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An Efficient Protocol for Solution- and Solid-Phase End-Group Differentiation of Spermidine

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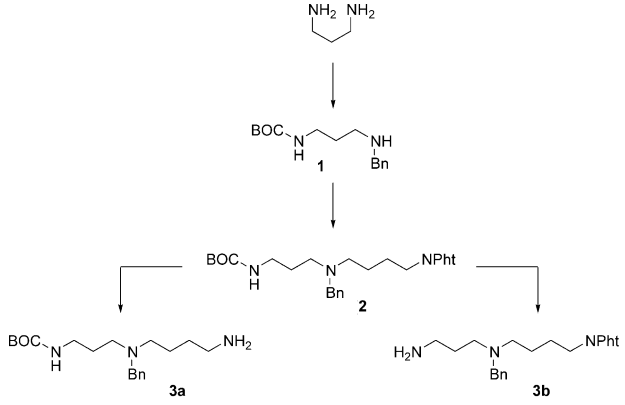
Abstract—The end-group differentiation of a selectively protected spermidine was achieved through a short sequence of steps. The functionalization of spermidine in solid-phase was monitored by FT-IR.

The range of biological activities displayed by conjugated polyamines has brought considerable attention to this class of compounds, making them attractive targets for synthesis.[1] The strategy commonly adopted to access these substrates lies on the synthesis of the polyamine backbone, and subsequent attachment of the desired chain to one of its terminal amino groups. In the case of unsymmetrical polyamines, such as spermidine, the differentiation of the primary amino groups is required. However, despite its seemingly simple structure, the selective functionalization of spermidine terminus frequently involves a series of protection and deprotection steps or the reduction of amino group equivalents.[2] As a result, these synthetic approaches usually suffer from low yields and long reaction sequences. Alternative syntheses of orthogonally protected spermidines is highly desirable.[3] As an outgrowth of our involvement with the solution- and solid-phase synthesis of spermidine conjugates we have developed a short, multigram synthesis of a selectively protected spermidine. Herein we describe a protocol for terminal amino group differentiation of spermidine, that has been successfully applied in our laboratories.

The route outlined in Scheme 1 begins with the monoprotection of 1,3-propanediamine with $(Boc)_2O$,[4] followed by the benzylation of the crude product,[5] to provide the protected diamine **1** in 59% yield (two steps) after purification by flash-chromathography. Alkylation of **1** with 4-bromobutylphtalimide using K_2CO_3 in refluxing acetonitrile over 24 h,[6] afforded the protected spermidine **2** as a colorless oil, in 73% yield.[7] To the best of our knowledge, this three-step sequence is one of the shortest syntheses described for a functionalized spermidine, and we have been performing it in batches of up to 7 g each.

Subsequent end-differentiation of spermidine **2** was accomplished either by the treatment with TFA in CH_2Cl_2 at room temperature for 19 h to afford amine **3a** in 99% yield, or by the hydrazinolysis of the phtalimide group in refluxing ethanol for 3 h to give amine **3b** in 82% yield, after purification by flash-chromatography. Alternatively, the hydrochloride salt of amine **3a** could be obtained in quantitative yield by the reaction with concentrated HCl in ethanol at room temperature



Scheme 1. Synthesis of a selectively functionalized spermidines.

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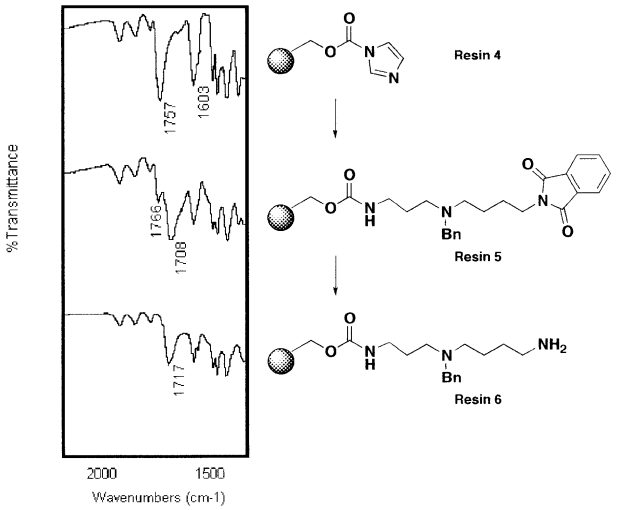

Scheme 2. Immobilization of spermidine **3a**.

overnight.[8] However, the ammonium salt proved hygroscopic and difficult to handle.

After securing comfortable amounts of spermidine **3a**, we turned our attention to its immobilization on solid support. The solid-phase reactions were monitored by FT-IR, and the diagnostic region is presented in Scheme 2. Initially, the Wang resin^{TM} was activated with carbonyl-diimidazole in THF for 4 h (Scheme 2).[9] Attachment of **3a** to resin **4** was carried out in refluxing CH_2Cl_2 for 10 h. The disappearance of the acyl-imidazole absorption at 1757 cm^{-1} and the appearance of two absorptions assigned to phtalimide (1766 cm^{-1}) and carbamate (1708 cm^{-1}) confirmed this step. Finally, removal of phtalimide from resin **5** was performed with aqueous hydrazine in EtOH:THF (1:1), under reflux for 6 h. Resin **6** was assigned based on the disappearance of the absorption at 1766 cm^{-1} and the positive ninhydrin test. The use of resin **6** in the synthesis of potential inhibitors of trypanosomatides' enzymes is currently under investigation and will be reported in due course.

In conclusion, we described a short synthesis of a selectively functionalized spermidine and its end-group differentiation in solution- and in solid-phase.

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7. Data for spermidine **2**: colorless oil; IR (thin film) 3393, 3026, 2973, 1771, 1713, 1511, 1396, 1366, 1250, 1172, 721, 530 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.61–7.80 (4H, m, Pht-H), 7.13–7.20 (5H, m, Ph–H), 3.56 (2H, t, $J=6.67$ Hz, $-CH_2NPht$), 3.41 (2H, s, $-CH_2Ph$), 3.35 (2H, q, $J=5{,}53$ Hz, $-CH_2NH$), 2.36 (4H, m, $-CH_2NCH_2-$), 1.40–1.60 (6H, m, three overlapping CH_2), 1.39 (9H, s, three CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.20, 26.37, 26.65, 28.47, 37.77, 39.60, 52.14, 53.19, 58.80, 78.61, 123.16, 126.94, 128.25, 128.90, 132.11, 133.88, 139.38, 156.01, 168.36; TLC $R_f=0.65$ (EtOAc/hexanes, 1:1); Exact mass calcd for $C_{27}H_{36}N_3O_4$: 465.2627, found: 465.2624.

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