[Chem. Pharm. Bull. 18(1) 217—218 (1970)] UDC 547.298.61.07

A Convenient Preparation of *tert*-Butyl Carbazate

Masayoshi Muraki and Tomishige Mizoguchi

Organic Chemistry Research Laboratories, Tanabe Seiyaku Co., Ltd.[1]

(Received August 20, 1969)

A variety of methods has been reported[2-7] for synthesis of *tert*-butyl carbazate (II), the precursor of *tert*-butyloxycarbonyl azide which is one of the most important protecting reagents of amino acids in peptide chemistry.

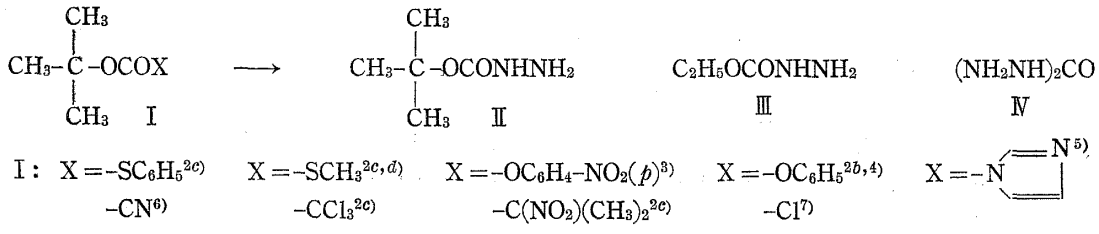

Chart 1

Because most of these methods require a large amount of poisonous gas, such as phosgene or carbonoxysulfide, or considerably low reaction temperature to avoid decomposition of the intermediates, other more convenient routes are desired.

Hydrazinolysis of *tert*-butyl ethylcarbonate (I: X=OC_2H_5)[2c] in five- to tenfold excess of hot hydrazine hydrate was found to give the carbazate (II) in a moderate yield. This reaction had formerly been reported to be unsuccessful.[2c]

In the earlier stage of the hydrazinolysis the product (II) was accompanied with ethyl carbazate (III), but the latter diminished with increase of reaction time, being converted to carbohydrazide (IV), and after heating for about ten hours, the desired *tert*-butyl derivative (II) was ultimately isolated as a single product. Although the carbazate (II) also reacts further with hydrazine,[8] difference between the stabilities of these two carbazates toward hydrazine is fairly enough to allow the isolation of the more stable compound (II).

The overall yield is somewhat low, but use of any dangerous gas, or special reaction condition or technique can be avoided in this preparative method.

1) Location: *2-2-50, Kawagishi, Toda-shi, Saitama.*
2) *a)* L.A. Carpino, *J. Org. Chem.*, **28**, 1909 (1963); *b)* L.A. Carpino, B.A. Carpino, C.A. Giza, R.W. Murray, A.A. Santilli and P.H. Terry, "Organic Syntheses," Vol. 44, ed. by John Wiley and Sons, Inc., New York, N.Y., 1964, p. 22; *c)* L.A. Carpino, *J. Am. Chem. Soc.*, **82**, 2725 (1960); *d)* L.A. Carpino, D. Collins, S. Göwecke, J. Mayo, S.D. Thatte and F. Tibbetts, "Organic Syntheses," Vol. 44, ed. by John Wiley and Sons, Inc., New York, N.Y., 1964, p. 20.
3) F. Eloy and C. Moussebois, *Bull. Soc. Chim. Belges*, **68**, 409 (1959) [*C.A.*, **54**, 3179*f* (1960)]; T. Inoue, M. Kanayama and H. Otsuka, *Nippon Kagaku Zasshi*, **85**, 599 (1964).
4) L.A. Carpino, *J. Am. Chem. Soc.*, **79**, 98 (1957); *idem, ibid.*, **79**, 4427 (1957).
5) W. Klee and M. Brenner, *Helv. Chim. Acta*, **44**, 2151 (1961).
6) M. Leplawy and W. Stec, *Bull. Acad. Poln. Sci. Ser. Sci. Chem.*, **12**, 21 (1964) [*C.A.*, **61**, 1933*g* (1964)].
7) Yu.A. Ovchinnikov, A.A. Kiryushkin and A.I. Miroshnikov, *Experientia*, **21**, 418 (1965); S. Sakakibara, I. Honda, K. Takada, M. Miyoshi, T. Onishi and K. Okumura, Presented at the 21th Meeting of Chemical Society of Japan, Osaka, Apr. 1968.
8) When a mixture of *tert*-butyl carbazate (II) and threefold excess of 100% hydrazine hydrate was refluxed for three hours, there was obtained carbohydrazide (IV) in 12.5% yield with 80% recovery of the starting carbazate.

Experimental

***tert*-Butyl Ethylcarbonate (I: $X=OC_2H_5$)**[2c]——A mixture of 69 g of powdered sodium and 1140 ml (12 moles) of *tert*-butanol was refluxed gently overnight to give a solution of sodium *tert*-butoxide in *tert*-butanol, to which was added slowly 325 g (3. 0 moles) of ethyl chloroformate in 285 ml (3.0 moles) of *tert*-butanol at 24—28° under cooling and vigorous stirring. The addition required about 2 hr, then stirring was continued for another 2 hr at room temperature. The resultant mixture was washed once with 600 ml of water, the separated aqueous layer was extracted with ether and the combined butanolic and ethereal solutions were dried and concentrated through a Widmer column at 130°(bath temperature). The remaining oil was distilled to give 297 g (65%) of I ($X=OC_2H_5$), bp 138—142° (lit.[2c] 140—142°).

***tert*-Butyl Carbazate (II)**——A mixture of 292 g (2.0 moles) of the foregoing carbonate (I) and 500 g (10 moles) of 100% hydrazine hydrate was refluxed for 13 hr under stirring. After cool, the mixture was diluted with 1 liter of water, saturated with sodium chloride and extracted repeatedly with ether. The combined extracts were washed with saturated sodium chloride solution, dried and evaporated to leave 124 g (47%) of crude II, mp 34—38°. Distillation afforded 114 g (43%) of a pure product of II, bp 70.5—72° (3.5 mmHg) and mp 38—40°, which was identified with authentic *tert*-butyl carbazate (mp 41—42°) by mixed melting test and IR spectra.

Occurence of Ethyl Carbazate (III) and Carbohydrazide (IV) as Byproducts——A mixture of 2.92 g (0.02 mole) of *tert*-butyl ethyl carbonate and 5.01 g (0.1 mole) of 100% hydrazine hydrate was heated as described above except that heating was discontinued after 3 hr. The mixture was then extracted with ether for 12 hr by a continuous extractor.

An oily residue from the ethereal extract was purified by silicic acid (Mallinckrodt, 100 mesh) chromatography using ether as an eluent, affording 0.88 g (45.6%) of *tert*-butyl carbazate (II) and 0.14 g (6.7%) of ethyl carbazate (III).[9] Each compound was identified with a respective authentic sample by IR analysis. The aqueous layer was evaporated to dryness *in vacuo* and dried to give 0.67 g (37%) of carbohydrazide (IV), mp 148—152° (decomp.) (lit.[10] mp 153—154° (decomp.)). Dibenzal derivative: mp 195—198° (lit.[10] mp 198°).

Acknowledgement The authors are grateful to Emeritus Professor S. Sugasawa, University of Tokyo for his guidance and to Mr. M. Yamazaki, Director of these laboratories for his interest throughout this work. Thanks are also due to Mr. N. Hoshino for IR data.

9) R. Stolle and A. Benrath, *J. Parkt. Chem.*, **70**, [2] 263 (1904).
10) E.B. Mohr, J.J. Brezinski and L.F. Audtieth, "Inorganic Syntheses," Vol. 4, ed. by McGraw-Hill Book Co., Inc., New York., N.Y., 1953, p. 32.