A one-pot preparation of isothiocyanates from amines using two phosgene substitutes: *bis*-(trichloromethyl) carbonate and trichloromethyl chloroformates

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A series of isothiocyanates have been prepared in high yields in a one-pot reaction from commercial amines and carbon disulfide under mild conditions using bis(trichloromethyl)carbonate (BTC) and trichloromethyl chloroformate (TCF) as reagents in the presence of base.

Keywords: isothiocyanates, bis (trichloromethyl) carbonate, trichloromethyl chloroformate, trichloromethyl chloroformate

Isothiocyanates are one of the most important synthetic intermediates for the preparation of both sulfur and nitrogen containing organic compounds especially for heterocycles.[1] The ITC functionality is frequently encountered in natural products, including marine susquiterpenes.[2] Additionally, synthetic isothiocyanates have been proved to have some biological activity, such as anti-proliferatives[3] and enzyme inhibitors for the HIV virus.[4] Numerous methods for the preparation of isothiocyanates have been reported from amines,[5] dithiocarbamates,[6] organic halides,[7] olefins[8] and aldoximes.[9] Among the literature methods, the most widely used procedure is for their synthesis by the decomposition of dithiocarbamates using heavy metals,[10] thiophosgene iodine, ethyl chlorocarbonate and claycop.[11] However, most of the methods suffer from low yields and the use of environmentally unattractive reagents.[10]

Bis-trichloromethyl carbonate (BTC) and trichloromethyl chloroformate (TCF) have emerged as versatile synthetic reagents and as important substitutes for phosgene in the synthesis of some important classes of organic compounds.[12] Both of them are more convenient to handle and store than phosgene, due to their low vapour pressure being in the liquid and the solid states. Recently, we have reported a facile one-pot preparation of isothiocyanates from formamides and sulfur powder using the phosgene substitute BTC.[13] Herein we wish to report the application of TCF and BTC for the preparation of various isothiocyanates from alkyl amines and carbon disulfide under mild conditions (Scheme 1).

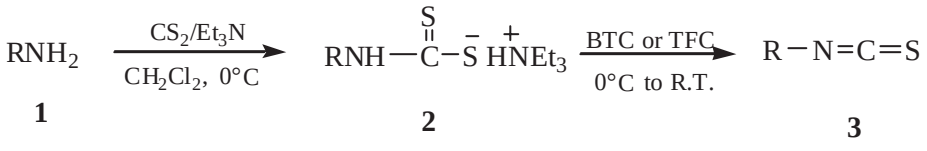
We have successfully employed the cheap reagents, BTC and TCF, for the one-pot preparation of isothiocyanates. The possible mechanism of this reaction is shown in Scheme 2. Firstly, the formation of the dithiocarbamate salt (**2**) from an amine (**1**), carbon disulfide and a base occurs and secondly, there is decomposition of the dithiocarbamate salt to form an isothiocyanate (**3**) by treatment of the salt with BTC and TCF. The first step of the synthesis proved to be more difficult with aromatic amines than aliphatic amines owing to their lower basicity.

From Table 1, isothiocyanates were obtained in high yields using either BTC or TCF within 4–6 h (entries 1 and 2). The corresponding thiourea was obtained as a side-product in the presence of triethylamine during the preparation of aromatic isothiocyanates, while we did not detect any urea in the course of the preparation of aliphatic isothiocyanates. When employing NaOH as base in THF, we obtained some aromatic isothiocyanates in good yields (entries 8 and 9). However, we also found that *p*-nitrobenzeneisothiocyanates could not be prepared by this method because of low nucleophilicity (entry 11).

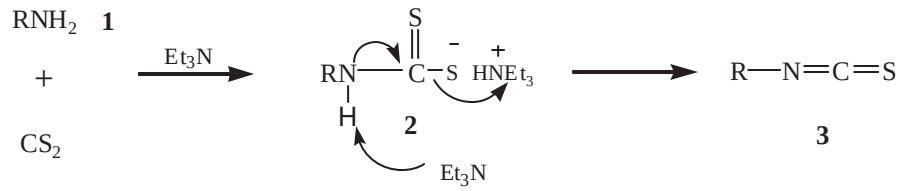
In conclusion, we have developed an efficient one-pot synthetic procedure for the preparation of isothiocyanates from commercially amines in good yields using BTC and TCF. This method is satisfactory in terms of time of reaction, yield, simplicity, safety, and environmental acceptability.

Experimental

Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately prior to use. All reactions were carried on under a dry nitrogen atmosphere. Melting points were obtained on a capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Thermo Nicolet Avatar 370 spectrophotometer, ^{1}H NMR spectra ($CDCl_3$) on a Varian Mercury plus-400 spectrometer using TMS as an internal standard. Organic solvents were obtained from commercial sources. Preparative TLC separations were carried out with silica gel GF-245 coated on glass plates.



Scheme 1



Scheme 2

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Table 1 Preparation of isothiocyanates from amines and carbon disulfide using BTC or TCF in dichloromethane

Entry	R	T/°C	Condition	Time/h	Yield[a] % (product)(Lit%[ref])
1	$PhCH_2CH(CO_2Et)$	0	BTC/Et_3N	5	85**(3a)** (65[11])
2	$PhCH_2CH(CO_2Et)$	0	TCF/Et_3N	5	86**(3a)** (65[11])
3	$C_6H_5CH_2$	0	TCF/Et_3N	4	86**(3b)** (73 [16])
4	C_6H_{11}	0	BTC/Et_3N	5	92**(3c)** (89[15])
5	4-$CH_3OC_6H_4CH_2$	5	BTC/Et_3N	4	92**(3d)** (82[15])
6	$C_6H_5CH(CH_3)$	5	TCF/Et_3N	5.5	95**(3e)** (85[11])
7	$C_6H_5CH_2CH_2$	5	TCF/Et_3N	4	90**(3f)** (86[14])
8	C_6H_5	10	BTC/Et_3N	6	25**(3g)** [b](89[13])
9	C_6H_5	10	BTC/NaOH[c]	6	81**(3g)** (89[13])
10	4-Cl-C_6H_4	10	TCF/NaOH[c]	6	65**(3h)** (75[11])
11	4-O_2N-C_6H_4	10	TCF/NaOH[c]	7	Trace ()

[a]Isolated yields based on amine; [b]The corresponding urea was obtained in 72%; [c]THF was used.

Representative procedure

Synthesis of isothiocyanates **3b**: To a solution of phenylmethanamine (1.5 mmol, 0.223 g) and triethylamine (3 mmol, 0.303 g) in dry dichloromethane (20 ml), carbon disulfide (2 mmol, 0.152 g) was added dropwise over 30 min at 0°C. After the mixture was stirred for 1 h at 0°C, a solution of BTC (0.5 mmol, 0.148 g) in dry dichloromethane (20 ml) was added at 0°C. Then the mixture was allowed to warm to room temperature and stirred for 4–6 h (monitored by TLC). The mixture was washed with water (20 ml), saturated aqueous Na_2CO_3 (15 ml) and dried over anhydrous $MgSO_4$. After evaporating the solvent under reduced pressure, the crude product was purified by preparative silica gel TLC using cyclohexane:ethyl acetate (10:1) as eluent (R_f = 0.9).

3a: Yellow oil, (lit., oil [11]); ^{1}H NMR ($CDCl_3$) δ: 7.18–7.31 (5H, m, ArH); 4.21 (2H, q, *J* = 6.8 Hz, CH_3); 2.77 (2H, m, CH_2); 2.18 (2H, m, CH_2); 1.28 (3H, t, *J* = 7.2 Hz, CH_3) ^{13}C NMR ($CDCl_3$) 168.69, 139.75, 137.89(NCS), 128.98, 128.88, 126.85, 62.85, 59.04, 35.18, 31.97, 14.47; IR ν_{max}/cm^{-1} (Nujol): 3062, 2981, 2862, 2059(NCS), 1745, 1496, 1453, 1204, 1022, 962, 700;

3b: Yellow oil, (lit., oil [16]); ^{1}H NMR ($CDCl_3$) δ: 7.20–7.35 (5H, m, ArH); 4.59 (2H, s, CH_2); ^{13}C NMR ($CDCl_3$) 134.30, 132.09(NCS), 129.00, 128.56, 126.90, 48.69; IR ν_{max}/cm^{-1} (Nujol) : 3063, 2924, 2858, 2088(NCS), 1605, 1531, 1494, 1447, 1199, 698;

3c: Yellow oil, (lit., oil [15]); ^{1}H NMR ($CDCl_3$) δ: 3.70 (1H, m, CH); 1.38–2.17 (10H, m, C_6H_{10}); ^{13}C NMR ($CDCl_3$) 129.58(NCS), 55.51, 32.95, 24.79, 22.97; IR ν_{max}/cm^{-1}: 2936, 2857, 2100(NCS), 1448, 1361, 1315, 1264, 720;

3d: Yellow oil, (lit., oil [15]); ^{1}H NMR ($CDCl_3$) (The AA'xx' system for the *para* substituted benzene ring appears as a pair of doublets) δ: 7.65 (2H, d, *J* = 8.8 Hz); 7.41 (2H, d, *J* = 8.8 Hz); 4.65 (3H, s, OCH_3); 3.84 (3H, s); ^{13}C NMR ($CDCl_3$) 159.60, 131.85(NCS), 128.39, 126.32, 114.29, 55.33, 48.26; IR ν_{max}/cm^{-1} (Nujol): 2957, 2836, 2086(NCS), 1733, 1611, 1586, 1513, 1250, 1032, 819;

3e: Yellow oil, (lit., oil [11]); ^{1}H NMR ($CDCl_3$) δ: 7.17–7.34 (5H, m, ArH; 4.99 (1H, q, *J* = 6.8 Hz, CH); 1.78 (3H, d, *J* = 4.8 Hz, CH_3); ^{13}C NMR ($CDCl_3$) 140.18, 132.35(NCS), 128.94, 128.24, 125.45, 57.07, 24.99; IR ν_{max}/cm^{-1} (Nujol): 3063, 2931, 2087(NCS), 1603, 1493, 1453, 1345, 1021, 699;

3f: Yellow oil, (lit., oil [14]); ^{1}H NMR ($CDCl_3$) δ: 7.16–7.32 (5H, m, ArH); 3.62 (2H, t, *J* = 7.2 Hz, CH_2); 2.90 (2H, t, *J* = 7.2 Hz, CH_2); ^{13}C NMR ($CDCl_3$) 137.25, 130.58(NCS), 129.03, 128.99, 127.38, 46.56, 36.61; IR ν_{max}/cm^{-1} (Nujol): 3027, 2929, 2086(NCS), 1734, 1603, 1496, 1348, 1079, 748;

3g: Yellow oil, (lit., oil [13]); ^{1}H NMR ($CDCl_3$) δ: 7.17–7.34 (5H, m, ArH); ^{13}C NMR ($CDCl_3$) 139.65, 132.17(NCS), 128.51, 128.38, 127.41; IR ν_{max}/cm^{-1} (Nujol): 2924, 2081(NCS), 1592, 1531, 1489, 1268, 927, 749;

3h: Yellow solid m.p. 42–43°C (lit., [11] 42°C); ^{1}H NMR ($CDCl_3$) δ: 7.09–7.42 (4H, m, ArH) ^{13}C NMR ($CDCl_3$) 138.16, 133.35(NCS), 130.23, 129.68, 127.56; IR (KBr) ν_{max}/cm^{-1} (flim): 2923, 2090(NCS), 1641, 1582, 1482, 1090, 928, 826.

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References

1 (a) A.K. Mukerjee and R. Ashare, *Chem. Rev.*, 1991, **91**, 1; (b) M. Dobosz and M. Wujec, *Heterocycles*, 2002, **57**, 1135.
2 (a) N. Kuhnert, G. Williamson and B. Holst, *J. Labl. Comp. Radiopharm.*, 2001. **44**, 347; (b) N. Kuhnert and Y. Lu, *J. Labl. Comp. Radiopharm.*, 2004. **47**, 501.
3 C. Nastruzzi, R. Cotesi, E. Eaposito, E. Menegatti, O. Leoni, R. Iori and S. Palmier, *J. Agric. Food. Chem.*, 2000, **48**, 3572.
4 K. Xu and P. Thornalley, *J. Biochem. Pharmacol*., 2000, **6**, 221.
5 X.C. Zhang, Y.K. Lee, J.A. Kelley and T.R. Burke, *J. Org. Chem*., 2000, **65**, 6237.
6 (a) J.E. Hodgkins and W.P. Reeves, J. *Org. Chem.*, **1956, 21,** 404; (b) J.E. Hodgkins and W.P. Reeves, *J. Org. Chem.*, **1964, 29,** 3098.
7 C.G. Cho and G.H. Posne, *Tetrahedron Lett.*, 1992, **33**, 3599.
8 T. Kitamura, S. Kobayashi and H. Taniguchi, *J. Org. Chem.*, 1990, **55**, 1801.
9 J.N. Kim, K.S. Jung, J.H. Lee and J.S. Son, *Tetrahedron Lett.*, 1997, **38**, 1597.
10 J. Goerdeler and C. Ho, *Chem. Ber*., 1984, **117**, 1636.
11 H.M. Mesheram, S. Dale and J.S. Yadav, *Tetrahedron Lett.*, 1997, **38**, 8743.
12 L. Cotarca, P. Delogu, A. Nardelli and V. Sunjic, *Synthesis*, **1996,** 533; (b) H. Eckert and B. Forster, *Angew. Chem., Int. Ed. Engl*., 1987, **26**, 894; (c) Q.D. You and Q.S. Wang, *Huaxue shiji*, 1992, **14**, 230; (d) K. Kurita, T. Matsumura and Y. Iwakura, *J. Org. Chem.*, 1976, **41**, 2070.
13 W.G. Shan. G.F. Bian. W.K. Su and X.R. Liang, *Org. Prep. Proced. Int.*, 2004, **36**, 284.
14 G. Dyson, H. George and R. Hunter, *J. Chem*. Soc., **1927**, 436.
15 S. Fujiwara, T. Shin-Ike, N. Sonoda, M. Aoki, K. Okada, N. Miyoshi and N. Kambe, *Tetrahedron Lett.*, 1991, **32,** 3503.
16 J.N. Kim, J.H. Song and E.K. Ryu, *Synth. Commun.*, 1994, **24**, 1101.