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Facile Synthesis of *o*-Nitrobenzylcarbamate and 1-(2-Nitrophenyl ethyl) Carbamate Protected α,ω-Diamines

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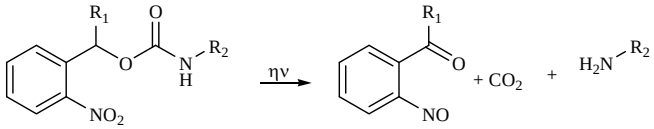
Abstract: A series of mono protected α,ω-diamines protected with photolabile carbamates has been synthesized by reaction between the corresponding α,ω-diamines and either *o*-nitrobenzyl or 1-(2-nitrophenyl)ethyl phenyl carbonate.

Keywords: Photocleavable protective groups, 2-nitrobenzylcarbamates, α,ω-diamines, mono protected diamines, *o*-nitrobenzyl phenyl carbonate, 1-(2-nitrophenyl)ethyl phenyl carbonate.

INTRODUCTION

Monoprotected α,ω-diamines are a versatile class of compounds, that can be used for synthesis of polyamines [1,2] or in the synthesis of dendrimers [3-5]. We have previously developed a general methodology for the synthesis of mono protected α,ω-diamines protected with Boc-, Alloc- or Z-groups [6] by reaction with alkyl phenyl carbonates enabling the use of stoichiometric amounts of reagents and a simple work-up based on extractions [7-9] , and the present paper expands this methodology and describes the synthesis of *o*-Nitrobenzyl- and 1-(2-Nitrophenyl)ethyl carbamate protected α,ω-diamines. The *o*-nitrobenzyl- and 1-(2-Nitrophenyl)ethyl carbamates are examples of protective groups, which can be cleaved photolytically [10, 11] (Fig. **1**) and are as such orthogonal to Boc- and Alloc-groups.

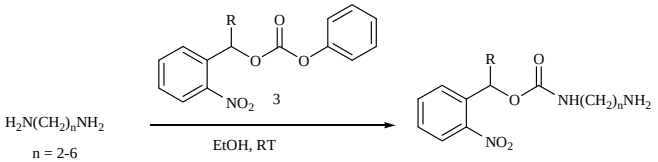


R_1 = H, CH_3

Fig. (1). Photolytic cleavage of *o*-nitrobenzyl carbamates.

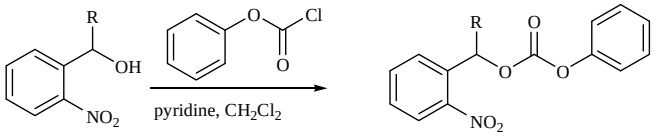
RESULTS

The carbamate protected α,ω-diamines were prepared by reaction of *o*-nitrobenzyl phenyl carbonate or 1-(2-nitrophenyl)ethyl phenyl carbonate with the appropriate diamine in Ethanol at room temperature as shown in Scheme (**1**) giving the monoprotected diamines shown in Table **1** in good yields. Various amounts of the bisprotected diamines were also formed, but these side products precipated during the reaction and were easily removed by filtration. The nitrobenzyl carbamates synthesized remain stable due to light under normal laboratory conditions, so no special measures were needed. The 2-nitrophenethyl carbamates (**2a - 2d**) all contained small amounts of CH_2Cl_2, which was impossible to remove completely even after extensive drying, but they were entirely pure by NMR otherwise.



Scheme (1). The synthesis of the monoprotected α,ω-diamines.

The required arylmethyl phenyl carbonates were synthesized as shown in Scheme **2** from the corresponding alcohols. 1-(2-Nitrophenyl)ethanol was synthesized in three steps from *o*-Nitrobenzoic acid via *o*-Nitroacetophenone[12] according to the published procedure [13].



Scheme (2). The synthesis of the nitrobenzyl carbonates **3a** and **3b**.

CONCLUSION

We have developed a simple procedure for the monoprotection of α,ω-diamines with photocleavable nitrobenzyl carbamates that is easy to use and proceeds in good yields.

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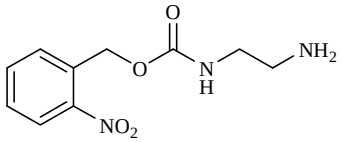
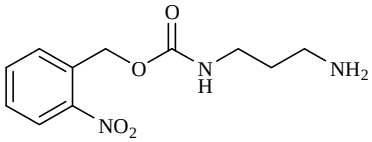
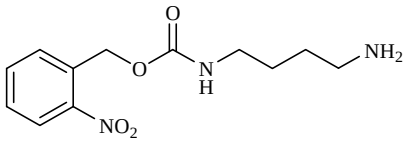
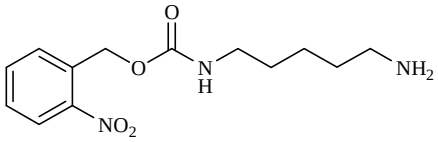
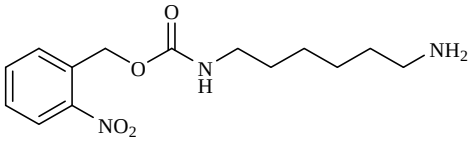
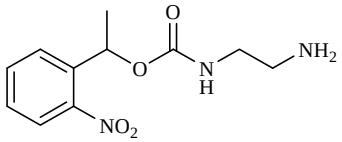
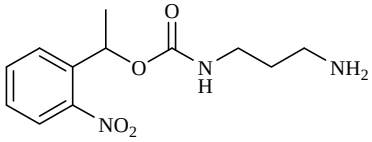
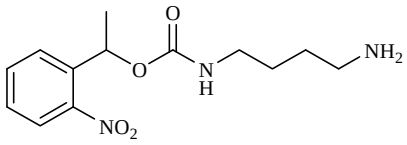
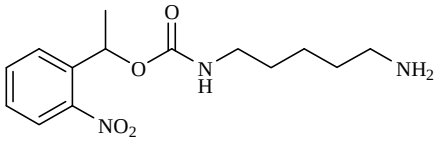
Table 1. Mono Protected α,ω-diamines Synthesized

Compound	Structure	Yield
1a		**58 %**
1b		**64 %**
1c		**72 %**
1d		**65 %**
1e		**53 %**
2a		**55 %**
2b		**84 %**
2c		**64 %**
2d		**50 %**

EXPERIMENTAL

Unless otherwise stated, all starting materials were obtained from commercial suppliers and used as received. Solvents were HPLC grade and used as received. Thin-layer chromatography was carried out using aluminum sheets precoated with silica gel 60F(Merck 5554). The plates were inspected under UV light and, if required, signals were induced by treatment with a 1 % solution of ninhydrin in EtOH. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian (300/75 MHz) instrumentor on a Bruker 500/125 MHz apparatus. Chemical shifts are reported in ppm down-

field of TMS using the resonance of residual solvent as internal standard and all coupling constants are reported in Hertz. Fast Atom Bombardment (FAB) spectra were obtained on a Jeol JMS-HX 110 Tandem Mass Spectrometer in the positive ion mode using 3-nitrobenzyl alcohol as the matrix. Elemental analyses were performed at the Microanalytical Laboratory at the Department of Chemistry, University of Copenhagen.

Melting points were measured on a Büchi melting point apparatus and are uncorrected.

GENERAL PROCEDURE FOR MONO PROTECTION OF DIAMINES

The diamine was dissolved in abs EtOH and cooled to 0 ºC before a solution of an equimolar amount of the alkyl phenyl carbonate in abs EtOH was added dropwise. The mixture was stirred at room temperature overnight. Any precipitate was removed by filtration and the filtrate was concentrated *in vacuo*. Water was added, and the solution was acidified with 2 M HCl and extracted with CH_2Cl_2. The aqueous solution was made alkaline with conc. NaOH (10 M) and extracted with CH_2Cl_2. The organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the monoprotected diamines **1a** – **1e**&**2a** -**2e**.

2-Nitrobenzyl (2-aminoethyl)carbamate (1a).

Yield: 58 %. Pale yellowsolid.Mp. 73–74 ºC.^{1}H-NMR (300 MHz, $CDCl_3$):8.15 – 8.01 (m, 1H), 7.67 – 7.56 (m, 2H), 7.50 –7.42 (m, 1H), 5.50 (s, 2H), 5.38 (br s, 1H), 3.25 (q, J=5.9, 2.84 (t, J=5.9, 2H), 1.38 (s,2H). ^{13}C-NMR (75 MHz, $CDCl_3$):156.31, 147.66, 133.89, 133.42, 129.05, 128.74,125. 12, 63.42, 44.00, 41.80. MS (FAB^+) m/z: 240.07 $[M+H]^+$. Elemental analysis (%) calculated for $C_{10}H_{13}N_3O_4$: C 50.21; H 5.48; N 17.56; Found: C 49.94; H 5.48; N 17.40.

2-Nitrobenzyl (3-aminopropyl)carbamate (1b).

Yield: 64 %. Pale yellow solid. Mp. 83–85 ºC.^{1}H-NMR (500 MHz, $CDCl_3$): 8.01 (dd, J=1.1, 8.2, 1H), 7.60 – 7.49 (m, 2H),7.39 (t, J=7.3, 1H), 5.55 (s, 1H), 5.43 (s, 2H), 3.25 (q, J=6.5, 2H), 2.74 (t, J=6.5, 2H),1.59 (p, J=6.5, 2H), 1.28 (s, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$):155.94, 147.46, 133.66, 133.37, 128.82, 128.49, 124.93, 63.15, 39.96, 39.55, 32.75. MS (FAB^+) m/z:254.18 $[M+H]^+$. Elemental analysis (%) calculated for $C_{11}H_{15}N_3O_4$: C 52.17; H 5.97;N 16.59; Found: C 51.90; H 5.84; N 16.18.

2-Nitrobenzyl (4-aminobutyl)carbamate (1c).

Yield: 72 %. Pale yellow solid.Mp. 72–73 ºC.^{1}H-NMR (300 MHz, $CDCl_3$):8.05 (d, J=8.2, 1H), 7.53-7.65 (m, 2H), 7.44 (t,J=7.5, 1H), 5.36-5.58 (m, 3H), 3.19 (q, J=6.4, 2H), 2.70 (t, J=6.6, 2H), 1.63-1.38 (m,4H), 1.17 (s, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$): 155.85, 147.51, 133.64, 133.30,128.87, 128.52, 124.93, 63.16, 41.74, 41.04, 30.75, 27.41. MS (FAB+) m/z: 268.21 $[M+H]^+$. Elemental analysis (%) calculated for $C_{12}H_{17}N_3O_4$: C 53.92; H 6.41; N15.72; Found: C 53.71; H 6.38; N 15.67.

2-Nitrobenzyl (5-aminopentyl)carbamate (1d)

Yield: 65 %. Yellow solid.Mp. 57–59 ºC.^{1}H-NMR (500 MHz, $CDCl_3$):8.01 (d, J=8.2, 1H), 7.63 – 7.48 (m, 2H), 7.40(t, J=7.6, 1H), 5.43 (s, 2H), 4.91 (br s, 1H), 3.14 (q, J=7.0, 2H), 2.63 (t, J=7.0, 2H),1.55 – 1.24 (m, 8H). ^{13}C-NMR (125 MHz, $CDCl_3$):155.82, 147.52, 133.64, 133.25,128.89, 128.54, 124.94, 63.18, 42.00, 41.09, 33.25, 29.77, 23.98. MS (FAB+) m/z:282.23 $[M+H]^+$.

Elemental analysis (%) calculated for $C_{13}H_{19}N_3O_4$: C 55.50; H 6.81;N 14.94; Found: C 54.98; H 7.02; N 15.00.

2-Nitrobenzyl (6-aminohexyl)carbamate (1e).

Yield: 53 %. Pale yellowsolid.Mp. 83–86 ºC.^{1}H-NMR (500 MHz, $CDCl_3$):8.01 (d, J=8.1, 1H), 7.64 – 7.48 (m, 2H), 7.40(t, J=7.5, 1H), 5.43 (s, 2H), 4.92 (br s, 1H), 3.13 (q, J=7.0, 2H), 2.61 (t, J=7.0, 2H),1.49 – 1.42 (m, 2H), 1.41 – 1.34 (m, 2H), 1.33 – 1.24 (m, 6H). ^{13}C-NMR (125 MHz,$CDCl_3$):155.82, 147.51, 133.64, 133.28, 128.87, 128.53, 124.93, 63.16, 42.07, 41.08,33.59, 29.88, 26.53, 26.48. MS (FAB+) m/z: 296.19 $[M+H]^+$. Elemental analysis (%) calculated for $C_{14}H_{21}N_3O_4$: C 56.94; H 7.17; N 14.23; Found: C 56.82; H 7.59; N 14.47.

1-(2-Nitrophenyl)ethyl (2-aminoethyl)carbamate (2a)

Yield: 55 %. Yellow oil.^{1}H-NMR (500 MHz, $CDCl_3$):7.85 (dd, J=0.8, 8.1, 1H), 7.59 – 7.50 (m, 2H),7.39 – 7.30 (m, 1H), 6.17 (q, J=6.5, 1H), 5.17 (br s, 1H), 3.17 – 3.04 (m,, 2H), 2.72(t, J=5.8, 2H), 1.55 (d, J=6.5, 3H), 1.35 (s, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$):155.58, 147.68, 138.70, 133.44, 128.16, 127.12, 124.38, 68.58, 43.51, 41.56, 22.24. MS(FAB+) m/z: 254.15 $[M+H]^+$. Elemental analysis (%) calculated for $C_{11}H_{15}N_3O_4$:C 52.17; H 5.97; N 16.59; Found: C 51.63; H 5.85; N 16.04.

1-(2-Nitrophenyl)ethyl (3-aminopropyl)carbamate (2b)

Yield: 84 %. Yellow oil.^{1}H-NMR (500 MHz, $CDCl_3$): 7.85 (d, J=8.0, 1H), 7.60 – 7.50 (m, 2H), 7.36 –7.32 (m, 1H), 6.16 (q, J=6.4, 1H), 5.34 (br s, 1H), 3.22 – 3.10 (m, 2H), 2.69 (t, J=6.4,2H), 1.62 – 1.50 (m, 5H), 1.43 (s, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$):155.45,147.67, 138.83, 133.42, 128.12, 127.07, 124.40, 68.49, 39.83, 39.26, 32.70, 22.24. MS(FAB+) m/z: 268.20 $[M+H]^+$. Elemental analysis (%) calculated for $C_{12}H_{17}N_3O_4$:C 53.92; H 6.41; N 15.72; Found: C 52.63; H 6.28; N 14.98.

1-(2-Nitrophenyl)ethyl (4-aminobutyl)carbamate (2c)

Yield: 64 %. Yellow oil.^{1}H-NMR (500 MHz, $CDCl_3$):7.92 (d, J=8.1, 1H), 7.63 – 7.59 (m, 2H), 7.46– 7.35 (m, 1H), 6.23 (q, J=6.4, 1H), 5.10 (br s, 1H), 3.23 – 3.06 (m, 2H), 2.69 (t,J=6.8, 2H), 1.61 (d, J=6.4, 3H), 1.56 – 1.48 (m, 2H), 1.48 – 1.40 (m, 2H), 1.17 (s,2H). ^{13}C-NMR (125 MHz, $CDCl_3$):155.34, 147.67, 138.81, 133.40, 128.12, 127.06,124.39, 68.47, 41.75, 40.85, 30.76, 27.38, 22.25. MS (FAB+) m/z: $[M+H]^+$. Elementalanalysis (%) calculated for $C_{13}H_{19}N_3O_4$: C 55.50; H 6.81; N 14.94; Found: C 54.02; H6.92; N 14.57.

1-(2-Nitrophenyl)ethyl (5-aminopentyl)carbamate (2d)

Yield: 50 %. Yellow oil.^{1}H-NMR (500 MHz, CDCl3): 7.85 (d, J=8.1, 1H), 7.54 (d, J=3.7, 2H), 7.40 –7.29 (m, 1H), 6.16 (q, J=6.5, 1H), 4.77 (s, 1H), 3.16 – 3.00 (m, 2H), 2.60 (t, J=6.9,2H), 1.54 (d, J=6.5, 3H), 1.50 – 1.18 (m, 8H). ^{13}C-NMR (125 MHz, $CDCl_3$):155.31, 147.68, 138.79, 133.39, 128.13, 127.05, 124.40, 68.51, 42.01, 40.90, 33.26, 29.78,23.96, 22.24. MS (FAB+) m/z: [M+H]+. Elemental analysis (%) calculated for$C_{14}H_{21}N_3O_4$: C 56.94; H 7.17; N 14.23; Found: C 56.23; H 6.87; N 13.79.

2-Nitrobenzyl phenyl carbonate (3a)

2-Nitrobenzyl alcohol (1.0011 g; 6.5372 mmol) was dissolved in a mixture of pyridine (5 mL) and CH_2Cl_2 (10 mL). Phenyl chloroformate (1.0 g; 6.6 mmol) was added dropwise while stirring. After stirring overnight, water (15 ml) was added and the solution was stirred for an additional 10 min. before the phases were separated. The organic phase was washed with 2 M H_2SO_4 (2 x 5 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was filtered through a plug of Silica using CH_2Cl_2 and concentrated*in vacuo*. Pale yellow oil.Yield 1.21 g; (68 %).

^{1}H-NMR (300 MHz, $CDCl_3$): = 8.16 (dd, J=7.5, 1.2, 1H), 7.76 – 7.68 (m, 2H),7.55 – 7.50 (m, 1H), 7.43 – 7.37 (m, 2H), 7.30 – 7.20 (m, 3H). ^{13}C-NMR (100 MHz,$CDCl_3$): = 152.97, 150.78, 146.99, 133.70, 130.80, 129.31, 129.10, 128.59, 126.22,124.96, 120.67, 66.48. MS (FAB^+) m/z: 274.31 $[M+H]^+$.Elemental analysis (%) calculated for $C_{14}H_{11}NO_5$: C 61.54; H 4.06; N 5.13; Found: C 61.75; H 4.05; N 5.02.

1-(2-Nitrophenyl)ethyl phenyl carbonate (3b)

To an ice-cooled solution of 1-(2-nitrophenyl)ethanol[D. M. Rothman, M. E. Vázquez, E. M. Vogel, B Imperiali, Org. Lett., 4, 2865–2868, 2002., G. A. Reynolds, C. R. Hauser, Org. Synth., Coll. Vol. 4, 708, 1963] (40.34 g; 241.3 mmol) in a mixture of pyridine(100 mL) and CH_2Cl_2 (200 mL) was phenyl chloroformate (37,24 g; 237.8 mmol) added dropwise at 0-10 ºC. After complete addition, the mixture was allowed to warm to room temperature and was stirred for 48 hours. 2 M H_2SO_4 (100 mL) was added and the mixture was stirred for 15 min before separation of the phases. The organic phase was washed with 2 M NaOH (1 x 50 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product crystallized upon cooling to 5 ºC, and recrystalization from EtOH and water which gave **3** bas pale yellow crystals (mp 69–70 ºC). Yield 44.69 g (65%).

^{1}H-NMR (300 MHz, $CDCl_3$): 7.99 (dd, J=1.3, 8.2, 1H), 7.79 (dd, J=1.5, 7.9, 1H),7.74 – 7.64 (m, 1H), 7.52 – 7.43 (m, 1H), 7.40 – 7.30 (m, 2H), 7.27 – 7.18 (m, 1H), 7.12(dt, J=2.4, 9.1, 2H), 6.36 (q, J=6.5, 1H), 1.78 (d, J=6.5, 4H). ^{13}C-NMR (100 MHz,$CDCl_3$): = 152.88, 151.14, 147.80, 137.46, 134.17, 129.70, 129.03, 127.30, 126.36, 124.84, 121.11, 72.95, 22.36. MS (FAB+) m/z: [M+H]+. Elemental analysis (%)calculated for $C_{15}H_{13}NO_5$: C 62.72; H 4.56; N 4.88; O 27.85; Found: C 62.90; H 4.47;N 4.81.

CONFLICT OF INTERESTS

The authors confirm that this article content has no conflicts of interest.

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