Pergamon

Tetrahedron Letters, Vol. 38, No. 49, pp. 8553-8556, 1997
© 1997 Elsevier Science Ltd
All rights reserved. Printed in Great Britain
0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10245-3

A New, Stereoselective Approach to Pyrrolidine-*N*-Oxides by Sequential Condensation of Sulfones with Nitrones and Reverse-Cope Elimination

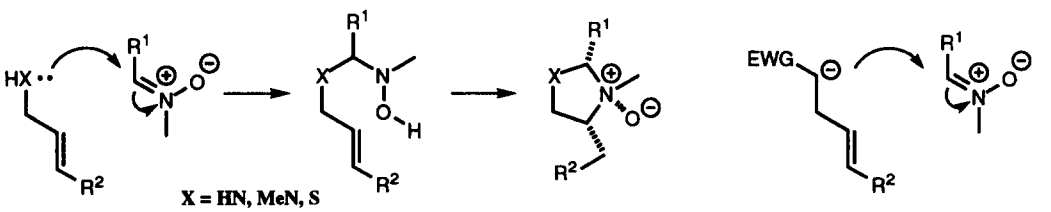
Andrew R. Wheildon,[a] David W. Knight*,[b] and Mathew P. Leese[b]

[a]Department of Chemistry, University Park, Nottingham, NG7 2RD, UK

[b]Department of Chemistry, Cardiff University, P.O. Box 912, Cardiff, CF1 3TB, UK

Abstract:- *Lithiosulfones **10** condense smoothly and highly stereoselectively with nitrones **11** to give unsaturated hydroxylamines **12** which undergo reverse-Cope cyclisations at varying rates leading to pyrrolidine-N-oxides **13** and **14** ; the former isomerized slowly to diastereoisomers **20**.* © 1997 Elsevier Science Ltd.

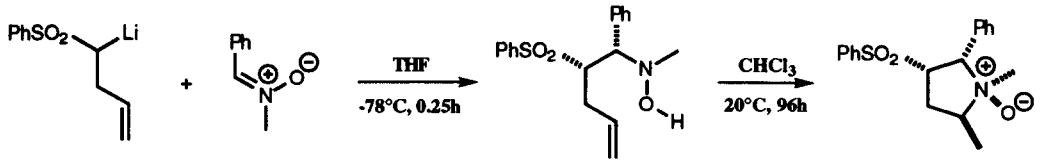
In the two foregoing papers,[1] we have outlined the reverse-Cope chemistry of hydroxylamines **3**, generated by nucleophilic addition of the heteroallylic precursors **1** to nitrones **2**, which leads to the *N*-oxides **4** and subsequent products, depending on the nature of the heteroatom X. These examples are related to a general method for the elaboration of unsaturated hydroxylamines which involves the addition of homoallylic Grignard reagents to nitrones.[2] This method forms the basis of Ciganek's seminal studies of the reverse-Cope elimination leading to a variety of pyrrolidine systems.[3] We reasoned that there might be considerable scope for the expansion of this methodology to include many other examples of stabilized homoallylic carbanions **5**; clearly, a potential attraction of this idea is that a wide range of homochiral systems could be suited to this chemistry.



1 **2** **3** **4** **5** **2**

It is perhaps surprising that such chemistry has been relatively little developed.[4] Our initial efforts focussed on a range of carboxylic acid derivatives as the electron withdrawing group [EWG in **5**] but met with little success. We subsequently found that lithiated sulfones add smoothly and rapidly to a range of nitrones to provide the hoped for unsaturated hydroxylamines[5] which subsequently cyclized in a reverse-Cope fashion.

Herein, we outline these results and give a preliminary account of this overall sequence as a stereoselective approach to pyrrolidine-*N*-oxides.



6 7 8 9

Scheme 1

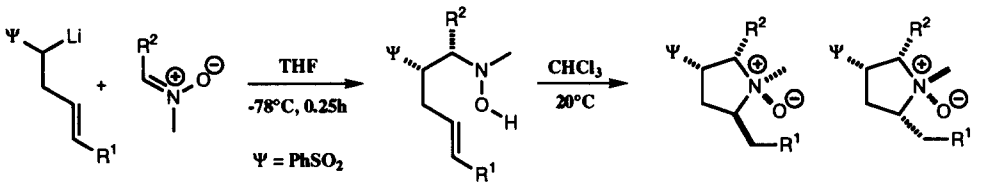
The lithiosulfone **6** was formed in THF at -78°C by treatment with BuLi and condensed rapidly and cleanly with the benzaldehyde nitrone **7** to provide an excellent yield of the hoped-for adduct **8** (Table; entry 1), somewhat to our surprise essentially as a single diastereoisomer. During characterization of this hydroxylamine, it slowly underwent the desired reverse-Cope cyclisation; this was best carried out at ambient temperature in chloroform to give an 88:12 mixture of the two pyrrolidine-*N*-oxides **13** and **14** (Entry 1) in essentially quantitative yield after 96h; the stereochemistry of these products was established largely by nOe measurements. The choice of solvent was important:[3] cyclisation was slower in toluene, was less stereoselective and less clean in DMSO or acetone and decomposition occurred in methanol, acetonitrile and ethyl acetate.

Attempts to extend this to the more substituted hydroxylamines led to very poor yields at the reverse-Cope stage (Entries 2,3); heating caused extensive decomposition. As outlined in the foregoing papers,[1] this rate retardation is a common feature of many reverse-Cope reactions; additionally, we also found that a phenyl substituent α-to the hydroxylamine function also has a very significant retarding effect. Hence, we turned to the nitrone derived from cyclopropanecarboxaldehyde and were delighted to find that, in the case of the 3-butenylsulfone, upon workup, the intermediate hydroxylamine had already undergone reverse-Cope cyclisation (Entry 4). Similarly, an *N*-butylnitrone reacted at a similar fast rate (Entry 5); the poorer yield at the condensation step may be due to proton exchange between the lithiosulfone and the protons α-to the nitrone in this case. With more substituted lithiosulfones, the cyclopropyl hydroxylamines did now undergo reverse-Cope cyclisations (Entries 6 and 7), albeit at a slower rate, but still with a good level of stereoselection.

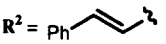
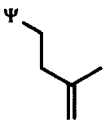
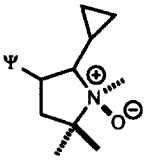
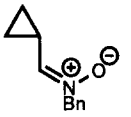
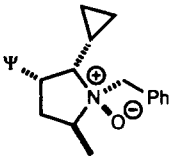
To try to understand these effects, we carried out similar reactions with isopropyl nitrone (Entries 8 and 9). The resulting hydroxylamines underwent cyclisation at very similar rates to the corresponding cyclopropyl nitrones, suggesting that the rate retardation by the phenyl group is due to electronic rather than steric reasons. The lower stereoselectivities of these cyclisations presumably reflects the greater steric bulk of the isopropyl group (see below). Confusingly, the nitrone derived from cinnamaldehyde also underwent rapid cyclisation (Entry 10), as it might be expected that the electronic effect of the phenyl group would have been transmitted by the connecting alkene; evidently, this is not the case. An internally substituted hydroxylamine also underwent slow cyclisation (Entry 11) but incorporation of an *N*-benzyl group into the benzaldehyde nitrone suppressed cyclisation (Entry 12; *cf.* entry 1); this again could be alleviated by use of the cyclopropyl nitrone (Entry 13), but there is clearly a significant retardation caused by the benzyl substituent (*cf.* Entry 4).

The stereoselectivity of the initial condensations of the lithiosulfones with the nitrones is consistent with

CONDENSATIONS OF LITHIOSULFONES WITH NITRONES AND REVERSE-COPE CYCLISATIONS



10 11 12 13 14

	Sulfone	Nitrone	% Yield 12	Time	% Yield N-Oxides	Ratio 13 : 14
Entry 1	10; R^1 = H	11; R^2 = Ph	93%	96h	>95%	88 : 12
Entry 2	10; R^1 = Me	11; R^2 = Ph	82%	> 120h	<5%	—
Entry 3	10; R^1 = Ph	11; R^2 = Ph	78%	> 120h	<5%	—
Entry 4	10; R^1 = H	11; R^2 = cyclopropyl	—	~0.5h	90%	90 : 10
Entry 5	10; R^1 = H	11; R^2 = *n*-propyl	—	~0.5h	68%	88 : 12
Entry 6	10; R^1 = Me	11; R^2 = cyclopropyl	76%	96h	>90%	82 : 18
Entry 7	10; R^1 = Ph	11; R^2 = cyclopropyl	83%	70h	>95%	76 : 24
Entry 8	10; R^1 = H	11; R^2 = *iso*-propyl	—	~0.5h	81%	66 : 34
Entry 9	10; R^1 = Me	11; R^2 = *iso*-propyl	67%	78h	89%	85 : 15
Entry 10	10; R^1 = H	11; R^2 = 	—	<0.5h	94%	69 : 31
Entry 11	 15	11; R^2 = cyclopropyl	65%	72h	90%	 16 *cis* : *trans* 76 : 24
Entry 12	10; R^1 = H	 17	65%	> 120h	<5%	—
Entry 13	10; R^1 = H	 18	89%	48h	92%	 [75% + 25% all *cis*]

When no yields or ratios are quoted [—], the hydroxylamines 12 cyclised upon isolation or the final reverse-Cope cyclisation gave too poor a yield of the *N*-oxides [13, 14] to measure these respectively.

Cram's rule[1] and suggests an approach as outlined in Fig 1. The subsequent reverse-Cope cyclisations then seem to occur largely *via* a boat-like transition state (Fig 2); at first sight, this seems surprising, but, when viewed end-on (Fig 3), the clear proximity of the hydroxylamine and alkene groups gives some credence to this idea.

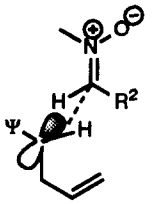
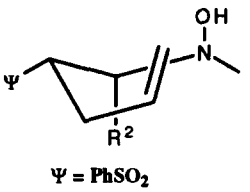


Fig 1



$\Psi = PhSO_2$

Fig 2

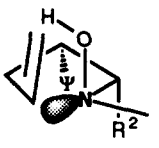
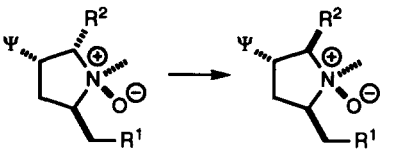


Fig 3



13 20

A final and significant finding was that the isolated isomers **13** slowly underwent isomerisation during a few weeks in chloroform to provide excellent yields of the corresponding 2,3-*trans* isomers **20**. This unexpected result thus allows access to an additional set of isomers of the the pyrrolidine-*N*-oxides but clearly could limit the synthetic utility of the initial *N*-oxides **13** as these will slowly isomerize during extended manipulation. It seems most likely that structures **20** represent the most thermodynamically stable arrangement of the pyrrolidine-*N*-oxides. It was fortunate that one of these [**20**; R^1 = H; R^2 = Ph] proved to be highly crystalline and hence the assigned stereochemistry could be confirmed by X-ray analysis.

In summary, this approach represents a rapid and efficient approach to a range of pyrrolidine-*N*-oxides with a variety of stereochemistries;[6] further, the highly stereoselective nature of the initial condensations between the lithiosulfones and nitrones could also have some more general applications.

Acknowledgements

We thank Dr J.A. Ballantine and his colleagues at the EPSRC Mass Spectrometry Service, Swansea University, for the provision of high resolution Mass Spectral data and BP Chemicals and the EPSRC for financial support through the CASE Award scheme.

References

1. Coogan, M.P.; Gravestock, M.B.; Knight, D.W.; Thornton, S.R. *Tetrahedron Lett.*, **1997**, *38*, 8549.
2. Chang, Z.-Y.; Coates, R.M. *J. Org. Chem.*, **1990**, *55*, 3464 and references cited therein.
3. Ciganek, E. *J. Org. Chem.*, **1990**, *55*, 3007; **1995**, *60*, 5803; Ciganek, E.; Read, J.M.; Calabrese, J.C. *J. Org. Chem.*, **1995**, *60*, 5795 and references cited therein.
4. Breuer, E.; Aurich, H.G.; Nielsen, A. "Nitrones, Nitronates and Nitroxides, Eds. Patai, S; Rappoport, Z., John Wiley and Sons, Chichester, 1989.
5. For an isolated example of the addition of a lithiated sulfone to a nitrone, see Annunziata, R.; Cinquini, M. *Synthesis*, **1982**, 929.
6. For an alternative approaches to pyrrolidine-*N*-oxides, see O'Neil, I.A.; Miller, N.D.; Barkley, J.V.; Low, C.M.R.; Kalindjian, S.B. *Synlett*, **1995**, 617, 619.

(*Received in UK* 12 *September* 1997; *accepted* 26 *September* 1997)