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LETTERS

Synthesis of an Azido Spermidine Equivalent

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Abstract: The synthesis and conversion of a new spermidine equivalent (**2**) to squalamine is reported. It is prepared in a practical manner, is stable to sodium borohydride reduction, is converted to spermidine under mild conditions, and is not prone to internal cyclization reactions.

Key words: polyamines; azides; reduction; amination

Spermidine is an abundant natural substance, which has multiple biological functions in the mammalian system[1] and is present in many natural products.[2] Due to its asymmetry, spermidine requires the selective masking of its termini in order to be incorporated regioselectively. Although there are many reports of differentially protected spermidine reagents,[3] none of them suited our purposes for the preparation of squalamine (**1**), which possesses a sensitive sulfate functionality. The protecting group had to be stable to reductive amination conditions and removed under mild conditions. Because we were developing a large-scale process, the synthesis and deprotection of the spermidine fragment had to be accomplished in an economical manner. We recently reported a nitrile containing spermidine synthon, which met these requirements.[4] However, it was deficient in that it contains an electrophilic nitrile function, leading to by-products of cyclization reactions. We wish to report here the synthesis and coupling of the azido-substituted spermidine equivalent **2**, which afforded squalamine more efficiently.

The synthesis of **2**[5] and its conversion to squalamine is shown below. Chlorobutanol was heated with 1,3-diaminopropane at 140-150°C (oil bath temp) for 24 hours and the monoalkylated product was separated by fractional distillation in 48% isolated yield. The primary and secondary amines were protected with BOC anhydride, and the alcohol was converted to its mesylate, which was then treated with sodium azide. The BOC protecting group was removed upon treatment with 4 M HCl in dioxane to give **2** as the hydrochloride salt.[6,7] Reductive alkylation on the primary amine of **2** with the steroid intermediate **6** was accomplished with sodium methoxide, 3Å sieves, and sodium borohydride to afford azido-squalamine, from which squalamine was obtained in 69% yield after hydrogenation and purification with RP-HPLC.

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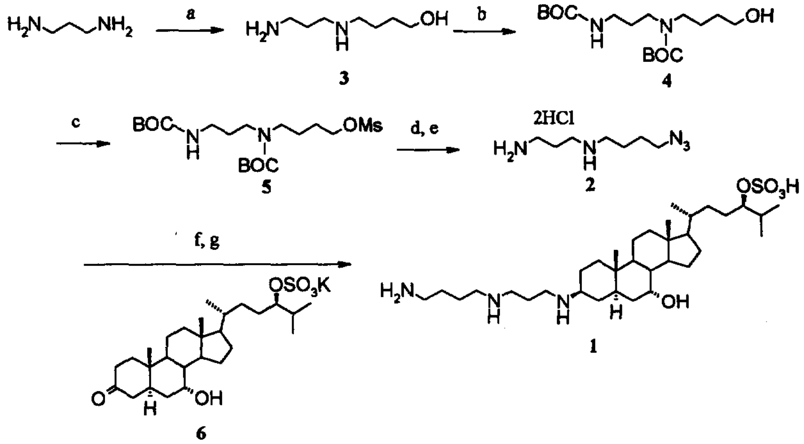
Reagent **2**, prepared without chromatography, possessed the advantages of yielding a less complex mixture of products in its reaction with the advanced intermediate **6** and of a higher yield of squalamine (69% vs 60%), than reported previously.[4] The azide, **2**, has little electrophilic character, making it immune to reaction with the secondary amine. This paper thereby demonstrates the potential of a novel spermidine equivalent.



a.) 0.37 equiv. 4-chlorobutanol, H_2O, 140-150°C oil bath, purification by distillation (0.2 mm, bp of **3**: 87-90°C), 48%; b.) BOC_2O, EtOH, rt, 48 h; c.) Et_3N, MsCl, CH_2Cl_2, rt, 16 hours; d.) NaN_3, DMF, rt, 48 h, 80% from **3**; e.) HCl, dioxane, 16 h, rt; f.) 2 equiv. NaOMe, 0.5 equiv. **6**, 3Å sieves, methanol, rt, 24 hours, then –78°C, $NaBH_4$; g.) H_2, RaNi, RP-HPLC, 69% from **6**.

References and Notes

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5.) Previous attempts to synthesize **2** by direct alkylation of sodium azide with a halogenated spermidine precursor were only partially successful due to the spontaneous cyclization of the aminobutylbromide. Protection of the secondary amine is critical to prevent the formation of the pyrrolidine by-product. Carboni, B.; Benalil, A.; Vaultier, M. *J. Org. Chem.* **1993**, *58*, 3736-3741.

6.) Spectral data for **2**: ^1H (δ, CD_3OD, 400 MHz): 3.38 (m, 2H), 3.10 (m, 2H), 3.04 (m, 4H), 2.07 (m, 2H), 1.77 (m, 2H), 1.65 (m, 2H); ^{13}C(δ, CD_3OD, 100 MHz): 52.0, 48.8, 46.0, 38.1, 27.1, 25.5, 24.8; Anal. Calcd for $C_7H_{17}N_5$-2HCl: C, 34.43; H, 7.84; N, 28.68. Found: C, 34.16; H, 7.68; N, 28.31; MS (+FAB): 172 (M+1, 100).

7.) An alternative procedure that utilized reductive amination of 4-azidobutanal and monoprotected 1,3-diaminopropane was abandoned, because of safety concerns. CAUTION: Alkyl azides in which the azide represents a significant portion of the molecular weight are prone to detonate.