SYNTHESIS OF REACTIVE $s$-TRIAZINES BEARING A CAGE SYSTEM DERIVED FROM ADAMANTANE AS PRECURSORS OF HEXAMETHYLMElamINE ANALOGUES

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Abstract - The synthesis of reactive $s$-triazines from cyanuric chloride and 1-adamantanamine, 1-adamantanol, 2-adamantanol, 1-adamantanemethanol and their use in the preparation of structural analogues of hexamethylmelamine are described.

Cyanuric chloride (1) is a well known and very important compound which has been used in $s$-triazines synthesis. Because of the polyfuctionality of cyanuric chloride, access to $s$-triazines by nucleophilic substitution with C-C, C-N or C-O bond formation has extendly been accomplished. Some $s$-triazine derivatives have been studied for their interesting biological properties, for example hexamethylmelamine (HMM) (Scheme 1) and 2-amino-4-morpholino-$s$-triazine are clinically used respectively for their antitumoral and antiviral activities.

![Scheme 1](image)

Other works report numerous investigations on molecules in which various biological activities are enhanced by the presence of an adamantyl bloc.
In connection with our studies on the introduction of an adamantyl bloc in biological structures,\textsuperscript{9,10} we describe in this paper the synthesis of new \textit{s}-triazines having adamantane as their substituents. These compounds are prepared by selective nucleophilic substitution of the cyanuric chloride (1) by 1-adamantanamine (2), 1-adamantanol (3), 2-adamantanol (4) and 1-adamantanemethanol (5), to obtain structural analogues of hexamethylmelamine (HMM), specially compounds (12) and (13).

1. **Substitution by 1-adamantanamine**: In order to obtain selectively the mono-, di- or tri-substitued \textit{s}-triazines (6), (7), (8), following acute experimental conditions have been determined.

1.1. **2-(1-Adamantanamino)-4,6-dichloro-s-triazine (6)**: Equimolar amounts of cyanuric chloride in acetone at 0°C reacted with 1-adamantanamine (2) in the presence of triethylamine and provided the mono-substituted compound (6) in good yield.

1.2. **2,4-Bis-(1-adamanminio)-6-chloro-s-triazine (7)**: When the reaction uses two equivalents or even a large excess of 1-adamantanamine with respect to cyanuric chloride in anhydrous THF at room temperature, the di-substituted compound (7) is isolated as the main product.

1.3. **2,4,6-Tris-(1-adamanminio)-s-triazine (8)**: The difficulty of substitution of the third chlorine atom of 7 and the deactivation effect of the adamantanamino group in 7 can be solved by heating cyanuric chloride in sulfolane at 285°C with a large excess of 1-adamantanamine, the tri-substituted product (8) \textsuperscript{18} is obtained in the conditions.

2. **Substitution by 1- or 2-adamantanol and 1-adamantanemethanol**: Compounds (9-11) are very easy to obtain using one, two or three equivalents of lithium alkoxide of 3, 4, 5 in boiling THF with one equivalent of cyanuric chloride, respectively.

3. **Synthesis of structural analogues of HMM, compounds (12), (13)**: Reaction of 6 in acetone with a large excess of dimethylamine leads the product (12) which reacts with \textit{n}-butyllithium and methyl iodide to give methylated compound (13).

In conclusion, this work describes the acute experimental procedure for a specific mono-, di- or tri-substitution of cyanuric chloride with amine or alcohols in the adamantane series in order to synthesize new compounds with potential biological activity.
Ad = 1-adamantyl
Ad' = 2-adamantyl

Scheme 2
EXPERIMENTAL

Melting points were uncorrected. IR spectra were recorded on a Nicolet 60 SX apparatus. $^1$H NMR spectra were obtained on a Bruker W 200 (200 MHz) using tetramethylsilane as an internal standard. MS were determined on a Finnigan Mat 800 ITD coupled with a CP-Sil 5GC column.

2-(1-Adamantanamino)-4,6-dichloro-s-triazine (6): Cyanuric chloride (1) (1.84 g, 10 mmol) was dissolved in 10 mL of anhydrous acetone at 0°C. A solution of 1-adamantanamine (2) (1.51 g, 10 mmol) and triethylamine (2.02 g, 20 mmol) in 10 mL of the same solvent was added slowly to the well-stirred solution. After the reactants were stirred for 1 h at rt, the reaction mixture was quenched by adding 50 mL of 10% HCl solution. The resulting precipitate was filtered and washed with water, dried over P$_2$O$_5$ and recrystallized (X 2) from n-hexane (1.85 g, 64%). mp 136-137°C; IR (KBr) 3411, 2909, 2848 (Ad) cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 8.30 (s, 1H, NH), 1.68-2.15 (m, 15H, Ad-H); MS (EI) m/z M$^+$ 299. Anal. Calcd for C$_{13}$H$_{16}$N$_2$Cl$_2$: C, 52.19; H, 5.35; N, 18.72. Found: C, 51.72; H, 5.35; N, 18.68.

2,4-Bis-(1-adamantanamino)-6-chloro-s-triazine (7): A solution of 1 (1.84 g, 10 mmol) and 2 (6.04 g, 40 mmol) in 40 mL of THF was stirred at rt for 7 h. The reaction mixture was quenched by adding 50 mL of 10% HCl solution. The resulting precipitate was filtered and washed with water, dried over P$_2$O$_5$ and recrystallized at first from ethanol then from n-hexane (2.83 g, 69%). mp 214-215°C; IR (KBr) 3420, 3202 (NH), 2915, 2854 (Ad) cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 8.30 (s, 2H, NH), 1.68-2.14 (m, 30H, Ad-H X 2); MS (EI) m/z M$^+$ 414. Anal. Calcd for C$_{23}$H$_{32}$N$_2$Cl: C, 52.19; H, 5.35; N, 18.72. Found: C, 51.72; H, 5.35; N, 18.68.

2,4,6-Tris-(1-adamantanamino)-s-triazine (8): A solution of 1 (1.84 g, 10 mmol) and 2 (10.57 g, 70 mmol) in 20 mL of sulfolane was refluxed for 2 h at 285°C. The reaction mixture was cooled to rt and quenched by adding 200 mL of 10% HCl solution. The precipitate was filtered, washed with water, dried over P$_2$O$_5$ and recrystallized from ethanol (2.79 g, 53%). mp 276-278°C; IR (KBr) 3419, 3273 (NH), 2906, 2850 (Ad) cm$^{-1}$; MS (EI) m/z M$^+$ 528. Anal. Calcd for C$_{33}$H$_{48}$N$_6$: C, 68.04; H, 9.27; N, 14.43. Found: C, 68.06; H, 8.76; N, 14.24.

2-(1-Adamantylxoy)-4,6-dichloro-s-triazine (9): A three-necked round bottomed flask equipped with a thermometer, reflux condenser, argon inlet is charged sequentially with 30 mL of anhydrous THF, 1-adamantanol (3) (1.52 g, 10 mmol) and n-butyllithium (10 mmol in suspension in n-hexane). After 15 min of stirring at rt, a solution of cyanuric chloride (1.84 g, 10 mmol) in 10 mL of THF is added. The system is stirred under reflux for 5 h. The precipitate of LiCl is filtered and the solution is evaporated in vacuo and
the crude residue is recrystallized from n-hexane (1.05 g, 35%): mp 195-196°C; IR (KBr) 2915, 2848 (Ad) cm⁻¹; ¹H NMR (CDCl₃) δ 1.61-2.14 (m, 15H, Ad-H); MS (EI) m/z M⁺ 300. Anal. Calcd for C₁₃H₁₅N₃O₂: C, 51.95; H, 4.99; N, 13.99. Found: C, 51.92; H, 5.09; N, 13.82.

2,4-Bis-(2-adamantyloxy)-6-chloro-s-triazine (10): This compound was isolated in a similar manner using 20 mmol of 2-adamantanol (4) and 20 mmol of n-butyllithium for 10 mmol of 1 (1.62 g, 37%): mp 193-194°C (n-hexane); IR (KBr) 2907, 2853 (Ad') cm⁻¹; ¹H NMR (CDCl₃) δ 1.61-2.19 (m, 30q Ad'-H); MS (EI) m/z M⁺ 416. Anal. Calcd for C₁₃H₁₅N₃O₂: C, 66.42; H, 7.22; N, 10.10. Found: C, 66.69; H, 7.35; N, 9.84.

2,4,6-Tris-(1-adamantanemethoxy)-s-triazine (11): This compound was prepared in a similar manner using 30 mmol of 1-adamantanemethanol (5) and 30 mmol of n-butyllithium for 10 mmol of 1 (2.29 g, 40%): mp >265°C (n-hexane); IR @3r) 2902, 2847 (Ad) cm⁻¹; ¹H NMR (CDCl₃) δ 3.96 (s, 6H, CH₂ X 3), 1.64-2.00 (m, 45H, Ad-H X 3). Anal. Calcd for C₃₆H₅₁N₃O₃: C, 75.39; H, 8.90; N, 7.33. Found: C, 75.29; H, 8.91; N, 7.35.

2-(1-Adamantanamino)-4,6-bis-(dimethylamino)-s-triaze (12): A solution of 6 (1.50 g, 5 mmol) in 5 mL of acetone was slurried in 25 mL of water at 0°C and NaOH (0.40 g, 10 mmol) was added under stirring. To this mixture maintained at 0°C, was added slowly dimethylamine chloride (1.21 g, 10 mmol) in 3 mL of water. NaOH (0.40 g, 10 mmol) was added and the mixture was heated for 1 h at 50°C. The resulting precipitate was filtered, washed with water, dried over P₂O₅ and purified by silica gel column chromatography (eluent: CHCl₃-EtOH: 95/5) (1.26 g, 40%): mp 165-166°C (n-heptane); IR (KBr) 3432 (NH), 2907, 2850 (Ad) cm⁻¹; ¹H NMR (CDCl₃) δ 3.17 (s, 12H, CH₂ X 5), 1.50-2.12 (m, 15H, Ad-H); MS (EI) m/z M⁺ 316. Anal. Calcd for C₁₇H₂₈N₆: C, 64.29; H, 8.80; N, 26.50. Found: C, 64.55; H, 8.86; N, 26.58.

2-(N-Methyl-1-adamantanamino)-4,6-bis-(dimethylamino)-s-triaze (13): To a solution of 12 (1.58 g, 5 mmol) in 10 mL of anhydrous THF, maintained under argon, were added at 0°C, 6 mmol of n-butyllithium. The mixture was stirred during 0.5 h, then iodomethane (2.13 g, 15 mmol) was added and the mixture was heated under reflux for 3 h. After cooling, the mixture was filtered, the solution evaporated under vacuo and the residue was purified by recrystallization from 96% ethanol (2.24 g, 68%): mp 137-138°C; IR (KBr) 2904, 2850 (Ad) cm⁻¹; ¹H NMR (CDCl₃) δ 3.14 (s, 15H, CH₃ X 5), 1.68-2.36 (m, 15H, Ad-H); MS (EI) m/z M⁺ 330. Anal. Calcd for C₁₈H₃₆N₆, ½H₂O: C, 63.97; H, 9.38; N, 24.52. Found: C, 63.71; H, 9.14; N, 24.77.
REFERENCES AND NOTES


Received, 1st March, 1999