Convenient Preparation of Alkyl Benzyl Imidodicarbonates, Useful Reagents for the Direct Synthesis of Protected Amines

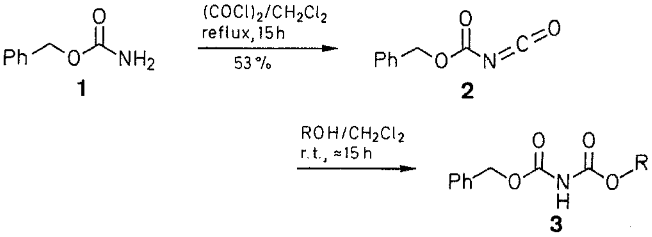
Leif Grehn, M. Lurdes S. Almeida, Ulf Ragnarsson*

Department of Biochemistry, University of Uppsala, Biomedical Center, P.O. Box 576, S-751 23 Uppsala, Sweden

New mixed alkyl benzyl imidodicarbonates were prepared by reaction of benzyloxycarbonyl isocyanate with appropriate alcohols. This simple procedure also furnished alternative, more convenient routes to dibenzyl and benzyl 9-fluorenylmethyl imidodicarbonates. The substances are of interest as potential Gabriel reagents. Completely selective removal of one of the alkoxycarbonyl groups from the N-atom of the imidodicarbonates was demonstrated in several instances, giving benzyl carbamate or the alternative carbamate.

Recent work indicated that various imidodicarbonates including di-*tert*-butyl[1] and benzyl *tert*-butyl[2] imidodicarbonate constitute versatile intermediates for improved one-step syntheses of protected amines from miscellaneous halides or alcohols using the Gabriel[3] and Mitsunobu[4] reactions, respectively. In the course of these investigations, a wider selection of such mixed imidodicarbonates was needed for related synthetic studies and, as an extension of this work, more general routes to this rather new class of compounds were sought. A crucial step in the synthesis of the aforementioned derivatives was the di-*tert*-butyl dicarbonate/4-dimethylaminopyridine(DMAP)-mediated *tert*-butoxycarbonylation of the amide nitrogen of a precursor. As other dicarbonates such as dimethyl, dibenzyl, and diallyl dicarbonate did not accomplish the corresponding alkoxycarbonylation (the presence of catalytic amounts of DMAP caused rapid decomposition of these reagents[5]), alternative approaches were required to prepare imidodicarbonates without a *tert*-butyl group.

The reaction between a suitably chosen alkoxycarbonyl isocyanate and an appropriate hydroxy compound appeared to be a promising strategy.[6] Furthermore, it was assumed that benzyloxycarbonyl isocyanate (**2**) would serve as a useful intermediate in this respect. Although compound **2** has previously been employed in synthetic work,[7] only scarce details regarding its synthesis and properties are available. We prepared **2** in acceptable yield from benzyl carbamate (**1**) and oxalyl chloride according to a known general procedure[8] which has been extended to carbamates.[9] Initial attempts to obtain isocyanate **2** by the 18-crown-6 catalyzed reaction of benzyloxycarbonyl chloride with potassium cyanate in dry dichloromethane furnished only intractable mixtures.[10]



3	R	3	R
a	$C_6H_5CH_2$	**f**	1-adamantyl
b	$4\text{-}CH_3OC_6H_4CH_2$	**g**	$CH_2=CH-CH_2$
c	$4\text{-}NO_2C_6H_4CH_2$	**h**	CCl_3CH_2
d	$C_6H_5C(CH_3)_2$	**i**	9-fluorenylmethyl
e	$(CH_3)_3C$		

As could be anticipated, compound **2** reacted readily with a wide range of alcohols to give the corresponding alkyl benzyl imidodicarbonates **3a–i** in 91–100% yields of nearly pure product after simple work-up. Besides the above-mentioned di-*tert*-butyl analogue and **3e**, also compound **3a** has been synthesized earlier in moderate overall yield by a rather laborious procedure starting from benzyloxycarbonyl chloride and benzaldehyde hydrazone.[11] The conversion **2** → **3** generally proceeded smoothly, but in the case of **3d** the crude product was contaminated with significant amounts of **1**. This was probably due to the presence of traces of acidic impurities in **2**,which might cause partial decomposition of the extremely acid-sensitive **3d** (see also below).

The facile *N*-alkylation of various diacylamides can be exploited in the amine syntheses discussed above and the application of **3e** to these conversions has already been demonstrated.[2] Preliminary experiments also indicated that the sodium salt of **3a** is a useful nucleophile in the Gabriel synthesis of *tert*-butyl *N,N*-bis(benzyloxycarbonyl)glycinate (94% yield of crude product) using *tert*-butyl bromoacetate as the starting material.[5] Further work to establish the potential of imidodicarbonates **3a–i** as amine precursors is now in progress. In this context, it is advantageous if one of the ester functions in the resultant *N,N*-bis(alkoxycarbonyl) compounds can be removed selectively under mild conditions. A preliminary study, employing our newly synthesized compounds as model substrates, indicated promising possibilities as regards the use of conventional deprotection conditions.[12] Thus, the usual catalytic hydrogenolysis (H_2/Pd, 1 atm, MeOH, 1 h, r.t.) of **3f** and **3h** led to quantitative elimination of the benzyloxycarbonyl group to give 1-adamantyl carbamate and 2,2,2-trichloroethyl carbamate, respectively. Strong acid [HF/anisole (9:1), 1 h, 0°C, or refluxing trifluoroacetic acid, 15 min] readily removed the benzyloxycarbonyl group in **3c**, thus furnishing 4-nitrobenzyl carbamate. Similarly, compound **3i** was smoothly converted to 9-fluorenylmethyl carbamate by treatment with 45% hydrogen bromide in acetic acid (3 h, r.t.). On the other hand, compound **1** was the sole product when **3i** was treated with 20% piperidine in dimethylformamide (1 h, r.t.). Mild acidolysis [trifluoroacetic acid/anisole (9:1), 1 h, 0°C] of **3b** afforded **1**. As expected, the very acid-labile compound **3d** required still milder conditions (1.5% trifluoroacetic acid in dichloromethane, 1 h, r.t.) for the complete removal of the 1-methyl-1-phenylethoxycarbonyl function, yielding **1**. The reductive cleavage of the 2,2,2-trichloroethoxycarbonyl moiety in **3h** was readily accomplished with zinc powder in acetic acid (4 h, r.t.) and gave carbamate **1**. The allyloxycarbonyl in **3g** readily underwent cleavage on treatment with $(Ph_3P)_3RhCl$ in 90% aqueous ethanol (1 h, 70°C) and only **1** was isolated.[13]

All deblocking reactions outlined above displayed excellent selectivity and in no case even traces of the anomalous deprotection product could be detected in the crude reaction mixtures as judged by TLC and ^{1}H-NMR. The observed yields in these conversions were also satisfactory after extractive work-up. From these results, we conclude that the alkyl benzyl imidodicarbonates **3a–i** as well as other related derivatives provide an interesting entry to miscellaneous fully protected amines by alkylation of the amide nitrogen.

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. TLC analyses were performed on 0.25 mm thick, precoated, UV-sensitive silica plates (Merck DC-Fertigplatten, Kieselgel 60 F_{254}) using toluene/MeCN (2:1), CH_2Cl_2/acetone (4:1), or Et_2O as eluents. Spots were visualized by inspection under UV light at 254 nm or, preferentially, after developing with Cl_2/dicarboxidine[14] (violet blue spots). Microanalyses were carried out by Mikro Kemi AB, Uppsala, Sweden. NMR spectra were recorded on a Jeol FX 90Q instrument; the signals were tentatively assigned by comparing the chemical shifts.

Benzyloxycarbonyl Isocyanate (2):

To a suspension of dry, finely ground benzyl carbamate[15] (**1**; 30.8 g, 0.20 mol) in dry CH_2Cl_2 (300 mL) under N_2 is added dropwise, with efficient stirring and with ice cooling, a solution of oxalyl chloride (38.1 g, 0.30 mol) in dry CH_2Cl_2 (150 mL) over a period of 1 h. The initially clear mixture gradually becomes turbid after stirring for 1 h at 0°C. Stirring is continued for 4 h at ambient temperature and overnight (15 h) under reflux. The mixture is then concentrated to about 2/3 of its original volume and the fine-grained precipitate is filtered off and washed with cold, dry CH_2Cl_2 (3 × 20 mL). The combined pale yellow filtrate is evaporated to dryness at room temperature with minimum exposure to atmospheric moisture and the residual yellowish turbid oil is distilled at reduced pressure. After a forerun, consisting largely of oxalyl chloride and benzyl chloride, product **2** is collected; yield: 18.9 g (53%); bp 78–80°C/0.15–0.20 Torr. This material, a colorless liquid containing < 1% of benzyl chloride, is suitable for further work, except for the synthesis of **3d** which requires the removal of remaining traces of acidic impurities by a second distillation. Compound **2** is very sensitive to moisture and should be stored below − 20°C in a sealed vessel.

^{1}H-NMR ($CDCl_3$): $\delta = 5.20$ (s, 2H, CH_2); 7.38 (s, 5H_{arom}).

^{13}C-NMR ($CDCl_3$): $\delta = 70.2$ (CH_2); 128.1, 128.2, 128.5, 133.6 (C_{arom}); 129.5 (N=C=O); 148.6 (O–CO).

The white precipitate from above (4.9 g) consists largely of *N,N'-bis(benzyloxycarbonyl)oxamide* (for related derivatives, see Lit.[9]); mp

Table 1. Alkyl Benzyl Imidodicarbonates **3** Prepared

Product	R	Yield[a] (%)	mp (°C) (solvent for recrystallization)	Molecular Formula[b] or Lit. Data (°C)
3a	$C_6H_5CH_2$	99	109–109.5 (CH_2Cl_2/Et_2O, 1:7; 50 mL/g)	105.5–106.5[11]
3b	$4\text{-}CH_3OC_6H_4CH_2$	≈100	92.5–93 (CH_2Cl_2/Et_2O, 1:7; 50 mL/g)	$C_{17}H_{17}NO_5$ (315.3)
3c	$4\text{-}NO_2C_6H_4CH_2$	97	113.5–114 (CH_2Cl_2/Et_2O, 1:4; 60 mL/g)	$C_{16}H_{14}N_2O_6$ (330.3)
3d	$C_6H_5C(CH_3)_2$	91[c]	83.5–84 (Et_2O/PE[d], 1:4; 30 mL/g)	$C_{18}H_{19}NO_4$ (313.3)
3e	*t*-C_4H_9	97[e]	oil (purified by column chromatography)	oil[2]
3f	1-adamantyl	98	112–112.5 (Et_2O; 10 mL/g)	$C_{19}H_{23}NO_4$ (329.4)
3g	$H_2C{=}CHCH_2$	94	79.5–80 (Et_2O/hexane, 1:1; 20 mL/g)	$C_{12}H_{13}NO_4$ (235.2)
3h	$Cl_3C{-}CH_2$	92	90–90.5 (Et_2O/PE[d], 1:4; 30 mL/g)	$C_{11}H_{10}Cl_3NO_4$ (326.6)
3i	9-fluorenylmethyl	92	112–113[f] (CH_2Cl_2/Et_2O, 1:10; 70 mL/g)	$C_{23}H_{19}NO_4$ (373.4)

[a] Yield of essentially pure product before recrystallization (< 1% impurities as judged from ^{1}H-NMR and TLC).

[b] Satisfactory microanalyses obtained for **3b**, **c**, **d**, **f–i**; C ± 0.2, H ± 0.2, N ± 0.1.

[c] Yield corrected for ≈4% of **1** in the crude product.

[d] PE = petroleum ether.

[e] The crude product contained 1–2% of **1**. Yield after chromatography 84%.

[f] Softens at ≈107°C.

Table 2. Spectral Data of Compounds 3

Compound	^{1}H-NMR (CDCl$_3$/TMS) δ, J (Hz)	^{13}C-NMR (CDCl$_3$/TMS) δ
3a	5.17 (s, 4H, CH_2); 7.34 (s, $\approx$11H, H_{arom} + NH)	67.8 (CH_2); 128.4, 128.6, 134.9 (C_{arom}); 150.5 (CO)
3b	3.78 (s, 3H, CH_3); 5.10 [s, 2H, CH_2 (Z(OMe)^b)]; 5.16 [s, 2H, CH_2 (Z)^a]; 6.85, 7.28 (2d, $J = 8.7$) + 7.33 (s, $\approx$10H, H_{arom} + NH)	55.2 (CH_3); 67.7 (CH_2); 113.9, 127.1, 130.4, 159.8 [C_{arom} (Z(OMe)^b)]; 128.4, 128.5, 134.9 [C_{arom} (Z)^a]; 150.6 (CO)
3c	5.20 [s, 2H, CH_2 (Z)^a]; 5.28 [s, 2H, CH_2 (Z(NO_2)^c)]; 7.35 [s, 5H_{arom} (Z)^a]; $\approx$7.40 (br s, $\approx$1H, NH); 7.51, 8.19 [2d, $J = 9.0$, 4H_{arom} (Z(NO_2)^c)]	66.2 [CH_2 (Z(NO_2)^c)]; 68.3 [CH_2(Z)^a]; 123.8, 128.5, 142.2, 147.8 [C_{arom} (Z(NO_2)^c)]; 128.5, 128.7, 134.7 [C_{arom} (Z)^a]; 150.4 (CO)
3d	1.81 (s, 6H, CH_3); 5.15 (s, 2H, CH_2); 7.20–7.40 (m) + 7.34 (s, $\approx$11H, H_{arom} + NH)	28.4 (CH_3); 67.6 (CH_2); 83.7 ($\underline{C}CH_3$); 124.3, 127.3, 128.3, 144.8 [C_{arom} (Ppoc^d)]; 128.4, 128.6, 135.1 [C_{arom} (Z)^a]; 148.9 (CO_{Ppoc})^d; 150.8 (CO_Z)^a
3e	as previously reported[2]	as previously reported[2]
3f	1.65, 2.12 (2br sign, 15H, H_{aliph}); 5.17 (s, 2H, CH_2); $\approx$7.10 (br s, $\approx$1H, NH); 7.34 (s, 5H_{arom})	30.9, 36.0, 41.2 ($C_{aliph, Adoc}$)^e; 67.4 (CH_2); 82.4 (C_{quart}); 128.4, 128.5, 128.6, 135.2 (C_{arom}); 148.9 (CO_{Adoc})^e; 150.9 (CO_Z)^a
3g	4.60, 4.67 (2t, 2H, $C\underline{H}_2CH$); 5.17 [s, 2H, CH_2 (Z)^a]; 5.30, 5.40 (2m, 2H, $=CH_2$); 5.70–6.12 (m, 1H, $=CH-$); 7.34 (s, 5H_{arom}); $\approx$7.50 (br s, $\approx$1H, NH)	66.8 ($\underline{C}H_2CH$); 67.8 [CH_2 (Z)^a]; 119.1 ($=CH_2$); 128.5, 128.6, 134.9 (C_{arom}); 131.3 ($=CH-$); 150.5, 150.6 (CO)
3h	4.78 [s, 2H, CH_2 (Troc)^f]; 5.22 [s, 2H, (Z)^a]; 7.37 (s, 5H_{arom}); $\approx$7.53 (br s, $\approx$1H, NH)	68.3 [CH_2, (Z)^a]; 74.7 (CH_2 (Troc)^f]; 94.3 (CCl_3); 128.6, 128.7, 128.8, 134.6 (C_{arom}); 149.0 (CO_{Troc})^f; 150.4 (CO_Z)^a
3i	4.14–4.28 [4 sign, 1H_{aliph}, (Fmoc)^g]; 4.45–4.53 [3 sign, 2H, CH_2 (Fmoc)^g]; 5.19 [s, 2H, CH_2 (Z)^a]; 7.18–7.80 (m) + 7.35 (s, together 14H, H_{arom} + NH)	46.6 [C_{aliph} (Fmoc)^g]; 67.8 (CH_2); 128.5, 128.6, 134.8 [C_{arom} (Z)^a]; 120.0, 124.9, 127.1, 127.9, 141.2, 142.2 [C_{arom} (Fmoc)^g]; 150.5, 150.7 (CO)

[a] Z = Benzyloxycarbonyl.
[b] Z(OMe) = 4-Methoxybenzyloxycarbonyl.
[c] Z(NO_2) = 4-Nitrobenzyloxycarbonyl.
[d] Ppoc = 2-Phenylisopropyloxycarbonyl.
[e] Adoc = 1-Adamantyloxycarbonyl.
[f] Troc = 2,2,2-Trichloroethoxycarbonyl.
[g] Fmoc = 9-Fluorenylmethoxycarbonyl.

211–212 °C [dec, from 1,2-dichloroethane ($\approx$ 1 L/g)]. The crystalline analytical specimen tenaciously retains solvent, even after drying in high vacuum for several days.

^{1}H-NMR (DMSO-d_6): δ = 5.17 (s, 4H, CH_2); 7.38 (s, 10H_{arom}); 11.60 (br s, $\approx$2H, NH).

^{13}C-NMR (DMSO-d_6): δ = 67.5 (CH_2); 128.4, 128.7, 135.3 (C_{arom}); 152.9 (O–CO); 165.0 (CO–CO).

Alkyl Benzyl Imidodicarbonates 3a–i; General Procedure:

To a vigorously stirred solution of the alcohol ROH (20 mmol) in dry CH_2Cl_2 (30 mL) under N_2 and cooled in ice, a solution of benzyloxycarbonyl isocyanate (**2**; 3.10 g, 19 mmol, in the preparation of **3a, b, d, e, g, h** involving volatile alcohols; 3.43 g, 21 mmol, for **3c, f, i**) in dry CH_2Cl_2 (30 mL) is added dropwise over a period of 30 min. In the preparation of **3d**, crude **2** is redistilled before use. After the addition, the colorless solution is stirred under N_2 in the ice bath for 1 h and at ambient temperature overnight. The solvent is evaporated and, except for **3e**, the residue thoroughly triturated with cold petroleum ether ($\approx$ 30 mL, for **3c** and **3i** cold Et_2O). The resultant solution is kept in the cold for several hours. The white crystalline solid is collected by suction, rinsed with small portions of cold solvent, and dried over paraffin chips at reduced pressure. Analytical samples are obtained by recrystallization (for **3e** by chromatography) (Table 1).

We acknowledge the Swedish Natural Science Research Council for generous support and the Swedish Institute for a research scholarship (to M.L.S.A.).

Received: 1 June 1988; revised: 28 July 1988

(1) Grehn, L., Ragnarsson, U. *Synthesis* **1987**, 275.
(2) Grehn, L., Ragnarsson, U. *Collect. Czech. Chem. Commun.* **1988**, *53*, 2778, and references cited therein.
(3) Gibson, M.S., Bradshaw, R.W. *Angew. Chem.* **1968**, *80*, 986; *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 919.
(4) Mitsunobu, O. *Synthesis* **1981**, 1.
(5) Grehn, L., Almeida, M.L.S., Ragnarsson, U., unpublished results.
(6) Kocovsky, P. *Tetrahedron Lett.* **1986**, *27*, 5521.
(7) Matsuda, K., Yasuda, N., Tsutsumi, H., Takaya, T. *J. Antibiot.* **1985**, *38*, 1719.
(8) Speziale, A.J., Smith, L.R. *J. Org. Chem.* **1962**, *27*, 3742; **1963**, *28*, 1805.
Speziale, A.J., Smith, L.R., Fedder, J.E. *J. Org. Chem.* **1965**, *30*, 4306.
(9) Zinner, G., Stoffel, R. *Arch. Pharm. (Weinheim, Ger.)* **1969**, *302*, 691.
(10) Childs, M.E., Weber, W.P. *J. Org. Chem.* **1976**, *41*, 3486.
(11) Milcent, R., Guevrekian-Soghomoniantz, M., Barbier, G. *J. Heterocycl. Chem.* **1986**, *23*, 1845.
For related imidodicarbonates, see also: Kupfer, R., Würthwein, E.U., Krestel, M., Allmann, R. *Chem. Ber.* **1986**, *119*, 3236.
The synthesis of **3a** was attempted by: Clarke, C.T., Elliott, J.D., Jones, J.H. *J. Chem. Soc. Perkin Trans. 1* **1978**, 1088.
(12) For a general survey of protective groups for amines, see: Greene, T.W. *Protective Groups in Organic Chemistry*, John Wiley & Sons, New York, 1981, p. 218.
Recent advances in the chemistry of base-labile protective groups have been reviewed:
Carpino, L.A. *Acc. Chem. Res.* **1987**, *20*, 401.
Novel aspects of acidolytic cleavage have been discussed by: Tam, J.P., Merrifield, R.B., in: *The Peptides*, Vol. 9, Udenfriend, S., Meienhofer, J. (eds.), Academic Press, New York, 1987, p. 185.
(13) Waldmann, H., Kunz, H. *Liebigs Ann. Chem.* **1983**, 1712.
(14) Svahn, C.M., Gyllander, J. *J. Chromatogr.* **1979**, *170*, 292.
(15) Carter, H.E., Frank, R.L., Johnston, H.W. *Org. Synth. Coll. Vol. III*, **1955**, 167.