Reagents for the Selective Acylation of Spermidine, Homospermidine, and Bis[3-aminopropyl]-amine

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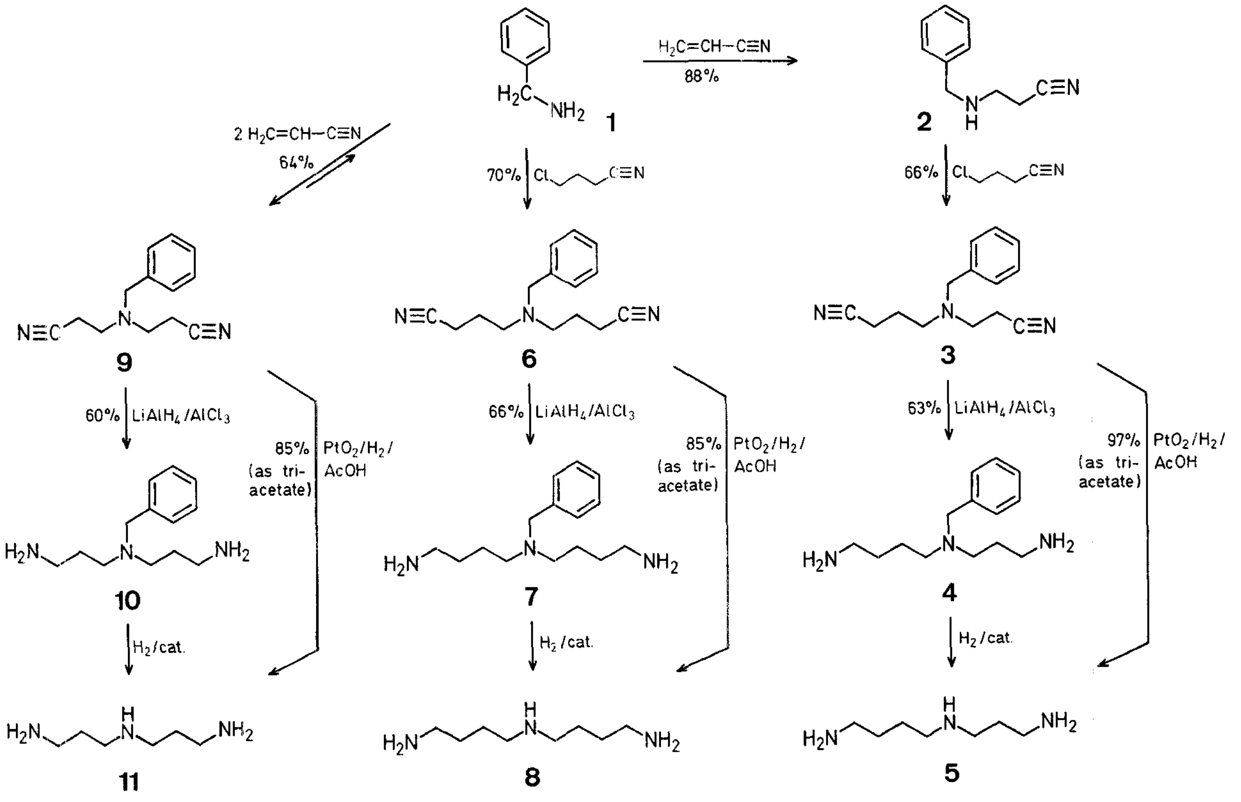
In recent years, a great deal of interest has been focused on the naturally occurring acyclic triamines: spermidine (**5**), homospermidine (**8**), bis[3-aminopropyl]-amine (**11**), and their derivatives[1-5]. The polyamines themselves are intimately involved in normal growth processes[6,7,8], while many of their derivatives have been shown to be potent iron chelators[9-12] and therefore of interest in chelation therapy. Although the triamines have all been synthesized in a variety of different ways, until recently effective methods for the synthesis of derivatives have been limited[2,3]. The major problem with derivatizing the amines is one of selectivity. While homospermidine and bis[3-aminopropyl]-amine both have two identical primary N-atoms and a secondary N-atom, spermidine has two different primary N-atoms as well as a secondary amine. Our interest in these polyamines focuses on compounds whose synthesis requires selective bis-functionalization of the primary N-atoms followed by acylation of the secondary amine.

There are currently three methods available for selective functionalization of these polyamines[13,14,15]. The oldest one employs N^4-tosyl-N^8-phthaloylspermidine which requires eight steps to synthesize[13]. This reagent is really designed to fix three different substituents to the spermidine backbone. This, coupled with the eight steps required to access the reagent, makes it somewhat impractical for the mode of acylation we require. A newer reagent, N^4,N^8-di-*t*-butoxycarbonylspermidine, was designed for the introduction of an acyl group at the N^1-position of spermidine[14]. It is accessible in 49% yield, in three steps. However, it still is not designed for the desired type[16] of terminal bis-acylation. The most recent and elegant method takes advantage of a "transiently protected" spermidine[15]. Cyclocondensation of the amine with aqueous formalin produces 1-(4-aminobutyl)-hexahydropyrimidine which can then be diacylated at N-3 and the primary N-atom. Deprotection (ring cleavage) affords the bis-terminal acylated compound. Unfortunately, the procedure cannot be applied to the synthesis of polyamines without at least one $(CH_2)_3$ bridge between the N-atoms. Furthermore, the conditions of deprotection (piperidine/ethyl hydrogen malonate/ethanol, 70 °C, 18 h) could lead to undesired side reactions.

An earlier procedure for selective acylation of spermidine[16] used N^4-benzylspermidine as substrate. The resultant N^1,N^8-diacylspermidines can be debenzylated quantitatively and the N^4-position can then also be acylated if desired. We have now extended the procedure to the selective acylation of homospermidine (**8**) and bis[3-aminopropyl]-amine (**11**). The method works well and nicely complements the procedure of Ref.[15] which is only applicable to polyamines having a 1,3-propanediamine moiety.

We describe here the synthesis of the benzyl-protected acylation substrates **7** (derived from homospermidine, **8**) and **10** (derived from bis[3-aminopropyl]-amine, **11**) starting from benzylamine (**1**) and 4-chlorobutanenitrile or acrylonitrile, respectively, and give one typical example of the *N*-acylation procedure which is analogous to that of Ref.[16]. In addition, we describe the direct conversion of 4-benzyl-4-azaoctanedinitrile [**3**, obtained from 3-benzylaminopropanenitrile (**2**) and 4-chlorobutanenitrile] into spermidine (**5**) triacetate via catalytic hydrogenation which represents a simplification of the two-step route **3**→**4**→**5**.

The dinitrile **9** may undergo some retro-Michael reaction during distillation. Purification by column chromatography does not present this problem. However, because of the simplicity of the synthesis and the low costs of the starting materials, we normally distill the dinitrile and take some loss.



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N^5-Benzylhomospermidine (7):

5-Benzyl-5-azanonanedinitrile (**6**): A solution of 4-chlorobutanenitrile (19.30 g, 0.186 mol) in dry butanol (100 ml) is added dropwise over 2 h to a stirred mixture of benzylamine (**1**; 10.30 g, 0.096 mol), anhydrous sodium carbonate (30.48 g, 0.288 mol), and potassium iodide (5.66 g, 0.034 mol) at 115 °C. After refluxing an additional 20 h under a nitrogen atmosphere, the mixture is allowed to cool to room temperature and filtered; the salts are washed well with ether. The combined filtrate and washings are extracted with 3 normal hydrochloric acid (3 x 100 ml) and water (2 x 100 ml). The acid and water extracts are combined and washed with ether (2 x 100 ml), made basic with sodium carbonate, and extracted with ether (3 x 100 ml). The resulting ethereal solution is dried with sodium sulfate, filtered, evaporated, and distilled; yield: 15.71 g (70%); b.p. 166 °C/0.05 torr. [An analytical sample was obtained by column chromatography using petroleum ether/ether (25/75) as eluent].

$C_{15}H_{19}N_3$	calc.	C 74.65	H 7.94	N 17.41
(241.3)	found	74.83	8.06	17.45

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.4$–2.1 (m, 4H); 2.1–2.8 (m, 8H); 3.50 (s, 2H); 7.22 ppm (s, 5H).

N^5-*Benzylhomospermidine* (**7**): A solution of aluminum chloride (5.05 g, 0.038 mol) in anhydrous diethyl ether (100 ml) is added to lithium aluminum hydride (1.44 g, 0.038 mol) in anhydrous ether (300 ml). The mixture is stirred under a nitrogen atmosphere for 15 min followed by the dropwise addition of 5-benzyl-5-azanonanedinitrile (**6**; 4.16 g, 0.017 mol) in anhydrous ether (50 ml). After stirring an additional 15 h, the mixture is cooled to 0 °C and quenched with aqueous 30% potassium hydroxide (w/v; 200 ml). The contents of the reaction vessel are loaded into a continuous extraction apparatus and extracted with diethyl ether for 48 h. The resulting solution is dried with sodium sulfate, filtered, evaporated, and distilled; yield: 2.79 g (65%); b.p. 185 °C/0.075 torr.

$C_{15}H_{27}N_3$	calc.	C 72.24	H 10.91	N 16.85
(249.4)	found	72.15	11.10	16.76

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.12$ (s, 4H); 1.2–1.6 (m, 8H); 1.9–2.7 (m, 8H); 3.40 (s, 2H); 7.10 ppm (s, 5H).

N,N-Bis[3-aminopropyl]-benzylamine (10):

4-Benzyl-4-azaheptanedinitrile (**9**): Benzylamine (**1**; 107.15 g, 1.0 mol) and acrylonitrile (150.2 g, 3.00 mol) are added to a 2000 ml Carius tube which is sealed and heated at 110 °C for 7 days. The reaction mixture is allowed to cool and distilled in vacuo; yield: 87.45 g (41%); b.p. 190 °C/0.05 torr. Alternately, the crude reaction mixture is reduced in vacuo and the residue chromatographed on silica gel eluting with diethyl ether to give **9** as an oil; yield: 136.50 g (64%, based on 5 g crude material).

$C_{13}H_{15}N_3$	calc.	C 73.21	H 7.09	N 19.70
(213.3)	found	73.29	6.94	19.65

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.1$–2.5 (m, 4H); 2.6–3.0 (m, 4H); 3.60 (s, 2H); 7.13 ppm (s, 5H).

N,N-*Bis[3-aminopropyl]-benzylamine* (**10**): A solution of aluminum chloride (11.1 g, 0.083 mol) in anhydrous diethyl ether (103 ml) is rapidly added to a suspension of lithium aluminum hydride (3.16 g, 0.083 mol) in anhydrous diethyl ether (165 ml). The mixture is vigorously stirred under a nitrogen atmosphere and a solution of 4-benzyl-4-azaheptanedinitrile (**9**; 7.00 g, 0.033 mol) in anhydrous ether (103 ml) is added over a 2 h period. After stirring 72 h, the mixture is cooled to 0 °C, quenched with 30% potassium hydroxide (w/v; 150 ml), and the ether layer decanted. The remaining emulsion is extracted with ether (5 x 100 ml). All the ethereal extracts are combined, dried with sodium sulfate, filtered, evaporated, and distilled; yield: 4.33 g (60%); b.p. 110 °C/0.025 torr.

$C_{13}H_{23}N_3$	calc.	C 70.54	H 10.47	N 18.98
(221.3)	found	70.37	10.56	18.96

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.00$ (s, 4H); 1.25–1.8 (m, 4H); 2.3–2.8 (m, 8H); 3.45 (s, 2H); 7.15 ppm (s, 5H).

***N^1,N^8*-Bis[acyl]-*N^4*-benzylspermidine; Typical Acylation Procedure:**

A solution of N^4-benzylspermidine in dry dichloromethene is cooled at 0 °C. A solution of the desired acid chloride (2.2 equiv.) dissolved in dry dichloromethane is added dropwise. The resultant mixture is allowed to warm to room temperature with continued stirring under a nitrogen atmosphere. After 18 h, the solution is washed with 1.1% hydrochloric acid (w/v) and water, dried, and evaporated to give the desired product as the hydrochloride salt. For specific examples, see Ref. [16].

Spermidine (5) Triacetate from 4-Benzyl-4-azaoctanedinitrile (3):

4-Benzyl-4-azaoctanedinitrile (**3**; 240 mg, 1.06 mmol) is added to a suspension of platinum oxide (36 mg, 15% by weight) in glacial acetic acid (10 ml) and stirred under a hydrogen atmosphere until no more hydrogen is taken up. The reaction mixture is then filtered through sintered glass and evaporated; yield of **5** triacetate as an oil: 333.5 mg (97%). [The spectral properties of the product thus obtained were identical with those of the triacetate of natural **5**.]

Homospermidine (**8**) *triacetate* and *bis[3-aminopropyl]-amine* (**11**) *triacetate* are similarly obtained from the dinitriles **6** and **9**, respectively, in yields of at least 85%.

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