*Christian Deshayes and Suzanne Gelin**

Laboratoire de Chimie Organique, Institut National des Sciences Appliquées,
20, Avenue Albert Einstein, 69621 Villeurbanne Cédex, France

Received October 31, 1978

The regioselective synthesis of new 3-alkenyl-1-phenylpyrazoles **4** from the reaction of phenylhydrazine with 2,3-dihydro-4*H*-pyran-4-ones **1** is described.

J. Heterocyclic Chem., **16**, 657 (1979).

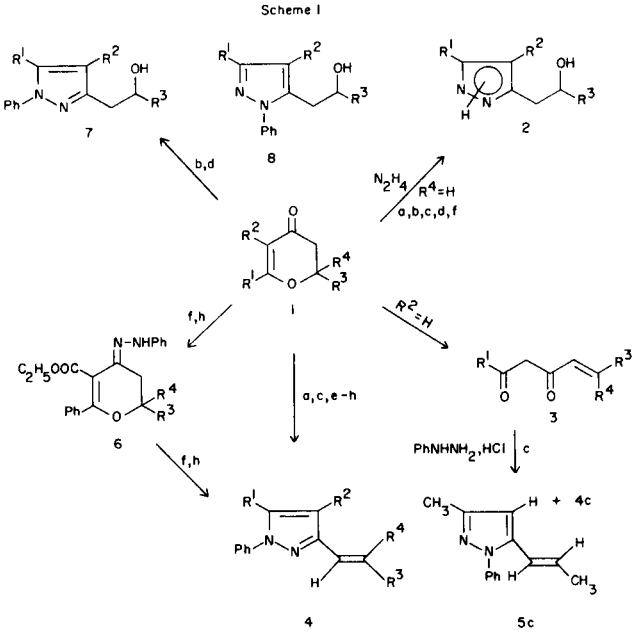
We have recently shown that the 2,3-dihydro-4*H*-pyran-4-ones **1** are readily converted into 3(5)-(2-hydroxyalkyl)pyrazole derivatives **2** by the action of hydrazine hydrate (1). This reaction involves the conjugate addition of hydrazine to the C-6 carbon atom. In continuation of this work, we report in this paper the behaviour of these compounds **1a-h** toward the action of phenylhydrazine. In most cases, the regioselective formation of 3-alkenyl-1-phenylpyrazole derivatives **4a,c,e-h** provides a new entry to this class of compounds; 1-phenyl-3-alkenylpyrazoles were only obtained from the action of *N*-phenylsydnone on conjugated enynes (2). Reaction of ethylenic β-diketones **3c,e,g** (open chain isomers of **1c,e,g**) and *p*-nitro or 2,4-dinitrophenylhydrazines has been investigated; this reaction afforded mixtures of both *N*-substituted isomeric 3- and 5-alkenylpyrazoles (3). By the action of various phenylhydrazines on 2,4-dioxohexenoates or hydroxymethyleneketone derivatives, *N*-substituted 5-alkenylpyrazoles were formed (4).

Results.

The nature of the products obtained by the reaction of phenylhydrazine on compounds **1** was found to be dependent on the substituents R^1 and R^2 and on the reaction conditions. Upon treatment of compounds **1a,c,e-h** with phenylhydrazine, catalyzed by acetic acid, 3-alkenyl-1-phenylpyrazole derivatives **4** were formed in good yields. Compounds **1f,h** under milder conditions, at room temperature, reacted to yield phenylhydrazones **6f,h**. These phenylhydrazones were unaffected on heating in ethanol, but in the presence of a catalytic amount of acetic acid, they afforded the corresponding alkenylpyrazoles **4f,h** in near quantitative yields.

However, under the same conditions, compound **1b** afforded a material wherein a mixture of the isomeric 3- and 5-(2-hydroxyethyl)pyrazoles **7b** and **8b** was detected. Fractional crystallization of the raw material yielded only crystallized pure compound **8b** in 30% yield; after several purifications of the residue (column chromatography) a small amount of an oily compound **7b** was isolated. The structures of compounds **7b** and **8b** were supported by ^{13}C-nmr (Table IV). Compound **1d** afforded a crude residue wherein a mixture of pyrazoles

Scheme I



	R^1	R^2	R^3	R^4
a	CH_3	H	H	H
b	CH_3	$CO_2C_2H_5$	H	H
c	CH_3	H	CH_3	H
d	CH_3	$CO_2C_2H_5$	CH_3	H
e	C_6H_5	H	CH_3	H
f	C_6H_5	$CO_2C_2H_5$	CH_3	H
g	C_6H_5	H	CH_3	CH_3
h	C_6H_5	$CO_2C_2H_5$	CH_3	CH_3

7d, **8d** and **4d** in a ratio (**7d** + **8d**/**4d**) of 7:3 was detected by ^{1}H-nmr (multiplet at 2.90-3.25 ppm, characteristic of methylenic protons at the C-3 and C-5 positions, respectively, for compounds **7d** and **8d**, and a doublet at 1.89 ppm, methyl protons of the propenyl group for **4d**). No further purification was undertaken.

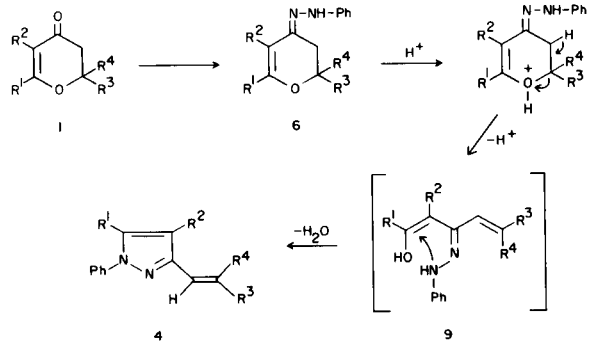
These results allow a plausible reaction scheme to be advanced to explain the synthesis of pyrazoles **4**. The formation of a phenylhydrazone suggested that the carbonyl at the C-4 position of the dihydro-γ-pyrones is reactive toward nucleophiles and competes with conjugate addition at the C-6 position. The intermediate open-chain

0022-152X/79/040657-04$02.25

© *HeteroCorporation*

compound **9**, as a result of the acid-catalyzed conversion of the hydrazone **6** (probably by initial *O*-protonation) can be expected to undergo exclusive formation of 3-alkenylpyrazoles **4** by a facile ring closure (Scheme 2). The reversibility of the ring chain tautomerism catalyzed by acids and bases in dihydro-γ-pyrones derivatives is known (5,6).

Scheme 2



In order to prepare the 5-alkenyl pyrazoles **5c,e**, we have examined the action of phenylhydrazine hydrochloride on β-diketones **3c,e**; only compound **3c** reacted to yield a mixture of two *N*-phenylpyrazoles **4c** and **5c** in a ratio of 1:4. The structures **4c** and **5c** were consistent with ^{13}C-nmr spectral comparison of these materials with previous findings concerning the carbon chemical shifts of methyl groups in isomeric pyrazole pairs (7); the C-3 methyl signal in compound **5c** is shifted to a lower field than the C-5 methyl signal in compound **4c** (Table III). The spectral properties of compound **4a** were similar with those of **4c**. The position of a 5-phenyl group in compounds **4e-h** was deduced from the observed singlet phenyl resonance, characteristic of an α-substituent (3,7).

EXPERIMENTAL

Melting points were determined on a Kofler hot plate and boiling points are uncorrected. Infrared and ultraviolet spectra were obtained with a Beckman Model Acculab 2 and DB spectrophotometers. ^{1}H-nmr spectra were taken on a Varian A-60; ^{13}C-nmr spectra were obtained with a Varian XL-100-12FT. The chemical shifts reported are in parts per million from internal TMS.

Elemental analysis were performed by Microanalytical Laboratory, Centre National de la Recherche Scientifique, Villeurbanne, France.

2,3-dihydro-4*H*-pyran-4-ones **1a-h** and β-diketones **3c,e** were prepared as previously described (6).

General Procedure for the Preparation of 3-Alkenyl-1-phenylpyrazoles (**4a,c,e-h**).

A mixture of **1** (10 mmoles) phenylhydrazine (10 mmoles) and two drops of acetic acid (for compound **1a**, *p*-quinone was added to prevent polymerization) was heated at 100° for an hour. The cooled residue was then dissolved in 50 ml. of benzene and the solution was dried. After evaporation *in vacuo*, the crude residue was distilled (**4a, c,e,g**) or recrystallized (**4f**). Compound **4h** was purified by column chromatography through a (24 mm x 69 cm) column of silica gel (95 g.) using hexane/ethyl acetate (2:8) as eluent. The product (2.15 g.) was obtained after elution of 200 ml. to 400 ml. (8). For physical data see Tables I, II, III.

Reaction of Compound **1b** with Phenylhydrazine.

The reaction mixture obtained as described above was

Table I

Physical Data for Compounds **4**

Compound No.	Yield	M.p. or B.p./Torr °C	Molecular Formula	Analyses Calcd. % Found % C	H	N	Uv in Ethanol λ Max (Nm) ε	Ir (Cm^{-1}) Chloroform
4a	75%	125-130/0.7	$C_{12}H_{12}N_2$	78.23	6.57	15.21	212 (10300)	1640
			(184.23)	78.33	6.74	15.11	258 (15000)	990
								910
4c	71%	130/0.7	$C_{13}H_{14}N_2$	78.75	7.12	14.13	212 (9200)	1675
			(198.26)	78.70	7.36	14.04	263 (14600)	965 (a)
4e	85%	172/0.5	$C_{18}H_{16}N_2$	83.04	6.20	10.76	212 (16700)	1670
			(260.32)	83.04	6.12	10.62	245 (27300)	965 (a)
4f	60%	113 (b)	$C_{21}H_{20}O_2N_2$	75.88	6.07	8.43	217 (21200) sh	1705
			(332.39)	75.97	6.11	8.18	236 (28600)	1660
								965 (a)
4g	80%	188-190/0.7	$C_{19}H_{18}N_2$	83.17	6.61	10.21	212 (17400)	1675
			(274.35)	82.72	6.69	10.22	245 (27600)	975
4h	62%	101 (c)	$C_{22}H_{22}O_2N_2$	76.27	6.40	8.09	219 (20100) sh	1705
			(346.41)	76.38	6.39	8.10	239 (23900)	1665
								975

(a) *E*-Configuration. (b) Solvent of crystallization: hexane. (c) Purified by column chromatography (see Experimental).

Table II

Proton Magnetic Resonance Parameters in Deuteriochloroform

δ (ppm)

Compound No.	
4a	2.18 (s, 3H), 5.26 (dd, 1H, J = 1.5 Hz, J = 11 Hz), 5.68 (dd, 1H, J = 1.5 Hz, J = 17.5 Hz), 6.28 (s, 1H), 6.78 (dd, 1H, J = 11 Hz, J = 17.5 Hz), 7.11-7.47 (m, 5H)
4c	1.87 (d, 3H, J = 5.5 Hz), 2.23 (s, 3H), 6.06-6.88 (m, 3H), 7.36-7.73 (m, 5H)
4e	1.83 (d, 3H, J = 5.5 Hz), 5.91-6.67 (m, 3H), [7.09 (s), 7.12 (s), 10H]
4f	1.06 (t, 3H, J = 7 Hz), 1.94 (d, 3H, J = 5.5 Hz), 4.10 (q, 2H, J = 7 Hz), 6.47-7.38 [(m, 12H, with 7.19 (s), 7.26 (s)]
4g	1.90 (d, 3H, J = 1.5 Hz), 2.06 (d, 3H, J = 1 Hz), 6.23 - 6.39 (m, 1H), 6.47 (s, 1H), [7.16 (s), 7.21 (s), 10H]
4h	1.05 (t, 3H, J = 7 Hz), 2.00 (d, 3H, J = 1.5 Hz), 2.18 (d, 3H, J = 1 Hz), 4.11 (q, 2H, J = 7 Hz), 6.65-6.85 (m, 1H), 7.18 (s, 5H), 7.27 (s, 5H).

Table III

Carbon-13 Chemical Shifts for **4c** and **5c** in Deuteriochloroform

Compound No.	C-3	C-4	C-5	CH_2 (R^1)	CH_3 (CH_3-CH=)
4c	150.8	103.5	139.6	12.3	18.3
5c	148.7	103.2	141.7	13.5	18.5

No attempt was made to assign the resonance to a specific carbon atom of the phenyl and vinyl groups.

dissolved in 50 ml. of ether. The solution was washed with 1*N* hydrochloric acid, 10% sodium hydroxide and water, and then dried. After evaporation *in vacuo*, the residue was recrystallized from hexane/ethyl acetate (4:1) to yield compound **8b** (0.8 g., 30%). The filtrate was evaporated *in vacuo* and purified on a silica gel column with ether as eluent; a small quantity of compound **7b** was obtained after several purifications.

4-Ethoxycarbonyl-5-(2-hydroxyethyl)-3-methyl-1-phenylpyrazole (**8b**).

This compound had m.p. 111°; uv (ethanol): λ nm (ε) 220 (10,000) sh, 241 (12,500); ir (potassium bromide): 3330, 1710 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 1.37 (t, 3H, J = 7 Hz), 2.47 (s, 3H), 3.11 (t, 2H, J = 6 Hz), 3.21-3.48 (m, 1H, CF_3COOH exchangeable), 3.78 (t, 2H, J = 6 Hz), 4.34 (q, 2H, J = 7 Hz), 7.41 (s, 5H).

Anal. Calcd. for $C_{15}H_{18}N_2O_3$ (274.31): C, 65.67; H, 6.61; N, 10.21. Found: C, 65.58; H, 6.69; N, 10.28.

4-Ethoxycarbonyl-3-(2-hydroxyethyl)-5-methyl-1-phenylpyrazole (**7b**).

This compound was a viscous oil; uv (ethanol): λ nm (ε) 218 (10,300), 245 (12,300); ir (chloroform): 3470, 1705 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 1.38 (t, 3H, J = 7 Hz), 2.53 (s, 3H), 3.03-3.50 (m, 3H, 1H, CF_3COOH, exchangeable), 4.01 (t, 2H, J = 6 Hz), 4.36 (q, 2H, J = 7 Hz), 7.44 (s, 5H).

Phenylhydrazones **6f,h**.

A mixture of compound **1** (10 mmoles) and phenylhydrazine (10 mmoles) in 20 ml. of ethanol was allowed to stand overnight at room temperature.

Compound **6f**.

The separated solid was recrystallized from ethanol to give compound **6f** (1.45 g., 42%), m.p. 127°; ir (chloroform): 3380, 1730 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 1.19 (t, 3H, J = 7 Hz), 1.67 (d, 3H, J = 6 Hz), 1.80-2.96 (m, 2H, 8 lines), 3.96-4.58 (m, 3H), 6.65-7.78 (m, 11H).

Anal. Calcd. for $C_{21}H_{22}N_2O_3$ (350.40): C, 71.98; H, 6.33; N, 8.00. Found: C, 72.06; H, 6.49; N, 7.96.

Table IV

Carbon 13 Chemical Shifts for **7b** and **8b** in Deuteriochloroform

Compound No.	C-3	C-4	C-5	CH_3	CO_2-CH_2-CH_3	CH_2-CH_2-OH	
7b	152.9	110.6	144.3	12.6	164.3-61.4-14.4	31.0-59.9	C′$_1$ 138.4 C′$_{2,6}$ 125.5 C′$_{3,5}$ 129.0 C′$_4$ 128.4
8b	151.1	110.6	146.0	14.4	164.6-61.2-14.4	29.0-60.0	C′$_1$ 138.4 C′$_{2,6}$ 126.2 C′$_{3,5}$ 129.0 C′$_4$ 128.6

The assigment of lines was determined according to reference (7).

Compound **6h**.

The reaction mixture was evaporated *in vacuo* and the residue was recrystallized from hexane to yield compound **6h** (1.4 g., 38%), m.p. 111°; ir (chloroform): 3370, 1730 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 1.17 (t, 3H, J = 7 Hz), 1.42 (s, 6H), 2.48 (s, 2H), 4.23 (q, 2H, J = 7 Hz), 6.61-7.69 (m, 11H).

Anal. Calcd. for $C_{22}H_{24}N_2O_3$ (364.43): C, 72.50; H, 6.64; N, 7.69. Found: C, 72.55; H, 6.50; N, 7.59.

3-Alkenyl-1-phenylpyrazoles **4f,h** from Phenylhydrazones **6f,h**.

A solution of compound **6** (1.4 mmoles), in ethanol (5 ml.) with acetic acid (two drops) was refluxed for two hours. The reaction mixture was evaporated *in vacuo* and the residue recrystallized from hexane ot give **4f** or **4h**.

Reaction of Phenylhydrazine Hydrochloride with β-Diketone **3c**.

Phenylhydrazine hydrochloride (69.2 mmoles) was dissolved in 150 ml. of water and compound **3c** (53.3 mmoles) was added dropwise with stirring at room temperature. After two hours of stirring at 50°, the mixture was cooled and extracted with ether; the ether layer was washed with 5% sodium bicarbonate and water. After drying and evaporation of the solvent, the residue was distilled *in vacuo* (135°/1.5 mm) leaving 8.25 g. (75%) of compounds **4c** and **5c** in a 1:4 ratio as shown by ^{1}H-nmr analysis (singlet at 2.37 ppm for **5c** and at 2.23 ppm for **4c**).

Anal. Calcd. for **4c** and **5c** ($C_{13}H_{14}N_2$): C, 78.75; H, 7.12 N, 14.13. Found: C, 78.78; H, 7.19; N, 14.05.

Preparative glc (using an aerograph 700 apparatus equipped with 18 ft. x 0.375 in. 20% DEGS column on 45:60 chromosorb w at 200°) yielded a pure sample of 5-mehtyl-1-phenyl-3-(*E*-1-propenyl)pyrazole **5c** (retention time 18 minutes); uv (ethanol): λ nm (ε) 212 (10,500), 257 (18,000); ir (chloroform): 1665, 960 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 1.84 (dd, 3H, J = 4 Hz and 1 Hz, allylic coupling of the propenyl group), 2.37 (s, 3H), 6.23-6.51 (m, 3H), 7.56-7.72 (m, 5H). Compound **4c** (retention time 32 minutes) was then collected. It was identical with the compound obtained from the dihydropyrone **1c** described in Tables I and II. In its ^{1}H-nmr spectrum, allylic coupling for the methyl protons of the propenyl group was not observed.

REFERENCES AND NOTES

(1) S. Gelin and C. Deshayes, *Synthesis*, **12**, 900 (1978).

(2) L. K. Vagina, V. N. Christokltev and A. A. Petrov, *Zh. Org. Khim.*, **1**, 1723 (1965); *Chem. Abstr.*, **64**, 725b (1966).

(3) J. Elguerro, R. Gelin, S. Gelin and G. Tarrago, *Bull. Soc. Chim. France*, 231 (1970).

(4) H. El Khadem, L. Rateb and H. Mokhtar, *J. Chem. Soc. C*, 1845 (1968); H. El Khadem, Z. El-Shafei, L. Rateb and H. Mokhtar, *J. Heterocyclic Chem.*, **10**, 15 (1973); L. Rateb, G. Mina and L. Soliman, *J. Chem. Soc. C*, 2173 (1968).

(5) R. P. Bell and S. M. Rybicka, *J. Chem. Soc.*, 25 (1947).

(6) S. Gelin and R. Gelin, *Bull. Soc. Chim. France*, 288 (1968).

(7) S. Gelin, R. Gelin and D. Hartmann, *J. Org. Chem.*, **43**, 2685 (1978); and references cited herein.

(8) An orange product (0.6 g.), m.p. 140°, was also obtained after elution of 540 to 740 ml. It was identified as 2,2-dimethyl-5(carbo-2-phenylhydrazide)-6-phenyl-2,3-dihydro-4*H*-pyran-4-one. ^{1}H-nmr (deuteriochloroform): 1.58 (s, 6H); 2.93 (s, 2H), 6.97-8.66 (m, 12H).