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Unexpected transformations: from 5-glyco-4-nitrocyclohexenes to bicyclic [3.3.1] oximes through isoxazoline *N*-oxides

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Abstract

Treatment of 5-glyco-4-nitrocyclohexenes with excess or equimolar sodium methoxide gave deacetylated sodium nitronates which, on reaction with Ac_2O/py, led to chiral isoxazoline *N*-oxides (cyclic nitronic esters). Depending on the configuration of their respective sugar side-chains, base-catalyzed deacetylation of these nitronate esters yielded either a bicyclic [3.3.1] oxime or a deacetylated isoxazoline *N*-oxide.

Keywords: nitro compounds; nitroglycocycloalkanes; isoxazoline *N*-oxides; cyclic nitronic esters; oximes.

The importance of functionalized aliphatic nitro compounds as reagents in organic synthesis is continuously being developed due to their increasing utilization as synthetic intermediates.[1] However, nitronic acids as well as their salts and esters, have been less frequently employed mainly because of the instability of these compounds,[2] although several authors have described unique uses of nitronates for the stereo- and regioselective construction of highly functionalized molecules,[3] for example, they can give 2-isoxazolines by deoxygenation,[4] or isoxazolizidines by cycloaddition reactions with alkenes, alkynes, and hetero-dipolarophiles.[2,5] These studies have also emphasized the need for efficient and specific methods for the preparation of alkyl nitronates.

In this paper, we report a simple and convenient procedure in which nitro sugar derivatives, via their corresponding nitronate salts, are the starting materials for the synthesis of highly stable chiral cyclic nitronic esters. Thus, when sodium methoxide was added in excess or in equimolar quantities to methanolic solutions of *trans*-5-glyco-1,2-dimethyl-4-nitro-1-cyclohexenes (**1a** or **1b**),[6] there was an immediate separation, in quantitative yields, of their corresponding deacetylated sodium nitronates (**2c** and **2d**) as white crystalline solids. These same nitronates were obtained when the starting materials were (4,5)-*trans*-nitropentitols **1c**, **1d** or their C-4 epimers (see Scheme 1).

On treatment with Ac_2O/py, **2c** and **2d** led to the chiral isoxazoline *N*-oxides **3e** (81% yield) and **3f** (91% yield), respectively (Scheme 1). Structures for these cyclic nitronic esters were in agreement with their analytical and spectroscopic data; thus, the ^{1}H NMR spectra showed *only* four acetate methyl

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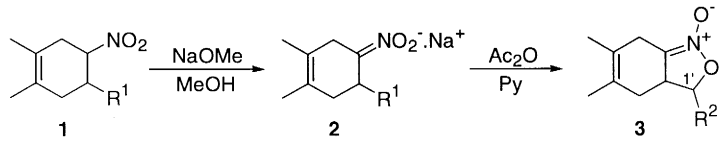
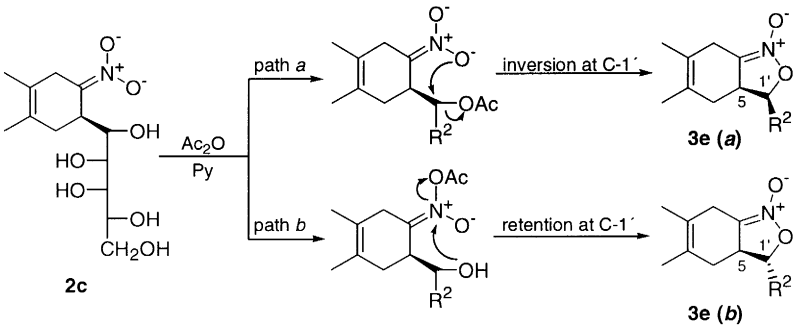


a), R^1=D-*galacto*-$(CHOAc)_4$-CH_2OAc e), R^2=D-*lyxo*-$(CHOAc)_3$-CH_2OAc
b), R^1=D-*manno*-$(CHOAc)_4$-CH_2OAc f), R^2=D-*arabino*-$(CHOAc)_3$-CH_2OAc
c), R^1=D-*galacto*-$(CHOH)_4$-CH_2OH g), R^2=D-*lyxo*-$(CHOH)_3$-CH_2OH
d), R^1=D-*manno*-$(CHOH)_4$-CH_2OH h), R^2=D-*arabino*-$(CHOH)_3$-CH_2OH

Scheme 1.

groups, whereas three olefinic carbons were evident from ^{13}C NMR spectra. The IR spectra were free from hydroxyl absorptions and showed ester carbonyl bands at 1740–1750 cm^{-1}, but they lacked those expected for the nitro group in the 1550 cm^{-1} region; instead, there were relatively intense bands at 1650–1670 cm^{-1} in the region where nitronic acids and their esters show strong C=N absorptions.

As we show in Scheme 2 for **2c**, two mechanisms could explain the conversion of compounds **2** into **3**. In one of them (path *a*), the sugar side-chain is acetylated and then one of the nitronate oxygens displaces the acetate group at C-1′ with configurational inversion at this carbon, leading to **3e** (***a***).[3a,3c,7] Path *b* implies the formation of a nitronic acid anhydride,[8] the acetate group on the nitrogen then being displaced by the free hydroxyl at C-1′ with retention at this carbon, yielding **3e** (***b***).[9]



Scheme 2.

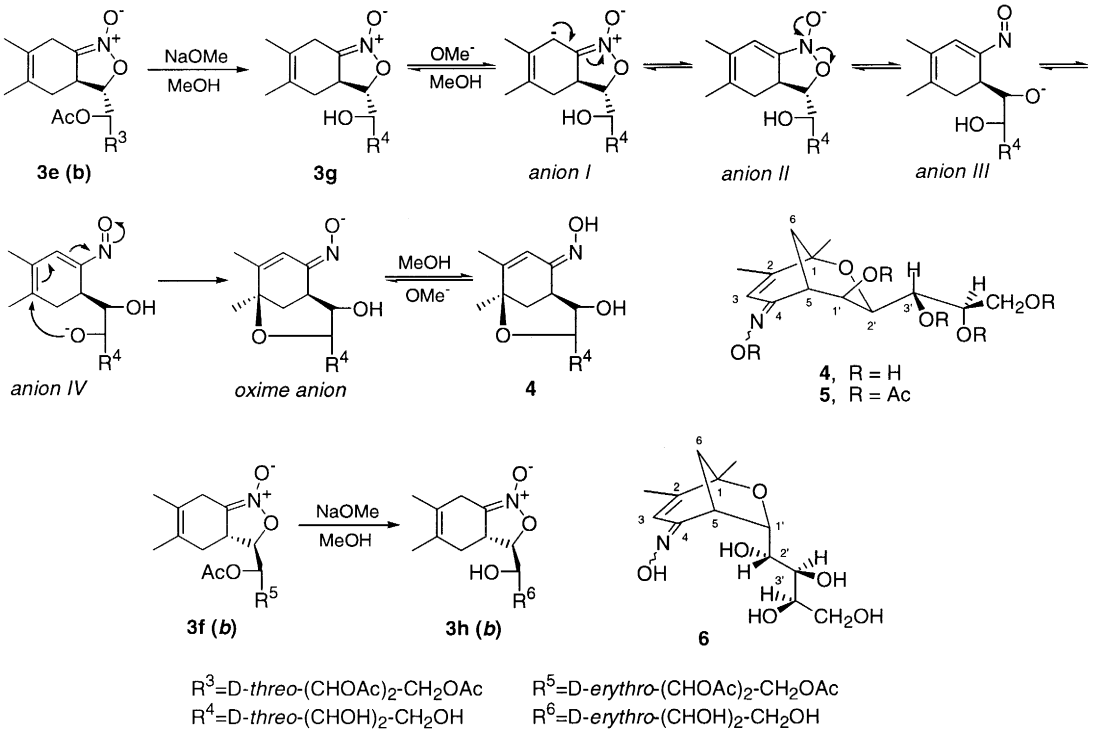
In spite of the H-1′ and H-5 protons being present with either a *cis*- or *trans*-relationship depending on the pathway (*a* or *b*) followed in the formation of compounds **3**, the $J_{1',5}$ couplings [7.7 Hz for **3e** (***b***) and 7.6 Hz for **3f** (***b***)] did not permit the differentiation between these two arrangements.[10]

Evidence supporting path *b* arose from treatment of methanolic solutions of **1a** or **1b** with a slight molar excess of non-nucleophilic bases, such as DBU or TMG. Although, as the proposed nitronate intermediates for path *a* should be formed under these conditions, we only obtained, after neutralization of the solutions, mixtures of the C-4 epimeric pentaacetylated starting materials, without any evidence of the presence of isoxazoline *N*-oxides (**3**); likewise, we did not observe any of these compounds in our previous work on Michael addition reactions of **1a** and **1b** using the above-mentioned bases.[11]

The cyclization could lead to heterocyclic rings with more than five members, but we only detected compounds in which the hydroxyl group on C-1′ seemed not to be acetylated; thus, the chemical shifts for H-1′ [δ 4.36 and 4.29 ppm for **3e** (***b***) and **3f** (***b***), respectively] were clearly different from those of H-2′, H-3′, or H-4′ which appeared between δ 5.5 and 5.1 ppm.

Although base-catalyzed decomposition of nitronic esters usually produces carbonyl compounds and oximes,[12] when **3e** (***b***) was treated with catalytic sodium methoxide in methanol, only the oxime **4** was obtained, in practically quantitative yield (see Scheme 3). The ^1H NMR spectrum of this compound exhibited signals at δ 10.85 (C=N–O*H*) and 6.07 ppm (H-3); ^{13}C NMR peaks were observed at δ

155.5 (*C*=N–OH), 139.8 and 124.7 (*C*=*C*), and 70.7 ppm (*C*-1, quaternary carbon). Treatment of **4** with Ac_2O/py yielded a pentaacetate (**5**), whose analytical and spectroscopic data were also in agreement with the proposed structure.



Scheme 3.

As shown in Scheme 3, formation of oxime **4**[13] could occur through **3g** which, under the alkaline conditions, would be in equilibrium with several anionic forms. Then, in *anion IV*, the oxygen at C-2′ could interact with the electrophilic C-1, thus leading to the bicyclic [3.3.1] *oxime anion*, again in equilibrium with its corresponding neutral form (**4**). It is noteworthy that the configuration at C-1′ does not change during this process. The other possibility we could consider, i.e., cyclization through oxygen at C-1′ in *anion III*, would lead to a bicyclic [3.2.1] oxime (**6**) in which the bulky sugar side-chain would be in the sterically crowded *endo* position.

Cyclization through the oxygen at C-2′ in *anion IV* was consistent with the chemical shift of H-2′ for **5** (δ 3.68 ppm), thus indicating this position had not been acetylated. Instead, H-1′, H-3′ and H-4′, whose corresponding carbons were acetylated, appeared at δ 4.73, 5.31 and 5.49 ppm, respectively.

With respect to the crucial point of the stereochemistry at C-1′, as we see above, it depends on the pathway (*a* or *b*) that was followed in the formation of **3e** and **3f** (Scheme 3). Both oxime **4** and its pentaacetate **5** showed couplings $J_{1',5}$ and $J_{1',2'}$ of ca. 2 Hz, in agreement with *gauche*-relationships between the H-1′/H-5 and H-1′/H-2′ protons; also, we observed long-range couplings (ca. 1 Hz) between H-1′ and H-6s, thus supporting a ‘W-path’ for the fragment H-1′/C-1′/C-5/C-6/H-6s. Bearing these data in mind, the stereochemistry at C-1′ should be as depicted for **5**; that is to say, the same as in its parent D-*galacto* compounds **1a** and **2c**. Hence, we conclude that the configuration at C-1′ was retained in the conversion of **2c** into **3e**, supporting pathway *b* for this reaction.

Concerning the step from *anion IV* to the *oxime anion*, the structure we propose for this latter compound arises from the attack of oxygen at C-2′ on C-1, on the same face of the cyclohexadiene

ring as the sugar side-chain. The other possibility, i.e., the attack on the opposite face, was discarded because it would lead to a geometrically non-viable product.

In contrast with the results observed for **3e** (***b***), treatment of **3f** (***b***) with catalytic sodium methoxide did not afford an oxime, but rather the isoxazoline *N*-oxide **3h** (***b***) as the only product (Scheme 3). The structure of this compound was based on its IR and NMR data, and was confirmed through acetylation, yielding **3f** (***b***). Although in the alkaline medium, the initially formed **3h** (***b***) would be in equilibrium with similar anionic forms shown in Scheme 3 (but with D-*arabino* sugar side-chains), the possible [3.3.1] or [3.2.1] bicyclic oximes arising from cyclizations through C-1′ or C-2′, would have their sugar side-chains in sterically crowded *endo* positions. Thus, we think that cyclization is precluded in this case, the product being the result of a straightforward protonation of *anion I*.

In summary, we have shown that acetylation of nitronate anions bearing hydroxyl groups at appropriate positions can yield isoxazoline *N*-oxides (cyclic nitronic esters) which, in turn, can be converted into cyclic oximes by treatment with a catalytic amount of sodium methoxide. Mechanistic discussions about these transformations have been supported by stereochemical considerations. Further studies, as well as applications of these efficient reactions are in progress in our laboratories and will be reported in due course.

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