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TRI-ARMED PODANDS AS EFFICIENT PRECURSORS FOR SUPRAMOLECULAR SYSTEMS

CORNELIA OPREA, VLAD PAŞCANU, CRINA CISMAŞ*, ANAMARIA TEREC, RICHARD ATTILA VARGA AND ION GROSU

ABSTRACT. The synthesis and structure of podands with isocyanurate core are described. The tosyl and azide terminal groups can ensure further functionalization towards supramolecular architectures. The tritosylated derivative was subjected to strong basic treatment to yield an *N*-tosyloxazolidin-2-one, thus providing a new route to *N*-substituted oxazolidinones. X-ray crystal structure of the triazide podand is discussed.

Keywords: *tripodands, isocyanurate, azides, x-ray diffraction, hydrogen bonding*

INTRODUCTION

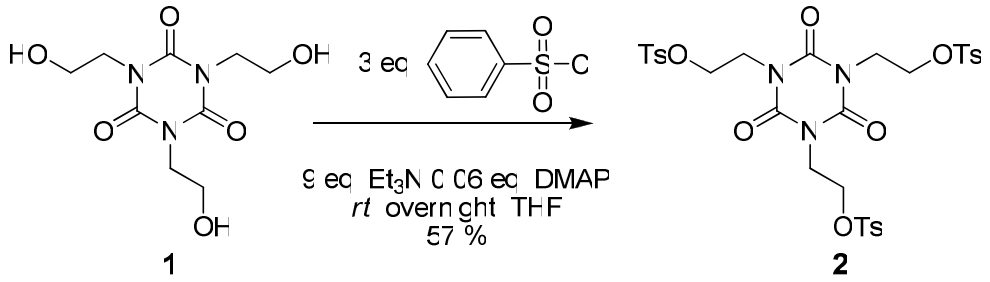
In the last decades, supramolecular chemistry [1] is one of the most dynamic areas in the chemical research. Its development requires rapid access to large molecules with well defined architectures. Tripodal structures represent smaller molecules which can be used as building blocks for macro- and supramolecular constructions. The elaboration of simple and efficient procedures for their synthesis is a continuous challenge for most of the researchers interested in this field. In this context, substrates with C_3 symmetry are of high interest, many studies being focused on the synthesis of derivatives with 1,3,5-trisubstituted benzene, [2] tertiary amines [3] or phosphines [4], cyclotriveratrilene [5] and 1,3,5-triazine[6] units. Transformation of C_3 symmetrical tripodal molecules into efficient hosts requires reactive terminal functional groups at the ends of the pendant arms. These peripheral groups have to exhibit: i) either the ability to participate in ring closure reactions with the formation of the corresponding cryptands; ii) or to allow reactions in which different units with high affinity for supramolecular interactions (*e.g.* by hydrogen bonding) can be attached to the pendant arms in order to promote the construction of supramolecular entities based on acyclic hosts. Recent developments in organic synthesis, *i.e.* click chemistry [7], suggest azide and tosylate as efficient terminal group candidates towards versatile tripodal intermediates.

* *Organic Chemistry Department, Faculty of Chemistry and Chemical Engineering, Babes-Bolyai University Cluj-Napoca, 11 Arany Janos str., RO-400028 Cluj-Napoca, Romania, csocaci@chem.ubbcluj.ro*

In our ongoing studies on the synthesis of various cryptand molecules we became interested in the synthesis of podands with isocyanuric platform. This central core may participate in hydrogen bonding interactions for highly functionalized supramolecular systems. We report hereafter the synthesis of two preorganized podands, as well as the solid state structure of one of them exhibiting already its supramolecular organization in the crystal.

RESULTS AND DISCUSSION

The synthesis of the tri-tosylated derivative **2** started from the commercially available 1,3,5-tris(hydroxyethyl) cyanuric acid **1** (*Scheme 1*). The substitution with tosyl chloride proceeded in the presence of triethylamine and *N,N*-dimethyl-aminopyridine (DMAP) as bases. The role of DMAP as an additional base is still obscure, however we observed a significant yield decrease (from 56 to 15 %) when the reaction was performed with the assistance of triethylamine only.



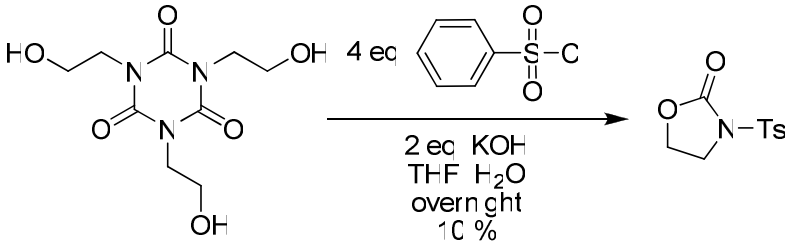
Scheme 1

The structure of tri-tosylate **2** has been proven by NMR Spectroscopy, meanwhile the ESI Mass Spectrum showed, besides the $[M+H]^+$ peak also the potassium adduct $[M+K]^+$ as well.

Even though the yield of **2** was not very high (57 %), this new podand represents, by its peripheral triple functionalities, an interesting precursor for various applications in the synthesis of supramolecular systems. Indeed, the ability of the tosylate fragment to be one of the best leaving group in the SN substitutions is already a classic concept in organic synthesis.

Next, using sodium hydroxide as base in aqueous tetrahydrofurane, a typical approach applied to **1** yielded the *N*-tosyl-oxazolidin-2-one **3** (*Scheme 2*). We have observed a similar behaviour of the commercially available compound **1** when propargylbromide, in strong basic protic media was employed.[8] Although compound **3** has been previously reported starting from dimethylenecyclourethane,[9] we considered our approach more facile in terms of synthetic methodology and

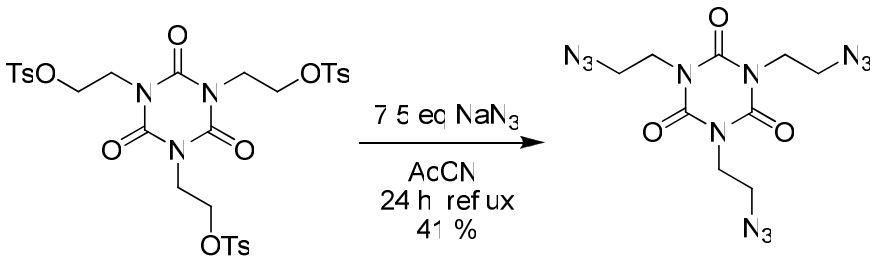
availability of the starting material. Nevertheless, the formation of derivative **3** can also be seen as a new route towards different *N*-substituted oxazolidinone derivatives, after optimizing the reaction.



1 **3**

Scheme 2

Finally, the synthesis of the triazide **4** was accomplished by nucleophilic displacement of tosyl groups of **2**, carried out with sodium azide, in acetonitrile (*Scheme 3*). The NMR spectra **4** are in accordance with the previously published ones by Sato *et al*.[10] In this case we were able to grow single crystals suitable for X-ray diffraction from an ethyl acetate/pentane (2/1) mixture.



2 **4**

Scheme 3

X-ray crystallographic analysis revealed the disposition of two of the pendant arms on one side of the isocyanuric plane, while the third one is facing the opposite direction, the last one showing unresolved nitrogen atoms of the azide group (**Figure 1**). The well resolved azide groups show a longer N(3)-N(4) [1.218 Å] and a shorter N(4)-N(5) [1.125 Å] bonds and the angle N(3)N(4)N(5) is slightly smaller (171.34^{o}). The crystal packing presents an antiparallel arrangement of the azide groups, with a long intermolecular distance (3.607 Å). This is in accordance with the previously observed data showing that specific intermolecular contacts in the polyazides crystals are either absent or very weak.[11] We also observe another type of intermolecular contacts, namely hydrogen bonds between the isocyanurate oxygen atom and the methylene protons (2.409 Å).

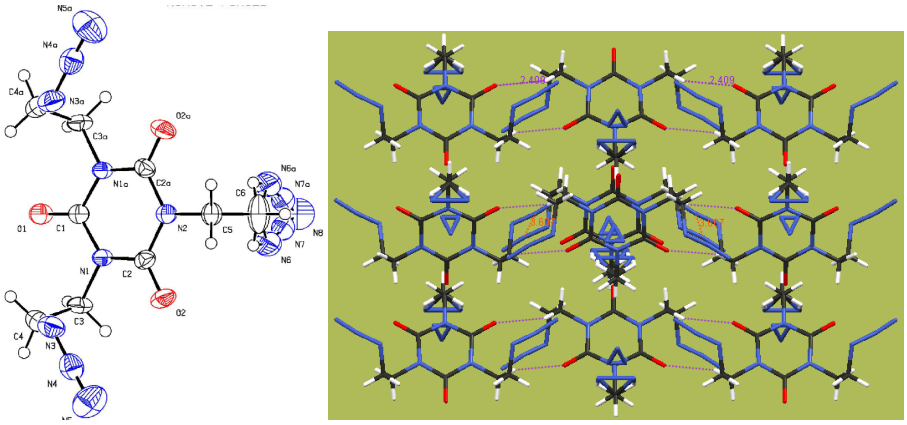


Figure 1. ORTEP diagram (left) and Mercury representation of the lattice (right) for compound **4**

Starting from the commercially available 1,3,5-tris(hydroxyethyl) cyanuric acid, two new podands with isocyanuric core were successfully obtained. The X-ray structure investigation of a triazide type tri-armed podand revealed the disposition of the pendant arms on both faces of the heterocyclic unit and the formation in the lattice of supermolecular aggregates by hydrogen bonding.

EXPERIMENTAL SECTION

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 spectrometer operating at 300 MHz (^{1}H) and 75 MHz (^{13}C) relative to TMS. MS were recorded on an ESI ion trap mass spectrometer (Agilent 6320) in positive mode. Solvents were dried and distilled under argon using standard procedures prior to use. Chemicals of commercial grade were used without further purification. Melting points are uncorrected. Column chromatography was carried out on Merck silica gel Si 60 (40–63 mm). TLC was carried out on aluminium plates coated with silica gel 60 F254 using UV lamp (254 nm) and $KMnO_4$ visualization.

The experimental conditions for the X-ray structure determination of compound **4** are as follows. The sample was studied on a Bruker SMART APEX with graphite monochromatized Mo Kα radiation. The structure was solved with SHELXS [12] which reveals the non hydrogen atoms of the molecule. The whole structure was refined with SHELXL-97 [12] by the full-matrix least-square techniques. Atomic scattering factors from International Tables for X-ray Crystallography (1992) [13]. ORTEP view was realized with ORTEP3 [14]. The structural data is deposited at the Cambridge Crystallographic Data Center.

2,2',2''-(2,4,6-Trioxo-1,3,5-triazinane-1,3,5-triyl)tris(ethane-2,1-diyl) tris(4-methylbenzenesulfonate) (2)

A solution of compound **1** (2.000 g, 7.600 mmol), triethylamine (4.000 ml, 28.000 mmol) and *N,N*-dimethylaminopyridine (0.049 g, 0.400 mmol) in THF (50 ml) was cooled at 0-3 ºC. After stirring for 90 minutes, a solution of tosyl chloride (4.130 g, 22.000 mmol) in THF (40 ml) was added dropwise with a push-syringe (rate: 0.5 ml/h). The resulting mixture was stirred overnight at room temperature, then extracted twice with ethyl acetate (2x35 ml). The organic phase was washed with water (2x50 ml), dried over sodium sulfate and concentrated in vacuo. The resulting powder was subjected to column chromatography using pethroleum ether/ethyl acetate 1/1 as a mobile phase (R_f = 0.6). Compound (**2**) was obtained as white solid (m.p. = 125ºC) in 57 %yield.

^{1}H-NMR: (300MHz, $CDCl_3$) δ ppm: 2.43 (s, 9H, CH_3), 4.13 (t, 6H, *J* = 5.3 Hz, N-CH_2), 4.26 (t, 6H, *J* = 5.3 Hz, CH_2-OTs), 7.32 (d, 6H, *J* = 8.3 Hz, CH-aromatic), 7.75 (d, 6H, *J* = 8.3 Hz, CH-aromatic)

^{13}C-NMR: (75 MHz, $CDCl_3$) δ ppm: 21.7 (CH_3), 41.6 (O-CH_2), 65.8 (CH_2-OTs), 127.9 (2 x CH-aromatic), 129.9 (2 x CH-aromatic), 132.6 (C-S), 145.1 (C-CH_3), 148.3 (C=O)

ESI-MS: m/z = 724 ($[M+H]^+$), 746 ($[M+Na]^+$), 762 ($[M+K]^+$)

***N*-Tosyl-oxazolidin-2-one (3)**

To a solution of 1,3,5-tris(hydroxyethyl)cyanuric acid **1** (2.00 g, 7.60 mmol) in THF (50 ml) a KOH solution (0.89 g, 16 mmol in 15 ml H_2O) was added. The mixture was cooled to 0^o C and a solution of tosyl chloride (5.56 g, 30.00 mmol) in THF (20 ml) was added dropwise. The mixture was extracted with ethyl acetate (2x50 ml) and the organic phase washed with water (2x70 ml) and aqueous solution of $NaHCO_3$ (50 ml), concentrated and the crude product subjected to column chromatography using petroleum ether/ethyl acetate 2/1 as a mobile phase (R_f = 0.23). Compound (**3**) was obtained as a white solid (m.p. = 183ºC (dec.)) 10% yield (for a 50% conversion).

^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm: 2.46 (s, 3H, CH_3), 4.05 (t, *J* = 7.8 Hz, 2H, N-CH_2), 4.37 (t, J = 7.8 Hz, 2H, O-CH_2), 7.37 (d, *J* = 8.2 Hz, 2H, CH-aromatic), 7.95 (d, *J* = 8.2 Hz, 2H, CH-aromatic)

^{13}C-NMR (75 MHz, $CDCl_3$) δ ppm: 21.7 (CH_3), 44.6 (N-CH_2), 62.2 (O-CH_2), 128.3 (CH-aromatic), 129.9 (CH-aromatic), 133.7 (C-S), 145.8 (C-CH_3), 152.0 (C=O)

1,3,5-Tris(2-azidoethyl)-1,3,5-triazinane-2,4,6-trione (4)

A mixture of compound **2** (1.00 g, 1.61 mmol), sodium azide (0.80 g, 12.00 mmol) in acetonitrile (25 ml) was refluxed for 24 hours under vigorous stirring. The reaction mixture was evaporated and the residue was dissolved in ethyl acetate (50 ml). The insoluble impurities were removed by filtration. The crude mixture was subjected to column chromatography pentane/ethyl acetate 2/1 (R_f = 0.64). The white solid was obtained in 41% yield (m.p. = 84 ºC).

^{1}H-NMR (300MHz, $CDCl_3$) δ ppm: 3.58 (t, *J* = 6.0 Hz, 6H, N-CH_2), 4.16 (t, *J* = 6.0 Hz, 6H, CH_2-N_3)

^{13}C-NMR (75MHz, $CDCl_3$) δ ppm: 41.7 (N-CH_2), 48.4 (CH_2-N_3), 148.6 (C=O)

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