tert-BUTOXYCARBONYLATION OF TYROSINE AND OTHER PHENOLIC AMINO ACIDS WITH DI-tert-BUTYL PYROCARBONATE

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UDC 547.466.493

Di-tert-butyl pyrocarbonate is a highly reactive N-tert-butoxycarbonylating reagent and has found wide use for obtaining N-tert-butoxycarbonyl (Boc) derivatives of compounds of various classes [1-7]. It is also known that tert-alkyl pyrocarbonates react fairly readily with phenols in the presence of bases [8-10]. It is therefore impossible by the usual method of tert-butoxycarbonylating amino acids with the aid of Boc_2O to obtain N-Boc-tyrosine without N,O-di-Boc-tyrosine as an impurity [1]. The attempts made in recent years to avoid the formation of di-Boc-tyrosine in the preparation of N-Boc-tyrosine by selecting appropriate reaction conditions have not given satisfactory results, although di-tert-amyl- and di-1-methyl-1-benzylethyl pyrocarbonates, [11] and [12], respectively, react with tyrosine to form N-protected derivatives with no contamination by N,O-diacyl products. As the result of investigations of the reaction of Boc_2O with tyrosine it has been found that under the action of approximately three equivalents of Boc_2O at pH 11-12, tyrosine is converted quantitatively into N,O-di-Boc-tyrosine, which was first obtained by E. Schnabel et al. [13] by the treatment of tyrosine with Boc fluoride. However, in contrast to the reaction conditions used by Schnabel et al. [13], the acylation of tyrosine with Boc_2O can be carried out at room temperature (20-25°). With vigorous stirring and maintenance of a pH of ~12, the exhaustive conversion of tyrosine into di-Boc-tyrosine requires about 2 hours. The isolation of the di-Boc-tyrosine was carried out by the methods usual in such cases of extraction and crystallization from petroleum ether. The crystalline product was obtained in almost quantitative yield, and its melting point was higher than that of a recrystallized analytical sample of di-Boc-tyrosine obtained by using Boc fluoride [13].

Under similar conditions (but in an atmosphere of nitrogen), using Boc_2O we have also obtained N,O-di-Boc-5-hydroxytryptophan and N,O,O'-tri-Boc-3,4-dihydroxyphenylalanine. In the presence of potassium carbonate, 3-nitrotyrosine reacts with Boc_2O with the formation of the N-Boc derivative exclusively.

N,O-Di-Boc-L-tyrosine. A solution of 27 mmole of Boc_2O in 15 ml of isopropanol was added to a suspension of 10 mmole of L-tyrosine in 25 ml of water and then, with vigorous stirring, an 8 M solution of KOH was added dropwise to pH 12. The reaction mixture was stirred at room temperature with the pH being kept at 11.5-12 until the spot of N-Boc-L-tyrosine on TLC [Silufol plates, benzene–acetone–glacial acetic acid (100:50:1)] had disappeared. Then the reaction mixture was diluted with water (approximately 75 ml) and extracted with ether, the extract was washed with 10 ml of 1 M sodium hydroxide solution, and the combined aqueous solutions were acidified to pH 2.5-3 and extracted with ethyl acetate (30 + 2 × 15 ml). The extract was washed with water, dried with Na_2SO_4, and evaporated in vacuum. The residue was triturated with several portions of petroleum ether and was left to complete crystallization under petroleum ether. The crystalline mass was filtered off washed with hexane, and dried in vacuum to give 3.6-2.8 g (94-99%) of N,O-di-Boc-L-tyrosine with mp 95-97°C, $[\alpha]_D^{20}$ +29.3° (c 1, dioxane) [13].

N,O-Di-Boc-DL-5-hydroxytryptophan. In an atmosphere of nitrogen, an 8 M solution of KOH was added to a suspension of 1 mmole of DL-5-hydroxytryptophan and 0.7 ml of Boc_2O in 6 ml of water and 4 ml of isopropanol to a pH of 12, and the mixture was stirred at this pH for 3-4 h (checked by TLC). Then the reaction mixture was worked up as in the preparation of di-Boc-tyrosine, and after the evaporation of the extract the resinous residue was dissolved in 5 ml of ether. To this solution was added 0.2 ml of dicyclohexylamine, and after an hour the mixture was diluted with hexane and the precipitate was filtered off, washed with hexane, and dried to give 0.58 g (96%) of the dicyclohexylammonium salt of N,O-di-Boc-DL-5-hydroxytryptophan with mp 154-155°C. $C_{35}H_{51}N_3O_7$.

Institute of Biological and Medicinal Chemistry, Academy of Medical Sciences of the USSR, Moscow. Translated from Khimiya Prirodnykh Soedinenii, No. 1, pp. 129-130, January-February, 1982. Original article submitted July 30, 1981.

0009-3130/82/1801-0125$07.50

N,O,O'-Tri-Boc-3,4-dihydroxyphenylalanine. In an atmosphere of nitrogen, a solution of KOH was added dropwise with stirring to a mixture of 5 mmole of DL-3,4-dihydroxyphenylalanine and 20 mmole of Boc_2O in 10 ml of water and 10 ml of isopropanol to a pH of 12, and stirring was carried out until the initial substances and the intermediate products had been completely converted into the tri-Boc derivative, with monitoring by TLC, the pH being kept at 11-12 with the addition of caustic soda. After a working up of the reaction mixture as in the preparation of di-Boc-tyrosine, a resinous chromatographically homogeneous product was obtained which, after trituration with several portions of petroleum ether was converted into a solid free-flowing powder having, after drying in vacuum, mp 64-66°C. $C_{24}H_{35}NO_{10}$. In another experiment, the residue after the evaporation of the extract was dissolved in ether (20 ml), 1 ml of dicyclohexylamine was added, and, after the crystalline mass had been diluted with petroleum ether, the solid matter was filtered off, washed with a mixture of ether and petroleum ether, and dried to give 2.8 g (97%) of the dicyclohexylammonium salt of N,O,O'-tri-Boc-DL-3,4-dihydroxyphenylalanine with mp 166-167°C. $C_{36}H_{58}N_2O_{10}$. The dicyclohexylammonium salt of N,O,O'-tri-Boc-L-3,4-dihydroxyphenylalanine was obtained similarly, with mp 141-143°C. $[\alpha]_D^{20}$ +27.6° (c 1; DMFA). $C_{36}H_{58}N_2O_{10}$.

N^α-Boc-L-3-Nitrotyrosine. A solution of 2.3 g of L-3-nitrotyrosine and 3 g of K_2CO_3 in 20 ml of water and 10 ml of isopropanol was treated with 3 ml of Boc_2O, and the mixture was stirred at ~20°C for 3 h. Then it was diluted with water to 80 ml, extracted with petroleum ether, acidified with 1 N H_2SO_4, and extracted with ethyl acetate. The extract was washed with water, dried, and evaporated in vacuum. The crystalline residue was recrystallized from a mixture of carbon tetrachloride and heptane. This gave 3.2 g (91%) of N^α-Boc-L-3-nitrotyrosine with mp 144-145°C, $[\alpha]_D^{20}$ +25.6° (c 1; CH_3OH).

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