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EVIDENCE FOR A PARC-ANRO MECHANISM IN HETEROCYCLIC RING CONVERSION OF FUNCTIONALIZED N-ALKOXYPYRIDINIUM SALTS

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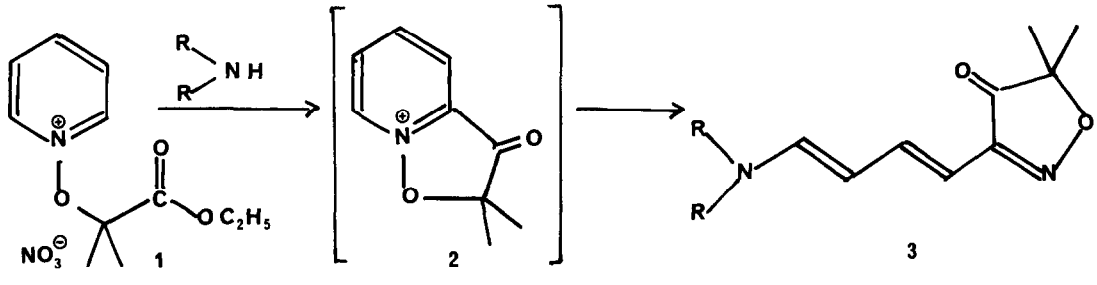
Summary : Isolation of intermediate isoxazolopyridinium salts ascertains earlier mechanistic assumption in a heterocyclic ring conversion of potential value for a new approach to terpenoid synthesis.

In an earlier study[1,2], we have postulated the mechanistic sequence Proton Abstraction, Ring Closure - Addition of a Nucleophile and Ring Opening (i.e. PARC-ANRO) in order to describe the ring conversion of functionalized N-alkoxypyridinium salts to isoxazoline derivatives. Since these latter are of potential value in various synthesis[3,4], we have further investigated this transformation both on mechanistic grounds and for applications in synthesis, especially to the terpenoid field.

Our previous work concerned the conversion of the salt 1 to isoxazolones 3, (scheme 1) for which we have postulated the intermediacy of the bicyclic ion 2 resulting from intramolecular attack of the ester group by an ylid formed by deprotonation of the pyridinium ion 1.

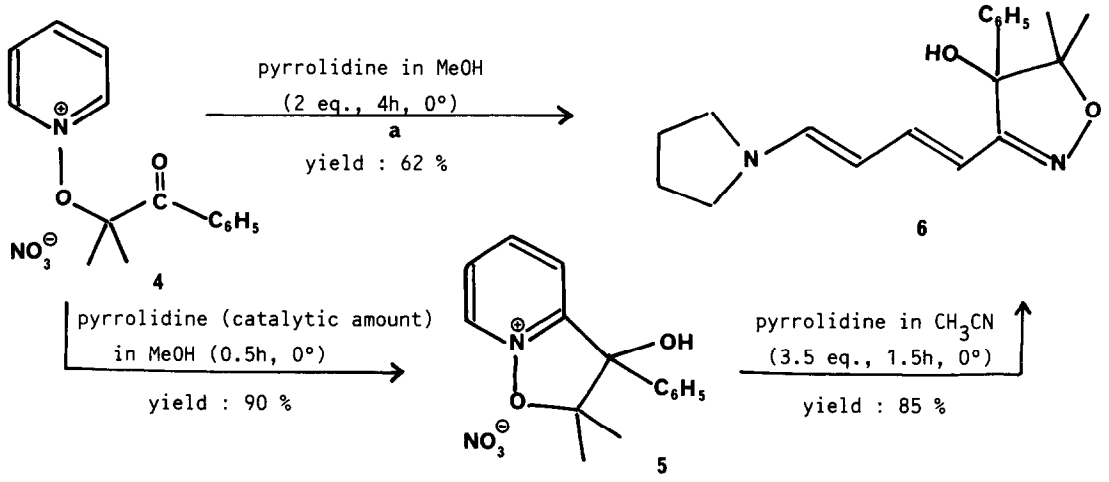


Scheme 1

Since the electron withdrawing keto group activates the alkoxypyridinium ion towards ring opening by a nucleophile such an amine, this bicyclic intermediate could not be isolated ; instead, it was converted to 3 according to mode D of the Katritzky's classification of reactions given by nucleophilic reagents on N-alkoxypyridnium salts[5,6]. This transformation (2⟶3) is reminiscent of the two first steps of the S_N (ANRORC) mechanism described by Van der Plas[7,8] for nucleophilic substitutions in heterocyclic series.

In order to make easier isolation of a bicyclic isoxazolopyridinium intermediate we have replaced the ester function of 1 by a keto group ; this latter was expected to still react with the ylid, even more easily, producing an alcohol function which would no more activate the resulting isoxazolopyridinium ion towards ring opening so that it could be isolated.

In effect, when N-benzoylisopropyloxy-pyridinium nitrate (4) was allowed to react with pyrrolidine, we observed the expected results which are summarized in scheme 2.

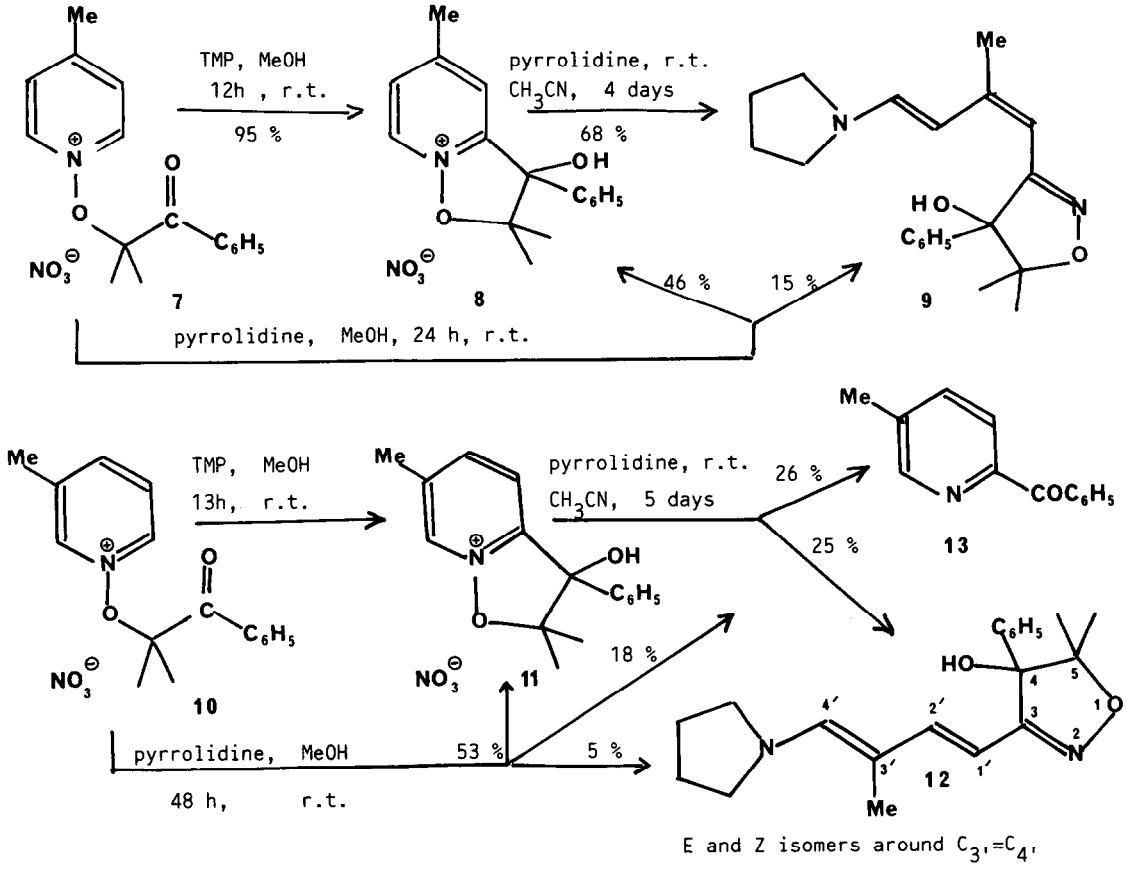


scheme 2

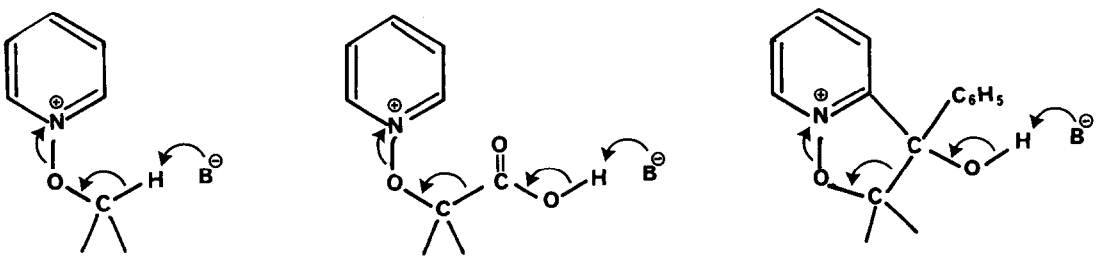
These results, joined to the fact that if reaction (a) is stopped after one hour, a mixture of products 5 and 6 is obtained, clearly demonstrate the two phases of the postulated PARC-ANRO sequence.

Extension of this heterocyclic ring transformation has been performed on similar salts derived from γ and β -picoline N-oxides (scheme 3). Although these are less reactive that the unsubstituted salt 1, very good yields in bicyclic intermediates[9] were obtained by use of 2, 2, 6, 6 tetramethylpiperidine (T.M.P.) since steric hindrance restricts reaction to the PARC phase of the process. The ANRO step was then performed by pyrrolidine in acetonitrile[10], but addition of the nucleophile (and subsequently ring opening) is disfavoured comparatively to the unsubstituted case both by electronic factors and by steric effects, especially for the β -picoline derivative. For this latter steric hindrance to this ANRO step allowed the observation of a competiting new mode of decomposition of N-alkoxypyridinium salts. This new mode can be depicted as "alcoxylog" of the mode A reported by Katritzky in the afore

mentioned classification[5,6], and compares rather well with decomposition occuring in a carboxylogous fashion described by Cohen[11] during oxidation of α -haloacids by pyridine N-oxide (scheme 4).



Scheme 3



Scheme 4

Stereochemistry of the opened products has been infered from ^1H n.m.r. analysis on the basis of vicinal coupling constants of ethylenic protons and deshielding introduced by the proximity of the OH group in -4 position, assuming an s-trans conformation about the single bonds as being the more stable. Data reported in the Table show that compound 6 possesses an all trans structure for its butadienyl chain, which is that of the thermodynamically more stable isomer. By contrast, the open product 9 has a trans cis syn geometry wich would be that of the primary product probably formed by a disrotatory opening of the adduct of pyrrolidine to the bicyclic ion 5, as we have shown in our previous work[1,2]. For compound 12, the cis configuration about the medium double bond is not maintained and a mixture of E and Z isomers (70-30) around the $C_{3'}$-$C_{4'}$ double bond is obtained.

Table : N.m.r. data for isozazolinols 6, 9 and 12 (in CDCl3, δ /TMS ppm, J Hertz)

	$-CH_2-CH_2-N$	Me (5)	C_6H_5(4)	OH(4)	1'	2'	3'	4'
6	1.86 m, 3.23 m	0.84 s, 1.44 s	7.40 s	3.2 s	5.76 d	6.64 dd	4.93 dd	6.48 d:
					$J_{1',2'}$:15.5	$J_{2',3'}$:11	$J_{3',4'}$:13	
9	1.94 m, 3.32 m	0.84 s, 1.44 s	7.42 s	3.36 s	4.9 s		7.02 d	6.4 d:
						Me 1.9 s	$J_{3',4'}$:13.5	
12 E:					5.7 d	6.7 d		6.13 s:
12	1.78 m, 3.32 m	0.82 s, 1.44 s	7.4 s	2.8 s	$J_{1',2'}$:16		Me 1.85 s	
Z:					5.86 d	7.15 d		6.08 s:

Since a dimethylisoxazoline ring can be visualized as a masked isoprenic unit, compounds 9 and 12 can be considered as structures related to functionalized terpenoids resulting respectively from head to tail or tail-to-tail fusion of two isoprenic moieties. In this respect the above results illustrate a novel approach to terpenoid synthesis.

References and Notes :

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9. The isolated isoxazolopyridinium salts 5, 8 and 11 (respective m.p. 137, 194 and 198°C) gave satisfactory elemental analysis and consistent n.m.r. spectra.
10. Our previous work[1,2] has shown that a protic solvent like methanol is necessary to observe the PARC step, otherwise the ANRO sequence occurs only on the starting N-alkoxypyridinium salt. These results, for which we gave an account by means of HSAB theory, explain the choice of the two solvents, MeOH and CH_3CN, used in this study.
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