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THERMAL ISOMERIZATION OF 1-MORPHOLINO-3-PHENYL (OR VINYL)-ALLENES: SYNTHESIS OF THE [1,4]OXAZINO-[4,3-a]AZEPINE FRAMEWORK

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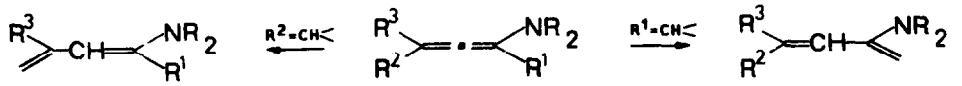
Key Words: Morpholinoallenes; Thermal rearrangement; Azomethine ylides; Azepine derivatives.

Abstract: 1-Morpholino-3-phenylallenes isomerize to 3,4,6,12b-tetrahydro-1*H*-[1,4]oxazino[4,3-a][2]benzazepines at ≥ 105 °C. Similarly, 1-morpholino-3-vinylallenes are transformed into 3,4,10,10a-tetrahydro-1*H*-[1,4]oxazino[4,3-a]azepines. Formation of these novel heterocycles is rationalized by a 1,3-proton shift in the morpholinoallenes, followed by 1,7-electrocyclization of the α,β,γ,δ-unsaturated azomethine ylide thus formed.

Aminoallenes 1 bearing a CHR_2 substituent at either one of the terminal allenic carbon atoms tautomerize thermally by a formal 1,3-H shift more or less rapidly to 1- or 2-dienamines:[1,2]



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As a consequence, such aminoallenes are of limited use for further synthetic transformations, especially when elevated temperatures are needed, and they may even escape their isolation. We report here that 1-morpholino-3-phenylallenes without CHR_2 substituents at the allene moiety, although perfectly stable at ambient temperature, undergo an unprecedented thermal isomerization which begins with a 1,4-hydrogen migration.

When a toluene solution of morpholinoallenes **2a-c** is heated at 120-130 °C in a Schlenk pressure tube, 3,4,5,12b-tetrahydro-1*H*-[1,4]oxazino[4,3-a][2]benzazepines **3a-c** are formed practically quantitatively.

2a-c **3a-c**

2,3	R	temp. [°C]	time [h]	yield of 3 [%]
a	Ph	120	1	92
b	tBu	138	12	93
c	$SiPh_2tBu$	138	7.5	91

The constitution of these novel heterocycles follows from their ^1H and ^{13}C NMR data.[3] In the 400 MHz ^1H NMR spectra, the morpholine protons form well-resolved ABXY and ABY spin systems. Assignments can be made based on the values of the ^2J and ^3J coupling constants[4] (Figure 1). It then becomes evident that 12b-H is in the equatorial position. The full relative stereochemistry (5α,6α,12α) of these molecules was suggested by NOE experiments and firmly established by an X-ray crystal structure analysis of **3a**[5] (Figure 2).

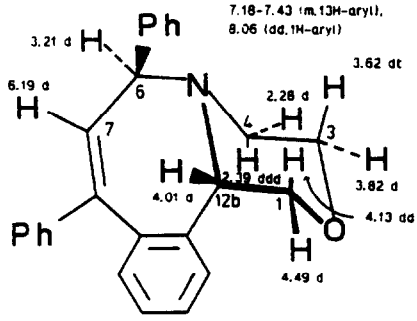


Fig. 1. ^1H NMR data of **3a**.
($CDCl_3$, 400 MHz); δ values are given.
Coupling constants [Hz]:[6]
$J(1\text{-}H^a,1\text{-}H^e) = -11.9$; $J(4\text{-}H^a,4\text{-}H^e) = -11.7$;
$J(1\text{-}H^a,12b\text{-}H) = 3.6$; $J(4\text{-}H^a,3\text{-}H^e) = 3.2$;
$J(3\text{-}H^a,3\text{-}H^e) = -11.0$; $J(4\text{-}H^a,3\text{-}H^a) = 11.0$;
$J(3\text{-}H^a,4\text{-}H^a) = 11.0$; $J(6\text{-H}, 7\text{-H}) = 5.5$;
$J(3\text{-}H^a,4\text{-}H^e) = 2.6$;

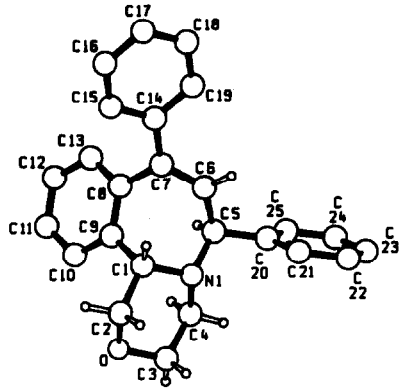
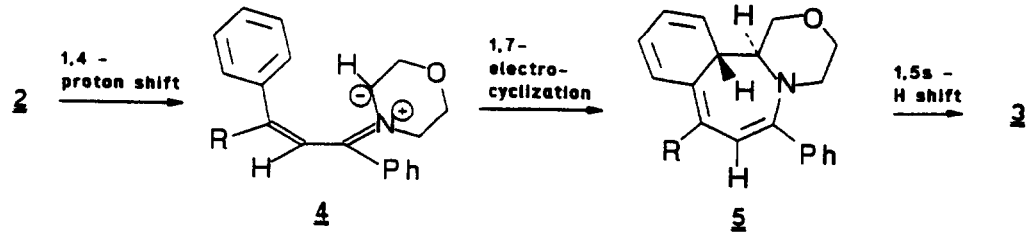
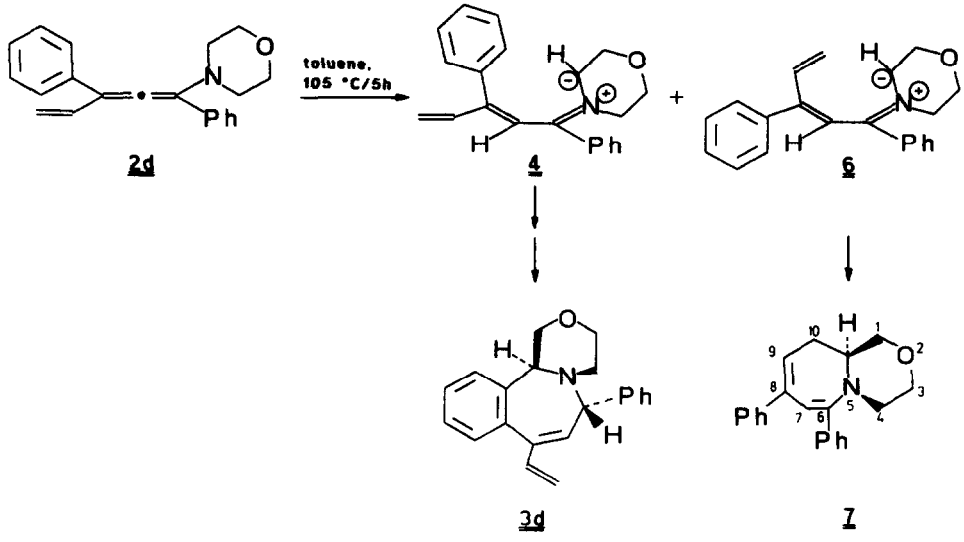


Fig. 2. SCHAKAL plot of **3a**.
Torsion angles in the seven-membered ring [°]:
C1-N1-C5-C6 41.7(2)
N1-C5-C6-C7 -77.7(2)
C5-C6-C7-C8 7.0(3)
C6-C7-C8-C9 42.1(3)
C7-C8-C9-C1 5.2(3)
C8-C9-N1-C1 -77.2(2)
C9-C1-N1-C5 44.6(2)

In mechanistic terms, the isomerization **2**⟶**3** is likely to begin with a 1,4-shift of a NCH_2 proton to the highly basic central allenic carbon atom. The α,β,γ,δ-unsaturated azomethine ylide (**4**) thus formed[7] is supposed to undergo a conrotatory 1,7-electrocyclization[8] to **5** which rearomatizes by a 1,5-suprafacial hydrogen shift. The isomerization **2**⟶**5** is reminiscent of the thermal ring-closure reactions taking place for certain ortho-alkenyl-N,N-dialkylanilines and 1-(N,N-dialkylamino)-1,3-dienes.[9] In those cases, however, it is a hydride rather than a proton shift which generates a 1,5- or 1,6-dipolar intermediate.



The electrocyclization step **4**⟶**5** suggests that the participating aromatic ring can be replaced by an olefinic double bond. This is indeed the case. Heating of 1-morpholino-3-phenyl-3-vinylallene **2d** at 105 °C (toluene) yields a 53:47 mixture of **3d** and the (5α,10α)-3,4,10,10a-tetrahydro-1*H*-[1,4]oxazino[4,3-a]azepine **7**.[10] An electrocyclization analogous to **6**⟶**7** has been proposed to be involved in the thermal isomerization of 2-acyl-1-dimethylamino-1,3,4-pentatrienes to 6-acyl-2,3-dihydroazepines.[11]



It is obvious that a broad range of substituted 2,3-dihydroazepines and 1*H*-[2]benzazepines will be accessible by appropriate modifications of aminoallenes **2**.

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References and Notes

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3. **3a**: mp. 201 °C. - ^{1}H NMR: See Fig. 1. - ^{13}C NMR ($CDCl_3$, 100 MHz): δ 47.0 (C-4), 56.1 (C-6), 67.1 (C-3), 67.6 (C-12b), 69.3 (C-1), 124.1 (C-7), 126.8-129.8, 139.0, 140.1, 140.8, 143.1, 144.4.
3b: mp. 108 °C. - ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.19 (s, CMe_3), 2.13-2.21 (m, 4-H^a, 4-H^e), 2.91 (d, *J* = 6.0, 6-H), 3.58 (ddd, *J* = 10.8, 10.4, 4.0, 3-H^a), 3.77 (d, *J* = 11.6, 3-H^e), 3.85 (d, *J* = 3.6, 12b-H), 4.11 (dd, *J* = 12.0, 3.6, 1-H^a), 4.46 (d, *J* = 12.0, 1-H^e), 5.84 (d, *J* = 6.0, 7-H), 7.25-7.35 (m, 7 H-aryl), 7.54 (m, 1 H-aryl), 7.95 (m, 1 H-aryl). - ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 31.1 (CMe_3), 36.3 (CMe_3), 46.7 (C-4), 55.4 (C-6), 66.6 (C-12b), 67.1 (C-3), 69.2 (C-1), 126.1-128.6, 136.9, 143.1, 145.1, 151.1 (C-8).
3c: mp. 167 °C. - ^{1}H NMR ($CDCl_3$, 400 MHz); δ 0.92 (s, CMe_3), 2.25-2.33 (m, 4-H^a, 4-H^e), 3.27 (broad s, 6-H), 3.63 (dd, broad lines, *J* = 10.1, 10.0, 3-H^a), 3.81 (d, *J* = 10.0, 3-H^e), 4.11 (broad s, 12b-H), 4.22 (dd, *J* = 11.8, 3.0, 1-H^a), 4.51 (d, *J* = 11.8, 1-H^e), 6.52 (d, *J* = 4.8, 7-H), 7.03-7.46 (m, 14 H-aryl), 7.68-7.75 (m, 2 H-aryl), 7.95 (m, 1 H-aryl). - ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 18.9

(SiCMe$_3$), 29.0 (C*Me*$_3$), 46.9 (C-4), 56.3 (C-6), 67.2 (C-3), 67.7 (C-12b), 69.2 (C-1), 126.3-129.4, 134.6-137.5, 141.9, 142.3, 147.2 (C-7).
All compounds gave correct microanalyses.

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5. $C_{25}H_{23}NO$, monoclinic, space group $P2_1/c$; a = 9.906(2), b = 8.772(2), c = 21.259(4) Å, ß = 92.40(2) °; Z = 4, d_{calc} = 1.272 g·cm^{-3}; T = 22 °C. Enraf Nonius CAD4 diffractometer, monochromatized Mo-Kα radiation, 3107 unique reflections in the range 4.0 ≤ 2θ ≤ 48.0 °. Full-matrix least-squares refinement with 2343 reflections [$I > 2\sigma(I)$] and 336 variables (H atoms refined with isotropic temperature factors); R = 0.047, R_w = 0.050; residual electron density 0.17 e·Å^{-3}. Atomic coordinates and thermal parameters, tables of bond lengths and angles, and structure factor tables are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K. Each request should be accompanied by the complete citation of this publication.
6. ^3J coupling constants between the equatorial protons of the morpholine ring were not found (≤ 1.5 Hz), in contrast to the geminal axial-equatorial coupling constants. This fact is due to a flattening of the ring as compared to an ideal chair conformation, so that the torsion angle involving these C-H bonds increases significantly above 60 °. For example, the following torsion angles are found in the crystal structure of **3a**: 1-H^a/C-1/C-12b/12b-H -49.0(1.5) °; 1-H^e/C-1/C-12b/12b-H 69.3(1.4) °.
7. For the formation of azomethine ylides and other 1,3-dipoles by prototropic 1,2 shifts, see: Grigg, R. *Bull. Soc. Chim. Belg.* **1984**, *93*, 593.
8. For 1,7-electrocyclic reactions of other α,ß,γ,δ-unsaturated 1,3-dipoles, see: Zecchi, G. *Synthesis* **1991**, 181.
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10. Compound **7** is isolated from the product mixture by Kugelrohr distillation at 230 °C / 0.002 mbar and subsequent crystallization from CH_3CN/ether (1:4); yield; 36 %; mp. 114 °C. Compound **2d** can be identified in the ^{1}H NMR spectrum of the reaction mixture; it decomposes during the distillation, however. - ^{1}H NMR of **7** ($CDCl_3$, 400 Mz): δ 2.65-2.78 (m, 10-H^a, 10a-H), 2.96 (ddd, J = 17.1, 8.5, 3.2, 10-H^e), 3.01-3.12 (m, NCH_2), 3.72 (ddd, J = 12.2, 10.3, 2.4, 3-H^a), 3.77 (dd, J = 12.2, 2,4, 3-H^e), 3.95 (dd, J = 11.5, 2.2, 1-H^e), 4.06 (dd, J = 11.5, 2.7, 1-H^a), 5.59 (d, J = 1.3, 7-H), 6.03 (ddd, J = 8.5, 3.6, 1.3, 9-H). - ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 32.6 (C-10), 47.5 (C-4), 57.9 (C-10a), 67.7 (C-3), 71.4 (C-1), 108.9 (C-7), 126.4 (C-9), 126.4-128.5, 138.2, 140.5, 145.8, 151.2 (C-6).
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