JOURNAL OF THE CHEMICAL SOCIETY

Chemical Communications

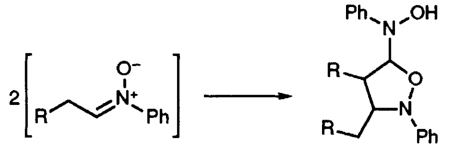
Number 22
1991

The Base Induced Dimerisation of α-Aryl-*N*-cyclohexylnitrones

Martin P. Cowling,[a] Paul R. Jenkins,*[a] Nicholas J. Lawrence[a] and Kelvin Cooper[b]

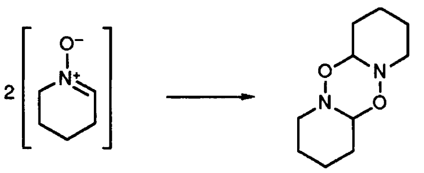
[a] *Department of Chemistry, The University, Leicester LE1 7RH, UK*
[b] *Pfizer Central Research, Sandwich, Kent CT13 9NJ, UK*

A series of α-aryl-*N*-cyclohexylnitrones undergo dimerisation on treatment with lithium diisopropylamide, by a process which may be explained in terms of deprotonation α to nitrogen followed by nucleophilic addition to the nitrone carbon atom and ring closure to give spirooxadiazinanes.



1

2



3

4

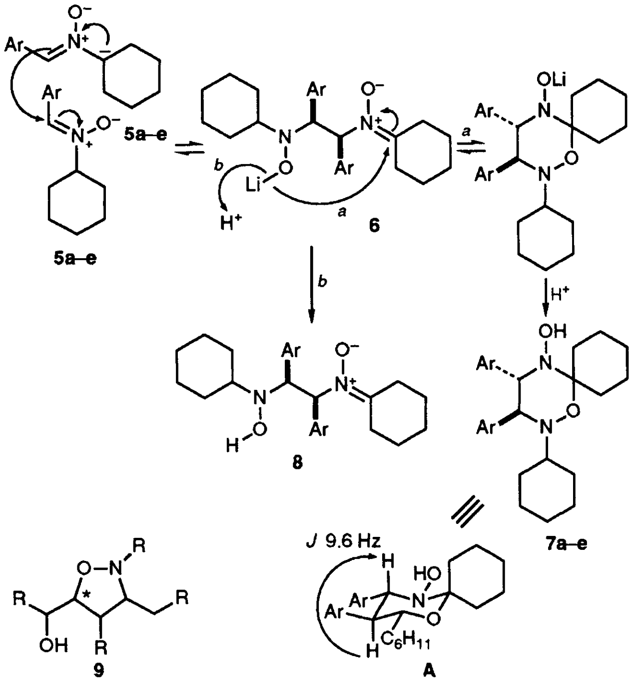
The dimerisation of nitrones falls into two classes:[1,2] the first involves an aldol-type condensation, in which the nitrone is both the nucleophile and electrophile,[3,4] in the sense **1** → **2**. The second class involves a dipole–dipole cycloaddition in the sense **3** → **4**.[5] A slight variation of the type **1** → **2**, involving the dimerisation of a nitrone that possesses a proton on the group directly attached to the nitrogen atom has been reported,[6] and since our results are different, we report our results herein.

As part of our studies on nucleophilic addition to racemic[7] and optically active nitrones[8] we treated α-aryl-*N*-cyclohexylnitrones **5a–e** with one equivalent of lithium diisopropylamide (LDA) (Scheme 1) and obtained crystalline products **7a–e** in the yields indicated in Table 1.† Although only 0.5 equiv. of LDA is required in theory the reaction was unsuccessful with this quantity of base. Our reasons for the assignment of **7** as the product are as follows (for **7e**).

First, a dimeric structure can be deduced from the ion at *m*/*z* 475 (75%) ($M^+ + H$) in the mass spectrum. Secondly, an alternative dimer, the open-chain **8**, can be ruled out by the lack of nitrone absorption in the UV spectrum. Thirdly, the ^{13}C NMR shifts are consistent with **7e**, the signals at δ 93.1 (s), 69.5 (d) and 70.8 (d) being the most significant and which we

Table 1 Preparation of the spiro compounds 7‡

	Ar	Yield (%) of 7a–e
a	$4\text{-Pr}^i\text{C}_6\text{H}_4$	100
b	Ph	90
c	$4\text{-BrC}_6\text{H}_4$	52
d	$3\text{-BrC}_6\text{H}_4$	100 (crude)
e	$4\text{-ClC}_6\text{H}_4$	98



Scheme 1

---

† All stable new compounds gave satisfactory spectroscopic data and microanalysis or accurate mass spectrum.

‡ General experimental procedure for the preparation of nitrone dimers **7a–e**. A freshly prepared solution of lithium diisopropylamide (2.1 mmol) in ether (2 cm^3) was added dropwise to a stirred solution of the nitrone **5a–e** (2.0 mmol) in diethyl ether (5 cm^3) at 0 °C. The reaction was monitored by TLC and when all the starting material had disappeared (20–90 min) water (4 cm^3) was added and the mixture was extracted with chloroform (5 × 10 cm^3). The combined extract was dried ($MgSO_4$) and the solvent was removed under reduced pressure to give the crude nitrone dimer which was purified by recrystallisation from ethanol–diethyl ether.

assign as the quaternary carbon and benzylic carbons, respectively. The signal at δ 93.1 correlates well with that of C* (δ 90–100) in 18 compounds of the type **9**.[4] Again **8** can be ruled out since the shift of the carbon atom of a nitrone is typically δ 135.[4] Our assignment of **7e** is consistent with the ^{1}H NMR spectrum, from which the relative stereochemistry of the two adjacent chiral centres bearing the aromatic groups can be deduced. The coupling constant of the two benzylic protons is 9.6 Hz, indicating that the aromatic groups are both equatorial, as in the conformation shown in structure **A**; Seebach[9] has shown that vicinal axial–axial coupling constants for 2,3-diphenylpiperazines are in the range 8.9–9.3 Hz, whereas those of axial–equatorial protons are 2.3–3.3 Hz. All attempts to obtain a crystal of **7e** suitable for X-ray structure determination proved unsuccessful. Our reasoning for assigning the dimer as **7e** equally well applies to the other examples. Thus we are confident that the dimers are indeed of the type **7**.

This is in contrast to the results of Hall and Gisler,[6] who isolated an open-chain dimer of the type **8**, in 30% yield by treating *N*-benzyl-α-phenylnitrone with lithium dimsylate (0.5 equiv.; 30 min; room temp.; Me_2SO). We have attempted to repeat this result, but without success, having always recovered the starting material. We further treated the nitrone **5b** with lithium dimsylate under similar conditions and again observed no reaction. Finally we treated *N*-benzyl-α-phenylnitrone with LDA (1.2 equiv.; 1 h; room temp.; tetrahydrofuran, THF) and isolated benzyl alcohol (88%) with no evidence of any dimeric products. In contrast to these findings our other results led to the formation of dimers **7a–e** in good yield.

We believe that the formation of **7a–e** is as a result of thermodynamic control. Both the initial dimerisation to the open chain **6** and subsequent ring closure that are presumably reversible will result in the formation of the product that has two equatorial aromatic groups in the conformation shown.

In conclusion, we have observed an unusual dimerisation reaction of nitrones which leads to reasonable yields of five spirooxadiazinanes.

We acknowledge the SERC and Pfizer for supporting this work (CASE studentship to M. P. C.).

Received, 3rd June 1991; Com. 1/02637B

References

1 J. Hammer and A. Macaluso, *Chem. Rev.*, 1964, **64**, 473.
2 E. Breuer, H. G. Aurich and A. Nielsen, *Nitrones, Nitronates and Nitroxides*, Wiley, Chichester, 1989.
3 F. H. Banfield and J. Kenyon, *J. Chem. Soc.*, 1926, 1612; R. F. C. Brown, V. M. Clark, I. O. Sutherland and A. Todd, *J. Chem. Soc.*, 1959, 2105, 2109 and 2116; R. Foster, J. Iball and R. Nash, *Chem. Commun.*, 1968, 1414; A. D. Baker, J. E. Baldwin, D. P. Kelly and J. DeBernardis, *Chem. Commun.*, 1969, 344; W. Kliegel, *Tetrahedron Lett.*, 1969, 2627; Y. K. Zhang and G. Z. Xu, *J. Chem. Res (S)*, 1991, 42.
4 H. G. Aurich, J. Eidel and M. Schmidt, *Chem. Ber.*, 1986, **119**, 18.
5 J. Thesing and H. Meyer, *Chem. Ber.*, 1956, **89**, 2159.
6 J. H. Hall and M. R. Gisler, *J. Org. Chem.*, 1977, **42**, 1133.
7 M. P. Cowling, P. R. Jenkins and K. Cooper, *J. Chem. Soc., Chem. Commun.*, 1988, 1503.
8 M. P. Cowling and P. R. Jenkins, to be published.
9 C. Betschart, B. Schmidt and D. Seebach, *Helv. Chim. Acta*, 1988, **71**, 1999.