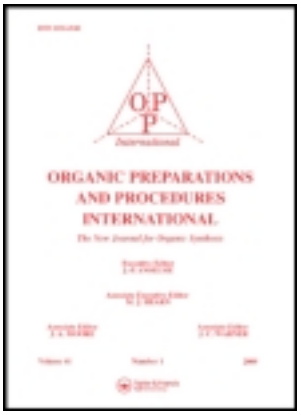

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Monoprotection of Triamines with Alkyl Phenyl Carbonates

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Historically we have been interested in developing simple procedures for the partial protection of polyamines using stoichiometric amounts of reagents and avoiding the use of chromatographic purification. We previously described the use of alkyl phenyl carbonates for the monoprotection of diamines and diprotection of triamines in fair to good yields.[1,2] Alkyl phenyl carbonates are easy to synthesize on a large scale and have a long shelf-life.[1] We were interested in the monoprotection of N^1-(2-aminoethyl)-1,2-diaminoethane (**1**), N^1-(3-aminopropyl)-1,3-diaminopropane (**6**) and N^1-(2-aminoethyl)-1,3-diaminopropane (**9**), which are commercially available, inexpensive and interesting as building blocks for a new family of dendrimers.

The regioselective acylation of polyamines has been the subject of considerable interest and is undoubtly related to the versatility of the products as well as the chemist's fascination with symmetry breaking in molecules. Since polyamines are polybasic, this suggests partial protonation as one of the strategies for providing temporary protection of some of the amino groups. However, this strategy requires strict pH control and prior knowledge of the individual pK_b-values. The monoacetylation of acyclic aliphatic α,ω-diamines with phenyl acetate was studied by Bruice and Willis,[3] who showed that the monoacetylation of 1,3-diaminopropane was twelve times faster than that of 1,2-diaminoethane. This is interesting considering that 1,2-diaminoethane is a stronger base than 1,3-diaminopropane and it would be expected that the strongest base should be the strongest nucleophile. The results were explained as a result of general base catalysis involving the ω-amino group of the α,ω-diamine, where the cyclic transition state was more favorable in the case of 1,3-diaminopropane than in 1,2-diaminoethane. Sayre and coworkers[4] also investigated the acylation of 1,2-diaminoethane with various acylating reagents and found that either high-dilution conditions or the use of weaker acylating reagents such as *N*-hydroxysuccinimide esters were necessary in order to keep diacylation to a minimum. They also carried out a kinetic study of the acetylation of a series of α,ω-diamines and derivatives, including α,ω-dimethylated and monoamides with 4-nitrophenyl acetate, and confirmed the findings of Bruice and Willis.[3] Acylation of one of the amino groups in an α,ω-diamine reduces

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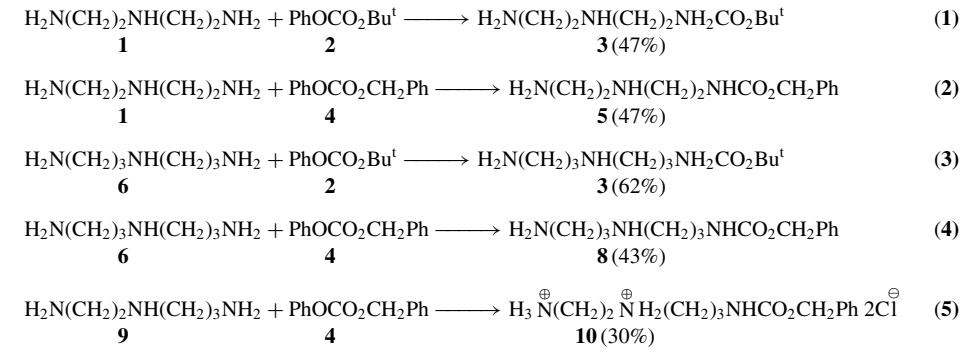
the reactivity of the remaining amino group, pointing toward the use of acylating reagents with reduced reactivity as a means to achieve selective discrimination in polyamines. Initial screening of solvents and conditions indicated the use of methanol at room temperature gave the best results. On the basis of these experiments, a series of monoprotected triamines were prepared from the triamines and alkyl phenyl carbonates shown in *Eqs. 1–5*.



Common to all the selected triamines is the fact that the corresponding monoprotected derivatives are known. They had been prepared by multi-step sequences with the exception of **8**, which had been obtained by reaction between the corresponding triamine (**2**) and Boc-azide.[8]

The reaction between the unsymmetrical N^1-(2-aminoethyl)propane-1,3-diamine (**9**) and benzyl phenyl carbonate (**2**) was expected to give a mixture of the two regioisomers. However, compound **10** could be isolated in pure form in 30% yield by crystallization of the mixture of dihydrochlorides from aqueous ethanol. This selectivity fits nicely with the predicted result based on the work of Bruice and Willis,[3] and of Sayre and coworkers,[4] predicting that the 1,3-diaminopropane component of the molecule would react considerably faster than the 1,2-diaminoethane end. In conclusion, a simple method for monoprotection of triamines with alkyl phenyl carbonates in methanol that avoids chromatographic work-up, has been developed.

Experimental Section

The triamines were purchased from Sigma-Aldrich. The alkyl phenyl carbonates were synthesized as previously described.[1,2] NMR Spectra were obtained in $CDCl_3$ or D_2O (TMS as internal standard) on either a Varian 300 MHz or a Bruker 500 MHz spectrometer equipped with a cryoprobe.

Typical Procedure for the Monoprotection of Triamines

To a solution of triamine (50.0 mmol) in 50 mL methanol was added dropwise a solution of alkyl phenyl carbonate[1,2] (51.5 mmol) in 50 mL methanol) over a period of 25 minutes. The reaction mixture was stirred at room temperature for 5 days and evaporated to dryness under reduced pressure. Upon addition of 50 mL CH_2Cl_2 and 50 ml 2M HCl, the *diprotected* triamine hydrochloride which precipitated, was collected on a sintered glass funnel (G3). The two-phase filtrate was separated (the methylene chloride layer was discarded) and the

aqueous layer was made alkaline (*pH 11*) with 12M NaOH and extracted with methylene chloride (4 × 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered and evaporated under reduced pressure to give the *mono*protected triamines.

t-Butyl 2-(2-Aminoethylamino)ethyl Carbamate (3).[6,7]

Pale yellow oil. Yield: 47%. ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.43 (s, 9 H); 1.56 (s, 3 H); 2.65–2.81 (m, 6 H); 3.18–3.24 (m, 2 H); 4.99 (s, 1 H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 28.54; 41.76; 49.16; 52.04; 79.05; 156.5.

Benzyl 2-(2-Aminoethylamino)ethyl Carbamate (5).[5]

Pale yellow oil. Yield: 49%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.82 (s, 3 H); 2.63–2.80 (m, 6 H); 3.28 (s, 2 H); 5.09 (s, 2 H); 5.40 (s, 1 H); 7.26 - 7.37 (m, 5 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 40.76; 41.56; 48.83; 51.78; 66.68; 128.06; 128.11; 128.51; 136.55; 156.37.

t-Butyl 3-(3-Aminopropylamino)propyl Carbamate (7).[7,8]

Pale yellow oil. Yield: 62%. ^{1}H NMR (500 MHz, $CDCl_3$): δ1.37 (s, 9 H); 1.57 (m, 4 H); 1.69 (broad s, 3 H); 2.59 (m, 4 H); 2.71 (t, J = 2.7 Hz, 2 H); 3.14 (m, 2 H); 5.17 (broad s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 28.44; 29.82; 33.57; 39.20; 40.40; 47.75; 47.82; 78.96; 156.14.

Benzyl 3-(3-Aminopropylamino)propyl Carbamate (8).[9]

Pale yellow oil. Yield: 43%. ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.51–1.68 (m, 4 H); 2.61–2.77 (m, 6 H); 3,27 (d, 2 H); 5.08 (s, 2 H); 7.26–7.35 (m, 5 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 29.54; 33.68; 40.05; 40.42; 47.73; 48.01; 66.44; 127.26; 128.04; 128.47; 136.82; 156.52.

N^1-[3-(Benzyloxycarbonylamino)propyl]-1,2-diaminoethane Dihydrochloride (10).[10]

Reaction of **9** with benzyl phenyl carbonate (**2**) according to the general procedure gave a pale yellow oil containing mainly N^1-(3-(benzyloxycarbonylamino)propyl)-1,2-diaminoethane. This crude material was converted to the dihydrochlorides by addition of a solution of HCl in EtOH (generated by cautious addition of 5 mL CH_3COCl to 50 mL EtOH). Evaporation of the solution to dryness *in vacuo* gave a mixture of the two hydrochlorides which was crystallized from 96% EtOH (***cooling only to room temperature***!) to afford white crystals (30% yield) of **10**, mp. 229–230°C (lit.[6]: 230–231°C). ^{1}H NMR (D_2O, 500 MHz): δ 1.83 (m, 2 H); 3.05 (t, 2 H, J = 7.5 Hz); 3.17 (t, 2 H, J = 6.5 Hz); 3.30 (br s, 4 H); 5.05 (s, 2 H); 7.37 (m, 5 H). ^{13}C NMR (D_2O, 125 MHz): δ 26.84; 35.91; 38.12; 44.76; 45.29; 65.99; 128.41; 128.47; 129.06; 137.78; 156.82.

Acknowledgements

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