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Regiochemical and stereochemical studies of the intramolecular dipolar cycloaddition of nitrones derived from quaternary aldehydes

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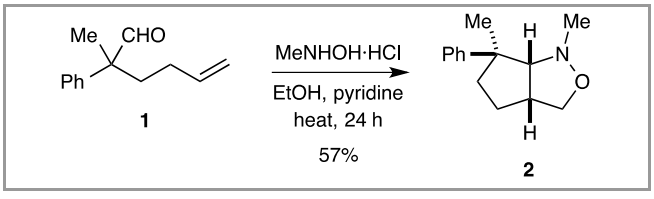
Abstract: Three aldehydes each with a quaternary α carbon stereocentre bearing an alkenyl, a phenyl, and a methyl ester group were treated with *N*-methylhydroxylamine. In each case bicyclic isoxazolidine products were formed by condensation to give intermediate nitrones that undergo intramolecular dipolar cycloaddition. The stereoselectivity was influenced by the α-carbonyl substituent, possibly by a hydrogen bond between CO and a nearby CH of the nitrone in the transition state (supported by DFT and X-ray studies), and the regioselectivity was affected by the length of the tether and by the presence of an ester on the alkene dipolarophile.

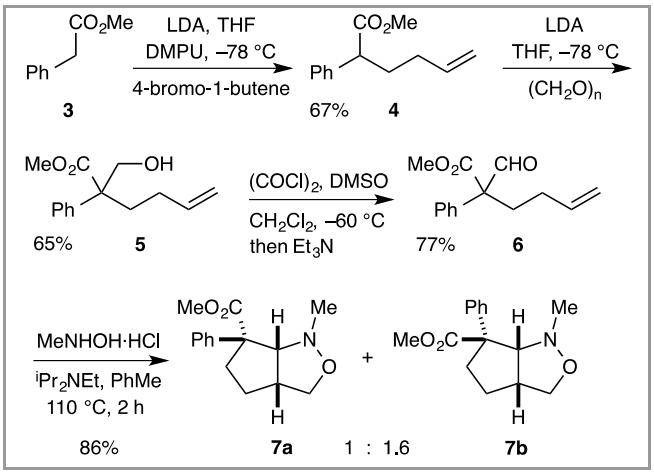
Key words: Cycloaddition; Diastereoselectivity; Domino reaction; Fused-ring systems; Heterocycles.

Intramolecular dipolar cycloaddition reactions of nitrones have been known for more than 50 years.[1] One of the attractions of this chemistry is that it allows the rapid synthesis of cyclic and polycyclic compounds with 1,3-amino-alcohol functionality. The presence of polycyclic amines in alkaloids has prompted a considerable number of studies into intramolecular nitrone cycloadditions,[2] including work in our own research group.[3] Many alkaloids contain not just an amino group but an aromatic ring, often derived from a β-arylethylamine precursor. Not surprisingly, therefore, there are reports of the intramolecular cycloadditions of nitrones bearing an aromatic substituent attached β to the nitrogen atom.[4,5] Of these examples, as far as we are aware, only one uses a quaternary aldehyde (compound **1**) which was heated with *N*-methylhydroxylamine hydrochloride salt and pyridine to give the cycloadduct **2** as a single stereoisomer (Scheme 1).[4a] We were interested in exploring further examples of this type of reaction of quaternary substituted aldehydes and report here our findings.



Scheme 1 Related literature example.[4a]

In related synthetic chemistry efforts, we wanted to test nitrone cycloadditions derived from aldehydes with an α-quaternary stereocentre bearing an aryl group and an ester group. We therefore prepared the aldehyde **6** by double alkylation of the ester **3** followed by Swern oxidation[6] (Scheme 2).



Scheme 2 Cycloaddition with aldehyde **6**.

Heating the aldehyde **6** with *N*-methylhydroxylamine hydrochloride salt and diisopropylethylamine in toluene gave a mixture of the cycloadducts **7a** and **7b** in a 1:1.6 ratio. The structures of both cycloadducts were determined by single crystal X-ray analysis (see Supporting Information, SI). This reaction is a direct comparison with the formation of the cycloadduct **2**, where a single stereoisomer was reported. This suggests that, although a phenyl group has a stronger preference for the *exo* position than a methyl group, there is a preference for a methyl ester, rather than a phenyl group, to be *exo*. A possible reason for this is evident in the X-ray crystal structure of **7b** (Fig. 1), in which the preference for this isomer might arise from a favorable interaction between the ester carbonyl oxygen atom and the proton at the ring junction α to the nitrogen atom.[7] These are only 2.35 Å apart in compound **7b** and this interaction could be present in the nitrone and in the transition state (see SI for DFT studies).

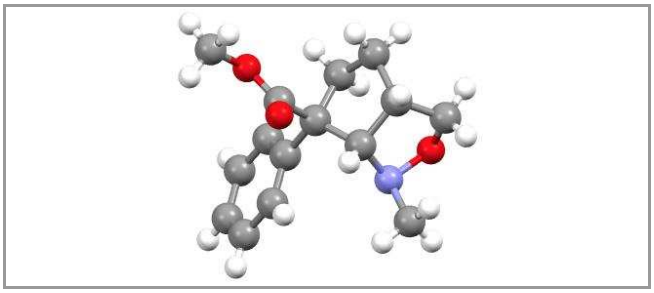
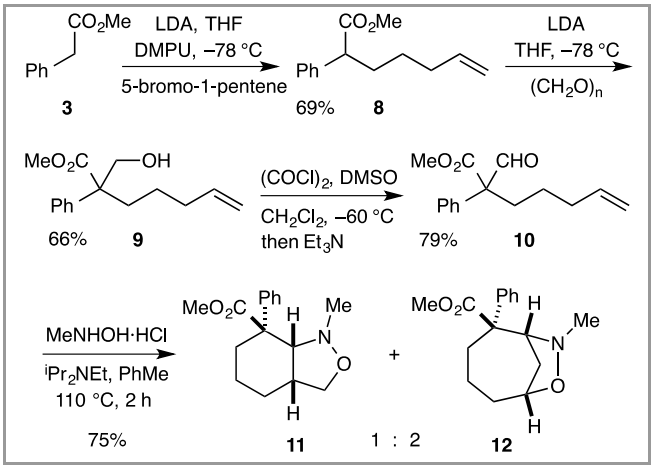


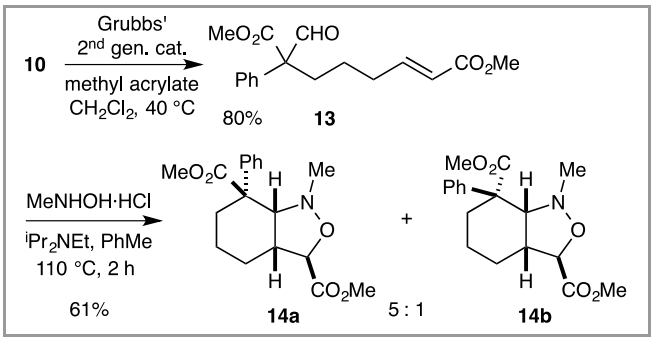
Figure 1 X-ray crystal structure of **7b**.

To test the cycloaddition to give a cyclohexane ring system, we prepared the aldehyde **10** from the same ester **3** (Scheme 3). This followed related chemistry but by using the homologous 5-bromo-1-pentene. Heating the aldehyde **10** with *N*-methylhydroxylamine hydrochloride and diisopropylethylamine in toluene gave a mixture of the cycloadducts **11** and **12** in a 1:2 ratio. Some of the isomer **12** could be separated by crystallization and single crystal X-ray analysis (see Supporting Information) confirmed the relative stereochemistry as shown for **12**, in which the methyl ester group prefers the *exo* position. We tentatively assign the stereochemistry of **11** to be the same relative configuration, as shown in Scheme 3. There is a preference for the bridged adduct **12** due to the longer carbon chain that gives flexibility to allow the opposite regiochemistry in the dipolar cycloaddition.



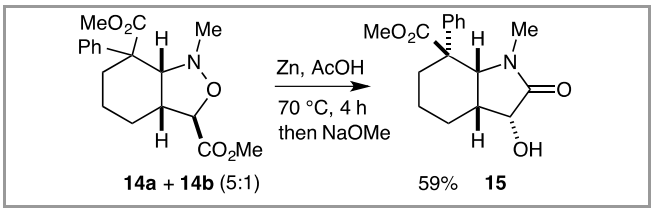
Scheme 3 Cycloaddition with aldehyde **10**.

We envisaged that the regioselectivity could be directed by altering the terminal alkene dipolarophile to have an electron-withdrawing group attached. Cross metathesis of the alkene **10** with methyl acrylate and Grubbs second generation catalyst[8] gave the new substrate **13** for cycloaddition (Scheme 4). We were pleased to find that heating the aldehyde **13** with *N*-methylhydroxylamine hydrochloride and diisopropylethylamine in toluene gave a single regioisomer and a high stereoselectivity in favour of the isomer **14a**.[9] Only the fused and none of the bridged regioisomer was formed, in contrast to the corresponding reaction with the aldehyde **10** (Scheme 3). The major isomer **14a** was crystalline and could be partially separated from **14b**. Single crystal X-ray analysis revealed the stereochemistry of **14a** as shown in Scheme 4. Therefore the methyl ester group favors the *exo* position in all cases studied. The presence of a terminal ester group has a significant effect, especially on the regioselectivity of the reaction.



Scheme 4 Cycloaddition with aldehyde **13**.

Finally, we treated the mixture of cycloadducts **14** with zinc in acetic acid to promote breakage of the N–O bond and subsequent cyclization of the resulting amine onto the ester to give the lactam **15** (Scheme 5). Cyclization was only partially complete but stirring with some sodium methoxide in methanol completed the process. The lactam **15** was isolated together with a small amount of the other stereoisomer. Recrystallization gave the isomer **15** as shown in Scheme 5 and the relative stereochemistry was verified by single crystal X-ray diffraction.



Scheme 5 Breaking the N–O bond of cycloadduct **14**.

In conclusion, we have demonstrated that intramolecular nitrone cycloadditions are amenable to aldehydes bearing α-quaternary centres in which one substituent is a methyl ester. The regioselectivities are affected by the length of the tether to the alkene dipolarophile and by the nature of the dipolarophile (terminal alkene or with attached electron-withdrawing group). The stereochemistry is influenced by the α carboxylic ester group that is thought to interact with the proton of the CHN group in the transition state, thereby favoring the stereoisomer with the ester group *exo* to the bicyclic ring system. The chemistry allows the synthesis of bicyclic isoxazolidines containing a β-phenylethylamine moiety.

Experimental details and spectroscopic data, including NMR spectra and X-ray crystal structures are provided in the Supporting Information.

Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

Primary Data for this article are available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083 and can be cited using the following DOI: (number will be inserted prior to online publication).

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(9) **Dimethyl 1-Methyl-7-phenyloctahydrobenzo[c]isoxazole-3,7-dicarboxylate (14a)** The aldehyde **13** (100 mg, 0.33 mmol), *N*-methylhydroxylamine hydrochloride (30 mg, 0.36 mmol) and diisopropylethylamine (0.12 mL, 0.66 mmol) in toluene (4 mL) was heated at 110 °C. After 2 h, the solvent was evaporated. Purification by column chromatography, eluting with petrol–EtOAc (7:2), gave the cycloadducts **14a** and **14b** (67 mg, 61%) as a mixture (ratio 5:1 by ^{1}H NMR spectroscopy) from which isomer **14a** was isolated by crystallization from CH_2Cl_2/hexane (1:1) as amorphous solid; m.p. 98−100 °C; R_f 0.28 [petrol–EtOAc (7:2)]; IR ν_{max}(film)/cm^{-1} 2950, 1750, 1725, 1435; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.34 (2H, m), 7.31–7.26 (3H, m), 4.13 (1H, s), 3.79 (3H, s), 3.67 (3H, s), 3.57 (1H, d, *J* 4 Hz), 3.23–3.19 (1H, m), 2.46−2.38 (1H, m), 2.35−2.26 (1H, m), 1.97−1.87 (5H, m), 1.74−1.59 (1H, m), 1.37−1.26 (1H, m); ^{13}C NMR (400MHz, $CDCl_3$) 175.1, 172.9, 140.7, 128.8, 127.7, 126.3, 80.4, 70.5, 53.2, 52.4, 52.2, 48.1, 47.8, 26.9, 26.5, 22.2; HRMS *m*/*z* (ES) Found: MH^+ 334.1646, $C_{18}H_{23}NO_5$ requires MH^+ 334.1649; LRMS *m*/*z* (ES) 334 (MH^+, 100%). X-ray analysis (see Supporting Information): CCDC 1422381.

Intramolecular nitrone cycloadditions from quaternary aldehydes