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A new efficient synthesis of isothiocyanates from amines using di-*tert*-butyl dicarbonate

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Abstract

Alkyl and aryl amines are converted smoothly to the corresponding isothiocyanates via the dithiocarbamates in good to excellent yields using di-*tert*-butyl dicarbonate (Boc_2O) and 1–3 mol % of DMAP or DABCO as catalyst. As most of the byproducts are volatile, the work-up involves simple evaporation of the reaction mixture.

Keywords: Isothiocyanate; Di-*tert*-butyl dicarbonate; Thiourea; Amine

Isothiocyanates constitute an important functional class in natural products and pharmaceutically active compounds. Furthermore, isothiocyanates are widely applied as chemoselective electrophiles in bioconjugate chemistry because of their tolerance towards aqueous reaction conditions,[1] and they are key intermediates in the synthesis of sulfur-containing heterocycles.[2,3] Therefore, numerous methods have been developed to synthesise isothiocyanates, the most well known being based on thiophosgene,[4,5] and later refinements of 'thiocarbonyl transfer' reagents such as thiocarbonylditriazole,[6] thiocarbonyldiimidazole[7] and dipyridyl-thionocarbonate (DPT).[8] Albeit, these reagents are found to be effective in the specific formation of isothiocyanates and occasionally as desulfurylating agents for thioureas, they are somewhat limited in scope, and lead to extensive formation of the corresponding thiourea as a byproduct in the case of less reactive amines. To avoid this side reaction, the desulfurylation of dithiocarbamates has been carried out by various reagents such as uronium- and phosphonium-based peptide coupling reagents,[9–11] triphenylphosphine dibromide[12] and tosyl chloride.[3] Although the previous methods are efficient, we were keen to develop a synthesis of isothiocyanates which would proceed cleanly without intermediate work-up, such as extraction or column chromatography, and which would leave no, or only traces of byproducts. A desulfurylation reagent leaving only gases and volatile byproducts should fit this purpose. Di-*tert*-butyl dicarbonate (Boc_2O) seemed a good candidate for the desulfurylation of the corresponding dithiocarbamate as this reagent may evolve CO_2 and COS during the reaction, and residual carbon disulfide and *tert*-butanol together with the solvent should be removed easily by evaporation. As the formation of dithiocarbamate in the case of most amines proceeds rapidly, the isothiocyanate can be synthesised directly from the amine in the presence of excess carbon disulfide.

In addition to Boc_2O, we found that a catalytic amount of DMAP or DABCO (1–3 mol %) increased the reaction rate significantly, with visible evolution of gas from the reaction mixture. The formation of an isothiocyanate from the corresponding amine was, in the case of aliphatic and activated aromatic amines, complete within a few minutes. In the reaction pathway, the electrophilic Boc_2O presumably reacts with the dithiocarbamate with evolution of

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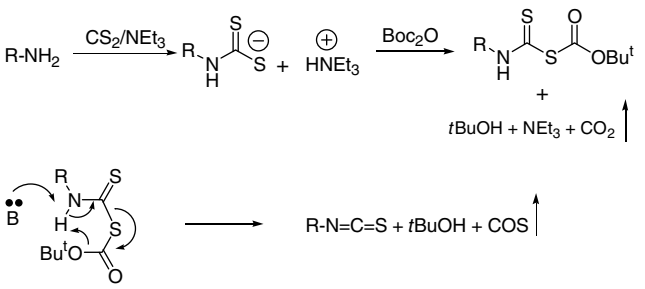
CO_2 to form an unstable 'mixed dithiocarbamate/carbonate' adduct that rapidly decomposes to the isothiocyanate, COS and *tert*-butanol (Scheme 1). One equivalent of triethylamine was needed for the stabilisation and complete formation of the dithiocarbamate in agreement with the earlier reports.[13] The reaction is usually carried out under polar conditions ethanol, aqueous ethanol or methanol, although it proceeds equally well in apolar solvents such as DCM, THF or in dipolar solvents like acetone or DMF.

Boc_2O was added in nearly stoichiometric amounts (0.99 equiv) to avoid residual di-*tert*-butyl dicarbonate as a byproduct. Although the reaction may proceed via other pathways, such as Boc-protection of the amine or conversion of the amine to the isocyanate,[14] these side reactions were rarely observed. However, formation of the Boc-protected amine was observed to some extent (14% in GCMS) in the case of 1-adamantylamine and poorly soluble arylamines, such as naphthyl and anthryl amines, and also in the case of deactivated aryl amines, for example, *para*-bromoaniline (8%). The Boc-protection of 1-adamantylamine (Table 1, entry 5) could, however, be avoided by cooling the dithiocarbamate prior to the addition of Boc_2O and catalyst.

In the case of entry 12 the desulfurylation proceeded without the addition of DMAP, albeit at a slower speed. In contrast, reaction with triphenylmethylamine did not give any isothiocyanate product even after prolonged reaction times.

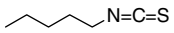
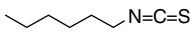
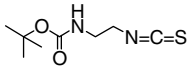
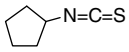
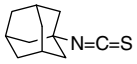
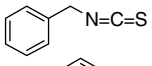
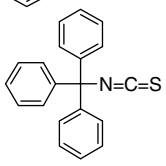
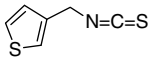
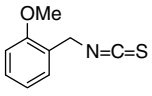
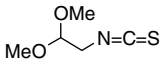
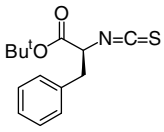
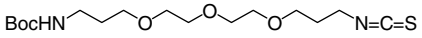
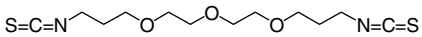
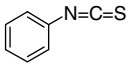
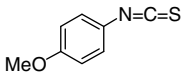
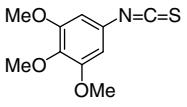
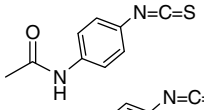
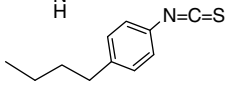
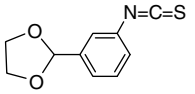
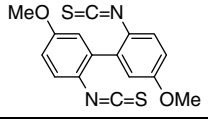
In the cases of amines having weak nucleophilic groups β to the amino functionality, for example, 2-(Boc-amino)-ethylenediamine, ethanolamine or in peptide substrates, the formation of a cyclised product was a competing reaction (e.g., formed in a 1:1 mixture with the isothiocyanate in the case of 2-(Boc-amino)-ethylenediamine).[32] Also in substrates containing electrophilic groups at the β-position such as 2-chloroethylamine, the cyclic dithiocarbamate was formed as the predominant product.

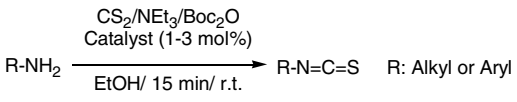
As an alternative, we applied dimethyl carbonate (DMC) instead of di-*tert*-butyl dicarbonate as the desulfurylating agent. However, DMC yielded the corresponding thioureas as the sole products. The formation of thiourea may be due to the lower reactivity of DMC compared to that of Boc_2O.



Scheme 1. Suggested mechanism for the base catalysed synthesis of isothiocyanates from the corresponding amines using di-*tert*-butyl dicarbonate. B: Base catalyst.

Table 1

Entry	Isothiocyanate	Yield (%)
1[15]		63
2[16]		98
3[17]		91
4[18]		Quant
5[19]		82
6[20]		86
7		0
8[21]		98
9[22]		Quant
10[23]		93
11[10]		81
12		Quant
13[24]		Quant
14[25]		Quant
15[26]		Quant
16[27]		Quant
17[28]		Quant
18[29]		Quant
19[30]		80
20[31]		96



Scheme 2.

In summary, a mild and chemoselective method for a rapid and clean preparation of isothiocyanates in high yields and purity without the need for subsequent work-up has been developed (Scheme 2).[33] The reaction proceeds within 15 min with aliphatic and activated aromatic substrates; however, deactivated arylamines need longer reaction times for the complete formation of the dithiocarbamate in order to prevent side reactions such as Boc-protection of the amine or thiourea formation. This method constitutes an interesting alternative in the synthesis of isothiocyanates (and thioureas) in complex synthetic sequences where a minimum work-up of the intermediate isothiocyanate should be carried out.

Acknowledgement

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References and notes

1. For examples, see: Fernández, J. M. G.; Mellet, C. O.; Blanco, J. L. J.; Mota, J. F.; Gadelle, A.; Coste Sarguet, A.; Defaye, J. *Carbohydr. Res.* **1995**, *268*, 57–71.
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21. *Analytical data for entry 8*: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (dd, ^3J 3 Hz, ^3J 5 Hz, 1H), 7.25 (s, 1H), 7.05 (d, ^3J 5 Hz, 1H), 4.70 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.2, 130.1, 127.4, 126.4, 123.0, 44.5. GCMS *m*/*z* 155. Anal. Calcd for $C_6H_5NS_2$ (155.24): C, 46.42; H, 3.25; N, 9.02. Found: C, 46.63; H, 3.43; N, 8.97.
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30. *Analytical data for entry 19*: Purified by filtering the crude through a plug of silica using 1:1 CH_2Cl_2/hexane containing 2% Et_3N. Pale brown oil, yield: 80%, ^{1}H NMR (400 MHz, $CDCl_3$, filtered through Al_2O_3 before use): 4.00–4.04 (m, 2H), 4.07–4.11 (m, 2H), 5.77 (s, 1H), 7.13 (d, ^3J 7.5 Hz, 1H), 7.29 (t, ^3J 7.5 Hz, 1H), 7.32–7.35 (m, 1H), 7.46–7.48 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 65.4, 104.7, 125.1, 125.2, 126.1, 130.4, 132.1, 137.0, 138.9. HRMS (ESI$^+$): [MH$^+$]: calcd for $C_{10}H_{10}NO_2S$ (*m*/*z*): 208.0432. Found: 208.0463.
31. *Analytical data for entry 20*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (m, 2H), 7.03–7.07 (m, 4H); 4.00 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.1; 140.3; 125.6; 120.4; 119.4; 110.1; 56.0. GCMS *m*/*z* 328. Anal. Calcd for $C_{16}H_{12}N_2O_2S_2$ (328.42): C, 58.52; H, 3.68; N, 8.53. Found: C, 58.42; H, 3.82; N, 8.71.
32. The cyclisation was indicated by elemental analysis, and in the ^{1}H NMR by two separate ^{t}Bu signals.
33. *General procedure*: Absolute ethanol (2–5 mL) was added to the amine (4.40 mmol). CS_2 (3.34 g, 44 mmol) and Et_3N (444 mg, 4.40 mmol, in the case of amine hydrochlorides an extra equivalent of triethylamine was added) were added while stirring, resulting in the precipitation of the dithiocarbamate. The reaction mixture was stirred for 5–30 min at room temperature and then cooled on an ice bath. Boc_2O (950 mg, 4.36 mmol), dissolved in absolute ethanol (1 mL), was added followed by the immediate addition of a catalytic amount of DMAP or DABCO (1–3 mol %) in absolute ethanol (1 mL). The reaction mixture was kept in the ice bath for 5 min, and was then allowed to reach room temperature. After evolution of gas from the reaction mixture had ceased (approximately 10 min), the reaction mixture was stirred for a further 5 min at rt and evaporated thoroughly in vacuo. In the case of amine hydrochlorides, the residue was taken up in diethyl ether and triethylammonium hydrochloride was filtered off, and the filtrate was evaporated in vacuo to afford the desired isothiocyanate in high purity.