Pergamon

Tetrahedron 54 (1998) 13997–14014

TETRAHEDRON

One-Pot Synthesis of the Hydroximoyl Chlorides and [3.3.0] Bicyclic Compounds from the Reactions of β-Nitrostyrenes with Stabilized Nucleophiles

Kuo-Hsi Kao, Cherng-Shi Yang, Ju-Tsung Liu, Wen-Wei Lin,
Hui-Yu Fang, Ching-Fa Yao,* and Kwunmin Chen*,#

*Department of Chemistry, National Taiwan Normal University
88 Sec. 4, Tingchow Road, Taipei, Taiwan, 117 R.O.C.

#Department of Applied Chemistry, Chaoyang University of Technology
168 Gifeng E. Road, Wufeng, Taichung, Taiwan, 413 R.O.C.

Received 18 August 1998; accepted 18 September 1998

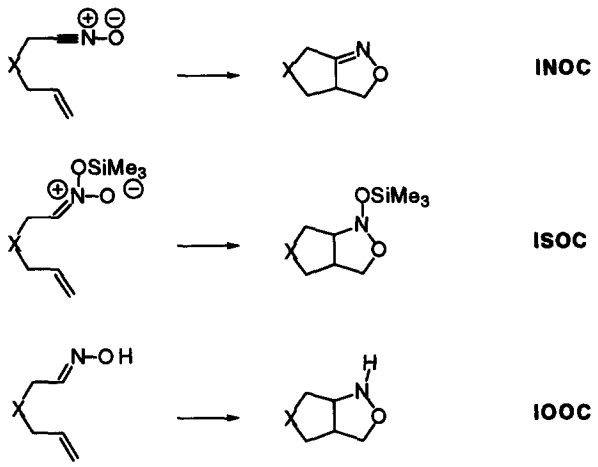
Abstract: β-Nitrostyrenes **1** react with various stabilized nucleophiles to generate hydroximoyl chlorides and nitroalkanes after workup with ice cold concentrated hydrochloric acid. One-pot synthesis of bicyclic products from the Michael addition of different nucleophiles with β-nitrostyrenes **1** is reported.

Introduction

Nitro olefins are useful intermediates in the synthesis of some biological active natural products.[1] Due to the strong electron withdrawing property of the nitro group, conjugated nitroalkenes are excellent Michael acceptors with a variety of nucleophiles. The nitro group of the molecules thus formed can be transformed to a variety of functionalities. These include silyl nitronates,[2] nitrile oxides,[3] and hydroximoyl chlorides.[4] Intramolecular 1,3-dipolar cycloadditions have been proved to be practical methods in synthetic utility.[5] Among these, intramolecular nitrile oxide-olefin cycloadditions (INOC),[3,5] intramolecular silyl nitronate-olefin cycloadditions (ISOC),[2] and intramolecular oxime-olefin cycloadditions (IOOC)[6] are valuable methods for the generation of [n.3.0] bicyclic compounds which can serve as versatile fragments in organic synthesis.

Our previous study found that hydroximoyl halides or nitrile oxides can be generated when β-nitrostyrenes react with nonstabilized nucleophiles such as Grignard or organolithium reagents.[7] Meanwhile, based on our observations and others,[1-7] the reactions of β-nitrostyrenes **1** with stabilized nucleophiles generate nitronates in high yields.[8] In this paper, an improved one-pot synthesis of bicyclic compounds involved the addition and chlorination to generate hydroximoyl chlorides, nitrile oxides is reported.

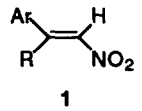
0040-4020/98/$ - see front matter
PII: S0040-4020(98)00883-7



Results and Discussion

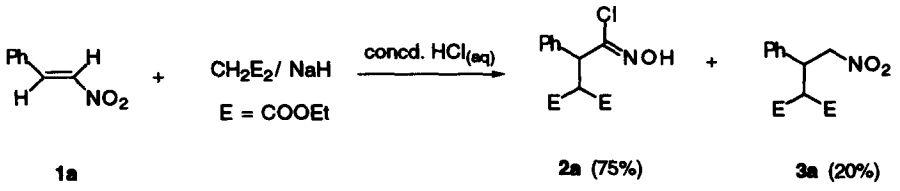
(a) Carbon nucleophiles

First we tried to add β-nitrostyrene **1a** to a diethyl malonate anion solution, prepared from diethyl malonate [$CH_2(COOEt)_2 = CH_2E_2$] and sodium hydride, in THF at room temperature (eq 1). After the starting material had disappeared, the nitronate was slowly added to an ice cold concentrated hydrochloric acid solution. The blue or green color was observed as previously described.[7,8] Hydroximoyl chloride **2a** was obtained (75%) together with nitroalkane **3a** (20%) after flash column chromatography purification. The structures of compounds **2a** and **3a** can be assigned according to their mass, ^{1}H- and ^{13}C-NMR spectra analysis. The formation of these products indicates that a proton from the hydrochloric acid solution can attack the oxygen of the nitro group to yield hydroximoyl chloride **2a** or the α-carbon to generate nitro compound **3a.** The mechanism was proposed to be similar to what we observed before.[7]



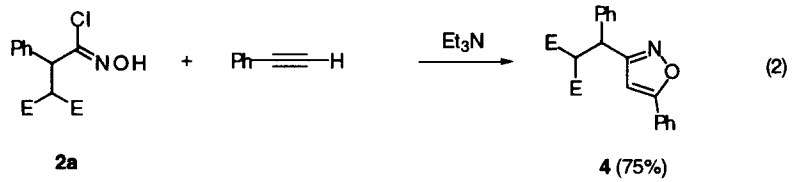
1

a: Ar = Ph, R = H
b: Ar = 4-MeC_6H_4, R = H
c: Ar = 4-$CF_3OC_6H_4$, R = H
d: Ar = 4-FC_6H_4, R = H
e: Ar = 2-thienyl, R = H
f: Ar = 2-furyl, R = H
g: Ar = Ph, R = Ph



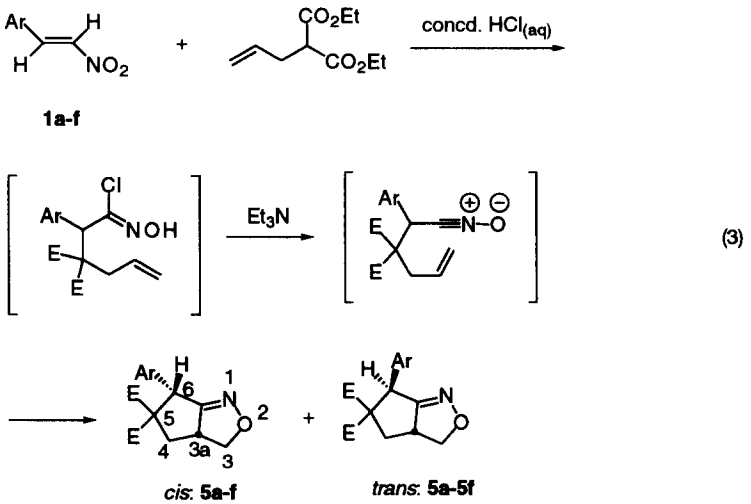
1a **2a** (75%) **3a** (20%) (1)

Hydroximoyl halides and nitrile oxides are important intermediates in organic synthesis.[2a] When compound **2a** reacted with phenylacetylene in the presence of triethylamine at room temperature for 3 hr, 75% of 1,3-dipolar cycloaddition product **4** was isolated (eq 2). After refluxing for 3 hr, only 20% of the same product **4** was generated and 75% of unreacted starting material was recovered when pure nitroalkane **3** reacted with phenylacetylene in the presence of phenylisocyanate and triethylamine (Mukaiyama-Hoshino method).[3a]



2a **4** (75%) (2)

It has been reported that bicyclic heterocyclic products can be prepared from the reactions of unsaturated nitro compounds with phenyl isocyanate and triethylamine to generate nitrile oxides (INOC) in a one-pot synthesis.[2c] Alternatively, reactions of unsaturated nitro compounds with chlorotrimethylsilane in the presence of triethylamine yield silyl nitronates (ISOC) in a multiple-step sequence.[2c] On the basis of equations 1 and 2, we also have succeeded in the preparation of the similar heterocyclic compounds from the reactions of β-nitrostyrenes **1a-1f** with [H_2C=CH-$CH_2CH(COOEt)_2$, E=COOEt] employing sodium hydride as a base. Treatment of the resulting hydroximoyl chlorides with triethylamine generated nitrile oxides which underwent intramolecular cycloaddition to give heterocyclic products as a mixture of *cis*- and *trans*-isomers **5a-f** (eq 3). This reaction failed when substrate **1g** reacted with the same nucleophile under similar conditions (entry 7). The presence of the two bulky phenyl groups that retard the attack of nucleophile might account for the result.



1a-f (3)

cis: **5a-f** *trans*: **5a-5f**

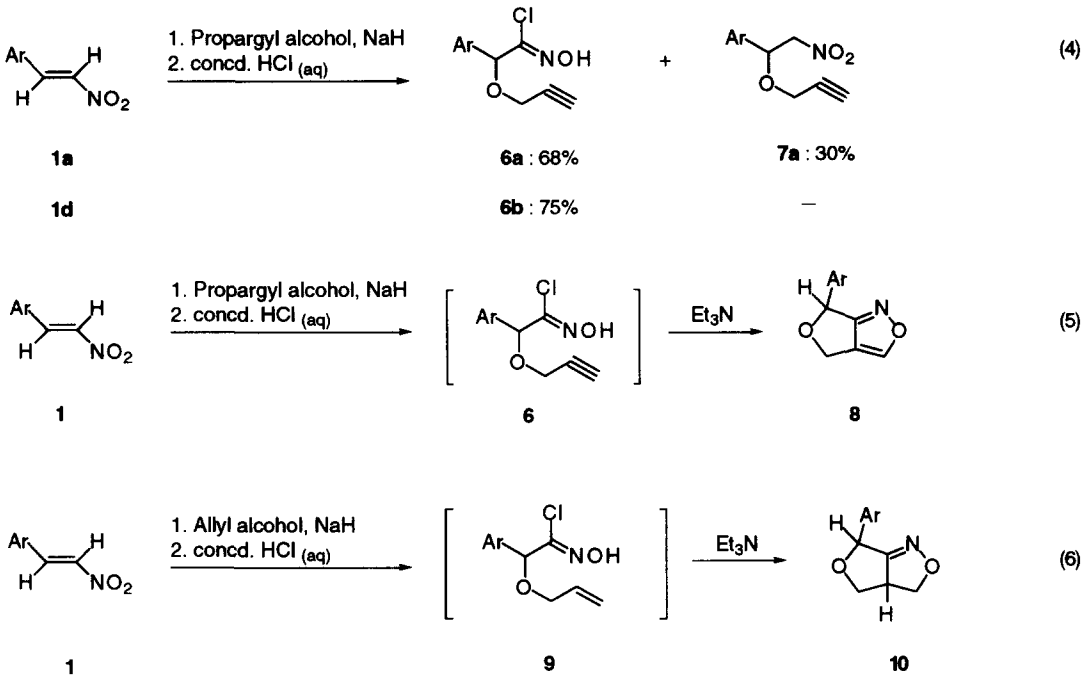
The ratio of *cis*- and *trans*- diastereomers generated by the reactions mentioned above is similar to what literature reported.[2c] The configuration of the *trans*-**5a** isomer was determined by 200 MHz NMR. The C3a methine proton of the *trans*-**5a** appeared at 4.60 ppm compared with that of 3.82 ppm in the *cis*-isomer. This might due to the deshielding effect of the phenyl group. The ratios of the *cis/trans* isomer ranging from 2.5/1 to 7.5/1 indicate that the steric factor of the aryl ring might play an important role to control the formation of the diastereomers. Electronic effect in the benzene ring apparently does not show much influence on the selectivity but actually has influence on the reaction rates. Compared with substrate **1a** (30 min at 0 °C), **1c** and **1d** reacted much faster (10 min at -78 °C) (entries 1, 3 and 4). In the cases of the heterocyclic rings **1e** and **1f** the diastereomeric ratios are somewhat low while the reaction rates are fast (entries 5 and 6) compared with those of **1a**.

Table 1 One-pot synthesis of [3.3.0] bicyclic products **5a-f** from the reactions of β-nitrostyrenes **1a-g** with $(H_2C{=}CH\text{-}CH_2)CH(COOEt)_2$/NaH

entry	β-nitrostyrene	condition	product	yield (%)	*cis* : *trans*
1	**1a**	0 °C, 30 min	**5a**	68	7.5 : 1
2	**1b**	r. t., 5 min	**5b**	85	7.5 : 1
3	**1c**	-78 °C, 10 min	**5c**	90	5.0 : 1
4	**1d**	-78 °C, 10 min	**5d**	56	5.5 : 1
5	**1e**	-78 °C, 10 min	**5e**	77	3.5 : 1
6	**1f**	-78 °C, 10 min	**5f**	85	2.5 : 1
7	**1g**	r. t., 10 hr	–	–	–

(b) Oxygen nucleophiles

It has been reported that unsaturated nitroalkyl ethers can be converted into cyclic ethers by intramolecular nitrile oxide-olefin cycloadditions (INOC) or intramolecular silyl nitronate-olefin cycloadditions (ISOC).[2c,9] When compounds **1a** reacted with propargyl alcohol and followed by workup with an ice cold concentrated hydrochloric acid solution, hydroximoyl chloride **6a** and nitroalkyl ether **7a** were isolated separately. However, none of the bicyclic product **8a** was observed (eq 4). Similarly, **9** was also observed in the crude proton NMR when β-nitrostyrenes **1** reacted with allyl alcohol. However, hydroximoyl chloride **9** was relatively unstable to silica gel and always underwent dehydrochlorination to generate bicyclic products **10** or went to decomposition directly. To solve these problems, we decided not to isolate the reactive intermediates **6** and **9** and just to treat the hydroximoyl chlorides with triethylamine directly. To our surprise, moderate to high yields of bicyclic products **8** and **10** were obtained (eqs 5 and 6).



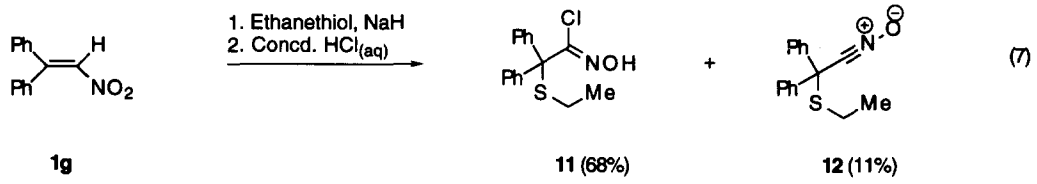
The ratio of the *cis/trans* isomers of **10a** is about 1:1.6 (table 2, entry 4) which is consistent with the literature report.[2c,9] The different ratios of the *cis/trans* isomers between **10a** (1:1.6) and **5d** (5.5:1) may be attributed to the longer bond length of C-O, leading to a less constrained transition state during the INOC cyclization process. It has been reported that the MM2 calculations predicts an energy difference of 0.96 kcal/mol in favor of the *trans* isomer of **10**.[9a,c]

Table 2 One-pot synthesis of [3.3.0] bicyclic products from the reactions of β-nitrostyrenes **1** with propargyl or allyl alcohol and NaH

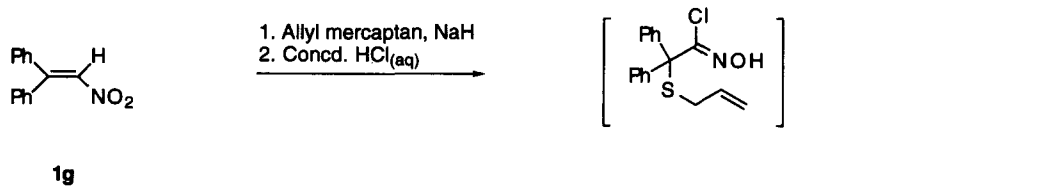
entry	β-nitrostyrene	alcohol	condition	**7** (%)	**8** or **10** (%)	*cis* : *trans*
1	**1a**	$HC{\equiv}CCH_2OH$	0 °C, 3 hr	–	**8a** (60)	–
2	**1d**	$HC{\equiv}CCH_2OH$	-78 °C, 25 min	–	**8b** (60)	–
3	**1g**	$HC{\equiv}CCH_2OH$	0 °C, 1.5 hr	7b (15)	**8c** (60)	–
4	**1d**	$H_2C{=}CHCH_2OH$	-78 °C, 20 min	–	**10a** (61)	1:1.6
5	**1g**	$H_2C{=}CHCH_2OH$	0 °C, 30 min	7c (30)	**10b** (64)	–

(c) Sulfur nucleophiles

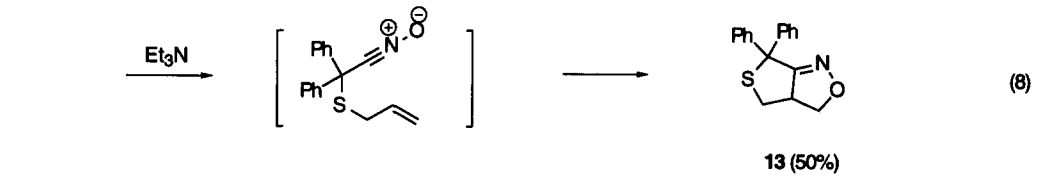
It has been reported that unsaturated nitro alkyl sulfides can be synthesized from the reactions of nitroalkenes with unsaturated mercaptans or from the reactions of aldehydes or ketones with nitromethane in the presence of unsaturated thiols.[2c,10] The unsaturated nitro sulfides are converted into tetrahydrothiophenol[3,4-c]isoxazoles or thiopyrans[2c,10] by intramolecular nitrile oxide-olefin cycloaddition with phenyl isocyanate and triethylamine (Mukaiyama-Hoshino method).[3a] According to equations 1-6, we also tried to react substrate **1 g** with ethanethiol or allyl mercaptan and to add the nitronates to an ice cold concentrated hydrochloric acid solution. Not only hydroximoyl chloride **11** but also nitrile oxide **12** was isolated when ethanethiol was used (eq 7). The isolation of the nitrile oxide **12** indicates that the presence of the two phenyl groups increase the steric hindrance to retard the reactive intermediate to form the furoxane, the dimer of the nitrile oxide. Moderate yields of bicyclic or tricyclic compounds **13** (50%) and **14** (35%) were obtained when substrate **1 g** reacted with allyl mercaptan and 3-acetylmercaptocyclohexene, respectively, in one-pot reaction (eqs 8, 9).



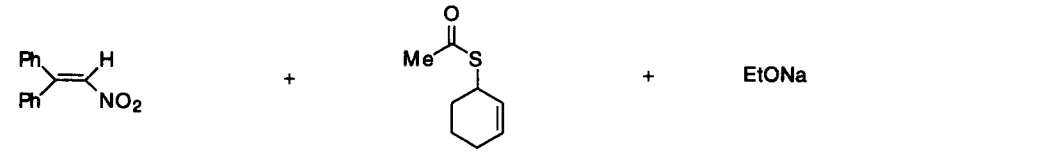
1g **11** (68%) **12** (11%)



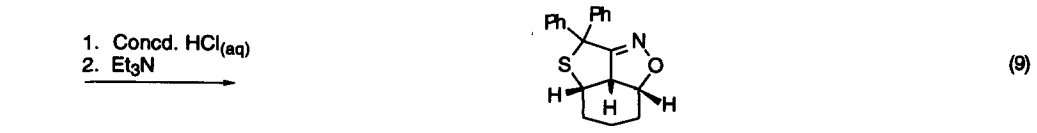
1g



13 (50%)



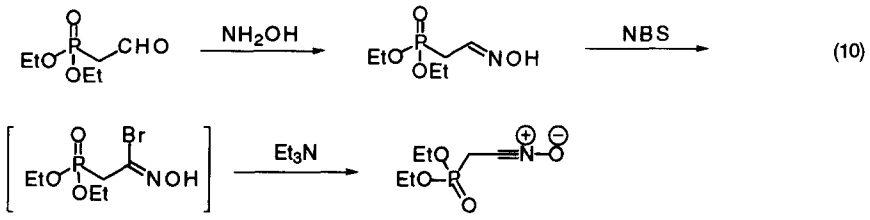
1g



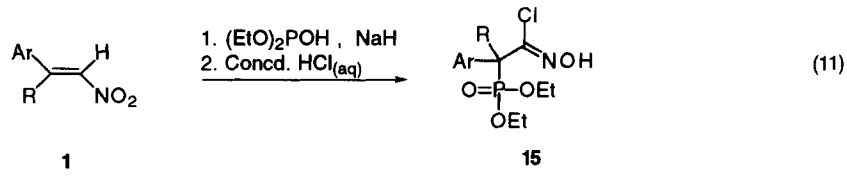
14 (35%)

(d) Phosphorus nucleophiles

It was in 1987 that the synthesis of (diethoxyphosphoryl)acetonitrile oxide and its subsequent reactions with olefins to prepare 3,5-disubstituted 2-isoxazoles were reported by Tsuge et al.[11] The strategy is to treat *N*-[2-(diethoxyphosphoryl)ethylene]hydroximoylamine, prepared from (diethoxyphosphoryl)acetaldehyde and hydroxyamine, with *N*-bromosuccinimide (NBS) to generate hydroximoyl bromide according to the Steven's method.[12] The hydroximoyl bromide is not isolated but is dehydrobrominated with triethylamine to generate nitrile oxide *in situ* (eq 10) which can react with various dipolarphiles. According to equations 1-9 and tables 1 and 2, we anticipated that similar intermediates could be prepared from the reactions of the conjugated nitroalkenes with diethyl phosphite. As expected, good to excellent yields (70-95%) of hydroximoyl chlorides **15a-c** were obtained when β-nitrostyrenes **1** reacted with diethyl phosphite in the presence of sodium hydride at -78 °C followed by the treatment of concentrated hydrochloric acid solution (eq 11).



(10)



(11)

1

a: Ar = Ph, R = H

b: Ar = 4-MeC$_6$H$_4$, R = H

g: Ar = Ph, R = Ph

15

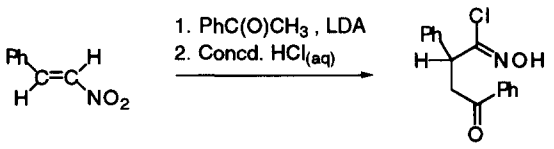
a: Ar = Ph, R = H (75%)

b: Ar = 4-MeC$_6$H$_4$, R = H (98%)

c: Ar = Ph, R = Ph (95%)

(e) Enolate nucleophile

One-pot synthesis of 1,4-diketones from the addition of lithium enolate of ketones to nitroalkenes and *in situ* hydrolysis of the resulting lithium salts of aci-nitro compounds with 10% aqueous hydrochloric acid in THF have been reported.[13] On the basis of the literature report and our study,[13,7] we predicted that different products could be generated when different concentration of a hydrochloric acid solution was used. As expected, when the lithium enolate of acetophenone which was generated from the corresponding ketone with lithium diisopropylamide (LDA) in THF at -78 °C reacted with β-nitrostyrene **1a** followed by workup with concentrated hydrochloric acid solution, 60% of hydroximoyl chloride **16** was isolated after flash column chromatography purification (eq 12).



1a 16 (12)

Conclusion

In summary, an efficient synthesis of hydroximoyl chlorides from the reactions of the β-nitrostyrenes **1** with various nucleophiles has been developed. We also had demonstrated the utility of this method for the synthesis of bicyclic or tricyclic compounds in a one-pot synthesis process. Compared with the literature procedures, several advantages are as follows: (a) the β-nitrostyrenes are easily synthesized or are commercially available, (b) the hydrochloric acid is inexpensive, and (c) the workup procedures are simple, the intermediates need not to be isolated, and the final products are easily purified. Further study using other nitroalkenes, nucleophiles and other reagents are now under investigation.

Experimental Section

General. All reactions were performed in flame or oven-dried glassware under a positive pressure of nitrogen. Air and moisture sensitive compounds were introduced by the use of a syringe or cannula through a rubber septum. Diethyl ether and THF were distilled from sodium/benzophenone ketyl. Analytical thin layer chromatography was performed with E. Merck silica gel 60F glass plates and flash chromatography by the use of E. Merck silica gel 60 (230-400 mesh). GCMS were recorded on a HP 5890 GC/HP 5970B MSD, MS or HRMS were measured by Jeol JMS-D300 or Jeol JMS-HX110 spectrometer. Elemental analysis were performed by a Perkin-Elemer 2400 instrument. IR spectra were recorded on JASCO FT/IR-5300. ^{1}H- and ^{13}C-NMR spectra were recorded on Jeol Ex-400 or Varian Gemini-200. All NMR data were obtained in $CDCl_3$ solution and chemical shifts (δ) were given in ppm relative to TMS. All melting points were determined on a MEL-TEMP II melting point apparatus and were uncorrected.

Materials. Compounds **1a-e** were purchased from Aldrich Chemical Co. Starting materials **1f-g** were prepared by modifying or according to the literature report.[14] 3-Acetylmercaptocyclohexene was prepared from 3-bromocyclohexene and thiolacetic acid according to literature procedures.[15]

1. Typical experimental procedures for the synthesis of compounds 2a and 3a (equation 1): Starting material **1a** 5 mmol was dissolved in 20 mL dry THF and was added to the diethyl malonate anion which was prepared from 10 mmol diethyl malonate and 10 mmol sodium hydride in 30 mL THF at rt. After

the starting material disappeared by checking the mixture with TLC plate, the solution was slowly added to a 50 mL ice cold concentrated hydrochloric acid solution and the blue or green color was observed during addition. The solution was stirred 30 minutes then poured into brine and extracted with dichloromethane, dried over $MgSO_4$, filtered and the solvent was evaporated to obtain an oily mixture. The crude products were purified by flash column chromatography by use of hexane-ethyl acetate (95 : 5) as eluent to obtain pure compounds **2a** (75%) and **3a** (20%).

3,3-Diethoxycarbonyl-2-phenylpropanohydroximoyl Chloride (2a): This compound was recrystallized from hexane and ethyl acetate solution and had mp 79-82 °C. ^{1}H NMR (200 MHz, $CDCl_3$) 8.72 (s, 1H), 7.32 (s, 5H), 4.51 (d, J = 12.0 Hz, 1H), 4.35 (d, J = 12.0 Hz, 1H), 4.33-4.18 (m, 2H), 3.91 (q, J = 7.2 Hz, 2H), 1.27 (t, J = 7.2 Hz, 3H), 0.94 (t, J = 7.2 Hz, 3H) ^{13}C NMR (50 MHz, $CDCl_3$) 167.4, 167.3, 140.7, 135.1, 128.8, 128.4, 62.1, 61.8, 55.9, 52.4, 13.8, 13.5. IR (cm^{-1}, neat) 3387, 1740. MS *m/z* (relative intensity) 329 ((M+2)$^+$, 9), 327 (M$^+$, 29), 237 (36), 168 (28), 77 (100). Elemental analysis calculated for $C_{15}H_{18}O_5NCl$: C, 54.97; H, 5.54; N, 4.27. Found: C, 55.01; H, 5.29; N, 4.31.

3,3-Diethoxycarbonyl-1-nitro-2-phenylpropane (3a): ^{1}H NMR (200 MHz, $CDCl_3$) 7.37-7.21 (m, 5H), 4.94 (dd, J = 13.0, 5.6 Hz, 1H), 4.85 (dd, J = 13.0, 8.6 Hz, 1H), 4.29-4.17 (m, 3H), 4.00 (q, J = 7.2 Hz, 2H), 3.82 (d, J = 9.2 Hz, 1H),1.26 (t, J = 7.2 Hz, 3H), 1.04 (t, J = 7.2 Hz, 3H) ^{13}C NMR (50 MHz, $CDCl_3$) 167.5, 166.9, 136.3, 128.9, 128.3, 128.0, 78.5, 62.1, 61.8, 54.9, 42.9, 13.8, 13.6. MS *m/z* (relative intensity) 310 (M$^+$, 13), 263 (97), 159 (22), 103 (100), 77 (66). HRMS (EI) *m/z* calculated for $C_{15}H_{19}O_6N$: 309.1213. Found: 309.1211. Elemental analysis calculated for $C_{15}H_{19}O_6N$: C, 58.25; H, 6.19; N, 4.53. Found: C, 58.02; H, 6.07; N, 4.55.

2. Typical experimental procedures for the synthesis of compound 4 (equation 2): Triethyl amine 2 mmol was dissolved in 10 mL dichloromethane and was slowly added to a 10 mL dichloromethane solution which contained hydroximoyl chloride **2** (1 mmol) and phenylacetylene (2 mmol) at room temperature. The solution was stirred for 3 hr and the solvent was evaporated to obtain the crude product. The mixture was purified by chromatography by use of hexane-ethyl acetate (95 : 5) as eluent to obtain pure compound **4** (75%). Only 20% of **4** was generated and 75% of unreacted starting material was recovered when compound **3** reacted phenylacetylene in the presence of phenylisocyanate and triethylamine under reflux for 3 hr.

3-(2,2-Diethoxycarbonyl-1-phenylethyl)-5-phenylisoxazole (4): mp 116-118 °C (hexane-ethyl acetate). ^{1}H NMR (200 MHz, $CDCl_3$) 7.72-7.67 (m, 2H), 7.42-7.24 (m, 8H), 6.30 (s, 1H), 4.86 (d, J = 11.8 Hz, 1H), 4.45 (d, J = 11.8 Hz, 1H), 4.21 (q, J = 7.2 Hz, 2H), 3.94 (q, J = 7.2 Hz, 2H), 1.24 (t, J = 7.2 Hz, 3H), 0.96 (t, J = 7.2 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) 170.0, 167.7, 167.5, 164.7, 137.7, 130.2, 128.9, 128.8, 128.7, 127.9, 127.4, 125.8, 99.5, 61.8, 61.4, 56.3, 43.8, 13.9, 13.6. IR (cm^{-1}, neat) 1752, 1736. MS *m/z* (relative intensity) 393 (M$^+$, 13), 320 (26), 274 (100), 245 (12), 105 (24), 77 (28). HRMS (EI) *m/z* calculated for $C_{23}H_{23}O_5N$: 393.1558. Found: 393.1577. Elemental analysis calculated for $C_{23}H_{23}O_5N$: C, 70.04; H, 6.13; N, 3.55. Found: C, 70.05; H, 5.96; N, 3.62.

3. Typical experimental procedures for the synthesis of compounds *cis*- and *trans*-5a-f (equation 3 and table 1) : Starting material **1a** 10 mmol was dissolved in 40 mL THF and was added to a $C(CH_2\text{-}CH{=}CH_2)(COOEt)_2$ solution which was prepared from 15 mmol $CH(CH_2\text{-}CH{=}CH_2)(COOEt)_2$ and 15 mmol NaH in 60 mL THF at 0 °C. After the starting material disappeared, the solution was slowly added to a 50 mL ice cold concentrated hydrochloric acid solution and the blue or green color was always observed as previously described. The solution was stirred for 30 min, poured into the brine, and extracted with dichloromethane. After treating the solution with excess amount of triethylamine, the dichloromethane solution was washed with distilled water (50 mL x 3), dried over $MgSO_4$, filtered and the solvent was evaporated to obtain oily mixture. The mixture was purified by flash column chromatography by use of hexane-ethyl acetate (95:5) as eluent to obtain pure compounds *cis*-**5a** (60%) and *trans*-**5a** (8%).

***cis*-5,5-Diethoxycarbonyl-3a,4-dihydro-6-phenyl-3H,6H-[3,4-c]isoxazole (*cis*-5a):** ^{1}H NMR (200 MHz, $CDCl_3$) 7.31-7.26 (m, 5H), 5.02 (d, J = 1.0 Hz, 1H), 4.65 (dd, J = 9.4, 8.0 Hz, 1H), 4.38-4.18 (m, 2H), 4.10 (dd, J = 12.2, 8.0 Hz, 1H), 3.96-3.64 (m, 2H), 3.41 (dq, J = 11.0, 7.2 Hz, 1H), 2.71 (dd, J = 13.4, 11.0 Hz, 1H), 2.56 (dd, J = 13.4, 8.0 Hz, 1H), 1.27 (t, J = 7.2 Hz, 3H), 0.78 (t, J = 7.2 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) 171.1, 171.0, 168.1, 135.7, 130.0, 128.1, 127.9, 75.1, 70.1, 62.4, 61.6, 51.8, 46.4, 35.2, 13.9, 13.2. IR (cm^{-1}, neat) 1730. MS *m/z* (relative intensity) 313 (M^+, 66), 258 (100), 143 (18), 115 (37), 77 (12). HRMS (EI) *m/z* calculated for $C_{18}H_{21}O_5N$: 331.1419. Found: 331.1429. Elemental analysis calculated for $C_{18}H_{21}O_5N$: C, 65.24; H, 6.39; N, 4.23. Found: C, 64.88; H, 6.44; N, 4.12.

***trans*-5,5-Diethoxycarbonyl-3a,4-dihydro-6-phenyl-3H,6H-[3,4-c]isoxazole (*trans*-5a):** ^{1}H NMR (200 MHz, $CDCl_3$) 7.27-7.21 (m, 5H), 5.02 (s, 1H), 4.73-4.49 (m, 2H), 4.40-4.15 (m, 2H), 3.91 (dd, J = 11.0, 7.0 Hz, 1H), 3.69 (dq, J = 11.0, 7.0 Hz, 1H), 3.32 (dq, J = 11.0, 7.0 Hz, 1H), 2.87 (dd, J = 12.8, 7.0 Hz, 1H), 1.80 (dd, J = 12.8, 11.0 Hz, 1H), 1.28 (t, J = 7.0 Hz, 3H), 0.74 (t, J = 7.0 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) 171.3, 170.3, 169.5, 136.8, 128.8, 128.3, 127.7, 75.1, 71.3, 62.0, 61.5, 55.3, 45.7, 36.5, 13.9, 13.1. IR (cm^{-1}, neat) 1728. MS *m/z* (relative intensity) 313 (M^+, 34), 258 (100), 185 (19), 173 (80), 143 (30). HRMS (EI) *m/z* calculated for $C_{18}H_{21}O_5N$: 331.1419. Found: 331.1415.

***cis*-5,5-Diethoxycarbonyl-3a,4-dihydro-6-(4-methylphenyl)-3H,6H-[3,4-c]isoxazole (*cis*-5b):** ^{1}H NMR (200 MHz, $CDCl_3$) 7.17 (d, J = 8.4, 2H), 7.08 (d, J = 8.4, 2H), 4.98 (s, 1H), 4.63 (dd, J = 9.4, 7.8 Hz, 1H), 4.40-4.18 (m, 2H), 4.08 (dd, J = 12.2, 7.8 Hz, 1H), 3.93-3.67 (m, 2H), 3.45 (dq, J = 11.0, 7.2 Hz, 1H), 2.69 (dd, J = 13.4, 11.0 Hz, 1H), 2.54 (dd, J = 13.4, 8.4 Hz, 1H), 2.29 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H), 0.81 (t, J = 7.2 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) 171.1, 168.2, 137.6, 132.7, 129.8, 128.8, 75.1, 70.1, 62.3, 61.5, 51.8, 46.2, 35.2, 21.0, 13.9, 13.2. IR (cm^{-1}, neat) 1727. MS *m/z* (relative intensity) 345 (M^+, 63), 272 (100), 224 (18), 169 (8), 91 (16). HRMS (EI) *m/z* calculated for $C_{19}H_{23}O_5N$: 345.1576. Found: 345.1596.

***trans*-5,5-Diethoxycarbonyl-3a,4-dihydro-6-(4-methylphenyl)-3H,6H-[3,4-c]isoxazole (*trans*-5b):** ^{1}H NMR (200 MHz, $CDCl_3$) 7.12 (d, J = 8.4, 2H), 7.06 (d, J = 8.4, 2H), 4.97 (d, J = 0.4 Hz, 1H), 4.71-4.47 (m, 2H), 4.40-4.14 (m, 2H), 3.90 (dd, J = 11.6, 6.7 Hz, 1H), 3.70 (dq, J = 11.0, 7.2 Hz, 1H), 3.37 (dq, J = 11.0, 7.2 Hz, 1H), 2.86 (dd, J = 12.8, 7.2 Hz, 1H), 2.29 (s, 3H), 1.78 (dd, J = 12.8, 11.0 Hz, 1H), 1.28 (t, J= 7.2 Hz, 3H), 0.77 (t, J = 7.2 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) 171.3, 170.4, 169.5, 137.3, 133.7, 128.9, 128.7, 75.1, 71.2, 62.0, 61.5, 55.3, 45.4, 36.4, 20.9, 13.9, 13.1. IR (cm^{-1},

neat) 1728. MS *m/z* (relative intensity) 345 (M^+, 52), 272 (100), 224 (15), 169 (11), 91 (8), 77 (8). HRMS (EI) *m/z* calculated for $C_{19}H_{23}O_5N$: 345.1576. Found: 345.1573.

***cis*-5,5-Diethoxycarbonyl-3a,4-dihydro-6-(4-trifluoromethoxyphenyl)-3H,6H-[3,4-c]isoxazole (*cis*-5c):** ^1H NMR (200 MHz, $CDCl_3$) 7.40-7.13 (m, 4H), 5.04 (d, J = 1.2 Hz, 1H), 4.66 (dd, J = 9.6, 8.0 Hz, 1H), 4.39-4.18 (m, 2H), 4.09 (dd, J = 12.2, 8.0 Hz, 1H), 3.92-3.67 (m, 2H), 3.45 (dq, J = 10.5, 7.2 Hz, 1H), 2.86 (dd, J = 13.4, 10.5 Hz, 1H), 2.55 (dd, J = 13.4, 8.0 Hz, 1H), 2.29 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H), 0.79 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 170.7, 170.1, 168.1, 148.8 (q, J = 1.8 Hz), 134.2, 131.5, 120.7, 120.5 (q, J = 258.2 Hz), 75.3, 69.8, 62.5, 61.8, 51.6, 45.8, 35.3, 14.0, 13.2. IR (cm^{-1}, neat) 1730. MS *m/z* (relative intensity) 415 (M^+, 68), 370 (4), 342 (100), 268 (15), 127 (11). HRMS (EI) *m/z* calculated for $C_{19}H_{20}O_6NF_3$: 415.1242. Found: 415.1243. Elemental analysis calculated for $C_{19}H_{20}O_6NF_3$: C, 54.94; H, 4.85; N, 3.37. Found: C, 55.04; H, 5.17; N, 3.22.

***trans*-5,5-Diethoxycarbonyl-3a,4-dihydro-6-(4-trifluoromethoxyphenyl)-3H,6H-[3,4-c]isoxazole (*trans*-5c):** ^1H NMR (200 MHz, $CDCl_3$) 7.37-7.28 (m, 2H), 7.14 (d, J = 8.6, 2H), 5.02 (s, 1H), 4.73-4.48 (m, 2H), 4.41-4.14 (m, 2H), 3.98 (dd, J = 12.6, 6.6 Hz, 1H), 3.73 (dq, J = 10.8, 7.2 Hz, 1H), 3.38 (dq, J = 10.8, 7.2 Hz, 1H), 2.86 (dd, J = 12.8, 7.4 Hz, 1H), 1.80 (dd, J = 12.8, 11.2 Hz, 1H), 1.27 (t, J = 7.2 Hz, 3H), 0.77 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 170.7, 170.1, 169.2, 148.7 (q, J = 2.3 Hz), 135.7, 130.4, 120.8, 120.4 (q, J = 255.7 Hz), 75.1, 71.3, 62.1, 61.6, 55.1, 45.0, 36.4, 13.7, 13.0. IR (cm^{-1}, neat) 1728. MS *m/z* (relative intensity) 415 (M^+, 36), 370 (4), 342 (100), 268 (29). HRMS (EI) *m/z* calculated for $C_{19}H_{20}O_6NF_3$: 415.1242. Found: 415.1250. Elemental analysis calculated for $C_{19}H_{20}O_6NF_3$: C, 54.94; H, 4.85; N, 3.37. Found: C, 54.75; H, 4.97; N, 3.04.

***cis*-5,5-Diethoxycarbonyl-3a,4-dihydro-6-(4-fluorophenyl)-3H,6H-[3,4-c]isoxazole (*cis*-5d):** ^1H NMR (200 MHz, $CDCl_3$) 7.34-7.27 (m, 2H), 7.02-6.94 (m, 2H), 5.02 (s, 1H), 4.66 (dd, J = 9.6, 8.0 Hz, 1H), 4.38-4.18 (m, 2H), 4.10 (dd, J = 12.0, 8.0 Hz, 1H), 3.91-3.70 (m, 2H), 3.47 (dq, J = 10.8, 7.2 Hz, 1H), 2.69 (dd, J = 13.4, 10.8 Hz, 1H), 2.55 (dd, J = 13.4, 8.0 Hz, 1H), 1.27 (t, J = 7.2 Hz, 3H), 0.85 (t, J = 7.2 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) 170.9, 170.7, 168.2, 162.4 (d, J = 246.2), 131.8 (d, J = 8.4), 131.3 (d, J = 3.4), 115.0 (d, J = 21.7), 75.2, 69.8, 62.4, 61.7, 51.6, 45.7, 35.1, 13.9, 13.3. IR (cm^{-1}, neat) 1728. MS *m/z* (relative intensity) 349 (M^+, 34), 276 (100), 246 (24), 173 (16), 145 (68). HRMS (EI) *m/z* calculated for $C_{18}H_{20}O_5NF$: 349.1326. Found: 349.1326. Elemental analysis calculated for $C_{18}H_{20}O_5NF$: C, 61.88; H, 5.77; N, 4.00. Found: C, 61.56; H, 6.04; N, 3.98.

***trans*-5,5-Diethoxycarbonyl-3a,4-dihydro-6-(4-fluorophenyl)-3H,6H-[3,4-c]isoxazole (*trans*-5d):** ^1H NMR (200 MHz, $CDCl_3$) 7.28-7.20 (m, 2H), 7.02-6.93 (m, 2H), 4.99 (s, 1H), 4.73-4.48 (m, 2H), 4.41-4.15 (m, 2H), 3.92 (dd, J = 11.6, 7.2 Hz, 1H), 3.74 (dq, J = 10.7, 7.2 Hz, 1H), 3.41 (dq, J = 10.7, 7.2 Hz, 1H), 2.86 (dd, J = 12.8, 7.2 Hz, 1H), 1.80 (dd, J = 12.8, 11.6 Hz, 1H), 1.28 (t, J = 7.2 Hz, 3H), 0.81 (t, J = 7.2 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) 171.1, 170.2, 169.4, 162.3 (d, J = 245.8), 132.5 (d, J = 3.5), 130.6 (d, J = 8.3), 115.1 (d, J = 21.2), 75.1, 71.3, 62.1, 61.6, 55.2, 45.0, 36.4, 13.9, 13.2. IR (cm^{-1}, neat) 1728. MS *m/z* (relative intensity) 349 (M^+, 52), 276 (6), 184 (13), 154 (8), 127 (11). HRMS (EI) *m/z* calculated for $C_{18}H_{20}O_5NF$: 349.1326. Found: 349.1321.

***cis*-5,5-Diethoxycarbonyl-3a,4-dihydro-6-(2-thienyl)-3H,6H-[3,4-c]isoxazole (*cis*-5e):** ^1H NMR (200 MHz, $CDCl_3$) 7.21 (dd, J = 5.0, 4.0, 1H), 7.11 (dd, J = 4.0, 3.6, 1H), 6.94 (dd, J = 5.0, 3.6, 1H), 5.28 (s, 1H), 4.65 (dd, J = 10.0, 8.0 Hz, 1H), 4.43-4.20 (m, 2H), 4.12 (dd, J = 12.2, 8.0 Hz, 1H), 3.95-3.79 (m, 2H), 3.65 (dq, J = 10.0, 7.2 Hz, 1H), 2.66 (dd, J = 13.8, 10.0 Hz, 1H), 2.51 (dd, J = 13.8,

8.0 Hz, 1H), 1.30 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) 170.5, 170.0, 168.1, 136.3, 128.3, 126.4, 125.6, 75.6, 69.8, 62.4, 61.9, 51.1, 42.0, 34.5, 14.0, 13.5. IR (cm^{-1}, neat) 1727. MS *m/z* (relative intensity) 337 (M^+, 100), 264 (83), 191 (11), 96 (56), 91 (40). HRMS (EI) *m/z* calculated for $C_{16}H_{19}O_5NS$: 337.0984. Found: 337.0966. Elemental analysis calculated for $C_{16}H_{19}O_5NS$: C, 56.96; H, 5.68; N, 4.15. Found: C, 56.98; H, 5.65; N, 4.12.

***trans*-5,5-Diethoxycarbonyl-3a,4-dihydro-6-(2-thienyl)-3H,6H-[3,4-c]isoxazole (*trans*-5e):** ^{1}H NMR (200 MHz, $CDCl_3$) 7.20 (t, J = 3.4, 1H), 6.94 (d, J = 3.4, 2H), 5.17 (s, 1H), 4.72-4.46 (m, 2H), 4.40-4.17 (m, 2H), 3.91 (dd, J = 12.0, 7.2 Hz, 1H), 3.82 (dq, J = 10.7, 7.2 Hz, 1H), 3.63 (dq, J = 10.0, 7.2 Hz, 1H), 2.90 (dd, J = 13.2, 7.2 Hz, 1H), 1.85 (dd, J = 13.2, 10.7 Hz, 1H), 1.30 (t, J = 7.0 Hz, 3H), 0.91 (t, J = 7.0 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) 170.0, 169.0, 137.8, 128.3, 127.0, 126.7, 125.2, 75.4, 70.8, 62.1, 61.8, 53.8, 41.4, 35.7, 13.9, 13.3. IR (cm^{-1}, neat) 1728. MS *m/z* (relative intensity) 337 (M^+, 94), 264 (86), 218 (100), 191 (13), 91 (23). HRMS (EI) *m/z* calculated for $C_{16}H_{19}O_5NS$: 337.0984. Found: 337.0988. Elemental analysis calculated for $C_{16}H_{19}O_5NS$: C, 56.96; H, 5.68; N, 4.15. Found: C, 56.97; H, 5.50; N, 4.03.

***cis*-5,5-Diethoxycarbonyl-3a,4-dihydro-6-(2-furyl)-3H,6H-[3,4-c]isoxazole (*cis*-5f):** ^{1}H NMR (200 MHz, $CDCl_3$) 7.34 (d, J = 1.2 Hz, 1H), 6.35 (d, J = 3.0 Hz, 1H), 6.31 (dd, J = 3.0, 1.2 Hz, 1H), 5.13 (d, J = 0.4 Hz, 1H), 4.63 (t, J = 8.8 Hz, 1H), 4.38-4.19 (m, 2H), 4.12-3.91 (m, 2H), 3.88-3.70 (m, 2H), 2.68 (dd, J = 13.4, 10.8 Hz, 1H), 2.52 (dd, J = 13.4, 8.0 Hz, 1H), 1.28 (t, J = 7.2 Hz, 3H), 1.02 (t, J = 7.2 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) 170.4, 168.9, 167.7, 148.7, 142.4, 110.4, 109.7, 75.2, 68.7, 62.5, 61.9, 51.3, 40.4, 34.9, 13.9, 13.6. IR (cm^{-1}, neat) 1730. MS *m/z* (relative intensity) 321 (M^+, 100), 230 (18), 175 (12), 146 (16), 91 (19). HRMS (EI) *m/z* calculated for $C_{16}H_{19}O_6N$: 321.1212. Found: 321.1208.

***trans*-5,5-Diethoxycarbonyl-3a,4-dihydro-6-(2-furyl)-3H,6H-[3,4-c]isoxazole (*trans*-5f):** ^{1}H NMR (200 MHz, $CDCl_3$) 7.32 (dd, J = 2.0, 0.8 Hz, 1H), 6.30 (dd, J = 3.4, 2.0 Hz, 1H), 6.23 (dd, J = 3.4, 0.8 Hz, 1H), 5.04 (s, 1H), 4.66 (dd, J = 10.0, 7.2 Hz, 1H), 4.56-4.40 (m, 1H), 4.35-4.17 (m, 2H), 4.06-3.86 (m, 2H), 3.82-3.66 (m, 1H), 2.99 (dd, J = 13.0, 8.4 Hz, 1H), 1.81 (dd, J = 13.0, 10.0 Hz, 1H), 1.27 (t, J = 7.2 Hz, 3H), 1.01 (t, J = 7.2 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) 169.7, 168.6, 168.1, 149.1, 142.3, 110.5, 108.7, 75.4, 68.8, 62.2, 62.1, 53.6, 40.2, 35.5, 13.9, 13.6. IR (cm^{-1}, neat) 1730. MS *m/z* (relative intensity) 321 (M^+, 65), 248 (100), 230 (27), 175 (18), 91 (35). MS *m/z* (relative intensity) 321 (M^+, 100), 230 (18), 175 (12), 146 (16), 91 (19). HRMS (EI) *m/z* calculated for $C_{16}H_{19}O_6N$: 321.1212. Found: 321.1210.

4. Typical experimental procedures for the synthesis of hydroximoyl chlorides 6a, 6b, and nitro ether 7a (equation 4) : Starting material **1a** 10 mmol was dissolved in 40 mL dry THF and was added to the propargyl alcohol (15 mmol) and sodium hydride (15 mmol) in 60 mL THF at 0 °C. After starting material disappeared, the solution was slowly added to a 50 mL ice cold concentrated hydrochloric acid solution and the blue or green color was always observed. The solution was stirred for 30 min, poured into brine, and extracted with dichloromethane. The dichloromethane solution was washed with distilled water (50 mL x 3), dried over $MgSO_4$, filtered and the solvent was evaporated to obtain an oily mixture. The crude products were purified by flash column chromatography by use of hexane-ethyl acetate (95:5) as eluent to obtain pure compounds 2-phenyl-2-propargyloxyethanohydroximoyl chloride **6a** (68%) and 1-nitro-2-phenyl-2-propagyloxyethane **7a** (30%).

2-Phenyl-2-propargyloxyethanohydroximoyl Chloride (6a): ^{1}H NMR (200 MHz, $CDCl_3$) 8.55 (s br, 1H), 7.47-7.28 (m, 5H), 5.49 (s, 1H), 4.26 (d, J = 1.6 Hz, 2H), 2.49 (t, J = 2.4 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) 141.5, 135.8, 128.8, 128.6, 127.0, 79.9, 78.4, 75.7, 56.2. IR (cm^{-1}, neat) 3293, 2120. MS *m/z* (relative intensity) 225 ($(M+2)^+$, 1), 223 (M^+, 3), 206 (10), 145 (100), 188 (70), 77 (100). HRMS (EI) *m/z* calculated for $C_{11}H_{10}O_2NCl$: 223.0400. Found: 223.0388.

2-(4-Fluorophenyl)-2-propargyloxyethanohydroximoyl Chloride (6b): ^{1}H NMR (200 MHz, $CDCl_3$) 8.08 (s br, 1H), 7.47-7.40 (m, 2H), 7.12-7.03 (m, 2H), 5.47 (s, 1H), 4.32 (dd, J = 17.0, 2.4 Hz, 1H), 4.22 (dd, J = 17.0, 2.4 Hz, 1H), 2.51 (t, J = 2.4 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) 160.3 (d, J = 246.6), 141.5, 131.7 (d, J = 3.0), 128.8 (d, J = 8.4), 115.5 (d, J = 22.0), 79.2, 78.3, 75.8, 56.3. IR (cm^{-1}, neat) 3391. MS *m/z* (relative intensity) 243 ($(M+2)^+$, 1), 241 (M^+, 3), 224 (3), 206 (13), 186 (26), 163 (76), 95 (25). HRMS (EI) *m/z* calculated for $C_{11}H_9O_2NFCl$: 241.0305. Found: 241.0298. Elemental analysis calculated for $C_{11}H_9O_2NFCl$: C, 54.67; H, 3.75; N, 5.80. Found: C, 54.59; H, 4.15; N, 5.85.

1-Nitro-2-phenyl-2-propagyloxyethane (7a): ^{1}H NMR (200 MHz, $CDCl_3$) 7.40 (s, 5H), 5.34 (dd, J = 9.8, 3.6 Hz, 1H), 4.69 (dd, J = 12.8, 9.8 Hz, 1H), 4.43 (dd, J = 12.8, 3.6 Hz, 1H), 4.18 (dd, J = 15.8, 2.4 Hz, 1H), 3.93 (dd, J = 15.8, 2.4 Hz, 1H), 2.45 (t, J = 2.4 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) 135.1, 129.4, 129.1, 127.1, 79.9, 78.2, 76.8, 75.3, 56.3. MS *m/z* (relative intensity) 205 (M^+, 1), 159 (8), 158 (20), 145 (100), 105 (20). Elemental analysis calculated for $C_{11}H_{11}O_3N$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.31; H, 5.53; N, 6.67.

2,2-Diphenyl-1-nitro-2-propargylethane (7b): ^{1}H NMR (200 MHz, $CDCl_3$) 7.40-7.29 (m, 10H), 5.32 (s, 2H), 4.07 (d, J = 2.2 Hz, 2H), 2.42 (t, J = 2.2 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) 140.1, 128.6, 128.5, 126.9, 82.5, 80.4, 79.3, 74.2, 52.5. MS *m/z* (relative intensity) 281 (M^+, 1), 165 (33), 154 (4), 152 (26), 77 (60). Elemental analysis calculated for $C_{17}H_{15}O_3N$: C, 72.58 ;H, 5.37; N, 4.98. Found: C, 72.32; H, 5.29; N, 5.12.

2,2-Diphenyl-1-nitro-2-allyloxyethane (7c): ^{1}H NMR (200 MHz, $CDCl_3$) 7.35-7.25 (m, 10H), 6.02-5.84 (m, 1H), 5.40 (dt, J = 3.4, 1.6 Hz, 1H), 5.34 (s, 2H), 5.31 (dt, J = 3.4, 1.6 Hz, 1H), 3.92 (t, J = 1.6 Hz, 1H), 3.89 (t, J = 1.6 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) 141.1.1, 133.9, 128.4, 128.1, 126.7, 116.5, 81.7, 80.4, 64.6. MS *m/z* (relative intensity) 283 (M^+, 1), 223 (27), 104 (25), 89 (5), 77 (30). Elemental analysis calculated for $C_{17}H_{17}O_3N$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.97; H, 5.96; N, 4.99.

5. Typical experimental procedures for the synthesis of hydroximoyl chloride 8 and bicyclic compound 10 (equations 5, 6 and Table 2) : Starting material **1a** 10 mmol was dissolved in 40 mL dry THF and was added to the propargyl alcohol (15 mmol) and sodium hydride (15 mmol) in 60 mL THF at 0 °C. After starting material disappeared, the solution was slowly added to a 50 mL ice cold concentrated hydrochloric acid solution. The solution was stirred for 30 min, poured into brine, and extracted with dichloromethane. The dichloromethane solution was treated with excess amount of triethylamine, washed with distilled water (50 mL x 3), dried over $MgSO_4$, filtered and the solvent was evaporated to obtain an oily mixture. The crude product was purified by flash column chromatography by use of hexane-ethyl acetate (95 : 5) as eluent to obtain pure compound **8a** (60%). Similar procedures were repeated when substrate **1d** reacted with allyl alcohol at -78 °C to obtain 61% of **10a** and the ratio of *cis/trans* was 1:1.6.

6-Phenyl-4H,6H-furo[3,4-c]isoxazole (8a): ^{1}H NMR (200 MHz, $CDCl_3$) 8.04 (dd, J = 1.4, 1.2 Hz, 1H), 7.48-7.25 (m, 5H), 6.11 (dd, J = 0.8, 0.6 Hz, 1H), 5.03 (ddd, J = 12.0, 1.4, 0.6 Hz, 1H), 4.95 (ddd, J = 12.0, 1.4, 0.8 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) 172.3, 148.1, 137.8, 128.6, 128.4, 126.2, 122.9, 76.3, 63.9. MS *m/z* (relative intensity) 187 (M^+, 43), 130 (12), 105 (100), 78 (8), 77 (28). HRMS (EI) *m/z* calculated for $C_{11}H_9O_2N$: 187.0633. Found: 187.0631.

6-(4-Fluorophenyl)-4H,6H-furo[3,4-c]isoxazole (8b): ^{1}H NMR (200 MHz, $CDCl_3$) 8.07 (dd, J = 1.4, 1.2 Hz, 1H), 7.47-7.40 (m, 2H), 7.12-7.02 (m, 2H), 6.11 (dd, J = 0.8, 0.6 Hz, 1H), 5.03 (ddd, J = 12.0, 1.4, 0.6 Hz, 1H), 4.95 (ddd, J = 12.0, 1.2, 0.8 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) 172.3, 162.9 (d, J = 246.6 Hz), 148.4, 133.7 (d, J = 3.1 Hz), 128.3 (d, J = 8.3 Hz), 123.0, 115.6 (d, J = 21.2 Hz), 75.8, 63.9. MS *m/z* (relative intensity) 205 (M^+, 10), 148 (7), 123 (100), 107 (8), 95 (25). HRMS (EI) *m/z* calculated for $C_{11}H_8O_2NF$: 205.0539. Found: 205.0542. Elemental analysis calculated for $C_{11}H_8O_2NF$: C, 64.39; H, 3.93; N, 6.83. Found: C, 63.76; H, 4.18; N, 6.81.

6,6-Diphenyl-4H-furo[3,4-c]isoxazole (8c): ^{1}H NMR (200 MHz, $CDCl_3$) 8.31 (s, 1H), 7.39-7.31 (m, 10H), 4.19 (s, 1H), 4.18 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) 166.6, 156.9, 143.1, 128.2, 128.1, 128.0, 127.8, 127.2, 118.1, 77.9, 53.9. MS *m/z* (relative intensity) 263 (M^+, 20), 234 (4), 183 (16), 151 (7), 77 (41). HRMS (EI) *m/z* calculated for $C_{17}H_{13}O_2N$: 263.0946. Found: 263.0938.

***cis*-3a,4-Dihydro-6-(4-fluorophenyl)-3H,6H-furo[3,4-c]isoxazole (*cis*-10a):** ^{1}H NMR (200 MHz, $CDCl_3$) 7.48-7.40 (m, 2H), 7.14-7.03 (m, 2H), 5.59 (s, 1H), 4.71-4.58 (m, 1H), 4.50-4.29 (m, 2H), 4.14-3.91 (m, 1H), 3.89-3.82 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) 170.4, 162.9 (d, J = 245.8 Hz), 133.0 (d, J = 3.0 Hz), 128.4 (d, J = 8.4 Hz), 115.6 (d, J = 22.0 Hz), 74.2, 72.6, 69.2, 55.9. MS *m/z* (relative intensity) 206 (M^+, 23), 177 (6), 123 (100), 107 (8), 95 (36). HRMS (EI) *m/z* calculated for $C_{11}H_{10}O_2NF$: 207.0696. Found: 207.0704.

***trans*-3a,4-Dihydro-6-(4-fluorophenyl)-3H,6H-furo[3,4-c]isoxazole (*trans*-10a):** ^{1}H NMR (200 MHz, $CDCl_3$) 7.45-7.36 (m, 2H), 7.13-7.02 (m, 2H), 5.58 (s, 1H), 4.66 (dd, J = 8.6, 7.4 Hz, 1H), 4.43 (td, J = 8.0, 0.8 Hz, 1H), 4.33-4.14 (m, 1H), 4.07 (dd, J = 12.0, 7.4 Hz, 1H), 3.81 (dd, J = 9.0, 8.0 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) 170.3, 162.8 (d, J = 246.5 Hz), 133.2 (d, J = 3.0 Hz), 127.6 (d, J = 7.6 Hz), 115.7 (d, J = 21.3 Hz), 73.6, 72.4, 69.9, 54.4. MS *m/z* (relative intensity) 206 (M^+, 10), 177 (48), 123 (100), 107 (8), 95 (39). HRMS (EI) *m/z* calculated for $C_{11}H_9O_2NF$: ($(M-1)^+$) 206.0617. Found: 206.0615.

3a,4-Dihydro-6,6-diphenyl-4H-furo[3,4-c]isoxazole (10b): mp 69-70 °C (hexane-ethyl acetate). ^{1}H NMR (200 MHz, $CDCl_3$) 7.58-7.20 (m, 10H), 4.62-4.50 (m, 1H), 4.50-4.17 (m, 2H), 4.07-3.88 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) 171.6, 141.3, 141.2, 128.6, 128.4, 128.2, 127.7, 126.4, 125.8, 82.4, 74.1, 68.2, 55.7. MS *m/z* (relative intensity) 265 (M^+, 1), 235 (18), 206 (15), 115 (2), 77 (37). HRMS (EI) *m/z* calculated for $C_{17}H_{15}O_2N$: 265.1103. Found: 265.1110. Elemental analysis calculated for $C_{17}H_{15}O_2N$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.99; H, 5.61; N, 5.60.

6. Typical experimental procedures for the synthesis of hydroximoyl chloride 11 and nitrile oxide 12 (equation 7) : Starting material **1g** 5 mmol was dissolved in 20 mL dry THF and was added to ethanethiol (10 mmol) and sodium hydride (10 mmol) in 30 mL THF at -78 °C. After the starting material disappeared, the solution was slowly added to a 50 mL ice cold concentrated hydrochloric acid solution. The

solution was stirred for 30 min, poured into brine, and extracted with dichloromethane. The dichloromethane solution was washed with distilled water (50 mL x 3), dried over $MgSO_4$, filtered and the solvent was evaporated to obtain an oily mixture. The crude product was purified by flash column chromatography by use of hexane-ethyl acetate (95 : 5) as eluent to obtain pure hydroximoyl chloride **11** (68%) and nitrile oxide **12**.(11%).

2,2-Diphenyl-2-ethylthioethanohydroximoyl Chloride (11): mp 108-109 °C (hexane-ethyl acetate). ^{1}H NMR (200 MHz, $CDCl_3$) 9.02 (s, 1H), 7.51-7.25 (m, 10H), 2.26 (q, J = 7.6 Hz, 2H), 1.05 (t, J = 7.6 Hz, 3H) ^{13}C NMR (50 MHz, $CDCl_3$) 145.2, 139.9, 129.5, 128.1, 127.8, 67.3, 26.0, 12.8. IR (cm^{-1}, neat) 3337. MS *m/z* (relative intensity) 307 ((M+2)$^+$, 3), 305 (M$^+$, 9), 270 (20), 244 (29), 151 (70), 77 (11). HRMS (EI) *m/z* calculated for $C_{16}H_{16}ClNOS$: 307.1105. Found: 307.1098.

2,2-Diphenyl-2-ethylthioethanenitrile Oxide (12): mp 104-105 °C (hexane-ethyl acetate). ^{1}H NMR (200 MHz, $CDCl_3$) 7.56-7.25 (m, 10H), 2.20 (q, J = 7.2 Hz, 2H), 1.23 (t, J = 7.2 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) 139.2, 128.9, 128.6, 127.4, 57.2, 26.7, 13.0. IR (cm^{-1}, neat) 2288. MS *m/z* (relative intensity) 269 (M$^+$, 25), 253 (74), 239 (41), 227 (25), 208 (100), 192 (21). HRMS (EI) *m/z* calculated for $C_{16}H_{15}NOS$: 269.0400. Found: 269.0395.

7. Typical experimental procedures for the synthesis of cyclic compounds 13 and 14 (equations 8, 9) : To 30 mL of THF was added 2 mL absolute ethanol and 0.23 g (10 mmol) of metallic sodium. When the reaction was completed, 10 mmol of 3-acetylmercaptocyclohexene was added and the reaction mixture was brought up to reflux for 15 min. The solution was then cooled to 0 °C and 5 mmol **1g** in 20 mL THF was added. After the starting material disappeared, the solution was slowly added to a 50 mL ice cold concentrated hydrochloric acid solution. The solution was stirred for 30 min, poured into the brine, and extracted with dichloromethane. The dichloromethane solution was treated with excess amount of triethyl amine then washed with distilled water (50 mL x 3), dried over $MgSO_4$, filtered and the solvent was evaporated to obtain an oily mixture. The crude product was purified by flash column chromatography by use of hexane-ethyl acetate (95:5) as eluent to obtain **14** (35%).

6,6-Diphenyl-3,3a,4-trihydrothiopheno[3,4-c]isoxazole (13): mp 132-133 °C (hexane-ethyl acetate). ^{1}H NMR (200 MHz, $CDCl_3$) 7.57-7.00 (m, 10H), 4.70-4.50 (m, 1H), 4.32-4.12 (m, 2H), 3.18-3.08 (m, 1H), 3.00-2.91 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) 170.0, 142.0, 141.0, 129.0, 128.7, 127.9, 127.8, 127.5, 75.5, 61.4, 55.8, 30.5. MS *m/z* (relative intensity) 281 (M$^+$, 31), 251 (15), 217 (45), 204 (21), 77 (8). HRMS (EI) *m/z* calculated for $C_{17}H_{15}ONS$: 281.0874. Found: 281.0887. Elemental analysis calculated for $C_{17}H_{15}ONS$: C, 72.57; H, 5.37; N, 4.98. Found: C, 72.52; H, 5.37; N, 4.81.

(14): ^{1}H NMR (200 MHz, $CDCl_3$) 7.55-7.16 (m, 10H), 4.82 (dt, J = 10.6, 6.6 Hz, 1H), 4.25 (dt, J = 10.6, 8.6 Hz, 1H), 3.50 (dt, J = 6.6, 8.6 Hz, 1H), 2.12-1.16 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) 169.7, 143.7, 142.1, 129.0, 128.6, 128.0, 127.6, 127.5, 127.3, 79.8, 61.2, 57.3, 39.8, 32.6, 28.4, 18.9. MS *m/z* (relative intensity) 321 (M$^+$, 94), 250 (55), 217 (45), 200 (17), 165 (100), 121 (68), 77 (45). HRMS (EI) *m/z* calculated for $C_{20}H_{19}NOS$: 321.1187. Found: 321.1189.

8. Typical experimental procedures for the synthesis of hydroximoyl chloride 15 (equation 11): Starting material **1a** (4 mmol) was dissolved in 20 mL dry THF and was added to the diethyl phosphite (8 mmol) and sodium hydride (10 mmol) in 30 mL THF at 0 °C. After the starting material disappeared (10 min), the solution was slowly added to a 50 mL ice cold concentrated hydrochloric acid solution. The solution was stirred for 30 min and extracted with dichloromethane. The dichloromethane solution was washed with brine, dried over $MgSO_4$, filtered and the solvent was evaporated to obtain solid product **15a** (75% of the NMR yield and 70% of the isolated yield) directly. After washing the crdue product with cold hexane, the solid was recrystallized from hexane and ethyl acetate solution to obtain colorless crystal.

2-(Diethoxyphosphinyl)-2-phenylethanohydroximoyl Chloride (15a): mp 117-118 °C (hexane-ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) 11.58 (s br, 1H), 7.44-7.33 (m, 5H), 4.24 (dq, J = 7.2, 1.0 Hz, 2H), 4.20 (d, J = 26.4 Hz, 1H), 4.07-3.89 (m, 1H), 3.88-3.69 (m, 1H), 1.32 (t, J= 7.2 Hz, 3H), 1.09 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 133.0, 131.9 (d, J = 7.3 Hz), 129.8 (d, J = 5.5 Hz), 128.7 (d, J = 2.3 Hz), 128.3 (d, J = 2.3 Hz), 63.8 (d, J = 6.9 Hz), 63.6 (d, J = 6.9 Hz), 53.3 (d, J = 139.6), 16.3 (d, J = 5.5 Hz), 16.0 (d, J = 5.5 Hz). IR (cm^{-1}, neat) 3177. MS *m/z* (relative intensity) 307 ((M+2)$^+$, 3), 305 (M$^+$, 9), 270 (6), 91 (100), 89 (70), 77 (48). HRMS (EI) *m/z* calculated for $C_{12}H_{17}O_4NPCl$: 305.0550. Found: 305.0559. Elemental analysis calculated for $C_{12}H_{17}O_4NPCl$: C, 47.15; H, 5.61; N, 4.58. Found: C, 47.25; H, 5.46; N, 4.59.

2-(Diethoxyphosphinyl)-2-(4-methylphenyl)ethanohydroximoyl Chloride (15b) : mp 162-163 °C (hexane-ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) 11.78 (s br, 1H), 7.30 (d, J = 7.8 Hz, 2H), 7.16 (d, J = 7.8 Hz, 2H), 4.25-4.20 (m, 2H), 4.16 (d, J = 24.0 Hz, 1H), 3.99-3.93 (m, 1H), 3.86-3.82 (m, 1H), 2.34 (s, 3H), 1.31 (t, J = 8.0 Hz, 3H), 1.11 (t, J = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 138.1 (d, J = 3.7 Hz), 133.2, 129.6 (d, J = 5.5 Hz), 129.4, 128.7 (d, J = 7.3 Hz), 63.8 (d, J = 5.5 Hz), 63.5 (d, J = 7.3 Hz), 53.0 (d, J = 141.5), 21.1, 16.4 (d, J = 7.3 Hz), 16.2 (d, J = 5.5 Hz). IR (cm^{-1}, neat) 3175. MS *m/z* (relative intensity) 321 ((M+2)$^+$, 28), 319 (M$^+$, 84), 302 (100), 284 (54), 274 (18). HRMS (EI) *m/z* calculated for $C_{13}H_{19}O_4NPCl$: 319.0740. Found: 319.0737. Elemental analysis calculated for $C_{13}H_{19}O_4NPCl$: C, 48.84; H, 5.99; N, 4.38. Found: C, 48.95; H, 5.89; N, 4.44.

2-(Diethoxyphosphinyl)-2,2-diphenylethanohydroximoyl Chloride (15c): mp 167-168 °C (hexane-ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) 7.65-7.64(m, 4H), 7.38-7.31 (m, 6H), 4.05-4.00 (m, 4H), 1.06 (t, J = 7.3 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) 137.7, 136.2 (d, J = 5.5 Hz), 130.7 (d, J = 5.5 Hz), 127.8, 64.7 (d, J = 136.1 Hz), 64.3 (d, J = 5.5 Hz), 16.0 (d, J = 5.5 Hz). IR (cm^{-1}, neat) 3160. MS *m/z* (relative intensity) 383 ((M+2)$^+$, 1), 381 (M$^+$, 3), 345 (9), 208 (84), 178 (85), 77 (7). Elemental analysis calculated for $C_{18}H_{21}O_4NPCl$: C, 56.63; H, 5.54; N, 3.67. Found: C, 56.35; H, 5.20; N, 3.63.

9. Typical experimental procedures for the synthesis of hydroximoyl chloride 16 (equation 12): To a solution of LDA (10 mmol) in THF, prepared from BuLi and diisopropylamine in THF (20 mL) at -78 °C, was added dropwise a solution of a acetophenone (10 mmol) in THF (10 mL) over 10 min at the same temperature under Ar. After stirring for 30 min, a solution of a β-nitrostyrene **1a** (5 mmol) in THF (20 mL) was added over a period of 10 min and the resulting mixture was stirred for an additional 2 hr at -78 °C, then warmed to 0 °C 1 hr. The mixture was added to an ice cold concentrated hydrochloric acid solution. The solution was stirred for 30 min, poured into brine, and extracted with dichloromethane. The dichloromethane

solution was washed with distilled water (50 mL x 3), dried over $MgSO_4$, filtered and the solvent was evaporated to obtain an oily mixture. The crude mixture was purified by chromatography to obtain pure product **16** (60%)

2-Acetophenonyl-2-phenylethanohydroximoyl Chloride (16): mp 117-118 °C (hexane-ethyl acetate). ^{1}H NMR (200 MHz, $CDCl_3$) 8.04 (s br, 1H), 7.70 (d, J = 7.4 Hz, 2H), 7.58-7.33 (m, 8H), 4.56 (dd, J = 8.4, 5.6 Hz, 1H), 3.92 (dd, J = 17.6, 8.4 Hz, 1H), 3.30 (dd, J = 17.6, 5.6 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) 197.1, 142.6, 138.8, 136.5, 133.4, 128.9, 128.6, 128.1, 128.0, 127.7, 48.1, 42.4. IR (cm^{-1}, neat) 3511, 1686. MS *m/z* (relative intensity) 287 (M^+, 1), 251 (11), 235 (50), 105 (100), 77 (100). HRMS (EI) *m/z* calculated for $C_{16}H_{14}O_2NCl$: 287.0713. Found: 287.0706.

Acknowledgment

Financial support by the National Science Council of the Republic of China (Grants NSC 87-2113-M-003-010 and NSC 87-2113-M-324-001) and X-ray data are collected and processed by Professor C.-H. Ueng of National Taiwan Normal University are gratefully acknowledged.

References and Notes

1. (a) Corey, E. J.; Estreicher, H. *J. Am. Chem. Soc.* **1978**, *100*, 6294. (b) Seebach, D.; Colvin, E. W.; Well, T. *Chimia* **1979**, *33*, 1. (c) Barrett, A. G. M.; Graboski, G. G. *Chem. Rev.* **1986**, *86*, 751. (d) Rosini, G.; Ballini, R. *Synthesis* **1988**, 833. (e) Barrett, A. G. M. *Chem. Soc. Rev.* **1991**, *20*, 95. (e) Several articles in *Tetrahedron: Symposia in Print* **1990**, *46* (21), Barrett, A. G. M. Ed.

2. (a) Torsell, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*, VCH; New York, 1988. (b) Gottlieb, L.; Hassner, A. *J. Org. Chem.* **1995**, *60*, 3759. (c) Dehaen, W.; Hassner, A. *Tetrahedron Lett.* **1990**, *31*, 743.

3. (a) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339. (b) Hassner, A.; Basel, Y. *Synthesis* **1997**, 309. (c) Maugein, N.; Wagner, A.; Mioskowski, C. *Tetrahedron Lett.* **1997**, *38*, 1547.

4. (a) Kamaran, G.; Kulkarni, G. H. *Tetrahedron Lett.* **1994**, *35*, 5517. (b) Kamaran, G.; Kulkarni, G. H. *Tetrahedron Lett.* **1994**, *35*, 9099. (c) Kamaran, G.; Kulkarni, G. H. *J. Org. Chem.* **1997**, *62*, 1516.

5. (a) Padwa, A. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A.; Ed.; Wiley-Interscience; New York, 1984; Vol. 2. (b) Curran, D. P. *Advances in Cycloaddition*; JAI Press; Greenwich , CT, 1988; p 129.

6. (a) Hassner, A.; Maurya, R.; Padwa, A.; Bullock, W. H. *J. Org. Chem.* **1991**, *56*, 2775. (b) Hassner, A.; Maurya, R.; Mesko, E. *Tetrahedron Lett.* **1988**, *29*, 5313. (c) Hassner, A.; Maurya, R. *Tetrahedron Lett.* **1989**, *30*, 5803. (d) Grigg, R. *Chem. Soc. Rev.* **1987**, *16*, 89. (e) Grigg, R.; Markandu, J.; Perrior, T.; Surendrakumar, S.; Warnock, W. J. *Tetrahedron Lett.* **1990**, *31*, 559.

7. (a) Yao, C.-F.; Chen, W.-C.; Lin, Y.-M. *Tetrahedron Lett.* **1996**, *37*, 6339. (b) Yao, C.-F.; Kao, K.-S.; Liu, J.-T.; Chu, C.-M.; Wang, Y.; Chen, W.-C.; Lin, Y.-M.; Yan, M.-C.; Liu, J.-Y.; Chuang, M.-C.; Shiue, J.-L. *Tetrahedron* **1998**, *54*, 791.

8. Yao, C.-F.; Yang C.-S, Fang, H.-Y. *Tetrahedron Lett.* **1997**, *38*, 6419.

9. (a) Hassner, A.; Dehaen, W. *Chem. Ber.* **1991**, *124*, 1181. (b) Hassner, A.; Friedman, O.; Dehaen, W. *Liebigs A.* **1997**, 587. (c) Hassner, A.; Murthy, K. S. K. *J. Org. Chem.* **1989**, *54*, 5277.

10. Hassner, A.; Dehaen, W. *J. Org. Chem.* **1990**, *55*, 5505.

11. Tsuge, O.; Kanemasa, S.; Suga, H.; Nakagawa, N. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2463.

12. Grundmann C.; Richter, R. *J. Org. Chem.* **1968**, *33*, 476.

13. (a) Miyashita, M.; Awen B. Z. E.; Yoshikoshi, A. *Synthesis*, **1990**, 563. (b) Ehrig, V.; Seebach, D. *Chem. Ber.* **1975**, *108*, 1961. (c) Seebach, D.; Leitz, H. R.; Ehrig, V. *Chem. Ber.* **1975**, *108*, 1924.

14. (a) Bouveault, L; Wahl, A. C. R. *Acad. Sci.* **1902**, *135*, 41. (b) Bordwell, F. G.; Garbisch, E. W. *J. Org. Chem.* **1962**, *27*, 2322, 3049.

15. Confalone, P. N.; Pizzolato, G.; Confalone, D. L.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1980**, *102*, 1954.