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High Yield Selective Acylation of Polyamines: Proton as Protecting Group

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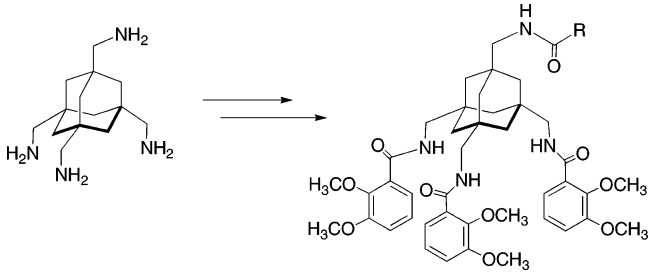
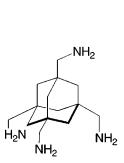
ABSTRACT



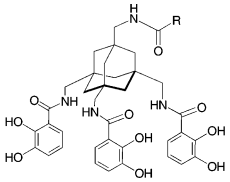
An advance in the selective acylation of polyamines having identical or similar amine functions is reported. While nucleophilicity differences between the various amine functions are slight, the corresponding conjugate acids exhibit pK_a values over a significant range. We have used proton as polyamine protecting group: the monoamine resulting from single deprotonation of a polyammonium compound has allowed for high yields of selective acylation.

Selective acylation of polyamines yielding unsymmetrical polyamides is an important transformation for making novel materials. The ubiquity of polyamide linkages in biological molecules also makes this transformation useful in the preparation of biomimetic compounds. Yet selective acylation of polyamines bearing more than one identical (or similar) amine function is a challenge and is generally accomplished by using a large excess of the polyamine, basing yield on the acylating agent.[1−5] This strategy results in only modest yields and is unattractive when using precious polyamines.

We recently prepared 1,3,5,7-tetrakis(aminomethyl)adamantane (**1**)[6] and are elaborating this tetrahedral assembly of four equivalent amine functionalities as the core of several families of compounds, including bifunctional analogues **2** of the *Escherichia coli* siderophore enterobactin (**3**).[7] We report here methodology for high yield selective acylation of symmetric polyamines.



1



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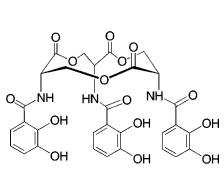

3

Compound **4**, a precursor to **2**, was first prepared through stoichiometric restriction (Scheme 1), but with unimpressive

(1) Stahl, G. L.; Walter, R.; Smith, C. W. *J. Org. Chem.* **1978**, *43*, 2285−2286.
(2) Roy, B. C.; Malik, S. *J. Org. Chem.* **1999**, *64*, 2969−2974.
(3) Cohen, S.; Raymond, K. N. *Inorg. Chem.* **2000**, *39*, 3624−3631.
(4) Bendavid, A.; Burns, C. J.; Field, L. D.; Hashimoto, K.; Ridey, D. D.; Sandanayake, K. R. A. S.; Wiesorek, L. *J. Org. Chem.* **2001**, *66*, 3709−3716.
(5) Cardner, R. Al.; Ghobrial, G.; Naser, S. S.; Phanstiel, O. *J. Med. Chem.* **2004**, *47*, 4933−4940.

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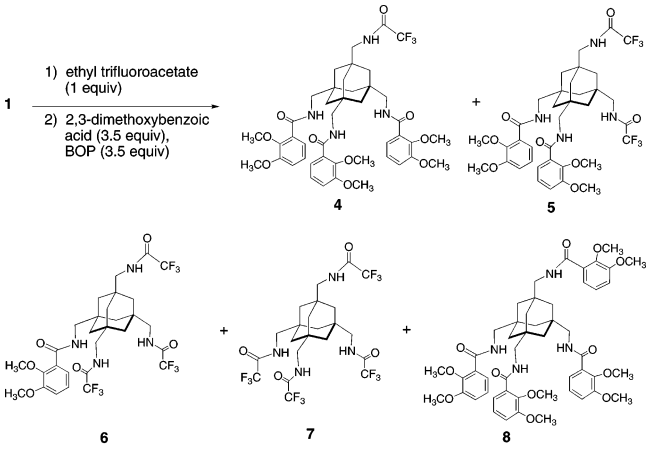
Scheme 1

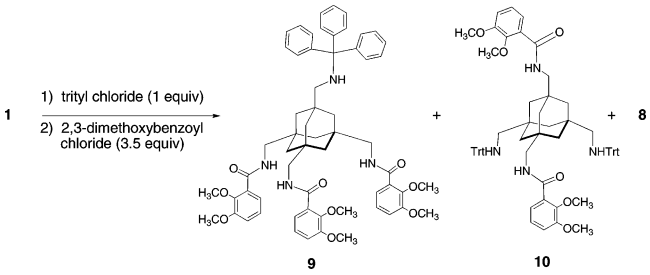


BOP: benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate

results. One equivalent of ethyl trifluoroacetate[8] was added to 1 equiv of **1** to introduce the first amide. Subsequently, 3.5 equiv of 2,3-dimethoxybenzoic acid activated by benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP, Castro's reagent)[9] was added to benzoylate the remaining free amines. Chromatographic separation of the reaction mixture provided the desired mono(trifluoroacetamide)tris(2,3-dimethoxybenzoylamide) **4** in 32% yield. We also isolated 16% of bis(trifluoroacetamide) **5** and 8% of tris(trifluoroacetamide) **6**. No tetrakis(trifluoroacetamide) **7** or tetrakis(2,3-dimethoxybenzamide) **8** were observed.[10] The modest selectivity underscores that the nucleophilicity of the four equivalent amine functions in **1** is similar to that of the residual free amines in the mono- and bis(trifluoroacetamides) toward ethyl trifluoroacetate. These results are consistent with reports of only modest success in selective acylation of compounds bearing more than one similar amino group.[1−5]

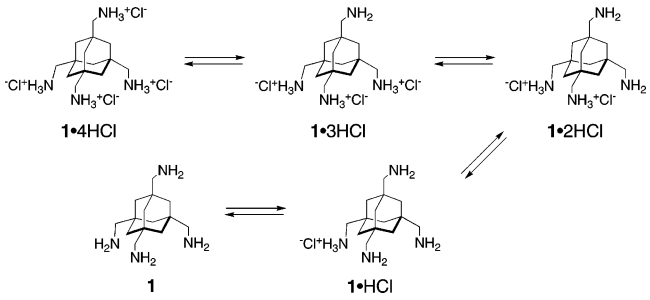
We attempted to bias the reaction toward selectivity by first introducing a bulky trityl group, with the expectation that it would preferentially monoalkylate, leaving the remaining three amines free for subsequent acylation (Scheme 2). However, reaction of tetraamine **1** with 1 equiv of trityl chloride, followed by 3.1 equiv of 2,3-dimethoxybenzoyl chloride, resulted in a product composition with largely unimproved selectivity in forming the desired mono(*N*-tritylaminomethyl)adamantane **9**. Separation of the crude reaction mixture provided a 40% yield of **9**, 6% of bis(*N*-tritylaminomethyl)adamantane **10**, and 5% of tetrakis(2,3-dimethoxybenzamide) **8**.

Scheme 2



While nucleophilicity differences between the various amine functions in polyamines are slight, the corresponding conjugate acids exhibit pK_a values over a significant range. For example, the conjugate diacid of ethylene diamine has pK_a values of 7.6 and 10.8; the conjugate triacid of 1,2,3-triaminopropane exhibits pK_a values of 3.6, 7.9, and 9.6.[11] The conjugate tetraacid of spermine has pK_a values of 8.1, 8.9, 10.1, and 10.9.[12] We observed pK_a values between 6.8 and 8.4 in the tetrahydrochloride of **1** (Table 1).

Table 1. Chemical Shifts for Exo- and Endocyclic Protons of **1**·4HCl Treated Sequentially with TEA in MeOD-d_4 (pK_a Values of Ammonium Protons were Determined in H_2O by Potentiometric Titration with KOH)



equiv of TEA	species	exocyclic CH_2, ppm	endocyclic CH_2, ppm	pK_a
0	**1**·4HCl	2.97	1.57	
1	**1**·3HCl	2.73	1.35	pK_{a1} = 6.8
2	**1**·2HCl	2.64	1.29	pK_{a2} = 7.9
3	**1**·HCl	2.29	1.27	pK_{a3} = 8.2
4	**1**	2.24	1.27	pK_{a4} = 8.4

In a ^{1}H NMR experiment, a solution of **1**·4HCl in methanol-d_4 was titrated with sequential equivalents of triethylamine. We observed rapid exchange of remaining ammonium protons among the amine functions after addition of each equivalent of base. In each case, we saw resonances corresponding to only one environment for all endocyclic methylene protons and only one for all exocyclic methylene protons (Table 1).

(6) Lee, G.; Bashara, J. N.; Sabih, G.; Oganesyan, A.; Godjoian, G.; Duong, H. M.; Marinez, E. R.; Gutierrez, C. G. *Org. Lett.* **2004**, *6*, 1705−1707.

(7) Marinez, E. R.; Salmassian, E. K.; Lau, T. T.; Gutierrez, C. G. *J. Org. Chem.* **1996**, *61*, 3548−3550.

(8) Geall, A. J.; Blagbrough, I. S. *Tetrahedron*. **2000**, *56*, 2449−2460.

(9) Castro, B.; Donmoy, T. R.; Elvin, G.; Selve, O. *Tetrahedron Lett.* **1975**, *16*, 1219−22.

(10) Compounds **4**−**6** containing the trifluoroacetamide moiety exhibited more complicated NMR spectra than expected (we suggest the involvement of intramolecular hydrogen bonding and also *cis*- and *trans*-trifluoroacetamide isomers). This will be elaborated in future reports.

(11) Weast, R. C. In *CRC Handbook of Chemistry and Physics*; Melvin, J. A., Beyer, H. W., Eds.; CRC Press, Inc.: Boca Raton, FL, 1984−1985; pp D-164−165.

(12) Geall, A. J.; Blagbrough, I. S.; Taylor, R. J.; Earll, M. E.; Eaton, M. A. W. *Chem. Commun*. **1998**, *13*, 1403−1404.

We considered the use of the proton as polyamine protecting group, testing the notion that the monoamine resulting from single deprotonation of a polyammonium compound could allow for selective acylation. We deprotonated **1**·4HCl in methanol with 1 equiv of triethylamine (TEA), and the resulting amine was trapped with 1 equiv of ethyl trifluoroacetate. Subsequent addition of excess TEA and 3.5 equiv of BOP-activated 2,3-dimethoxybenzoic acid resulted in 69% yield of mono(trifluoroacetamide) **4**, 12% of di(trifluoroacetamide) **5**, 2% of tris(trifluoroacetamide) **6**, and 5% of tetrakis(2,3-dimethoxybenzamide) **8**. These results show a marked improvement in selectivity and yield of **4**.

In deprotonations with TEA, each equivalent produced an equivalent of the conjugate acid, TEA·H^+(pK_a in water = 11.1).[11] To avoid the possible back-protonation of aminomethyl groups on the adamantane core by TEA·H^+, we switched the base to an alkoxide, whose (alcohol) conjugate acids have considerably higher pK_a. One equivalent of potassium *t*-butoxide (*t*-BuOK) was used to deprotonate **1**·4HCl, followed sequentially by addition of 1 equiv of ethyl trifluoroacetate, excess TEA, and 3.5 equiv of BOP-activated 2,3-dimethoxybenzoic acid to produce unsymmetric monotrifluoroacetamide **4** in 92% yield. We also isolated 2% of symmetric tetrakis(2,3-dimethoxybenzamide) **8**. Under these reaction conditions, we did not observe di(trifluoroacetamide) **5** or tris(trifluoroacetamide) **6**. Data in Table 2 summarize

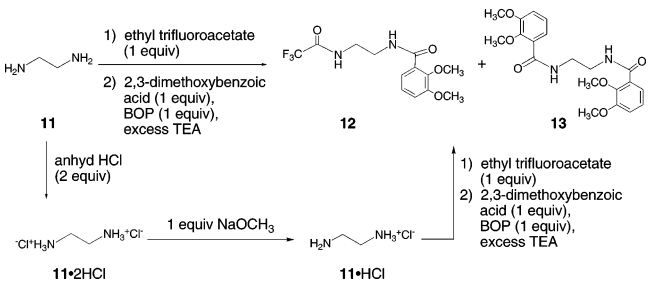
Table 2. Isolated Yields (Based on Amine) for Selective Acylation by Deprotonation of **1**·4HCl (Data for Acylation of Neutral Tetraamine **1** Are Given for Comparison; the Compounds Refer to Structures in Scheme 1)

substrate	base	% **4**	% **5**	% **6**	% **7**	% **8**
1	none	32	8	16	0	0
1·4HCl	TEA	69	12	2	0	5
1·4HCl	*t*-BuOK	92	0	0	0	2

the degree of selectivity in acylation obtained under our various conditions.

We applied this procedure to ethylenediamine (**11**) (Scheme 3). As reference, we reacted free diamine **11** with 1 equiv

Scheme 3



of ethyl trifluoroacetate, followed by an equivalent of BOP-activated 2,3-dimethoxybenzoic acid, which produced a 30% yield of the unsymmetric mono(trifluoroacetamide)−mono-(2,3-dimethoxybenzamide) **12** and 62% of symmetric bis-(2,3-dimethoxybenzamide) **13**. However, monodeprotonation of the ethylene diamine dihydrochloride (**11**·2HCl) with 1 equiv of sodium methoxide followed sequentially by reaction with 1 equiv of ethyl trifluoroacetate, excess base, and 1 equiv of BOP-activated 2,3-dimethoxybenzoic acid gave markedly better results. Chromatographic separation of the crude mixture provided unsymmetric **12** in 86% yield and 10% of symmetric diamide **13** (Table 3).

Table 3. Isolated Yields for Selective Acylation of Ethylene Diamine Starting from the Neutral Amine and from the Bis(ammonium) Salt

substrate	base	solvent	% **12**	% **13**
11	none	CH_2Cl_2	30	62
11·2HCl	$NaOCH_3$	CH_3OH	86	10

Additional examples suggest the generality of the procedure (Table 4). The two primary amine functions in 1,2-diaminopentane (**14**) are unsymmetrically acylated by this procedure to produce **15** in 83% yield (entry 1).

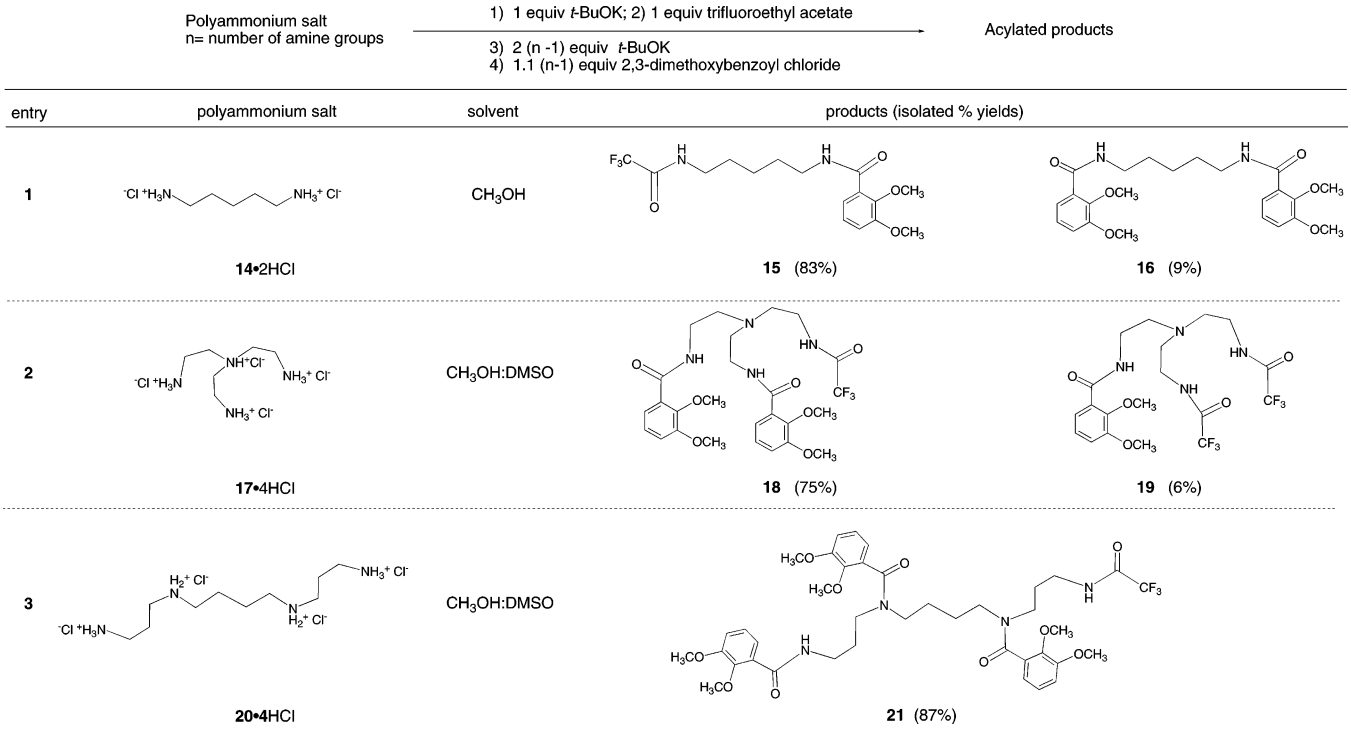
Tris(2-aminoethyl)amine (TREN) (**17**) has long been used as a backbone for the synthesis of polydentate ligands, including some where the three amines have been selectively acylated to bear different amide units.[3] The present procedure allows for differentiation of the equivalent primary amine groups in TREN to produce **18** in good yield (entry 2).

Discrimination between primary and secondary amines in polyamines such as spermine (**20**) has been readily accomplished by earlier workers; however, differentiation between the two primary amines has been more difficult.[12] The proton here is a useful protecting group. The pK_a difference between the two primary ammonium ions in **20**·4HCl is sufficient (8.1 and 8.9) to allow for the production of unsymmetrically acylated **21** in 87% yield as the only product with a spermine backbone (entry 3). The location of the trifluoroacetamide on a primary amine was established by ^{1}H NMR: the spectrum of **21** exhibited a one-proton signal at 8.42 ppm for the primary benzamide and a one-proton triplet for the primary trifluoroacetamide proton at 6.82 ppm.

We have extended the use of the proton as a protecting group to selectively alkylate a diamine (Scheme 4). Piperazine (**22**) has been used to link disparate molecular fragments. The preparation of **23** where one of the two equivalent amines has been selectively attached to an NBD unit has been reported in quantitative yield based on NBD chloride and a 3-fold excess of piperazine.[13] We produced this molecule in 96% yield by the reaction of NBD chloride with an equimolar amount of the monoamine resulting from single deprotonation of bisammonium salt **22**·2HCl.

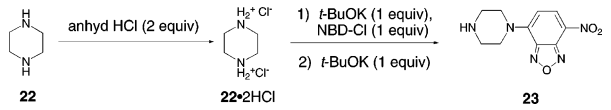
(13) Nudelman, R.; Ardon, O.; Hader, Y.; Chen, Y. l.; Libman, J.; Shanzer, A. *J. Med. Chem.* **1998**, *41*, 1671−1678.

Table 4. Selective Acylation of Additional Polyammonium Salts



To summarize, the proton is an attractive and atom-efficient protecting group for discriminating among nitrogen functions in polyamines. This new methodology produces high yields of selective acylation (or alkylation) of polyamines in one-pot reactions, which affords readily separable mixtures. The number and amount of possible byproducts are greatly reduced. We are currently studying the scope and useful application of reactions that result from controlled deprotonation of poly(ammonium) ions to effect selective functionalization.

Scheme 4



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Supporting Information Available: Experimental details and data characterizing all new compounds are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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