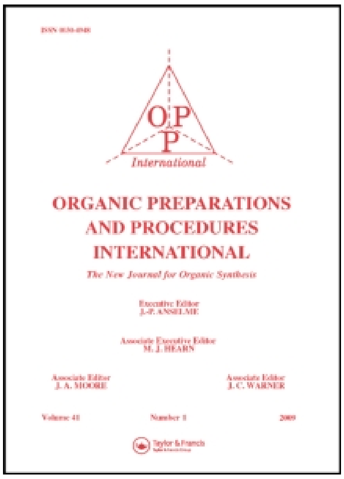

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

A FACILE ONE-POT PREPARATION OF ISOTHIOCYANATES FROM *N*-FORMAMIDES AND SULFUR POWDER WITH *bis*(TRICHLOROMETHYL) CARBONATE

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To cite this Article Shan, W. G. , Bian, G. F. , Su, W. K. and Liang, X. R.(2004) 'A FACILE ONE-POT PREPARATION OF ISOTHIOCYANATES FROM *N*-FORMAMIDES AND SULFUR POWDER WITH *bis*(TRICHLOROMETHYL) CARBONATE', Organic Preparations and Procedures International, 36: 3, 283 — 286

To link to this Article: DOI: 10.1080/00304940409355967

URL: http://dx.doi.org/10.1080/00304940409355967

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6. *N*-Bromosuccinimide was substituted for molecular bromine which was used in the reported synthesis of **2c** (see ref. 3).
7. In contrast the *N*-methyl analog of **3** undergoes electrophilic bromination at the allylic position when using *N*-bromosuccinimide (see ref. 4).

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A FACILE ONE-POT PREPARATION OF ISOTHIOCYANATES FROM *N*-FORMAMIDES AND SULFUR POWDER WITH *bis*(TRICHLOROMETHYL) CARBONATE

Submitted by (04/16/04)

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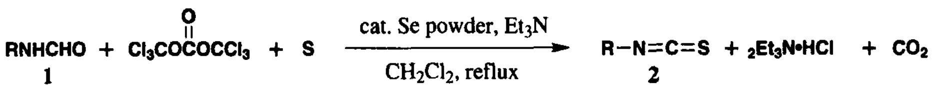
Isothiocyanates are one of the most important synthetic intermediates for the preparation of both sulfur and nitrogen containing organic compounds and especially heterocycles.[1] The synthesis of isothiocyanates has been extensively studied over the past decades, because they play an important role as anti-proliferatives[2] and in the therapy of blood cancer, as enzyme inhibitors for the HIV virus.[3] Numerous methods for the synthesis of isothiocyanates have been reported from amines,[4] organic halides,[5] olefins,[6] and aldoximes.[7] Most of them suffer from low yields and the use of environmentally unattractive reagents such as thiophosgene and its derivatives.[4,8] The direct conversion from isocyanides with elemental sulfur have been reported previously.[9] However, it is difficult to prepare and purify isocyanides because almost all of them are volatile and have a repulsive odor.[10]

Herein, we report a facile one-pot method for the preparation of isothiocyanates from formamides and sulfur powder, which use the environmentally friendly reagent *bis*(trichloromethyl) carbonate (BTC) in the presence of selenium powder and triethylamine (*Scheme 1*). The intermediate isocyanide is not isolated from reaction because it reacts with

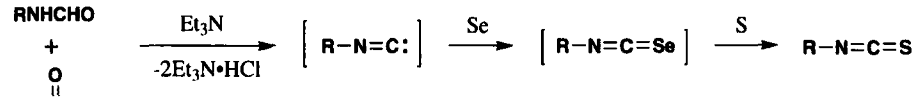


a) R = C_6H_5; b) R = 2-$CH_3C_6H_4$; c) R = 3-$CH_3OC_6H_4$; d) R = 4-$CH_3OC_6H_4$; e) R = 4-ClC_6H_4;
f) R = 2,6-$[(CH_3)_2CH]_2C_6H_3$; g) R = 4-$CH_3COC_6H_4$; h) R = 2,4-$(CH_3)_2C_6H_3$

Scheme 1

elemental sulfur to the isothiocyanate under mild conditions in the presence of catalytic amounts of elemental selenium.

BTC has been used as a substitute for toxic gaseous phosgene in the preparation of many important classes of organic compound since its re-introduction by Eckert *et al.*[11] It is a stable solid (mp. 79-80°C, bp. 205-207°C; only slight decomposition to phosgene occurs at its boiling point[11]), making it safer to handle and convenient to transport and to store. Triethylamine is used not only to neutralize the by-product HCl, but also to promote the formation of isothiocyanates; without triethylamine, the reaction times are much longer and the yields much lower. A possible mechanism may be proposed as shown in *Scheme 2*.



Scheme 2

Although, only 1/3 of a mole of BTC should be sufficient to react with one mole of formamide, even when a 5% excess of BTC was used, 10% of the formamides remained unreacted. The use of 10% excess of BTC resulted in the total conversion of formamides to isothiocyanates. The results are summarized in *Table 1*. The reaction was complete within 5-7 hours and gave isothiocyanates **2** in excellent yields. It was also found that the by-product triethylamine hydrochloride was formed nearly in quantitative yields.

In summary, we have developed an efficient one-pot procedure for the preparation of isothiocyanates from easily available formamides and this method is satisfactory in time, yields, simplicity, safety and environmental acceptability.

EXPERIMENTAL SECTION

Melting points were obtained on a capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Thermo Nicolet Avatar 370 spectrophotometer, H^1NMR spectra ($CDCl_3$) on a Varian Mercur plus-400 spectrometer using TMS as an internal standard. Organic solvents were obtained from commercial sources. Preparative TCL separations were carried out with silica gel GF-245 coated glass plates.

General Procedure. Synthesis of Isothiocyanates 4.- A solution of *bis*(trichloromethyl) carbonate (1.1 mmol) dissolved in dry dichloromethane (20 mL), was added dropwise over 1 h to a boiling suspension of the formamide (3 mmol), selenium powder (0.5% mol of the

Table 1. Preparation of Isothiocyanates from Formamides and Sulfur Powder with BTC[a]

Cmpd	Yield[b] (%)	Time (hrs)	mp. (°C)	*lit.* (°C)	IR(NCS)^1 (cm^{-1})	H NMR (δ)
2a	89	6.5	oil[b]	oil[12]	2924 2081	7.17~7.34 (5H, m, ArH)
2b	92	6.0	oil	oil[13]	2921 2089	7.18~7.23 (4H, m, ArH); 2.28 (3H, s, CH_3)
2c	92	5.5	oil	oil[12]	2939 2109	7.21 (1H, t, J = 8.0 Hz, ArH); 6.81~6.69 (3H, m, ArH); 2.77 (3H, s)
2d	93	6.5	oil	oil[12]	2958 2111	7.13 (2H, d, J = 8.8 Hz, ArH); 6.82 (2H, d, J = 8.8 Hz, ArH); 3.78 (3H, s, OCH_3)
2e	85	7.0	42-43	42[13]	2923 2090	7.33 (2H, d, J = 8.8Hz, ArH); 7.16 (2H, d, J = 8.8 Hz, ArH)
2f	90	6.5	oil	oil[13]	2928 2098	7.21~7.11 (3H, m, ArH); 3.27~3.23 (2H, m, ArH); 1.26 (6H, s, CH_3); 1.25 (6H, s, CH_3)
2g	84	7.0	74-76	76[12]	2921 2190	7.96 (2H, d, J = 8.4 Hz); 7.27 (2H, d, J = 8.4 Hz); 2.60(3H, s, CH_3)
2h	93	6.0	oil	oil[14]	2921 2099	7.06 (1H,d, J = 8 Hz ArH); 6.97 (2H,d, J = 8 Hz ArH);2.31 (3H, s, CH_3); 2.28 (3H, s, CH_3)

a) Formamides (3 mmol), sulfur powder (3 mmol), selenium powder (0.015 mmol), *bis*(trichloromethyl) carbonate (1.1 mmol), triethylamine (6.6 mmol) and dichloromethane (40mL) were used. b) Yields based on formamides. c) All are yellow oils and solids.

formamide), sulfur powder (3 mmol), triethylamine (6.6 mmol) and dichloromethane (40 mL). Then the mixture was stirred at reflux for specified time (monitored by TLC), the reaction mixture was allowed to cool to room temperature. The mixture was washed with water (20 mL), and the deposited selenium powder was removed by vacuum filtration. Triethylamine hydrochloride was obtained by evaporation of the aqueous phase. The organic phase was washed with saturated aqueous Na_2CO_3 and dried over anhydrous $MgSO_4$. After evaporating the solvent, the crude product was purified by preparative silica gel TLC using cyclohexane:ethyl acetate (10:1) as eluent.

Acknowledgement: We are grateful to the Natural Science Foundation of Zhejiang province (Project NO.2002095) and the center of engineering research of Zhejiang University of Technology for financial help.

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