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

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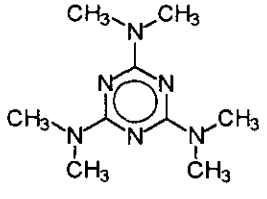
Abstract - The synthesis of reactive *s*-triazines from cyanuric chloride and 1-adamantanamine, 1-adamantanol, 2-adamantanol, 1-adamantanemethanol and their use in the preparation of structural analogues of hexamethylmelamine are described.

Cyanuric chloride (**1**) is a well known and very important compound which has been used in *s*-triazines synthesis.[1] Because of the polyfonctionality of cyanuric chloride, access to *s*-triazines by nucleophilic substitution with C-C, C-N or/and C-O bond formation has extendly been accomplished.[2]

Some *s*-triazine derivatives have been studied for their interesting biological properties, for example hexamethylmelamine (HMM) (Scheme 1) [3] and 2-amino-4-morpholino-*s*-triazine [4] are clinically used respectively for their antitumoral and antiviral activities.



(HMM)

Scheme 1

Other works report numerous investigations on molecules in which various biological activities are enhanced by the presence of an adamantyl bloc.[5-17]

In connection with our studies on the introduction of an adamantyl bloc in biological structures,[9, 10] we describe in this paper the synthesis of new *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 *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-substitued compound (**6**) in good yield.

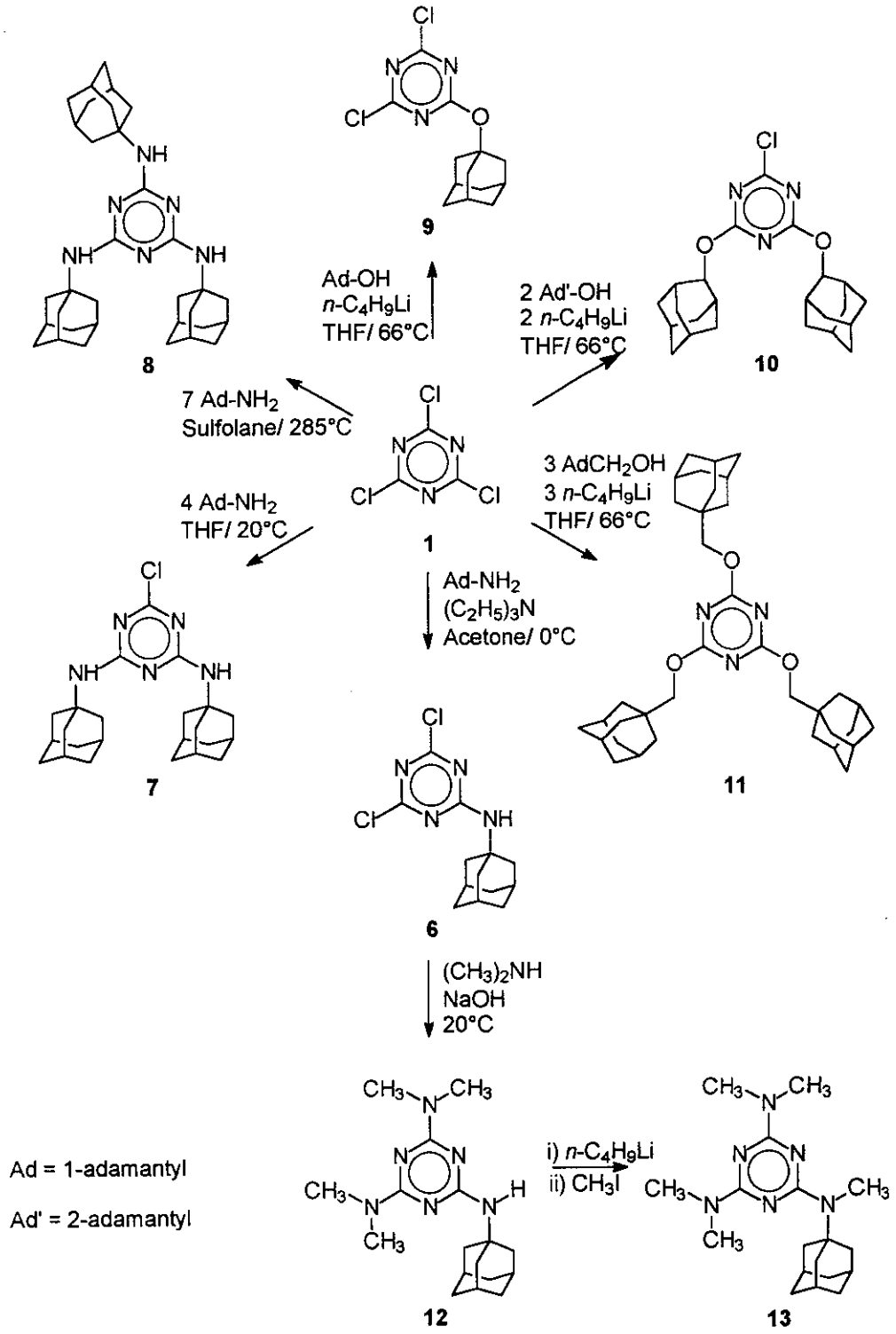
1.2. *2,4-Bis-(1-adamantanamino)-6-chloro-s-triazine* (**7**) : When the reaction uses two equivalents or even a large excess of 1-adamantanamine with respect to cyanuric chloride in anhydrous THF at room temperature, the di-substituted compound (**7**) is isolated as the main product.

1.3. *2,4,6-Tris-(1-adamantanamino)-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**) [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 *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.


Cl
N
N
Cl
N
O
9
NH
NH
NH
8
Ad-OH
n-C4H9Li
THF/ 66°C
2 Ad'-OH
2 n-C4H9Li
THF/ 66°C
10
7 Ad-NH2
Sulfolane/ 285°C
1
4 Ad-NH2
THF/ 20°C
3 AdCH2OH
3 n-C4H9Li
THF/ 66°C
Ad-NH2
(C2H5)3N
Acetone/ 0°C
7
11
6
(CH3)2NH
NaOH
20°C
CH3
N
H
12
i) n-C4H9Li
ii) CH3I
13
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_2O_5 and recrystallized (X 2) from *n*-hexane (1.85 g, 64%) : mp 136-137°C ; IR (KBr) 3411 (NH), 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 $C_{13}H_{16}N_4Cl_2$: 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_2O_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 $C_{23}H_{32}N_5Cl$: C, 66.74 ; H, 7.73 ; N, 16.92. Found : C, 66.58 ; H, 7.82 ; N, 16.80.

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. The precipitate was filtered, washed with water, dried over P_2O_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 $C_{33}H_{48}N_6$, $3H_2O$: C, 68.04 ; H, 9.27 ; N, 14.43. Found : C, 68.06 ; H, 8.76 ; N, 14.24.

2-(1-Adamantyloxy)-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 ($CDCl_3$) δ 1.61-2.14 (m, 15H, Ad-H) ; MS (EI) *m/z* M^+ 300. Anal. Calcd for $C_{13}H_{15}N_3OCl_2$: 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, 39%) : mp 193-194°C (*n*-hexane) ; IR (KBr) 2907, 2853 (Ad') cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.61-2.19 (m, 30H, Ad'-H X 2) ; MS (EI) *m/z* M^+ 416. Anal. Calcd for $C_{23}H_{30}N_3O_2$: 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 (KBr) 2902, 2847 (Ad) cm^{-1} ; ^1H NMR ($CDCl_3$) δ 3.96 (s, 6H, CH_2 X 3), 1.64-2.00 (m, 45H, Ad-H X 3). Anal. Calcd for $C_{36}H_{51}N_3O_3$: 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*-triazine (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 P_2O_5 and purified by silica gel column chromatography (eluent : $CHCl_3$-EtOH : 95/5) (1.26 g, 40%) : mp 165-166°C (*n*-heptane) ; IR (KBr) 3432 (NH), 2907, 2850 (Ad) cm^{-1} ; ^1H NMR ($CDCl_3$) δ 3.17 (s, 12H, CH_3 X 4), 1.50-2.12 (m, 15H, Ad-H) ; MS (EI) *m/z* M^+ 316. Anal. Calcd for $C_{17}H_{28}N_6$: 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*-triazine (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 ($CDCl_3$) δ 3.14 (s, 15H, CH_3 X 5), 1.68-2.36 (m, 15H, Ad-H) ; MS (EI) *m/z* M^+ 330. Anal. Calcd for $C_{18}H_{30}N_6$, $\frac{1}{2}H_2O$: C, 63.97 ; H, 9.38 ; N, 24.52. Found : C, 63.71 ; H, 9.14 ; N, 24.77.

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