THE USE OF T-BUTYLCARBONIC DIETHYLPHOSPHORIC ANHYDRIDE FOR ACYLATING AMINES: A NEW WAY OF PREPARING, T-BUTOXYCARBONYL DERIVATIVES*

By D. STANLEY TARBELL AND MICHAEL A. INSALACO

DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER

Communicated December 23, 1966

Among the mixed carboxylic carbonic anhydrides whose preparation and mode of reaction we have studied¹ was p-nitrobenzoic t-butylcarbonic anhydride² (II). This compound was prepared from t-butyl chlorocarbonate and p-nitrobenzoic acid or, much more conveniently, by the method indicated below, which involves the carbonation of potassium t-butoxide and treatment of the resulting carbonate with p-nitrobenzoyl chloride. We wished to prepare a carbonic phosphoric anhydride³

$$(CH_3)_3COK + CO_2 \rightarrow (CH_3)_3COCOOK \qquad I$$

$$O$$

$$(C_2H_5O)_2P-Cl \qquad O_2NC_6H_4COCl$$

$$(CH_3)_3CO-C-O-P(OC_2H_5)_2 \qquad O_2NC_6H_4C-O-C-OC(CH_3)_3$$

$$III$$

$$O$$

$$(CH_3)_3COC-NHR \qquad (C_2H_5O)_2P-OC(CH_3)_3 \qquad IV$$

$$V, R = H$$

$$VI, R = p-CH_3C_6H_4$$

$$VII, R = CH_2COOC_2H_5$$

$$VIIII, R = CH_2COOH$$

for studies on reaction mechanisms, and we have therefore treated the carbonate (I) with diethyl phosphorochloridate. The reaction yielded potassium chloride and the expected anhydride (III), *t*-butylcarbonic diethylphosphoric anhydride. The structure of the latter was proved by determining its infrared spectrum in carbon tetrachloride, which showed the following absorption bands, in agreement with the expected values for organophosphorus compounds:⁴

Infrared Absorption of t-Butylcarbonic Diethylphosphoric Anhydride (III) in Carbon Tetrachloride

С—Н	$3010-3020 \text{ cm}^{-1}$
C=0	1755 - 1765
CH_3	1370-1380
P=0	1250-1300
C0	1145 - 1155

In order to prove that the carbonyl absorption in the product was not that of potassium *t*-butyl carbonate, the infrared spectrum of the latter was run in tetra-hydrofuran (THF) and compared with that of the anhydride in the same solvent. The anhydride has its carbonyl peak at 1760–1780 cm⁻¹ in THF as compared with 1610–1630 cm⁻¹ for the carbonyl group in *t*-butyl carbonate.

Further infrared evidence for the structure of the anhydride was obtained by comparison of its spectrum with that of diethyl *t*-butyl phosphate (IV), which was prepared from potassium *t*-butoxide and diethyl phosphochloridate. The spectra of the ester and the anhydride differed sharply in the carbonyl region, the ester having no absorption in this region.

The structure of the anhydride (III) was supported by the NMR spectrum,⁵ run neat at 0° and 10°. It showed a singlet (nine protons, $C(CH_3)_3$) at 1.5 ppm; triplet (six protons, CH_3 of the C_2H_5 groups) at 1.3 ppm, and a multiplet (seven lines distinguishable) resulting from the four CH_2 protons of the C_2H_5 group, which were split to a quartet by the CH_3 group, and the quartet was split further by coupling⁶ with the phosphorus atom, J_{P-H} 8.6 cps.

The anhydride was characterized chemically by treatment with anhydrous ammonia to form the carbamate⁷ (V), and by conversion to the p-toluidine derivative (VI). The widespread use of the *t*-butoxycarbonyl group^{8, 9} as a protecting residue in the synthesis of polypeptides¹⁰ suggested an examination of the anhydride (III) as a reagent for the introduction of this group. We have found that (III) reacts with glycine ethyl ester to give a good yield of the corresponding carbamate (VII), which can be saponified to the corresponding carbamate of glycine itself⁹ (VIII). L-phenylalanine ethyl ester also reacts well; we have not examined exhaustively other amino acids, but the reaction is presumed to be general.

Our interest in the carbonic phosphoric anhydrides such as (III) is not primarily in their possible use as reagents in peptide syntheses, and we are therefore reporting the present observations so that other workers may utilize them if they wish.

t-Butylcarbonic Diethylphosphoric Anhydride (III).—It was found that potassium t-butylcarbonate (I) was best prepared for this synthesis in THF rather than in dimethylformamide (DMF).²

Potassium t-butylcarbonate was prepared from 11.6 gm (0.1 mol wt) of potassium t-butoxide dissolved in 250 ml of THF (purified by two distillations from lithium aluminum hydride) by addition of CO_2 from dry ice at 0°. The CO_2 was allowed to bubble through the solution for 1.5 hours with continuous stirring. The volume of solution was brought back to 250 ml, and 17.2 gm (0.1 mol wt) of diethyl phosphorochloridate¹¹ dissolved in 50 ml of dry THF was added slowly with stirring. After 0.5 hour of further stirring, the reaction was complete, as determined by running several reactions for various times and measuring the yield of potassium chloride. The THF was removed under water-pump vacuum with no application of external heat. To the residual gelatinous mass, 300 ml of anhydrous ethyl ether was added, and the resultant solution with fine potassium chloride in suspension was centrifuged; the yield of potassium chloride was 6.0 gm, which indicates a maximum yield of 80 per cent of anhydride. The ether solution was evaporated under a water-pump vacuum at room temperature and yielded 20 gm of oil (79% of the anhydride).

A sample of the anhydride (III) was converted to the carbamate (V) by treatment with anhydrous ammonia in dry ether. Ammonium diethyl phosphate (identified by the infrared absorption in a potassium bromide disk) was obtained in 91 per cent yield. The ether filtrate was extracted three times with water and dried; evaporation gave 54 per cent of the crude carbamate, which melted, after recrystallization from ether-petroleum ether, at $106-107^{\circ}$, in agreement with reported values.^{2, 7} Its infrared spectrum was identical with that of a known sample.²

N-t-Butoxycarbonyl Glycine Ethyl Ester and the Free Acid (VIII).—Glycine ethyl ester hydrochloride (9.5 gm, 0.068 mol wt) was suspended in 160 ml of chloroform, stirred and cooled in an ice bath, and 6.85 gm (0.068 ml wt) of triethylamine was added with stirring. The anhydride (III) (19.0 gm, 0.068 mol wt, assuming a purity of 91%) was added, followed by 5.6 gm more of triethylamine. After stirring for 20 minutes more and cooling in an ice bath, the solvent was evaporated. Anhydrous ether (500 ml) was added, and 10 gm of white salt was collected by filtration. The filtrate was extracted with three 15-ml portions of water, dried, and the solvent was removed. The crude product (11 gm) was distilled, bp 93–97° (0.65–0.70 mm), to give 9.8 gm (71%) of practically colorless product (VII).

The infrared spectrum showed absorption (in cm⁻¹) at 3400–3500 (N—H), 3005– 3015 (C—H), 1700–1730 (C=O), 1380 (CH₃), and 1150–1160 (C—O). The NMR spectrum showed the following absorption: triplet (one proton, N—H) at 6.0 ppm; quartet (two protons, OCH₂) at 4.15 ppm; doublet (two protons, —NCH₂) at 3.8 ppm; singlet (nine protons, $C(CH_3)_3$) at 1.4 ppm; triplet (three protons, CH₃ of C_2H_5) at 1.3 ppm.

Saponification in aqueous THF with sodium hydroxide gave N-t-butoxycarbonylglycine (VIII); this melted, after recrystallization from ether, at 85–87°, and showed the expected infrared spectrum. The reported⁹ mp is 89–90°.

N-t-butoxycarbonyl-p-toluidine was prepared similarly, and melted at 88-88.5°. Its infrared and NMR spectra were in complete agreement with the proposed structure.

Analysis: Calcd. for C₁₂H₁₇NO₂: C, 69.57; H, 8.21. Found: C, 69.50; H, 8.20.

* Supported by grant GP-4961 from the National Science Foundation.

¹ Longosz, E. J., and D. S. Tarbell, J. Org. Chem., 26, 2161 (1961); Michejda, C. J., D. S. Tarbell, and W. H. Saunders, J. Am. Chem. Soc., 84, 4113 (1962); Tarbell, D. S., and T. Parasaran, J. Org. Chem., 29, 2471 (1964), for example.

² Michejda, C. J., and D. S. Tarbell, J. Org. Chem., 29, 1168 (1964).

³ D. L. Griffith and M. Stiles (J. Am. Chem. Soc., 87, 3710 (1965)) have reported an excellent study on p-nitrobenzylcarbonic dibenzylphosphoric anhydride.

⁴ Bellamy, L. J., and L. Beecher, J. Chem. Soc., 475 (1952).

⁵ We are indebted to Professor L. D. Colebrook for the NMR spectra.

⁶ Axtmann, R. C., W. E. Shuler, and J. H. Eberly, J. Chem. Phys., 31, 850 (1959).

⁷ Choppin, A. R., and J. W. Rogers, J. Am. Chem. Soc., 70, 2967 (1948).

⁸ Carpino, L. A., J. Am. Chem. Soc., 79, 98 (1957).

⁹ Anderson, G. W., and A. C. McGregor, J. Am. Chem. Soc., 79, 6180 (1957).

¹⁰ For a recent example, see Marglin, A., and R. B. Merrifield, J. Am. Chem. Soc., 88, 5051 (1966).

¹¹ Obtained from the Stauffer Chemical Co.