ALKALI METAL FLUORIDE PROMOTED GENERATION OF NITRILE OXIDES FROM HYDROXIMOYL CHLORIDES

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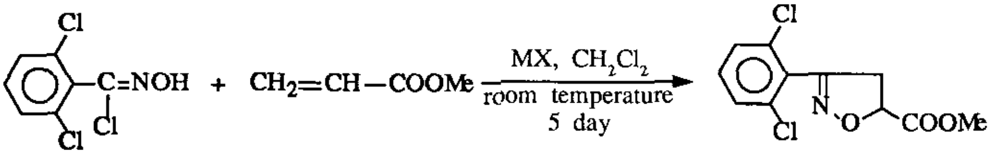
Abstract - Some nitrile oxides were generated from hydroximoyl chlorides by alkali metal fluoride in the presence of methyl acrylate to give isoxazoline derivatives **2** in high yields.

The fluoride ion has frequently been employed in organic synthesis based on its characteristic property of forming a strong hydrogen bond with various protic organic compounds.[1] The fluoride ion appears to be acting as a base even in nonpolar media,[2] and particurarly, there was certain report on the use of cesium fluoride as an acid captor instead of triethylamine.[3] On the other hand, generation of nitrile oxides from the corresponding hydroximoyl chlorides is an easy but an important synthetic transformation.[4] In general, slow generation of nitrile oxide in the presence of dipolarophile in the 1,3-dipolar cycloaddition reaction is crucial due to its relative unstability. Dropwise addition of triethylamine,[5] use of inorganic base,[6] and photochemical generation method[7] are the reported ones. Recently, we have reported another method using molecular sieves as an acid captor.[8] In our continuous work, we report herein a useful method of generation of nitrile oxides from hydroximoyl chlorides in the presence of alkali metal fluoride.

Thus, we examined the reaction of 2,6-dichlorobenzohydroximoyl chloride (**1a**) with methyl acrylate in methylene chloride using various metal halides, and the results were summarized in **Table I**.

As shown in **Table I**, sodium fluoride, potassium fluoride, cesium fluoride, and lithium iodide gave good yields of **2a**, whereas with other metal halides no reaction products or trace amounts of **2a** was observed on tlc. In view of yields, the ease of handling, and price of metal halide, we chose potassium fluoride or sodium fluoride as an acid captor and the results were summarized in **Table II**.

Table I. Effect of Metal Halide MX



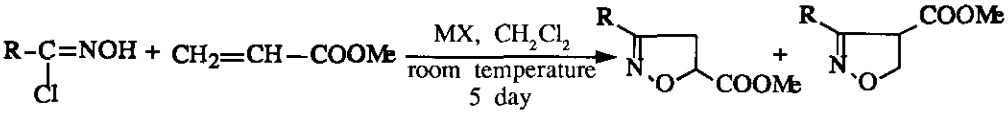
1a (1 mmol) (3 mmol) 2a

Entry	MX	Yield(%)[a]	Entry	MX	Yield(%)[a]
1	LiF	b	8	NaI	b
2	LiCl	b	9	KF	93
3	LiBr	b	10	KCl	b
4	LiI	80	11	KBr	b
5	NaF	92	12	KI	b
6	NaCl	b	13	CsF	94
7	NaBr	b	14	CaF_2	b

a. Isolated yield of pure product.

b. Trace amounts of product were observed on tlc.

Table II. Synthesis of Some Isoxazolines



1 (5 mmol) (15 mmol) **2** (major) **3** (minor)

Entry	R	MX	Yield(%)[a]	2 : 3[b]
1	$2,6\text{-}Cl_2C_6H_3$	NaF	96	90.8 : 9.2
2	$2,6\text{-}Cl_2C_6H_3$	KF	93	93.3 : 6.7
3	$2\text{-}Cl, 6\text{-}FC_6H_3$	KF	98	96.5 : 3.5
4	EtO_2C	KF	94	>99 : 1
5	C_6H_5	NaF	99[c]	>99 : 1
6	MeCO	NaF	97	>99 : 1
7	Br[d]	NaF	89[c]	94.9 : 5.1

a. Isolated yield, and the products were all identical with the authentic samples as prepared according to the previous method.[8]

b. The ratio was determined by glc using HP-1 column.

c. See : reference 10.

d. Dibromoformaldoxime[9] was used instead of the corresponding chloride.

Desired isoxazolines **2** together with small amounts of regioisomeric **3** were obtained in good to excellent yields. Although relatively long reaction times are required to complete the reaction, there were observed little or no dimerization products.

Potassium fluoride mediated regeneration method of nitrile oxides from *O*-(trimethylsilyl)hydroximoyl chlorides has been reported in the literature,[11] where preparation of *O*-silylhydroximoyl chlorides from the corresponding nitrile oxides and chlorotrimethylsilane is needed. However, our method includes the direct use of easily obtainable hydroximoyl chloride and can be applied conveniently in synthesizing various isoxazoline and isoxazole derivatives.

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. 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).

Materials. Metal halides were purchased from Aldrich Chem. Co. and used as it. Starting dibromoformaldoxime and hydroximoyl chlorides were prepared according to the literature method (see references 8 and 9).

Synthesis of Methyl 3-(2,6-dichlorophenyl)-Δ^2-isoxazoline-5-carboxylate (2a); Typical Procedure: To a stirred solution of 2,6-dichlorobenzohydroximoy chloride (**1a**; 1.13 g, 5 mmol) and methyl acrylate (1.30 g, 15 mmol) in methylene chloride (15 ml) was added sodium fluoride (700 mg) and the mixture was stirred at room temperature for 5 days. The reaction mixture is filtered through a Celite pad and washed with CH_2Cl_2 (2 x 5 ml). The filtrates and washings were combined and evaporated to afford nearly pure isoxazoline. Column chromatographic separation (silica gel, 70% CH_2Cl_2 in hexane) gave analytically pure isoxazoline (**2a**; 1.32 g, 96%) containing small amounts of regioisomeric methyl 3-(2,6-dichlorophenyl)-Δ^2-isoxazoline-4-carboxylate.

ACKNOWLEDGEMENT

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10. Methyl 3-phenyl-Δ^2-isoxazoline-5-carboxylate : ^{1}H-Nmr ($CDCl_3$) δ 3.57-3.71(m, 2H), 3.80 (s, 3H), 5.18(dd, J=10.1 and 8.2 Hz, 1H), 7.28-7.70(m, 5H); ms (m/z, %) 51(36), 77(65), 118(80), 146(100), 205(M^+, 26), 206(32).
    Methyl 3-bromo-Δ^2-isoxazoline-5-carboxylate : ^{1}H-Nmr ($CDCl_3$) δ 3.50-3.66(m, 2H), 3.83 (s, 3H), 5.13(dd, J=9.8 and 8.7 Hz, 1H); ms (m/z, %) 41(100), 43(96), 59(64), 122 (32), 124(31), 148(42), 150(41), 208(M^++1, 10), 210(9).
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