Synthesis of α-Functionalized and Nonfunctionalized Hydroximoyl Chlorides from Conjugated Nitroalkenes and Nitroalkanes

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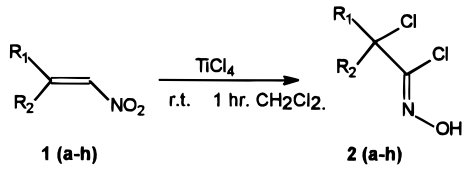
During the last few decades the dipolar cycloaddition reaction has received much attention for the construction of five-membered rings.[1] Amongst the known 1,3-dipoles, the nitrile oxides have contributed[2] significantly, over a long time, since they readily undergo a variety of 1,3-dipolar cycloaddition reactions. The heterocycles *viz.* isoxazolines and isoxazoles formed, respectively, from olefinic and acetylenic compounds with nitrile oxides have various synthetically useful functionalities such as *β*-hydroxy ketones,[3] *γ*-amino alcohols,[4] *β*-hydroxy nitriles,[5] *β*-hydroxy acids,[6] α,*β*-unsaturated ketones,[7] etc.

Several methods have been described in the literature for the *in situ* generation[8] of nitrile oxides, amongst which Mukaiyama's[8a] dehydration of primary nitro compounds using phenyl isocyanate with a catalytic amount of Et_3N and Huisgen's[8b] base-induced dehydrohalogenation of hydroximoyl chlorides are the most frequently used. Hence, hydroximoyl chlorides, which are precursors of nitrile oxides, have generated considerable interest in organic synthesis.

Usually hydroximoyl chlorides are prepared by chlorination of aldoximes, for which a number of chlorinating reagents such as chlorine,[9a] nitrosyl chloride,[9b] *tert*-butyl hypochlorite,[9c] *N*-chlorosuccinimide[9d] in *N*,*N*-dimethylformamide and HCl/*N*,*N*-dimethylformamide/oxone[9e] have been employed for improving the yield, simplifying the experimental conditions and avoiding polyhalogenation.

Scheme 1



1 (a-h) **2 (a-h)**

The synthetic versatility of heterocycles *viz.* isoxazolines and isoxazoles described above can be enhanced by introducing more functionalities in the ring. It is well known that in the 2-isoxazolines the functionalities at 5-position can be introduced by selecting appropriate dipolarophiles for cycloaddition, whereas for the introduction of functionalities at the 3-position functionalized nitrile oxides or hydroximoyl chlorides are needed. A literature survey revealed that very few hydroximoyl chlorides/nitrile oxides possessing α-functionalities have been reported[10] so far, and such compounds have always been obtained by multistep synthesis, involving routine reactions. Herein we report[11] our detailed study on the synthesis of several new α-functionalized and nonfunctionalized hydroximoyl chlorides from conjugated nitroalkenes and nitroalkanes, which do not involve the conventional chlorination of aldoximes.

Although the utility of nitrile oxides in organic synthesis has been investigated extensively,[2] the synthesis of their precursors has received only limited attention. Hence the development of an effective method for the synthesis of hydroximoyl chlorides has still remained a task far from perfection. The only method for the synthesis of hydroximoyl chlorides is based on the chlorination of aldoximes. We have developed a new route for the synthesis of hydroximoyl chlorides from conjugated nitroalkenes by reaction with $TiCl_4$.[12]

Thus, reaction of conjugated nitroalkenes with $TiCl_4$ in dry CH_2Cl_2 at room temperature under an inert atmosphere afforded α-chloro hydroximoyl chlorides in good yields (Scheme 1).

The general applicability of this reaction has been demonstrated by carrying out the reaction of $TiCl_4$ on various nitroalkenes **1a**−**h** to get the corresponding hydroximoyl chlorides **2a**−**h** (Table 1).

A plausible mechanism for the formation of α-chlorohydroximoyl chlorides by reaction of conjugated nitroalk-

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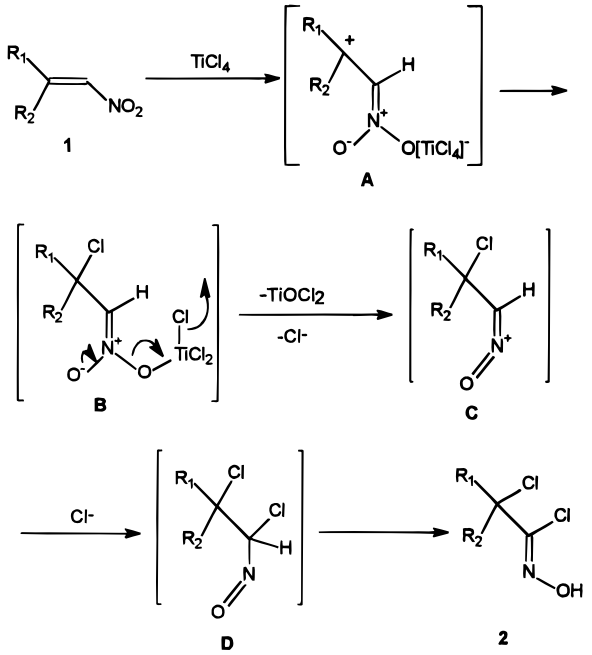
Table 1. Preparation of α-Chlorohydroximoyl Chlorides

compd no.	R_1	R_2	mp (°C)	isolated yield (%)
2a	isopropyl	H	oil	68
2b	methyl	methyl	oil	64
2c	cyclohexyl		51−52	65
2d	C_6H_5	H	79	78
2e	4-ClC_6H_4	H	96	80
2f	4-FC_6H_4	H	84	82
2g	4-$NO_2C_6H_4$	H	114	72
2h	2-$NO_2C_6H_4$	H	117	87

Scheme 2



ene **1** with $TiCl_4$ has been suggested, which involves[11a] an electrophilic attack of $TiCl_4$ on the nitro group of nitroalkene giving initially the intermediate **A**, which by chloride transfer affords the intermediate **B**. The latter gives α-halonitroso derivative **D** *via* **C** by loss of $TiOCl_2$ and chloride transfer. Intermediate **D** then isomerizes[13] to hydroximoyl chloride **2** (Scheme 2).

In the mechanism suggested above, an intermolecular chloride transfer to the carbocationic intermediate **A** is postulated, and if it is so, the intermediate may become amenable to attack by an external nucleophile leading to a different type of hydroximoyl chloride. Support for this hypothesis comes from the use of Et_3SiH[14] as a coreactant which is a source of hydride ion, when phenylacetohydroximoyl chloride was formed as the sole product.

Thus, treatment of a mixture of 1-nitro-2-phenylethene (**1d**) and Et_3SiH in dry CH_2Cl_2 with $TiCl_4$ gave phenylacetohydroximoyl chloride (**3d**) in good yield. Similarly, several other arylacetohydroximoyl chlorides **3e**−**m** were prepared from their respective 1-nitro-2-phenylethenes **1e**−**m** as evident from Table 2 (Scheme 3).

Further support for the mechanism proposed for the formation of α-chloro hydroximoyl chlorides from conjugated nitroalkenes (Scheme 2) involving the nitronate intermediate **B** was provided by generating a similar type of nitronate intermediate $\mathbf{B_1}$ from primary nitroalkanes

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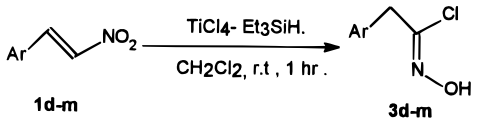
Table 2. Preparation of Arylacetohydroximoyl Chlorides 3d−m

compd. no.	Ar	mp (°C)	isolated yield (%)
3d	C_6H_5	87	76
3e	4-ClC_6H_4	83	65
3f	4-FC_6H_4	90	69
3g	4-$NO_2C_6H_4$	108	63
3h	2-$NO_2C_6H_4$	123	84
3i	3-BrC_6H_4	36	80
3j	2-ClC_6H_4	107	70
3k	3,4-$Cl_2C_6H_4$	66	65
3l	4-$EtOC_6H_4$	semisolid	52
3m	4-MeC_6H_4	82	80

Scheme 3



Scheme 4

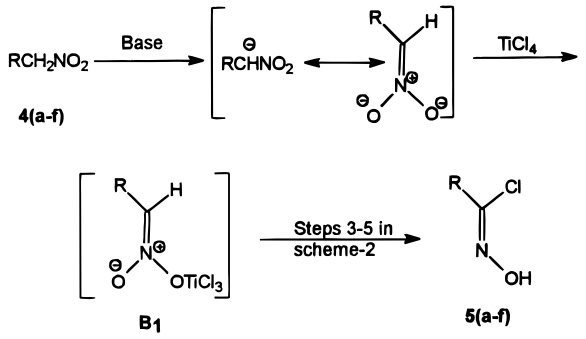


Table 3. Synthesis of Hydroximoyl Chlorides from Primary Nitroalkanes

compd no.	R	Solvent	Base	mp (°C)	isolated yield (%)
5a	benzyl	CH_2Cl_2	NaOMe	89	75
5b	*p*-methylbenzyl	CH_2Cl_2	NaOMe	82	71
5c	1-naphthyl	CH_2Cl_2	NaOMe	113	78
5d	2-naphthyl	CH_2Cl_2	NaOMe	127	65
5e	ethyl	CH_2Cl_2	NaOMe	oil	68[a]
5f	carbomethoxy	benzene	NaH	59	70
5a	benzyl	benzene	NaH	89	75
5b	*p*-methylbenzyl	benzene	NaH	82	72
5a	benzyl	benzene	KH	89	63
5a	benzyl	benzene	CaH_2	−	no reaction
5a	benzyl	benzene	Et_3N	−	no reaction

[a] Since this hydroximoyl chloride was found to be unstable, it was immediately converted into the corresponding 2-isoxazoline derivative *via*. nitrile oxide, and the yield is based on the isolated yield of 2-isoxazoline derivative.

4 by initial treatment with base followed by reaction with $TiCl_4$ to get the expected hydroximoyl chlorides **5** (Scheme 4).

Initially bases like NaOMe, NaH, and KH were used for generating metal nitronates from primary nitroalkanes, and their subsequent reaction with $TiCl_4$ gave hydroximoyl chlorides in good yields. However, weak bases like CaH_2 and Et_3N failed to give the required product, and the starting material was recovered unchanged. It was also observed that the reaction works well for both aliphatic as well as aromatic substrates (Table 3).

As shown earlier the carbocationic intermediate **A** can be trapped by a nucleophilic hydride ion using Et_3SiH. Analogously, we have used azide and cyanide ions to get a straightforward route for the synthesis of α-azido/

Scheme 5

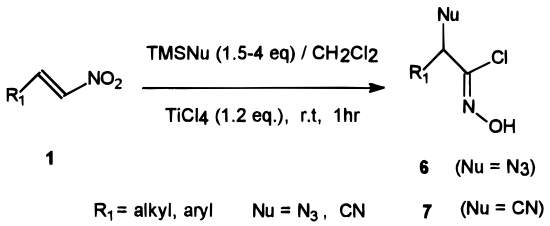
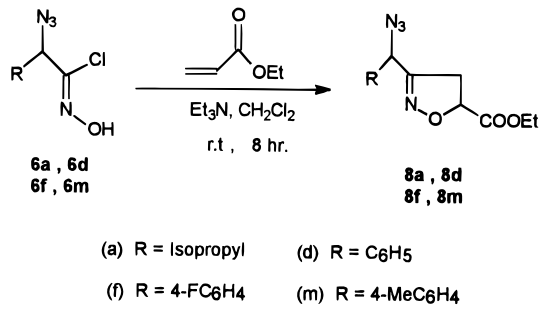


Table 4. Synthesis of α-Azido/Cyano-Functionalized Hydroximoyl Chlorides

compd no.	R_1	Nu[a]	isolated yield (%)
6a	isopropyl	N_3 (2)	87
6d	C_6H_5	N_3 (1.5)	78
6f	4-FC_6H_4	N_3 (1.5)	73
6j	2-ClC_6H_4	N_3 (1.5)	81
6k	3,4-$Cl_2C_6H_3$	N_3 (1.5)	75
6m	4-MeC_6H_4	N_3 (1.5)	71
7a	isopropyl	CN (4)	10[b]
7d	C_6H_5	CN (3)	59
7f	4-FC_6H_4	CN (3)	57
7m	4-MeC_6H_4	CN (3)	69

[a] The value in the parentheses indicates the molar equivalent of TMSNu (Nu = N_3, CN) used. [b] Along with α-cyano hydroximoyl chloride **7a**, its corresponding α-chloro hydroximoyl chloride was also obtained (30%).

Scheme 6



cyano-functionalized hydroximoyl chlorides. Thus, reaction of conjugated nitroalkenes with TMSNu (Nu = N_3, CN) and $TiCl_4$ gave α-azido/cyano-functionalized hydroximoyl chlorides in one step from conjugated nitroalkenes (Scheme 5) (Table 4).

We believe that azide and cyanide ion transfer to the carbocationic intermediate **A** from TMSNu (Nu = N_3, CN) is probably taking place by the mechanism suggested by Zieger[15] *et al*. It was also observed that an excess of (1.5−4 equiv) of TMSNu (Nu = N_3, CN) is required for getting good yields of the respective α-azido/cyano-functionalized hydroximoyl chlorides (Table 4). However, in the reaction of 3-methyl-1-nitrobut-1-ene (**1a**) with a mixture of $TiCl_4$−TMSCN, a poor yield (∼10%) of the desired product *viz*. 2-cyano-3-methyl-butanohydroximoyl chloride (**7a**) was obtained even when 4 equiv of TMSCN was used.

With a view to ascertaining whether the corresponding nitrile oxides can be generated with the α-functionalities intact and also to study their cycloaddition reactions with dipolarophiles, these hydroximoyl chlorides were treated with Et_3N in the presence of a dipolarophile like ethyl acrylate. For example, generation of nitrile oxide from **6d** by treating it with triethylamine in the presence of ethyl acrylate afforded 2-isoxazoline-5-carboxylate **8d**, identified by spectral data (Scheme 6).

However, under identical conditions, the α-cyano-functionalized hydroximoyl chlorides **7** failed to give the expected 2-isoxazolines-5-carboxylates, which may be attributed to the possible cyano group participation[16] with the nitrile oxide cycloaddition reaction.

In conclusion, we have developed a general, one step, easy route for the synthesis of several α-functionalized and nonfunctionalized hydroximoyl chlorides without involving the conventional chlorination of aldoximes. The methodology described herein has several advantages over the previously reported multistep routes, as both α-functionalities and hydroximoyl chloride function can be introduced in a single step. The method utilizes commercially available reagents and easily accessible starting materials *viz*. conjugated nitroalkenes[17] and nitroalkanes.[18] The reaction takes place at ambient temperature in a relatively short period.

Experimental Section

General. All the reactions were performed in oven (140 °C) dried glasswares under an inert atmosphere of argon unless otherwise specified. All purifications were carried out by column chromatography using 100−200 mesh silica gel activated at 100 °C for 2 h. Solvents for extraction and chromatography were technical grade and distilled before use. Anhydrous solvents were obtained following the standard procedure. All chemicals used in this study were of commercial grade and used after distillation. $TiCl_4$ was purchased from the Aldrich Chemical Co. diluted with CH_2Cl_2 to 1 M. Melting points were determined with a microscope hot-stage apparatus and uncorrected. IR spectra were recorded in Nujol or neat and reported in cm^{-1}. ^1H NMR spectra were recorded at 200, 90, 60 MHz. ^{13}C NMR spectra were recorded at 75 MHz. Chemical shifts were reported in ppm (δ) using TMS as internal standard, and coupling constants were expressed in hertz. All the starting nitroalkenes and a few nitroalkanes were synthesized following known procedures. Elemental analysis were performed by the microanalytical division, National Chemical Laboratory.

Representative Procedure for the Preparation of α-Chlorophenylacetohydroximoyl Chloride (2d). To a stirred solution of 1-nitro-2-phenylethene (**1d**) (1.4 g, 0.01 mol) in dry CH_2Cl_2 (10 mL), was added dropwise a slight excess of $TiCl_4$ (0.012 mol as 1 M solution in CH_2Cl_2) at room temperature under argon atmosphere. The resulting mixture was stirred for 1 h, water was added by syringe, and the product was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was washed with water, brine and dried (Na_2SO_4). Removal of solvent gave TLC pure α-chlorophenylacetohydroximoyl chloride (**2d**), further purified by crystallization and identified by elemental analysis and spectral data. Yield 78%. Mp 79 °C (*n*-hexane). IR (Nujol): 3270, 1670 cm^{-1}. ^1H NMR ($CDCl_3$): 5.6 (s, 1H), 7.3 (s, 5H), 8.4 (br, 1H, D_2O exchangeable). ^{13}C NMR ($CDCl_3$): 61.90, 127.91, 128.97, 129.51, 135.51, 141.87. Mass spectrum (*m*/*z*): 204 (M^+, ^{35}Cl), 206 (M^+, ^{37}Cl), 132 (100%). Anal. Calcd for $C_8H_7NOCl_2$: C, 47.08; H, 3.45; N, 6.86; Cl, 34.74. Found: C, 47.48; H, 3.83; N, 7.05; Cl, 34.81.

The other α-chloro-functionalized hydroximoyl chlorides were prepared by an analogous procedure, which showed the following properties.

2-Chloro-3-methylbutanohydroximoyl Chloride (2a). Yield: 68%. IR (neat): 3360, 1632, 1180, 990 cm^{-1}. ^1H NMR ($CDCl_3$): 0.93, 1.11 (d each, J = 6 Hz each, 2 × 3H), 2.0−2.40 (m, 1H), 4.2 (d, J = 9 Hz, 1H), 8.26 (br, 1H, D_2O exchangeable). ^{13}C NMR ($CDCl_3$): 19.18, 19.31, 33.16, 66.87, 142.15. Anal. Calcd for $C_5H_9NOCl_2$: C, 35.31; H, 5.33; N, 8.23; Cl, 41.70. Found: C, 35.36; H, 5.19; N, 8.35; Cl, 41.95.

2-Chloro-2-methylpropanohydroximoyl Chloride (2b). Yield: 64%. IR (neat): 3400, 1630, 1560 cm^{-1}. ^1H NMR

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($CDCl_3$): 1.84 (s, 6H), 8.52 (br, 1H, D_2O exchangeable). Anal. Calcd for $C_4H_7NOCl_2$: C, 30.79; H, 4.52; N, 8.97; Cl, 45.54. Found: C, 30.47; H, 4.27; N, 8.69; Cl, 45.27.

2-Chloro-2,2-cyclohexylacetohydroximoyl Chloride (2c). Yield: 65%. Mp: 51−52 °C (*n*-hexane). IR (Nujol): 3300, 1640, 1560 cm^{-1}. ^1H NMR ($CDCl_3$): 1.2−1.88 (m, 6H), 2.04−2.68 (m, 4H), 8.0 (br, 1H, D_2O exchangeable). Anal. Calcd for $C_7H_{11}NOCl_2$: C, 42.87; H, 5.65; N, 7.14; Cl, 36.16. Found: C, 42.99; H, 5.79; N, 7.06; Cl, 36.25.

α-Chloro(4-chlorophenyl)acetohydroximoyl Chloride (2e). Yield: 80%. Mp: 96 °C (*n*-hexane). IR (Nujol): 3290, 1640, 1600 cm^{-1}. ^1H NMR ($CDCl_3$): 5.76 (s, 1H), 7.0−7.24 (m, 4H), 7.68 (br, 1H, D_2O exchangeable). ^{13}C NMR ($CDCl_3$): 61.16, 129.19, 129.27, 134.00, 135.58, 141.52. Anal. Calcd for $C_8H_6NOCl_3$: C, 40.28; H, 2.53; N, 5.87. Found: C, 40.51; H, 2.88; N, 5.79.

α-Chloro(4-fluorophenyl)acetohydroximoyl Chloride (2f). Yield: 82% Mp: 84 °C (*n*-hexane). IR (Nujol): 3300, 1652, 1615 cm^{-1}. ^1H NMR ($CDCl_3$): 5.76 (s, 1H), 6.88−7.20 (m, 2H), 7.36−7.68 (m, 2H), 8.04 (s, 1H, D_2O exchangeable). ^{13}C NMR ($CDCl_3$): 61.19, 115.78, 116.22, 129.78, 129.94, 131.42, 131.48, 141.73, 160.84. Anal. Calcd for $C_8H_6NOCl_2F$: C, 43.27; H, 2.72; N, 6.30. Found: C, 43.10; H, 2.97; N, 6.49.

α-Chloro(4-nitrophenyl)acetohydroximoyl Chloride (2g). Yield: 72%. Mp: 114 °C (petroleum ether−benzene). IR (Nujol): 3250, 1630, 1615, 1535 cm^{-1}. ^1H NMR ($CDCl_3$): 5.88 (s, 1H), 7.64−7.84 (m, 2H), 8.16−8.44 (m, 3H, two aromatic protons and one OH). ^{13}C NMR ($CDCl_3$): 61.34, 123.72, 129.30, 136.39, 143.14, 148.03. Anal. Calcd for $C_8H_6N_2O_3Cl_2$: C, 38.57; H, 2.42; N, 11.25. Found: C, 38.92; H, 2.80; N, 11.32.

α-Chloro(2-nitrophenyl)acetohydroximoyl Chloride (2h). Yield: 87%. Mp: 117 °C (petroleum ether−benzene). IR (Nujol): 3280, 1645, 1610, 1520 cm^{-1}. ^1H NMR ($CDCl_3$): 6.56 (s, 1H), 7.4−7.84 (m, 2H), 7.96−8.24 (m, 3H, two aromatic protons and one OH). ^{13}C NMR ($CDCl_3$): 59.28, 124.98, 130.30, 130.83, 131.63, 133.90, 136.54, 147.69. Anal. Calcd for $C_8H_6N_2O_3Cl_2$: C, 38.57; H, 2.42; N, 11.25. Found: C, 38.72; H, 2.37; N, 10.98.

General Procedure for the Synthesis of Arylacetohydroximoyl Chlorides. Titanium tetrachloride (0.012 mol as 1 M solution in CH_2Cl_2) was added dropwise to a stirred mixture of 1-nitro-2-phenylethene (0.01 mol) and Et_3SiH (0.01 mol) at room temperature under argon atmosphere. The reaction mixture was stirred for 1 h at the same temperature and quenched by addition of water, and the product was extracted with CH_2Cl_2 (3 × 15 mL). The combined CH_2Cl_2 extract was washed with water and brine and dried over sodium sulfate. Evaporation of the solvent in vacuo afforded arylacetohydroximoyl chlorides, purified by crystallization and characterized by spectral data.

Phenylacetohydroximoyl Chloride (3d). Yield: 76%. Mp: 87 °C (*n*-hexane). IR (Nujol): 3300, 1670 cm^{-1}. ^1H NMR ($CDCl_3$): 3.75 (s, 2H), 7.23 (s, 5H), 8.5 (br, 1H, D_2O exchangeable). ^{13}C NMR ($CDCl_3$): 42.95, 127.68, 128.91, 129.27, 134.46, 142.10. Anal. Calcd for C_8H_8NOCl: C, 56.65; H, 4.75; N, 8.25; Cl, 20.90. Found: C, 56.47; H, 4.82; N, 8.27; Cl, 20.68.

General Procedure for the Preparation of Hydroximoyl Chlorides from Primary Nitroalkanes Using NaOMe as a Base. To a stirred solution of NaOMe (0.01 mol) in dry methanol (2 mL) was added dropwise primary nitroalkane (0.01 mol) in dry methanol (1 mL) at room temperature under argon atmosphere. The mixture was stirred for 20 min, the solvent was removed, and the resulting sodium salt was dried in vacuo for 3 h. To this was added dry CH_2Cl_2 (10 mL), the suspension was cooled to 0 °C, and a slight excess of $TiCl_4$ (0.012 mol, 1 M solution in CH_2Cl_2) was added dropwise. The resulting mixture was stirred at room temperature for 0.5 h and quenched by addition of water. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extract was washed with water and brine and dried over sodium sulfate. Evaporation of solvent under reduced pressure afforded hydroximoyl chloride, purified by column chromatography and characterized by spectral data.

The phenyl/(4-methylphenyl)acetohydroximoyl chlorides (**5a**/**5b**) obtained by this method were found to be identical with compounds **3d**/**3m**, respectively, obtained by the reaction of 1-nitro-2-phenylethene/1-nitro-2-(4′-methyl phenyl)ethene with $TiCl_4$−Et_3SiH (compared by IR, ^1H MNR, and ^{13}C NMR).

1-Naphthylacetohydroximoyl Chloride (5c). Yield: 78%, Mp: 113 °C. IR (Nujol): 3280, 1610 cm^{-1}. ^1H NMR ($CDCl_3$): 4.25 (s, 2H), 7.40−7.55 (m, 4H), 7.75−8.00 (m, 3H), 8.02−8.10 (m, 1H). ^{13}C NMR ($CDCl_3$): 39.36, 112.84, 124.52, 124.83, 125.32, 127.04, 127.68, 130.31, 130.96, 132.73, 135.74. Anal. Calcd for $C_{12}H_{10}NOCl$: C, 65.61; H, 4.59; N, 6.38. Found: C, 65.45; H, 4.71; N, 6.15.

2-Naphthylacetohydroximoyl Chloride (5d). Yield: 65%. Mp: 127 °C. IR (Nujol): 3420, 1600 cm^{-1}. ^1H NMR ($CDCl_3$): 3.8 (s, 2H), 7.00−7.80 (m, 7H), 8.30 (br, 1H, D_2O exchangeable). ^{13}C NMR ($CDCl_3$): 42.64, 126.40, 126.78, 127.58, 128.05, 128.61, 132.65, 133.56, 136.92. Anal. Calcd for $C_{12}H_{10}NOCl$: C, 65.61; H, 4.59; N, 6.38. Found: C, 65.72; H, 4.67; N, 6.51.

Since the hydroximoyl chloride **5e** was found to be rather unstable, it was immediately converted into the corresponding 2-isoxazoline derivative *viz*. ethyl 3-ethyl-2-isoxazoline-5-carboxylate, by generating the nitrile oxide followed by its cycloaddition reaction with ethyl acrylate.

Ethyl 3-Ethyl-2-isoxazoline-5-carboxylate. Yield: 68%. IR (neat): 1735, 1440 cm^{-1}. ^1H NMR ($CDCl_3$): 1.1 (t, J = 7.5 Hz, 3H), 1.25 (t, J = 7.5 Hz, 3H), 2.35 (q, J = 7.5 Hz, 2H), 3.15 (d [with minor splitting], J = 10 Hz, 2H), 4.2 (q, J = 7.5 Hz, 2H), 4.95 (t, J = 10 Hz, 1H). Anal. Calcd for $C_8H_{13}NO_3$: C, 56.63; H, 7.57; N, 8.09. Found: C, 56.35; H, 7.62; N, 8.23.

General Procedure for the Preparation of Hydroximoyl Chlorides from Primary Nitroalkanes Using NaH or KH as a Base. To a stirred solution of NaH or KH (0.01 mol) in dry benzene (5 mL) was added primary nitroalkane (0.01 mole) in dry benzene slowly at room temperature under argon atmosphere. After stirring the reaction mixture for 0.5 h at the same temperature, it was cooled to 0 °C. Then $TiCl_4$ (0.012 mol) was added slowly, and the resulting mixture was stirred for additional 0.5 h at room temperature. The reaction mixture was quenched with water, and the organic layer was extracted with benzene (3 × 5 mL), and the combined organic layer was washed with water and brine, dried, filtered, and concentrated in vacuo to get the crude product, which was purified by column chromatography over silica gel to afford pure product, characterized by spectral data.

The phenyl/(4-methylphenyl)acetohydroximoyl chlorides (**5a**/**5b**) obtained by using NaH or KH as a base were found to be identical with compound **3d**/**3m** obtained by the reaction of 1-nitro-2-phenylethene/1-nitro-2-(4′-methylphenyl)ethene with $TiCl_4$−Et_3SiH (compared by IR, ^1H MNR, and ^{13}C NMR).

Carbomethoxyacetohydroximoyl Chloride (5f). Yield: 59%. IR (neat): 3310, 1740, 1620 cm^{-1}. ^1H NMR ($CDCl_3$): 3.5 (s, 3H), 10.0 (br, 1H, D_2O exchangeable). Anal. Calcd for $C_3H_4NO_3Cl$: C, 26.20; H, 2.93; N, 10.18. Found: C, 26.51; H, 3.15; N, 9.93.

Representative Procedure for the Preparation of α-Azidophenylacetohydroximoyl Chloride (6d). To a stirred solution of nitroalkene (**1d**) (0.745 g, 5 mmol) and $TMSN_3$ (0.99 mL, 7.5 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise a solution of $TiCl_4$ (5.2 mmol, 1 M solution in CH_2Cl_2) over a period of 0.5 h at room temperature under argon atmosphere. After stirring for additional 1 h, water was added and the product extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was washed with water and brine and dried (Na_2SO_4). Removal of solvent gave a residue which was purified by column chromatography over silica gel (5% ethyl acetate in petroleum ether) to obtain the α-azidohydroximoyl chloride (**6d**) (0.819 g). Yield: 78%. Mp: 51 °C (*n*-hexane). IR (Nujol): 3270, 2100, 1600 cm^{-1}. ^1H NMR ($CDCl_3$): 5.40 (s, 1H), 7.48 (m, 5H), 8.44 (s, 1H, D_2O exchangeable). ^{13}C NMR ($CDCl_3$): 67.60, 127.63, 129.18, 129.51, 134.03, 140.25. Anal. Calcd for $C_8H_7N_4OCl$: C, 45.61; H, 3.35; N, 26.60. Found: C, 45.49; H, 3.43; N, 26.63.

By an analogous procedure, the other α-azidohydroximoyl chlorides were prepared which showed the following properties.

2-Azido-3-methylbutanohydroximoyl Chloride (6a). Yield: 87%. IR (neat): 3200, 2100, 1640, 1610 cm^{-1}. ^1H NMR ($CDCl_3$): 0.95, 1.10 (d each, J = 7.5 Hz each, 2 × 3H), 2.05−2.25 (m, 1H), 4.32 (d, J = 10 Hz, 1H), 8.35 (br, 1H, D_2O exchangeable). ^{13}C NMR ($CDCl_3$): 18.80, 18.97, 30.39, 71.02, 140.88. Anal. Calcd for $C_5H_9N_4OCl$: C, 34.00; H, 5.14; N, 31.72. Found: C, 34.27; H, 5.31; N, 31.69.

α-Azido-(4-fluorophenyl)acetohydroximoyl Chloride (6f). Yield: 73%. Mp: 65 °C (petroleum ether). IR (Nujol): 3280, 2100, 1660, 1610 cm^{-1}. ^1H NMR ($CDCl_3$) 5.32 (s, 1H), 6.88−

7.52 (m, 4H), 8.48 (br, 1H, D_2O exchangeable). Anal. Calcd for $C_8H_6N_4OClF$: C, 42.02; H, 2.64; N, 24.50. Found: C, 42.23; H, 2.71; N, 24.35.

α-Azido-(2-chlorophenyl)acetohydroximoyl Chloride (6j). Yield: 81%. IR (neat): 3200, 2100, 1630 cm^{-1}. ^1H NMR ($CDCl_3$): 5.84 (s, 1H), 7.20−7.68 (m, 4H), 8.64 (s, 1H, D_2O exchangeable). Anal. Calcd for $C_8H_6N_4OCl_2$: C, 39.20; H, 2.46; N, 22.86. Found: C, 39.35; H, 2.61; N, 22.69.

α-Azido-(3,4-dichlorophenyl)acetohyroximoyl Chloride (6k). Yield: 75%. IR (neat): 3300, 2100, 1630 cm^{-1}. ^1H NMR ($CDCl_3$): 5.36 (s, 1H), 7.08−7.65 (m, 3H), 8.48 (br, 1H, D_2O exchangeable). Anal. Calcd for $C_8H_5N_4OCl_3$: C, 34.37; H, 1.80; N, 20.04. Found: C, 34.51; H, 1.75; N, 20.17.

α-Azido-(4-methylphenyl)acetohydroximoyl Chloride (6m). Yield: 71%. Mp: 85 °C (petroleum ether). IR (Nujol): 3250, 2090, 1650 cm^{-1}. ^1H NMR ($CDCl_3$): 2.28 (s, 3H), 5.32 (s, 1H), 7.2 (bs, 4H), 8.32 (s, 1H, D_2O exchangeable). ^{13}C NMR ($CDCl_3$): 20.31, 67.39, 127.55, 129.82, 131.04, 139.46, 140.08. Anal. Calcd for $C_9H_9N_4OCl$: C, 48.12; H, 4.03; N, 24.94. Found: C, 48.28; H, 4.31; N, 24.69.

Cycloaddition Reaction of Nitrile Oxide Generated from 6d with Ethyl Acrylate. To a stirred solution of α-azidophenylacetohydroximoyl chloride (**6d**) (2.1 g, 0.01 mol) and ethyl acrylate (4.04 g, 0.04 mol) in dry CH_2Cl_2 (30 mL) was added triethylamine (1.2 g, 0.012 mole) in dry CH_2Cl_2 (20 mL), dropwise over a period of 30 min at room temperature. The mixture was stirred for additional 8 h at the same temperature. After diluting with water, the organic layer was washed with HCl (5%) and brine and dried over sodium sulfate. The solvent was evaporated to afford a residue, which was purified by column chromatography over silica gel using 5% ethyl acetate in petroleum ether as an eluent to get ethyl 3-(α-azidobenzyl)-2-isoxazoline-5-carboxylate (**8d**) as a diastereomeric mixture (2.4 g). Yield: 88%. IR (neat): 2100, 1740 cm^{-1}. ^1H NMR ($CDCl_3$): 1.23, 1.32 (t each, J = 7.5 Hz, 3H, CH_3 of the diastereomers), 2.92−3.10 (m, 1H, one of the CH of the allylic CH_2), 3.17−3.35 (m, 1H, another CH of the allylic CH_2), 4.17, 4.25 (q each, J = 7.5 Hz, 2H), 4.95−5.10 (m, 1H), 5.65 (s, 1H, benzylic CH), 7.42 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$): 13.88, 13.93, 37.45, 61.29, 61.34, 61.75, 61.83, 78.04, 126.70, 126.81, 129.05, 134.64, 134.76, 156.70, 169.42, 169.56. Anal. Calcd for $C_{13}H_{14}N_4O_3$: C, 56.92; H, 5.14; N, 20.42. Found: C, 56.79; H, 5.21; N, 20.49.

By an analogous procedure the other isoxazolines *viz*. **8a**, **8f**, and **8m** were synthesized and characterized by spectral data and elemental analysis.

Ethyl 3-(1-Azido-2-methyl-propyl)-2-isoxazoline-5-carboxylate (8a). Yield: 43%. IR (neat): 2100, 1740 cm^{-1}. ^1H NMR ($CDCl_3$): 0.90, 0.94 (d each, J = 7.5 Hz each, 3H, one of the methyls of isopropyl of diastereomers), 1.05, 1.10 (d each, J = 7.5 Hz, 3H), 1.30, 1.35 (t each, J = 7.5 Hz each, 3H), 1.75−2.97 (m, 1H), 3.10−3.42 (m, 2H), 4.05 (d, J = 10 Hz, 1H), 4.25, 4.27 (q each, J = 7.5 Hz, 2H), 4.97−5.12 (m, 1H). ^{13}C NMR ($CDCl_3$): 14.08, 18.81, 18.98, 19.11, 19.23, 31.15, 31.53, 37.46, 37.79, 61.99, 65.11, 65.26, 77.70, 77.75, 156.74, 169.78, 169.87. Anal. Calcd for $C_{10}H_{16}N_4O_3$: C, 49.98; H, 6.71; N, 23.32. Found: C, 50.13; H, 6.59; N, 23.17.

Ethyl 3-(α-Azido-4-fluorobenzyl)-2-isoxazoline-5-carboxylate (8f). Yield: 74%. IR (neat): 2120, 1740, 1620 cm^{-1}. ^1H NMR ($CDCl_3$): 1.25, 1.37 (t each, J = 7.5 Hz, 3H), 2.92−3.10 (m, 1H), 3.17−3.35 (m, 1H), 4.17, 4.25 (q each, J = 7.5 Hz, 2H), 4.95−5.10 (m, 1H), 5.60, 5.62 (s each, 1H), 7.02−7.15 (m, 2H), 7.25−7.43 (m, 2H). ^{13}C NMR ($CDCl_3$): 13.98, 37.37, 37.43, 60.71, 60.77, 61.90, 61.98, 78.12, 78.17, 116.32, 128.63, 128.77, 128.92, 130.63, 130.69, 156.67, 169.57. Anal. Calcd for $C_{13}H_{13}N_4O_3F$: C, 53.42; H, 4.48; N, 19.17. Found: C, 53.71; H, 4.61; N, 19.31.

Ethyl 3-(α-Azido-4-methylbenzyl)-2-isoxazoline-5-carboxylate (8m). Yield: 69%. IR (neat): 2100, 1740 cm^{-1}. ^1H NMR ($CDCl_3$): 1.25, 1.30 (t each, J = 7.5 Hz, 3H), 2.37 (s, 3H), 2.95−3.12 (m, 1H), 3.16−3.31 (m, 1H), 4.17, 4.25 (q each, J = 7.5 Hz, 2H), 4.92−5.07 (m, 1H), 5.57 (s, 1H), 7.24 (bs, 4H). ^{13}C NMR ($CDCl_3$): 14.12, 14.17, 21.25, 37.64, 61.37, 61.44, 62.02, 62.11, 78.18, 78.24, 126.80, 126.90, 129.94, 131.85, 139.10, 157.00, 169.85. Anal. Calcd for $C_{14}H_{16}N_4O_3$: C, 58.32; H, 5.59; N, 19.43. Found: C, 58.27; H, 5.67; N, 19.59.

Representative Procedure for the Preparation of α-Cyanophenylacetohydroximoyl Chloride (7d). To a stirred solution of 1-nitro-2-phenylethene (**1d**) (0.745 g, 5 mmol) and TMSCN (1.99 mL, 15 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise a solution of $TiCl_4$ (5.2 mmol, 1 M solution in CH_2Cl_2) over a period of 0.5 h at room temperature under argon atmosphere. After stirring for additional 1 h, water was added and the product extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was washed with water and brine and dried (Na_2SO_4). Removal of solvent gave a residue which was purified by column chromatography over silica gel (5% ethyl acetate in petroleum ether) to obtain TLC pure α-cyanophenylacetohydroximoyl chloride (**7d**) as a solid (0.819 g). Yield: 59%. Mp: 65 °C (*n*-hexane). IR (Nujol): 3240, 2260, 1635, 1570 cm^{-1}. ^1H NMR ($CDCl_3$): 4.96 (s, 1H), 7.4 (m, 5H), 8.52 (br, 1H, D_2O exchangeable). Anal. Calcd for $C_9H_7N_2OCl$: C, 55.53; H, 3.62; N, 14.39. Found: C, 55.71; H, 3.91; N, 14.17.

By an analogous procedure the other α-cyano-functionalized hydroximoyl chlorides were prepared and identified by spectral data.

2-Cyano-3-methylbutanohydroximoyl Chloride (7a). Yield: 10%. IR (neat): 3300, 2260, 1634, 1560 cm^{-1}. ^1H NMR ($CDCl_3$): 1.06, 1.24 (d each, J = 6 Hz each, 2 × 3H), 2.11−2.62 (m, 1H), 3.46 (d, J = 7 Hz, 1H), 8.20 (br, 1H, D_2O exchangeable). Anal. Calcd for $C_6H_9N_2OCl$: C, 44.86; H, 5.64; N, 17.44. Found: C, 44.63; H, 5.81; N, 17.45.

α-Cyano(4-fluorophenyl)acetohydroximoyl Chloride (7f). Yield: 57%. Mp: 129 °C (*n*-hexane). IR (Nujol): 3260, 1640, 1600 cm^{-1}. ^1H NMR ($CDCl_3$): 4.91 (s, 1H), 6.91−7.44 (m, 4H), 8.11 (br, 1H, D_2O exchangeable). Anal. Calcd for $C_9H_6N_2OClF$: C, 50.83; H, 2.84; N, 13.18. Found: C, 50.49; H, 2.92; N, 13.27.

α-Cyano(4-methylphenyl)acetohydroximoyl Chloride (7m). Yield: 69%. Mp: 109 °C (*n*-hexane). IR (Nujol): 3300, 1640 cm^{-1}. ^1H NMR ($CDCl_3$): 2.33 (s, 3H), 4.88 (s, 1H), 7.13 (m, 4H), 8.28 (br, 1H, D_2O exchangeable). Anal. Calcd for $C_{10}H_9N_2OCl$: C, 57.56; H, 4.34; N, 13.42. Found: C, 57.22; H, 4.32; N, 13.27.

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Supporting Information Available: Spectral data of compounds **3e**−**m** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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