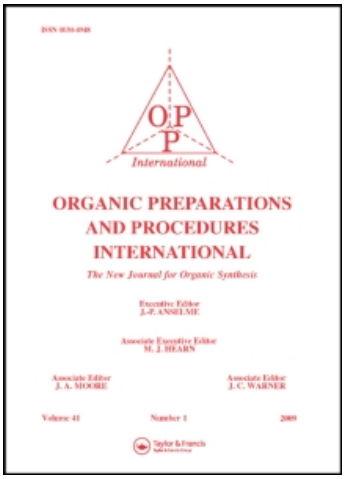

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A CONVENIENT SYNTHESIS OF *t*-BUTYL N-(2-BROMOETHYL)CARBAMATE

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8. A steady pH of 11 indicates completion of the neutralization and readiness for alkylation which is best performed at pH 11-12.
9. This packing was purchased as tubular cartridges from Metex Corporation, 970 New Durham Road, Edison, NJ 08817. Other packing materials such as glass beads or porcelain berl saddles should also be effective.

A CONVENIENT SYNTHESIS OF t-BUTYL N-(2-BROMOETHYL)CARBAMATE

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(05/29/86)

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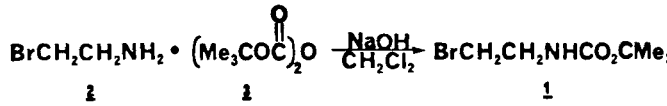
While evaluating various β-aminoethylating agents, we focused on t-butyl N-(2-bromoethyl)carbamate (1) since the protecting t-carbobutoxy (BOC) group can be removed under mild conditions. This reagent has been used in the synthesis of modified peptides as a "reduced" glycine analogue.[1] Unfortunately, we could not find a convenient literature method which could be used on a preparative scale or a complete description of its physical and analytical characteristics. The compound is reported[2] to have been prepared

from t-butyl azidoformate and 2-bromoethanamine hydrochloride in the presence of triethylamine in 66% yield and used without purification. Attempted distillation under vacuum led to largely decomposition.[3] This note describes a convenient method for the preparation of 1 which utilizes a two-phase reaction mixture (dichloromethane–water).



$$\underset{2}{BrCH_2CH_2NH_2} \cdot \underset{3}{(Me_3COC(=O))_2O} \xrightarrow[CH_2Cl_2]{NaOH} \underset{1}{BrCH_2CH_2NHCO_2CMe_3}$$

During the study of different stoichiometric ratios of 2 and di-t-butyl dicarbonate (3), it was found that the product was usually contaminated with 3, which is very difficult to remove from 1 because of their similar physical properties (mp., solubility, etc.). In order to avoid this problem and to completely consume the more expensive 3, a two-fold excess of 2 was used. The excess of 2-bromoethanamine was easily separated from the organic phase by washing with dilute hydrochloric acid. This procedure afforded the product 1 (99% pure by GC) in 71% yield after recrystallization from hexane; this method is recommended for large scale preparations.

EXPERIMENTAL SECTION

t-Butyl N-(2-bromoethyl)carbamate.- A two-phase mixture of 2-bromoethanamine hydrobromide (68.3 g, 0.333 mol) in 250 ml of water and di-t-butyl dicarbonate (36.4 g, 0.167 mol) in 600 ml of dichloromethane was vigorously stirred with a mechanical stirrer in a 3 l., three-necked flask. A solution of NaOH (26.7 g, 0.667 mol) was added dropwise to the stirred reaction mixture over 40 min. The mixture was stirred at room temperature for an additional 2.5 hrs after which time TLC (SiO_2, CH_2Cl_2, I_2) showed absence of 3. The layers were separated and the organic layer was washed with water, 0.2 N HCl (to pH 1), again with water (to pH 6-7) and then dried over $MgSO_4$. Removal of the solvent on a rotary evaporator provided 36.4 g of an oily residue which crystallized on cooling (5°). The solid was dissolved in 100

ml of hexane. The warm solution (30-35°) was cooled down to -25° for 15 min. to start precipitation and then was left overnight at -15°. The white crystalline solid was collected, washed on the filter with small portions of cold hexane, dried in vacuum (0.3 mm) at room temperature to furnish 26.6 g (71%) of 1, mp. 33-35°.

IR(KBr): 3350, 1689 cm^{-1}; ^{1}H-NMR($CDCl_3$,200 MHz): δ 1.45 (s, 9H, CH_3), 1.68 (small s, traces of 3), 3.57-3.45 (m, 4H, CH_2), 4.95 (broad s, 1H, NH). MS: m/z 226 (22.6%), 224 (22.4%), 170 (82.5%); 168 (68%), 57 (100%).

GC, (Shimadzu, MINI-3,OV-101): 98.6%; (Varian-6500, DB-1): 100%.

Anal. Calcd for $C_7H_{14}BrNO$: C, 37.54; H, 6.30; N, 6.25; Br, 35.65

Found: C, 37.34; H, 6.12; N, 6.11; Br, 35.44

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CHLORINATION OF PYRIDAZINONES WITH CHLOROCARBONYL ISOCYANATE

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Chlorocarbonyl isocyanate (CCI), a versatile reactive isocyanate with two functional groups has been extensively employed for the synthesis of a wide variety of heterocyclic systems.[1] In view of our earlier observation that chlorosulfonyl isocyanate (CSI) acts as a chlorinating agent with