Powerful *N*-Monoalkylation of Linear Tetraamines via Bisaminal Intermediates

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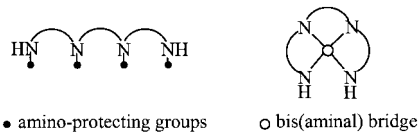
The bisaminals obtained through the condensation of two linear tetraamines with glyoxal or pyruvic aldehyde were selectively alkylated with bromo- or α,ω-dibromoalkanes in good yields at one of the secondary amino functions to give rise to *N*-monoalkylated tetraamines or linear octaamines.

Introduction

In the last three decades naturally occurring polyamines and their synthetic analogues have been widely studied because of their various biological and medical applications, notably as antineoplastic,[1] antimicrobial[2] and antimalarial[3] agents. These studies have highlighted the large potential of polyamine functionalisation in the generation of important applications. Since the publications of Ganem[4] and Bergeron,[5] few articles covering the main synthetic routes to polyamines have been published. Two recent reviews have exhaustively reported the methods used in the synthesis of polyamines and their derivatives.[6,7] Many of the methods used for the selective *N*-alkylation of polyamines involve one-pot syntheses which necessitate the tedious separation of the resulting mixtures,[8] step-by-step approaches with the complete elaboration of the polyamine skeleton[9] or multi-step routes that involve classical *N*-protecting groups.[10] Moreover, few examples of the direct and efficient *N*-monofunctionalisation of polyamines have been described with the exception of two methods based on the temporary triprotection of triamines[11] or tetraamines.[12] In recent years, the bisaminals of cyclic and linear tetraamines have been extensively studied. In numerous cases, they have enabled the successful synthesis of tetraazamacrocycles[13−17] (cyclen, cyclam and homocyclen) and the *N*-mono-[18−20] and *N*,*N*′-dialkylation[21] of these macrocycles. The use of bisaminals has also allowed the synthesis of specific α,ω-dialkylated linear tetraamines.[22]

The selective *N*-monoalkylation of primary amines of classically protected linear polyamines (with, for example, the Ts and Boc groups) is tricky because the independent and statistical reactions of the two terminal nitrogen atoms lead to mixtures of products and lower the yields. These drawbacks could be considerably reduced by bringing the two remaining secondary amino functions closer together to form a rigid intermediate: in this way, the alkylation of the first nitrogen atom could influence the alkylation of the second one, and thus limit its reactivity (Scheme 1). The properties of the bisaminal intermediates appear to be appropriate for such a purpose owing to their geometry. Moreover, their preparation is quantitative and, after reaction, can easily be deprotected.



Scheme 1

Results and Discussion

Herein, we describe the *N*-monoalkylation of bisaminals readily obtained through the condensation of the two linear tetraamines, 1,4,7,10-tetraazadecane and 1,4,8,11-tetraazaundecane, respectively denoted in the literature as **222** (trien or VE2896) and **232** (NSC19173), with glyoxal and pyruvic aldehyde. These tetraamines and their *N*-functionalised derivatives have been extensively studied because of their biological importance.[23−25] Hence, it is essential to control the selective alkylation. Reports concerning the synthesis of these bisaminals indicate that one or several isomers can be isolated in variable proportions depending on the experimental conditions.[14,15,26,27] Scheme 2 lists the bisaminals synthesized under our own conditions.

Bisaminals **1**−**5**, eventually used as a mixture of isomers, were engaged in *N*-alkylation reactions with benzyl bromide

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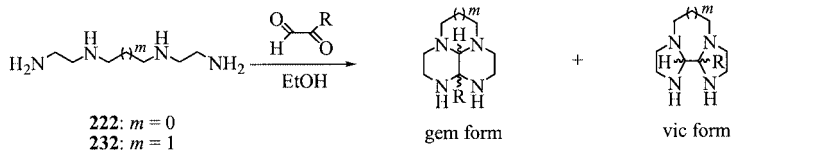
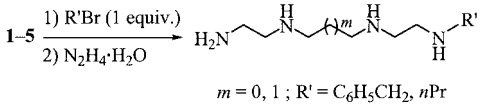


1: $m = 0$, R = H gem-(*cis* + *trans*) + vic-(*cis* + *trans*)
2: $m = 0$, R = CH_3 gem-(*cis* + *trans*) + vic-(*cis* + *trans*)
3: $m = 1$, R = H gem-*trans*
4: $m = 1$, R = H gem-*cis*
5: $m = 1$, R = CH_3 gem-*cis*

Scheme 2. Bisaminals obtained under our experimental conditions

or 1-bromopropane as the electrophile (Scheme 3). Under our conditions, the reactivity of the first secondary nitrogen atom of these bisaminals, which have all been previously used as precursors in cyclisation reactions with dihaloalkanes,[16,17,28] showed high selectivity: The reaction of 1 equiv. of the electrophilic agent with the different bisaminals led, after deprotection performed in hydrazine hydrate,[28] to *N*-monoalkylated compounds and a few dialkylated products which were easily removed during the purification step. The monoalkylation was easy to perform and was achieved with good yields irrespective of the electrophile (activated or not) and starting bisaminal (single compound or a mixture of isomers). The overall yields for compounds **6**−**9** are reported in Table 1.



Scheme 3. Selective *N*-monoalkylation of bisaminals **1**−**5**

Table 1. *N*-Monoalkylation of linear tetraamines

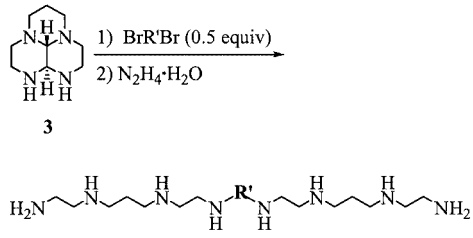
Starting tetraamine	Bisaminal	Product No.	R′	Yield (%)[a]
222	**1**	**6**	$C_6H_5CH_2$	60
	2			63
	1	**7**	*n*Pr	62
	2			65
232	**3**	**8**	$C_6H_5CH_2$	86
	4			76
	5			74
	3	**9**	*n*Pr	76
	4			74
	5			72

[a] Isolated yield after purification.

The proximity of the two secondary amino functions in the bisaminals is likely to introduce geometrical constraints and steric hindrance; these effects added to those induced by the first-linked R′ substituent, prevent the access of the second electrophile equivalent to the free secondary nitrogen atom. The nature of the bisaminal bridge does not influence the course of the reaction since similar results were obtained with glyoxal or pyruvic aldehyde derivatives.

Among the dialkylated products obtained, dissymmetrical ones, obtained by reaction with the tertiary amino groups of the bisaminals, were also detected. This fact precludes the formation of selectively α,ω-dialkylated tetraamines with 2 equiv. of the electrophile.

We took advantage of the selective reactivity of these bisaminals towards electrophiles to synthesize linear octaamines by using bis(electrophilic) reagents. Since compound **3** gave the best monoalkylation yields, it was used in alkylation reactions with α,α′-dibromo-*p*-xylene and 1,5-dibromopentane. Accordingly, very good yields were also secured for the expected octaamines **10** and **11**, respectively (Scheme 4).



Scheme 4. Synthesis of two linear octaamines

Conclusions

In summary, the use of bisaminal intermediates of linear tetraamines to discriminate between the two terminal nitrogen functions constitutes a new and efficient route to the *N*-monoalkylation of linear tetraamines. The synthesis of bisaminals is quasiquantitative, and deprotection, after al-

kylation, is facile. It should be easy to extend this process to other electrophilic reagents and linear tetraamines. The two linear octaamines described here constitute an interesting application of the method as they are used as starting materials in the synthesis of large macrocycles. Further investigations are in progress.

Experimental Section

General: All reagents were of commercial quality and solvents were dried using standard procedures. ^{1}H and ^{13}C NMR spectra were recorded with an AC 300 or a DX Avance 400 Bruker spectrometer. The mass spectra were recorded with a ZABSpec TOF Micro-Mass spectrometer

Experimental Procedures for the Synthesis of Bisaminals 1−5

Bisaminal 1: A solution of 40% aqueous glyoxal (726 mg, 5 mmol) in EtOH (10 mL) was added to a solution of **222** (730 mg, 5 mmol) in EtOH (10 mL). The resulting mixture was stirred for 2 h and then the solvent was removed under reduced pressure. Following the addition of CH_3CN (20 mL) and a few drops of water, the resulting solution was stirred under reflux overnight. Then, the solvent was evaporated, and the residual oil was taken up in toluene (20 mL). Insoluble polymers were eliminated by filtration. When required, this procedure was repeated twice. The filtrate was concentrated to give an oily residue composed of the four isomers of bisaminal **1** in 90% yield (755 mg). The gem-*cis* isomer was the major product (about 70%).

Bisaminal 2: A solution of 40% aqueous pyruvic aldehyde (901 mg, 5 mmol) in EtOH (10 mL) was added to a solution of **222** (730 mg, 5 mmol) in EtOH (10 mL) and stirred at room temperature for 2 h. After removal of the solvent, the residual oil was purified by treatment with toluene according to the same procedures as those used for compound **1**. Bisaminal **2** was obtained in 90% yield (820 mg) as a mixture of four isomers of which the gem-*cis* isomer was the major one (about 75%).

Bisaminal 3: A solution of 40% aqueous glyoxal (726 mg, 5 mmol) with a few drops of glacial acetic acid in EtOH (10 mL) was added to a stirred solution of **232** (800 mg, 5 mmol) in EtOH (10 mL). The solution was refluxed overnight. After evaporation of the solvent and removal of polymers (see details for the preparation of compound **1**), a white solid was obtained in 90% yield (818 mg) as a single gem-*trans* isomer.

Bisaminal 4: A mixture of 40% aqueous glyoxal (726 mg, 5 mmol) in EtOH (10 mL) was added at 0 °C to a solution of **232** (800 mg, 5 mmol) in EtOH (10 mL). The mixture was stirred at this temperature for 2 h. After evaporation of the solvent and removal of polymers (see details for the preparation of compound **1**), an oily residue was obtained in 90% yield (822 mg) as a single gem-*cis* isomer.

Bisaminal 5: A solution of 40% aqueous pyruvic aldehyde (901 mg, 5 mmol) was added to **232** (800 mg, 5 mmol) according to the same procedure as described for the synthesis of compound **2** to give the oily gem-*cis* bisaminal **5** in 90% yield (880 mg).

Typical Procedure for the Synthesis of *N*-Monoalkylated Tetraamines 6−11: K_2CO_3 (6.91 g, 10 equiv.) and the electrophile (1 equiv.) or biselectrophile (0.5 equiv.) were added to a solution of the bisaminal (5 mmol) in CH_3CN. After stirring at room temperature for 4 h for benzyl bromide or α,α′-dibromo-*p*-xylene, or at 50 °C for 2 d in the case of 1-bromopropane or 1,5-dibromopentane, the solution was filtered and the solvent evaporated. Then the residue was dissolved in hydrazine monohydrate (10 mL) and the solution refluxed for 2 h. Excess hydrazine was removed in vacuo and the residual oil was taken up in $CHCl_3$ (20 mL); insoluble polyhydrazones were discarded. The solvent was evaporated in vacuo and the residue was purified to obtain the *N*-mono-alkylated tetraamine. The crude product was dissolved in EtOH and the *N*-monoalkylated derivative was precipitated as the sulfate salt for **222** derivatives (solution of 5% H_2SO_4 in EtOH) or as the chloride salt for **232** derivatives (12 M HCl). The solid was washed with EtOH (3 × 20 mL) and the salt was dissolved in the minimum amount of water (5 mL). The pH of this solution was raised to 14 (NaOH pellets) with cooling and after extraction with CH_2Cl_2 (3 × 20 mL), drying ($MgSO_4$) and concentrating, the oily residue was found to be pure and free *N*-monoalkylated tetraamine. For microanalyses and NMR studies, **222** derivatives were also isolated as the chloride salts.

Tetraamine 6: ^{1}H NMR (300.13 MHz, $CDCl_3$, 25 °C): δ = 2.62−2.78 (m, 12 H, $C_\alpha H$-N), 3.84 (s, 2 H, CH_2Ph), 7.26−7.30 (m, 5 H, CH_2Ph) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$, 25 °C): δ = 41.2 (C_α−NH_2), 48.3, 48.8 (3 C), 52.0 (C_α−N), 53.4 ($CH_2C_6H_5$), 126.4, 127.5, 127.7, 140.0 (C_6H_5) ppm. HRMS (ESI): calcd. for $C_{13}H_{25}N_4$: 237.2079 $[M + H]^+$; found: 237.2081.

Tetraamine 6·4HCl: ^{13}C NMR (100.62 MHz, D_2O, 25 °C): δ = 38.2 (C_α−NH_2), 45.3, 46.2, 46.5, 47.5, 47.9 (C_α−N), 54.5 ($CH_2C_6H_5$), 132.2, 132.8 (3C) (C_6H_5) ppm. $C_{13}H_{28}Cl_4N_4$ (382.2): calcd. C 40.85, H 7.38, N 14.66; found C 40.92, H 7.49, N 14.38.

Tetraamine 7: ^{1}H NMR (400.13 MHz, $CDCl_3$, 25 °C): δ = 0.87 (t, J = 7.3 Hz, 3 H, CH_3), 1.46 (m, 2 H, CH_2CH_3), 2.50−2.65 (m, 14 H, $C_\alpha H$−N) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$, 25 °C): δ = 10.5 (CH_3), 21.9 (CH_2CH_3), 40.5 (C_α−NH_2), 48.1 (3 C), 50.5, 51.2 (2 C) (C_α−N) ppm.

Tetraamine 7·4HCl: ^{1}H NMR (400.13 MHz, D_2O, 25 °C): δ = 0.82 (t, J = 7.1 Hz, 3 H, CH_3), 1.57−1.58 (m, 2 H, CH_2CH_3), 3.27−3.38 (m, 14 H, $C_\alpha H$−N) ppm. ^{13}C NMR (100.62 MHz, D_2O, 25 °C): δ = 13.3 (CH_3), 22.1 (CH_2CH_3), 38.4 (C_α−NH_2), 45.7, 46.2 (2 C), 46.5, 47.5, 52.7 (C_α−N) ppm. $C_9H_{28}Cl_4N_4$ (334.2): calcd. C 32.35, H 8.45, N 16.77; found C 32.68, H 8.45, N 16.52.

Tetraamine 8: ^{1}H NMR (400.13 MHz, $CDCl_3$, 25 °C): δ = 1.67 (m, 2 H, $C_\beta H$−N), 2.59−2.79 (m, 12 H, $C_\alpha H$−N), 3.77 (s, 2 H, $CH_2C_6H_5$), 7.29−7.31 (m, 5 H, C_6H_5) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$, 25 °C): δ = 29.6 (C_β−N), 40.9 (C_α−NH_2), 47.4, 47.5, 47.9, 48.6, 51.8 (C_α−N), 53.0 ($CH_2C_6H_5$), 125.9, 127.2, 127.4, 139.7 (C_6H_5) ppm. HRMS (ESI): calcd. for $C_{14}H_{27}N_4$: 251.2236 $[M + H]^+$; found: 251.2241. $C_{14}H_{27}N_4 \cdot 1.4H_2O$ (276.6): calcd. C 61.01, H 10.53, N 20.33; found C 61.03, H 10.07, N 20.54.

Tetraamine 8·4HCl: ^{1}H NMR (400.13 MHz, D_2O, 25 °C): δ = 1.99 (m, 2 H, $C_\beta H$−N), 3.03−3.09 (m, 4 H, $C_\alpha H$−N), 3.23−3.26 (m, 4 H, $C_\alpha H$−N), 3.31 (s, 4 H, $C_\alpha H$−N), 4.16 (s, 2 H, $CH_2C_6H_5$), 7.35 (m, 5 H, C_6H_5) ppm. ^{13}C NMR (75.47 MHz, D_2O, 25 °C): δ = 25.5 (C_β−N), 38.2 (C_α−NH_2), 45.3, 46.1, 47.1, 47.7, 47.8 (C_α−N), 54.6 ($CH_2C_6H_5$), 132.2, 132.7, 132.8, 132.9 (C_6H_5) ppm.

Tetraamine 9: ^{1}H NMR (400.13 MHz, $CDCl_3$, 25 °C): δ = 0.87 (t, J = 7.4 Hz, 3 H, CH_3), 1.45 (m, 2 H, CH_2CH_3), 1.64 (m, 2 H, $C_\beta H$−N), 2.52 (t, J = 7.1 Hz, 2 H, $C_\alpha H$−N), 2.60 (m, 8 H, $C_\alpha H$−N), 2.75 (t, J = 5.8 Hz, 4 H, $C_\alpha H$−N) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$, 25 °C): δ = 11.2 (CH_3), 22.6 (CH_2CH_3), 29.9 (C_β−N), 41.2 (C_α−NH_2), 47.7, 47.8, 48.8, 49.0, 51.3, 52.1 (C_α−N) ppm. HRMS (LSIMS): calcd. for $C_{10}H_{27}N_4$: 203.2236 $[M + H]^+$; found 203.2234.

Tetraamine 9·4HCl: ^{1}H NMR (400.13 MHz, D_2O, 25 °C): δ = 1.02 (t, J = 7.4 Hz, 3 H, CH_3), 1.76 (m, 2 H, CH_2CH$_3$), 2.20 (m, 2 H, C$_\beta H$−N), 3.13 (t, J = 7.7 Hz, 2 H, C$_\alpha H$−N), 3.29 (t, J = 7.7 Hz, 4 H, C$_\alpha H$−N), 3.46 (m, 8 H, C$_\alpha H$−N) ppm. ^{13}C NMR (100.62 MHz, D_2O, 25 °C): δ = 13.1 (*C*H$_3$), 22.0 (*C*H$_2$CH$_3$), 25.5 (*C*$_\beta$−N), 38.3 (*C*$_\alpha$−NH$_2$), 45.8, 46.1, 47.2, 47.8 (2 C), 52.7 (*C*$_\alpha$−N) ppm. $C_{10}H_{30}Cl_4N_4$·0.5H_2O (215.4): calcd. C 56.83, H 12.88, N 26.51; found C 56.65, H 12.38, N 26.53.

Octaamine 10: ^{1}H NMR (400.13 MHz, $CDCl_3$, 25 °C): δ = 1.62 (m, 4 H, C$_\beta H$−N), 2.58−2.61 (m, 12 H, C$_\alpha H$−N), 2.67 (s, 8 H, C$_\alpha H$−N), 2.74 (m, 4 H, C$_\alpha H$−N), 3.72 (s, 4 H, C$H_2C_6H_4$), 7.18−7.21 (m, 4 H, C$_6H_4$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$, 25 °C): δ = 29.7 (*C*$_\beta$−N), 41.0 (*C*$_\alpha$−NH$_2$), 47.5 (2 C), 48.0, 48.7, 51.9 (*C*$_\alpha$−N), 52.8 (*C*H$_2$C$_6$H$_4$), 127.2, 138.3 (*C*$_6$H$_4$) ppm.

Octaamine 10·8HCl: ^{13}C NMR (100.62 MHz, D_2O, 25 °C): δ = 28.0 (*C*$_\beta$−N), 40.8 (*C*$_\alpha$−NH$_2$), 48.1, 48.6, 49.6, 50.3 (2 C) (*C*$_\alpha$−N), 56.5 (*C*H$_2$C$_6$H$_4$), 136.1, 137.0 (*C*$_6$H$_4$) ppm. $C_{22}H_{54}Cl_8N_8$ (714.3): calcd. C 36.99, H 7.62, N 15.69: found C 36.95, H 7.61, N 15.31.

Octaamine 11: ^{13}C NMR (100.62 MHz, $CDCl_3$, 25 °C): δ = 25.5 (C$_\gamma$−N), 23.9, 29.9 (*C*$_\beta$−N), 39.9 (*C*$_\alpha$−NH$_2$), 44.1, 46.2, 46.6, 52.1, 54.2, 58.1 (*C*$_\alpha$−N) ppm.

Octaamine 11·8HCl: ^{13}C NMR (100.62 MHz, D_2O, 25 °C): δ = 26.4 (C$_\gamma$−N), 28.2, 28.4 (*C*$_\beta$−N), 41.1 (*C*$_\alpha$−NH$_2$), 45.8, 48.6 (2 C), 49.5, 57.2, 59.6 (*C*$_\alpha$−N) ppm.

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