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HETEROCYCLIC SYNTHESIS BY ELECTROCYCLIZATION OF EXTENDED DIPOLES: A NOVEL ACCESS TO THE INDOLIZINE AND QUINOLIZINE SYSTEMS

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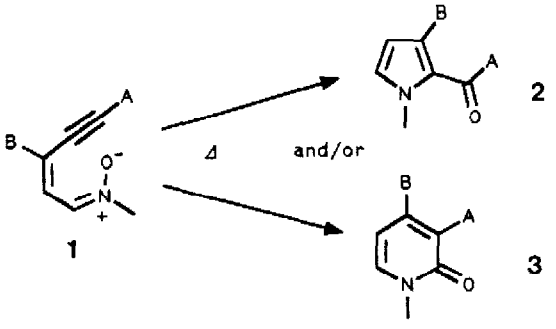
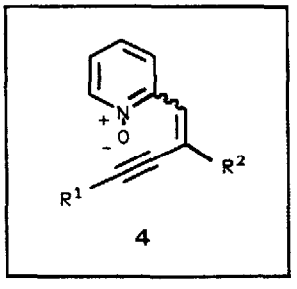
SUMMARY. On thermal activation α-butenynyl substituted pyridine-N-oxides **4** undergo a multistep rearrangement affording 4-oxo-4H-quinolizines (8) and 2-acylindolizines (9). In the geometrical isomeriziation of **E-4** to **Z-4** annulated isoxazolidines (7) are involved as unstable intermediates.

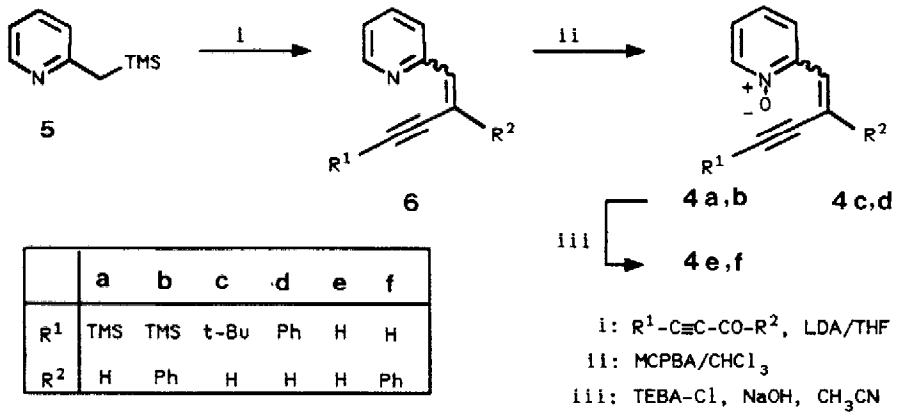
Quinolizines and indolizines are of considerable interest due to their widespread occurrence in natural products, particularly in the field of alkaloids [1]. Although many routes to the basic ring systems are known [2] new general synthetic approaches are still highly desirable.

Based on recent results on the tranformation of butenynyl nitrones **1** into 2-acyl pyrroles **2** and/or α-pyridones **3**, respectively,[3] we have investigated the analogous reaction of α-substituted pyridine-N-oxides **4**, a special class of nitrones, which should lead to derivatives of the title compounds (*i.e.* benzoannulated pyrroles and pyridones) by a similar reaction sequence. Here we communicate our findings with the pyridine oxides **4c-f**, and discuss some further informations on the reaction mechanism of these unusual rearrangement processes.





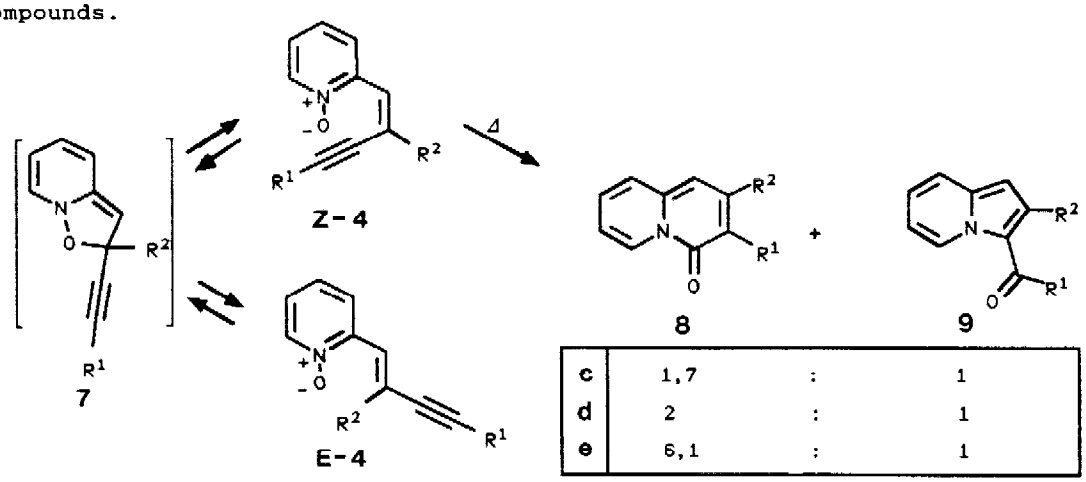
The synthesis of the dipolar compounds was performed using 2-(trimethylsilylmethyl)-pyridine (5) as a common precursor [4]. Peterson reaction of 5 with the corresponding carbonyl alkynes led to the olefination products **6a-d** [5] which subsequently were treated with MCPBA yielding the butenynyl substituted pyridine-N-oxides **4a-d** [6]. Finally, protodesilylation of **4a,b** under phase transfer conditions [7] gave the terminal alkynes **4e,f** [6]. Although the separation of the E/Z-diastereomers could be achieved by careful flash chromatography on the stage of the butenynyl pyridines **6a-d**, the preparative isolation of the pure compounds turned out to be unnecessary because both isomers serve equally well as starting material for the desired transformation. Nevertheless, for the purpose of an unambigous identification one diastereomer in each case has been isolated and fully characterized [6,8].



	a	b	c	d	e	f
R^1	TMS	TMS	t-Bu	Ph	H	H
R^2	H	Ph	H	H	H	Ph

Heating up the Z-configurated dipolar systems **4c,d,e** to 380°C under short-time-thermolysis conditions (contact time ca. 10s)[9] afforded a mixture of two new products, namely the quinolizines **8c,d,e** and the indolizines **9c,d,e**, in 50-60% yield. However, the very same result was obtained when the corresponding **E**-compounds of **4c,d,e** were treated the same way. This observation was specially intriguing with regard to the necessity of having a syn-configuration of the extended dipole **4** in order to enable the 8e-ring closure as initiating step of the over all transformation (see below). Whereas a direct geometrical isomerization between **E-4** and **Z-4** seems to be less probable under the reaction conditions [10] we rather propose the intermediacy of the annulated isoxazolidine **7**, formed by reversible 6π-electrocyclisation [12], as relay species.

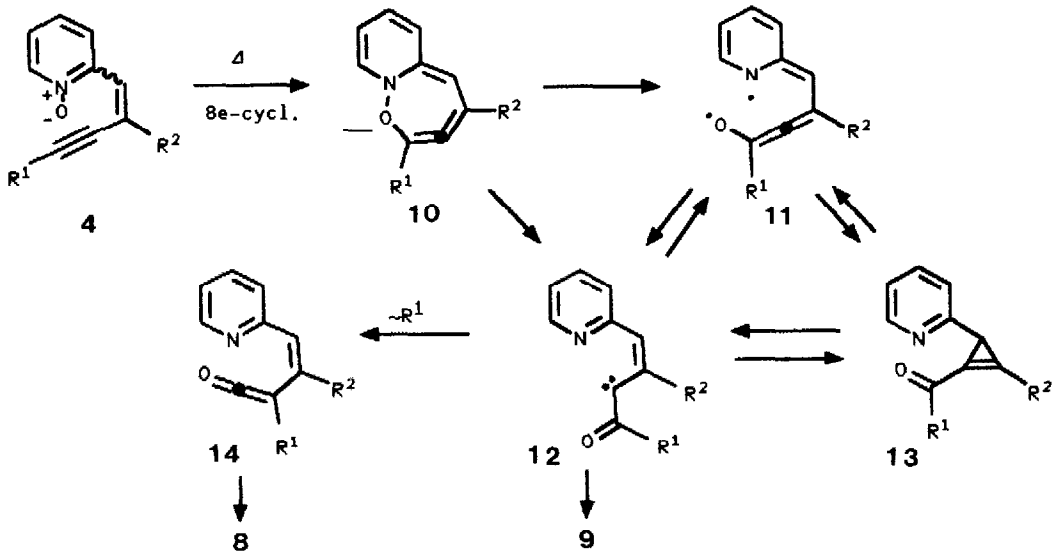
The structure of the reaction products has been confirmed by the usual analytical techniques including MS as well as IR-and NMR-spectroscopy [8,14]; on the basis of these data **8e** [15a] and **9e** [15b] have been identified as known compounds.



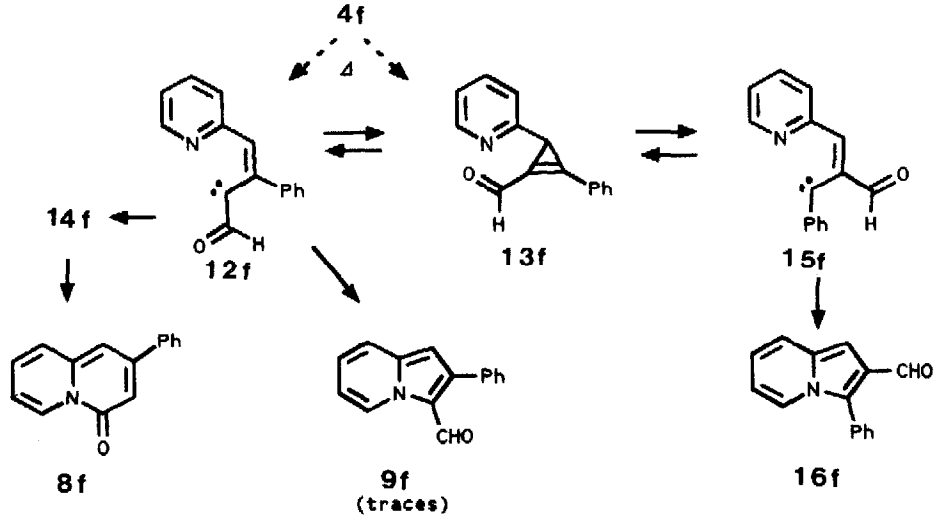
c	1,7	:	1
d	2	:	1
e	6,1	:	1

For the transformation of the pyridine-N-oxides **4** into quinolizinones (**8**) and indolizines (**9**), respectively, the same general mechanism holds as proposed in the case of simple butenynyl nitrones [3]: After 1,7-cyclization of the dipolar system the labile N-O bond of the bicyclic allene **10** is cleaved affording directly or, after rearrangement of the diradical **11**, the keto carbene **12** which then reacts by 6π-cyclization (leading to **9**) or by initial Wolff migration of R^1 and subsequent concerted ring closure of the ketene **14** to yield **8**. It is interesting to note that all electrocyclization

steps, i.e. **4** → **10** as well as **12** → **9** and **14** → **8**, take place with dearomatization of the pyridine nucleus.



Cyclopropenes of type **13** were already discussed as intermediates in the transformation of other butenynyl dipoles [9,11,16]. *With the phenyl substituted* pyridine-N-oxide **4f** as starting material we have now accumulated further indications for their possible intervention on the reaction coordinate. After thermolysis of **4f** at 380°C/10s two major products were isolated, the quinolizinone **8f** [17a] and the indolizine **16f** [17b] (60%, ratio 1:1.1), the latter one showing a different substitution pattern compared to the "normal" indolizine **9f** [17c], which is formed only in traces. This result is best explained by assuming the intermediacy of the cyclopropene **13f**: Due to the stabilizing effect of the phenyl group the vinylcyclopropene-vinyl carbene rearrangement [18] takes place with similar efficiency producing the carbenes **12f** and **15f**, which then give rise to the formation of the observed products.



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REFERENCES

1) A.S. Howard, J.P. Michael in *The Alkaloids* (E. Brossi, Ed.), Vol. **28**, p. 183, Academic Press, New York, 1986).

2) N. Campbell in *Rodd's Chemistry of Carbon Compounds* (S. Coffey, Ed.), Vol. IV^{B}, p. 259, Elsevier, Amsterdam, 1978; F.J. Swinbourne, J.H. Hunt, G. Klinkert, Adv.Heterocycl.Chem. **23**, 103 (1978).

3) W. Eberbach, J. Roser, Tetrahedron Letters **28**, 2689 (1987).

4) T. Konakahara, Y. Takagi, Synthesis **1979**, 192.

5) **6a**: 71%, E:Z= 1:1; **6b**: 81%, E:Z= 1:3; **6c**: 61%, E:Z= 10:1; **6d**: 35%, E:Z= 2:1; yields are not optimized.

6) **4a**: 54%; **E-4a**: mp 93-94°C (ether/hexane); ^{1}H-NMR ($CDCl_3$, 250 MHz): σ= 8.23/7.43/7.2 (Pyr-H), 7.49/6.75 (HC=CH, J= 16,5 Hz), 0.25 (Me_3Si). **4b**: 77%; **Z-4b**: oil; ^{1}H-NMR: σ= 8.59/8.29/7.3 (Pyr-H), 7.95 (C=CH), 0.27 (Me_3Si). **4c**: 77%; **E-4c**: mp 103-104°C (ether/hexane);^{1}H-NMR: σ= 8.22/7.43/7.20/7.15 (Pyr-H), 7.40/6.67 (HC=CH, J= 16.5 Hz); 1,28 (Me_3C). **4d**: 71%; **E-4d**: mp 143-145°C (ether/hexane); ^{1}H-NMR: σ= 8.23/7.36/7.2 (Pyr-H), 7.3/7.5 (Ph-H), 7.53/6.98 (HC=CH, J= 16.5 Hz). **E-4e**: mp 90-91°C; ^{1}H-NMR: σ= 8.22/7.43/7.2 (Pyr-H), 7.50/6.80, HC=CH, J= 16.5), 3.28 (C=CH, J= 2.3, 0.8 Hz). **Z-4f**: mp 112-113°C (ether/hexane); ^{1}H-NMR: σ= 8.50/8.29/7.30/7.20 (Pyr-H), 7.8/7.3 (Ph-H), 7.97 (C=CH, J=0.8), 3.70 (C=CH, J= 0.8 Hz).

7) J. Roser, W. Eberbach, Synth.Commun. **16**, 983 (1986).

8) All new compounds gave satisfactory C,H,N analyses.

9) W. Eberbach, J. Roser, Tetrahedron **42**, 2221 (1986).

10) In the case of E-butenynyl carbonyl ylides the corresponding geometrical isomerization has been observed only to a very minor extent in special examples [11].

11) J. Roser, Dissertation, University of Freiburg, 1987.

12) The proposed isoxazolidines are probably very unstable, as judged by the limited number of known 1,5-cyclization products [13].

13) A.R. Forrester, S.P. Hepburn, J.Chem.Soc. (C) **1970**, 1277; N.S. Ooi, D.A. Wilson, J.Chem.Res. **1980**, (S) 394; (M) 4726; H.G. Aurich, M.Schmidt, T. Schwerzel, Chem.Ber.**118**, 1105 (1985).

14) **8c**: mp 62-64°C (ether/hexane); ^{1}H-NMR ($CDCl_3$, 250 MHz): σ = 9.12 (dd, 5-H), 7.67 (d, 2-H), 7.38 (d, 8-H), 7.20 (dt, 7-H), 6.90 (dt, 6-H), 6,58 (d, 1-H), 1.46 (s, Me_3C); $J_{1,2}$= $J_{2,3}$= 8.3, $J_{5,6}$= 7.5, $J_{6,7}$= 6.8, $J_{7,8}$= 9.0 Hz. **8d**: mp 135-136°C (ether/hexane); ^{1}H-NMR : σ = 9.27 (dd, 5-H), 7.90 (d, 2-H), 7.48 (d, 8-H), 7.45 (dt, 7-H), 7.3/7.8 (m, Ph-H) 7.04 (dt, 6-H), 6.76 (d, 1-H); J-values as for **8c**. **9c**: mp 64-65°C(ether/hexane); ^{1}H-NMR : σ = 9.99 (ddd, 5-H), 7.69 (dd, 2-H), 7.51 (dd, 8-H), 7.10 (dt, 7-H), 6.84 (dt, 6-H), 6.52 (dd, 1-H), 1.44 (s, Me_3C); $J_{1,2}$= 4.5, $J_{5,6}$= 7.5, $J_{6,7}$=6.8, $J_{7,8}$= 8.3 Hz. **9d**: mp 91-92°C (ether/hexane); ^{1}H-NMR : σ = 9.99 (ddd, 5-H), 7.83 (dd, 8-H), 7.29 (dd, 2-H), 7.20 (dt, 7-H), 7.4-7.6 (m, Ph-H) 6.95 (dt, 6-H), 6.53 (dd, 1-H); J-values as for **9c**.

15) [15a] L. Forti, M.L. Gelmi, D. Pocar, M. Varallo, Heterocycles **24**, 1401 (1986). [15b] O. Fuentes, W.W. Paudler, J.Heterocycl.Chem. **12**, 379 (1975).

16) W. Eberbach, J. Roser, Tetrahedron Lett. **28**, 2685 (1987).

17) [17a] H.N. Al-Jallo, F.W. Al-Azawi, J.Heterocycl.Chem.10, 139 (1973). [17b] E. Pohjala, Acta Chem.Scand. **B 29**, 1079 (1975). [17c] Y.Yamashita, D.Suzuki, M. Masumura, Heterocycles **16**, 1499 (1981).

18) W.M. Jones, U.H. Brinker in *Pericyclic Reactions*, Vol. 1, p. 123, Academic Press, New York, 1977; B. Halton, M.G. Banwell, Top.Curr.Chem. **144**, 138 (1988).

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