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THE STEREOCHEMISTRY AND MECHANISM OF THE RING OPENING REACTION OF 3-ARYLTETRAZOLOPYRIDINIUM SALTS AND THEIR v-TRIAZOLO ANALOGUES[1]

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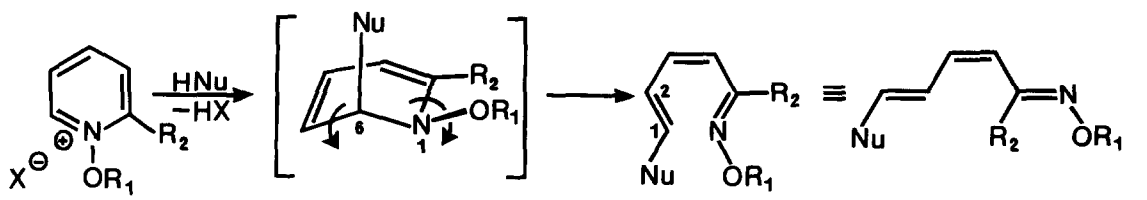
Abstract. Contrary to earlier reports, the title reaction was found to yield both 1E and 1Z configured dienic products predicted for a disrotatory process. A novel degradation giving, via the loss of one carbon unit, tetrazolyl- and triazolyl-acrolein was also observed.

The cleavage of C-N bond in the ring opening reaction of pyridine-N-oxides[2,3] and N-aryl-pyridinium salts[4] following the addition of nucleophiles has been interpreted in terms of retro-electrocyclization of intermediates like (2) in Scheme 1. The basis to this contention was provided by the 1E configuration of dienic products[2,3] and kinetic data of the inverse reaction.[4] More recently, the analogous two-step reaction of N-alkoxy-pyridinium salts[5] (1a) with amines has been discussed on the basis of the same proposals by Sliwa and Tartar.[6] In particular, to account for the stereospecific formation of dieneamines (3), the initially detectable products of ring opening, they claimed that disrotation[7] can only take place with intermediates (2) possessing *cis*-1,6 relative stereochemistry and should proceed in the sense portrayed in Scheme 1. These authors argued that, on steric grounds, disrotation in the opposite sense and/or disrotation with intermediates of any other 1,6-stereochemistry has to be excluded. Consequently, the ring opening of condensed systems like (1b) should not lead, *via* disrotation, to products with 1Z configuration.



(1a), (1b) (2a), (2b) (3a), (3b)

a: R_1 = ethoxycarbonyl-alkyl, R_2 = H
b: R_1, R_2 = $-C(CH_3)_2-CO-$

Scheme 1 Nu: sec. amine

Contrary to these assumptions, we had previously found[8] that the ring opening of condensed pyridinium salts, like 3-aryl-tetrazolo-pyridinium tetrafluoroborate (4), with methoxide ions as the nucleophile yields both 1E and 1Z isomers, (7a) and (6a), and does so with net predominance of the "unexpected" (6a). Some of our more recent experiments revealed that with cyanide ions (tetrabutylammonium cyanide in dry acetonitrile at t<-20°) the reaction proceeds with the same unusual stereoselectivity: it yields a pair of non-interconvertible isomers (6b) and (7b), with 1Z configured product being the dominant component again.

In an attempt to solve the apparent contradiction regarding the mechanism[9] and gain more information on the determinants of ring opening, we have extended our former studies on (4). To this end, we have analysed the variations in the isomeric composition of dienic products upon changing the nucleophilic agent. The experimental results, including the diagnostic ^{1}H NMR data of olefinic side chain, are summarized in Table 1.

Since, as noted above, nitrogen nucleophiles were found to yield 1E isomers stereospecifically,[5,6] the reaction of (4) with imidazole-sodium and its analogues (obtained with NaH in dry THF) has been studied first. (The choice of this particular reagent was motivated by the fact that, under the conditions of the usually facile Z → E conversion of enamines,[10] N-styryl-imidazoles are known to retain their configuration,[11] a property that eliminates the ambiguities about the initial configuration of products.) According to the respective entries of Table 1, ring opening with this type of nucleophiles gave, in fact, exclusively 1E isomers. Exactly the same result was obtained for the reaction of (4) with sodium-morpholide (carried out under rigorously aprotic conditions). As there seemed no reason to assume drastic alterations either in the reaction mechanism or the conformation of intermediate (5) by merely changing the attacking atom of the entering nucleophilic agent, in the following, the effects of the steric demand of nucleophiles on the isomeric composition of products have been studied. A convenient experimental approach was provided by increasing the bulkiness of the alkyl group of alkoxide ions. The reactions were carried out under identical conditions, at t<-40°, by adding equivalent amounts of

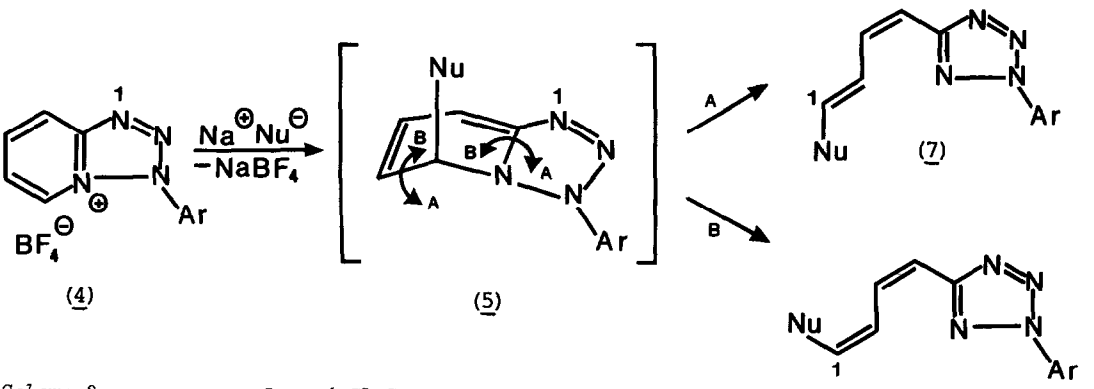
Table 1. Ring Opening Products (6) and (7) of Salt (4)

	Nucleophile (Nu)	Δ[1]	M.p. [°C]	Yield[a)12)] [%]	^{1}H NMR of Diene Protons[b)c)] Chemical Shifts (ppm) H1	H2	H3	H4	^{3}J coupling Constants (Hz) $J_{1,2}$	$J_{2,3}$	$J_{3,4}$
(6a)[e)]	$^{\ominus}$OMe	Z	164	38	6.46	7.02	6.55	6.29	6.05	10.52	11.21
(7a)[e)]		E	97	12	7.13	6.91	6.61	6.20	11.51	10.98	11.48
(6b)	$^{\ominus}$CN	Z	160	67	4.75	8.08	6.78	6.40	11.22	10.92	11.62
(7b)		E	142	15	4.92	8.11	6.42	6.54	15.82	11.20	11.88
(7c)	imidazole	E	151	92	7.17	7.96	6.60	6.67	13.86	10.91	10.74
(7d)	benzimidazole	E	198	82	7.28	7.92	6.67	6.89	13.26	10.78	10.82
(7e)	indole	E	164	85	6.93	8.05	6.58	6.71	13.26	10.78	10.82
(7f)	7-chloro-phenotiazine	E	179	89	d	8.11	d	6.65	13.1	10.8	10.82
(7g)[f)]	morpholine	E	94	69	6.65	7.27	6.81	6.22	12.92	10.81	10.15
(6h)[e)]	$^{\ominus}$OEt	Z	67	34	6.76	7.05	6.58	6.21	6.08	10.61	11.21
(7h)		E	54	12	6.91	7.30	6.48	6.21	11.82	10.48	11.32
(6i)	$^{\ominus}$OPr^i	Z	84	5	6.81	6.94	6.52	6.18	6.05	10.51	11.42
(7i)		E	77	75	6.44	6.84	6.49	6.21	10.85	10.84	11.23
(6k)	$^{\ominus}$OBu^t	Z	-	0	-	-	-	-	-	-	-
(7k)		E	106	79	6.82	7.78	6.39	6.18	11.62	11.09	10.85

a) Yields of isolated products after fractional crystallization. b) Proton NMR spectra were recorded at 100 MHz and ambient temp. in deuteriobenzene with TMS (0 ppm). c) Unless otherwise stated, NMR parameters were obtained by first-order approximation. Protons not indicated in the Table gave signals in agreement with structure. d) Unresolved multiplets. e) Spectral parameters were obtained by iterative spectral analysis. f) In DMSO-d_6 with 0.5% KOBu^t.

alcohol-free sodium-alcoholates in dry THF to (4) dissolved in dry acetonitrile. The results in Table 1 clearly show that the bulkiness of the entering group is indeed a principal determinant of the isomeric composition of products. Ring opening with ethoxide ions, as with methoxide ions, yields the 1Z isomer (6h) preferentially. A drastic change in the isomeric ratio can be seen with the larger isopropoxide nucleophile (6i, 7i) and, finally, the 1E isomer (7k) is the only dienic product in the reaction of (4) with t-butoxide ions.[13]

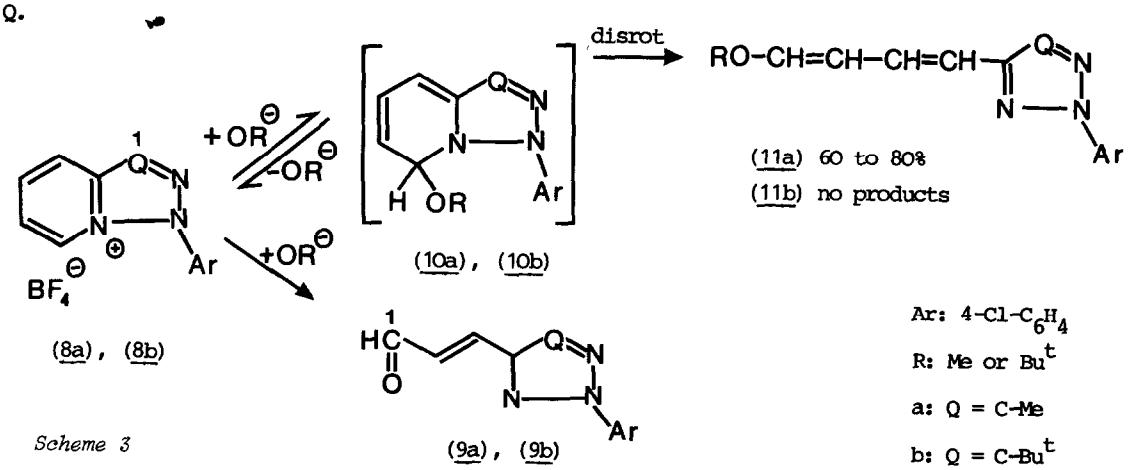
To rationalize the above findings, one has to assume that, contrary to earlier views,[2,3,6] disrotation of intermediate (5) may occur in *both senses* A and B (see Scheme 2); stereospecificity (*i.e.* high preferences for sense A), regardless of the attacking atom, is to be expected with bulky entering groups only.



(4) (5) (7) (6)

Scheme 2 Ar: 4-Cl-C_6H_4

The disrotation of (5) necessarily involves the rotational motion of the condensed tetrazole ring as a whole. Consequently, steric hindrance due to the size of group Q in position 1 (Scheme 3) might also affect the course of ring opening reaction. To test this hypothesis, (8a, Q = = C-Me) and (8b, Q = C-Bu^t), the *v*-triazolo-analogues of (4, Q = N) were reacted with methoxide and t-butoxide ions. (The reactivity towards nucleophiles of these 3-aryl-[1,2,3]triazolo[5,1-a] pyridinium salts[14a] was found[14b] to be essentially the same as that of (4).) Product analysis disclosed the formation of (9), a novel olefinic product the yield of which varied with the size of Q.



(8a), (8b) (10a), (10b) (11a) 60 to 80%
(11b) no products
(9a), (9b)

Ar: 4-Cl-C_6H_4
R: Me or Bu^t
a: Q = C-Me
b: Q = C-Bu^t

Scheme 3

Thus, reaction of (8a) with methoxide or t-butoxide ions gave, apart from the expected isomeric dienes (11a), 8 to 10% (9a),[15a] whereas, under identical conditions, the ring opening of (8b) with the same nucleophiles yielded no detectable amounts of dienes; product (9b)[15b] instead was found in 35 to 40% yields. The search for an analogous product in the reactions of (4) with these nucleophiles resulted in the isolation of small (1 to 3%) amounts of (9c, Q = N).[15c] These variations in the yield of (9) with the increasing size of Q indicate that steric hindrance at position 1 is capable to render the ring opening reaction according to Schemes 1 and 2 disadvantageous to the extent that the competitive degradation process becomes the predominant route.

In complete agreement with the consequences of a general disrotatory process, the above results strongly suggest that the ring opening reaction of these and simular systems is governed by an electrocyclization mechanism. The formation of the novel degradation product and the stereoselectivity leading to 1Z configured dienes must await further studies. These are now in progress in our laboratories.

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12. On the nitrogen elimination reaction of (4), observed with $^{\ominus}$OMe and $^{\ominus}$OEt nucleophiles, which reduces the overall yield of ring opening products, will be reported elsewhere.
13. The incomplete stereospecifity observed with $^{\ominus}OPr^{i}$ may be due to the ability of Pr^{i} group to avoid steric hindrance. See: M. Simonyi, I. Kovács, J. Kardos and S. Holly, *Tetrahedron Letters*, 1632 (1975).
14. (a) R. Kuhn and W. Münzig, *Chem. Ber.*, 86, 858 (1953). (b) Unpublished results from this laboratory.
15. (a) M.p.:104°C; ^{1}H NMR($CDCl_3$): δ ppm:9.77(H1,d,J_{12} 7.7 Hz); 6.98(H2,dd); 7.54(H3,d,J_{23}15.5 Hz); 2.54(3H,s); 8.05 and 7.41(4H,AA'BB',J(ortho) 8.1 Hz). (b) M.p.:85°C; ^{1}H NMR($CDCl_3$): δ ppm:9.72 (H1,d,J_{12} 7.6 Hz); 7.05(H2,dd); 7.61(H3,d,J_{23} 15.2Hz); 1.48(9H,s); 8.08 and 7.47(4H,AA'BB', J(ortho) 8.1 Hz). (c) M.p.:87°C; ^{1}H NMR($CDCl_3$): δ ppm:9.74(H1,d,J_{12} 7.6 Hz); 7.05(H2,dd); 7.62(H3,d,J_{23} 15.5 Hz); 8.08 and 7.44(4H,AA'BB', J(ortho) 8.1 Hz).

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