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Hydrazides as Tunable Reagents for Alkene Hydroamination and Aminocarbonylation

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Hydrazides as Tunable Reagents for Alkene Hydroamination and Aminocarbonylation

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Thesis submitted to the Faculty of Graduate & Postdoctoral Studies, University of Ottawa
in partial fulfillment of the requirements for the M.Sc. degree in the
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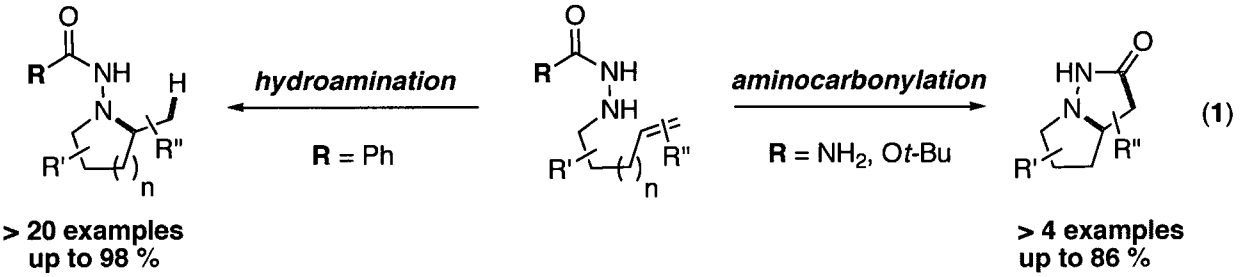
Abstract



(1)

Intramolecular hydroamination and aminocarbonylation of alkenes are highly desirable synthetic transformations providing access to structures frequently used in medicinal chemistry. Most research efforts currently focus on achieving this reactivity through transition metal catalysis. Our approach involves using hydrazides under thermal (metal-free) conditions to achieve hydroamination or aminocarbonylation upon selection of the appropriate hydrazide substituent (**R**). Upon substitution when **R**=Ph, various different compounds were synthesized and isolated in moderate to excellent yields (39 to 98%). Primary and secondary hydrazides pyrrolidines were cyclized and terminal or internal substituted double bonds were tolerated. Morpholine, piperazine, piperidine and azepane moieties were also cyclised with increased heat. This methodology was also consistent with hydroamination on a benzylic olefin. Aminocarbonylation products were obtained in good to excellent yields (52-86%), when **R**= NH_2 and O-*t*Bu. Substituted terminal bonds are obtained with retention of alkene stereochemistry, suggesting a novel concerted reaction pathway. Such reactions are very practical: the starting materials are accessed readily, and both starting materials and products are easy to handle and purify. Such products are also remarkably stable at high temperatures.

Acknowledgements

Well... WOW, already two years and a master's done. Time flies when you are in good company of classmates, colleagues and even friends. I started my master's being a bit pessimistic about this WHOLE research thing, however, within a few weeks of RESEARCH, I new that I wanted to undergo research for the rest of my life in Organic Chemistry or other domains. Nevertheless, this love that have I acquired for organic chemistry can be attributed in large part to André Beauchemin, my supervisor. Andre is passionate to the max about organic chemistry even so, that sometimes; i used to wonder how he managed to do everything. I would like to thank Andre for believing in me, even more then sometimes I would believe in my self. I would also like to thank Andre for the motivational speeches that were welcomed with open arms (yeppers that's organic chemistry, it doesn't always work!).

The first few weeks in the lab involved the training aspect (how to!) and, without the help of Pam and her profound commitment, this would have been impossible. Thank you Pam for being there and helping me out! I would also thank Isabelle, Joseph and Joffré for the odd questions. Francis, my ex-lab mate, is passionate and helpful. Even if he doesn't know the answer he will go out of his way to find it. Francis, I would like to thank you for all those long conversations about life, chemistry and everything else we talked about, you are truly a genuinely GOOD person and I wish you much success in Organic Chemistry. Whenever I got into arguments with my girlfriend or colleagues, Toni was the one to go to. Thank you Toni for listening to my BS. I would also like to thank Hao, Jenn, Christian, Ashley, Peter and the rest for putting up with my somewhat hard headedness! Finally, my parents and friends for believing in me and supporting through this life experience.

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Abbreviations

ΔG	activation free energy
AM	anti-Markovnikov
approx.	approximately
aq.	aqueous
Ar	argon
BHT	butylated hydroxytoluene
calcd	calculated
cat.	catalyst or catalyzed
$CHCl_3$	chloroform
COSY	correlation spectroscopy
Cp	cyclopentadiene
G	Gibbs free energy
GCMS	gas chromatograph/mass spectrometry
eq.	equation
equiv.	molar equivalents
Et_2O	diethyl ether
EtOAc	ethyl acetate
h	hours
i-Pr	isopropyl
$KMnO_4$	potassium permanganate
M	Markovnikov
MHz	megahertz
mL	millilitres

HMBC	heteronuclear multiple bond correlation experiment
HRMS	high resolution mass spectrometry
M	molarity
MeOH	methanol
mg	milligrams
min	minutes
mmol	millimolar
n-Bu	normal butyl
NMR	nuclear magnetic resonance spectroscopy
NOESY	nuclear Overhauser effect spectroscopy
$PhCF_3$	α,α,α-trifluorotoluene
PhCl	chlorobenzene
ppm	parts per million
R_f	rate of flow (coelution coefficient)
r.t.	room temperature
t-Bu	tertiary butyl
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilane
TS	transition state
μL	microlitre
vs	versus

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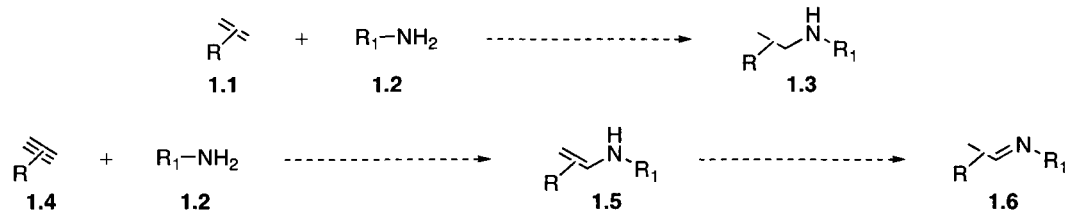
Chapter 1. General hydroamination reactivity

1.1 Amination reactions

The frequent incidence of amines, imines, enamines and nitrogen heterocycles in commercial pharmaceutical and natural products, as well as other chemicals makes the formation of C-N bond a desirable synthetic transformation. These have traditionally been categorized as amination reactions.[1] An amination reaction is the process by which a nitrogen atom is introduced into a molecule, this process can occur in a number of ways which include reactions with ammonia or other types of amines such as alkylations (with acyl chloride or alkyl halide), reductive amination, Mannich reaction, Mitsunobu reaction, and Ritter amination.

1.1.1 Hydroamination reactions

Contrary to the reactions just mentioned, hydroamination has been thought to be an atom-efficient reaction where a nitrogen atom and a hydrogen atom are added onto a carbon-carbon double or triple bond. The hydroamination of alkenes gives rise to the corresponding amine (**1.3**) moiety and the hydroamination of alkynes results in the enamine, which after tautomerization gives the imine (**1.6**).



Scheme 1.1: General hydroamination of alkyne and alkene

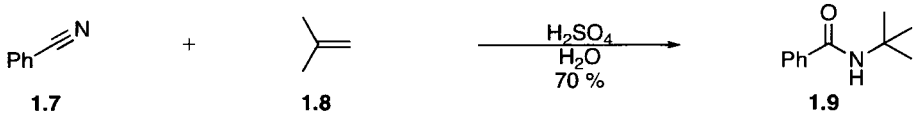
Even though this reaction is atom-efficient, the transformation has a high activation barrier due to electrostatic repulsions between the nitrogen lone pair and the corresponding alkyne or alkene. Also, the intermolecular variants are generally thermodynamically neutral due to the negative entropy of the reaction therefore, increasing the temperature would revert to the starting material. In order to overcome this, catalysis by either transition metals or strong acidic conditions are employed. These reactions tend not to be used in organic synthesis by industry due to poor substrate scope and problems of functional group compatibility. The

[1] (a) Dugger, R. W.; Ragan, J. A.; Brown Ripin, D. H. *Org. Proc. Res. Dev.* **2005**, *9*, 253.
(b) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337.

current developments in hydroamination will be described in the following sections. Even though the interest in hydroaminations has increased during the last decade there is still no general method that circumvents the issues of thermodynamics, substrate scope and limited reactivity.

1.1.2 Bronsted acid catalyzed hydroamination

Bronsted acids have not been used significantly for catalysis in the hydroamination of alkenes and alkynes due to an atom inherent buffering problem. The basic character of the nitrogen atom compared to the π-system of the double or triple bond favors formation of the conjugate acid over that of the carbocation. In this way, the nucleophilicity of the nitrogen is obliterated and protonation (activation) of the alkene or alkyne followed by attack of the nitrogen is inhibited. Nevertheless, use of catalytic amounts of acids and deactivated amines has shown to allow the inter- and intramolecular hydroamination of alkenes and alkynes.[2] Previously published results in this area include, the intermolecular hydroamination, known as the Ritter amination, which relies on acid catalysis. As seen in equation **1.1**, upon protonation of the alkene with a strong acid, the nitrile attacks and renders the Markovnikov product (**1.9**) in moderate yield. From this reaction, poor functional group compatibility and substrate scope limitation is observed.[3]



1.7 **1.8** **1.9** **(1.1)**

Reactions that use acids necessarily require the use of a system that is biased by using an alkene that is generally very reactive or strained (e.g. norbornene) and a nitrogen nucleophile that is slightly deactivated. Schlummer and Hartwig[4] reported the first example of intramolecular hydroamination in 2002. Under the presence of substochiometric amounts of triflic acid, reaction of aminoalkenes (**1.10**) led to the formation of the

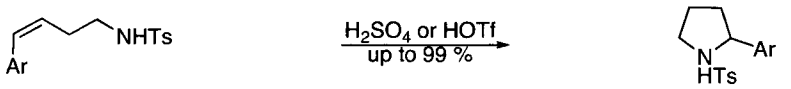
---

[2] (a) Muller, T. E.; Berger, M.; Grosche, M.; Herdtweck, E.; Schmidtchen, F. P. *Organometallics* **2001**, *20*, 4384–4393 (b) Penzien, J.; Su, R. Q.; Mu¨ller, T. E. *J. Mol. Catal. A: Chem.* **2002**, *182-183*, 489–498 (c) Mizuno, N.; Tabata, M.; Uematsu, T.; Iwamoto, M. *J. Catal.* **1994**, *146*, 249–256.

[3] (a) Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045 (b) Ritter, J. J.; Kalish, J. *J. Am. Chem. Soc.* **1948**, *70*, 4048.

[4] Schlummer, B.; Hartwig, J. F. *Org. Lett.* **2002**, *4*, 1471–1474.

corresponding pyrrolidines (**1.11**) and piperidines in excellent yields. Nevertheless, in order to reduce the basicity of the amine and prevent its protonation, tosylation of the amine was performed.



1.10 **1.11** **(1.2)**

From these studies, Yin and Zhao applied the former methodology to the synthesis of indoles and quinolines.[5] Ackermann et al.[6] were the first to introduce an intramolecular hydroamination reaction of nonactivated alkenes with alkylamine, using Bronsted acid catalysis. Nevertheless, the system was biased: Thorpe-Ingold effect was needed in order to achieve excellent yields for the cyclization.

The Bergman group reported the intermolecular hydroamination of a handful of alkenes (equation 1.3) with only 5 mol % of catalyst.[7]

1.12 **1.13** **1.14** 13 %, 1:1 ratio **1.15** **(1.3)**

Similar to those reported by Bergman, Hartwig reported the addition of a deactivated amine nucleophile onto norbornene,[8] which could be performed under milder conditions and lower catalyst loading. The He group also demonstrated similar results.[9]

---

[5] Yin, Y.; Zhao, G. *Heterocycles* **2006**, *68*, 23–31.

[6] Ackermann, L.; Kaspar, L. T.; Althammer, A. *Org. Biomol. Chem.* **2007**, *5*, 1975–1978.

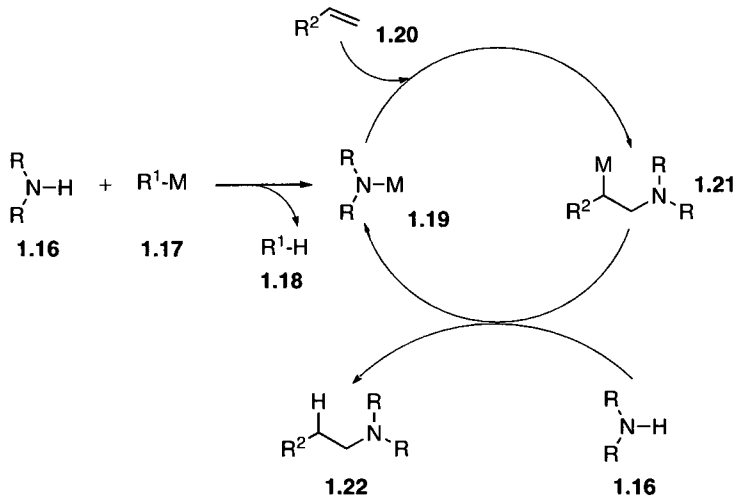
[7] Anderson, L. L.; Arnold, J.; Bergman, R. G. *J. Am. Chem. Soc.* **2005**, *127*, 14542

[8] Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett.*, **2006**, *8*, 4179.

[9] Li, Z.; Zhang, J.; Brouwer, C.; Yang, C.-G.; Reich, N. W.; He, C. *Org. Lett.* **2006**, *8*, 4175.

1.1.3 Base/alkali metal-catalyzed hydroamination

Another method that has been employed to access amination products is the base/alkali metal-catalyzed hydroamination. Firstly, this involves the deprotonation of the amine. From this, the deprotonated amine is able to attack the unactivated alkene or alkyne. The proposed mechanism (Scheme 1.2), shows deprotonation of the amine with a strong alkali base, and leads to the alkali amide **1.19** (initiation step). Following the initiation step, the highly reactive intermediated adds onto the alkene to form a more reactive organometallic species **1.21**, which deprotonates another amine in the reaction medium and the alkali amide is regenerated (**1.19**).

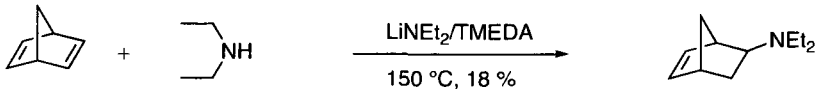


Scheme 1.2 : General base metal catalyzed hydroamination

Similar to the acid catalysis, the base catalysis utilizes harsh condition, and high temperatures and pressures are also needed.[10] Reasonable yields were obtained when the developing charge was stabilized by an sp^2 carbon alpha to the alkene. Reinehr and Lemkuhl reported a reaction with 2,5-norbornadiene (**1.23**) and

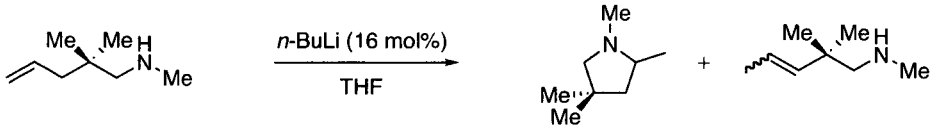
[10] Howk, B. W.; Little, E. L.; Scott, S. L.; Whitman, G. M. *J. Am. Chem. Soc.* **1954**, *76*, 1899.

diethylamine (**1.24**), which gave the hydroamination product in low yields (equation 1.4).[11]



1.23 + **1.24** → **1.25** **(1.4)**

Similar conditions were reported by the Narducy group in which 2,5-norbornadiene was replaced by styrene; lower temperatures and higher yields were also observed.[12] Intramolecular variants were shown to be possible; Ates and Quinet[13] reported the first cyclization of primary and secondary amines onto an alkene in THF at 50 °C or 20 °C using *n*-BuLi (5 – 16 mol%) as the precatalyst.



1.26 → **1.27** + **1.28** **(1.5)**

Olefin isomerisation and solvent specificity[14] were problems that were encountered nevertheless; Hultzch et al. demonstrated the first asymmetric bas-catalysed intramolecular hydroamination reactions of aminoalkenes.[15] Others have also shown different variants, which utilize a chiral amine and a strong alkali metal (ex. Li,[16] *n*-BuLi[17], CsOH[18]).

---

[11] Lemkuhl, H.; Reinehr, D. *J. Organomet. Chem.* **1973**, *55*, 215.

[12] Schlott, R. J.; Falk, J. C.; Narducy, K. W. *J. Org. Chem.* **1972**, *37*, 4243.

[13] Ates, A.; Quinet, C. *Eur. J. Org. Chem.* **2003**, 1623.

[14] Quinet, C.; Jourdain, P.; Hermans, C.; Ates, A.; Lucas, I.; Marko, I. E. *Tetrahedron* **2008**, *64*, 1077.

[15] Horrillo Martinez, P.; Hultzsch, K. C.; Hampel, F. *Chem. Commun.* **2006**, 2221.

[16] Ogata, T.; Ujihara, A.; Tsuchida, S.; Shimizu, T.; Kaneshige, A.; Tomioka, K. *Tetrahedron Lett.* **2007**, *48*, 6648.

[17] van Otterlo, W. A. L.; Pathak, R.; de Koning, C. B.; Fernandes, M. A. *Tetrahedron Lett.* **2004**, *45*, 9561.

[18] Tzalis, D.; Koradin, C.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 6193.

1.1.4 Transition metal-catalyzed hydroamination

Up to date, hydroamintion has proven to be most efficient with the use of metal catalysts, which tend to lower the high activation barrier. The hydroamination of alkenes is harder than that of alkynes due to the lower reactivity and lower electron density of the double bond.[19] There are three classes of metals used to perform hydroaminations: the Lanthanides and Actinides,[20] the early transition metals[21] and finally the late transition metals.[22] While most alkali and lanthanide metal catalysts were used in early studies, focus has recently shifted to the use zirconium, titanium and late transition metals catalysts.

Rare-earth metal complexes are highly efficient catalysts for intramolecular hydroamination of various C-C unsaturations such as alkenes, alkynes,[23] allenes[24] and dienes[25] but reduced rates are observed in the intermolecular hydroamination process. The general hydroamination mechanism for those reactions involves a rate-limiting C-C double bond insertion in the Ln-N bond (**1.30-1.31**), followed by a rapid protonolysis by the amine (Scheme 1.3).

---

[19] Haggins, J. *Chem. Eng. News* **1993**, *71* (22), 23–27.

[20] For reviews on lanthanides and actinides please see (a) Hultzsch, K. C. *Org. Biomol. Chem.* **2005**, *3*, 1819–1824 (b) Hultzsch, K. C.; Gribkov, D. V.; Hampel, F. *J. Organomet. Chem.* **2005**, *690*, 4441–4452 (c) Kim, Y. K.; Livinghouse, T.; Horino, Y. *J. Am. Chem. Soc.* **2003**,*125*, 9560–9561. (d) Kim, J. Y.; Livinghouse, T. *Org. Lett.* **2005**, *7*, 4391–4393. (e) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673–686.

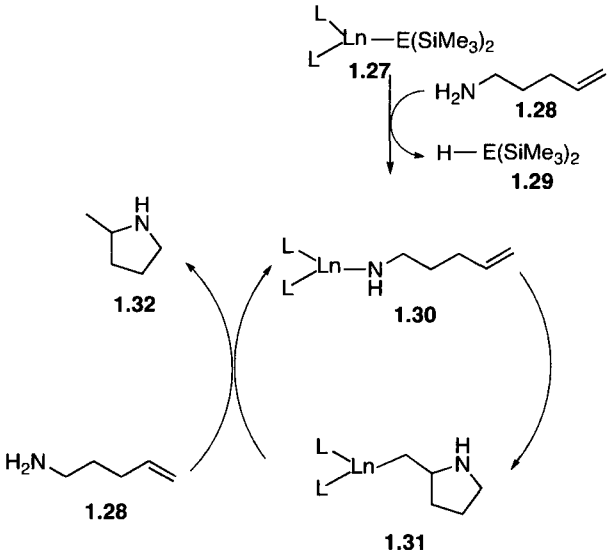
[21] For a review on early transition metal catalysts Lee, A. V.; Schafer, L. L. *Eur. J. Inorg. Chem.* **2007**, 2245–2255.

[22] For reviews on late transition metal catalysts (a) Brunet, J.-J.; Chu, N.-C.; Rodriguez-Zubiri, M. *Eur. J. Inorg. Chem.* **2007**, 4711–4722 (b) Liu, C.; Bender, C. F.; Han, X.; Widenhoefer, R. A. *Chem. Commun.* **2007**, 3607–3618 (c) Widenhoefer, R. A.; Han, X. *Eur. J. Org. Chem.* **2006**, 4555–4563.

[23] Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 9295–9306.

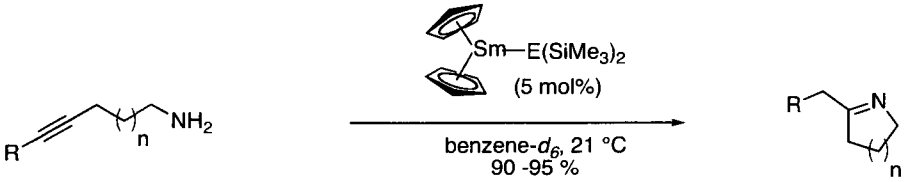
[24] Arredondo, V. M.; Tian, S.; McDonald, F. E.; Marks, T. J. *J. Am.Chem. Soc.* **1999**, *121*, 3633–3639.

[25] (a) Hong, S.; Marks, T. J. *J. Am. Chem. Soc.* **2002**, *124*, 7886–7887 (b) Hong, S.; Kawaoka, A. M.; Marks, T. J. *J. Am. Chem. Soc.* **2003**,*125*, 15878–15892 (c) Stubbert, B. D.; Marks, T. J. *J. Am. Chem. Soc.* **2007**, *129*, 4253–4271.



Scheme 1.3 : General rare-earth metal catalyzed hydroamination of an aminoalkene

The catalytic activity generally increases as the ionic radius of the rare-earth metal ion increases (i.e. La, Sm and Lu).[26] Marks and Li[23] reported in 1996 a catalyzed hydroamination of aliphatic (**1.32**) and aromatic aminoalkynes to yield the corresponding imines (**1.33**). They were able to synthesize five, six and seven membered rings in reasonable yields (equation 1.6).



1.32 (a-g)
R= Ph, Me_3Si, H
n= 1,2, 3

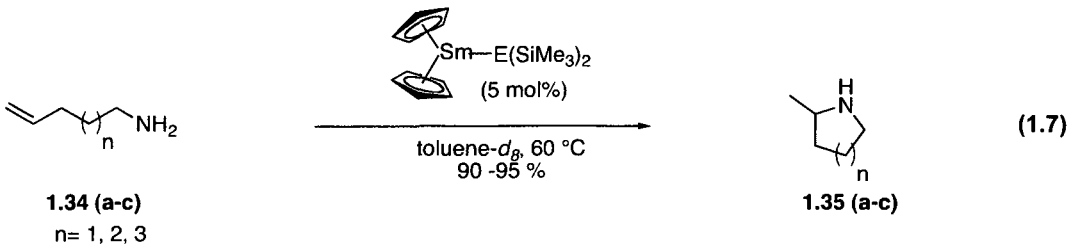
1.33 (a-g)

(1.6)

Alkenes were also subject to cyclization with lanthanides[26] or actinides base catalysts. Even though alkenes required higher temperatures, pyrroldines, piperidines and azepane rings were all synthesized in excellent yields (equation 1.7).

---

[26] Gagné, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **1989**, *111*, 4108–4110. (b) Gagné, M. R.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 275–294.



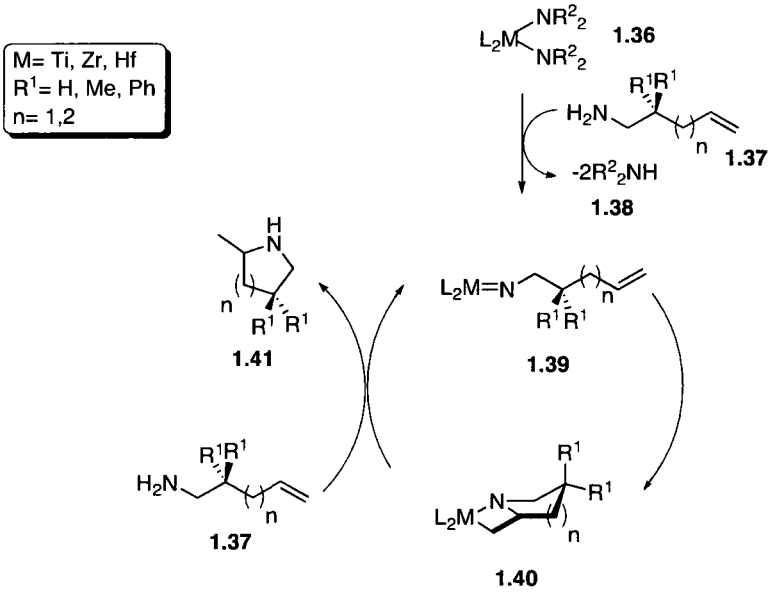
1.34 (a-c)
n= 1, 2, 3

1.35 (a-c)

(1.7)

Rare earth metals have through these studies and others shown to be very efficient catalysts for hydroamination, however their sensitivity to oxygen and moisture have limited their use in many synthetic applications.

Lately, early transition metals have been used extensively including titanium and zirconium. The mechanism at play is suggested to involve a [2 + 2] cycloaddition of the metal imido species (**1.39**) to the olefin, followed by subsequent protonation of the azametallacycobutane (**1.40**) by another aminoalkene substrate (**1.37**).



Scheme 1.4 : Mechanism for the hydroamination of primary aminoalkenes using goup 4 (early) metal catalysis

Bergman[27] and Livinghouse[28] reported the first titanium-based hydroamination catalyst systems. From these initial reports numerous titanium-based hydroamination catalysts have been developed. Titanium catalysts are particularly useful in inter- and intramolecular hydroaminations of alkynes and allenes.[29] This regioselectivity challenge was addressed successfully with internal and external alkynes. Nevertheless, for industrial applications the functionalization of compounds with an unsaturation at the terminal position was of most significance.[30] There were therefore intensive studies and a wide range of catalysts developed in the field. The n^2-alkyne titanocene $Cp^2Ti(n^2\text{-}Me_3SiCCSiMe_3)$ was found by the Beller group[31] to catalyze the anti-Markovnikov addition of the sterically hindered *tert*-butyl amine to terminal aliphatic alkynes with high regioselectivity (Table 1, entries 1-3). Sterically less demanding aliphatic amines also produced anti-Markovnikov products with lower regioselectivities (Table 1.1, entries 4 and 5) and aromatic amines led predominantly to the Markovnikov adduct (Table 1, 6-10).

---

[27] (a) Walsh, P. J.; Baranger, A. M.; Bergman, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 1708–1719. (b) Baranger, A. M.; Walsh, P. J.; Bergman, R. G. *J. Am. Chem. Soc.* **1993**, *115*, 2753–2763. (c) Walsh, P. J.; Hollander, F. J.; Bergman, R. G. *Organometallics* **1993**, *12*, 3886 (d) Lee, S. Y.; Bergman, R. G. *Tetrahedron* **1995**, *51*, 4255–4276. (e) Polse, J. L.; Andersen, R. A.; Bergman, R. G. *J. Am.Chem. Soc.* **1998**, *120*, 13405–13414.

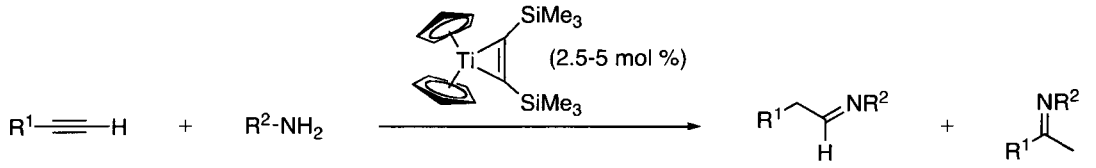
[28] (a) McGrane, P. L.; Livinghouse, T. *J. Am. Chem. Soc.* **1993**, *115*, 11485–11489. (b) McGrane, P. L.; Livinghouse, T. *J. Org. Chem.* **1992**, *57*, 1323–1324. (c) McGrane, P. L.; Jensen, M.; Livinghouse, T. *J. Am. Chem. Soc.* **1992**, *114*, 5459–5460. (d) Fairfax, D.; Stein, M.; Livinghouse, T.; Jensen, M. *Organometallics* **1997**, *16*, 1523–1525. (e) Duncan, A. P.; Livinghouse, T. *Organometallics* **1999**, *18*, 4421–4428.

[29] For reactions that involve allenes please see (a) Johnson, J. S.; Bergman, R. G. *J. Am. Chem. Soc.* **2001**, *123*, 2923–2924 (b) Ackermann, L. *Organometallics* **2003**, *22*, 4367–4368. (c) Anderson, L. L.; Arnold, J.; Bergman, R. G. *Org. Lett.* **2004**, *6*, 2519–2522. (d) Anderson, L. L.; Arnold, J.; Bergman, R. G. *Org. Lett.* **2006**, *8*, 2445–2445. (e) Ayinla, R. O.; Schafer, L. L. *Inorg. Chim. Acta* **2006**, *359*, 3097–3102. (f) Ackermann, L.; Bergman, R. G. *Org. Lett.* **2002**, *4*, 1475–1478. (g) Ackermann, L.; Bergman, R. G.; Loy, R. N. *J. Am. Chem. Soc.* **2003**, *125*, 11956–11963.

[30] Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368–3398.

[31] (a) Tillack, A.; Castro, I. G.; Hartung, C. G.; Beller, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 2541–2543. (b) Tillack, A.; Jiao, H.; Castro, I. G.; Hartung, C. G.; Beller, M. *Chem. Eur. J.* **2004**, *10*, 2409–2420.

Table 1.1 : Anti-Markovnikov hydroamination reactions



Entry	R^1	R^2	Temperature (°C)	Time (h)	Yield (%)	A/B
1	*n*-Bu	*t*-Bu	85	2	90	>99:1
2	*n*-Octyl	*t*-Bu	85	24	93	63:1
3	$PhCh_2$	*t*-Bu	85	24	88	100:0
4	*n*-Bu	*s*-Bu	85	24	86	3:1
5	*n*-Bu	CH(Me)Ph	100	24	79	2:1
6	*n*-Bu	Ph	85	24	94	1:3
7	*n*-Hex	$4\text{-}MeOC_6H_4$	85	24	61	50:50
8	*n*-Hex	$2\text{-}EtOC_6H_4$	100	24	80	9:91
9	*n*-Hex	$2\text{-}MeC_6H_4$	85	24	93	12:88
10	*n*-Hex	$2,6\text{-}Me_2C_6H_3$	85	24	68	2:98

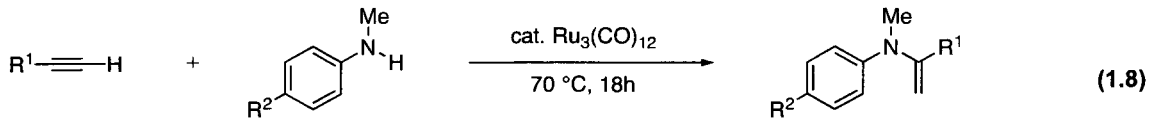
Computational studies revealed that the regioselectivity is determined by the relative stability of the imido alkyne complex that precedes the [2+2] cycloaddition step. Even though regioselectivity was controlled with early transition metals, low functional group tolerance for early transition metal catalyst has been observed.

The use of late transition metals has been extensively researched and has shown to have a broader application than the rare earth metals and early transition metals. Metal complexes with Lewis acidic character and with d^8 and d^{10} electron configurations appear to have a particularly high affinity in the hydroamination process. Thus, Ru^0, Rh^I and Ir^I, Pd^{II} and Pt^{II}, Cu^I and Zn^{II} catalysts show high activity. Generally in all catalyzed hydroaminations, the addition of the amine to the alkene or alkyne precedes with Markovnikov regioslectivity. Unlike the lanthanides and early transition metals, various mechanistic models have been suggested for hydroaminations using late transition metals. These models can be classified in four different groups:

nucleophilic attack on a coordinated alkenes or alkynes,[32] nucleophilic attach on allylic alkenes,[33] insertion of the alkenes or alkynes into a metal-hydride bond[34] and oxidative addition of the amine.[35]

Knowing the extensive research efforts in the field of late transition metals, only a brief overview will be discussed.

Firstly, the intermolecular hydroamination of alkynes using three different late transition metals. In 1999 Uchimara reported the first ruthenium-catalysed hydroamination.[36] The terminal alkynes (**1.46**) would undergo hydroamination with and aromatic amine (**1.47**) in the presence of catalytic amount of $Ru_3(CO)_{12}$.



1.46 (a-d) **1.47 (a-b)** **1.48 (aa-db)** **(1.8)**

R^1= Ph, *p*-MeC_6H_4, *p*-FC_6H_4, cyclohex-1-enyl
R^2= H, Me

5 examples, 76-85 %

---

[32] (a) Seul, J. M.; Park, S. *J. Chem. Soc., Dalton Trans.* **2002**, 1153–1158 (b) Muller, T. E.; Berger, M.; Grosche, M.; Herdtweck, E.; Schmidtchen, F. P. *Organometallics* **2001**, *20*, 4384–4393. (c) Muller, T. E.; Grosche, M.; Herdtweck, E.; Pleier, A.-K.; Walter, E.; Yan, Y.-K. *Organometallics* **2000**, *1*, 170–183. (d) Penzien, J.; Su, R. Q.; Mu¨ller, T. E. *J. Mol. Catal. A: Chem.* **2002**, *182-183*, 489–498. (e) Ambuehl, J.; Pregosin, P. S.; Venanzi, L. M.; Consiglio, G.; Bachechi, F.; Zambonelli, L. *J. Organomet. Chem.* **1979**, *181*, 255. (e) Seligson, A. L.; Trogler, W. C. *Organometallics* **1993**, *12*, 744. (f) Senn, H. M.; Block, P. E.; Togni, A. *J. Am. Chem. Soc.* **2000**, *122*, 4098.

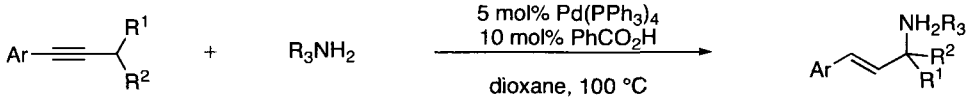
[33] (a) Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 5421–5424. (b) Al-Masum, M.; Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* **1997**, *38*, 6071–6074. (c) Besson, L.; Gore, J.; Cases, B. *Tetrahedron Lett.* **1995**, *36*, 3857–60. (d) Loeber, O.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4366–4367. (e) Johns, A. M.; Utsunomiya, M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 1828–1839. (f) Minami, T.; Okamoto, H.; Ikeda, S.; Tanaka, R.; Ozawa, F.; Yoshifuji, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 4501–4503. (g) Pawlas, J.; Nakao, Y.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 3669–3679. (h) Sakai, N.; Ridder, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 8134–8135.

[34] (a) Sievers, C.; Jimenez, O.; Knapp, R.; Lin, X.; Muller, T. E.; Wierczinski, B.; Lercher, J. A. *J. Mol. Catal. A. Catal.* **2007** (b) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9546–9547

[35] (a) Sappa, E.; Milone, L. *J. Organomet. Chem.* **1973**, *61*, 383–388. (b) Beller, M.; Trauthwein, H.; Eichberger, M.; Breindl, C.; Muller, T. E. *Eur. J. Inorg. Chem.* **1999**, 1121–1132. (c) Beller, M.; Trauthwein, H.; Eichberger, M.; Breindl, C.; Herwig, J.; Muller, T. E.; Thiel, O. R. *Chem. Eur. J.* **1999**, *5*, 1306–1319. (d) Beller, M.; Eichberger, M.; Trauthwein, H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2225–2227. (e) Zhao, J.; Goldman, A. S.; Hartwig, J. F. *Science* **2005**, *307*, 1080–1082. (f) Tsipis, C. A.; Kefalidis, C. E. *Organometallics* **2006**, *25*, 1696–1706. (g) Cowan, R. L; Trogler, W. C. *Organometallics* **1987**, *6*, 2451–2453. (h) Cowan, R. L.; Trogler, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4750–4761.

[36] Uchimaru, Y. *Chem. Commun.* **1999**, 1133–1134.

The Yamamoto group demonstrated the use of palladium and benzoic acid to catalyze the hydroamination of internal alkynes (**1.49**). The product obtained was the corresponding allylic amines (**1.51**) instead of the desired hydrazone due to formation of a π-allyl intermediate.[37]

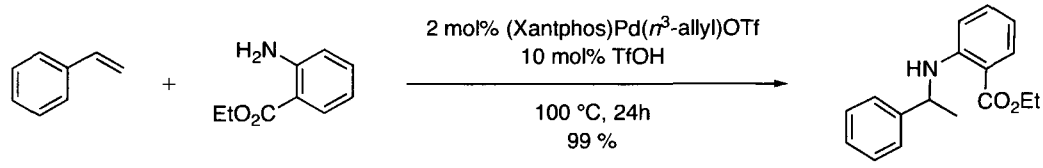


1.49 (a-d) **1.50 (a-d)** **1.51 (aa-dd)** **(1.9)**

Ar= Ph, *p*-$MeOC_6H_4$
R^1= H, OMe
R^2= H
R^3= Bn, Ts, CH_2CO_2Et, $(CH_2CH_2)_2O$

5 examples, 61-98 %

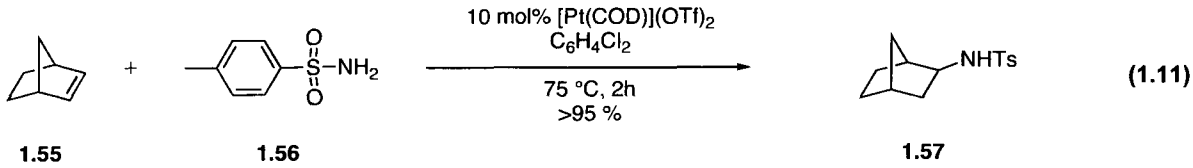
The intermolecular hydromamination of alkenes is often less successful than the equivalent intramolecular variants, because of the increased energy required to achieve this process, combined with the inherent thermodynamic issues that need to be addressed. Generally, methods include hydroamination with activated alkenes such as styrenes (**1.52**) and strained alkenes (**1.55**). Typically, lanthanide catalysts have higher reactivity towards olefins nevertheless, in spite of this, the Hartwig group was able to catalyze the addition of aniline derivatives to styrene based alkenes in the presence of free alcohols, free carboxylic acid, free amides and esters (equation **1.10**), which would most probably not have been possible with lanthanides.



1.52 **1.53** **1.54** **(1.10)**

Prior to Hartwig's published results, the Tilley group demonstrated that the electrophilic Pt(II) complexes catalyze efficient hydroamination of olefins by sulfonamides (**1.56**) and weakly basic amines (equation **1.11**).

[37] (a) Kadota, I.; Shibuya, A.; Mpaka Lutete, L.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 4570. (b) Mpaka Lutete, L.; Kadota, I.;Shibuya, A.; Yamamoto, Y. *Heterocycles* **2002**, *58*, 347.



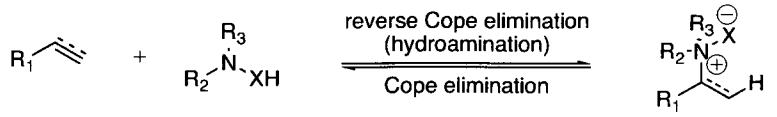
In conclusion, efficient lanthanide and actinide catalysts have been developed, but their intermolecular use gives generally slow and low yielding (≤15 %) reactions. Early transition metals (group 4) have similar reactivity, but are easier to handle. Late transition metal catalysts are known for this reactivity being less sensitive to air and more tolerant[38] towards polar functional groups. However, intermolecular hydroaminations of alkenes that are catalyzed by late transition metals provide low rates and have limited scope. Also, intramolecular variants require the installation of deactivating groups at the amine position in order to cyclise at lower temperature. Newly developed intramolecular reactions with rhodium do not require the use of deactivated amines, nevertheless, Thorpe-Ingold effects are needs in order to obtain reasonable yields. Finally, no general method has been employed and in the next section a *metal-free* variant will be proposed, along with initial results reported, that are in accordance with a more general substrate scope.

1.2 The Cope-type hydroamination reaction

The Cope-type hydroamination is a reaction that has not been widely documented as a hydroamination reaction; in essence, the reaction is the microscopic reverse of the Cope elimination.[39] Such a concerted hydroamination is, like other hydroaminatons previously discussed, adding both nitrogen and a hydrogen atom onto an unsaturated C-C bond, while using a bifunctional compound such as a hydroxylamine, hydrazine or hydrazide. In equation 1.12 are shown the addition of such bifunctional reagents **1.59** onto an alkene or alkyne substituant.

[38] Johns, A. M.; Utsunomiya, M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 1828.

[39] For a review on the reverse Cope elimination: Cooper, N. J.; Knight, D. W. *Tetrahedron* **2004**, *60*, 243.



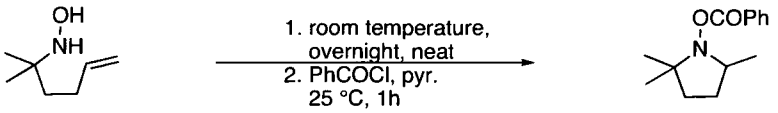
1.58 **1.59** **1.60** **(1.12)**

X = O, NH or $NCOR_4$

Also depicted is the proposed mechanism for such reactions involving a concerted 5-membered transition state that is supported by experimental DFT calculations.[42,43] These same DFT calculations revealed the reaction as an asynchronous process.[40] The compound **1.63** can be furthermore subjected to a proton transfer to get to the hydroamination product (**1.64**).

1.61 **1.62** **1.63** **1.64** **(1.13)**

House and co-workers reported the intramolecular version of the Cope-type hydroamination[41] in 1976, it was postulated that the mechanism went through a radical intermediate. Depicted in equation 1.14 is the formation of a pyrrolidine (**1.66**) from the corresponding alkenylhydroxylamine (**1.65**). The derived product was obtained in 34 % yield.



1.65 **1.66** **(1.14)**

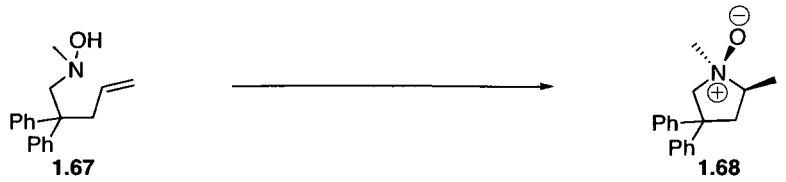
Following these studies, Ciganek[42] cyclized a similar, methyl-substituted hydroxylamine (**1.67**) to afford a single diastereoisomer.

---

[40] Beauchemin, A. M.; Moran, J.; Lebrun, M.-E.; Séguin, C.; Dimitrijevic, E.; Zhang, L.; Gorelsky, S. I. *Angew. Chem. Int. Ed.* **2008**, *47*, 1410.

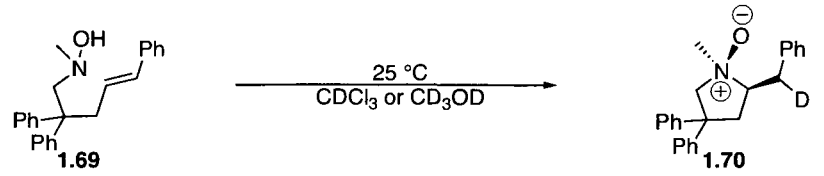
[41] (a) House, H. O.; Manning, D. T.; Melillo, D. G.; Lee, L. F.; Haynes, O. R.; Wilkes, B. E. *J. Org. Chem.* **1976**, *41*, 855. (b) House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863.

[42] Ciganek, E. *J. Org. Chem.* **1990**, *55*, 3007.



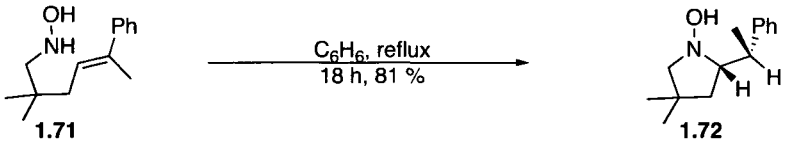
(1.15)

Upon analysis of the compound, the cyclized pyrrolidine displayed a cis relationship between the N-oxide and the beta methyl susbstituents. From this stereochemistry, the nitrogen and hydrogen atom were assumed to be delivered from the same face because no loss of stereochemistry was observed. This implied the reaction was a concerted process. To prove this theory Ciganek cyclized a similar deuterated methyl-substituted hydroxylamine (**1.69**) and upon isolation of the *N*-oxide (**1.70**) the deuterium transfer was consistent with a concerted proton transfer.

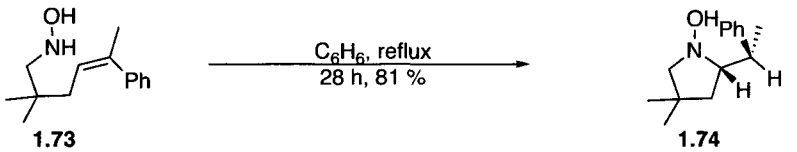


(1.16)

The Oppolzer[43] group reported the cyclization of the *E* and *Z*-alkenylhydroxylamines (**1.71** and **1.73**) and this provided both diastereoisomers (**1.72** and **1.74**) with complete retention of stereochemistry (equation **1.17** and **1.18**). These findings are once again consistent with the fact that the nitrogen and hydrogen are introduced suprafacially on the olefin.



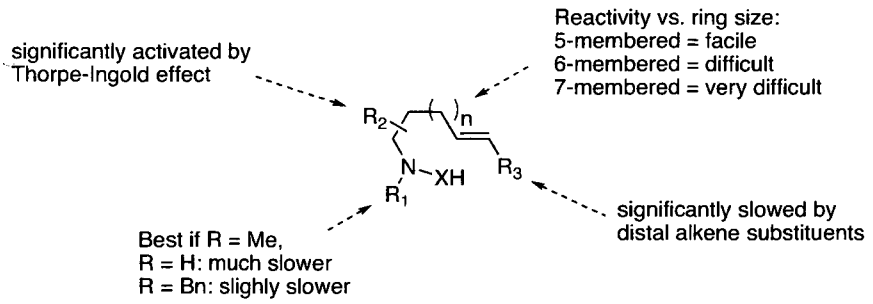
(1.17)



(1.18)

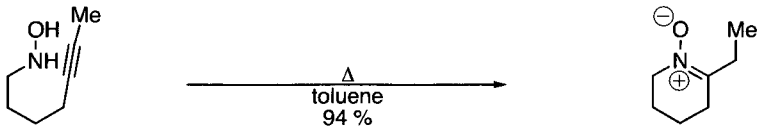
[43] Oppolzer, W.; Spivey, A. C.; Bochet, C. G. *J. Am. Chem. Soc.* **1994**, *116*, 3139.

In a recent review article, knight summarized the reactivity trend observed for intramolecular Cope-type hydroamination as depicted in Scheme 1.5.



Scheme 1.5 : General trends for Cope-type cyclizations

The cyclization that requires the least energy is a 5-membered methyl-substituted hydroxylamine, which can be accelerated by a Thorpe-Ingold effect. The alkenylhydroxylamine is cyclized onto a terminal double bond. Nevertheless, a few examples of more complex systems have been shown throughout the years. The Homes group[44] demonstrated the cyclization of a six membered ring onto an alkyne (**1.75**), even though distal substitution on alkynes are known to require harsher reaction conditions the *N*-oxide **1.76** was isolated in good yields.



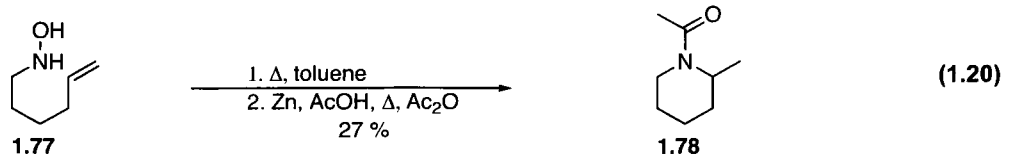
1.75 **1.76** **(1.19)**

Cyclization of a six membered ring to form piperadine followed by the cleavage of the N-O bond and production of the amine (**1.78**) in 27 % yield. House[45] reported this in 1976, mentioning that compared to the 5-membered ring systems, the 6-membered required higher temperatures and resulted in lower yields.

---

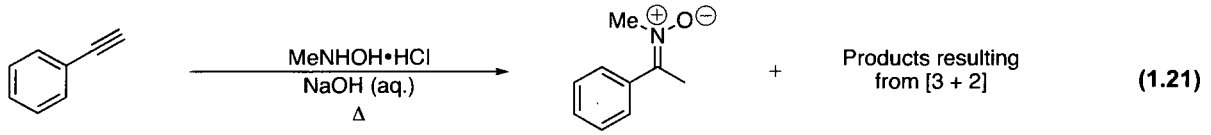
[44] Fox, M. E.; Holmes, A. B.; Forbes, I. T.; Thompson, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3379.

[45] (a) House, H. O.; Manning, D. T.; Melillo, D. G.; Lee, L. F.; Haynes, O. R.; Wilkes, B. E. *J. Org. Chem.* **1976**, *41*, 855. (b) House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863.



1.77 1.78 **(1.20)**

Up to now, only intramolecular variants have been shown, and in order to understand the problems and limitations of the Cope-type hydroamination as a general tool for synthesis, intermolecular variants will be shortly discussed. Padwa and Wong[46] reported three examples of intermolecular Cope-type hydroamination of aryl acetylene (**1.79**) with *N*-alkylhydroxylamines to form a nitrone intermediate (**1.80**) in poor yield. Following the reaction, the "nitrone intermediate" can further react to give a [3 + 2] product, yielding a complex mixture of products.



1.79 1.80 **(1.21)**

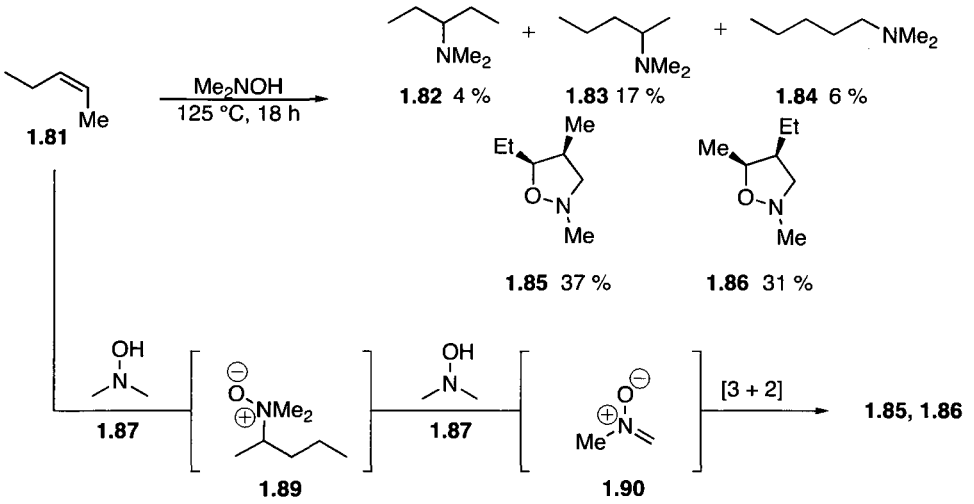
traces 69 %

The intermolecular Cope-type hydromamination of alkenes has been more obscure; Laughlin[47] reported the first example in 1973. The reaction involved *N,N*-dimethylhydroxylamine and (*Z*)-pent-2-ene (**1.81**), which gave a mixture of products, some of which had to originate from an initial Cope-type hydroamination (Scheme 1.6). The amines produced are obtained from different hydroamination regioisomeric products, which are further transformed by reduction by another hydroxylamine (**1.87**) in solution to give the corresponding amine (**1.82-1.84**) and nitrone (**1.90**). The resulting nitrone here again can undergo [3 + 2] cycloaddition reaction to give the isoxazolidines, that were observed by Laughlin as major products for this intermolecular reactivity (**1.85, 1.86**).

---

[46] Padwa, A.; Wong, S. K. *J. Org. Chem.* **1986**, *51*, 3125.

[47] Laughlin, R. G. *J. Am. Chem. Soc.* **1973**, *95*, 3295.

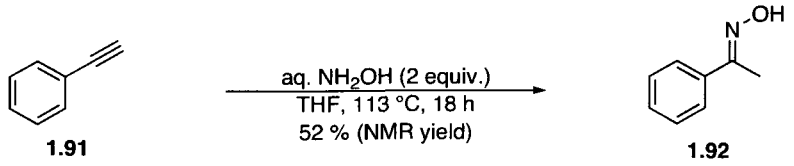


Scheme 1.6: Preliminary intermolecular Cope-type hydroamination onto an alkene

This latter reaction has shown significant potential for intermolecular Cope-type hydroaminations, however no use for synthetic purposes has surfaced in the literature, undoubtedly related to the uncontrollable side reactions and poor yields observed.

1.2.1 Previous work done by the Beauchemin group: using hydroxylamines

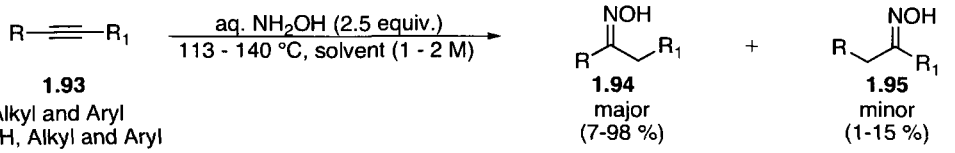
Marie-Eve Lebrun and Catherine Séguin observed the first example of intermolecular Cope-type hydroamination within the Beauchemin research group. Like previously stated, the π-bond of an alkyne is generally more reactive than that of an alkene, it was first used, in conjunction with aqueous hydroxylamine, that would minimize side reactions by generating stable oximes as the products of the reaction. Upon heating phenylacetylene (**1.91**) and hydroxylamine in THF at 113 °C, an NMR yield of 52 % was obtained for the *E*-oxime (**1.92**).



(1.22)

Subsequent optimization was done, and alcoholic solvents such as i-PrOH were found to be optimalfor intermolecular Cope-type hydroamination. The scope of these conditions is quite general, with terminal alkynes

reacting well, with both steric and electronic differences on the ring. Also, alkylacetylene, enynes and alkynes bearing a pryridine group, free hydroxyl groups, and common protecting groups were also well tolerated (equation 1.23).



1.93
R = Alkyl and Aryl
R_1 = H, Alkyl and Aryl

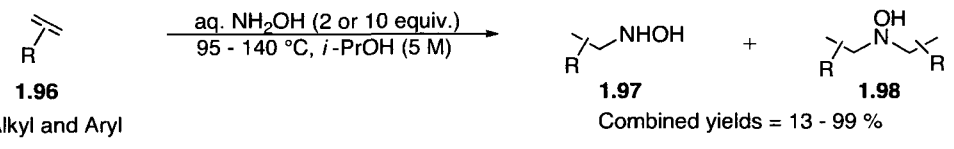
1.94
major
(7-98 %)

1.95
minor
(1-15 %)

(1.23)

22 examples

Encouraged by these results, the Beauchemin group focused on more challenging substrates. The hydroxylamine reacted well with substituted reactive norbornene derivatives; needless to say, alkenes substituants reacted much better in the presence of alcoholic solvents. Also styrene and vinylarenes having a free hydroxyl group and nitro were tolerated, as well as unconjuguated allylphenols (equation 1.24).



1.96
R = Alkyl and Aryl

1.97

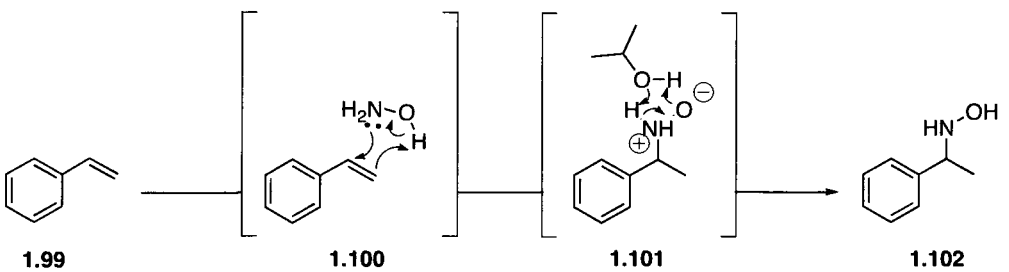
1.98

Combined yields = 13 - 99 %

(1.24)

10 examples

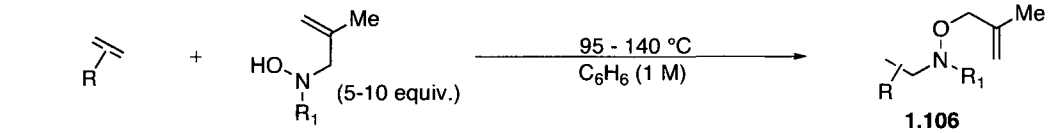
In order to increase our understanding of the Cope-type hydroamination, DFT calculations were performed in collaboration with Serge Gorlesky. The calculations suggested that protic solvents could be attributed to a more facile proton transfer (**1.101**) following Cope-type hydroamination (Scheme 1.7).



1.99 **1.100** **1.101** **1.102**

Scheme 1.7: Bimolecular proton transfer

These studies, like others[48] demonstrate that intermolecular hydroamination reactions of vinylarenes are nearly thermoneutral. Since the intermolecular hydroamination has negative entropy which in contrast with its high temperature requirement these limit the synthetic reach of intermolecular hydroamination. In order to resolve this important problem, the Beauchemin group was drawn to a tandem process where the hydroamination reaction is followed by an irreversible reaction, which provides a more stable hydroamination product. Mr. Joffré Bourgeois from the Beauchemin group reported a proof of concept that is now known as a Cope-type hydroamination/Mesenheimer rearrangement sequence.[49] This method is shown to be quite efficient with strained and less efficient with unstrained (4-flurostyrene and vinyltriphenylsilane) alkenes and also, substitution on the hydroxylamine was also well tolerated (equation 1.25).

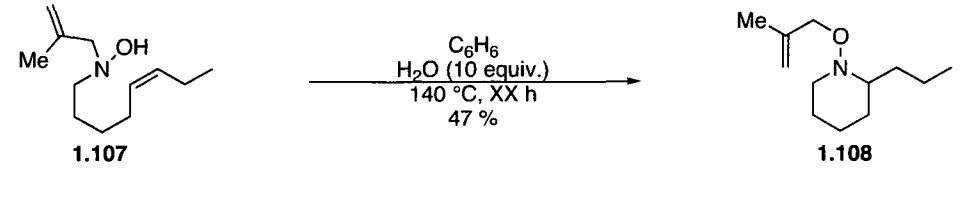


1.104 **1.105** **1.106** **(1.25)**

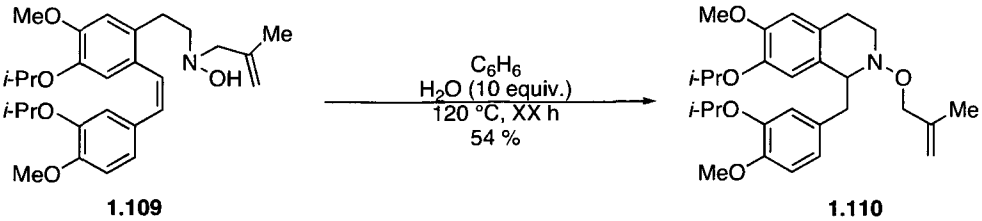
R = Alkyl and Aryl
R_1 = Alkyl

21-86 % yield
11 examples

This methodology has proven itself to be quite versatile and to illustrate the potential synthetic purpose of this cyclization, the syntheses of coniine (**1.108**) and norreticuline (**1.110**) were carried out as proof of concept.



1.107 **1.108** **(1.26)**



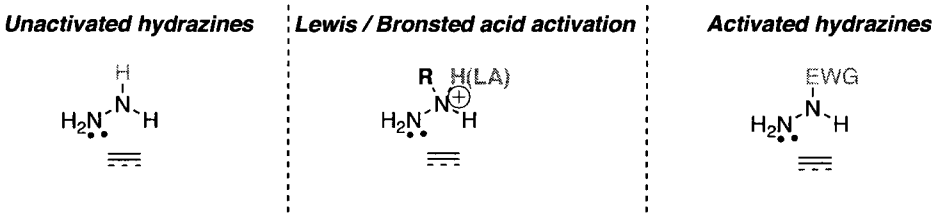
1.109 **1.110** **(1.27)**

[48] Johns, A. M.; Sakai, N.; Ridder, A.; Hartwig, J. F. *J. Am. Chem. Soc.***2006**, *128*, 9306.
[49] Bourgeois, J.; Dion, I.; Cebrowski, P. H.; Loiseau, F.; Bédard, A.-C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 874-875.

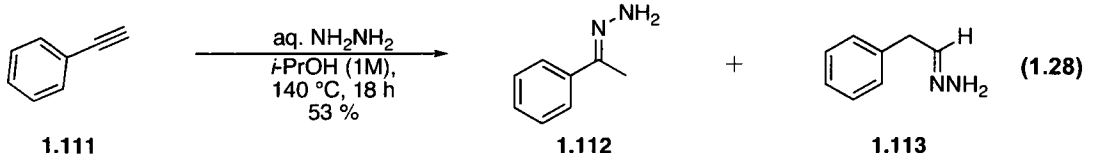
The hydroamination/Meisenheimer rearrangement sequence was developed to address the thermodynamic issue of the intermolecular reaction of alkenes and to improve the synthetic use of the Cope-type hydroamination.

1.2.2 Previous work done by the Beauchemin group: using hydrazines

Hydrazines have been considered as possible alternatives in the Cope-type hydroamination. Three different classes of hydrazines can be considered: unactivated hydrazines, activated hydrazines and Lewis/ Bronsted acid activated hydrazines.



Unactivated hydrazines have shown to be a possible contender in the Cope-type hydroamination. It was hypothesized that the use of substituted hydrazines (or hydroxylamines) could lead to a change in regioselectivity. Preliminary results where reported by Ms. Pamela Cebrowski who discovered that aqueous hydrazine and phenylacetyene (**1.111**) react together giving a 53 % NMR yield in a 2.5/1 (**1.113/1.112**) mixture of regioisomers favoring the "anti-Markovnikov" hydrazone.[50]



1.111 **1.112** **1.113** **(1.28)**

In order to optimize regioselectivity, the substituted hydrazine, methylhydrazine was used. This hydrazine led to increased conversions and regioselectivity. Having optimized conditions in hand, the substrate scope was evaluated and also derivatization of the linear hydrazone was done to allow its isolation by column chromatography (equation 1.29).

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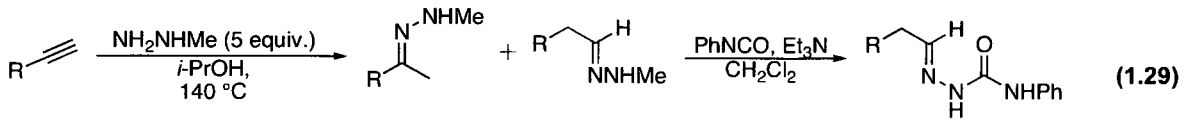
[50] Cebrowski, P. H.; Roveda, J.-G.; Moran, J.; Gorelsky, S. I.; Beauchemin, A. M. *Chem. Commun.* **2008**, 492.



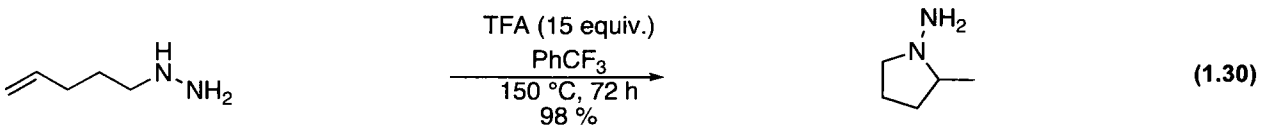
1.114 **1.115** **1.116** **1.117** **(1.29)**

R = Aryl

31-58 % yield
10 examples

Hydroamination of aromatic acetylenes and substituted arenes were generally well tolerated. Also, heterocyclic acetylenes react efficiently under the same reaction conditions. In all cases, the semicarbazone derivative of the major regioisomer was isolated after derivatization. DFT calculations were performed and are in good agreement with the observed regioselectivity.

It was also thought that protonation of one of the nitrogen atoms by a strong acid would increase the reactivity of the Cope-type hydroamination. However, there would a chance of protonating both nitrogen atoms thus, inhibiting the reaction. Nevertheless, Ms. Anna Chkrebtii has shown preliminary results of the intramolecular Cope-type hydroamination using Bronsted acid activation (equation 1.30).[51]



1.118 **1.119** **(1.30)**

Upon heating the reaction, the alkenylhydrazine in the presence of TFA for 72 hours gave an NMR yield of 98 %. Due to the fact that unprotected hydrazines are not stable and can lead to radical formation, The Beauchemin group sought out to use a different class of hydrazines; the protected hydrazine.

1.3 Conclusion

A lot of strategies have emerged in recent year: base/acid catalysis, catalysis using early or late transition metals, lactinides etc... Cope-type hydroamination is a metal-free alternative that requires modified reagents: hydroxylamines are commonly used and hydryzides appear to hold potential for their development. Currently, Late transition metals catalysts and Cope-type hydroamination likely show the best synthetic

[51] Chkrebtii, A.; Whipp, C.; Beauchemin, A. M. *Unpublished results*

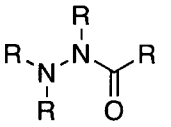
potential, due to functional group compatibility. However, important synthetic are still present even for intramolecular reactions of alkenes such as 6 and 7 membered ring formation (especially substituted alkenes) and in stereoselective variants. Presented in Chapter 2 of this thesis is the further development of the Cope-type hydroamination method to achieve an increased scope for the reaction using activated hydrazines.

Chapter 2. Intramolecular Cope-type hydroamination of alkenes.[52]

[52] Portion of this chapter has been published: Roveda, J.-G.; Clavette, C.; Hunt, A. D.; Gorelsky, S. I.; Whipp, C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, 131, 8740.

2.1 Introduction

Hydrazides or *N*-acyl hydrazides are a class of organic compounds sharing a common functional group. They are characterized by a nitrogen-to-nitrogen covalent bond with usually four substituents, one of which is an acyl group (equation 2.1). The remaining substituents can be hydrogens, alkly chains and even aryl groups.



(2.1)

R= H, Alkyl and Aryl

Hydrazides are a very old class of molecules. The first example of hydrazides in chemistry was reported in 1850.[53] There is now a large selection of commercially available mono-, di- and trisubstituted hydrazides. Hydrazides are a multipurpose class of nitrogen-substituted molecules with a high level of chemical reactivity. They have been used as intermediates and precursors in accessing many important organic molecules and drug candidates as well as being used for many transformations,[54] some of which will be described in the following sections.

2.1.1 Structural characteristics

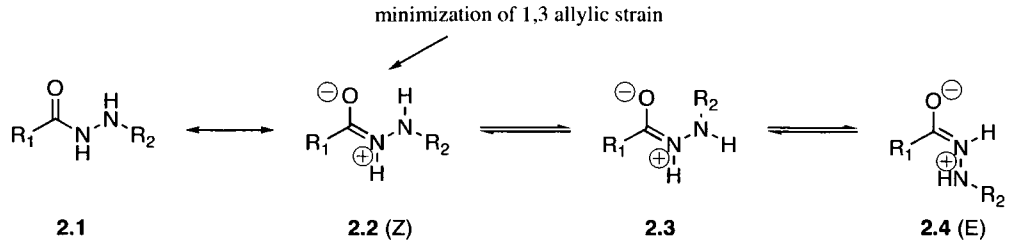
Hydrazides have chemical properties comparable to those of amides (Scheme 2.1). Like them, hydrazides can have partial double bond character in the carbon-nitrogen bond. In order to minimize the 1,3 allylic strain[55] the hydrogen is positioned in a trigonal planar fashion as shown in compounds **2.2** and **2.3**.

---

[53] K. Schöfer, S. Schwan, *J. Prak. Chem.* **1850**, *51*, 185

[54] Hydrazine and its Derivatives, in *Kirk-Othmer Encyclopedia Chemical Technology*, 4th edn., vol. 13, John Wiley & Sons, New York, **1995**

[55] Broeker, J. L.; Hoffmann, R. W.; Houk, K. N. *J. Prak. Chem.* **1991**, *113*, 5006

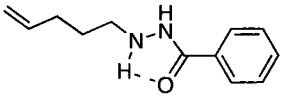


2.1 **2.2** (Z) **2.3** **2.4** (E)

Scheme 2.1: Minimization of 1,3 allylic strain and E or Z isomers

Due to the partial double bond character, the hydrazide can exist in two configurations: the Z isomer (**2.2**) and the E isomer (**2.4**). As a general rule, the hydrazides usually adopt the E configuration if the nitrogen atoms are fully substituted. However, if the size of the carbonyl group substituent (Scheme 2.1, R_1) is increased, a mixture of E and Z isomers can be observed.[56]

Samdal and Mollendal performed ab-initio and density functional theory on formic-hydrazide.[57] The computational data demonstrated that the Z isomer was more stable than the E isomer by 10-14 kJ/mol for that compound. The author argues that the internal hydrogen bonding (**2.6**) is involved in the stabilization the Z isomer (Scheme 2.2). From this, depending on the substitution hydrazides can adopt the E isomer or the Z isomer. Therefore, the Z isomer is preferred if the alpha nitrogen can do H-bonding with the carbonyl. In our case, this involves solely a primary monosubstited hydrazide as indicated in Scheme 2.2.



2.6

Scheme 2.2: Hydrogen bonding of the amine with the carbonyl

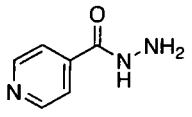
[56] (a) Knapp, S.; Toby, B. H.; Sebastian, M.; Krogh-Jespersen, K.; Potenza, J. A. *J. Org. Chem.* **1981**, *46*, 2490. (b) Ghelfi, F.; Parsons, A. F. *J. Org. Chem.* **2000**, *65*, 6249

[57] Samdal, S.; Mollendal, H. *J. Phys. Chem.* **2003**, *107*, 8845

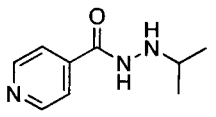
2.1.2 General reactivity and purpose

Hydrazides have been used in different areas of chemistry and specific uses will be shown below. Some of them have been used in drug therapy like Iproniazid and others have been used as mediators in organic reactions.

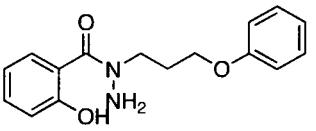
Hydrazides have been used in drug therapy (Scheme 2.2). Isoniazid (**2.7**) is a strong antituberculosis agent.[58] The drug is used as a mixture of the hydrazide itself and of other drugs.



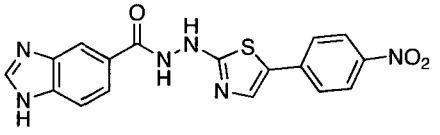
2.7



2.8



2.9



2.10

Scheme 2.3: Hydrazides 2.7, 2.8, 2.9 and 2.10 used as therapeutic agents

In 1952, Iproniazid (**2.8**) was developed and was shown to be an antituberculosis medication. During treatment it was observed that this drug had a significant impact on the central nervous system and was therefore subsequently used as an antidepressant.

In 1997, the Burke[59] group discovered that *N*-(2-hydroxybenzoyl)-*N*-(2-hydroxy-3-phenoxypropyl)hydrazine (**2.9**) is a potent HIV integrase inhibitor displaying excellent antagonist capability with an IC_{50} of 0.6 μg/mL. This hydrazide was chosen as a lead candidate solely based on its three pharmacaphores: the terminal amine of the hydrazide, the corresponding carbonyl group and finally the phenolic moiety.

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[58] Seydel, J. K.; Schaper, K.-J.; Wempe, E.; Cordes, H. P. *J. Med. Chem.* **1976**, *19*, 483.

[59] Zhao, H.; Neamati, N.; Sunder, S.; Hong, H.; Wang, S.; Milne, G. W. A.; Pommier, Y.; Burke, T. R. *J. Med. Chem.* **1997** *40*, 937.

Recently, it has been shown that hydrazides are promising therapeutic agents for another very interesting target, Alzeihmer's disease. One of the key pathological features of the Alzeihmer's disease is the aggregation of the Tau protein. The Tau protein has been shown to from aggregates toxic to neurons, and contributes to their degeneration. In turn, this prevents the transmission of acetylcholine, which is needed as neurotransmitter. In 2007, the Mandelcow[60] group demonstrated that hydrazide **2.10** and some of its derivatives have a potential inhibitory effect on the aggregation of this protein.

Other drugs have been used as antagonists on the lucagon[61] and cannabinoid CB_1 receptors.[62] Hydrazides have also been used as protecting groups,[63] cross linkers,[64] chain transfer reagents[65] and ligands.[66]

In recent times, self-assembling molecular capsules, which are formed through non-covalent interactions, have attracted considerable interest due to their potential as molecular storage, sensors, catalysts or reaction chambers in the field of supramolecular chemistry.[67] The Paek group demonstrated the ability to form robust molecular capsules from a benzoylhydrazide derivative (equation 2.2).[68]

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[60] Pickhardt, M.; Larbig, G.; Khlistunova, I.; Coksezen, A.; Meyer, B.; Mandelkow, E.-M.; Schimdt, B.; Mandelkow, E. *Biochemistry* **2007**, *46*, 10016.

[61] Madsen, P. et al. *J. Med. Chem.* **2002**, *45*, 4555.

[62] Francisco, M. E. Y.; Seltzman, H. H.; Gilliam, A. F.; Mitchell, R. A.; Rider, S. L.; Pertwee, R. G.; Stevenson, L. A.; Thomas, B. F. *J. Med. Chem.* **2002**, *45*, 2708.

[63] Cheung, H. T.; Blout, E. R. *J. Org. Chem.* **1965**, *30*, 315.

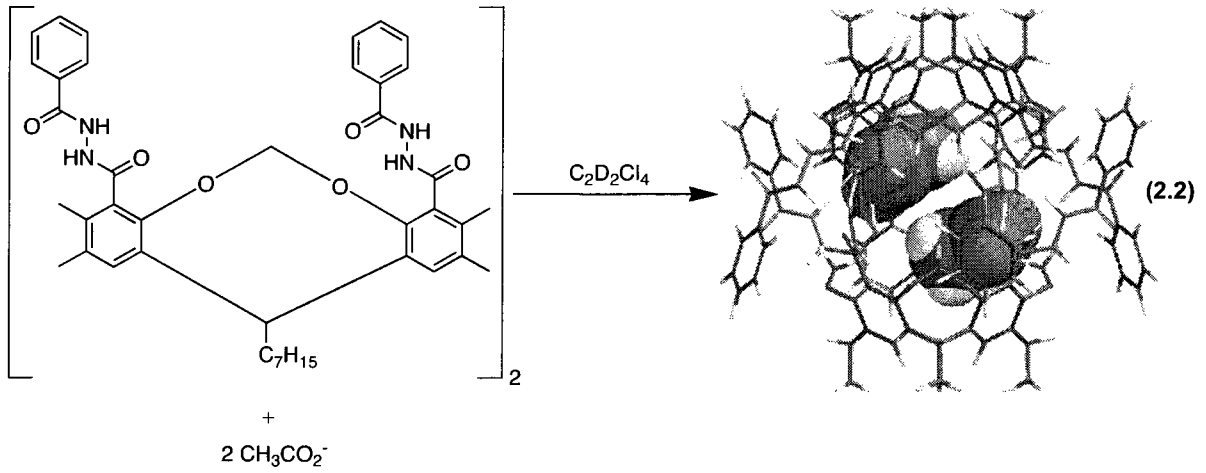
[64] Ansell, S. M.; Tardi, P. G.; Buchowsky *Bioconjuguate Chem.* **1996**, *7*, 490.

[65] Costioli, M. D.; Berdat, D.; Freitag, R.; André, X.; Muller, A. H. E. *Macromolecules* **2005**, *38*, 3630

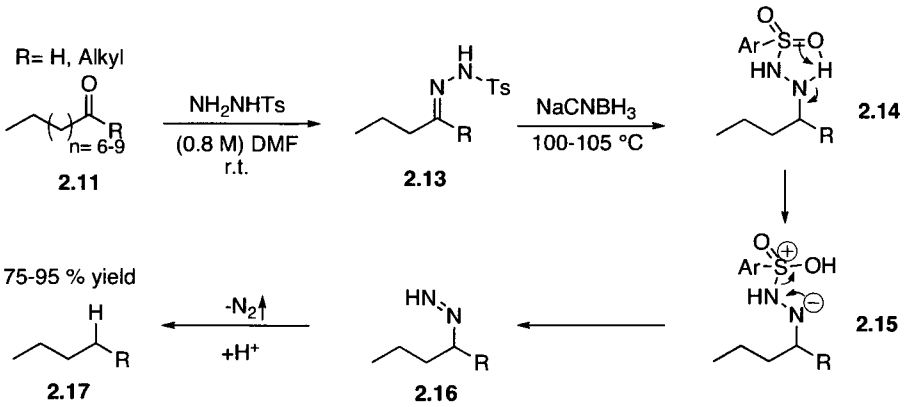
[66] Kost, D.; Kalikhman, I. *Acc. Chem. Res.* **2009**, *42*, 303.

[67] (a) Brunsveld, L.; Folmer, B. J. B.; Meijer, E. W.; Sijbesma, R. P. *Chem. Re*V. **2001**, *101*, 4071. (b) Prins, L. J.; Reinhoudt, D. N.; Timmerman, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 2382. (c) Bong, D. T.; Clark, T. D.; Granja, J. R.; Ghadiri, M. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 988. (d) Balzani, V.; Credi, A.; Raymo, F. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2000**, *39*, 3348. (e) Lehn, J. M. *Chem.sEur. J.* **2000**, *6*, 2097. (f) Whitesides, G. M.; Boncheva, M. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4769. (g) Clark, T. D.; Tien, J.; Duffy, D. C.; Paul, K. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **2001**, *123*, 7677. (h) Pease, A. R.; Jeppesen, J. O.; Stoddart, J. F.; Luo, Y.; Collier, C. P.; Heath, J. R. *Acc. Chem. Res.* **2001**, *34*, 433.

[68] Park, Y. S.; Paek, K. *Org. Let.* **2008**, *10*, 4867.



Finally, to our knowledge, hydrazides are used in only a handful of organic reactions. One of the first organic reactions published was in 1970 by the Hutchins group. [69] This formal reduction reaction incorporated the use of *para*-toluenesulfonyl hydrazide as starting material and an aliphatic ketone or aldehyde (Scheme 2.4). Upon introduction of the hydrazide to the aldehyde or ketone (**2.11**) a primary or secondary hydrazone (**2.13**) is formed. Addition of sodium borohydride to the newly formed hydrazone in dimethylformamide at reflux afforded the deoxygenated version of the starting carbonyl compound in moderate to excellent yields.

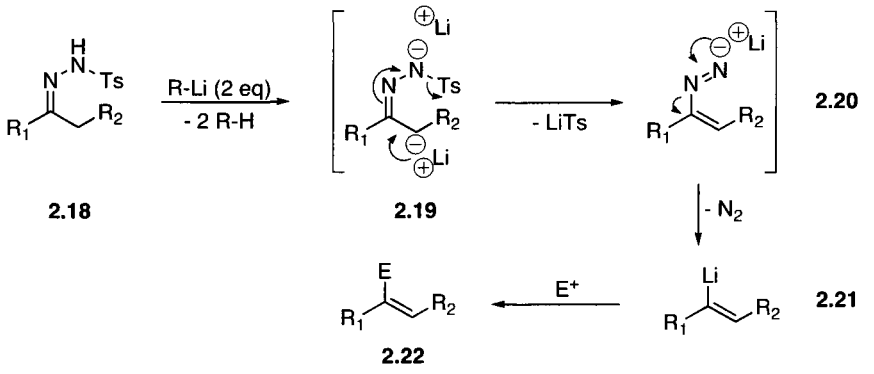


Scheme 2.4: Selective reduction of aliphatic ketone and aldehyde to hydrocarbons with sodium cyanoborohydride and *p*-toluensulfonyl hydrazide

[69] Hutchins, R. O.; Maryanoff, B.; Milewski, C. *J. Am. Chem. Soc.* **1971**, *93*, 1793.

The proposed mechanism involves initial reduction to the tosylhydrazide (**2.14**) followed by elimination of *p*-toluenesulfonic acid (**2.15**) and subsequent decomposition of the diimide intermediate (**2.16**) to the hydrocarbon (**2.17**).

In 1976, the Shapiro[70] group demonstrated that a ketone or aldehyde could be converted to an alkene through the same type of hydrazone intermediate (**2.18**) in the presence of two equivalents of strong base (Scheme 2.5).



Scheme 2.5: The Shapiro reaction and mechanism[71]

The mechanism involves the deprotonation of the tosylhydrazone (**2.19**) at the nitrogen and the alpha-carbon with two equivalents of alkyllithium. An alkenyllithium intermediate (**2.21**) is formed via a carbanion mechanism. Afterwards, the protonation of the alkenyllitium gives rise to an alkene (**2.22**).

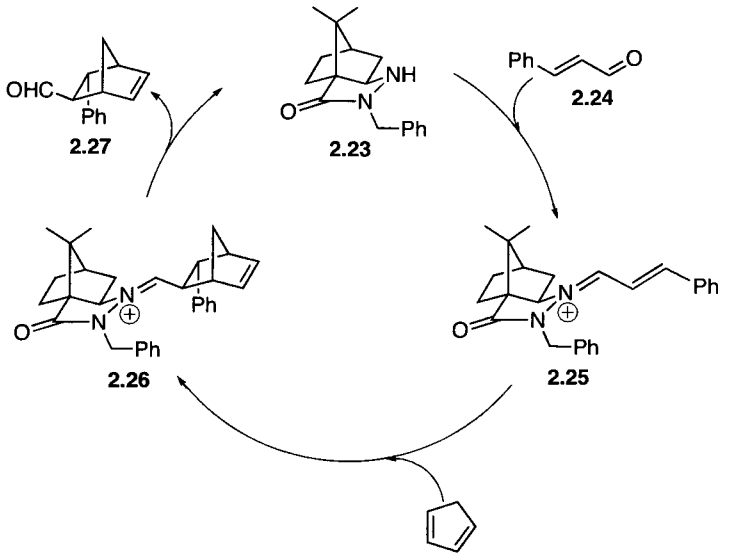
Recently, Lemay and Ogilive[72] were able to perform Diels-Alder reactions with a camphor based hydrazide used as an organocatalyst (Scheme 2.6).

---

[70] Shapiro, R. H.; Lipton, M. F.; Kolonko, K. J.; Buswell, R. L.; Capuano, L. A. *Tetrahedron* **1975**, *16*, 1822.

[71] László Kurti and Barbara Czakó, Unviversity of Pennsylvania, *Strategic Applications of Named Reactions in Organic Synthesis: background and detailed mechanism*, (Burlington, Elsevier Academic Press, 2005), 36-37

[72] (a) Lemay, M.; Ogilvie, W. W. *Org. Lett.* **2005**, *93*, 1793, (b) Lemay, M.; Ogilvie, W. W. *J. Org. Chem.* **2006**, *71*, 463.



Scheme 2.6: Enantioselective organocatalytic Diels-Alder reaction employing hydrazide catalyst

Lemay and Ogilvie describe this transformation as an enantioselective Diels-Alder reaction with ee's ranging from 3 to 82 %. The camphor-derived hydrazide (**2.23**) is shown in Figure 9. Upon addition of the α,β unsaturated ketone (**2.24**), there is a rapid formation of the iminium compound (**2.25**). This iminium lowers the energy of the dienophile LUMO, thus accelerating the concerted reaction. Since the reaction is done in water, intermediate **2.26** is hydrolyzed, which gives the desired product (**2.27**) and hence regenerates the initial catalyst (**2.23**).[73]

2.2 Toward the development of hydroamination reactivity of hydrazides

2.2.1 Introduction

As previously discussed, hydrazides are used in several different types of chemistry. Different methods to synthesize functionalized hydrazides have been applied depending on the substitution (mono, di and tri). Also, hydrazides have been shown to be possible therapeutic agents (section 2.1.2) therefore; thousands[74] of

[73] For other reactions that involve hydrazides please visit this microreview: Licandro, E.; Perdicchia, D. *Eur. J. Org. Chem.* **2004**, 665.

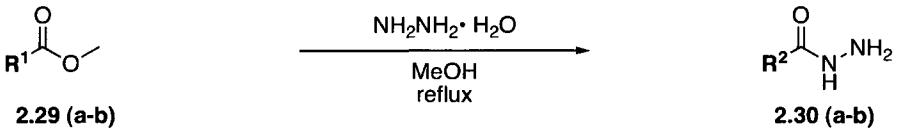
[74] Based on the Aldrich search "hydrazide", 2854 are currently available

derivatives are currently commercially available. Nevertheless, our chemistry involves the use of specific di-substituted hydrazines or mono-substituted hydrazides.

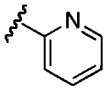
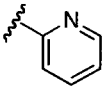
2.2.2 Synthesis of hydrazides

There are many different methods for accessing unsubstituted and monosubstituted hydrazides, some of which are an acylation reaction between the hydrazine and the corresponding acyl chloride or ester. However, the use of acyl chlorides and anhydrous compounds can often give diacylated hydrazide derivatives, or mixtures of mono- and diacylated derivatives when employing aqueous hydrazine.[75] The hydrazides used for the presented research were synthesised from the corresponding methylester (Figure 12) following the procedure developed by the Wieczorek[76] group.

Table 2.1: Formation of the acylated hydrazine (hydrazide)



2.29 (a-b) **2.30 (a-b)**

Starting Material	Product	Yield (%) and Product
R^1= 	R^2= 	> 99 (2.30a)
		> 99 (2.30b)

All other hydrazides or carbamates have been purchased and used without purification (refer to Chapter 5 for more details).

[75] Nesterova, E. Y.; Voevudsky, M. V.; Samukha, A. V.; Zubatyuk, R. I.; Shishkin, O. V. *Chemistry of Heterocyclic Compounds* **2005**, *41*, 1511

[76] Kazuyuki, O.; Yamamoto, T.; Okuma, M.; Horiuchi, T.; Imanishi, H.; Odagaki, Y.; Kawabata, K.; Sekioka, T.; Hirota, Y.; Matsuka, S.; Nakai, H.; Cheronis, M. T.-J. C.; Spruce, L. W.; Gyorkos, A.; Wieczorek, M. *J. Med. Chem.* **2001**, *40*, 1268.

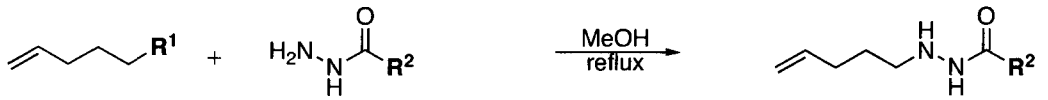
2.2.3 Synthesis of alkenylhydrazides

To the best of our knowledge, no viable method has been developed to accommodate an alkenyl chain on the terminal amine of similar hydrazide functionalities. In 1999, Hansen[77] demonstrated that boc-hydrazine would react with 1-bromo-3-phenyl propane via a direct alkylation to afford the mono-boc protected hydrazine in an 85 % yield using a two-fold excess of the hydrazide. The first attempt was with 5-bromopent-1-ene and *t*-butyl carbazate (Table 2.2). The corresponding alkenyl hydrazide (entry 3) was obtained in an 89 % yield. Following this, it was of interest to synthesize the corresponding alkenyl ethyl carbazate (entry 4). Once again due the substantial alkylation, the compound was isolated in 68 % yield. The alkenyl benzoic hydrazide was obtained in a 59 % yield. 1-Bromopent-4-ene was replaced with more simple and inexpensive but-3-enyl-4-methylbenzenesulfonate (entries 1-2, which was synthesized according to Sirett's procedure).[78]

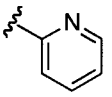
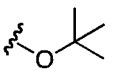
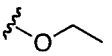
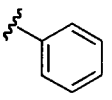
[77] Hansen, T. K. *Tetrahedron* **1999**, *40*, 9119

[78] Ashley, J. N.; Collins, M. D.; Sirett, N. E. *J. Org. Chem.* **1999**, *183*, 897.

Table 2.2: Alkylation products

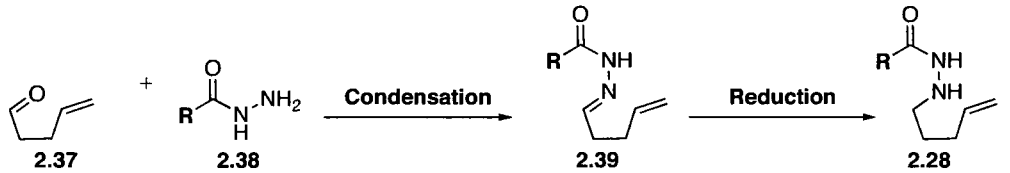


2.31 (a-b) **2.30 (a-e)** **2.32 (a-e)**

Entry	R^1	R^2	Yield (%) and Product
1	OTs (b)		18 (2.32a)
2	OTs (b)		6 (2.32b)
3	Br (a)		89 (2.32c)
4	Br (a)		68 (2.32d)
5	Br (a)		59 (2.32e)

Typically, sulfonates should be better alkylating agent than bromides, however this is not found to be the case in this situation. Pivalohydrazide (entry 1, **2.36**) and picolinohydrazide (entry 2, **2.35**) were subjected to the same reaction condition as previously reported; the respective alklenylhydrazides were obtained in deceiving 18 and 6 % yields, respectively. Having observed low reactivity and poor yields, it was of primary interest to explore other for the preparation of the substrates.

A reductive amination approach was investigated (equation 2.3) as an alternative. The corresponding hydrazone (**2.39**) can be formed via a simple condensation followed by reduction to the corresponding hydrazide (**2.28**).

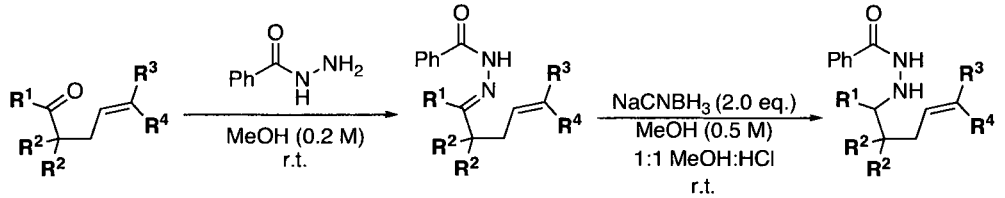


2.37 2.38 2.39 2.28 (2.3)

R= Alkyl and Aryl

The results of the reductive amination of the five membered ring precursors are summarized in Table 2.3. Due to an increase in steric hindrance of secondary hydrazones (entry 1) the reduction seemed tends to give less dialkylation product. Entries 2 and 3 were synthesized from the corresponding alcohol. The hydrazones and hydrazides were obtained in reasonable yields (Table 2.3).

Table 2.3: Synthesis of five membered ring precursors



2.40 (a-d) 2.42 (a-d) 2.43 (a-d)

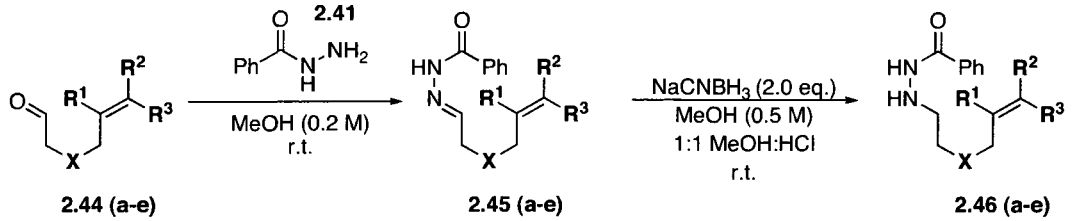
Entry	R^1	R^2	R^3	R^4	Hydrazone yield (%)	Reduction yield (%)
1	Me	H	H	H	86 (2.42a)	90 (2.43a)
2[a]	H	H	Me	H	69 (2.42b)	42 (2.43b)
3[a]	H	H	H	Me	63 (2.42c)	48 (2.43c)
4	H	Me	H	H	100 (2.42d)	52 (2.43d)

[a] This work was performed by Ms. Ashley D. Hunt

Finally, the hydrazone of entry 4 was synthesized form the commercially available 2,2-dimethylpent-4-enal. The hydrazone is isolated in excellent yield. Once again reduction of a primary hydrazone gave a lower yield of the hydrazide.

The following six and seven membered ring cyclization precursors were synthesized via the same method as previously described. The hydrazones (**2.45**) and hydrazides (**2.46**) in Table 2.4 were isolated in varying yields.

Table 2.4: Six and seven membered ring precursors

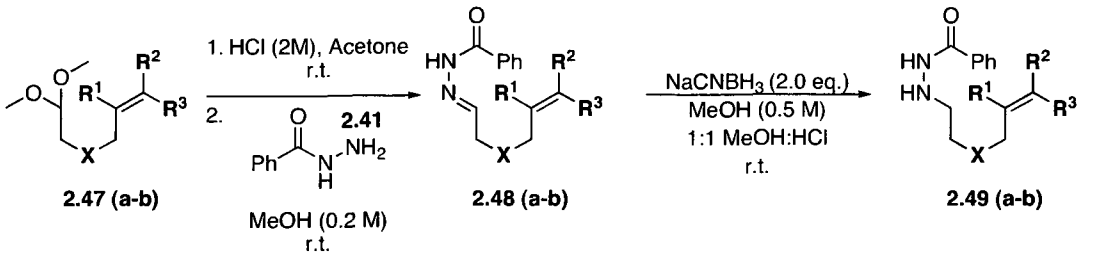


2.44 (a-e) 2.45 (a-e) 2.46 (a-e)

Entry	R^1	R^2	R^3	X	Hydrazone yield (%)	Hydrazide yield (%)
1	H	H	H	CH_2	70 (2.45a)	38 (2.46a)
2	H	H	H	O	69 (2.45b)	77 (2.46b)
3	H	Et	H	CH_2	63 (2.45c)	26 (2.46c)
4	H	H	Et	CH_2	61 (2.45d)	38 (2.46d)
5	H	H	H	$(CH_2)_2$	94 (2.45e)	32 (2.46e)

The hydrazones were generally isolated in good to excellent yields. Once again, reduction of primary hydrazones (entries 1, 2, 3 and 5) gives poor isolated yields. For the most part, this is due to the fact that upon reduction of the hydrazone to hydrazide, dialkylation of the hydrazide is observed as a competitive pathway. In order to validate the method other precursors are considered. It was also of interest to synthesize piperazine precursors. The compound (**2.49**) in Table 2.5 was obtained from a simple alkylation procedure (please see chapter 5). In order to form the desired aldehyde in situ, these compounds (entries 1 and 2) were subjected to a 2M HCl solution followed by addition of the benzoic hydrazide (**2.41**). The hydrazone was isolated in poor yield due to the fact that aldehyde formation was not complete. The reduction is accomplished in good yield.

Table 2.5: Six membered ring piperazine precursor



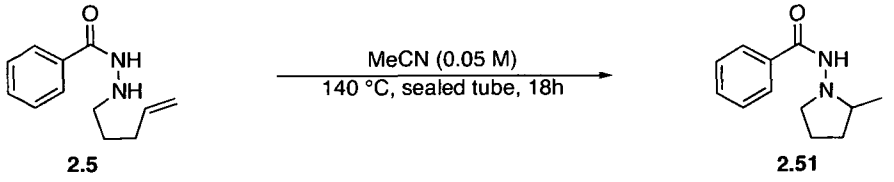
Entry	R^1	R^2	R^3	X	Hydrazone yield (%)	Hydrazide yield (%)
1	H	H	H	NTs	46 (2.48a)	87 (2.49a)
2	Me	H	H	NTs	32 (2.48b)	73 (2.49b)

Finally, it is found that upon fast addition HCl to the reaction better yields were observed. Nevertheless, reduction of hydrazones to their respective hydrazides still require further optimization. Improving the yields of the reduction would have beneficial result in future work.

2.3 Substitution and optimization

2.3.1 Cope-type hydroamination: general optimization

The first reaction was performed with the hydrazide cyclization precursor **2.5**, which was heated to 140 °C for 18 hours. The result proved to be quite promising, the desired product (**2.51**) being obtained in 70 % yield.



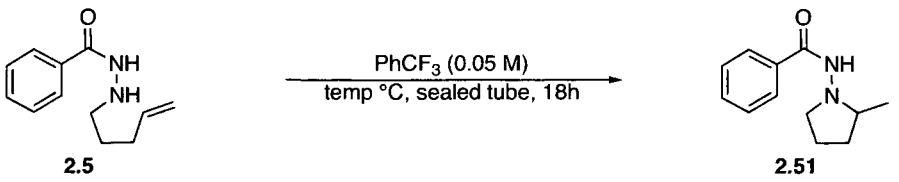
(2.4)

The first optimization study concentrated on the effect of solvent in the hydroamination product formation. Given the importance of solvent effect seen in previous work by our group,[79] both protic and aprotic, as well as polar and non-polar solvent were surveyed. Shown in Table 2.6 are the solvents used in the scan,

[79] (a) Beauchemin, A. M.; Moran, J.; Lebrun, M.-E.; Séguin, C.; Dimitrijevic, E.; Zhang, L.; Gorelsky, S. I. *Angew. Chem., Int. Ed.* **2008**, *47*, 1410. (b) Moran, J.; Gorelsky, S. I.; Dimitrijevic, E.; Lebrun, M.-E.; Bédard, A.-C.; Séguin, C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 17893.

including water (entry 6), which has shown to give the least efficient NMR yield, with only 34 %. Interestingly, compared to the hydroxylamines,[79] *i*-PrOH (entry 2) is one of the least efficient solvents with an NMR yield of 52 %. On the other hand, both the use of dioxane (entry 5) and acetonitrile (entry 7), give higher NMR yields.

Table 2.6: Cope-type hydroamination solvent scan

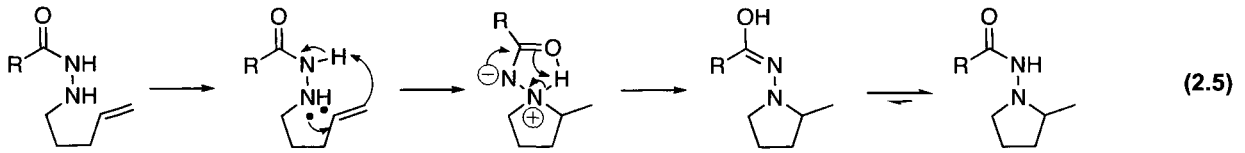


2.5 **2.51**

Entry	Solvent	NMR yield (%)[a]
1	**$PhCF_3$**	**84**
2	*i*-PrOH	52
3	DMF	34
4	$PhCH_3$	71
5	Dioxane	60
6	H_2O	31
7	MeCN	58

[a]Determined by ^1H NMR using 1,4-dimethoxybenzene as int. std.

Finally, aromatic and aprotic (entry 1 and 4) solvents show more efficient NMR yields. α,α,α-trifluorotoluene ($PhCF_3$) attested to be the solvent of choice for this transformation. A plausible alternative to the previously discussed bimolecular proton transfer is that instead the hydrazide could undergo an intramolecular proton transfer (see **2.30** to **2.31**, equation **2.5**, also section 2.4.2).



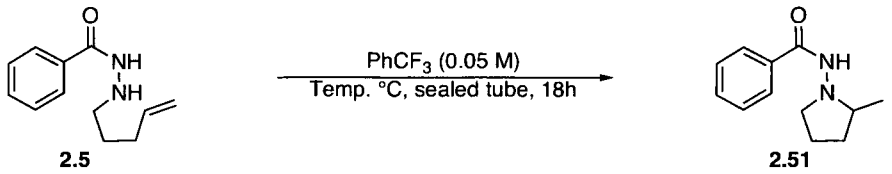
2.28 **2.29** **2.30** **2.31** **2.32** **(2.5)**

R= Alkyl and Aryl

Upon formation of the hydroamination product (**2.29**), adduct **2.30** executes a fast irreversible proton transfer in an aprotic solvent. Following this, the amide isomer (**2.31**) is formed and then tautomorizes to the stable Cope-type hydroamination product (**2.32**). In addition to the solvent scan a temperature scan compels to

be performed. In concurrence with past results, high NMR yields are observed; entry 2 of Table 2.7 gave a NMR yield of 93 %.

Table 2.7: Cope-type hydroamination: temperatures scan



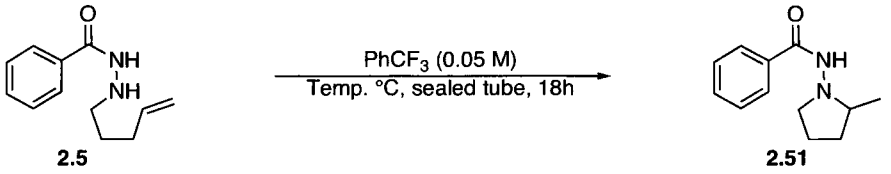
2.5 **2.51**

Entry	Temperature (°C)	NMR yield (%)[a]
1	140	87
2	**120**	**93**
3	110	84
4	80	traces

[a]Determined by ^{1}H NMR using 1,4-dimethoxybenzene as int. std.

Subjecting hydrazide **2.5** to higher temperatures gave a lower yield for the transformation, as is shown in entry 1 of Table 6. Decomposition of the product at higher temperatures is the only valuable explanation. A short concentration scan shows that increasing the concentration to 0.3 M yields similar NMR yields (Table 2.8).

Table 2.8: Cope-type hydroamination: concentrations scan



2.5 **2.51**

Entry	Concentration (M)	NMR yield (%)[a]
1	0.05	93
2[b]	0.30	91

[a]Determined by ^{1}H NMR using 1,4-dimethoxybenzene as int. std.

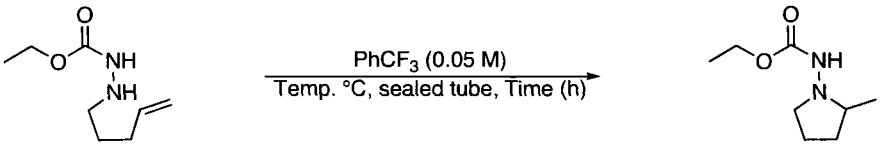
[b]This experiment was performed by Ms. Ashley D. Hunt

Finally, with the temperature, concentration and solvent scans completed we could evaluate the scope of the developed hydroamination further by substituting at the terminal acyl position.

2.3.2 Cope-type hydroamination: tuning the carbonyl moiety[80]

Firstly, 1-(pent-4-enyl) ethylcarbazate (**2.51**) was subjected to several different temperatures and different reaction times (Table 2.9). The ethoxy group at the terminal position yielded poor results (entry 1) at 120 °C compared to the phenyl moiety.

Table 2.9: 1-(Pent-4-enyl) ethylcarbazate optimization

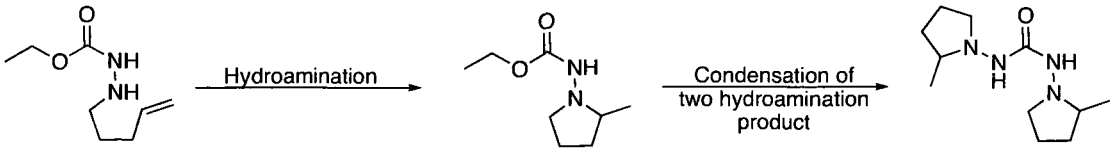


2.52 **2.53**

Entry	Temperature (°C)	Time (h)	NMR yield (%)[a]
1	120	16	13
2	**140**	**16**	**76**
3	150	16	53
4	150	42	48
5	150	16	59

[a]Determined by ^{1}H NMR using 1,4-dimethoxybenzene as int. std.

To our surprise entry 2 demonstrates the best results with a NMR yield of 76 %, as determined by ^{1}H NMR. Isolation of this compound proved extremely difficult and only 28 % of the desired material was obtained. The crude sample, when subjected to GC/MS analysis, allowed us to see that the hydroamination product can condense during purification to give product **2.53** and ethanol.[81] Product **2.53** was furthermore isolated.



2.52 **2.53** **2.54** **(2.6)**

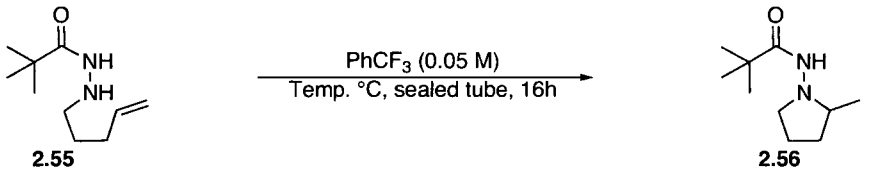
This accounted for the previously mentioned NMR yield (Table **2.9**, entry 2); roughly all the mass was accounted for, and the resonance for the various pyrrolidine ring systems was similar, suggesting a more

[80] Synthesis of the starting material will not be discussed but for more details please refer to chapter 5

[81] Ethanol was NOT observed by NMR nor GC/MS analysis

efficient reaction. Hence, the carbazates are not stable compounds after or even before hydroamination. It is of interest to synthesize another akyl chain that would lack in its ability to act as a good leaving group. In order to prevent attack on the carbonyl group of the hydrazide, *N*'-(pent-4-enyl)pivalhydrazide (**2.55**) was synthesized and submitted to the hydroamination conditions at two different temperatures. The first temperature (entry 1) was used to compare reactivity with the phenyl group (**2.5**), which demonstrates to be poor compared to its opponent (**2.5**). Despite our efforts, the corresponding product (**2.56**) is isolated in a 70 % yield at 150 °C. This could be due to sterics of the *tert*-butyl group or the electronics of the sp^3 hybridized carbon alpha to the carbonyl.

Table 2.10: *N*'-(Pent-4-enyl)pivalhydrazide optimization

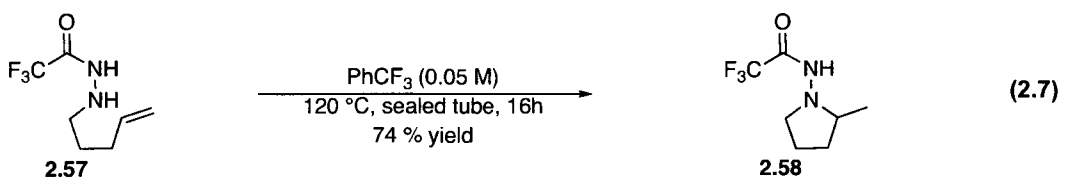


2.55 **2.56**

Entry	Temperature (°C)	NMR yield (%)[a]
1	120	55
2	**150**	**70**

[a]Determined by ^{1}H NMR using 1,4-dimethoxybenzene as int. std.

By comparing the aryl and alkyl groups (Table 2.4, 2.8, 2.9 and 2.10), it can be reasoned that the increased electron withdrawing character of the acyl moiety had a positive effect on the reaction. Substitution with a strong electron-withdrawing group (EWG) would inductively increase the acidity of the proton located on the nitrogen. Assuming hydroamination is a concerted process (section 2.4.3) and abstraction of the proton is involved in the rate-determining step (section 2.4.2), increased proton acidity and increased stabilization may lower the energy of activation of the whole reaction.

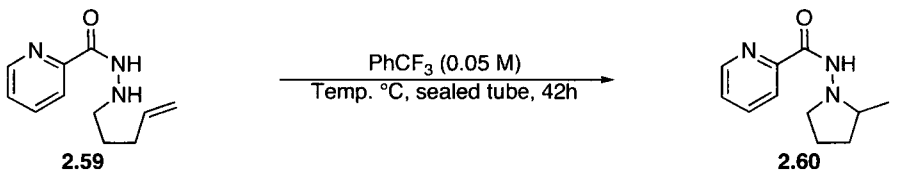


2.57 **2.58** **(2.7)**

To test this hypothesis, 2,2,2-Trifluoro-*N*'-(pent-4-enyl) acetohydrazide **2.58** was submitted to the same conditions as *N*'-(pent-4-enyl) benzohydrazide and the reaction was heated for 16 hours in $PhCF_3$ The hydroamination product was isolated in a 74 % yield. Even after addition of a stronger EWG, no improvement was observed. Therefore, after extensive work done on the tuning of the carbonyl moiety with sp^3 carbons, it was deicided that the use of a sp^2 center at this position, from which better results had been previously observed, would be more beneficial.

The first substrate synthesized to that effect was *N*'-(pent-4-enyl) picolinohydrazide **2.59**. The following alkenylhydrazide was subjected to a suitable temperature scan. The aryl-substituted hydrazide was found to be a very stable molecule and could be the best test subjects for a Lewis acid catalyzed process.

Table 2.11: *N*'- (Pent-4-enyl) picolinohydrazide optimization



2.59 **2.60**

Entry	Temperature (°C)	NMR yield (%)[a]
1	120	0
2	150	36
3	**170**	**70**

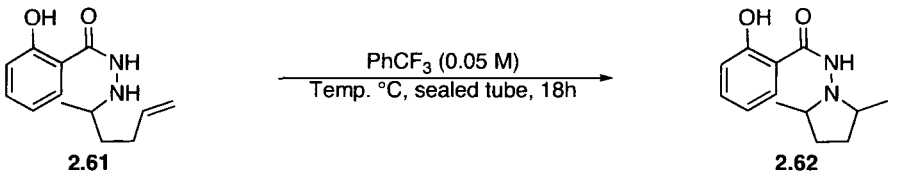
[a]Determined by ^1H NMR using 1,4-dimethoxybenzene as int. std.

Surprisingly, the picolinohydrazide required higher temperature and increased reaction time to cyclize efficiently. The starting material **2.59** was heated at 170 °C for 42 hours to afford the desired product in 70 % NMR yield. Due to poor yields, it was postulated that the nitrogen of the 2-pyridyl moieties could be hydrogen bonding with the protons of the hydrazide group (either intra- or intermolecularly). Prior to the hydroamination, the hydrogen bond needs to be broken thus explaining why higher temperatures are needed.

The alkenylhydrazide chosen as a substrate was one capable of accommodating a possible bidentate Lewis acid. Fortunately, the hydroamination temperature of the substrate alone, without addition of any lewis acid, is reduced by 30 °C, when compared to its earlier version the *N*'- (pent-4-enyl)benzohydrazide **(2.5)**. Mr.

Francis Loiseau and Mr. Michael Raymond will undertake future work on this recent discovery.

Table 2.12: 2-hydroxy-*N*- (2-methylpyrrolidin-1-yl) benzamide optimization



2.61 **2.62**

Entry	Temperature (°C)	NMR yield (%)[a]
1	50	13
2	**90**	**90**
3	110	65

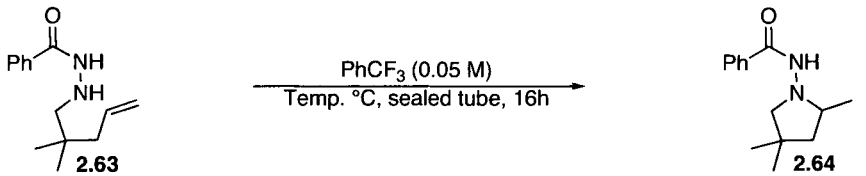
[a]Determined by ^{1}H NMR using 1,4-dimethoxybenzene as int. std.

After tuning the carbonyl moiety, we were then able to test the diversity of this method by incorporating different substitutions on the five membered rings. Also six and seven membered ring, which are known to be hard to cyclize, as a result the limits of this transformation will be tested. Even though product **2.62** demonstrated better results the following reactions were performed with the phenylhydrazide derived substrates as the latter discovery occurred recently.

2.3.3 Cope-type hydroamination: substitution patterns

The obvious modification is to incorporate a Thorpe-Ingold effect where the alkene and the hydrazine are forced to be in close proximity of each other. Using the method previously mentioned, the hydroamination precursor (**2.63**) was formed relatively easily. The precursor is subjected to the same optimized concentration and solvent but lower temperature of 80 °C because Thorp-Ingold effects generally require less energy.

Table 2.12: *N*- (2,4,4-Trimethylpyrrolidin-1-yl) benzamide optimization



2.63 **2.64**

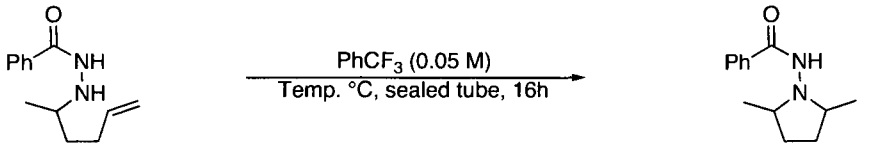
Entry	Temperature (°C)	Yield (%)
1	80	67[a]
2	**85**	**96**
3	95	91[a]

[a]Determined by ^{1}H NMR using 1,4-dimethoxybenzene as int. std.

After 16 hours, the NMR yield obtained was approximately 67 % (entry 1), due to low NMR yield and presence of unreacted starting material; this implies that the reaction can be optimized. After two other scans (entry 2 and 3), the corresponding product (**2.64**) was isolated with a 96 % yield.

We had yet, at this point to cyclize a hydroamination product via a secondary hydrazide. This would give rise to a 2,5 alkyl relationship. Using a simple methyl group at the 2 position the corresponding secondary hydrazide (2.65) was subjected to the same reaction conditions (Table 2.7) as previously mentioned (Table 2.13).

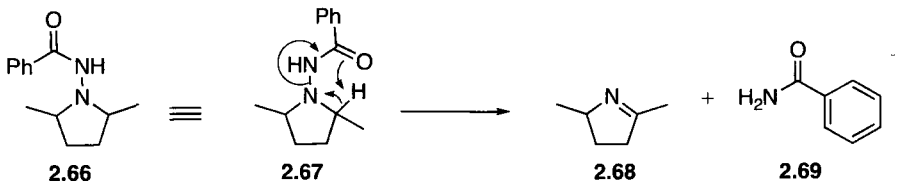
Table 2.13: (±)-*N*- (2,5-dimethylpyrrolidin-1-yl) benzamide optimization



2.65 **2.66**

Entry	Temperature (°C)	Yield (%)
1	**120**	**98**
2	150	62

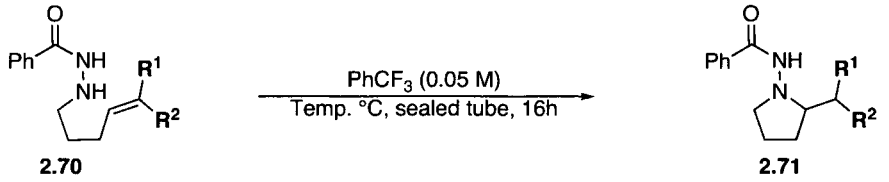
The secondary hydrazide displayed in table **2.13** was subjected to two different temperatures from which entry 1 had the highest isolated yield of 98%. However, at 150 °C all the starting material had reacted but upon isolation on 62 % of the desired product was obtained. This observation can be explained: Upon formation of the desired hydroamination product, the product can undergo another reaction, which involves elimination of the benzamide moiety-giving rise to an oxidative Cope-type hydroamination product (**2.68,** equation 2.8), which is observed by GC/MS and ^{1}H NMR, current studies are being undertaken by Ms Ashley D. Hunt to optimize this reactivity.



2.66 **2.67** **2.68** **2.69** **(2.8)**

Another possible substitution is on the terminal double bond. A substrate with a cis and trans double bond, which had a terminal methyl group was chosen.

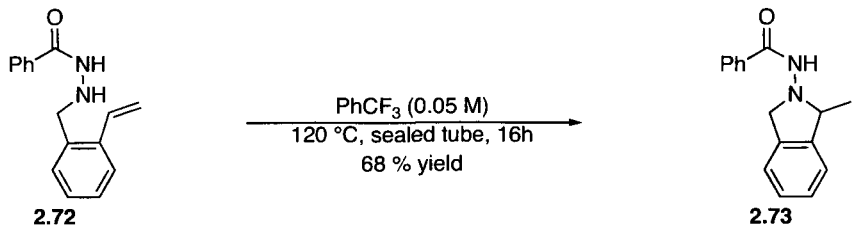
Table 2.14: The cyclisation onto disubstituted alkenes



2.70 2.71

Entry	R^1	R^2	Yield (%)
1	H	CH_3	75
2	CH_3	H	61

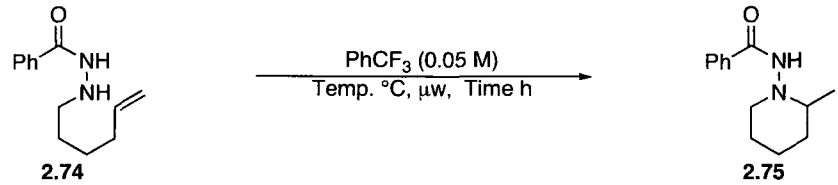
Ms. Ashley D. Hunt was able to isolate the product **2.71** in reasonable yields (entries 1 and 2). Once again formation of the corresponding oxidative hydroamination product (**2.68**) was also observed, which upon elevated heating, seemed to increase the by-product (**2.68**). Before moving on to more demanding substrates, it was important to consider if the hydroamination of alkenes could tolerate an alkene moiety which is benzylic. Interestingly the product cyclized at the same temperature as the unsubstituted pyrrolidine (equation 2.9). Therefore, benzylic substrate seems compatible with this transformation.



2.72 2.73 **(2.9)**

Having successfully cyclised the five membered ring, we set our sight on cyclizing a six membered ring. Our first attempt was cyclizing the piperadine at temperatures similar to the pyrrolindines (entry 1). It was found that heating the reaction at 200 °C for 5 hours resulted in an overall NMR yield of 80 % (entry 2) with 15 % of the starting material still remaining.

Table 2.15: *N*- (2-methylpiperidin-1-yl) benzamide optimization



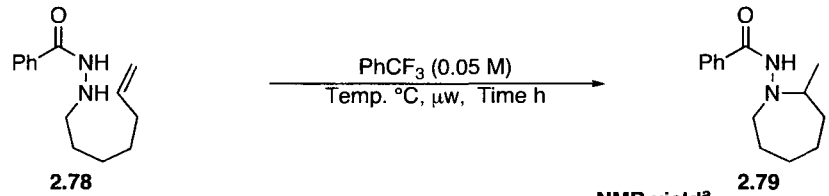
2.74 2.75

Entry	Temperature (°C)	Time (h)	Yield (%)
1	120	5	traces
2	200	5	80[a]
3	**200**	**10**	**90**

[a]Determined by ^{1}H NMR using 1,4-dimethoxybenzene as int. std.

The reaction time of the corresponding hydrazide (**2.75**) was doubled and the hydrazide isolated in a 90 % yield. In order to test the limits of this newly developed method with respect to ring size, the seven membered ring (**2.79**) precursor was submitted to the reaction conditions (Table 2.16). The following was obtained in 39 % NMR yield (entry 4).

Table 2.16: *N*- (2-Methylazepan-1-yl) benzamide optimization



2.78 2.79

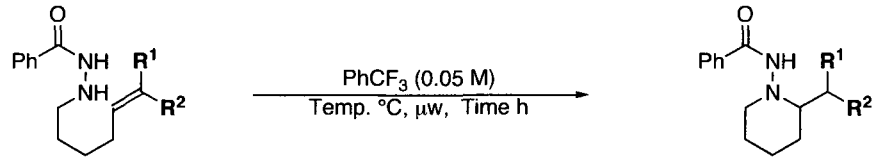
				NMR yield[a]	
Entry	Solvent	Time (h)	Temp. (°C)	S.M (%)	Product (%)
1	$PhCF_3$	14	200	52	15
2	$PhCF_3$	15	210	65	35
3	PhCl	12	225	46	34
4	**PhCl**	**24**	**235**	**19**	**39**

[a]Determined by ^{1}H NMR using 1,4-dimethoxybenzene as int. std.

Finally, having reasonable yields for the piperidine moieties (table **2.15**), our interest focused on substitution of the terminal alkene, which proved to be quite challenging. Since our group had previously synthesized coniine with hydroxylamine (chapter 1, equation **1.26**), it was of great interest to test the efficiency of the hydrazide methodology for difficult cyclizations. After subjecting the precursors to several temperature and time scans it became evident that the product proved to be quite challenging (Table **2.17**). The first

condition tried is 200 °C for 10 hours (entry 1). Previously, it is shown that terminal alkenes would cyclize nearly quantitavely (Table **2.15**). Substituted multiple bonds tend to be harder to cyclize then the terminal triple or douple bond which is probably due to steric hinderance

Table 2.17: Optimization in the coniine system



2.76 **2.77**

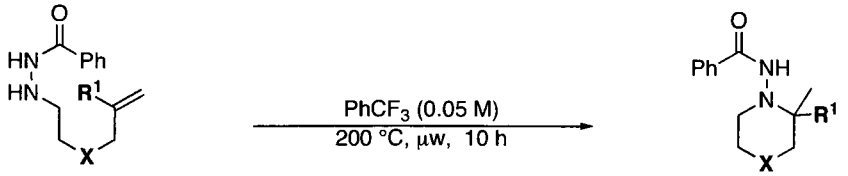
Entry	Solvent	Time (h)	Temp. (°C)	R^1	R^2	NMR yield[a] S.M (%)	NMR yield[a] Product (%)
1	$PhCF_3$	10	200	C_2H_5	H	70	18
2	$PhCF_3$	12	220	C_2H_5	H	33	33
3	**$PhCF_3$**	**19**	**220**	**C_2H_5**	**H**	**23**	**51**
4	$PhCF_3$	12	220	H	C_2H_5	37	30
5	**PhCl**	**10**	**235**	**H**	**C_2H_5**	**29**	**47**
6	PhCl	10	250	C_2H_5	H	13	11
7	PhCl	24	235	H	C_2H_5	8	29
8	PhCl	5	250	C_2H_5	H	15	29
9	PhCl	24	220	C_2H_5	H	17	33

[a]Determined by ^1H NMR using 1,4-dimethoxybenzene as int. std.

Entries 2 and 4 demonstrate that at elevated temperatures, both alkene isomers cyclized with similar efficiency. The alkenylhydrazide **2.76** was heated at 250 °C for 10 hours (entry 6); starting material and product are still observed by NMR. One can conclude by affirming that the hyrazides are thermally very stable but, tend to degrade at excessively elevated temperatures. The trans and cis alkene gave the product in 51 and 47 % yields, respectively (entries 3 and 5). Once again it is evident that more optimization is needed for these substrates. One can suggest improvements with auxiliary substitution or maybe Lewis acid catalysis.

Like previously mentioned, morpholines and piperazines are attractive molecules and are characterized by another heteroatom in the ring, whether an oxygen or nitrogen respectively. Table **2.18** shows the optimization for piperazine and morpholine formation.

Table 2.18: Optimization of the piperazine and morpholine systems



2.80 (a-c) 2.81 (a-c)

Entry	R^1	X	Yield (%) and Product
1	H	NTs	81 (2.81a)
2	Me	NTs	84 (2.81b)
3	H	O	75 (2.81c)

The precursors (table **2.18**) were subjected to the same reaction conditions as the previous piperidine reactions (table **2.15**). Morpholine and piperazine were isolated in good yields (entries 1 and 3). Interestingly, disubstitution at the internal position of the alkene was found to also be well tolerated (entry 2).

Hydrazides proved to be versatile substrates in the formation of substituted rings nevertheless; formation of a substituted six membered ring (coniine) is known to require harsh reaction condition. The *N*-(2-methylazepan-1-yl) benzamide is also a substrate that will benefit from the newly developed modification of the carbonyl moiety (Table **2.11**).

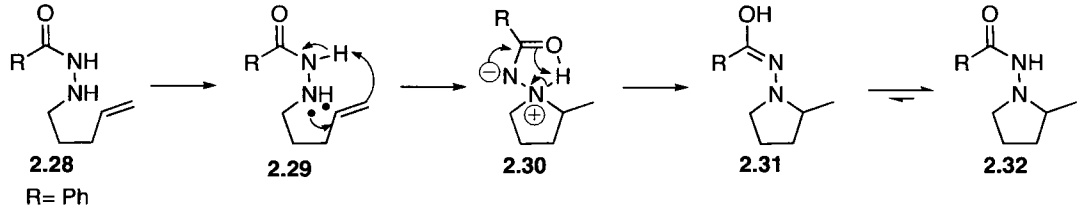
2.4 In efforts toward mechanism elucidation with Density Functional Theory Calculation

2.4.1 Introduction

In order to understand a reaction fully, one must identify the reaction pathway, in other words its mechanism. Mechanistic insight is desirable once generality of the method has been shown experimentally, and increased understanding can often lead to subsequent improvements in reactivity, scope or applications. For example, trapping intermediates, labeling atoms and monitoring their progression over time can be performed with various experiments. In addition, density functional theory (DFT) can also been a practical tool in reaction pathway elucidation.

2.4.2 Intramolecular Cope-type hydroamination: DFT calculations

To develop an understanding of the reactions of hydrazides and hydroxylamines, DFT calculations were performed in collaboration with Dr. Serge Gorelsky. The DFT calculations were performed using the *Gaussian 03* program[82] in the gas phase at the B3LYP[83]/TZVP[84] level of theory. In general hydrazides, when compared to hydroxylamines, have a tendency to need increased temperatures (roughly 100 °C) to undergo Cope-type hydroamination. Using DFT calculation Dr. Serge Gorelsky is able to illuminate this aspect. The calculated activation energies for a concerted, planar, 5-membered Cope-type hydroamination transition state were previously determined to be 22.9 kcal/mol for the hydroxylamine. By comparison, the calculated values for the parent hydrazides are 28.7 kcal/mol. Depicted in Scheme 2.5 is the calculated free energy of reaction and transition states for the intramolecular Cope-type hydroamination of hydrazides. The calculations are in agreement with the participation of the hydrazide carbonyl group in the proton transfer (**2.30**). This is also in harmony with the experimental observation that hydroamination is compatible with different types of solvents, likely because the solvent is not involved in the proton transfer step.[79]

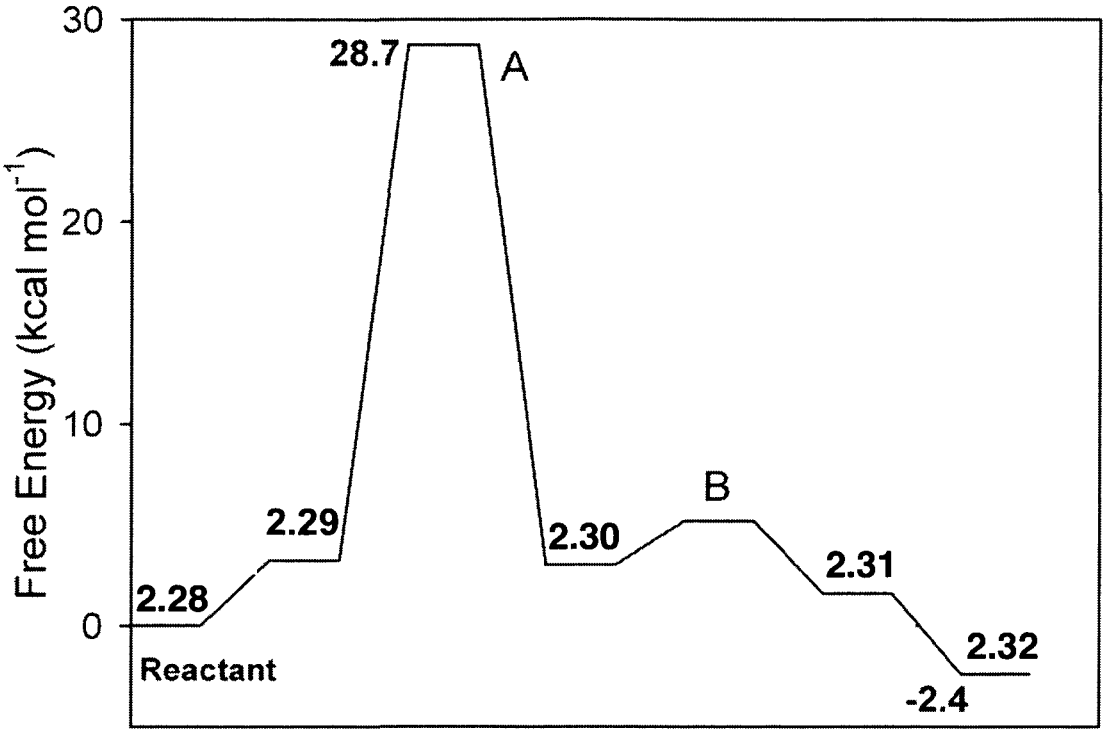


2.28 **2.29** **2.30** **2.31** **2.32**

[82] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J., J. A. ; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Lyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A.; Gaussian, Inc.: 2003.

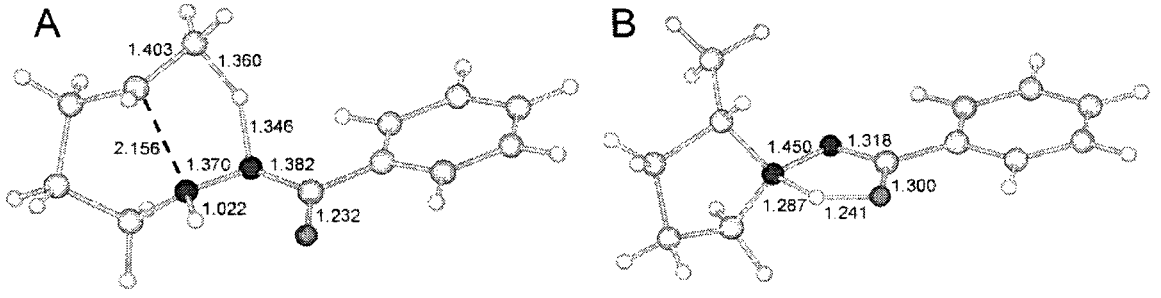
[83] Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

[84] Schafer, A.; Huber, C.; Ahlrichs, R. *J. Chem. Phys.* **1994**, *100*, 5829.



Scheme 2.7: Free energy of reaction species and transition states for the intramolecular cope-type hydroamination of hydrazides at the B3LYP/TZVP level of theory.

Transition state structures for the hydroamination and proton transfer are shown in Scheme **2.8**.



Scheme 2.8: Transition state structures for the intramolecular Cope-type hydroamination (**A**) and subsequent proton transfer (**B**) at the B3LYP/TZVP level of theory. The internuclear distances (Å) are shown only for relevant chemical bonds.

Also, TS A (Scheme 2.8) depicts a concerted asynchronous process and supports the involvement of the hydrazide moiety in the proton transfer step. From this, during the transition state the HOMO of the alkene interacts first with the hydrogen followed by attack of the other nitrogen in the LUMO of this same alkene. Mechanistics insights are currently being investigated experimentally by Ms. Ashley D. Hunt and will be briefly discussed in the subsequent section.

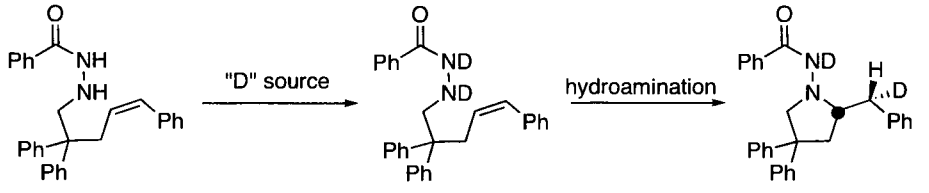
2.4.3 Intramolecular Cope-type hydroamination: mechanistic insight

Previous reports have shown the hydroamination of hydroxylamines to be a concerted process.[85] In order to demonstrate this aspect, the hydrogen was replaced by a deuterium and submitted to the reaction conditions. The Ciganek group performed this reaction in order to shed light on the possible radical mechanism, however they observed a mixture of deuteration of products on both diastereotopic benzyl groups.

2.82 **2.83** **(2.10)**

Interestingly, Ciganel did observe that the reaction was stereospecific with both alkene isomers (**2.83**, shown is the trans product). This fascinating discovery supported a concerted mechanism.

Current work is being undertaken by Ms. Ashley D. Hunt, which should elucidate and confirm if the intramolecular Cope-type hydroamination using hyrazides truly goes through a concerted reaction.

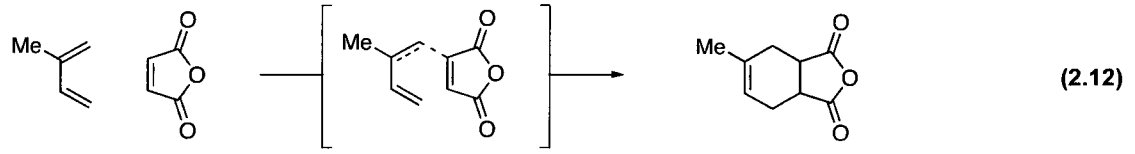


2.84 **2.85** **2.86** **(2.11)**

[85] (a) Ciganek, E.; Read, J. M.; *J. Org. Chem.* **1995**, *60*, 5795, (b) Oppolzer, W.; Spivey, A. C.; Bochet, C. G. *J. Am. Chem. Soc.* **1994**, *116*, 3139, (c) Oppolzer, W. *Gazz. Chim. Ital.* **1995**, *125*, 207

Ms. Hunt is currently synthesizing compound **2.84**, which will be deuterated at the amine and amide position as displayed in compound **2.85**. Following this, submission to the thermal reaction conditions should give rise to product **2.86**. If the stereochemistry of the product is preserved a concerted mechanism is supported. If the process is judged to be concerted, further investigation to determine whether the Cope-type hydroamination is asynchronous or synchronous can be done.

In 1995 the Singleton[86] group developed an analytical method that can calculate isotope effects at natural abundance. With this method, the group was able to determine that this Diels-Alder reaction (**2.87**) is a concerted asynchronous process (**2.88**); as seen in Scheme **2.12**, **2.88** displays the formation of one bond over the other one during the transition state.



2.87 **2.88** **2.89** **(2.12)**

With time, this method could be employed in the hydroamination reaction. One could prove or disprove the DFT calculations that suggest that the hydroamination reactivity of hydrazides is a asynchronous concerted reaction.

2.5 Conclusion

Hydrazides have proven to be an important tool in the intramolecular Cope-type hydroamintion. Their stability at elevated temperature, their capacity to withstand substitution at different positions and finally the ease synthesizing the starting material make them a good alternative in the hydroamination reactions. The reactivity has shown to be quite general in the formation of five membered rings, where substitutions at the terminal alkene was tolerated, the gem-dimethyl displayed lower temperatures and finally secondary hydrazides were also well tolerated in the formation of five membered rings. The method has also been shown promising

[86] Singleton, D. A.; Thomas, A. A. *J. Chem. Soc.* **1995**, *117*, 9357

results in the cylization of six and seven membered rings onto a terminal alkene moiety. Also, terminal and internal substitution of the alkene was also tolerated. The developed methodology has also been applied to the synthesis of morpholine and piperazines. The reactivity shown is only preliminary results, the focus of further experimentation on this method should be on fine tuning hydrazide structure, possible catalysis and on developing intermolecular variants.

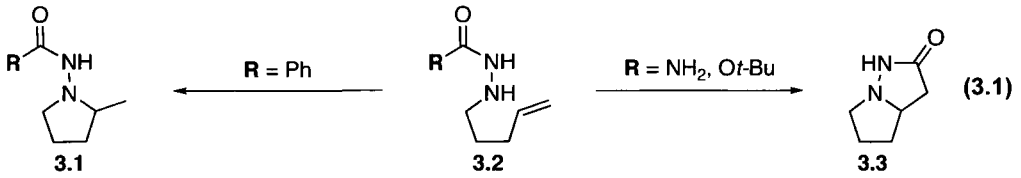
Chapter 3:

Preliminary alkene aminocarbonylation reactivity and future work

3.1 Towards controlled aminocarbonylation reactivity

3.1.1 Introduction

Hydrazides have proven themselves to be desirable reagents in several different transformations.[87] Nevertheless, upon a simple modification, different reactivity was observed. The Beauchemin Group discovered that upon substitution of the R group, aminocarbonylation compound **3.3** is obtained in addition to the Cope-type hydroamination product (equation 3.1) at lower temperatures (125-150 °C) and overwhelming favored at higher temperatures (180-200 °C).



(3.1)

This aminocarbonylation process has been shown experimentaly to be stereospecific, leading to the addition of the nitrogen and carbonyl group onto a double bond. Through precedence from the literature it has been proposed to go through an aminoisocyanate intermediate and, DFT calculations suggest that aminoisocyanate could undergo a facile intramolecular cycloaddition.[88]

3.1.2 Palladium-catalyzed alkene aminocarbonylation

Aminocabonylation reactions have been studied in the 1980's by the Hegedus[89] group (equation 3.2). They demonstrated that upon addition of the desired compound **3.4 (a-f)** and Pd^{II} species a fast equilibrium is formed between compound **3.5** and **3.4**. Upon addition of carbon monoxide and methanol, the aminocarbonylation product can be obtained in reasonable yields. Due to the fact that the β-hydride elimination is a competitive pathway, the reactions needed to be done at lower temperatures in order to favor the CO insertion product (**3.6**).

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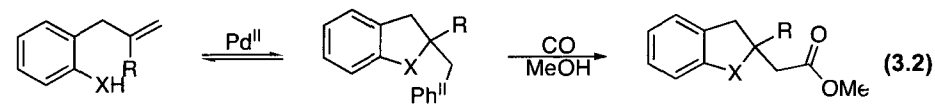
[87] Please refer to chapter 1 and 2 for more details

[88] Serge Gorelsky, *unpublished results*

[89] Hegedus, L. S.; Allen, G. F.; Olsen, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 3583.

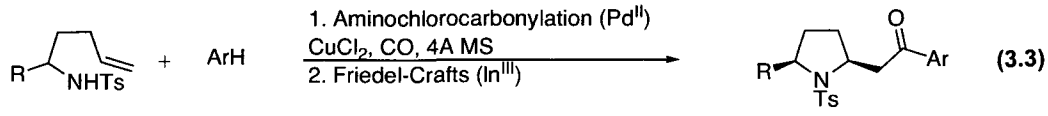


3.4 (a-f)
R = H, Me
X = NH, NMe, NAc, CO_2

3.5

3.6

Recently the Lambert[90] group demonstrated a similar metal-catalyzed tandem sequence (equation **3.3**), which is complementary to Hegedus aminocarbonylation reaction.

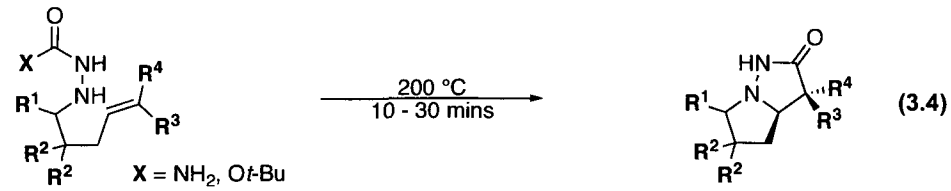


3.7

3.8

3.9

The Lambert group demonstrated that *N*-tosylpentenamine (**3.7**), when exposed to Palladium (II) and $CuCl_2$ under a carbon monoxide (CO) atmosphere gave rise to an acid chloride. Following this, Indium (III) triflate catalyzed Friedel-Crafts reaction gave rise to product **3.9**. The methods employed by Hegedus and Lambert required a two-step process to yield the desired aminocarbonlyation product. Herein, in equation **3.4**, we report a one-step aminocarbonylation reaction that is conducted under metal free conditions.



3.9 (a-b)

3.10 (a-b)

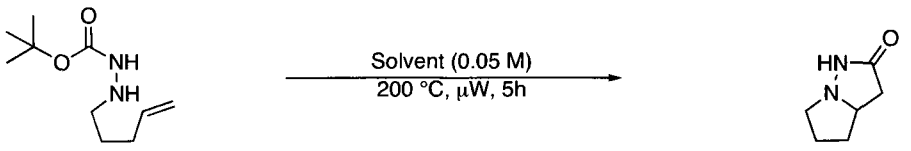
3.1.3 Metal-Free Aminocarbonylation Reactivity of Hydrazides:[91] Optimization and Mechanistic reasoning

[90] Cernak, T. A.; Lambert, T. H. *J. Am. Chem. Soc.* **2009**, *131*, 3124.

[91] Throughout this section, substantial work as been done by Christian Clavette.

In order to improve the preliminary results observed by Christopher Whipp a solvent scan was preformed on the alkenylhydrazide (**3.11**).

Table 3.1: Aminocarbonylation: solvent scan



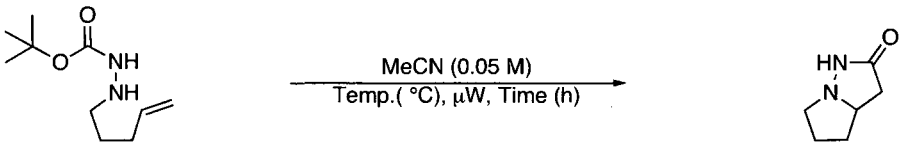
3.11 **3.12**

Entry	Solvent	NMR yield (%)[a]
1	$PhCF_3$	50
2	*i*-PrOH	0
3	Dioxane	43
4	PhCl	57
5	H_2O	0
6	DMF	50
7	**MeCN**	**74**
8	*n*-BuOH	39

[a]Determined by ^1H NMR using 1,4-dimethoxybenzene as int. std.

Running the reaction under Mr. Whipp's lead results, the alkenylhydrazide (**3.11**) was subjected to the reaction conditions in eight different solvents (Table 3.1). From these results, aprotic and polar solvents (entries 4, 6 and 7) were found to dominate over the others. Nevertheless, acetonitrile (entry 7) demonstrated the best results with a conversion of 74 %. Following this, a temperature and time scan was performed. Even though the yields were not drastically improved, the reaction time at 200 °C diminished from 5 hours to just 10 mins (entry 5).

Table 3.2: Aminocarbonylation: temperature and time scan

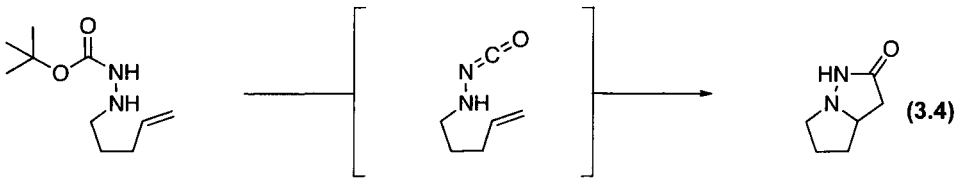


Entry	Temperature (°C)	Time	Conversion (%)[a]
1	200	5.0 h	74
2	200	1.0 h	35
3	200	1.0 h	60
4	200	30 min	69
5	**200**	**10 min**	**76**
6	200	5 min	71
7	190	10 min	45
8	190	10 min	70
9	190	30 min	67
10	180	12.0 h	64
11	180	10 min	51
12	150	12.0 h	53
13	150	5.0 h	52
14	150	3.0 h	51
15	150	1.0 h	37
16	150	10 min	12

[a]Determined by ^{1}H NMR using 1,4-dimethoxybenzene as int. std.

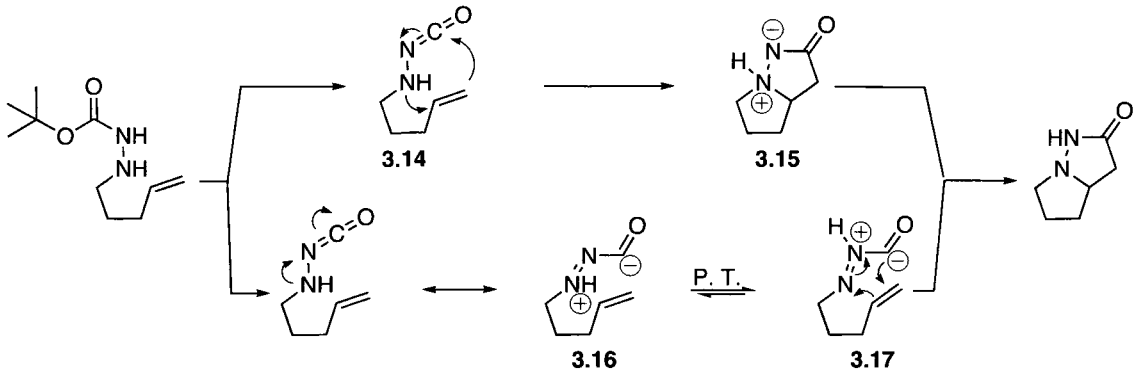
Unlike hydroamination, which requires several hours to fully react, the aminocarbonylation reaction only needs a minimum amount of time (entry 6). This can be explained with a mechanistic rational where upon formation of a highly reactive species the reaction time would drastically diminish. When subjected to elevated temperatures, substantial evidence suggests the formation of a reactive species: aminoisocyanate species (**3.13**). Such an intermediate could be quite reactive and react readily, intramolecularly under the dilute conditions used to form the aminocarbonylation product (**3.12**).[92]

[92] For more details please refer to: (a) Clavette, C. *A Novel, Metal-Free Aminocarbonylation of Alkenes* (Honours thesis, University of Ottawa, 2009) (b) Maier, G; Teles, H. *Chem. Ber.* **1989**, *122*, 745 (c) For a an overview of aminoisocyanates and their reactivity see: Reichen, W. *Chem. Rev.* **1978**, *78*, 569 (d) For more details on the thermolysis of semicarbazides and their reactivity see: Pinner, G. *Ber.* **1908**, *21*, 1225. (e) For similar reactivity of aminoisocyanate with acetylenes see: Lockley, W. J. S.; Lwowski, W. *Tetrehedron* **1974**, *48*, 4263



3.13

Current DFT calculations done in collaboration with Dr. Serge Gorelsky explore two possible pathways (Scheme 3.1). Upon expulsion of a good leaving group (i.e. *tert*-butyl), formation of a reactive aminoisocyanate intermediate could be possible (Scheme 3.1, pathway **A** and **B**).[93] Depicted in pathway A is a simple 3 + 2 cycloaddition to form the zwitterionic intermediate **3.15**, where upon proton transfer the aminocarbonylation product is obtained. Pathways B explored resonance structures (**3.14** to **3.16**) to farm a dipole, followed by a 1,3 dipolar cycloaddition. Nevertheless, pathway B is or was proposed in accordance with the fact that zwertterionic intermediates are lower in energy when the charges are contiguous.



Scheme 3.1: Aminocarbonylation proposed pathways for novel aminocarbonylation reactivity

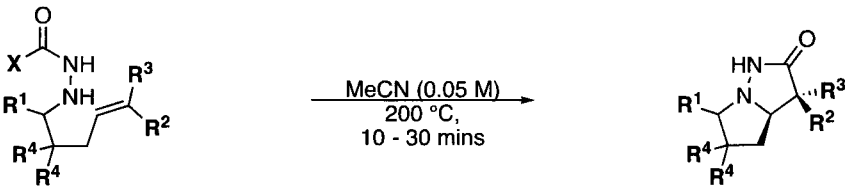
Nevertheless, whether the desired or correct pathway is A or B, the aminoisocyanate species is present in both, and seems like a reasonable intermediate. Serge Gorlesky demonstrated the reaction to favor pathway A, using DFT calculations. Current studies by Christian Clavette will probe this mechanistic proposal experimentally.

[93] Wadsworth, W. S.; Emmons, W. D. *J. Org. Chem.* **1967**, *32*, 1279

3.1.4 Metal-free aminocarbonylation reactivity of hydrazides[91]: substrate scope[94]

In order to explore the scope of this novel reactivity, the reaction was performed on precursors with different substitution patterns on the alkenyl chain.

Table 3.3: Aminocarbonylation reaction: substrate scope



3.9 (a-h) 3.10 (a-h)

Entry	R^1	R^2	R^3	R^4	X	Yield (%)
1	H	H	H	H	O*t*-Bu	70 (3.10 a)
2	H	H	H	H	NH_2	86 (3.10 b)
3	Me	H	H	H	O*t*-Bu	76 (3.10 c)
4	Me	H	H	H	NH_2	84 (3.10 d)
5	H	Me	H	H	O*t*-Bu	66 (3.10 e)
6	H	Me	H	H	NH_2	52 (3.10 f)
7	H	H	Me	H	NH_2	71 (3.10 g)
8	H	H	H	Me	NH_2	33 (3.10 h) (+47 % HA)[a]

[a] Hydroamination product

The unsubstituted alkenylhydrazide was cyclized with both the semicarbazide and tert-butylcarbazate (entries 1 and 2). The semicarbazide (entry 2) precursor yielded the product in better yields than with the carbazate (entry 1) derivative. A branched hydrazide was also cyclized and the resulting product was isolated in good yields (entries 3 and 4). Following this the trans alkenylhydrazide was subjected to similar reactivity with the same hydrazide functionalities (entries 5 and 6). Once again the semicarbazide displayed better reactivity over its carbazate counterpart.

Noesy experiments (Chapter 5) have established the reaction to be stereospecific; for the trans and cis alkenes (entries 5, 6 and 7). Unfortunately, the gem dimethyl substitution gave rise to poor yields (entry 8). This can be rationalized by a more favourable (but reversible) hydroamination occurring at lower temperature, and

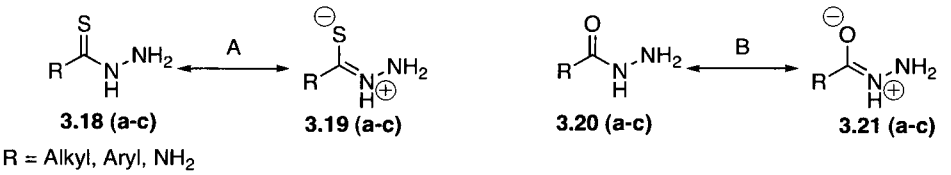
[94] For details on the synthesis the carbazates and semicarbazides please see chapter 5

that the aminocarbonylation can occur at the higher temperature required for aminoisocyanate formation. The Aminocarbonylation is relatively new chemistry in the Beauchemin group and current studies by Mr. Christian Clavette will try to further our understanding this transformation. Intermolecular variants are currently tested with similar reaction conditions. Nonetheless, little is known on the intramolecular aminocarbonlyation even less on the intermolecular variants therefore, and efforts are being undertaken to elucidate this reactivity and increase its reaction scope.

3.2 Preliminary results for hydroamination with thiosemicarbazides

3.2.1 Introduction

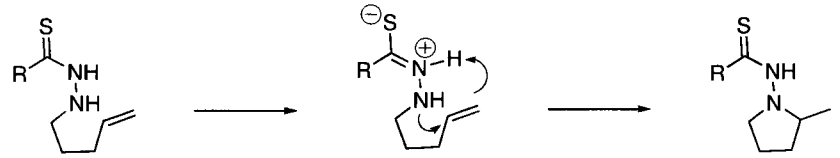
While working to improve the Cope-type hydroamination reactivity, it was hypothesized that thiohydrazides could be better reagents than hydrazides.[95] Comparing the two resonance structures A and B (Scheme **3.2**) helps to illustrate this hypothesis.



Scheme 3.2: Resonance structure of thiohydrazide and hydrazide

Both the acyl hydrazines and their thio equivalents can be expressed as their corresponding zwitterionic resonance structures. They only differ by the fact that structure **3.19** has negatively charged sulfur and the other one has an oxygen. Sulfur, as in compound **3.18**, is known to be a bigger and more diffused atom and is generally expected to be better at stabilizing the negative charge that is building up in the transition state of the reaction. From this, when compared to the hydrazide the resonance structure should predominate, making its corresponding iminium more apt to get deprotonated (ex: Cope-type hydroamination).

[95] For more details please refer to Chapter two of this thesis



3.22 (a-c) 3.23 (a-c) 3.24 (a-c)

R = Alkyl, Aryl, NH_2

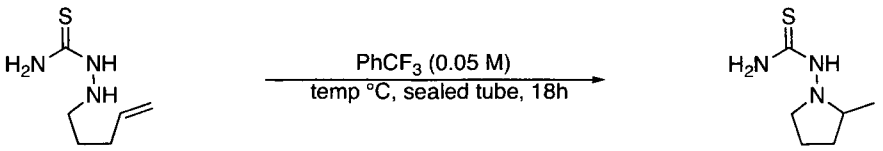
(3.4)

It was of interest to cyclize the corresponding hydrazide (equation 3.4) and to test this hypothesis. From an inexpensive, commercially available thio semi-carbazide, the alkenylthiohydrazide was synthesized in the same manner as previously discussed (oxidation followed by reductive amination, see chapter 2).

3.2.2 Cope-type hydroamination with a thiohydrazide

The corresponding thiohydrazide was subjected to tow different temperatures (Table 3.4), in order to compare to its forerunner.

Table 3.4: Cope-type hydroamination: temperatures scan

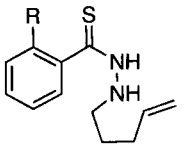


3.25 3.26

Entry	Temperature (°C)	Yield (%)
1	**150**	**82**
2	100	traces[a]

[a]Determined by ^{1}H NMR using 1,4-dimethoxybenzene as int. std.

The corresponding alkenylthiohydrazide was heated to 150 °C and the desired product was isolated in a 82 % yield. This is quite promising because the previous alkenylhydrazide at 150 °C displayed only 50 % conversion on top of a 20 % conversion to the aminocarbonylation product. Unlike the alkenylhydrazide, the alkenylthiohydrazide did not show any formation of the aminocarbonylation product. This could be explained by the deficiency of orbital interaction where there is not a good orbital interaction; the 3p orbital of sulfur and the 2p orbital of oxygen. In order to allow direct comparison, a thio analog of the one used in Chapter 2 must be synthesized (equation 3.5).



3.27 (a-b)

R = OH, H

$PhCF_3$ (0.05 M)
temp °C, sealed tube, 18h...

? (3.5)

Mr. Francis Loiseau is undertaking current work in this area, where he will test the compound (**3.27b**), as well as others to see if the reaction conditions for hydrazide hydroamination can be optimized. As a possible avenue for this type of chemistry, some Lewis acids have been shown to be nearly exclusively thiophilic. Therefore, a thorough Lewis acid scans could be undertaken in this area.

3.3 Conclusion

As demonstrated in this chapter, upon a simple modification of the terminal acyl substituent, the Cope-type hydroamination reactivity can be suppressed from which new aminocarbonylation reactivity is obtained. Both alpha-unsubsituted and alpha-substituted primary carbazates (or carbazides) display the desired reactivity, cis or trans substitution and of the olefin was also tolerated.

Preliminary results displayed that the use of thiosemicarbazide could possibly be an alternative to the intramolecular Cope-type hydroamination using hydrazides. Initial results show high conversions; however, further research is currently being undertaken to explore the synthetic utility of those reagents.

Chapter 4: Conclusion

4.1 General conclusion

The work resented in this thesis has described the development of certain aspects of intramolecular Cope-type hydroamination of alkenes using hydrazides as bifunctional reagents. Parallel to this work, was the development of intramolecular aminocarbonylation of alkenes. The goal of this work was in line with attempts to ultimately develop simple, metal free hydroamination or aminocarbonylation methods that are general to all types of alkenes.

In Chapter 2, a methodology project was presented on the intramolecular of alkenes with hydrazines. The development of Cope-type hydroamination achieved reliably five and six membered azacycles, using various primary hydrazides also, heteroatoms, such as morpholines and piperazines. Several substitution patterns on the alkene where well tolerated, although the higher reaction temperatures. The hydroamination procedure is simple and the cyclized precursors are typically bench-stable and the products can be purified by chromatography. DFT studies calculation done support the proposed intramolecular hydroamination followed by a subsequent proton transfer of the dipolar intermediate. Given that hydroxylamines can be sensitive and prone to decomposition, we have developed more a practical reagent.

In Chapter 3, another methodology was developed in parallel to the hydroamination Cope-type hydroamination that is the intramolecular aminocarbonylation of alkenes of hydrazines. In contrast to the benzoic hydrazides, carbazates and semicarbazides form the aminocarbonylation; a preliminary substrate scope was presented. Primary and secondary semicarbazides (or carbazates), alkene substitution at the distal position have shown to be well tolerated. Through DFT calculations, this reactivity appears to be consistent with in situ formation of an aminoisocyanate intermediate. To the best of our knowledge, this is the first metal free aminocarbonylation reaction.

4.2 Contributions to research

1) Was implicated in the first examples of intermolecular metal-free Cope-type Hydroamination of aryl

alkynes with hydrazines and obtained anti-Markovnikov selectivity, which is rare in transition metal catalysts.

2) Obtained initial results on the intramolecular alkene hydroamination reactivity of hydrazides. Several extensions are currently being investigated in the group

3) Was implicated in the discovery and optimization of the aminocarbonylation reactivity.

4.2.1 Publications

1) "Intermolecular Cope-Type Hydroamination of Alkynes Using Hydrazines" Cebrowski, P. H.; **Roveda, J.-G.**; Moran, J.; Gorelsky, S. I.; Beauchemin, A. M. *Chem. Commun.* **2008**, 492-493.

2) "Hydrazides as Tunable Reagents for Alkene Hydroamination and Diamination" **Roveda, J-G.**; Clavette, C.; Hunt, A.; Gorelsky, S. I.; Whipp, C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, 131, 8740

4.2.2 Presentations

1) "Towards Controlled Amination: Hydroamination vs. Diamination" Synthesis Day, University of Ottawa, ON, Ottawa, June 16, **2008**

2) "Towards Controlled Amination: Hydroamination vs. Diamination" Ottawa-Carleton Chemistry Institute (OCCI), University of Ottawa, ON, Ottawa, May 15, **2008**

3) "Towards Controlled Amination: Hydroamination vs. Diamination" Quebec-Ontario Minisymposium in Synthetic and Biological Chemistry (QOMSBOC), University of Toronto, ON, Ottawa, November 8, **2008**

Chapter 5: Experimental

5.1 General Information

Purification of reaction products was carried out by flash column chromatography using Silicycle silica gel (40-63 μm), unless otherwise noted. Analytical thin layer chromatography (TLC) was performed on aluminum, cut to size. Visualization was accomplished with UV light followed by staining with a potassium permanganate solution and heating.

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AVANCE 300 MHz and 400 MHz spectrometers at ambient temperature, unless otherwise indicated. Spectral data was reported in ppm using solvent as the reference ($CDCl_3$ at 7.26 ppm, C_6D_6 at 7.15 ppm or DMSO-d_6 at 2.50 ppm for ^{1}H NMR and $CDCl_3$ at 77.0 ppm or DMSO-d_6 at 39.43 for ^{13}C NMR). ^{1}H NMR data was reported as: multiplicity (ap = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, sept = septuplet, m = multiplet), integration and coupling constant(s) in Hz. Infrared (IR) spectra were obtained with neat thin films on a sodium chloride disk and were recorded on a Bomem Michelson 100 Fourier transform infrared spectrometer (FTIR). High resolution mass spectroscopy (HRMS) was performed on a Kratos Concept-11A mass spectrometer with an electron beam of 70ev at the Ottawa-Carleton Mass Spectrometry Centre.

Materials. Unless otherwise noted, all commercial materials were purchased from commercial sources and used without further purification. Pivalohydrazide and picolinohydrazide were synthesized using Wieczorek's method. [96] Pent-4-enyl 4-methylbenzenesulfonate was synthesized according to Sirett's procedure.[97]

(96) Kazuyuki, O.; Yamamoto, T.; Okuma, M.; Horiuchi, T.; Imanishi, H.; Odagaki, Y.; Kawabata, K.; Sekioka, T.; Hirota, Y.; Matsuka, S.; Nakai, H.; Cheronis, M. T.-J. C.; Spruce, L. W.; Gyorkos, A.; Wieczorek, M. *J. Med. Chem.* **2001**, *40*, 1268.
(97) Ashley, J. N.; Collins, R. F.; Davis, M.; Sirett, N. E. *J. Chem. Soc.* **1959**, 897.

5.1.1 General procedure for the formation of the hydrazone (Chapter 2)

General Procedure A: Prepared according to the procedure of the Mukai group.[98] To a flame-dried round bottom flask (250 mL) charged with a magnetic stir bar, alkenol (0.50 mL, 4.9 mmol), DMSO (1.12 mL, 15.8 mmol) and Et_3N (2.20 mL, 16.1 mmol) in dry CH_2Cl_2 (22.4 mL) was added SO_3·Pyr (2.35 g, 14.8 mmol) at 0 °C. The reaction was monitored by TLC until judged to be complete. The reaction was quenched by addition of saturated aqueous NH_4Cl, and the mixture was extracted with CH_2Cl_2. The extract was washed with H_2O and brine. The crude mixture was evaporated *in vacuo*, and the aldehyde was used without any purification. The hydrazone was prepared according to the procedure of the Leighton group.[99] The corresponding hydrazide (0.318 g, 2.32 mmol) and acetic acid (0.133 mL, 2.32 mmol) were added in methanol (13.0 mL) to the unpurified aldehyde mixture. The mixture was refluxed until consumption of the aldehyde or hydrazide was judged to be complete by TLC. The corresponding product was concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding product(s).

General Procedure B: Prepared according to the procedure of the Mukai group.[98] To a flame-dried round bottom flask (250 mL) charged with a magnetic stir bar, alkenol (1.0 mL, 9.8 mmol), DMSO (2.7 mL, 30 mmol) and Et_3N (5.5 mL, 39 mmol) in dry CH_2Cl_2 (60.0 mL) was added SO_3·Pyr (4.7 g, 30 mmol) at 0 °C. The reaction was monitored by TLC until completion. The reaction was quenched by addition of saturated aqueous NH_4Cl, and the mixture was extracted with CH_2Cl_2. The extract was washed with H_2O and brine. The crude mixture was evaporated *in vacuo*, and the aldehyde was used without any purification.The hydrazone was prepared according to a modified procedure of the Leighton group.[99] To the crude mixture the corresponding semicarbazide (1.0 g, 9.0 mmol) and pyridine (0.712 g, 9.00 mmol) were added in methanol (13.0 mL). The mixture was refluxed until consumption of the aldehyde or hydrazide was judged to be complete by TLC. The

(98) Mukai, C.; Nomura, I.; Katagaki, S. *J. Org. Chem.* **2003**, *68*, 1376.
(99) Berger, R.; Duff, K.; Leighton, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 5686.

corresponding product was concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding products.

General Procedure C: Prepared according to the procedure of the Leighton group.[99] The corresponding ketone (0.250 g, 2.55 mmol,), hydrazide (0.318 g, 2.32 mmol) and acetic acid (0.133 mL, 2.32 mmol) were added in methanol (13.0 mL). The mixture was refluxed until consumption of the aldehyde or hydrazide was judged to be complete by TLC. The corresponding product was concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding product(s).

General Procedure D: Prepared according to the procedure of the Naito group.[100] To a solution of the acetal (0.356 g, 1.190 mmol) in acetone (12.0 mL) was added 2.0 M HCl (7.2 mL) under an argon atmosphere at room temperature. After being stirred for 1h, 2.0 M HCl (7.2 mL) was again added to the reaction mixture. After being stirred for 1 hour, the reaction mixture was extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to give the crude aldehyde as a yellow oil. The aldehyde was subjected to benzoic hydrazide (0.147 g, 1.080 mmol) in MeOH (5.4 mL). The mixture was refluxed until consumption of the aldehyde or hydrazide is judged to be complete by TLC. The corresponding product was concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding product(s).

5.1.2 General procedure for the formation of the alkylhydrazide

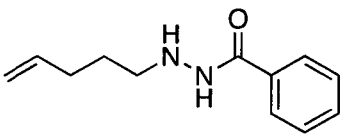
General Procedure A (via reduction): Prepared by a modification of Lane's procedure.[101] The corresponding hydrazone (0.346 g, 1.60 mmol) was combined with $NaCNBH_3$ (0.132 g, 1.92 mmol), a pinch of methyl orange

(100) Miyata, O.; Muroya, K.; Kobayashi, T.; Yamanaka, R.; Kajisa, S.; Koide, J.; Naito, T. *Tetrahedron* **2002**, *58*, 4459.
(101) Lane, C. F. *Synthesis* **1974**, 135.

and a clean stir bar in methanol (2.0 mL) (the mixture is orange). The solution was capped with a septum and purged with argon for 5 minutes. A solution of 1:1 MeOH:HCl was added drop wise until the solution turned red (the reaction must stay red). The reaction mixture is stirred for 3 hours. NaOH is added until pH is around 8. Extraction was done with CH_2Cl_2, the organic phase was washed with brine and dried over Na_2SO_4. The corresponding product was concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding product(s).

General Procedure B (via alkylation): Prepared according to the procedure of Hansen.[102] The alkenyl tosyl (0.775 g, 3.22 mmol) and corresponding hydrazide (0.131 g, 9.66 mmol) were stirred at 100 °C in DMF (16 mL) for 5 hours. The solvent was removed by heating the reaction flask under reduced pressure. The residue was dissolved in EtOAc and the organic phase was washed with a mixture of 1:1 brine: H_2O. The organic phase was dried over Na_2SO_4. The corresponding product was concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding product(s).

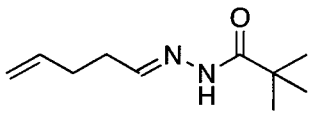
5.1.3 Characterization of hydrazide and hydrazone



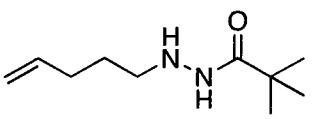
***1-N*-(Pent-4-enyl)benzohydrazide (Table 1, entry 5, 2.32e).** Synthesized according to general procedure 2B. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (20 % EtOAc in toluene and 1 % Et_3N). The title compound was obtained as a clear oil (0.220 g, 33 % yield). TLC R_f

(102) Hansen, T. K. *Tetrahedron* **1999**, *40*, 9119.

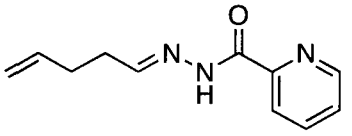
0.1 in 20 % EtOAc in toluene; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.78 (d, J = 7.3 Hz, 2H), 7.50 (t, J = 7.3 Hz, 1H), 7.41 (t, J = 7.3 Hz, 2H), 5.79 (tdd, J = 16.9, 10.2, 6.7 Hz, 1H), 5.01 (ddd, J = 17.1, 3.5, 1.6 Hz, 1H), 4.94 (tdd, J = 10.2, 2.1, 1.2 Hz, 1H), 2.95 (t, J = 7.3 Hz, 2H) 2.1 (q, J = 7.2 Hz, 2H), 1.63 (q, J = 7.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 167.3 (C), 138.0 (CH), 132.8 (C), 131.8 (CH), 128.6 (CH), 126.8 (CH), 115.0 (CH_2), 52.0 (CH_2), 31.1 (CH_2), 27.12 (CH_2); IR (film) 3279, 3070, 2937, 2861, 1641, 1580, 1550, 1458, 1367, 1314, 1284, 1154, 1075, 1022, 991, 908, 793, 691 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{12}H_{16}N_2O$ $[M]^+$: 204.1263. Found: 204.1255.



***2-N*-(Pent-4-enylidene)pivalohydrazide:** Synthesized according to general procedure 1A. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (60 % EtOAc in hexanes). The title compound was obtained as a white solid (0.500 g, 62 % yield).TLC R_f 0.36 in 60 % EtOAc in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) * denotes minor isomer δ ppm 9.27 (s, 1H), 7.59 (t, J = 5.3 Hz, 1H), 5.77 (tdd, J = 16.7, 10.1, 6.4 Hz, 1H), 5.13-4.92 (m, 2H), 2.43-2.17 (m, 4H), *1.25 (s, 9H), 1.21 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 174.4 (C), 151.1 (CH), 136.8 (CH), 115.4 (CH_2), 38.0 (C), 31.5 (CH_2), 30.5 (CH_2), 27.3 (CH_3); IR (film) 3238, 3065, 2969, 1656, 1546, 1481, 1399, 1368, 1288, 1198, 1066, 991, 944, 913 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{10}H_{18}N_2O_1$ $[M]^+$: 182.1419. Found: 182.1411.

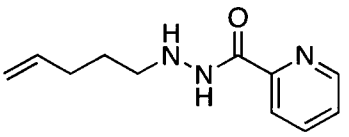


***3-N*-(Pent-4-enyl)pivalhydrazide (Table 1, entry 2, 2.32b):** Synthesized according to general procedure 2A. Procedure as indicated above but used 2.40 eq. (0.290 g) of $NaCNBH_3$ and decreased the concentration to 0.05 M (3.5 mL). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (40 % EtOAc in toluene with 1 % Et_3N). The title compound was obtained as a white solid (0.150 g, 46 %). TLC R_f 0.13 in 40 % EtOAc in toluene; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.65 (s, 2H), 5.74 (tdd, J = 13.5, 10.2, 6.6 Hz, 1H), 5.02-4.85 (m, 2H), 4.72 (br (s), 1H), 2.80-2.71 (m, 2H), 2.05 (dt, J = 13.6, 6.7 Hz, 2H), 1.58-1.45 (m, 1H), 1.15 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 177.7 (C), 138.0 (CH), 114.8 (CH_2), 51.5 (CH_2), 37.8 (C), 31.1 (CH_2), 27.2 (CH_3), 27.1 (CH_2); IR (film) 3296, 3078, 2960, 2869, 1642, 1534, 1482, 1455, 1398, 1367, 1303, 1227, 1086, 1021, 993, 912, 812, 641 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{10}H_{20}N_2O_1$ $[M]^+$: 184.1576. Found: 184.1553.

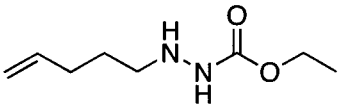


***4-N*-(Penten-4-enylidene)picolinohydrazide**: Synthesized according to general procedure 1A. Observed a mixture of E and Z in a ratio of 8:1, respectively. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (40 % EtOAc in toluene with 1 % Et_3N). The title compound was obtained as a clear oil (0.510 g, 109 % yield). TLC R_f 0.60 in 100 % EtOAc; ^1H NMR (300 MHz, $CDCl_3$) *denotes minor isomer δ ppm *10.91 (s, 1H), 10.70 (s, 1H), 8.56-8.46 (m, 1H), 8.28-8.20 (m, 1H), 7.87-7.79 (m, 1H), 7.59 (t, J = 5.6 Hz, 1H), 7.48-7.39 (m, 1H), *6.94 (t, J = 4.0 Hz, 1H), 2.61-2.43 (m, 2H), 2.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) * denotes minor isomer δ ppm 160.0 (C), 152,14 (CH), *150.8 (CH), 149.1 (C), *148.1 (CH), 147.9 (CH), 137.5 (CH), 136.8 (CH), *136.0 (CH), *126.7 (CH), 126.6 (CH), 122.9 (CH), *116.5 (CH_2), 115.8 (CH_2), 31.5 (CH_2), 30.7 (CH_2), *29.8 (CH_2), *26.0 (CH_2); IR (film) 3249, 3245, 3067,

3000, 2914, 1679, 1588, 1568, 1527, 1436, 1360, 1284, 1238, 1143, 1090, 1048, 995, 911, 812, 752 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{11}H_{13}N_3O$ $[M]^+$: 203.1059. Found: 203.1033.

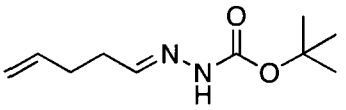


5-*N*-(Pent-4-enyl)picolinohydrazide (Table 1, entry 1, 2.32a): Procedure as indicated above but used 2.40 equiv. (0.57 g) of $NaCNBH_3$ and decreased the concentration to 0.05 M (7.9 mL). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (40 % EtOAc in toluene with 1 % Et_3N). The title compound was obtained as a white oil (0.330 g, 47 %) TLC R_f 0.28 in 40 % EtOAc in toluene; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.52 (ddd, J = 4.8, 1.6, 0.9 Hz, 2H), 8.16-8.11 (m, 1H), 7.83 (dt, J = 7.8 1.7 Hz, 1H), 7.41 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 6.78 (s, 1H), 5.79 (tdd, J = 16.9, 10.2, 6.7 Hz, 1H), 5.01 (ddd, J = 17.1, 3.5, 1.6 Hz, 1H), 4.94 (tdd, J = 10.2, 2.1, 1.2 Hz, 1H), 2.95 (t, J = 6.9 Hz, 1H), 2.09 (q, J = 6.9 Hz, 1H), 1.65 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 163.2 (C), 149.2 (C), 148.2 (CH), 138.0 (CH), 137.3 (CH), 126.3 (CH), 122.2 (CH), 115.0 (CH_2), 51.6 (CH_2), 31.1 (CH_2), 27.1 (CH_2); IR (film) 3283, 3078, 2941, 2865, 1660, 1588, 1569, 1516, 1455, 1428, 1288, 1246, 1086, 991, 908, 809, 740 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{11}H_{15}N_3O$ $[M]^+$: 205.1215. Found: 205.1193.

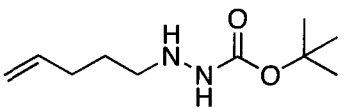


6-1-(Pent-4-enyl)ethylcarbazate (Table 1, entry 4, 2.32d): Synthesized according to general procedure 2B. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (40 %

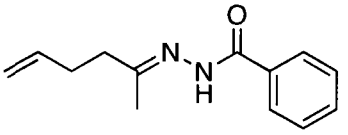
EtOAc in toluene with 1 % Et_3N). The title compound was obtained as a clear oil (1.10 g, 50 % yield). TLC R_f 0.22 in 40 % EtOAc in toluene; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 5.79 (tdd, J = 16.9, 10.2, 6.7 Hz, 1H), 5.01 (ddd, J = 17.1, 3.5, 1.6 Hz, 1H), 4.94 (tdd, J = 10.2, 2.1, 1.2 Hz, 1H), 4.18 (q, J = 7.0 Hz, 1H), 2.95 (t, J = 7.3 Hz, 2H) 2.1 (q, J = 7.2 Hz, 2H), 1.63 (q, J = 7.3 Hz, 2H), 1.26 (t, J = 7.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 157.6 (C), 138.3 (CH), 115.0 (CH_2), 61.4 (CH_2), 51.6 (CH_2), 31.3 (CH_2), 27.1 (CH_2), 14.7 (CH_3); IR (film) 3264, 2971, 1705, 1375, 1253, 1178, 1060 cm^{-1}; HRMS (EI): Exact mass calcd for $C_8H_{16}N_2O_2$ $[M]^+$: 172.1212. Found: 172.1210.



***7-N*-(Pent-4-enylidene)*tert*-butylcarbazate:** Synthesized according to general procedure 1A. Observed a mixture of E and Z isomers in a ratio of 5:1, respectively. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (40 % EtOAc in toluene with 1 % Et_3N). The title compound was obtained as a clear oil (0.340 g, 66 % yield). TLC R_f 0.57 in 40 % EtOAc in toluene; ^1H NMR (300 MHz, $CDCl_3$) * denotes minor isomer δ ppm 7.76 (s, 1H), 7.16 (t, J = 5.3 Hz, 1H), *6.63 (t, J = 5.0 Hz, 1H), 5.79 (tdd, J = 16.9, 10.2, 6.7 Hz, 1H), 5.01 (ddd, J = 17.1, 3.5, 1.6 Hz, 1H), 4.94 (tdd, J = 10.2, 2.1, 1.2 Hz, 1H), 2.46-2.15 (m, 4 H), *1.53 (s, 9H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) * denotes minor isomer δ ppm 156.8 (C), 146.5 (CH), *145.5 (CH), 137.0 (CH), *136.1 (CH), 116.4 (CH_2), *115.6 (CH_2), 80.0 (C), 31.4 (CH_2), 30.8 (CH_2), *29.8 (CH_2), 28.3 (CH_3), *25.4 (CH_2); IR (film) 3249, 2979, 2941, 1699, 1534, 1393, 1367, 1271, 1251, 1168, 1044, 1017, 912, 866, 763 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{10}H_{18}N_2O_2$ $[M]^+$: 198.1368. Found: 198.1385.

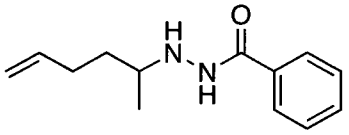


***8-N*-(Pent-4-enyl)*tert*-butylcarbazate (Table 1, entry 3, 2.32e):** Synthesized according to general procedure 2A. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (20 % EtOAc in toluene with 1 % Et_3N). The title compound was obtained as a clear oil (0.110 g, 35 % yield). TLC R_f 0.45 in 40 % EtOAc in toluene; 1H NMR (300 MHz, $CDCl_3$) δ ppm 6.22 (s, 1H), 5.79 (tdd, J = 16.9, 10.2, 6.7 Hz, 1H), 5.01 (ddd, J = 17.1, 3.5, 1.6 Hz, 1H), 4.94 (tdd, J = 10.2, 2.1, 1.2 Hz, 1H), 3.93 (s, 1H), 2.83 (t, J = 7.2 Hz, 1H), 2.09 (q, J = 6.9 Hz, 1H), 1.55 (m, 1H), 1.44 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 156.8 (C), 138.3 (CH), 114.8 (CH_2), 80.4 (C), 51.5 (CH_2), 31.2 (CH_2), 28.4 (CH_3), 27.0 (CH_2); IR (film) 3317, 3078, 2979, 2937, 2873, 1706, 1641, 1478, 1455, 1364, 1284, 1254, 1159, 1048, 1014, 991, 912, 870, 775 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{10}H_{20}N_2O_2$ $[M]^+$: 200.1524. Found: 200.1512.

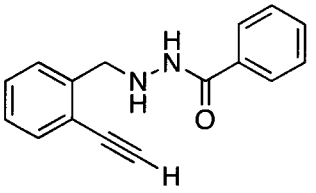


***9-N*-(Hex-5-en-2-ylidene)benzohydrazide (Table 2, entry 1, 2.42a):** Synthesized according to general procedure 1B. Observed a mixture of E and Z isomers in a 5:1 ratio, respectively. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (40 % EtOAc in toluene with 1 % Et_3N). The title compound was obtained as a white crystalline solid (3.17 g, 86 % yield). TLC R_f 0.29 in 40 % EtOAc in toluene; ^1H NMR (300 MHz, $CDCl_3$) * denotes minor isomer δ ppm *8.85 (s, 1H), 8.69 (s, 1H), 7.79 (d, J = 5.4 Hz, 2H), 7.55-7.46 (m, 1H), 7.42 (t, J = 7.3 Hz, 2H), 5.83 (tdd, J = 12.9, 10.5, 6.4 Hz, 1H), 5.18-4.93 (m, 2H), 2.65-2.20 (m, 4H), *2.13 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 163.9 (C), 158.2 (C), 137.2 (CH), 131.7 (CH), 128.6 (CH), 127.1 (CH), 115.4 (CH_2), 38.4 (CH_2), 30.7 (CH_2), 15.2 (CH_3);

IR (film) 3230, 2975, 2918, 1660, 1641, 1580, 1546, 1489, 1451, 1378, 1291, 1173, 1136, 1075, 999, 912, 790, 718, 691 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{13}H_{16}N_2O_1$ $[M]^+$: 216.1263. Found: 216.1268.

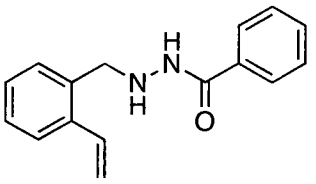


***10-N*-(Hex-5-en-2-yl)benzohydrazide (Table 2, entry 2, 2.43a):** Synthesized according to general procedure 2A. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (40 % EtOAc in hexanes). The title compound was obtained as white solid (2.88 g, 90 %). TLC R_f 0.67 in 60 % EtOAc in hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.15 (s, 1H), 7.78 (d, J = 7.4 Hz, 2H), 7.56-7.38 (m, 3H), 5.82 (tdd, J = 16.8, 10.1, 6.6 Hz, 1H), 5.10-4.90 (m, 3H), 3.15-3.03 (m, 1H), 2.28-2.00 (m, 2H), 1.76-1.32 (m, 2H), 1.10 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 164.4 (C), 138.2 (CH), 132.8 (C), 131.8 (CH), 128.6 (CH), 126.9 (CH), 114.7 (CH_2), 55.4 (CH), 34.1 (CH_2), 30.0 (CH_2), 18.4 (CH_3); IR (film) 3287, 3067, 2975, 2918, 2858, 1641, 1580, 1489, 1451, 1379, 1314, 1291, 1136, 1075, 1026, 999, 912, 790, 717, 691 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{14}H_{20}N_2O_1$ $[M]^+$: 218.1419. Found: 218.1402.

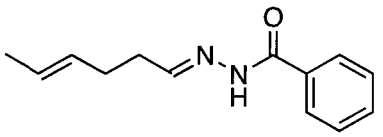


***11-N'*-(2-ethynylbenzyl)benzohydrazide:** Synthesized according to general procedure 2A. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (40 % EtOAc in hexanes). The title compound was obtained as white solid (0.300 g, 75 %). TLC R_f 0.54 in 60 % EtOH in

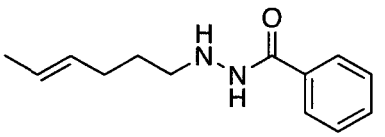
hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.69 (d, J = 7.3 Hz, 2H), 7.59-7.15 (m, 7H), 5.62 (s, 1H), 4.27 (s, 2H), 3.26 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 167.3 (CH), 139.5 (C), 133.1 (CH), 132.7 (C), 131.9 (CH), 129.6 (CH), 129.1 (CH), 128.6 (CH), 127.7 (CH), 126.9 (CH), 122.4 (C), 81.7 (C), 81.5 (CH), 54.1 (CH_2); IR (film) 3291, 3067, 2922, 2854, 1649, 1580, 1535, 1455, 1345, 1310, 1158, 1026, 763, 683 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{16}H_{14}N_2O_1$ $[M]^+$: 250.1106. Found: 250.1105.



12-2-hydroxy-*N*'-(pent-4-enyl)benzohydrazide (equation 2.9, 2.72): The title compound (0.37 g, 1.48 mmol) was dissolved in a mixture of 1:1 hexene:EtOAc (150 mL), Palladium on carbon was added to the mixture. Following this, Hydrogen was bubbled into the reaction. The reaction was monitored by TLC and usually took around 10 to 15 minutes. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (40 % EtOAc in hexanes). The title compound was obtained as white solid (0.100 g, 27 %). TLC R_f 0.7 in EtOAc in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.78-7.17 (m, 10H), 5.72 (dd, J= 17.4, 1.32 Hz, 1H), 5.36 (dd, J=11.0, 1.3 Hz), 4.19 (s, 1H), 4.15 (s, 1H), 2.81 (q, J= 7.7 Hz, 1H), 1.25 (t, J= 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 167.3 (CH), 139.5 (C), 133.1 (CH), 132.7 (C), 131.9 (CH), 129.6 (CH), 129.1 (CH), 128.6 (CH), 127.7 (CH), 126.9 (CH), 125.9 (CH), 122.4 (C), 116.4 (CH_2), 54.1 (CH_2); IR (film) 3287, 3063, 3029, 2972, 2918, 2877, 1637, 1603, 1577, 1523, 1451, 1349, 1311, 1079, 1026, 988, 908, 756, 691 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{16}H_{16}N_2O_1$ $[M]^+$: 252.1263. Found: 252.1248.

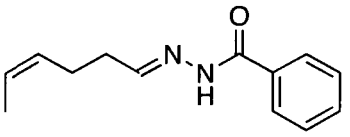


***13-N*-((*E*)-Hex-4-enylidene)benzohydrazide (Table 2, entry 2, 2.42b):** Synthesized according to general procedure 1A. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (50 % EtOAc in toluene with 1 % Et_3N). The title compound was obtained as a yellow solid (2.03 g, 69 % yield). TLC R_f 0.14 in 20 % EtOAc in hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 9.17 (s, 1H), 7.80 (d, J = 7.1 Hz, 1H), 7.64-7.35 (m, 4H), 5.59-5.32 (m, 2H), 2.32 (ddd, J = 19.1, 11.9, 6.2 Hz, 1H), 1.64 (d, J = 4.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) * denotes minor isomer δ ppm 164.0 (C), 152.2 (CH), 133.2 (CH), 131.9 (CH), 131.9 (CH), *129.8 (CH), 129.3 (CH), 128.6 (CH), 127.2 (CH), *126.9 (CH), 126.4 (CH), 32.2 (CH_2), *29.8 (CH_2), 29.6 (CH_2), *28.8 (CH_2), 17.9 (CH_3); IR (film) 3068, 3028, 2915, 1695, 1682, 1649, 1572, 1562, 1439, 1359, 1286, 1084, 964, 692, 668 cm^{-1}; LRMS m/z (relative intensity): 105.0339 (100 %), 77.0399 (34.9 %).

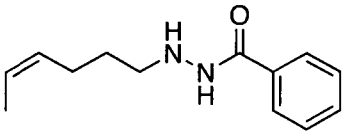


***14-N*-((*E*)-Hex-4-enyl)benzohydrazide (Table 2, entry 2, 2.43b):** Synthesized according to general procedure 2A. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (15 % EtOAc in toluene with 1% Et_3N). The title compound was obtained as a white solid (0.863 g, 42 % yield). TLC R_f 0.24 in 30 % EtOAc in hexanes; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.15 (br, 1H), 7.81-7.71 (m, 2H), 7.53-7.46 (m, 1H), 7.45-7.38 (m, 2H), 5.51-5.32 (m, 2H), 4.81 (br, 1H), 2.96-2.87 (m, 2H), 2.09-1.99 (m, 2H), 1.64-1.60 (m, 3H), 1.56 (dd, J = 14.8, 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3 (C), 132.9 (C), 131.8

(CH), 130.5 (CH), 128.6 (CH), 126.9 (CH), 125.5 (CH), 51.84 (CH_2), 30.1 (CH_2), 27.9 (CH_2), 17.9 (CH_3); IR (film) 3859, 3746, 3255, 3103, 3018, 2936, 2846, 1705, 1638, 1561, 1463, 1315, 1167, 1097, 1085, 1066, 961, 929, 692, 668 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{13}H_{18}N_2O$ $[M]^+$ = 218.1419. Found 218.1400.

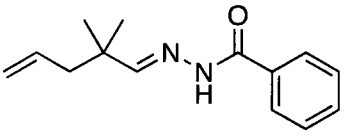


***15-N*-((*Z*)-Hex-4-enylidene)benzohydrazide (Table 2, entry 3, 2.42c):** Synthesized according to general procedure 1A. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (30 % EtOAc in toluene with 1 % Et_3N). The title compound was obtained as a white solid (1.86 g, 63 % yield). TLC R_f 0.18 in 40 % EtOAc; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.89 (s, 1H), 7.87-7.73 (m, 2H), 7.68-7.36 (m, 4H), 5.59-5.47 (m, 1H), 5.46-5.35 (m, 1H), 2.65-2.18 (m, 4H), 1.71-1.55 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) * denotes minor isomer δ ppm 164.0 (C), *152.0 (CH), 152.0 (CH), 133.2 (CH), 132.0 (CH), *130.0 (CH), *129.0 (CH), 128.7 (CH), 128.4 (CH), *128.2 (CH), *127.6 (CH), 127.2 (CH), 125.4 (CH), *60.4 (CH_2), 32.2 (CH_2), *30.9 (CH_2), 24.0 (CH_2), *23.2 (CH_3), 12.8 (CH_3); IR (film) 3236, 3060, 2920, 2846, 1775, 1701, 1646, 1580, 1557, 1490, 1448, 1354, 1284, 1143, 1070, 1023, 925, 801, 696 cm^{-1}; LRMS m/z (relative intensity): 105.0323 (100 %), 77.0407 (40.9 %), 51.0235 (11.3 %).

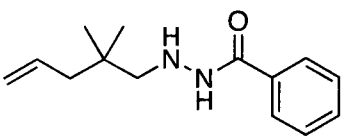


***16-N*-((*Z*)-Hex-4-enyl)benzohydrazide (Table 2, entry 3, 2.43c):** Synthesized according to general procedure 2A. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (15 % EtOAc in toluene with 1 % Et_3N). The title compound was obtained as a white solid (0.894 g, 48 % yield).

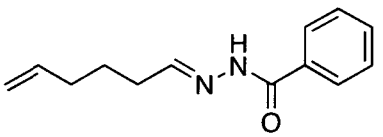
TLC R_f 0.22 in 30 % EtOAc; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.75 (d, J = 7.1 Hz, 2H), 7.55-7.47 (m, 1H), 7.46-7.39 (m, 2H), 5.52-5.42 (m, 1H), 5.42-5.32 (m, 1H), 2.94 (t, J = 7.3 Hz, 1H), 2.12 (dd, J = 14.4, 7.2 Hz, 1H), 1.66-1.54 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2 (C), 132.8 (C), 131.8 (CH), 129.7 (CH), 128.6 (CH), 126.8 (CH), 124.5 (CH), 51.8 (CH_2), 27.8 (CH_2), 24.3 (CH_2), 12.7 (CH_3); IR (film) 3290, 3064, 3010, 2940, 2862, 1631, 1572, 1529, 1455, 1315, 1085, 1023, 887, 797, 688 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{13}H_{18}N_2O$ $[M]^+$ = 218.1419. Found 218.1409.



***17-N*-(2,2-Dimethylpent-4-enylidene)benzohydrazide (Table 2, entry 4, 2.42d):** Synthesized according to general procedure 1B. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (30 % EtOAc in toluene with 1 % Et_3N). The title compound was obtained as a white solid (1.73 g, 100 % yield). TLC R_f 0.64 in 60 % EtOAc in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 11.32 (s, 1H), 7.92 (d, J = 7.5 Hz, 2H), 7.74 (s, 1H), 7.40 (t, J = 7.1 Hz, 1H), 7.30 (t, J = 7.4 Hz, 2H), 5.68 (dt, J = 16.7, 7.5 Hz, 1H), 4.94 (d, J = 13.0 Hz, 2H), 2.08 (d, J = 7.2 Hz, 2H), 1.00 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 164.6 (C), 160.0 (CH), 134.0 (CH), 133. 2 (C), 131.4 (CH), 128.2 (CH), 127.6 (CH), 117.7 (CH_2), 44.9 (CH_2), 37.8 (C), 24.7 (CH_3); IR (film) 3197, 3060, 3033, 2963, 2928, 2866, 1647, 1568, 1490, 1377, 1357, 1307, 1288, 1187, 1147, 1046, 914, 867, 796, 688 cm^{-1}; LRMS m/z (relative intensity): 105.0327 (100 %), 77.0403 (7.5 %).

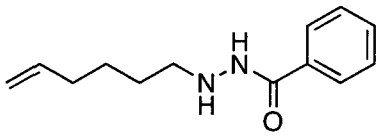


***18-N*-(2,2-Dimethylpent-4-enyl)benzohydrazide (Table 2, entry 4, 2.43d)**: Synthesized according to general procedure 2A. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (40 % EtOAc in hexanes). The title compound was obtained as a white oil (0.800 g, 52 %). TLC R_f 0.2 in 40 % EtOAc in Hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.75 (d, J = 7.0 Hz, 2H), 7.54-7.36 (m, 3H), 5.84 (tdd, J = 20.2, 9.0, 7.5 Hz, 1H), 5.11-4.98 (m, 2H), 2.74 (s, 2H), 2.05 (d, J = 7.5 Hz, 2H), 0.95 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 167.2 (C), 134.9 (CH), 132.8 (C), 131.7 (CH), 128.6 (CH), 126.8 (CH), 117.3 (CH_2), 62.3 (CH_2), 44.7 (CH_2), 34.0 (C), 25.3 (CH_3); IR (film) 3287, 3072, 2963, 2920, 2870, 1634, 1580, 1463, 1311, 1077, 906, 789, 692 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{14}H_{20}N_2O_1$ $[M]^+$: 232.1576. Found: 232.1575.

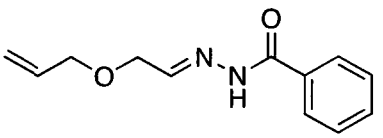


***19-N*-(Hex-5-enylidene)benzohydrazide (Table 3, entry 1, 2.45a):** Synthesized according to general procedure 1A. Observed a mixture of E and Z isomers in a 6:1 ratio, respectively. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (40 % EtOAc in toluene with 1 % Et_3N). The title compound was obtained as a clear oil (2.32 g, 70 % yield). TLC R_f 0.43 in 60 % EtOAc in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) * denotes minor isomer δ ppm 10.19 (s, 1H), *9.14 (s, 1H) 7.77 (d, J = 7.2 Hz, 2H), 7.71 (t, J = 4.7 Hz, 1H), 7.53 (t, J = 7.3 Hz, 1H), 7.45 (t, J = 7.3 Hz, 2H), 5.79 (tdd, J = 16.9, 10.2, 6.7 Hz, 1H), 5.01 (ddd, J = 17.1, 3.5, 1.6 Hz, 1H), 4.94 (tdd, J = 10.2, 2.1, 1.2 Hz, 1H), 2.32 (dd, J = 13.6, 7.0 Hz, 2H), 2.07 (dd, J = 14.1, 7.0 Hz, 2H), 1.63 (q, J = 7.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 164.4 (C), 152.8 (CH), 137.8 (CH), 133.1 (C), 131,7 (CH), 128.4 (CH), 127.4 (CH), 115.4 (CH_2), 33.1 (CH_2),

31.9 (CH_2), 25.8 (CH_2); IR (film) 3230, 3070, 2934, 2858, 1653, 1546, 1489, 1444, 1360, 1287, 1143, 1075, 991, 912, 798, 687 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{13}H_{16}N_2O$ $[M]^+$: 216.1263. Found: 216.1263.

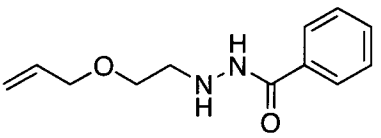


***20-N*-(Hex-5-enyl)benzohydrazide (Table 3, entry 1, 2.46a):** Synthesized according to general procedure 2A. Procedure as indicated above but used 2.40 eq. (1.71 g) of $NaCNBH_3$ and decreased the concentration to 0.05 M (20.7 mL). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (60 % EtOAc in hexanes). The title compound was obtained as a white solid (0.870 g, 38 %). TLC R_f 0.46 in 60 % EtOAc in hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.99 (s, 1H), 7.77 (d, J = 7.2 Hz, 1H), 7.53 (t, J = 7.3 Hz, 1H), 7.45 (t, J = 7.3 Hz, 1H), 5.79 (tdd, J = 16.9, 10.2, 6.7 Hz, 1H), 5.01 (ddd, J = 17.1, 3.5, 1.6 Hz, 1H), 4.94 (tdd, J = 10.2, 2.13, 1.2 Hz, 1H), 2.95 (t, J = 6.9 Hz, 1H), 2.09 (q, J = 6.9 Hz, 1H), 1.65-1.40 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 167.3 (C), 138.5 (CH), 132.8 (C), 131.8 (CH), 128.6 (CH), 126.8 (CH), 114.6 (CH_2), 52.1 (CH_2), 33.5 (CH_2), 27.4 (CH_2), 26.3 (CH_2); IR (film) 3272, 3074, 2934, 2858, 1637, 1577, 1546, 1535, 1455, 1314, 1155, 1064, 1026, 995, 908, 790 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{13}H_{18}N_2O$ $[M]^+$: 218.1419. Found: 218.1405.

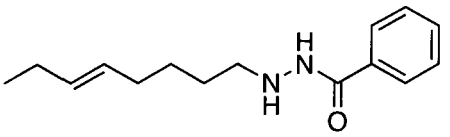


***21-N*-(2-(Allyloxy)ethylidene)benzohydrazide (Table 3, entry 2, 2.45b):** Synthesized according to general procedure 1A. The reaction mixture was concentrated under reduced pressure and isolated using flash

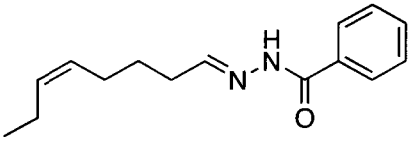
chromatography (40 % EtOAc in toluene with 1 % Et_3N). The title compound was obtained as a white crystalline solid (0.806 g, 40 % yield). TLC R_f 0.20 in 40 % EtOAc in hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.98 (s, 1H), 7.82 (d, J = 7.2 Hz, 2H), 7.66 (s, 1H), 7.59-7.51 (m, 1H), 7.47 (t, J = 7.4 Hz, 2H), 5.92 (ddd, J = 22.6, 10.9, 5.6 Hz, 1H), 5.45-5.05 (m, 2H), 4.28 (d, J = 3.6 Hz, 2H), 4.05 (d, J = 5.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 164.7 (C), 148.6 (CH), 134.0 (CH), 132.7 (CH), 132.0 (C), 128.5 (CH), 127.5 (CH), 117.6 (CH_2), 71.7 (CH_2), 69.2 (CH_2); IR (film) 3234, 3070, 2914, 2854, 1656, 1546, 1352, 1284, 1132, 1284, 1132, 1075, 1048, 923, 790, 691 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{12}H_{14}N_2O_2$ $[M]^+$: 218.1055. Found: 218.1052.



***22-N*-(2-(Allyloxy)ethyl)benzohydrazide (Table 3, entry 2, 2.46b):** Synthesized according to general procedure 2A. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (50 % EtOAc in toluene with 1 % Et_3N). The title compound was obtained as white solid (0.628 g, 77 %). TLC R_f 0.57 in 100 % EtOAc; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.88 (s, 1H), 7.76 (dd, J = 8.2, 1.4 Hz, 2H), 7.57-7.50 (m, 1H), 7.49-7.42 (m, 2H), 5.97 (tdd, J = 17.2, 10.4, 5.7 Hz, 1H), 5.32 (ddd, J = 17.2, 3.2, 1.6 Hz, 1H), 5.23 (ddd, J = 10.4, 2.9, 1.2 Hz, 1H), 4.07 (td, J = 5.7, 1.4 Hz, 2H), 3.70-3.65 (m, 2H), 3.18 (dd, J = 9.9, 5.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.5 (C), 134.5 (CH), 132.9 (C), 131.7 (CH), 128.6 (CH), 126.8 (CH), 117.3 (CH_2), 72.1 (CH_2), 69.0 (CH_2), 51.3 (CH_2); IR (film) 3286, 3064, 2920, 2854, 1642, 1572, 1541, 1451, 1311, 1101, 1081, 1023, 921, 789, 692 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{12}H_{16}N_2O_2$ $[M]^+$: 220.1212. Found: 220.1192.

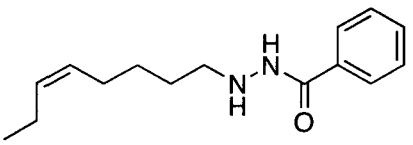


***23-N*-((*E*)-Oct-5-enyl)benzohydrazide (Table 3, entry 3, 2.46c):** Synthesized according to general procedure 2A. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (20 % EtOAc in toluene with 1 % Et_3N). The title compound was obtained as a white solid (0.529 g, 26 %). TLC R_f 0.30 in 30 % EtOAc in hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.09 (s, 1H), 7.77 (d, J = 7.0 Hz, 1H), 7.56-7.49 (m, 1H), 7.48-7.40 (m, 2H), 5.52-5.32 (m, 2H), 4.94 (br (s), 1H), 2.94 (t, J = 7.1 Hz, 2H), 2.06-1.93 (m, 4H), 1.63-1.36 (m, 4H), 0.96 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 167.2 (C), 132.9 (C), 132.4 (CH), 131.8 (CH), 128.7 (CH), 128.6 (CH), 126.8 (CH), 52.2 (CH_2), 32.3 (CH_2), 27.4 (CH_2), 27.0 (CH_2), 25.5 (CH_2), 14.0 (CH_3); IR (film) 3244, 3022, 2961, 2926, 2858, 1626, 1579, 1502, 1482, 1325, 1082, 965, 900, 797, 690, 654, 615 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{15}H_{22}N_2O$ $[M]^+$: 246.1732. Found: 246.1724.

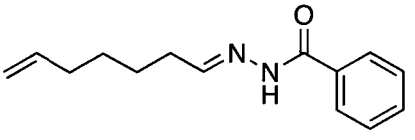


***24-N*-((*Z*)-Oct-5-enylidene)benzohydrazide (Table 3, entry 4, 2.45d):** Synthesized according to general procedure 1A. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (20 % EtOAc in toluene with 1 % Et_3N). The title compound was obtained as a white crystalline solid (1.18 g, 61 % yield). TLC R_f 0.15 in 20 % EtOAc in hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.82 (s, 1H), 7.80 (d, J = 6.4 Hz, 2H), 7.60-7.49 (m, 2H), 7.45 (t, J = 7.4 Hz, 2H), 5.49-5.24 (m, 2H), 2.43 (s, 2H), 2.12 (dd, J = 14.5, 6.9 Hz, 1H), 2.03 (td, J = 14.9, 7.3 Hz, 2H), 1.69-1.57 (m, 2H), 0.96 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 164.6 (C), 152. 6 (CH), 133.2 (C), 132.6 (CH), 131.8 (CH), 128.5

(CH), 127.9 (CH), 127.9 (CH), 127.3 (CH), 32.1 (CH_2), 26.6 (CH_2), 20.5 (CH_2), 14.3 (CH_3); IR (film) 3228, 3072, 3017, 2963, 2936, 2850, 1653, 1622, 1552, 1494, 1459, 1358, 1280, 1136, 1073, 882, 797, 691 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{15}H_{20}N_2O_1$ $[M]^+$: 244.1576. Found: 244.1557.

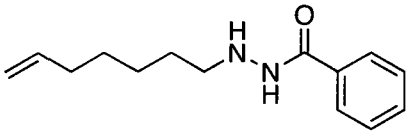


***25-N*-((*Z*)-Oct-5-enyl)benzohydrazide (Table 3, entry 4, 2.45d):** Synthesized according to general procedure 2A. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (20 % EtOAc in toluene with 1 % Et_3N). The title compound was obtained as a white solid (0.868 g, 38 %). TLC R_f 0.30 in 30 % EtOAc in hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.75 (d, J = 6.9 Hz, 2H), 7.62 (s, 1H), 7.57-7.40 (m, 3H), 5.45-5.26 (m, 1H), 4.90 (s, 1H), 2.95 (t, J = 7.1 Hz, 2H), 2.12-1.98 (m, 4H), 1.66-1.35 (m, 4H), 0.95 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 167.2 (C), 132.9 (C), 132.0 (CH), 131.8 (CH), 128.6 (CH), 126.8 (CH), 52.2 (CH_2), 27.6 (CH_2), 27.1 (CH_2), 26.9 (CH_2), 20.5 (CH_2), 14.3 (CH_3); IR (film) 3275, 3006, 2959, 2932, 2858, 1623, 1556, 1455, 1319, 1288, 1077, 890, 793, 688 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{15}H_{22}N_2O$ $[M]^+$: 246.1732. Found: 246.1703.

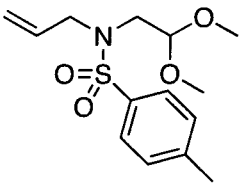


***26-N*-(Hept-6-enylidene)benzohydrazide (Table 3, entry 5, 2.45e):** Synthesized according to general procedure 1A. Observed a mixture of E and Z isomers in an 11:1 ratio, respectively. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (40 % EtOAc in hexanes and 1 %

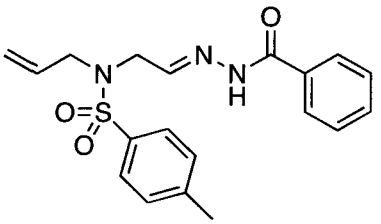
Et_3N). The title compound was obtained as a white crystalline solid (1.60 g, 94 % yield). TLC R_f 0.15 in 30 % EtOAc in hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.86 (s, 1H), 7.80 (d, J = 6.9 Hz, 2H), 7.60-7.49 (m, 2H), 7.45 (t, J = 7.3 Hz, 2H), 5.80 (tdd, J = 17.0, 10.4, 6.7 Hz, 1H), 5.08-4.90 (m, 2H), 2.54-2.34 (m, 2H), 2.09 (q, J = 6.7 Hz, 2H), 1.69-1.32 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) * denotes minor isomer δ ppm 164.2 (C), 152.7 (CH), 138.4 (CH), 133.1 (C), 131.8 (CH), 128.5 (CH), 127.3 (CH), 114.7 (CH_2), 33.4 (CH_2), *33.2 (CH_2), 32.3 (CH_2), 28.4 (CH_2), 26.0 (CH_2), 25.3 (CH_2); IR (film) 3228, 3068, 2940, 2862, 1648, 1557, 1490, 1436, 1354, 1290, 1148, 1070, 991, 902, 801, 717, 684 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{14}H_{18}N_2O_1$ $[M]^+$: 230.1419. Found: 230.1418.



***27-N*-(Hept-6-enyl)benzohydrazide (Table 3, entry 5, 2.46e):** Synthesized according to general procedure 2A. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (30 % EtOAc in toluene with 1 % Et_3N). The title compound was obtained as a white solid (0.422 g, 32 %). TLC R_f 0.26 in 30 % EtOAc in hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.17 (s, 1H), 7.77 (dd, J = 8.3, 1.3 Hz, 1H), 7.56-7.48 (m, 1H), 7.47-7.40 (m, 2H), 5.80 (tdd, J = 16.9, 10.2, 6.7 Hz, 1H), 5.05-4.91 (m, 3H), 2.93 (t, J = 7.3 Hz, 2H), 2.11-2.00 (m, 2H), 1.61-1.48 (m, 2H), 1.48-1.32 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 167.7 (C), 139.2 (CH), 133.3 (C), 132.2 (CH), 129.1 (CH), 127.3 (CH), 114.8 (CH_2), 52.7 (CH_2), 34.1 (CH_2), 29.2 (CH_2), 28.3 (CH_2), 27.0 (CH_2); IR (film) 3274, 3084, 3018, 2927, 2858, 1628, 1557, 1498, 1471, 1323, 1291, 1081, 1023, 988, 902, 797 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{14}H_{20}N_2O_1$ $[M]^+$: 232.1576. Found: 232.1574.

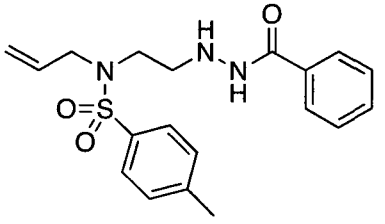


***28*-*N*-(2,2-Dimethoxyethyl)-*N*-tosylprop-2-en-1-amine (Table 4, entry 1, 2.47a):** Prepared according to the procedure of the Naito group.[103] An oven dried round bottom flask and condenser were assembled and charged with a stir bar, capped with a septum and purged with argon and an outlet for 10 minutes. To a solution of 2-aminoacetaldehyde dimethyl acetal (3.15 g, 30.0 mmol) in CH_2Cl_2, Et_3N (4.05 g, 40.0 mmol) and TsCl (7.64 g, 40.0 mmol) in CH_2Cl_2 were added (50.0 mL) under argon atmosphere at 0 °C. After being stirred for 2 hours at room temperature the reaction mixture was diluted with water and extracted with $CHCl_3$. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to give the crude tosylate. To a solution of the crude tosylate and K_2CO_3 (5.60 g, 40.0 mmol) in acetone was added 4-bromo-1-butene (4.05 g, 30 mmol) under argon atmosphere. After being refluxed for 5 hours, the crude mixture was diluted with H_20 and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The title compound was obtained as a clear oil (0.353 g, 32 % yield). The spectral data is in agreement with previously reported data by Miyata et al.[103]



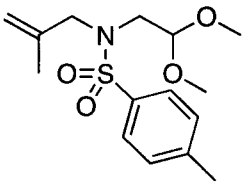
[103] Miyata, O.; Muroya, K.; Kobayashi, T.; Yamanaka, R.; Kajisa, S.; Koide, J.; Naito, T. *Tetrahedron* **2002**, *58*, 4459.

***29-N*-(2-(Allyltosylamino)ethylidene)benzohydrazide (Table 5, entry 1, 2.48a):** Synthesized according to general procedure 1D. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (60 % EtOAc in toluene with 1 % Et_3N). The title compound was obtained as a clear oil (0.913 g, 46 % yield). TLC R_f 0.33 in 60 % EtOAc in hexanes; ^1H NMR (300 MHz, $CDCl_3$) * denotes minor isomer δ ppm 9.27 (s, 1H), *8.02 (d, J = 7.2 Hz, 2H), 7.84 (d, J = 7.3 Hz, 2H), 7.72 (d, J = 8.2 Hz, 2H), 7.67-7.51 (m, 2H), 7.46 (t, J = 7.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 5.65 (tdd, J = 16.3, 9.8, 6.25 Hz, 1H), 5.31-5.11 (m, 2H), 4.00 (d, J = 4.3 Hz, 2H), *3.88 (d, J = 5.0 Hz, 2H), 3.83 (d, J = 6.3 Hz, 2H), *2.48 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 164.3 (C), 147.7 (CH), 143.9 (C), 135.6 (C), 132.6 (C), 132.0 (CH), 129.9 (CH), 128.5 (CH), 127.5 (CH), 127.2 (CH), 119.8 (CH_2), 51.3 (CH_2), 49.1 (CH_2), 21.5 (CH_3); IR (film) 3230, 3066, 2922, 2854, 1652, 1550, 1348, 1284, 1158, 1090, 1037, 930, 854, 805, 759, 660 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{19}H_{21}N_3O_3S_1$ $[M]^+$-Tosyl: 216.1140 Found: 216.1250



***30-N*-(2-(Allyltosylamino)ethyl)benzohydrazide (Table 5, entry 1, 2.49a):** Synthesized according to general procedure 2A. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (20 % EtOAc in toluene with 1 % Et_3N). The title compound was obtained as a clear oil (0.512 g, 87 % yield). TLC R_f 0.43 in 60 % EtOAc in hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.48 (s, 1H), 7.81 (d, J = 6.9 Hz, 2H), 7.72 (d, J = 8.3 Hz, 2H), 7.55-7.37 (m, 3H), 7.27 (d, J = 8.4 Hz, 2H), 5.59 (tdd, J = 16.6, 10.0, 6.5 Hz, 1H), 5.21-5.07 (m, 2H), 4.99 (s, 1H), 3.84 (d, J = 6.5 Hz, 2H), 3.35 (t, J = 5.9 Hz, 2H), 3.05 (t, J = 5.8 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.7 (C), 143.3 (C), 136.4 (C), 132.5 (C),

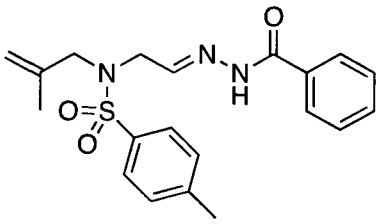
132.4 (CH), 131.6 (CH), 129.6 (CH), 128.4 (CH), 126.9 (CH), 126.8 (CH), 119.2 (CH_2), 50.6 (CH_2), 48.7 (CH_2), 44.8 (CH_2), 21.3 (CH_3); IR (film) 3290, 3068, 2983, 2920, 2866, 1650, 1572, 1533, 1459, 1337, 1155, 1089, 1023, 988, 922, 883, 805, 750, 692 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{19}H_{23}N_3O_3S_1$: $[M]^+$-Tosyl: 218.1290. Found: 218.1291.



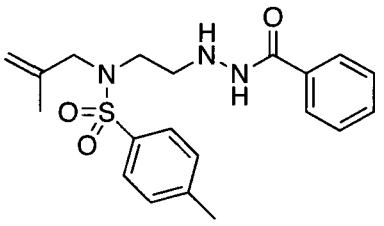
***31-N*-(2,2-Dimethoxyethyl)-2-methyl-*N*-tosylprop-2-en-1-amine (Table 5, entry 2, 2.47b):** Tosylation was done according to the previously mentioned procedure (see above). Metallylation was performed according to the procedure of Beauchemin *et al.* [104] An oven dried round bottom flask and condenser were assembled and charged with a stir bar, capped with a septum and purged with argon and an outlet for 10 minutes. 2,2-Dimethoxy-*N*-tosylethanamine (1.64 g, 6.32 mmol) and 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 1.06 g, 6.96 mmol) were dissolved in a minimum of THF. 3-chloromethylpropene (1.72 g, 19.0 mmol) and 23 mL of THF:DMF (4:1), were added to the reaction flask, which was then heated at reflux for 2.5 hours. The reaction mixture was extracted with EtOAc and washed with water, then brine. The organic layer was dried over Na_2SO_4, filtered, concentrated under reduced pressure and isolated using flash chromatography (20 % EtOAc in hexanes). The title compound was obtained as a white solid (1.38 g, 70 % yield). TLC R_f 0.48 in 20 % EtOAc in hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.65 (d, J = 8.04 Hz, 2H), 7.24 (d, J = 7.95 Hz, 2H), 4.79 (d, J = 19.36 Hz, 2H), 4.41 (t, J = 5.27 Hz, 1H), 3.76 (s, 2H), 3.25 (s, 6H), 3.15 (d, J = 5.28 Hz, 2H), 2.35 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 143.0 (C), 140.1 (C), 137.0 (C), 129.3 (CH), 127.0 (CH), 114.1 (CH_2), 103.4 (CH), 54.9 (CH_2), 54.3 (CH_2), 48.4 (CH_2), 21.2 (CH_3), 19.6 (CH_3); IR (film) 3076, 2939, 2835,

(104) Bourgeois, J.; Dion, I.; Cebrowski, P. H.; Loiseau, F.; Bédard, A.-C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 874.

1658, 1599, 1495, 1443, 1338, 1160, 1124, 995, 920, 816, 772, 710, 657 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{15}H_{23}N_1O_4S_1$: $[M]^+$-Tosyl: 158.1180. Found: 158.1187.

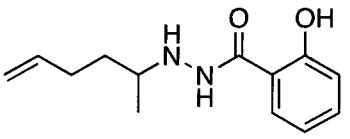


***32-N*-(2-(2-Methylallyltosylamino)ethylidene)benzohydrazide (Table 5, entry 2, 2.48b):** Synthesized according to general procedure 1D. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (40 % EtOAc in hexanes). The title compound was obtained as a clear oil (0.244 g, 32 % yield). TLC R_f 0.43 in 60 % EtOAc in hexanes; ^1H NMR (300 MHz, $CDCl_3$) * denotes minor isomer δ ppm 10.27 (s, 1H), *7.94 (d, J = 7.5 Hz, 2H), 7.81 (d, J = 7.3 Hz, 2H), 7.69-7.59 (m, 3H), 7.49-7.18 (m, 5H), 4.81 (d, J = 16.9 Hz, 2H), 3.84 (d, J = 4.6 Hz, 2H), *3.63 (s, 2H), 3.60 (s, 2H), 2.38 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 164.3 (C), 147.8 (CH), 143.8 (C), 139.3 (C), 135.0 (C), 132.5 (C), 131.8 (CH), 129.7 (CH), 129.7 (CH), 128.3 (CH), 127.5 (CH), 127.2 (CH), 115.2 (CH_2), 54.9 (CH_2), 49.3 (CH_2), 21.4 (CH_3), 19.7 (CH_3); IR (film) 3228, 3065, 2987, 2924, 2858, 1646, 1553, 1490, 1439, 1335, 1299, 1283, 1161, 1085, 1011, 906, 805, 762, 699 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{20}H_{23}N_3O_3S_1$: $[M]^+$-Tosyl: 230.1290. Found: 230.0633.



***33-N*-(2-(2-Methylallyltosylamino)ethyl)benzohydrazide (Table 5, entry 2, 2.49b):** Synthesized according to general procedure 2A. The reaction mixture was concentrated under reduced pressure and isolated using flash

chromatography (60 % EtOAc in hexanes). The title compound was obtained as a clear oil (0.179 g, 73 % yield). TLC R_f 0.35 in 60 % EtOAc in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.34 (s, 1H), 7.82 (d, J = 6.8 Hz, 2H), 7.75 (d, J = 6.8 Hz, 2H), 7.58-7.41 (m, 3H), 7.30 (d, J = 6.8 Hz, 2H), 4.99 (s, 1H), 4.88 (s, 2H), 3.73 (s, 2H), 3.34 (t, J = 5.9 Hz, 2H), 3.03 (t, J = 5.8 Hz, 2H), 2.42 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.8 (C), 143.5 (C), 140.7 (C), 136.6 (C), 132.7 (C), 131.8 (CH), 129.7 (CH), 128.7 (CH), 127.2 (CH), 126.9 (CH), 115.1 (CH_2), 55.0 (CH_2), 49.1 (CH_2), 45.7 (CH_2), 21.5 (CH_3), 19.8 (CH_3); IR (film) 3290, 3068, 2983, 2920, 2866, 1650, 1572, 1533, 1459, 1337, 1155, 1089, 1023, 988, 922, 883, 805, 750, 692 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{20}H_{25}N_3O_3S_1$: $[M]^+$-Tosyl: 232.1450. Found: 232.1441.



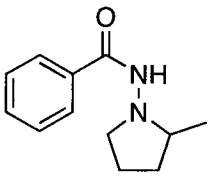
34-2-hydroxy-*N*'-(pent-4-enyl)benzohydrazide (Table 11, 2.61): Synthesized according to general procedure 2A. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (30 % EtOAc in hexanes). The title compound was obtained as white solid (3.84 g, 88 %). TLC R_f 0.7 in 100 % EtOH; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.48-7.31 (m, 2H), 6.99 (d, J = 8.7 Hz, 1H), 6.84 (t, J = 7.6 Hz, 2H), 5.80 (tdd, J = 16.8, 10.2, 6.6 Hz, 1H), 5.10-4.92 (m, 2H), 3.15-3.02 (m, 1H), 2.32-1.97 (m, 2H), 1.74-1.57 (m, 1H), 1.50-1.35 (m, 1H), 1.11 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 169.5 (C), 161.0 (C), 138.0 (C), 134.4 (CH), 125.2 (CH), 118.9 (CH), 118.5 (CH), 114.9 (CH), 113.1 (C), 55.6 (CH), 34.0 (CH_2), 30.0 (CH_2), 18.4 (CH_3); IR (film) 3287, 3074, 2975, 2922, 2873, 1641, 1604, 1550, 1482, 1455, 1375, 1309, 1253, 1151, 1102, 1033, 991, 913, 824, 754 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{13}H_{18}N_2O_2$ $[M]^+$: 234.1368. Found: 234.1362.

5.1.4 General procedures for the Cope-type hydroamination or aminocarbonylation of alkenes (Chapter 2)

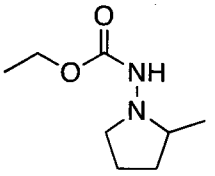
General Procedure A (sealed tube): An oven dried 15 mL sealed tube was charged with a stir bar, capped with a septum and purged with argon and an outlet for 5 minutes. The alkenyl hydrazide (1.00 equiv) and α,α,α-trifluorotoluene (such that the concentration of the alkenyl hydrazide is 0.05 M) were added to the sealed tube, while keeping it under an argon atmosphere. The septum was removed and the tube was then quickly sealed with a screw cap and Teflon tape and heated while stirring in a wax bath for 18-42 hours at 120-170°C. The reaction solution was cooled to ambient temperature, concentrated under reduced pressure and analyzed by ^{1}H NMR using styrene or 1,4-dimethoxybenzene as an internal standard, then again concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding products.

General Procedure B (microwave): An oven dried 5 - 20 mL μw tube was charged with a stir bar, capped with a septum and purged with argon and an outlet for 5 minutes. The alkenyl hydrazide (1.00 equiv) α,α,α-trifluorotoluene, chlorobenzene or acetonitrile (such that the concentration of the alkenyl hydrazide was 0.05 M) were added to the sealed tube, while keeping it under an argon atmosphere. The septum was removed and the tube was then quickly sealed with a microwave cap and heated for 0.25-5 hours at 150-200°C. The reaction solution was cooled to ambient temperature, concentrated under reduced pressure and analyzed by ^{1}H NMR using styrene or 1,4-dimethoxybenzene as an internal standard, then again concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding products.

5.1.5 Characterization: tuning the carbonyl moiety (2.3.2 Cope-type hydroamination)

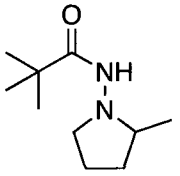


***35-N*-(2-Methylpyrrolidin-1-yl)benzamide (Table 5-7, 2.51).** Synthesized according to general procedure A (120 °C, 18h) using hydrazide **1a** (0.156 g, 0.762 mmol). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (40 % EtOAc in toluene with 1% Et_3N). The title compound was obtained as a white solid (0.128 g, 82 % yield). TLC R_f 0.21 in 60 % EtOAc in hexanes. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 9.23 (s, 1H), 7.79 (d, J = 6.9 Hz, 2H), 7.45-7.55 (m, 3H), 3.15 (td, J = 8.4, 5.8 Hz, 1H), 3.06 (td, J = 9.1, 6.6 Hz, 1H), 2.83 (q, J = 8.7 Hz, 1H), 1.94 (td, J = 18.9, 7.1 Hz, 1H), 1.74 (ddd, J = 14.7, 8.5, 6.1 Hz, 2H), 1.36 (qd, J = 12.0, 9.0 Hz, 1H), 1.03 (d, J = 6.1 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 165.5 (C), 134.3 (C), 131.3 (CH), 128.4 (CH), 127.4 (CH), 59.5 (CH), 53.8 (CH_2), 30.4 (CH_2), 20.3 (CH_2), 18.7 (CH_3) IR (film) 3211, 3079, 2972, 2922, 2868, 2842, 1668, 1641, 1303, 1210, 1140, 1075, 1029, 908, 805, 699 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{12}H_{16}N_2O$ $[M]^+$: 204.1263. Found: 204.1249.

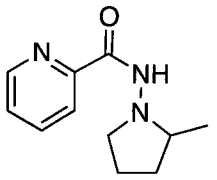


***36-N*-(2-Methylpyrrolidin-1-yl)ethylcarbamate (Table 8, entry 2, 2.53)**. Synthesized according to general procedure A (150 °C, 18h) using hydrazide **1d** (0.214 g, 1.24 mmol). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (20-30 % EtOAc in hexanes). The title compound was obtained as a yellow oil (0.059 g, 27 % yield). TLC R_f 0.53 in 100 % EtOAc. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 5.48-5.13 (m, 1H), 4.26-4.10 (m, 2H), 3.35 (dt, J = 8.5, 3.0 Hz, 1H), 2.74-2.32 (m, 2H),

2.05-1.66 (m, 3H), 1.62-1.43 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H), 1.16 (d, J = 6.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 62.1 (CH), 61.0 (CH_2), 55.9 (CH_2), 30.1 (CH_2), 20.0 (CH_2), 18.0 (CH_3), 14.6 (CH_3); IR (film) 3264, 2971, 1705, 1375, 1253, 1178, 1060 cm^{-1}; HRMS (EI): Exact mass calcd for $C_8H_{16}N_2O_2$ $[M]^+$: 172.1212. Found: 172.1203.

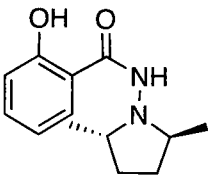


***37-N*-(2-Methylpyrrolidin-1-yl)pivalamide (Table 9, entry 2, 2.56)**. Synthesized according to general procedure A (150 °C, 18h) using hydrazide **1b** (0.067 g, 0.360 mmol). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (40 % EtOAc in toluene with 1% Et_3N). The title compound was obtained as a brown oil (0.043 g, 65 % yield). TLC R_f 0.21 in 60 % EtOAc in hexane; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 6.20 (s, 1H), 3.29 (dt, J = 8.4, 3.4 Hz, 1H), 2.85-2.71 (m, 1H), 2.64 (q, J = 8.8 Hz, 1H), 2.05-1.65 (m, 3H), 1.58-1.38 (m, 1H), 1.20 (s, 9H), 1.09 (d, J = 6.1 Hz, 3H); ^{13}NMR (75 MHz, $CDCl_3$) δ ppm 176.6 (C), 61.4 (CH), 55.1 (CH_2), 30.4 (CH_2), 27.6 (CH_3), 20.3 (CH_2), 18.2 (CH_3); IR (film) 3245, 3067, 2964, 2926, 2859, 2831, 1648, 1550, 1459, 1288, 1193, 995, 927 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{10}H_{20}N_2O$ $[M]^+$: 184.1576. Found: 184.1433.

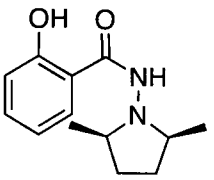


***38-N*-(2-Methylpyrrolidin-1-yl)picolinamide (Table 10, entry 3, 2.60).** Synthesized according to general procedure A (170 °C, 42h) using hydrazide **1c** (0.117 g, 0.568 mmol). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (60 % EtOAc in hexane). The title compound

was obtained as a white solid (0.074 g, 64 % yield). TLC R_f 0.32 in 100 % EtOAc.; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.57-8.44 (m, 2H), 8.23 (d, J = 7.8 Hz, 1H), 7.84 (dt, J = 7.8, 1.6 Hz, 1H), 7.47-7.39 (m, 1H), 3.45 (dt, J = 8.5, 2.7 Hz, 1H), 2.92-2.78 (m, 1H), 2.72 (q, J = 8.8 Hz, 1H), 2.12-1.74 (m, 3H), 1.70-1.52 (m, 1H), 1.19 (d, J = 6.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 162.5 (C), 149.8 (C), 147.9 (CH), 137.3 (CH), 126.3 (CH), 122.6 (CH), 62.5 (CH), 56.0 (CH_2), 30.2 (CH_2), 20.3 (CH_2), 18.2 (CH_3); IR (film) 3245, 2964, 2900, 2873, 1679, 1584, 1565, 1523, 1466, 1379, 1280, 1238, 1139, 1068, 1037, 991, 908, 824, 763, 726, 664 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{11}H_{15}N_3O$ $[M]^+$: 205.1215. Found: 205.1207.



2.62-anti



2.62-syn

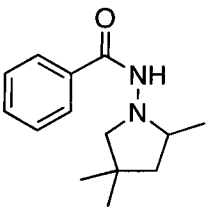
39 a et b(±)-2-hydroxy-*N*-((2*S*,5*S*)-2,5-dimethylpyrrolidin-1-yl)benzamide and (±)-2-hydroxy-*N*-((2*R*,5*S*)-2,5-dimethylpyrrolidin-1-yl)benzamide (Table 11, entry 2, 2.62): Synthesized according to general procedure A (90 °C, 16h) using hydrazide **2.61** (0.207 g, 0.883 mmol). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (20-40 % EtOAc in hexanes). The title compounds were obtained as a brown oils (0.036 g and 0.144 g, 87 % yield).

Diastereoisomer **2.62-anti**: TLC R_f 0.4 in 40 % EtOAc in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$)* denotes minor isomer δ ppm *12.56 (s, 1H), 12.15 (s, 1H), 7.48-7.31 (m, 2H), 7.01 (d, J = 8.3 Hz, 1H), 6.85 (t, J = 7.7 Hz, 2H), 6.57 (s, 1H), *3.54 (s, 1H), 2.83 (dd, J = 11.3, 5.9 Hz, 2H), *2.68-2.56 (m, 2H), 2.41-2.29 (m, 2H), 2.02-1.90 (m, 2H), 1.69-1.51 (m, 2H), *1.43-1.32 (m, 2H), 1.19 (d, J = 6.1 Hz, 6H); ^{13}NMR (75 MHz, DMSO-d_6) δ ppm 168.6 (C), 159.7 (C), 133.4 (CH), 127.5 (CH), 118.4 (CH), 117.2 (CH), 115.0 (C), 59.9 (CH), 28.4

(CH_2), 18.8 (CH_3); IR (film) 3295, 3067, 2968, 2930, 2873, 2705, 2588, 1637, 1603, 1550, 1493, 1455, 1371, 1311, 1238, 1151, 1098, 1037, 908, 752 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{13}H_{18}N_2O$ $[M]^+$: 234.1368. Found: 234.1377.

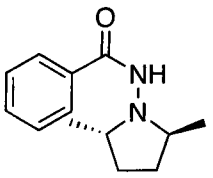
Diastereoisomer **2.62-syn**: TLC R_f 0.11 in 40 % EtOAc in hexanes; ^1H NMR (300 MHz, DMSO-d_6)* denotes minor isomer δ ppm *12.40 (s, 1H), 12.10 (s, 1H), *7.94 (d, J = 7.6 Hz, 1H), 7.47-7.30 (m, 1H), 6.99 (d, J = 8.5 Hz, 1H), 6.94-6.77 (m, 2H), *4.04-3.79 (m, 1H), *3.71-3.49 (m, 1H), 3.44-3.26 (m, 2H), *2.44-2.21 (m, 2H), 2.20-2.04 (m, 2H), 1.62-1.44 (m, 2H), *1.44-1.27 (m, 1H), *1.26-1.21 (m, 6H), 1.10 (d, J = 6.4 Hz, 6H); ^{13}NMR (75 MHz, DMSO-d_6) δ ppm 167,2 (C), 159.2 (CH), 133.23 (CH), 127.9 (CH), 118.5 (CH), 117.1 (CH), 115.3 (C), 55.7 (CH), 28.9 (CH_2), 17.1 (CH_3); IR (film) 3295, 3067, 2968, 2930, 2873, 2705, 2588, 1637, 1603, 1550, 1493, 1455, 1371, 1311, 1238, 1151, 1098, 1037, 908, 752 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{13}H_{18}N_2O_2$ $[M]^+$: 234.1368. Found: 234.1377.

5.1.6 Characterization: substitution patterns (2.3.4 Cope-type hydroamination)

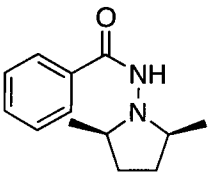


***40-N*-(2,4,4-Trimethylpyrrolidin-1-yl)benzamide (Table 11, entry 2, 2.64):** Synthesized according to general procedure A (85 °C, 18h) using hydrazide **2.63** (0.071 g, 0.300 mmol). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (40 % EtOAc in hexanes). The title compound was obtained as a white solid (0.068 g, 96 % yield). TLC R_f 0.24 in 20 % EtOAc in hexanes; ^1H NMR (300 MHz, $CDCl_3$)* denotes minor isomer δ ppm *7.81 (d, J = 6.7 Hz, 2H), 7.73 (d, J = 7.1 Hz, 2H), 7.55-7.32 (m,

3H), 6.83 (s, 1H), *6.17 (s, 1H), 3.29-3.09 (m, 2H), *3.01 (d, J = 8.2 Hz, 1H), 2.68 (d, J = 8.7 Hz, 1H), *2.41 (d, J = 8.0 Hz, 1H), 1.83-1.63 (m, 1H), 1.43 (dd, J = 12.2, 10.2 Hz, 1H), 1.16 (d, J = 4.9 Hz, 3H), 1.11 (s, 6H), *1.04 (s, 6H), *0.92 (d, J = 5.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) * denotes minor isomer δ ppm 166.5 (C), 134.1 (C), 131.4 (CH), *129.0 (CH), 128.5 (CH), *127.3 (CH), 126.9 (CH), 69.9 (CH_2), 61.5 (CH), 46.7 (CH_2), 34.6 (C), 30.4 (CH_3), 29.9 (CH_3), 18.5 (CH_3); IR (film) 3251, 3060, 3037, 2959, 2928, 2862, 1650, 1576, 1541, 1494, 1455, 1374, 1292, 1218, 1026, 898, 805, 692 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{11}H_{15}N_3O$ $[M]^+$: 205.1215. Found: 205.1207.



2.66-anti

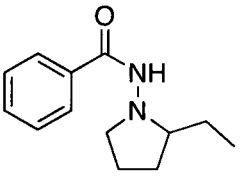


2.66-syn

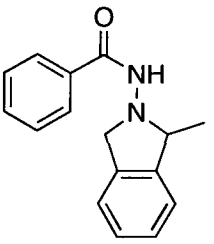
41 a et b(±)-*N*-((2*S*,5*S*)-2,5-Dimethylpyrrolidin-1-yl)benzamide and (±)-*N*-((2*R*,5*S*)-2,5-dimethylpyrrolidin-1-yl)benzamide (Table 12, entry 1, 2.66): Synthesized according to general procedure A (120 °C, 18h) using hydrazide **2.65** (0.160 g, 0.784 mmol). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (40 % EtOAc in hexanes). The title compounds were obtained as a brown oils (0.033 g and 0.065 g, 98 % yield).

Diastereoisomer **2.66-anti**: TLC R_f 0.5 in 60 % EtOAc in hexanes; ^{1}H NMR (300 MHz, DMSO-d_6)* denotes minor isomer δ ppm 8.95 (s, 1H), 7.79 (d, J = 6.8 Hz, 2H), 7.57-7.40 (m, 3H), 3.13-2.97 (m, 2H), 1.94-1.80 (m, 2H), 1.42-1.29 (m, 2H), 1.00 (d, J = 6.1 Hz, 6H), *0.94 (d, J = 5.8 Hz, 6H); ^{13}NMR (75 MHz, DMSO-d_6) δ ppm 166.4 (C), 134.6 (C), 131.2 (CH), 128.5 (CH), 127.4 (CH), 58.9 (CH), 28.7 (CH_2), 19.3 (CH_3); IR (film) 3220, 3068, 2971, 2920, 2920, 2846, 1658, 1638, 1553, 1451, 1369, 1303, 1015, 903, 696 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{13}H_{18}N_2O$ $[M]^+$: 218.1419. Found: 218.1411.

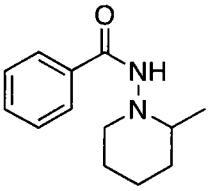
Diastereoisomer **2.66-syn**: TLC R_f 0.33 in 60 % EtOAc in hexanes; ^{1}H NMR (300 MHz, DMSO-d_6)* denotes minor isomer δ ppm 9.04 (s, 1H), *7.87 (d, J = 7.2 Hz, 2H), 7.78 (d, J = 7.1 Hz, 2H), 7.56-7.40 (m, 3H), 3.45-3.28 (m, 2H), 2.03-1.89 (m, 2H), 1.40-1.28 (m, 2H), 0.97 (d, J = 6.3 Hz, 6H), *0.81 (d, J = 5.6 Hz, 6H); ^{13}NMR (75 MHz, DMSO-d_6) δ ppm 166.2 (C), 135.3 (C), 131.8 (CH), 129.0 (CH), 128.2 (CH), 56.5 (CH), 29.9 (CH_2), 18.2 (CH_3); IR (film) 3220, 3068, 2971, 2920, 2920, 2846, 1658, 1638, 1553, 1451, 1369, 1303, 1015, 903, 696 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{13}H_{18}N_2O$ $[M]^+$: 218.1419. Found: 218.1405.



***42-N*-(2-Ethylpyrrolidin-1-yl)benzamide (Table 13, entry 1-2, 2.71):** Synthesized according to general procedure A (175 °C, 10h) using hydrazide **2.70** (0.050 g, 0.230 mmol) and **4d** (0.200 g, 0.920 mmol), for entries 3 and 4, respectively. The reaction mixture was concentrated under reduced pressure and the product was isolated using flash chromatography (75 % Et_2O in pentane with 1 % Et_3N). The title compound was obtained as a white solid (0.031 g, 61 % yield and 0.150 g, 75 % yield, respectively). TLC R_f 0.51 in 100 % EtOAc; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.75 (d, J = 7.0 Hz, 2H), 7.57-7.32 (m, 3H), 3.45 (dt, J = 8.5, 3.2 Hz, 1H), 2.83-2.66 (m, 2H), 2.10-1.66 (m, 4H), 1.65-1.36 (m, 2H), 0.90 (t, J = 7.5, 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.9 (C), 134.3 (C), 131.9 (CH), 128.9 (CH), 127.4 (CH), 68.6 (CH), 56.3 (CH_2), 28.3 (CH_2), 26.5 (CH_2), 20.9 (CH_2), 11.0 (CH_3); IR (film) 3855, 3746, 3220, 3060, 2963, 2932, 2878, 1697, 1646, 1584, 1541, 1487, 1463, 1307, 1284, 1089, 941, 914, 688 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{13}H_{18}N_2O$ $[M]^+$: 218.1419. Found 218.1398.

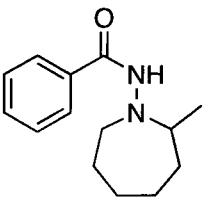


43-1-(2-methylpyrrolidin-1-yl)thiourea (Figure 20, 2.73): Synthesized according to general procedure A (120 °C, 16h) using hydrazide **2.72** (0.99 g, 0.396 mmol). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography with silver nitrate silica (5 % MeOH in CH_2Cl_2). The title compound was obtained as a brown solid (0.062 g, 68 % yield). TLC R_f 0.38 in 30 % EtOAc in toluene. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.92-7.61 (m, 3H), 7.56-6.92 (m, 5H), 4.60 (dd, J = 11.6, 6.3 Hz, 1H), 4.45 (s, 2H), 1.45 (d, J = 6.17 Hz, 3H), 1.27-1.20 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 167.0 (C), 142.2 (C), 137.1 (C), 133.5 (C), 131.6 (C), 128.5 (CH), 127.2 (CH), 127.0 (CH), 122.3 (CH), 122.0 (CH), 64.5 (CH), 58.5 (CH_2), 18.1 (CH_3); IR (film) 3241, 3063, 3032, 2968, 2926, 2839, 1653, 1546, 1482, 1379, 1307, 1181, 1094, 1079, 1022, 995, 904, 743, 694 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{16}H_{16}N_2O$ $[M]^+$: 252.1263. Found: 252.1248.



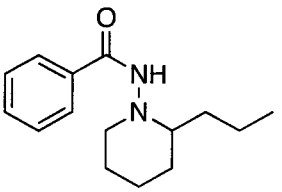
***44-N*-(2-Methylpiperidin-1-yl) benzamide (Table 14, entry 3, 2.75):** Synthesized according to general procedure B (200 °C, 10h) in α,α,α-trifluorotoluene using hydrazide **2.74** (0.179 g, 0.821 mmol) . The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (40 % EtOAc in

hexanes). The title compound was obtained as a white solid (0.159 g, 89 % yield). TLC R_f 0.43 in 60 % EtOAc in hexanes. The spectral data is in agreement with previously reported data by Charette and Legault.[105]

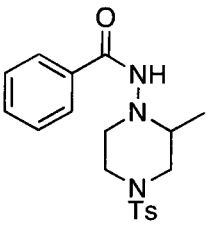


***45-N*-(2-Methylazepan-1-yl)benzamide (Table 15, entry 4, 2.79):** Synthesized according to general procedure B (235 °C, 24h) in α,α,α-trifluorotoluene from the corresponding hydrazide **2.78** (0.055 g, 0.240 mmol). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (40 % EtOAc in hexanes). The title compound was obtained as a mixture of starting material and product (39 % yield by NMR).[106] TLC R_f 0.26 in 30 % EtOAc in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) * denotes starting material δ ppm 8.17 (s, 1H), 7.77 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.56-7.48 (m, 2H), 7.47-7.40 (m, 4H), *5.80 (tdd, *J* = 16.9, 10.2, 6.7 Hz, 1H), *5.05-4.91 (m, 3H), 3.26-3.20 (m, 1H), 3.17 (m, 2H), *2.93 (t, *J* = 7.3 Hz, 2H), *2.11-2.00 (m, 2H), 1.61-1.48 (m, 4H), 1.48-1.32 (m, 8H), 1.15 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) * denotes starting material δ ppm *167.2 (C), 166.4 (C), *138.9 (CH), 138.8 (CH), 134.2 (CH), *132.9 (CH), 132.8 (CH), *131.8 (C), 131.5 (C), 130.0 (CH), 128.7 (CH), *128.6 (CH), 128.3 (CH), *127.0 (CH), *126.8 (CH), *114.4 (CH_2), 61.2 (CH), 56.7 (CH_2), *52.2 (CH_2), *33.6 (CH_2), 33.5 (CH_2), *28.7 (CH_2), *27.8 (CH_2), 27.8 (CH_2), *26.5 (CH_2), 26.3 (CH_2), 25.4 (CH_2), 20.9 (CH_3); IR (film) 3277, 3085, 3050, 3000, 2878, 1640, 1567, 1500, 1474, 1322, 1290, 1080, 1024, 1000, 900, 800 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{14}H_{20}N_2O_1$ $[M]^+$: 232.1576. Found: 232.1578.

(105) Legault, C. Y.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 8966.
(106) Several different solvent systems and columns were attempted but isolation of the desired pure product was not possible.

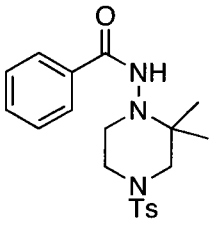


***46-N*-(2-Propylpiperidin-1-yl)benzamide (Table 16, entry 3 and 5, 2.77):** Synthesized according to general procedure B (220 °C, 19h) in α,α,α-trifluorotoluene from the corresponding hydrazide **2.76** (0.060 g, 0.240 mmol) and **2.76** (0.051 g, 0.210 mmol). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (30 % EtOAc in hexanes). The title compound was obtained as a white solid (0.025 g, 42 % yield). TLC R_f 0.56 in 60 % EtOAc in hexanes. The spectral data is in agreement with data reported by Charette and Legault.[105]

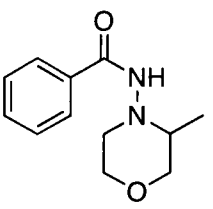


***47-N*-(2-Methyl-4-tosylpiperazin-1-yl)benzamide (Table 17, entry 1, 2.81a):** Synthesized according to general procedure B (200 °C, 10h) in α,α,α-trifluorotoluene from the corresponding hydrazide **2.80a** (0.077 g, 0.259 mmol). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (50 % EtOAc in toluene with 1% Et_3N). The title compound was obtained as a dark oil (0.773 g, 80 % yield). TLC R_f 0.30 in 60 % EtOAc in hexanes; ^1H NMR (300 MHz, $CDCl_3$)* denotes minor isomer δ ppm 7.73 (d, *J* = 7.1 Hz, 2H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.55-7.31 (m, 5H), 7.02 (s, 1H), 3.72-3.58 (m, 2H), 3.19 (td, *J* = 10.5, 2.36 Hz, 1H), 3.03-2.89 (m, 2H), 2.72 (dt, *J* = 11.5, 2.6 Hz, 1H), 2.50-2.38 (m, 3H), 2.34 (t, *J* = 10.9 Hz, 1H), *1.24 (d, *J* = 3.8 Hz, 3H), 1.11 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.1 (C),

144.2 (C), 133.3 (C), 131.8 (C), 131.7 (C), 129.8 (CH), 128.6 (CH), 127.8 (CH), 127.1 (CH), 58.4 (CH), 54.8 (CH_2), 51.8 (CH_2), 45.9 (CH_2), 21.5 (CH_3), 16.2 (CH_3); IR (film) 3271, 3057, 2983, 2924, 2854, 1654, 1537, 1455, 1338, 1299, 1171, 1109, 1000, 925, 812, 758 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{19}H_{23}N_3O_3S_1$: $[M]^+$-Tosyl: 218.1290. Found: 218.1279.



***48-N*-(2,2-Dimethyl-4-tosylpiperazin-1-yl)benzamide (Table 17, entry 2, 2.81b):** Synthesized according to general procedure B (225 °C, 10h) in chlorobenzene from the corresponding hydrazide **2.80b** (0.037 g, 0.090 mmol). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (70 % EtOAc in hexanes). The title compound was obtained as a dark oil (0.031 g, 84 % yield). TLC R_f 0.28 in 60 % EtOAc in hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.70 (d, J = 6.6 Hz, 2H), 7.62 (d, J = 7.6 Hz, 2H), 7.57-7.38 (m, 3H), 7.34 (d, J = 7.6 Hz, 2H), 6.69 (s, 1H), 3.42-2.73 (m, 6H), 2.54-2.27 (m, 3H), 1.19 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 144.0 (C), 132.1 (C), 131.8 (CH), 129.8 (CH), 128.7 (CH), 127.7 (CH), 127.1 (CH), 57.3 (C), 56.6 (CH_2), 49.9 (CH_2) 46.2 (CH_2), 21.5 (CH_3), 20.8 (CH_3); IR (film) 3310, 3066, 3032, 2983, 2922, 2857, 2226, 1661 1534, 1459, 1352, 1329, 1284, 1168, 1147, 1097, 959, 915, 765, 731, 659 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{20}H_{25}N_3O_3S_1$: $[M]^+$-Tosyl: 232.1450. Found: 232.1435.



***49-N*-(3-Methylmorpholino)benzamide (Table 17, entry 3, 2.81c):** Synthesized according to general procedure B (200 °C, 10h) in α, α, α- trifluorotoluene using hydrazide **2.80c** (0.057 g, 0.260 mmol). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (3 % MeOH in CH_2Cl_2). The title compound was obtained as a white solid (0.042g, 75 % yield). TLC R_f 0.36 in 100 % EtOAc; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.72 (d, J = 7.3 Hz, 1H), 7.50-7.43 (m, 1H), 7.41-7.34 (m, 2H), 7.17 (br, 1H), 3.86-3.70 (m, 3H), 3.41-3.32 (m, 1H), 3.04 (dt, J = 10.6, 1.9 Hz, 1H), 2.97-2.82 (m, 2H), 1.02 (d, J = 6.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 166.2 (C), 133.6 (C), 131.5 (CH), 128.5 (CH), 127.0 (CH), 72.1 (CH_2), 66.6 (CH_2), 59.1 (CH), 55.8 (CH_2), 14.22 (CH_3); IR (film) 3488, 3230, 3065, 2972, 2858, 1652, 1542, 1303, 1117, 984, 904, 699 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{12}H_{16}N_2O_2$ $[M]^+$ = 220.1212. Found 220.1188.

5.2 General information

Please refer to section **5.1**

5.2.1 General procedures for the formation of the hydrazone

General Procedure A: Prepared according to the procedure of the Mukai group.[98] To a flame-dried round bottom flask (250 mL) charged with a magnetic stir bar, alkenol (0.500 mL, 4.9 mmol), DMSO (1.12 mL, 15.8 mmol) and Et_3N (2.24 mL, 16.1 mmol) in dry CH_2Cl_2 (22.4 mL) was added SO_3·Pyr (2.35 g, 14.8 mmol) at 0 °C. The reaction was monitored by TLC until completion. The reaction was quenched by addition of saturated aqueous NH_4Cl, and the mixture was extracted with CH_2Cl_2. The extract was washed with H_2O and brine. The crude mixture was evaporated *in vacuo*, and the aldehyde was used without any purification. The hydrazone was prepared according to the procedure of the Leighton group.[99] The corresponding hydrazide (0.318 g, 2.32 mmol) and acetic acid (0.133 mL, 2.32 mmol) were added in methanol (13.0 mL) to the unpurified aldehyde

mixture. The mixture was refluxed until consumption of the aldehyde or hydrazide was judged to be complete by TLC.

General Procedure B: Prepared according to the procedure of Mukai group.[98] To a flame-dried round bottom flask (250 mL) charged with a magnetic stir bar, alkenol (1.0 mL, 9.8 mmol), DMSO (2.7 mL, 29.5 mmol) and Et_3N (5.5 mL, 39.3 mmol) in dry CH_2Cl_2 (60.0 mL) was added SO_3·Pyr (4.7 g, 29.5 mmol) at 0 °C. The reaction was monitored by TLC until completion. The reaction was quenched by addition of saturated aqueous NH_4Cl, and the mixture was extracted with CH_2Cl_2. The extract was washed with H_2O and brine. The crude mixture was evaporated *in vacuo*, and the aldehyde was used without any purification. The hydrazone was prepared using a modified procedure of the Leighton group.[99] To the crude mixture the corresponding semicarbazide (1.0 g, 9.0 mmol,) and pyridine (0.71 g, 9.00 mmol,) were added in methanol (13.00 mL). The mixture was refluxed until consumption of the aldehyde or hydrazide was judged to be complete by TLC.

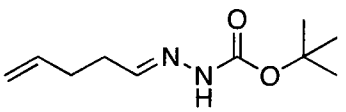
General Procedure C: Prepared according to the procedure of the Leighton group.[99] The corresponding ketone (0.255 g, 2.55 mmol), hydrazide (0.318 g, 2.32 mmol) and acetic acid (0.133 mL, 2.32 mmol) were added in methanol (13.0 mL). The mixture was refluxed until consumption of the aldehyde or hydrazide was judged to be complete by TLC. The corresponding product is concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding product(s).

5.2.2 General procedure for the formation of the alkylhydrazide

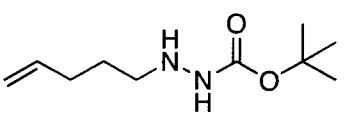
Prepared via a modification of Lane's procedure.[101] The corresponding hydrazone (0.346g, 1.60 mmol) was combined with $NaCNBH_3$ (0.132 g, 1.92 mmol), a pinch of methyl orange and a clean stir bar in methanol (2.0 mL) (the mixture is orange). The solution was capped with a septum and purged with argon for 5 minutes. A

solution of 1:1 MeOH:HCl was added drop wise until the solution turned red (the reaction must stay red). The reaction mixture was stirred for 3 hours. NaOH was added until the pH was around 8. Extraction was done with CH_2Cl_2, the organic phase was washed with brine and dried over Na_2SO_4. The corresponding product was concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding product(s).

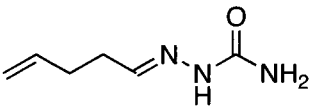
5.2.3 Characterization: aminocarbonylation and thiohydrazide precursor



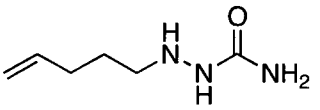
***56-N*-(Pent-4-enylidene)*tert*-butylcarbazate:** Synthesized according to general procedure 5.2.3A. Observed a mixture of E and Z isomers in a 5:1 ratio, respectively. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (40 % EtOAc in toluene with 1 % Et_3N). The title compound was obtained as a clear oil (0.339 g, 66 % yield). TLC R_f 0.57 in 40 % EtOAc in toluene; ^{1}H NMR (300 MHz, $CDCl_3$) * denotes minor isomer δ ppm 7.76 (s, 1H), 7.16 (t, J = 5.3 Hz, 1H), *6.63 (t, J = 5.0 Hz, 1H), 5.79 (tdd, J = 16.9, 10.2, 6.7 Hz, 1H), 5.01 (ddd, J = 17.1, 3.5, 1.6 Hz, 1H), 4.94 (tdd, J = 10.2, 2.1, 1.2 Hz, 1H), 2.46-2.15 (m, 4 H), *1.53 (s, 9H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) * denotes minor isomer δ ppm 156.8 (C), 146.5 (CH), *145.5 (CH), 137.0 (CH), *136.1 (CH), 116.4 (CH_2), *115.6 (CH_2), 80.0 (C), 31.4 (CH_2), 30.8 (CH_2), *29.8 (CH_2), 28.3 (CH_3), *25.4 (CH_2); IR (film) 3249, 2979, 2941, 1699, 1534, 1393, 1367, 1271, 1251, 1168, 1044, 1017, 912, 866, 763 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{10}H_{18}N_2O_2$ $[M]^+$: 198.1368. Found: 198.1385.



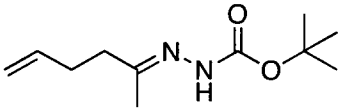
***57-N*-(Pent-4-enyl)*tert*-butylcarbazate (3.9a):** Synthesized according to general procedure 5.2.4. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (20 % EtOAc in toluene with 1 % Et_3N). The title compound was obtained as a clear oil (0.113 g, 35 % yield). TLC R_f 0.45 in 40 % EtOAc in toluene; 1H NMR (300 MHz, $CDCl_3$) δ ppm 6.22 (s, 1H), 5.79 (tdd, J = 16.9, 10.2, 6.7 Hz, 1H), 5.01 (ddd, J = 17.1, 3.5, 1.6 Hz, 1H), 4.94 (tdd, J = 10.2, 2.1, 1.2 Hz, 1H), 3.93 (s, 1H), 2.83 (t, J = 7.2 Hz, 1H), 2.09 (q, J = 6.9 Hz, 1H), 1.55 (m, 1H), 1.44 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 156.8 (C), 138.3 (CH), 114.8 (CH_2), 80.4 (C), 51.5 (CH_2), 31.2 (CH_2), 28.4 (CH_3), 27.0 (CH_2); IR (film) 3317, 3078, 2979, 2937, 2873, 1706, 1641, 1478, 1455, 1364, 1284, 1254, 1159, 1048, 1014, 991, 912, 870, 775 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{10}H_{20}N_2O_2$ $[M]^+$: 200.1524. Found: 200.1412.



58-1-(Pent-4-enylidene)semicarbazide: Synthesized according to general procedure 5.2.3B. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (100 % EtOAc). The title compound was obtained as a white solid (0.826 g, 60 % yield). TLC R_f 0.29 in 100 % EtOAc; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.88 (s, 1H), 7.12 (t, J = 4.8 Hz, 1H), 5.84 (tdd, J = 16.4, 10.4, 6.2 Hz, 1H), 5.13-5.00 (m, 2H), 2.42-2.24 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 158.7 (C), 144.6 (CH), 137.0 (CH), 115.4 (CH_2), 31.4 (CH_2), 30.3 (CH_2); IR (film) 3454, 3283, 3165, 3063, 2930, 1681, 1633, 1596, 1504, 1428, 1352, 1128, 994, 919, 774 cm^{-1}; HRMS (EI): Exact mass calcd for $C_6H_{11}N_3O_1$ $[M]^+$: 141.0902. Found: 141.0915.

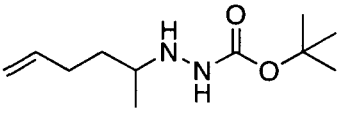


59-1-(Pent-4-enyl)semicarbazide (3.9b): Synthesized according to general procedure 5.2.4. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (10 % MeOH in CH_2Cl_2). The title compound was obtained as a white solid (0.460 g, 56 %). TLC R_f 0.10 in 100 % EtOAc; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.00 (s, 1H), 5.88-5.71 (m, 3H), 5.01 (ddd, J = 17.2, 3.3, 1.5 Hz, 1H), 4.97-4.91 (m, 1H), 4.58 (s, 1H), 2.67-2.56 (m, 2H), 2.05 (dd, J = 14.6, 6.9 Hz, 2H), 1.52-1.39 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 161.7 (C), 137.9 (CH), 114.9 (CH_2), 51.7 (CH_2), 31.1 (CH_2), 26.6 (CH_2); IR (film) 3450, 3290, 3263, 3209, 3080, 2983, 2940, 2858, 1662, 1646, 1576, 1428, 1100, 988, 911, 773 cm^{-1}; HRMS (EI): Exact mass calcd for $C_6H_{13}N_3O_1$ $[M]^+$: 143.1059. Found: 143.1071.

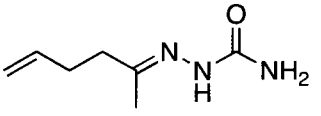


***60-N*-(Hex-5-en-2-ylidene)*tert*-butylcarbazate.** Synthesized according to general procedure 5.2.3C. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (20 % EtOAc in toluene with 1 % Et_3N). The title compound was obtained as a clear oil (0.957 g, 53 % yield). TLC R_f 0.43 in 30 % EtOAc in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) * denotes minor isomer δ ppm 7.35 (s, 1H), 5.82 (tdd, J = 16.5, 10.3, 6.4 Hz, 1H), 5.09-4.92 (m, 2H), 2.46-2.22 (m, 4H), *2.05-1.98 (m, 4H), 1.79 (s, 3H), *1.59 (s, 9H), 1.51 (s, 9H), *1.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) * denotes minor isomer δ ppm 178.7 (C), 175.5 (C), 152.8 (C), 137.5 (CH), *136.44 (CH), *116.3 (CH_2), 115.2 (CH_2), 80.9 (C), 38.3 (CH_2), *30.9 (CH_2), 30.7 (CH_2), *29.0 (CH_3), 28.3 (CH_3), *28.2 (CH_2), *23.4 (CH_3), 14.77 (CH_3); IR (film) 3234, 3044, 3013, 2979,

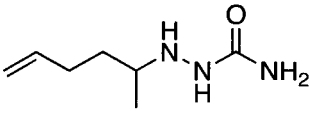
2949, 1725, 1706, 1637, 1542, 1451, 1364, 1295, 1238, 1147, 1044, 1021, 995, 911, 774, 729 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{11}H_{20}N_2O_2$ $[M]^+$: 212.1525. Found: 212.1506.



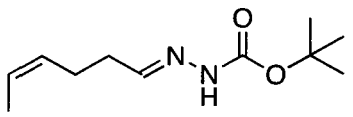
***61-N*-(Hex-5-en-2-yl)*tert*-butylcarbazate (3.9c):** Synthesized according to general procedure 5.2.4. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (20 % EtOAc in toluene with 1 % Et_3N). The title compound was obtained as a white solid (0.900 g, 94 %). TLC R_f 0.48 in 30 % EtOAc in hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 6.18 (s, 1H), 5.82 (tdd, J = 16.8, 10.2, 6.6 Hz, 1H), 5.03 (ddd, J = 17.1, 3.5, 1.7 Hz, 1H), 4.99-4.92 (m, 1H), 3.96 (s, 1H), 3.08-2.93 (m, 1H), 2.22-1.99 (m, 1H), 1.70-1.22 (m, 11H), 1.03 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 156.8 (C), 138.5 (CH), 114.5 (CH_2), 80.3 (C), 54.9 (CH), 33.9 (CH_2), 30.0 (CH_2), 28.3 (CH_3), 18.2 (CH_3); IR (film) 3341, 3084, 2979, 2932, 2873, 1712, 1642, 1475, 1451, 1362, 1276, 1253, 1155, 1097, 1046, 1011, 914, 863, 769 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{11}H_{22}N_2O_2$ $[M]^+$: 214.1681. Found: 214.1676.



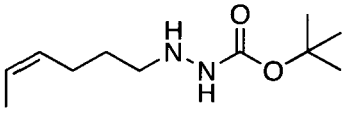
62-1-(Hex-5-en-2-ylidene)semicarbazide: Synthesized according to general procedure 5.2.3C. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (5 % MeOH in CH_2Cl_2). The title compound was obtained as a white solid (2.12 g, 100 % yield). TLC R_f 0.33 in 5 % MeOH in CH_2Cl_2; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm * denotes minor isomer 8.20 (s, 1H), 5.81 (dd, J = 17.0, 10.3 Hz, 1H), 5.00 (dd, J = 18.1, 13.7 Hz, 2H), 2.32 (dd, J = 9.3, 6.2 Hz, 4H), *1.94 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 161.0 (C), 138.1 (CH), 115.2 (CH_2), 56.1 (CH), 33.6 (CH_2), 30.3 (CH_2), 18.4 (CH_3); IR (film) 3419, 3197, 1677, 1638, 1592, 1444, 1132, 910 cm^{-1}; HRMS (EI): Exact mass calcd for $C_7H_{14}N_3O_1$ $[M]^+$: 155.1059. Found: 155.1062.



63-1-(Hex-5-en-2-yl)semicarbazide (3.9d): Synthesized according to general procedure 5.2.4. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (5 % MeOH in CH_2Cl_2 with 1% Et_3N). The title compound was obtained as a white solid (0.541 g, 49 % yield). TLC R_f 0.60 in 10 % MeOH in CH_2Cl_2; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 5.90 (s, 1H), 5.87-5.71 (m, 1H), 5.79 (tdd, J = 16.9, 10.1, 6.7 Hz, 1H), 5.08-4.93 (m, 1H), 5.07-4.93 (m, 2H), 3.63-3.55 (m, 1H), 2.84 (sext., J = 7.1 Hz, 1H), 2.21-1.99 (m, 2H), 1.65-1.52 (m, 1H), 1.45-1.31 (m, 1H), 1.07 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4 (C), 115.5 (CH), 56.4 (CH_2), 33.9 (CH), 31.3 (CH_2), 30.6 (CH_3), 18.6 (CH_2); IR (film) 3454, 3267, 3080, 2917, 1670, 1580, 1432, 902 cm^{-1}; LRMS m/z (relative intensity); 102.0663 (100%), 59.0623 (50.5%), 41.0390 (49.2%), 55.0561 (35.9%), 85.0422 (25.2 %), 42.0341 (25.0%).

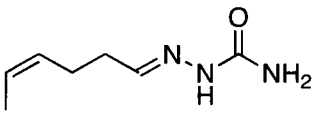


***64-N*-((*Z*)-Hex-4-enylidene)*tert*-butylcarbazate:** Synthesized according to general procedure 5.2.3A. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (30 % EtOAc in hexanes). The title compound was obtained as a white solid (0.639 g, 34 % yield). TLC R_f 0.3 in 30 % EtOAc in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm * denotes minor isomer 7.66 (s, 1H), 7.13 (t, J = 5.2, 5.2 Hz, 1H), 5.49 (td, J = 17.4, 6.7 Hz, 2H), 5.37 (dtd, J = 10.4, 6.7, 1.4 Hz, 2H), 2.35 (dd, J = 13.2, 6.3 Hz, 2H), 2.25 (dd, J = 14.3, 7.0 Hz, 2H), 1.59 (d, J = 6.4 Hz, 3H), 1.49 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.9 (CH), *145.9 (CH), 128.8 (CH), *128.0 (CH), *126.3 (CH), 125.3 (CH), *81.2 (CH), 77.4 (CH), 32.2 (CH_2), 28.4 (CH_3), 26.4 (C), 24.3 (CH_2), 23.4 (CH_2), 13.0 (CH_3); IR (film) 3244, 3010, 2983, 2932, 1710, 1529, 1367, 1251, 1166, 1039, 1007, 863, 770 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{11}H_{20}N_2O_2$ $[M]^+$: 212.1525. Found: 212.1521.

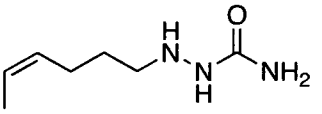


65-1-((*Z*)-Hex-4-enyl)*tert*-butylcarbazate (3.9e): Synthesized according to general procedure 5.2.4. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (20 % EtOAc in hexanes). The title compound was obtained as a white solid (3.74 g, 59 % yield). TLC R_f 0.26 in 20 % EtOAc; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 6.04 (s, 1H), 5.54-5.33 (m, 2H), 3.80 (s, 1H), 2.86 (t, J = 7.3 Hz, 2H), 2.11 (q, J = 7.4, 7.3 Hz, 2H), 1.62 (dd, J = 6.1, 0.9 Hz, 3H), 1.55 (p, J = 7.4 Hz, 2H), 1.48 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.1 (CH), 124.5 (CH), 51.8 (CH_2), 28.5 (CH_3), 27.9 (CH_2), 24.5 (CH_2), 12.9

(CH_3); IR (film) 3306, 3014, 2983, 2944, 2862, 1701, 1448, 1366, 1280, 1259, 1253, 1156, 1046, 1015, 871 cm^{-1}; LRMS m/z (relative intensity): 57.0705 (100%), 45.0458 (48%), 158.1070 (37%), 89.0366 (24.8%).

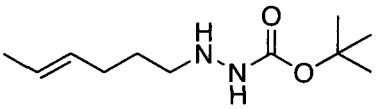


66-1-((*Z*)-Hex-4-enylidene)semicarbazide: Synthesized according to general procedure 5.2.3B. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (100 % EtOAc). The title compound was obtained as a white solid (0.985 g, 47 % yield). TLC R_f 0.33 100 % EtOAc; ^1H NMR (300 MHz, $CDCl_3$) δ ppm * denotes minor isomer 8.86 (s, 1H), *8.16 (s, 1H), 7.09 (t, J = 4.5 Hz, 1H), *6.46 (t, J = 5.2 Hz, 1H), 5.51 (td, J = 17.5, 6.6 Hz, 1H), 5.43-5.29 (m, 1H), 2.36-2.17 (m, 4H), 1.61 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm *158.8 (C), 158.7 (C), 145.0 (CH), *144.8 (CH), 128.8 (CH), *128.3 (CH), *125.9 (CH), 125.2 (CH), 32.2 (CH_2), *26.8 (CH_2), 23.9 (CH_2), *23.4 (CH_2), *13.0 (CH_3), 12.9 (CH_3); IR (film) 3442, 3275, 3177, 3018, 2924, 2854, 1681, 1588, 1506, 1432, 1342, 1132, 980, 910, 770, 703 cm^{-1}; HRMS (EI): Exact mass calcd for $C_7H_{13}N_3O_1$ $[M]^+$: 155.1059. Found: 155.1054.

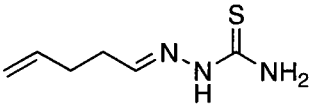


67-1-((*Z*)-Hex-4-enyl)semicarbazide (3.9f): Synthesized according to general procedure 5.2.4. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (100 % EtOAc). The title compound was obtained as a white solid (0.286 g, 33 % yield). TLC R_f 0.4 in 7.5 % MeOH in CH_2Cl_2; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 5.82 (s, 1H), 5.55-5.43 (m, 1H), 5.41-5.30 (m, 1H), 3.91-3.48 (m, 1H), 2.83 (t,

J = 7.2 2H), 2.10 (q, J = 7.5 Hz, 2H), 1.64-1.51 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3 (C), 129.6 (CH), 124.8 (CH), 52.4 (CH_2), 27.4 (CH_2), 24.4 (CH_2), 12.9 (CH_3); IR (film) 3454, 3271, 3076, 3014, 2940, 2862, 1666, 1642, 1576, 1436, 1105, 914, 781, 700 cm^{-1}; LRMS m/z (relative intensity); 45.0450 (100%), 88.0514 (76%), 98.0953 (45%), 55.0555 (27%).

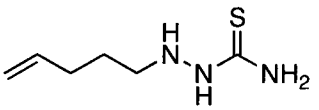


68-1-((*E*)-Hex-4-enyl)*tert*-butylcarbazate (3.9g): Synthesized according to general procedure 5.2.4. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (20 % EtOAc in hexanes). The title compound was obtained as a white solid (0.105 g, 22 % yield). TLC R_f 0.3 in 20 % EtOAc in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 6.07 (s, 1H), 5.50-5.32 (m, 2H), 3.93 (s, 1H), 2.82 (t, J = 7.2 Hz, 2H), 2.02 (dd, J = 12.1, 6.4 Hz, 2H), 1.63 (d, J = 4.1 Hz, 3H), 1.57-1.45 (m, 2H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9 (C), 130.9 (CH), 125.4 (CH), 80.6 (C), 51.8 (CH_2), 30.2 (CH_2), 28.5 (CH_3), 27.8 (CH_2), 18.0 (CH_3); IR (film) 3318, 2979, 2834, 2854, 1701, 1451, 1367, 1284, 1254, 1158, 1042, 964, 871, 766 cm^{-1}; LRMS m/z (relative intensity): 57.0698 (100%), 45.0464 (57.6%), 41.0398 (48.9%), 55.0561 (27.5%), 29.0389 (28.7%).



69-1-(pent-4-enylidene)thiosemicarbazide. Synthesized according to general procedure 5.2.3A. Observed a mixture of E and Z isomers in a 33:1 ratio, respectively. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (40 % EtOAc in toluene with 1 % Et_3N). The title compound

was obtained as a white crystalline solid (0.997 g, 65 % yield). TLC R_f 0.29 in 10 % MeOH in CH_2Cl_2; ^1H NMR (300 MHz, $CDCl_3$) * denotes minor isomer δ ppm 10.58 (s, 1H), *9.13 (s, 1H), 7.44 (t, J = 4.8 Hz, 1H), 7.08 (s, 1H), 6.90 (s, 1H), *6.56 (t, J = 5.1 Hz, 1H), 5.78 (tdd, J = 16.4, 10.2, 6.2 Hz, 1H), 5.09-4.95 (m, 2H), 2.42-2.20 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 177.4 (C), 148.0 (CH), 136.5 (CH), 115.7 (CH_2), 31.3 (CH_2), 29.9 (CH_2); IR (film) 3417, 3390, 3268, 3211, 3166, 2987, 2919, 1596, 1538, 1535, 1471, 1364, 1284, 1239, 1098, 912, 828 cm^{-1}; HRMS (EI): Exact mass calcd for $C_6H_{11}N_3S_1$ $[M]^+$: 157.0674. Found: 157.0690.



70-1-(pent-4-enyl)thiosemicarbazide (3.25): Synthesized according to general procedure 5.2.4. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (40-60 % EtOAc in hexanes with 1 % Et_3N). The title compound was obtained as white solid (0.700 g, 74 %). TLC R_f 0.49 in 10 % MeOH in CH_2Cl_2; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.80 (s, 1H), 7.10 (s, 1H), 6.36 (s, 1H), 5.77 (tdd, J = 16.9, 10.1, 6.7 Hz, 1H), 5.07-4.93 (m, 2H), 3.89 (t, J = 5.3 Hz, 1H), 2.91-2.82 (m, 2H), 2.15-2.05 (m, 2H), 1.58 (tt, J = 7.3, Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 182.1 (C), 137.5 (CH), 115.4 (CH_2), 51.1 (CH_2), 31.1 (CH_2), 26.6 (CH_2); IR (film) 3412, 3287, 3204, 3169, 3101, 2991, 2934, 2892, 2846, 1637, 1595, 1561, 1459, 1265, 934, 889, 851, 801 cm^{-1}; HRMS (EI): Exact mass calcd for $C_6H_{13}N_3O_1$ $[M]^+$: 159.0830. Found: 159.0859.

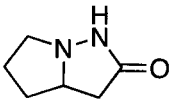
5.2.4 General procedures for the Cope-type hydroamination or aminocarbonylation of alkenes (Chapter 3)

General Procedure A (microwave): An oven dried 5- 20 mL μw tube was charged with a stir bar, capped with a septum and purged with argon and an outlet for 5 minutes. The alkenyl hydrazide (1.00 equiv) and acetonitrile (such that the concentration of the alkenyl hydrazide was 0.05 M) were added to the sealed tube, while keeping

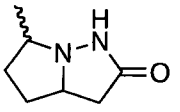
it under an argon atmosphere. The septum was removed and the tube was then quickly sealed with a microwave cap and heated for 0.5 hours at 200°C. The reaction solution was cooled to ambient temperature, concentrated under reduced pressure and analyzed by ^{1}H NMR using styrene or 1,4-dimethoxybenzene as an internal standard, then again concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding product(s).

General Procedure B (sealed tube): An oven dried 15 mL sealed tube was charged with a stir bar, capped with a septum and purged with argon and an outlet for 5 minutes. The alkenyl hydrazide (1.00 equiv) and α,α,α-trifluorotoluene (such that the concentration of the alkenyl hydrazide is 0.05 M) were added to the sealed tube, while keeping it under an argon atmosphere. The septum was removed and the tube was then quickly sealed with a screw cap and Teflon tape and heated while stirring in a wax bath for 18-42 hours at 120-170°C. The reaction solution was cooled to ambient temperature, concentrated under reduced pressure and analyzed by ^{1}H NMR using styrene or 1,4-dimethoxybenzene as an internal standard, then again concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding products.

5.2.5 Characterization of cyclised substrates



50-Tetrahydro-1*H*-pyrrolo[1,2-*b*]pyrazol-2(3*H*)-one (3.10a-b). Synthesized according to general procedure 5.2.1A (200 °C, 0.5 h) in acetonitrile from the corresponding hydrazide **3.9b** (0.033 g, 0.230 mmol). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (10 % MeOH in CH_2Cl_2). The title compound was obtained as a white solid (0.027 g, 85 % yield). TLC R_f 0.47 in 10 % MeOH in CH_2Cl_2; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 4.13-4.01 (m, 1H), 3.11 (td, *J* = 11.1, 6.4 Hz, 1H), 2.88 (td, *J* = 11.0, 6.5 Hz, 1H), 2.64 (dd, *J* = 17.1, 9.3 Hz, 1H), 2.43 (dd, *J* = 17.1, 7.8 Hz, 1H), 2.15-1.97 (m, 2H), 1.85-1.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 174.5 (C_4), 61.9 (CH), 57.9 (CH_2), 37.6 (CH_2), 31.3 (CH_2), 23.7 (CH_2); IR (film); 3181, 2967, 2873, 1682, 1574, 1422, 1356, 1063, 917 cm^{-1}; HRMS (EI): Exact mass calcd for $C_6H_{10}N_2O[M]^+$: 126.0793. Found: 126.0813.

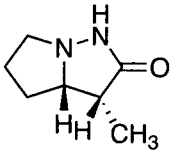


51 a and b-Tetrahydro-6-methyl-1*H*-pyrrolo[1,2-*b*]pyrazol-2(3*H*)-one (3.10c-d): Synthesized according to general procedure 5.2.1A (200 °C, 0.5h) in acetonitrile from the corresponding hydrazide **6c** (0.210 g, 0.978 mmol) and **6d** (0.152 g, 0.966 mmol). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (7.5 % MeOH in CH_2Cl_2). The title compound was obtained as a white solid (0.091 g and 0.046 g, 74 % yield and 0.075 g and 0.037 g, 84 % yield).

Diastereoisomer **a**: TLC R_f 0.33 in 7.5 % MeOH in CH_2Cl_2; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 6.49 (s, 1H), 4.04 (ddd, *J* = 13.4, 8.9, 4.3 Hz, 1H), 3.14 (qd, *J* = 13.4, 6.8, 6.6, Hz, 1H), 2.75 (dd, *J* = 17.1, 9.5 Hz, 1H), 2.36 (dd, *J* = 17.1, 4.7 Hz, 1H), 2.17-1.99 (m, 1H), 1.88-1.54 (m, 3H), 1.23 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 174.6 (C), 62.6 (CH_2), 62.2 (CH_2), 38.8 (CH), 32.4 (CH), 30.2 (CH), 15.9 (CH_3); IR (film)

3131, 3053, 2967, 2917, 2846, 1699, 1650, 1346, 1284, 1241, 1120 cm^{-1}; HRMS (EI): Exact mass calcd for $C_7H_{12}N_2O_1$ $[M]^+$: 140.0950. Found: 140.0949.

Diastereoisomer **b**: TLC R_f 0.24 in 7.5 % MeOH in CH_2Cl_2; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.89 (s, 1H), 4.12 (ddd, *J* = 18.2, 9.3, 5.0 Hz, 1H), 2.95 (td, *J* = 10.5, 5.9 Hz, 1H), 2.60-2.42 (m, 2H), 2.19 (dtd, *J* = 12.8, 8.4, 8.3, 2.5 Hz, 1H), 2.11-1.99 (m, 1H), 1.79-1.65 (m, 1H), 1.61-1.44 (m, 1H), 1.13 (d, *J* = 6.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5 (C), 64.3 (CH), 62.2 (CH), 38.1 (CH_2), 32.3 (CH_2), 29.5 (CH_2), 18.7 (CH_3); IR (film) IR (film) 3131, 3053, 2967, 2917, 2846, 1699, 1650, 1346, 1284, 1241, 1120 cm^{-1}; HRMS (EI): Exact mass calcd for $C_7H_{12}N_2O_1$ $[M]^+$: 140.0950. Found: 140.0949.



52-(±)-(3*R*,3*S*)-Tetrahydro-3-methyl-1*H*-pyrrolo[1,2-*b*]pyrazol-2(3*H*)-one (3.10g): Synthesized according to general procedure 5.2.1A (200 °C, 0.5h) in acetonitrile from the corresponding hydrazide (0.217 g, 1.01 mmol) and **3.9g** (0.042 g, 0.265 mmol). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (7.5% MeOH in CH_2Cl_2). The title compound was obtained as a white solid (0.014 g, 66 % yield and 0.024 g, 58 % yield, respectively). TLC R_f 0.2 in 7.5 % MeOH in CH_2Cl_2; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 3.91 (dd, *J* = 15.0, 8.8 Hz, 1H), 3.07 (td, *J* = 12.2, 7.3 Hz, 1H), 2.99-2.90 (m, 1H), 2.84 (qd, *J* = 9.1, 7.5 Hz, 1H), 2.03-1.68 (m, 4H), 1.22 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 66.6 (CH), 57.8 (CH), 39.8 (CH_2), 24.8 (CH_2), 24.0 (CH_2), 11.6 (CH_3); IR (film) 3213, 3068, 2967, 2874, 1699, 1455, 1374, 1265, 1097, 1066 cm^{-1}; HRMS (EI): Exact mass calcd for $C_7H_{11}N_2O_1$ $[M]^+$: 140.0950. Found: 140.0959.

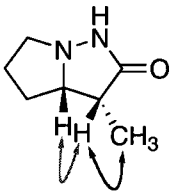
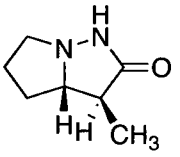


Figure S1: Selected NOE correlations observed for pyrazolidinone product **3.10g**



53-(±)-(3*S*,3*S*)-Tetrahydro-3-methyl-1*H*-pyrrolo[1,2-*b*]pyrazol-2(3*H*)-one (3.10e-f): Synthesized according to general procedure A (200 °C, 0.5h) in acetonitrile from the corresponding hydrazide **3.9e** (0.054 g, 0.253 mmol). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (10 % MeOH in CH_2Cl_2). The title compound was obtained as a white solid (0.028 g, 72 % yield). TLC R_f 0.33 in 10 % MeOH in CH_2Cl_2; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.19 (s, 1H), 3.68 (dd, J = 10.1, 7.1 Hz, 1H), 3.67 (dd, J = 9.9, 7.6 Hz, 1H), 3.21 (td, J = 6.4, 5.8 Hz, 1H), 2.88-2.78 (m, 1H), 2.50 (qd, J = 9.8, 7.2 Hz, 1H), 2.20-1.98 (m, 2H), 1.94-1.74 (m, 2H), 1.21 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9 9 (CH), 71.0 (CH), 57.7 (CH_2), 41.4 (CH), 29.1 (CH_2), 24.1 (CH_2), 14.0 (CH_3); IR (film) 3213, 3068, 2967, 2874, 1699, 1455, 1374, 1265, 1097, 1066 cm^{-1}; HRMS (EI): Exact mass calcd for $C_7H_{11}N_2O_1$ $[M]^+$: 140.0950. Found: 140.0959.

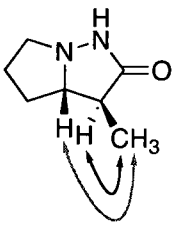
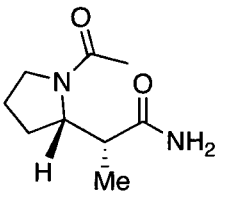


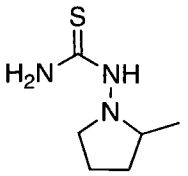
Figure S2: Selected NOE correlations observed for pyrazolidinone product **3.10e-f**

Proof of Structure (derivatization of aminocarbonylation product)



54-(±)-(*R*)-2-((*S*)-1-Acetylpyrrolidin-2-yl)propanamide: The title compound was obtained from amino-carbonylation product **3.10g** using the procedure by Rabiczko and Chmielewski.[107] The pyrazolidinone product **3.10g** (0.0661 g, 0.472 mmol) was treated with Raney nickel (0.7373 g suspension in ethanol). The residue was acetylated using acetic anhydride (0.2444 g, 2.394 mmol). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (5 % MeOH in CH_2Cl_2). The title compound was obtained as a brown oil (0.0205 g, 28 % yield). TLC R_f 0.52 in 10 % MeOH in CH_2Cl_2; ^{1}NMR (300 MHz, $CDCl_3$) δ ppm 6.01 (s, 1H), 5.42 (s, 1H), 4.07 (dd, J =12.31, 5.60 Hz, 1H), 3.53-3.34 (m, 2H), 3.33-3.22 (m, 1H), 2.26-2.15 (m, 1H), 2.08 (s, 3H), 2.02-1.85 (m, 3H), 1.85-1.71 (m, 1H), 1.12 (d, J = 7.09 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 177.1 (C), 60.8 (CH_3), 49.0 (CH_2), 41.1 (CH), 26.9 (CH_2), 24.2 (CH_2), 23.6 (CH), 14.5 (CH_3), ; IR (film); 3397, 3184, 2971, 2934, 2885, 1672, 1624, 1452, 1402, 1352, 1257, 1200, 1018, 911, 854, 740 cm^{-1}; HRMS (EI): Exact mass calcd for $C_9H_{16}N_2O_2$ $[M]^+$: 184.1193; found: 184.1212. This spectral data is in excellent agreement with the data reported for related compounds.[107]

(107) Rabiczko, J.; Chmielewski, M. *J. Org. Chem.* **1999**, *64*, 1347.



55-1-(2-methylpyrrolidin-1-yl)thiourea (3.26): Synthesized according to general procedure 5.2.1B (150 °C, 16h) using hydrazide **3.25** (0.156 g, 0.762 mmol). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (40 % EtOAc in hexanes). The title compound was obtained as a brown solid (0.048 g, 82 % yield). TLC R_f 0.29 in 60 % EtOAc in hexanes. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.04 (s, 2H), 6.26 (s, 1H), 3.31-3.19 (m, 1H), 2.82-2.66 (m, 1H), 2.59 (q, J = 9.5 Hz, 1H), 1.98 (ddd, J = 14.6, 12.6, 7.3 Hz, 1H), 1.84-1.72 (m, 2H), 1.50-1.33 (m, 1H), 1.11 (d, J = 6.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 181.9 (C), 62.4 (CH), 55.1 (CH_2), 30.0 (CH_2), 20.1 (CH_2), 18.3 (CH_3); IR (film) 3416, 3241, 3158, 2971, 2872, 2838, 1587, 1584, 1523, 1451, 1378, 1257, 1207, 1136, 1056, 995, 839 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{16}H_{13}N_3S$ $[M]^+$: 159.0830. Found: 159.08417.

5.3 Computational details

Density functional theory (DFT) calculations have been performed using the *Gaussian 03* program.[108] Optimized molecular geometries were calculated using the B3LYP[109] exchange-correlation functional.

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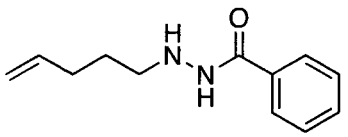
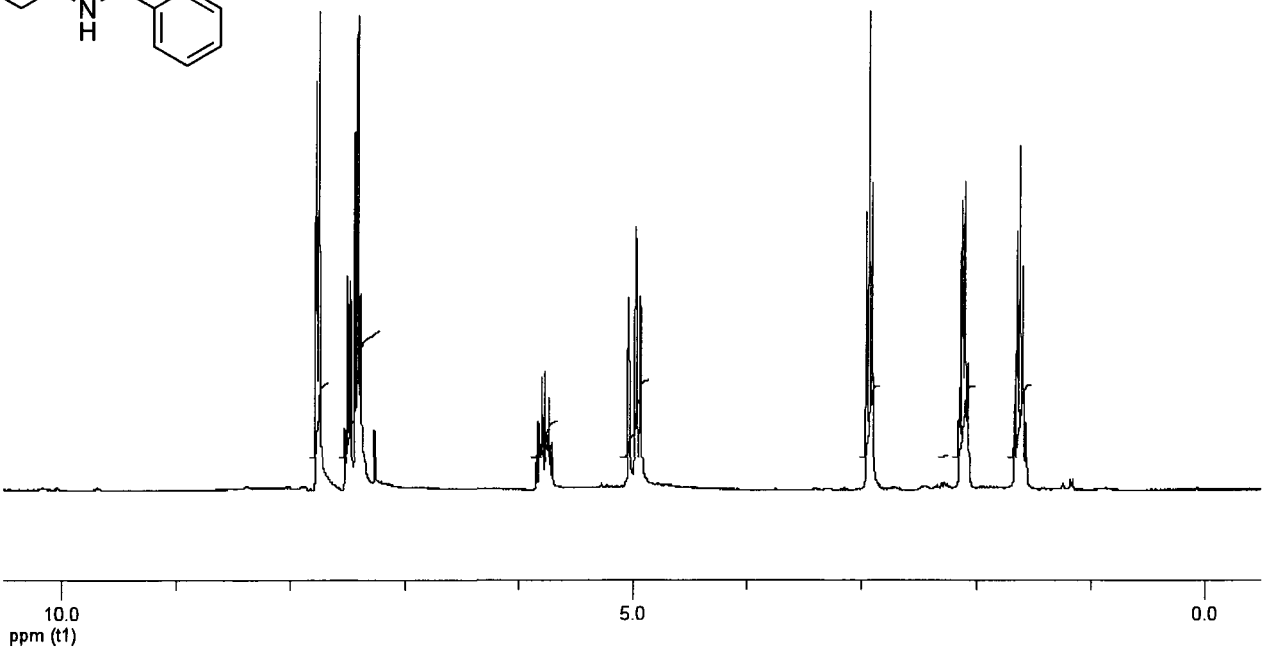
(108) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J., J. A. ; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Lyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A.; Gaussian, Inc.: 2003.
(109) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

The triple-zeta TZVP[110] basis set and tight SCF convergence criteria were used for calculations. Wave function stability calculations were performed to confirm that the calculated wave functions corresponded to the ground state. Harmonic frequency calculations were performed to ensure that the stationary points were true energy minima or transition states (TSs) and to calculate vibrational zero point energy and thermal corrections. The unscaled frequencies were used for calculating Gibbs free energies of the species (at 298K and 1 atm). Intrinsic reaction coordinate (IRC)[111,112] calculations were used to confirm the reaction pathways through the CMD transition states (TSs) for all reactants.

(110) Schafer, A.; Huber, C.; Ahlrichs, R. *J. Chem. Phys.* **1994**, *100*, 5829.
(111) Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154.
(112) Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523.

2.32e

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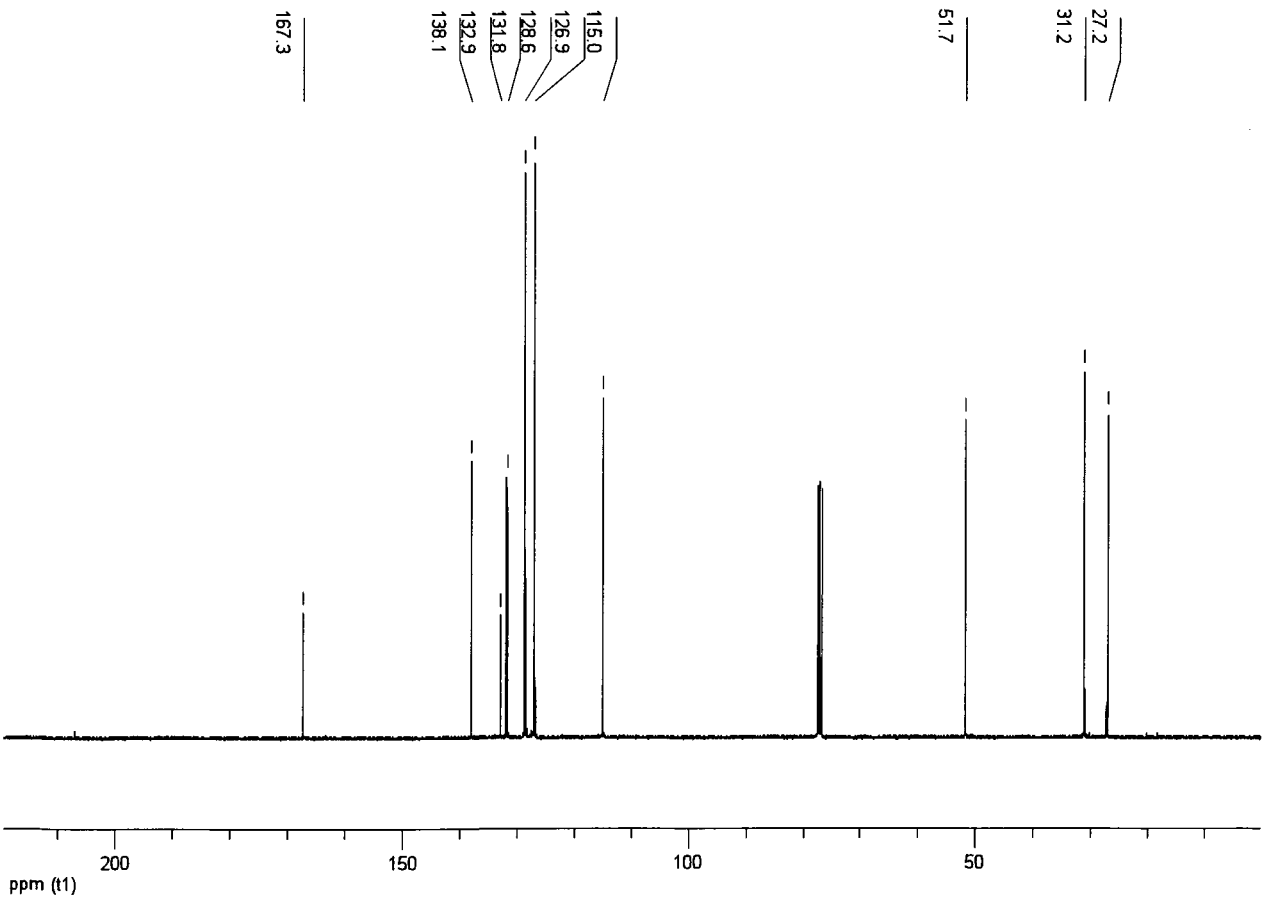
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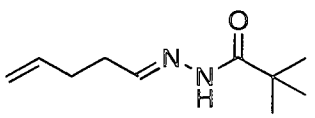
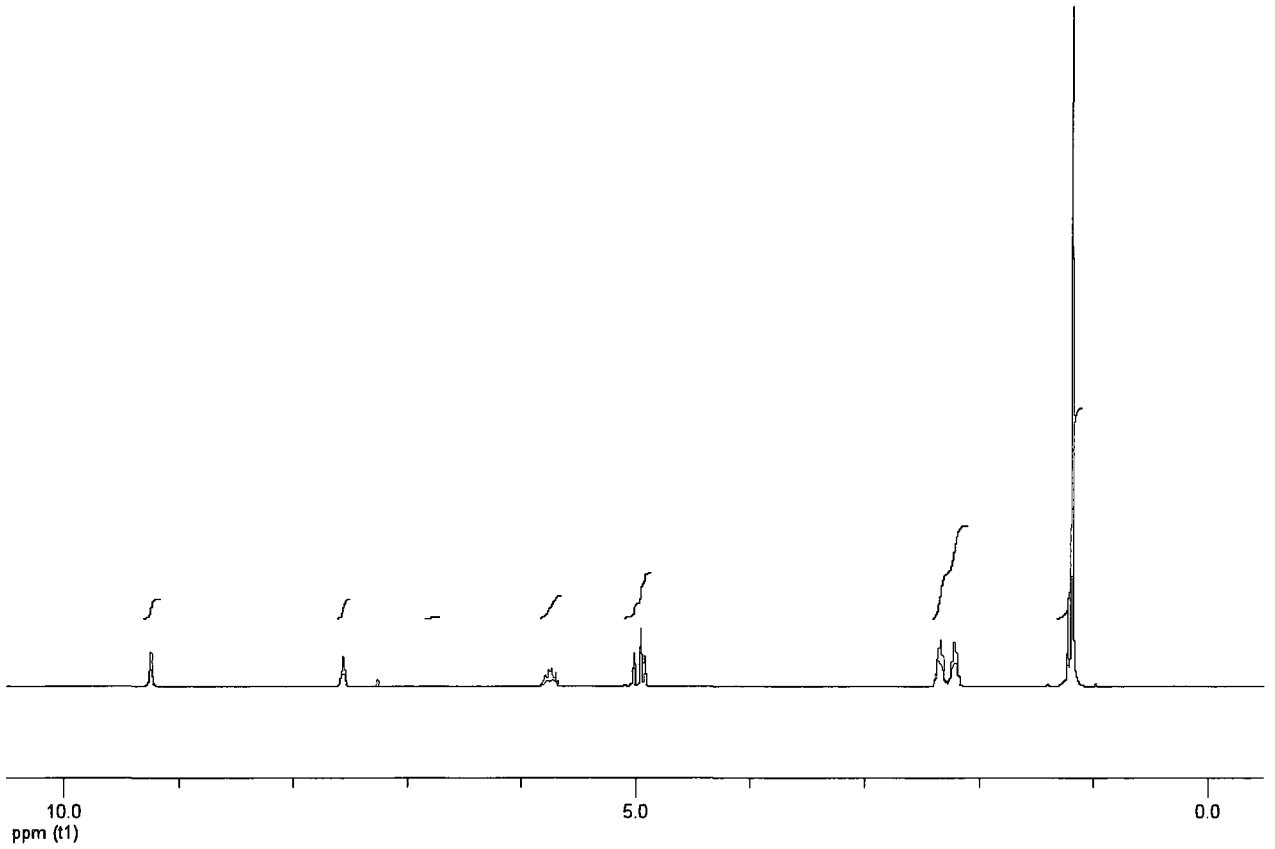
ppm (t1)

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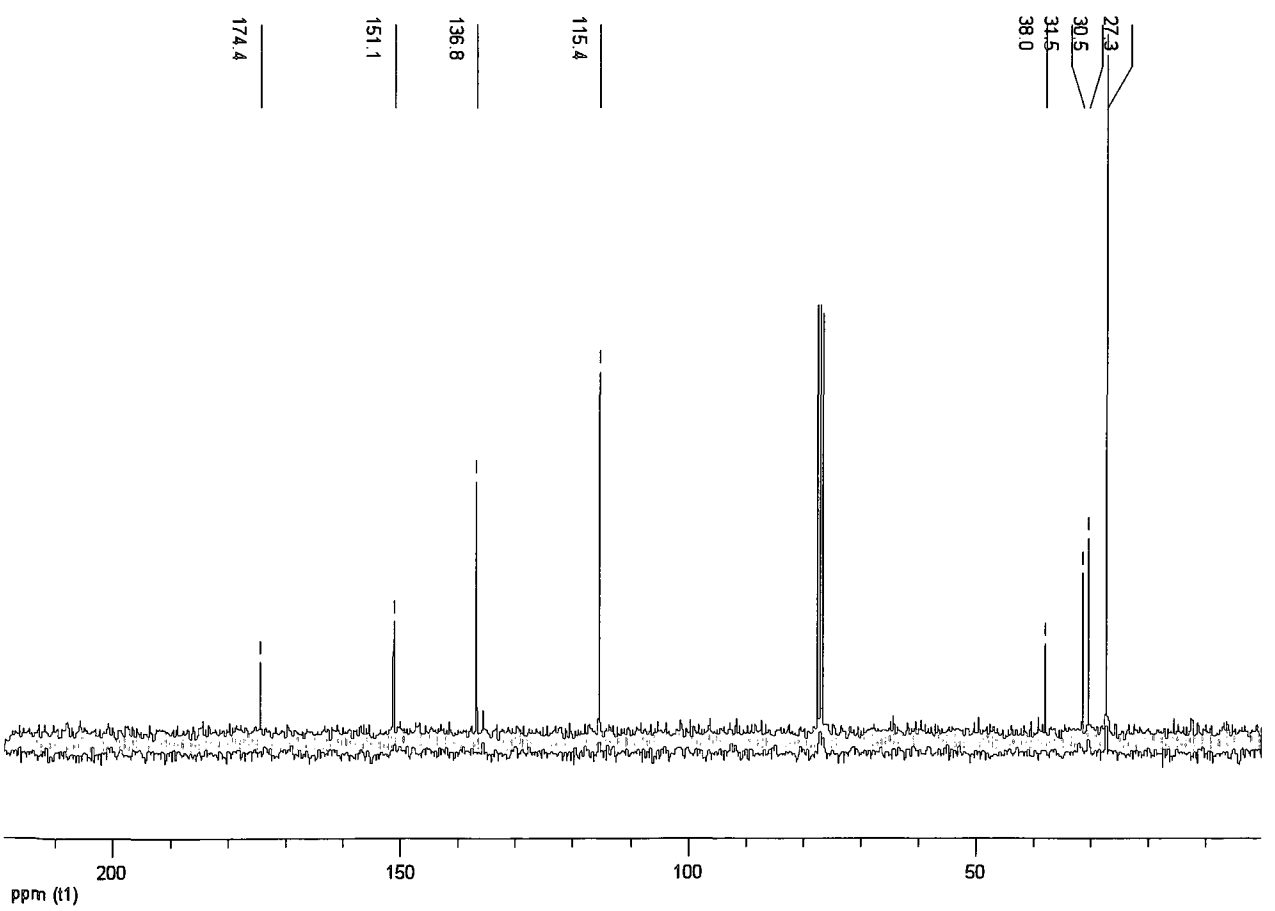
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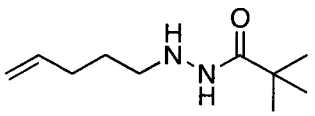
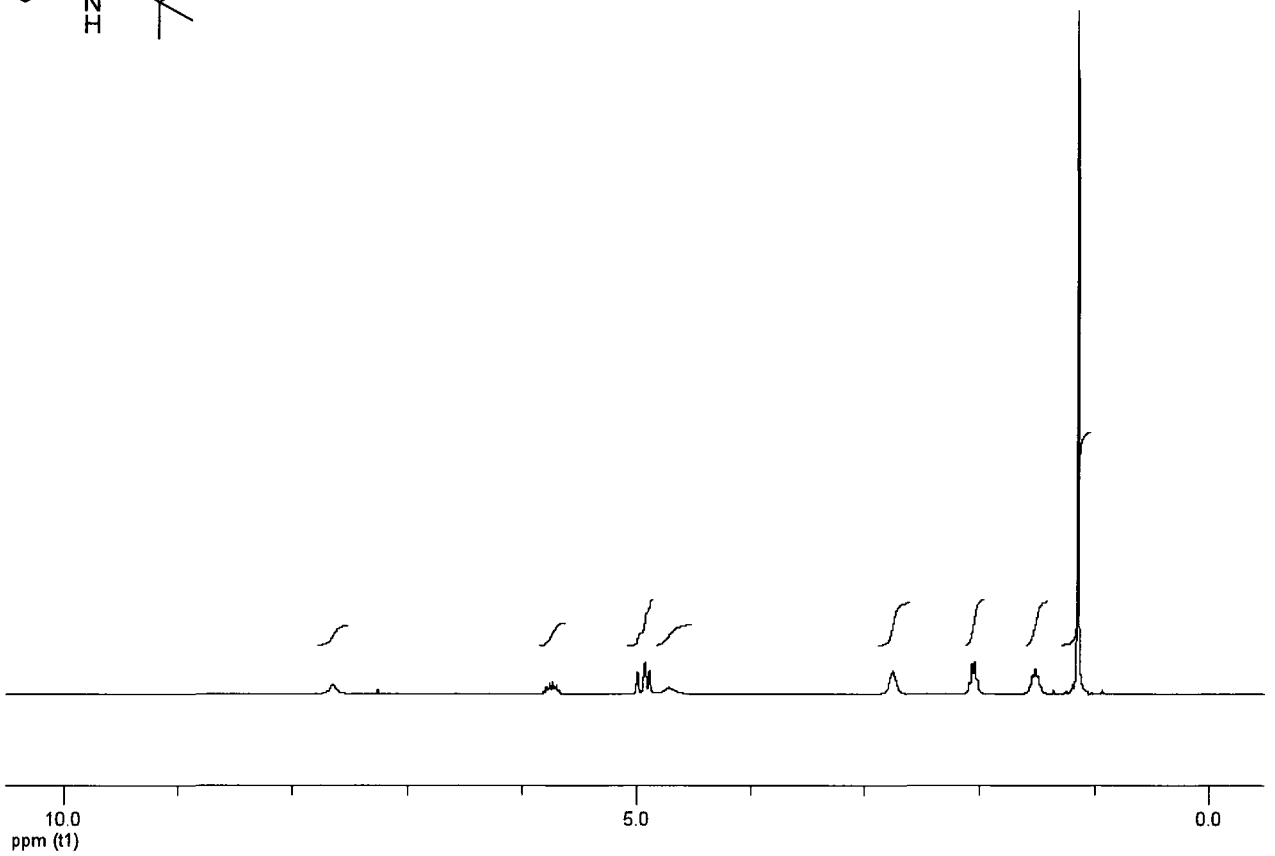
2.32b

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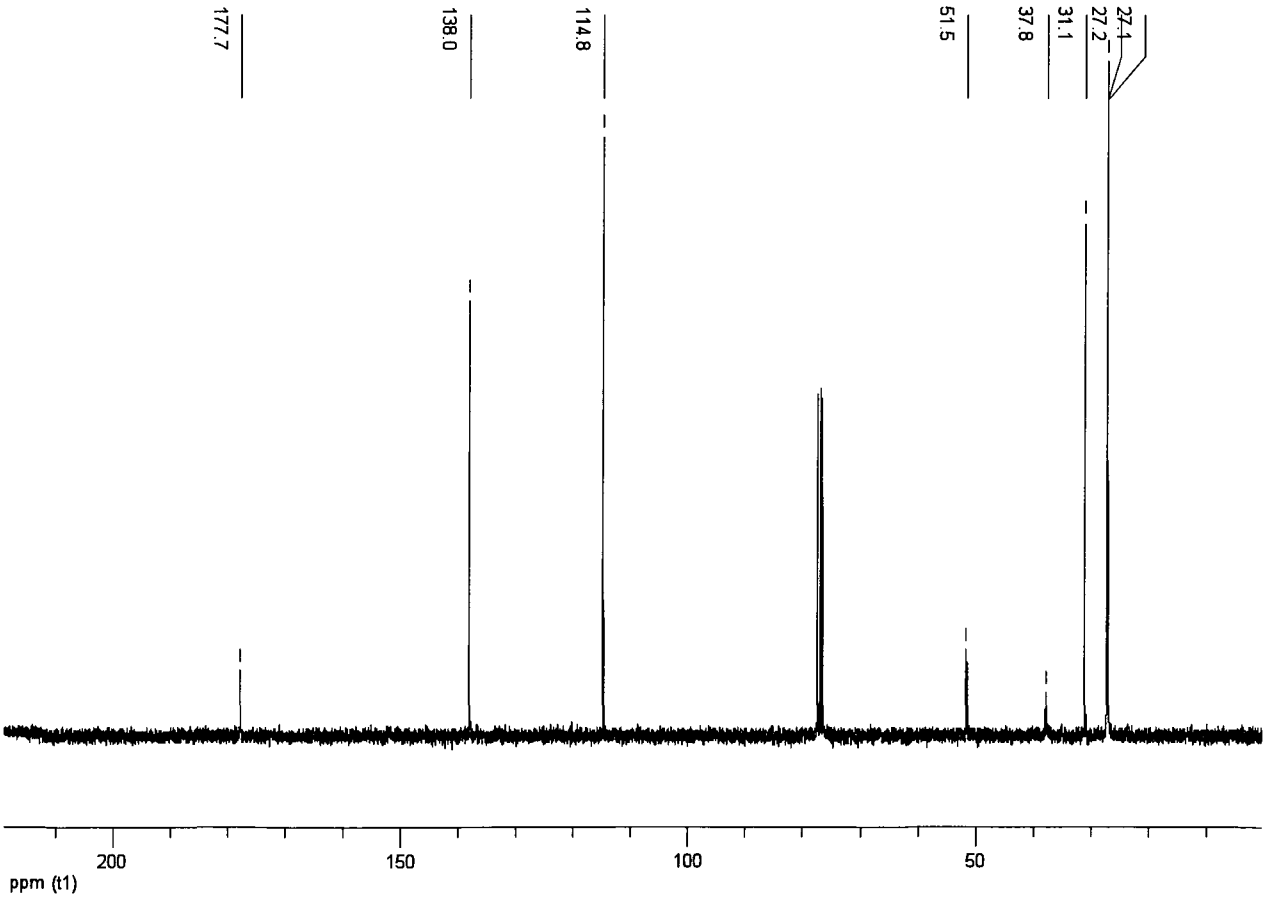
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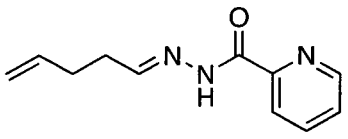

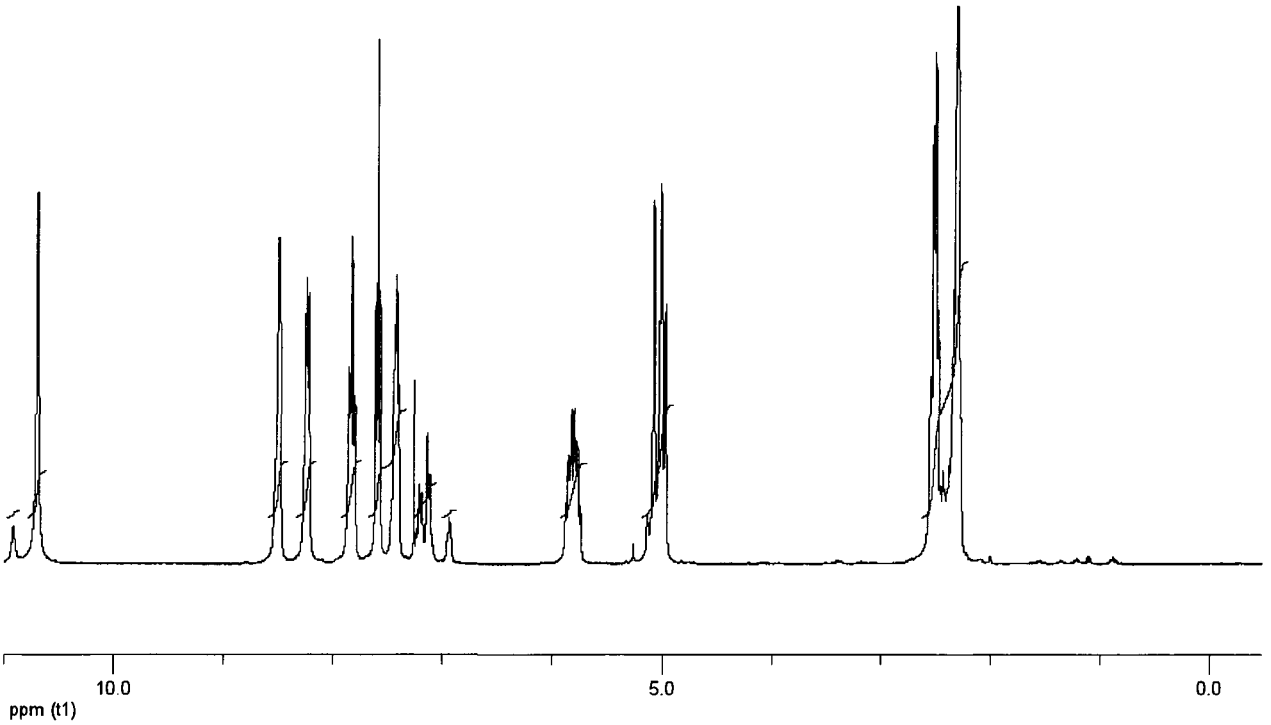

159.9
152.1
150.8
149.1
148.1
147.9
137.5
137.6
136.8
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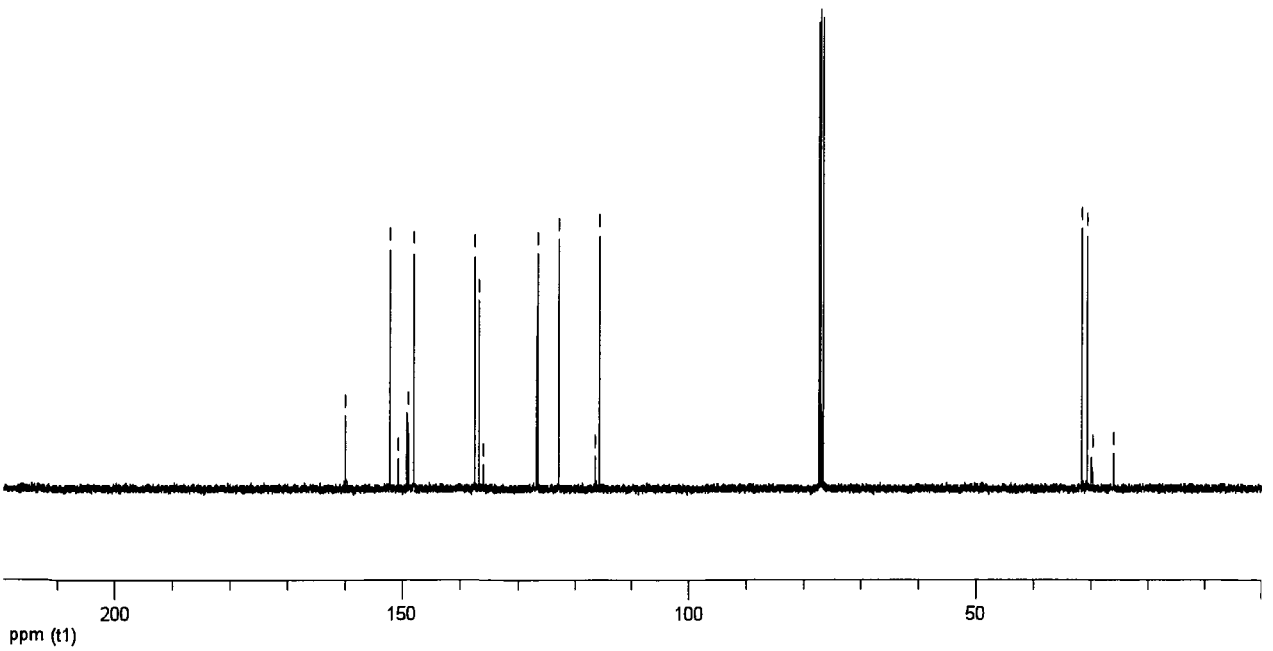
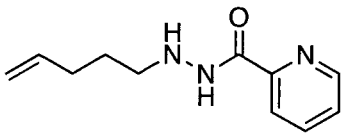
126.7
126.6
122.9
122.9
116.5
115.7
31.5
30.7
29.8
26.0



2.32a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N
N
H
O
N

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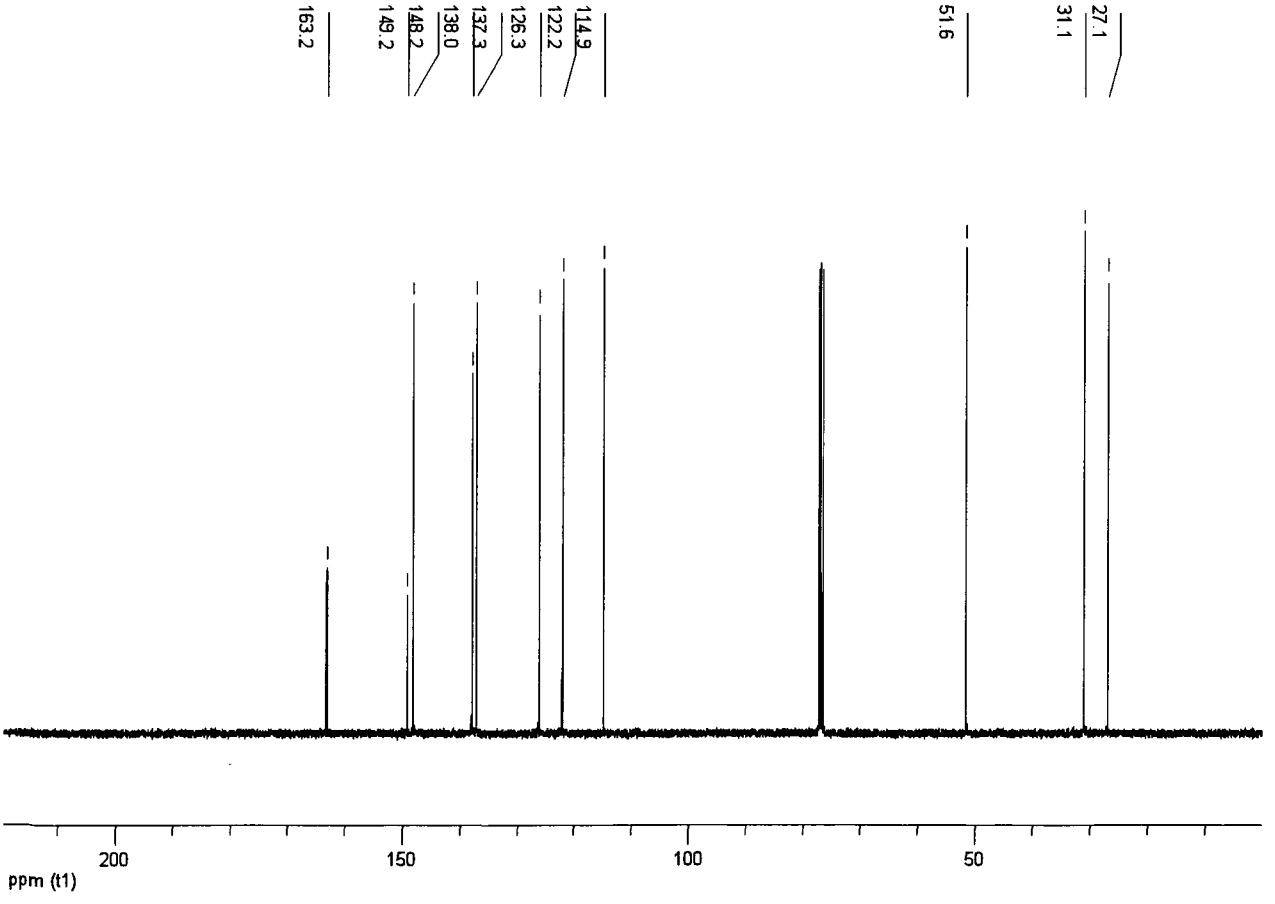
ppm (t1)
5.0
0.0


163.2
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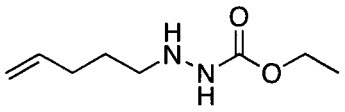
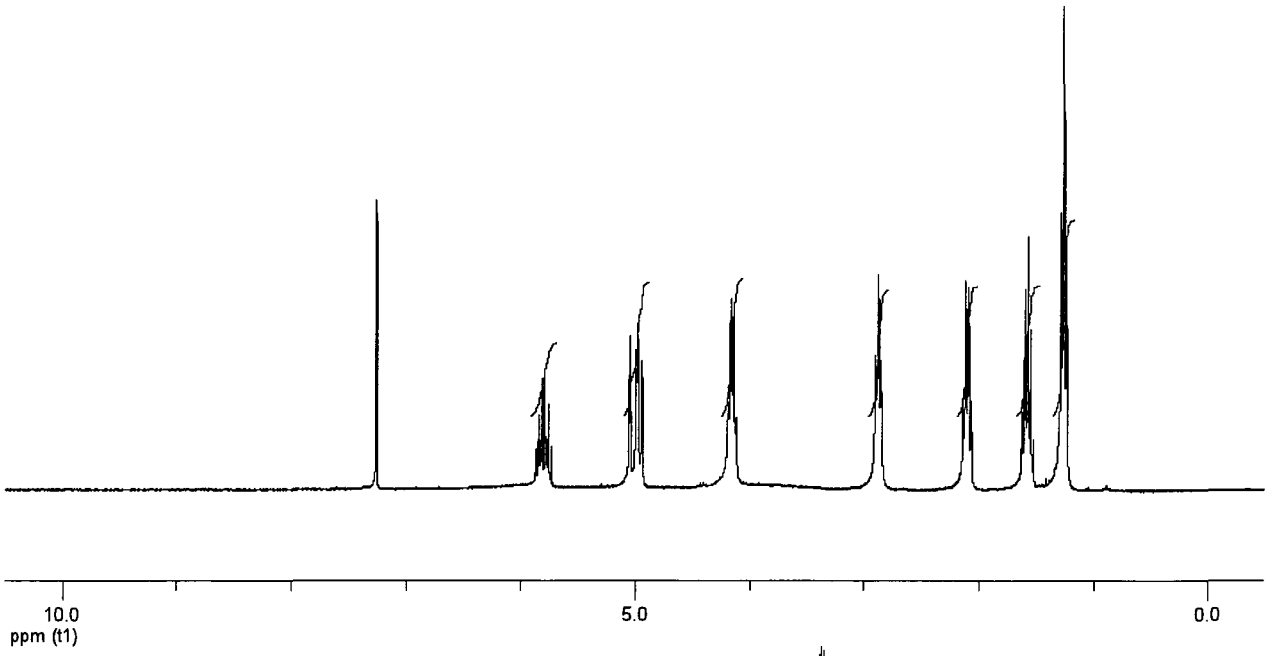
126.3
122.2
114.9
51.6
31.1
27.1
200
ppm (t1)
150
100
50

2.32d

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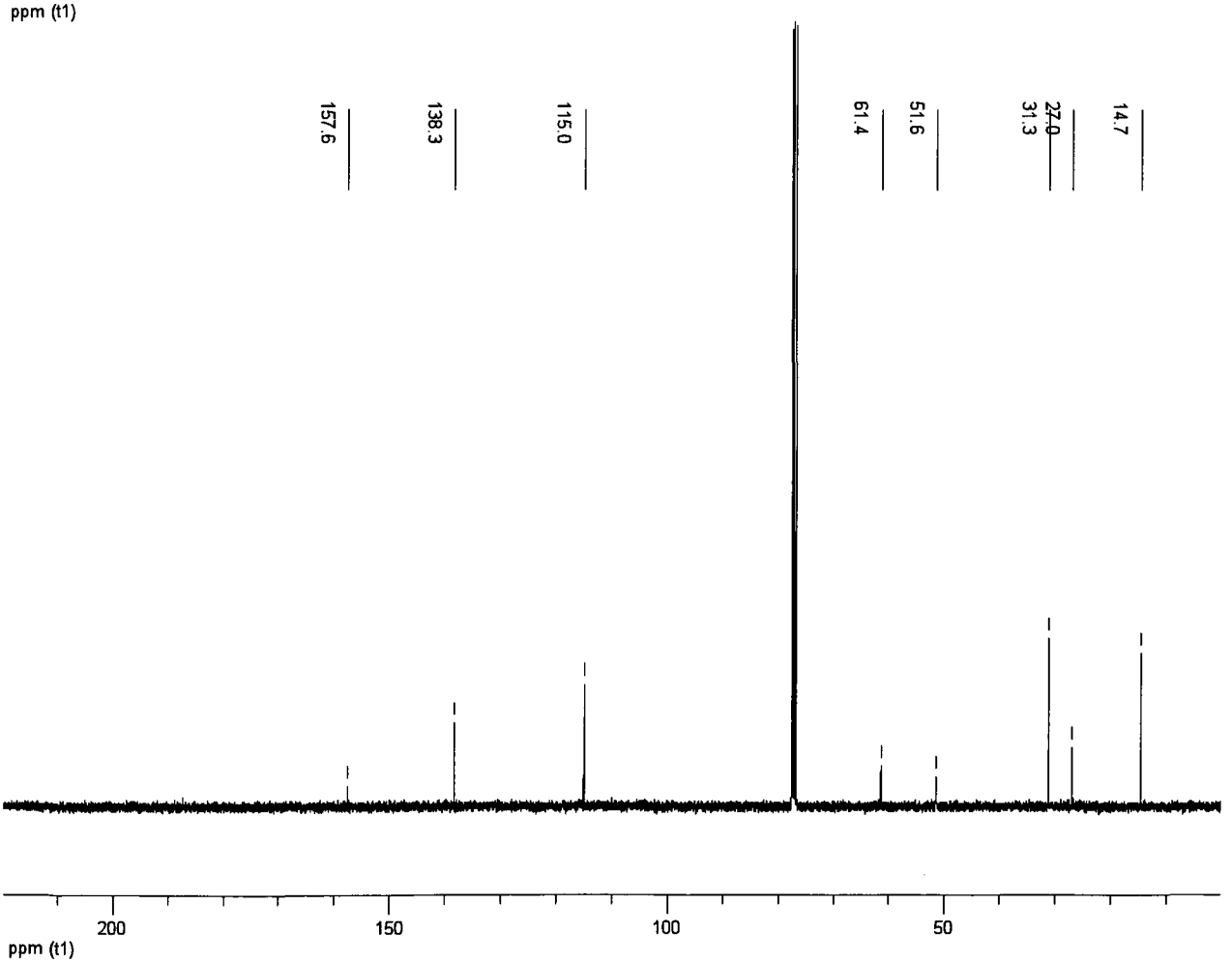
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31.3
27.0
14.7
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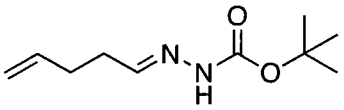
ppm (t1)
150
100
50



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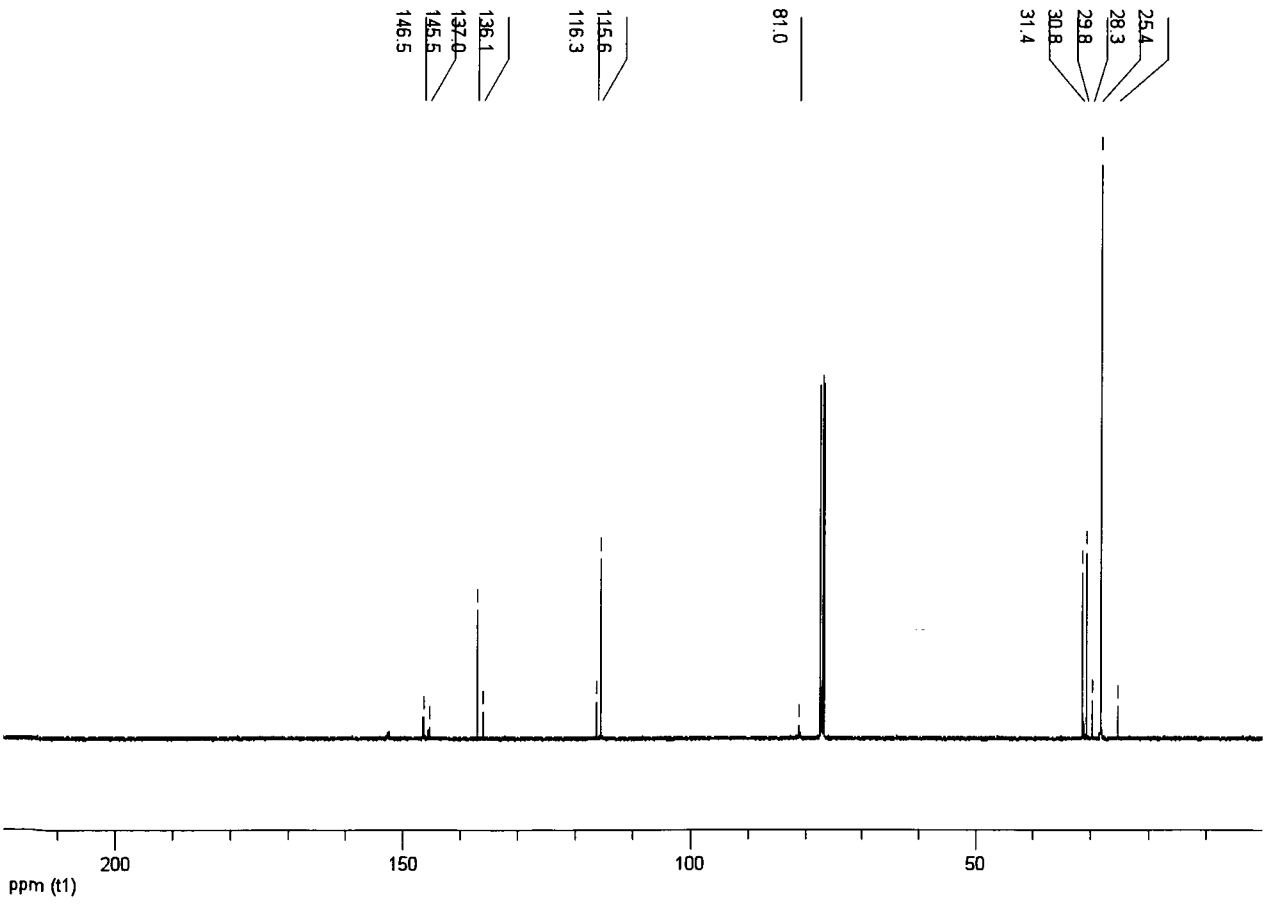
146.5
145.5
137.0
136.1
116.3
115.6
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31.4
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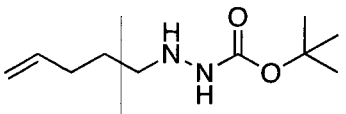
29.8
28.3
25.4
200
ppm (t1)
150
100
50

2.32e



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5.0
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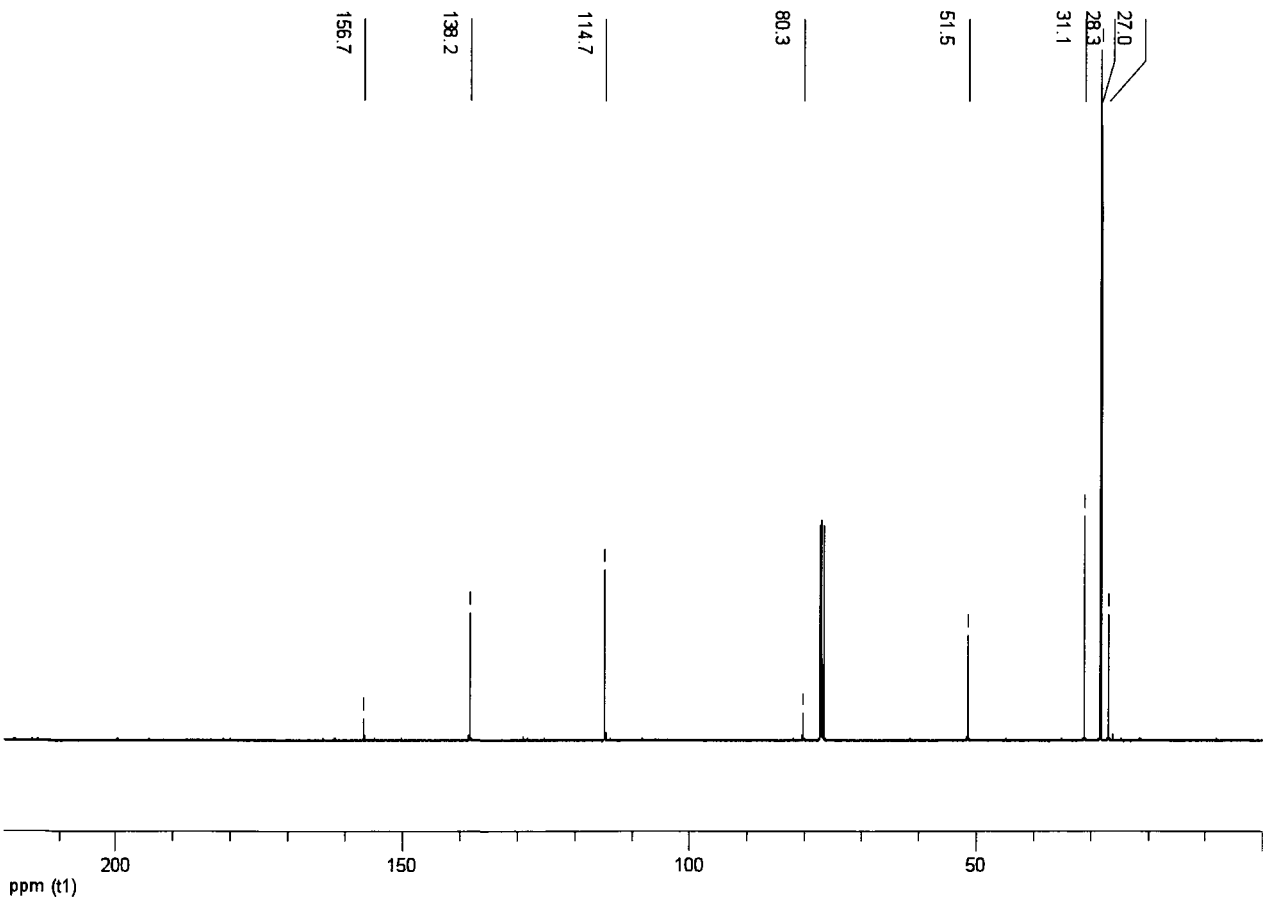
156.7
138.2
114.7
80.3
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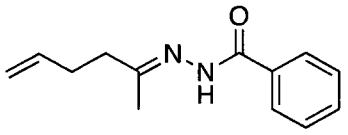
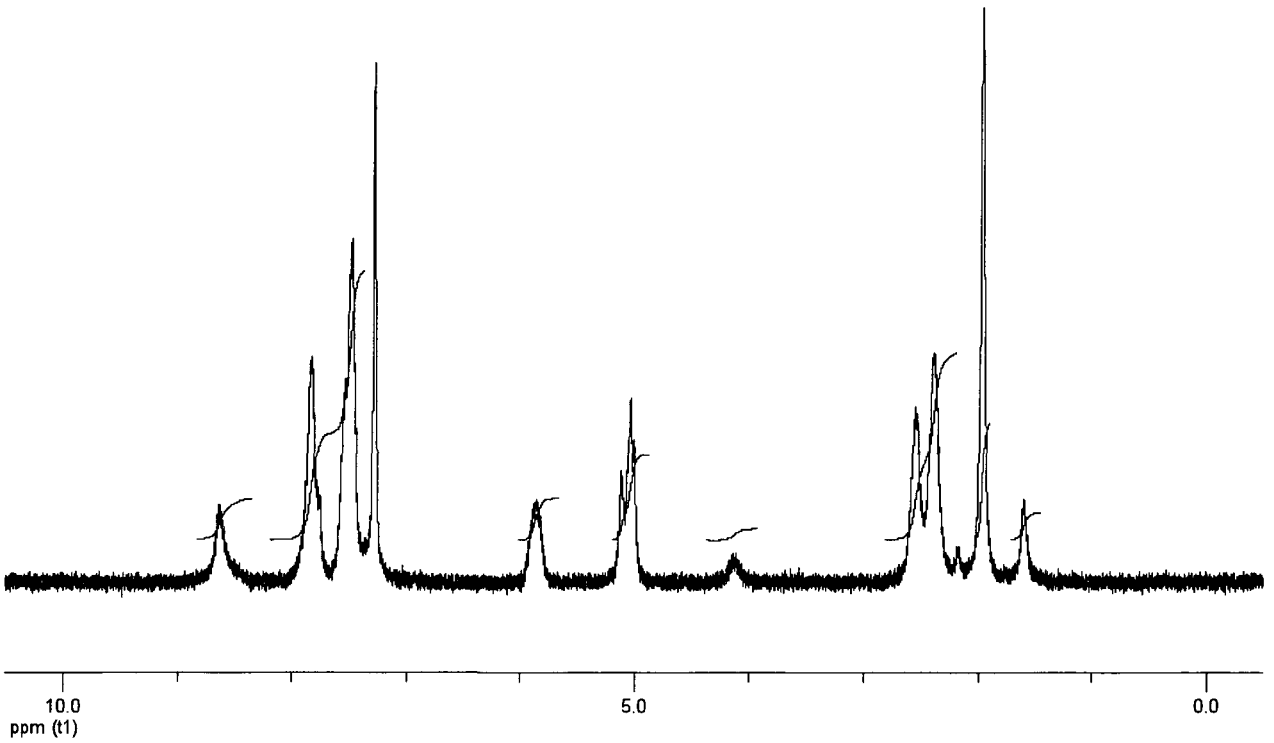
28.3
27.0
200
150
100
50
ppm (t1)

2.42a

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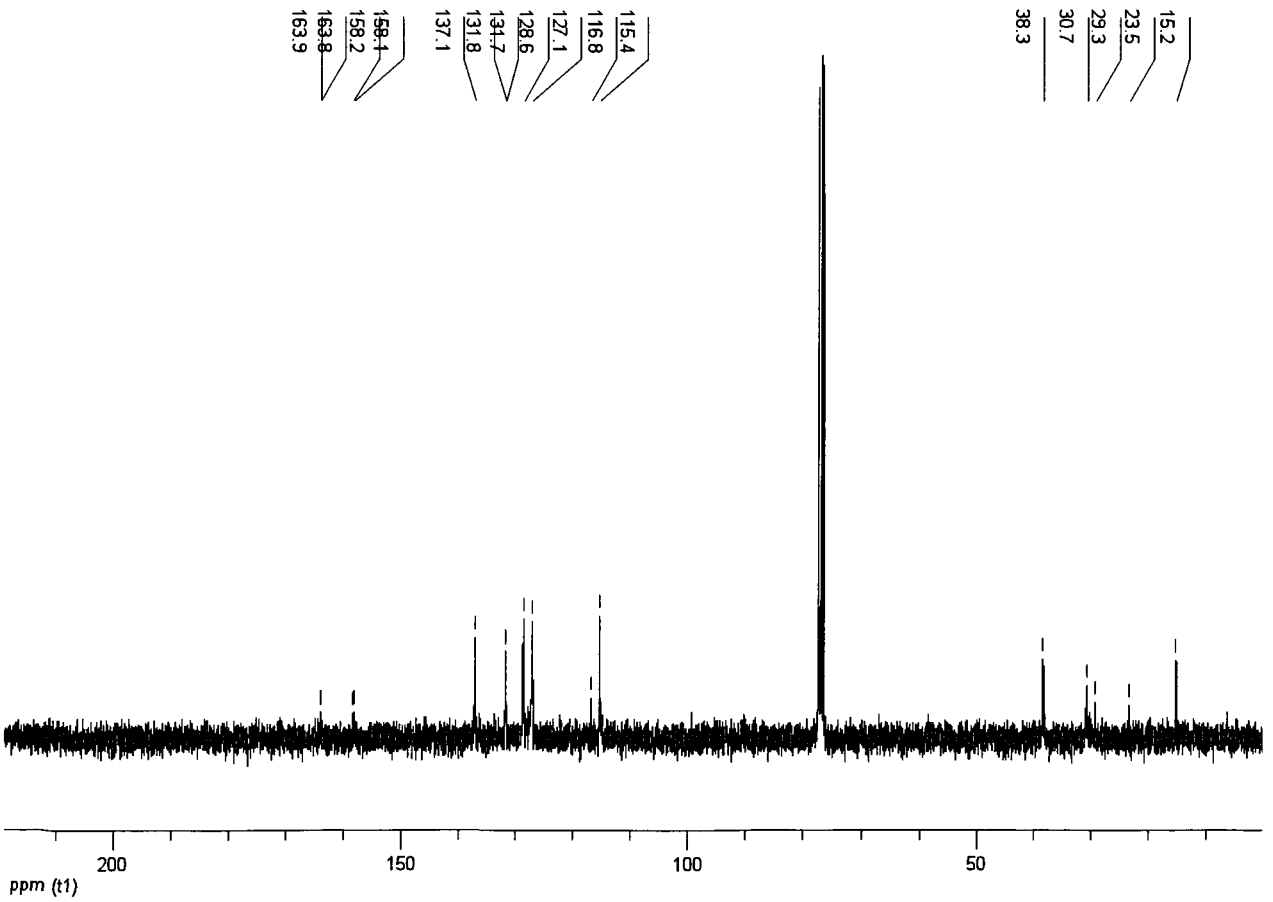
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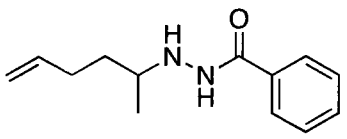
158.1
137.1
131.8
131.7
128.6
127.1
116.8
115.4
38.3
30.7
29.3
23.5
15.2
200
150
100
50
ppm (t1)

2.43a



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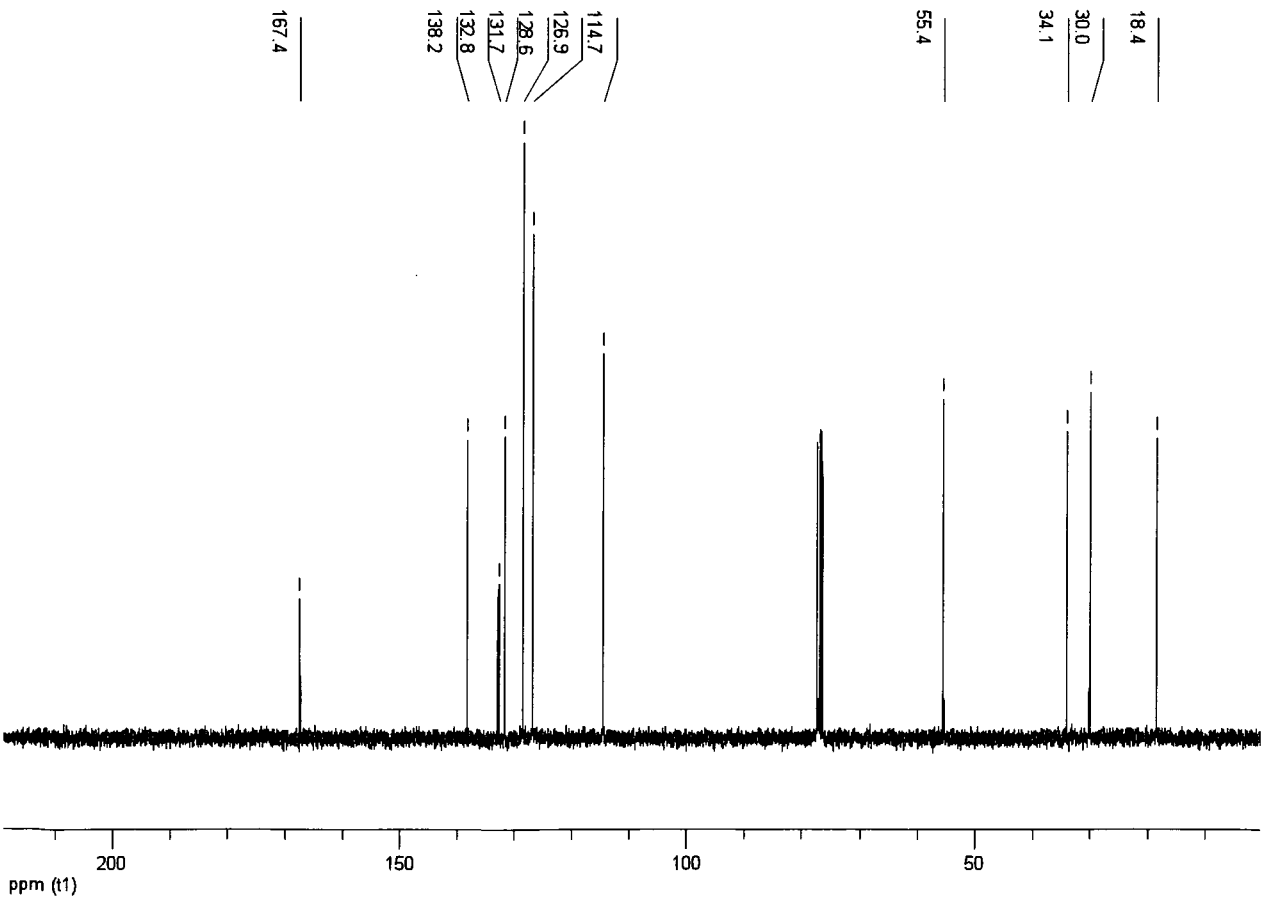
0.0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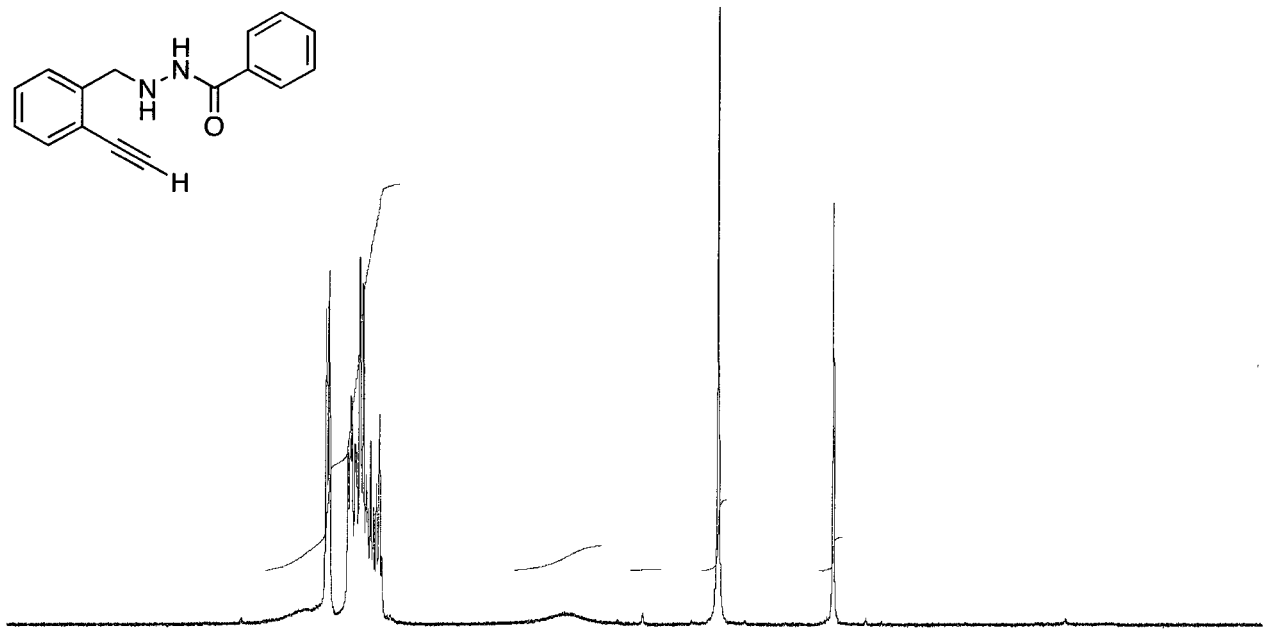
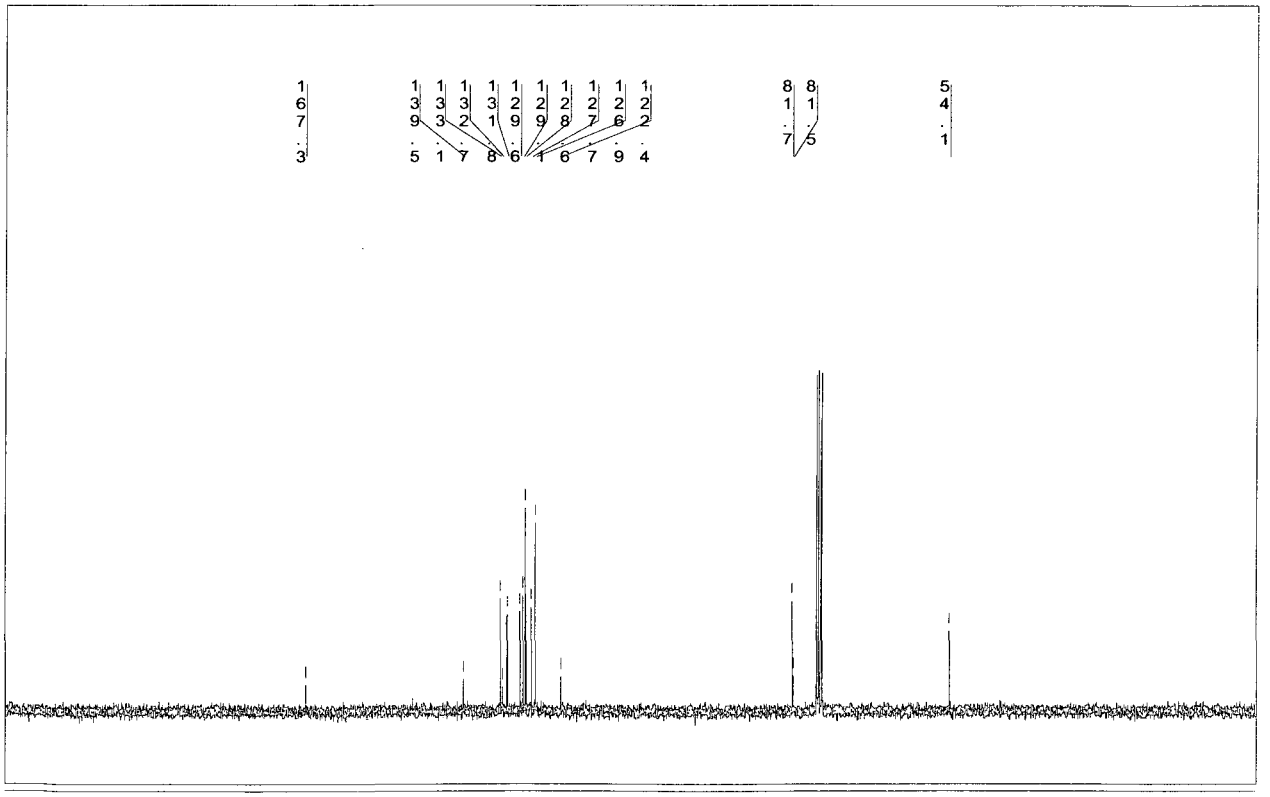
126.9
114.7
55.4
34.1
30.0
18.4
200
150
100
50
ppm (t1)

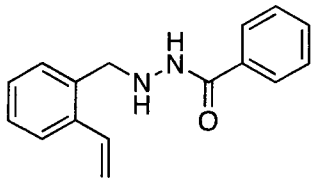


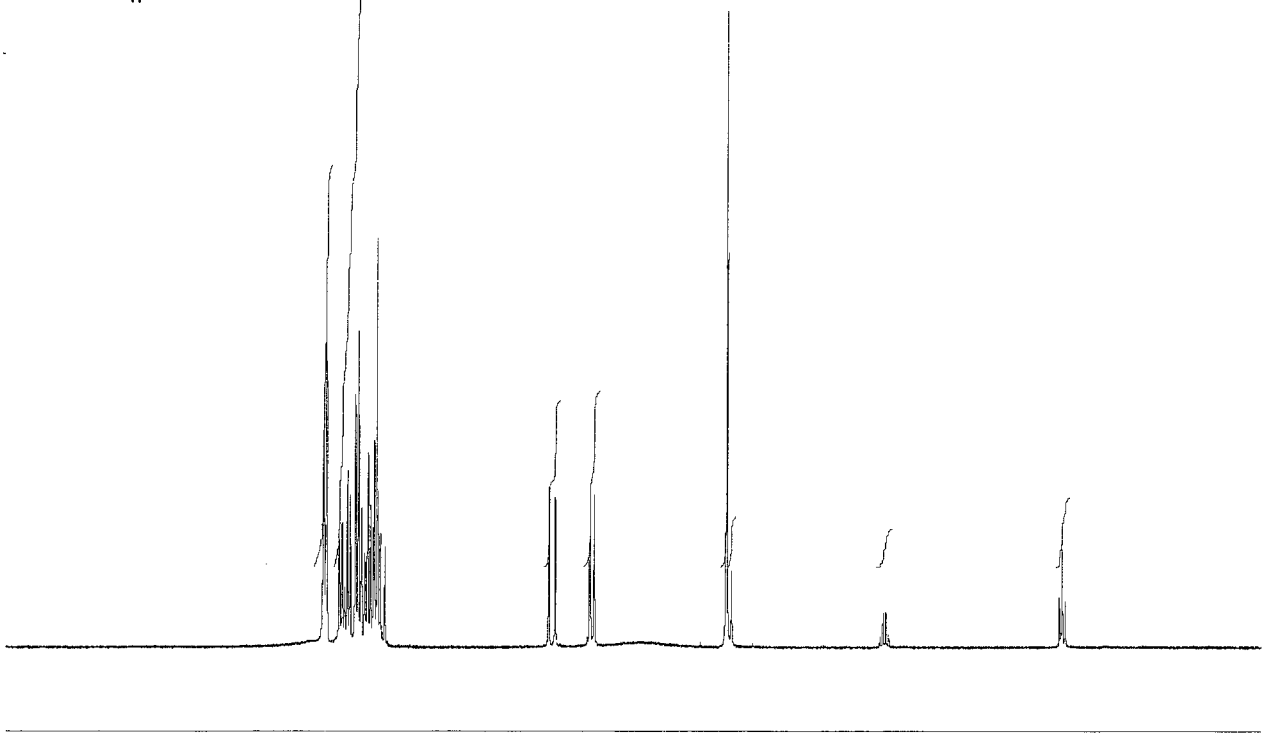
ppm (t1)



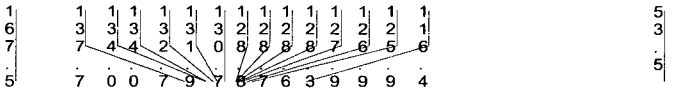
ppm (t1)

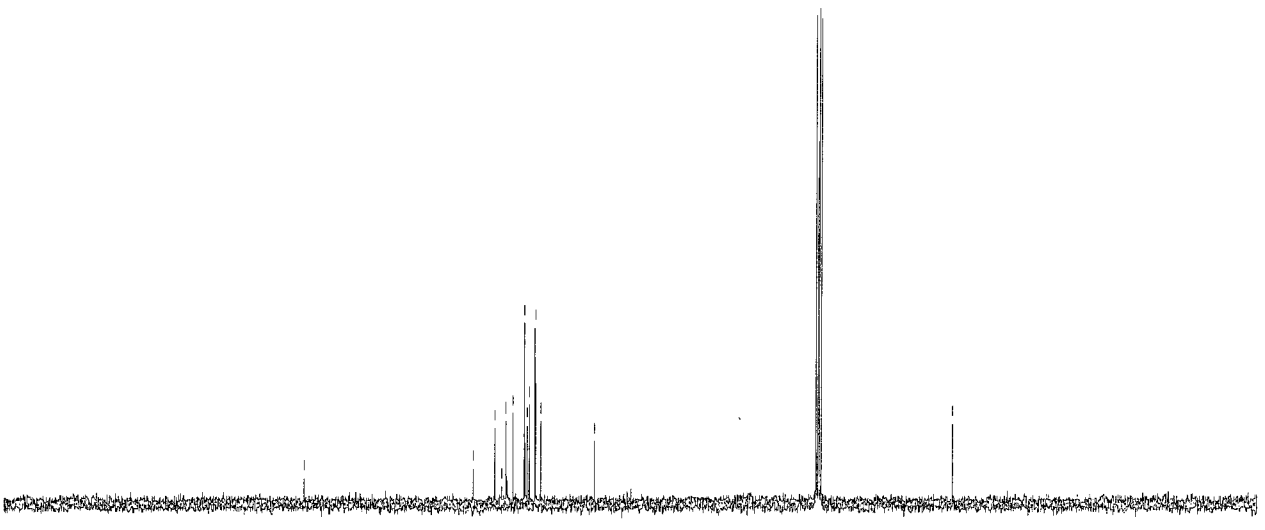
2.72





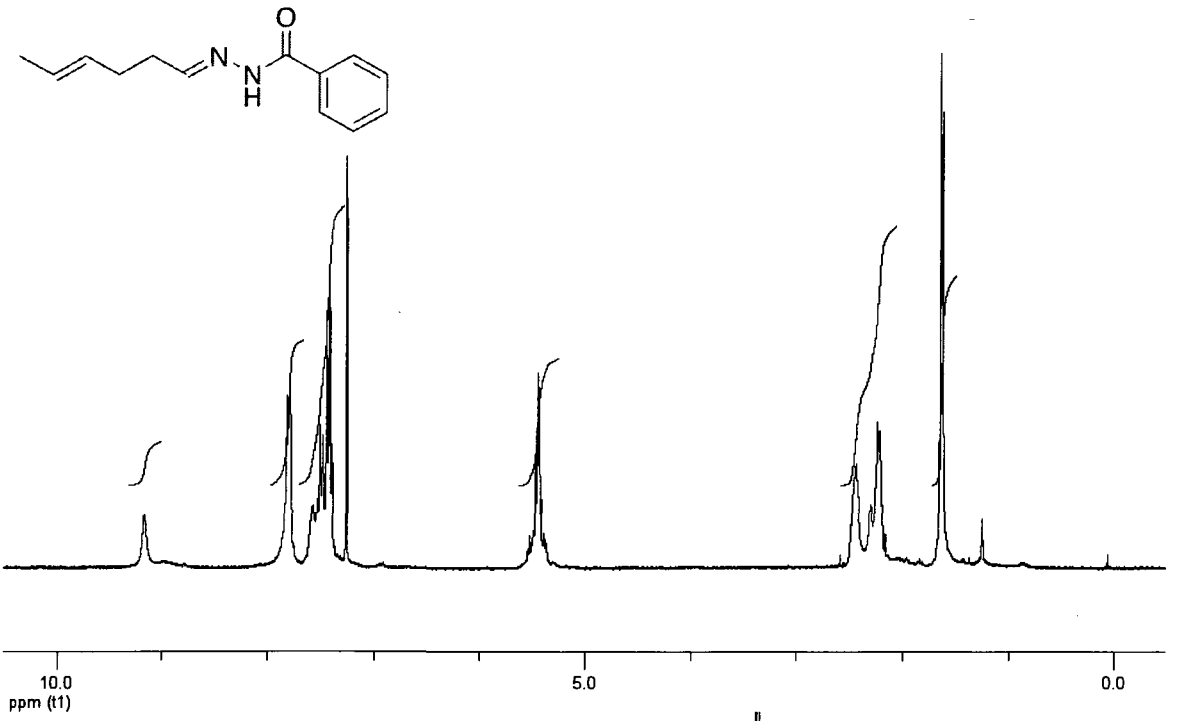
ppm (t1)





ppm (t1)

2.42b


O
N
N
H

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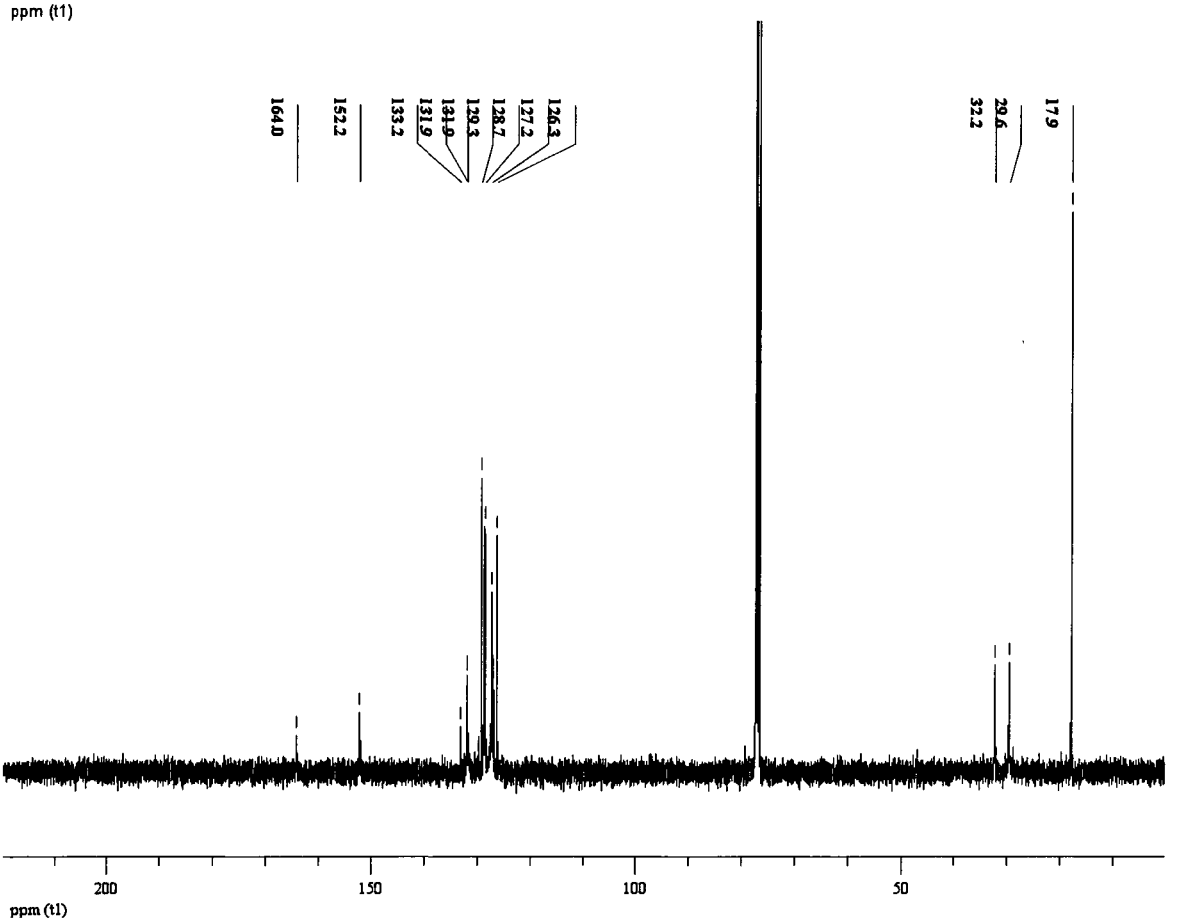
0.0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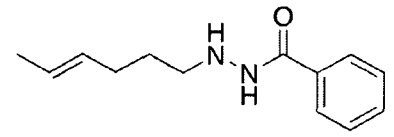
131.9
131.9
129.3
128.7
127.2
126.1
32.2
29.6
17.9
200
150
100
50
ppm (t1)

2.43b



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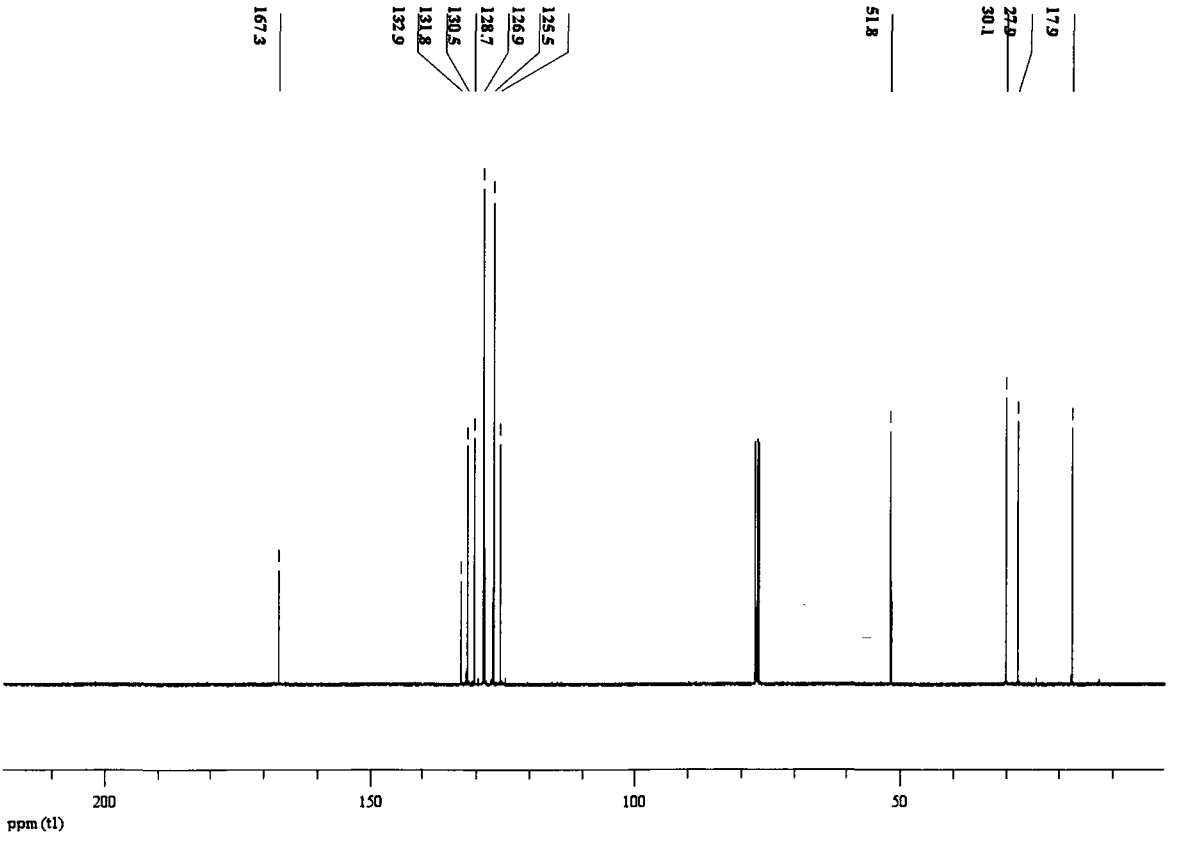
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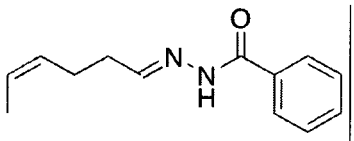
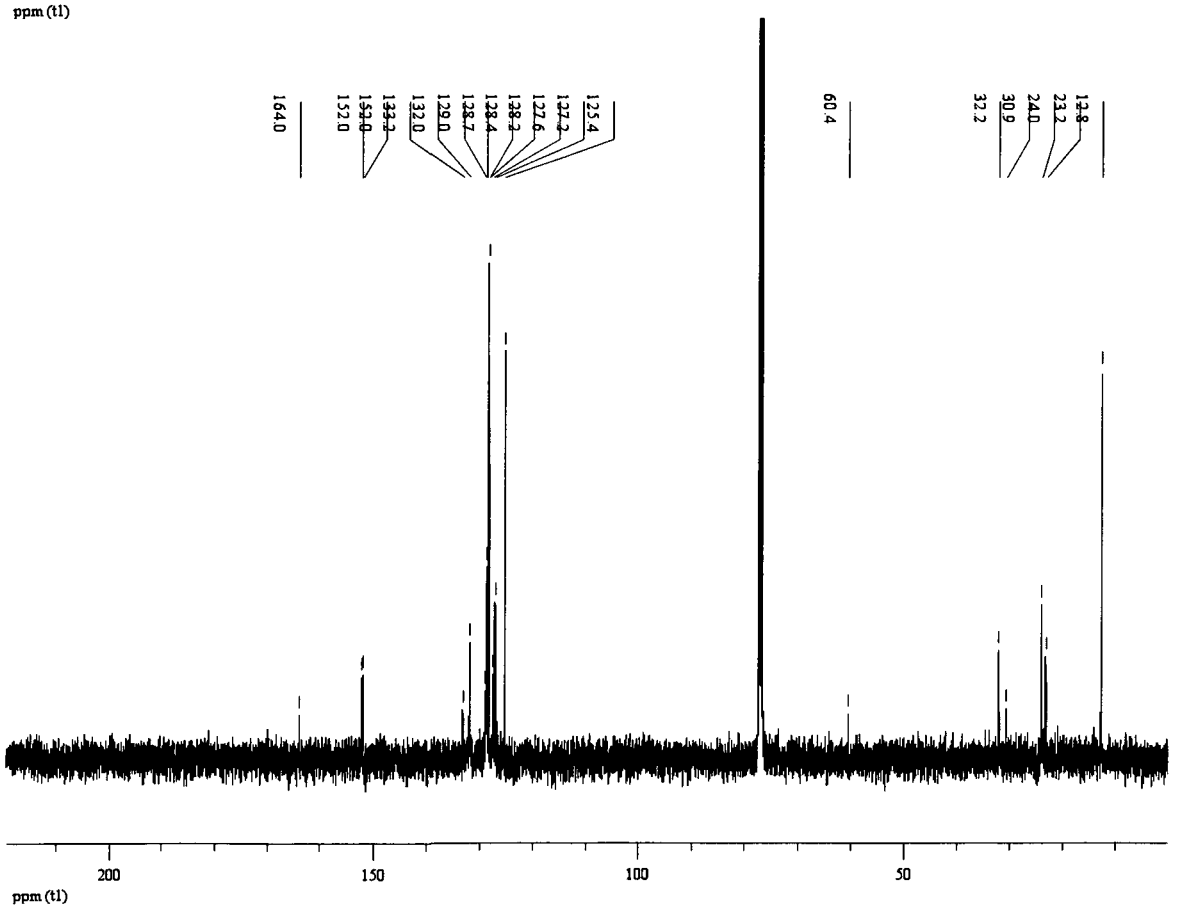
131.8
130.5
128.7
126.9
125.5
51.8
30.1
27.9
17.9
200
150
100
50
ppm (t1)

2.42c


O
N
N
H

10.0
5.0
0.0
ppm (t1)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129.0
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128.4
128.2
127.6
127.2
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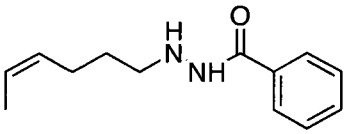
32.2
30.9
24.0
23.2
13.8
200
150
100
50
ppm (t1)

2.43c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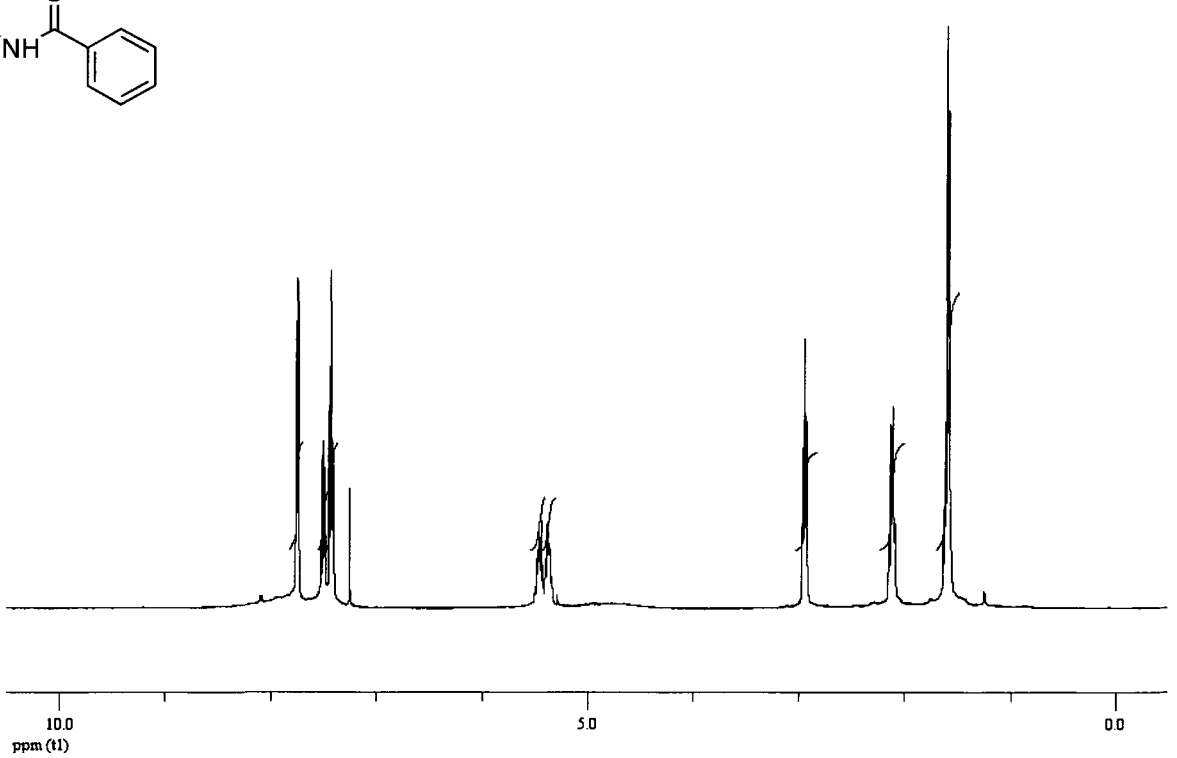
NH
O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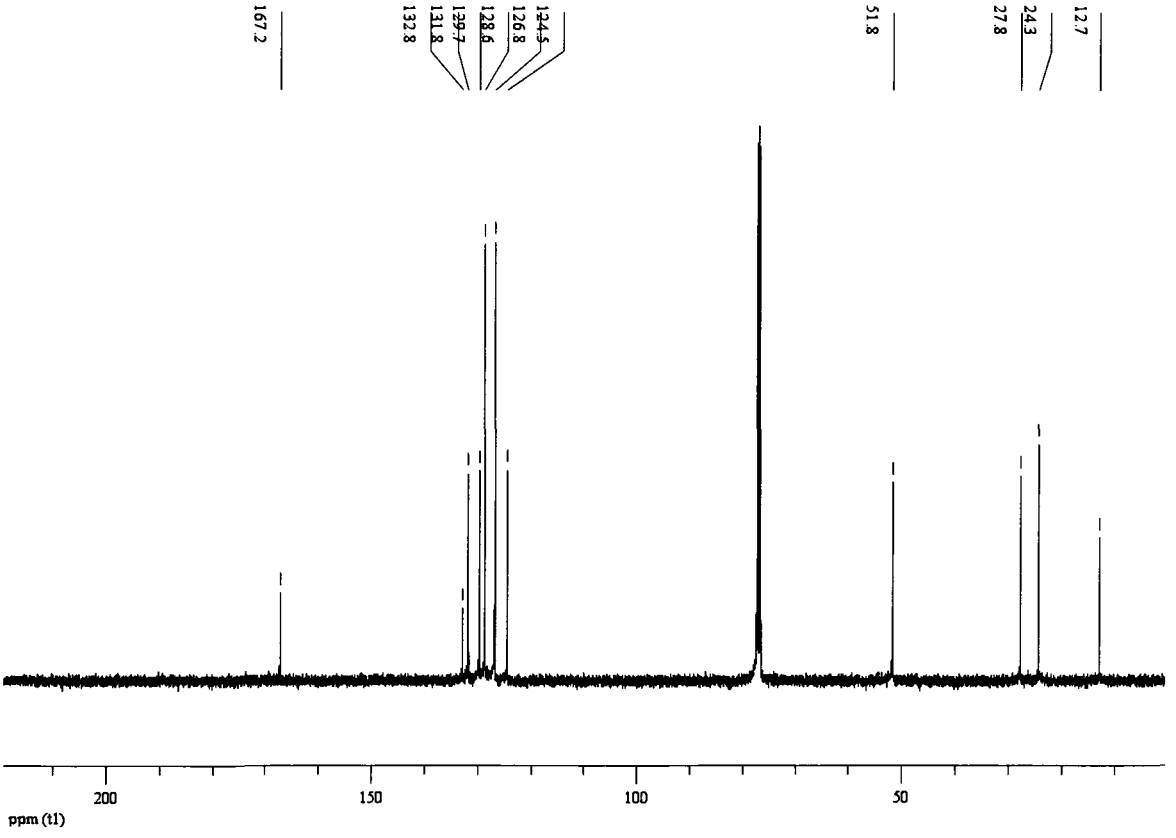
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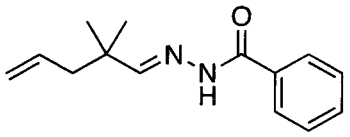
129.7
128.6
126.8
124.5
51.8
27.8
24.3
12.7
200
150
100
50
ppm (t1)

2.42d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N
H

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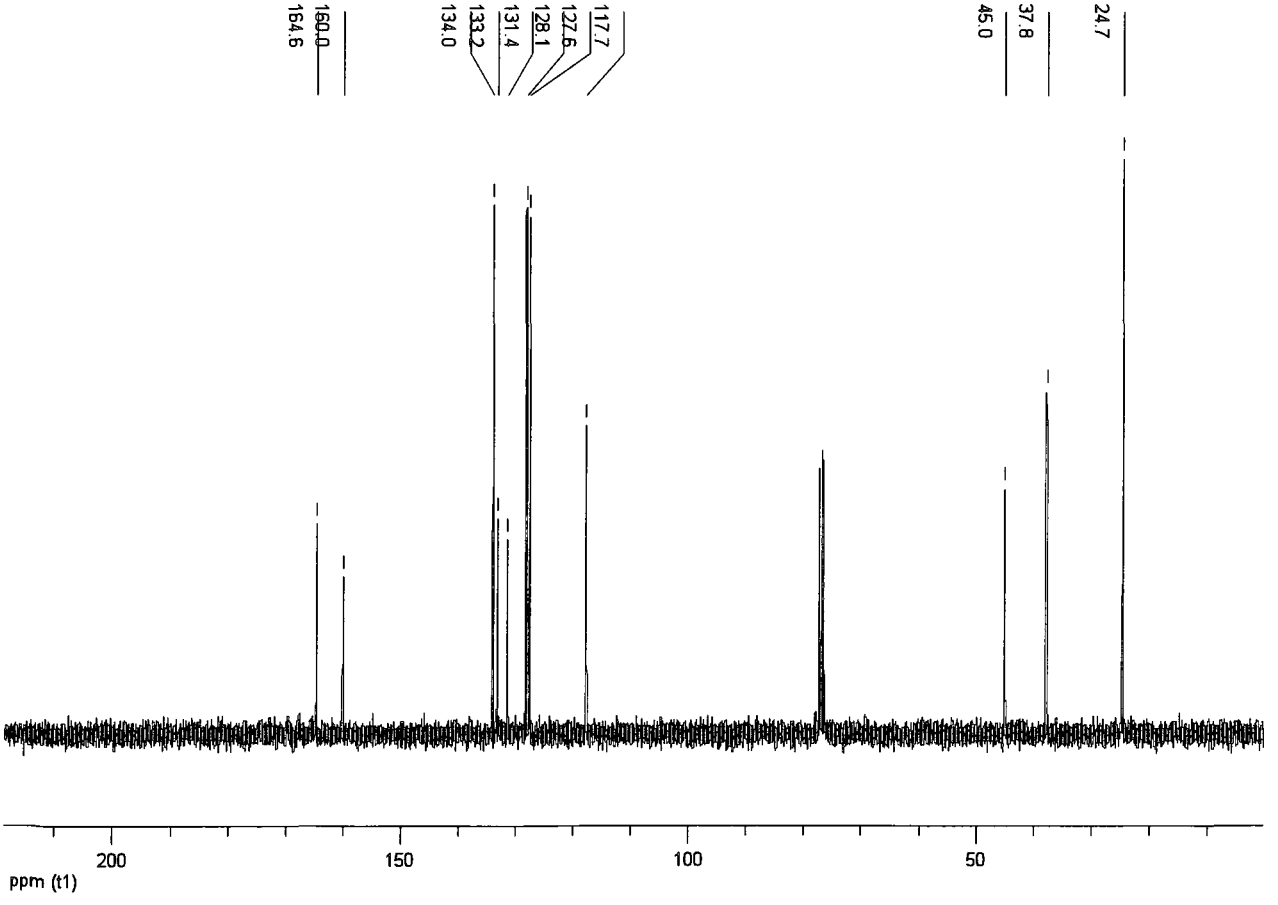
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127.6
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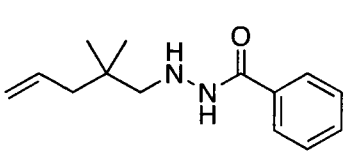
37.8
24.7
200
ppm (t1)
150
100
50

2.43d



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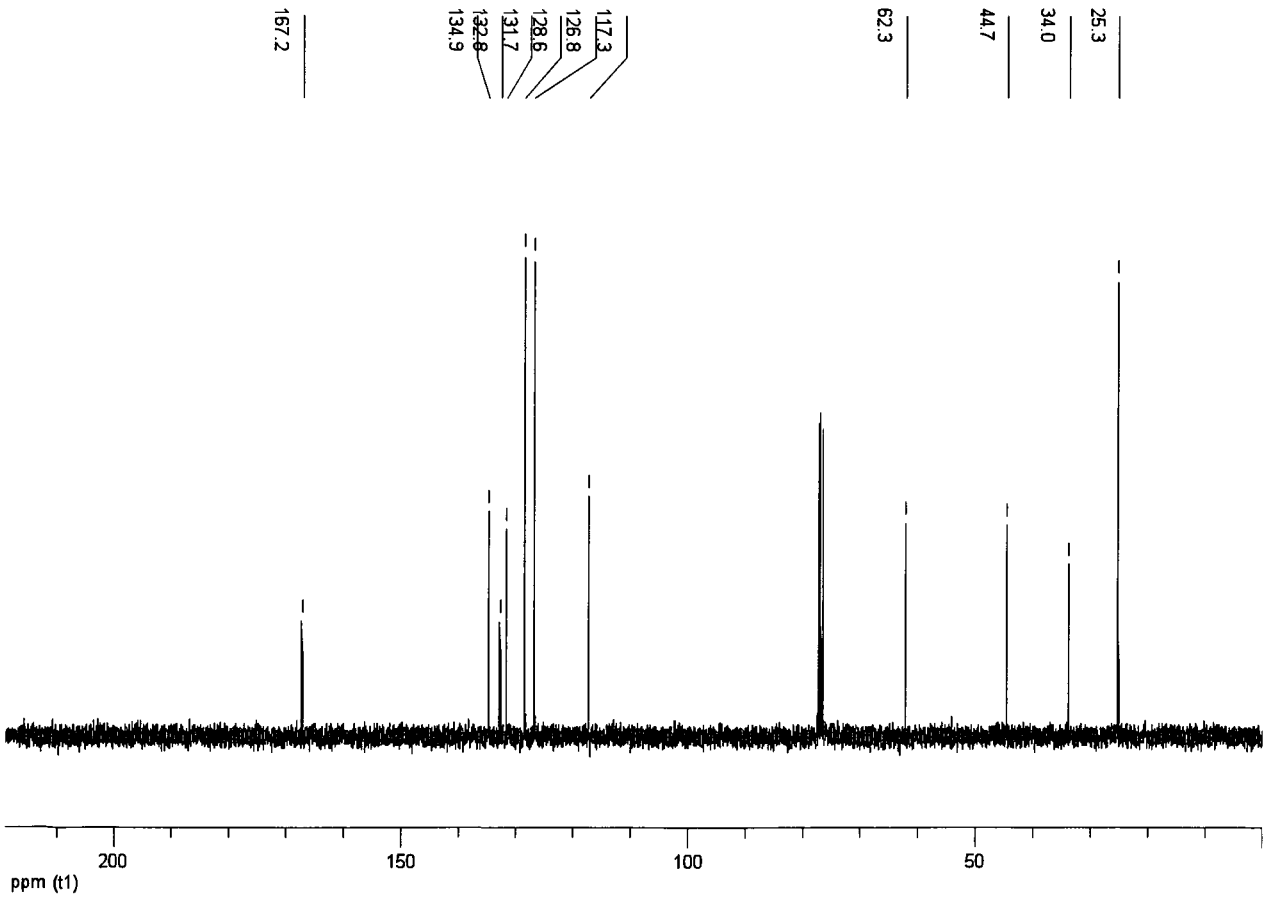
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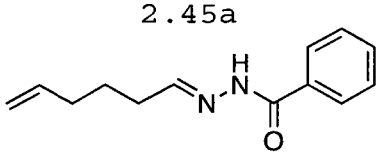
132.8
131.7
128.6
126.8
117.3
62.3
44.7
34.0
25.3
200
ppm (t1)
150
100
50

2.45a



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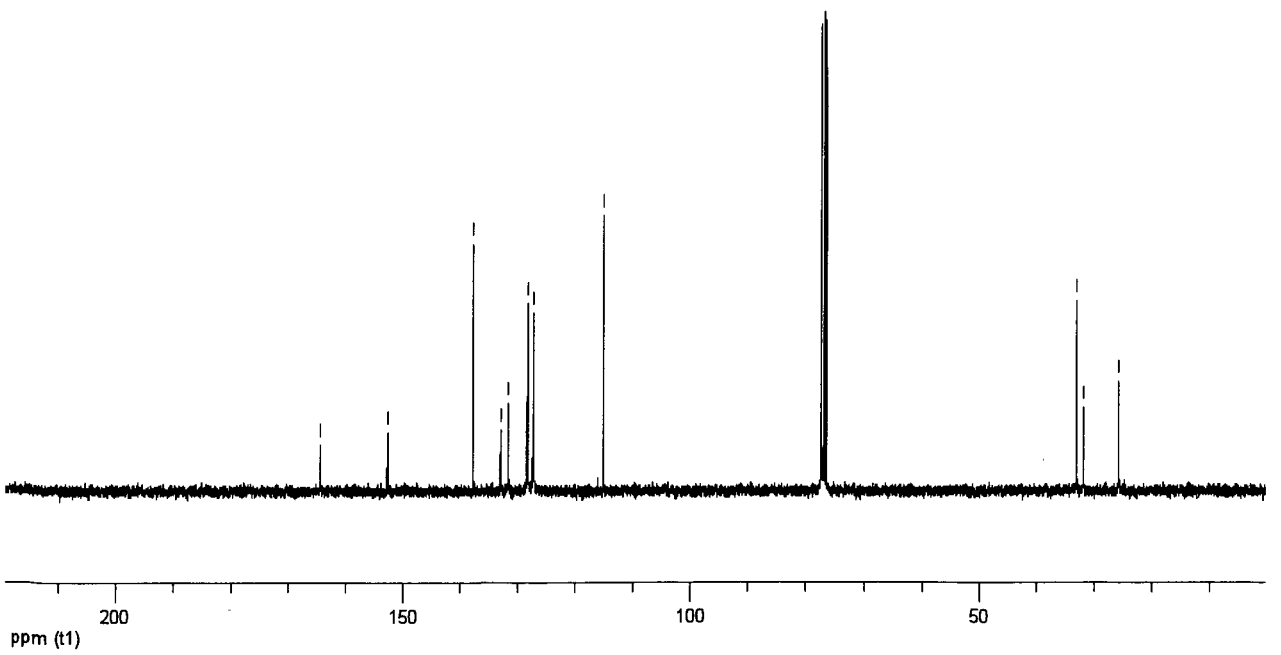
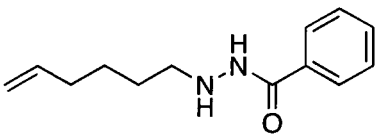
128.4
127.4
115.1
33.1
31.9
25.8



2.46a



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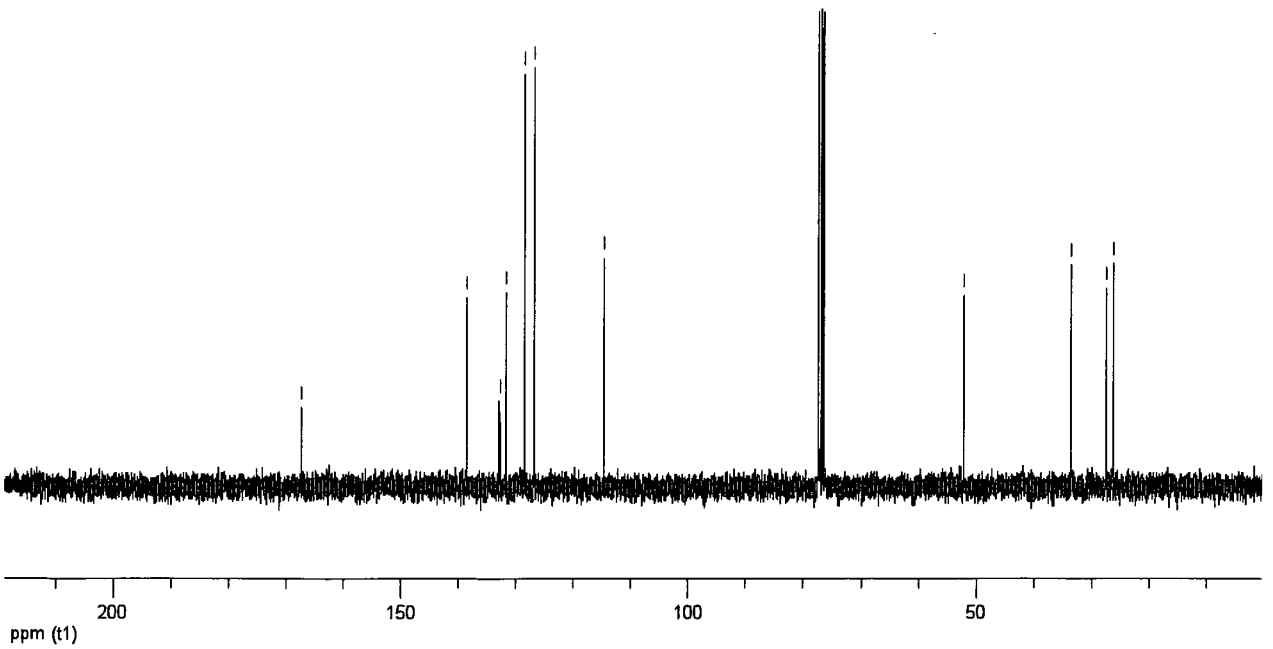
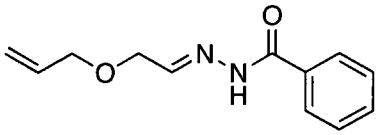
131.8
128.6
126.8
114.6
52.1
33.5
27.4
26.3



2.54b



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ppm (t1)
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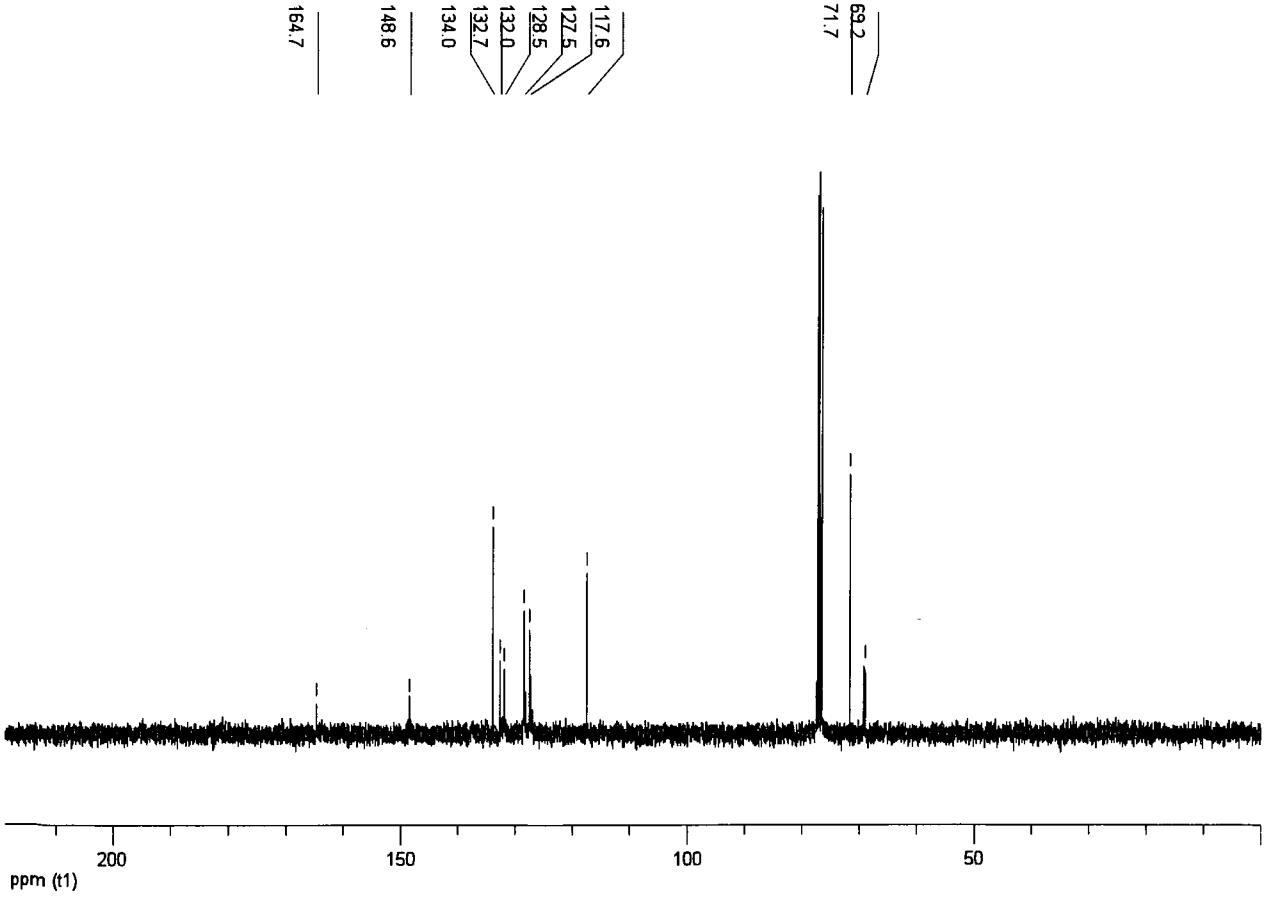
0.0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132.7
132.0
128.5
127.5
117.6
71.7
69.2
200
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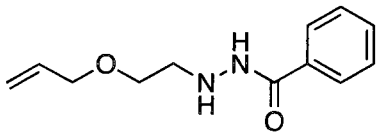
100
50
ppm (t1)

2.46b



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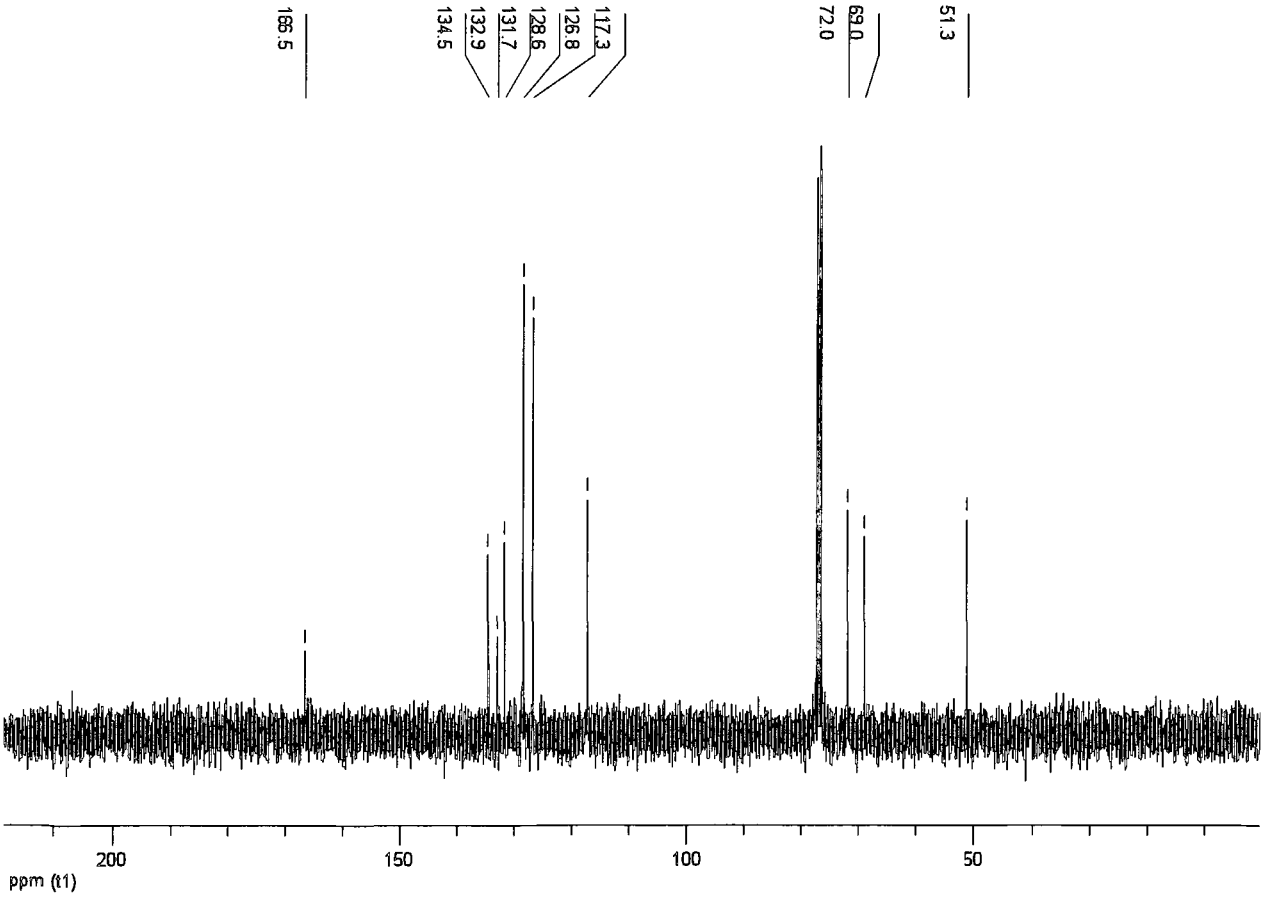
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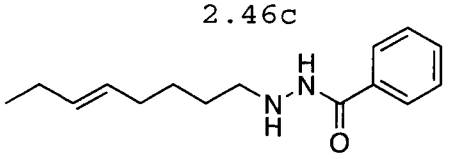
134.5
132.9
131.7
128.6
126.8
117.3
72.0
69.0
51.3
200
ppm (t1)
150
100
50

2.46c



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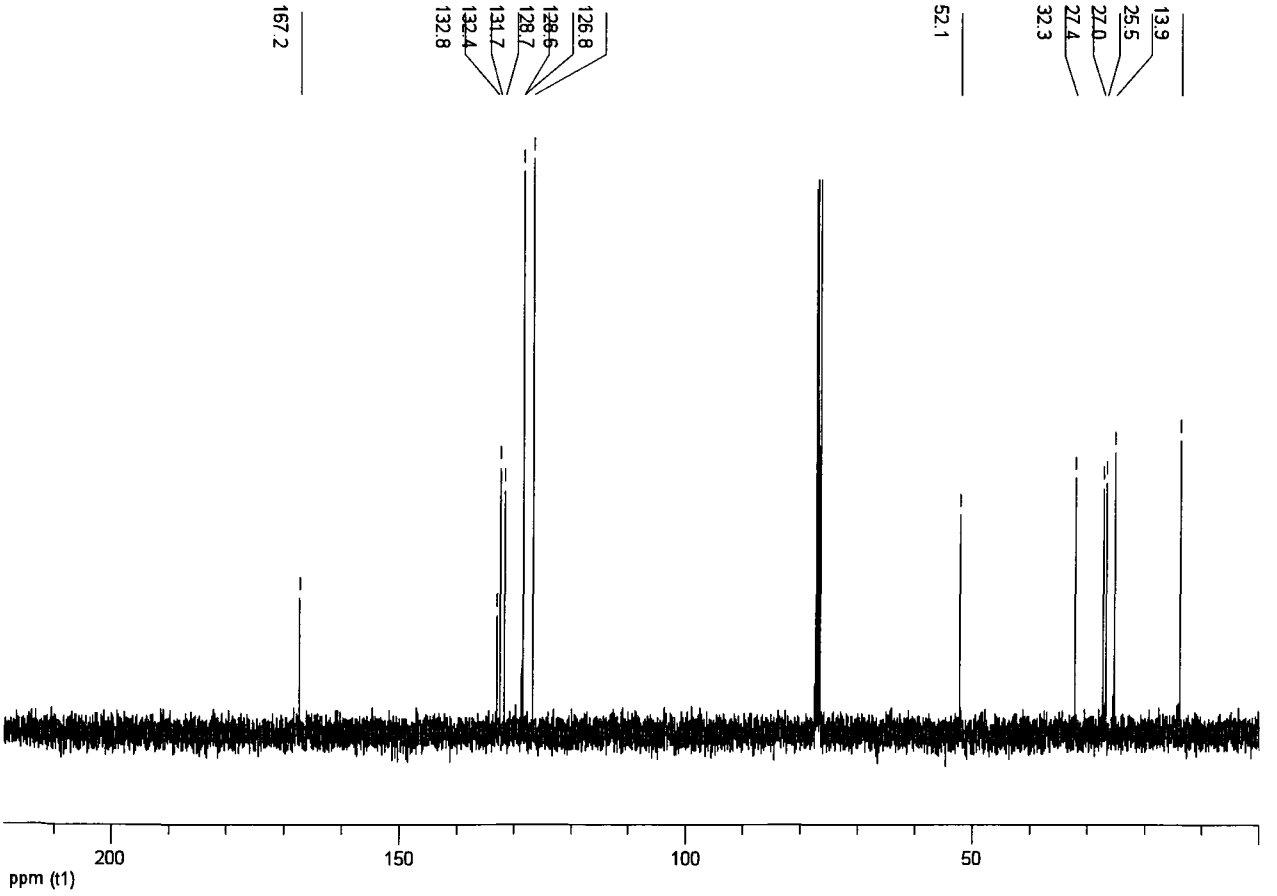
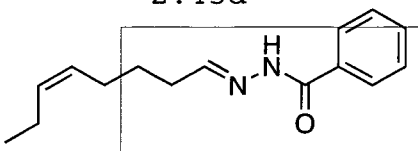
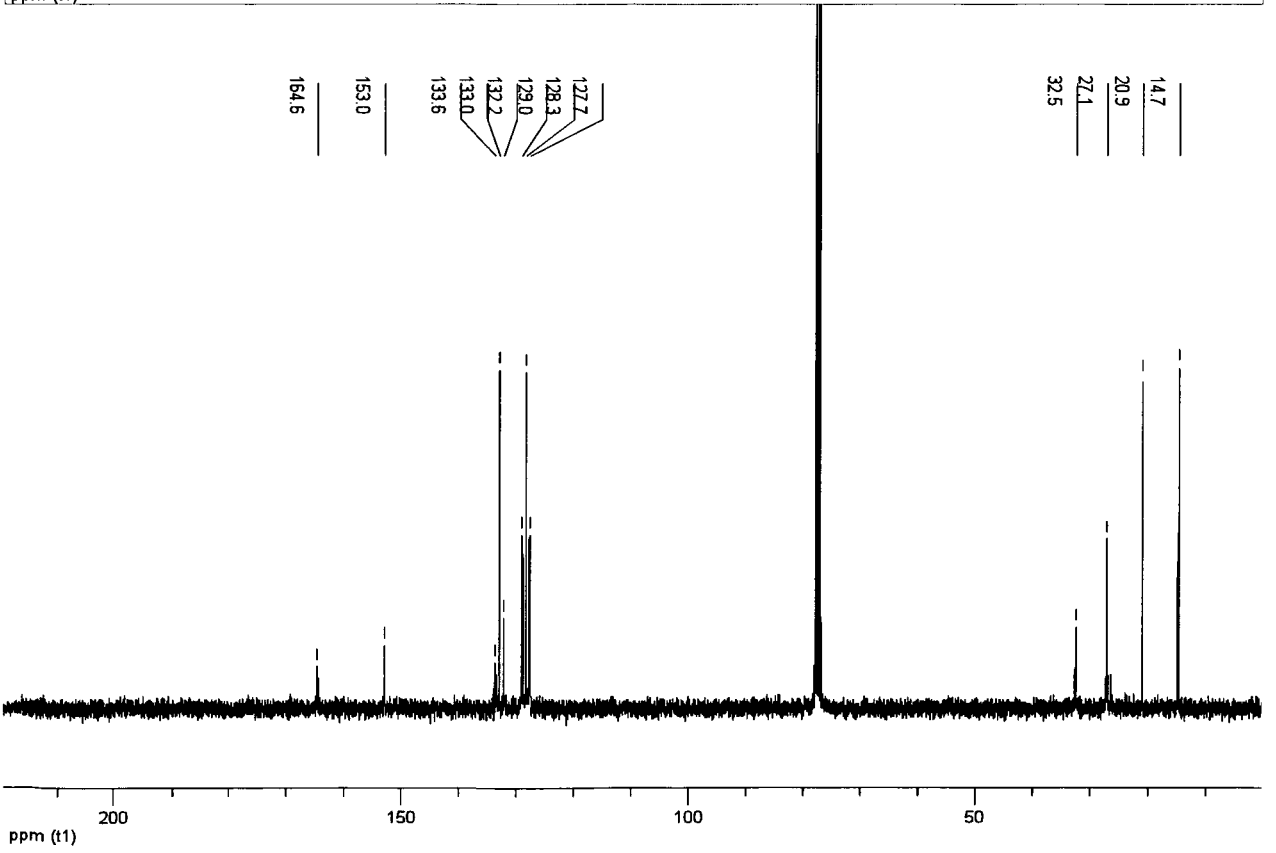

167.2
132.8
132.4
131.7
128.7
128.6
126.8
52.1
32.3
27.4
27.0
25.5
13.9
200
150
100
50
ppm (t1)

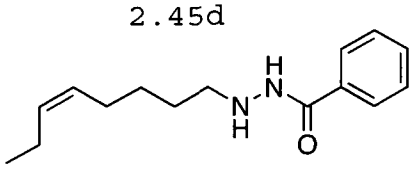
2.45d



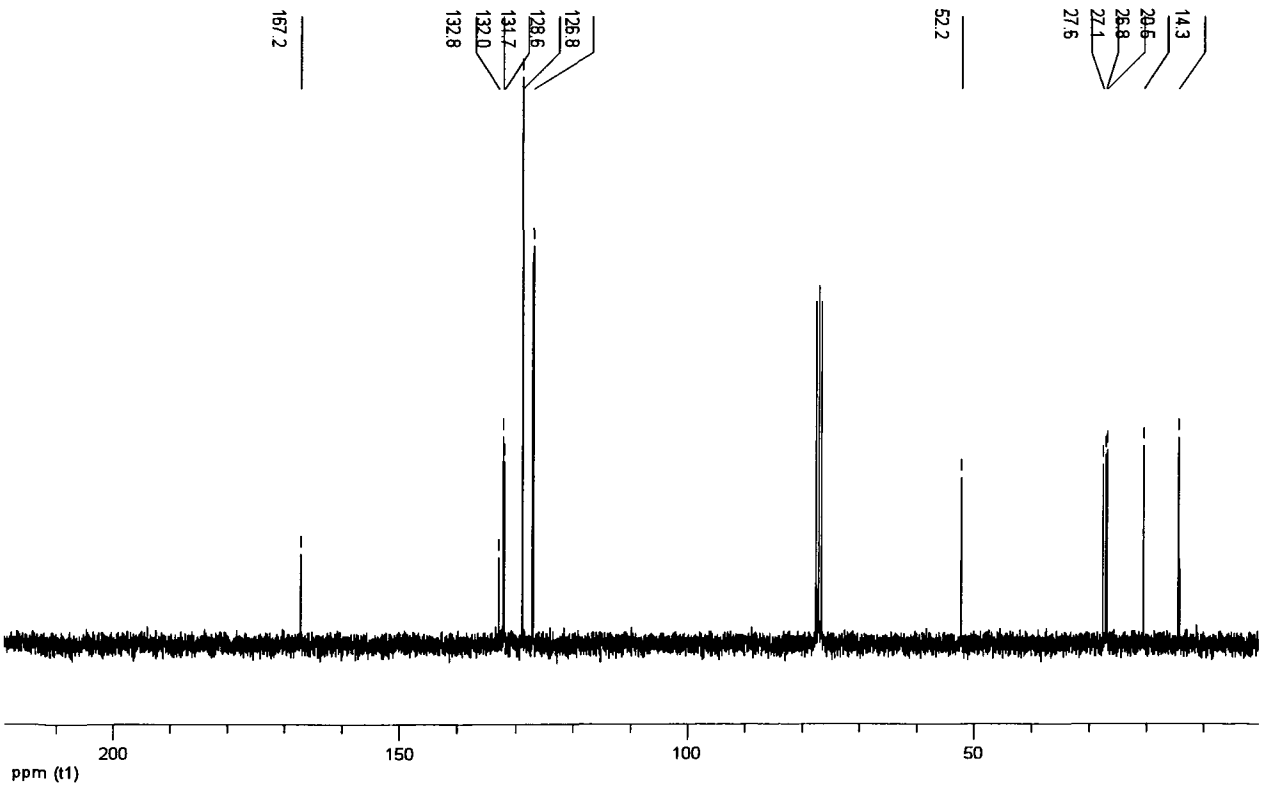
10.0
ppm (t1)
5.0
0.0


164.6
153.0
133.6
133.0
132.2
129.0
128.3
127.7
32.5
27.1
20.9
14.7
200
150
100
50
ppm (t1)

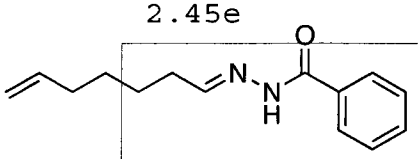
2.45d



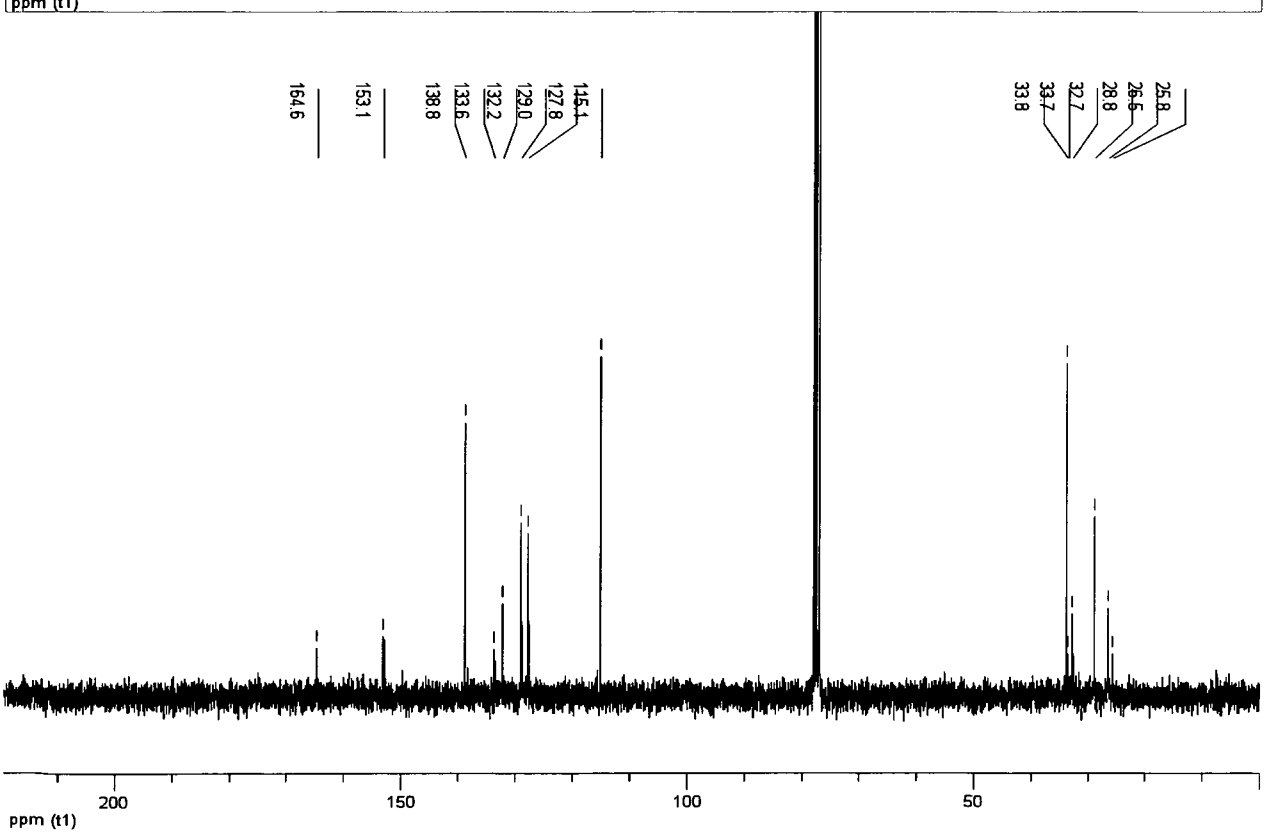
10.0
5.0
0.0
ppm (t1)


167.2
132.8
132.0
131.7
128.6
126.8
52.2
27.6
27.1
26.8
20.6
14.3
200
150
100
50
ppm (t1)

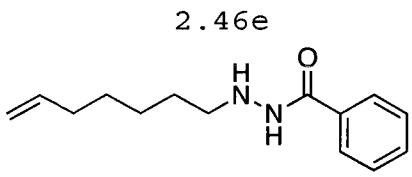
2.45e



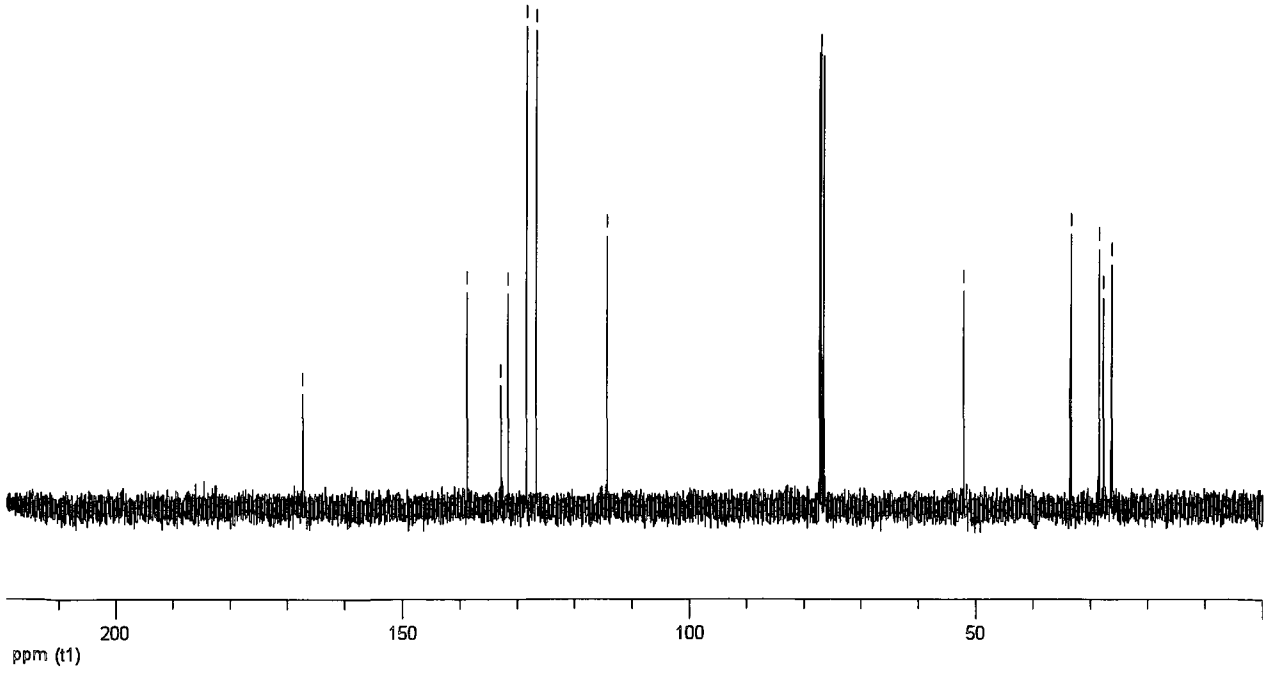
10.0
5.0
0.0
ppm (t1)


164.6
153.1
138.8
133.6
132.2
129.0
127.8
115.1
33.8
33.7
32.7
28.8
26.5
25.8
200
150
100
50
ppm (t1)

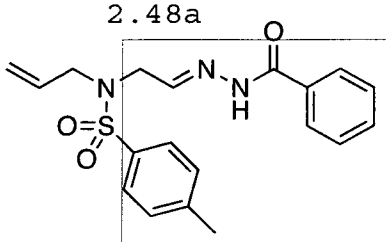
2.46e



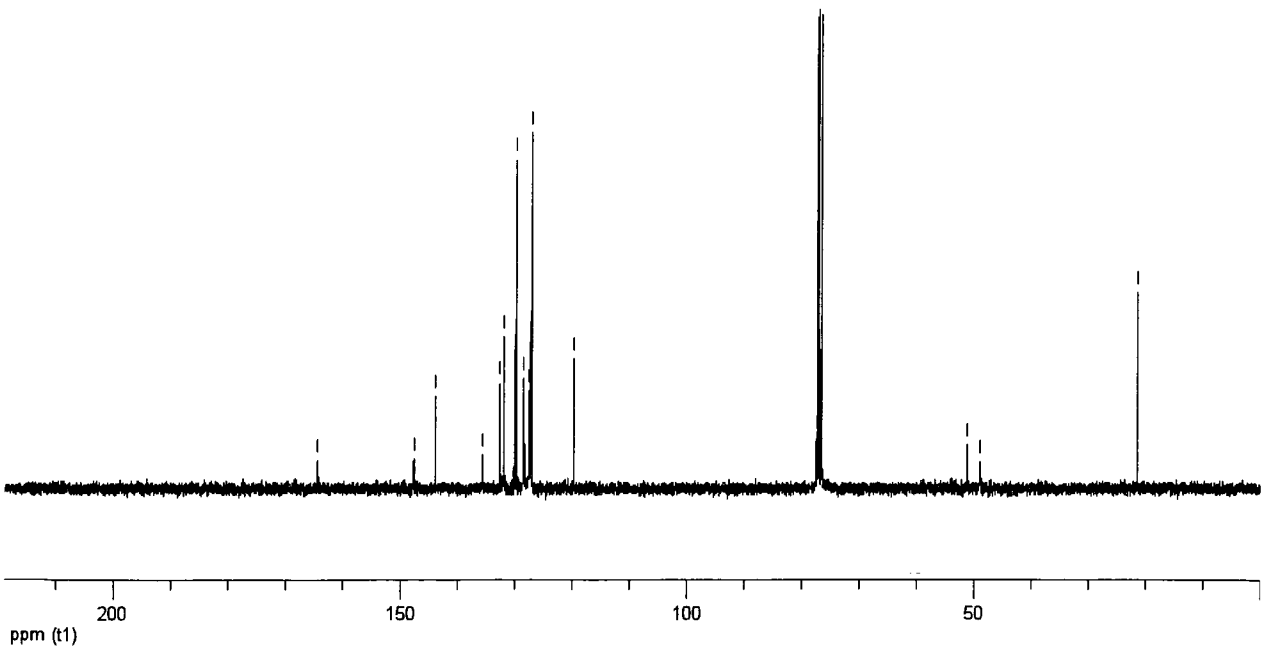
167.2
138.8
132.8
131.7
128.6
126.8
144.4
52.2
33.6
28.7
27.8
26.5



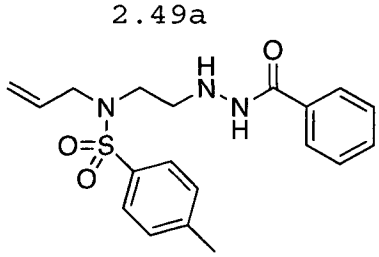
2.48a



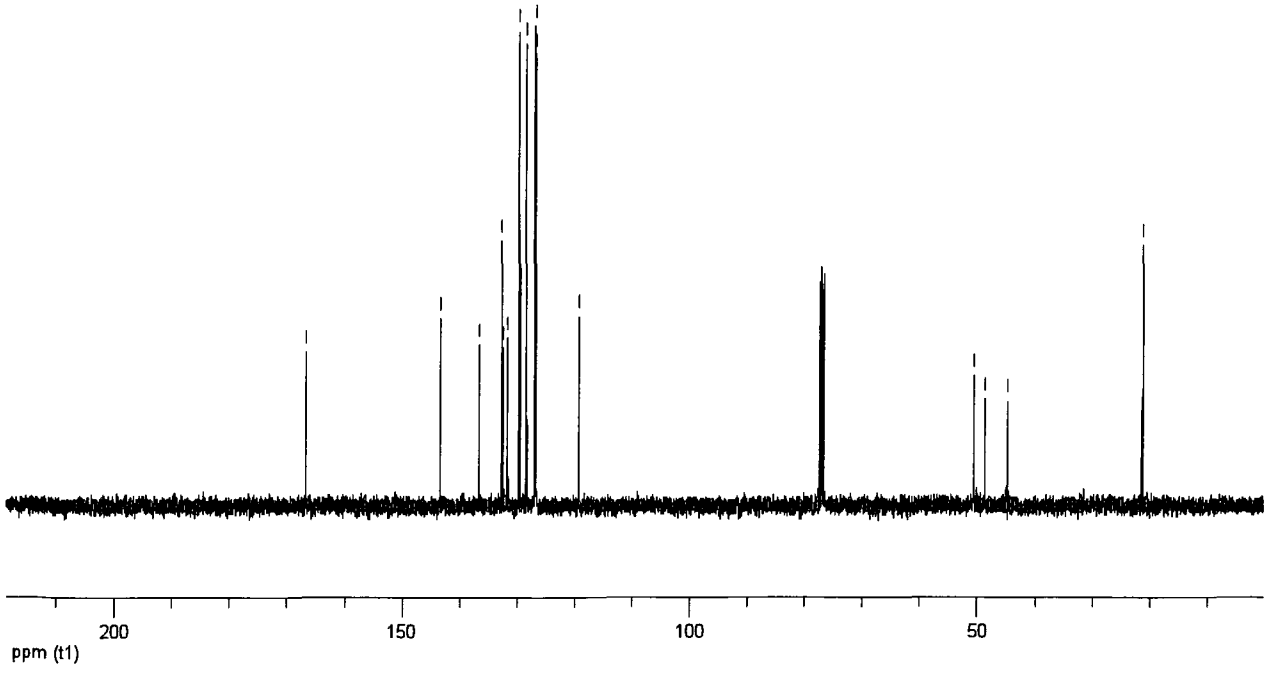
164.3
147.7
143.9
135.6
132.6
132.0
130.1
129.9
128.5
127.5
127.2
127.2
119.8
51.3
49.1
21.5



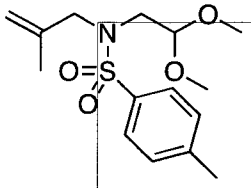
2.49a



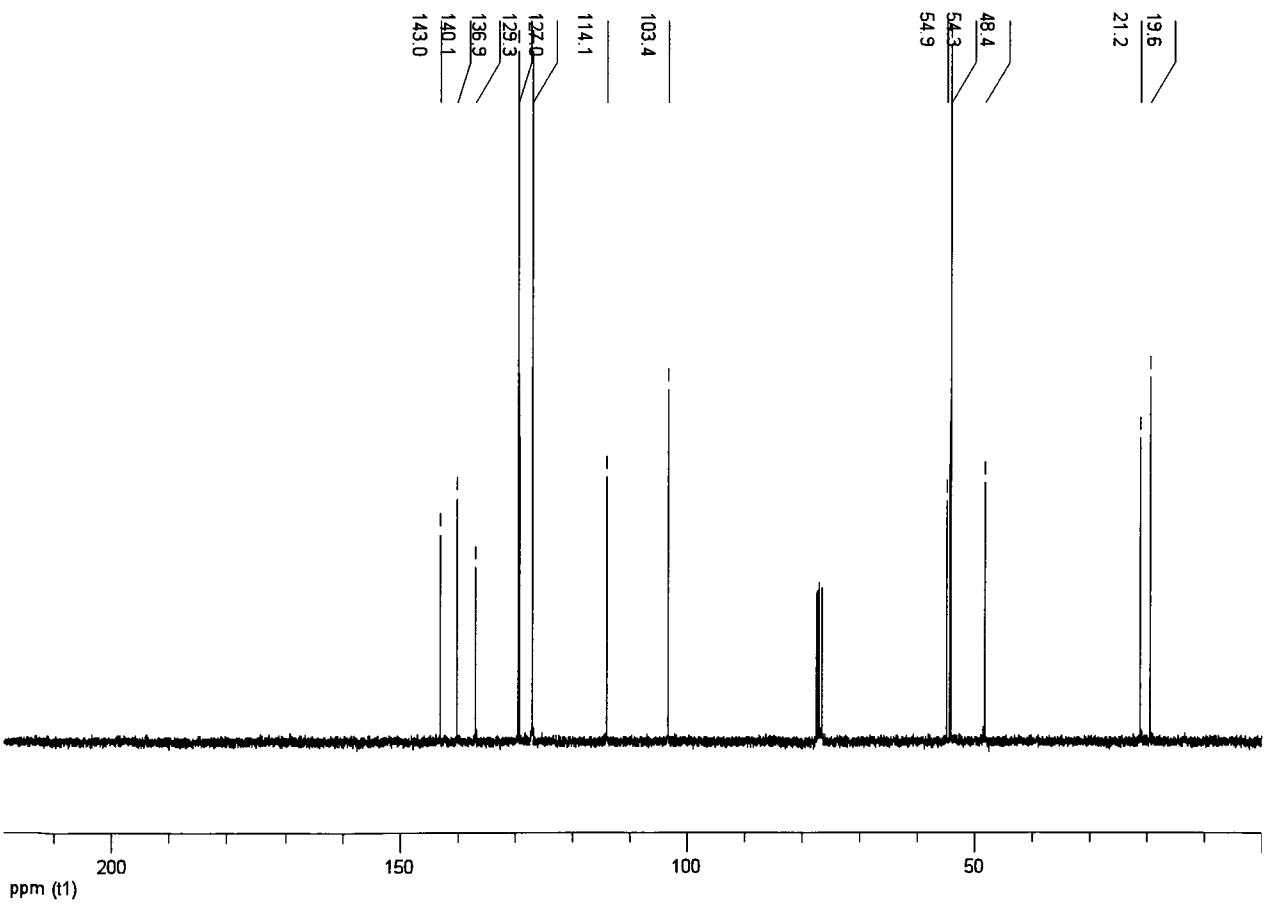
166.7
143.3
136.4
132.5
132.4
131.5
129.6
128.4
126.9
126.8
119.2
50.6
48.7
44.8
21.3



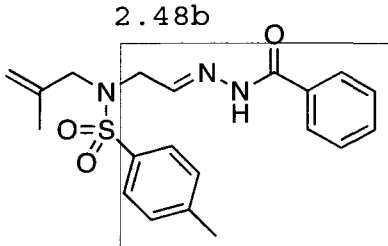
2.47b


N
O
O=S
O
O

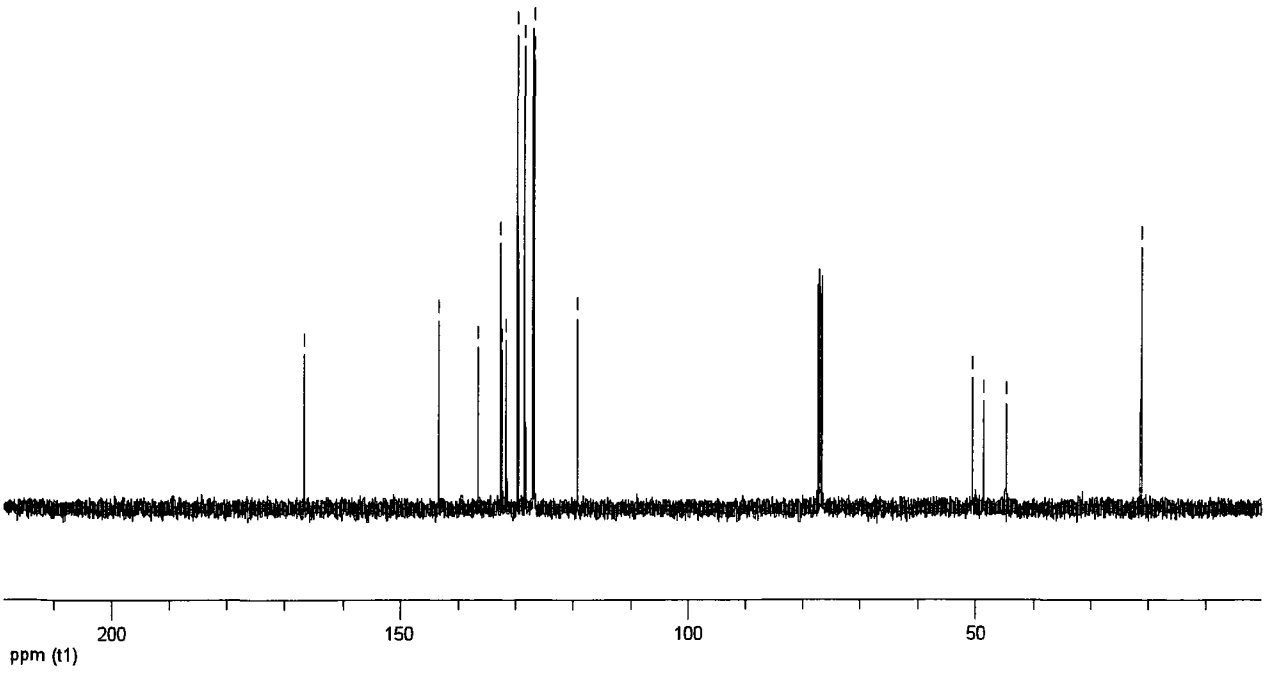
10.0
5.0
0.0
ppm (t1)


143.0
140.1
136.9
129.3
127.0
114.1
103.4
54.9
54.3
48.4
21.2
19.6
200
150
100
50
ppm (t1)

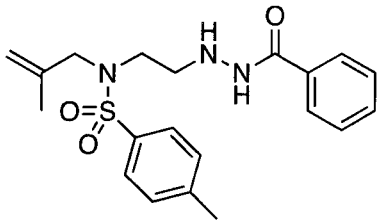
2.48b



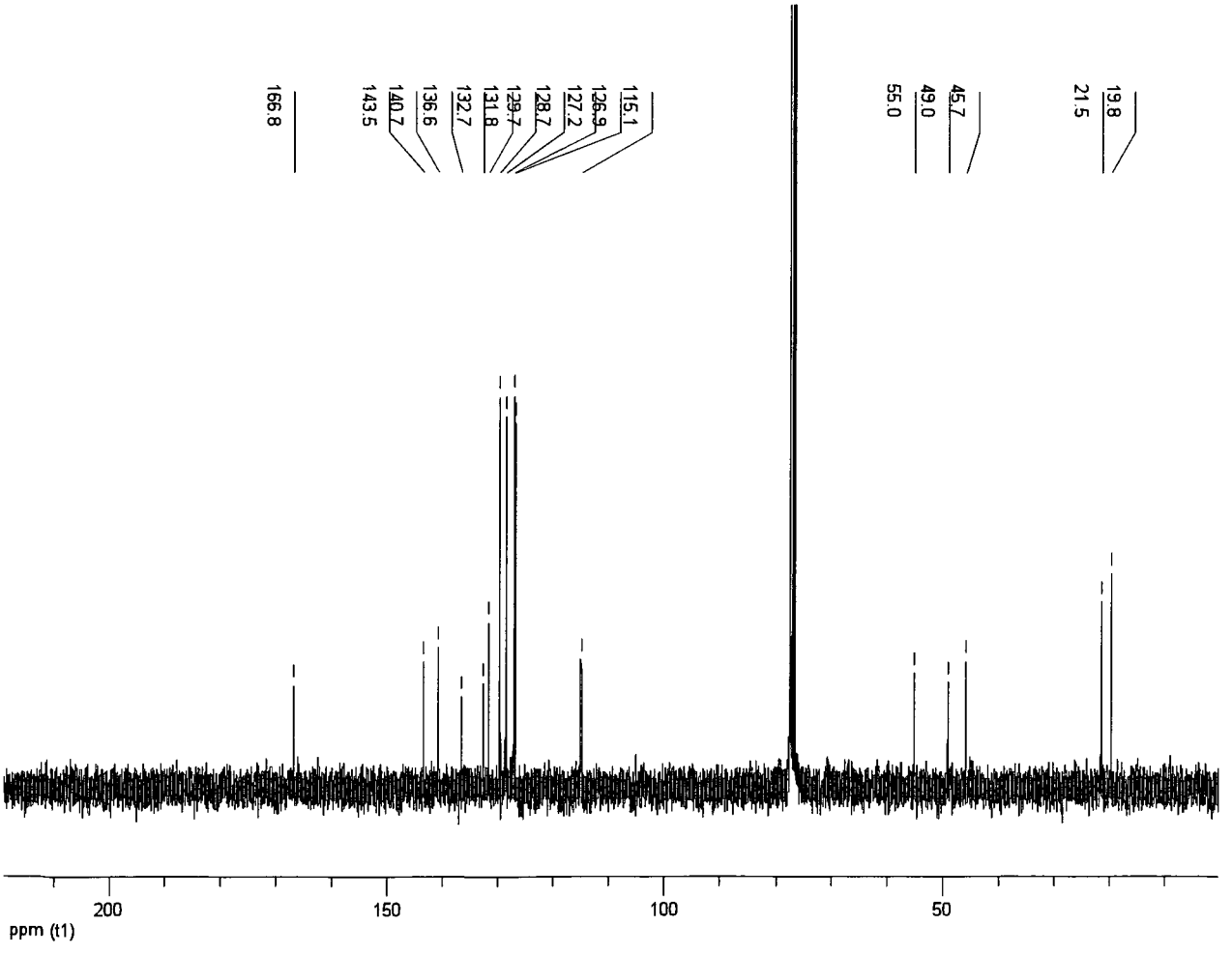
166.7
143.3
136.4
132.5
132.4
131.5
129.6
128.4
126.9
126.8
119.2
50.6
48.7
44.8
21.3



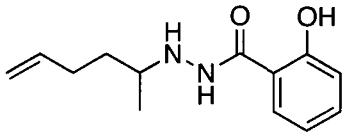
2.49b

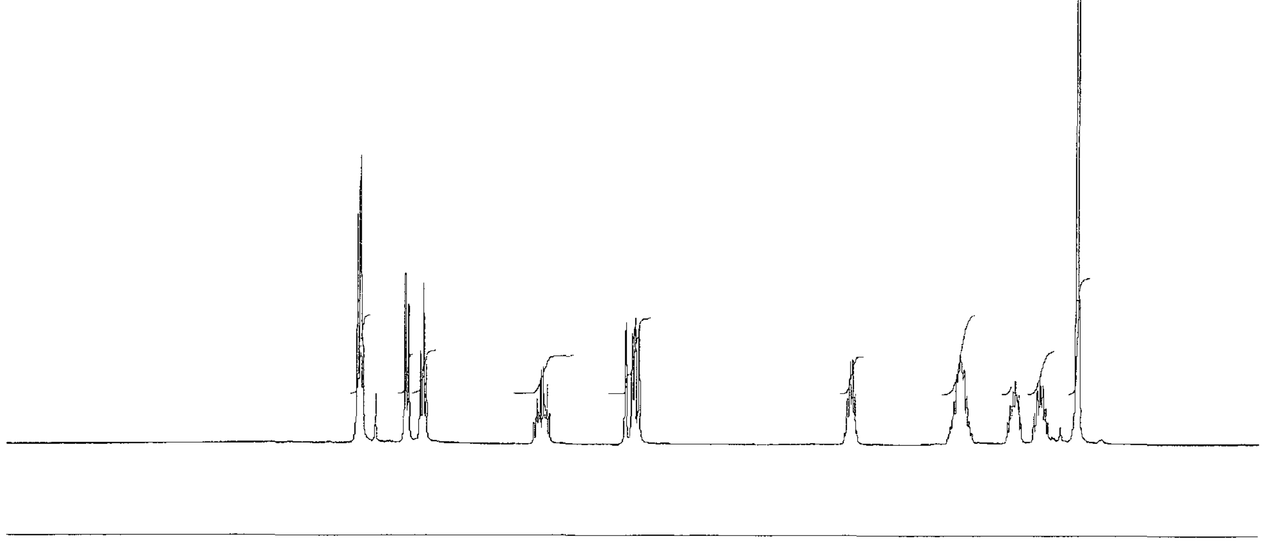


10.0
ppm (t1)
5.0
0.0

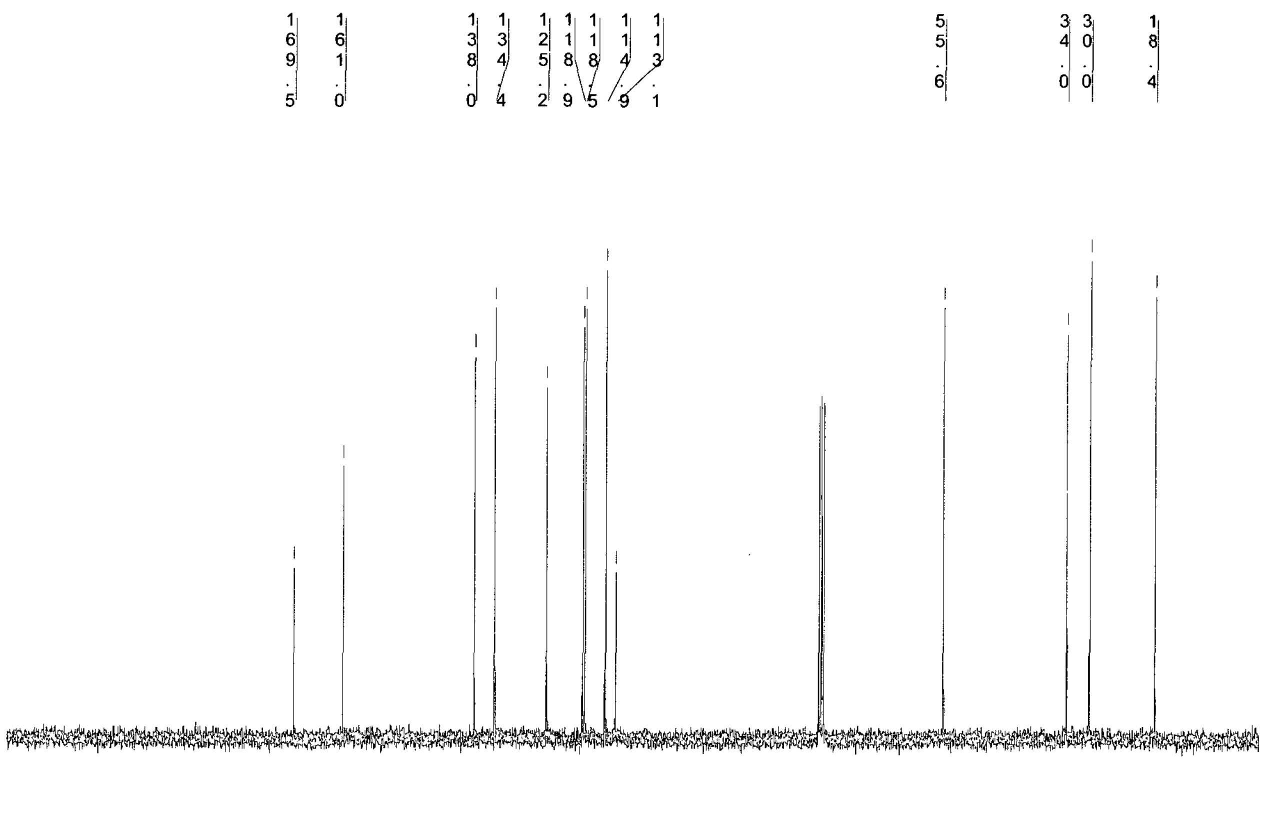

166.8
143.5
140.7
136.6
132.7
131.8
129.7
128.7
127.2
126.9
115.1
55.0
49.0
45.7
21.5
19.8
200
150
100
50
ppm (t1)

2.61



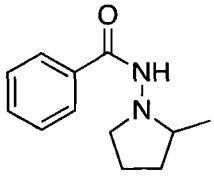


ppm (t1)

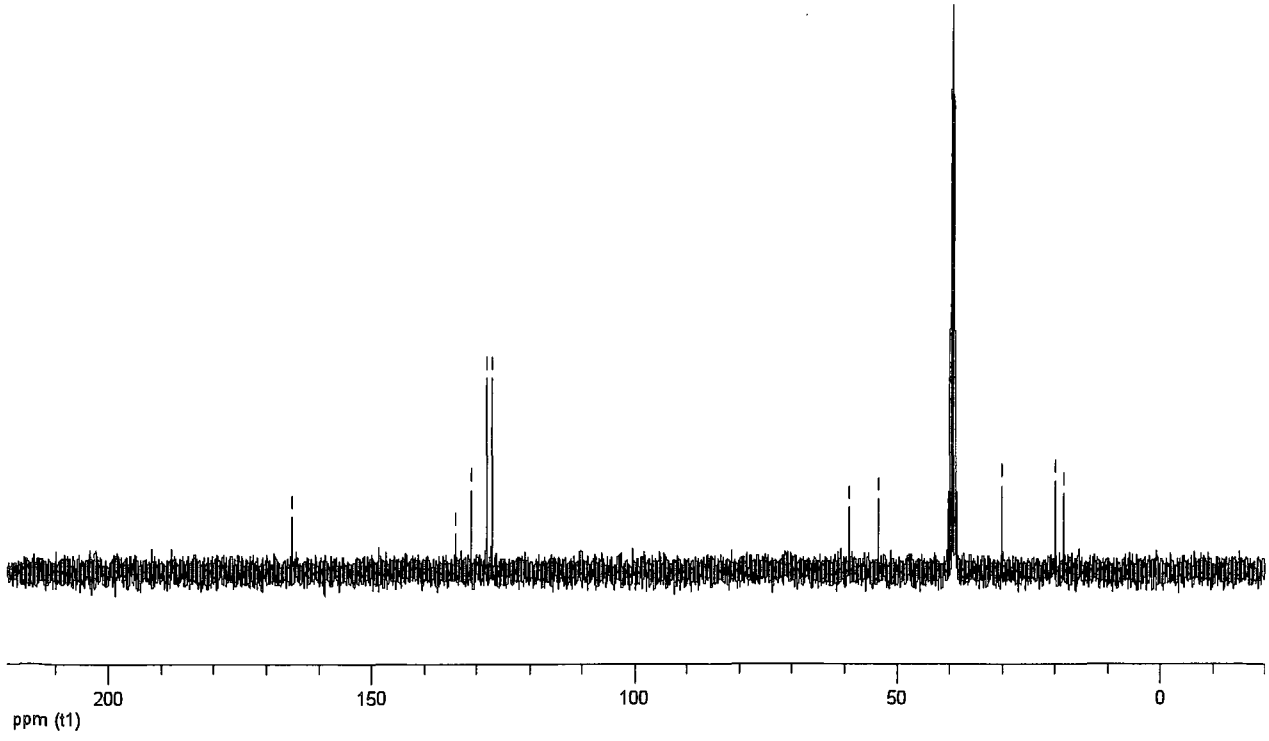


ppm (t1)

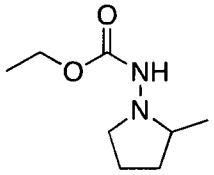
2.51



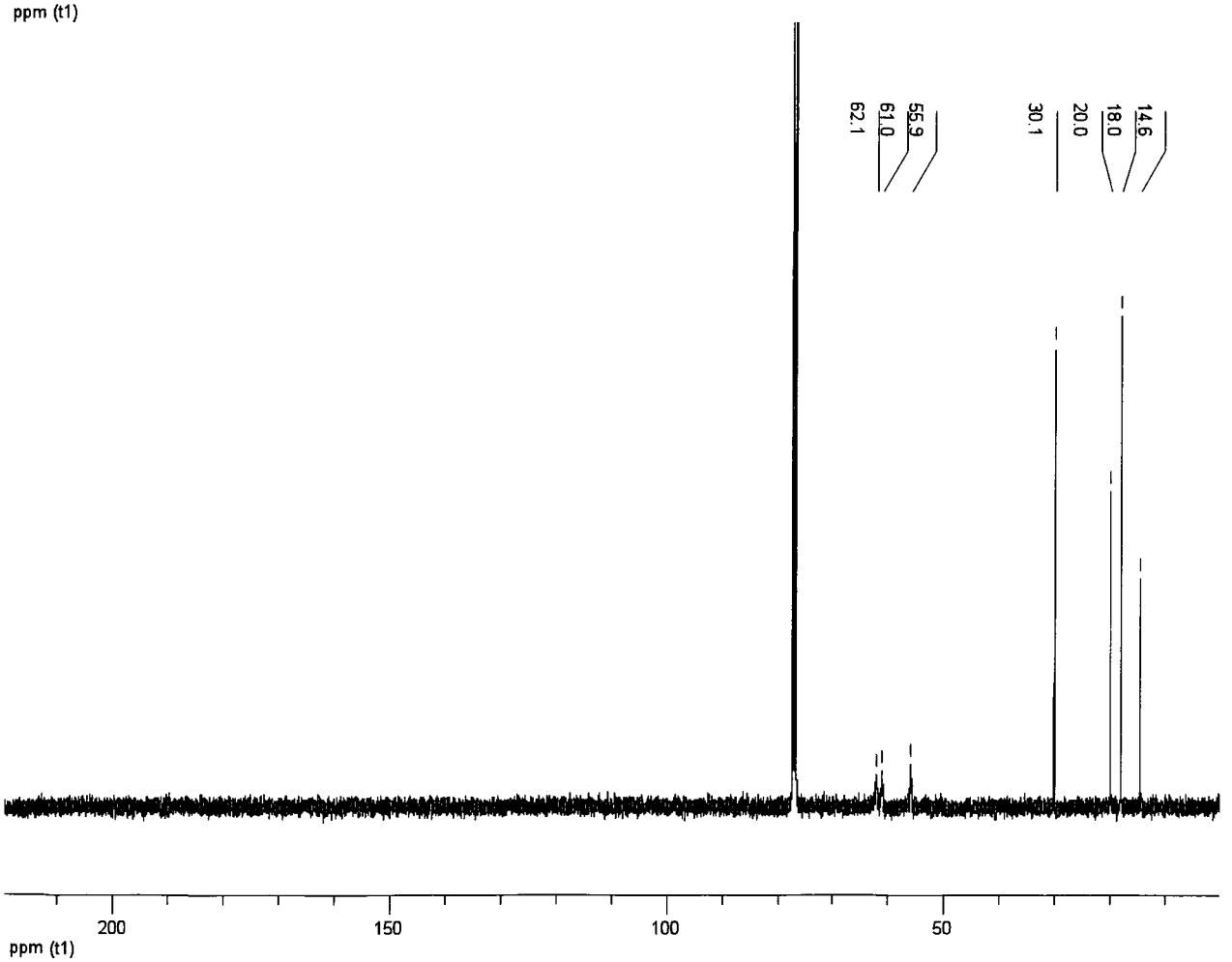
165.3
134.1
131.0
128.2
127.2
59.2
53.6
30.1
20.0
18.4



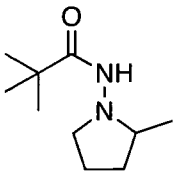
2.53


O
O
NH
N

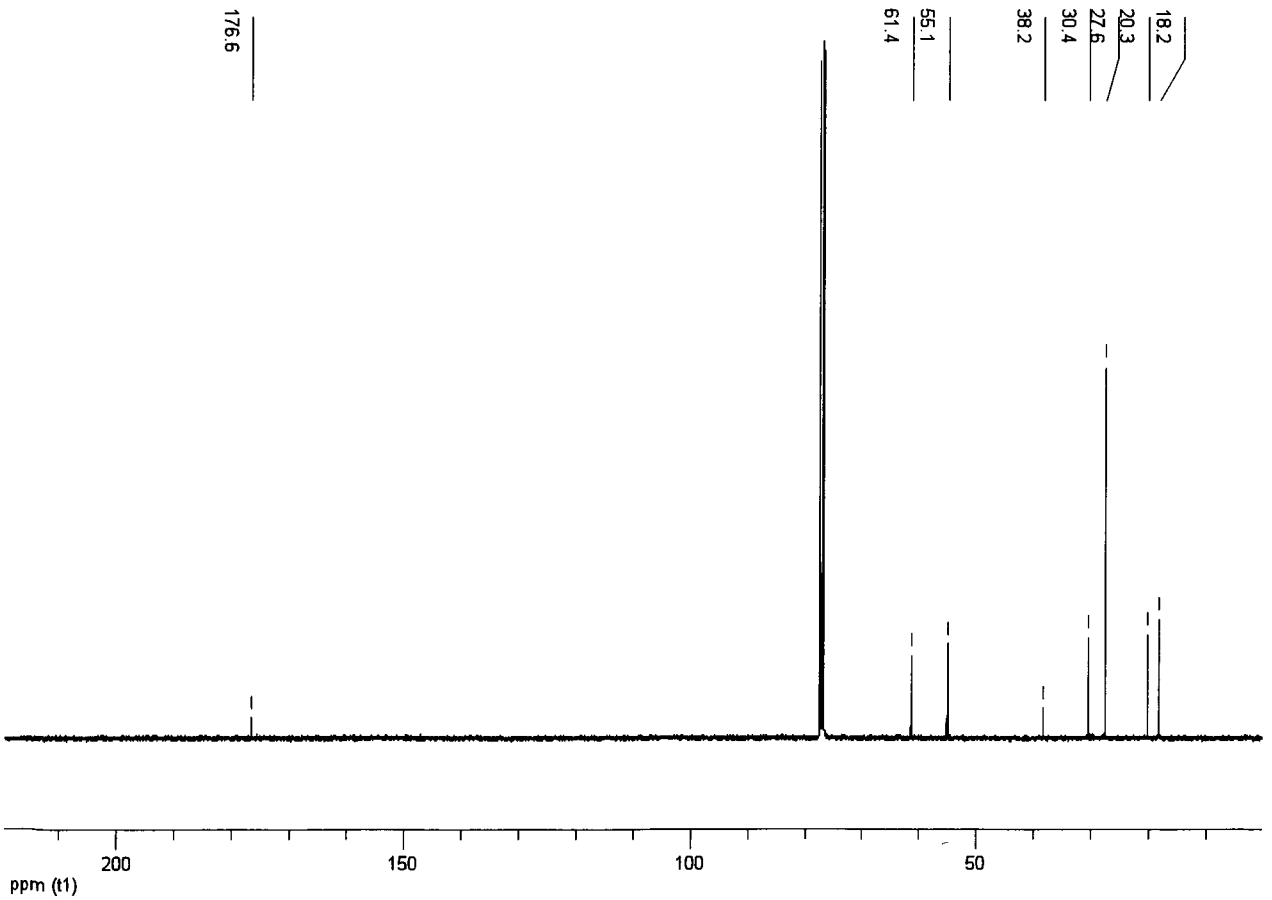
10.0
5.0
0.0
ppm (t1)


62.1
61.0
55.9
30.1
20.0
18.0
14.6
200
150
100
50
ppm (t1)

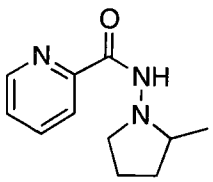
2.56


O
NH
N

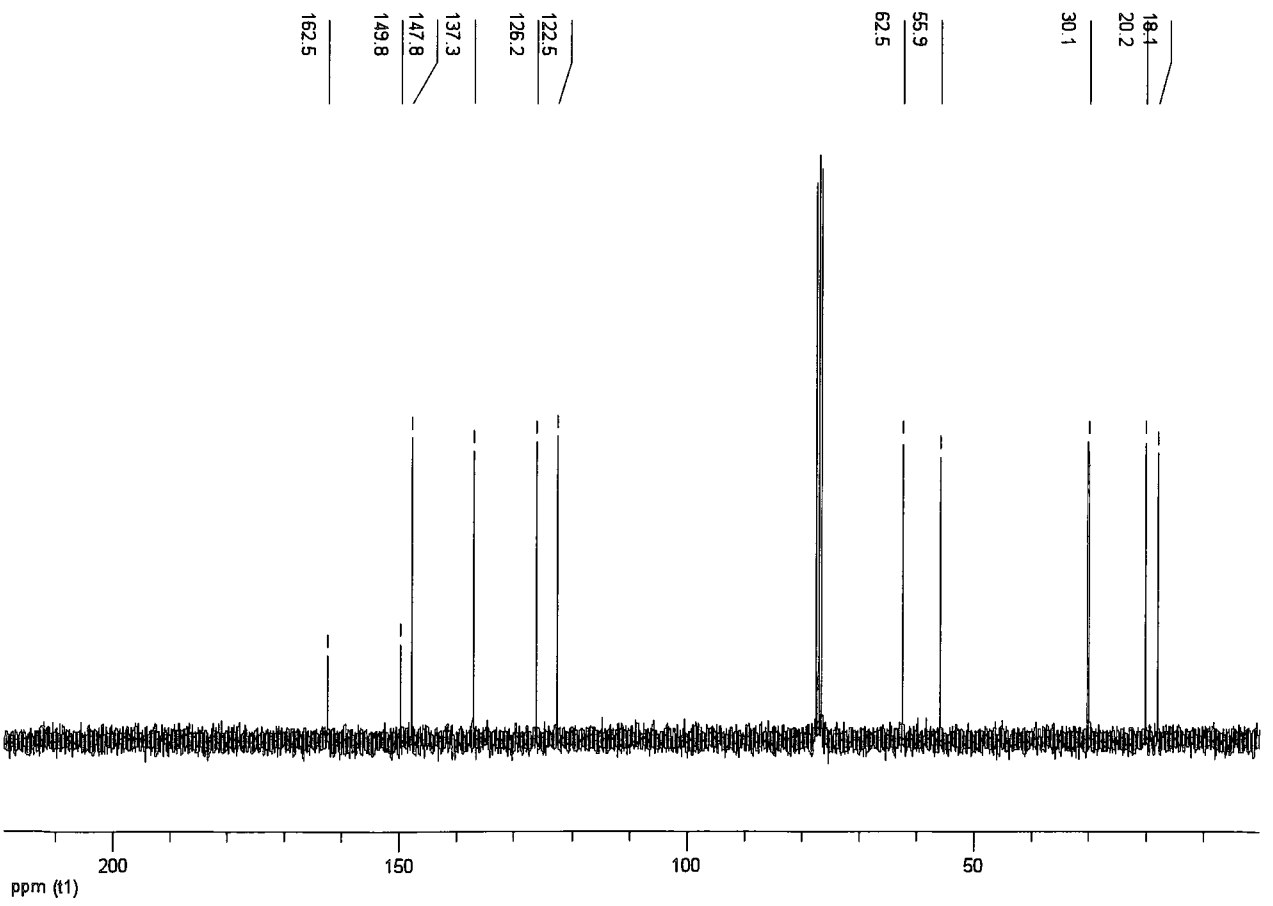
10.0
ppm (t1)
5.0
0.0


176.6
61.4
55.1
38.2
30.4
27.6
20.3
18.2
200
150
100
50
ppm (t1)

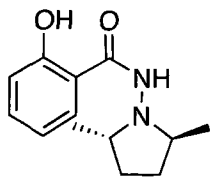
2.60


O
N
NH
N

10.0
ppm (t1)
5.0
0.0


162.5
149.8
147.8
137.3
126.2
122.5
62.5
55.9
30.1
20.2
18.1
200
150
100
50
ppm (t1)

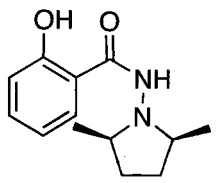
2.62-anti



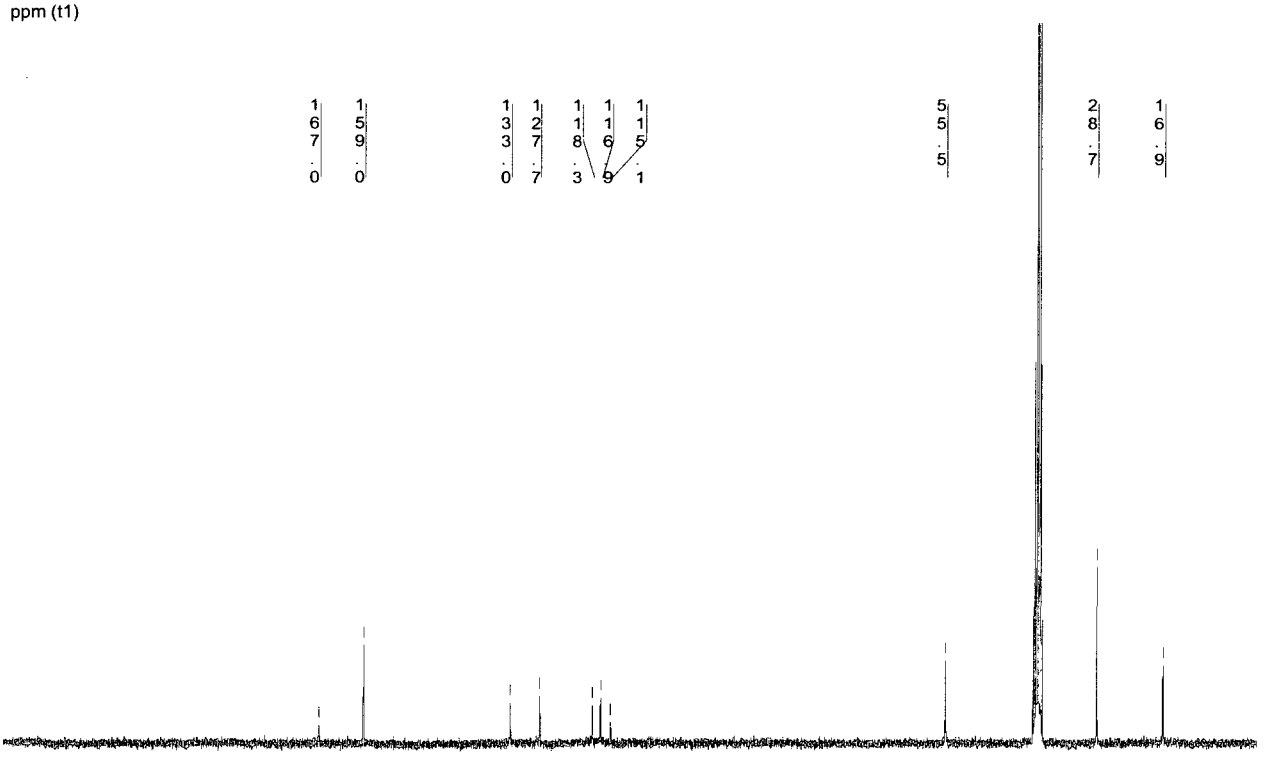
ppm (t1)

ppm (t1)

2.62-syn

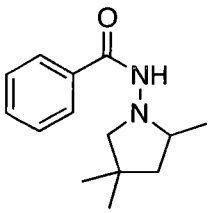


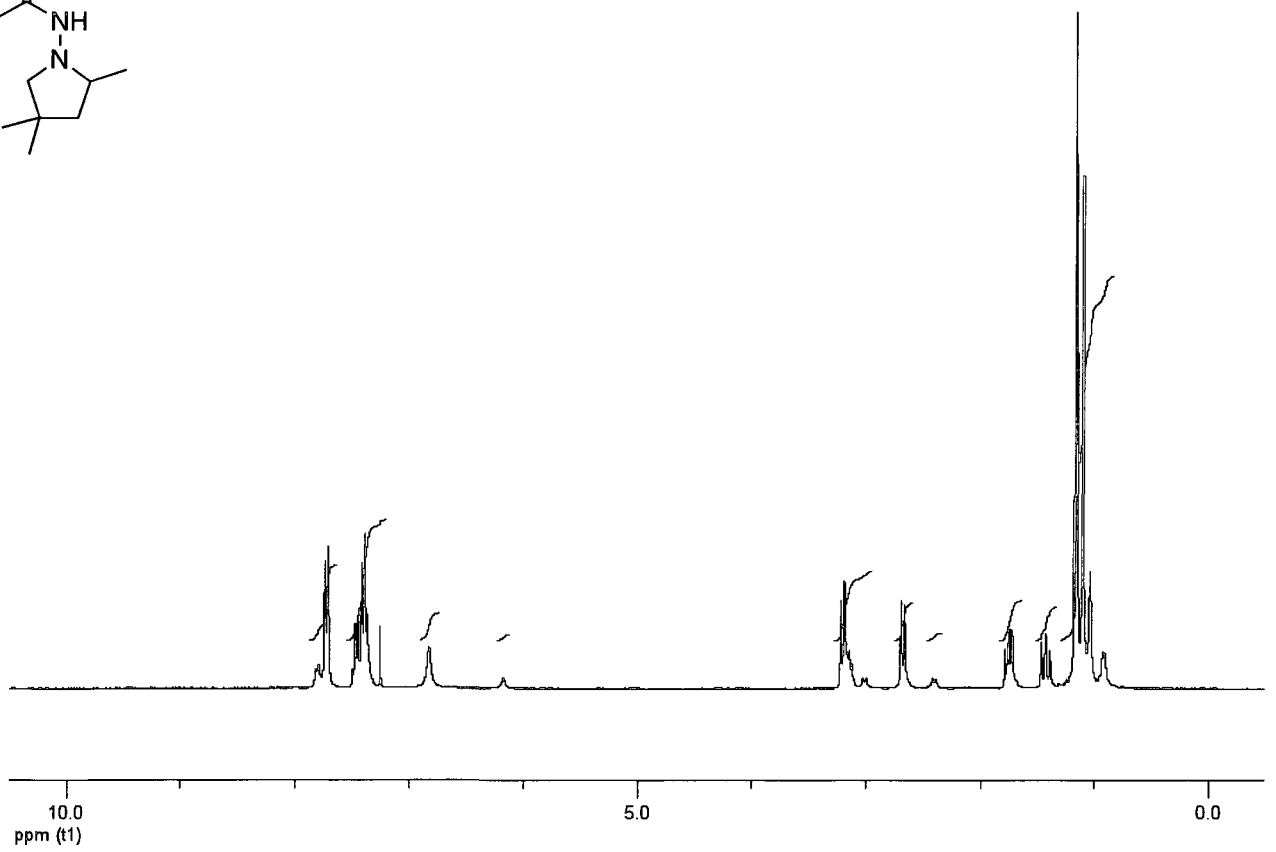
ppm (t1)

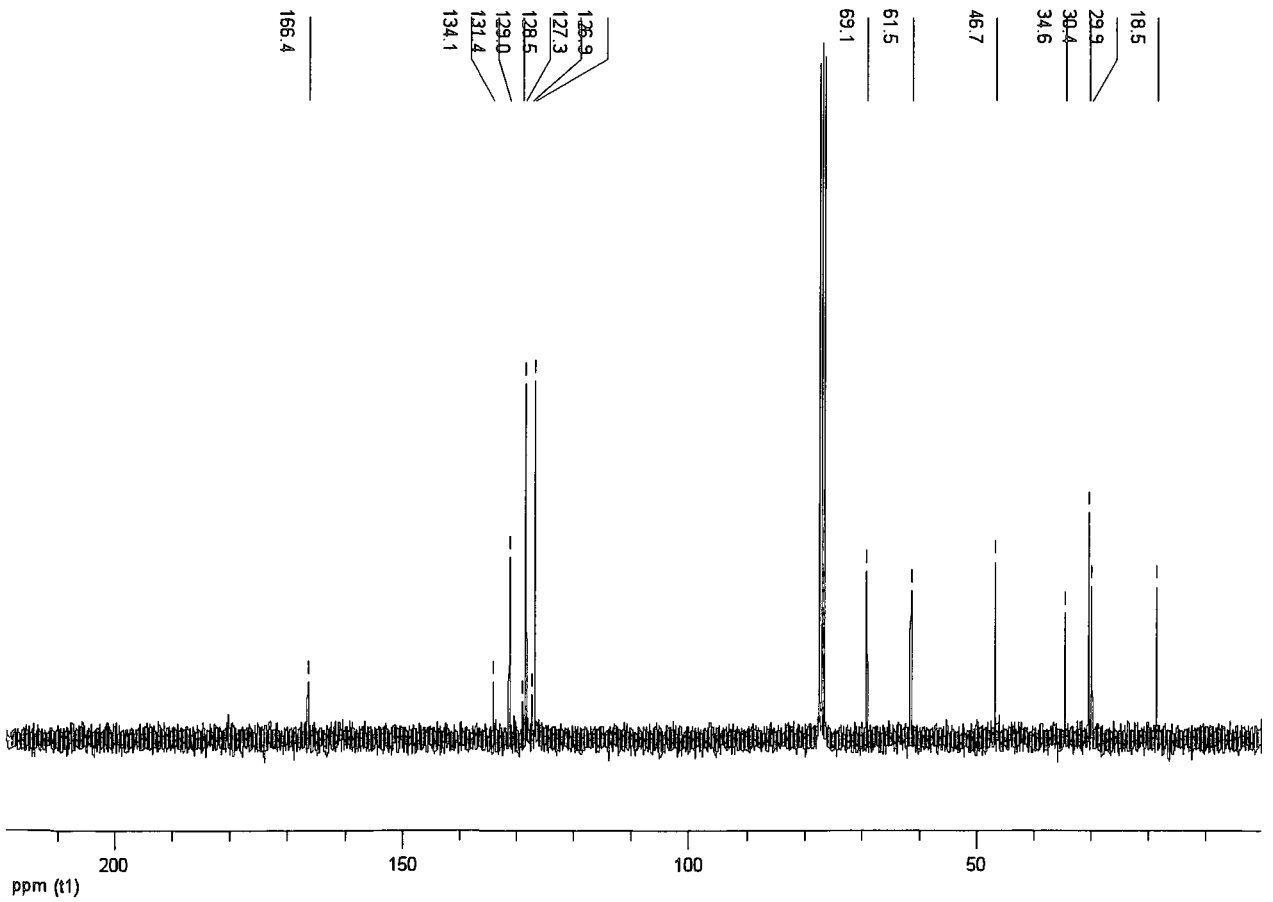


ppm (t1)

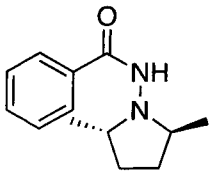
2.64

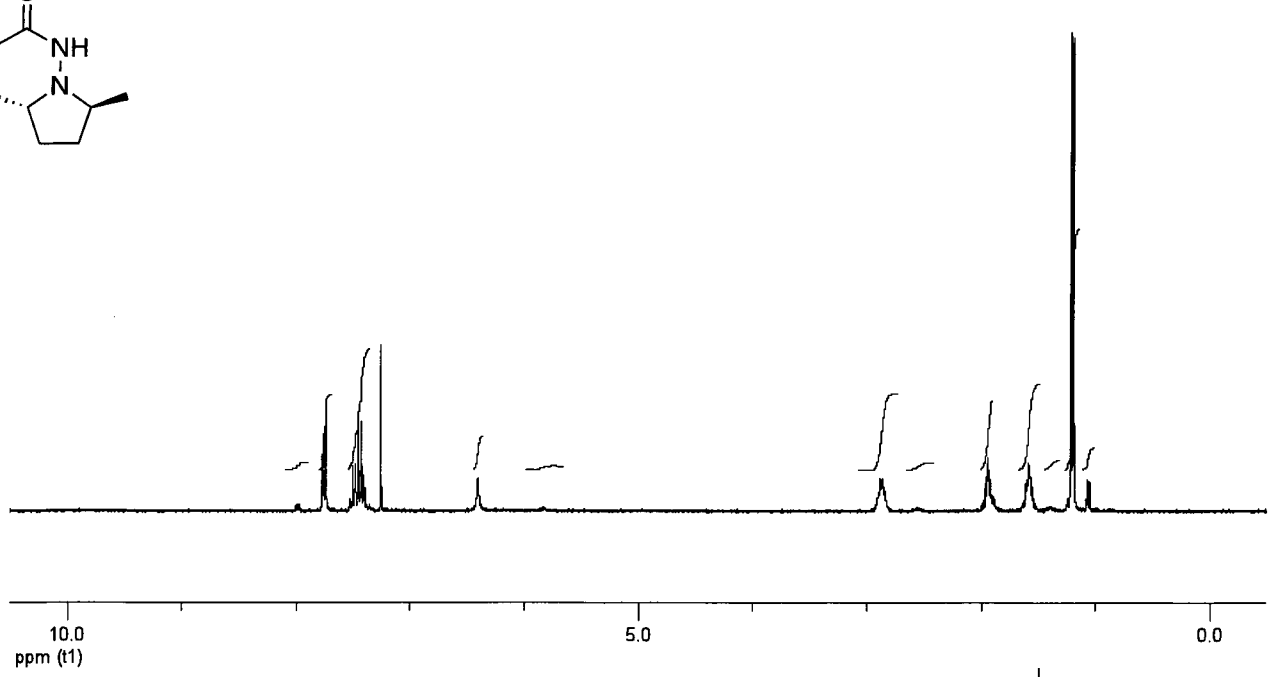

O
NH
N

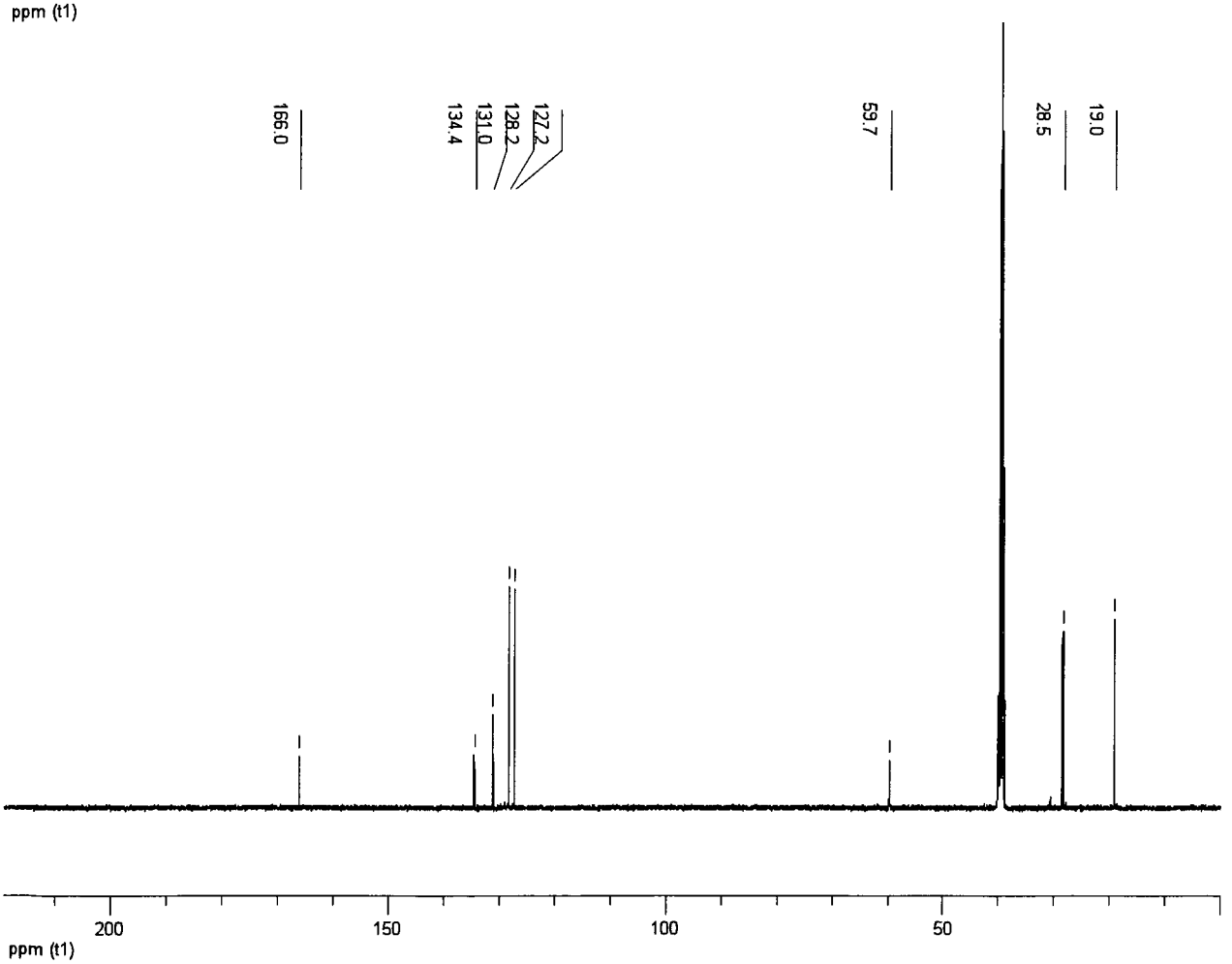

10.0
ppm (t1)
5.0
0.0


166.4
134.1
131.4
129.0
128.5
127.3
69.1
61.5
46.7
34.6
30.4
29.9
18.5
200
ppm (t1)
150
100
50

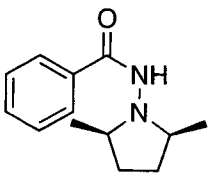
2.66-anti

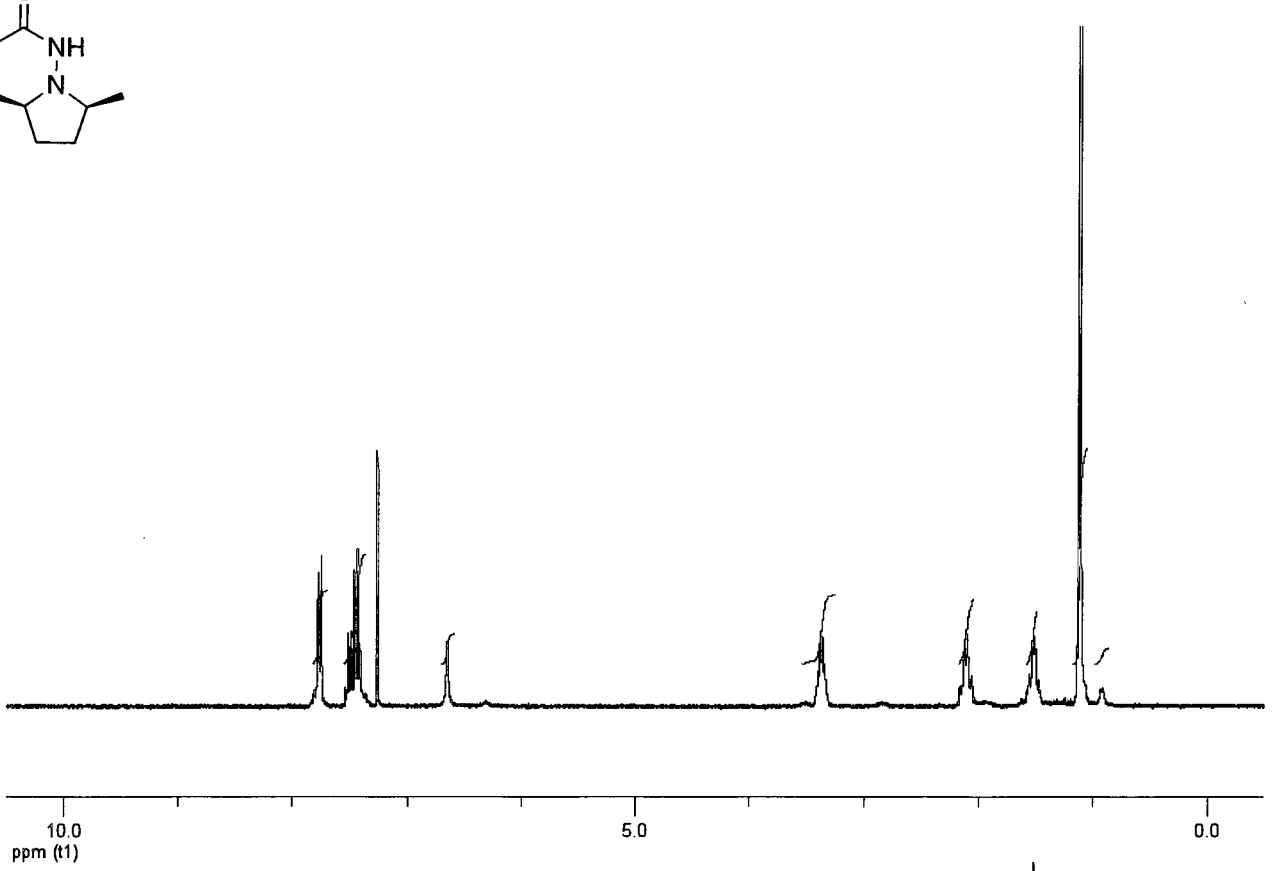

O
NH
N

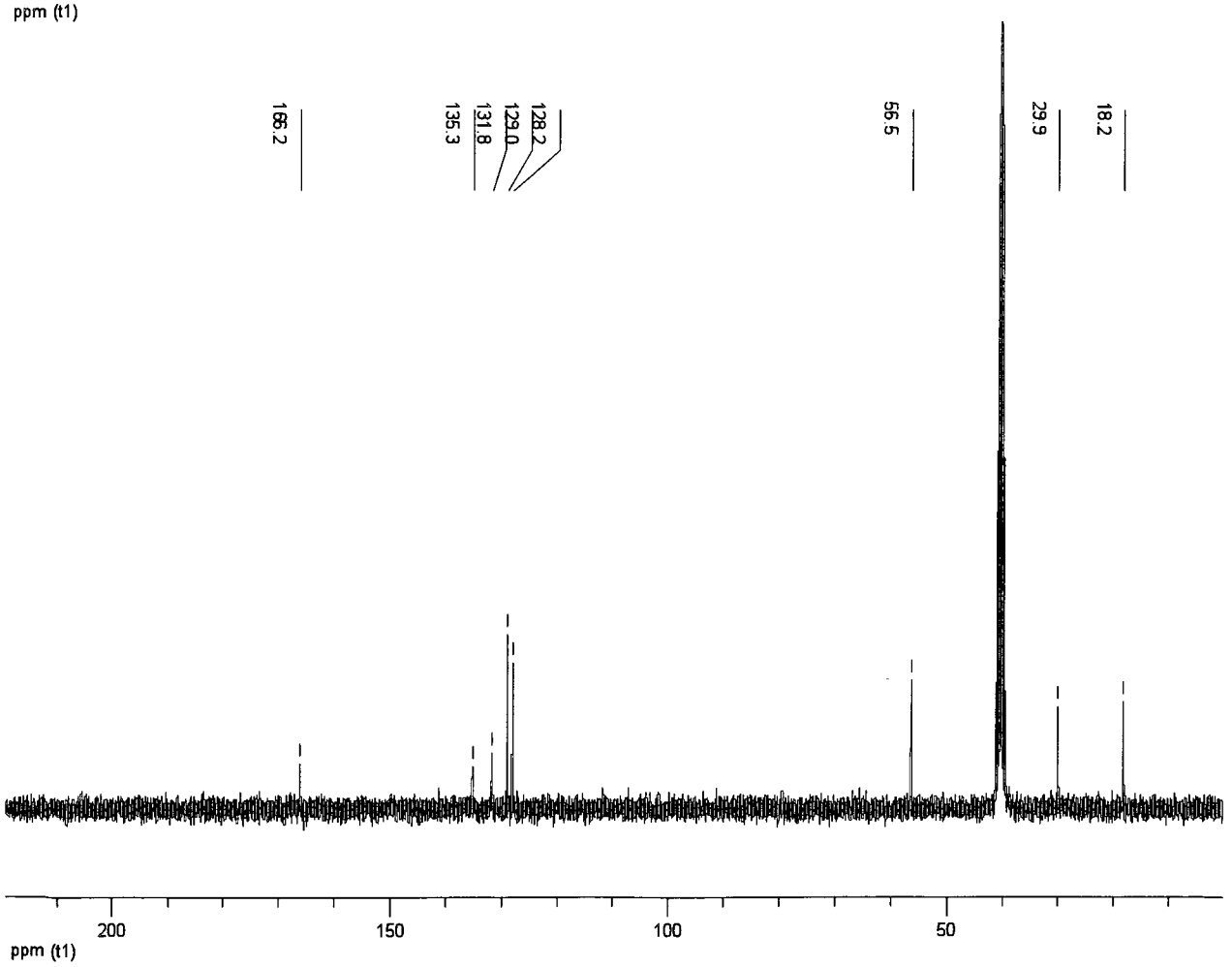

10.0
ppm (t1)
5.0
0.0


166.0
134.4
131.0
128.2
127.2
59.7
28.5
19.0
200
ppm (t1)
150
100
50

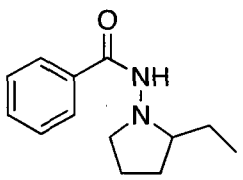
2.66-syn


O
NH
N

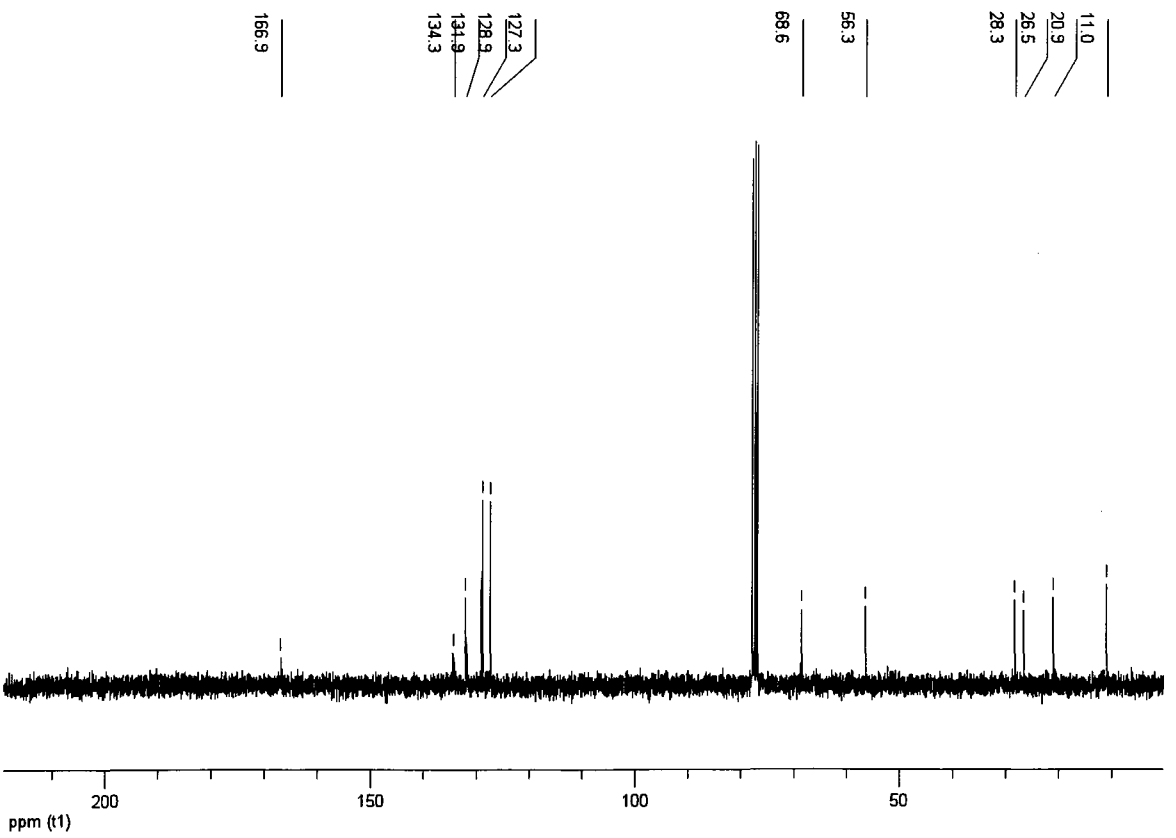

10.0
ppm (t1)
5.0
0.0


166.2
135.3
131.8
129.0
128.2
55.5
29.9
18.2
200
ppm (t1)
150
100
50

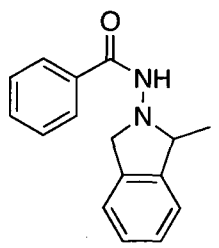
2.71


O
NH
N

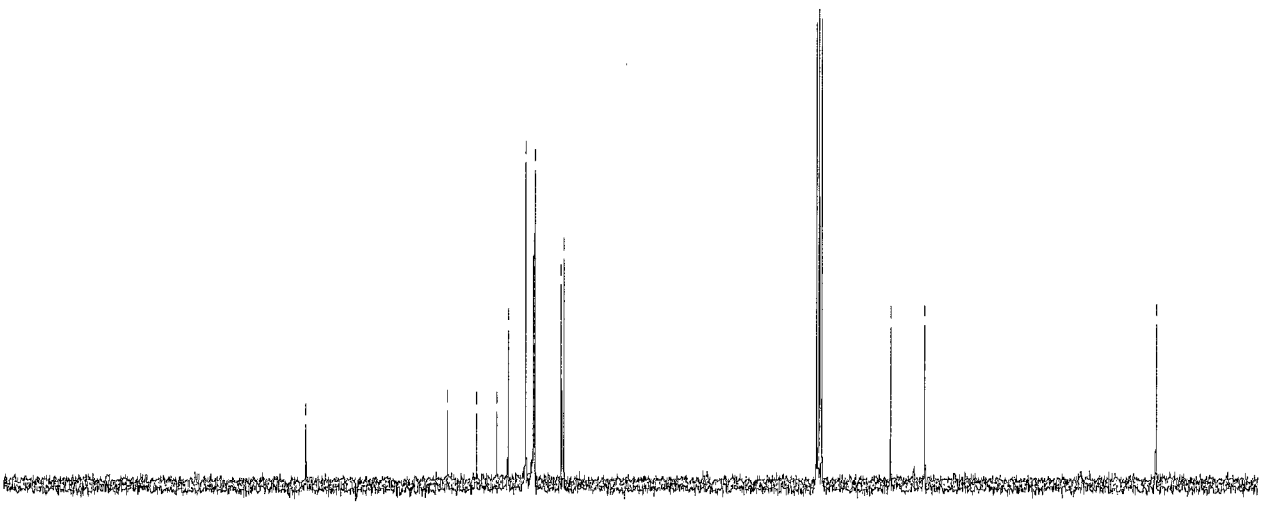
10.0
ppm (t1)
5.0
0.0


166.9
134.3
131.9
128.9
127.3
68.6
56.3
28.3
26.5
20.9
11.0
200
ppm (t1)
150
100
50

2.73

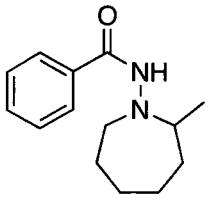


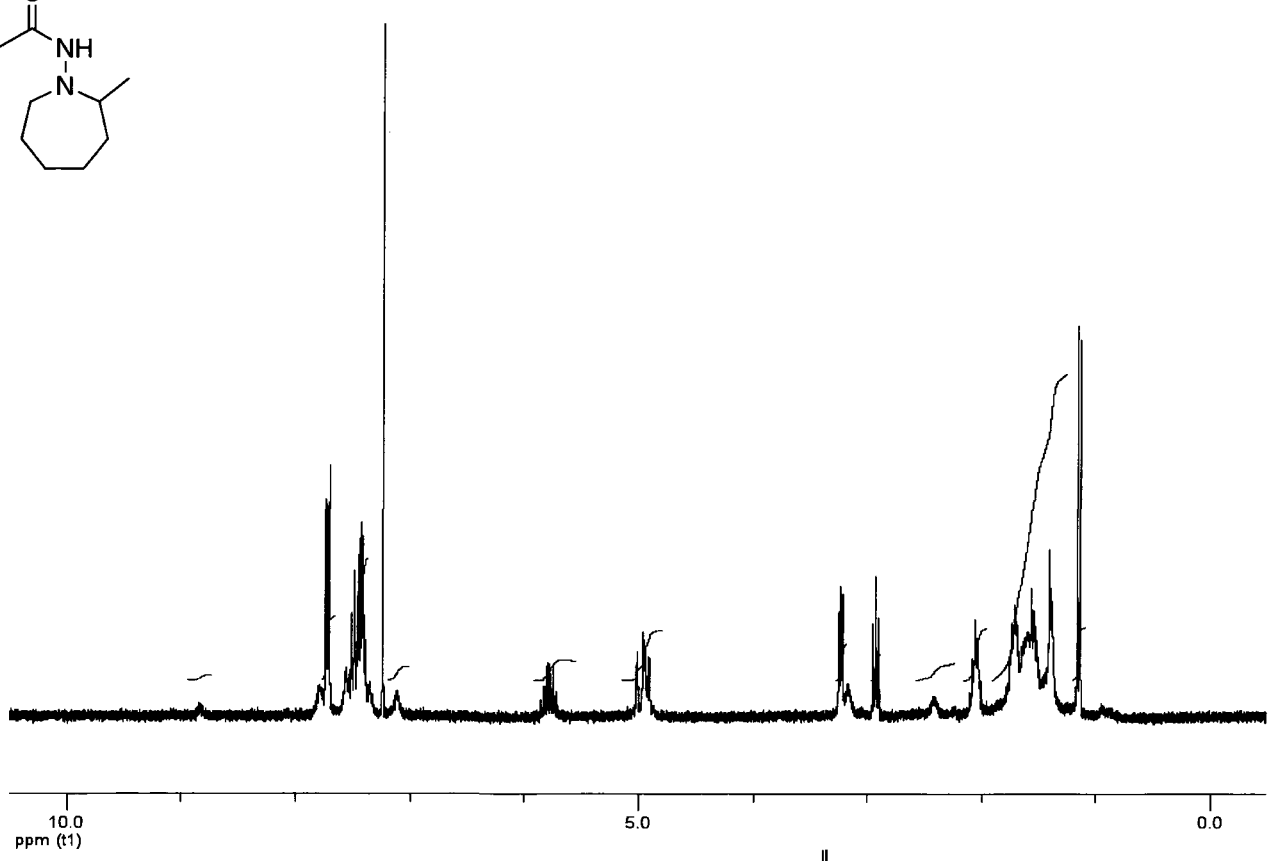
ppm (t1)

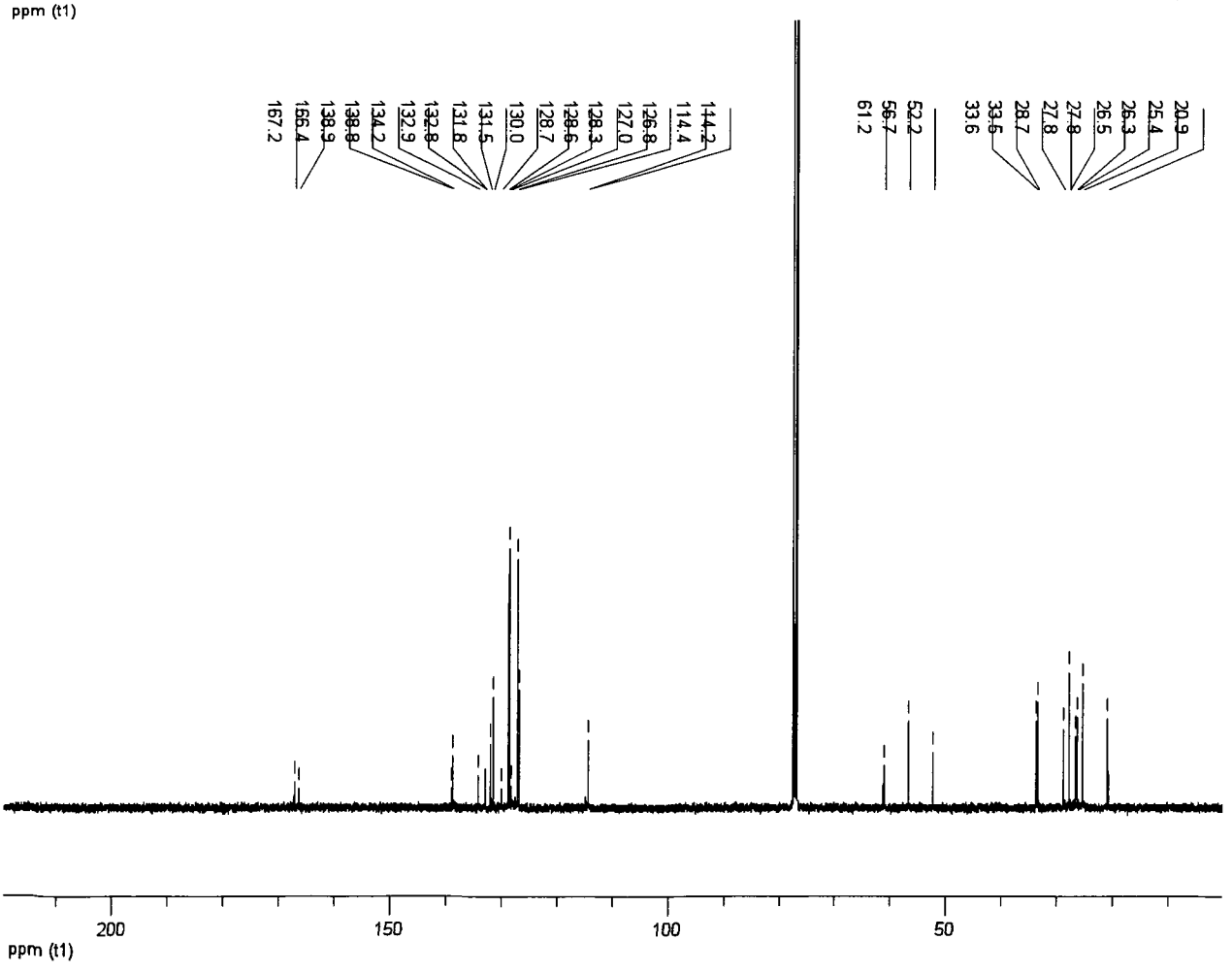


ppm (t1)

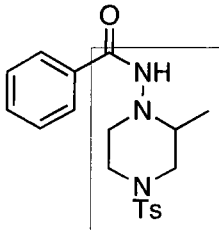
2.79


O
NH
N

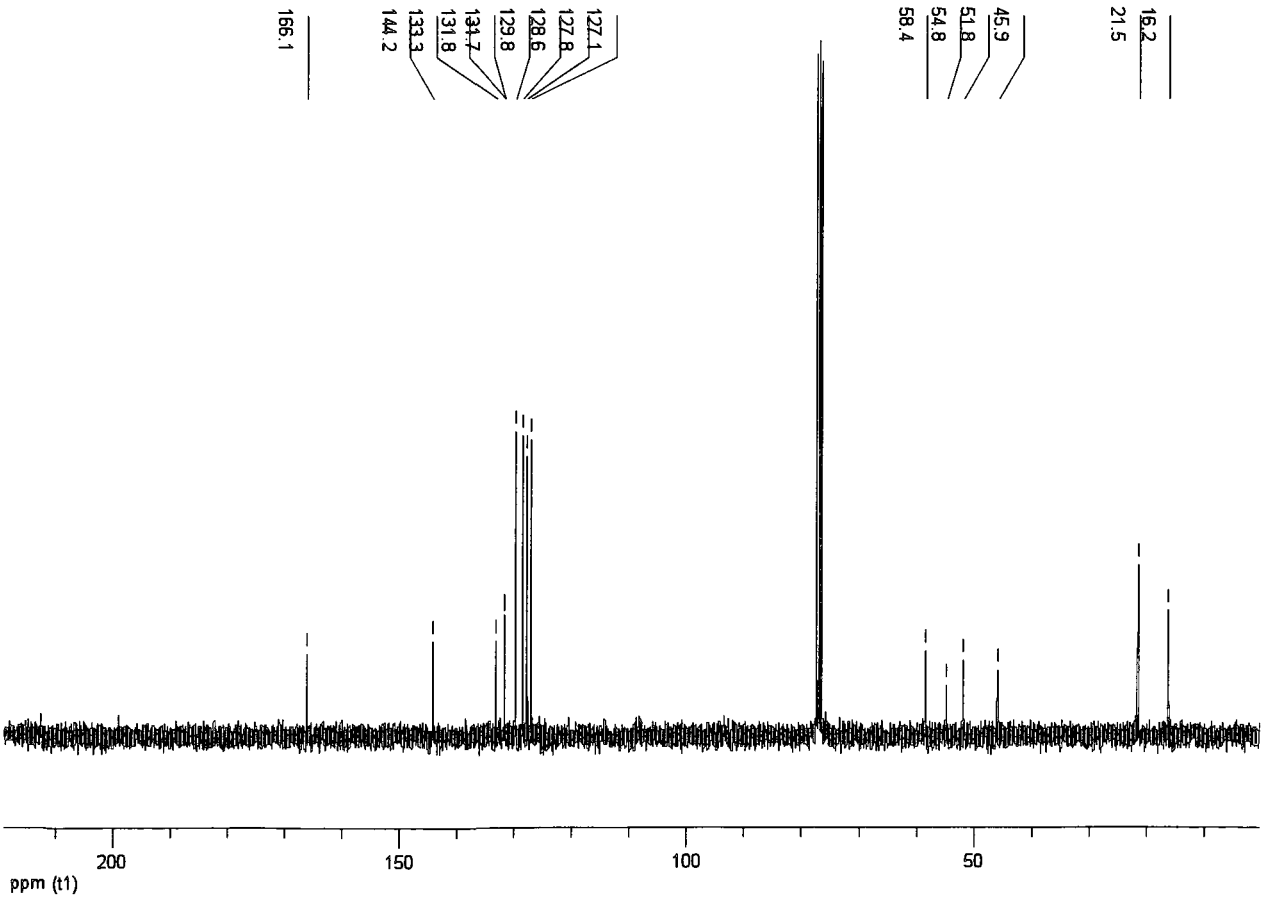

10.0
ppm (t1)
5.0
0.0


167.2
166.4
138.9
138.8
134.2
132.9
132.8
131.8
131.5
130.0
128.7
128.6
128.3
127.0
126.8
114.4
114.2
61.2
56.7
52.2
33.6
33.5
28.7
27.8
27.8
26.5
26.3
25.4
20.9
200
150
100
50
ppm (t1)

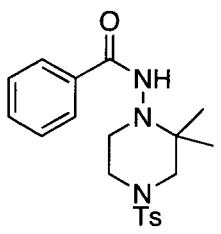
2.81a

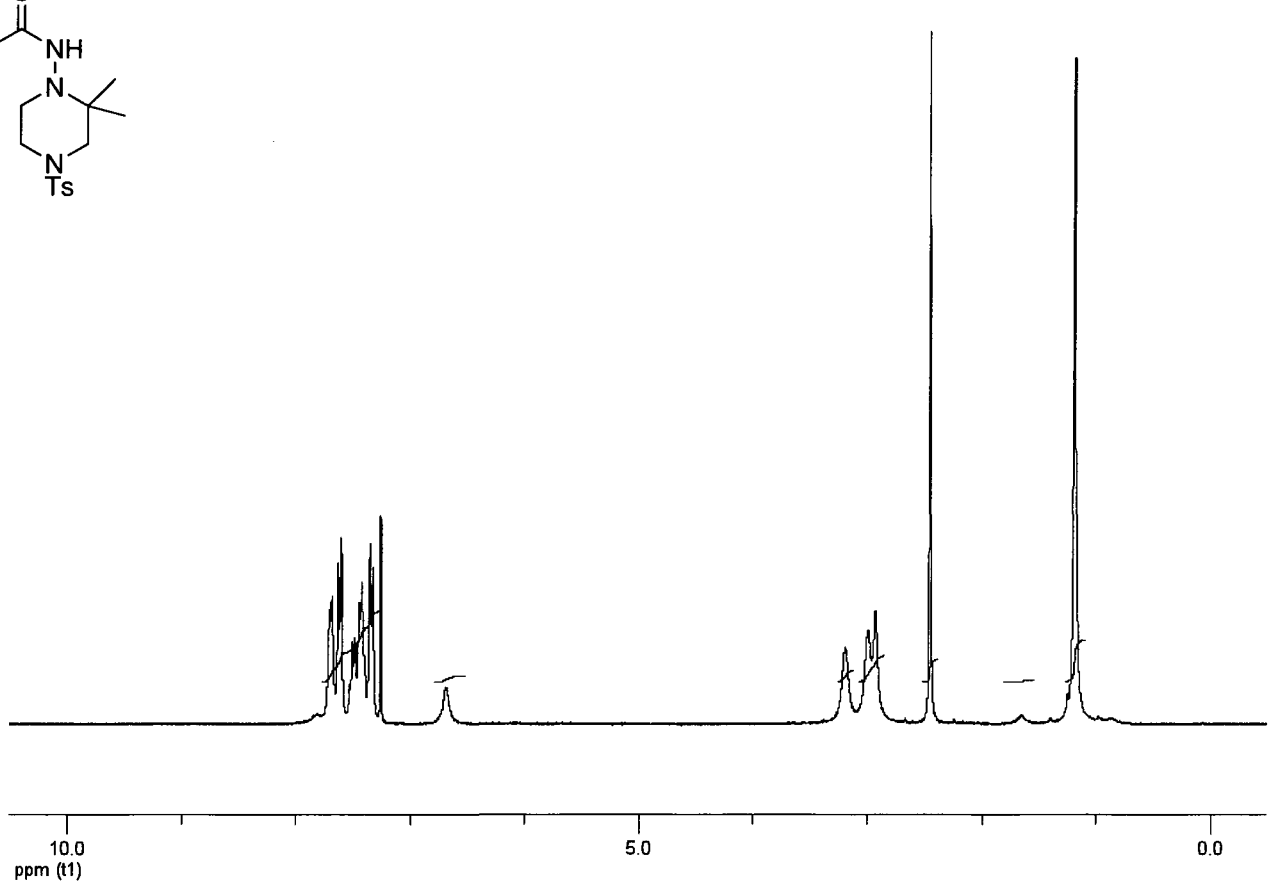

O
NH
N
N
Ts

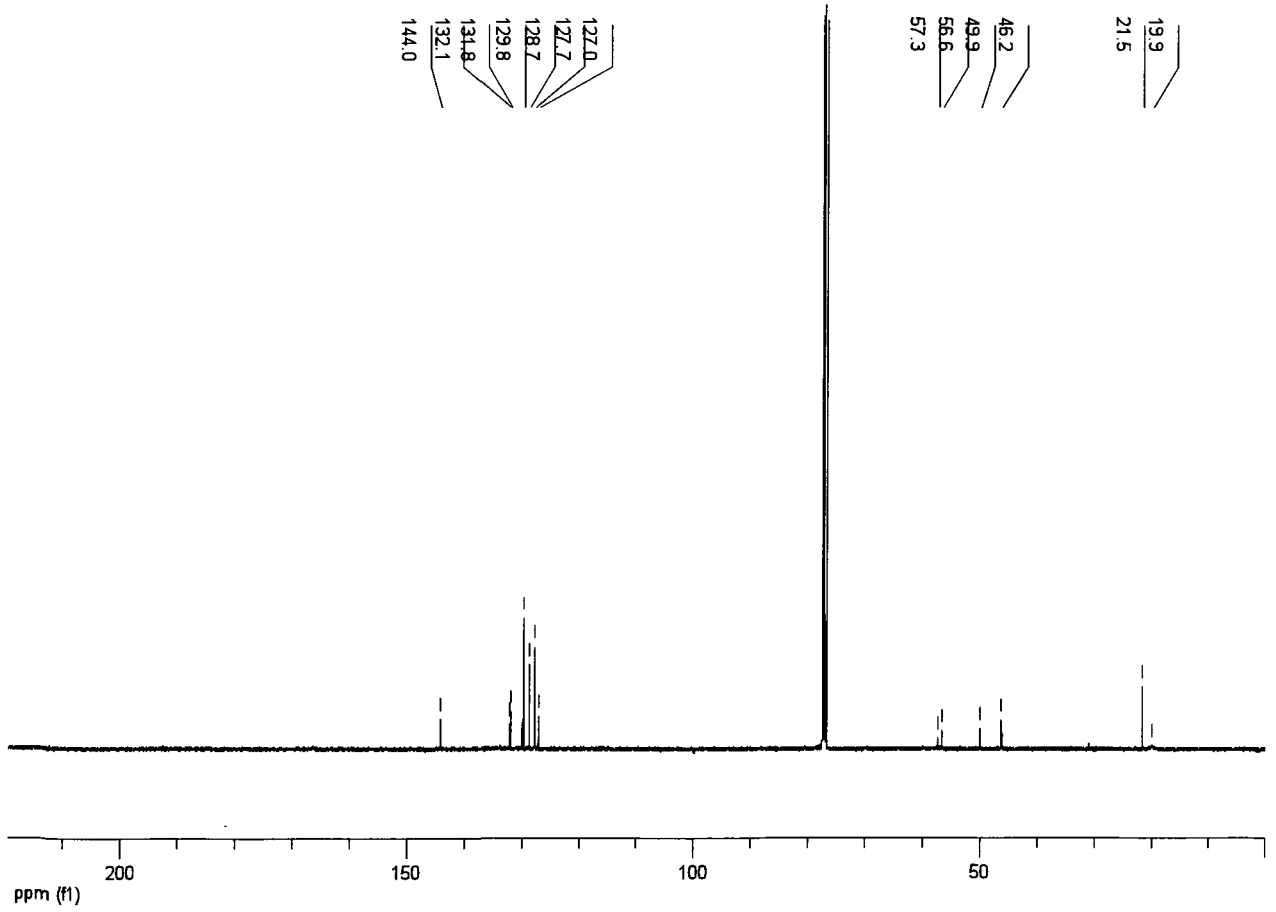
10.0
ppm (t1)
5.0
0.0


166.1
144.2
133.3
131.8
131.7
129.8
128.6
127.8
127.1
58.4
54.8
51.8
45.9
21.5
16.2
200
150
100
50
ppm (t1)

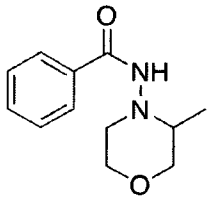
2.81b


O
NH
N
N
Ts

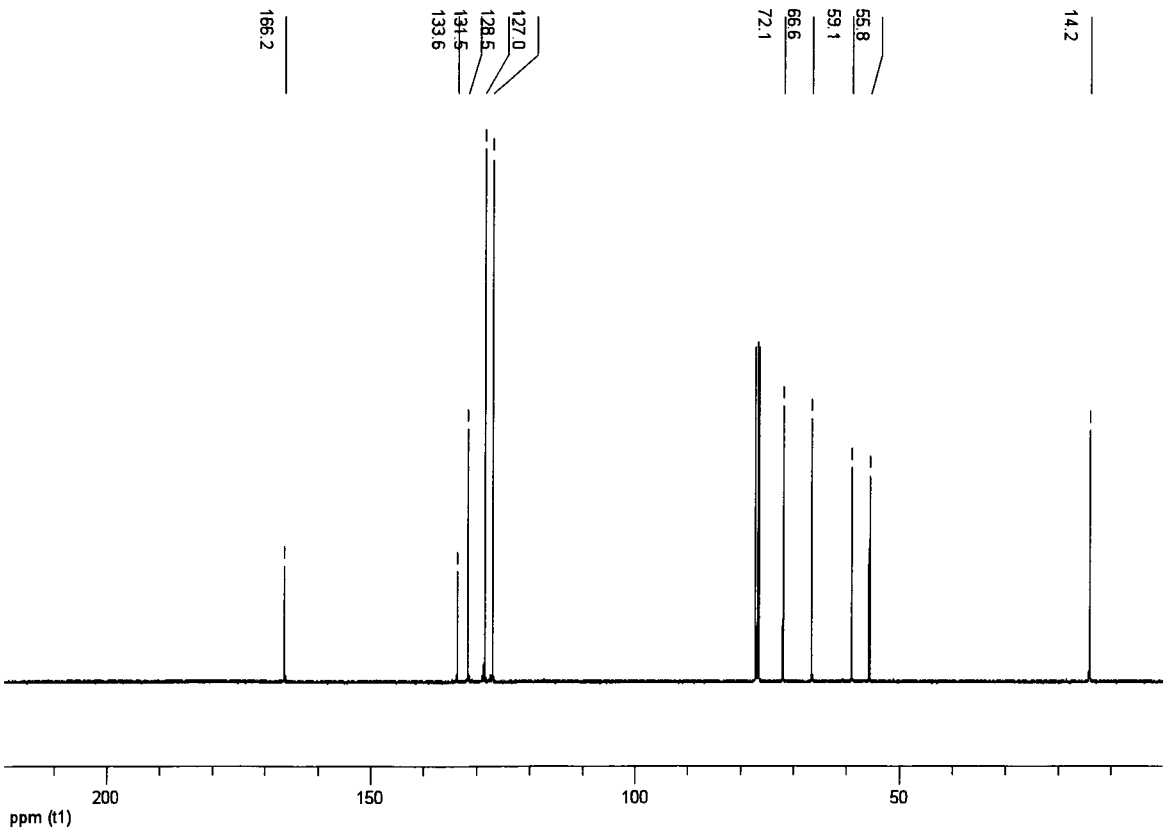

10.0
ppm (t1)
5.0
0.0

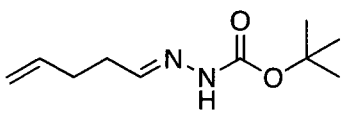

144.0
132.1
131.8
129.8
128.7
127.7
127.0
57.3
56.6
49.9
46.2
21.5
19.9
200
150
100
50
ppm (f1)

2.81c

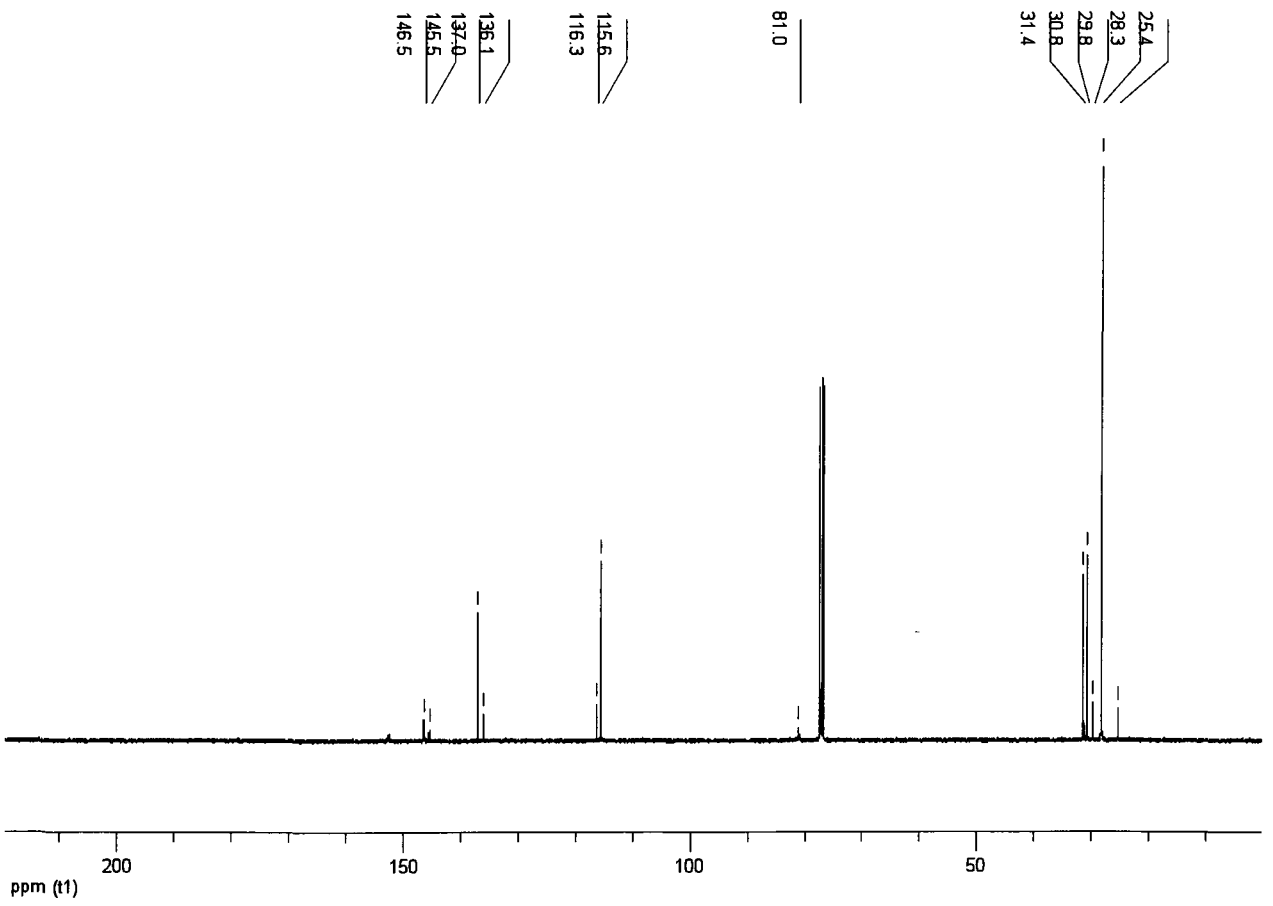

O
NH
N
O

10.0
ppm (t1)
5.0
0.0

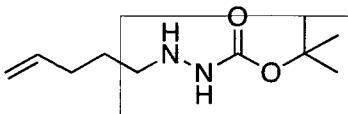

166.2
133.6
131.5
128.5
127.0
72.1
66.6
59.1
55.8
14.2
200
150
100
50
ppm (t1)


O
N
N
H
O

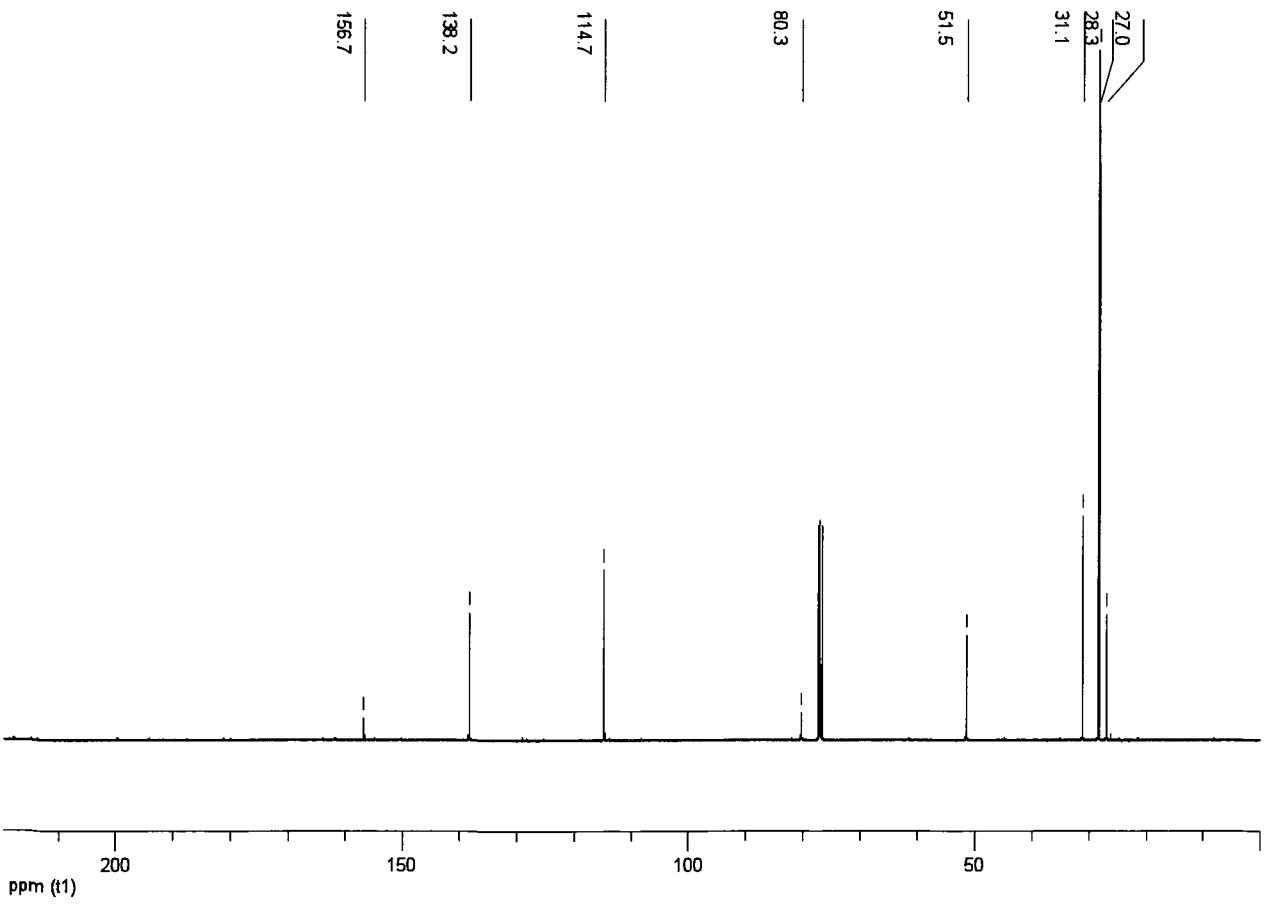
10.0
ppm (f1)
5.0
0.0

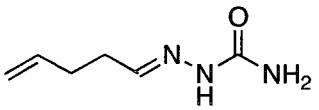

146.5
145.5
137.0
136.1
116.3
115.6
81.0
31.4
30.8
29.8
28.3
25.4
200
ppm (t1)
150
100
50

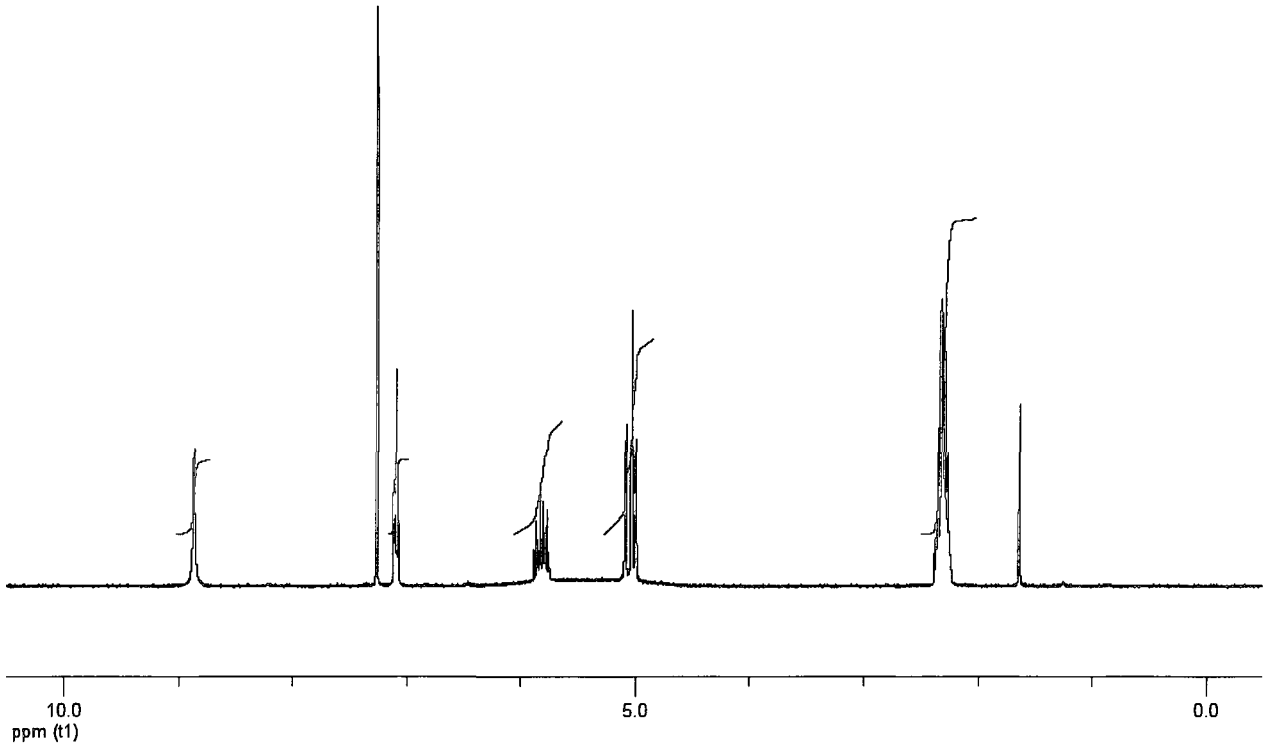
3.9a

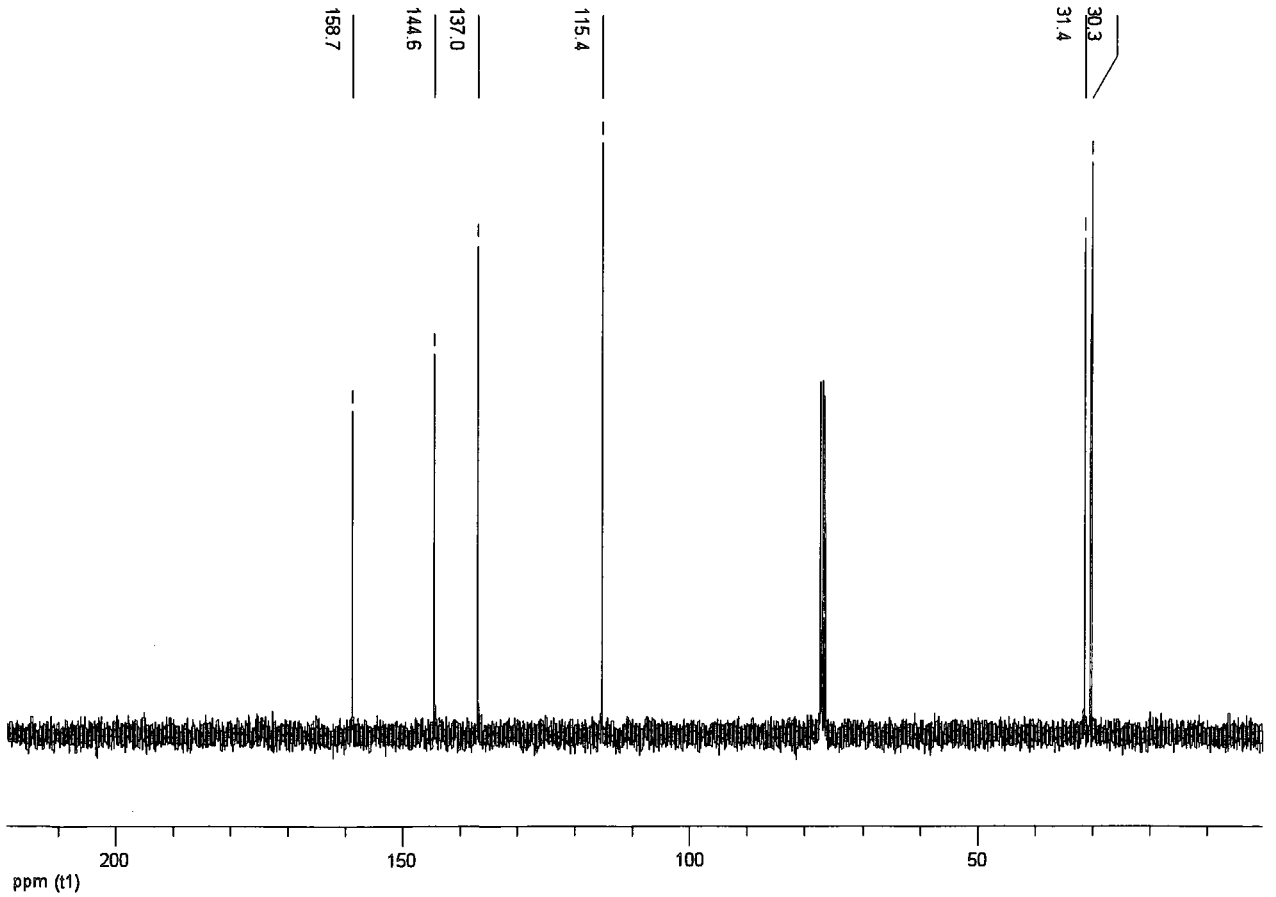


10.0
ppm (t1)
5.0
0.0

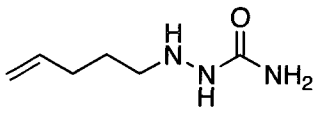

156.7
138.2
114.7
80.3
51.5
31.1
28.3
27.0
200
150
100
50
ppm (t1)


O
N
N
H
NH2

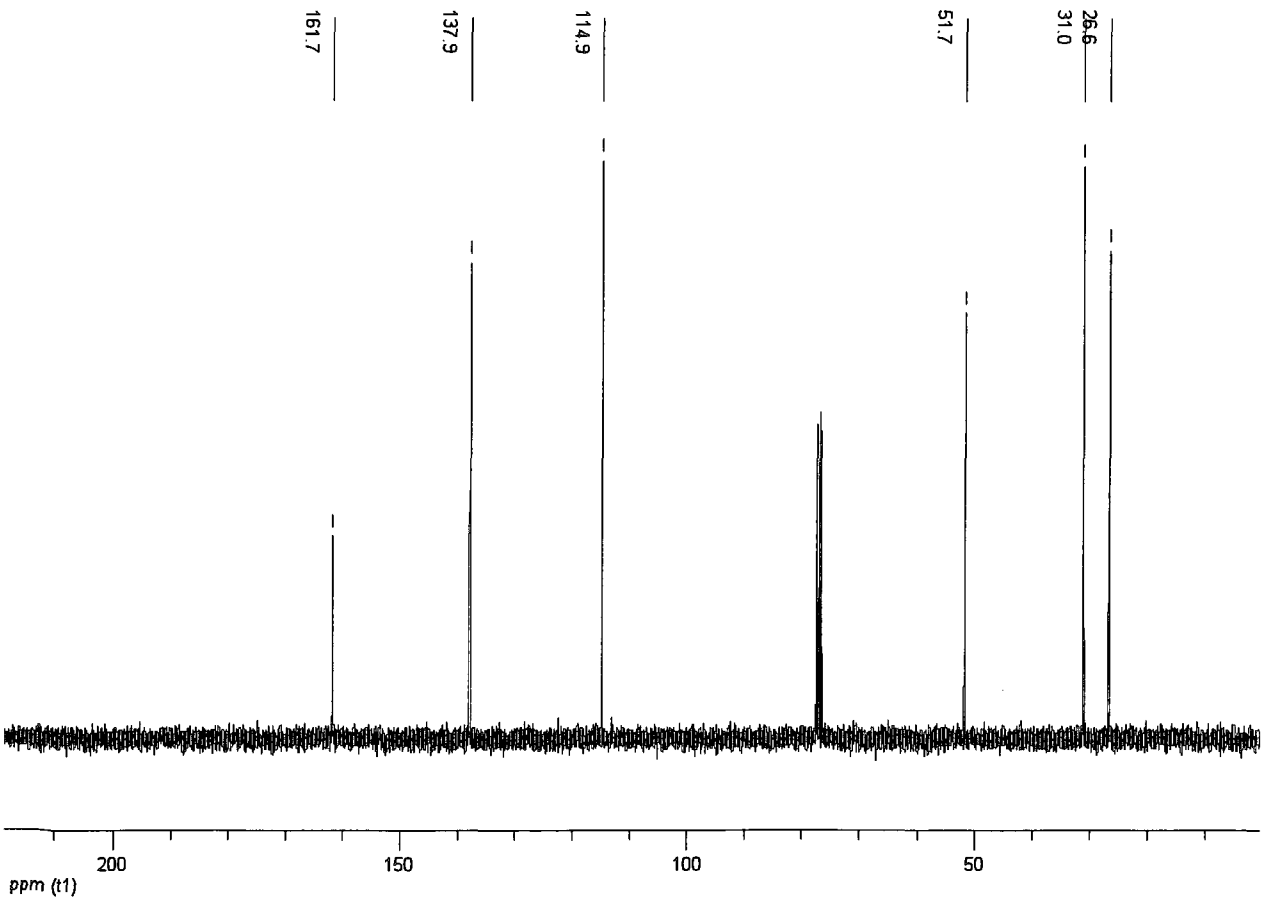

10.0
ppm (t1)
5.0
0.0

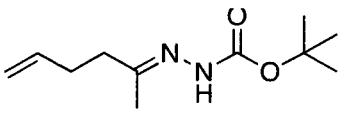

158.7
144.6
137.0
115.4
31.4
30.3
200
ppm (t1)
150
100
50

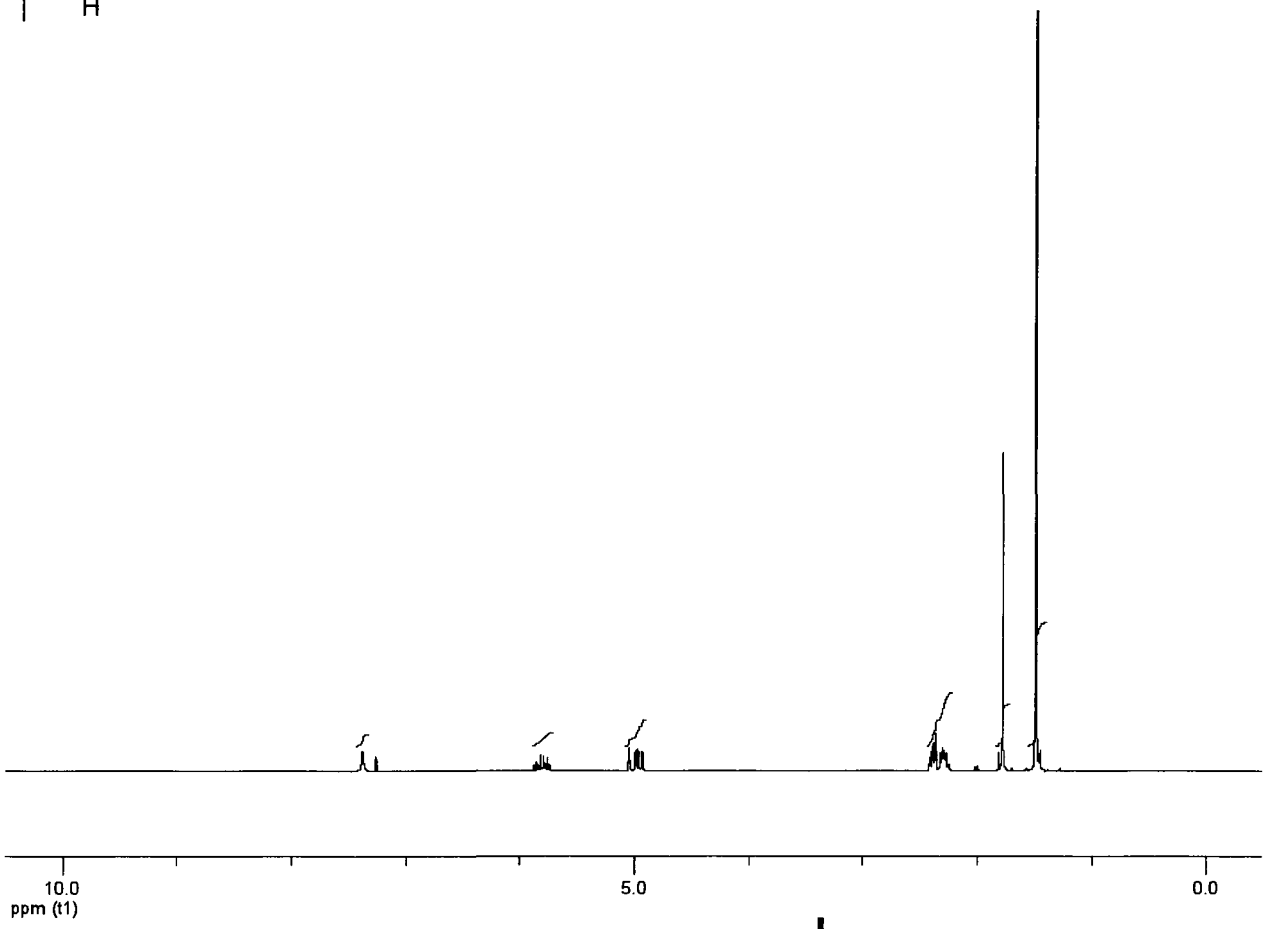
3.9b

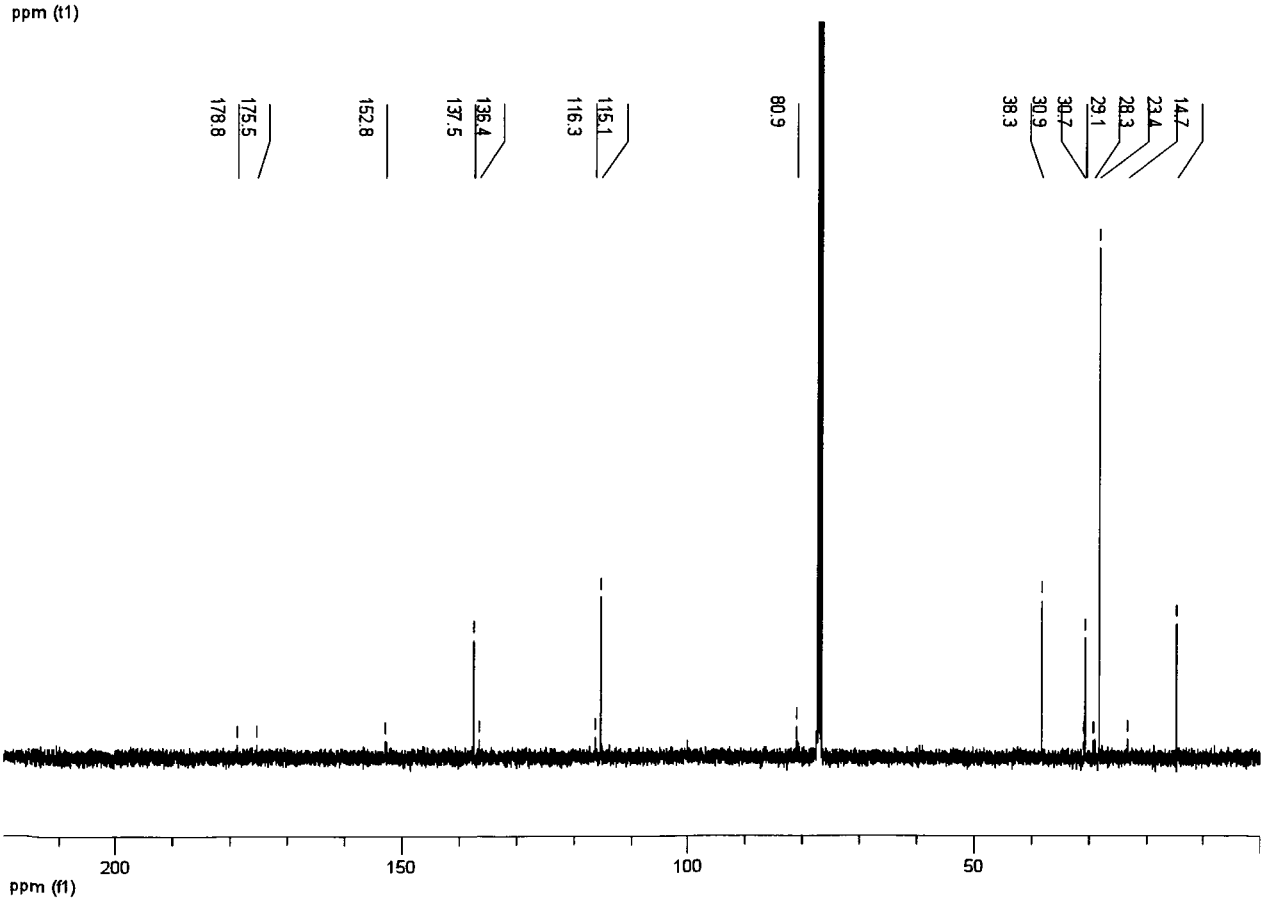

H
N
N
H
O
NH2

10.0
ppm (t1)
5.0
0.0

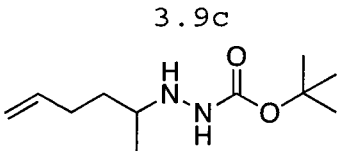

161.7
137.9
114.9
51.7
31.0
26.6
200
150
100
50
ppm (t1)



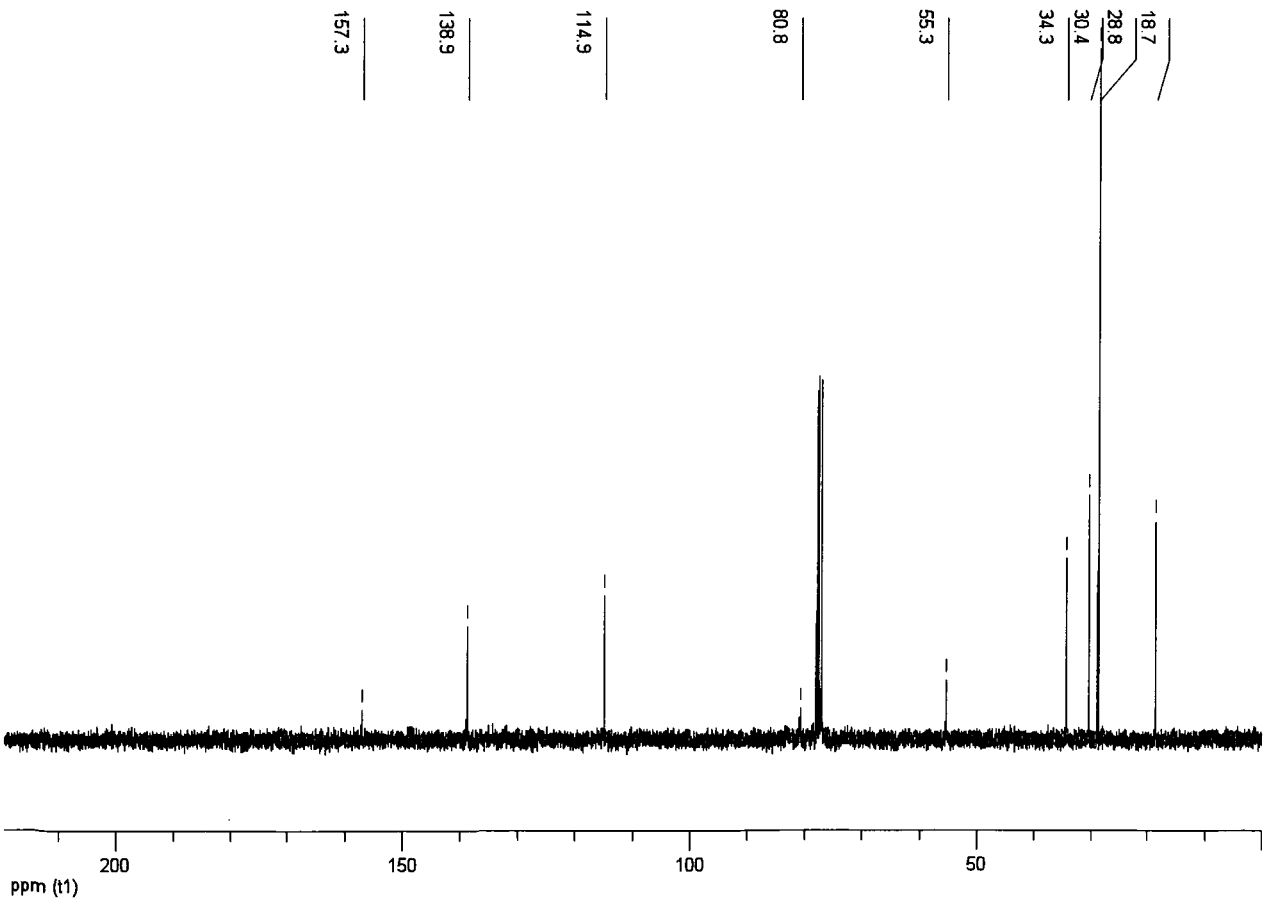

10.0
ppm (t1)
5.0
0.0

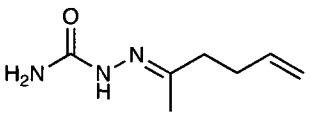

178.8
175.5
152.8
137.5
136.4
116.3
115.1
80.9
38.3
30.9
30.7
29.1
28.3
23.4
14.7
200
150
100
50
ppm (f1)

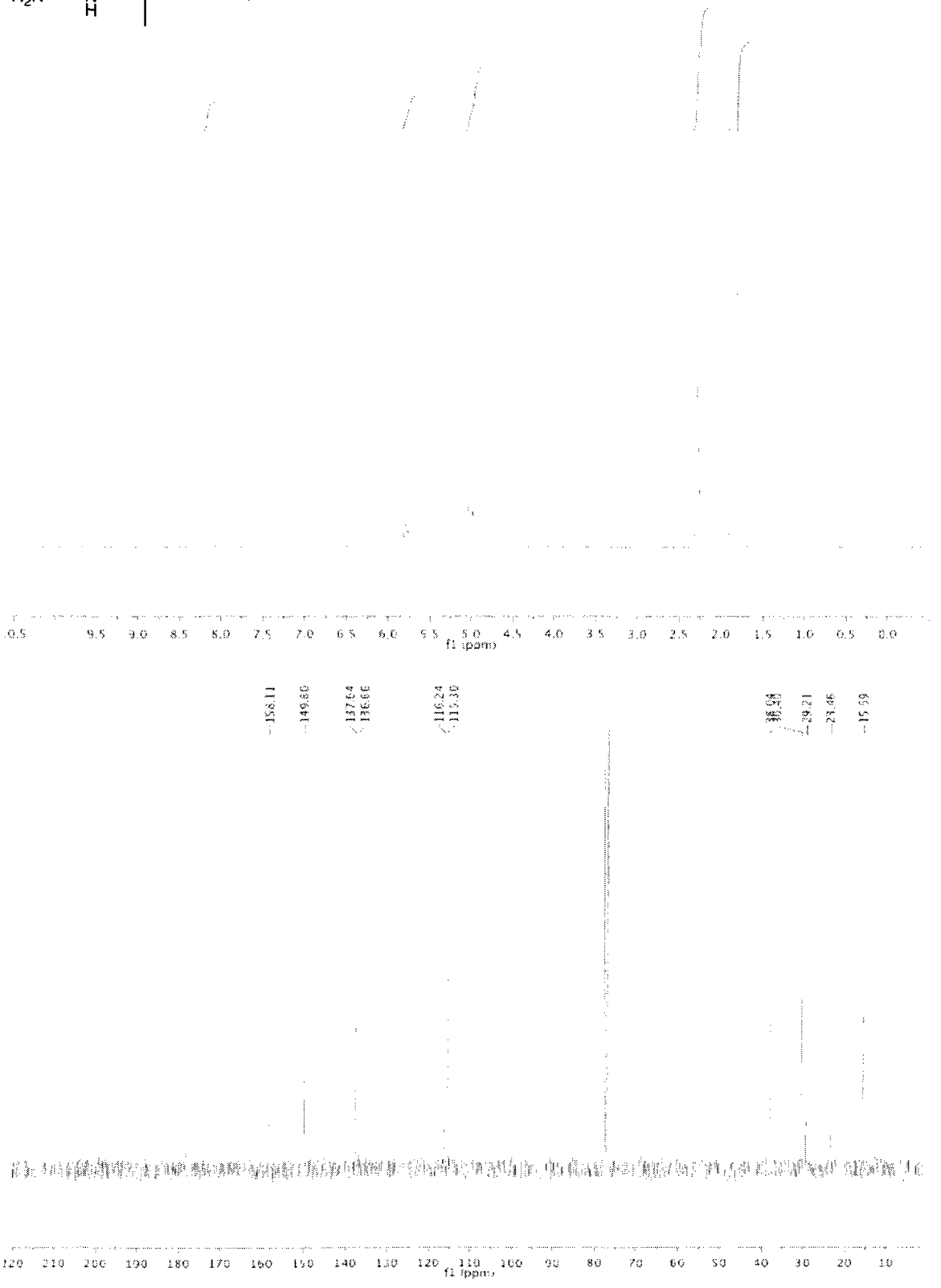
3.9c



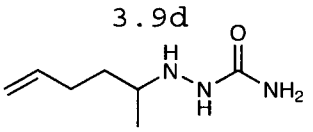
10.0
ppm (t1)
5.0
0.0

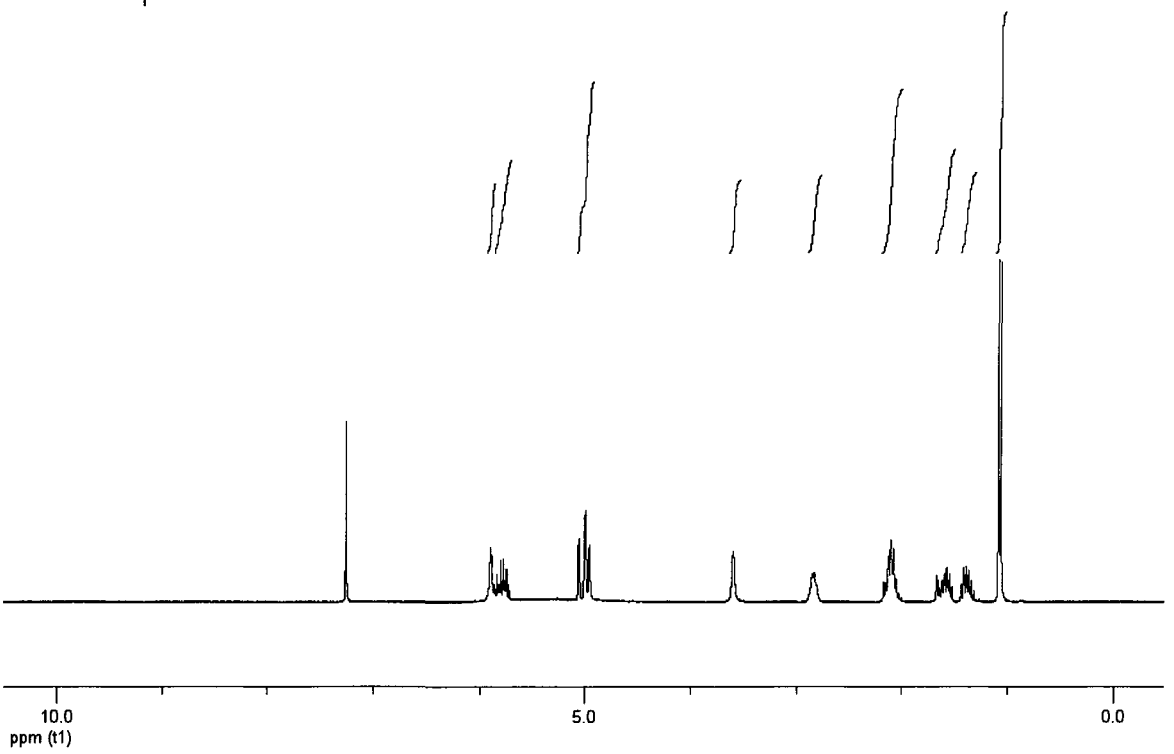

157.3
138.9
114.9
80.8
55.3
34.3
30.4
28.8
18.7
200
150
100
50
ppm (t1)

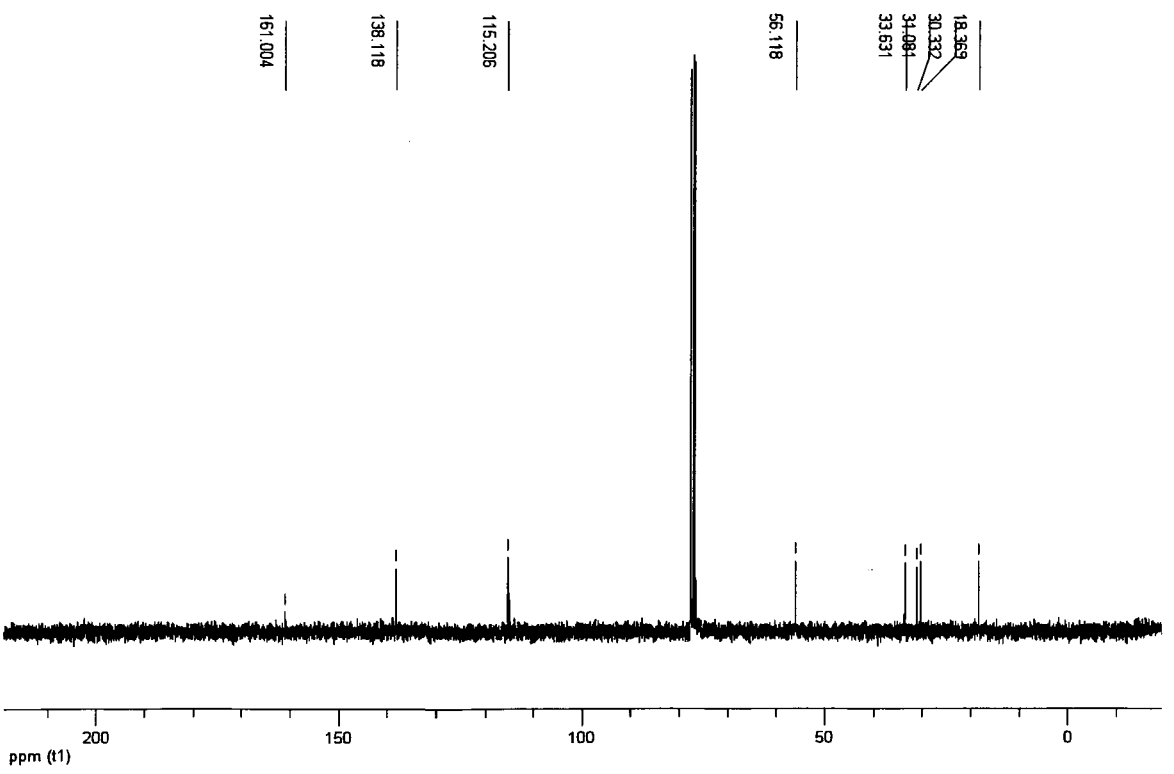


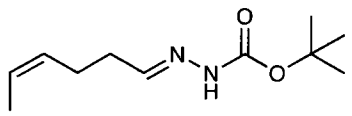

f1 (ppm)
158.11
149.60
137.64
136.66
116.24
115.30
36.49
36.24
29.21
23.46
15.59
f1 (ppm)

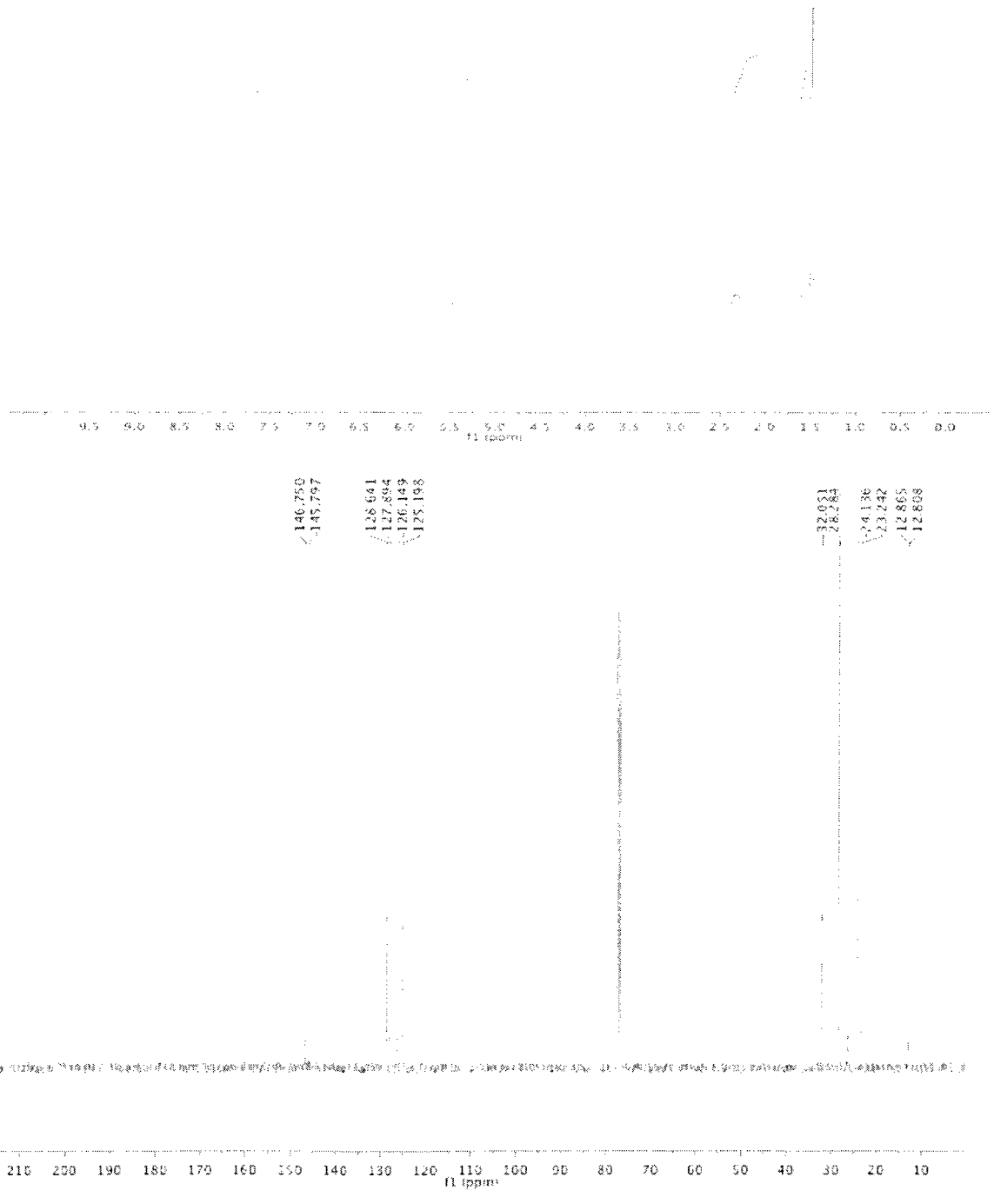
3.9d


H
N
O
N
H
NH2

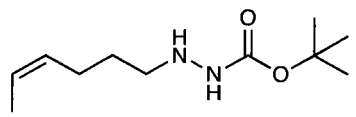

10.0
ppm (t1)
5.0
0.0

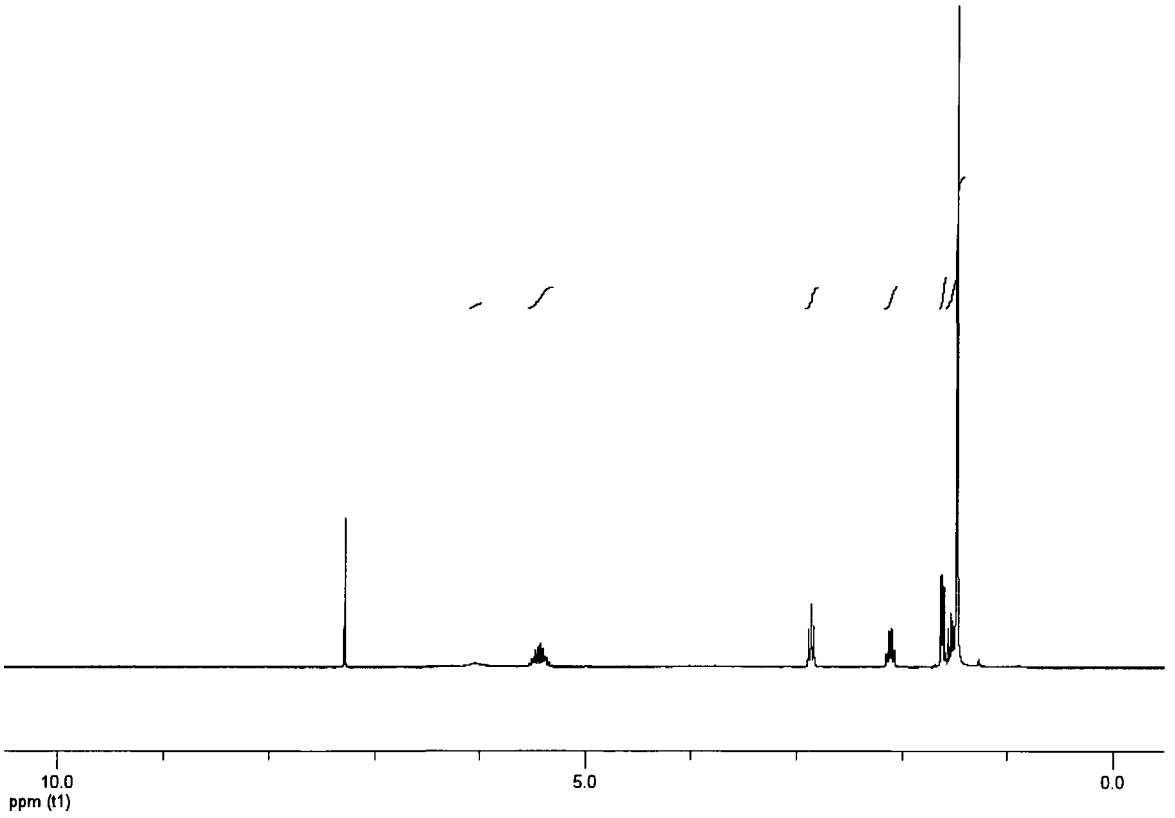

161.004
138.118
115.206
56.118
33.631
31.081
30.332
18.369
200
ppm (t1)
150
100
50
0

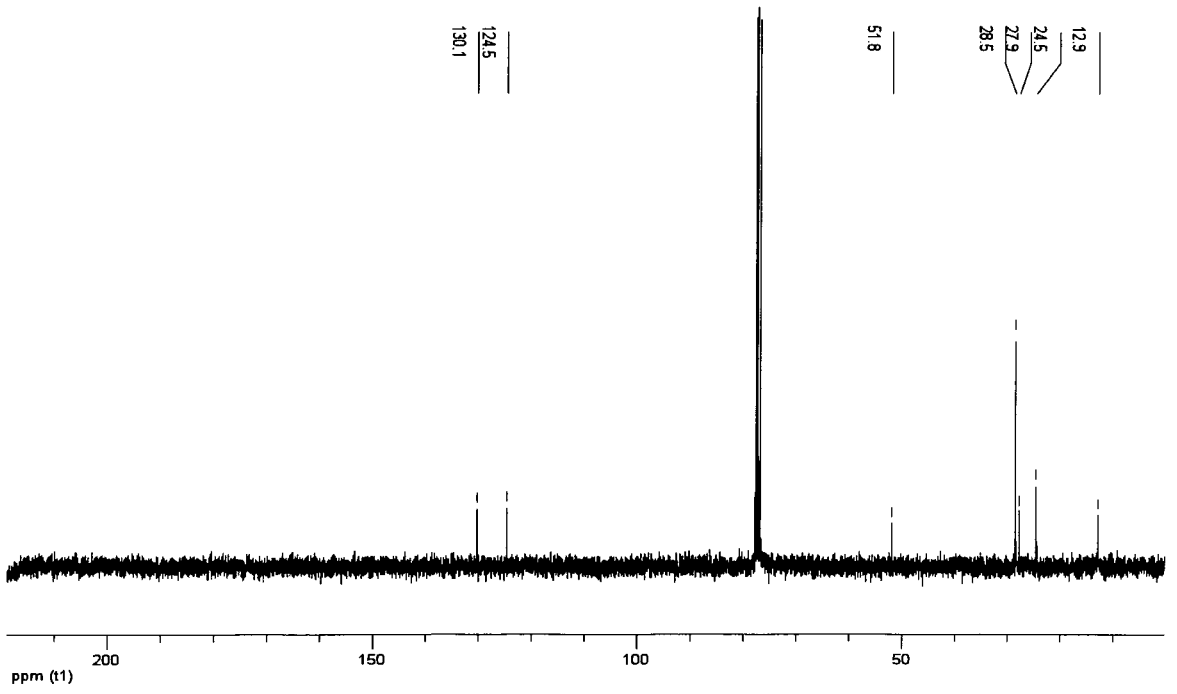


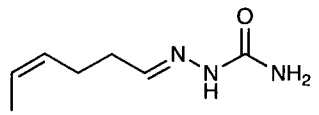

f1 (ppm)
146.750
145.797
128.641
127.894
126.149
125.198
32.031
28.783
24.136
23.242
12.865
12.808
f1 (ppm)

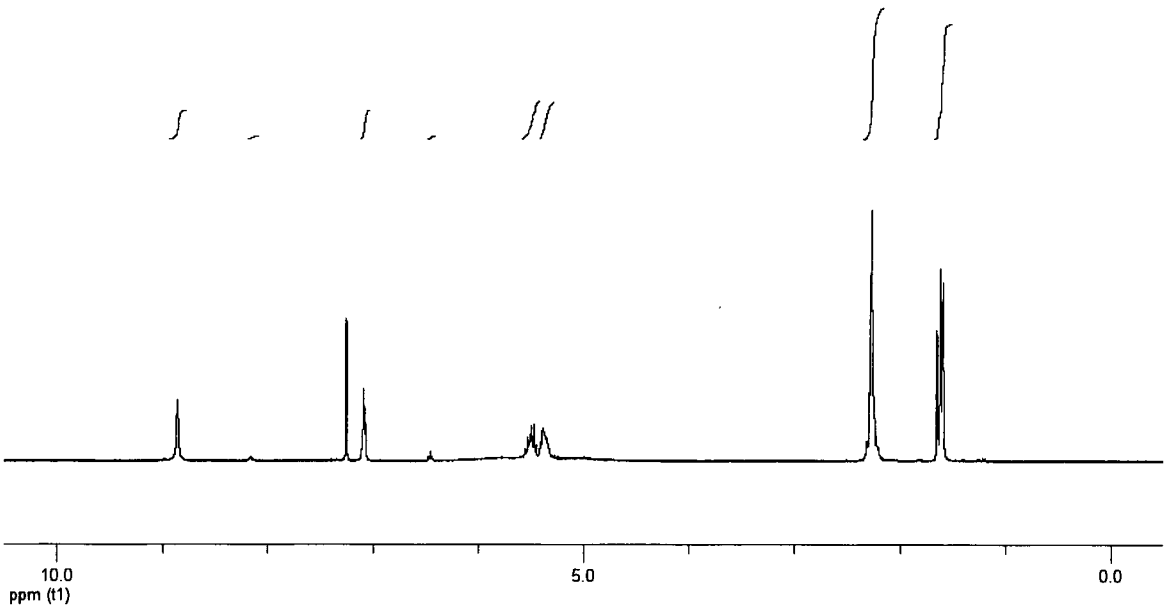
3.9e

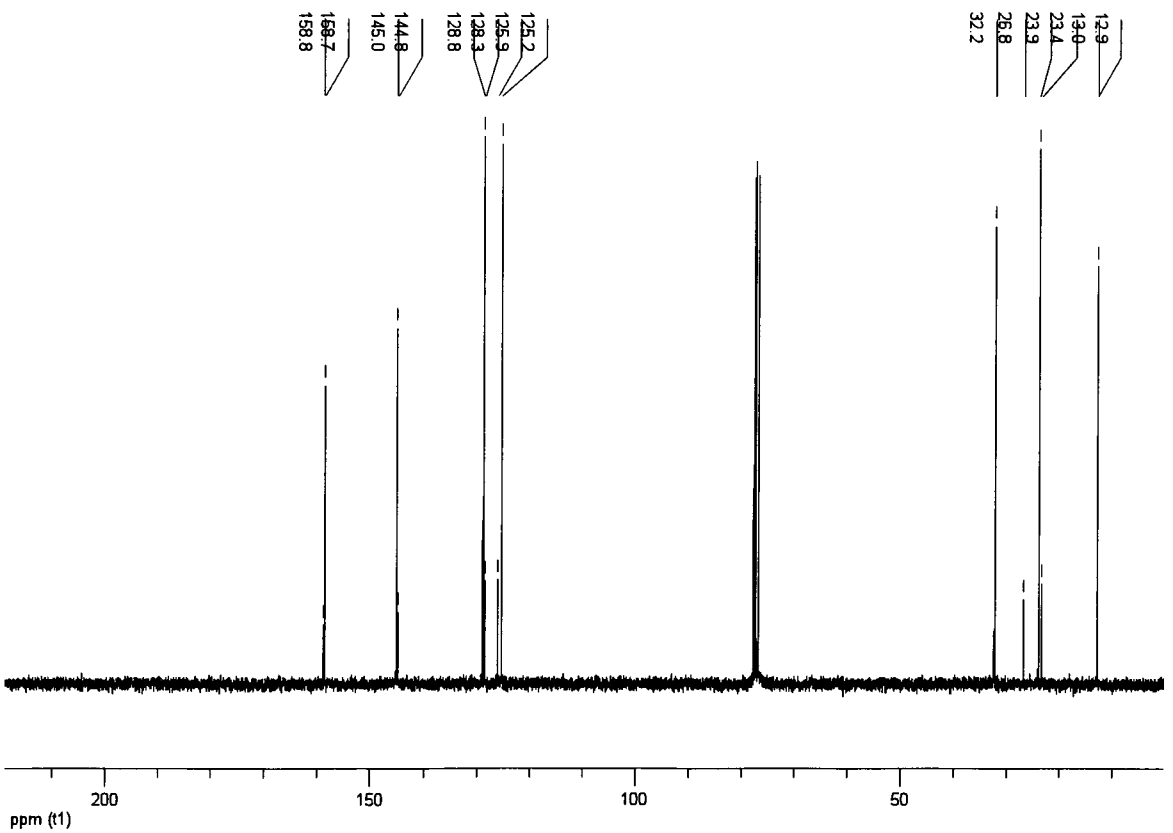



10.0
ppm (t1)
5.0
0.0

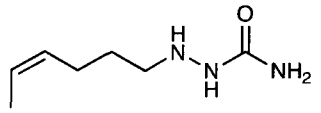

130.1
124.5
51.8
28.5
27.9
24.5
12.9
200
ppm (t1)
150
100
50

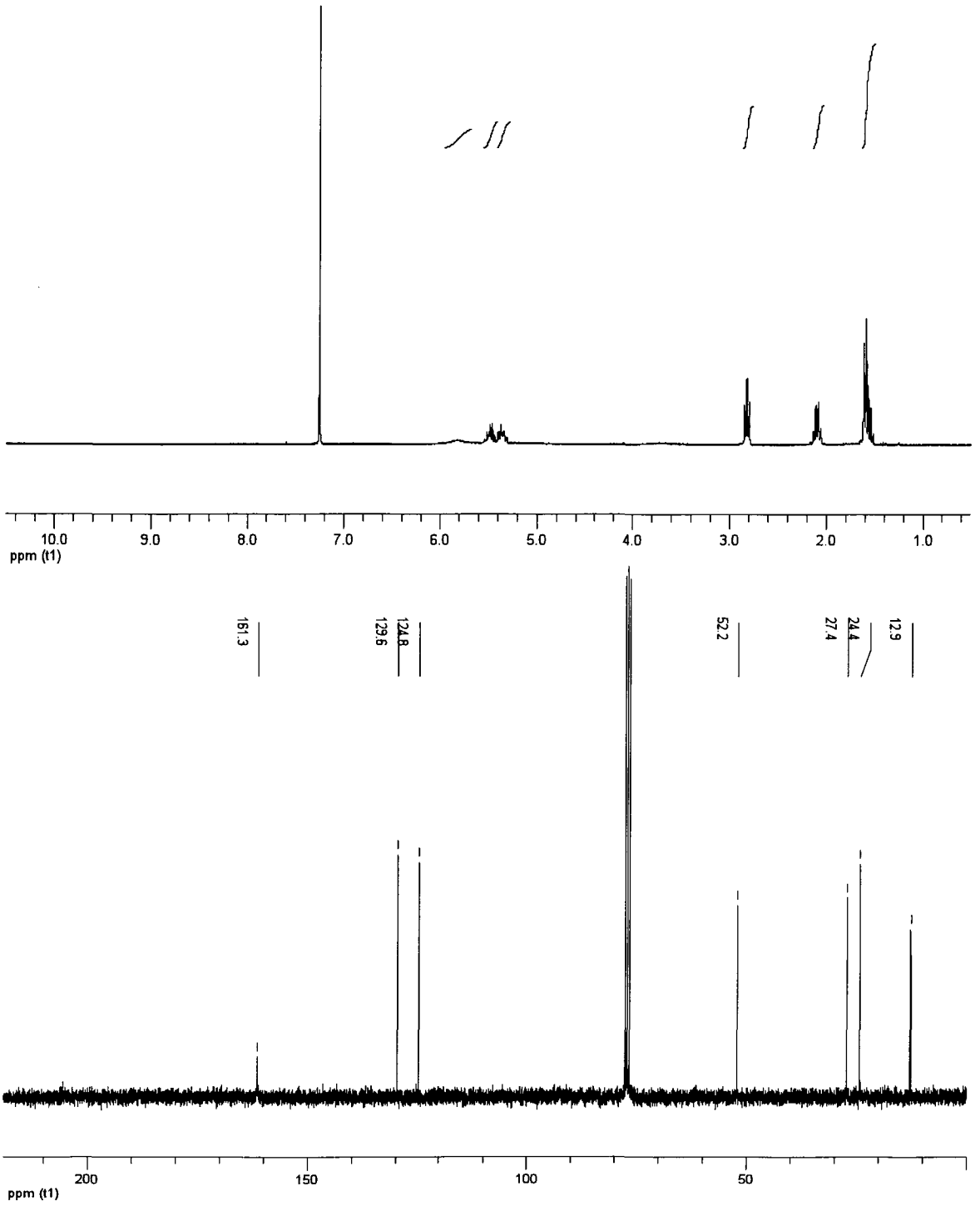

O
N
N
H
NH2


10.0
ppm (t1)
5.0
0.0

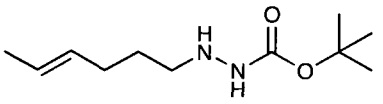

158.8
145.0
144.8
128.8
32.2
26.8
23.9
23.4
13.0
12.9
200
150
100
50
ppm (t1)

3.9f

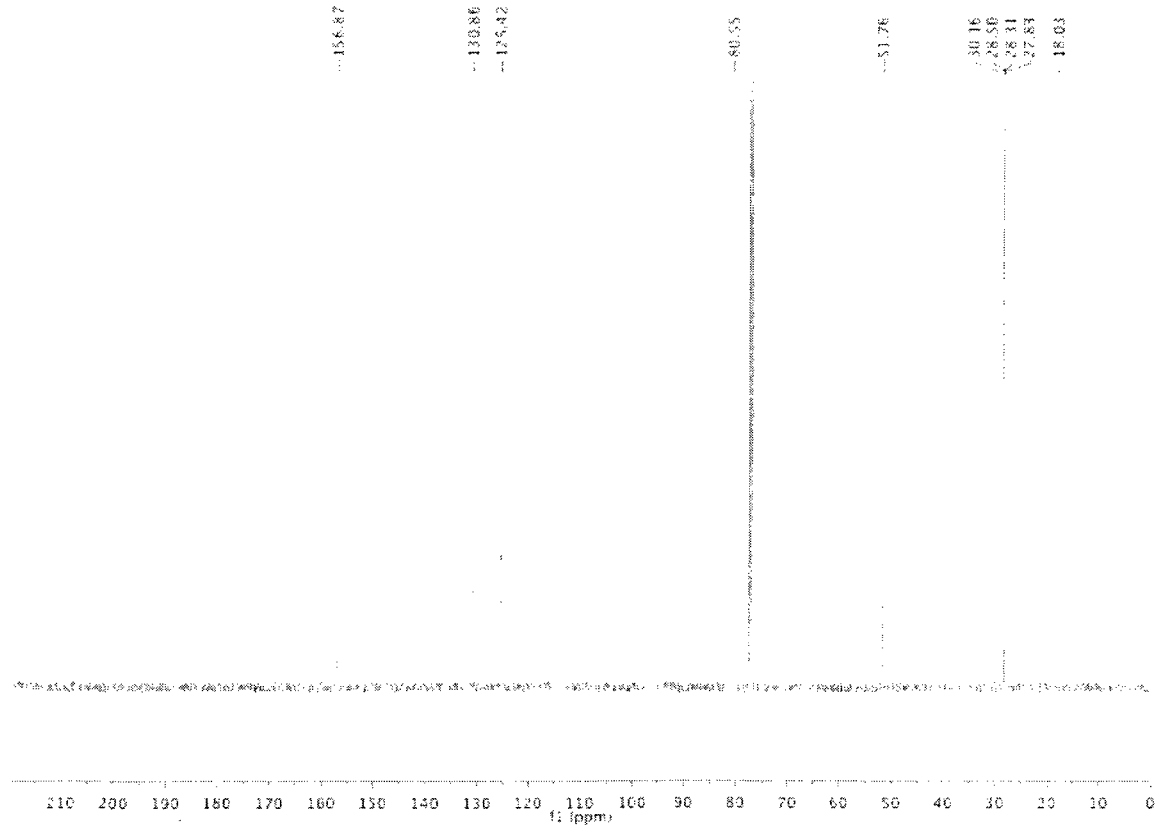

H
N
O
N
H
NH2

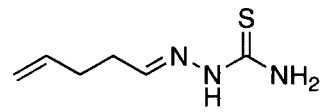

10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)
161.3
129.6
124.8
52.2
27.4
24.4
12.9
200
150
100
50
ppm (t1)

3.9g

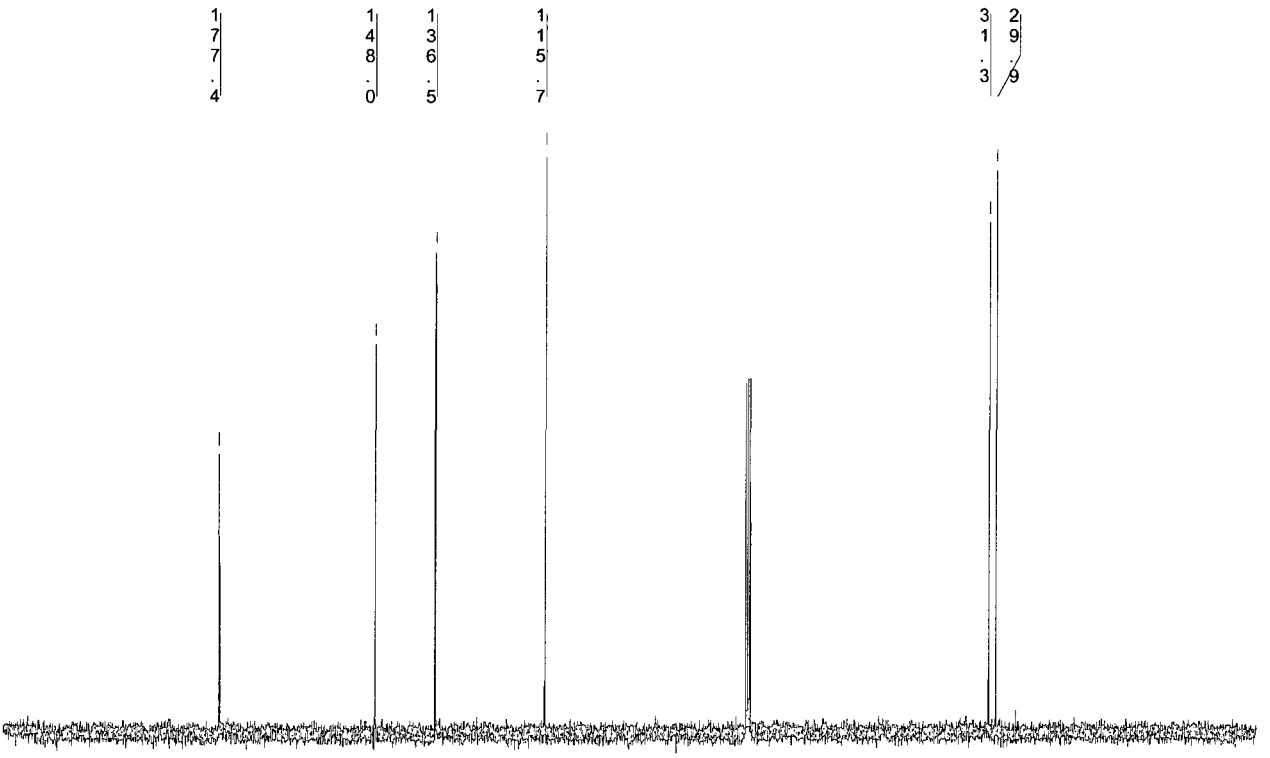


10.0
ppm (t1)
5.0
0.0


156.87
138.86
129.42
80.55
51.78
30.16
28.58
28.31
27.83
18.03
f1 (ppm)

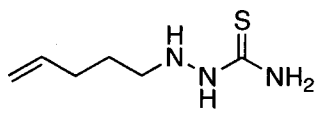


ppm (t1)

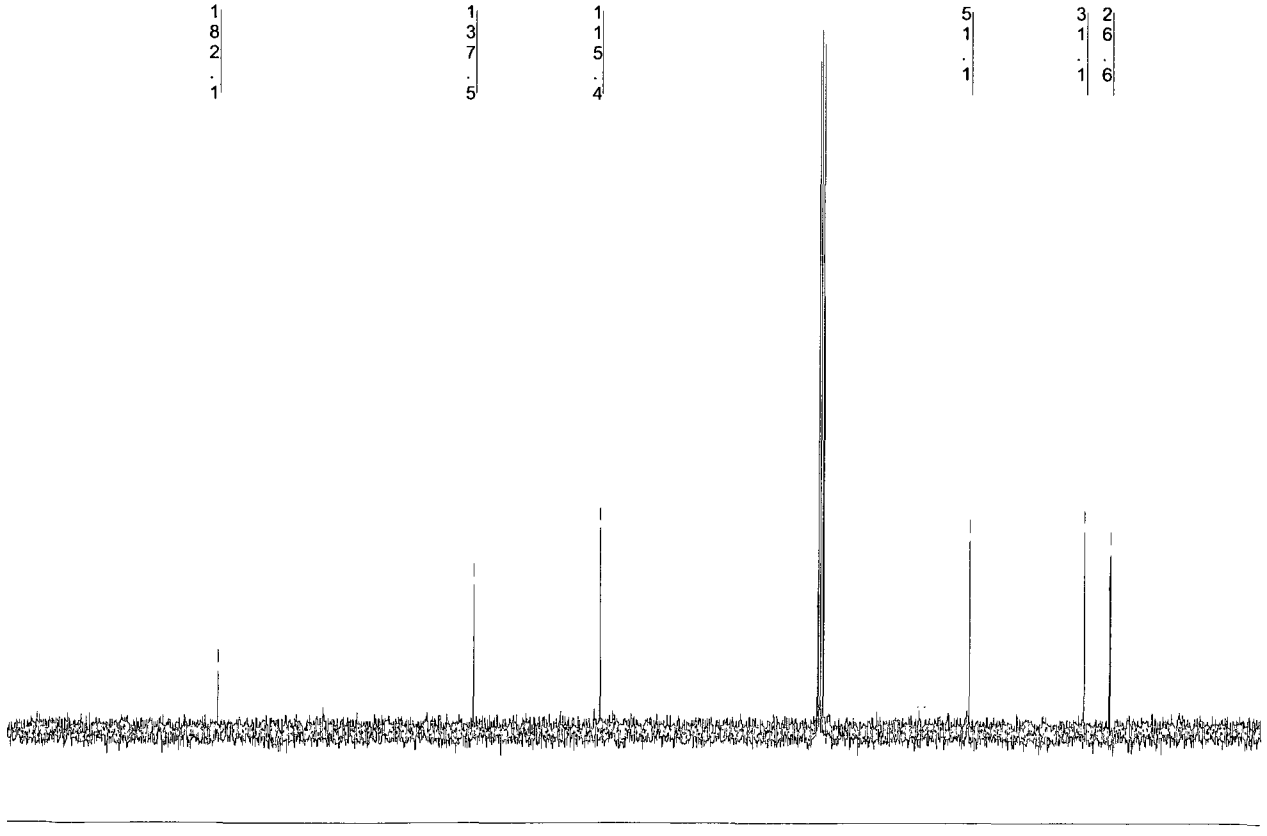


ppm (t1)

3.25

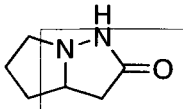


ppm (t1)

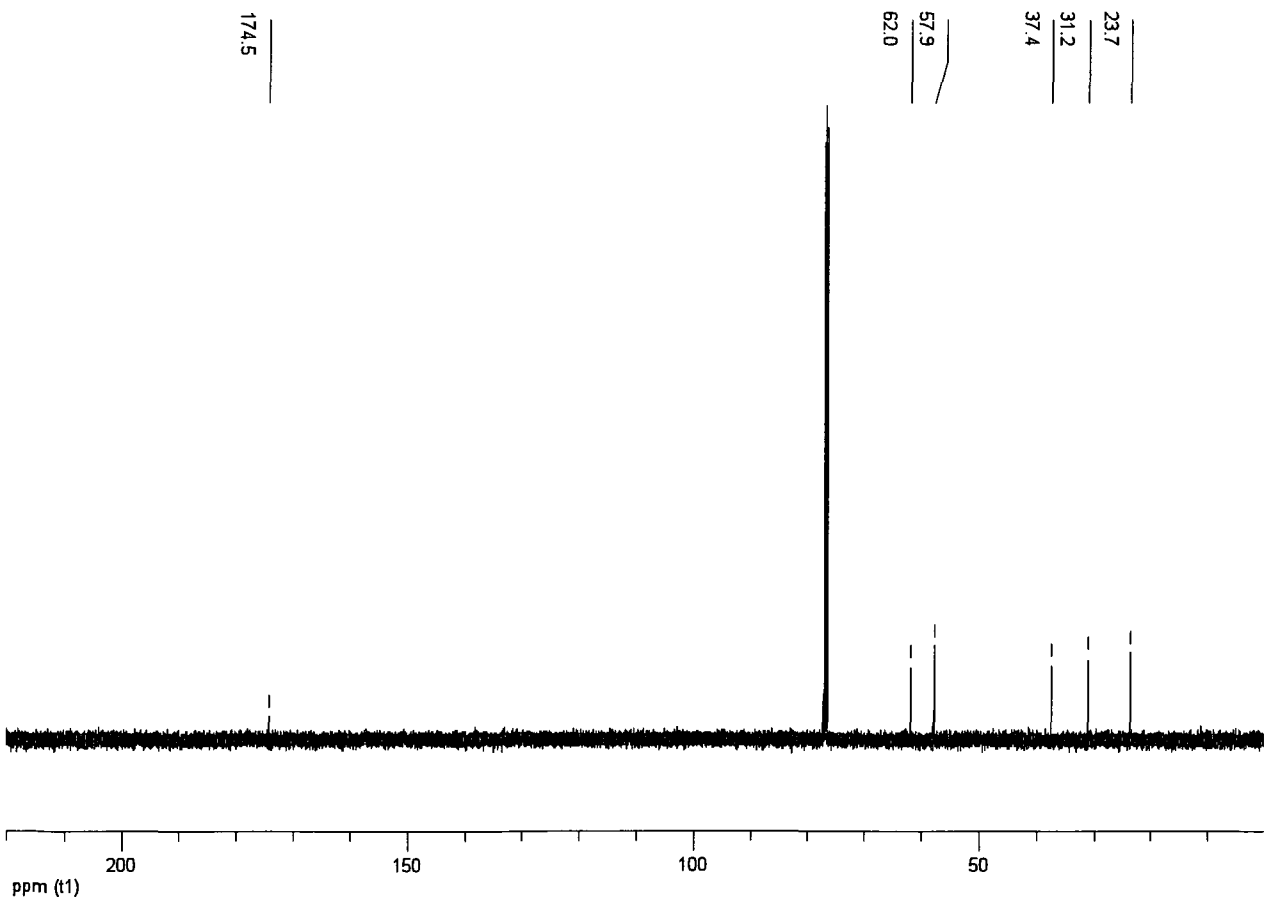


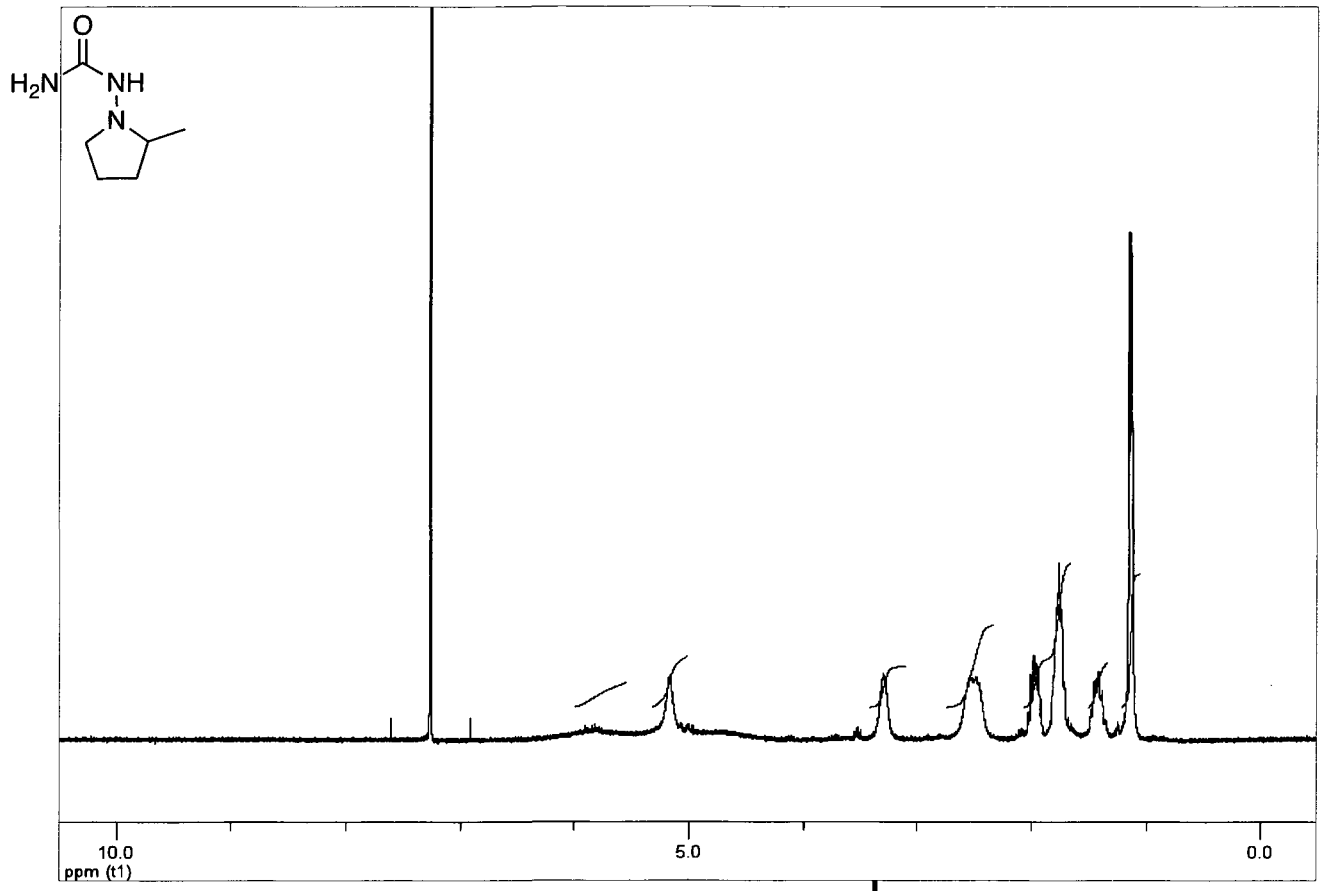
ppm (t1)

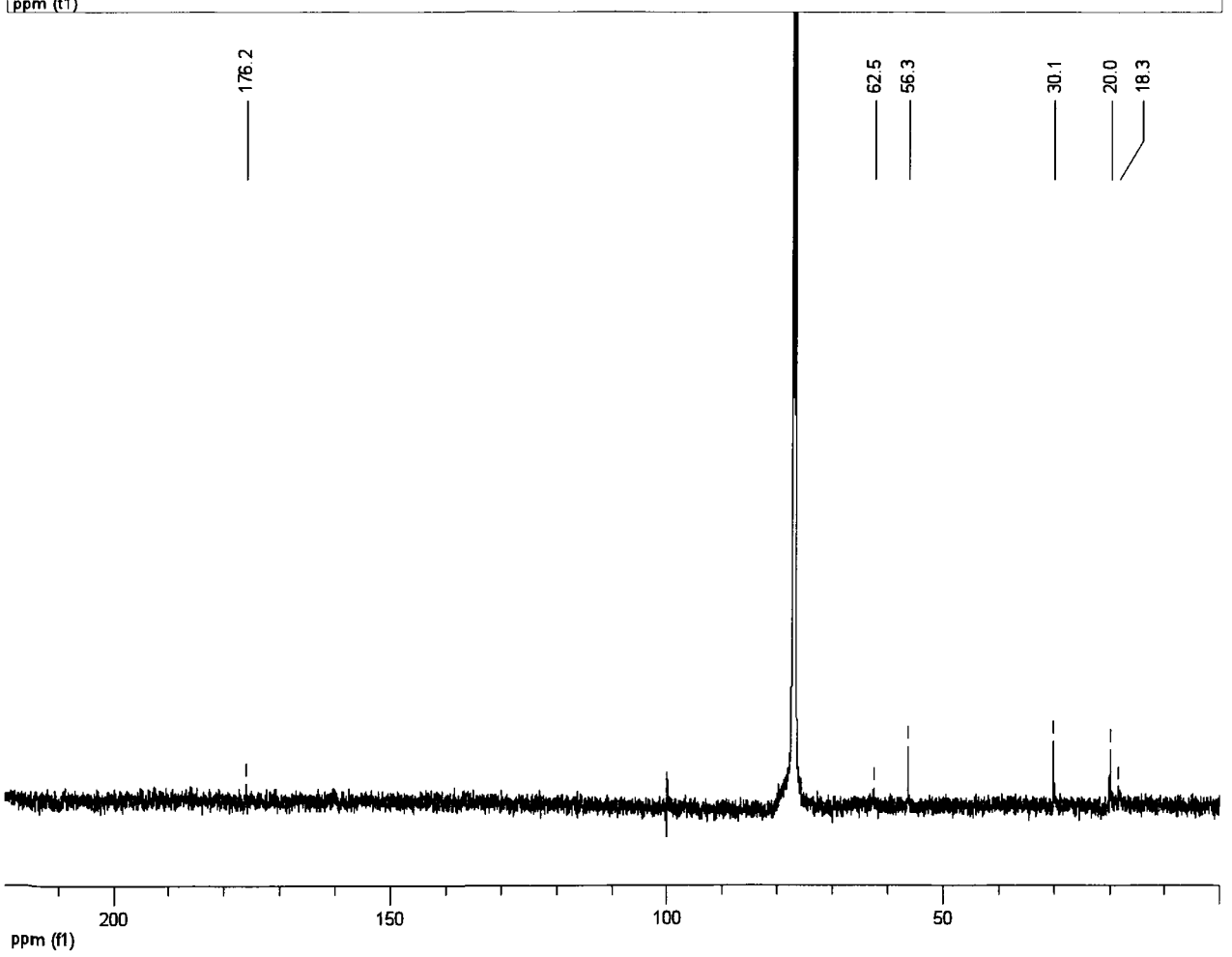
3.10a-b


H
N
N
O

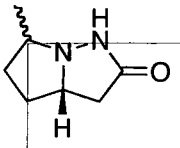
10.0
ppm (t1)
5.0
0.0

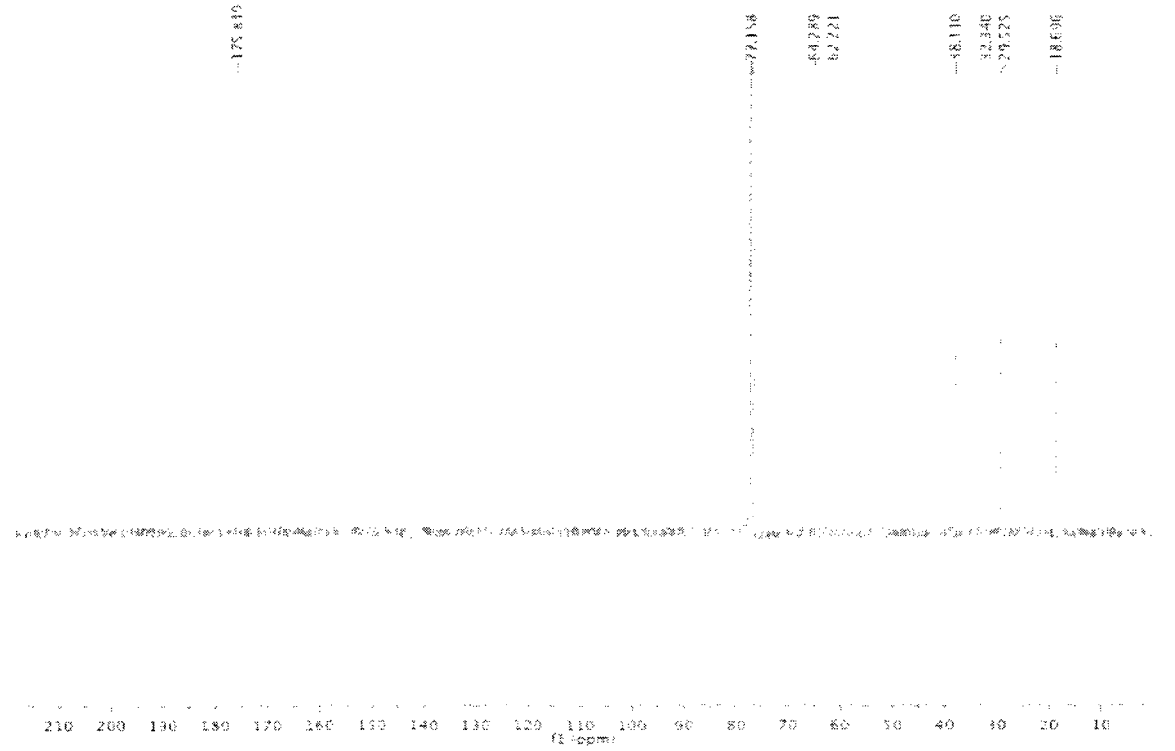

174.5
62.0
57.9
37.4
31.2
23.7
200
150
100
50
ppm (t1)


O
H2N
NH
N
10.0
ppm (t1)
5.0
0.0

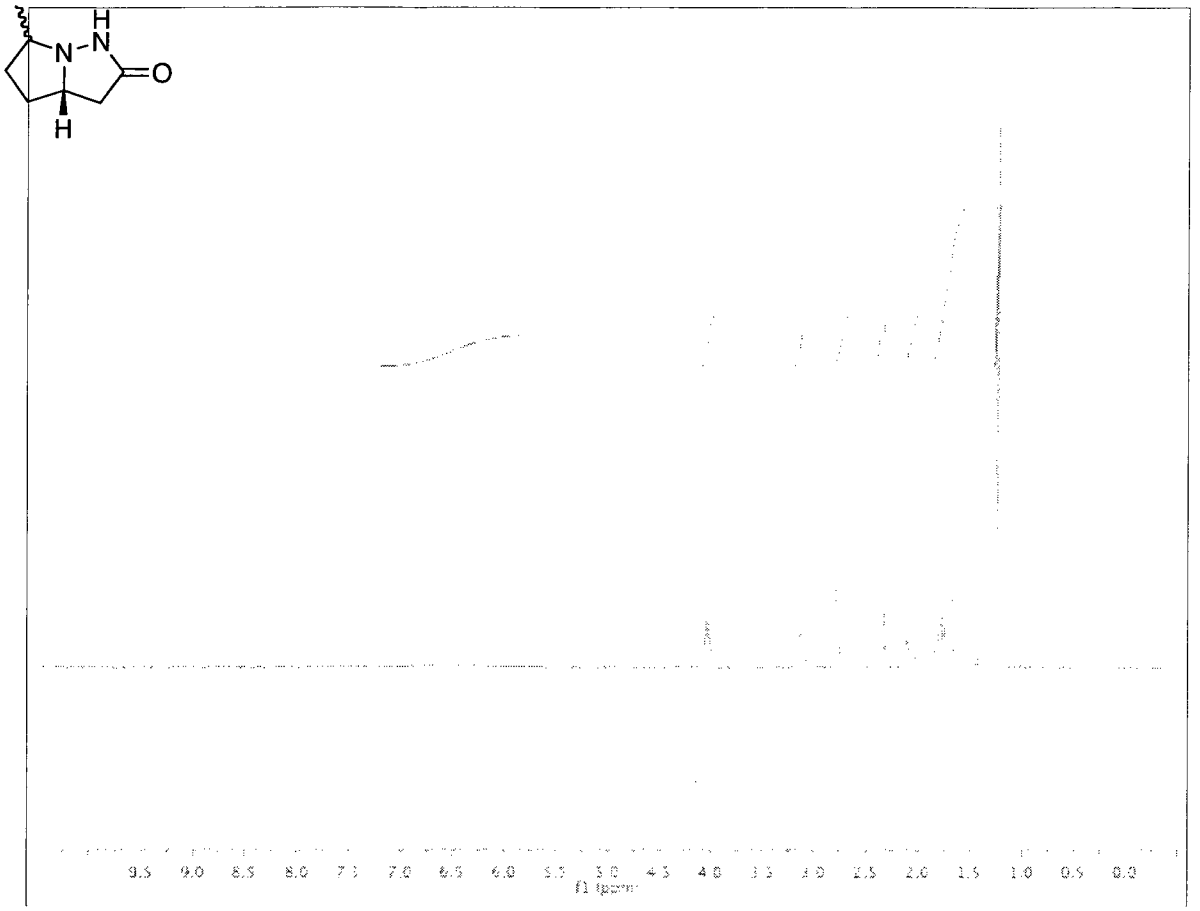

176.2
62.5
56.3
30.1
20.0
18.3
200
150
100
50
ppm (f1)

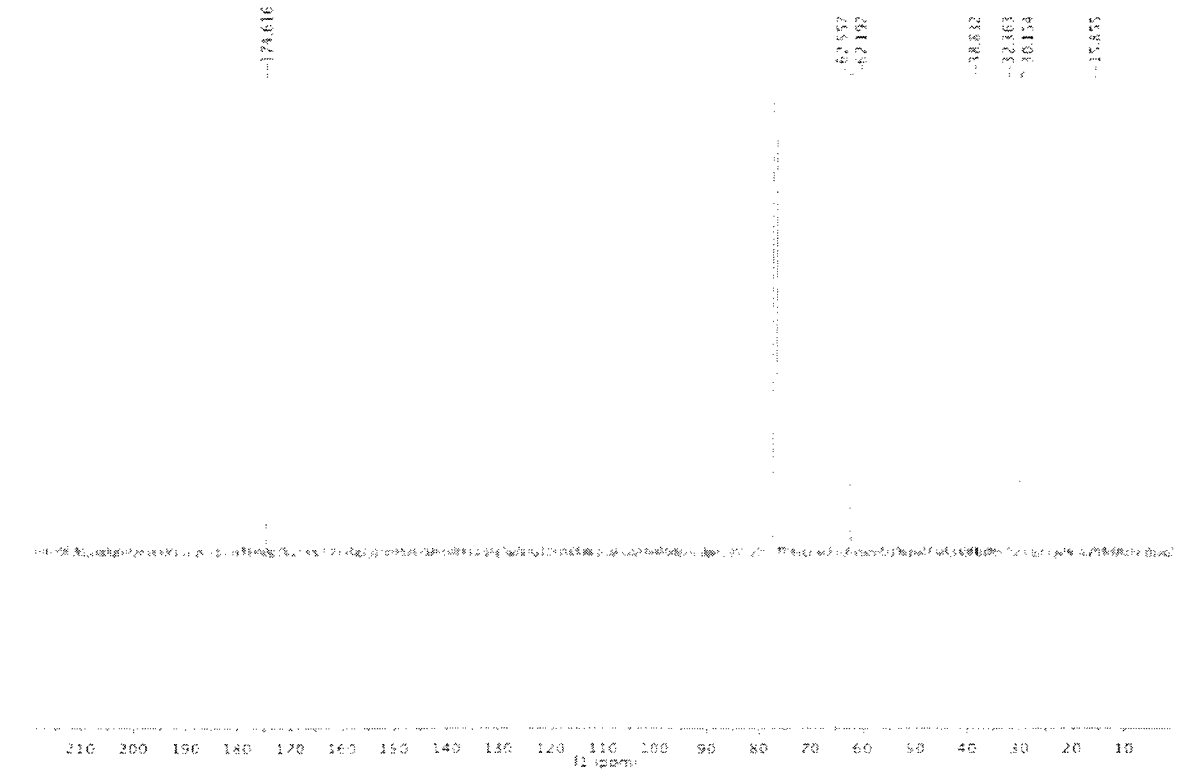
3.10c-d



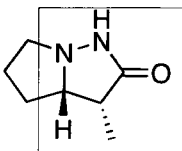


3.10c-d

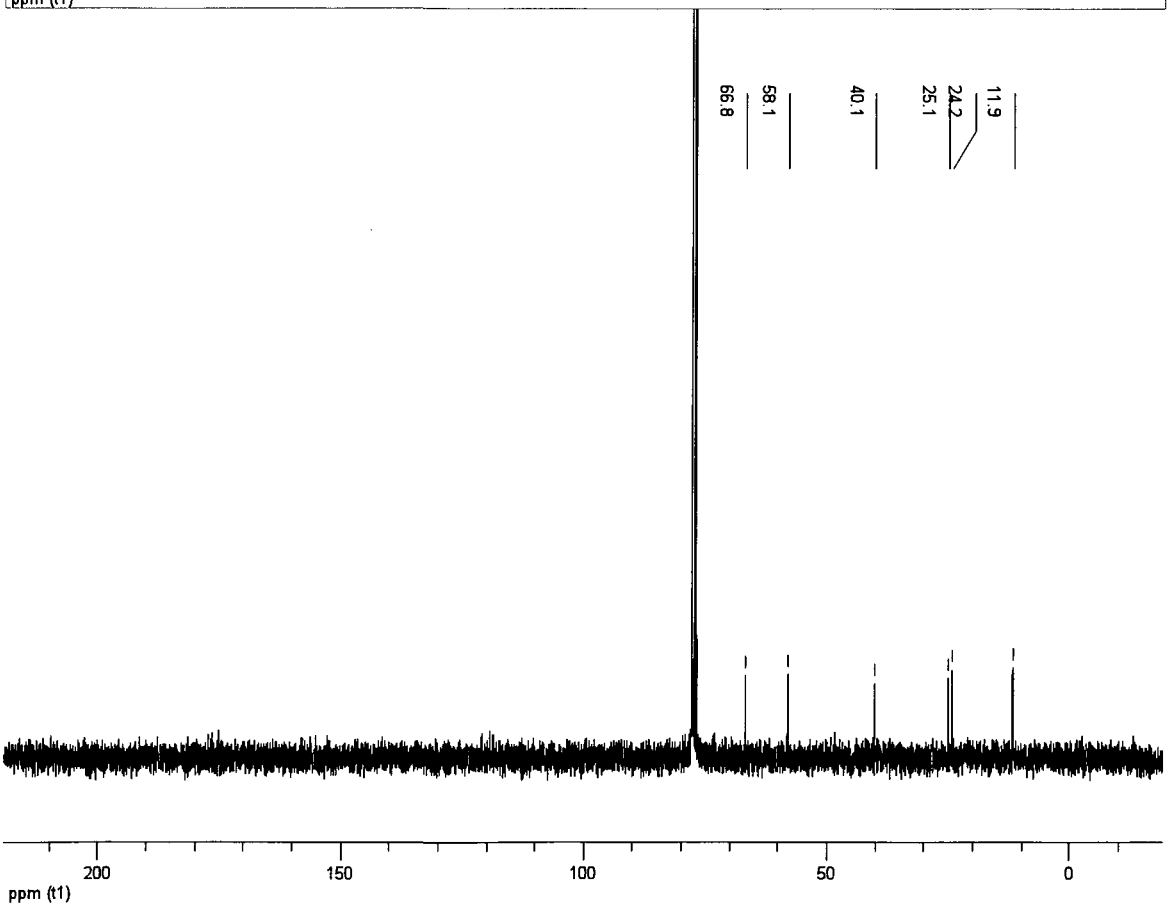

H
N
N
O
H
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


174.616
62.552
62.192
38.832
32.363
28.134
15.855
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

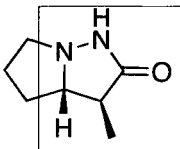
3.10g


H
N
N
O
H

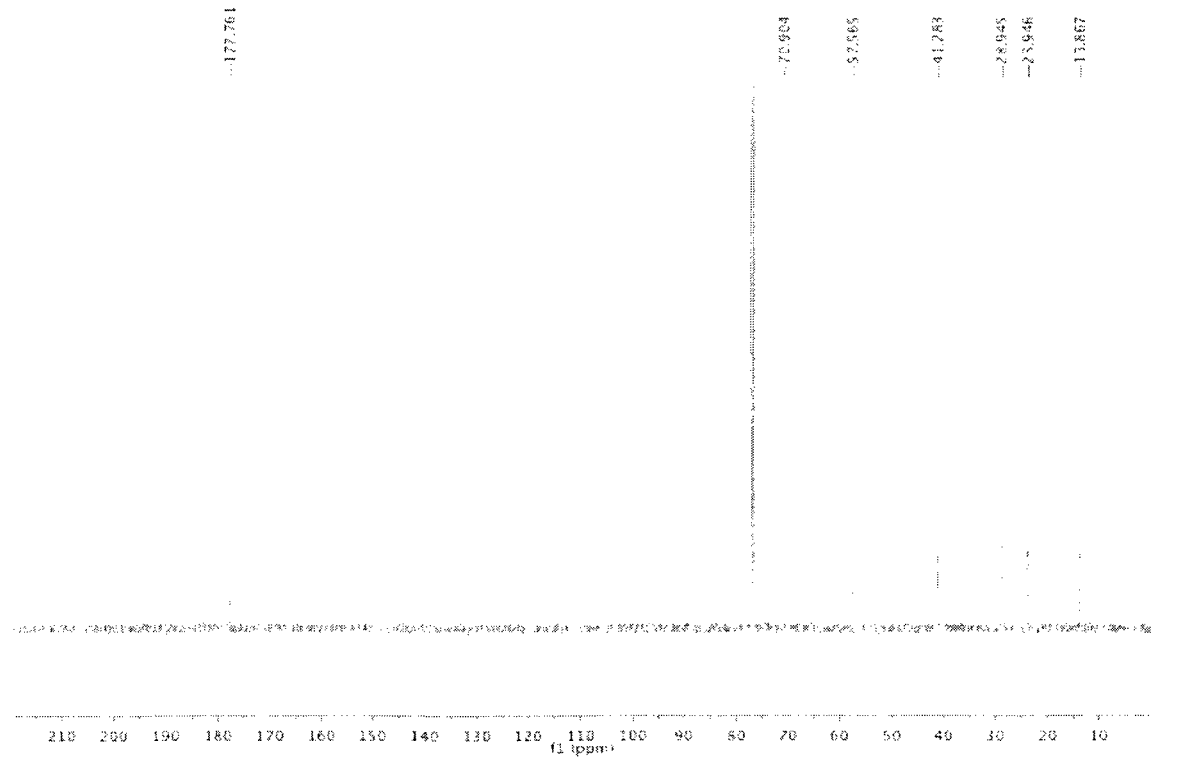
10.0
5.0
0.0
ppm (t1)


66.8
58.1
40.1
25.1
24.2
11.9
200
150
100
50
0
ppm (t1)

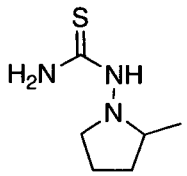
3.10e-f


H
N
N
O
H

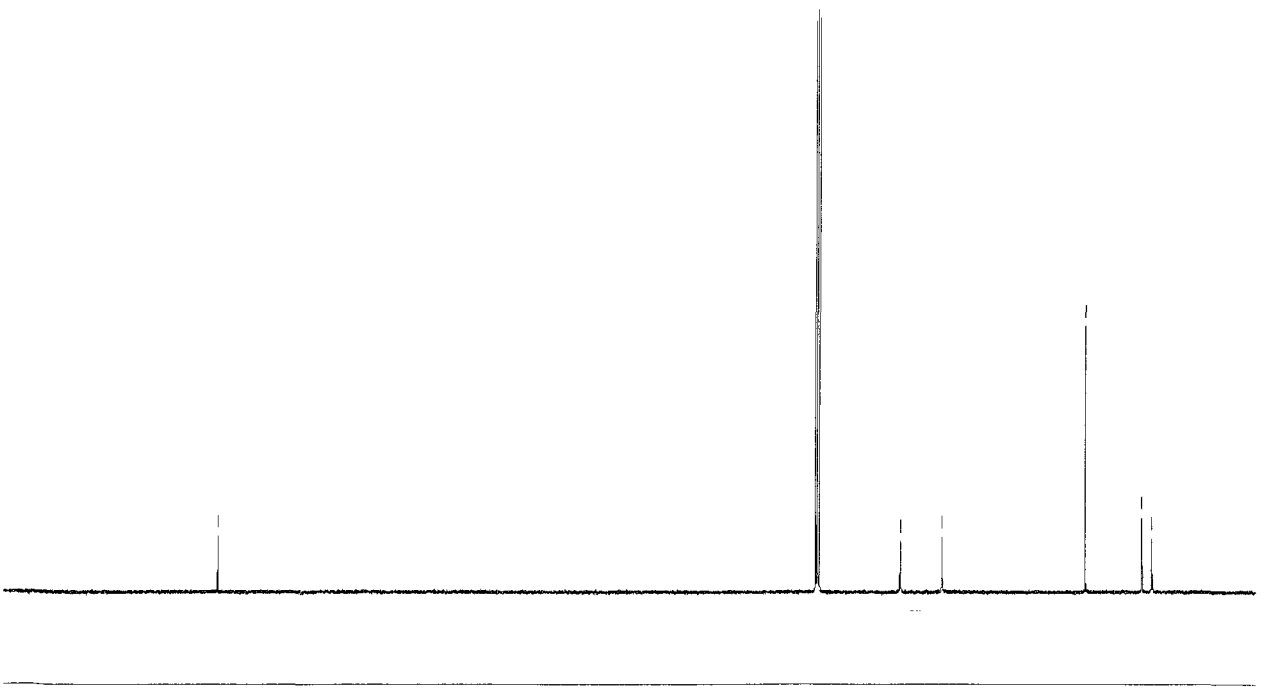
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


177.761
75.984
57.165
41.283
28.945
25.846
13.867
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

3.26



ppm (t1)



ppm (t1)