Chemistry of Heterocycles; 7. Synthesis of Isoxazolopyridines by 6π-Electrocyclization[1]

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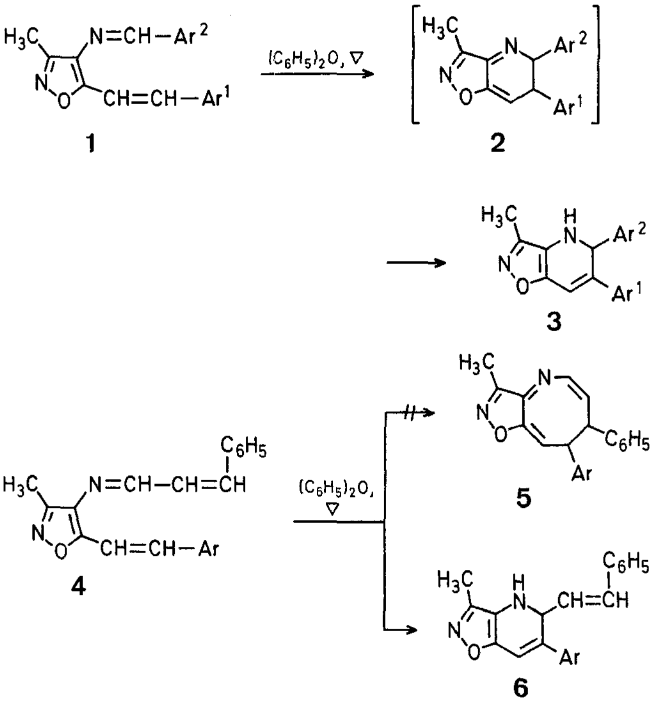
Electrocyclic ring-closures of aza-1,3,5-hexatriene to aza-1,3-cyclohexadiene which amount to isomerization, have not been reported sofar. The only known related reactions are the electrocyclic-ring closures accompanied by eliminations, which have been exhaustively reviewed[2], and transformations of these trienes into five-membered rings[3]. In this communication, we report a thermal electrocyclic reaction of 3-methyl-4-benzylideneamino-5-styrylisoxazoles **1**, strictly an isomerization, leading to isoxazolopyridines **3**. This is a convenient, one-step, general synthesis of compounds **3**, which hitherto required a multistep sequence[4-7].

Diphenyl ether solutions of 3-methyl-4-benzylideneamino-5-styrylisoxazoles **1**[8] were heated under reflux for 3 h. Removal of the solvent followed by crystallization furnished T.L.C.-pure products which have been characterized as 3-methyl-5,6-diaryl-4,5-dihydroisoxazolo[4,5-*b*]pyridines (**3**, Table) rather than the expected 3-methyl-5,6-diaryl-5,6-dihydroisoxazolo[4,5-*b*]pyridines (**2**). In the latter, the isoxazole ring is not aromatic but has an *o*-quinonoid structure and hence it might be isomerizing to the more stable structure **3**. The 1,2-dihydropyridine structure assigned to the product **3** is supported by I.R. (3400-3300 cm^{-1}) and ^{1}H-N.M.R. (a broad one-proton peak in the downfield area which disappears on shaking with deuterium oxide) spectra which point to the presence of NH. A 1,4-dihydropyridine structure for the product is ruled out as the ^{1}H-N.M.R. spectrum does not show any methylene protons.



With a view to extend the reaction to aza-1,3,5,7-octatetraenes, the vinylogue of **1**, namely, 3-methyl-4-cinnamylideneamino-5-styrylisoxazole (**4**) was subjected to thermal cyclization in diphenyl ether to get the azocine **5**. Instead of the expected **5**, the product was again the pyridine **6**. I.R. and ^{1}H-N.M.R. spectral data show the presence of the NH group. The ^{1}H-N.M.R. spectrum displays a doublet of doublets at $\delta = 7.1$ ppm ($J = 15$ Hz) which is diagnostic of a *trans*-1,2-disubstituted ethylene, thus strongly supporting the structure **6**. The reason as to why **4** is behaving like a hexatriene rather than a octatetraene is not clear, but cyclooctatrienes are obtained[9] only by the electrocyclic ring-closure of 2,4,6,8-decatetraenes.

3-Methyl-5,6-diaryl-4,5-dihydroisoxazolo[4,5-*b*]pyridines 3; General Procedure:

A solution of 3-methyl-4-benzylideneamino-5-styrylisoxazole **1** (5 mmol) in diphenyl ether (15 ml) is refluxed for 3 h. The dark brown substance obtained after the removal of solvent by steam distillation is triturated with benzene (20 ml). Crystallization from a large excess of benzene gives isoxazolopyridines **3**.

3-Methyl-5-styryl-6-phenyl-4,5-dihydroisoxazolo[4,5-*b*]pyridines (6); General Procedure:

3-Methyl-4-cinnamylideneamino-5-styrylisoxazole **4** (4 mmol) is refluxed in diphenyl ether (15 ml) for 3 h, cooled, and the solid formed is filtered and purified by crystallization.

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Table. 4,5-Dihydro-isoxazolo[4,5-*b*]pyridines **3** and **6** prepared

Product No.	Ar^1	Ar^2	Yield [%]	m.p. [°C] (solvent)	Molecular formula[a]	I.R. (KBr) ν [cm^{-1}]	^1H-N.M.R. ($CDCl_3$) δ [ppm]	M.S. *m/e* (rel. int. %)
3a	C_6H_5	C_6H_5	25	212° (C_6H_6)	$C_{19}H_{16}N_2O$ (288.4)	3350-3400 (NH)	2.6 (s, 3H); 6.9-8.0 (m, 12H); 12.0 (br. s, 1H)	288 (M^+, 100); 211 (30), 185 (20), 104 (22)
3b	C_6H_5	4-H_3C—C_6H_4	60	220° (C_6H_6)	$C_{20}H_{18}N_2O$ (302.4)	3250-3280 (NH)	—[b]	—[b]
3c	C_6H_5	4-Cl—C_6H_4	45	257° (CH_3OH/H_2O)	$C_{19}H_{15}ClN_2O$ (322.8)	3300-3360 (NH)	—[b]	—[b]
3d	4-H_3C—C_6H_4	C_6H_5	35	215° (C_6H_6)	$C_{20}H_{18}N_2O$ (302.4)	3270-3300 (NH)	2.4 (s, 3H); 2.6 (s, 3H); 7.3-8.2 (m, 11H); 11.5 (br. s, 1H)	—[b]
6a	C_6H_5	—	20	194-196° (C_6H_6/PE)	$C_{21}H_{18}N_2O$ (314.4)	3300-3370 (NH) 970 (*trans*-CH=CH)	2.5 (s, 3H); 7.1 (2d, 2H, $J = 15$ Hz); 7.0-8.1 (m, 12H); 9.5 (br. s, 1H)	314 (M^+, 100); 285 (24), 209 (40), 103 (17)
6b	4-H_3C—C_6H_4	—	25	226° (C_6H_6)	$C_{22}H_{20}N_2O$ (328.4)	3320-3380 (NH)	—[b]	—[b]

[a] Satisfactory microanalyses obtained: C ±0.50, H ±0.20, N ±0.06.

[b] Not recorded.

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