Retro-Cope Eliminations in the Synthesis of 1,2,5-Oxadiazinanes from Allylamines and Nitrones: a Method for the Amination of Unactivated Alkenes

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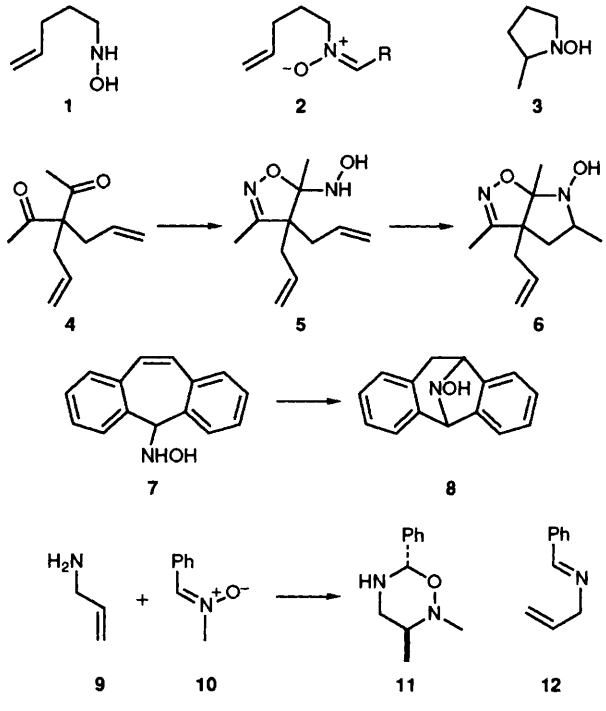
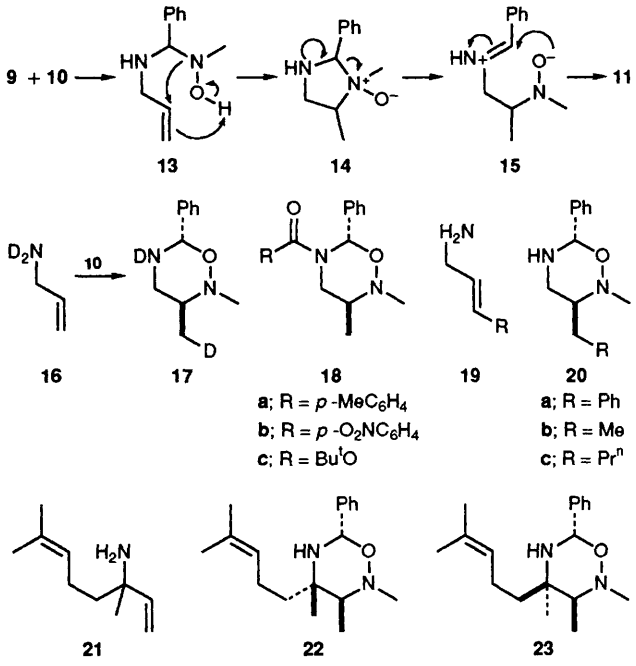
Heating an allylamine (*e.g.* **9**) and a nitrone (*e.g.* **10**) in an inert solvent produces often excellent yields of a 1,2,5-oxadiazinane (*e.g.* **11**) by a pathway which features a retro-Cope elimination and a Meisenheimer rearrangement; reduction of the oxadiazinanes leads to vicinal diamines and hence overall amination of the alkene function in the original allylamine.

A standard route to unsaturated nitrones **2**, useful as substrates for intramolecular [1,3]-dipolar cycloadditions leading to annulated isoxazolidines, consists of condensations between the corresponding hydroxylamines **1** and an aldehyde. Some time ago, it was observed that such hydroxylamines were unstable to storage, undergoing cyclisation to the cyclic system **3**, apparently *via* a retro-Cope elimination.[1] Just prior to this, it was reported that attempts to prepare a bis-oxime of the dione **4** lead instead to the heterocycle **6**, presumably *via* an intermediate hydroxylamine **5**, and again a retro-Cope elimination.[2a] Applications of the latter to simpler unsaturated hydroxylamines have resulted in novel approaches to alkyl-pyrrolidines and piperidines.[2b,3] The only other area where retro-Cope chemistry has been exploited in synthesis is in the elaboration of the dibenzoazabicyclic systems **8** from the corresponding hydroxylamines **7**.[4]

One approach to the unsaturated hydroxylamines (*cf.* **1**) required for this reaction consists of addition of appropriate alkenyl Grignard reagent to a nitrone.[3] We have recently been examining some aspects of the [1.3]-dipolar cycloaddition chemistry of selected nitrones with masked allylamine derivatives[5] and were intrigued by the prospect of triggering retro-Cope eliminations by the nucleophilic addition of an allylamine to a nitrone. Herein, we report our preliminary results in this area, together with some mechanistic and synthetic implications of the sequence.

We have discovered that when a solution of equivalent amounts of allylamine **9** and nitrone **10** was left in chloroform at ambient temperature for seven days, the reactants were completely transformed into a single product **11** containing no more than a trace of impurity (*vide infra*). The same product could be obtained more rapidly by keeping the solution at 45 °C for 36 h (100%) or by using toluene as the solvent (110 °C, 17 h). Under these conditions, the yield of the new product was 80%, accompanied by 20% of the imine **12**. The identity of the 1,2,5-oxadiazinane **11** was established mainly by ^{1}H and ^{13}C NMR data, together with a variety of subsequent transformations (*vide infra*).[6] The stereochemistry was determined by difference nuclear Overhauser effect (NOE) experiments, which indicated that the ring system adopts a chair-like conformation in solution at ambient tempertures. A possible mechanism consists of an initial nucleophilic attack by the amine onto the nitrone function,



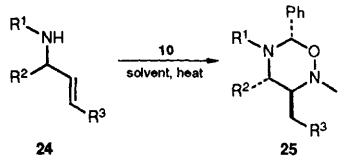


leading to an intermediate amino-hydroxylamine **13**, following proton transfer. This could then undergo a retro-Cope elimination as indicated to give the *N*-oxide **14**. The leaving ability of the latter function, coupled with the nucleophilicity of the amine group, would then result in an overall Meisenheimer rearrangement,[7] *via* the *N*-oxide **15**, to give the observed product **11**. Although it was originally speculated that the retro-Cope reaction involved radical intermediates,[2a] more recent observations suggest that it is best regarded as a purely pericyclic process.[3,8,9] It is more likely that the Meisenheimer rearrangement is at least partly radical in nature; the ionic pathway shown may be an over simplification.[7] Some evidence in favour of the mechanism is that the *N*-deuteriated allylamine **16** was smoothly transformed into the *C*-deuteriated product **17** in essentially quantitative yield when reacted with the nitrone **10** in deuteriochloroform (20 °C, 120 h). Presumably, the imine **12** is formed by exchange between the allylamine **9** and hydroxylamine as an alternative pathway following the initial nucleophilic attack by the amine. Very recently, a related cyclisation of an acetylenic hydroxylamine, leading to a cyclic nitrone, has been reported[10] as well as cyclisations of unsaturated oximes, which also result in the formation of cyclic nitrones, apparently by a similar mechanism.[11] It has been proposed that all such 'retro-Cope' processes should be referred to as '1,3-azaprotio cyclotransfer reactions'.[11]

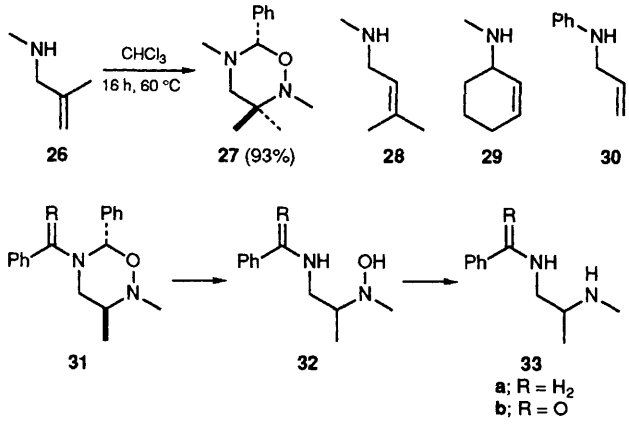
The initial adduct **11** was relatively sensitive to chromatographic purification but could be derivatized by *N*-acylation [Hunig's base, CH_2Cl_2, 0–20 °C, slowly add ArCOCl or $(Boc)_2O$, (Boc = *tert*-butoxycarbonyl)] to give the more stable derivatives **18** in 65–70% isolated yields. The structure of the nitrobenzoyl derivative **18b** was confirmed by X-ray crystallographic analysis, details of which will be reported elsewhere.†

Attempts to extend this type of chemistry to more highly substituted examples were only partly successful as the exchange reaction leading to imines related to **12** became the dominant pathway. For example, reaction between (*E*)-cinnamylamine **19a** and the nitrone **10** in refluxing toluene for 72 h led to a 1:1 mixture (82% combined yield) of the oxadiazinane **20a** and the imine. However, the two alkyl-

Table 1 Reactions between nitrone **10** and *N*-substituted allylamines



Allylamine **24**	Solvent	*t*/h	*T*/°C	Yield **25** (%)
a R^1 = Me, R^2 = R^3 = H	$CHCl_3$	20	60	95
b R^1 = Allyl, R^2 = R^3 = H	$CHCl_3$	72	60	100
c R^1 = Benzyl, R^2 = R^3 = H	$CHCl_3$	48	60	95
d R^1 = Me, R^2 = H, R^3 = Ph	Toluene	48	110	65
e R^1 = Benzyl, R^2 = H, R^3 = Ph	$CHCl_3$	120	110 (sealed tube)	12
f R^1 = Me, R^2 = H, R^3 = Pr^n	Toluene	21	110	45
g R^1 = Me, R^2 = H, R^3 = Me	Benzene	120	80	95
h R^1 = R^2 = Me, R^3 = H	Benzene	20	80	93
i R^1 = Bu^n, R^2 = Ph, R^3 = H	Toluene	17	110	89



substituted allylic amines **19b,c** both gave essentially only imines under the same conditions. By contrast, the more hindered linalylamine **21**[12] reacted slowly with nitrone **10** (toluene, reflux, 170 h) to give the two diastereoisomeric oxadiazinanes **22** and **23** (3:1) in 70% combined yield, together with *ca.* 9% of the corresponding imine.‡ The use of more hindered phenyl nitrones, including the *N*-benzyl and *N*-*tert*-butyl analogues, resulted in slower reaction rates and more or exclusive imine formation.

In order to prevent competing imine formation, we examined similar reactions of the corresponding secondary allylic amines **24** from which imine formation is not possible. We were pleased to find that 1,2,5-oxadiazinanes **25** were formed in often excellent yields and that in no examples so far studied have any more than traces of products arising from [1.3]-dipolar cycloadditions been observed. The results are collected in Table 1. Both *N*-allyl and *N*-benzyl substituents in the allylamine tend to slow the reaction rate as do substituents at the distal end of the allylamine. Alone, these do not prevent the eventual realization of excellent yields but, in combination, lead to much reduced returns (**25e**). All the reactions were essentially stereospecific;‡ the proton NMR spectra of the 'trisubstituted' oxadiazinanes **25h** and **25i** indicated that all three groups (*i.e.* Ph, R^2 and R^3CH_2) occupied equatorial

† We are grateful to Dr M. J. Begley (University of Nottingham) for these data.

‡ The stereochemistries were determined by proton coupling constant measurements and NOE experiments.

positions in a well-behaved chair conformation in deuteriochloroform at ambient temperature.[6] Although we have not conducted a comprehensive survey of solvents, at present chloroform and toluene appear to be the best.[3] We were somewhat surprised to find that the more sterically congested methylamine **26** also reacted smoothly with nitrone **10** under relatively mild conditions to give an excellent yield of the oxadiazinane **27**. However, similar reactions failed or gave no more than traces of products when attempted using the prenyl amine **28**, the cyclohexenylamine **29** and *N*-allylaniline **30**. Steric hindrance and/or rigidity may explain the first two observations while reduced nucleophilicity may be responsible for the failure of the aniline **30** to react.

Finally, we have briefly examined some methods for ring opening of the oxadiazinanes. As expected, both the initial products (*e.g.* **31a**) and the corresponding *N*-aroyl derivatives (*e.g.* **31b**) are rather acid sensitive. For example, brief exposure to 2 mol dm^{-3} HCl leads to excellent (~ 95%) yields of the amino-hydroxylamines **32** which, in turn, can be efficiently reduced to the diamine derivatives **33** using zinc in 2 mol dm^{-3} HCl (80 °C, 1 h; >90%). Direct treatment of the oxadiazinanes **31** with zinc and 2 mol dm^{-3} HCl also leads smoothly to the diamines **33**.

Overall, therefore, these model reactions indicate that this procedure can be regarded as a method for the amination of unactivated alkene functions in allylamines, leading to vicinal diamines wherein the two amine groups can be differently substituted. Further studies are in progress.

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