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Factors Influencing the Reverse-Cope Approach to 1,2,5-Oxadiazinanes from Allylamines and Nitrones : Optimization of a New Vicinal Diamine Synthesis

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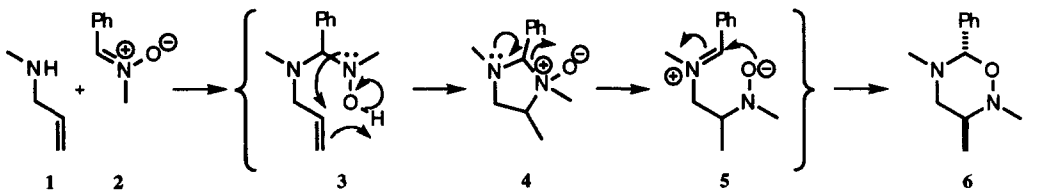
Abstract:- *Nitrones generated from formaldehyde and N-alkyl-hydroxylamines are particularly suitable reactants in tandem reverse-Cope~Meisenheimer reactions leading to oxadiazinanes and thence N-hydroxydiamines and vicinal diamines, from allylamines.*

We have recently reported[1] that reaction between *N*-methylallylamine **1** and the nitrone **2** leads to the oxadiazinane **6** by a sequence which appears to involve sequential nucleophilic attack by the amine to generate the hydroxylamine **3** and a reverse-Cope elimination;[2] subsequent Meisenheimer rearrangement[3] of the resulting *N*-oxide **4** *via* the iminium species **5** to give the final product **6**, in essentially quantitative yield as a single *trans* diastereoisomer (Scheme 1). In synthetic terms, one significance of this sequence is that it results in overall amination of an "unactivated" alkene; hydrolysis of the oxadiazinanes leads to the corresponding *N*-hydroxydiamines while reduction leads to vicinal diamines.

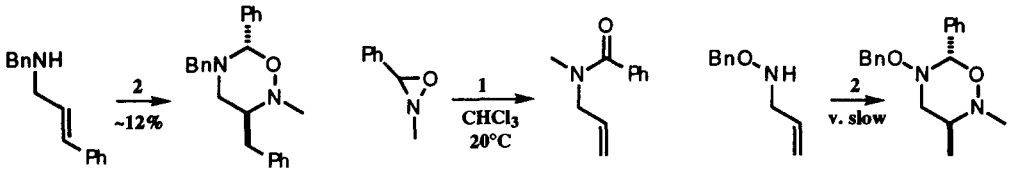


Scheme 1

We were interested in extending this sequence to include more highly substituted examples and ones incorporating more readily removable amino groups, such as benzyl. Unfortunately, a serious limitation of the reverse-Cope elimination[2] is retardation by additional substituents on the alkene; further, we have found that *N*-benzyl analogues of both reactants **1** and **2** react more slowly. Taken together, these were obstacles to such extensions; in this paper, we outline some solutions to these. This retardation by additional substituents is illustrated by the conversion of *N*-benzyl-cinnamylamine **7** into the oxadiazinane **8** using *C*-phenyl nitrone **2**: after thermolysis at 110°C in chloroform (sealed tube), a 12% yield was realized. In contrast, the sequence shown in Scheme 1 leads to a quantitative yield of oxadiazinane **6** after heating in the same solvent at 60°C for 15h; at ambient temperature, a similar yield can be recovered after five days.

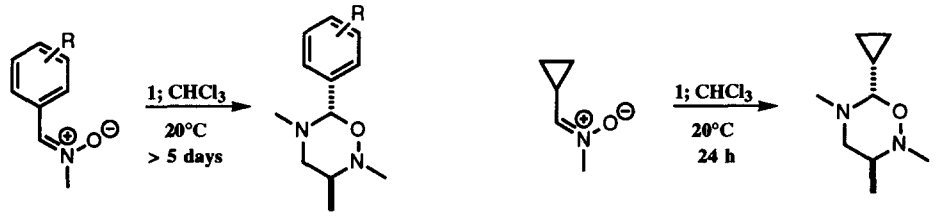
No evidence for the existence of any of the proposed intermediates was obtained when the process was

followed by ^{1}H NMR spectroscopy. However, it seems reasonable that the scheme is triggered by nucleophilic attack by the amine and the Oppolzer group has provided excellent evidence that the central reverse-Cope reaction



7 8 9 10 11 12

is a concerted process.[2] One doubt was that an oxaziridine, not a nitrone, was an initial reactant.[4] We therefore reacted oxaziridine **9**[5] with *N*-methylallylamine **1** in chloroform; after 10 days at 20°C, the only product isolated was *N*-allylamide **10**, formed by an oxaziridine to amide rearrangement[6] to give *N*-methylbenzamide and transamination with amine **1**. Given the nitrone is the electrophile in the first step (Scheme 1), a more nucleophilic allylamine should react faster; the *N*-benzyloxy derivative **11**[7] appeared suitable. However, under comparable conditions ($CHCl_3$, 20°C), this reacted three times *slower* than the *N*-methylamine **1** but still gave a quantitative return of the expected oxadiazinane **12**. Further mechanistic considerations led us to examine the behaviour of nitrones **13** derived from substituted benzaldehydes. Unexpectedly, these all reacted at similar (R = *p*-alkyl, *m*-halo) or *slower* rates than the parent nitrone **2**. Two electronically extreme examples (R = *p*-NMe_2 or NO_2) reacted the slowest of all! Perhaps the former retards the initial nucleophilic attack while the latter destabilizes the intermediate **5** and hence adversely affects the Meisenheimer rearrangement, given that these are rate-determining steps. Alternatively, both types of substituent could adversely affect the central reverse-Cope process by donation or withdrawal through the sigma framework of the intermediate hydroxylamines (*cf* **3**).

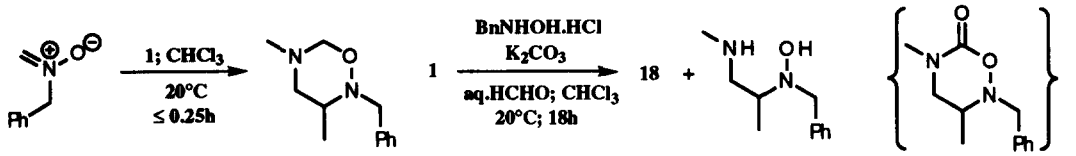


13 14 15 16

We therefore turned to other nitrones and were pleased to find that *C*-cyclopropyl nitrone **15**[8] reacted at 20°C during 24h in $CHCl_3$ with amine **1** to give the oxadiazinane **16** in >95% yield. Unfortunately, this greater reactivity was insufficient to overcome the lower reactivity of substituted allylamines at ambient temperature; no reaction was observed between nitrone **15** and *N*-benzyl-cinnamylamine **7** at 20°C in $CHCl_3$ (an optimum solvent for this type of chemistry[2]); heating led to extensive decomposition. We reasoned that there could be an advantage in having no *C*-substituent and thus reacted nitrone **17**[9] with *N*-methylallylamine **1** and were delighted to find that reaction was complete in less than 0.25h at 20°C and gave only the oxadiazinane **18** with >95% purity. The absence of *C*-substitution is thus sufficient to largely overcome the rate retarding effect of the *N*-benzyl substituent. As nitrone **17** is rather unstable, it occurred to us that its isolation might not be necessary. Thus, we found that stirring a mixture of amine **1** with equivalents of benzylhydroxylamine hydrochloride, potassium carbonate and 37% formalin for 18h at 20°C gave the oxadiazine **18** along with amino-hydroxylamine **19** in >95% combined yield in a ratio of 1.3:1. The latter was presumably formed by interception of the iminium intermediate [*cf* **5**, Scheme 1] by water and was characterized as the corresponding oxadiazinanone **20**.

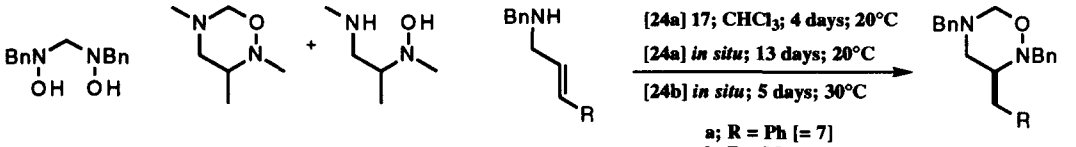
A minor impurity using this method was the aminal **21**.[10] As expected, a similar reaction using *N*-methylhydroxylamine gave the related products **22** and **23**. Thus, although more convenient, the *in situ* method

proceeded at a significantly slower rate than when using the isolated nitrone **17**. The was also true when *N*-benzylcinnamyl- and crotylamines **24** were used as substrates. In the former case, the reaction was complete in



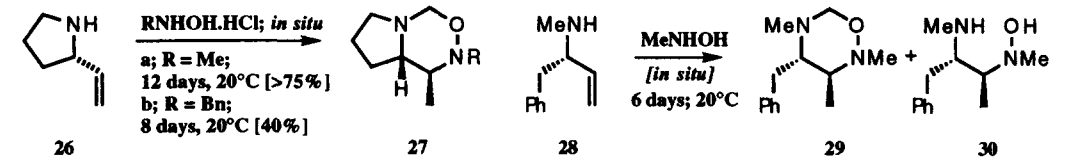
17 **18** **19** **20**

4 days with isolated nitrone **17** and gave the oxadiazine **25a** in 86% yield, but took 13 days to reach completion (yield >95%) using the *in situ* method; the crotyl analogue reacted somewhat more rapidly. In these two examples, only traces of the corresponding amino-hydroxylamines were formed. The benefit of enhanced rates when the mixtures were heated was offset by the resulting generation of a number of byproducts. The formation of excellent yields (>90%) of the oxadiazinanes **25** was in direct contrast to the forgoing examples using *C*-substituted nitrones [*eg* **7** to **8**] and indicates that this is a method with some considerable generality.

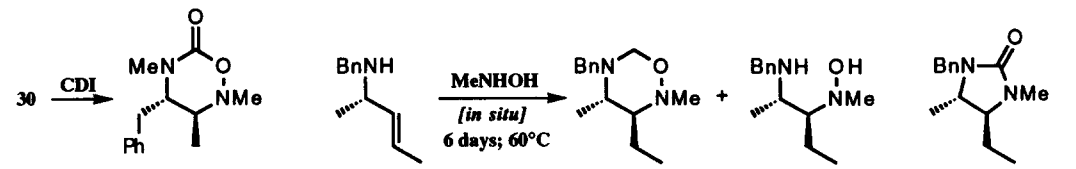


21 **22** **23** **24** **25**

More highly substituted allylamines can also be used in the *in situ* method. The vinylpyrrolidine **26**, derived from (*S*)-proline, gave single annulated oxadiazinanes **27** when reacted with *N*-methyl or *N*-benzyl-hydroxylamine, the latter, as expected, proceeding more slowly. Similarly, the benzyl-substituted allylamine **28** derived from (*S*)-phenylalanine, reacted slowly but smoothly under the *in situ* conditions using two equivalents



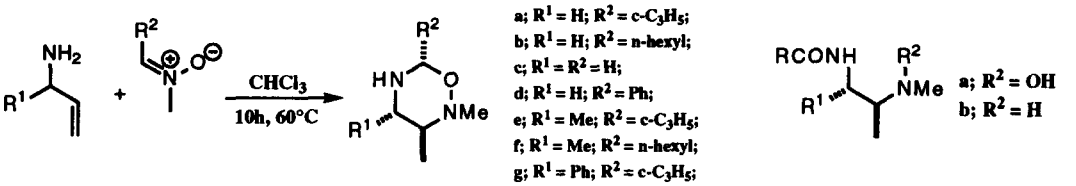
26 **27** **28** **29** **30**



31 **32** **33** **34** **35**

of the hydroxylamine to give a 1:1 mixture of oxadiazinane **29** and amino-hydroxylamine **30**, both as single *trans* enantiomers, in a combined yield of 90% relative to allylamine **28**; again, the latter was characterized as the corresponding oxadiazinanone **31**. The more substituted crotylamine **32** required heating at 60°C to achieve an efficient conversion (90%) to a 1.7:1 mixture of the oxadiazinane **33** and the amino-hydroxylamine **34**, again both as single *trans* diastereoisomers. Presumably, the *N*-benzyl group, in combination with the disubstituted alkene, combine to slow the overall reaction. In this example, the products were not separated but reduced to the related vicinal diamine using $NiCl_2$-$NaBH_4$,[11] which was characterized as a single imidazolidinone **35**.

In our original work,[1] we found that the overall scheme was only successful with primary allylamines in the case of allylamine [**36**; R^1 = H] itself; the incorporation of substituents on the double bond resulted instead in an exchange reaction with the *C*-phenylnitrone used to give the corresponding imine. Unfortunately, this also proved to be the case with both *C*-alkyl and formaldehyde-derived nitrones **37**. However, reactions between these nitrones and the primary allylamines **36** were clean and rapid in chloroform at 60°C and led to excellent yields (80-100%) of the oxadiazinanes **38**. These were also characterized as the corresponding *N*-acyl derivatives as well as the *N*-acylamino-hydroxylamines **39a**, formed by brief treatment of the former with 2M HCl and as the monoacyl diamines **39b**, obtained by reducing the acylated oxadiazines with $TiCl_3$. In all cases, only the *trans*-oxadiazines were isolated. Attempts to effect asymmetric induction by using α-methylbenzyl derivatives of either the allylamine or the nitrone were not successful.



36 **37** **38** **39**

These reactions should find use for the preparation of a range of oxadiazines, vicinal aminohydroxylamines and diamines with, if required, differential protection; the latter are of particular interest as chiral ligands.

Acknowledgements

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