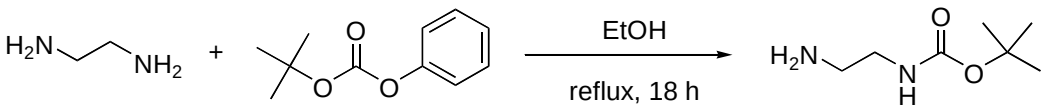
# MONO CARBAMATE PROTECTION OF ALIPHATIC DIAMINES USING ALKYL PHENYL CARBONATES

## [(2-Aminoethyl)carbamic acid *tert*-butyl ester]

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Checked by Cara Cesario and Marvin J. Miller.

## 1. Procedure

*(2-Aminoethyl)carbamic acid tert-butyl ester*. *tert*-Butyl phenyl carbonate (Note 1) (64.62 g, 61.6 mL, 0.33 mol) is added to a solution of 1,2-ethanediamine (Note 2) (20.0 g, 22.3 mL, 0.33 mol) in absolute EtOH (Note 3)(200 mL) in a 500-mL, single-necked, round-bottomed flask equipped with a stirring bar and a reflux condenser. The reaction mixture is heated gently to reflux overnight (18 h) (Note 4) ensuring that the temperature of the oil bath is at a maximum of 80 °C resulting in a yellow solution. The reaction mixture is cooled to room temperature and the solution concentrated to approximately 150 mL using a rotary evaporator (20 °C, 20 mmHg), which leaves a yellow solution. Water (300 mL) is added and the pH is adjusted to approximately 3 (Note 5) by careful addition of aqueous HCl (2M, approximately 110 mL) followed by extraction with $CH_2Cl_2$ (3 × 400 mL) (Note 6). The aqueous phase is adjusted to pH 12 by addition of aqueous NaOH (2M, 150 mL) and extracted with $CH_2Cl_2$ (5 × 500 mL). The combined organic extracts are dried ($Na_2SO_4$), filtered and concentrated using a rotary evaporator (20 °C, 20 mmHg) to afford 27.0 g (51%) of the title compound as a yellow oil (Notes 7, 8, 9, and 10).

## 2. Notes

1. *tert*-Butyl phenyl carbonate (98%) was purchased from Aldrich Chemical Company, Inc. and used as received. *tert*-Butyl phenyl carbonate


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is a low melting solid that should be stored in a refrigerator. It is convenient to allow it to melt before handling.

2. 1,2-Ethanediamine was purchased from Aldrich Chemical Company, Inc. (99%). Distillation before use is recommended if the compound has a deep yellow color. Otherwise it can be used as received.

3. Absolute Ethanol (99.9%) was purchased from De Danske Spritfabrikker and was used without further efforts to remove water. The checkers used 200 proof ethanol from Aaper Alcohol and Chemical Company; the solvent was used as received.

4. The Boc protection group is known to be thermally unstable and temperatures above 85–90 °C for prolonged periods should be avoided.[2]

5. The acid labile protective group should not be exposed to acidic aqueous media for prolonged periods of time, otherwise unwanted cleavage of the group may occur.

6. Thorough extraction was needed at this stage to remove unreacted alkyl phenyl carbonate and side products including the bis-carbonate-protected diamine and phenol. Also, it was important to conduct this extraction immediately after addition of 2M HCl, as the Boc group is known to be acid sensitive.

7. The product had the following physical data: $^{1}$H NMR (300 MHz, $CDCl_3$) δ: 1.23 (br s, 2 H, $NH_2$), 1.37 (s, 9 H, $(CH_3)_3$), 2.78 (t, 2 H, $J$ = 6.0 Hz), 3.09 (q, 2 H, $J$ = 6.0 Hz), 5.18 (br s, 1 H, NHCO); $^{13}$C NMR (125 MHz, $CDCl_3$) δ: 28.2, 41.7, 42.2, 78.9, 156.1. MS (FAB): $m/z$ 161 ($MH^+$). IR (film) 3350, 2977, 1693, 1524, 1391, 1366, 1252, 1172. Anal. Calcd for $C_7H_{16}N_2O_2$: C, 52.48; H, 10.07; N, 17.48. Found: C, 52.54; H, 9.83; N, 17.28.

8. The level of phenol in the product was below the level that could be detected by the human nose. No other products were detected by NMR and TLC (visualized either by UV light at 256 nm or 316 nm, by oxidation with $I_2$ or by ninhydrin test).

9. If long-term storage of the product is required, it should be stored under an inert atmosphere as it is prone to react with $CO_2$ from the air to produce a solid compound.

10. The checkers also performed the procedure on half-scale and obtained 14.4 g (54%) of the title compound as a yellow oil.

## Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

## 3. Discussion

A challenge often encountered in the synthesis, or in the synthetic use of polyamines, is selective protection of the amino groups. This synthetic challenge has been dealt with in a number of ways and elegant multi-step synthetic procedures have been developed to strategically incorporate protection groups in polyamines.[2-4]

The most widely used procedure for mono carbamate protection of aliphatic diamines is that of Krapcho and co-workers that uses an excess of diamine as compared to di-*tert*-butyl dicarbonate to achieve high yield with respect to the di-*tert*-butyl dicarbonate.[5,6] This procedure, however, is not attractive if the diamine is a valuable intermediate; in general, the use of a large excess of a reagent should be avoided if possible. Other reagents such as 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON)[7] and *O*-alkyl-*O'*-(*N*-succinimidyl) carbonates[8] have also been successful for similar transformations, but issues with strict temperature control and pH control complicates these procedures. The use of alkyl chloroformates has also been described, but these generally give statistical mixtures of products.

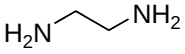
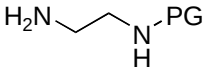
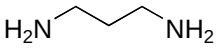
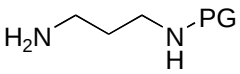
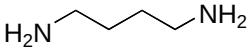
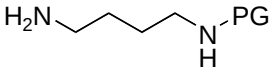
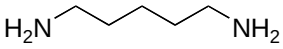
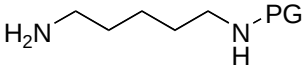
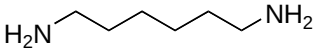
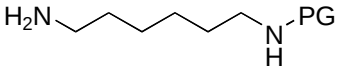
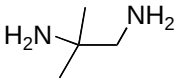
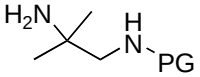
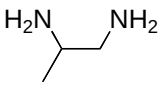
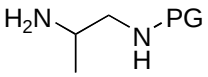
This procedure, which uses alkyl phenyl carbonates as the electrophiles, is a simple, efficient and selective method for the preparation of mono-carbamate-protected diamines. It is applicable for large laboratory scale preparations and the purification of the product proceeds without the need for column chromatography, distillation or recrystallization. The procedure has been shown to work almost equally well for the introduction of Boc, Cbz and Alloc protecting groups.[9]

The selectivity in the introduction of carbamate protecting groups has further been tested by reaction with unsymmetrical aliphatic diamines.[9] Selectivity towards reaction with primary amines located on a primary carbon in the presence of a primary amine located on either a secondary or a tertiary carbon was studied by reaction of the alkyl phenyl carbonates with the two diamines, 2-methyl-1,2-propanediamine and 1,2-propanediamine.

Both of these diamines were successfully mono-carbamate-protected on the primary amino groups located on the primary carbon atom in high yields with the three carbonates tested (Table 1).

Some representative examples of mono-carbamate-protected diamines prepared by this method are compiled in Table 1, which illustrates the possibility to incorporate the Boc, Cbz and Alloc protecting groups by the same procedure.

**Table 1** Selective Carbamate Protection of Aliphatic Diamines.[9]

| Amine | Protected Amine | Yield[a] | |
|---|---|---|---|
|  |  | PG = Boc<br>PG = Cbz<br>PG = Alloc | 65%<br>64%<br>67% |
|  |  | PG = Boc<br>PG = Cbz<br>PG = Alloc | 68%<br>72%<br>86% |
|  |  | PG = Boc<br>PG = Cbz<br>PG = Alloc | 63%<br>63%<br>77% |
|  |  | PG = Boc<br>PG = Cbz<br>PG = Alloc | 50%<br>56%<br>51% |
|  |  | PG = Boc<br>PG = Cbz<br>PG = Alloc | 49%<br>48%<br>46% |
|  |  | PG = Boc<br>PG = Cbz<br>PG = Alloc | 91%<br>97%<br>96% |
|  |  | PG = Boc<br>PG = Cbz<br>PG = Alloc | 70%[b]<br>69%[b]<br>75%[b] |

a) PG =Protection Group: Boc = $(CH_3)_3COCO$, Cbz = $PhCH_2OCO$, Alloc = $CH_2CHCH_2OCO$
b) Yields are based on the polyamine; two equivalents of alkyl phenyl carbonate were used.

**1.** Department of Chemistry, University of Copenhagen, Universitetsparken 5, DK-2100, Copenhagen Ø, Denmark. E-mail: jbc@kiku.dk

**2.** Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, **1999**.
**3.** Kuksa, V.; Buchan, R.; Lin, P. K. T. *Synthesis* **2000**, 1189.
**4.** Bergeron, R. J.; Stolowich, N. J.; Porter, C. W. *Synthesis* **1982**, 689.
**5.** Krapcho, A. P.; Maresch, M. J.; Lunn, J. *Synth. Commun.* **1993**, *23*, 2443.

**6.** Krapcho, A. P.; Kuell, C. S. *Synth. Commun.* **1990**, *20*, 2559.
**7.** Phanstiel, O.; Price, H. L.; Wang, L.; Juusola, J.; Kline, M.; Shah, S. M. *J. Org. Chem.* **2000**, *65*, 5590.
**8.** Adamczyk, M.; Fishpaugh, J. R.; Heuser, K. J. *Org. Prep. Proced. Int.* **1998**, *30*, 339.
**9.** Pittelkow, M.; Lewinsky, R.; Christensen, J. B. *Synthesis* **2002**, 2195.

## Appendix
## Chemical Abstracts Nomenclature; (Registry Number)

*tert*-Butyl phenyl carbonate: Carbonic acid, 1,1-dimethylethyl phenyl ester; (6627-89-0)
1,2-Ethanediamine; (107-15-3)

Jørn B. Christensen was born in 1960 in Rødovre, Denmark. He received his PhD under the supervision of Professor Klaus Bechgaard in 1994, and became an assistant professor at University of Copenhagen in 1994. He has been associate professor at University of Copenhagen since 1997. He worked part-time in industry at Niels Clauson-Kaas A/S from 1985–1987 and was a visiting scientist at the Technical University of Eindhoven in 1997 and 2001.

Michael Pittelkow was born in 1977 in Brøndby Strand, Denmark. He received his undergraduate education at the University of Copenhagen and he performed his doctoral work in the laboratories of Associate Professor Jørn B. Christensen. During his studies he has worked in the research groups of Dr. Kevin Winzenberg at CSIRO in Melbourne (Australia), Professor E. W. Meijer the Technical University in Eindhoven (The Netherlands) and Professor J.K.M. Sanders at Cambridge University (United Kingdom). Since November 2006, he has been a FNU postdoctoral scholar working with dynamic combinatorial chemistry at the University of Copenhagen and Cambridge University.

Rasmus Lewinsky was born in 1976 in Gentofte, Denmark. He received his BS at the University of Copenhagen in 2001 after doing his thesis at the University of Adelaide, Australia. He then joined the group of Jørn B. Christensen at the University of Copenhagen where he carried out research in host-guest systems involving dendrimers. Here he received his MS in 2003. He is currently employed at Acadia Pharmaceuticals where he works as a medicinal chemist.

Cara Cesario was born in New York City on November 16, 1979. She received her B.S. degree in 2001 from Stonehill College in North Easton, MA. Cara developed as a synthetic organic chemist at OSI Pharmaceuticals, where she worked on several oncology-driven medical chemistry programs prior to entering the graduate program at The University of Notre Dame. She is currently a graduate student in the laboratory of Marvin J. Miller and is developing novel allylindium methodologies to synthesize highly functionalized carbocyclic scaffolds as novel precursors to biologically important molecules.