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PHOTOCYCLIZATION OF 5-(1-ALKENYL)-1-PHENYLPYRAZOLES : A CONVENIENT SYNTHESIS OF 4,5-DIHYDROPYRAZOLO[1,5-*a*]QUINOLINES

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Summary: The photocyclization of some 5-(1-alkenyl)-4-ethoxycarbonyl-1-phenylpyrazoles affords 3-ethoxycarbonyl-4,5-dihydropyrazolo[1,5-*a*]quinolines which are decarboxylated to the 3-unsubstituted analogs.

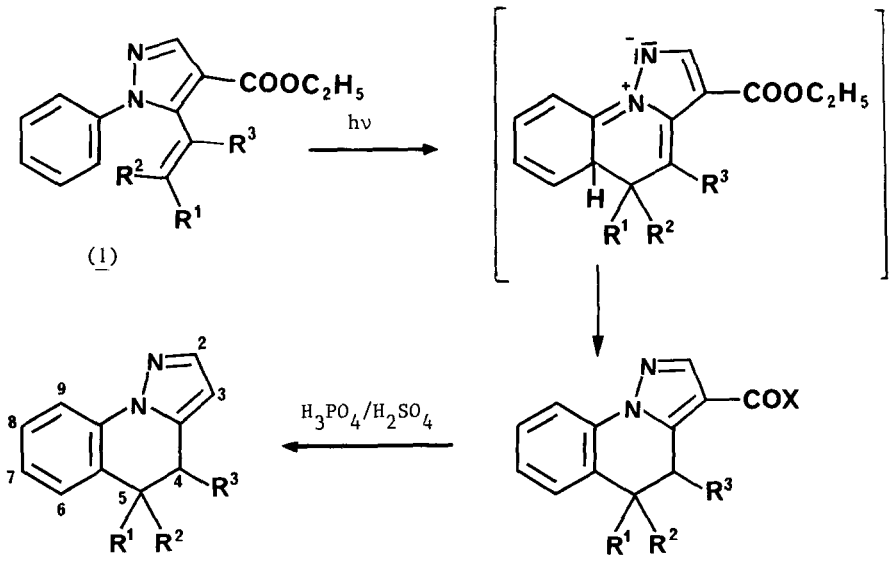
There are few synthetic routes to 4,5-dihydropyrazolo[1,5-*a*]quinolines[1-6]. Only one report in the literature describes the use of photocyclization in the synthesis of 3,4-dimethyl-2-phenyl-4,5-dihydropyrazolo[1,5-*a*]quinoline from 5-isopropenyl-4-methyl-1,3-diphenylpyrazole[4]. The potential usefulness of 5-(1-alkenyl)-1-phenylpyrazoles was hitherto limited since their synthesis were rather difficult[4,7,8]. Recent work from our laboratory has centered on the preparation of this class of pyrazoles[5,6]. Electrophilic ring closure to afford the pyrazoloquinolines was only successful in the case of 1-phenylpyrazoles bearing a styryl or 2-methyl-1-propenyl group at the C-5 position[5,6]. Consequently, we have explored the photoreactivity of a series of various 5-alkenyl or dialkenyl-1-phenyl-pyrazoles (1), to allow a general entry to 4,5-dihydropyrazolo[1,5-*a*]quinolines.

Irradiation of compounds (1a-e) under nitrogen, in benzene as solvent, for one hour, gives rise, in all cases, to complete conversion to 3-ethoxycarbonyl-4,5-dihydro[1,5-*a*]quinolines (2a-e)[9].

Table. Physical constants and spectral data of compounds (3) and (4).

Compd	Yield %	Mp °C	UV (C_2H_5OH) λ_{max} nm (ε)	^{1}H NMR, δ ppm (DMSO-d_6 for 3, $CDCl_3$ for 4). H-2	H-3	H-4 (m)	H-5 (m)	H-9 (m)
3a[f]	69[b]	149	268 (14400)	8.08[d]		3.5-4.0 (1H)	2.8-3.5 (1H)	7.8-8.0
3b	65[b]	177	267 (15900)	8.14[d]		3.7-4.2 (1H)	2.7-3.5 (2H)	7.8-8.1
3c	68[b]	190	268 (16100)	8.08[d]		3.23[d] (2H)		7.8-8.0
3d	65[b]	183	268 (15000)	8.14[d]		2.9-3.7 (3H)		7.8-8.1
3e[g]	62[b]	168	267 (14800)	8.05[d]		2.8-4.4 (3H)		7.7-8.0
4a[f]	75[c]	oil	263 (13500)	7.65[e]	6.20[e]	2.5-3.5 (2H)		7.8-8.1
4b	70[c]	oil	261 (13100)	7.65[e]	6.20[e]	2.4-3.4 (3H)		7.8-8.1
4c	77[c]	oil	263 (14700)	7.68[e]	6.20[e]	2.86[d] (2H)		7.9-8.1
4d	79[c]	oil	262 (15400)	7.65[e]	6.20[e]	2.5-3.3 (3H)		7.9-8.1

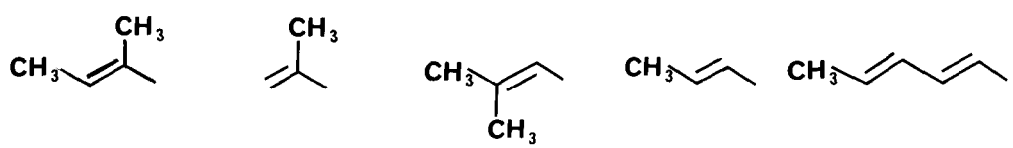
[a] All products give satisfactory elemental analyses. [b] Irradiation of a solution of (1) (5 mmol), in benzene (500 ml) for 1 h through a quartz tube with a 400 W high pressure mercury lamp, as nitrogen is bubbled through it, yields the dihydropyrazoloquinolines (2). The esters (2) are converted to the acids (3) by refluxing with 10% KOH for 4 h and acidifying. Analytical samples are obtained by recrystallization from methanol (3b), acetonitrile (3c-e) or by column chromatography on silica gel using ethyl acetate as eluent (3a). [c] Decarboxylation of (2) obtained as described above, by heating for 15 min at 190°C in 85% phosphoric acid (5g) and concentrated sulfuric acid (0.75 g), followed by extractive work up with chloroform and column chromatography on silica gel using hexane/ethyl acetate 4:1 as eluent affords (4). [d] (s). [e] (d, J = 1.5 Hz). [f] Mixture of *cis/trans* isomers in a ratio respectively of 2:1. [g] Mixture of E/Z isomers in a ratio of 1:1.



	a	b	c	d	e
R^1	CH_3	H	CH_3	CH_3	CH_3-CH=CH
R^2	H	H	CH_3	H	H
R^3	CH_3	CH_3	H	H	H

When the reaction is stopped after ten minutes, analysis of the reaction mixture shows that the ratio (2):(1) is slighty substituent dependent : a methyl substituent on the α position of the alkenyl chain decreases the reactivity.

Product ratio (2):(1) after ten min.



(2):(1) 44:56	47:53	69:31	72:28	74:26
a	b	c	d	e

The formation of the new bond closing the ring of pyrazole between an aromatic ring and an alkenyl group appears to derive of a conrotatory process[10], involving a zwitterionic intermediate. Subsequent thermal suprafacial [1,5] (or [1,9]) sigmatropic shift of a hydrogen atom gives rise to the dihydropyrazoloquinoline. Following this mechanism, *trans* 3-ethoxycarbonyl-4,5-dimethyl-4,5-dihydropyrazolo[1,5-*a*]quinoline should be obtained

starting from (E) 5-(1-methyl-1-propenyl)-1-phenylpyrazole (1a). Surprisingly, a mixture of inseparable *cis/trans* isomers (2a) in a ratio respectively 2:1 is obtained[11]. It is not clear how the *cis* product is formed. A possible explanation for this stereochemical feature could be due to a partial E/Z isomerisation of the side chain prior to ring closure. However, no evidence of the presence of the Z isomer can be obtained from analysis of the partially photocyclized mixture. It is possible that the Z isomer is more reactive than its precursor E isomer. The isomeric composition of the products of irradiation of (1a), analyzed at various intervals of time (10 min, 30 min, 1 h, 5 h) remains the same. *Trans/cis* isomerization post to the cyclization seems unlikely in anaerobic conditions and aprotic solvent.

Decarboxylation of the dihydropyrazoloquinolines (2a-d), by heating, in acidic medium affords easily the corresponding 3-unsubtituted derivatives (4). Compound (3e) polymerizes.

Additionnal studies concerning substituent effects and mechanistic details of this reaction are in progress.

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9 The oily esters (2)are converted to the cristalline acids (3) for purification.

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11 Based on the coupling constants H_4-H_5 observed in the 350 MHz ^{1}H-NMR spectrum of the isomeric mixture (3a): J_{cis}= 1.3 Hz ; J_{trans}= 5.6 Hz. This is in accordance with the general principle of stereochemical assignment by examination of molecular models (M. J. Karplus, J. Am. Chem. Soc., 85, 2870 (1963); L. M. Jackman and S. Sternhell, " Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: New York, 1969).

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