



Diastereoselective synthesis of *cis*-2,5-disubstituted pyrrolidine *N*-oxides by the retro-Cope elimination

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Abstract—Nitrones were reacted with 3-butenylmagnesium bromide to give alkenylhydroxylamines that were cyclised by retro-Cope elimination. Heating the diastereomeric mixtures of pyrrolidine *N*-oxides in the absence of solvent affected a highly diastereoselective isomerisation to provide the *cis*-2,5-disubstituted products in excellent yield. © 2000 Elsevier Science Ltd. All rights reserved.

Since its independent discovery by House¹ and Oppolzer² in the 1970s, the thermal cyclisation of alkenylhydroxylamines has been known as a method to prepare pyrrolidine and piperidine *N*-oxides from acyclic precursors. Initially postulated to proceed by a radical mechanism, it was only within the last decade that the reaction's true relationship to the Cope elimination³ was established.^{4,5} The retro-Cope elimination is a concerted and reversible process, involving the suprafacial addition of a hydroxylamine across a carbon–carbon double bond. However, in spite of understanding the mechanism of reaction, there have only been a few applications of this methodology in the synthesis of nitrogen-containing heterocycles.⁶

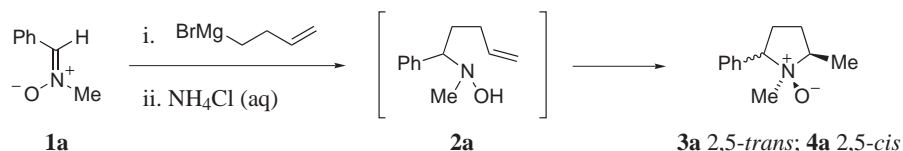
As part of our interest in the preparation of pyrrolidine-based alkaloids and in order to develop an asymmetric variant of this process, we embarked upon reviewing the use of the retro-Cope elimination for the stereoselective synthesis of 2,5-disubstituted pyrrolidine *N*-oxides. Although there have been a few relevant examples of alkenylhydroxylamine cyclisation that proceeded with good diastereocontrol at ambient tempera-

ture,^{5b,6h} it has been found that, in general, for simple systems the diastereoselectivity of this reaction is quite poor.⁵ Ciganek illustrated the limitations of this process by reacting 3-butenylmagnesium bromide with *Z*-nitron **1a**, the hydroxylamine intermediate **2a** cyclising spontaneously under the reaction conditions to yield a mixture of *trans*-**3a** and *cis*-2,5-disubstituted pyrrolidine *N*-oxide **4a/3a** in a 3:2 ratio (Scheme 1).^{5a}

Table 1. Isomerisation of pyrrolidine *N*-oxides **3a** and **4a** at elevated temperatures

Entry	Solvent	Time (day)	D.r. ^a
1	Ethanol	1	72:28
2	Chloroform	1	57:43
3	Chloroform	2	86:14
4	Chloroform	4	93:7
5	Toluene	1	93:7
6	95°C, none	0.06	98:2

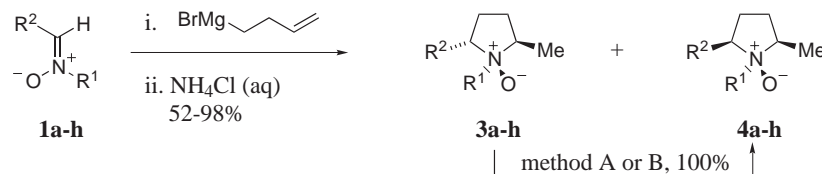
^a Refers to the ratio of *cis*/*trans*-2,5-disubstituted products as determined by 400 MHz ¹H NMR assay.



Scheme 1.

Keywords: Cope elimination; cyclisation; diastereoselection; nitrones; *N*-oxides; pyrrolidines.

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Scheme 2. Method A, CHCl_3 , Δ , 1 day; method B, 95°C , 15–90 min.

Since the diastereoselectivity of this process is critical for application to the synthesis of pyrrolidine-based natural products, we decided to develop a general method to improve the stereoselectivity of this transformation that took advantage of the reversibility of the retro-Cope elimination. It was postulated that should the reaction be operating under conditions of thermodynamic control then the diastereoselectivity of this process would favour the formation of the more stable *cis*-2,5-disubstituted pyrrolidine *N*-oxide products. O'Neil and Jäger have already shown that the solvent employed for the retro-Cope elimination has a marked effect upon the diastereoselectivity of reaction.^{6m-o} Prompted by this result, we now wish to report that the highly diastereoselective formation of functionalised pyrrolidine *N*-oxides may be achieved by the use of elevated temperatures.

Using Ciganek's study as a starting point, 3-butenylmagnesium bromide was added to a solution of nitrone **1a** in ether at room temperature to give an inseparable mixture of pyrrolidine *N*-oxide **3a** and **4a** in the same ratio as reported in the original paper.^{5a} Taking a solution of this crude reaction product and submitting it to conditions that promote the retro-Cope elimination, namely heating at reflux for a number of days in a range of different solvents, favoured the formation of *cis*-2,5-disubstituted pyrrolidine *N*-oxide **4a** (Table 1). The highest diastereoselectivity was observed when heating in toluene at reflux for 1 day to provide the *cis*-2,5-disubstituted product **4a** in a diastereomeric ratio of 93:7 (although significant decomposition accompanied cyclisation). The most promising and reproducible results were obtained in chloroform until,

in a fortuitous experiment, the solution was allowed to boil dry by accident. It was observed that heating the crude reaction mixture to 95°C for 1.5 h optimised the diastereoselectivity of reaction, generating *N*-oxide **4a**/**3a** in 98:2 d.r. and excellent yield without any need for further purification. This procedure is remarkable as it has been reported that heating *N*-oxides in the absence of solvent promotes the Cope elimination process, and yet it is our finding that this is a highly efficient method for the diastereoselective formation of functionalised pyrrolidine *N*-oxides.

Following this observation the scope and limitations of this new method were investigated. 3-Butenylmagnesium bromide was added to a range of nitrones **1a–h**, prepared by condensing *N*-alkylhydroxylamine with the corresponding aldehyde, to give mixtures of *trans*- and *cis*-pyrrolidine *N*-oxides, **3a–h** and **4a–h**, respectively (Scheme 2). The isomerisation of each of these mixtures was studied using our new methodology, namely heating at reflux in chloroform or heating to 95°C for up to 90 min in the absence of solvent (Table 2). Reactions conducted in toluene routinely gave complex mixtures of products, whereas the use of chloroform as a solvent (method A) was only successful for the synthesis of **4b**/**3b** and **4c**/**3c** in 83:17 and 94:6 d.r., respectively. Of the procedures studied, the direct application of heat (method B) was the superior method, preparing **4a–h**/**3a–h** in up to >98:2 d.r. Where possible, the *cis*-2,5-disubstituted products **4a–h** were identified by NOE experiments, observing an enhancement of the signal arising from H-2 or H-5 (and from protons in substituent R^1) upon irradiation of the other α -proton. It was evident from the tabulated data that, in general, as

Table 2. The isomerisation of pyrrolidine *N*-oxides **3a–h** and **4a–h** at elevated temperatures

Nitrone	R^1	R^2	D.r. before heating ^a	Method A d.r. ^a	Method B d.r. ^a	Yield %
1a	Me	Ph	40:60	57:43	98:2	96
1b	Me	Me	58:42	83:17	96:4	52
1c	Me	Et	50:50	94:6	94:6	94 ^d
1d	Me	<i>i</i> -Pr	67:33	^b	96:4	62 ^c
1e	Me	<i>t</i> -Bu	94:6	^c	96:4	73
1f	Bn	Ph	75:25	^c	83:17	95
1g	Ph	Ph	93:7	^b	95:5	98 ^d
1h	Cyclohexyl	Ph	>98:2	^c	>98:2	71 ^c

^a Refers to the ratio of *cis*/*trans*-2,5-disubstituted products as determined by 400 MHz ^1H NMR assay.

^b Significant decomposition prevented calculation of d.r.

^c No 2,5-disubstituted pyrrolidine *N*-oxides were detected.

^d Some decomposition occurred on heating.

^e Heat was required to produce fully cyclised material.

the steric bulk of substituents R¹ and R² increased the diastereoselectivity of the initial cyclisation at ambient temperature improved, such that *N*-oxide **4h** was formed as a single diastereoisomer according to 400 MHz ¹H NMR spectroscopic analysis.

For many of the cases studied when substituents R¹ and R² were relatively small, the use of elevated temperatures, either in solution or in the absence of solvent, must promote the formation of the thermodynamic product in a reversible cyclisation. This finding has enabled a variety of *cis*-2,5-disubstituted pyrrolidine *N*-oxides **4a–h** to be prepared in good yield and with excellent diastereocontrol, in a reliable process that can now tolerate a wide range of different substituents. This represents the first report of heat alone promoting the retro-Cope elimination and the first example of a pyrrolidine *N*-oxide diastereomeric ratio being changed by the use of elevated temperatures. Studies are now underway to develop an asymmetric variant of this process and apply this new methodology to the synthesis of a range of pyrrolidine based natural products.

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