Synthesis of the *N*-Alkyl Isomers of 4-Ethoxycarbonyl- or -acetyl-3(5)-alkyl- or -aryl-5(3)-acylpyrazoles from 3(2*H*)-Furanones. Structure Determination.[1,2]

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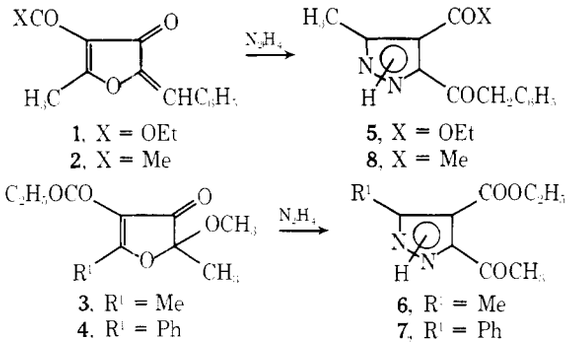
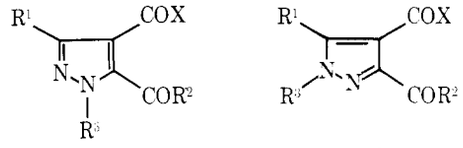
Synthesis of isomeric *N*-alkyl-3,4,5-trisubstituted pyrazoles are described from reaction of 3(2*H*)-furanones with alkylhydrazines or alternatively by alkylation of corresponding N-unsubstituted pyrazoles. Their structures are unambiguously established by ^1H and ^{13}C NMR studies. By comparison of the data of the *N*-alkylpyrazoles with those of the N-unsubstituted pyrazoles, the 5-methyl and 5-phenyl structures were found as the predominant form for these pyrazoles.

Recently, we have reported that the 3(2*H*)-furanones are interesting substrates which undergo ring opening by nucleophilic reagents, leading to new cyclic compounds.[1-3] Our studies concerning the reaction of hydrazine hydrate with 3(2*H*)-furanones **1–4** have led to a useful procedure to obtain 3(5)-acyl-4-ethoxycarbonyl- or -acetyl-5(3)-substituted pyrazoles **5–8**.[1,2]



1, X = OEt
2, X = Me
5, X = OEt
8, X = Me
3, R^1 = Me
4, R^1 = Ph
6, R^1 = Me
7, R^1 = Ph

The preparation and structure determination of corresponding N-substituted isomeric pyrazoles **9–16a,b** are described in this paper. Two routes have been investigated: first, the reaction of **1–4** with alkylhydrazines; second, the alkylation of the pyrazoles **5–8**.



9–16a **9–16b**

	R^1	R^2	R^3	X
9	Me	CH_2Ph	Me	OEt
10	Me	CH_2Ph	CH_2Ph	OEt
11	Me	Me	Me	OEt
12	Me	Me	CH_2Ph	OEt
13	Ph	Me	Me	OEt
14	Ph	Me	CH_2Ph	OEt
15	Me	CH_2Ph	Me	Me
16	Me	CH_2Ph	CH_2Ph	Me

Table I. Spectral Data of Pyrazoles

Compd	Registry no.	UV, nm ($\epsilon \times 10^{-3}$)	^1H NMR chemical shifts ($CDCl_3$) δ, ppm
9a	65969-58-6	212 (9.3) 235 (6.4)	1.37 (3 H, t, J = 7 Hz), 2.47 (3 H, s), 3.47 (3 H, s), 4.37 (2 H, s), 4.40 (2 H, q, J = 7 Hz), 7.31 (5 H, s)
9b	65942-77-0	212 (13.7) 243 (6.8)	1.30 (3 H, t, J = 7 Hz), 2.40 (3 H, s), 3.78 (3 H, s), 4.30 (2 H, s), 4.37 (2 H, q, J = 7 Hz), 7.35 (5 H, s)
10a	65942-78-1	211 (14.1) 241 (6.6)	1.37 (3 H, t, J = 7 Hz), 2.49 (3 H, s), 4.07 (2 H, s), 4.42 (2 H, q, J = 7 Hz), 5.16 (2 H, s), 7.0–7.5 (10 H, m)
10b	65942-79-2	217 (14.2) 236 (7.4)	1.28 (3 H, t, J = 7 Hz), 2.32 (3 H, s), 4.33 (2 H, q, J = 7 Hz), 4.37 (2 H, s), 5.35 (2 H, s), 7.3–7.5 (10 H, m)
11a	65942-80-5	254 (5.4)	1.38 (3 H, t, J = 7 Hz), 2.43 (3 H, s), 2.61 (3 H, s), 3.86 (3 H, s), 4.41 (2 H, q, J = 7 Hz)
11b	65942-81-6	213 (6.3) 245 (5.3)	1.35 (3 H, t, J = 7 Hz), 2.46 (3 H, s), 2.56 (3 H, s), 3.87 (3 H, s), 4.36 (2 H, q, J = 7 Hz)
12a	65942-82-7	214 (9.0) 250 (6.7)	1.35 (3 H, t, J = 7 Hz), 2.35 (3 H, s), 2.50 (3 H, s), 4.31 (2 H, q, J = 7 Hz), 5.41 (2 H, s), 7.13–7.56 (5 H, m)
12b	65942-83-8	216 (13.0) 243 (7.0)	1.31 (3 H, t, J = 7 Hz), 2.38 (3 H, s), 2.61 (3 H, s), 4.36 (2 H, q), 5.40 (2 H, q), 7.11–7.56 (5 H)
13a	65942-84-9	239 (17.5)	1.20 (3 H, t, J = 7 Hz), 2.60 (3 H, s), 4.03 (3 H, s), 7.4–7.63 (3 H, m), 7.63–8.0 (2 H, m)
13b	65942-85-0	239 (14.3)	1.11 (3 H, t, J = 7 Hz), 2.63 (3 H, s), 3.81 (3 H, s), 4.25 (2 H, q, J = 7 Hz), 7.55 (5 H, s)
14a	65942-86-1	213 (12.8) 240 (17.2)	1.18 (3 H, t, J = 7 Hz), 2.35 (3 H, s), 4.30 (2 H, q, J = 7 Hz), 5.58 (2 H, s), 7.33 (5 H, s), 7.45 (3 H, m), 7.85 (2 H, m)
14b	65942-87-2	230 (14.7)	1.11 (3 H, t, J = 7 Hz), 2.68 (3 H, s), 4.25 (2 H, q, J = 7 Hz), 5.33 (2 H, s), 7.00–7.70 (10 H)
15a	65942-88-3	217 (7.4) 259 (6.3)	2.50 (3 H, s), 2.52 (3 H, s), 3.43 (3 H, s), 4.18 (2 H, s), 7.35 (5 H, s)
15b	65942-89-4	218 (9.2) 258 (6.4)	2.34 (3 H, s), 2.45 (3 H, s), 3.81 (3 H, s), 4.40 (2 H, s), 7.37 (5 H, s)
16a	65942-90-7	214 (13.2) 260 (8.3)	2.40 (3 H, s), 2.50 (3 H, s), 3.87 (2 H, s), 5.12 (2 H, s), 7.0–7.5 (10 H, m)
16b	65942-91-8	222 (15.1) 258 (8.5)	2.35 (3 H, s), 2.48 (3 H, s), 4.45 (2 H, s), 5.45 (2 H, s), 7.2–7.5 (10 H, m)

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Table II. Eu(fod)$_3$ Induced Chemical Shifts

Compd	CH_3 (C-3)	NCH_3	CH_2 in CO_2Et at C-4	CH_3 or CH_2 at C-5
9a	2.41	1.49	3.40	2.08
9b	1.82	2.15	3.22	4.09
11a	2.58	2.39	3.59	3.09[20]
11b	2.13	2.65	3.33	4.54[20]

Results and Discussion

The reaction of methylhydrazine with the 3(2*H*)-furanones **1–4** gave mixtures in which the **a** isomers were the major products (about 3:1 **a/b**) with **9, 11, 13,** and **15.** Benzylhydrazine gave only the **a** isomers **10a,**[4] **12a, 14a, 16a.**

On the other hand, the alkylation of the anions from pyrazoles **5–8** with methyl iodide and benzyl chloride produced, in the most cases, a material wherein the main products of the reaction (70–80%) were the isomeric pyrazoles **9,11–15b** or only **10b** and **16b.** The treatment of **6** and **7** with ethereal diazomethane yielded a 4:1 mixture of **11** and **13 a/b,** respectively. In the same conditions, **5** generated **9a** accompanied by another unidentified product.

The presence of two isomers is clearly revealed in the ^1H NMR spectra, which generally consist of two sets of signals. Simply by comparing the relative signal intensities, the isomeric composition of the crude reaction mixture was determined. The pure isomeric pyrazoles **a** or **b** were obtained by distillation, crystallization, or column chromatography. The pyrazole structure of these compounds was evident from the alkylation reaction and by their ready conversion into pyrazolo[3,4-*d*]pyridazine derivatives with hydrazine hydrate.[5] Proton NMR data for all compounds are collected in Table I and are completely consistent with the assigned structures. The problem remains of deciding which belong to series **a** and which to series **b.**

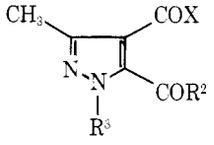
A great deal of work has been done on the structural assignment to *N*-alkyl derivatives of unsymmetrical pyrazoles.[6–17] However, no general solution is available. ^1H NMR studies have dealt with this problem. The 1-alkyl-3- or -5-methylpyrazole pairs show a diamagnetic shift of the methyl peak in going from the 3-methyl to the 5-methyl isomer.[12] However, the methyl peak undergoes a paramagnetic instead of a diamagnetic displacement in pairs of 3- or 5-methylpyrazole carboxylates.[14] Tensmeyer and Ainsworth[15] state that the phenylpyrazoles fall into two groups: those with essentially singlet phenyl peaks and those with multiplet phenyl resonances. A phenyl group attached to a nitrogen or a carbon atom of the pyrazole ring has a multiplet resonance, except in the presence of a substituent α to it; in this case, the phenyl resonance is a singlet, because of the impossibility of the coplanarity of the two rings. When multiplet resonances occur, the *o*-phenyl protons reside preferentially near the plane of the pyrazole ring and are shifted by the magnetic field of the pyrazole ring current.

The position of the phenyl group in the pyrazoles assigned structures **13–14a,b** is indicated by the splitting pattern of the aryl protons. The two ortho protons are seen at δ 7.82 and 7.85 in **13a** and **14a** (see Table I). In UV spectra, the hypochromic effect on going from **13a** to **13b** and hypochromic and hypsochromic effects from **14a** to **14b** were characteristic of ortho-substituted diphenyls and analogous heterocyclic compounds.[18,19]

In 3- or 5-methyl series **9–12, 15,** and **16,** the structural assignment could not be made on the basis of their ^1H NMR spectra. In order to find further support for the alternative structures **a** or **b,** we have measured the lanthanide shift data of the two pairs of the pyrazoles **9** and **11.** The LIS extrapolated for a 1:1 complex with Eu(fod)$_3$ in $CDCl_3$, given in parts per million, are presented in Table II.

It is well established that the 4 position in the pyrazole nucleus has a greater electron density than the 3 and 5 positions.[18,19] A considerable contribution of a dipolar structure with a negative charge on the carbonyl of the ethoxycarbonyl group and a positive charge on the N-1 atom explains the large LIS of the methylene of this group. The most significant differences are observed between the two isomers **a** and **b** on the methylene and the methyl of the acyl groups **9** and **11,** respectively. It seems reasonable to presume that the acyl groups more affected by the complexation must be the less hindered,

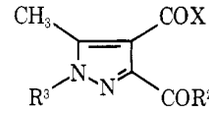
Table III. Carbon-13 Chemical Shifts for Derivatives of the 3-Methyl Series of Pyrazoles ($CDCl_3$)



Compd	C-3	C-4	C-5	CH_3	COX: CO	COX: X	COR^2: CO	COR^2: R^2	NR^3
11a	149.3	110.6	143.0	13.56	162.9	OCH_2: 60.5; CH_3: 14.2	194.3	CH_3: 31.12	CH_3: 38.2
9a	149.3	111.2	143.4	13.5	162.8	OCH_2: 60.5; CH_3: 14.2	194.8	CH_2: 50.6; Ph: C′-1, 132.3; C′-2,6, 129.4;[a] C′-3,5, 128.6;[a] C′4, 127.2	CH_3: 37.3
10a	149.6	112.4	143.6	13.8	163.0	OCH_2: 60.6; CH_3: 14.3	195.3	CH_2: 50.1; Ph: C′-1, 132.5; C′-2,6, 129.6;[a] C′-3,5, 128.6;[a] C′-4, 127.1[b]	CH_2: 54.1; Ph: C′-1, 135.6; C′-2,6, 127.6;[a] C′-3,5, 128.5;[a] C′-4, 127.9[b]
15a	147.0	121.9	144.0	14.6	192.9	CH_3: 29.8	195.4	CH_2: 50.2; Ph: C′-1, 132.5; C′-2,6, 129.6;[a] C′-3,5, 128.6;[a] C′-4, 127.2	CH_3: 36.94
16a	147.1	122.5	143.6	14.7	193.1	CH_3: 29.8	195.5	CH_2: 49.6; Ph: C′-1, 132.6; C′-2,6, 129.7;[a] C′-3,5, 128.5;[a] C′-4, 127.0[b]	CH_2: 54.0; Ph: C′-1, 135.4; C′-2,6, 127.8;[a] C′-3,5, 128.3;[a] C′-4, 128.0[b]

[a,b] These values might be interchanged.

Table IV. Carbon-13 Chemical Shifts for Derivatives of the 5-Methyl Series of Pyrazoles ($CDCl_3$)



					COX		COR^2		
Compd	C-3	C-4	C-5	CH_3	CO	X	CO	R^2	NR^3
11b	149.1	111	143.4	10.4	163.0	OCH_2: 60.3; CH_3: 14.1	193.5	CH_3: 28.2	CH_3: 36.7
6	150.3	110.6	145.5	11.3	163.7	OCH_2: 60.7; CH_3: 14.1	195.2	CH_3: 28.7	H
9b	148.9	112	143.4	10.5	163.2	OCH_2: 60.5; CH_3: 14.0	193.4	CH_2: 47.2; Ph: C′-1, 134.3; C′-2,6, 129.6;[a] C′-3,5, 128.2;[a] C′-4, 126.5	CH_3: 36.7
10b	149.1	112.5	143.5	10.6	163.3	OCH_2: 60.5; CH_3: 14	193.7	CH_2: 47.5; Ph: C′-1, 134.3; C′-2,6, 129.7;[a] C′-3,5, 128.2;[a] C′-4, 126.5[b]	CH_2: 53.7; Ph: C′-1, 135; C′-2,6, 126.7;[a] C′-3,5, 128.7;[a] C′-4, 127.9[b]
5	149.9	111.2	145.6	11.3	163.4	OCH_2: 60.7; CH_3: 14.1	192.2	CH_2: 47.7; Ph: C′-1, 134.0; C′-2,6, 129.6;[a] C′-3,5, 128.3;[a] C′-4, 126.6[a]	H
15b	147.0	121.6	143.1	10.5	196.9	CH_3: 31.1	193.7	CH_2: 46.2; Ph: C′-1, 134.4; C′-2,6, 129.6;[a] C′-3,5, 128.2;[a] C′-4, 126.5	CH_3: 36.7
16b	147.6	122.2	143.2	10.7	197.0	CH_3: 31.2	193.8	CH_2: 46.4; Ph: C′-1, 134.4; C′-2,6, 129.7;[a] C′-3,5, 128.3;[a] C′-4, 126.6	CH_2: 53.7; Ph: C′-1, 134.8; C′-2,6, 126.9;[a] C′-3,5, 128.8;[a] C′-4, 128.1
8	149.3	120.4	144.4	11.2	197.6	CH_3: 31.2	194.8	CH_2: 49.6; Ph: C′-1, 134.0; C′-2,6, 129.6;[a] C′-3,5, 128.4;[a] C′-4, 126.7	H

[a,b] These values might be interchanged.

in best agreement with the 3 position in β of the *N*-methyl group.

The 3- or 5-methyl isomeric structures were also inferred by ^{13}C NMR spectroscopy. All compounds studied gave well-resolved lines which could be assigned by application of the usual shift parameters,[21] from the obtained signal multiplicities in the off resonance spectrum and consultation of the pyrazole literature.[22-25] The assigned structures are first based on the carbon chemical shifts of the observed δ values of the methyl groups in the pairs of the isomeric pyrazoles with those of the model systems: 1,3- or 1,5-dimethylpyrazoles, 1,3,5-trimethylpyrazole.[23] The C-3 methyl signals are shifted on about 2–3 ppm to lower field than the C-5 methyl signals. Moreover, it has been shown[22-24] that the carbon-13 chemical shift for a pyridinic environment N=C< occurs at lower field than for a pyrrolic environment N–C=. Consequently, the signals of the C-3 or C-5 carbons bonded with a methyl group can be attributed, the C-4 signals are easily assigned by their larger shieldings. The remaining signal is assigned to the C-3 or C-5 carbons bonded to an acyl group. The chemical shifts are presented in Tables III and IV. In summary, the comparison of the chemical shifts from two N-alkylated isomeric pyrazoles shows that the C-3 and C-5 shifts change in opposite directions (Table V). The carbons 3, 4, and 5 in series **a** must correspond to carbons 5, 4, and 3, respectively, in series **b**. For all compounds examined, methyl or acyl substitution causes a similar effect at the carbon adjacent to the site of the substitution. The replacement of a *N*-methyl group (**9** and **15**) by a benzyl group (**10** and **16**) gives very weak deshieldings ($\Delta\delta^{max}$ < 1.2 ppm). The effect caused by replacing an ethoxycarbonyl group by an acetyl group at the C-4 position is higher at C-3 than at C-5 and appears dominated by inductive effects (Table VI).

The structures of **13a** and **13b** are consistent with ^{13}C NMR spectral comparisons of these materials with previous findings concerning the 1,3- or 1,5-dimethyl-5- or -3-phenylpyrazoles.[23] The C′-1 atom of a phenyl group in the 3 position is more deshielded than in the 5 position. The assignments of the chemical shift values to specific carbon atoms C-3, C-4, and C-5 are determined as above (see Table VII).

We have already shown that the formation of pyrazoles from 3(2*H*)-furanones involves a Michael addition of the

Scheme I

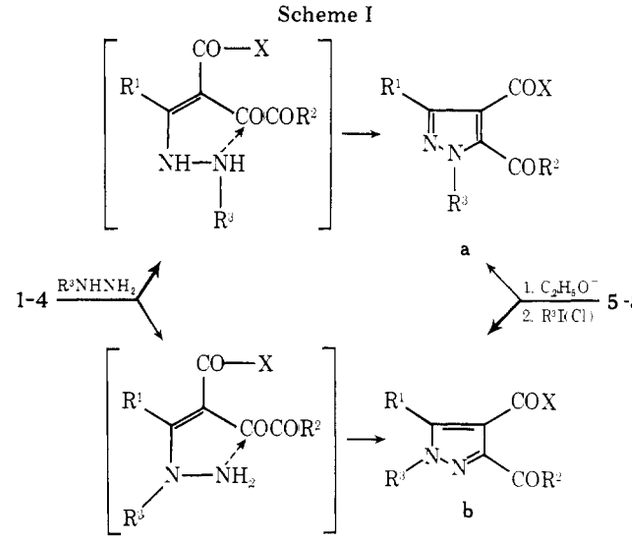
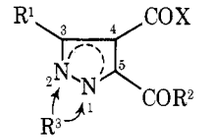


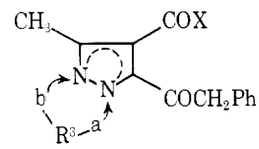
Table V. Change in the Carbon-13 Chemical Shifts ($\Delta\delta$)[a] for Derivatives of N(1)- or N(2)-Alkylated Pyrazoles



Compds compared	C-3	C-4	C-5	R^1	COX		COR^2		NR^3
					CO	X	CO	R^2	
11a, 11b	5.9	−0.4	−6.1	CH_3: 3.2	−0.1	OCH_2: 0.2; CH_3: 0.1	0.8	CH_3: 2.92	CH_3: 1.5
9a, 9b	5.9	−0.9	−5.6	CH_3: 3	−0.4	OCH_2: 0; CH_3: 0.1	1.4	CH_2: 3.4; Ph[b]	CH_3: 0.6
10a, 10b	6.1	−0.4	−5.5	CH_3: 3.2	−0.3	OCH_2: 0.1; CH_3: 0.3	1.6	CH_2: 2.6; Ph[b]	CH_2: 0.5; Ph[b]
15a, 15b	3.9	0.3	−3	CH_3: 4.2	−1.5	CH_3: −1.3	0.8	CH_2: 4; Ph[b]	CH_3: 0.2
16a, 16b	3.9	0.3	−3.9	CH_3: 4	−1.5	CH_3: −1.36	−0.7	CH_2: 3.2; Ph[b]	CH_2: 0.2; Ph[b]
13a, 13b	4.8	−0.4	−6.7	Ph[b]	0.3	OCH_2: 0.5; CH_3: 0	−1	CH_3: 2.8	CH_3: 1.5

[a] $\Delta\delta = \delta C_a - \delta C_b$. Negative numbers represent shift changes to lower field as compared to the chemical shifts observed for the corresponding position in the reference compound. [b] The aromatic carbon absorptions are omitted.

Table VI. Substitution Effects on Replacement of Ethoxycarbonyl by Acetyl Group at the C-4 Position ($\Delta\delta$)[a]



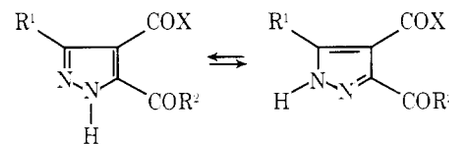
Compds compared	R^3	C-3	C-4	C-5	CH_3	CO	CH_2
9a, 15a	CH_3	2.3	−10.7	−0.6	−1.1	−0.6	0.4
9b, 15b	CH_3	1.9	− 9.6	0.3	0	−0.3	1
10a, 16a	CH_2Ph	2.5	−10.1	0	−0.9	−0.2	0.5
10b, 16b	CH_2Ph	1.5	− 9.7	0.3	−0.1	−0.1	0.9

[a] $\Delta\delta = \delta C(X = OEt) - \delta C(X = CH_3)$.

hydrazine to the C-5 position of the furanone ring.[1,2,26] The composition of the isomeric mixtures obtained with unsymmetrical hydrazines reflects approximatively the relative reactivities of the two nitrogen atoms. Our results imply that the conjugate addition occurs preferentially or exclusively at the unsubstituted nitrogen atom (Scheme I). Although the secondary nitrogen atom is the more nucleophilic,[27-29] the reaction is principally controlled by steric effects. Analogous orientations in conjugate additions were already reported.[30-32]

The factors that influence the site of alkylation of ambident anions from pyrazole derivatives are complex. In most cases studied, both *N*-alkyl isomers were produced.[12,17,30,33-35] The prevailing formation of the isomers **b**, in all cases studied in this paper, suggests that this orientation may be attributed to electronic rather than steric effects. With diazomethane, methylation proceeds on the nitrogen atom nearer to the acyl-withdrawing group as expected from previous findings.[36,37]

The predominance of one tautomeric form for several unsymmetrical pyrazoles has been shown.[12,15-17,38,39] The carbon chemical shifts of the N(1)H and N(2)H tautomers of pyrazole derivatives have been recently reported.[24] Chemical shift comparisons of 3,5-dimethylpyrazole in a reduced tautomeric exchange rate with our 3- or 5-methylpyrazoles **9a,b, 11a,b,** and **15a,b** (Tables III and IV) indicate that the chemical shift alterations induced by the *N*-methyl substitution have a limited effect on the C-3 or C-5 methyl signals: δ CH_3 (C-3) 13.8, CH_3(C-5) 10.6. The methyl carbon chemical shifts in **5, 6,** and **8** are closer in magnitude to the corresponding chemical shifts in **9b, 11b,** and **15b** than to those in **9a, 11a,** and **15a.** The phenyl resonance in **7** is very similar to the values shown for the corresponding *N*-methylpyrazole **13b** (Table VII).



tautomer **a**, N(1)H tautomer **b**, N(2)H

Furthermore, these tables show the obvious similarity of the acyl methylene in **5** and **8** and methyl in **6** and **7** as compared with those of **9** and **15** and **11b** and **13b,** respectively. These findings would strongly suggest that the unalkylated pyrazoles **5–8** exist predominantly, at least in deuteriochloroform, in the tautomeric form N(2)H (**b**).

Experimental Section

Melting points were determined on a Kofler hot plate and boiling points are uncorrected. Infrared and ultraviolet spectra were obtained with a Beckmann Model Acculab 2 and DB spectrophotometers. NMR spectra were recorded on Varian A-60 (^{1}H NMR) and Varian X-100-12 FT (^{13}C NMR) spectrometers at 35 °C, using deuteriochloroform solution 0.2 M in pyrazoles and tetramethylsilane as internal reference. The lanthanide induced shift study was done by adding small portions of Eu(fod)$_3$ (25 mg) to a $CDCl_3$ solution containing the pyrazole (0.125 mM in 1 mL). Plots of the chemical shifts vs. ratio Eu(fod)$_3$/pyrazole (0.385, 0.578, 0.771, 0.963) are nearly linear. Elemental analyses were performed by Microanalytical Laboratory, Centre National de la recherche Scientifique, Villeurbanne, France.

3(2*H*)-Furanones **1**[3] and **2**[40] and pyrazoles **5–8**[1,2] were prepared as described in the literature.

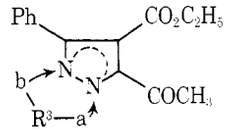
3(2*H*)-Furanones 3 and 4. A solution of 2-acetoxy-2,5-dimethyl-4-ethoxycarbonyl-3(2*H*)-furanone or 2-acetoxy-2-methyl-4-ethoxycarbonyl-5-phenyl-3(2*H*)-furanone (0.05 mol), prepared as described[41,42] in 100 mL of dry methanol acidified with acetyl chloride (0.2 mL), was heated at reflux temperature for 5 h. After evaporation of the methanol, the residue was distilled in vacuo to afford **3** or **4.**

4-Ethoxycarbonyl-2-methoxy-2,5-dimethyl-3-(2*H*)-furanone (3) (9.1 g, 85%): bp 110 °C (0.1 mm); mp 43 °C (hexane); IR (CCl_4) 1745, 1720, 1700 cm^{-1}; UV max (EtOH) 216 nm (ϵ 11 700), 270 (12 000); ^{1}H NMR ($CDCl_3$) δ 1.37 (3 H, t, J = 7 Hz), 1.50 (3 H, s), 2.68 (3 H, s), 3.27 (3 H, s), 4.32 (2 H, q, J = 7 Hz). Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.05; H, 6.66.

4-Ethoxycarbonyl-2-methoxy-2-methyl-5-phenyl-3-(2*H*)-furanone (4) (12.4 g, 90%): bp 165 °C (0.5 mm); mp 54 °C (hexane); IR (CCl_4) 1730 cm^{-1}; UV max (EtOH) 212 nm (ϵ 9200), 254 (5500), 306 (15 200); ^{1}H NMR ($CDCl_3$) δ 1.32 (3 H, t, J = 7 Hz), 1.61 (3 H, s), 3.34 (3 H, s), 4.34 (2 H, q, J = 7 Hz), 7.45–8.15 (5 H, m). Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.19; H, 5.75.

Preparation of 1-Alkyl-3-methyl(or phenyl)pyrazoles. Series a. Reaction of 3(2*H*)-Furanones with Methylhydrazine. General Procedure. To a stirred solution (0.02 mol) of **1–4** in acetonitrile (20 mL for **1, 3,** and **4,** 100 mL for **2**) was added slowly methylhydrazine (0.92 g, 0.02 mol). The reaction mixture was allowed to stir at room temperature for 1 h and acetonitrile was evaporated. The crude products were analyzed by GLC or ^{1}H NMR. After further purification pyrazoles **a** were obtained as described below.

Table VII. Carbon-13 Chemical Shifts for Derivatives of 3- and 5-Phenyl Series of Pyrazoles ($CDCl_3$)



				$COOCH_2CH_3$			$COCH_3$			
Compd	C-3	C-4	C-5	CO	OCH_2	CH_3	CO	CH_3	Ph	NR^3
13a	150.0	113.2	141.6	163.5	61.1	13.7	191.9	30.3	C′-1, 131.7; C′-2,6, 128.4;[a] C′-3,5, 127.8;[a] C′-4, 128.6[a]	CH_3: 39.2
13b	148.3	113.6	145.2	163.2	60.6	13.7	192.9	27.5	C′-1, 128.8; C′-2,6, 129.4;[a] C′-3,5, 128.3;[a] C′-4, 127.9	CH_3: 37.7
7	148.9	111.8	145.3	164.8	61.6	13.7	193.6	27.4	C′-1, 129.3; C′-2,6, 129.4; C′-3,5, 128.3; C′-4, 129.3	H

[a,b] These values might be interchanged.

Reaction of 3(2*H*)-Furanones with Benzylhydrazine. General Procedure. The resulting solutions of **1–4** with benzylhydrazine (2.44 g, 0.02 mol) were run as described above for **1** and **2;** the reaction mixture was heated under reflux for 30 min for **3** and **4.** Evaporation of the solvent afforded the crude pyrazoles **b.** Final purification by recrystallization or fractional distillation at reduced pressure gave the pure pyrazoles **a.**

Their spectra are listed in Tables I, III, and VII.

4-Ethoxycarbonyl-1,3-dimethyl-5-phenylacetylpyrazole (9a). The distillation of crude product mixture **9a/9b,** 65:35, afforded **9a:** 3.37 g (59%); bp 170 °C (1 mm). Anal. Calcd for $C_{16}H_{18}O_3N_2$: C, 67.11; H, 6.34; N, 9.78. Found: C, 67.12; H, 6.42; N, 9.66.

1-Benzyl-4-ethoxycarbonyl-3-methyl-5-phenylacetylpyrazole (10a). The residual solid was extracted with boiling hexane (200 mL). The residue obtained by evaporation of the hexane extract was recrystallized from ethyl acetate–hexane, 70:30, to give 5 g (66%) of **10a.**

5-Acetyl-4-ethoxycarbonyl-1,3-dimethylpyrazole (11a). The distillation of the mixture **11a/11b,** 80:20, gave a first fraction [2.5 g; bp 120–130 °C (0.2 mm)] which crystallized. The raw crystals were recrystallized from water–ethanol, 80:20, to afford **11a:** 1.5 g (35%; mp 65 °C). Anal. Calcd for $C_{10}H_{14}O_3N_2$: C, 57.13; H, 6.71; N, 13.33. Found: C, 57.42; H, 6.48; N, 13.61.

5-Acetyl-1-benzyl-4-ethoxycarbonyl-3-methylpyrazole (12a). The residue afforded the pure pyrazole **12a** by distillation 180–182 °C (0.5 mm); 3.4 g (60%). Anal. Calcd for $C_{16}H_{18}O_3N_2$: C, 67.11; H, 6.34; N, 9.78. Found: C, 67.21; H, 6.35; N, 9.96.

5-Acetyl-4-ethoxycarbonyl-1-methyl-3-phenylpyrazole (13a). The crude mixture product **13a/13b,** 92:8, gave by distillation **13a** (2.2 g, 40%): bp 160 °C (1 mm). Anal. Calcd for $C_{15}H_{16}O_3N_2$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.44; H, 5.91; N, 10.34.

5-Acetyl-1-benzyl-4-ethoxycarbonyl-3-phenylpyrazole (14a). The crude product was purified by distillation: 4.4 g(63%); bp 230 °C 0.1 mm). Anal. Calcd for $C_{21}H_{20}O_3N_2$: C, 72.39; H, 5.79; N, 8.04. Found: C, 71.83; H, 5.79; N, 8.04.

4-Acetyl-1,3-dimethyl-5-phenylacetylpyrazole (15a). The residue **15a/16b,** 75:25, was distillated at 180–200 °C (0.5 mm) to give a solid distillate which was recrystallized from ethyl acetate–hexane, 20:80 (3 g, 58%); mp 86°C. Anal. Calcd for $C_{15}H_{16}O_2N_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.05; H, 6.25; N, 11.02.

4-Acetyl-1-benzyl-3-methyl-5-phenylacetylpyrazole (16a). The residual solid was recrystallized from ethyl acetate–hexane, 20:80 (4.8 g, 72%); mp 94 °C. Anal. Calcd for $C_{21}H_{20}O_2N_2$: C, 75.88; H, 6.07; N, 8.43. Found: C, 76.00; H, 6.10; N, 8.43.

Preparation of 1-Methyl(or benzyl)-5-methyl(or phenyl)-pyrazoles. Series b. General Procedure. A stirred solution of pyrazoles **5–8** (0.02 mol) in ethanol (50 mL) containing sodium ethylate (from 0.46 g of sodium) was treated dropwise with methyl iodide (3.5 g, 0.025 mol) or benzyl chloride (2.8 g, 0.022 mol). The mixture was then heated under reflux for 2 h. Solvent was removed in vacuo. The residue was diluted with 20 mL of water, made alkaline, and extracted with ether. After washing with water the solvent was removed by evaporation and the residues were analyzed by ^1H NMR. The crude products were purified by recrystallization, distillation, or chromatography on basic alumina to give pure pyrazoles **b.**

Their spectra are reported in Tables I, IV, and VII.

4-Ethoxycarbonyl-1,5-dimethyl-3-phenylacetylpyrazole (9b) was obtained by recrystallization of residual solid mixture **9a/9b,** 20:80, from ethyl acetate–hexane, 30:70: 3.7 g (65%); mp 71 °C. Anal. Calcd for $C_{16}H_{18}O_3N_2$: C, 67.11; H, 6.34; N, 9.78. Found: C, 66.88; H, 6.28; N, 9.87.

1-Benzyl-4-ethoxycarbonyl-5-methyl-3-phenylacetylpyrazole (10b). The crude pyrazole **10b,** 3.55 g (71%), was purified by chromatography over basic alumina and elution with ethyl acetate. Anal. Calcd for $C_{22}H_{22}O_3N_2$: C, 72.91; H, 6.12; N, 7.33. Found: C, 72.67; H, 6.06; N, 7.55.

3-Acetyl-4-ethoxycarbonyl-1,5-dimethylpyrazole (11b). The residual mixture **11a/11b,** 20:80, 3.4 g, was purified by chromatography; 0.6 g was chromatographed on 50 g of basic alumina (activity III). Elution with 7% ethyl acetate in hexane gave **11a** (0.11 g) and then **11b** (0.42 g, 56%). Anal. Calcd for $C_{10}H_{14}O_3N_2$: C. 57.13; H, 6.71; N, 13.33. Found: C, 56.91; H, 6.64; N, 13.24.

3-Acetyl-1-benzyl-4-ethoxycarbonyl-5-methylpyrazole (12b). The solid crude product **12a/12b,** 25:75, afforded **12b** by recrystallization from hexane: 2.6 g (46%); mp 75 °C. Anal. Calcd for $C_{16}H_{18}O_3N_2$: C, 67.11; H, 6.34; N, 9.78. Found: C, 67.01; H, 6.26; N, 9.81.

3-Acetyl-4-ethoxycarbonyl-1-methyl-5-phenylpyrazole (13b). The solid crude product **13a/13b,** 20:80, afforded **13b** by recrystallization from hexane–ethyl acetate, 90:10; 2.2 g (40%); mp 68 °C. Anal. Calcd for $C_{15}H_{16}O_3N_2$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.22; H, 5.92; N, 10.26.

3-Acetyl-1-benzyl-4-ethoxycarbonyl-5-phenylpyrazole (14b) was obtained by crystallization of crude mixture **14a/14b,** 10:90, from hexane–ethyl acetate, 80:20: 3.75 g (54%); mp 76 °C. Anal. Calcd for $C_{21}H_{20}O_3N_2$: C, 72.39; H, 5.79; N, 8.04. Found: C, 72.41; H, 5.79; N, 8.09.

4-Acetyl-1,5-dimethyl-3-phenylacetylpyrazole (15b). Distillation of mixture **15a/15b,** 20:80, gave **15a** [0.8 g; bp 180–185 °C(0.5 mm)] and **15b** [3.1 g; 60%; bp 210–215 °C (0.5 mm)]. Anal. Calcd for $C_{15}H_{16}O_2N_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 69.35; H, 6.45; N, 10.15.

4-Acetyl-1-benzyl-5-methyl-3-phenylacetylpyrazole (16b) was obtained by recrystallization from ethyl acetate–hexane, 20:80; 4.3 g (65%); mp 95 °C. Anal. Calcd for $C_{21}H_{20}O_2N_2$: C, 75.88; H, 6.07; N, 8.43. Found: C, 75.60; H, 6.04; N, 8.46.

Registry No.—**1,** 53252-49-6; **2,** 62723-14-2; **3,** 62538-46-9; **4,** 62538-48-1; **5,** 65942-92-9; **6,** 62538-27-6; **7,** 62538-29-8; **8,** 63195-08-4; 2-acetoxy-2,5-dimethyl-4-ethoxycarbonyl-3(2*H*)-furanone, 53252-54-3; 2-acetoxy-2-methyl-4-ethoxycarbonyl-5-phenyl-3(2*H*)-furanone, 53252-56-5; methylhydrazine, 60-34-5; benzylhydrazine, 555-96-4.

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A New and Facile Synthesis of Trialkylketenimines

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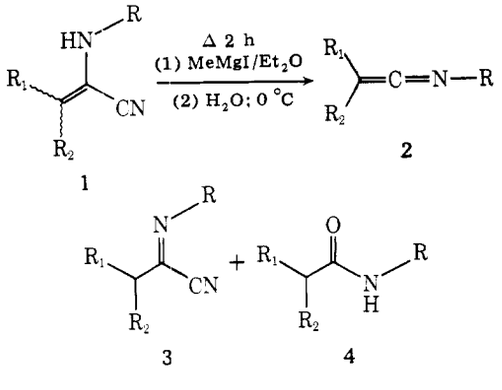
Trialkylketenimines were prepared by reaction of α-cyano enamines with methylmagnesium iodide in ethereal solution. Condensation of trialkylketenimines with primary amines afforded the corresponding amidines.

Ketenimines are an important class of organic compounds, which are apt to undergo a variety of photochemical and thermal cycloadditions.[2a] Several entries into this cumulenic system have been described,[2a] but the overwhelming number of ketenimines described hitherto are substituted with one or more aromatic substituents. A few trialkylketenimines have been prepared from aliphatic imidoyl chlorides and triethylamine[2b,3] or by dehydration of amides.[4] These trialkylketenimines have been used as catalysts for the low-temperature polymerization of ϵ-caprolactam.[5] It was claimed[2a] that the lower trialkylketenimines are not readily accessible due to the easy formation of resinous material. For instance dimethyl-*N*-*n*-butylketenimine was reported to decompose rapidly at −20 °C.[3]

We now report a new and facile synthesis of trialkylketenimines starting from α-cyano enamines **1**, which are easily accessible from disubstituted acetaldehydes via α-chloroaldimines.[6,7] Treatment of α-cyanoenamines **1** with methylmagnesium iodide in diethyl ether afforded, after usual workup with an aqueous ammonium chloride solution, a reaction mixture in which trialkylketenimines **2** were the predominant compounds (Scheme I). When the reaction mixture was subjected to a GC–MS coupling, using on-column injection in order to minimize polymerization of the title compounds, small amounts of imidoylcyanides **3** and *N*-alkylamides **4** were also detected.

Scheme I



Careful distillation in vacuo over a 10-cm Vigreux column allowed separation of ketenimines **2** from compounds **3** and **4**. Trialkylketenimines **2** were obtained in 27–61% yield as colorless liquids and were fully characterized by NMR, IR, and MS. Compounds **2a–e** are stable for several weeks when kept in the refrigerator.

Table I gives a survey of the synthesis of ketenimines **2**, while Table II compiles the spectral properties of compounds **2**. Up to now, NMR data from only one trialkylketenimine, i.e., dimethyl-*N*-cyclohexylketenimine, have been reported.[4]

From the mechanistic point of view, the synthesis of ketenimines **2** can be visualized by methane production and formation of a magnesium salt **5**, from which cyanide is expelled (Scheme II). In this respect the expulsion of cyanide from enamine anion **6** parallels the mechanistic behavior of α-halo enamines, which react as ketenimmonium halides.[8] The production of side products such as imidoylcyanides **3** and amides **4** is interpreted as derived from protonation of salt **5** (workup with water)[9] and addition of water to the ketenimine system, respectively. Surprisingly, reaction of 2-*tert*-butylamino-3-methyl-2-butenenitrile (**1a**) with methylmagnesium iodide in tetrahydrofuran resulted in a complete recovery of

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