ChemComm

A simple entry towards novel bi- and tricyclic *N*-oxy-β-lactams by high pressure promoted tandem [4 + 2]/[3 + 2] cycloadditions of enol ethers and β-nitrostyrene

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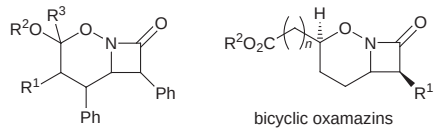
Received (in Liverpool, UK) 23rd February 1999, Accepted 11th March 1999

A high pressure promoted tandem [4 + 2]/[3 + 2] cycloaddition of β-nitrostyrene with a variety of enol ethers followed by a base catalysed rearrangement provided a novel class of di- and tricyclic *N*-oxy-β-lactam compounds.

Since the discovery of heteroatom activated β-lactams several reports mention the unique properties of this class of compound which show potential antibacterial activity. The biological activity of *N*-oxy-β-lactams has been attributed to electronic activation of the azetidinone ring. The oxygen atom directly attached to the ring makes the β-lactam more susceptible to nucleophilic attack than the corresponding *N*-alkyl-β-lactams.[1] Although polycyclic *N*-oxy-β-lactams can be considered as attractive targets in the search for new antibiotics only a few articles describing their synthesis have been reported.[2,3]

Here we describe a stereoselective route towards novel di- and tricyclic heteroatom activated β-lactams **1** from easily accessible building blocks such as enol ethers and β-nitrostyrene. The bi- and tricyclic *N*-oxo-β-lactams described are new compounds strongly resembling the biologically active bicyclic oxamazins.[2,4]



1a R^1 = H, R^2 = Et, R^3 = H
b R^1 = H, R^2 = PMB, R^3 = H
c R^1–R^3 = $(CH_2)_4$, R^2 = Me
d R^1–R^2 = $(CH_2)_2$, R^3 = H

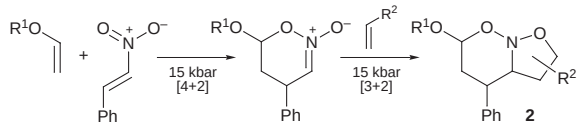
Recently, we reported the one-pot three-component tandem [4 + 2]/[3 + 2] cycloaddition of nitroalkenes, enol ethers and mono-substituted electron-poor alkenes (Scheme 1).[5] The powerful effect of high pressure resulted in the formation of the nitroso-acetals **2** without the need of stoichiometric amounts of Lewis acid catalysts as reported by Denmark and Seebach.[6,7] Furthermore it is reported that 1,2-disubstituted olefins are unreactive under Lewis acid conditions at ambient pressure in this type of tandem [4 + 2]/[3 + 2] cycloaddition.[7] This stimulated us to study the reactivity of 1,2-disubstituted olefins under high pressure conditions.

Here we report the high pressure promoted tandem cycloaddition of enol ethers and β-nitrostyrene in which β-nitrostyrene reacts both as heterodiene and 1,2-disubstituted dipolarophile. In general, the tandem cycloaddition of the enol ether with an excess of β-nitrostyrene (4 equiv.) resulted in the formation of regioisomers **3** and **4** (Scheme 2). β-Nitrostyrene first reacts as an electron-poor diene in an inverse electron demand Diels–Alder reaction with an electron-rich enol ether and thereafter as an electron-poor dipolarophile with the *in situ* formed mono-adduct in a 1,3-dipolar cycloaddition. The reaction was studied with mono-substituted and cyclic enol ethers.

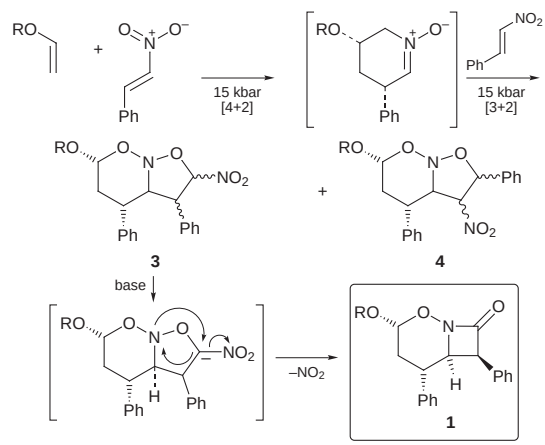
Surprisingly the main regioisomer **3** was converted in one step into β-lactam **1** during purification on silica gel using an eluent containing Et_3N, pointing to a base catalysed rearrangement (Scheme 2). This was further confirmed by stirring the crude reaction mixture in CH_2Cl_2 with a catalytic amount of Et_3N. In this way the same mixture of products was obtained. In agreement with these results it is suggested that first the acidic proton adjacent to the nitro group is removed by the base followed by N–O bond cleavage and elimination of nitrite (Scheme 2).[8] Table 1 shows the regioisomeric ratios of cycloadducts **1a**–**d** in the crude reaction mixture (measured by ^{1}H NMR).

The stereochemistry of the cycloadducts has been elucidated by high field 2D-NOESY ^{1}H NMR experiments. It was found that the [4 + 2] cycloaddition proceeded with complete regio- and *endo*-selectivity while the [3 + 2] cycloaddition proceeded with variable regioselectivity and with moderate *exo*-selectivity. However β-lactam **1** was formed after a completely *endo*-selective [4 + 2] and *exo*-selective [3 + 2] cycloaddition.

The stereochemistry of the cycloadducts is discussed on the basis of a representative example (entry 2, Table 1). The main product **7** and regioisomers **5a**† and **6** (Scheme 3) were detected by NMR analysis of the crude reaction mixture in a 7 : 2 : 1 ratio. After purification, β-lactam **1b**‡ and nitroso-acetals **5b** and **6** were isolated in a 7 : 2 : 1 ratio, indicating a complete conversion of **7** to **1b** and **5a** to **5b**. Product **5b** is the NO_2 epimer of the *endo*[4 + 2]-*anti-endo*[3 + 2]-isomer **5a** and product **6** is the



Scheme 1

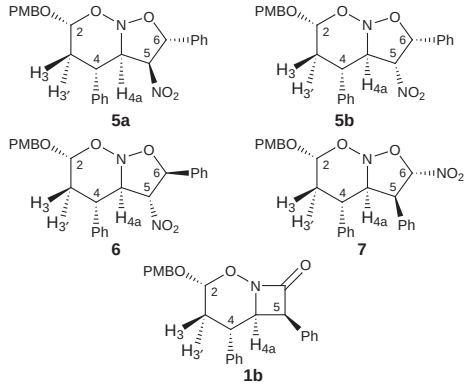


Scheme 2

Table 1 Synthesis of *N*-oxy-β-lactams **1a–d**

Entry		Ratio **3** : **4**	Yield (%)[a]	β-Lactam (%)[b]
1	**1a**	6 : 4	63	38
2	**1b**	7 : 3	87	61
3	**1c**	7 : 3	90	63
4	**1d**	3 : 7	68	20

[a] Combined yield of β-lactam **1** and regioisomer **4**. [b] Chemical yield of β-lactam after purification.

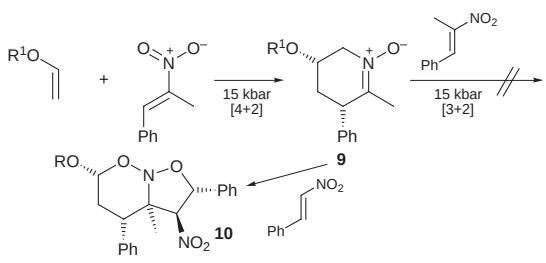


Scheme 3

endo[4 + 2]-*anti*-*exo*[3 + 2]-isomer.[9] Some crystals of compound **7** were obtained from the crude reaction mixture and the structure of **7** was assigned by 2D-NMR as depicted in Scheme 3. The C-5 epimer of β-lactam **1b** was not detected. NOE contact between H-4a and H-5 of **1b** indicate a *cis* configuration for these protons. The formation of regioisomers **5b** and **6** however proceeded with less selectivity (**5b** : **6** = 2 : 1). NOE-contacts between H-2 and H-3, H-3 and H-4, and H-2 and H-4 indicate a chair-like conformation of the 6-membered ring formed after the *endo*-selective hetero Diels–Alder reaction. These NOE contacts were observed for both regioisomers **5b**, **6** and β-lactam **1b**. X-Ray analysis of compound **1b** confirmed the configuration of the 6-membered ring. In all cases the attack of β-nitrostyrene in the [3 + 2] dipolar cycloaddition was *anti* (with respect to the phenyl group) since a *trans* relationship between H-4a and H-4 was found in the cycloadducts.

The formation of regioisomer **7** is rather unexpected since literature data concerning the 1,3-dipolar cycloaddition of nitrones and olefins with unequally electron-withdrawing groups such as nitro and phenyl substituents predict opposite regioselectivity (*e.g.* **5** and **6**).[10] AM1 calculations predict a HOMO-dipole controlled formation of regioisomers **5** and **6**.[11] The experimental regioisomeric outcome could be explained on the basis of charge distribution between dipole and dipolarophile obtained through AM1 calculations which is in agreement with calculations reported by Baskaran *et al.*[12,13]

1-Phenyl-2-nitropropene and *p*-methoxybenzyl vinyl ether reacted stereoselectively to give *endo* [4 + 2] adduct **9**. This mono-adduct failed to react with another molecule of 1-phenyl-2-nitropropene (15 kbar, 50 °C, 48 h) probably because of steric hindrance but it reacted completely regio- and stereoselectively with β-nitrostyrene in accordance with the predicted regioselectivity towards bicyclic nitroso-acetal **10**[13] (Scheme 4).



Scheme 4

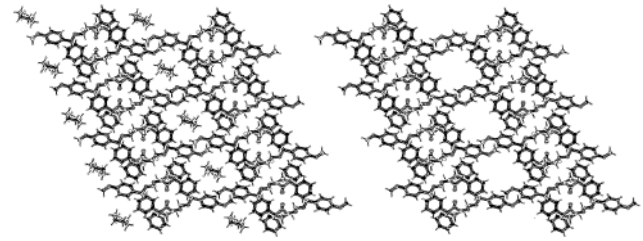


Fig. 1 2D depiction of the X-ray structure of β-lactam **1b** with (left) and without (right) cyclohexane.

Interestingly the X-ray structure of **1b** showed parallel oriented channels with aromatic walls holding cyclohexane molecules present in the solvent from which the compound was crystallised (Fig. 1). It seems that **1b** acts as an organic zeolite since complete selectivity for the inclusion of cyclohexane was found after crystallisation from *n*-hexane–CH_2Cl_2 (*n*-hexane contains 3–10% cyclohexane by GC analysis). The zeolite properties of this compound are under investigation (*e.g.* inclusion of other solvents or chiral compounds).

We gratefully acknowledge the support of NWO-CW and Solvay Pharmaceuticals.

Notes and references

† *Crystal data* for **5a**: $C_{26}H_{26}N_2O_6$, M = 462.49, triclinic, a = 8.9646(6), b = 9.4791(8), c = 14.7752(4) Å, α = 95.628(5), β = 100.8151(5), γ = 103.968(6)°, U = 1183.00(12) Å^3, T = 293 K, $P\bar{1}$, Z = 2, μ(Cu-Kα) = 0.765 mm^{-1}, 4780 reflections, 4471 unique (R_{int} = 0.0072) which were used in all calculations. The final $wR(F^2)$ was 0.1169 (all data).
‡ *Crystal data* for **1b**: $C_{26}H_{25}NO_4$, M = 415.49, monoclinic, a = 18.7886(4), b = 7.41628(19), c = 19.3640(3) Å, β = 116.2092(16)°, U = 2420.80(8) Å^3, T = 208 K, $P2_1/a$, Z = 4, μ(Cu-Kα) = 0.664 mm^{-1}, 4736 reflections, 4583 unique (R_{int} = 0.0257) which were used in all calculations. The final $wR(F^2)$ was 0.1367 (all data). CCDC 1202. See http://www.rsc.org/suppdata/cc/1999/855/ for crystallographic data in .cif format.

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13 Further investigations concerning the regioselectivity of the [3 + 2] cycloadditions are in progress.

Communication 9/01505A

Typeset and printed by Black Bear Press Limited, Cambridge, England