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SYNTHESIS OF tert-BUTYL AMINOCARBONATE, A NEW TYPE OF COMPOUND THAT CAN BE USED TO ACYLATE AMINES

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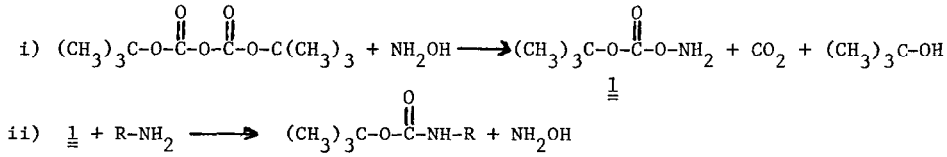
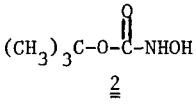
SUMMARY: tert-Butyl aminocarbonate (tert-butyloxycarbonyloxyamine) was prepared by reaction of hydroxylamine with excess di-tert-butyl dicarbonate. Amino carbonates have not previously been described. This compound rapidly acylates amines in both organic and aqueous solutions.

While using di-tert-butyl dicarbonate to acylate the amino and imidazole groups in proteins, we found that the acylation occured much more rapidly in the presence of hydroxylamine (2). It seemed likely that hydroxylamine catalyzed the reaction of the dicarbonate with amines via the sequence:



Although tert-butyl hydroxycarbamate, $\underline{2}$, has been synthesized (3), $\underline{1}$ has not been prepared. Indeed, no amino carbonates have yet been described. We therefore undertook the synthesis of $\underline{1}$, both because it represents a new class of compound and because this type of compound may prove to be a useful reagent for protecting amino groups.



We prepared the amino carbonate as follows. 28.8 mmol $NH_2OH \cdot HCl$ in 50 ml 50% (v/v) dioxane at 0° was brought to pH 10.3 with 4N NaOH. 72 mmol of solid di-tert-butyl dicarbonate (Pierce Chemical Co.) was added and the pH was maintained at 10.3 with a pH stat. After 30 min., the uptake of base had greatly slowed and the temperature was allowed to rise to room temperature

A small precipitate was dissolved by adding a little distilled water. After 90 min., the solution was acidified to pH 2 with 3N HCl and the product was extracted into 50 ml $CHCl_3$, 3 times. The $CHCl_3$ solution was washed with water, dried over Na_2SO_4, and the chloroform was removed under reduced pressure to yield a heavy liquid that solidified in the freezer, yield 98%. The product was 98% pure as judged by high performance liquid chromatography (C_{18} μBondapak reverse-phase column, isochratic elution, 0.1% H_3PO_4-50% CH_3CN). The 2% impurity was unreacted di-tert-butyl dicarbonate.

Compounds 1 and 2 can be separated readily because 1 is extracted from an aqueous solution by $CHCl_3$ and 2 is not extracted. If the synthesis is attempted with considerable excess NH_2OH, only compound 2 is obtained (3) but if equimolar amounts of NH_2OH and the dicarbonate are used, comparable quantities of 1 and 2 are obtained. Compound 1 is a semi-solid, m.p. 22°C and compound 2 is a crystalline solid, m.p. 56-58°C (3). 1 is soluble in water and organic solvents but 2 is readily soluble in water but not in organic solvents. Compounds 1 and 2 are readily distinquished by HPLC. Using a linear gradient (10min., 1.5 ml/min.) of 0.1% H_3PO_4 to 0.1% H_3PO_4-50% CH_3CN, 1 elutes in 11.8 min., 2 in 8.8 min., and di-tert-butyl dicarbonate in 10.7 min. The ^1H NMR spectrum of 1 (in $CDCl_3$ or d_6-DMSO) and 2 (in D_2O or d_6-DMSO) shows only the distinctive tert-butyl hydrogens, δ1.5. In the I.R., 1 shows a carbonyl stretching band at 1780 cm^{-1} corresponding to a carbonate. 2 shows a carbonyl stretching band at 1727 cm^{-1} (3), corresponding to a carbamate. The identity of 1 is further supported by its equivalent weight determined by chemical ionization mass spectrometry (M+1 ion, 134; calculated 134) or by using a weighed quantity of 1 to acylate a weighed amount of leucine that was in 100% excess. The amount of unreacted leucine was measured with the ninhydrin assay (4). The equivalent weight of 1 determined by this method was 129 (calculated 133). The identity of 1 was further established by its conversion to 2 (70%) using 5% of its equivalence of NH_2OH in 50% (v/v) dioxane at pH 9.3.

Compound 1 is an acylating agent in organic and aqueous solutions but compound 2 is not an acylating agent. Compound 1 acylates amines 1.5-2.5 times more rapidly than di-tert-butyl dicarbonate. Compound 1 has the remarkable property of maintaining its ability to acylate amines rapidly in acid solutions, even at pH 5.5.

REFERENCES AND NOTES

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