FIRST SYNTHESIS, ROTAMERISM AND HERBICIDAL EVALUATION OF SUBSTITUTED *s*-TRIAZINES WITH AMINO-1,3-DIOXANE GROUPS

Marijana Fazekas,[a] Mircea Darabantu,[a,b] Monica Pintea,[a] Pedro Lameiras,[b]
Constantin Bele,[c] Camelia Berghian[a,b] and Nelly Plé[b]
[a]"Babes-Bolyai" University, Department of Organic Chemistry, 11 Aranyi Jànos str., RO-400028 Cluj-Napoca, Romania
[b]Université de Rouen, Institut de Recherche en Chimie Organique Fine (I. R. C. O. F.), BP-08, F- 76131 Mont Saint-Aignan Cedex, France
[c]University of Agricultural Sciences and Veterinary Medicine, 3-5 Manastur str., RO-400375 Cluj-Napoca, Romania
E-mail : darab@chem.ubbcluj.ro; darabantu@cluj.astral.ro; FAX: 00 40 264 59 08 18; Tel.: 00 40 264 59 38 33

Abstract: First pure enantiomeric 5-amino-1,3-dioxane, obtained by total diastereospecific ring closure of (1*S*,2*S*)-2-amino-1-(4-ni-trophenyl)-1,3-propanediol (*"nitrophenylserinol"*) reacted with cyanuryl chloride to afford *N*-substituted amino-*s*-triazines and melamine. Their rotameric behaviour around the C^{sp2}(*s*-triazine)-N(1,3-dioxane) bond is discussed in terms of NMR, as steric and electronic influence of the substituents. The herbicidal evaluation of one of the new compounds is also described.

Introduction

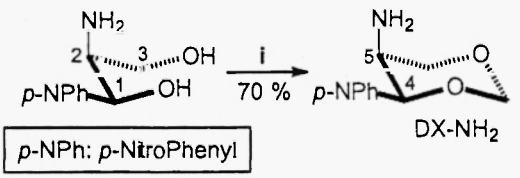
We have previously reported our methodology to prepare pure enantiomeric 5-amino-1,3-dioxanes (1-5) by direct diastereospecific ring closure of (1*S*,2*S*)-2-amino-1-(4-nitrophenyl)-1,3-propanediol (the so called *"nitrophenylserinol"*) and its *N,N*-dimethyl analogue upon treatment with certain aldehydes in strong acidic media (98 % H_2SO_4, 0 °C). These aminodioxanes exhibited useful reactivity upon treatment with typical electrophiles: aryl(di)aldehydes and acid (poly)chlorides (1-3).

For the present preliminary communication, our outstanding attention is dedicated to the reaction between one representative compound in this class and cyanuryl chloride with a concise stereochemical approach of the products. To the best of our knowledge, amino-1,3-dioxanes were never considered as nucleophiles against cyanuryl chloride though some *N*-subsituted-amino-*s*-triazines bearing an acetal motif are mentioned in the literature to be potential anticancer agents (6).

Results and Discussions

1. Synthesis

The starting amino-1,3-dioxane (hereafter abbreviated as DX-NH_2) was prepared from the enantiomerically pure (1*S*,2*S*)-2-amino-1-(4-nitrophenyl)-1,3-propanediol (*ni- trophenylserinol*) (**Scheme-1**). The synthesis and stereochemistry of DX-NH_2 we reported elsewhere (1,4). The compound is a stable crystalline solid and an ananchomeric structure, possessing the aromatic group in equatorial position. It is already useful to observe that in DX-NH_2 the amino group is placed in axial position flanked by the preferred bisectional orientation of the aromatic ring (*cis* relationship).

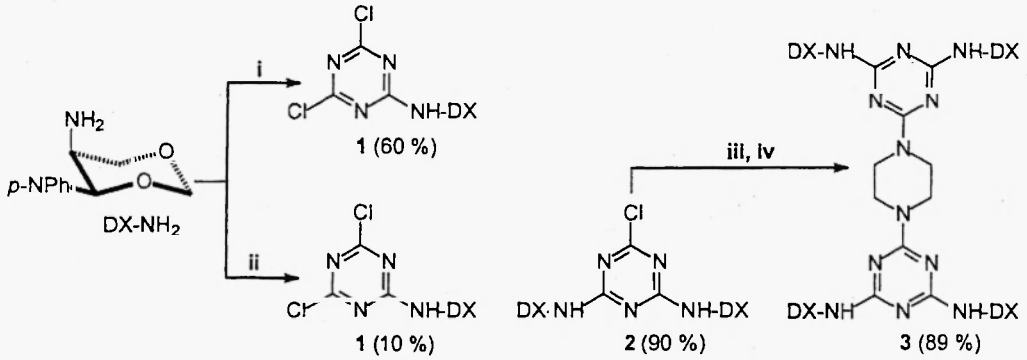


i: 1 eq. CH_2O / 10 eq. H_2SO_4 98 % / 24 hrs. from 0 °C to r.t.

Scheme-1

The nucleophilicity of DX-NH_2 against chloro-*s*-triazines was straightforward (**Scheme 2**, the partial conversions of cyanuryl chloride are presented in round brackets).

In a first effort (route **i**) we obtained the expected **1** with a satisfactory yield; TLC monitoring of the reaction evidenced also the noticeable presence of the unreacted starting materials. Attempting at a melamine based exclusively on DX-NH_2 (route **ii**) failed:



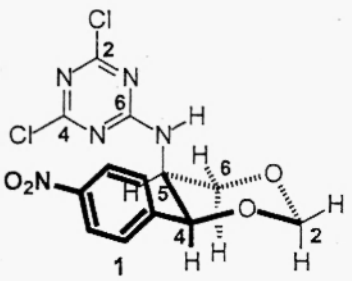
i: 1.05 eq. $C_3N_3Cl_3$ / 1.00 eq. anh. K_2CO_3 / THF / 24 hrs. from 0 °C to r.t.; **ii:** 0.33 eq. $C_3N_3Cl_3$ / 1.00 eq. anh. K_2CO_3 / toluene / 24 hrs. at reflux; **iii:** 0.49 eq. piperazine hexahydrate, 1.15 eq. HCl / *i*-PrOH; **iv:** 0.49 eq. piperazine hydrochloride / 2.00 eq. anh. K_2CO_3 / toluene / 12 hrs. at reflux.

Scheme-2

the successive replacement of chlorine in cyanuryl chloride stopped after the second substitution. Instead, the chloro-diamino-*s*-triazine **2** was isolated with excellent yield, together with **1** as side product. They were separated by flash column chromatography. Matching results we reached when the proton scavenger was the "proton sponge" (1,8-bis-dimethylaminonaphthalene). However, if reducing the amount of cyanuryl chloride (0.47 eq., 1.00 eq. K_2CO_3), the partial conversions changed as 47 % **1** and 53 % **2**. Thus, it was impossible to link three DX-NH units to the triazine ring, presumably because the intimate stereochemistry of the DX-NH_2 which influenced the nucleophilicity of the 5-amino group. Consequently, in order to access melamines based on aminodioxane DX-NH_2, our option focused on a stronger nucleophile, piperazine (**Scheme-2**, routes **iii, iv**). Its hygroscopicity was avoided by preliminary conversion into hydrochloride. The "dimeric" melamine **3** was prepared in good yield in a very clean reaction.

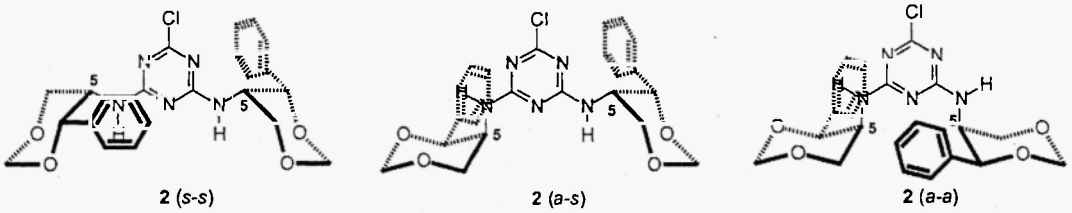
2. Stereochemistry and Rotameric Behaviour

The compound **1** was an ananchomeric structure exhibiting a double bond character of the linkage C-6(*s*-triazine)-N(1,3-dioxane), hence a restricted rotation in this sequence (**Scheme-3**). Thus, in the ^{13}C NMR spectrum, the triazinic positions 2 and 4 were found diastereotopic, $\Delta\delta$=0.5 ppm. In the ^1H NMR spectrum, the protons N*H* displayed a typical splitting ^3J=9.4 Hz to support a fixed location and an *anti* arrangement against the proton H-5. Next, one can also anticipate some hindered rotation about the axial C-5-N bond, due to the proximity of the ligands H-6-eq. and *p*-NPh, predicting an *out* orientation of the triazinic moiety.



Scheme-3

In the case of compound **2**, the NMR analysis revealed the diastereomerism issued from the restricted rotation about the C^{sp2}(triazine)-N(dioxane) bond as mixtures of three blocked rotamers (8,9) designed as: *syn-syn* (*s-s*), *syn-anti* (*s-a*) and *anti-anti* (*a-a*). The dioxane fragments and the triazine chlorine were chosen as references for these descriptors (**Scheme-4**, **Table-1**, **Figure-1**; in **Scheme-4** the *p*-nitro group was omitted for reason of simplicity).

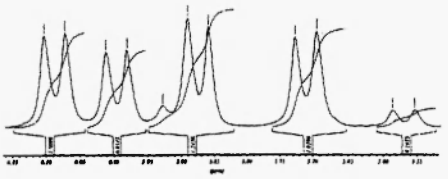


2 (*s-s*) 2 (*a-s*) 2 (*a-a*)

Scheme-4

Table-1: Relevant ^{1}H NMR data and contributions of the blocked rotamers for the compound **2**

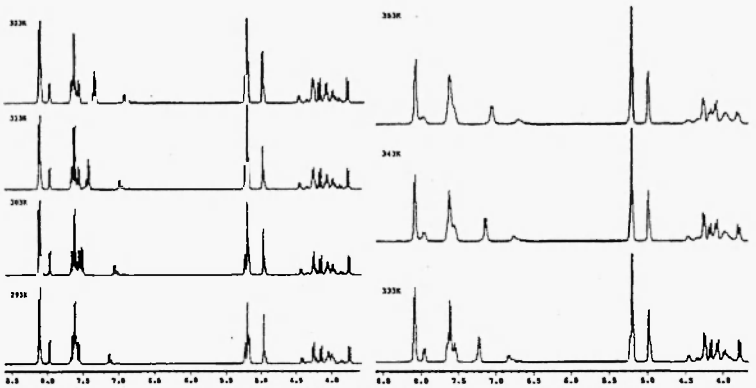
Solvent	Rotamers (%) according to N*H* signals			δ_{NH} (ppm) (^3J N*H*-*H*-5 Hz)		
	(*s*-*s*)	(*s*-*a*)	(*a*-*a*)	(*s*-*s*)	(*s*-*a*)	(*a*-*a*)
DMSO-d_6	34	53	13	7.55 (8.8)	7.55, 7.13 (8.8), (9.6)	7.10 (11.6)
C_6D_6	53	24	23	6.48 (8.3)	5.57, 5.78 (9.1), (9.8)	5.85 (9.8)
$CDCl_3$	26	54	20	6.09 (9.4)	5.88, 5.71 (9.4), (9.8)	6.00 (9.8)



^{1}H NMR spectrum of the compound **2** (300 MHz, $CDCl_3$, 293 K), detail in the region of the protons N*H*.
Figure-1

As expected, the "reference" protons were N*H* and used for the calculations (**Table-1**): isochronous doublets in environments (*s*-*s*) and (*a*-*a*) but anisochronous in (*s*-*a*). The rotamerism appeared influenced by the stereochemistry of the axial linkage dioxane-triazine, (**Figure-1**). Surprisingly, the NMR spectra of **2** clearly indicated that this molecule, arising from a bulky nucleophile, can adopt all possible spatial arrangements (*s*-*s*, *s*-*a*, *a*-*a*) suggested by the manipulation of the Drieding models (**Scheme-4**, **Figure -1**). Moreover, as shown in **Figure-1**, in $CDCl_3$, another pair of doublets was revealed to indicate a fourth minor rotamer which was not assigned. It must be observed that, in all stereoisomers, the magnitude of the coupling pattern ^3J between protons N*H* and H-5-eq. was significant, in agreement with some hindrance to rotation about the axial *C*-5-*N*H bond (**Table-1**). A major dependence on the solvent was determined related to the content of rotamers: the statistically favoured (*s*-*a*) rotamer was dominant in polar and chelating solvent (DMSO-d_6) or only polar ($CDCl_3$). In contrast, the A.S.I.S. (10) interactions required the rotamer (*s*-*s*) as prevailing.

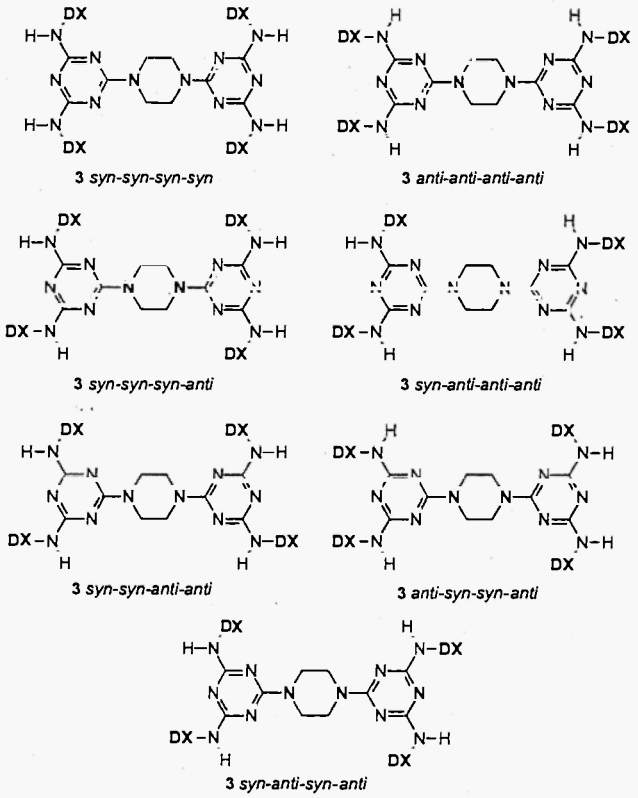
The NMR experiments carried out in DMSO-d_6 by increasing the temperature (293→353 K) provided the results depicted in **Figure-2**: one can not assume that even at 80 °C the compound **2** reached complete flexibility.



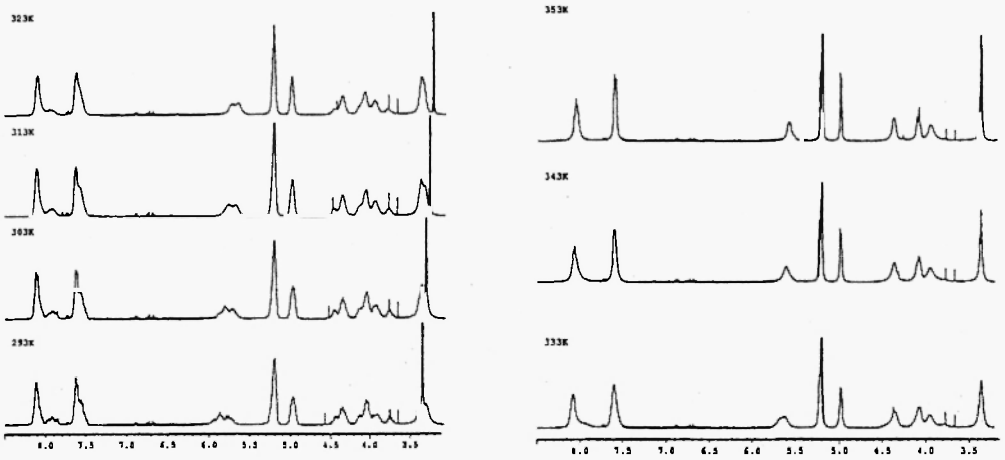
^{1}H DNMR spectrum of the compound **2** (400 MHz, 353 K, see also **Scheme-3**) from downfield to upfield δ (ppm), *J* (Hz): 8.08 (d, ^3J=8.0 Hz, H-*p*-NPh), 7.97 (bs, *p*-NPh), 7.62 (d, ^3J=6.8 Hz, *p*-NPh), 7.06 (d, ^3J=8.4 Hz, N*H*), 6.69 (bs, N*H*), 5.21 (s, H-4-ax.), 5.20 (d, ^2J=6.0 Hz, H-2-eq.), 4.99 (d, ^2J=6.0, H-2-ax.), 4.46 (bs, H-5-eq.), 4.35 (d, ^2J=7.6 Hz, H-5-eq.), 4.26 (d, ^3J=8.4 Hz, H-5-eq.), 4.17 (d, ^2J=10.8 Hz, H-6-eq.), 4.09 (d, ^2J=11.2 Hz, H-6-eq.), 3.97 (bs, H-6-ax.), 3.80 (d, ^2J=10.8 Hz, H-6-ax.).
Figure-2

Indeed, at 353 K, three correlations between N*H*-*H*-5-eq. were assigned by COSY Experiments, consistent with three unequal environments for the proton H-5-eq.: two doublets and one broad singlet.

The "dimeric" melamine **3** can exist as seven distinct rotamers (**Scheme-5**, the 1,3-dioxane and piperazine rings as references; the *syn* and *anti* descriptors are cited clockwise) (8). At room temperature, the ^{1}H NMR 300 MHz spectra ($CDCl_3$ and DMSO-d_6) were complex and allowed only to identify the type of compound as the envisaged one. The ^{1}H DNMR (400 MHz, DMSO-d_6) recorded by rising the temperature (ΔT=10 K) provided at 80 °C a single deblocked structure in a slow exchange domain between sites (**Figure-3**).



Scheme-5



^{1}H DNMR spectrum of the compound **3** (400 MHz, 353 K, see also **Scheme-5**) from downfield to upfield δ (ppm), *J* (Hz): 8.06 (8 H, bs, H-*p*-NPh), 7.59 (8 H, d, ^3J=7.6 Hz, H- *p*-NPh), 5.58 (4 H, d, ^3J=7.6 Hz, N*H*), 5.22 (4 H, d, ^2J=6.0 Hz, H-2-eq.), 5.20 (4 H, s, H-4-ax.), 4.99 (4 H, d, ^2J=6.0 Hz, H-2-ax.), 4.37 (4 H, d, ^3J=7.6 Hz, H-5-eq.), 4.10 (4 H, d, ^2J=10.4 Hz, H-6-eq.), 3.97 (4 H, bs, H-6-ax.), 3.36 (8 H, s, CH_2, piperazine).

Figure-3

3. Herbicidal evaluation

Compound **2** was in addition tested as potential herbicide on seeds of *Cucumis sativus* and *Raphanus sativus*. Literature methods were straightforward (11). Atrazine® was used for testing biological activity along with the synthesised compound **2**. The results, as mean (±SD) percentage values of germination inhibition and root length are collected in **Table-2**.

Table-2: Percent inhibitions of seeds germination and root length of *Cucumis sativus* and *Raphanus sativus* in response to different concentrations of the compound **2** as compared to those of Atrazine®

Tested species	Conc.	Germination		Root length	
		2	Atrazine®	2	Atrazine®
Cucumis sativus	0.50 mM	57 ± 4.9	62 ± 4.2	67 ± 5.6	69 ± 6.5
	0.75 mM	84 ± 2.3	89 ± 2.5	86 ± 3.4	91 ± 3.3
	1.00 mM	100 ± 0.0	100 ± 0.0	-	-
Raphanus Sativus	0.50 mM	65 ± 6.2	71 ± 5.6	72 ± 4.8	74 ± 6.2
	0.75 mM	87 ± 3.7	90 ± 2.4	91 ± 4.6	93 ± 5.8
	1.00 mM	100 ± 0.0	100 ± 0.0	-	-

Our opening data evidenced an important inhibition in germination seeds of the tested species, even complete (c. 1mM), quite similar to Atrazine®. The root length was also significantly reduced.

Experimental

General

Melting points were uncorrected; they were carried out on ELECTROTHERMAL® instrument. Current NMR spectra were recorded on Brucker® AM 300 instrument operating at 300 and 75 MHz for ^{1}H and ^{13}C nuclei respectively. The ^{1}H DNMR spectra were run on Brucker® AM 400 instrument operating at 400 MHz for ^{1}H nuclei with each step 10 K increasing the temperature. 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® 16 PC FT-IR spectrometer. Only relevant absorptions are listed in cm^{-1}[weak (w), medium (m) or (s) strong]. Mass spectrum (MS) was recorded on an ATI-Unicam Automass® apparatus, fitted (or not) with a GC-mass coupling (high-resolution J&W column, 30 m, 0.25 mm ID, flow rate: 1.2 mL min^{-1}).

2,4-Dichloro-6-[(4*S*,5*S*)-4-(4-nitrophenyl)-1,3-dioxan-5-yl]-amino-*s*-triazine (1): (60 %) yellowish crystalline powder; m.p.=194-195 °C (Et_2O); [Found: C, 42.11; H, 2.77; N, 19.09. $C_{13}H_{11}N_5Cl_2O_4$ requires C, 41.96; H, 2.98; N, 18.82 %]; IR (ν_{max}, KBr) 3305 (s), 2875 (m), 1585 (s), 1556 (s), 1510 (s), 1410 (s), 1346 (s), 1325 (s), 1240 (m), 1183 (s), 1167 (s), 1103 (s), 1043 (m), 1028 (m), 964 (m), 842 (m), 798 (m), 713 (m) cm^{-1}; ^{1}□ □□R (300 MHz, $CDCl_3$, 293 K): 8.18 (2 H, d, ^{3}J=8.7 Hz, H-*p*-NPh), 7.51 (2 H, d, ^{3}J=8.7 Hz, H- *p*-NPh), 6.65 (1 H, d, ^{3}J=9.4 Hz, N*H*), 5.35 (1 H, d, ^{2}J=6.4 Hz, H-2eq.), 5.11 (1 H, s, H-4-ax.), 5.02 (1 H, d, ^{2}J=6.4 Hz, H-2-ax.), 4.56 (1 H, d, ^{3}J=9.8 Hz, H-5-eq.), 4.24 (1 H, d, ^{2}J=12.1 Hz, H-6-eq.), 4.14 (1 H, d, ^{2}J=11.3 Hz, H-6-ax.); ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): 171.1 (1 C, C-Cl), 170.6 (1 C, C-Cl), 165.8 (1 C, C-N), 148.0 (1 C, Cq.- *p*-NPh), 144.4 (1 C, Cq.- *p*-NPh), 126.8 (2 C, CH- *p*-NPh), 124.0 (2 C, CH- *p*-NPh), 94.9 (1 C, C-2), 78.9 (1 C, C-4), 70.6 (1 C, C-6), 50.2 (1 C, C-5); MS (EI, 70 eV); m/z (rel. int. %): 371 (40) [M^{+}-1], 341 (25), 311 (100), 277 (18), 218 (39), 190 (25), 164 (27).

2-Chloro-4,6-bis[(4*S*,5*S*)-4-(4-nitrophenyl)-1,3-dioxan-5-yl]-amino-s-triazine (2): (90 %) yellow crystalline powder; m.p.=154-155 °C (flash column chromatography, eluent ligroine : acetone 1.5:1 v/v); [Found: C, 48.97; H, 4.14; N, 17.99. $C_{23}H_{22}N_7ClO_8$ requires C, 49.34; H, 3.96; N, 17.51 %]; IR (ν_{max}, KBr) 3404 (m), 3314 (m), 2859 (s), 1573 (s), 1518 (s), 1510 (s), 1346 (s), 1240 (m), 1174 (s), 1167 (s), 1094 (s), 1026 (s), 1028 (s), 987 (s), 851 (m), 805 (m), 711 (m) cm^{-1}; ^{1}□ □□R (300 MHz, $CDCl_3$, 293 K): 8.12-8.05 (12 H, m, H- *p*-NPh), 7.45-7.39 (12 H, m, H- *p*-NPh), 6.09 (2 H, d, ^{3}J=9.4 Hz, N$H_{s\text{-}s}$), 6.00 (2 H, d, ^{3}J=9.8 Hz, N$H_{a\text{-}a}$), 5.88 (1 H, d, ^{3}J=9.4 Hz, N$H_{s\text{-}a}$), 5.71 (1 H, d, ^{3}J=9.8 Hz, N$H_{s\text{-}a}$), 5.35-5.30 (3 H, m, H-2eq.), 5.25-5.20 (3 H, m, H-2eq.), 4.99-4.91 (12 H, m, H-2-ax., H-4-ax.), 4.41-3.88 (18 H, m, H-5-eq., H-6-eq., H-6-ax.); ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): 169.5 (3 C, C-

Cl), 165.8, 165.4, 165.3, 165.2 (6 C, C-N), 147.9, 147.7 (6 C, C-q.- *p*-NPh), 145.2, 145.0 (6 C, Cq.- *p*-NPh), 126.9, 126.73, 126.66 (12 C, CH- *p*-NPh), 123.80, 123.77, 123.73 (12 C, CH- *p*-NPh), 94.9, 94.8 (6 C, C-2), 79.33, 79.27, 79.21, 79.1 (6 C, C-4), 71.1, 70.8, 70.7, 70.5 (6 C, C-6), 49.6, 49.5, 49.3, 49.2 (6 C, C-5); MS (ESI, 35 eV); m/z (rel. int. %): 559 (100) [M^+], 541 (27), 529 (22), 511 (10).

1,4-Bis{4,6-bis[(4*S*,5*S*)-4-(4-nitrophenyl)-1,3-dioxan-5-yl]-amino-s-triazin-2-yl}-piperazine (3): (89 %) yellow crystalline powder; m.p.=224-225 °C (flash column chromatography, eluent ligroine : acetone 1.25:1 v/v); [Found: C, 53.37; H, 5.02; N, 19.69. $C_{50}H_{52}N_{16}O_{16}$ requires C, 53.00; H, 4.63; N, 19.78 %]; IR (ν_{max}, KBr) 3414 (m), 2855 (m), 1576 (s), 1548 (s), 1520 (s), 1442 (s), 1346 (s), 1244 (w), 1173 (s), 1095 (m), 1027 (m), 985 (m), 852 (w), 810 (m), 742 (w), 711 (w) cm^{-1}; ^{1}□ □□R (400 MHz, DMSO-d_6, 353 K): 8.06 (8 H, bs, H-*p*-NPh), 7.59 (8 H, d, ^3J=7.6 Hz, H- *p*-NPh), 5.58 (4 H, d, ^3J=7.6 Hz, N*H*), 5.22 (4 H, d, ^2J=6.0 Hz, H-2eq.), 5.20 (4 H, s, H-4-ax), 4.99 (4 H, d, ^2J=6.0 Hz, H-2-ax.), 4.37 (4 H, d, ^3J=7.6 Hz, H-5-eq.), 4.10 (4 H, d, ^2J=10.4 Hz, H-6-eq.), 3.94 (4 H, bs, H-6-ax.), 3.36 (8 H, s, CH_2 piperazine); ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): 165.7 (4 C, C-N), 165.5 (2 C, C-N), 147.6 (4 C, Cq.- *p*-NPh), 146.0 (4 C, Cq.- *p*-NPh), 127.0 (8 C, CH- *p*-NPh), 123.4 (8 C, CH- *p*-NPh), 94.7 (4 C, C-2), 79.8 (4 C, C-4), 71.4 (4 C, C-6), 49.0 (4 C, C-5), 42.8 (4 C, CH_2-piperazine); MS (FAB^+); m/z (rel. int. %): 1132 (95) [M^+-1], 952 (20), 663 (33), 551 (33), 459 (100).

Conclusions

As demonstrated by our first example, a 5-amino-1,3-dioxane built on *p*-nitrophenyserinol skeleton reacts with cyanuryl chloride to yield amino-*s*-triazines in medium to good yields. However, the substitution of the third chlorine appears not possible due to the axial orientation of the nucleophilic group linked to an anancomeric skeleton. At room temperature, all *N*-substituted-amino-*s*-triazines with a 1,3-dioxane group are distinct type of rotamers due to the partial double bond character of the C^{sp2}(s-triazine)-N(1,3-dioxane) site. The content of rotameric species is also dependent on the solvent. The herbicidal activity in this class of *s*-triazines was tested. The full report of our complete results is under consideration for the near future.

References

1. M. Darabantu; S. Mager; C. Puscas; M. Bogdan; E. Cotora; G. Plé and I. Bratu, *Rev. Rom. Chim.* **39**, 955-965 (1994).
2. M. Darabantu; S. Mager; C. Puscas; M. Bogdan; G. Plé; E. Cotora and D. Kovacs, *Rev. Rom.Chim.* **40**, 453-461 (1995).
3. M. Darabantu; S. Mager; C. Puscas; G. Plé; M. Bogdan and E. Cotora, *Rev. Rom. Chim.* **40**, 907-916 (1995).
4. M. Darabantu; C. Maiereanu; G. Plé; C. Berghian; E. Condamine and Y. Ramondenc, *Heterocyclic Commun.* *7*(6), 593-596 (2001).
5. M. Darabantu; G. Ple; S. Mager; C. Puscas and E. Cotora, *Tetrahedron* **53**, 1909-1922 (1997).
6. B. O. Kraiz and A. L. Remizov, *Zh. Org. Khim.* **15**(16), 1282-1283 (1979).
7. Recent data, for example : G. Boncic-Caricic; Z. D. Tadic and M. Muskatirovic, *J. Serb. Chem. Soc.* **59**(12), 929-933 (1994); N. D. Reddy; A. Elias and A. Vic, *J. Chem. Res. Synop.* **9**, 504-505 (1998).
8. See our preceding communication.
9. **a)** A. R. Katritzky; I. Ghiviriga; D. C. Oniciu and A. Barkock, *J. Chem. Soc. Perkin Trans.* **2**, 785-792 (1995); **b)** A. R. Katritzky; I. Ghiviriga; P. G. Steel and D. C. Oniciu, *J. Chem. Soc. Perkin Trans.* **2**, 443-447 (1996); **c)** I. Ghiviriga and D. Oniciu, *Chem. Comm.* **22**, 2718-2719 (2002).
10. **a)** P. Laszlo, *Bull. Soc. Chim. Fr.* **10**, 2658-2661 (1964); **b)** K. Nikki, *Magn. Res. Chem.* **28**, 385-388 (1990).
11. **a)** K. Grossmann; S. Tresch and Z. Plath, *Naturforsch*, **56c**, 559-569 (2001); **b)** H. Omokawa and M. Konnai, *Pestic. Sci.* **35**, 83-86 (1992); **c)** H. Omokawa; N. Ichizen and T. Takematsu, *Agric. Biol. Chem.* **51**, 2563-2568 (1987).

Received on January 20, 2005