Dipolar Cycloaddition Reactions of *N*-Tetrahydropyranylnitrone

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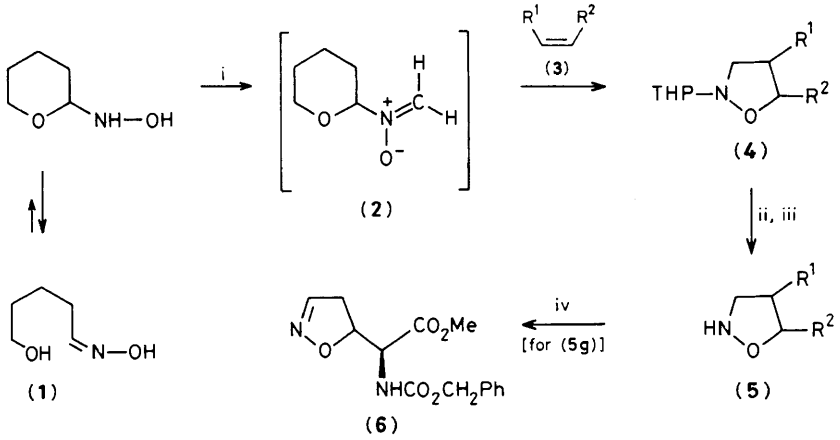
Paraformaldehyde and the oxime of 5-hydroxypentanal react with alkenes at elevated temperatures to give dipolar cycloadducts arising from *N*-tetrahydropyran-2-ylnitrone.

The dipolar cycloaddition of nitrones to alkenes has been studied for over 20 years from both an experimental[1] and a theoretical[2] perspective. In general the majority of nitrones studied to date bear alkyl or aryl groups on nitrogen which cannot subsequently be removed with ease from the resulting cycloadduct; as a consequence *N*-unsubstituted isoxazolidines have not been readily available through dipolar cycloaddition reactions with alkenes. The notable exceptions are the studies



Scheme 1. THP = tetrahydropyranyl. i, $(CH_2O)_n$, $CHCl_3$, reflux; ii, 60% $HClO_4$, MeOH or EtOH, reflux; iii, aq. Na_2CO_3; iv, *N*-Chlorosuccinimide, CH_2Cl_2.

of Vasella[3] on *N*-glycosylnitrones as chiral 1,3-dipoles and Morita[4] on the reaction of formaldehyde oxime with conjugated alkenes. As a consequence of our interest in natural products containing isoxazolidines, and related heterocycles, we have examined the dipolar reactivity of *N*-tetrahydropyran-2-ylnitrone generated *in situ*. The preliminary results are reported herein as outlined in Scheme 1.

The oxime (**1**) of 5-hydroxypentanal, readily prepared[5] from dihydropyran and hydroxylamine hydrochloride, has been shown[6] to exist in solution (D_2O) predominantly as the acyclic oxime rather than the cyclic tetrahydropyran-2-ylhydroxylamine. However, when a mixture of the oxime, paraformaldehyde, and an alkene (**3a—g**) (in a molar ratio of 1.5 : 2 : 1) was heated at reflux under a nitrogen atmosphere in chloroform, toluene, or tetrahydrofuran for *ca.* 1.5 days, cycloaddition products (**4a—g**) arising from *N*-tetrahydropyran-2-ylnitrone (**2**) were obtained. While we have no direct evidence for the intermediacy of (**2**), the ^1H n.m.r. spectra of the crude cycloadducts showed, in some instances, a low field pair of doublets (*J* 7.5 Hz) centred at δ 6.7 attributable to unreacted nitrone; no attempt has been made to isolate and characterize this compound. The cycloadducts were obtained in satisfactory yields upon purification as indicated in Table 1.

The presence of the tetrahydropyranyl group in the isoxazolidines complicated the n.m.r. spectral analysis of these compounds; however the facile alcoholysis of this group under acidic conditions (1.1 equiv. 60% $HClO_4$, MeOH or EtOH, reflux, 0.5 h) allowed the *N*-unsubstituted isoxazolidines (**5a—g**) to be isolated and purified after neutralization. Unambiguous assignment of the regiochemistry of the nitrone cycloaddition was then possible on the basis of proton–proton coupling; in all cases the 5-substituted isoxazolidine was obtained as indicated in Scheme 1.

The facile oxidation of *N*-unsubstituted isoxazolidines with *N*-chlorosuccinimide[3] (NCS) allows subsequent access to 2-isoxazolines;† for example, treatment of isoxazolidine (**5g**) with NCS in dichloromethane gave (**6**) in 90% yield as a 3 : 2 mixture of diastereoisomers separable upon chromatographic purification. Since 2-isoxazolines are usually prepared by the dipolar cycloaddition of nitrile oxides to alkenes, the procedure herein described offers an alternative to the use of fulminic acid[7] in the preparation of isoxazolines.

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Table 1. Cycloaddition products of *N*-tetrahydropyranylnitrone.

Compound	B.p./°C (0.05 Torr)[a]	% Yield	Compound	B.p./°C (14 Torr)[a]	% Yield
(**4a**)	95—105	89	(**5a**)	80—90	81
(**4b**)	100—110	89	(**5b**)	135—145	75
(**4c**)	95—105	78	(**5c**)	100—110	70
(**4d**)	80—100	59	(**5d**)	105—120	60
(**4e**)	100—105	72	(**5e**)	100—120	83
(**4f**)	90—105	81	(**5f**)	125—135	71
(**4g**)	oil[b]	90	(**5g**)	oil[b]	84

[a] Purified by kugelrohr distillation, oven temperature range given. [b] Purified by column chromatography (silica gel).

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† 4,5-Dihydroisoxazoles (*Pure Appl. Chem.*, 1983, **55**, 409).