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SYNTHESIS OF NEW POTENTIAL DENDRITIC CORES: (4-OXOPIPERIDIN-1-YL)-*s*-TRIAZINES

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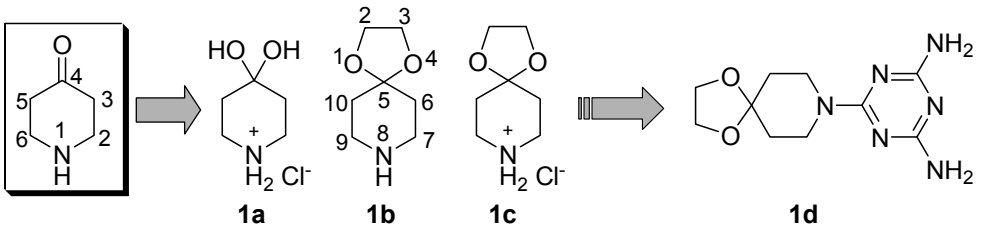
ABSTRACT. Starting from 4-piperidone monohydrate hydrochloride or the hydrochloride of its ethylene ketal, the synthesis of new (4-oxopiperidin-1-yl)-*s*-triazine derivatives (potential C_2, C_3 symmetric dendritic cores) based on amination of cyanuric chloride is for the first time reported.

Keywords: *s-triazine, 4-piperidone monohydrate hydrochloride, 1,4-dioxa-8-azaspiro[4.5]decane hydrochloride, amination, dendritic cores*

INTRODUCTION

Following our recent findings in *s*-triazine chemistry [1], particularly in dendrimers [2] and dendrons [3] based on *N*-substituted 2,4,6-triamino-*s*-triazines (*melamines*), we were recently interested in testing the nucleofilicity of 4-piperidone as nucleophile in reaction with cyanuric chloride.

The instability, as free base, of 4-piperidone against autocondensation is well-known as early as 1949 [4]; hence, its monohydrate hydrochloride **1a** and its ethylene ketal (free base **1b** or hydrochloride **1c**), are commercially available (Scheme 1).



1a **1b** **1c** **1d**

Scheme 1

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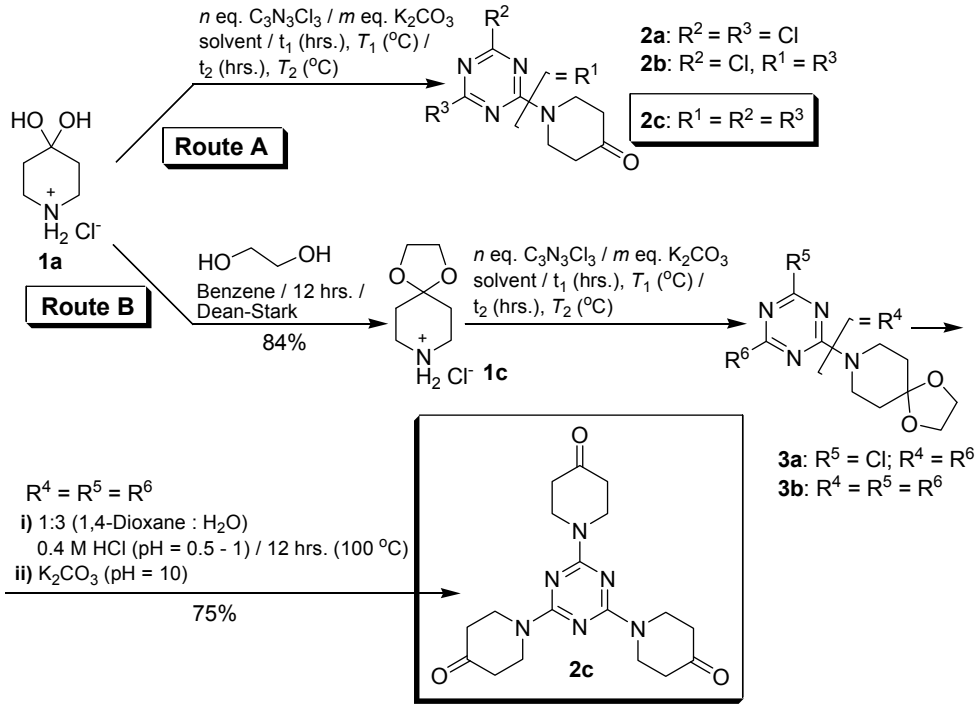
On the other hand, there is nowadays a noticeably highlighting interest in nucleophilic substitution of the reminder chlorine in chlorodiamino-*s*-triazines carried out with 4-piperidone derivatives, providing pharmaceutical compositions for treating pathological states which arise from or are exacerbated by angiogenesis [5] (*e.g.* compound **1d**, Scheme 1).

The aim of this communication is to account on the first synthesis of a melamine built entirely from 4-piperidone, namely 2,4,6-tris(4-oxopiperidin-1-yl)-*s*-triazine, together with some of its useful precursors.

RESULTS AND DISCUSSION

Firstly, our attempts were dedicated to direct amination of cyanuric chloride by using 4-piperidone monohydrate hydrochloride **1a** (Scheme 1) as source of nucleophile in the presence of potassium carbonate as proton scavenger (Scheme 2, **Route A**, Table 1, Entries 1 - 4).



Scheme 2

As shown by the partial conversions of cyanuric chloride, preliminary results in **Route A** (Scheme 2) were not promising at all (Table 1, Entries 1 – 3): its maximum global conversion was about 26% only. Selectivity of chlorine replacement was also poor.

Table 1. Quantitative and qualitative results of amination of cyanuric chloride starting from 4-piperidone hydrochloride **1a** (Scheme 2, **Route A**) or its ethylene ketal hydrochloride **1c** (Scheme 2, **Route B**)

Entry	Molar ratios		Conditions			(Partial) conversions
Route	*n* eq. $C_3N_3Cl_3$	*m* eq. K_2CO_3	Solvent	t_1 (hrs.) t_2 (hrs.)	T_1 (^oC) T_2 (^oC)	of cyanuric chloride (%)
1 **A**	0.98	1.97	THF	72 -	r.t. -	16 (**2a**); 9 (**2b**); 1(**2c**)*
2 **A**	0.33	1.97	THF	24 29	r.t. reflux	11(**2b**); 4(**2c**)*
3 **A**	0.33	1.97	$CHCl_3$	48 -	reflux -	12(**2b**); 7(**2c**)*
4 **A**	0.50	2.00	THF + 10% H_2O	12 24	-10 r.t.	68(**2b**)**
5 **B**	0.50	2.00	THF + 10% H_2O	10 24	-10 r.t.	62(**3a**)**
6 **B**	0.32	2.00	DMF	24 12	0 → r.t. reflux	63(**3b**)**

*calculated based on effective amounts isolated by flash column chromatography; **isolated yields

Indeed, 4-piperidone monohydrate hydrochloride **1a** exhibited a very reduced solubility in solvents usually recommended for amination of cyanuric chloride (THF, 1,4-dioxane, chloroform and dichloromethane). Combined with the insolubility of the proton scavenger (K_2CO_3) in the same solvents, at room temperature, 4-piperidone was too slowly generated from **1a**. Upon heating (Table 1, Entries 2, 3), the poorer results obtained inferred us that decomposition of the nucleophile rather occurred instead ofthe desired S_N2Ar process.

A pivotal improvement of our strategy in **Route A** consisted of the use of aqueous THF (10% water) as solvent (Table 1, Entry 4), able to ensure a rapid acid-base interchange between potassium carbonate and 4-piperidone monohydrate hydrochloride **1a**. Thus, in very mild and carefully controlled conditions, the highly selective double replacement of chlorine in cyanuric chloride by two 4-oxopiperidin-1-yl units was achieved, affording the bis(ketone) **2b** with an satisfactory yield. We note that conditions in Table 1 (Entry 4) were appropriate only for the double substitution of chlorine (spot to spot TLC monitoring). They also demonstrated the high reactivity as nucleophile of 4-piperidone in the depicted methodology.

Therefore, the exploitation as nucleophile of the freshly prepared ethylene ketal of 4-piperidone **1b** (Scheme 1) was straightforward. Surprisingly, in our hands, **1b** was very volatile during the usual work-up of its hydrochloride **1c**. Consequently, we had to opt for the direct use of **1c** (Scheme 2, **Route B**) and the *in situ* generation of **1b** [6].

Furthermore, our methodology was classic and resumed to three steps: protection by acetalisation of **1a** (→ **1c**), selective aminations (→ **3a**, **3b**) and deprotection of **3b** (→ **2c**).

Protection of the masked carbonyl group of **1a** as ethylene ketal **1c** occurred in 84% yield. Thus, **1c** was routinely prepared. As **1a**, **1c** was also highly insoluble in THF and 1,4-dioxane.

Accordingly, the selectivity as twofold amination of cyanuric chloride by the free base **1b** generated *in situ* from **1c** was achieved (Scheme 2, **Route B**, Table 1, Entry 5) only in similar conditions as in the case of 4 piperidone (Scheme 2, **Route A**, Table 1, Entry 4).

Next, DMF was the suitable solvent for **1c** in order to perform the complete substitution of chlorine in cyanuric chloride in one-pot synthesis (Scheme 2, **Route B**, Table 1, Entry 6) in 63% yield. That is, the generation *in situ* of the nucleophile **1b** from **1c** in the presence of potassium carbonate also occurred in DMF. No problem we encountered during isolation of the triple spirane **3b** as pure analytical sample by simple crystallisation.

In contrast, deprotection of **3b**, carried out in refluxing aqueous 1,4-dioxane at pH = 0.5 – 1.0, required an unexpected long time, about 12 hrs, as indicated by its spot to spot evolution in TLC monitoring. The desired tris(ketone) **2c** was also isolated simply, by direct crystallisation.

CONCLUSIONS

The synthesis of the first melamine based entirely on 4-piperidone and of some of its precursors was realised in three steps by using a classical chemistry in an overall 40% global yield. The study of compound **3b** as dendritic core is in advanced progress.

EXPERIMENTAL SECTION

General. Melting points are uncorrected; they were carried out on ELECTROTHERMAL® instrument. Conventional NMR spectra were recorded on a Bruker® AM 300 instrument operating at 300 and 75 MHz for ^{1}H and ^{13}C nuclei respectively (a Bruker® DMX500 instrument was also used in the case of compound **2b**). All NMR spectra were measured in anhydrous commercially available deuteriated solvents. No $SiMe_4$ was added; chemical shifts were measured against the solvent peak. All chemical shifts (δ values) are given throughout in ppm; all coupling patterns ($^{n}J_{H,H}$ values) are given throughout

in Hz.TLC was performed by using aluminium sheets with silica gel 60 F_{254} (Merck®); flash column chromatography was conducted on Silica gel Si 60 (40–63 μm, Merck®). IR spectra were performed on a Perkin-Elmer® Paragom FT-IR spectrometer. Only relevant absorptions are listed [throughout in cm^{-1}: weak (w), medium (m) or (s) strong]. Microanalyses were performed on a Carlo Erba® CHNOS 1160 apparatus. Mass spectra (MS) were recorded a Bruker® Esquire Instrument.

*Preparation of compounds **2a – c** (Scheme 2, **Route A**, Table 1, Entry 1)*

Cyanuric chloride (1.673 g, 9.07 mmol) and anh. K_2CO_3 (2.502 g 18.10 mmol) in dry THF (80 mL) were stirred at room temperature meanwhile 4-piperidone monohydrate hydrochloride **1a** (1.462 g, 9.524 mmol) was added portionwise within 5 hrs. with vigorous stirring. The reaction mixture was kept at room temperature for additional 72 hrs. until no more evolution was observed by TLC monitoring. The resulted suspension was filtered off and solids were well washed with dry THF (100 mL). The THF filtrate was evaporated under reduced pressure to yield 2.300 g crude solid material which was separated by column chromatography (eluent ligroin: acetone 3.8:1 v/v) yielding the title compounds as follows: **2a** (0.363 g, as the first fraction, 16 % conversion of cyanuric chloride), **2b** (0.251 g, as the second fraction, 9 % conversion of cyanuric chloride) and **2c** (0.030 g, as the third fraction, 1 % conversion of cyanuric chloride).

*Alternative preparation of compound **2b** (Scheme 2, **Route A**, Table 1, Entry 4)*

To a 10 % v/v aq. in THF suspension (100 mL) containing cyanuric chloride (0.922 g, 5 mmol) and anh. K_2CO_3 (2.762 g, 20 mmol), cooled at –15 °C, solid piperidone monohydrate hydrochloride **1a** (1.536 g, 10 mmol) was added slowly and portionwise within 12 hrs with vigorous stirring and keeping temperature to not exceed –10 °C. The reaction mixture was then allowed to reach very slowly room temperature and was kept as such for additional 24 hrs. until TLC monitoring showed completion of reaction (eluent ligroin : acetone 1.5:1 v/v, single spot, R_f = 0.70). The reaction mixture was filtered off, minerals were well washed with dichloromethane (50 mL) then dichloromethane (75 mL) was added to the filtrate with stirring. The organic layer was separated, and then washed several times with water (× 50 mL) to neutrality. After drying over anh. Na_2SO_4, and filtering off, the organic solution was evaporated to dryness under vacuum. The solid residue was crystallised from dry ether (5 mL) at –20 °C to yield 1.053 g pure **2b** (68 % yield).

*In a similar procedure, compound **3a** was prepared (Scheme 2, **Route B**, Table 1, Entry 5).*

2,4-Dichloro-6-(4-oxopiperidin-1-yl)-*s*-triazine (2a) (16%) white crystalline powder, mp 219.1 - 220.2 °C (flash column chromatography, eluent ligroin : acetone 3.8:1 v/v). [Found: C, 38.55; H, 3.55; N, 23.05; $C_8H_8Cl_2N_4O$ (246.01) requires: C, 38.89; H, 3.26; N, 22.68%]. R_f 0.50 (80% ligroin/acetone). IR ν_{max} (KBr) = 1726 (s), 1591 (s), 1479 (s), 1366 (s), 1356 (s), 1229 (s), 1176 (s), 1155 (s), 1053 (s), 980 (s), 846 (s), 785 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H = 4.14 (4 H, t, $^3J_{H,H}$ = 6.4 Hz, H-2, -6, -a, -e), 2.56 (4 H, t, $^3J_{H,H}$ = 6.4 Hz, H-3, -5, -a, -e) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 205.9 (1 C, C-4, 4-piperidone), 171.1 (2 C, C-2, -4, *s*-triazine), 164.7 (1 C, C-6, *s*-triazine), 43.2 (2 C, C-2, -6, 4-piperidone), 40.6 (2 C, C-3, -5, 4-piperidone) ppm. ^1H NMR (300 MHz, [D_8]THF) δ_H = 4.12 (4 H, t, $^3J_{H,H}$ = 6.4 Hz, H-2, -6, -a, -e), 2.50 (4 H, t, $^3J_{H,H}$ = 6.4 Hz, H-3, -5, -a, -e) ppm; ^{13}C NMR (75 MHz, [D_8]THF) δ_C = 202.4 (1 C, C-4, 4-piperidone), 168.7 (2 C, C-2, -4, *s*-triazine), 162.9 (1 C, C-6, *s*-triazine), 41.0 (2 C, C-2, -6, 4-piperidone), 37.9 (2 C, C-3, -5, 4-piperidone) ppm. MS (EI, 70 eV), m/z (rel. int. %) 246.01 (100) [M^+].

2-Chloro-4,6-bis(4-oxopiperidin-1-yl)-*s*-triazine (2b) (9%) white crystalline powder, mp 188.1–189.0 °C (flash column chromatography, eluent ligroin : acetone 3.8:1 v/v). [Found: C, 50.79; H, 4.90; N, 22.71; $C_{13}H_{16}ClN_5O_2$ (309.10) requires: C, 50.41; H, 5.21; N, 22.61%]. R_f 0.35 (80% ligroin/ acetone) R_f 0.70 (60% ligroin/acetone). IR ν_{max} (KBr) = 3007 (w), 2974 (w), 2900 (w), 1714 (s), 1592 (s), 1492 (s), 1450 (s), 1367 (m), 1331 (m), 1231 (s), 1211 (s), 1016 (m), 982 (m), 967 (m), 827 (m), 793 (m), 753 (w), 685 (w), 556 (w), 497 (w) cm^{-1}. ^1H NMR (500 MHz, [D_8]THF, 303 K) δ_H = 4.10 (8 H, t, $^3J_{H,H}$ = 6.5 Hz, H-2', -2", -6', -6", -a, -e), 2.45 [4 H, bt, H-5'(3'), -5"(3"), -a, -e], 2.44 [4 H, bt, H-3'(5'), -3"(5"), -a, -e] ppm; ^1H NMR (500 MHz, [D_8]THF, 263 K) δ_H = 4.08 [4 H, t, $^3J_{H,H}$ = 5.8 Hz, H-6'(2'), -6"(2"), -a, -e], 4.07 [4 H, t, $^3J_{H,H}$ = 5.8 Hz, H-2'(6'), -2"(6"), -a, -e], 2.43 [4 H, t, $^3J_{H,H}$ = 6.3 Hz, H-5'(3'), H-5"(3"), -a, -e], 2.41 [4 H, t, $^3J_{H,H}$ = 6.3 Hz, H-3'(5'), -3"(5"), -a, -e] ppm; QC NMR (125 MHz, [D_8]THF, 303 K) δ_C = 205.1 (2 C, C-4', -4"), 170.3 (1 C, C-2, *s*-triazine), 165.2 (2 C, C-4, -6, *s*-triazine), 42.7, 42.6 (4 C, C-2', -2", -6', -6"), 40.6, 40.3 (4 C, C-3', -3", -5', -5") ppm; ^1H NMR (500 MHz, [D_6]DMSO, 343 K) δ_H = 4.03 (8 H, t, $^3J_{H,H}$ = 6.3 Hz, H-2', -2", -6', -6", -a, -e), 2.48 (8 H, t, $^3J_{H,H}$ = 6.3 Hz, H-3', -3", -5', -5", -a, -e) ppm. MS (EI, 70 eV): *m/z* (%) = 309 [M^+] (100), 281 (58), 253 (78), 240 (70), 225 (40), 197 (33), 184 (29), 70 (37).

2,4,6-Tris(4-oxopiperidin-1-yl)-*s*-triazine (2c) (1%) yellowish crystalline powder, mp 234.2 °C (dec.) (flash column chromatography, eluent ligroin : acetone 3.8:1 v/v). [Found: C, 57.75; H, 6.88; N, 22.71; $C_{18}H_{24}N_6O_3$ (372.19) requires: C, 58.05; H, 6.50; N, 22.57%]. R_f 0.20 (80% ligroin/acetone). IR ν_{max} (KBr) = 2958 (w), 2862 (w), 1709 (s), 1530 (s), 1490 (s), 1455 (s), 1371 (m), 1316 (m), 1231 (s), 1068 (m), 991 (m), 967 (m), 806 (m), 762 cm^{-1}. ^1H NMR

(300 MHz, $CDCl_3$) δ_H = 4.08 (12 H, t, $^3J_{H,H}$ = 6.0 Hz, H-2', -2", -2"', -6', -6", -6"', -a, -e), 2.47 (12 H, t, $^3J_{H,H}$ = 6.0 Hz, H-3', -3", -3"', -5', -5", -5"', -a, -e) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 208.9 (3 C, C-4', -4", -4"'), 165.8 (3 C, C-2, -4, -6, *s*-triazine), 43.0 (6 C, C-2', -2", -2"', -6', -6", -6"'), 41.5 (6 C, C-3', -3", -3"', -5', -5", -5"') ppm. MS (EI, 70 eV): *m/z* (%) = 372 [M^+] (100), 344 (20), 329 (18), 316 (58), 303 (75), 288 (47), 275 (45), 260 (50), 247 (60), 232 (25), 219 (28), 203 (26), 177 (25), 163 (21), 122 (33), 94 (32), 80 (46), 68 (28).

*Preparation of compound **1c** (Scheme 2, **Route B**)*

4-Piperidone monohydrate hydrochloride **1a** (4.70 g, 30.06 mmol) and ethyleneglicol (3.94 g, 60.12 mmol, 3.54 mL) in benzene (125 mL) were refluxed with vigorous stirring and azeotropic removal of water in a Dean-Stark trap until no more water separated (about 12 hrs.). The resulted brownish suspension was cooled at room temperature with stirring then crude **1c** was filtered off and well washed with dry ether (× 25 mL) to complete removal of benzene. Crude **1c** was taken with isopropanol : ether 1:1 v/v (24 mL), stirred 1 hr. at room temperature then the suspension was cooled at -20 °C for 12 hrs. After filtering off, washing with cooled isopropanol : ether 1:1 v/v (20 mL) and dry ether (2 × 25 mL) pure **1c** was obtained (4.62 g, 84% yield with respect to **1a**).

1,4-Dioxa-8-azaspiro[4.5]decane hydrochloride (1c) (84%) yellowish crystalline powder, mp 192.5 – 192.9 °C (Compd. No. 94532 Fluka mp193 - 197 °C and mp 193 - 198 °C see also CAS Number 42899-11-6 Beilstein Registry Number 7304914). [Found: C, 47.11; H, 7.77; N 8.19; $C_7H_{14}ClNO_2$ (179.07) requires: C, 46.80; H, 7.86; N, 7.80%]. IR ν_{max} (KBr) = 3394 (s), 2948 (s), 2788 (s), 2616 (s), 2465 (s), 1586 (s), 1474 (m), 1449 (s), 1428 (m), 1376 (s), 1347 (m), 1309 (s), 1228 (m), 1189 (s), 1178 (s), 1110 (s), 1045 (s), 1028 (s), 942 (s), 888 (s), 834 (m), 656 (m) cm^{-1}. ^{1}H NMR (300 MHz, [D_6]DMSO) δ_H = 9.30 (2 H, bs, NH_2^+), 3.90 (4 H, s, 2 × H-2, 2 × H-3), 3.05 (4 H, s, H-7, -9, -a, -e), 1.84 (4 H, t, $^3J_{H,H}$ = 5.6 Hz, H-6, -10, -a, -e) ppm; ^{13}C NMR (75 MHz, [D_6]DMSO) δ_C = 104.5 (1 C, C-5), 64.4 (2 C, C-2, -3), 42.2 (2 C, C-7, -9), 31.6 (2 C, C-6, -10) ppm. MS (EI, 70 eV), m/z (rel. int. %) 143 [M^+ - HCl] (40), 112 (10), 98 (78), 87 (100), 82 (28), 80 (8), 73 (5), 71 (14), 68 (8).

2-Chloro-4,6-bis(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-*s*-triazine (3a) (62%) yellowish crystalline powder, mp 143 – 145 °C (Et_2O). [Found: C, 50.98; H, 5.88; N 17.31; $C_{17}H_{24}ClN_5O_4$ (397.15) requires: C, 51.32; H, 6.08; N, 17.60%]. IR ν_{max} (KBr) = 2964 (m), 2932 (m), 2870 (m), 1655 (m), 1571 (s), 1492 (s), 1458 (s), 1364 (m), 1310 (m), 1230 (s), 1146 (m), 1116 (s), 1078 (s), 1034 (m), 979 (m), 944 (m), 908 (m), 796 (m), 660 (w) cm^{-1}. ^{1}H NMR (300 MHz, [D_6]DMSO) δ_H = 3.95 (8 H, s, H-2', -2", -3', -3"), 3.79 (8 H, bs, H-7', -7" -9', -9", -a, -e), 1.66 (8 H, bs, H-6', -6", -10', -10", -a, -e) ppm; ^{1}H NMR

(300 MHz, $CDCl_3$) δ_H = 3.97 (8 H, s, H-2', -2", -3', -3"), 3.85 (8 H, bs, H-7', -7" -9', -9", -a, -e), 1.66 (8 H, t, $^3J_{H,H}$ = 5.3 Hz, H-6', -6", -10', -10", -a, -e) ppm; ^{13}C NMR (75 MHz, [D_6]DMSO) δ_C = 169.2 (1 C, C-2, *s*-triazine), 163.9 (2 C, C-4, -6, *s*-triazine), 106.7 (2 C, C-5', -5"), 64.2 (4 C, C-2', -2", -3', -3"), 41.5 (4 C, C-7', -7", -9', -9"), 34.6 (4 C, C-6', -6", -10', -10") ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 170.1 (1 C, C-2, *s*-triazine), 164.5 (2 C, C-4, -6, *s*-triazine), 107.5 (2 C, C-5', -5"), 64.8 (4 C, C-2', -2", -3', -3"), 41.8 (4 C, C-7', -7", -9', -9"), 35.2 (4 C, C-6', -6", -10', -10") ppm. MS (EI, 70 eV), m/z (rel. int. %) 397 [M^+] (100), 354 (30), 325 (25), 310 (10), 297 (50), 284 (70), 252 (10), 225 (20), 212 (15), 197 (10), 184 (20), 170 (15), 158 (5), 142 (8), 127 (5), 99 (65), 86 (13), 70 (18).

*Preparation of compound **3b** (Scheme 2, **Route B**, Table 1, Entry 6)*

1,4-Dioxa-8-azaspiro[4.5]decane hydrochloride **1c** (3.60 g, 20 mmol) was dissolved in dry and freshly distilled DMF (125 mL), then anh. K_2CO_3 (5.60 g, 40 mmol) was added. The resulted suspension was cooled at 0 ^{o}C when solid cyanuric chloride (1.18 g, 6.35 mmol) was rapidly introduced with vigorous stirring. The reaction mixture was let very gently to reach room temperature (about 24 hrs.) then heated at reflux until TLC monitoring (eluent ligroin : acetone 1.5 : 1 v/v) indicated no more evolution of the reaction and the crude product **3b** as a main spot (about 12 hrs.). The reaction mixture was poured on water (100 mL) then extracted with chloroform (100 ml). After separation, the organic layer was well washed with water (7 × 100 mL) to complete removal of DMF, then dried over anh. Na_2SO_4. After filtering off and washing minerals with chloroform, the organic solution was evaporated under reduced presure to dryness yielding the crude product which was taken with dry ether (5 mL) with stirring. The resulted suspension was cooled at -20 ^{o}C for 12 hrs. then filtered off and washed with dry and cooled ether to yield the title compound **3b** (2.00 g, 63% yield with respect to cyanuric chloride).

2,4,6-Tris(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-*s*-triazine (3b) (63%) yellowish crystalline powder, mp 259 – 263 ^{o}C (Et_2O). [Found: C, 56.98; H, 7.33; N 17.01; $C_{24}H_{36}N_6O_6$ (504.27) requires: C, 57.13; H, 7.19; N, 16.66%]. IR ν_{max} (KBr) = 2954 (w), 2927 (w), 2875 (w), 1684 (w), 1539 (s), 1493 (s), 1450 (s), 1360 (w), 1333 (w), 1309 (w), 1234 (m), 1120 (m), 1080 (s), 1038 (w), 947 (m), 908 (m), 804 (w), 661 (w) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 4.00 [12 H, s, 2 × (H-2', -2", -2'"), 2 × (H-3', -3", -3'")], 3.86 [12 H, t, $^3J_{H,H}$ = 5.2 Hz, H-7', -7", -7'", -9', -9", -9'", -a, -e), 1.70 (12 H, t, $^3J_{H,H}$ = 5.2 Hz, H-6', -6", -6'", -10', -10", -10'", -a, -e) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 165.3 (3 C, C-2, -4, -6, *s*-triazine), 107.8 (3 C, C-5', -5", -5'"), 64.3 (6 C, C-2', -2", -2'", -3', -3", -3'"), 41.1 (6 C, C-7', -7", -7'", -9', -9", -9'"), 34.8 (6 C, C-6', -6", -6'", -10', -10", -10'") ppm.

Alternativ preparation of compound ***2c*** *(Scheme 2,* ***Route B****)*

To 2,4,6-tris(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-*s*-triazine **3b** (1.446 g, 2.86 mmol) suspended in aqueous 1,4-dioxane (water 21 mL + 1,4-dioxane 7 mL), concd. aq. hydrochloric acid (1.00 mL, 1.18 g soln. 37%, 12 mmol HCl) was added and the reaction mixture, having the pH = 0.5 – 1.0, was heated at reflux for 12 hrs. The reaction was monitored spot to spot by TLC (eluent ligroin : acetone 1.5:1 v/v) and stopped when no more evolution was observed and the desired **2c** as largely major spot. The reaction mixture was cooled at room temperature and made alkaline (pH = 10) with solid K_2CO_3 when crude **2c** precipitated abundantly. After filtering off, washing with water to neutrality and drying, pure **2c** (0.800 g, 75 % yield) was obtained after crystallisation from ether at -20 ^{o}C. The pure analytical sample obtained by the above methodology was identical with that obtained in **Route A** (Table 1, Entries 1 – 3).

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