

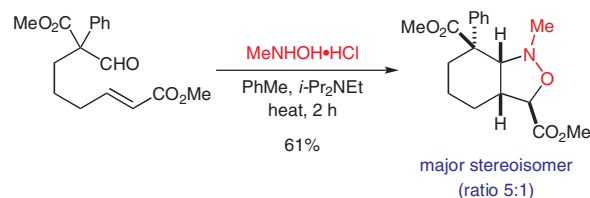
# Regiochemical and Stereochemical Studies of the Intramolecular Dipolar Cycloaddition of Nitrones Derived from Quaternary Aldehydes

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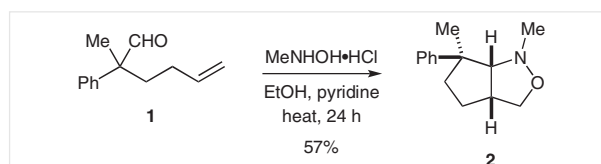


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**Abstract** Three aldehydes each with a quaternary  $\alpha$ -carbon stereocentre bearing an alkenyl, a phenyl, and a methyl ester group were treated with *N*-methylhydroxylamine. In each case bicyclic isoxazolidine products were formed by condensation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

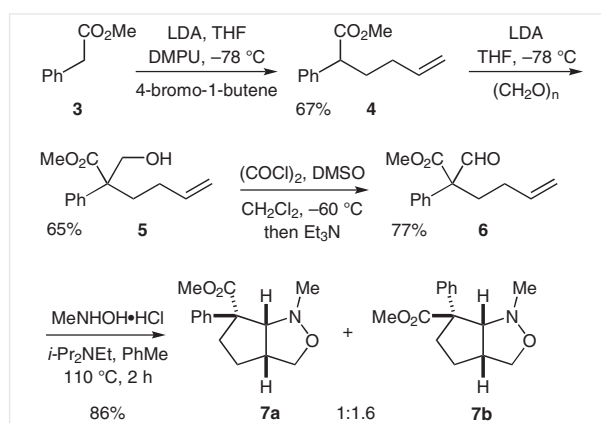
**Key words** cycloaddition, diastereoselectivity, domino reaction, fused-ring systems, heterocycles

Intramolecular dipolar cycloaddition reactions of nitrones have been known for more than 50 years.<sup>1</sup> 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,<sup>2</sup> including work in our own research group.<sup>3</sup> Many alkaloids contain not just an amino group but an aromatic ring, often derived from a  $\beta$ -arylethylamine precursor. Not surprisingly, therefore, there are reports of the intramolecular cycloadditions of nitrones bearing an aromatic substituent attached  $\beta$  to the nitrogen atom.<sup>4,5</sup> 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).<sup>4a</sup> 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<sup>4a</sup>

In related synthetic chemistry efforts, we wanted to test nitrone cycloadditions derived from aldehydes with an  $\alpha$ -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<sup>6</sup> (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