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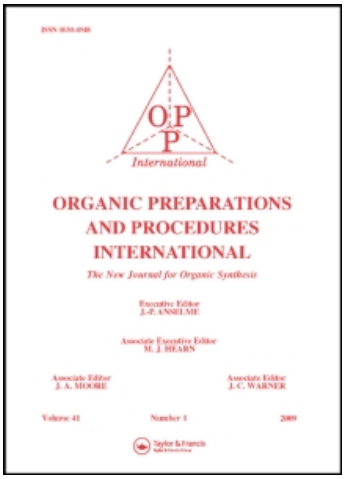

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AN EFFICIENT SYNTHESIS OF BOC-AMINOACETALDEHYDE AND ITS APPLICATION TO THE SYNTHESIS OF *N*-(2-BOC-AMINOETHYL)GLYCINE ESTERS

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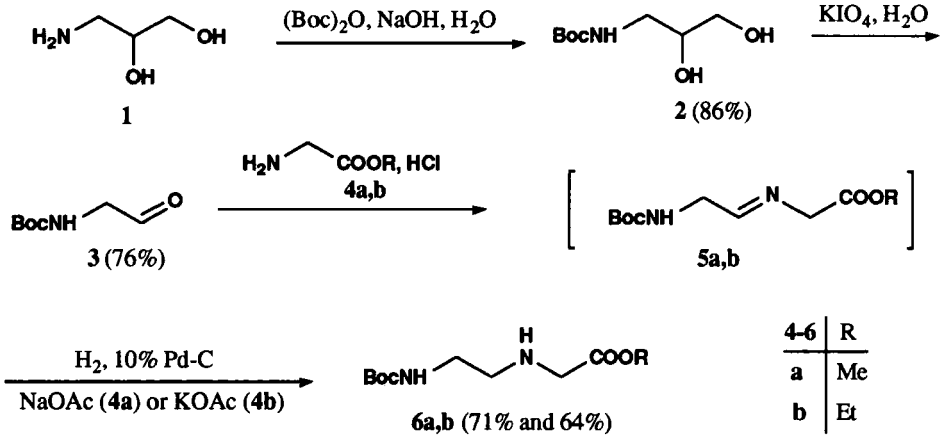
The number of applications for compounds able to recognize specific sequences in DNA and/or RNA is vast.[1] Recent reports from this laboratory have described the design, synthesis, and properties of a new class of such reagents, *i.e.*, peptide nucleic acid (PNA).[2-4] PNA is a DNA-analogue in which the carbohydrate backbone is replaced by an oligopeptide consisting of *N*-(2-aminoethyl)glycine units while retaining only the nucleobases of DNA. PNA was found to bind to complementary sequences in single and double stranded DNA with a binding strength and specificity unprecedented by oligonucleotides or related analogues. In order to obtain large amounts of starting material for the syntheses of the monomers employed in preparations of PNA, we needed an efficient synthetic route to the backbone Boc-aminoethylglycine esters. The result of this work is described herein.

Reductive amination of Boc-aminoacetaldehyde with glycine esters afforded a good yield of pure *N*-(2-Boc-aminoethyl)glycine esters. Protection of the amino group of 3-amino-1,2-propandiol (**1**) with *tert*-butyloxycarbonyl (Boc) was achieved in 86% yield by subjecting **1** to di-*tert*-butyl dicarbonate. Subsequent periodate oxidation of the crude protected diol **2** yielded 76% of pure



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Boc-aminoacetaldehyde (**3**) after Kugelrohr distillation of the crude product. Reductive amination of **3** with glycine esters **4** was performed by *in situ* reduction of the intermediate imines **5**. Hydrogenation in the presence of 10% palladium on activated carbon afforded the amines **6**. This approach allowed the isolation of methyl ester **6a** and ethyl ester **6b** in 71% and 64% yield, respectively. Boc-Amino-acetaldehyde has been prepared a number of times previously,[5-10] most frequently by ozonolysis of the corresponding allyl compound,[5,7,9,10] but also by the Swern oxidation[11] (activated dimethyl sulfoxide) of 2-Boc-aminoethanol[8] as well as by oxidation of the latter[6] with Corey's reagent[12] (pyridinium chlorochromate). A common trend in these procedures is the difficulty encountered in the isolation, purification and storage of **3**. In the few instances in which successful isolation of **3** was accomplished, column chromatography was necessary for purification. In addition, aldehydes with a chiral center in place of the methylene group in Boc-aminoacetaldehyde are described as possessing chiral lability[13-15] and as being subject to slow decomposition when stored in organic solvents at room temperature.[16] These observations further emphasize the general instability of compounds of this type.

The reductive amination described herein requires an efficient synthesis of **3**. After having obtained unsatisfactory yields and purity when attempting to synthesize **3** as previously described in the literature, we decided to use periodate oxidation of 3-Boc-amino-1,2-propanediol (**2**), as periodate oxidations are known to proceed cleanly. This approach with its simple workup and purification procedures, allowed **3** to be isolated pure and in good yield. However, the instability of **3** was confirmed by the observation that decomposition was observed in the NMR spectra of both DMSO-d_6 and $CDCl_3$ solutions when these were stored at room temperature. NMR spectra of a $CDCl_3$ solution recorded immediately, one hour, three hours and four days after dissolution, indicated that appreciable decomposition had already occurred after one hour and that the decomposition progressed over time. After completion of this manuscript, Simon *et al.*[17] published a reductive amination analogous to the one reported herein for the synthesis of **6** from Boc-aminoacetaldehyde. However, they did not produce the aminoethylglycine entity, but rather employed analogues of **3** with alkyl substituents in place of the Boc-amino function.

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EXPERIMENTAL SECTION

NMR spectra were recorded on a Bruker AM 250 spectrometer. Chemical shifts are in parts per million (δ) relative to TMS. Commercial reagents, di-*tert*-butyl dicarbonate, potassium m-periodate, 10% Pd/C, glycine methyl ester hydrochloride (Aldrich) and glycine ethyl ester hydrochloride (Aldrich) and 3-amino-1,2-propandiol (Sigma) were used for the reactions.

3-(Boc-Amino)-1,2-propanediol (2).- To 3-amino-1,2-propandiol (**1**, 80.00 g, 0.880 mol, 1.0 eqv) dissolved in water (1500 mL) and cooled to 0°, was added di-*tert*-butyl dicarbonate (230.0 g, 1.052 mol, 1.2 eqv) in one portion. The reaction mixture was heated to room temperature with stirring on a water bath. The pH was maintained at 10.5 with a solution of sodium hydroxide (70.24 g, 1.760 mol, 2.0 eqv) in water (480 mL). When the addition of aqueous sodium hydroxide was completed, the reaction mixture was stirred overnight at room temperature. Subsequently, ethyl acetate (1000 mL) was

added to the reaction mixture followed by cooling to 0°. The pH was adjusted to 2.5 with 4 N hydrochloric acid with vigorous stirring and the phases were separated. The aqueous phase was washed with additional ethyl acetate (8x500 mL). The volume of the organic phase was reduced to 1500 mL by evaporation under reduced pressure and washed successively with a saturated aqueous solution of potassium hydrogen sulfate diluted to twice its volume (1 x 1500 mL) and with saturated aqueous sodium chloride (1 x 1000 mL). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure to yield 145.3 g (86%) of the title compound. The product which could be made to solidify by evaporation from methylene chloride and subsequent cooling, was not purified[18] prior to use in the synthesis of **3**. ^{1}H NMR ($CDCl_3$): δ 1.43 (s, 9H, Me_3C), 3.25 (m, 2H, CH_2), 3.57 (m, 2H, CH_2), 3.73 (m, 1H, CH). ^{13}C NMR ($CDCl_3$): δ 28.2 (Me_3C), 42.6 (CH_2), 63.5, 71.1 (CH_2OH, CHOH), 79.5 (Me_3C), 157.0 (C=O).

Boc-Aminoacetaldehyde (3).- 3-(Boc-Amino)-1,2-propanediol (**2**, 20.76 g, 0.109 mol, 1 eqv) was suspended in water (150 mL). Potassium *m*-periodate (24.97 g, 0.109 mol, 1 eqv) was added and the reaction mixture was stirred for 2 hrs at room temperature under nitrogen. The reaction mixture was filtered and the water phase extracted with chloroform (6 x 250 mL). The organic phase was dried ($MgSO_4$) and evaporated to afford crude Boc-aminoacetaldehyde as a golden oil. This oil was kugelrohr distilled at 80° and 0.2 mbar to yield 13.19 g (76%) of the title compound as a semicrystalline solid. ^{1}H NMR (DMSO-d_6): δ 1.47 (s, 9H, Me_3C), 3.81 (d, J = 6 Hz, 2H, CH_2), 7.22 (b, 1H, NH), 9.54 (s, 1H, CHO). ^{13}C NMR (DMSO-d_6): δ 28.2 (Me_3C), 50.5 (CH_2), 78.4 (Me_3C), 156.1 (carbamate C=O), 200.6 (CHO).

Anal. Calcd for $C_7H_{13}NO_3$: C, 52.82; H, 8.23; N, 8.80. Found: C, 52.73; H, 8.20; N, 8.82

N-(2-Boc-Aminoethyl)glycine Methyl Ester (6a).- Boc-Aminoacetaldehyde (**3**, 23.00 g, 144 mmol, 1 eqv) was dissolved in MeOH (1000 mL). Glycine methyl ester hydrochloride (**4a**, 18.14 g, 144 mmol, 1 eqv) and anhydrous sodium acetate (23.71 g, 289 mmol, 2 eqv) each dissolved in MeOH (150 mL) were added to the solution. The mixture was cooled to 0° and nitrogen was bubbled through for 10 min., then 10% palladium on activated carbon (4.6 g) was added under nitrogen with vigorous stirring. The reaction mixture was hydrogenated at atmospheric pressure and room temperature with vigorous stirring until hydrogen uptake had ceased (when 3.18 L, 144 mmol, 1 eqv, had been consumed) after ca. 5 hrs. The reaction mixture was filtered and the solvent removed under reduced pressure. The residue was suspended in water (225 mL) and with vigorous stirring, the pH was adjusted to 8 by addition of 1N NaOH. The water phase was extracted with methylene chloride (5 x 200 mL). The organic phase was dried (Na_2SO_4), filtered and evaporated under reduced pressure to yield 30.6 g of crude title compound as a golden oil. The crude product was kugelrohr distilled at 100° and 0.2 mbar to afford 23.59 g (71%) of *N*-(2-Boc-aminoethyl)glycine methyl ester as a colorless liquid. ^{1}H NMR ($CDCl_3$): δ 1.44 (s, 9H, Me_3C), 2.05 (s, 1H, NH), 2.75 (t, J = 6 Hz, 2H, $NHCH_2$), 3.22 (q, J = 6 Hz, 2H, $NHCH_2$), 3.43 (s, 2H, CH_2COO), 3.73 (s, 3H, OMe), 5.15 (b, 1H, carbamate NH). ^{13}C NMR ($CDCl_3$): δ 28.2 (Me_3C), 40.0, 48.6 ($NHCH_2$), 50.1 (CH_2COO), 51.6 (OMe), 79.0 (Me_3C), 155.9 (carbamate C=O), 172.7 (ester C=O).

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Anal. Calcd for $C_{10}H_{20}N_2O_4$: C, 51.71; H, 8.68; N, 12.06. Found: C, 51.44; H, 8.78; N, 12.10

N-(2-Boc-Aminoethyl)glycine Ethyl Ester (6b).- This compound was prepared as with **4a** from Boc-aminoacetaldehyde (**3**, 10.00 g, 62.8 mmol, 1 eqv) and glycine ethyl ester (**4b**, 8.77 g, 62.8 mmol, 1 eqv) in ethanol (625 mL) in the presence of potassium acetate (12.33 g, 126 mmol, 2 eqv) and 10% palladium on activated carbon (2.5 g). The hydrogenation required 2 hrs (to consume 1.38 L, 62.8 mmol, 1 eqv) yielding 17.03 g of crude title compound as a yellow oil. The crude product was kugelrohr distilled at 110° and 0.2 mbar to afford 9.88 g (64%) of *N*-(2-Boc-aminoethyl)glycine ethyl ester as a colorless liquid. ^{1}H NMR ($CDCl_3$): δ 1.28 (t, J = 7 Hz, 3H, CH_3CH_2O) 1.44 (s, 9H, Me_3C), 2.09 (s, 1H, NH), 2.75 (t, J = 6 Hz, 2H, $NHCH_2$), 3.22 (q, J = 6 Hz, 2H, $NHCH_2$), 3.41 (s, 2H, CH_2COO), 4.19 (q, J = 7 Hz, 2H, CH_3CH_2O), 5.32 (b, 1H, carbamate NH). ^{13}C NMR ($CDCl_3$): δ 13.8 (CH_3CH_2O) 28.0 (Me_3C), 39.8, 48.4 ($NHCH_2$), 50.0 (CH_2COO), 60.4 (CH_3CH_2O), 78.6 (Me_3C), 155.8 (carbamate C=O), 172.0 (ester C=O).

Anal. Calcd for $C_{11}H_{22}N_2O_4$: C, 53.64; H, 9.00; N, 11.37. Found: C, 53.37; H, 9.07; N, 11.15

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18. Although satifactory (±0.30) data were obtained for the carbon and hydrogen analyses, the results for nitrogen were beyond acceptable limits for **2**.

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