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Regiochemical and Stereochemical Studies of the Intramolecular Dipolar Cycloaddition of Nitrones Derived from Quaternary Aldehydes

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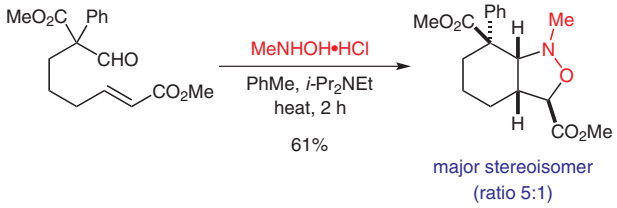

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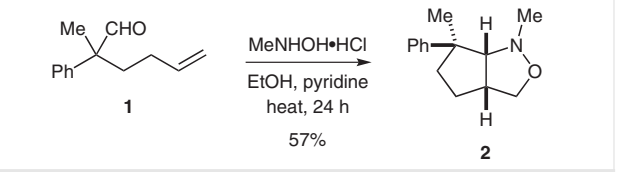
Abstract Three aldehydes each with a quaternary α-carbon stereocentre bearing an alkenyl, a phenyl, and a methyl ester group were treated with *N*-methylhydroxylamine. In each case bicyclic isoxazolidine products were formed by condensation to give intermediate nitrones that undergo intramolecular dipolar 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.

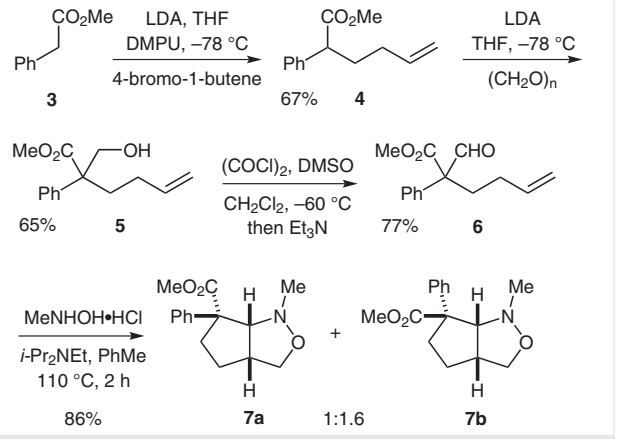
Key words cycloaddition, diastereoselectivity, domino reaction, fused-ring systems, heterocycles

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). 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** (Figure 1), in which the preference for this isomer might arise from a favourable 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 Supporting Information for DFT studies).

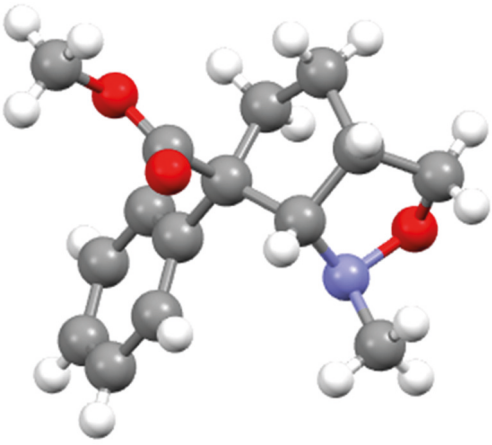
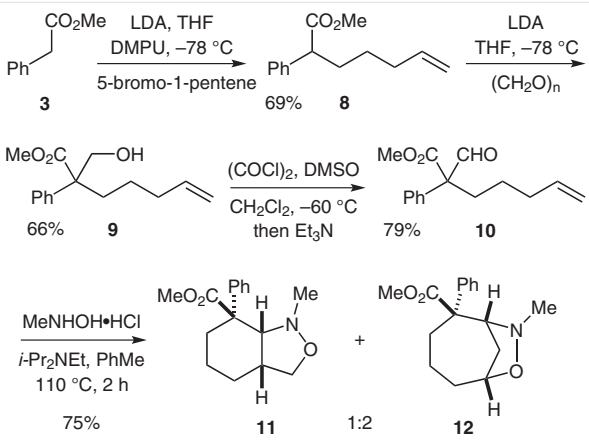


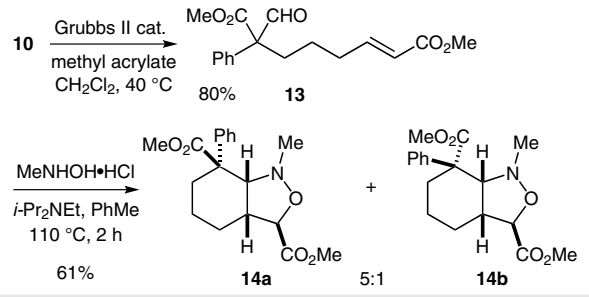
Figure 1 X-ray crystal structure of **7b**

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.

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 favours 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.

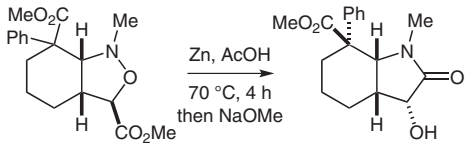


Scheme 3 Cycloaddition with aldehyde **10**



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 favouring 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.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560906. Experimental details and spectroscopic data, including NMR spectra and X-ray crystal structures are provided .

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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 DIPEA (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 PE–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; mp 98–100 °C; R_f = 0.28 [PE–EtOAc (7:2)]. IR (film): ν_{max} = 2950, 1750, 1725, 1435 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.34 (2 H, m), 7.31–7.26 (3 H, m), 4.13 (1 H, s), 3.79 (3 H, s), 3.67 (3 H, s), 3.57 (1 H, d, *J* = 4 Hz), 3.23–3.19 (1 H, m), 2.46–2.38 (1 H, m), 2.35–2.26 (1 H, m), 1.97–1.87 (5 H, m), 1.74–1.59 (1 H, m), 1.37–1.26 (1 H, m). ^{13}C NMR (400MHz, $CDCl_3$): δ = 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 (ES): *m*/*z* calcd for $C_{18}H_{23}NO_5$ [MH$^+$]: 334.1649; found [MH$^+$]: 334.1646. LRMS (ES): *m*/*z* (%) = 334 (100) [MH$^+$]. X-ray crystal structure analysis (see Supporting Information): CCDC 1422381.