1,3-Azaprotio Cyclotransfer. Nitrone-forming Oxime–Alkyne Cyclisations

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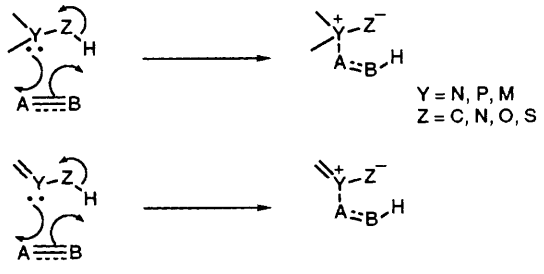
δ-Alkynyl oximes undergo a concerted 2n + 2π + 2σ 1,3-azaprotio cyclotransfer (APT) reaction generating cyclic *N*-vinyl nitrones which have been trapped in cycloaddition reactions; MNDO and AM1 calculations and transition-state modelling provide support for the observed greater facility of oxime–alkyne reactions compared to oxime–alkene reactions.

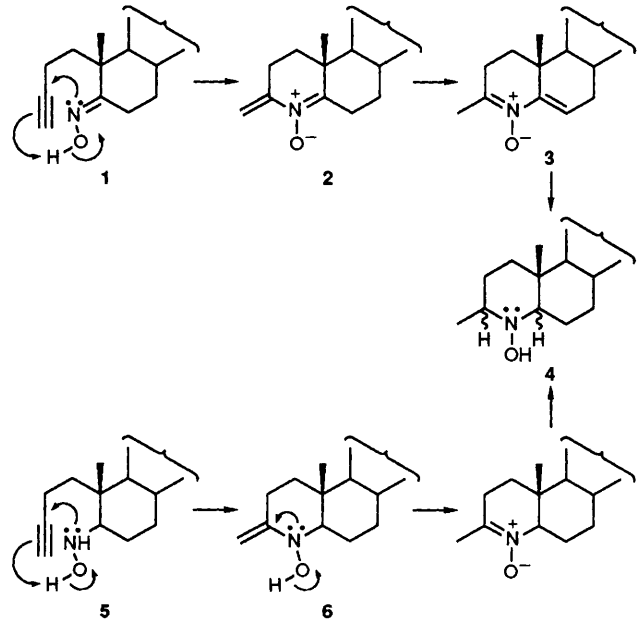
We have recently proposed that the facile and synthetically useful reactions of hydroxylamines and oximes with alkenes be designated 1,3-azaprotio cyclotransfer (APT) reactions (Scheme 1, Y = N, Z = O).[1] These 2n + 2π + 2σ processes can be generalised, as indicated in Scheme 1, and can conceptually encompass other Y and Z atoms including cases where Y is a metal centre capable of undergoing a 2e redox process. The hydroxylamine APT reactions were shown by Ciganek[2] to occur under exceptionally mild conditions and Holmes *et al.* have reported elegant applications of nitrone-forming hydroxylamine–alkyne APT cyclisations,[3] many of which occur at room temperature. Indeed, it was shown that in certain competitive situations cyclisation of the hydroxylamine onto an alkyne occurred in preference to cyclisation onto an alkene.[3] We now report our observation on the related oxime–alkyne reactions.

An intramolecular oxime–alkyne APT reaction was postulated in the borohydride reduction of the secosteroid oxime **1** to a stereoisomeric mixture of the hydroxylamines **4** (Scheme 2).[4] Convincing circumstantial evidence was provided that **4** was formed *via* **1** → **3** and not *via* **5** → **6** although nitrone intermediates were not detected.

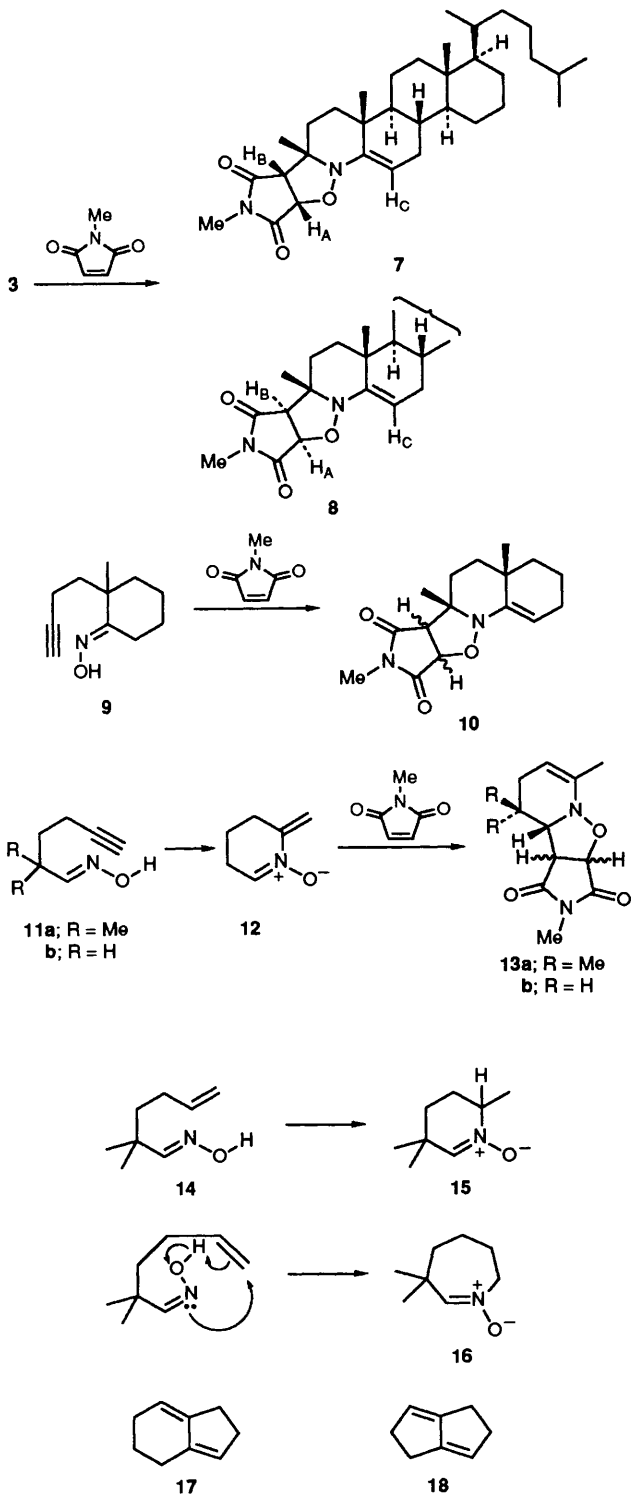
The suggested sequence **1** → **4**, if correct, indicated that intramolecular oxime–alkyne APT reactions might be considerably more facile than the corresponding oxime–alkene reactions.[1] When 4,5-secocholest-3-yn-5-one oxime was allowed to react with *N*-methylmaleimide (NMM) in chloroform at room temperature it afforded a 2 : 1 mixture (68%) of the *endo*-(**7**) and *exo*-(**8**) cycloadducts arising from nitrone **3** (Scheme 2). Product regiochemistry and stereochemistry were assigned on the basis of NMR data and by comparison with other related *endo–exo*-isomer pairs (see below). In particular although the olefinic proton H_C resonates at δ *ca.* 5.35 in both isomers, protons H_A and H_B have characteristically different chemical shifts in the *endo* [δ 4.82(H_A), 3.13(H_B)] and *exo*



Scheme 1



Scheme 2



[δ 5.25(H_A), 3.43(H_B)] isomers. Failure to observe cycloadducts derived from **2** is a result of steric retardation of the cycloaddition step. Oxime **9** reacts in analogous manner with NMM ($CHCl_3$, 25 °C, 48 h) to give cycloadduct **10** (75%) as 2 : 1 mixture of *endo*- and *exo*-isomers whilst **11a** with NMM ($CHCl_3$, 60 °C, 23 h) gave **13a** (84%) as a 1 : 1 mixture of *endo*- and *exo*-cycloadducts. In previous studies of intramolecular APT reactions involving alkenes we demonstrated the importance of *gem*-disubstitution adjacent to the oxime moiety[1] in promoting the process. A similar effect is observed in the oxime–alkyne reactions. Thus, in contrast to **11a**, oxime **11b** does not give **13b** on heating with NMM in boiling chloroform

Table 1 Calculated enthalpies (ΔH/kcal mol^{-1})[a] of APT reactions

	11a → 12a	**14 → 15**	**14 → 16**
MNDO	5.1	15.1	21.7
AM1	−6.0	1.7	4.5

[a] 1 cal = 4.184 J.

Table 2 Calculated enthalpies (ΔH/kcal mol^{-1})[a] of activation for APT reactions

	11a → 12a	**14 → 15**
MNDO	64.8	72.8
AM1	50.8	55.1

[a] 1 cal = 4.184 J.

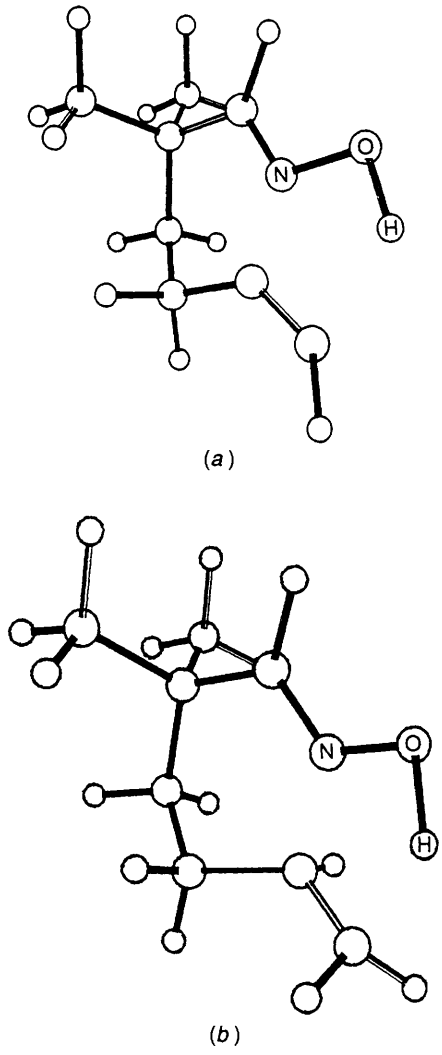


Fig. 1 Calculated transition state geometries (*a*) for **11a** → **12a** and (*b*) for **14** → **15**

for 48 h. The oxime–alkyne reaction **11a** → **12a** occurs under much milder conditions (60 °C) than the corresponding oxime–alkene process **14** → **15** (140 °C). Moreover in the oxime–alkene reaction none of the alternative regioisomeric product **16** is observed. It was of interest to calculate the enthalpies of reaction of these three processes (Table 1) and to attempt to locate their respective transition states using the semiempirical MNDO and AM1 methods. Thus although the absolute enthalpies are unreliable the trend is clear with

formation of **12a** some 8–10 kcal mol^{-1} more exothermic than formation of **15** which, in turn, is 3–6 kcal mol^{-1} more exothermic than formation of **16**.

Transition states were readily located for the concerted APT processes **11a** → **12a** and **14** → **15** (Table 2) but a transition state could not be located for **14** → **16**. Both methods indicate that the activation energy for **11a** → **12a** is lower than that for **14** → **15** by 4–8 kcal mol^{-1}. The calculated transition states are shown in Fig. 1. In both transition states the calculations indicate that the new C–N bond is forming more rapidly than the new C–H bond. Thus in transition state (*a*) the calculated C–N and C–H distances of the two forming bonds are 1.49 and 1.76 Å respectively (AM1) whilst the corresponding distances for **14** → **15** are 1.64 and 1.60 Å. There is noticeable bending of the alkyne moiety in transition state (*a*) and both transition states resemble the 6/5-ring fused system (**17**).

It is clear from the work on the hydroxylamine–alkene (alkyne) APT reaction that 5-membered ring formation occurs readily.[2,3] In contrast, 5-membered ring formation has not been observed in oxime–alkene (alkyne) APT processes. Thus in such oxime–alkene cases, 1,2-prototropy–cycloaddition intervenes.[1] The absence of 5-membered ring formation in oxime–alkyne reactions clearly relates to the higher strain energy of the analogous 5/5-fused ring system (**18**). Thus AM1 and MNDO calculations show **17** to be 14–19 kcal mol^{-1} less strained than **18**.

Further work on these and related processes is underway.[5]

We thank the SERC and ICI Agrochemicals for support.

Received, 14th December 1992; Com. 2/06629G

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