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SELECTIVE PROTECTION OF THE PRIMARY AMINE FUNCTIONS OF LINEAR TETRAAMINES USING THE TRITYL GROUP

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Abstract: Treatment of linear tetraamines 3,6-diaza-1,8-octanediamine (**1**); 4,7-diaza-1,10-decanediamine (**2**); and 4,9-diaza-1,12-dodecanediamine (spermine) (**3**) with equimolar amounts of trityl chloride allowed preparation of the α,ω-bistrityl-protected tetraamines **4, 6** and **8** in good to excellent yields. A 2:1 ratio of trityl chloride to tetraamine gave a tritrityl-substituted by-product. An internal N,N′-ditrityl-substituted tetraamine, 5,8-ditrityl-1,5,8,12-tetraazadodecane (**10**), was also prepared as a further proof of the structures of the α,ω-ditrityl-substituted tetraamines.

Selective protection of primary amine functions in the presence of secondary amines is an important synthetic organic chemistry problem.[1,2] Certain acylating reagents selectively react with primary amines but they are expensive or have other deficiencies. For example, the primary amine derivatives of 1,3-thiazolidine-2-thione or poly(3-acyl-2-oxazolone)[3-8] form hydrogen bonds with neighboring secondary amines thereby preventing desired reactions on the secondary amine functions.[9] Primary amine protection reagents such as phenylbis(2-thiono-1,3-thiazoline-3-

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yl)phosphine oxide or triphenylphosphine 2,2′-dipyridyl disulfide require multistep syntheses before use.[9-11] Other reported protection methods include using acylimidazoles for the direct bisacylation of the primary amine functions of spermidine and other linear triamines,[12] the esters of 1-hydroxypiperidine,[13,14] and ruthenium catalyzed condensation of nitriles or acyl cyanides to give the 1,8-N,N′-disubstituted diamides.[15,16] N-Ethoxycarbonylphthalimide, first reported twelve years ago,[17] is easily removed at the end of a synthetic sequence by a treatment with hydrazine but is not used because it is difficult to separate the protected amine from the starting amine.

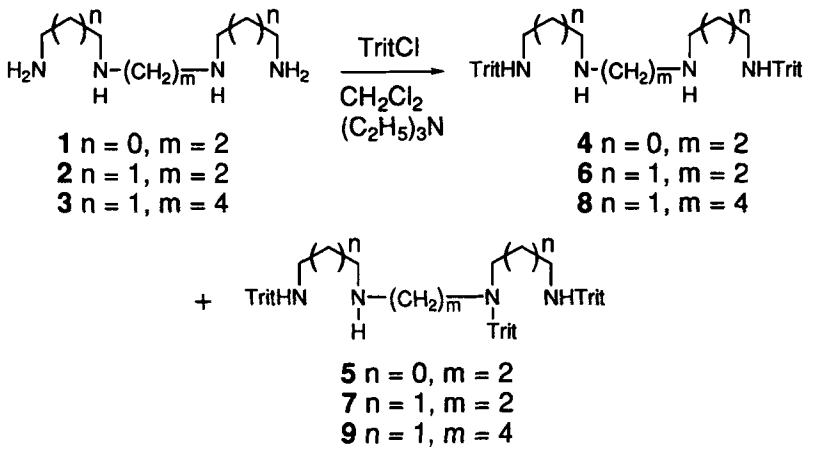
Ethyl trifluoroacetate, which only reacts with primary amine functions to form trifluoroacetamides, is an important new primary amine protecting group.[18-21] The trifluoroacetamide function is easily hydrolyzed in a weak base so that deprotection at the end of a synthetic sequence is straight forward. This easy hydrolysis causes the trifluoroactyl protecting group to not be useful when the protected compounds need to be subsequently reacted in basic media.

The ideal primary amine protecting group for a polyamine needs to be inexpensive, very selective for primary over secondary amines, stable in acidic or basic conditions, and easily removed at a later stage. We have chosen trityl chloride as a protecting group for the primary amine functions of unsubstituted tetraamines where the protected compound will be subsequently reacted in base media. This group is a known amine protecting group.[22] The trityl-protected amines are lipophilic and can be purified by flash column chromatography or extraction by a nonpolar solvent, which will not coextract the starting tetraamines. In addition, the trityl

groups are easily removed in acidic media or by hydrogenolysis in a subsequent step. In contrast to the trifluoroacetate group, trityl-substituted amines are stable in any basic pH solution which allows the protected polyamine to be used in many further reactions. The trityl alcohol by-product of the deprotection step can be isolated and converted back to trityl chloride if this process is used on a large scale. Trityl chloride has been used to protect primary amines in the presence of a secondary amine in the case of diethylenetriamine.[23-25] To our knowledge, this is the only example of selective primary amine protection by the trityl group. Herein, we report the facile preparation of three α,ω-dityrityl-protected tetraamines, namely those of 3,6-diaza-1,8-octanediamine (triethylenetetraamine) (**1**), 4,7-diaza-1,10-decanediamine (**2**), and 4,9-diaza-1,12-dodecanediamine (spermine) (**3**). This is the first example of protecting the primary amine functions of a polyamine using an alkyl group.

Treatment of tetraamines **1-3** with trityl chloride in the presence of triethylamine in methylene chloride gave the desired α,ω-dityrityl-substituted tetraamines **4, 6,** and **8** as well as tritrityl-substituted tetraamines **5, 7,** and **9** as shown in Scheme I. We did not isolate mono- or tetratrityl-substituted products although trace amounts were observed in the TLC analysis. In the case of diethylene-triamine, we have found by careful spectral analysis that, even in an excess of trityl chloride, only the primary amines reacted.[26] With the tetraamines used in this study, the higher ratio of secondary to primary amines provides more opportunity for the secondary amines to react producing tritrityl-substituted **5, 7,** and **9**.

As shown in Table I, the best results were obtained when equimolar amounts of trityl chloride and the tetraamine were used. Wanting to obtain the best possible



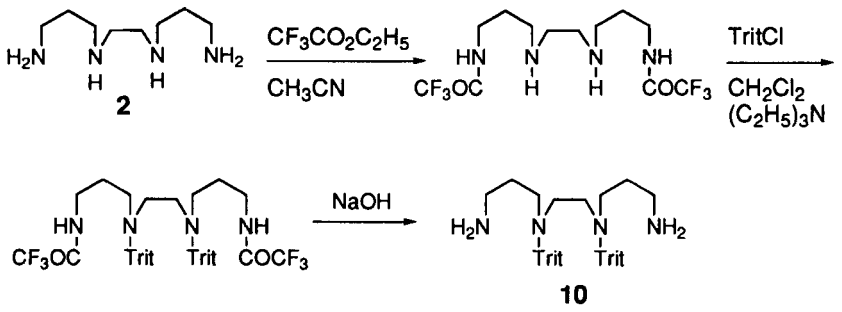
Scheme 1. Reaction of trityl chloride with linear tetraamines.

Table I. Results of the Reaction of Tetraamines with Trityl Chloride

Amine	Molar Ratio of Amine to Chloride	% yield[a] 4, 6 or 8	% yield[a] 5, 7 or 9
1	1:1	62	trace
1	1:2	25	20
2	1:1	78	trace
2	1:2	10	39
3	1:1	64	trace
3	1:2	15	28

[a]yield based on amount of trityl chloride used.

yields of the diprotected products, our first reactions used a 1:2 molar ratio of tetraamine to trityl chloride. As shown in Table I, this ratio produced a considerable amount of the undesired trityl-substituted products. Using a 1:1 molar ratio of reactants gave good to excellent yields of the desired dityl products. In this case,



Scheme 2. Preparation of dityityl-substituted **10**

trace amounts of the monotrityl products were observed but not isolated. Compound **8** was prepared before by a three step process,[27] but no spectral data was published.

To provide further proof that products **4, 6,** and **8** had trityl substituents on the primary amine functions and not on the internal amines, we prepared **10** with trityl substituents on the internal amine groups (Scheme 2). This material was prepared via the bis(trifluoroacetamide) as shown. In the second step, the two trityl groups reacted with the secondary amines of the diamide forming **10** after removing the trifluoroacetyl protecting groups in base. ^{1}H and ^{13}C NMR spectra of ditrityl-substituted compounds **6** and **10** are very different. The shielding effects of the large trityl groups are more pronounced in **10** than in **6**. The signals for the internal methylene protons shift from δ 1.6 in compound **6** to δ 1.15 in compound **10,** while those on carbons next to the nitrogen atoms substituted with trityl groups shift from δ 2.65 in compound **6** to δ 2.05 in ditrityl compound **10**.

EXPERIMENTAL SECTION

Preparation of Ditrityl- and Tritrityl-substituted Tetraamines. A solution of 0.02 mol of trityl chloride in 50 mL of CH_2Cl_2 was slowly dropped into

a stirred mixture of 0.02 mol (or 0.01 mol) of tetraamine **1, 2,** or **3** and 0.022 mol (or 0.011 mol) of triethylamine at -5 to -10°C for 1-2 h. The mixture was stirred overnight at rt. The CH_2Cl_2 layer was washed three times with 20-mL portions of water, dried ($MgSO_4$) and evaporated. The residue was dissolved in a $C_6H_5CH_3$:EtOH/ 20:1 mixture and purified on silica gel using the same solvent mixture and then methanol as eluants to give first the trisubstituted and then disubstituted products as shown in Table 1. The collected fractions were evaporated, disolved in CH_2Cl_2, filtered and evaporated again for analyses. The spectral and elemental analyses for products **4** to **9** are as follows:

Compound **4**, ^{1}H NMR δ: 1.8 (b, 4 H), 2.28 (t, 4 H), 2.6 (s, 4 H), 2.71 (t, 4 H), 7.1-7.5 (m, 30 H); mp 120-122 °C; Anal. Calcd for $C_{44}H_{46}N_4$: C, 83.76; H, 7.35. Found: C, 83.98; H, 7.26; MS(FAB), 631.

Compound **5**, ^{1}H NMR δ: 1.6 (b, 2 H), 1.8 (b, 1 H), 2.1-2.5 (m, 12 H), 7.1-7.6 (m, 45 H); mp 100-102 °C; Anal. Calcd for $C_{63}H_{60}N_4$: C, 86.65; H, 6.95; N, 6.41. Found: C, 86.48; H, 7.11; N, 6.36; MS(FAB), 873.

Compound **6**, ^{1}H NMR δ: 1.5-1.8 (m+b, 8 H), 2.18 (t, 4 H), 2.6-2.7 (t+s, 8 H), 7.1-7.5 (m, 30 H); ^{13}C NMR δ: 30.94, 42.25, 48.64, 49.50, 71.07, 126.36, 127.92, 128.79, 146.31; mp 91-93 °C; Anal. Calcd for $C_{46}H_{50}N_4$: C, 83.83; H, 7.65. Found: C, 83.64; H, 7.43.

Compound **7**, ^{1}H NMR δ: 1.6 (m, 7 H), 2.0 (m, 2 H), 2.15 (t, 2 H), 2.6 (t, 4 H), 2.6 (t, 2 H), 2.75 (t, 2 H), 7.1-7.5 (m, 45 H); mp 89-91 °C; *Anal.* Calcd for $C_{65}H_{64}N_4$: C, 86.62; H, 7.16. Found: C, 86.63; H, 7.24.

Compound **8**, ^{1}H NMR δ: 1.5 (m, 6 H), 1.65 (b + t, 6 H), 2.2 (t, 4 H), 2.6 (m, 4 H), 2.65 (t, 4 H), 7.1-7.5 (m, 30 H); ^{13}C NMR δ: 28.05, 31.03, 42.08, 48.51, 49.98,

70.88, 126.16, 127.73, 128.62, 146.17; mp 119-120 °C; *Anal.* Calcd for $C_{48}H_{54}N_4$: C, 83.92; H, 7.92. Found: C, 83.77; H, 7.84.

Compound **9,** ^{1}H NMR δ: 1.3 (m, 3 H), 1.5 (m, 4 H), 1.65 (m, 4 H), 2.0 (t, 2 H), 2.2 (t, 2 H), 2.3 (t, 2 H), 2.45 (m, 4 H), 2.6 (t, 2 H), 7.1-7.5 (m, 45 H); ^{13}C NMR δ: 28.18, 28.46, 30.98, 31.86, 41.85, 42.09, 48.50, 50.07, 51.37, 53.18, 70.76, 70.89, 79.16, 9 peaks (126.0 to 130.0), 144.0, 146.0; mp 86-88 °C; *Anal.* Calcd for $C_{67}H_{68}N_4$: C, 86.59; H, 7.38. Found: C, 86.35; H, 7.27.

Preperation of 5,8-Dityityl-1,5,8,12-tetraazadodecane 10. To a solution of 1.74 g (10 mmol) of 1,5,8,12-tetraazadodecane in 200 mL of acetonitrile was added 2.84 g (20 mmol) of ethyl trifluoroacetate at 0 °C. The mixture was stirred for 4 h, followed by the addition of 2.1 g (20 mmol) of Et_3N and 5.6 g (20 mmol) of trityl chloride. After stirring overnight at rt, the mixture was added to 5 g of NaOH in 20 mL of H_2O and heated for 2 h at 60 °C. The mixture was cooled and evaporated. The residue was dissolved in CH_2Cl_2 and washed three times with H_2O. The organic layers were dried ($MgSO_4$) and evaporated. The residue was purified using silica gel and MeOH to give 3.5 g (53%) of **10**; mp 198 °C; ^{1}H NMR δ: 0.8 (b, 4 H), 1.15 (m, 4 H), 2.05 (t, 4 H), 2.2 (t, 4 H), 2.6 (s, 4 H), 7.1-7.5 (m, 30 H); ^{13}C NMR δ: 35.58, 40.67, 52.38, 55.54, 79.22, 126.09, 127.61, 129.40, 144.17. *Anal.* Calcd for $C_{46}H_{50}N_4 \bullet 1.5\ H_2O$: C, 80.55; H, 7.48. Found: C, 80.64; H, 7.27.

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