CHEMISTRY LETTERS, pp. 237-238, 1984.

# t-BUTYL 2-PYRIDYL CARBONATE. A USEFUL REAGENT FOR t-BUTOXYCARBONYLATION OF AMINO ACIDS

Sunggak KIM* and Jae In LEE

Department of Chemistry, Korea Advanced Institute of Science and Technology, Seoul 131, Korea

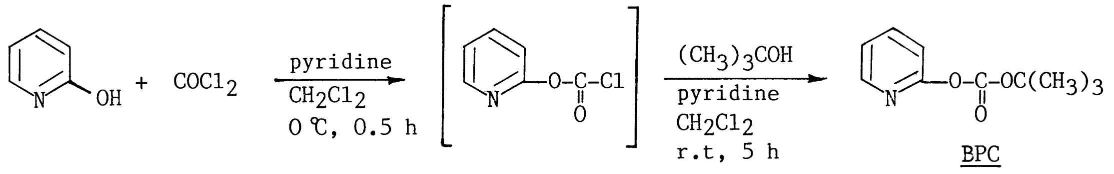
t-Butyl 2-pyridyl carbonate, a stable crystalline compound, is found to be very effective in the t-butoxycarbonylation of amino acids.

The t-butoxycarbonyl (Boc) group is one of the most important amino protective groups along with benzyloxycarbonyl (Cbz) group because N-Boc amino acids are resistant to racemization during peptide syntheses and the t-butoxycarbonyl group is cleanly cleaved by cold trifluoroacetic acid, hot formic acid, or hydrochloric acid.1) Since t-butyl chloroformate is only fairly stable above -30 °C, considerable efforts have been devoted to the development of a variety of useful and reliable reagents for the introduction of the t-butoxycarbonyl group during last 30 years.1,2)

In the course of studies on the synthetic utility of 2-pyridyl esters,3) we have found that t-butyl 2-pyridyl carbonate (BPC) is very effective in the t-butoxycarbonylation of amino acids (Eq. 1). BPC was conveniently prepared by the reaction of 2-pyridyl chloroformate, generated from phosgene and 2-hydroxypyridine in the presence of pyridine, with equimolar amounts of t-butanol and pyridine in methylene chloride and was obtained in 70% yield as colourless crystals (Eq. 2). BPC was a stable compound and could be stored at room temperature for one month without any decompositions.4)

Reaction of amino acids with BPC was examined and BPC was found to be very reactive toward amino acids. Among the solvents employed, aqueous dimethylformamide gave the best results in terms of the rapidity and the yield of the reaction and is generally recommended. For instance,

$$H_2N\text{-CHR-COOH} + \text{BPC} \xrightarrow{Et_3N} \xrightarrow{H^+} \text{Boc-HN-CHR-COOH} + \text{HO-2-Py} \qquad (1)$$



(2)

Table 1. Preparation of N-Boc Amino Acids in Aqueous DMF at Room Temperature

| Amino acid | Time/h | Yield/% | Amino acid | Time/h | Yield/% |
|---|---|---|---|---|---|
| Leu | 4 | 99 | Thr | 8 | 98 |
| Pro | 6 | 96 | Met | 7 | 96 |
| Phe | 12 | 96 | Try | 4 | 98 |
| Tyr | 6 | 88 | CyS | 10 | 85 |
| Ser | 7 | 95 | CyS.SCy | 8 | 87 |

t-butoxycarbonylation of L-leucine in aqueous dimethylformamide was complete within 4 h at room temperature, whereas the reaction in aqueous dioxane required 16 h. Thus, the reactions were carried out with an equimolar mixture of an amino acid and BPC in the presence of triethylamine in aqueous dimethylformamide at room temperature. As shown in Table 1, the t-butoxycarbonylation of amino acids was normally complete within 12 h at room temperature and the corresponding N-Boc amino acids were obtained in high yields. The identities of N-Boc amino acids were confirmed by comparison of mp, NMR, and IR data and $[\alpha]_D$ values with reported data.

The following procedure is representative for the preparation of N-Boc amino acids. A solution of L-proline (2 mmol), BPC (2 mmol), and $Et_3N$ (3 mmol) in 50% aqueous DMF (8 ml) was stirred at room temperature for 6 h. The reaction mixture was acidified with oxalic acid, extracted with methylene chloride, and evaporated to afford Boc-proline (96%). Mp 133-135 °C, $[\alpha]_D^{20}$ -60.7° (c 1.0, AcOH) (lit,[2b]) mp 136-137 °C, $[\alpha]_D^{25}$ -60.57° (c 0.97, AcOH).

In conclusion, BPC should be valuable for the t-butoxycarbonylation of amino acids and offers the advantages of the easy prepration and the stability of BPC, the high-yield and the mildness of the reaction, and simple workup for the isolation of the product.

We are very grateful to the Korea Advanced Institute of Science and Technology for financial support.

## References

1) J.F.W. McOmie, " Protective Groups in Organic Chemistry," Plenum Press, London (1973); T.W. Greene, " Protective Groups in Organic Synthesis," Wiley, New York (1981); E. Gross and J. Meienhofer, " The Peptides," Academic Press, New York (1981), Vol.3.

2) For recently developed reagents, see: a) T. Kunieda, T. Higuchi, Y. Abe, and M. Hirobe, Tetrahedron Lett., 1980, 3065 ; b) Y. Kita, J. Haruta, H. Yasuda, K. Fukunaga, Y. Shirouchi, and Y. Tamura, J. Org. Chem., 47, 2697 (1982); c) R.B. Harris and I.B. Wilson, Tetrahedron Lett., 1983, 231 ; d) S. Kim and H. Chang, J. Chem. Soc., Chem. Commun., in press (1983).

3) S. Kim and J.I. Lee, J. Org. Chem., 48, 2608 (1983); S. Kim and J.I. Lee, ibid., in press (1984).

4) Mp 48-49 °C; NMR ($CDCl_3$) $\delta$ 1.60 (9H, s), 7.00-7.39 (2H, m), 7.62-7.97 (1H, m), 8.30-8.50 (1H, m); IR (KBr) 1755 $cm^{-1}$. Calcd for $C_{10}H_{13}O_3N$: C, 61.53; H, 6.71; N, 7.17%. Found: C, 62.03; H, 6.86; N, 6.98%.

(Received November 18, 1983)