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Mono-(BOC)-Protected Diamines. Synthesis of tert-Butyl-N-alkyl-N-(2-aminoethyl)carbamates and tert-Butyl-N-[2-(alkylamino)ethyl] Carbamates

A. P. Krapcho [a], Martin J. Maresch [a] & James Lunn [a]
[a] Department of Chemistry, The University of Vermont, Burlington, Vermont, 05450
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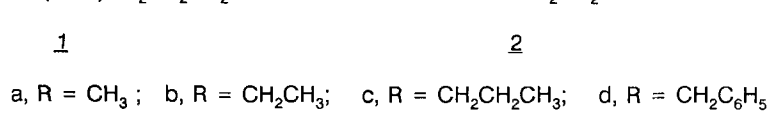
MONO-(BOC)-PROTECTED DIAMINES. SYNTHESIS OF tert-BUTYL-N-ALKYL-N-(2-AMINOETHYL)CARBAMATES AND tert-BUTYL-N-[2-(ALKYLAMINO)ETHYL] CARBAMATES

A. Paul Krapcho*, Martin J. Maresch and James Lunn

Department of Chemistry, The University of Vermont
Burlington, Vermont 05450

Abstract We wish to report preparative pathways to the mono-(BOC)-protected diamines 1a-d and 2a-c.

The tert-butoxycarbonyl (BOC) group is an important protective group for amines [1] which can readily be removed by anhydrous hydrogen chloride gas to yield the corresponding amine hydrochloride salts. During the course of another study, we had need for diamines with a free primary amino group and a BOC-protected secondary amino fuctionality such as 1 [2] and those with a free secondary amino group with a BOC-protected primary amino group such as 2. We wish to report synthetic strategies leading to analogues related to 1 and 2.



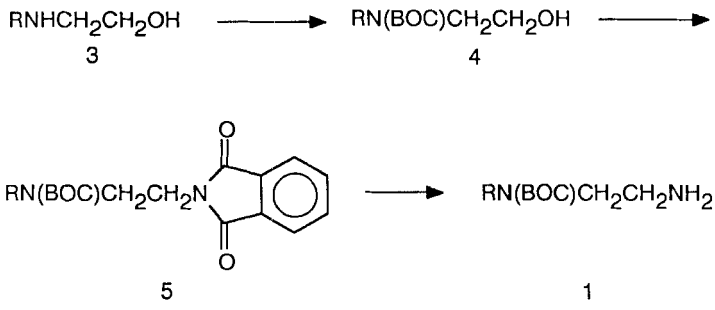
1 2

a, R = CH_3 ; b, R = CH_2CH_3; c, R = $CH_2CH_2CH_3$; d, R = $CH_2C_6H_5$

tert-Butyl-N-alkyl-N(2-aminoethyl)carbamates (1)

The syntheses of these N-(BOC) protected diamines 1a-d are outlined in Scheme I.

SCHEME I. Synthesis of N-alkyl-N-(BOC)-Protected Diamines 1



Treatment of N-alkylaminoethanols 3a-d with di-tert-butyl dicarbonate in dichloromethane as solvent led to excellent yields of the N-(BOC)-protected N-alkylamino ethanols 4a-d (86-96%) [3]. These analogues on treatment with phthalimide under Mitsunobu conditions [4,5] were converted into the phthalimido derivatives 5a-d in good yields (78-91%). The removal of the triphenylphosphine oxide and 1,2-dicarbethoxyhydrazine by-products was readily accomplished by silica gel chromatography of the crude reaction mixture. The conversion of the N-BOC-phthalimides to the desired N-(BOC)-diamines 1a-d (60-90%) was accomplished by treatment with aqueous hydrazine at room temperature. The crude products which were obtained were quite pure as shown by ^{1}H NMR analysis. The carbamates 1a and 1b could be distilled under vacuum while 1c and 1d undergo partial decomposition.

tert-Butyl N-[2-(alkylamino)ethyl] carbamates 2

It has previously been reported [6] that treatment of N-methylethylenediamine with di-tert-butyl dicarbonate (1/3 molar equivalent) led to 1a (12%) and 2a (38%) which were

separated by silica gel chromatography. Our examination of the crude reaction mixture from this procedure indicated a 1a:2a product ratio of 23:77 (THF) and 15:85 (dichloromethane). These values were obtained by ^{1}H NMR integration of the methyl proton singlets for 1a and 2a, respectively.

On the other hand, the diamines N-ethyl- and N-propylethylenediamine on treatment with di-tert-butyl dicarbonate led to 2b and 2c, respectively, as beautiful crystalline solids in good yields (60-62%). Presumably the regioselective increase in attack at the primary amino group in the ethyl and propyl analogues is steric in nature.

EXPERIMENTAL

The amines, reagents and solvents were obtained from the Aldrich Chemical Company. The ^{1}H NMR spectra were obtained on a Brucker WP270SY pulsed FT spectrometer, All ^{1}H NMR data are reported in δ units using TMS as an internal standard with deuterochloroform as solvent. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Satisfactory analytical data were obtained for all new compounds.

tert-butyl-N-methyl-(2-hydroxyethyl) carbamate(4a):

A solution of di-tert-butyl dicarbonate (15.2 g, 69.7 mmol) in dichloromethane (30 mL) was added dropwise over 1 h to a solution of N-methylaminoethanol (3a, 6.20 g, 82.7 mmol) in dichloromethane (30 mL) which was cooled in an ice bath. The mixture was allowed to stir at room temperature for 24 h and the solvent was removed by rotary evaporation. A saturated sodium chloride solution (20 mL) was added to the resultant oily material and the mixture was extracted with ethyl acetate (3 x 30 mL). The extracts were

TABLE I. Mono-BOC-amino alcohols 4a-d

4	% Yield	bp °C (mm)	^{1}H NMR
a	96	79-80 (0.30)	1.45 (s, 3H), 2.92 (s, 3H), 3.40 (t, 2H), 3.75 (t, 2H)
b	96	74-78 (0.25)	1.10 (t, 3H), 1.46 (s, 9H), 3.26 (q, 2H), 3.73 (t, 2H)
c	86	83-85 (0.25)	0.87 (t, 3H), 1.46 (s, 9H), 1.54 (q, 2H), 3.18 (t, 2H), 3.39 (t, 2H), 3.73 (t, 2H)
d	91	108-112 (0.25)	1.47 (s, 9H), 3.52 (m, 2H), 3.70 (m, 2H), 4.48 (s, 2H), 7.27-7.40 (m, 5H)

washed with a saturated sodium chloride solution, dried over magnesium sulfate and concentrated under vacuo. The viscous oil was distilled under reduced pressure to yield 4a (11.7 g, 96%).

Carbamates 4b-d were prepared according to the methodology utilized for 4a. The yields, boiling points and ^{1}H NMR data are tabulated in Table I.

tert-butyl-N-ethyl-(2-phthalimidoethyl) carbamate (5b)

A solution of diethyl azodicarboxylate (6.96 g, 0.04 mol) in THF (40 mL) was added dropwise to a stirred suspension of 4b (8.16 g, 0.04 mol), triphenylphosphine (10.48 g, 0.04 mol) and phthalimide (5.88 g, 0.04 mol) in THF (40 mL). The yellow solution was stirred for 14 h and the THF was removed by rotary evaporation. Ether (50 mL) was added and the insoluble by-products were removed by filtration (13.0 g). Purification was accomplished by partially dissolving crude 5b in ethyl acetate-hexane (10:90) followed by chromatography over silica gel (70-230 mesh) using this solvent mixture as eluant. The removal of the solvents led to 5b (11.14 g, 81%).

Phthalimides 5a, 5c and 5d were prepared as in the typical procedure for 5b. The yields, pertinent properties and ^{1}H NMR data are tabulated in Table II.

TABLE II. Phthalimides 5a-d

5	% Yield	mp, °C	^{1}H NMR
a	80	94-95	1.20 (s, 9H), 2.80 (s, 3H), 3.50 (m, 2H), 3.85 (m 2H), 7.70 (m, 2H), 7.85 (m, 2H)
b	81	50-52	1.03 (m, 3H), 1.22 (s, 9H), 3.25 (m, 2H), 3.42 (m, 2H), 3.78 (t, 2H), 7.65 (m, 2H), 7.80 (m, 2H)
c	91	62-64	0.87 (t, 3H), 1.31 (s, 9H), 1.54 (m, 2H), 3.18 (m, 2H), 3.52 (m, 2H), 3.87 (m, 2H), 7.69 (m, 2H), 7.83 (m, 2H)
d	78	111-113	1.29 (m, 9H), 3.50 (m, 2H), 3.83 (m, 2H), 4.45 (m, 2H), 7.16-7.26 (m, 5H), 7.69 (m, 2H), 7.82 (m, 2H)

tert-butyl-N-ethyl-N-(2-aminoethyl) carbamate (1b)

Hydrazine hydrate (55%; 0.74 g, 7.6 mmol) was added to a solution of 2b (2.0 g, 0.28 mmol) in ethanol (20 mL) at room temperature. After 0.5 h phthalhydrazide filled the flask. After stirring for 24 h, the mixture was added to a solution of sodium carbonate (10%, 30 mL) and the product was extracted into dichloromethane (3 x 20 mL). The combined extracts were dried over potassium carbonate and the solvent removed under reduced pressure. The resultant product (1.12 g, 94%) which was quite pure on ^{1}H NMR analysis was distilled rapidly under reduced pressure to yield 1b (0.83 g, 70%).

The carbamates 1a, 1c and 1d were prepared via similar procedures given for 1b. In some experiments the phthalhydrazide was removed by filtration of the crude reaction mixture followed by concentration and addition of chloroform. Refiltration followed by concentration of the chloroform led to high purity (BOC) analogues. The yields, physical properties and ^{1}H NMR data are presented in Table III.

TABLE III. Carbamates 1a-d

1	% Yield	bp °C (mm)	^{1}H NMR
a	70	40-41 (0.25)	1.22 (s, 2H), 1.46 (s, 9H), 2.82 (t, 2H), 2.88 (s, 3H), 3.27 (t, 2H)
b	72	47-48 (0.07)	1.09 (t, 3H), 1.27 (br, 2H), 1.45 (s, 9H), 2.80 (t, 2H), 3.22 (m, 4H)
c	75	-[a]	0.90 (t, 2H), 1.46 (s, 9H), 1.54 (q, 2H), 2.82 (t, 2H), 3.18 (m, 2H), 3.26 (m, 2H)
d	90	-[b]	1.34 (br s, 2H), 1.47 (s, 9H), 2.77 (m, 2H), 3.26 (m, 2H), 4.46 (s, 2H), 7.24-7.26 (m, 5H)

[a] Partial decomposition on attempted distillation.

[b] Crude viscous oil.

TABLE IV. Carbamates 2a-c

2	mp	^{1}H NMR
a	oil	methyl singlets at 2.87 (1a) and 2.42 (2a)
b	54-55	1.10 (t, 3H), 1.42 (s, 9H), 2.62 (m, 2H), 2.72 (t, 2H), 3.20 (m, 2H), 4.90 (br s, 1H)
c	35-36	0.90 (t, 3H), 1.42 (s, 9H), 1.52 (m, 2H), 2.55 (t, 2H), 2.71 (t, 2H), 3.20 (m, 2H), 4.90 (br s, 1H)

tert-butyl N-[2-(ethylamino)ethyl] carbamate (2b)

A solution of di-tert-butyl dicarbonate (3.27 g, 15 mmol) in THF (30 mL) was added dropwise over a 0.5 h period to a solution of N-ethylethylenediamine (4.41 g, 50 mmol) in THF (100 mL) which was cooled in an ice bath. After stirring at room temperature for

24 h, the mixture was concentrated by rotary evaporation. A saturated sodium chloride solution (30 mL) was added and the product was extracted into ethyl acetate (3 x 30 mL). The extracts were washed with a saturated sodium chloride solution (30 mL), dried over anhydrous sodium sulfate and concentrated to yield a yellowish oily material. Upon cooling in the freezer this material solidified (2.6 g). Recrystallization from pentane with cooling in the freezer led to beautiful crystals of 2b (1.8 g, 64%).

The preparation of carbamate 2c (62%) was performed in a similar fashion and the pertinent data for these compounds are tabulated in Table IV.

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