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A Facile One-Pot Preparation of Isothiocyanates from Aldoximes

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Summary : Isothiocyanates **2a-l** were prepared in excellent yields in a one-pot reaction from aldoxime derivatives **1a-l** by successive treatment of aldoxime with *N*-chlorosuccinimide (NCS), thiourea, and triethylamine. The use of HCl / DMF / Oxone system in the reaction instead of NCS was equally effective.

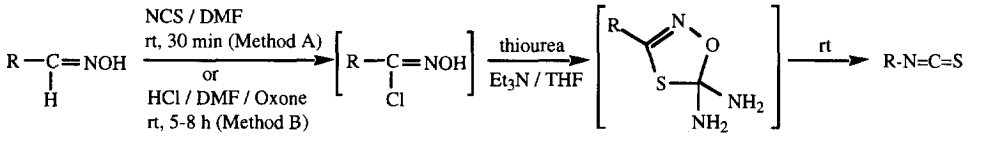
Isothiocyanates have been used extensively in organic synthesis,[1] particularly in the synthesis of various heterocyclic compounds[1a] as well as for the synthesis of various agrochemicals that have antifungal and anthelmintic activities.[2] Some isothiocyanates such as sulforaphane and phenethyl isothiocyanate (PEITC) have antitumor activities,[2] and several sesquiterpene isothiocyanates have been isolated from marine natural products.[3]

There have been reported numerous methods for the synthesis of isothiocyanates.[4-7] Most of the reported methods involve the use of amines or amine derivatives as starting materials.[4] Synthesis of isothiocyanates from isocyanides,[5] organic halides,[6] or olefins[7] have also been reported. However, these methods suffer from low yields, the use of toxic materials, and/or contaminations with isocyanate derivatives. In these regards development of a facile synthetic procedure for the preparation of isothiocyanates is important.

Recently, we have reported a useful method for the preparation of isothiocyanates from nitrile oxides,[8] which use hydroximoyl chlorides[8a] or primary nitroalkanes[8b] as nitrile oxide precursors. In the reactions, nitrile oxides reacted with thiourea to afford unstable 1,4,2-oxathiazolines, which decomposed instantaneously to urea and the corresponding isothiocyanates. Thus we envisioned that isothiocyanates could be prepared from the easily prepared aldoximes and thiourea in a one-pot reaction. Firstly, we tried the reaction of 2,6-dichlorobenzaldoxime (**1d**) and thiourea in the presence of various oxidizing agents such as MnO_2, Ag_2CO_3, chloramin-T, $Pb(OAc)_4$ in order to oxidize aldoxime into nitrile oxide *in situ*. However, all attempts have failed presumably due to oxidative decomposition of thiourea. Secondly, we examined the possibility that *in situ* generated hydroximoyl chlorides from aldoximes could be used efficiently as nitrile oxide precursors in the above reaction. 2,6-Dichlorobenzaldoxime (**1d**, 10 mmol) in *N,N*-dimethylformamide (10 mL) was treated with *N*-chlorosuccinimide (1.34 g, 10 mmol) in water bath to afford the corresponding hydroximoyl chloride (**Method A**).[9] After 30 min the reaction mixture was diluted with tetrahydrofuran (50 mL), and treated with thiourea (0.85 g, 11 mmol) and triethylamine (1.2 g in 5 mL THF, 11 mmol). The reaction mixture was poured into cold water (200 mL) after 10 min and extracted with ether (2 x 200 mL). 2,6-Dichlorophenyl isothiocyanate (**2d**) was obtained after usual workup process without any detcetable side products on TLC. Analytically pure product was obtained in excellent yield (99%) by passing through short path silica column. During the course of the reaction we found that DMF was the best solvent for the praration of hydroximoyl chlorides, and in the second manipulation step dilution with THF was necessary to obtain the highest yield of the products. Without THF decomposition of the oxathiazoline was somewhat retarded. The use of HCl / DMF / Oxone system (**Method B**)[10] to prepare the corresponding hydroximoyl chlorides was found to be

equally effective : higher yields of products were obtained in most of the cases, however, longer reaction time (5-8 h) was required. The representative results were summarized in **Scheme 1** and **Table 1**.

In conclusion, we developed an efficient one-pot synthetic procedure for the preparation of isothiocyanates from easily available aldoximes. The reaction have some merits over the published methods such as one-pot reaction from aldoximes, short reaction time, high yields, mild reaction conditions, and the ease of separation.



1a-l **2a-l**

Scheme 1

Table 1. Synthesis of Isothiocyanates from Aldoximes.

Entry	Product	R	Yield (%, **Method A**)	Yield (%, **Method B**)
1	**2a**	C_6H_5-	94	92
2	**2b**	2-ClC_6H_4-	92	95
3	**2c**	4-ClC_6H_4-	93	98
4	**2d**	2,6-$Cl_2C_6H_3$-	99	99
5	**2e**	4-$CH_3C_6H_4$-	93	94
6	**2f**	2,4,6-$Me_3C_6H_2$-	99	99
7	**2g**	4-$CH_3OC_6H_4$-	94	88
8	**2h**	4-$CF_3C_6H_4$-	97	97
9	**2i**	C_6H_4-1,4-$(NCS)_2$	84	61
10	**2j**	C_6H_5-$CH(CH_3)$-	85	90
11	**2k**	$(C_6H_5)_2CH$-	91	98
12	**2l**	$CH_3(CH_2)_4$-	76	89

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