Synthesis of Some 1-Substituted-3-or-5-Styrylpyrazoles

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The synthesis of the title compounds by the Wittig-Horner reaction is described, using the 3-or-5-hydroxymethylpyrazole derivatives as precursors.

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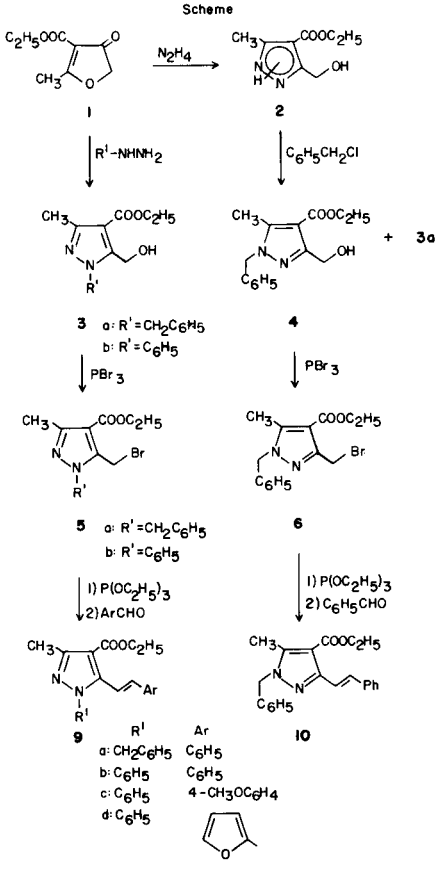
Synthetic methods for the preparation of 1-substituted-3-or-5-alkenylpyrazoles are relatively few in numbers. They involve the formation of the pyrazole ring by action of classical reagents on unsaturated compounds [reaction of various phenylhydrazines with γ,δ-unsaturated β-diketo-compounds (1,2), or of *N*-phenylsydnone with conjugated enynes (3)] or the formation of the pyrazole ring and of the alkenyl chain in a one step process [action of phenylhydrazine on 2,3-dihydro-4-pyrones (4)].

Scheme



We now report an alternative method of introducing the styryl moiety into the pyrazole ring by the Wittig-Horner reaction from the 1-substituted 3-or-5-hydroxymethylpyrazoles as precursors. Our earlier studies have shown that these compounds can be synthesized either by reacting the 3-oxo-2,3-dihydrofuran derivatives with an appropriate hydrazine or by alkylation of 3(or-5)-hydroxymethylpyrazoles (5,6). As anticipated, treatment of 4-ethoxycarbonyl-5-methyl-3-oxo-2,3-dihydrofuran **1** with benzylhydrazine or phenylhydrazine affords the 1-benzyl or 1-phenylpyrazole derivatives **3a** or **3b**. On the other hand, benzylation of the 4-ethoxycarbonyl-5(or-3)-hydroxymethyl-3(or-5)-methylpyrazole **2** carried out with potassium carbonate and benzyl chloride in cyclohexanone as solvent produces a mixture of the isomeric pyrazoles **3a** and **4**, respectively in a 3:7 ratio, from which the pure compound **4** is obtained by chromatography. The structures of compounds **3a, 3b** and **4** are unequivocally established by ^{13}C nmr spectral comparison with our previous results (4,6,7) (see Table I).

Table I

Pertinent ^{13}C Nmr Spectral Data δ (ppm) (deuteriochloroform)

Compound No.	C-3	C-4	C-5	CH_3	CH_2 (OH)
3b	150.99	111.72	147.15	14.22	54.91
3a	150.17	110.29	146.66	14.19	54.01
4	153.74	109.33	144.18	11.25	58.67

The 3-or-5-hydroxymethylpyrazoles **3** or **4** are easily converted into the corresponding 5 or 3-bromomethylpyrazoles **5** or **6**, by reaction with phosphorus tribromide. Treatment of the bromides **5a,b** or **6** with triethyl phosphite (Arbusov reaction) affords the diethylphosphonomethylpyrazoles **7a,b** or **8** respectively. Reaction of compounds **7a** or **7b** with sodium hydride and various aromatic aldehydes (benzaldehyde, anisaldehyde, furfural), in dimethoxyethane, leads to the formation of 4-ethoxycarbonyl-3-methyl-5-styryl-1-substitutedpyrazoles **9a-d** with good yields. Similarly, reaction of compound **8** with benzaldehyde affords the 3-styrylpyrazole derivative **10**. Reaction of the diethylphosphonomethylpyrazole **7b** with an aliphatic aldehyde (propanal), under a variety of conditions, gives no satisfactory yield in alkenylpyrazole derivative (<20%).

The structures of compounds are consistent with the microanalysis and spectral data (uv, ir, and ^1H nmr) see Tables II and III. An analysis of the nmr spectra indicates

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that the compounds **9a-d** possess the *E*-configuration. No conclusion is possible for the compound **10** since the AB system of the carbon-carbon double bond is completely masked by the phenyl and benzyl groups.

EXPERIMENTAL

Melting points were determined on a Kofler hot plate. Infrared and ultraviolet spectra were obtained with a Beckmann Model Acculab 2 and DB spectrometers. ^1H nmr spectra were taken on a Brucker WP 80 spectrometer, ^{13}C nmr spectra were obtained with a Varian XL 100 12 FT. The chemical shifts reported are in parts per million from internal TMS as an internal standard. Elemental analysis were performed by Microanalytical Laboratory, Centre National de la Recherche Scientifique, 69390 Vernaison, France.

1-Substituted-4-ethoxycarbonyl-5-hydroxymethyl-3-methylpyrazoles (**3**). General Procedure.

To a solution of 4-ethoxycarbonyl-5-methyl-3-oxo-2,3-dihydrofuran (5) **1** (1.7 g, 10 mmoles) in ethanol (10 ml) is added in one portion benzylhydrazine or phenylhydrazine (11 mmoles). The mixture is heated under reflux for 2 hours and then evaporated under reduced pressure. Compound **3b** is recrystallized from hexane. Compound **3a** is recrystallized from water/ethanol (1:1) and then from hexane.

1-Benzyl-4-ethoxycarbonyl-3-hydroxymethyl-5-methylpyrazole (**4**). General Procedure.

To a stirred solution of 4-ethoxycarbonyl-5(or 3)-hydroxymethyl-3(or 5)-methylpyrazole (5) (1.84 g, 10 mmoles) in cyclohexanone (20 ml) is added potassium carbonate (1.5 g, 11 mmoles) and benzyl chloride (1.3 g, 11 mmoles). The mixture is refluxed for 3 hours. The solid is filtered off and washed with acetone (10 ml) and the filtrate rotoevaporated. The residue is taken up with chloroform (50 ml) and the solution washed with 1*N* sodium hydroxide (10 ml), and water, then dried and evaporated to leave a mixture of isomeric pyrazoles **3a** and **4**, respectively, in a ratio of 3:7 (as monitored by nmr). This mixture is purified through a column (50 cm × 30 mm) of silica gel (150 g) using ether as eluent; compound **3a** is obtained from the 300 to 450 ml fraction (yield, 0.5 g) and compound **4** is obtained from the 500 to 700 ml fraction (yield, 1.1 g).

1-Substituted-5-or-3-bromomethyl-4-ethoxycarbonyl-3-or-5-methylpyrazoles (**5** or **6**). General Procedure.

To a stirred suspension of the hydroxymethyl pyrazole **3** or **4** (10 mmoles) in anhydrous toluene (20 ml) is added phosphorus tribromide (1.08 g, 4 mmoles). The mixture is heated under reflux for 1 hour. The clear toluene layer is decanted and evaporated. The residual solid is recrystallized from hexane to afford compounds **5a, 5b** or **6**.

1-Substituted-4-ethoxycarbonyl-3-or-5-methyl-5-or-3-styrylpyrazoles (**9** or **10**). General Procedure.

A mixture of the bromomethylpyrazole **5** or **6** (10 mmoles) and triethyl phosphite (1.66 g, 10 mmoles) is heated at 130° for 1 hour. The ethyl bromide is removed under reduced pressure, leaving the crude diethylphosphonomethylpyrazole **7** or **8** (yield 100%), which is pure enough for the next step (as shown by the ^1H-nmr spectrum). Anhydrous dimethoxyethane (10 ml) and then the aldehyde (benzaldehyde, anisaldehyde or furfural, 10 mmoles) in dimethoxyethane (5 ml) are added. This solution is added dropwise at room temperature to a suspension of sodium hydride (10 mmoles, 50% dispersion washed with hexane) in dimethoxyethane (10

Table II

Physical Data for 4-Ethoxycarbonyl-3-and-5-methyl-and-1,3-disubstituted pyrazoles

Compound No.	Yield %	M.p. (°C)	Molecular Formula	Analyses Calcd. % / Found % C	H	N	Br	Ir, cm^{-1} Chloroform	Uv (in ethanol) δ max (nm) ϵ
3a	90	96	$C_{15}H_{18}N_2O_3$	65.67	6.61	10.21	—	3420, 2980, 1680	237 (9400)
			(274.3)	65.64	6.86	10.29			219 (6700)
3b	80	59	$C_{14}H_{16}N_2O_3$	64.60	6.20	10.76	—	3460, 2980, 1690	252 (12100)
			(260.3)	64.47	6.17	10.87			214 (8700)
4	40	72	$C_{15}H_{18}N_2O_3$	65.67	6.61	10.21	—	3460, 2980, 1680	232 (11200)
			(274.3)	65.84	6.67	10.17			216 (8700)
5a	87	70	$C_{15}H_{17}N_2O_2Br$	53.42	5.08	8.31	23.70	2980, 1710	248 (10300)
			(337.2)	53.35	5.00	8.18	23.47		208 (14800)
5b	78	53	$C_{14}H_{15}N_2O_2Br$	52.03	4.67	8.67	24.73	2980, 1710	256 (12100)
			(323.2)	51.95	4.79	8.47	24.60		209 (15800)
6	86	59	$C_{15}H_{17}N_2O_2Br$	53.42	5.08	8.31	23.70	2980, 1710	212 (19600)
			(337.2)	53.60	5.08	8.07	23.69		
9a	80	78	$C_{22}H_{22}N_2O_2$	76.27	6.40	8.09	—	1715, 1650, 965	300 (18400)
			(346.4)	76.04	6.32	8.03			
9b	80	57-59 (subl.)	$C_{21}H_{20}N_2O_2$	75.88	6.07	8.43		1715, 1650, 970	274 (16400)
			(332.4)	76.01	6.05	8.29			
9c	94	83-84	$C_{22}H_{22}N_2O_3$	72.91	6.12	7.73		1710, 1640, 965	274 (16300)
			(362.4)	73.07	6.07	7.72			
9d	80	64	$C_{19}H_{18}N_2O_3$	70.79	5.63	8.69		1710, 1640, 955	273 (16600)
			(322.4)	70.78	5.72	8.46			
10	72	92-93	$C_{22}H_{22}N_2O_2$	76.27	6.40	8.09		1715, 1645, 965	310 (16300)
			(346.4)	76.23	6.50	7.89			

ml). After stirring overnight at room temperature, water (150 ml) is added.

Work-Up Procedure for Products **9a,b,c,d**.

The solid that separates is collected, washed with water (2 × 10 ml) and dried. Analytical samples are obtained by recrystallization from hexane (**9a,c**), or hexane/ethyl acetate 9:1 for **9b** and 4:1 for **9d**.

Table III

Proton Magnetic Resonance Parameters in Deuteriochloroform

Compound No.	δ (ppm)
3a	1.35 (t, 3H, J = 7 Hz), 2.45 (s, 3H), 4.15-4.60 (m, 2H + 1 H CF_3COOH, exchangeable), 4.80 (br, 2H), 5.41 (s, 2H), 7.16-7.50 (m, 5H) (a).
3b	1.44 (t, 3H, J = 7 Hz), 2.54 (s, 3H), 4.07 (br, 1H, CF_3COOH exchangeable), 4.47 (q, 2H, J = 7 Hz), 4.79 (s, 2H), 7.60 (s, 5H) (a).
4	1.33 (t, 3H, J = 7 Hz), 2.43 (s, 3H), 4.06 (s, 1H, CF_3COOH exchangeable), 4.33 (q, 2H, J = 7 Hz), 4.82 (d, 2H, J = 7 Hz), 5.25 (s, 2H), 7.03-7.46 (m, 5H) (a).
5a	1.37 (t, 3H, J = 7 Hz), 2.50 (s, 3H), 4.35 (q, 2H, J = 7 Hz) 4.70 (s, 2H), 5.40 (s, 2H), 7.13-7.50 (m, 5H).
5b	1.47 (t, 3H, J = 7 Hz), 2.60 (s, 3H), 4.52 (q, 2H, J = 7 Hz), 4.81 (s, 2H), 7.75 (s, 5H) (a).
6	1.40 (t, 3H, J = 7 Hz), 2.48 (s, 3H), 4.37 (q, 2H, J = 7 Hz), 4.78 (s, 2H), 5.33 (s, 2H), 7.07-7.25 (m, 2H), 7.32-7.49 (m, 3H).
9a	1.35 (t, 3H, J = 7 Hz), 2.53 (s, 3H), 4.34 (q, 2H, J = 7 Hz), 5.45 (s, 2H), 6.77-7.50 (m, 12H, with two lines of an AB system, J_{AB} = 17 Hz).
9b	1.40 (t, 3H, J = 7 Hz), 2.55 (s, 3H), 4.39 (q, 2H, J = 7 Hz), (2d, 2H, AB system, δ_A 6.77 δ_B 7.40, J_{AB} = 17 Hz), 7.32 (s, 5H), 7.50 (s, 5H).
9c	1.41 (t, 3H, J = 7 Hz), 2.55 (s, 3H), 3.82 (s, 3H), 4.40 (q, 2H, J = 7 Hz), (2d, 2H, AB system, δ_A 6.76, δ_B 7.26, J_{AB} = 17 Hz), (2d, 4H, A_2B_2 system, δ_A 6.86, δ_B 7.28, J_{AB} = 9 Hz), 7.51 (s, 5H).
9d	1.41 (t, 3H, J = 7 Hz), 2.54 (s, 3H), 4.40 (q, 2H, J = 7 Hz), 6.30-6.45 (m, 2H), (2d, 2H, AB system, δ_A 6.82, δ_B 7.24, J_{AB} = 17 Hz), 7.31-7.63 (m, 6H).
10	1.40 (t, 3H, J = 7 Hz), 2.45 (s, 3H), 4.34 (q, 2H, J = 7 Hz), 5.34 (s, 2H), 7.04-7.84 (m, 12H).

(a) Measured on a Varian A-60 spectrometer.

Work-Up Procedure for Product **10**.

The resulting mixture is acidified with 1*N* sulfuric acid (5 ml), extracted with ether and the extracts washed with water, dried and evaporated. The residue is chromatographed through a column (39 cm × 24 mm) of silica gel (60 g) using hexane/ethyl acetate (7:3) as eluent. Compound **10** is obtained from the 130 to 215 ml fraction (yield, 2.5 g).

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