Alkoxycarbonyl groups transfer to amines by the *N,N'*-dibenzyl- and *N,N'*-di-*tert*-butyl-carbamates of cyclic thioureas

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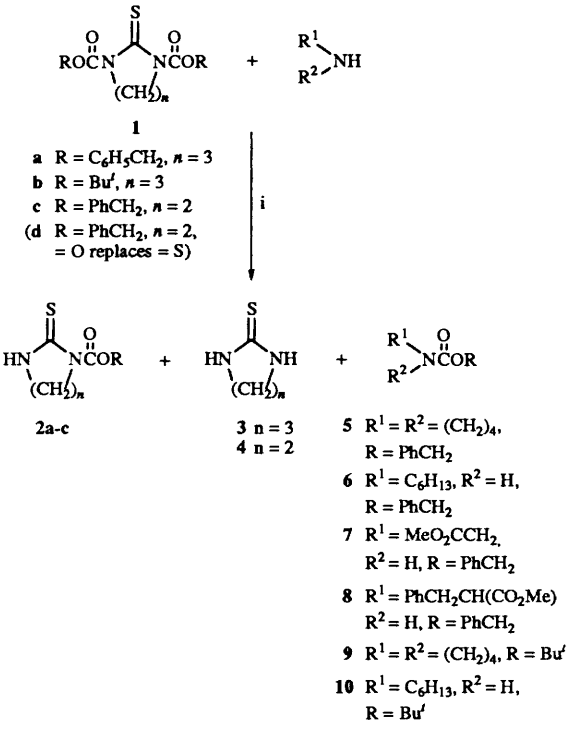
The use of the dicarbamates of cyclic thioureas as alkoxycarbonyl-transfer reagents for the protection of amino groups is described.

The development of effective reagents for the protection of amino groups is of importance, particularly in respect of peptide synthesis. Since certain alkoxycarbonyl groups, *e.g.* benzyloxycarbonyl and *tert*-butoxycarbonyl (Boc), have been recognized[1] as good protecting groups, there is a growing demand for the development of reagents which introduce them under mild and neutral conditions.

Recently, we have found that the *N,N'*-dibenzyl- and *N,N'*-di-*tert*-butyl-carbamates **1a–c** of cyclic thioureas effectively transfer their alkoxycarbonyl groups to pyrrolidine, hexylamine and the methyl esters of glycine and L-phenylalanine to give the corresponding carbamates **5–10** (Scheme 1).

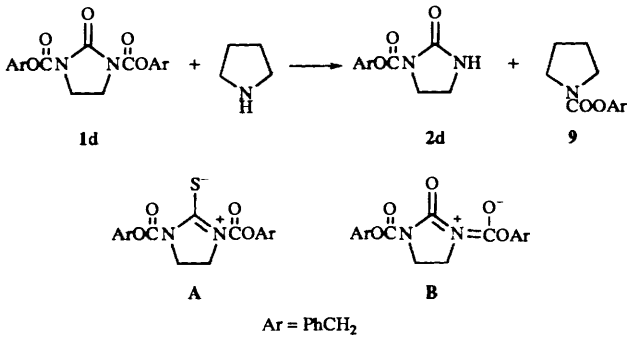


Scheme 1 *Conditions:* i, dioxane; reflux; 7 h

We now report that **1a–c** function as alkoxycarbonyl-transfer reagents on reaction with amines.

The reactions of **1a–c** with amines were carried out in refluxing dioxane and the results are summarized in Table 1. The reaction of 1,3-bis(benzyloxycarbonyl)-3,4,5,6-tetrahydropyrimidine-2-thione **1a** with pyrrolidine in a 1:1 molar ratio gave 1-benzyloxycarbonylpyrrolidine **5** and 1-benzyloxycarbonyl-3,4,5,6-tetrahydropyrimidine-2-thione **2a** in nearly quantitative yield (entry 1), thus indicating that the benzyloxycarbonyl-transfer ability of **1a** is superior to that of **2a**. When the reaction of **1a** with pyrrolidine was carried out in 1:2 molar ratio, two benzyloxycarbonyl groups of **1a** were transferred to pyrrolidine to give **5** (entry 2). The reaction of **1a** with hexylamine and the methyl esters of glycine and L-phenylalanine also proceeded smoothly to give **6**, **7** and **8**, respectively (entries 3, 4 and 5).

The Boc group of **1b** was less efficiently transferred than the benzyloxycarbonyl group of **1a**, probably owing to its greater bulk (entries 2 and 7). Furthermore, **1c** having a 5-membered ring was less reactive than **1a** having a 6-membered ring (entries 2 and 9). The benzyloxycarbonyl-transfer ability of **1c** and **1d** towards pyrrolidine under similar conditions were significantly different, the latter (1 mol equiv.) giving 0.20 mol equiv. each of **9** and **2d**, with 75% recovery of **1d**. Whilst the ν(CO) absorption for the benzyloxycarbonyl groups of **1c** and **1d** appeared at 1760 and 1700 cm^{-1} respectively, that for the imidazolidinone ring of **1d** appeared at 1780 cm^{-1}. Furthermore, the ^1H NMR spectra of **1c** and **1d** in $CDCl_3$ exhibited signals for the methylene protons of the heterocyclic rings of 4.00 and 3.84 ppm, respectively, as a singlet each. These spectral results suggest that the resonance forms **A** and **B** contribute to the structures of **1c** and **1d**, thus indicating that the N–CO bond of **1c** is cleaved more easily by amines as compared with that of **1d**.



In summary, compounds **1a–c** efficiently transfer alkoxycarbonyl groups to amino groups under mild and neutral conditions. Since, in addition, **1a–c** are reasonably stable to air, moisture and heat, properties which make them much easier to handle than, for instance, benzyl chloroformate and di-*tert*-butyl pyrocarbonate, they are regarded as new and useful reagents for the protection of amino groups.

Experimental

General procedure for the reaction of *N,N'*-dibenzyl- and *N,N'*-di-*tert*-butyl-carbamates 1a–d with amines

A dioxane solution (5 cm^3) of the amine (0.54 mmol) was added under argon to a dioxane solution (5 cm^3) of **1a–d** (0.27 mmol)

Table 1 Reaction of **1a**, **b** with amines[a]

Entry	Dicarbamate	Amine R[1]	Amine R[2]	Molar ratio 1:amine	Product (mol)/**1a–c** (mol)		
1	**1a**	$(CH_2)_4$		1:1	**2a** (0.90)	**3** (–)	**5** (0.97)
2	**1a**	$(CH_2)_4$		1:2	**2a** (—)	3 (0.98)	**5** (1.97)
3	**1a**	C_6H_{13}	H	1:2	**2a** (—)	**3** (0.96)	**6** (1.94)
4	**1a**	CH_3OOCCH_2	H	1:1	**2a** (0.64)	**3** (—)	**7** (0.65)
5	**1a**	$PhCH_2CH(CO_2Me)$	H	1:1	**2a** (0.70)	**3** (—)	**8** (0.80)
6	**1b**	$(CH_2)_4$		1:1	**2b** (0.82)	**3** (–)	**9** (0.85)
7	**1b**	$(CH_2)_4$		1:2	**2b** (0.12)	**3** (0.80)	**9** (1.72)
8	**1b**	C_6H_{13}	H	1:2	**2b** (0.17)	**3** (0.77)	**10** (1.72)
9	**1c**	$(CH_2)_4$		1:2	**2c** (0.19)	**4** (0.69)	**5** (1.76)

[a] All reactions were carried out under argon in refluxing dioxane for 7 h. [b] The dash (—) signifies that the product was not isolable.

at room temperature. The mixture was refluxed for 7 h and then evaporated under reduced pressure. The residue was chromatographed on silica gel with dichloromethane–ethyl acetate (4:1) to give the corresponding products **2a–c** and **3–10**. The structures of the compounds were established by comparison of their mps and IR, ^{1}H NMR and mass spectra with those of authentic specimens.

Dicarbamates of cyclic thioureas 1a–c

The dicarbamates **1a–c** were synthesized by the reactions of the dianions of cyclic thioureas with benzyl chloroformate or di-*tert*-butyl pyrocarbonate at −40 °C in good yields. Compound **1a**; mp 94.5–95.5 °C (Found: C, 62.45; H, 5.12; N, 7.3. $C_{20}H_{20}N_2O_4S$ requires C, 62.48; H, 5.24; N, 7.29); ν_{max}(KBr)/cm^{-1} 1745 (C=O) and 1220; δ_H(270 MHz, $CDCl_3$) 2.16 (2 H, quint, *J* 7.0, $NCH_2CH_2CH_2N$), 3.76 (4 H, t, *J* 6.7, $NCH_2CH_2CH_2N$), 5.28 (4 H, s, 2 × $CH_2C_6H_5$) and 7.32–7.45 (10 H, m, ArH); *m*/*z* 384 (M^+).

Compound **1b**; mp 93–94 °C (Found: C, 53.15; H, 7.9; N, 9.0. $C_{14}H_{24}N_2O_4S$ requires C, 53.14; H, 7.65; N, 8.85); ν_{max}(KBr)/cm^{-1} 1722 (C=O) and 1280; δ_H(270 MHz, $CDCl_3$) 1.54 [18 H, s, 2 × $C(CH_3)_3$] 2.15 (2 H, quint, *J* 6.7, $NCH_2CH_2CH_2N$) and 3.68 (4 H, t, *J* 6.7, $NCH_2CH_2CH_2N$); *m*/*z* 316 (M^+).

Compound **1c**; mp 133–134 °C (Found: C, 61.8; H, 4.9; N, 7.65. $C_{19}H_{18}N_2O_4S$ requires C, 61.61; H, 4.90; N, 7.56); ν_{max}(KBr)/cm^{-1} 1760 (C=O) and 1268; δ_H(270 MHz, $CDCl_3$) 4.00 (4 H, s, NCH_2CH_2N), 5.30 (4 H, s, 2 × $CH_2C_6H_5$) and 7.33–7.43 (10 H, m, ArH); *m*/*z* 370 (M^+).

1,3-Bis(benzyloxycarbonyl)imidazolidin-2-one 1d

The reaction of 1-benzyloxycarbonyl-3-trimethylsilylimidazolidin-2-one, which is derived from 1-benzyloxycarbonylimidazolidin-2-one and trimethylsilyl chloride in the presence of triethylamine, with benzyl chloroformate was carried out in refluxing benzene for 16 h. After work-up, **1d** was obtained as a white solid (75%), mp 124–125 °C (Found: C, 64.7; H, 4.95; N, 8.1. $C_{19}H_{18}N_2O_5$ requires C, 64.40; H, 5.12; N, 7.91); ν_{max}(KBr)/cm^{-1} 1780 and 1700 (C=O); δ_H(270 MHz, $CDCl_3$) 3.83 (4 H, s, NCH_2CH_2N), 5.30 (4 H, s, 2 × $CH_2C_6H_5$) and 7.29–7.45 (10 H, m, ArH); *m*/*z* 354 (M^+).

References

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