

Halogen-induced Formation of Nitrones from Oximes and Alkenes

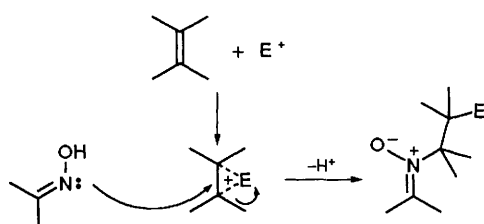
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Oximes possessing γ -, δ -, or ω -alkenyl substituents are cyclised by *N*-bromosuccinimide or iodine to the corresponding cyclic nitrones or their dimeric H-bonded hydriodide salts in good yield; facially specific cycloaddition of these nitrones, and others derived by cyclisation of a δ,δ -bis(alkenyl) ketoxime or addition of acetaldoxime to cyclohexene, furnish isoxazolidines.

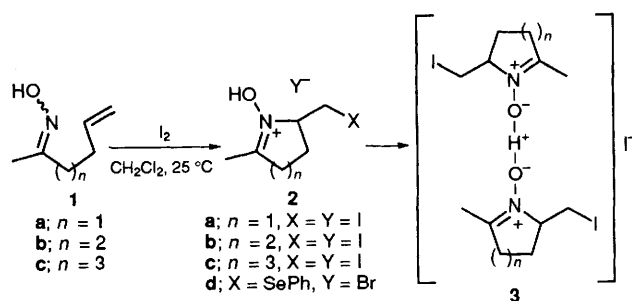
Electrophile induced heteroatom cyclisations onto carbon-carbon π -bonds constitutes a valuable and versatile method for the construction of 3-6 membered rings.¹ We recently proposed a related general inter- and intra-molecular electrophile induced addition of oximes to alkenes (Scheme 1) that has the potential for incorporation into oxime-nitrono-cycloaddition cascades.² The latter cascades, in favourable cases, may be achievable in four tactically distinct synthetic variants (Table 1). Examples employing mercuric acetate² and



Scheme 1

phenylselenenyl bromide³ have already been reported by us. We now report related studies employing *N*-bromosuccinimide (NBS) and iodine as electrophiles.

Oximes react readily with alkenes when treated with either NBS or iodine in methylene chloride at room temperature. Interesting differences arise because the reaction liberates a



Scheme 2

Table 1 Synthetic variants of tandem oxime processes

Class	Nitrone generation	Cycloaddition
I	Intermolecular	Intermolecular
II	Intermolecular	Intramolecular
III	Intramolecular	Intermolecular
IV	Intramolecular	Intramolecular

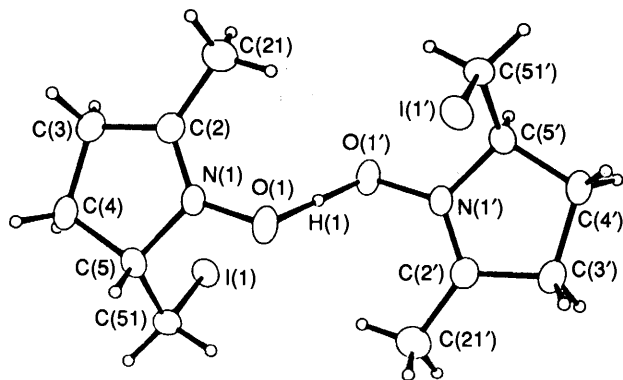


Fig. 1

proton from the oxime hydroxy group which is scavenged as succinimide in the former case but, unless a base is added, results in salt formation in the latter case. Thus, **1a–c** react with iodine (CH_2Cl_2 , 25°C , 2 h) to produce the nitron salts **2a–c** in essentially quantitative yield (Scheme 2).† Work-up without addition of base followed by crystallisation from methylene chloride–hexane affords the linear H-bonded dimeric salts **3a–c**. A crystal structure of **3a** established the structure unequivocally (Fig. 1).‡

The stability of the salts **2** and **3** caused us to re-evaluate our previously reported reactions of alkenyl oximes with phenylselenenyl bromide³ which we had interpreted as proceeding *via* addition of the reagent to the alkene followed by nucleophilic displacement of the bromide by the oximes. The phenylselenenyl bromide–alkene adducts are now reformulated as the analogous nitron salts **2d**.

Oxime **4** is a single stereoisomer and undergoes cyclisation (CH_2Cl_2 , I_2 , 25°C , 6 h) to a 5 : 1 mixture of *cis*- and *trans*-**5** in essentially quantitative yield. After washing with aqueous sodium thiosulfate and reduction (2 equiv. LiAlH_4 , Et_2O , 35°C , 16 h) the major *cis*-isomer **6** was obtained in 50% overall yield from **4**. An analogous sequence on **1a** afforded a 4 : 1 mixture of *cis*- and *trans*-**7a** in 53% yield whilst **1b** affords a

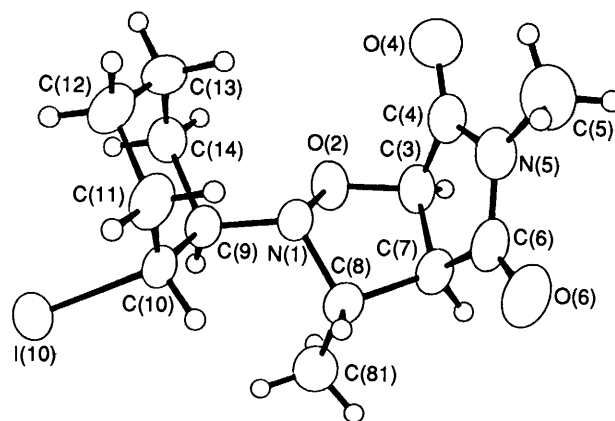
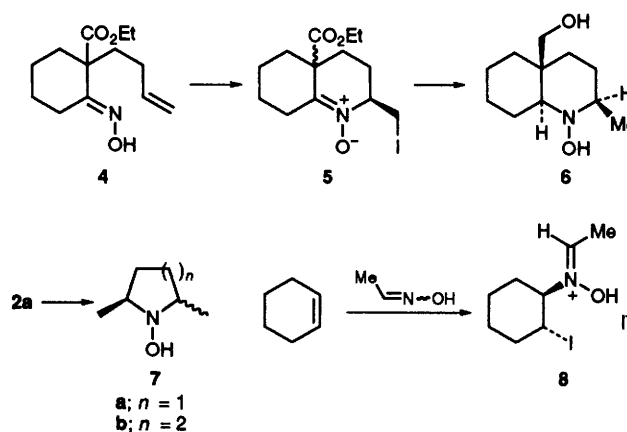
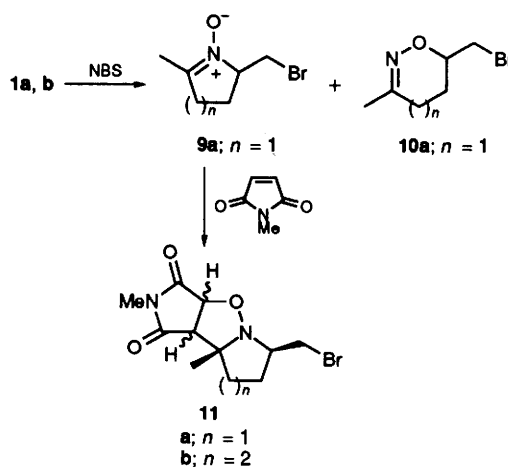


Fig. 2



Scheme 3



Scheme 4

† The oximes **1a, b** are approximately 2 : 1 mixtures of *anti*- and *syn*-isomers but no oxazines are observed in these cases when cyclisation is mediated by iodine.

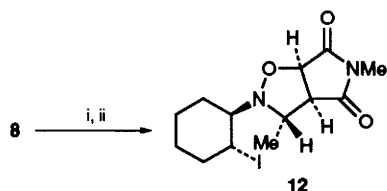
‡ Crystal data for **3a**: $\text{C}_{13}\text{H}_{19}\text{I}_2\text{N}_2\text{O}_3$, $M = 378.20$, orthorhombic, space group $Pbca$, $a = 9.7403(14)$, $b = 13.950(2)$, $c = 21.889(2)$ Å, $U = 2974.2(2)$ Å³, $Z = 8$, $D_x = 1.689$ g cm⁻³, $F(000) = 1504$, $\mu = 2.159$ mm⁻¹, $\lambda = 0.71069$ Å (Mo-K α). Scan mode: ω/θ ; range: $4.0 < 2\theta < 50.0^\circ$; T : 293 K. Crystal dimensions $0.72 \times 0.38 \times 0.20$ mm (pale brown blocks). 2092 observed data [$I \geq 2.0\sigma(I)$] from 5228 were refined to $R_1 = 0.0459$, $\omega R_2 = 0.0876$.

For **12**: $[\text{C}_{12}\text{H}_{21}\text{I}_2\text{N}_2\text{O}_2]^+\text{I}^-$, $M = 606.01$ monoclinic space group $I2/a$, $a = 14.9833(14)$, $b = 11.1692(7)$, $c = 14.9833(8)$ Å, $\beta = 92.700(7)^\circ$, $U 1823.2(2)$ Å³, $Z = 4$, $D_x = 2.208$ g cm⁻³, $F(000) = 1132$, $\mu = 5.038$ mm⁻¹, $\lambda = 0.71069$ Å (Mo-K α). Scan mode: ω/θ ; range: $4.0 < 2\theta < 50.0^\circ$; T : 160 K. Crystal dimensions $0.46 \times 0.30 \times 0.27$ mm (colourless blocks) 1536 observed data [$I \geq 2.0\sigma(I)$] from 3323 were refined to $R_1 = 0.0202$, $\omega R_2 = 0.0436$.

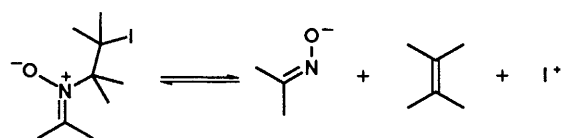
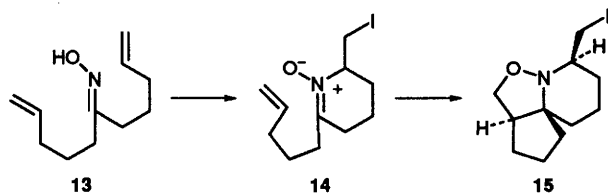
Atomic coordinates, bond lengths and angles, and thermal parameters for both structures have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

3 : 1 mixture of *cis*- and *trans*-**7b** (57%). An intermolecular example is provided by the addition of acetaldehyde oxime to cyclohexane (I_2 , CH_2Cl_2 , 25°C , 5 h) which affords **8** (Scheme 3) as a single stereoisomer but in low yield. In this case the oxime is a 40 : 60 mixture of *syn*- and *anti*-isomers and only the *anti*-isomer undergoes addition.

In contrast to the iodine induced cyclisation the reaction of **1a** with NBS (CH_2Cl_2 , 25°C , 2 h) afforded a 2 : 1 mixture of nitron **9a** and oxazine **10a** which reflected the 2 : 1 ratio of *anti*- and *syn*-oximes in the starting material. Reaction of this product mixture (C_6H_6 , 60°C , 13 h) with *N*-methylmaleimide (NMM) afforded cycloadduct **11a** (78%) Scheme 4 as a 2 : 1 mixture of *endo*- and *exo*-stereoisomers together with **10a**



Scheme 5 Reagents and conditions: i, $\text{Na}_2\text{S}_2\text{O}_3$ (aq); ii, NMM, C_6H_6 , 80°C



Scheme 6

(61%). These isolated yields are based on the *anti/syn*-ratio of the oxime **1a**. Oxime **1b** treated in an analogous manner afforded **11b** (33%) as a 2.3:1 mixture of *endo*- and *exo*-stereoisomers but no oxazine was isolated in this case. Formation of **11a,b** constitute examples of Class III processes (Table 1).

The free base derived from the salt **8** undergoes cycloaddition with NMM (C_6H_6 , 80°C , 1h) to give **12** as a single stereoisomer in 36% overall yield from acetaldoxime.

This is an example of a Class I process (Table 1). The stereochemistry of **12** was established by an X-ray crystal structure determination (Fig. 2).[‡]

A Class IV example is provided by the conversion (I_2 , CH_2Cl_2 , 25°C) of **13** to the nitronium salt in essentially quantitative yield followed by a sodium thiosulfate wash to give **14**, which on heating (C_6H_6 , 80°C , 5 h) afforded **15** (53%).

The disappointing yields of cycloadducts from the iodoneitronium salts are probably due to the tendency of these nitronium salts to fragment by ionic (Scheme 6) or radical pathways.⁴ Therefore, if the iodine induced nitronium formation is to be followed by a cycloaddition step the iodine should be replaced by a more thermally stable atom or group.

Further work on these and related electrophile induced formation of nitronium salts from oximes and alkenes is underway. We thank Roussel, the SERC and Leeds University for support.

Received, 26th May 1993; Com. 3/03021K

References

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- 2 R. Grigg, M. Hadjisoteriou, P. Kennewell, J. Markandu and M. Thornton-Pett, *J. Chem. Soc., Chem. Commun.*, 1992, 1388.
- 3 R. Grigg, M. Hadjisoteriou, P. Kennewell and J. Markandu, *J. Chem. Soc., Chem. Commun.*, 1992, 1537.
- 4 Addition of iodine to alkenes is known to be equilibrium process dependant on alkene structure, solvent and temperature. R. C. Fahey, *Top. Stereochem.*, 1968, 3, 237; P. B. D. de la Mare and R. Bolton, *Electrophilic Additions to Unsaturated Systems*, Elsevier, New York, 2nd edn., 1982; for an up-to-date discussion of the more thoroughly studied addition of bromine to alkenes see M.-F. Ruasse, *Adv. Phys. Org. Chem.*, 1993, 28, 207.