A Novel Synthesis of Cyclic Nitrones *via* a Nitrosoketene Intermediate

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Nitrosoketene generated by thermolysis of hydroxyimino Meldrum's acid **1** reacts with various ketones including the chiral ketone (+)-nopinone to produce cyclic nitrones **2–5** as novel 1,3-dipolar molecules.

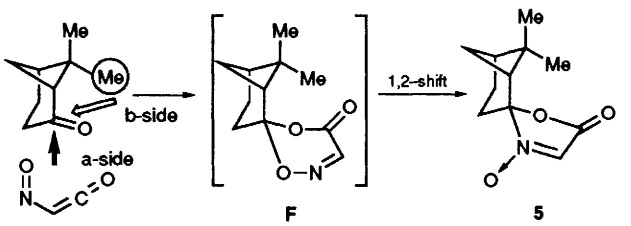
The 1,3-dipolar cycloaddition of nitrones to C–C double bonds is a versatile reaction in organic synthesis because the isoxazolidines thus obtained are important precursors in the synthesis of natural products.[1] Most nitrones have so far been synthesized by the condensation reaction of hydroxylamines with aldehydes or ketones.[2] We now report a novel synthesis of cyclic nitrones including an optically pure nitrone from 5-hydroxyimino-2,2-dimethyl-1,3-dioxane-4,6-dione (isonitroso Meldrum's acid) **1**.[3]

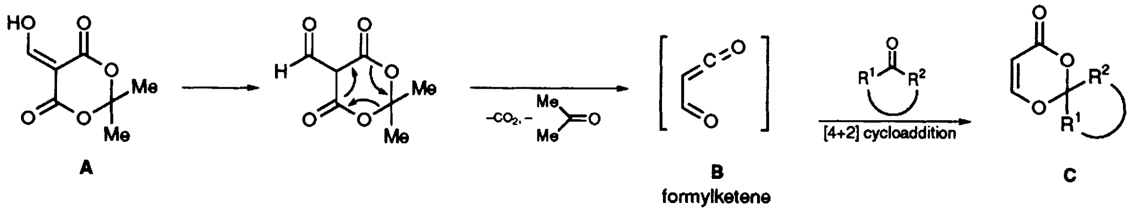
Previously, we reported that formylketene **B** generated by heating hydroxymethylene Meldrum's acid **A** underwent [4 + 2] cycloaddition to ketones to produce the synthetically versatile 1,3-dioxin-4-ones **C**.[4] The use of hydroxyimino Meldrum's acid **1** instead of **A** for this reaction would formally be expected to lead to 1,3,4-dioxazin-6-ones **F** by the [4 + 2] cycloaddition of ketones with nitrosoketene **D**,[5] which would be formed by thermolysis of **1**. In fact, however, the products were the dihydrooxazole 3-oxides **2–5** (cyclic nitrones) instead of **F**.

Heating of **1** with cyclohexanone (4 equiv.) in refluxing toluene for 2 h gave the nitrone in 60% yield as a crystalline substance, mp 87–87 °C. Its IR spectrum showed strong absorptions at 1776 and 1560 cm^{-1} due to the carbonyl and *N*-oxide groups, respectively. Its NMR spectrum showed a signal at δ 7.04 due to –N=C*H*– as well as cyclohexane ring proton signals. The cyclic nitrone structure **2** was assigned to the product on the basis of these data. Similar treatment of **1** with acetophenone gave the nitrone **3** as an oil in 54% yield. However, the same reaction using acetone as the ketone gave only a trace of the nitrone **4**.† While direct [3 + 2] cycloaddition (*e.g.* **E** → **2–4**) cannot be rigorously excluded at present,[6] we propose the mechanism in Scheme 2 for the formation of the nitrones **2–4**, nitrosoketene **D** undergoes [4 + 2] cycloaddition with ketones to yield 1,3,4-dioxazin-6-ones **F**, which are transformed to nitrones **2–4** by 1,2-rearrangement. This mechanism is supported by the facile ring contraction of 5,6-dihydro-1,2-oxazin-4-ones to 4,5-dihydropyrrol-3-one 1-oxides.[7]

The reaction of **1** with the chiral ketone (+)-nopinone produced the chiral nitrone **5**, m.p. 77–78 °C, $[\alpha]_D$ −136.4 (*c* 1.0) as the sole product. Crystallographic results supported the structure shown for compounds **5**.[8] This nitrosoketene **D** approached from the less hindered side (a-side) of (+)-nopinone to form exclusively the nitrone **5** as shown in Scheme 3.

The potential utility of these cyclic nitrones in natural product synthesis is clear, since these nitrones can act as 1,3-dipoles to form isoxazolidines. Wide applicability in asymmetric synthesis also seems possible.





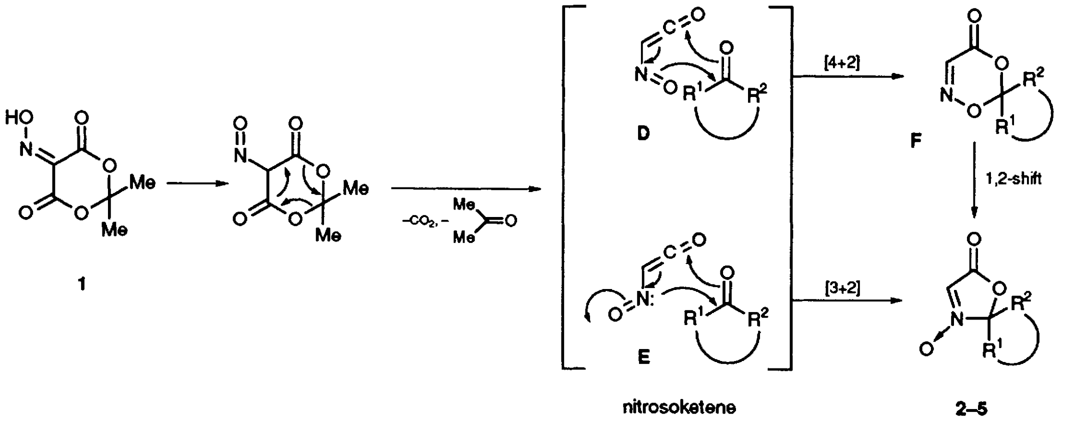
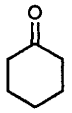
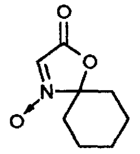
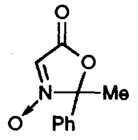
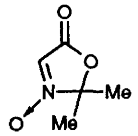
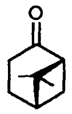
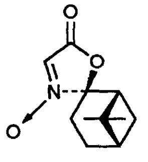


Table 1 Synthesis of nitrones **2**–**5** from **1** and ketones

Ketone	Product	Yield (%)	ν_{max} cm^{-1} (C=O)	(=N→O)	δ (–C$\underline{H}$=N–)
	 **2**	60	1776	1560	7.04
PhCOMe	 **3**	54	1781	1566	7.16
MeCOMe	 **4**	trace	1784	1568	6.96
	 **5**	62	1779	1565	6.98

^{a} In $CHCl_3$. ^{b} ^1H NMR in $CDCl_3$.

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Footnote

† The low yield may well be due to the low boiling point of acetone.

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5 Although numerous papers have dealt with the chemistry of ketene intermediates, to the best of our knowledge, none has mentioned cycloadditions involving nitrosoketene as a reactive intermediate: R. S. Ward, *The Chemistry of Ketenes, Allenes, and Related Compounds*, ed. S. Patai, Wiley, New York, 1980, p. 223.

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8 Details will be reported in a full paper.