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SYNTHESIS OF SOME 3-OXO-2-PHENYL-6,7-DIHYDRO-2*H*-PYRANO[4,3-c]PYRAZOLE DERIVATIVES

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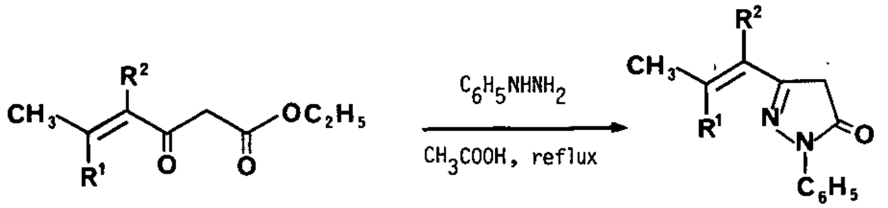
Abstract---- Acylation reaction of 3-(2-methyl-1-propenyl)-1-phenyl-2-pyrazolin-5-one provides a route to 6,6-dimethyl-3-oxo-2-phenyl-6,7-dihydro-2*H*-pyrano[4,3-c]pyrazole derivatives.

Recent work in this laboratory has centered on the synthesis of biologically active pyranopyrazoles[1,2]. To provide further insight into this class of fused-pyrazoles, we have examined the utility of suitably functionalized 2-pyrazolin-5-one derivatives, as precursors, based on the annulation of the pyrone ring.

Traditionnally, preparation of 3-alkyl-1-phenyl-2-pyrazolin-5-ones involves the condensation of β-keto esters with phenylhydrazine. Interest in the pharmacology of these compounds has resulted in numerous compounds having various substituents[3,4]. Surprisingly, this route has not been applied hitherto to the synthesis of 3-alkenyl derivatives. We now report a successful conversion of γ,δ-unsaturated β-keto esters (1) into new 3-alkenyl-1-phenyl-2-pyrazolin-5-ones (2-4)



(1)

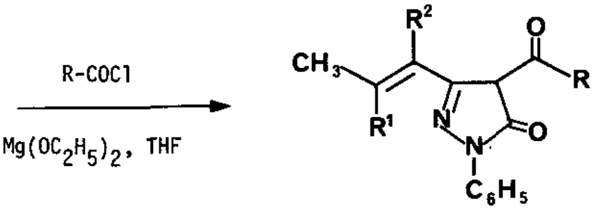
(2) $R^1 = R^2 = H$

(3) $R^1 = H$, $R^2 = CH_3$

(4) $R^1 = CH_3$, $R^2 = H$

The acylation reaction of 1-aryl-2-pyrazolin-5-ones has been extensively studied during the past decade. In the most cases, the C-acylation has been carried out using acyl chlorides in the presence of $Ca(OH)_2$[5-8]. We have found that the compounds (2-4) can be readily acylated, using magnesium ethoxide as base and tetrahydrofuran as solvent, by various acyl chlorides, to afford the corresponding 4-acyl derivatives (5-7).

(2-4)



R

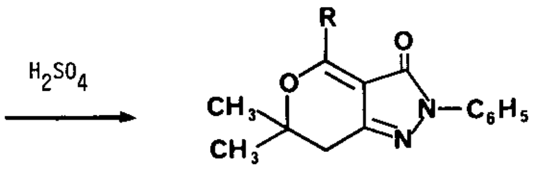
a, CH_3
b, C_2H_5
c, C_6H_5
d, (E,E) CH_3-CH=CH-CH=CH
e, (E) C_6H_5-CH=CH

(5c) $R^1 = R^2 = H$
(6c) $R^1 = H$, $R^2 = CH_3$
(7a-e) $R^1 = CH_3$, $R^2 = H$

The expected ring closure of the enol hydroxyl of the side chain upon the double bond, in the presence of concentrated sulfuric acid, can be realized only in the case of the compounds (7), $R^1 = CH_3$, $R^2 = H$, whereas, from (5c) and (6c), under the same reaction conditions, only the starting materials were recovered. These results could be explained by postulating that the cyclization proceeds via a tertiary carbonium ion intermediate.

Compounds (7a-e) bearing diversified acyl groups were successfully converted into 6,6-dimethyl-3-oxo-2-phenyl-6,7-dihydro-2*H*-pyrano[4,3-c]pyrazole derivatives (8a-e), a novel class of fused-pyrazoles.

(7a-e)



(8a-e)

Table Physical Data of New Compounds (2-8)

Compd.	Yield %	MP °C[a]	Molecular Formula[b]	IR ($CHCl_3$) ν CO cm^{-1}	UV (C_2H_5OH) λ nm (ε. 10^{-3})
2	60	135-136 (A)	$C_{12}H_{12}N_2O$	1715	260 (18.5)
3	60	114-115 (A)	$C_{13}H_{14}N_2O$	1715	258 (22.7)
4	80	121-122 (A)	$C_{13}H_{14}N_2O$	1715	266 (19.8)
5c	60	90-92 (A)	$C_{19}H_{16}N_2O_2$	1610	250 (20.6)
6c	70	78-79 (A)	$C_{20}H_{18}N_2O_2$	1605	250 (21.9)
7a	60	88-89 (A)	$C_{15}H_{16}N_2O_2$	1620	259 (22)
7b	65	79-80 (A)	$C_{16}H_{18}N_2O_2$	1620	259 (20.6)
7c	50	73-74 (A)	$C_{20}H_{18}N_2O_2$	1600	252 (19.9)
7d	70	135-136 (A)	$C_{19}H_{20}N_2O_2$	1635	340 (21.5), 272 (17.7), 264 (17)
7e	70	144-145 (A)	$C_{22}H_{20}N_2O_2$	1640	340 (21.2), 296 (17.2), 252 (19.2)
8a	80	109-110 (B)	$C_{15}H_{16}N_2O_2$	1680	264 (19.7)
8b	80	97-98 (C)	$C_{16}H_{18}N_2O_2$	1680	275 (19.6)
8c	70	150-151 (D)	$C_{20}H_{18}N_2O_2$	1675	305 (18.4), 256 (19.2)
8d	80	136-137 (A)	$C_{19}H_{20}N_2O_2$	1670	350 (31), 254 (15.3)
8e	70	167-168 (A)	$C_{22}H_{20}N_2O_2$	1670	360 (31), 246 (18.9)

[a] Recrystallization solvent; A: ethanol; B: ethyl acetate/hexane 1:9; C: hexane; D: ethyl acetate/hexane 1:1. [b] All products gave satisfactory microanalyses. ^{1}H-nmr data are in good agreement with proposed structures; compounds (5-7) exist, in solution, as the enol tautomers.

EXPERIMENTAL SECTION

All melting points were determined on a Kofler block. Infrared and ultraviolet spectra were obtained with Beckman Model Acculab 2 and DB spectrometers. NMR spectra were recorded on a Brucker WP 80 spectrometer. Elemental analyses were performed by microanalytical laboratory, Centre National de la Recherche Scientifique, 69390 Vernaison, France.

3-Alkenyl-1-phenyl-2-pyrazolin-5-ones (2-4); General Procedure

A mixture of the appropriate γ,δ-unsaturated β-keto ester (1) (0.1 mol), phenylhydrazine (10.8 g, 0.1 mol), in acetic acid (250 ml) was refluxed for 1.5 h. After evaporation under reduced pressure of the solvent, the residue was recrystallized from ethanol.

4-Acyl-3-alkenyl-1-phenyl-2-pyrazolin-5-ones (5-7); General Procedure

A mixture of 3-alkenyl-1-phenyl-2-pyrazolin-5-one (2, 3, or 4) (0.02 mol), magnesium ethoxide (2.28 g, 0.02 mol) and dry tetrahydrofuran (100 ml) was stirred and heated to reflux for 4 h. The mixture was then cooled to 0-5°C and a solution of the acyl chloride (0.02 mol) in tetrahydrofuran (25 ml) was added dropwise with stirring. The mixture was then allowed to stand at room temperature for 3 h and poured onto cold 10% hydrochloric acid (300 ml) and extracted with chloroform (3 X 50 ml). The combined extracts were washed with water. After drying and evaporation of the solvent, the residue was recrystallized from ethanol.

6,6-Dimethyl-3-oxo-6,7-dihydro-2*H*-pyrano[4,3-c]pyrazoles (8); General Procedure

4-Acyl-3-(2-methyl-1-propenyl)-1-phenyl-2-pyrazolin-5-one (7) (0.01 mol) was added to concentrated sulfuric acid (50 ml) with stirring. The mixture was allowed to stand at room temperature overnight. The mixture was then poured onto ice water (400 g) and extracted with chloroform (3 X 50 ml). The combined extracts were washed with 10% aqueous potassium carbonate (2 X 30 ml), dried and evaporated. The residue was recrystallized from a suitable solvent (table).

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