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A FACILE SYNTHESIS OF STABLE DIHYDROINDOLIZINES VIA INTRAMOLECULAR 1,5-CYCLIZATION OF YLIDES

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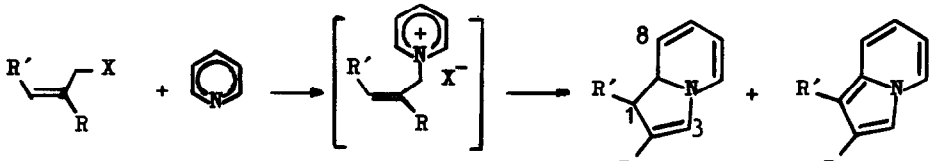
A few syntheses of indolizines by intramolecular 1,5-cyclization have been reported[1,2,3,4,5]. Dihydroindolizine intermediates were not obtained due to rapid oxidation to indolizines, except in special cases[3,4]. 1,3-Cycloaddition reactions of ylides with dipolarophile acetylenes[6] and ethylenes[7] yield in certain cases resonance stabilized dihydroindolizine derivatives.

In this investigation acyl- and aryl-substituted allyl halides and esters I were refluxed with K_2CO_3 in pyridine under N_2 to give dihydroindolizines II and/or indolizines III. The advantage of the procedure is its simplicity; isolation of the pyridine salts IV is not necessary. The overall conversion of I is high.

The structures of the new cyclization products were determined mainly on the basis of spectral data. Thus dihydroindolizines IId,e(=h),i show a typical 1,2-dihydropyridine pattern at δ6.6-5.1[8], absent in IIj. The protons 1 and 8a give a broad singlet (δ4.45 in IId and δ4.15 in IIe,i) in agreement with an analogous dihydropyrrolo[1,2-b]pyridazine[9]. In IIj this signal corresponds to one proton. A singlet near δ7.3 arises from H_3. Indolizines IIId-i show very similar NMR-absorptions to those of 1-substituted indolizine-2-carboxylic esters[10], H_3 appearing at δ7.7 instead of $\delta\approx$6.7, where H_1 would be found in 2-acyl-3-aryl-indolizines, formed by allylic rearrangement before cyclization. Both compounds II and III have an absorption maximum at 380-400nm, but II with larger extinction than III. The carbonyl bands in the IR-spectra of III are at 1650cm^{-1} (in IIId at 1620cm^{-1}), whereas those of II are found in the cluster

of strong bands between 1600-1500cm^{-1}. Significantly, the mass spectra of compounds IIi, IIIi and IIj, IIIj exhibit molecular peaks at 267, 265 and 272, 269 m/e, respectively. Indolizines IIId-j are not soluble in dilute acid and show a bright green to blue-green fluorescence, particularly in benzene, and are stable in the pure state. Dihydroindolizines IId-j can be stored for variable lenghts of time when air is excluded.



I IV II III

	X	R	R'	Ref. of I	%II	%III		Ref. of III
a	Br	Ph	H	11	-	84		17
b	Br	H	Ph	12	-	63		18
c	Br	Ph	PhCO	13	-	91		5
d	Br	PhCO	Ph	14	94	2		
e	Br	Ac	Ph		93	-		
f	OAc	Ph	H	15	-	100	x)	19
g	OAc	PhCO	H	16		45		
h	OAc	Ac	Ph		68	23	xx)	
i	OAc	Ac	p-MeO-Ph		73	16		
j	OAc	Ac	p-MeO-Ph		86	5	xxx)	

x) Cyclization with isoquinoline
xx) Exposed to air
xxx) Cyclization with D_5-pyridine

The role of the group R is dual; it activates the allylic double bond and stabilizes via N-C=C-CO -system the dihydroindolizines formed, e.g. If does not react with refluxing pyridine but does with refluxing isoquinoline, giving only the indolizine derivative IIIf. A large group R'does probably not permit full coplanarity of III thus decreasing the driving force in the formation of of III. In the case of Ig, the absence of a large R'accelerates the consumption

of Ig manifold, but after work-up only resin-contaminated IIIg could be obtained, although the presence of IIg was suggested by a typical red dihydroindolizine spot on TLC plate developed with H_2SO_4.

The ease of aerial oxidation of II to III varied with the nature of the group R'. When R' is electron releasing, p-anisyl in IIi, oxidation to IIIi occured even in neutral petroleum spirit at room temperature. In the case of IIj the expected retarding deuterium effect is observed. The electron withdrawing phenyl group in IId,e retarded the oxidation to IIId,e, and several hours' refluxing with base catalyst (e.g. pyridine) was required.

These cyclization reactions were notably selective, as beside II and III, the presence of only a few minor components was demonstrated on TLC plates. Some resinous material was formed in reactions a, b and g. Tentatively one of the byproducts is the epimer of II and another a dimeric product from I of an aromatic nature, as was indicated by its NMR- and mass spectra. Cyclization of other allylic compounds with pyridines is now being studied.

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