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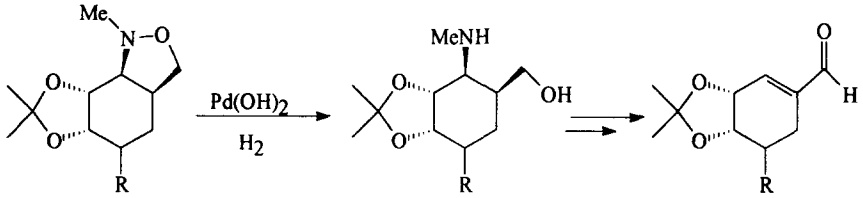
Synthesis of α,β-Unsaturated Aldehydes from the Fragmentation of Isoxazolidines with Methyl Iodide

Michel P. van Boggelen, Bart F.G.A. van Dommelen, Shende Jiang, and Gurdial Singh*

School of Science and Technology, University of Teesside, Middlesbrough TS1 3BA, UK

Abstract: Isoxazolidines when treated with methyl iodide in THF, under reflux readily afford α,β-unsaturated aldehydes and quaternary ammonium iodide alcohols.

The early pioneering studies by LeBel[1] made use of the intramolecular nitrone cycloaddition (INC) reactions to prepare a wide range of heterocyclic compounds. Utilisation of these and other 1,3-dipolar reactions have thus become important as methods for synthesis of heterocyclic ring systems containing one or more heteroatoms. This ready accessibility to a wide range of structures makes these reactions attractive for the preparation of heterocyclic systems for use as intermediates in synthesis.[2] In order to exploit successfully these attributes, one must cleanly liberate the masked functionality inherent in their structures. This unmasking is generally accomplished by reductively breaking the N-O bond, in cases where a nitrone cycloaddition reaction has been employed.[3] In the case of our recent synthesis of (-)-5-*epi*-shikimic acid and (-)-shikimic acid we accomplished a reductive cleavage of the isoxazolidine N-O bond in **1a,b** to afford the corresponding amino alcohol **2a,b** which was subsequently oxidised to the α,β-unsaturated aldehyde **3a,b** as detailed in scheme 1. In this note we wish to report a novel fragmentation reaction involving an oxidative / reductive cleavage of the N-O bond of isoxazolidines.



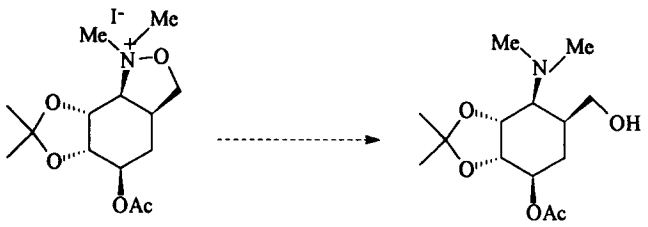
1a R=α OAc
1b R=β OAc

2a R=α OAc
2b R=β OAc

3a R=α OAc
3b R=β OAc

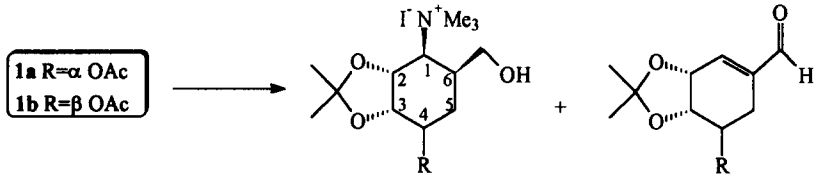
Scheme 1

As a part of these and other ongoing studies we examined the preparation of the quaternary dimethyl ammonium salt **4** which we reasoned on reductive cleavage would lead to the N,N-dimethyl amino alcohol **5**. Methylations of **1a,b** were conducted with one equivalent of methyl iodide in THF, however the reaction was very sluggish. As a result of this finding we increased the methyl iodide to 20eq and conducted the reaction for 18 hours. To our surprise this resulted in the formation of two new compounds. The less polar of these was readily isolated by chromatography and its spectroscopic data were consistent with the α,β-unsaturated aldehyde structures **3a,b**, which had previously been prepared by a Swern oxidation procedure.[4]



4 5

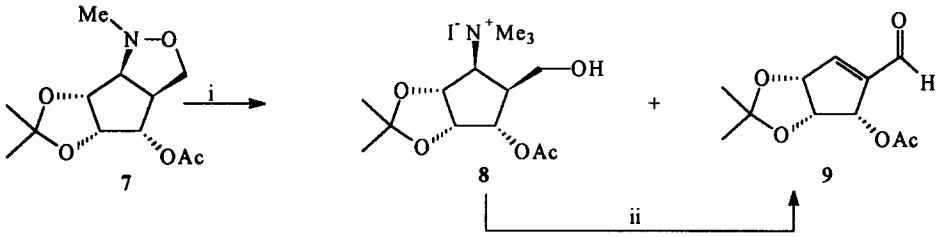
In the case of **1b**, from the aqueous phase of the reaction we isolated the quaternary ammonium alcohol assigned as **6b** in 58% yield. In its ir spectrum absorptions were evident at 3381 and 1734 cm^{-1}. These data alongside its ^1H nmr and high resolution FAB ms confirmed the structure as **6b**.[5] Methylation of **2a,b** with methyl iodide gave rise to material whose spectral and physical properties were identical to the salt **6a,b**.[4]



6a R=α OAc
6b R=β OAc

3a R=α OAc
3b R=β OAc

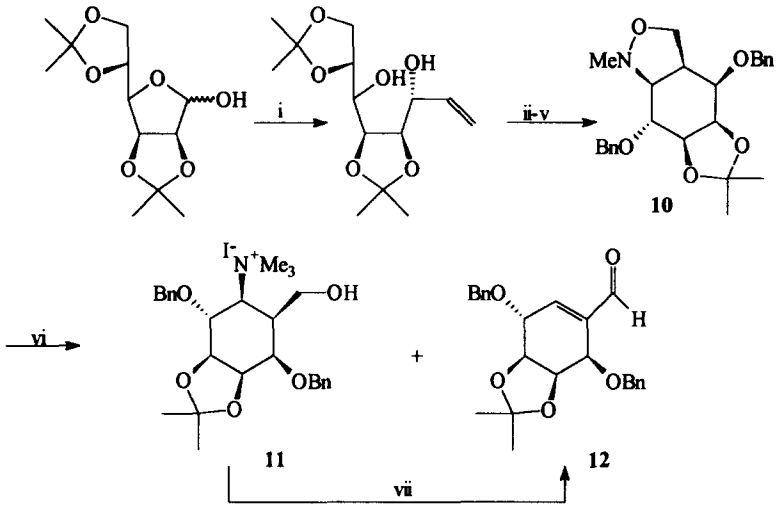
Armed with these findings we sought to investigate this reaction further. We thus prepared the isoxazolidines **7** and **10**.[6]



Scheme 2 i, MeI, 20 eq, THF, Δ, 16h; ii, $(COCl)_2$, DMSO, CH_2Cl_2, NEt_3, -78 °C, 30 mins.

Subjection of the isoxazolidine **7** to the same methylation procedure gave the aldehyde **9** in 24% yield; $[\alpha]_D$-183.9° (c 0.77, $CHCl_3$); along with the ammonium salt **8** in 67% yield, which could be readily converted to the aldehyde **9** in 75% yield.

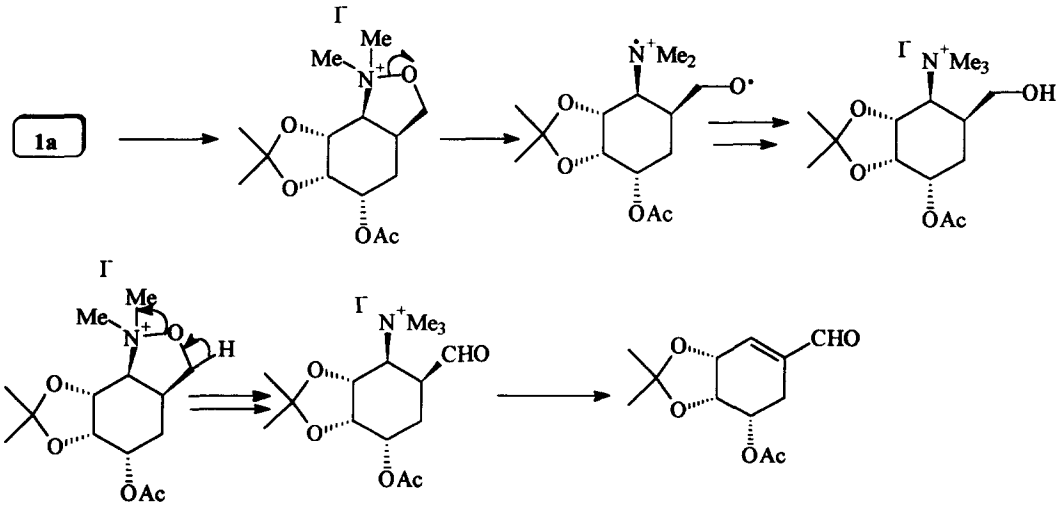
The six membered isoxazolidine analogue(s) were synthesised by a somewhat shorter, more efficient route, than reported in the literature.[6] Treatment of di-isopropylidene-D-mannofuranose with vinyl magnesium chloride gave rise to two epimeric diols, in a ratio of (5:1), which were separated by chromatography. The major diastereoisomer was assigned the structure as indicated in scheme 3 on the basis of spectroscopic data and correlation.[6] The terminal isopropylidene group was selectively cleaved and oxidised by the action of periodic acid.[7] The resultant hemi-acetal was then converted to the tricycle **10**. The minor isomer from the Grignard reaction was similarly converted to the analogous isoxazolidine. The action of methyl iodide on **10** resulted in the production of the aldehyde **12** and the ammonium alcohol **11** in 30% and 25% yields respectively. This lower yield for the ammonium salt we believe is a reflection of its solubility in organic solvents. This was smoothly converted to the aldehyde **12**, in 72% yield, under Swern conditions.



Scheme 3. i, vinyl MgCl, THF, 0°C, 3h; ii, $PhCH_2Br$, Bu_4NI, NaH, THF, iii, H_5IO_6, Et_2O, Δ, 12h; iv, MeNHOH.HCl, Py, r.t., 16h; v, $PhCH_3$, Δ, 16h; vi, MeI, 20eq, THF, Δ, 18h; vii, $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, -78° C to r.t., 1h.

The formation of these products can be rationalised as occurring *via* a radical pathway as outlined in scheme 4.[8] However the aldehyde formation can also be explained by deprotonation at the methylene carbon of the isoxazolidine ammonium salt with concomitant N-O bond cleavage followed by elimination of trimethylamine. It is noteworthy that this mechanism does not explain the formation of the corresponding ammonium alcohols whose formation must be as a result of a reduction process taking place. Our initial findings do not lead us to an unequivocal conclusion, and it is probable that a mixed pathway is the most likely result. An additional point of note is that iodine is formed in the reaction.

Our studies suggest that this fragmentation is applicable to both 5,5 and 6,5-fused isoxazolidines. This provides ready access to highly functionalised cylopentane and cyclohexane derivatives.



Scheme 4

Acknowledgements- We thank Dr R. H. Wightman (Heriot-Watt University) for invaluable discussions, and the EPSRC for access to central facilities for high resolution mass spectrometry at the University of Wales, Swansea (Director, Dr. J.A. Ballantine).

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5. Selected data:**3b:** $[\alpha]_D$ -84.6°; (c 1.38, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.39 (3H, s), 1.40 (3H, s), 2.04 (3H, s), 2.31 (1H, dd, *J* 17.7, 6.0 Hz), 2.65 (1H, ddt, *J* 17.7, 4.5, 1.4 Hz), 4.30 (1H, t, *J* 6.0 Hz), 4.83 (1H, m), 5.20 (1H, dt, *J* 6.0, 4.6 Hz), 6.69 (1H, m), 9.54 (1H, s).**6b:** m.p. 105-110°, $[\alpha]_D$ +12.2°; (c 1.31, H_2O); I R (KBr) 3381, 1734; HRMS (FAB) M^+-I Found 302.1969; $C_{15}H_{28}NO_5$ requires 302.1967; δ_H (270 MHz, $CDCl_3$) 1.41 (3H, s), 1.57 (3H, s), 1.83 (1H, dt, *J* 15.2, 3.8, Hz, H-5β), 2.07 (3H, s), 2.27 (1H, dt, *J* 15.2, 5.8 Hz, H-5α), 2.82 (1H, m, H-6), 3.41 (9H, s), 3.68 (1H, dd, *J* 11.9, 3.6, H-7α), 3.81-3.95 (2H, m, H-7β, H-1), 4.41 (1H, m, H-3), 5.05-5.17 (2H, m, H-2, H-4) **9:** m.p. 97.5-98°C $[\alpha]_D$ -183.9°; (c 0.77, $CHCl_3$); δ_H (200 MHz, $CDCl_3$) 1.30 (3H, s), 1.34 (3H, s), 2.07 (3H, s), 4.95 (1H, dd, *J* 5.6 Hz), 5.07 (1H, dd, *J* 5.72, 2.02 Hz), 5.62 (1H, dd, *J* 5.56, 1.30 Hz), 6.88 (1H, t, *J* 1.6 Hz), 9.80 (1H, S). **12:** $[\alpha]_D$ -52.4°;(c 1.36, $CHCl_3$); δ_H (200 MHz, $CDCl_3$) 1.38 (3H, s), 1.53 (3H, s), 4.15 (1H, dd, *J* 8.40, 3.8 Hz), 4.41 (1H, d, *J* 12.1 Hz, OBn), 4.44 (1H, dd, *J* 8.2, 5.0 Hz), 4.62 (1H, d, *J* 12.1 Hz, OBn), 4.69 (1H, d, *J* 11.6 Hz, OBn), 4.77 (1H, dd, *J* 3.75, 1.0 Hz), 4.82 (1H, dd, *J* 5.0, 2.05 Hz), 4.92 (1H, d, *J* 11.6 Hz, OBn), 6.93 (1H, dd, *J* 2.0, 1.15 Hz), 7.32 (10H, m), 9.81(1H, s).

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