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Oxidative Azidonation of Glycals Using the Reagent Combination PhIO/$TMSN_3$: Synthesis of Diaminopyrans

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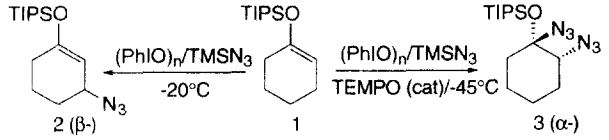
Abstract: Dihydropyran and derivatives react with $(PhIO)_n/TMSN_3$ to give 3-azido adducts and with $(PhIO)_n/TMSN_3$/TEMPO(cat) to give 2,3-*bis*-azido adducts which can be further elaborated into aminopyrans.

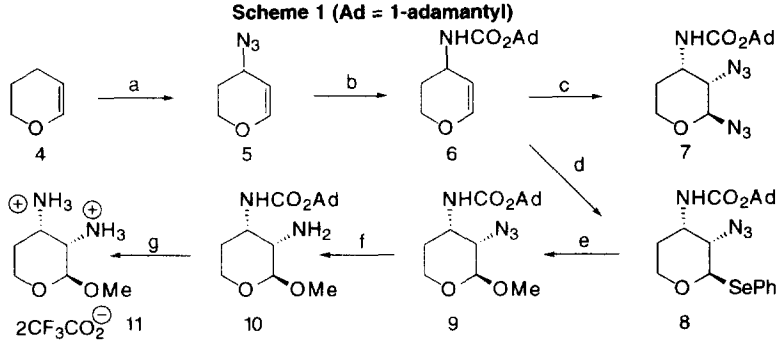
We have reported that the reagent combination PhIO/$TMSN_3$ reacts with triisopropylsilyl (TIPS) enol ethers **1** at -20°C to give β-azido TIPS enol ethers **2** (β-functionalization), **Eqn 1**.[1] This regiochemical outcome can be diverted into a novel α-functionalization pathway by conducting the above reaction in the presence of a catalytic amount of the stable radical TEMPO to give **3**.[2] These two azidonation reactions appeared to be particularly suitable for the introduction of azide, and subsequently amine functionality, into glycals with potential applications for the synthesis of aminoglycoside antibiotics.



Eqn. 1

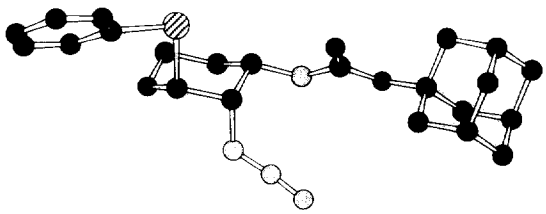
The recent report by Kirschning describing the application of the β-azidonation process for the introduction of azide functionality into 3-deoxyglycals prompts us to disclose our own results in this area.[3]

Scheme 1 (Ad = 1-adamantyl)



Conditions:- a) $(PhIO)_n/TMSN_3/CH_2Cl_2$/-20°C. b) i. $LiAlH_4/Et_2O$. ii. AdOCOCl/py/CH_2Cl_2 (27% from **4**). c) $(PhIO)_n/TMSN_3$/TEMPO (10%)/toluene/-45°C (66%). d) $PhI(OAc)_2/(PhSe)_2/NaN_3/CH_2Cl_2$/25°C (44%). e) H_2O_2/MeOH (94%). f) H_2/PtO_2/MeOH (99%). g) CF_3CO_2H/CH_2Cl_2 (76%).

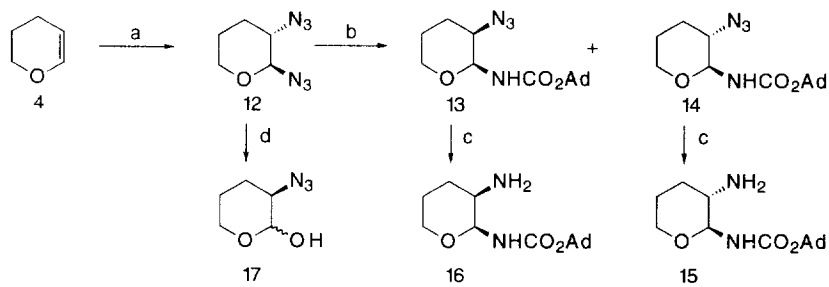
Figure 1



Chem 3D representation of **8** from X-ray coordinates

Preliminary experiments were carried out on the simplest glycal, dihydropyran. Treatment of dihydropyran **4** with $(PhIO)_n/TMSN_3/CH_2Cl_2$/-20°C (β-azidonation) gave the labile allylic azide **5** which was immediately reduced, and the resulting amine protected as the 1-adamantyl carbamate derivative **6**, **Scheme 1**. When **6** was treated with $(PhIO)_n/TMSN_3/CH_2Cl_2$ at -45°C in the presence of TEMPO (10%) (α-azidonation), the *trans-bis*-azide **7** was isolated in 66% yield.[4] The 1,2-diaxial *bis*-azide **7** is the product of azide-radical addition to the 2-position of **6**, followed by combination of the resulting anomeric radical with $N_3^{\bullet}$. It was found that the anomeric azide in **7** was extremely resistant to hydrolysis (replacement by -OMe), presumably because the azide group is highly electronegative (three N atoms in a row) and reluctant towards protonation. Consequently, it was decided to treat **6** with $PhI(OAc)_2/(PhSe)_2/NaN_3$ to give **8**.[5] The stereochemistry of **8** was confirmed by X-ray crystallography, and **Figure 1** shows a Chem 3D representation from the X-ray coordinates. Oxidation of the selenide **8** with H_2O_2/MeOH gave the axial anomeric methyl ether **9** (stereochemistry by X-ray), which was hydrogenated to the protected *cis*-diamine **10**. Deprotection of **10** with trifluoroacetic acid yielded the *cis*-diamine **11**, which was isolated as its *bis*-ammonium trifluoroacetate salt.

Scheme 2



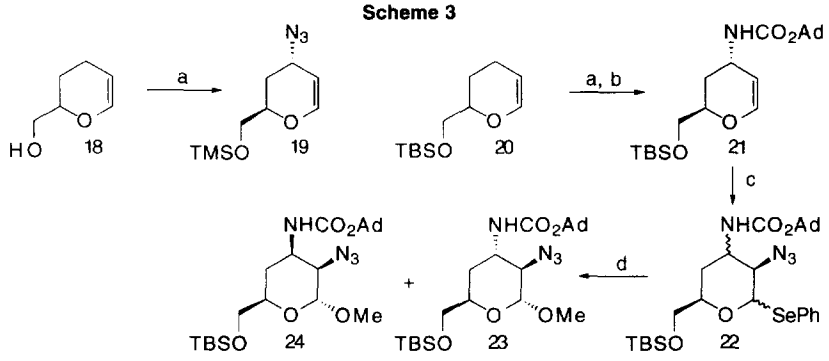
Conditions:- a) $(PhIO)_n/TMSN_3$/TEMPO (10%)/toluene/-45°C (60%). b) i. Ph_3P/CH_2Cl_2/0-25°C. ii. MeOH/aqueous NH_4OH. iii. AdOCOCl/py/CH_2Cl_2, **13** (11%) and **14** (20%). c) H_2/Rh/Al_2O_3/MeOH **15** (100%) and **16** (90%). d) i. Ph_3P (1 eq)/CH_2Cl_2/0-25°C. ii. THF/H_2O/reflux **17** (40%, 3:2 *trans:cis*).

Dihydropyran **4** reacted with $(PhIO)_n/TMSN_3$/TEMPO (10%) (α-azidonation) at -45°C to give the *trans-bis*-azide **12** (60%), **Scheme 2**. The anomeric azide in **12** also proved to be extremely resistant towards hydrolysis. Treatment of **12** with Ph_3P followed by aqueous hydrolysis gave **17** (40%), presumably *via* an alpha-amino dihydropyran. Reduction of **12** with Ph_3P, followed by successive treatment with mild base, and then 1-adamantyl chloroformate gave a

mixture of **13** (11%) and **14** (20%). Hydrogenation of **13** and **14** gave the *trans*- and *cis*-monoprotected diamines **15** (100%) and **16** (90%) respectively.

Extension of these reactions to 5-hydroxymethyldihydropyran **18** was studied. The Treatment of **18** with $(PhIO)_n/TMSN_3/CH_2Cl_2$ at -20°C gave the 3-azido derivative **19** as a 3:1 *trans*:*cis* mixture (only the major *trans*-isomer is shown), **Scheme 3**. Reaction of the protected derivative **20** under the standard β-functionalization conditions, followed by reduction and protection gave **21** (41% overall) 3:1 *trans*:*cis* mixture. The mixture could not be separated and consequently was directly exposed to $PhI(OAc)_2/(PhSe)_2/NaN_3$ to give **22** (34%). Oxidation of **22** in methanol gave **23** (44%) and **24** (24%).

Scheme 3

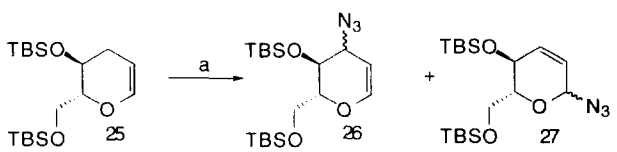


Conditions:- a) $(PhIO)_n/TMSN_3CH_2Cl_2$/-20°C, **19** (62%, 3:1 *trans*:*cis*). b) i. $LiAlH_4/Et_2O$. ii. $AdOCOCl/py/CH_2Cl_2$, **21** (41%, 3:1 *trans*:*cis*). c) $PhI(OAc)_2/(PhSe)_2/NaN_3/CH_2Cl_2$, **22** (34%, 3:5 ratio of major isomers). d) H_2O_2/MeOH, **23** (44%) and **24** (24%).

In the β-functionalization reaction of **20** it was noticed that minor by-product(s) were present that were less evident in the 5-unsubstituted dihydropyran case, **Scheme 1**.

Treatment of **25** with $(PhIO)_n/TMSN_3/CH_2Cl_2$/-20°C gave **26** and **27** (1:1). Carrying out the β-azidonation in the presence of 3Å molecular sieves changed the ratio of **26** and **27** to 2:1, **Scheme 4**.[6] Kirschning reported that **25** gave **26** (-78° to 25°C), (3:1 epimers) and **27** was not detected. We have always found that low temperatures greatly favor α-azidonation over the β-azidonation reaction.[1,2] Attempts to equilibrate **26** and **27** using $LiBPh_4/CH_2Cl_2$ were unsuccessful.[7]

Scheme 4



Conditions:- a) $(PhIO)_n/TMSN_3CH_2Cl_2$/-20°C/3Å mol sieves, **26** (1:1 epimers) and **27** (3:1 epimers), **26**:**27**, 2:1.

The α-azidonation reaction and the β-azidonation reaction, combined with the azidoselenation, provides a convenient method to construct diaminopyrans that is not based on the classical nucleophilic displacement methodology.

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References and footnotes

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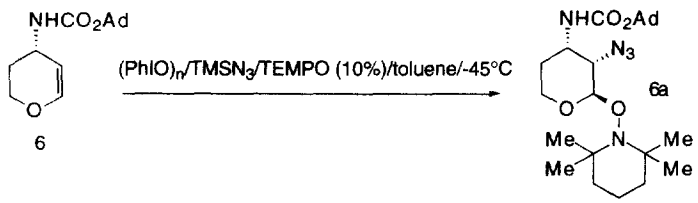
4. The α-azidonation reaction in the presence of TEMPO produces by-product(s) that result from the anomeric radical combining with TEMPO to give a covalent adduct. In the example of **6** we have isolated **6a** in 7% yield, which corresponds to 70% based on the amount of TEMPO present.



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6. We have detected small amounts of allylic azide isomers (anomeric azide) corresponding to **31** in the reactions to give **5**, **19** and **21**, and we have not observed subsequent allylic rearrangement of these azides.

7. We have frequently observed that the β-azido group can be ionized in the presence of a Lewis acid, Jérôme Lacour, Ph. D thesis, The University of Texas at Austin, 1993.

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