A Convenient One-Flask Preparation of Di-tert-butyl Iminodicarbonate: A Versatile Gabriel Reagent

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An improved synthesis of di-tert-butyl iminodicarbonate from formamide and di-tert-butyl dicarbonate with dimethylaminopyridine as a catalyst followed by aminolytic removal of the formyl group is described as well as a few applications related to the synthesis of primary amines.

The Gabriel reaction is a well established procedure which still competes favourably with other methods for the preparation of primary amines.1 Its utility is, however, severely restricted by the inherent high stability of the phthaloyl group which necessitates the use of a strong acid or base, alternatively the nucleophile hydrazine, at elevated temperatures for the final deprotection step.2 Therefore it was highly desirable to design a Gabriel reagent with protective groups which could easily be removed under mild conditions. Of particular interest among miscellaneous Gabriel reagents with acid-labile and other selectively removable protecting groups that have been studied3-9 is di-tert-butyl iminodicarbonate (3), containing tert-butoxycarbonyl (Boc) groups which can be cleaved rapidly with acid under mild conditions. In recent years, the sodium- and potassium salts of di-tert-butyl iminodicarbonate (3) have emerged as promising Gabriel reagents,3,8,10 but the use of 3 in this context has hitherto been restricted by the limited accessibility of this compound.

An early method of preparation of 3 exploited tert-butyl oxalylhydrazide. After conventional conversion to the corresponding azide, the latter compound was made to undergo a Curtius rearrangement in tert-butanol to give 3 in a moderate overall yield.1 Later, an improved synthesis appeared in which the readily accessible tert-butyl oxamate was oxidized with lead tetraacetate to give 3 in high yield.8 We now present a favourable alternative method which enables the large-scale preparation of 3 by a convenient one-flask procedure using commercially available starting materials. Thus, when formamide 1 was allowed to react with 2 equivalents of di-tert-butyl dicarbonate11 in dry acetonitrile in the presence of catalytic amounts of 4-dimethylaminopyridine (DMAP), the hydrogens of the amide moiety were completely replaced by tert-butoxycarbonyl groups with the formation of di-Boc-formamide 2. Similar DMAP-catalyzed tert-butoxycarbolations of various amide derivatives under comparable conditions have previously been investigated by us in some detail.12,13 The yields in such conversions are generally excellent. Moreover, the resulting Boc-acylamides are susceptible to aminolysis to various extent.14 Therefore, as expected, the initially formed 2 was quite unstable and could not be isolated pure. However, in agreement with earlier findings, the direct addition of 2-diethylaminoethylamine (DEAEA) to the reaction mixture after complete tert-butoxycarbonylation smoothly cleaved the formyl group of 2, and 3 of high purity could be isolated in satisfactory yield after a simple work up.

As mentioned above, the potential of the potassium- and sodium salts of 3 and related reagents has already been investigated and it was shown that a variety of halides could be transformed into the corresponding aminides by this approach.8,10 Dimethylformamide seems to be the solvent of choice and, in most cases, the reaction is complete after a few hours. Sometimes gentle heating facilitates this conversion and the isolated yields are generally acceptable. A similar reaction was also carried out in refluxing benzene under phase transfer conditions with a related Gabriel reagent.9 With respect to the isolation of products, Carpinò3 did not isolate the fully protected amines but instead preferred to deprotect them with acid directly to form the free amines. Allan et al.10 on the other hand, fully characterized a bis-Boc-amine derivative. Clarke et al.8 have isolated previously mixed bis-protected amines.

In addition to preparing 3 we also carried out a few conversions with this reagent. Thus, we have found that benzyl chloride as well as benzyl bromoacetate reacts smoothly with the potassium salt of 3 in dry dimethylformamide under mild conditions and the yields of the desired, fully protected products 4 and 5, respectively, are excellent (see experimental). Furthermore, this reaction has also been extended to a polymeric halide. Thus, when a chloromethylated styrene polymer was treated with excess of potassium salt of 3 in dry dimethylformamide using our standard conditions, a product was obtained which exhibited satisfactory elemental analyses (nitrogen, chlorine). In the future, this Boc₂N—CH₂ — styrene polymer 6, after due deprotection of the amino function, might find applications in solid phase peptide synthesis.

Di-tert-butyl Iminodicarbonate (3):
To a well-stirred solution of dry 4-dimethylaminopyridine (6.1 g, 0.05 mol) in dry acetonitrile (50 ml) is added slowly formamide (22.5 g, 0.50 mol, dried over a molecular sieve 4A) and di-tert-butyl dicarbonate (240 g, 1.1 mol) dissolved in dry acetonitrile (200 ml) at ambient temperature. The resulting mixture is gently heated to 35—40 °C to initiate the reaction. The evolution of carbon dioxide becomes brisk after a few minutes but ceases virtually after 1 h. After stirring for 5 h at room temperature, the clear, brandy-coloured solution is cooled in ice. Next 2-diethylaminoethylamine (69.7 g, 0.60 mol) is then cautiously introduced with vigorous stirring while maintaining the reaction temperature below 25 °C and the resulting yellowish mixture is stirred overnight at room temperature. Removal of the solvent at reduced pressure below 30 °C affords a brown syrup which is partitioned between ether (1.5 l) and 1 mol aqueous potassium hydrogen sulfate (1.0 l). The orange coloured aqueous phase containing precipitated salts is discarded and the light-yellow ether extract is washed in turn with 1 mol aqueous potassium hydrogen sulfate (3 x 500 ml), 1 mol aqueous sodium hydrogen carbonate (3 x 500 ml) and saturated brine (3 x 500 ml). After drying with magnesium sulfate and treatment with decolorizing carbon, the filtrate is evaporated to dryness and the residual crystalline mass is thoroughly dried in vacuo at 40 °C; yield: 96.2 g (89%). TLC (toluene/acetonitrile, 2:1, silica gel) gives essentially one spot with R₂ = 0.35 after development with dichloroacetic spray. 1H-NMR (CD₂Cl₂) confirms the high purity (a minor peak at δ = 1.40 ppm corresponds to < 1% of Boc-NH₂). Recrystallization of the crude product from petroleum ether (8 ml/g, decolorizing carbon) gives white needles after cooling at 0 °C overnight: total yield: 77.0 g (71%); m. p. 118—119 °C (Ref.3, m. p. 88.5—90.5 °C or 119—121 °C (Ref.4, m. p. 118—120 °C).
reduced pressure below 30 °C and the residual semisolid jelly is partitioned between ether (40 ml) and 1 molar aqueous potassium hydrogen sulfate (20 ml). The clear ethereal extract is washed in turn with 1 molar aqueous potassium hydrogen sulfate (3 × 10 ml), 1 molar aqueous sodium hydrogen carbonate (3 × 10 ml) and brine (3 × 10 ml) and dried with magnesium sulfate. Evaporation to complete dryness at 40 °C leaves a colourless oil which soon solidifies in the cold after seeding with authentic sample. The crude product is essentially pure; yield: 563 mg (92%). Recrystallization from petroleum ether (5 ml/g; decolorizing carbon, cooling to −70 °C) affords an analytical specimen as pale, yellow, soft crystals, in all respects identical with a sample prepared by an alternative synthesis.16 mp. 30–31 °C.

C₇H₈N₂O₆ calc. C 66.4 H 8.2 N 4.6 (307.4) found 66.3 8.3 4.7

1H-NMR (CD₂CN/TMS): δ = 1.42 (s, 18 H); 4.73 (s, 2 H); 7.29 ppm (s, 5 H).

Benzyl N,N-di-Boc-glycinate (Boc₂-Gly-OBzl, 5): A vigorously stirred suspension of fine-grained, thoroughly dried potassium salt of 3 (25.5 g, 0.10 mol) in dry dimethylformamide (150 ml) is slowly treated with benzyl bromoacetate (23.4 g, 0.102 mol), dissolved in dry dimethylformamide (100 ml). The resulting light-yellow slurry becomes lukewarm and the stirring is continued for 10 H at 40 °C. Most of the solvent is stripped off in vacuo and the semisolid yellowish residue is worked up as described above for compound 4. The resulting ethereal extract is treated with decolorizing carbon and the filtrate is evaporated to complete dryness at reduced pressure below 40 °C to afford crude 5 as a colourless oil; yield: 34.1 g (93%). 1H-NMR of the product reveals the presence of 3 and benzyl bromoacetate (~ 2% of each). Recrystallization from petroleum ether gives pure 5, identical with that obtained earlier.17 mp. 26–29 °C.

C₉H₁₀N₂O₆ calc. C 62.4 H 7.5 N 3.8 (365.4) found 62.3 7.9 3.8

1H-NMR (CD₂CN/TMS): δ = 1.43 (s, 18 H); 4.32 (s, 2 H); 5.16 (s, 2 H); 7.37 ppm (s, 5 H).

Polymeric N,N-di-Boc-Benzylamine (Boc₂N – CH₂ – Styrene Polymer, 6): Prepolymer of Polymer: Commercial polymer (Bio-Beads S-X1, chloromethylated, 200–400 mesh, 20 g) is meticulously rinsed on a glass filter with 100 ml portions of dimethylformamide, dimethylformamide/ethanol (1:1) and ethanol (twice each with 5 min shaking in every wash). The polymer is then thoroughly dried in a stream of air for a few hours and then in vacuo overnight at ambient temperature.

Elemental analysis: CI 5.0 % (1.40 mmol Cl/g) N 38 ppm

Gabriel Synthesis: The above washed and dried polymer (1.00 g, 1.40 mmol Cl) is suspended in dry dimethylformamide (15 ml). Fine-grained potassium salt of 3 (678 mg, 2.66 mmol) is added and the slurry is vigorously stirred for 20 h at 50 °C. The solid is filtered and thoroughly washed in turn with dimethylformamide (2 × 10 ml), dimethylformamide/water (1:1, 3 × 10 ml), dimethylformamide/ethanol (1:1, 2 × 10 ml), 99% ethanol (3 × 10 ml), dimethylformamide/ethyl acetate (2 × 10 ml), dimethylformamide/ethanol (1:1, 2 × 10 ml) and finally with 99% ethanol (5 × 10 ml). After careful drying as described above, the yield of 6 is 1.10 g (theoretical yield 1.25 g).

Elemental analysis: CI 0.03 % N 1.42 % (1.27 mmol N/g)

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