COMMUNICATION

Synthesis of cyclitols fused with a furoxan ring from alditols by intramolecular nitrile oxide dimerization

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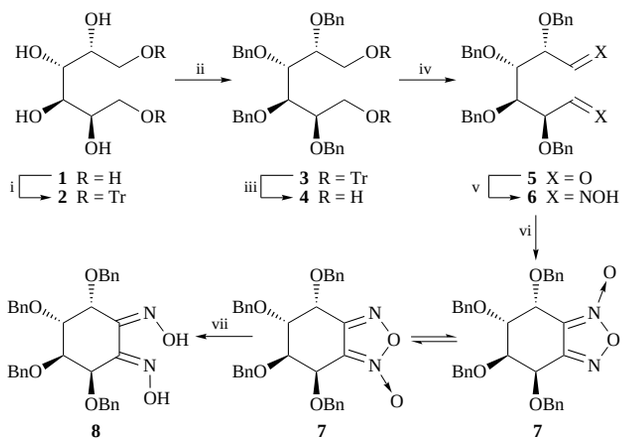
The synthesis of cyclitols fused with a furoxan ring has been achieved by conversion of an alditol to a bis-(aldoxime) and further oxidation of the oxime groups with *N*-chlorosuccinimide to nitrile oxides, which spontaneously dimerize intramolecularly to form a furoxan ring.

Furoxans (furazan *N*-oxides) and their fused derivatives are of considerable importance in organic synthesis, since they are excellent precursors for the synthesis of a large number of heterocyclic compounds.[1] In addition, furoxans themselves have attracted remarkable biological and pharmaceutical interest, as many have been shown to possess antibacterial, antihelmintic, fungicidal, anticonvulsant and vasodilator activities.[2] Recent studies[3] have shown that the biological activity of furoxans is related to their ability to liberate *in vivo* nitric oxide (NO). This finding correlates the action of furoxans with one of the most important biological discoveries made in the last decade, namely the revelation of the major role of nitric oxide in a variety of physiological pathways,[4] such as muscle relaxation, macrophage activation, neurotransmission, vasodilation and blood pressure control. This has refreshed the interest of organic chemists in this class of compounds[5] from both the understanding of their pharmacochemical action at a molecular level and the synthesis of new furoxan derivatives with potential biological applications.

One of the methods to prepare furoxan derivatives is the dimerization of nitrile oxides,[5d,6] which are furthermore prepared by oxidation of aldoximes, or dehydration of aliphatic primary nitro compounds. Despite the fact that the nitrile oxide dimerization to furoxans involves a carbon–carbon bond formation, it has attracted surprisingly little attention by synthetic chemists. It is apparent that the intermolecular dimerization of nitrile oxides produces symmetrically substituted furoxans, whereas furoxans prepared by an intramolecular process could be unsymmetrically substituted. The last type of reaction could moreover generate a carbocyclic ring fused with the furoxan ring. To the best of our knowledge, the intramolecular dimerization of nitrile oxides has been successfully applied only once, in the total synthesis of biotine.[7]

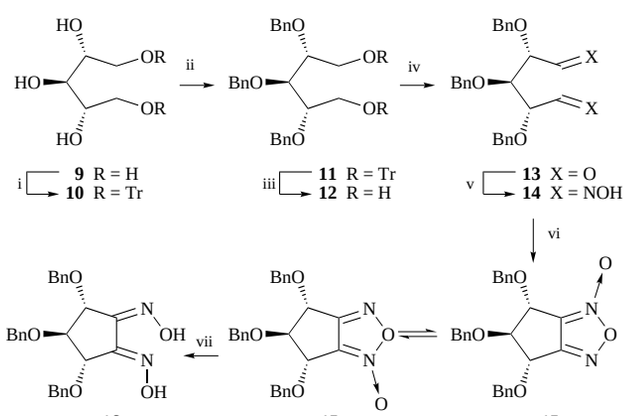
Further to our recent work[8] on the synthesis of polyhydroxylated carbocycles from carbohydrates, we report here two examples of the synthesis of five- and six-membered cyclitols fused with a furoxan ring by intramolecular dimerization of nitrile oxides in sugar derivatives. There are two interesting features in the novel compounds reported here: (a) after the removal of the protecting group, the hydroxy groups will increase the solubility of the furoxans in water making them capable of study under physiological conditions, and (b) reductive ring opening of the furoxan ring results in the formation of a densely substituted cyclopentane or cyclohexane ring.

In this preliminary study, we selected D-mannitol (C_2-symmetry) and xylitol (*meso* compound) as starting compounds to avoid the formation of isomers because of the equilibrium existing between the *N*-oxides.[1] Both alditols were converted to compounds **4** and **12** (Schemes 1 and 2, respectively), which have free primary and protected secondary hydroxy groups by standard sugar manipulations:[9] the primary hydroxy groups were tritylated, the secondary hydroxy groups were subsequently benzylated and then the triphenylmethyl (trityl) groups were selectively removed by acidic hydrolysis. Swern oxidation of the free hydroxy groups[10] in both **4** and **12** afforded the respective dialdehydes **5** and **13**, and further treatment with NH_2OH gave the bis(aldoximes) **6** and **14**, which were shown by ^1H and ^{13}C NMR spectroscopy to be mixtures of all possible oxime geometric isomers. Finally, the dioximes



Tr = triphenylmethyl

Scheme 1 *Reagents and conditions*: i, Ph_3CCl, Et_3N, DMAP, DMF, 0 °C, 70%; ii, DMF, NaH, 0 °C, then BnCl, 80%; iii, H_2SO_4, MeOH, CH_2Cl_2, 0 °C, 91%; iv, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −70 °C; v, $NH_2OH·HCl$, $NaHCO_3$, MeOH–H_2O, 20 °C, 93% from **4**; vi, NCS, pyridine, $CHCl_3$, reflux, 1 h, 92%; vii, H_2, Pd–C, EtOH, 20 °C, 20 min, 92%



Scheme 2 *Reagents and conditions*: i, Ph_3CCl, Et_3N, DMAP, DMF, 0 °C, 63%; ii, DMF, NaH, 0 °C, then BnCl, 84%; iii, H_2SO_4, MeOH, CH_2Cl_2, 0 °C, 95%; iv, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −70 °C; v, $NH_2OH·HCl$, $NaHCO_3$, MeOH–H_2O, 20 °C, 60% from **12**; vi, NCS, pyridine, $CHCl_3$, reflux, 1 h, 66%; vii, H_2, Pd–C, EtOH, 20 °C, 20 min, 52%

were oxidized[11] with *N*-chlorosuccinimide in the presence of Et_3N to give directly the furoxans **7** and **15**, in very good overall yields.†

Because of the C_2-symmetry of the starting D-mannitol the two *N*-oxide isomeric forms of furoxan **7** are identical and retain the chirality of D-mannitol. On the other hand, the dimerization of the bis(nitrile) oxide derived from the *meso*-xylitol produces a racemate.

The furoxan ring can be easily opened or transformed in a variety of ways.[1] To demonstrate this possibility, the furoxan ring in compounds **7** and **15** was reductively opened by selective hydrogenolysis over Pd–C in EtOH. As shown by NMR spectroscopy, the resulting dioxime exists exclusively in the *amphi*-configuration in both products **8** and **16**, thus reflecting their formation pathway.

In conclusion, the method reported here offers a simple and efficient way for preparing five- and six-membered cyclitol derivatives from cheap, commercially available alditols, demonstrating the potential of the carbon–carbon bond formation reaction in the dimerization of nitrile oxides. A cyclitol of a desired stereochemistry can be prepared by selecting the appropriate alditol and transferring its stereochemistry to the products.

Experimental

(4*S*,5*S*,6*S*,7*S*)-4,5,6,7-Tetrahydro-4,5,6,7-tetra(benzyloxy)-benzofurazan 1-oxide

A solution of dry DMSO (1.8 ml, 25 mmol) in dry CH_2Cl_2 (10 ml) was added to a solution of $(COCl)_2$ (1.15 ml, 13 mmol) in dry CH_2Cl_2 (20 ml) which had been cooled to −60 °C under an argon atmosphere. The resulting mixture was further stirred at the same temperature for another 2 min and a solution of **4** (2.6 g, 4.8 mmol) in dry CH_2Cl_2 (15 ml) was subsequently added carefully during a period of 5 min, while the temperature was kept at −60 °C. The stirring was continued for 15 min and then Et_3N (7.7 ml, 55 mmol) was added at the same temperature. After another 10 min stirring at low temperature the mixture was allowed to warm to room temperature. CH_2Cl_2 (200 ml) was subsequently added and the solution was washed with saturated aqueous NaCl (2 × 100 ml). The organic layer was dried over Na_2SO_4, the solvent was removed on a rotary evaporator and a mixture of the resulting residue along with $NH_2OH·HCl$ (2.0 g, 28.8 mmol) and $NaHCO_3$ (2.45 g, 28.8 mmol) in MeOH (45 ml) was vigorously stirred overnight at 20 °C. The reaction mixture was then transferred to a separatory funnel, H_2O (100 ml) and CH_2Cl_2 (100 ml) were added and the organic layer was separated, while the aqueous layer was extracted with CH_2Cl_2 (2 × 100 ml). The combined organic layers were dried over Na_2SO_4, the solvent was then evaporated and the mixture chromatographed on silica gel with hexane–ethyl acetate as the eluent to give dioxime **6** as an oil (2.55 g) in 93% overall yield.

A solution of the dioxime **6** (1.137 g, 2 mmol) in $CHCl_3$ (100 ml) was added dropwise through a dropping funnel to a refluxing solution of *N*-chlorosuccinimide (NCS) (0.614 g, 4.6 mmol) and pyridine (0.363 g, 4.6 mmol) in $CHCl_3$ (100 ml) in a two-necked flask equipped with a reflux condenser, during a period of 1 h. The mixture was allowed to cool at room temperature, the solvent was evaporated and the product purified by chromatography (silica gel, ethyl acetate–hexane 1:4) to give the oily furoxan **7** (1.04 g, 92%).

† All new compounds gave satisfactory CHN microanalyses and spectral data consistent with their assigned structures. Selected analytical data for compounds prepared (*J* values are given in Hz): Compound **7**: oil $[\alpha]_D$ −155.9 (*c* 1 in $CHCl_3$); δ_H(300 MHz, $CDCl_3$) 3.95 (1H, dd, *J* 3.7 and 7.2), 4.02 (1H, dd, *J* 3.0 and 7.2), 4.56 (1H, d, *J* 12.0), 4.59 (1H, d, *J* 11.8), 4.67 (1H, d, *J* 12.0), 4.69 (1H, d, *J* 11.8), 4.75 (1H, d, *J* 12.1), 4.7 (1H, d, *J* 11.4), 4.83 (1H, d, *J* 3.7), 4.84 (1H, d, *J* 3.0), 4.90 (1H, d, *J* 11.5), 4.98 (1H, d, *J* 12.1) and 7.3 (20H, m); δ_C(75 MHz, $CDCl_3$) 68.81, 69.33, 72.68, 73.77, 74.04, 74.64, 75.56, 75.96, 111.13, 127.81, 127.86, 127.92, 127.95, 128.10, 128.15, 128.20, 128.37, 128.45, 128.50, 137.08, 137.31, 137.58, 137.66 and 154.56. Compound **8**: oil, $[\alpha]_D$ −0.8 (*c* 2.4 in $CHCl_3$); δ_H(300 MHz, $CDCl_3$) 4.10 (1H, dd, *J* 10.1 and 2.3), 4.17 (1H, dd, *J* 10.1 and 3.0), 4.28 (1H, d, *J* 3.0), 4.6 (8H, m), 5.26 (1H, d, *J* 2.3), 7.3 (20H, m) and 9.81 (2H, s); δ_C(75 MHz, $CDCl_3$) 66.90, 69.64, 71.69, 72.87, 73.14, 74.80, 77.04, 77.61, 127.49, 127.63, 127.66, 127.69, 128.08, 128.13, 128.21, 128.25, 128.34, 137.18, 137.65, 138.24, 138.28, 147.08 and 148.09. Compound **15**: oil, δ_H(300 MHz, $CDCl_3$) 4.55 (1H, dd as t, *J* 3.6), 4.58 (2H, s), 4.68 (4H, m), 4.88 (1H, d, *J* 11.9), 4.96 (1H, d, *J* 11.5) and 7.3 (15H, m); δ_C(75 MHz, $CDCl_3$) 72.27, 72.60, 73.01, 75.11, 75.67, 93.87, 112.72, 127.76, 128.01, 128.10, 128.15, 128.36, 128.42, 128.44, 136.24, 136.27, 136.64 and 160.74. Compound **16**: oil, δ_H(300 MHz, $CDCl_3$) 4.01 (1H, s), 4.35 (1H, s), 4.39 (2H, s), 4.62 (1H, d, *J* 12.3), 4.70 (1H, d, *J* 11.7), 4.74 (1H, s), 4.80 (1H, d, *J* 11.7), 4.82 (1H, d, *J* 12.3), 7.3 (15H, m), 9.75 (1H, br s) and 12.13 (1H, br s); δ_C(75 MHz, $CDCl_3$) 70.61, 71.55, 72.90, 76.96, 79.10, 82.74, 127.65, 127.71, 127.83, 127.91, 127.94, 128.13, 128.31, 128.37, 128.42, 137.08, 137.42, 137.71, 149.85 and 153.54.

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