t-Butyl Methyl Iminodicarboxylate Potassium Salt: a Modified Gabriel Reagent for the Introduction of t-Butoxycarbonylamino Groups

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Summary t-Butyl methyl iminodicarboxylate potassium salt is a stable, easily prepared, non hygroscopic compound; it undergoes smooth *N*-alkylation in dipolar aprotic solvents to give derivatives which suffer loss of the methoxycarbonyl group on mild treatment with alkali, enabling the direct conversion R–X → R–NHBoc (Boc = t-butoxycarbonyl) to be achieved.

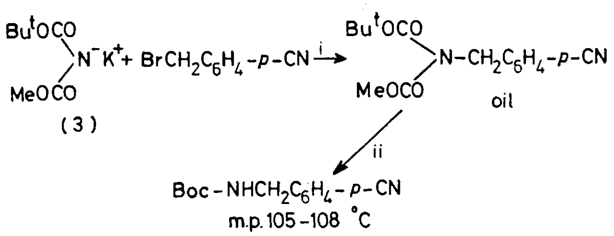
THE conventional Gabriel synthesis of primary amines[1] suffers from the disadvantage that the standard conditions for cleavage of phthaloyl protection are undesirably vigorous.[2] This has prompted investigations[3] of a number of alternatives to potassium phthalimide which yield *N*-alkyl derivatives amenable to milder deprotection, but so far the procedures devised either require reagents which are not conveniently accessible, or involve rather complex chemistry, or both. We have found that the potassium salt of t-butyl methyl iminodicarboxylate is a useful modified Gabriel reagent which is not open to these objections.

t-Butyl methyl iminodicarboxylate (**1**) is easily prepared by lead tetra-acetate oxidation of t-butyl oxamate (**2**) (which is itself simple to prepare starting from commercial ethyl oxalyl chloride) in the presence of methanol.† The reaction (Scheme 1),‡ which no doubt proceeds by generation of t-butoxycarbonyl isocyanate *in situ*, is an extension of one which has previously been applied to simple primary amides.[4] The potassium salt (**3**) is obtained by dissolving (**1**) in slightly less than 1 equiv. of 1 M potassium hydroxide, evaporation, trituration with ether, and drying *in vacuo*; it is a white crystalline non-hygroscopic material of m.p. > 250 °C which is indefinitely stable at room temperature. The salt (**3**) is only sparingly soluble in dimethylformamide (DMF) and dimethylsulphoxide but can be alkylated as a suspension in either of these solvents. We have examined its reactions with a range of alkyl bromides and chlorides, bromoesters, *etc.* Except when the alkylating agent was susceptible to base catalysed side-reactions (*e.g.* ethyl β-bromopropionate which gave ethyl acrylate), excellent yields of *N*-t-butoxycarbonyl-*N*-methoxycarbonylamino compounds were obtained. Treatment of these fully substituted intermediates with 1 equiv. of 1 M sodium hydroxide at room temperature gave the corresponding *N*-t-butoxycarbonyl derivatives. Two representative examples are shown in Schemes 2 and 3. The salt (**3**) appears to have considerable potential as a simple, stable, and accessible Gabriel type reagent with which the transformation R–X → R–NHBoc can be achieved in two operations with a good overall yield.

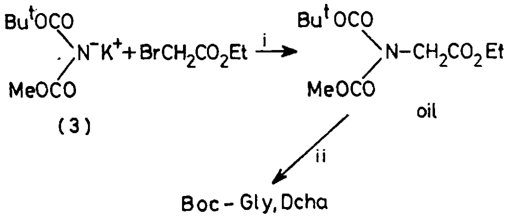
$$\mathrm{Bu^tOCOCONH_2} \xrightarrow{\text{i}} \mathrm{Bu^tOCONHCO_2Me}$$

(**2**) (**1**); m.p. 75—77 °C

Scheme 1. i, $\mathrm{Pb(OAc)_4}$-dry tetrahydrofuran (THF)–MeOH; 83% yield.



Scheme 2. i, $\mathrm{Me_2SO}$, 3 h at 50 °C, then 2 days at 20 °C; ii, 1 equiv. 1 M NaOH, 20 °C, 1 h; 69% overall yield.



Scheme 3. i, DMF, 20 °C, 3 h; ii, 2 equiv. 1 M NaOH, 20 °C, 1 h, followed by isolation as dicyclohexylammonium (Dcha) salt; 71% overall yield. Gly = a glycine residue.

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† Spectral and analytical data in accordance with the structures shown were obtained for all new compounds.

‡ $\mathrm{Pb(OAc)_4}$ (6·8 g) was added in one portion at 20 °C to a solution of $\mathrm{Bu^tOCOCONH_2}$ (2·0 g) in a mixture of dry THF (30 ml) and dry MeOH (20 ml). An orange colour developed. The mixture was brought to reflux (the colour was discharged), solvents were evaporated, and the product was isolated by washing an ether extract of the residue with water and sodium bicarbonate (taking care appropriate to the fact that the product is somewhat soluble in water) followed by recrystallisation from light petroleum.

[1] M. S. Gibson and R. W. Bradshaw, *Angew. Chem. Internat. Edn.*, 1968, **7**, 919.

[2] See S. Kukolja and S. R. Lammert, *J. Amer. Chem. Soc.*, 1975, **97**, 5582.

[3] L. A. Carpino, *J. Org. Chem.*, 1964, **29**, 2820; T. Mukaiyama and T. Taguchi, *Tetrahedron Letters*, 1970, 3411; T. Taguchi and T. Mukaiyama, *Chem. Letters*, 1973, 1; J. B. Hendrickson and R. Bergeron, *Tetrahedron Letters*, 1973, 3839.

[4] H. E. Baumgarten, H. L. Smith, and A. Staklis, *J. Org. Chem.*, 1975, **40**, 3554; B. Acott, A. L. J. Beckwith, and A. Hassanali, *Austral. J. Chem.*, 1968, **21**, 197.