Convenient Preparations of Di-t-butyl and Methyl t-Butyl Iminodicarboxylates. The Use of Methyl t-Butyl Iminodicarboxylate Potassium Salt as a Modified Gabriel Reagent †

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The oxidation of t-butyl oxamate in the presence of t-butyl alcohol or methanol is a convenient means of preparing di-t-butyl and methyl t-butyl iminodicarboxylate respectively. The latter forms a crystalline, stable, non-hygroscopic potassium salt. The salt undergoes smooth *N*-alkylation in dipolar aprotic solvents, except with alkylating agents which are susceptible to base catalysed side reactions. The fully substituted derivatives produced give *N*-t-butoxycarbonylamino compounds on mild treatment with alkali, thus permitting the direct conversion R–X ⟶ R–NHBoc.

THE Gabriel synthesis [1] of primary amines is a classic procedure which has stood the test of time,[2] but it suffers from the disadvantage that the usual conditions for cleavage of the phthaloyl group are undesirably vigorous.[3] This has prompted investigation of several alternatives [4-7] to phthalimide in which an acidic N–H is flanked by protecting groups amenable to selective removal after *N*-alkylation. One such alternative is the di-t-butyl iminodicarboxylate reagent (1) devised by Carpino,[7] who prepared it as shown in Scheme 1. However, as Carpino himself has observed,[8] the exploitation of the reagent has been hindered by the lack of a convenient preparation. We have recently had occasion to prepare (1) and some related reagents, and report our experience.

$$\underset{}{\mathrm{Bu^tOCOCONHNH_2}} \longrightarrow \underset{(1)}{\mathrm{Bu^tOCONHCOOBu^t}}$$

SCHEME 1 Reagents: $NaNO_2$–H^+ then Bu^tOH

In our hands, Carpino's procedure [7] (see Scheme 1) for the preparation of (1) was difficult to execute reproducibly, and the best yield we were able to obtain was 24%. We therefore investigated alternatives and found that the lead tetra-acetate induced oxidation of t-butyl oxamate (2) in t-butyl alcohol (Scheme 2) was a great improvement, giving an excellent yield of (1) by a simple procedure. This reaction is an extension of one which has previously only been used [9,10] for the preparation of simple carbamates from the corresponding primary amides: its application to oxamates appears to be without complication. t-Butyl oxamate can be made easily on a large scale from commercial ethyl oxalyl chloride, and di-t-butyl iminodicarboxylate thus becomes a freely accessible reagent.

$$\underset{(2)}{\mathrm{Bu^tOCOCONH_2}} \longrightarrow \underset{(1)}{\mathrm{Bu^tOCONHCOOBu^t}}$$

SCHEME 2 Reagents: $Pb(OAc)_4$–Bu^tOH

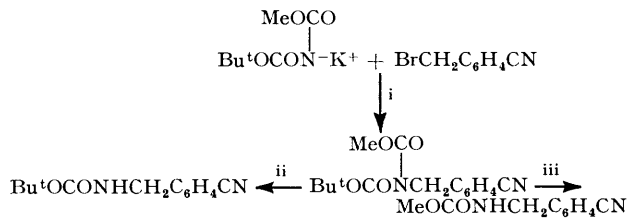
We have also attempted the preparation of the iminodicarboxylates (3)—(6) by appropriate reactions related to those shown in Schemes 1 and 2. We failed to obtain (3)—(5) except as components of complex mixtures, but methyl t-butyl iminodicarboxylate (6) proved very easy to prepare by the oxidation of t-butyl oxamate in the presence of methanol as shown in Scheme 3 or, somewhat less satisfactorily, by the oxidation of methyl oxamate in t-butyl alcohol. The iminodicarboxylate (6) seems to have considerable potential as a modified Gabriel reagent, with the advantage over Carpino's reagent (1) that it forms a stable, crystalline, non-hygroscopic potassium salt. Carpino's reagent has only been used as its sodium salt, generated *in situ* with sodium hydride: we find this inconvenient and attempts to find a suitable isolable salt have only given poorly defined and impure materials. The *N*-alkylation of the potassium salt of (6) in dimethyl sulphoxide or dimethylformamide proceeds smoothly except in cases where strong base-induced alternative courses of reaction are open. The fully substituted derivatives produced can be converted to t-butoxycarbonylamino compounds by

$\underset{(3)}{\mathrm{PhCH_2OCONHCOOCH_2Ph}}$ $\underset{(4)}{\mathrm{Bu^tOCONHCOOCH_2Ph}}$

$\underset{(5)}{\mathrm{Bu^tOCONHCOOCH_2CCl_3}}$

$$\underset{(2)}{\mathrm{Bu^tOCOCONH_2}} \longrightarrow \underset{(6)}{\mathrm{Bu^tOCONHCOOMe}}$$

SCHEME 3 Reagents: $Pb(OAC)_4$–THF–MeOH



SCHEME 4 Reagents: i, DMSO for 3 h at 50° then 2 days at 20°; ii, 1 equiv. M-NaOH at 20° for 1 h; iii, CF_3CO_2H

† Preliminary communication, J. D. Elliott and J. H. Jones, *J.C.S. Chem. Comm.*, 1977, 758.

[1] S. Gabriel, *Ber.*, 1887, **20**, 2224.
[2] M. S. Gibson and R. W. Bradshaw, *Angew. Chem. Internat. Edn.*, 1968, **7**, 919.
[3] See, however, S. Kukolja and S. R. Lammert, *J. Amer. Chem. Soc.*, 1975, **97**, 5582.
[4] T. Mukaiyama and T. Taguchi, *Tetrahedron Letters*, 1970, 3411.
[5] T. Taguchi and T. Mukaiyama, *Chem. Letters*, 1973, 1.
[6] J. B. Hendrickson, R. Bergeron, and D. D. Sternbach, *Tetrahedron*, 1975, **31**, 2517.
[7] L. A. Carpino, *J. Org. Chem.*, 1964, **29**, 2820.
[8] L. A. Carpino, *Accounts Chem. Res.*, 1973, **6**, 191.
[9] H. E. Baumgarten, H. L. Smith, and A. Staklis, *J. Org. Chem.*, 1975, **40**, 3554.
[10] B. Acott, A. L. J. Beckwith, and A. Hassanali, *Austral. J. Chem.*, 1968, **21**, 1971.

mild treatment with an equivalent amount of molar sodium hydroxide at room temperature: Scheme 4 shows an example. This sequence permits the direct introduction of a usefully protected amino function by the novel conversion R–X ⟶ R–NHBoc. As the circumstances under which the alkylation fails include the situation which we were originally interested in, we have not conducted an exhaustive examination of the utility of the reagent, but the examples collected together in the Table serve to delineate its reactivity and limitations.

Reactions of methyl t-butyl iminodicarboxylate potassium salt with some alkylating agents

Alkylating agent	Conditions [a]	Yield of *N*-alkyl derivative (%) [b]
$CH_3CH_2CH_2CH_2Br$	DMF–60°–1 h	59
$H_2C{=}CH{\cdot}CH_2Br$	DMSO–20°–2 h	71
$HC{\equiv}CCH_2Br$	DMSO–20°–1 h	68
p-Bromobenzyl bromide	DMF–60°–1 h	95 [c]
p-Cyanobenzyl bromide	DMSO–3 h–50° then 20°–2 days	73 [d]
2,4-Dichlorobenzyl chloride	DMSO–20°–16 h	*ca.* 65 [e]
$BrCH_2CO_2Et$	DMF–20°–3 h	80 [d]
$CH_3CHBrCO_2Me$	DMF–20°–16 h	83 [f]
$(CH_3)_2CBrCO_2Et$	DMF–20°–3 days	0 [g]
$BrCH_2CH_2CO_2Et$	DMF–20°–30 min	*h*
$BrCH(CO_2Et)_2$	DMF–20°–3 h	0 [i]
p-Phenylphenacyl bromide	DMF–20°–90 min	A complex mixture was obtained
Propylene oxide [j]	DMF–20°–16 h	0 [g,k]

[a] 1 equiv. of each reactant in all except the last case; salt suspended in a solution of the alkylating agent (concentrations *ca.* 100 mg per 0.25—0.5 ml). In no case have the conditions been optimised. [b] Except where indicated, all the products (which were isolated by conventional extraction and washing procedures) were oils which had n.m.r. spectra consistent with purity and the expected structures. [c] Treatment with anhydrous trifluoroacetic acid for 30 min at 20° gave *N-methoxycarbonyl-*p*-bromobenzylamine* in 87% overall yield, m.p. 93—96° (Found: C, 44.4; H, 4.0; N, 5.7; Br, 32.6. $C_9H_{10}BrNO_2$ requires C, 44.3; H, 4.1; N, 5.7; Br, 32.8%). Treatment with 1 equiv. M-NaOH in aqueous MeOH for 1 h gave *N-t-butoxycarbonyl-*p*-bromobenzylamine* in 60% overall yield, m.p. 84—85° (Found: C, 50.5; H, 5.7; N, 5.0; Br, 28.0. $C_{12}H_{16}BrNO_2$ requires C, 50.35; H, 5.6; N, 4.9; Br, 28.0%). [d] For full details of this reaction and the alkaline cleavage of the product see Experimental section. [e] Contaminated with *ca.* 15% of unchanged chloride. [f] A trace of an unidentified contaminant was present. Treatment with 2 equiv. M-NaOH gave Boc-DL-Ala in 60% overall yield as an essentially pure oil. [g] Methyl t-butyl iminodicarboxylate was recovered in good yield on work-up. [h] Ethyl acrylate was formed. [i] Tetraethoxycarbonylethylene was formed. [j] A ten-fold excess of propylene oxide was used. [k] More vigorous conditions gave complex mixtures.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. I.r. and n.m.r. spectra were determined with Perkin-Elmer 257 and R32 (operating at 90 MHz) spectrometers. Tetrahydrofuran was dried with lithium aluminium hydride and redistilled; light petroleum was of AnalaR grade, sodium-dried, b.p. 40—60°; methanol was dried with magnesium–iodine and distilled; dimethyl sulphoxide was Fison's 'dried distilled solvent'; dimethylformamide was fractionally distilled before use.

t-Butyl Oxamate.—The following simplified modification of Carpino's procedure [11] proved convenient. Commercial ethyl oxalyl chloride (203 g, 1.49 mol) was added over 1 h to a stirred mixture of t-butyl alcohol (110.6 g, 1.49 mol), pyridine (118.1 g, 1.49 mol), and dichloromethane (314 ml) which was cooled in ice. The liquid remaining after washing with water (2 × 150 ml), drying, and evaporation of most of the dichloromethane, was added dropwise with stirring to liquid ammonia (*ca.* 750 ml). The mixture was allowed to evaporate after 2 h reflux, giving an off-white solid which was dissolved in methanol. Removal of the insoluble material (presumed to be oxamide) and evaporation gave chromatographically pure t-butyl oxamate (126.4 g, 58%), m.p. 90—91° (lit.,[11] 89.5—90.5°).

Di-t-butyl Iminodicarboxylate.—Lead tetra-acetate (6.8 g, 15.3 mmol) was added to a solution of t-butyl oxamate (2.0 g, 13.8 mmol) in dry t-butyl alcohol (40 ml) and the mixture was warmed to 55°, when an orange colour developed. Dry triethylamine (5 ml) was added dropwise. The colour was discharged. The mixture was maintained at reflux temperature for 30 min and then filtered into a mixture of ice (60 g), water (200 ml), and acetic acid (10 ml). The mixture was extracted with ether (3 × 80 ml) and the combined extracts were washed with water (100 ml), saturated aqueous sodium hydrogencarbonate (50 ml), and brine (50 ml). Removal of solvent after drying gave an oil which crystallised on standing. Recrystallisation from light petroleum gave di-t-butyl iminodicarboxylate (2.1 g, 70%) as needles, m.p. 118—120° (lit.,[7] two polymorphic modifications, 88.5—90.5 and 119—121°), i.r. and n.m.r. identical to those of material obtained by Carpino's method.

Methyl t-Butyl Iminodicarboxylate.—Lead tetra-acetate (6.8 g, 15.3 mmol) was added to a solution of t-butyl oxamate (2.0 g, 13.8 mmol) in a mixture of dry tetrahydrofuran (30 ml) and dry methanol (20 ml). An orange colour, which was discharged on bringing the mixture to reflux, developed. Solvents were removed and the residue was distributed between ether (100 ml) and water (100 ml). The aqueous layer was separated and further extracted with ether (2 × 50 ml). The combined ether extracts were washed with saturated aqueous sodium hydrogencarbonate; since some product passed into the aqueous phase the washings were extracted with ether. The combined ether extracts were dried and evaporated to give chromatographically pure *methyl t-butyl iminodicarboxylate* (2.1 g, 83%) as a solid, m.p. 70—73°. Recrystallisation from ether–light petroleum gave needles, m.p. 75—77°; $\nu_{max.}$ ($CHCl_3$) 3 445 (N–H), 1 805, 1 770, and 1 735 (C=O) cm^{-1}; τ($CDCl_3$) 3.0br (1 H, NH), 6.21 (3 H, s, CO_2CH_3), and 8.47 (9 H, s, Bu^t) (Found: C, 48.3; H, 7.5; N, 8.1. $C_7H_{13}NO_4$ requires C, 48.0; H, 7.4; N, 8.0%). The compound could also be prepared by oxidation of methyl oxamate in t-butyl alcohol using a procedure analogous to that described above for the case of di-t-butyl iminodicarboxylate, but the crude product was slightly discoloured and the yield was lower (55%).

Methyl t-Butyl Iminodicarboxylate Potassium Salt.—Methyl t-butyl iminodicarboxylate (0.62 g, 3.5 mmol) was treated with 0.88M aqueous potassium hydroxide (3.75 ml, 3.29 mmol). Filtration, evaporation, trituration with ether, and drying at 20° and 0.1 mmHg gave *methyl t-butyl iminodicarboxylate potassium salt* (0.60 g, 85%) as a crystalline solid which did not melt below 250°; $\nu_{max.}$ (Nujol) 1 690 cm^{-1} (C=O), N–H stretch absent; τ[$(CD_3)_2SO$] 6.69 (3 H, s, CO_2CH_3) and 8.68 (9 H, s, Bu^t), no other bands (Found: C, 38.8; H, 5.6; K, 18.3, N, 6.5. $C_7H_{12}KNO_4$ requires C, 39.4; H, 5.6; K, 18.3; N, 6.6%).

[11] L. A. Carpino, *J. Amer. Chem. Soc.*, 1960, **82**, 2725.

Alkylation of Methyl t-Butyl Iminodicarboxylate Potassium Salt with p-*Cyanobenzyl Bromide*.—(a) A suspension of methyl t-butyl iminodicarboxylate potassium salt (120 mg, 0.56 mmol) in a solution of *p*-cyanobenzyl bromide (110 mg, 0.56 mmol) in dry dimethyl sulphoxide (0.5 ml) was stirred for 3 h at 55° and then 2 days at 20°. The mixture was partitioned between chloroform (25 ml) and water (10 ml); the chloroform layer was separated, washed with water (2 × 10 ml), and dried. Removal of solvent gave N-*t-butoxycarbonyl*-N-*methoxycarbonyl*-p-*cyanobenzylamine* (120 mg, 73%) as a chromatographically pure oil, τ($CDCl_3$) 2.3—2.7 (4 H, ABq, ArH), 5.12 (2 H, s, CH_2), 6.18 (3 H, s, CO_2CH_3), and 8.55 (9 H, s, Bu^t).

(b) A suspension of methyl t-butyl iminodicarboxylate potassium salt (295 mg, 1.4 mmol) in a solution of *p*-cyanobenzyl bromide (275 mg, 1.4 mmol) in dry dimethyl sulphoxide (0.5 ml) was stirred at 55° for 3 h and then for 2 days at 20°. Methanol (2 ml) and sodium hydroxide (2 ml) were then added. After 1 h at 20° the mixture was diluted with water (20 ml) and extracted with ether (3 × 20 ml). The ethereal layer was separated and the ether was evaporated. Trituration of the residue with water followed by recrystallisation from light petroleum gave N-*t-butoxycarbonyl*-p-*cyanobenzylamine* (225 mg, 69%), m.p. 105—108°; $\nu_{max.}$ 3 460 (N–H), 2 240 (C≡N), and 1 715 (C=O) cm^{-1}; τ($CDCl_3$) 2.3—2.7 (4 H, ABq, ArH), 4.1br (1 H, NH), 5.65 (2 H, d, *J* 7 Hz, CH_2), and 8.55 (9 H, s, Bu^t) (Found: C, 66.95; H, 6.9; N, 12.2. $C_{13}H_{16}N_2O_2$ requires C, 67.2; H, 6.9; N, 12.1%).

Alkylation of Methyl t-Butyl Iminodicarboxylate Potassium Salt with Ethyl Bromoacetate.—Methyl t-butyl iminodicarboxylate potassium salt (160 mg, 0.75 mmol) was suspended in a solution of ethyl bromoacetate (125 mg, 0.75 mmol) in dry dimethylformamide (0.5 ml) for 3 h at 20°. Dimethylformamide was evaporated and the residue was distributed between ether (20 ml) and water (10 ml). The ethereal layer was separated and dried. Removal of the ether gave N-*t-butoxycarbonyl*-N-*methoxycarbonylglycine ethyl ester* as a chromatographically pure oil (195 mg, 80%), τ($CDCl_3$) 5.51 (3 H, s, CH_2CO), 5.77 (2 H, q, CH_2CH_3), 8.50 (9 H, s, Bu^t), and 8.72 (3 H, t, CH_2CH_3). The oil was dissolved in dioxan (2 ml) and M-sodium hydroxide (1.5 ml, 1.5 mmol) was added. The solution was stirred at 20° for 1 h and the dioxan was evaporated. The residue was distributed between ether (20 ml) and 7% aqueous citric acid (20 ml). The ethereal layer was separated and the aqueous phase was further extracted with ether (2 × 20 ml). Dicyclohexylamine (270 mg, 1.5 mmol) was added to the combined ether extracts after drying. Evaporation of the ether and trituration with light petroleum gave t-butoxycarbonylglycine dicyclohexylammonium salt (188 mg, 71%) identical in every respect (m.p., i.r., n.m.r.) to authentic material.

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