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A NEW TERT-BUTYLOXYCARBONYLATING REAGENT, 2-TERT-BUTYLOXYCARBONYLOXYIMINO-2-PHENYLACETONITRILE.

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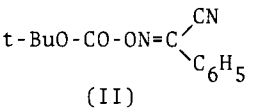
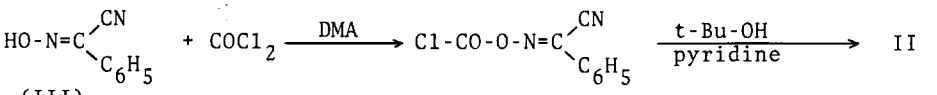
The tert-butyloxycarbonyl (Boc) group is one of the most important amino-protecting groups in peptide synthesis, and there are so many methods and reagents proposed for its introduction because the most widely utilized reagent, tert-butyl azidoformate (I), has several disadvantages[1,2].

Now the present authors wish to propose a new promising reagent, 2-tert-butyloxycarbonyloxyimino-2-phenylacetonitrile (II), which is easy to prepare, stable but highly reactive crystals, and affords contaminant-free Boc-amino acids in high yield by conventional procedure.

In course of studies on the application of N-hydroxy compounds to peptide synthesis, it was noticed that some oximes are suitable as an activator and carrier of Boc group. From the attempts to screen a most prominent one, finally chosen was 2-hydroxyimino-2-phenylacetonitrile (III)[3] which was prepared in 80% yield by introducing methyl nitrite into a solution of benzyl cyanide and sodium hydroxide in methanol.



(II)

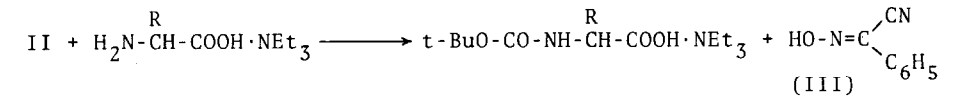


(III)

The preparation of II from III is exemplified as follows: To a solution of phosgene (9.9 g, o.1 M) or an equivalent of trichloromethyl chloroformate in benzene (60 ml) was added dropwise a solution of III (14.6 g, 0.1 M), N,N-dimethylaniline (12.0 g) and dioxane (5 ml) in benzene (100 ml) at 3-5°C. The mixture was stirred for 1 hour at the same temperature, allowed to stand overnight, and added a solution of tert-butanol (14.8 g) and pyridine (16.0 ml) in benzene (30 ml) at 5-10°C. The mixture was allowed to react at room temperature for 1 hour, at 35°C for 3 hours and to stand overnight at room temperature, and then was worked up by following usual manner. Evaporation of benzene and subsequent trituration of the residue with 90% aqueous methanol gave crude product of mp 84-86°C. Recrystallization from methanol gave 13.9 g

of pure II; mp 84-86°C. IR (nujol) cm^{-1}; 1785. NMR ($CDCl_3$)δ; 1.62 (9H, s), 7.2-8.2 (5H, m). Calcd for $C_{13}H_{14}O_3N_2$; C, 63.40; H, 5.73; N, 11.38. Found; C, 63.69; H, 5.71; N, 11. 20.

tert-Butyloxycarbonylation of amino acids was carried out by using 10% excess of II and 50% excess of triethylamine in 50% aqueous dioxane or aqueous acetone. The reaction was usually brought to completion within 4-5 hours at room temperature or within 1 hour at 45°C. By-product III was



easily and completely removed from the reaction mixture by extraction with ether, benzene or ethyl acetate.

In comparison with I and a leading ready-for-use type reagent, 2-tert-butyloxycarbonylthio-4,6-dimethylpyrimidine (IV)[1], II showed much higher reactivity than the others. When IV required, for example, more than 20 hours for the completion of a Boc-introducing reaction at room temperature, II completed it within 2 hours under the same conditions. A typical procedure is as follows: To a solution of glycine (0.75 g, 10 mM), triethylamine (2.10 ml, 15 mM) in 50% aqueous dioxane (12 ml) was added II (2.71 g, 11 mM) with stirring at room temperature. After stirring for 2 hours, water (15 ml) and ethyl acetate (20 ml) was added to the mixture. Aqueous phase was washed with ethyl acetate (20 ml), and worked up following usual manner to give 1.52 g (86.9%) of Boc-glycine; mp 86.5-87.5°C (Lit.[1]: mp 86-88°C).

To secure high purity and high yield of the products, the authors recommend to distil off dioxane or acetone before the extraction of III from the reaction mixture, though direct extraction of III may not cause problems in most of cases

Other Boc-amino acids prepared by this method are N^{α}-Boc-N^{ε}-benzyloxycarbonyl-L-lysine (oil, 92%), N^{α}-Boc-N^{G}-nitro-L-arginine (mp 123-5°C, 80.0%), N-Boc-L-proline (mp 133-4°C, 87.8%), N-Boc-L-methionine dicyclohexylamine salt (mp 137-9°C, 82.1%) and N-Boc-L-asparagine (mp 167-8°C (decomp), 79.0%).

This concept was also applicable to the preparation of p-methoxybenzyloxycarbonylamino acids in good yield.

References

1. T. Nagasawa, K. Kuroiwa, K. Narita, and Y. Isowa, Bull. Chem. Soc. Japan, 46, 1269 (1973).
2. G. Bram, Tetrahedron Lett., 469 (1973).
3. A. Meyer, Chem. Ber., 21, 1314 (1888).