Tetrahedron Letters, Vol. 34, No. 51, pp. 8283-8284, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

A Convenient Synthesis of Isothiocyanates from Nitrile Oxides

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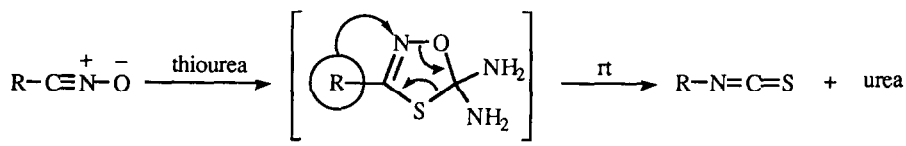
Summary: *Isothiocyanats were prepared in quantitative yields from the reaction of nitrile oxides with thiourea in tetrahydrofuran at room temperature in short time.*

Isothiocyanates are important reagents in organic synthesis, particularly in the synthesis of various heterocyclic compounds.[1a] There have been reported numerous methods for the synthesis of isothiocyanates.[1-3] Most of the reported methods involve the use of amines or amine derivatives as starting materials.[2] Converting methods of isocyanide to isothiocyanates have also been reported.[3] To our best knowledge, however, there have no efficient method for the preparation of isothiocyanates from aldehydes or aldehyde derivatives.

On the other hand, the reactions of nitrile oxides with compounds containing carbon-sulfur double bond have been investigated in many reports,[4] in which the isothiocyanates were obtained from the reactions of nitrile oxides with C=S bond containing compounds including thioaldehydes, thioketones, thioamides, thiono esters, thionocarbonates, thioketenes, sulfonyl isothiocyanates, and carbon disulfide.[4] 1,4,2-Oxathiazoline derivatives were formed via [3+2] cycloaddition reaction of nitrile oxide and thiocarbonyl compounds, which could be easily decomposed into isothiocyanates and the corresponding carbonyl compounds. Most of attention was paid to converting the thiocarbonyl functionality into the corresponding carbonyl functional group, thus the formation of isothiocyanates have received little attention. Moreover, the generated isothiocyanates were contaminated with the desired C=O containing compounds and/or other side products, which make purification of the isothiocyanates tedious. The reaction of nitrile oxides with thiocyanate ion also produce isothiocyanates, which was not valuable as a general method for the preparation of isothiocyanates due to the similar reasons described above.[5]

During the course of our investigation on the reaction of nitrile oxide with nucleophiles,[6] we decided to examine the reaction of nitrile oxides with thiourea, the neutral nucleophile. The reaction of 2,6-dichlorobenzonitrile oxide with thiourea (1.0 equiv) in tetrahydrofuran at room temperature afforded 2,6-dichlorophenyl isothiocyanate quantitatively within 1 min. Analogously 2,4,6-trimethylphenyl isothiocyanates was obtained quantitatively. The mechanism for the formation of isothiocyanates could be explained as shown below.

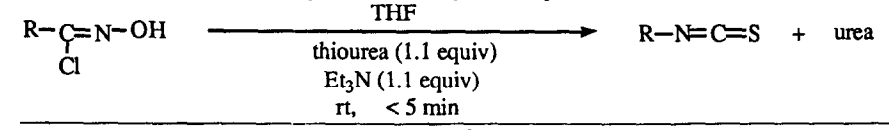


R = 2,6-$Cl_2C_6H_3$- or 2,4,6-$Me_3C_6H_2$-

The reaction can also be conducted effectively in CH_3CN, EtOH, DMF, acetone with equal facility. The reaction can not be completed in methylene chloride or ether due to the limited solubility of thiourea in these solvents. In methylene chloride, however, the use of 1,3-dimethyl-2-thiourea gave good yields of isothiocyanates. The reactions of various hydroximoyl chlorides[7] and thiourea in the presence of triethylamine are summarized in **Table 1**. As shown in **Table 1**, the mixture of hydroximoyl chloride and thiourea (1.1 equiv)

in THF was treated with triethylamine (1.1 equiv) and stirred at room temperature in a few min to afford the corresponding isothiocyanates in excellent yields. In the reactions, isothiocyanates can be prepared readily under mild conditions in short time in contrast to the most of the reported methods which involve heating of nitrile oxides with thiocarbonyl compounds at elevated temperature for a long time.[4,5] Most of all, the generated side product, urea, can be easily removed by simple extractive workup (H_2O/ether) and we could obtain the isothiocyanates in analytically pure state.

Table 1. Synthesis of Isothiocyanates from Hydroximoyl Chlorides.



Entry	R	Yield(%)[a]	Entry	R	Yield(%)[a]
1	C_6H_5	99	6	2,4,6-$Me_3C_6H_2$	100
2	2-ClC_6H_4	99	7	2-$MeOC_6H_4$	98
3	3-ClC_6H_4	99	8	4-$MeOC_6H_4$	99
4	4-ClC_6H_4	100	9	4-$CF_3C_6H_4$	98
5	2,6-$Cl_2C_6H_3$	100	10	*tert*-butyl	98

a)Isolated yields of pure products.

In conclusion, we have developed an efficient synthetic method of isothiocyanates from hydroximoyl chlorides which could be prepared easily from aldehydes in two steps.

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(Received in Japan 19 July 1993; accepted 20 September 1993)