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FIRST REPORT ON 3,7-DIOXA-*r*-1-AZABICYCLO[3.3.0]OCT-*c*-5-YLMETHOXY SYSTEM SUBSTITUTING *s*-TRIAZINE

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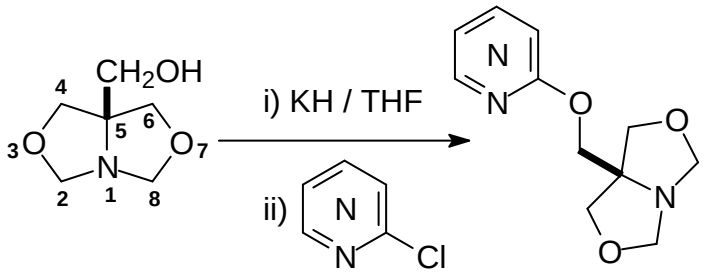
ABSTRACT. The nucleophilicity of two representative *c*-5-hydroxymethyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]octanes against cyanuryl chloride was investigated. Surprisingly, the C-2, -8 substitutions on the bicyclic system was found to decide the type of reactive species involved in the nucleophilic displacement of chlorine.

1. INTRODUCTION

We have recently reported the *O*-functionalisation of *c*-5-hydroxymethyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]octane *via* alkoxide form upon treatment with chlorodiazines (**Scheme 1**).[1,2]



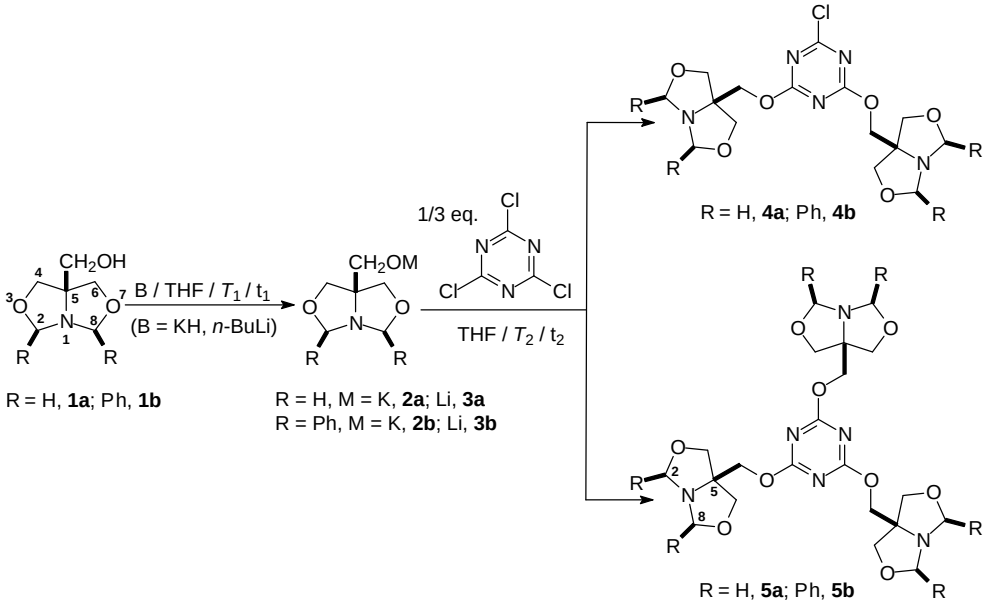
Scheme 1

By developing the Broadbent pioneering work,[3] our methodology extrapolated the clean and selective access to a large variety of π-deficient systems (pyrazines and pyrimidines) bearing 1-3 3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-ylmethoxy groups linked at the α-positions to the (di)azine nitrogen atoms.

Following the above up to date promising results, the present work focused on the reactivity of certain *c*-5-hydroxymethyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]octanes against cyanuryl chloride. Thus, if the nucleophilic displacement of its chlorine atoms by simple alcohols in neutral or basic conditions is already "classic",[4-6] the same reaction in our dedicated class of compounds is inexistent so far.

2. RESULTS AND DISCUSSIONS

The selected *c*-5-hydroxymethyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]octanes were **1a**, **b** (**Scheme 2**) because of their previously very well documented synthesis, stereochemistry and applications.[2] The strategy we used is resumed below and the results are collected in **Table 1**.



Scheme 2

The target compounds were the *s*-triazines **5a**, **b**.

Preliminary attempts already demonstrated unexpected great differences (reactivity, chemioselectivity, analytical control, NMR behaviour etc.) with respect to the previously described by us chlorodiazines: pyrimidine and pyrazine.[1,2]

As shown by the data collected in **Table 1**, starting from **1a**, a strong dependence of the nucleophilicity with respect to the *O*-metallated form (as **2a** or **3a**) was observed.* Thus, **2a** allowed only the disubstitution of chlorine to yield the *s*-triazine **4a** (entry 1) with poor yield. In fact, one may assume, as main process, rather the decomposition of cyanuryl chloride since, besides the unreacted **1a** and **4a**, no intermediate originating from the monosubstitution of chlorine we detected. By varying the temperature, as milder conditions (entries 3-5), it appeared to us that the ring opening of *s*-triazine occurred to provide exclusively resins structures with complex NMR spectra of the crude reaction mixtures.

In contrast, the use of **3a**, seen as soft nucleophile, permitted rapidly the optimisation of the synthesis towards **5a** (entry 6→7) in mild and reproducible conditions.

* the sodium hydride was *a priori* ruled out since it promotes only partial deprotonation of **1a, b**, as we earlier pointed out.[1,2]

Table 1

Results of the synthesis of the compounds **4a**, **b**, **5a**, **b**

Starting material	Entry	B	T_1 (^oC)	t_1 (hrs.)	T_2 (^oC)	t_2 (hrs.)	Results	
							Compd.	Yield (%)
1a	1	KH	45	2	65	36	**4a**	34
	2				-78→r.t. 40	19 24	**1a**	44
	3				-78→r.t. 65	18 72	dec.	-
	4				-78→r.t. r.t. 45	19 24 24	dec.	-
	5				40 65	1 48	dec.	-
	6	*n*-BuLi	-78	0.3	-78→r.t. r.t. 65	19 24 24	**5a** (70)[a] **1a** (30)	39[b]
	7				-78→r.t.	20	**5a**	82
1b	8	KH	45	2	0 65	1 40	**5b** (51) **4b** (10) **1b** (39)	37
	9	*n*-BuLi	-60	0.3	r.t.	68	**5b** (24) **4b** (4)[c] **1b** (65)	15
	10				-60→r.t. r.t. 65	20 48 4	**5b** (46) **4b** (8)[d] **1b** (29)	29

[a]as molar percentages issued from the ^{1}H NMR spectra of the crude reaction mixture; [b]the recovered amounts of the starting materials **1a**, **b** were not taken into account; [c]7% assigned comparatively as non isolable product of monosubstitution *s*-triazine; [d]17 % assigned comparatively as non isolable product of monosubstitution.

Analytical discrimination between the *s*-triazines **4a** and **5a** was less simple than would expect. In the ^{13}C-NMR spectrum of **4a**, the triazine carbons were found accidentally isochronous at 171.0 in $CDCl_3$ and 170.6 ppm in DMSO-d_6 (75 MHz) meanwhile in **5a** the most deshielded resonance was 173.3 ppm. The ^{1}H singlet assigned to 5-CH_2O group in **4a** was located 0.52 ppm downfield than in the starting **1a** whereas in **5a** the same deshielding was 0.87 ppm. That is, only the mass spectra of **4a**, **5a** (ESI and FAB$^+$ respectively) fully validated the envisaged structures.

The TLC monitoring of the reaction was very cumbersome because of the very weak absorption in UV (254 nm) of the compounds and almost absent during flash column chromatography. Moreover, the routine as typical visualisation of the starting **1a** in I_2-bath was quite difficult in the case of **4a** and **5a**.

These serious complications arose presumably from the retention of the products on silica gel: indeed, this behaviour is already known to be useful methodology to access silica gel HPLC chiral *s*-triazines selectors for enantiomeric separation.[8-11]

They were also encountered in the synthesis of the compound **5b**. The starting **1b** was used as pure *all cis*-2,5,8 diastereomer (*meso* form, **Scheme 1**).[2,12] The potassium alkoxide derivative **2b** of **1b**, afforded this time the highest content of **5b** in the crude reaction mixture (entry 8): the depicted yield in **Table 1** refers to isolated amounts after flash column chromatography (eluent ligroin : acetone 3.5:1 v/v) as follows: the unreacted **1b** was recovered as a first fraction then pure **5b**. Complete elution of the column with pure acetone yielded supplementary amounts of **5b** as a non separable mixture with the **4b** in about 2:1 molar ratio. Discrimination between **4b** and **5b** was solved by MS-(FAB^+) only: the spectrum clearly displayed both the peaks 967.9 [M^++1] (100 % abundance of **5b**) and 704 [M^+-1] (20 % abundance of **4b**). In the ^{1}H NMR spectra ($CDCl_3$), the most influenced signals were again those belonging to 5-CH_2O group: the corresponding singlet was located at 3.45 ppm in **1b**, 4.24 ppm in **5b** and 4.31 ppm in **4b**. Similarly, the triazine carbons were accidentally isochronous in **4b** (171.8 *vs.* 172.9 ppm in **5b**).

Finally we note that, according to data in **Table 1** issued from the ^{1}H NMR spectra of the crude reaction mixtures, the major components in all successful cases were the desired trisubstituted compounds **5a** (or **5b**) together with the corresponding starting materials **1a** (or **1b**). This supports our hypothesis about the partial uncontrollable decomposition of the cyanuryl chloride, as ring cleavage, in the depicted protocols. Thus, agreement was found with its related behaviour against dimethylformamide and active methylene compounds.[13]

3. CONCLUSION

The nucleophilic displacement of chlorine in cyanuryl chloride by the *c*-5-hydroxymethyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]octanes as *O*-potassium- or *O*-lithio-derivatives can be successfully achieved in mild conditions, to promote the di- or trisubstitution. The fezability of the syntheses depends on the C-2, -8 functionality of the bicycle and the base (KH or *n*-BuLi) used to deprotonate the hydroxymethyl group.

4. EXPERIMENTAL

Melting points are not corrected; they were determined on an ELECTROTHERMAL® instrument.

NMR spectra were recorded on Brucker® AM 300 instrument operating at 300 and 75 MHz for ^{1}H and ^{13}C nuclei respectively. No $SiMe_4$ was added; chemical shifts were measured against the solvent peak. All NMR spectra were measured in anhydrous commercially available deuterated solvents. All chemical shifts (δ values) were given throughout in ppm; all coupling patterns (*J* values) were given throughout in Hz. In the stereochemical assignment based on ^{1}H NMR spectra of the compounds **4a**, **b**, **5a**, **b**, the lone pair of the bridged N-1 was designed as fiducial substituent (reference); the bicyclic protons are labelled as H-*c* (*cis*) or H-*t* (*trans*) with respect to the fiducial substituent.

IR spectra were performed on a Perkin-Elmer® 16 PC FT-IR spectrometer. Only relevant absorptions were listed [throughout in cm^{-1}: weak (w), medium (m) or (s) strong].

Mass spectra (MS) were 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}).

All syntheses were performed under dry nitrogen atmosphere. THF was freshly distilled from Na/benzophenone prior to use. All solvents and starting materials were of commercial quality. The synthesis of the starting materials **1a** and **1b** were reported elsewhere.[2,12]

Preparation of the compound 4a

A solution of *c*-5-hydroxymethyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]octane **1a** (1.450 g, 10.0 mmol) in THF (50 mL) was added to potassium hydride isolated by repeated washing with dry ligroin of 1.337 g as 30 % KH in mineral oil suspension (0.401 g 100 %, 10.0 mmol). The resulted suspension was stirred at 45 ^{o}C for 2 hrs. until no more hydrogen was formed. Cyanuryl chloride (0.571 g, 3.1 mmol) was added as THF (20 mL) solution. The reaction mixture was heated at 65 ^{o}C for 36 hrs. with vigorous stirring, until the starting **1a** was reasonably absent, as shown by the TLC monitoring (eluent ligroin : acetone 2:1 v/v). The reaction was quenched with isopropanol (1 mL) with stirring for additional 30 min. The mineral compounds were filtered off and washed with excess of THF. The combined THF solution was evaporated under vacuum to dryness to provide the crude product as yellow oil. Purification by flash column chromatography (eluent ligroin : acetone 2:1 v/v visualisation in I_2-bath) afforded the desired **4a** as a yellowish crystalline powder: 0.420 g (34 % yield).

2-Chloro-4,6-bis[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]*s*-triazine 4a (34 %) yellowish crystalline powder, m.p. 91.8-93.4 ^{o}C; (flash column chromatography, eluent ligroin : acetone 2:1 v/v); R_f 0.75 (66 % ligroin/acetone); [Found: C, 44.91; H, 5.19; N, 17.63. $C_{15}H_{20}N_5O_6Cl$ requires: C, 44.84; H, 5.02; N, 17.43 %]; ν_{max} (KBr) 2971 (m), 2868 (s), 1731 (s), 1390 (m), 1252 (s), 1138 (m), 1038 (s), 926 (s), 885 (w), 792 (m), 673 (s), 610 (s), 505 (w) cm^{-1}; δ_H (300 MHz $CDCl_3$) 4.39 (4 H, s, H-2, -8-*c*), 4.37 (4 H, s, H-2, -8-*t*), 4.06 (4 H, s, 5-OCH_2), 3.73 (4 H, d, *J*=9.0 Hz, H-4, -6-*c*), 3.68 (4 H, d, *J*=9.0 Hz, H-4, -6-*t*); δ_C (75 MHz $CDCl_3$) 171.0 (3 C, C-2, -4, -6 triazine), 88.6 (4 C, C-2, -8), 74.2 (4 C, C-4, -6), 71.5 (2 C, C-5), 66.9 (2 C, 5-OCH_2); δ_H (300 MHz DMSO-d_6) 4.47 (4 H, d, *J*=5.7 Hz, H-2, -8-*c*), 4.33 (4 H, d, *J*=5.7 Hz, H-2, -8-*t*), 4.10 (4 H, s, 5-OCH_2), 3.80 (4 H, d, *J*=8.7 Hz, H-4, -6-*c*), 3.67 (4 H, d, *J*=8.7 Hz, H-4, -6-*t*); δ_C (75 MHz DMSO-d_6) 170.6 (3 C, C-2, -4, -6 triazine), 87.8 (4 C, C-2, -8), 73.5 (4 C, C-4, -6), 71.0 (2 C, C-5), 66.2 (2 C, 5-OCH_2); MS (EI), m/z (rel. int. %) 402 (< 1) [M^++1], 324 (38), 256 (57), 145 (58), 127 (100).

Preparation of the compound 5a

A solution of *c*-5-hydroxymethyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]octane **1a** (0.740 g, 5.10 mmol) in THF (25 mL) was cooled at -78 ^{o}C with stirring, then *n*-BuLi (1.6 M in hexane, 3.35 mL, 5.35 mmol) was injected to provide a clear white fine suspension. After 20 min., cyanuryl chloride (0.320 g, 1.70 mmol) was injected as THF (15 mL) solution. The reaction mixture was let very gently to reach the room temperature (20 hrs.) with vigorous stirring. The reaction was quenched with water (5 mL). The reaction mixture was evaporated to dryness then water (50 mL) and dichloromethane (50 mL) were added with stirring. After separation, the dichloromethane solution was washed with water to neutrality and then dried over $MgSO_4$. After

filtering and washing with dichloromethane, the organic solution was concentrated in vacuum to provide the crude product which was taken with Et_2O to yield the compound **5a** as white crystalline powder: 0.720 g (82 % yield).

2,4,6-Tris[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]*s*-triazine 5a (82 %) white crystalline powder, m.p. 238.9-239.5 ^oC; (direct crystallization from Et_2O); R_f 0.30 (50 % ligroin/acetone); [Found: C, 49.44; H, 5.98; N, 16.44. $C_{21}H_{30}N_6O_9$ requires: C, 49.41; H, 5.92; N, 16.46 %]; ν_{max} (KBr) 3444 (m), 2969 (w), 2858 (s), 1589 (s), 1414 (s), 1334 (s), 1189 (m), 1141 (m), 1096 (s), 1044 (s), 1028 (s), 943 (m), 807 (s), 750 (m), 718 (w), 676 (m), 572 (m) cm^{-1}; δ_H (300 MHz $CDCl_3$) 4.49 (6 H, d, *J*=5.6 Hz, H-2, -8-*c*), 4.42 (6 H, d, *J*=5.6 Hz, H-2, -8-*t*), 4.41 (6 H, s, 5-OCH_2), 3.85 (12 H, s, H-4, -6-*c*, -*t*); δ_C (75 MHz $CDCl_3$) 173.3 (3 C, C-2, -4, -6 triazine), 88.5 (6 C, C-2, -8), 74.3 (6 C, C-4, -6), 71.5 (3 C, 5-OCH_2) 71.3 (3 C, C-5); δ_H (300 MHz D_2O) 4.56 (6 H, d, *J*=6.0 Hz, H-2, -8-*c*), 4.51 (6 H, s, 5-OCH_2) 4.48 (6 H, d, *J*=6.8 Hz, H-2, -8-*t*), 3.99 (6 H, d, *J*=9.2 Hz, H-4, -6-*c*), 3.91 (6 H, d, *J*=9.2 Hz, H-4, -6-*t*); MS (ESI), m/z (rel. int. %) 532 [M^+-1+Na^+] (100), 511 (40) [M^+], 384(10).

Preparation of the compounds 4b and 5b

A solution of *c*-5-hydroxymethyl-*c*-2,*c*-8-diphenyl-3,7-dioxa-*r*-1-azabicyclo [3.3.0]octane **1b** (1.48 g, 5.00 mmol) in THF (50 mL) was added to potassium hydride isolated by repeated washing with dry ligroin of 0.668 g as 30 % KH in mineral oil suspension (0.200 g 100 %, 5.00 mmol). The resulted yellow-greenish suspension was stirred at 45 ^oC for 2 hrs. until no more hydrogen was formed, then cooled at 0 ^oC. Cyanuryl chloride (0.302 g, 1.64 mmol) was rapidly added as THF (30 mL) solution. The reaction mixture was gently heated at 65 ^oC for 40 hrs. with vigorous stirring, until the starting **1a** was reasonably absent, as shown by the TLC monitoring (eluent ligroin : acetone 3.5:1 v/v, visualisation in UV-254 nm). The reaction was quenched with water (50 mL) and dichloromethane (125 mL) with stirring for additional 30 min. After separation, the aqueous layer was extracted with dichloromethane (3 $\times$ 25 mL) and the combined dichloromethane solution was washed with water to neutrality. After drying on $MgSO_4$, the organic solution was evaporated in under vacuum to yield 1.10 g of the crude reaction mixture. Purification by flash column chromatography (eluent ligroin : acetone 3.5:1 v/v visualisation in UV-254 nm) afforded the following fractions: 0.137 g recovered **1b**; 0.370 g desired **5b** as a white crystalline powder. The column was then completely eluted with pure acetone to afford 0.310 g mixture **5b** (66 %) + **4b** (34 %), according to the ^1H NMR spectrum.

2,4,6-Tris[(*c*-2,*c*-8-diphenyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy] *s*-triazine 5b (37 %) white crystalline powder, m.p. 162.5-164.2 ^oC; (flash column chromatography, eluent ligroin : acetone 3.5:1 v/v); R_f 0.40 (78 % ligroin/acetone); [Found: C, 70.61; H, 5.70; N, 8.44. $C_{57}H_{54}N_6O_9$ requires: C, 70.80; H, 5.63; N, 8.69 %]; ν_{max} (KBr) 3063 (w), 2871 (m), 1571 (s), 1417 (s), 1334 (s), 1210 (m), 1131 (s), 1088 (m), 1068 (m), 922 (m), 820 (w), 762 (m), 735 (s), 698 (s) cm^{-1}; δ_H (300 MHz $CDCl_3$) 7.51 (12 H, m, phenyl), 7.32-7.26 (18 H, m, phenyl), 5.59 (6 H, s, H-2, -8-*t*), 4.24 (6 H, s, 5-OCH_2), 4.06 (6 H, d, *J*=9.2 Hz, H-4, -6-*c*), 3.98 (6 H, d, *J*=9.2 Hz, H-4, -6-*t*); δ_C (75

MHz $CDCl_3$) 172.9 (3 C, C-2, -4, -6 triazine), 139.5 (6 C, Cq., phenyl), 129.1 (6 C, CH, phenyl), 128.8 (12 C, CH, phenyl), 127.5 (12 C, CH, phenyl), 97.6 (6 C, C-2, -8), 73.6 (6 C, C-4, -6), 72.8 (3 C, 5-OCH_2), 72.2 (3 C, C-5); MS (FAB^+), m/z (rel. int. %) 968 (100) [M^++1].

2-Chloro-4,6-bis[(*c*-2,*c*-8-diphenyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl) methoxy]*s*-triazine 4b (8 %) white crystalline powder (flash column chromatography, eluent ligroin : acetone 3.5:1 v/v; δ_H (300 MHz $CDCl_3$) as detected from the mixture with **5b**: 5.59 (4 H, s, H-2, -8-*t*), 4.31 (4 H, s, 5-OCH_2), 4.06 (4 H, d, *J*=9.2 Hz, H-4, -6-*c*), 3.98 (4 H, d, *J*=9.2 Hz, H-4, -6-*t*); δ_C (75 MHz $CDCl_3$), 171.8 (3 C, C-2, -4, -6 triazine), 139.3 (4 C, Cq., phenyl), 127.5 (8 C, CH, phenyl); MS (FAB^+), m/z (rel. int. %) 704 (20) [M^+-1].

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