THE N-tert-BUTOXYCARBONYLATION OF AMINO ACIDS BY tert-BUTYL DINITROPHENYL CARBONATE

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The introduction of alkoxycarbonyl protective groupings into amino acids with the aid of alkyl aryl carbonates is widely used in synthetic practice [1-8]. Carbonates are more stable and accessible than alkoxycarbonyl azides. The difficulties that arise in a number of cases in the separation of the N-protected amino acids and phenols can be avoided by condensing the components into activated aryl esters [2, 3].

We have investigated the possibility of using as N-tert-butoxycarbonylating reagent tert-butyl 2,4-dinitrophenyl carbonate (BOC-ODNP), a method for synthesizing which we have proposed previously [9]. It has been found that in the reaction of BOC-ODNP with salts of amino acids, in addition to the BOC-amino acids and 2,4-dinitrophenol, two other substances are produced in the form of slight impurities which can be detected chromatographically (Silufol, UF-254). One of them forms on a plate a yellow spot the R_f value of which coincides with a standard sample of the 2,4-dinitrophenyl derivative of the corresponding amino acid. The second substance, distinguished by a higher chromatographic mobility and colored on plates by ninhydrin at 120° C is apparently the tert-butyl ester of the BOC-amino acid. However, both impurities are readily eliminated in the working up of the reaction mixture, after which the mixture of BOC-amino acid and 2,4-dinitrophenol is separated on a column of silica gel or is converted into the 2,4-dinitrophenyl esters.

Crystalline BOC-ODNP (11-12 mmole) was added to a solution of 10 mmole of an amino acid and 1.5 g of K_2CO_3 in 20 ml of aqueous dimethylformamide (1 : 1), and the mixture was stirred at 45-50° C for 2 h. Then it was diluted with 20 ml of water and extracted with benzene (20 ml), acidified with citric acid, saturated with NaCl, and extracted with benzene again (30 + 2 × 15 ml). The extract was dried with $MgSO_4$ and, to separate the contaminating DNP derivative of the amino acid, it was filtered through a layer (~2 g) of finely ground activated carbon. The carbon was washed with benzene (30 ml) and the filtrate was evaporated in vacuum to ~20 ml. To isolate the BOC-amino acid, the benzene solution was filtered through silica gel (7.5 × 2.5 cm) and the 2,4-dinitrophenol was eluted with benzene (~100 ml). The BOC-amino acid was eluted with chloroform–ethanol (9 : 1). The eluate was evaporated and the residue was crystallized from a mixture of CCl_4 and isooctane. By this method we have obtained BOC-Gly (yield 63%, mp 86-87° C), BOC-Ala (53%, mp 80-82° C), BOC-Leu (69%, mp 78-80° C from aqueous ethanol), BOC-Phe (65%, mp 82-84° C), and BOC-Trp (63%, mp 138-139° C).

In order to obtain the 2,4-dinitrophenyl esters of the BOC-amino acids, another 500 mg of 2,4-dinitrophenol and a solution of dicyclohexycarbodiimide (10 mmole) in methylene chloride were added to the benzene solution of the mixture of BOC-amino and 2,4-dinitrophenol after filtration through carbon and evaporation. After 6-10 h, the dicyclohexylurea was filtered off, the solution was evaporated in vacuum, the residue was dissolved in ethyl acetate (50 ml), and the solution was washed with 5% $NaHCO_3$ solution (2 × 20 ml), water, 10% citric acid solution, water again, and brine, and was dried with $MgSO_4$. The ethyl acetate was evaporated in vacuum, the residue was crystallized, and for analysis it was recyrstallized. In this way BOC-Ala-ODNP was obtained (yield 66.0%, mp 109-110° C, CCl_4–hexane). After recrystallization from the same mixture of solvents, mp 109-110° C. BOC-Gly-ODNP (64%, 84-86° C, ether–heptane). BOC-Phe-ODNP (69%, mp 85-86° C from cyclohexane). The results of elementary analysis for C, H, and N corresponded to the calculated figures. The esters of BOC-Leu and BOC-Pro were obtained in the form of noncrystallizing oils.

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LITERATURE CITED

1. G. W. Anderson and A. McGregor, J. Amer. Chem. Soc., 79, 6180 (1957).
2. W. Broadbent, J. S. Morley, and B. E. Stone, J. Chem. Soc., C, 2632 (1967).
3. J. Wolman, D. Ladkany, and M. Frankel, J. Chem. Soc., C, 689 (1967).
4. B. Rzeszotarska and S. Wiejak, Ang. Chem., 80, 364 (1968).
5. E. Klieger, Ann. Chem., 724, 204 (1969).
6. Yajima Ha i ki, Tamura Fusako, and Kiso Yoshiaki, Chem. Pharm. Bull., 18, 2574 (1971).
7. C. Bir, W. Lochinger, G. Stahnke, and P. Lang, Ann. Chem., 763, 163 (1972).
8. U. Ragnarsson, S. M. Karlsson, and B. E. Sandberg, Acta Chem. Scand., 26, 2550 (1972).
9. V. F. Pozdnev, Zh. Organ. Khim., 10, 1753 (1974).