1,3-DIPOLAR CYCLOADDITION: MOLECULAR SIEVES ASSISTED GENERATION OF NITRILE OXIDES FROM HYDROXIMOYL CHLORIDES

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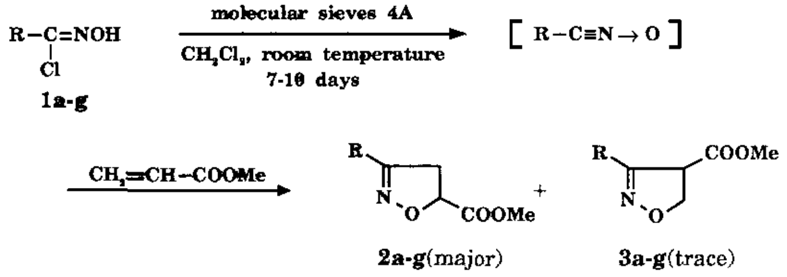
Abstract - Molecular sieves irrespective of their pore size convert hydroximoyl chlorides into the corresponding nitrile oxides very slowly and cleanly in the presence of dipolarophiles to give isoxazolines in good to excellent yields.

Nitrile oxides are important synthetic intermediates in organic synthesis, particularly in [3+2] cycloaddition reaction to form isoxazolines or isoxazoles.[1] Nitrile oxides can be generated by many methods. Among several methods developed for the *in situ* generation of nitrile oxides, two have been extensively used: a) the dehydration of primary nitro derivatives (Mukaiyama procedure)[2] and b) the base-induced dehydrohalogenation of hydroximoyl halides (Huisgen's methodology).[3] In general, nitrile oxides are relatively unstable, so low concentration in the reaction medium is necessary to increase the yields of cycloaddition products with alkenes or alkynes and to minimize the dimerization of nitrile oxides. In continuing our study on nitrile oxides,[4] we found that molecular sieves convert hydroximoyl chlorides into nitrile oxides very slowly in the presence of dipolarophiles and give good yields of cycloaddition products. Molecular sieves have received much attention by synthetic organic chemists as well as chemists in the field of petrochemistry and oil processing.[5] There have been reported the catalytic activity of molecular sieves in organic synthesis;[6] particularly Weinstock *et al.* have used molecular sieves to trap the hydrogen chloride generated from the acylation of amides with acetyl chlorides.[7]

Thus, we have prepared several isoxazolines from methyl acrylate and nitrile oxides which were generated from the corresponding hydroximoyl chlorides in the presence of molecular sieves 4A (**Scheme 1**).



Scheme 1

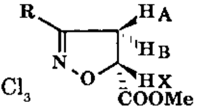
Desired isoxazolines (**2a-g**) together with small amount of regioisomeric (**3a-g**) were obtained in good to excellent yields. The results and spectroscopic data are given in **Tables I-III**.

Table I. Synthesis of Isoxazolines **2a-g**/**3a-g**

Entry	R	Time(day)	Yield(%)	Ratio(2:3)[a]
a	COMe	7	72	99.3 : 0.7
b	COOEt	7	80	99.3 : 0.7
c	COPh	7	99	99.5 : 0.5
d	2,6-$Cl_2C_6H_3$	10	95	93.9 : 6.1
e	2-Cl, 6-FC_6H_3	8	99	92.4 : 7.6
f	2,6-$F_2C_6H_3$	9	94	94.1 : 5.9
g	2,4,6-$Me_3C_6H_2$	9	99	94.5 : 5.5

[a] The ratio was determined by gc.

Table II. ^{1}H-Nmr Data of Products **2a-g** in $CDCl_3$



Product[a]	H_X	J_{AX}	J_{BX}	AB part[b]	COOMe	Others
2a	5.22(dd)	10.3	9.0	3.37-3.51(m)	3.82	2.53(s, 3H)
2b	5.24(apparent t, J=9.7)			3.52(apparent d, J=9.7)	3.82	1.37(t, J=7.1, 3H), 4.38(q, J=7.1, 2H)
2c	5.21(dd)	10.7	8.5	3.59-3.73(m)	3.80	7.30-8.22(m, 5H)
2d	5.28(dd)	10.9	7.1	3.51-3.69(m)	3.84	7.30-7.41(m, 3H)
2e	5.26(dd)	10.2	8.0	3.56-3.73(m)	3.84	7.06-7.42(m, 3H)
2f	5.20(dd)	9.7	8.9	3.66-3.75(m)	3.83	6.95-7.45(m, 3H)
2g	5.17(dd)	10.1	7.1	3.43-3.57(m)	3.84	2.23(s, 6H), 2.29 (s, 3H), 6.90(s, 2H)

[a] Contaminated by regioisomeric **3a-g**.

[b] Geminal coupling constant J_{AB} was not determined.

Table III. Ms Spectral Data and Elemental Analyses for **2a-g**

Product[a]	Molecular Formular	Ms (70 eV) m/z (%)	Analyses (Calcd/Found) C	H	N
2a	$C_7H_9NO_4$	43(100), 112(7), 172(M$^+$+1, 1)	49.12	5.30	8.18
			48.81	5.13	8.41
2b	$C_8H_{11}NO_5$	49(100), 142(11), 202(M$^+$+1, 13)	47.76	5.51	6.96
			47.38	5.47	6.70
2c	$C_{12}H_{11}NO_4$	77(39), 105(100), 174(3),	61.80	4.75	6.01
		205(2), no M$^+$	61.81	4.75	5.95
2d	$C_{11}H_9NO_3Cl_2$	185(100), 186(95), 188(67),	48.20	3.31	5.11
		214(69), 215(49), 216(47),	48.06	3.25	4.97
		273(M$^+$, 15), 275(12)			
2e	$C_{11}H_9NO_3ClF$	49(100), 170(9), 198(8),	51.28	3.52	5.44
		257(M$^+$, 1)	50.94	3.51	5.19
2f	$C_{11}H_9NO_3F_2$	49(54), 154(99), 182(100),	54.78	3.76	5.81
		241(M$^+$, 35), 242(30)	54.62	3.62	5.74
2g	$C_{14}H_{17}NO_3$	49(100), 84(30), 188(22),	67.99	6.93	5.66
		247(M$^+$, 7)	67.82	6.93	5.55

[a] Contaminated by regioisomeric **3a-g**.

Although relatively long reaction times are required, our procedure can minimize dimerization of nitrile oxide to furoxane, presumably due to slow generation of nitrile oxide by interaction of molecular sieves and hydroximoyl chloride, which may be beneficial for maintaining low concentration of nitrile oxide during the cycloaddition reactions.[7,8] Consequently the desired isoxazolines can be obtained in high yields and high purity after simple work-up of the reaction mixtures. It is noteworthy that molecular sieves 3A, 5A, and 13X also conducted the cycloaddition reaction effectively, whereas silica gel, Celite, charcoal, and alumina (acidic or basic) do not effect at all under the same reaction conditions.

EXPERIMENTAL

General Remarks. ^{1}H Nmr spectra were recorded on a Bruker AM-300 Nmr Spectrometer with TMS as an internal standard. Mass spectra were recorded on a Shimadzu QP 1000 Spectrometer. Elemental analyses for C, H, and N were performed with Perkin-Elmer 240C Elemental Analyzer. Vapor-phase chromatography was performed on a Hewlett-Packard HP 5890A gas chromatograph equipped with a Hewlett-Packard HP-1 capillary column (crosslinked methylsilicone gum, 25 m x 0.2 mm x 0.33 μm film thickness), FID detector, and a Hewlett-Packard 3390A integrator. The column was used with the following temperature program: 150 °C (2 min), 150-290 °C (10 °C/min). Thin layer chromatography (tlc) was carried out with precoated silica gel plates (Kieselgel 60 F-254, Merck). Flash chromatography was performed using 230-400 mesh Kieselgel 60 (E. Merck).

Materials. Molecular sieves (3A, 4A, 5A, and 13X, 4-8 mesh) were purchased from Aldrich Chem. Co. and used as it. Starting hydroximoyl chlorides were prepared according to the literature method (see reference 4b).

Synthesis of Methyl 3-(2,6-dichlorophenyl)-Δ^2-isoxazoline-5-carboxylate (2d); Typical Procedure: To a stirred solution of 2,6-dichlorobenzohydroximoyl chloride (**1d**; 1.13 g, 5 mmol) and methyl acrylate (1.30 g, 15 mmol) in methylene chloride (10 ml) were added molecular sieves 4A (4.0 g) and stirred at room temperature for 10 days. The reaction mixture is filtered through a Celite pad and washed with CH_2Cl_2 (3 x 10 ml). The filtrates and washings were combined and evaporated to afford nearly pure isoxazoline. Column chromatographic separa

CH_2Cl_2 in hexane) gave analytically pure **2d+3d** (1.30 g, 95%, **2d/3d** = 93.9 : 6.1) as an oil. Further separation of **2d** and **3d** was not performed.

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