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Nucleophilic cationization reagents

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ABSTRACT

Nucleophilic cationization reagents fitted with aminooxy groups are described. Practical syntheses of mono- and bis-aminooxy tetraalkylammonium iodides including *N*-hydroxyethyl-functionalized analogs are reported. An oximation example using one of the reagents is presented to illustrate their use in synthesis of cationic materials.

A wide variety of materials have been modified by the covalent attachment of quaternary ammonium functionality to furnish derivatives with overall positive charge.[1] This process, a derivatization known as cationization, typically proceeds via reaction of the substrate with an electrophilic reagent containing a quaternary ammonium salt. For example, the cationization of proteins is performed to enhance their intracellular delivery via adsorptive-mediated endocytosis.[2] The cationization of cellulose fibers (e.g., cotton) can improve the uptake of dyes in subsequent coloring operations.[3] These applications and others principally rely on cationization reagents of the type **1**–**5** depicted in Figure 1. Indeed, chlorohydrin **1**[4] and epoxide reagents **2**[5] and **3**[6] have been particularly useful for the cationization of carbohydrate domains in reactions with bases at elevated temperatures. The reagents **4**[7] and **5**[8] illustrate other permutations of reactive electrophilic groups used in reactions to derivatize materials with ammonium salts.

Of particular interest to us[9] is the use of quaternary ammonium salts attached to lipid- or polymer-frameworks as vehicles for the intracellular delivery of polynucleotides to mammalian cells.[10] We felt that a mild, more convenient procedure for direct attachment of ammonium ions to substrates would greatly improve our abilities to access new cationic materials. On considering alternative strategies, the chemospecific reaction between aminooxy and ketone or aldehyde carbonyl groups appeared to be an ideal, nucleophilic counterpart to current methods.[11] Given the ease of oximation and the robust nature of the oxime ether linkage, we targeted aminooxy reagents **6.1** and **6.2** (Fig. 2) for synthesis. Our interest in gene transfer materials also led us to prepare hydroxyethyl-functionalized analogs **7.1** and **7.2**. The benefit of hydroxyethylated polar domains in gene delivery is well documented.[12] Consequently, we disclose herein a general synthesis of the novel nucleophilic cationization reagents **6** and **7**.

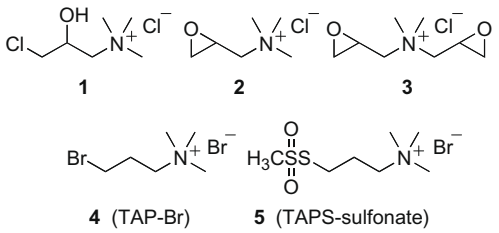


Figure 1. Common cationization reagents.

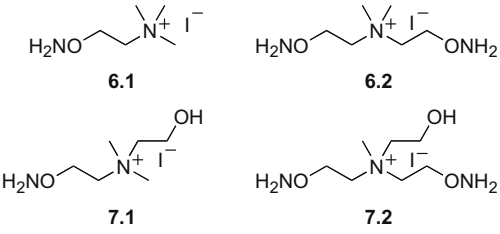
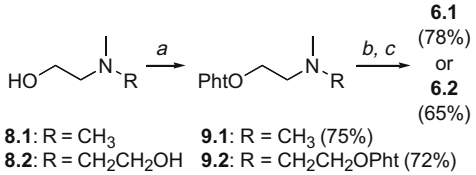


Figure 2. Cationic aminooxy reagents.

Reaction of the commercially available ethanolamines **8.1** and **8.2** (Scheme 1) with *N*-hydroxypthalimide (NHP) under Mitsunobu



Scheme 1. Reagents and conditions: Pht = phthalimidoyl; (a) *N*-hydroxyphthalimide, PPh_3, DIAD, THF, 0 °C to rt, 12 h; (b) CH_3I, sealed tube, 45 °C, 2 h; (c) $H_2NNH_2{\cdot}H_2O$, EtOH, H_2O, rt, 12 h.

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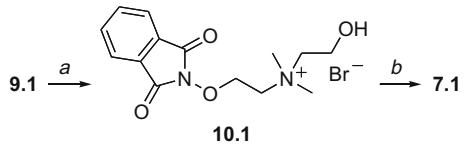
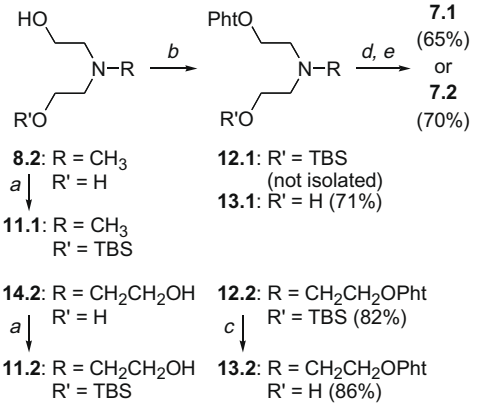


Scheme 2. Reagents and conditions: (a) 2-bromoethanol, CH_3CN, 60 °C; (b) $H_2NNH_2{\cdot}H_2O$, EtOH, rt, 12 h.

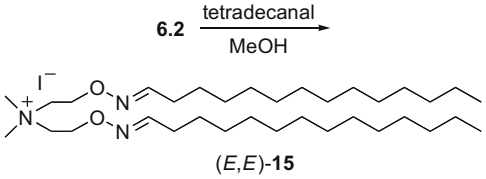


Scheme 3. Reagents and conditions: TBS = *t*-BuMe$_2$Si; (a) TBSCl (0.2 equiv), Et_3N (1 equiv), CH_2Cl_2; (b) *N*-hydroxyphthalimide, PPh_3, DIAD, THF, 0 °C to rt, 12 h; (c) 48% aq HF, THF, 0 °C to rt, 12 h; (d) CH_3I, sealed tube, 60 °C, 2 h; (e) $H_2NNH_2{\cdot}H_2O$, EtOH, rt, 12 h.

conditions[13] (equimolar amounts of NHP/PPh_3/DIAD) furnished phthaloyloxy amines **9.1** and **9.2**, respectively. Amine quaternization was best accomplished by gently warming the amines in methyl iodide (ca. 0.2 M). The resultant, crude ammonium iodides were treated directly with hydrazine in ethanol to cleave the phthaloyl groups. After work-up, the water-soluble aminooxy reagents **6.1** and **6.2** were isolated by lyophilization of the aqueous layer and then purified using reverse phase HPLC.

By analogy to previous syntheses of *N*-(2-hydroxyethyl)ammonium salts,[14] we expected the N-alkylation of **9.1** using 2-bromoethanol to be a convenient route to hydroxyethyl-functionalized reagent **7.1** (Scheme 2). However, the N-alkylation required heating the reactants at 60 °C, and this resulted in a complex mixture of products containing ammonium bromide **10.1**. Subsequent hydrazinolysis failed to deliver a product mixture that was more amenable to purification. Consequently, **7.1** was obtained in only poor yields (ca. <20%). Due to these complications, we opted to rely again on N-methylation as the penultimate, ammonium salt-forming step.

Monosilylation of di- (**8.2**) and triethanolamine (**14.2**, Scheme 3) was accomplished by reacting an excess of each ethanolamine with TBSCl as the limiting reagent. The resultant, mono-protected ethanolamines **11.1** and **11.2** were then transformed to the corresponding *N*-(2-hydroxyethyl)-functionalized aminooxy reagents using the path established for synthesis of reagents **6**. While desilylation of the more polar phthaloyloxy amine **12.1** proceeded smoothly on work-up by stirring with aq HCl, this approach did not work for phthaloyloxy amine **12.2**. Furthermore, standard TBAF-mediated deprotection of **12.2** resulted in double N–O cleavage, giving **14.2** as the principal product. Other attempts (e.g., AcOH- or TsOH-mediated deprotections) were equally disappointing. We were gratified to find, however, that prolonged reaction with aqueous HF furnished the desired product **13.2**. The amine quaternizations, this time using methyl iodide, and subsequent hydrazinolyses proceeded without incident, and the cationic aminooxy reagents **7.1** and **7.2** were isolated in good overall yield.



Scheme 4. Cationic lipid synthesis.

To demonstrate the synthetic utility of the aminooxy cationization reagents in a representative oximation reaction, we used bis(aminooxy) ammonium salt **6.2** to prepare a new cationic lipid. Simple mixing of **6.2** with tetradecanal in methanol furnished the corresponding bis(oxime ether) lipid **15** (Scheme 4) as a 2.7:1 mixture of diastereomers in 82% yield. By comparison to the literature reports[15] on oximyl proton shifts in ^{1}H NMR, we assigned the major isomer the (*E*,*E*)-configuration of oxime ether stereochemistry as depicted in Scheme 4 and the (*E*,*Z*)-configuration to the minor isomer.[16] The utility of the prototypic oxime ether lipid **15** as an agent for gene delivery is ongoing and will be reported elsewhere.

In summary, we report a general synthesis of novel ammonium ion-based aminooxy reagents that complement existing reagents for cationization applications. The unfunctionalized and hydroxyethyl-functionalized aminooxy reagents as well as the bis(aminooxy) analogs prepared herein can serve as nucleophilic counterparts for reaction with aldehydes and ketones in oximation reactions designed to modify carbonyl surfaces, such as those formed on partial periodate oxidation of carbohydrate domains. In contrast to the harsh conditions typically employed for reaction with the electrophilic cationization reagents, the mild conditions of oxime ether formation should make the present aminooxy approach an attractive alternative. In one demonstration, we prepared a representative member of a new class of cationic lipids that features an oxime ether as the tethering moiety between hydrophobic and hydrophilic domains.

Acknowledgments

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Supplementary data

Supplementary data (experimental details for all reactions and spectral data for new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.094.

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16. The oximyl proton shift for the (*E*)-oxime ether sidechain in **15** occurs at δ 7.58, (*Z*)-isomer at δ 6.91.