Synthesis of 3-(1,5-Diphenyl-3-pyrazolyl)aryl Propanoates

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New procedures for the synthesis of 3-(1,5-diphenyl-3-pyrazolyl)aryl propanoates and related 2-(1,5-diphenyl-3-pyrazolyl)aryl propanoates from a common 3-hydroxymethylpyrazole intermediate are described. These new procedures include an improved method for carrying out pyridinium chlorochromate oxidations under ultrasonic conditions. These syntheses also utilize lithium triethylphosphonoacetate formed from *n*-butyllithium and triethylphosphonoacetate as a Wittig-Horner reagent to improve olefination yields.

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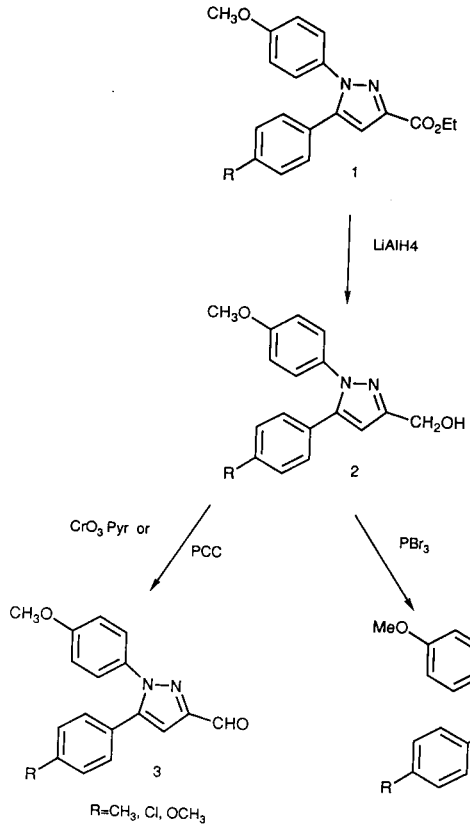
In our continuing efforts towards the synthesis of tepoxalin [1a-d], and related 1,5-diarylpyrazole antiinflammatory agents, we required an efficient synthesis of 3-(1,5-diaryl-3-pyrazolyl)-2-aryl propanoates and 3-(1,5-diaryl-3-pyrazolyl)-3-arylpropanoates. These compounds were not available through our initial synthetic approach to tepoxalin and related analogs [1a]. We felt the most efficient synthesis of these compounds would be through a common intermediate, the hydroxymethyl derivative **2**.

We have recently described an improved synthesis of 3-carboethoxy-1,5-diarylpyrazoles **1** [2]. The ester **1** was then reduced with lithium aluminum hydride to the pyrazole methyl alcohol **2** (Scheme 1) in 90-100% yields. Compound **2** was then oxidized to its requisite aldehyde **3** using Collins reagent in 80-90% yield. Later we found pyridinium chlorochromate, (PCC) to be an effective oxidative reagent when a sonicative work up procedure is used [3]. Without sonication we would routinely obtain yields of less than 50%. With sonication we routinely observed yields of greater than 90%. One problem that has been encountered with PCC reactions is the recovery of oxidized product from the chromium tars. By sonicating these tars in ether, during workup, they are converted to a dark gray granular solid which is easily filtered. We have found that PCC reaction yields are enhanced by sonication during the workup and during the course of the reaction [4]. Sonication also tends to speed up the reaction probably due to enhanced mixing, and energy addition. Compound **2** was also converted to the bromide **4** with phosphorus tribromide.

Aldehyde **3** proved to be a suitable intermediate for the synthesis of 3-(1,5-diaryl-3-pyrazolyl)-3-aryl propanoates **9** (Scheme II). Addition of an aryl Grignard reagent or an aryllithium to **3** afforded **5** in generally good yields (Table 1). The lower yields observed in **5h** and **5k** were due to incomplete formation of the aryllithium. This was evidenced by the isolation of the requisite 3-(1-hydroxypentyl)-1,5-diphenylpyrazole as the major side product. This product arises from incomplete reaction of *n*-butyllithium with the aryl bromide or anisole, and subsequent addition of *n*-butyllithium to the aldehyde **3**. This can be averted by longer formation times for the aryllithium. In later examples, *i.e.* **5i**, this problem was overcome. The pertinent spectral characteristics of **5** are outlined in Table 2.

Scheme I



The oxidation of the pyrazole aryl alcohols **5** to their requisite ketones **6** was carried out by our sonicative PCC oxidation. The results of these reactions are outlined in Table 3. The yields of these reactions are generally good to excellent with the exceptions of the furyl derivative **6l**, which undergoes a ring opening [5], and the 4-methoxyphenyl derivative **6o** which partially decomposes. Some pertinent spectral features of these molecules are shown in Table 4.

Scheme II

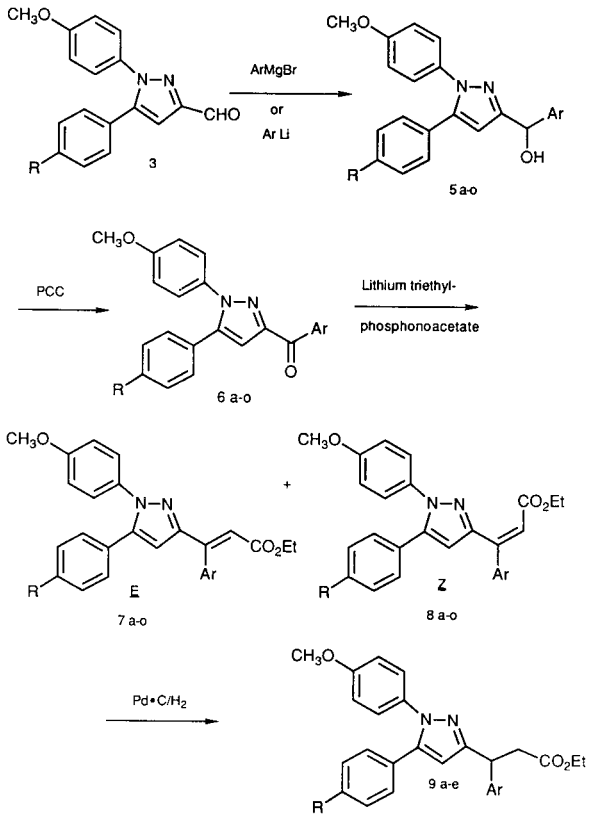
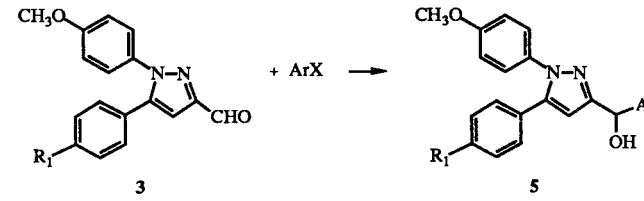


Table 1

Addition of Aryl Grignard Reagents to 1,5-Diphenyl-pyrazole-3-aldehydes

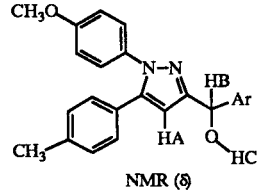


No.	R_1	Ar	X	Yield
5a	CH_3	phenyl	MgBr	99
5b	CH_3	4-fluorophenyl	MgBr	91
5c	CH_3	4-biphenyl	MgBr	91
5d	CH_3	4-chlorophenyl	MgBr	92
5e	CH_3	4-methylphenyl	MgBr	89
5f	CH_3	1-naphthyl	MgBr	73
5g	CH_3	2-naphthyl	Li	64
5h	CH_3	4-methoxyphenyl	Li	49
5i	CH_3	2-thienyl	Li	82
5j	CH_3	2-methoxyphenyl	Li	63
5k	CH_3	2-methoxy-6-naphthyl	Li	53
5l	CH_3	2-furyl	Li	70
5m	OCH_3	4-methylphenyl	MgBr	88
5n	OCH_3	2-methoxyphenyl	Li	61
5o	OCH_3	4-methoxyphenyl	Li	67

In synthesizing **7** and **8**, we found that Wittig-Horner olefination using lithium triethylphosphonoacetate gave the best results [7] [8]. Further, better results were obtained when we formed the lithio salt of the phosphonate ester from triethylphosphonoacetate and *n*-butyllithium at -78°. When LDA or lithium hexamethyldisilazide was used, we found varying degrees of transamidation in the olefin products. This is not unexpected since the amine, *i.e.* diisopropylamine, is present in stoichiometric quantities during a 24 hour reflux period. At - 78° we saw no evidence of addition of *n*-butyllithium to the phosphonate ester, we only observed deprotonation. The olefination reactions are outlined in Table 5. In general, there is a small degree of selectivity toward the *E* isomer **7**. The assignments of *E* and *Z* were made by comparison with (*E*)-Ethyl 3-[1,5-bis(methoxyphenyl)-3-pyrazolyl]propenoate which was prepared by reaction of the aldehyde **3** with sodium triphenylphosphonoacetate. Related Wittig reactions are reported to give only the *E* isomer [8]. Pertinent spectral features of **7** and **8** are shown in Table 6. Mixtures of **7**

Table 2

Pertinent Spectral Features of Representative Compounds

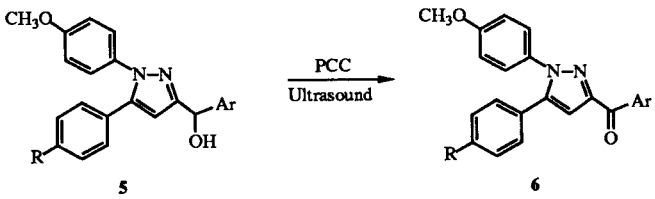


NMR (δ)

No	HA	HB	HC	IR cm^{-1}
5c	6.30 (1H, s)	6.02 (1H, d, J = 4 Hz)	3.22 (1H, d, J = 4 Hz)	3400
5d	6.19 (1H, s)	5.94 (1H, d, J = 4 Hz)	3.28 (1H, d, J = 4 Hz)	3208
5e	6.24 (1H, s)	5.93 (1H, d, J = 4 Hz)	3.10 (1H, d, J = 4 Hz)	3205
5f	6.10 (1H, s)	6.70 (1H, d, J = 4 Hz)	3.30 (1H, d, J = 4 Hz)	3284
5h	6.23 (1H, s)	5.92 (1H, d, J = 4 Hz)	3.18 (1H, d, J = 4 Hz)	3274
5j	6.30 (1H, s)	6.25 (1H, d, J = 4 Hz)	3.54 (1H, d, J = 4 Hz)	3512

Table 3

Oxidation of Diarylalcohols with Pyridinium Chlorochromate



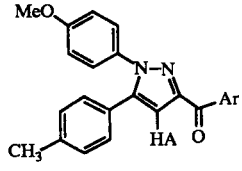
5 6

Compound	R	Ar	Yield (%)
6a	CH_3	phenyl	96
6b	CH_3	4-fluorophenyl	98
6c	CH_3	4-biphenyl	91
6d	CH_3	4-chlorophenyl	92
6e	CH_3	4-methylphenyl	88
6f	CH_3	1-naphthyl	80
6g	CH_3	2-naphthyl	99
6h	CH_3	2-thienyl	98
6i	CH_3	4-methoxyphenyl	59
6j	CH_3	2-methoxyphenyl	69
6k	CH_3	6-methoxy-2-naphthyl	72
6l [a]	CH_3	2-furyl	24
6m	OCH_3	2--methoxyphenyl	60
6n	OCH_3	4-methylphenyl	77
6o	OCH_3	4-methoxyphenyl	41

[a] Furyl cleavage was noted in this oxidation. It can be averted by oxidizing with aluminum triisopropoxide/cyclohexanone in toluene [6]. This reaction affords a 80% yield.

Table 4

Pertinent Spectral Features of Representative Compounds



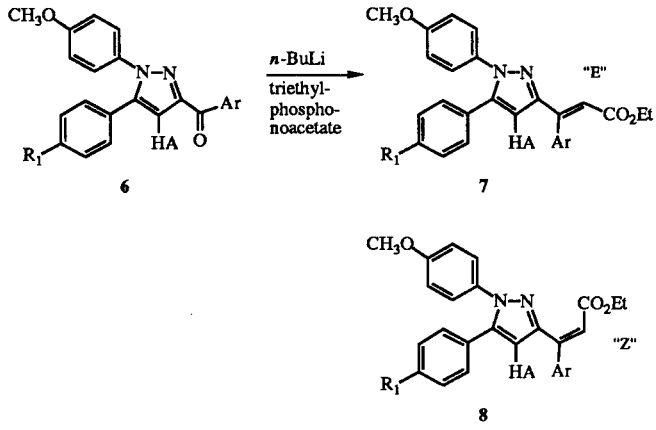
Compound	HA δ	IR cm^{-1}
6c	7.15 (1H, s)	1638
6d	7.15 (1H, s)	1644
6e	7.20 (1H, s)	1636
6f	7.12 (1H, s)	1648
6i	7.12 (1H, s)	1635
6j	7.01 (1H, s)	1663

and **8** can be readily hydrogenated to our target **9** in greater than 90% yield.

In order to generate the 2-aryl isomer **10** we alkylated aryl alkyl acetates with **4** (Scheme III). These reactions are carried out in DMF using sodium hydride as base. The yields for these reactions are fair to good and are outlined in Table 7. Attempts to improve the yields by varying solvents were unsuccessful. Use of amide bases such as

Table 5

Addition of Lithium Triethylphosphonoacetate to Diphenylpyrazole Aryl Ketones [9]



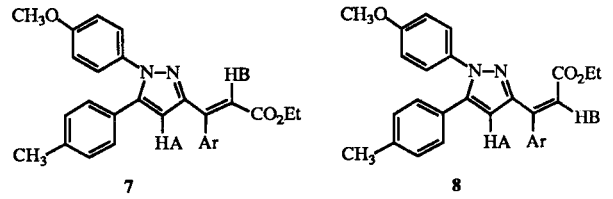
6 7 8

No. 7 + 8	R_1	Ar	Yield 7 (%)	Yield 8 (%)
a	CH_3	phenyl	48	27
b	CH_3	4-fluorophenyl	41	36
c	CH_3	4-biphenyl	48	37
d	CH_3	4-chlorophenyl	38	43
e	CH_3	4-methylphenyl	51	40
f [a]	CH_3	1-naphthyl	36	27
g	CH_3	2-naphthyl	39	13
h	CH_3	4-methoxyphenyl	50	40
i	CH_3	2-methoxyphenyl	45	45
j	CH_3	2-thienyl	51	22
k	CH_3	2-furyl	20	43
l [b]	OCH_3	2-methoxyphenyl	50	10
m	OCH_3	4-methoxyphenyl	44	0
n	CH_3	6-methoxy-2-naphthyl	47	24
o	CH_3	4-methylphenyl	46	24

[a] Isolated as a 4:3 mixture of *E* to *Z*, total yield 63%. [b] Isolated as a 5:1 mixture of *E* to *Z*, total yield 60%.

Table 6

Representative NMR Resonacnes of 7,8 Pairs [a]

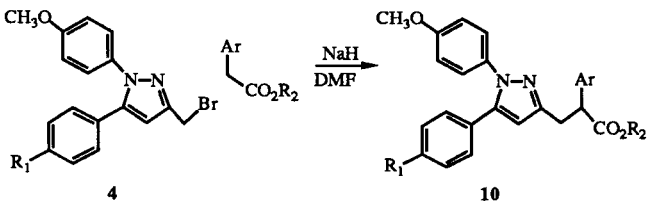


7 8

No.	HA δ	HB δ
7d	6.55	6.31
8d	6.89	6.21
7e	6.51	6.34
8e	6.86	6.20
7g	6.58	6.48
8g	7.00	6.18
7h	6.51	6.34
8h	6.85	6.20

[a] All reonances are singlets which integrate for 1 proton.

Table 7
Reactions of 4-Bromomethyl-1,5-diphenylpyrazoles **4** with Anions of Aryl Alkyl Acetates

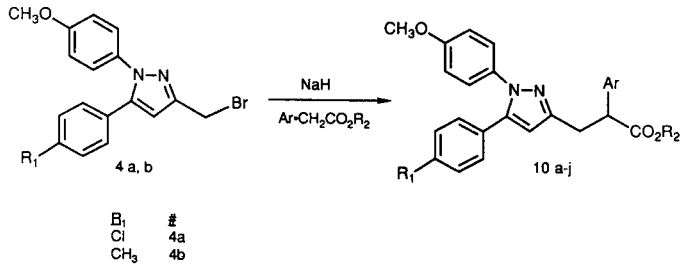


4 **10**

Compound	R_1	R_2	Ar	Yield
10a	Cl	Et	Phenyl	51
10b	Cl	Et	3,4-Dimethoxyphenyl	52
10c	Cl	Et	4-Chloropophenyl	72
10d	Cl	Et	4-methoxyphenyl	59
10e	CH_3	Et	2-naphthyl	84
10f	CH_3	Et	1-naphthyl	33
10g	CH_3	Et	2-methoxyphenyl	61
10h	CH_3	Et	2-pyridyl	49
10i	CH_3	Et	4-biphenyl	31
10j	CH_3	CH_3	2-carbomethoxyphenyl	92

LDA were avoided because of the transamidation reactions mentioned above.

Scheme III



The procedures described afforded us a range of 2- and 3-arylpropanoic and propenoic acids. These compounds were then used as intermediates in the preparation of analogs of the potent antiinflammatory dual inhibitor tepoxalin. In synthesizing these compounds we have described useful procedures for the oxidation of heterocyclic benzhydrols and for Wittig-Horner additions of lithium phosphonoacetates to heterocyclic benzophenones.

Table 8
Melting Points and Combustion Analysis of Compound **5a-o** and **6a-0**

No.	Formula	MP °C	Theoretical	Found
5a	$C_{24}H_{22}N_2O_2$	101-103	C, 77.81 H, 5.99 N, 7.56	C, 77.49 H, 6.24 N, 7.22
5b	$C_{24}H_{21}N_2O_2F$	101-104	C, 74.20 H, 5.45 N, 7.21	C, 73.80 H, 5.29 N, 7.17
5c	$C_{30}H_{26}N_2O_2$	135-137	C, 80.69 H, 5.87 N, 6.27	C, 80.70 H, 5.84 N, 6.28
5d	$C_{24}H_{21}N_2O_2Cl$	130-132	C, 71.19 H, 5.23 N, 6.92	C, 70.98 H, 5.33 N, 6.85
5e	$C_{25}H_{24}N_2O_2$	138-140	C, 78.10 H, 6.29 N, 7.29	C, 78.15 H, 6.46 N, 7.33
5f	$C_{28}H_{21}N_2O_2$	156-159	C, 79.98 H, 5.75 N, 6.66	C, 79.59 H, 5.85 N, 6.50
5g	$C_{28}H_{21}N_2O_2$	142-143	C, 79.98 H, 5.75 N, 6.66	C, 80.06 H, 5.70 N, 6.64
5h	$C_{25}H_{24}N_2O_3$	109-111	C, 74.98 N, 6.04 N, 7.00	C, 75.04 H, 5.85 N, 7.09
5i	$C_{22}H_{20}N_2O_2S$	134-136	C, 70.19 H, 5.35 N, 7.44	C, 70.24 H, 5.36 N, 7.82
5j	$C_{25}H_{214}N_2O_3$	109-111	C, 74.98 H, 6.04 N, 7.00	C, 74.80 H, 6.08 N, 6.99
5k	$C_{29}H_{26}N_2O_3$	170-172	C, 77.31 H, 5.82 N, 6.22	C, 76.98 H, 5.87 N, 5.96
5l	$C_{22}H_{20}N_2O_3$	127-130	C, 73.32 H, 5.59 N, 7.77	C, 73.07 H, 5.74 N, 7.60
5m	$C_{25}H_{24}N_2O_3$	138-139	C, 74.98 H, 6.04 N, 7.00	C, 74.72 H, 5.96 N, 6.88
5n	$C_{25}H_{24}N_2O_4$	--	C, 72.10 H, 5.81 N, 6.73	C, 71.84 H, 5.75 N, 6.43
5o	$C_{25}H_{24}N_2O_4$	148-149	C, 72.10 H, 5.81 N, 6.73	C, 72.15 H, 5.77 N, 6.73
6a	$C_{24}H_{20}N_2O_2$	101-103	C, 78.24 H, 5.47 N, 7.60	C, 77.93 H, 5.29 N, 7.63
6b	$C_{24}H_{19}N_2O_2F$	138-139	C, 74.60 H, 4.96 N, 7.25	C, 74.70 H, 4.81 N, 7.23
6c	$C_{30}H_{24}N_2O_2$	146-148	C, 81.06 H, 5.44 N, 6.30	C, 80.97 H, 5.58 N, 6.36
6d	$C_{24}H_{19}N_2O_2Cl$	157-159	C, 71.55 H, 4.75 N, 6.96	C, 71.29 H, 4.72 N, 6.86
6e	$C_{25}H_{22}N_2O_2$	136-138	C, 78.51 H, 5.80 N, 7.32	C, 78.22 H, 5.71 N, 7.25
6f	$C_{28}H_{19}N_2O_2$	158-160	C, 80.36 H, 5.30 N, 6.69	C, 80.21 H, 5.55 N, 6.67
6g	$C_{28}H_{19}N_2O_2$	158-159	C, 80.36 H, 5.30 N, 6.69	C. 80.18 H, 5.21 N, 6.59
6h	$C_{22}H_{18}N_2O_2S$	161-162	C, 70.57 H, 4.85 N, 7.72	C, 70.55 H, 4.74 N, 7.42
6i	$C_{25}H_{22}N_2O_3$	127-128	C, 75.36 H, 5.57 N, 7.03	C, 75.35 H, 5.66 N, 7.32
6j	$C_{25}H_{22}N_2O_3$	141-143	C, 75.36 H, 5.57 N, 7.03	C, 75.11 H, 5.55 N, 6.91
6k	$C_{29}H_{24}N_2O_3$	175-176	C, 77.66 H, 5.39 N, 6.25	C, 77.74 H, 5.26 N, 6.05
6l	$C_{22}H_{18}N_2O_3$	139-141	C, 73.73 H, 5.06 N, 7.82	C, 73.84 H, 4.88 N, 7.56
6m	$C_{25}H_{22}N_2O_4$	141-143	C, 72.45 H, 5.35 N, 6.76	C, 72.35 H, 5.45 N, 6.80
6n	$C_{25}H_{22}N_2O_3$	137-138	C, 75.36 H, 5.57 N, 7.03	sC, 75.30 H, 5.51 N, 7.04
6o	$C_{25}H_{22}N_2O_4$	138-139	C, 77.45 H, 5.35 N, 6.76	C, 72.26 H, 5.47 N, 6.69

Table 9

Melting Points and Elemental Analysis of 7,8 Isomer Pairs

No.	Formula	MP° C	Theoretical	Found
7a	$C_{28}H_{26}N_2O_3$	---	C, 76.69 H, 5.98 N, 6.39	C, 76.89 H, 6.04 N, 6.25
8a	"	143-144	C, 76.69 H, 5.98 N, 6.39	C, 76.82 H, 6.00 N, 6.48
7b	$C_{28}H_{25}N_2O_3F$	---	C, 73.67 H, 5.52 N, 6.14	C, 73.90 H, 5.59 N, 6.10
8b	"	131-133	C, 73.67 H, 5.52 N, 6.14	C, 74.04 H, 5.53 N, 6.25
7c	$C_{34}H_{30}N_2O_3$	---	C, 79.35 H, 5.88 N, 5.44	C, 79.37 H, 6.01 N, 5.41
8c	"	147-149	C, 79.35 H, 5.88 N, 5.44	C, 79.54 H, 5.96 N, 5.42
7d	$C_{28}H_{25}N_2O_3Cl$	---	C, 71.11 H, 5.33 N, 5.92	C, 71.49 H, 5.30 N, 5.88
8d	"	141-143	C, 71.11 H, 5.33 N, 5.92	C, 71.09 H, 5.40 N, 5.96
7e	$C_{29}H_{28}N_2O_3$	---	C, 76.97 H, 6.24 N, 6.19	C, 76.69 H, 6.32 N, 6.11
8e	"	118-119	C, 76.97 H, 6.24 N, 6.19	C, 77.24 H, 6.42 N, 6.20
7f & 8f [a]	$C_{32}H_{28}N_2O_3$	---	C, 78.67 H, 5.78 N, 5.73	C, 78.47 H, 5.84 N, 5.63
7g	$C_{32}H_{28}N_2O_3$	123-125	C, 78.67 H, 5.78 N, 5.73	C, 78.74 H, 5.63 N, 5.80
8g	"	171-173	C, 78.67 H, 5.78 N, 5.73	C, 78.91 H, 5.69 N, 5.78
7h	$C_{29}H_{28}N_2O_4$	---	C, 74.32 H, 6.02 N, 5.98	C, 74.32 H, 6.09 N, 5.88
8h	"	104-107	C, 74.32 H, 6.02 N, 5.98	C, 74.46 H, 6.12 H, 5.98
7i & 8i [a]	$C_{29}H_{28}N_2O_4$	---	C, 74.32 H, 6.02 N, 5.98	C, 74.21 H, 6.09 N, 5.92
7j	$C_{26}H_{24}N_2O_3S$	---	C, 70.25 H, 5.44 N, 6.30	C, 69.98 H, 5.38 N, 6.26
8j	"	---	C, 70.25 H, 5.44 N, 6.30	C, 69.90 H, 5.73 N, 6.01
7k	$C_{26}H_{24}N_2O_4$	---	C, 76.43 H, 5.83 N, 5.40	C, 76.18 H, 5.76 N, 5.25
8k	"	125-127	C, 76.43 H, 5.83 N, 5.40	C, 76.14 H, 5.66 N, 5.27
7l	$C_{29}H_{28}N_2O_5$	---	C, 72.88 H, 5.65 N, 6.54	C, 76.14 H, 5.66 N, 5.27
8l	"	---	C, 72.88 H, 5.65 N, 6.54	C, 72.55 H, 5.96 N, 6.38
7m	$C_{29}H_{28}N_2O_5$	---	C, 71.88 H, 5.83 N, 5.78	C, 71.79 H, 5.94 N, 5.77
7n & 8n	$C_{32}H_{28}N_2O_4$	---	C, 71.88 H, 5.83 N, 5.78	C, 71.78 H, 4.78 N, 5.72
7o	$C_{29}H_{28}N_2O_4$	---	C, 74.34 H, 6.02 N, 5.98	C.74.39 H, 6.09 N, 5.92
8o	"	211-214	C, 74.34 H, 6.02 N, 5.98	C, 74.29 H, 6.19 N, 6.14

[a] Mixture was not separated.

Table 10

Elemental Analysis of Compounds **9a-e** and **10a-j** [a]

No.	Formula	Theoretical	Found
9a	$C_{28}H_{28}N_2O_3$	C, 76.33 H, 6.41 N, 6.36	C, 75.98 H, 6.80 N, 6.00
9b	$C_{28}H_{27}N_2O_3F$	C, 73.34 H, 5.94 N, 6.11	C, 72.87 H, 6.25 N, 5.85
9c	$C_{34}H_{32}N_2O_3$	C, 79.04 H, 6.24 N, 5.42	C, 79.06 H, 6.39 N, 5.43
9d	$C_{29}H_{30}N_2O_3$	C, 76.63 H, 6.65 N, 6.16	C, 76.74 H, 6.98 N, 6.08
9e	$C_{28}H_{27}N_2O_3Cl$	C, 70.80 H, 5.73 N, 5.90	C, 70.93 H, 5.79 N, 5.92
10a	$C_{27}H_{25}N_2O_3Cl$	C, 70.35 H, 5.47 N, 6.08	C, 70.06 H, 5.53 N, 6.02
10b	$C_{29}H_{29}N_2O_5Cl$	C, 66.85 H, 5.61 N, 5.38	C, 67.06 H, 5.82 N, 5.24
10c	$C_{27}H_{24}N_2O_3Cl_2$	C, 65.46 H, 4.88 N, 5.65	C, 65.18 H, 4.90 N, 5.49
10d	$C_{28}H_{27}N_2O_4$	C, 66.07 H, 5.74 N, 5.50	C, 66.06 H, 5.36 N, 5.43
10e	$C_{32}H_{30}N_2O_3$	C, 78.34 H, 6.16 N, 5.71	C, 78.49 H, 6.19 N, 5.65
10f	$C_{32}H_{30}N_2O_3$	C, 78.34 H, 6.16 N, 5.71	C, 78.20 H, 6.40 N, 5.76
10g	$C_{29}H_{30}N_2O_3$	C, 74.02 H, 6.43 N, 5.95	C, 73.63 H, 6.32 N, 5.89
10h	$C_{27}H_{27}N_3O_3$	C, 70.57 H, 6.36 N, 9.14	C, 70.26 H, 6.29 N, 8.93
10i	$C_{34}H_{32}N_2O_3$	C, 79.04 H, 6.24 N, 5.42	C, 78.02 H, 6.20 N, 5.07
10j	$C_{29}H_{28}N_2O_5$	C, 71.88 H, 5.82 N, 5.78	C, 71.60 H, 5.86 N, 5.95

[a] None of these compounds were crystalline.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. The infrared spectra (ir) were recorded on a Beckman InstrumentsIR-B spectrophotometer and are expressed in reciprocal centimeters. Nuclear magnetic resonance (nmr) spectra for hydrogen atoms were measured in the indicated solvent with tetramethylsilane (TMS) as the internal standard on a GE QE 300 or an IBM WP-100 spectrometer. The values are expressed in parts per million downfield from TMS. Parenthesized, underlined hydrogens were assigned to the resonance positions immediately before the parentheses. EI and CI mass spectra were obtained on a Finnigan MAT 8230 Double Focusing high resolution mass spectrometer. Sonications were carried out using a L+R model T 14-B 400 watt ultrasonic cleaner or a Branson DHA 1000 200 watt cleaner.

5-(4-Chlorophenyl)-3-hydroxymethyl-1-(4-methoxyphenyl)pyrazole **2a**.

A solution of 3-carboethoxy-1-(4-chlorophenyl)-5-(4-methoxyphenyl)pyrazole (7.12 g, 0.02 mole) in tetrahydrofuran (250 ml) was cooled to 0°. Lithium aluminum hydride (1.9 g, 0.05 mole) was slowly added with vigorous stirring. After 15 minutes ethyl acetate (15 ml) was added with vigorous stirring. With continued stirring saturated aqueous ammonium chloride (100 ml) was added. The gray precipitate was then filtered through a celite pad. The celite was washed twice with 100 ml portions of ether. The combined organic fractions were separated from the aqueous phase, washed with 5% aqueous hydrochloric acid, and then saturated aqueous sodium chloride. The solution was dried over sodium sulfate, filtered and concentrated to a yellow oil which crystallized from ethyl acetate/hexane to afford the title compound as a white solid (5.9 g, 94%) melting point 95-97°; ms: (m/z) 315 (M+H); ^{1}H nmr (deuteriochloroform): δ 3.80 (3H, s), 4.78 (2H, s), 6.50 (1H, s), 6.95 (2H, d, J = 8 Hz), 7.05-7.40 (6H, m).

Anal. Calcd. for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.88; N, 8.90. Found: C, 64.75; H, 4.83; N, 8.84.

3-Hydroxymethyl-1-(4-methoxyphenyl)-5-(4-methylphenyl)pyrazole **2b**.

Compound **2b** was prepared by the same procedure as **2a**. Compound **2b** was isolated as a white solid (94%) melting point 100-102°; Mass ms: (m/z) 295 (M+H).

Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.24; H, 6.16; N, 9.57.

1-(4-Methoxyphenyl)-5-(4-methylphenyl)pyrazol-3-ylcarboxyaldehyde **3a**.

Pyridine (54.6 ml, 0.68 mole) was dissolved in methylene chloride (450 ml), cooled to 0° and chromium trioxide (34 g, 0.23 mole) was added with stirring. 3-Hydroxymethyl-1-(4-methoxyphenyl)-5-(4-methylphenyl)pyrazole **2b** (16.66 g, 0.0457 mole) dissolved in methylene chloride (400 ml) was added to the mixture with stirring at 0°. After 30 minutes at 0°, the mixture was allowed to warm to room temperature and stirred for an additional 7 hours. The solvent was decanted and filtered through Florosil [10] (100-200 mesh). The residual black tar was sonicated three times with 150 ml portions of ethyl acetate. The combined organic layers were concentrated *in vacuo* to afford a brown oil. The oil was dissolved in ether, washed with 10% sodium hydroxide, 4*N* hydrochloric acid and saturated sodium chloride. The solution was dried with sodium sulfate, filtered and concentrated *in vacuo* to a tan solid which upon recrystallization from ether/hexane afforded the title compound as a white solid (14.2 g, 83%) melting point 100-102°; ms: (m/z) 295 (M+H); ^{1}H nmr (deuteriochloroform): δ 2.35 (s, 3H), 3.84 (s, 3H), 6.83 (d, 2H, J = 8 Hz), 6.98 (s, 1H), 7.15 (s, 4H), 7.23 (d, 2H, J = 8 Hz), 10.05 (s, 1H).

Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.24; H, 6.16; N, 9.57.

3-Bromomethyl-5-(4-chlorophenyl)-1-(4-methoxyphenyl)pyrazole **4**.

To a solution of 5-(4-chlorophenyl)-3-hydroxymethyl-1-(4-methoxyphenyl)pyrazole (3.14 g, 0.01 mole) in benzene (100 ml) was added phosphorous tribromide (1.35 g, 0.005 mole) in benzene (10 ml) dropwise with stirring. The reaction mixture was refluxed for 1 hour, cooled, poured into ice water (100 ml) and extracted with 2 x 100 ml portions of ether. The combined organic layer was washed with 10% aqueous sodium bicarbonate, dried over sodium sulfate, filtered and concentrated to give a tan oil which crystallized on standing to afford the title compound (3.25 g, 86%). Recrystallization afforded a tan solid mp 88-90°; ms: (DCI, m/z) 377 (M+H); ^{1}H nmr (deuteriochloroform): δ 3.81 (s, 3H), 4.57 (s, 2H), 6.55 (s, 1H); 6.92 (d, 2H, J = 8 Hz), 7.0-7.45 (m, 6H).

Anal. Calcd. for $C_{17}H_{14}ON_2ClBr$: C, 54.06; H, 3.74; N, 7.42. Found: C, 53.72; H, 4.01; N, 7.06.

3-Bromomethyl-1-(4-methoxyphenyl)-5-(4-methylphenyl)pyrazole **4b**.

Compound **4b** was prepared following the same procedure as **4a**. Compound **4b** was isolated as a tan solid (88%) melting point 119-121°.

Anal. Calcd. for $C_{18}H_{17}BrN_2O$: C, 60.52; H, 4.80; N, 7.84. Found: C, 60.61; H, 4.97; N, 7.57.

1-Aryl-1-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-methanols **5**.

Procedure A.

A solution of aryl bromide (0.1 mole) in tetrahydrofuran (250 ml) was added dropwise to a sonicating suspension of magnesium (0.1 mole) iodine (20 mg) and ethylene bromide (3 drops) in tetrahydrofuran. The mixture was sonicated at room temperature for 3 hours. The solution was then cooled to 0° and a solution of **3** (7.3 g, 0.025 mole) in tetrahydrofuran (100 ml) was slowly added. The reaction was stirred for 1 hour at 0°, quenched by slow addition of saturated aqueous ammonium chloride and then diluted with ether (200 ml). The organic layer was isolated, washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered and concentrated to a solid which was recrystallized from ether/hexane.

1-(4-Biphenylyl)-1-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]methanol **5c**.

Compound **5c** was prepared by Procedure A and afforded a white solid mp 135-137°; ms: (m/z) 447 (M+H); ir (potassium bromide): 3400, 1513 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.31 (3 H, s), 3.22 (1H, d, J = 4 Hz), 3.81 (3H, s), 6.02 (1H, d, J = 4 Hz), 6.30 (1H, s), 6.84 (2H, d, J = 9 Hz), 7.05 (4H, s), 7.24 (2H, d, J = 9 Hz), 7.30-7.70 (9H, m).

Procedure B.

n-Butyllithium (0.04 mole) was added by syringe to a solution of the bromoaryl or methoxyphenyl compound (0.04 mole) in tetrahydrofuran at -78° under nitrogen. The solution was stirred for 1 hour at -78°. A solution of **3** (0.02 mole) in tetrahydrofuran (100 ml) was added dropwise to the reaction mixture and stirred for 30 minutes at -78°. The reaction mixture was warmed to room temperature, diluted with ether (150 ml) and quenched with water (100 ml). The organic layer was separated, dried over sodium sulfate, filtered and concentrated. The concentrate was flash chromatographed on silica gel with hexane/20% ethyl acetate to afford a solid which was recrystallized from acetone/hexane.

General Synthesis of 3-Aroyl-1,5-diphenylpyrazoles using Pyridinium Chlorochromate and Sonication **6** [9].

The alcohol (0.02 mole) was dissolved in methylene chloride (200 ml). Pyridinium chlorochromate (0.03 mole) was added and the resultant mixture was sonicated for 1 hour. Ether (200 ml) was added while sonicating and the mixture was sonicated for an additional 10 minutes while scraping the tarry residue with a spatula. The supernatant was filtered through a 10 centimeter column of Florisil (100-200 mesh) [10]. The tarry residue was then treated 3 times with ether (50 ml), sonicated for 10 minutes and scraped and filtered through Florisil each time. The Florisil [10] pad was rinsed with ether and the combined supernatants were concentrated to a solid residue which generally was recrystallized from an appropriate solvent.

3-(4-Chlorobenzoyl)-1-(4-methoxyphenyl)-5-(4-methylphenyl)-pyrazole **6d**.

Compound **6d** was prepared following the general synthesis of **6** shown above and afforded a white solid mp 157-159°; ms: (m/z) 445 (M + H); ir (potassium bromide): 1644, 1513 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.35 (3H, s), 3.82 (3H, s), 6.88 (2H, d, J = 9 Hz), 7.15 (1H, s), 7.15 (4H, s), 7.28 (2H, d, J = 9 Hz), 7.45 (2H, d, J = 8 Hz), 8.48 (2H, d, J = 8 Hz).

Synthesis of Ethyl 3-[(1,5-Diphenyl-3-pyrazolyl)-3-aryl-2-propenoates] **7** & **8**.

Triethylphosphonoacetate (0.04 mole) was dissolved in tetrahydrofuran (200 ml) and cooled to -78° under a nitrogen atmosphere. 1.6 Molar *n*-butyllithium (25 ml, 0.04 mole) was added to the solution by syringe. The clear solution was kept at -78° for 45 minutes. At this time the 3-aryl-1,5-diphenylpyrazole (0.01 mole) in tetrahydrofuran (100 ml) was added by syringe. The solution was allowed to warm to room temperature and then fitted with a reflux condensor and heated under reflux for 24 hours. At this time the reaction mixture was allowed to cool to room temperature. Ether (40 ml) and 5% hydrochloric acid were added consecutively. The ether layer was separated, washed once each with 100 ml portions of 5% hydrochloric acid and saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated *in vacuo* to a residue which was a mixture of *E* and *Z* isomers. The residue was flash chromatographed on silica gel using hexane/15% ethyl acetate as the mobile phase. The *Z* isomer generally elutes first and crystallizes from the mobile phase. The *E* isomer is isolated by concentration *in vacuo*.

Ethyl 3-(4-Methoxyphenyl)-3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]propenoate **7h**, *Z* Isomer.

Compound **7h** was prepared by the general synthesis of **7** as shown above and isolated as a colorless oil; ms: m/z 469 (M + H); ir (potassium bromide): 1714, 1515 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.15 (3 H, t, J = 7 Hz), 2.31 (3H, s), 3.81 (3H, s), 3.84 (3H, s), 4.07 (2H, q, J = 7 Hz), 6.23 (1H, s), 6.84 (2H, d, J = 9 Hz), 6.85 (1H, s), 6.94 (2H, d, J = 9 Hz), 7.05 (4H, s), 7.24 (2H, d, J = 9 Hz), 7.33 (2H, d, J = 9 Hz).

Ethyl 3-(4-Methoxyphenyl)-3-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]propenoate **8h**. *E* Isomer.

Compound **8h** was synthesised by the general synthesis of **8** shown above and isolated as a white solid mp 104-107°; ms: (m/z) 469 (M + H); ir (potassium bromide): 1718, 1515 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.20 (3H, t, J = 7 Hz), 2.34 (3H, s), 3.80 (3H, s), 3.82 (3H, s), 4.14 (2H, q, J = 7 Hz), 6.31 (1H, s), 6.51 (1H, s), 6.83 (2H, d, J = 9 Hz), 6.88 (2H, d, 9 Hz), 7.09 (2H, d, J = 8 Hz), 7.14 (2H, d, J = 8 Hz), 7.24 (2H, d, J = 9 Hz), 7.45 (2H, d, J = 9 Hz).

General Procedure for the Synthesis of Ethyl 3-(1,5-Diphenyl-3-pyrazolyl)-3-propanoates **9**.

The ethyl 3-(1,5-diphenyl-3-pyrazolyl)-3-arylpropenoate (0.01 mole) was dissolved in absolute ethanol (100 ml) and glacial acetic acid (10 ml). 10% Palladium on carbon (100 mg) was added and the mixture was shaken on a Parr hydrogenator at 50 pounds per square inch for 48 hours. The reaction mixture was filtered through celite and concentrated *in vacuo* to give the desired propanoate generally as an oil.

Ethyl 3-[1-(4-Methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-3-phenylpropanoate **9a**.

This compound was prepared following the above procedure and afforded **9a** as a colorless oil (96%); ms: (m/z) 441 (M + H); ir (potassium bromide): 1733, 1515, cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.14 (3H, t, J = 7 Hz), 2.31 (3H, s), 2.99 (1H, dd, J = 8 Hz, JAB = 15 Hz), 3.27 (1H, dd, J = 8 Hz, JAB = 15 Hz), 3.80 (3H, s), 4.09 (2H, q, J = 7 Hz); 4.63 (1H, dd, J = 8 Hz), 6.16 (1H, s), 6.85-7.40 (13H, m).

Ethyl 3-Fluorophenyl-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]propanoate **9b**.

This compound was prepared by the above procedure and afforded **9b** as a pale yellow oil (98%); ms (m/z) 459 (M + H); ir (potassium bromide): 1733, 1515, cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.14 (3H, t, J = 7 Hz), 2.30 (3H, s), 2.99 (1H, dd, J = 8 Hz, JAB = 15 Hz), 3.29 (1H, dd, J = 8 Hz, JAB = 15 Hz), 3.80 (3H, s), 4.08 (2H, q), 4.63 (1H, dd, J = 8 Hz), 6.16 (1H, s), 6.87-7.45 (12H, m).

Ethyl 3-Biphenylyl-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]propanoate **9c**.

This compound was prepared by the above procedure and afforded **9c** as a colorlss oil (91%); ms: (m/z) 517 (M + H); ir (potassium bromide): 1735, 1514 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.14 (3H, t, J = 7 Hz), 2.31 (3H, s), 2.99 (1H, dd, J = 8 Hz, JAB = 15 Hz), 3.36 (1H, dd, J = 8 Hz, JAB = 15 Hz), 3.80 (3H, s), 4.12 (2H, q), 4.70 (1H, dd, J = 8 Hz), 6.83-7.59 (17H, m).

Ethyl 3-[1-(4-Methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]-3-(4-methylphenyl)propanoate **9d**.

This compound was prepared by the above procedure and afforded **9d** as a colorless oil; ms: (m/z) 455 (M + H); ir (potassium

bromide): 1733, 1516 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.14 (3H, t, J = 7 Hz), 2.30 (3H, s), 2.31 (3H, s), 2.99 (1H, dd, J = 8 Hz, JAB = 15 Hz), 3.27 (1H, dd, J = 8 Hz, JAB = 15 Hz), 3.79 (3H, s), 4.08 (2H, q, J = 7 Hz), 4.62 (1H, dd, J = 8 Hz), 6.16 (1H, s), 7.11 (2H, d, J = 8 Hz), 7.18 (2H, d, J = 9 Hz), 7.27 (2H, d, J = 8 Hz).

Ethyl 3-Chlorophenyl-[1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-pyrazolyl]propanoate **9e**.

This compound was prepared by the above procedure and afforded **9e** as a colorless oil (99%); ms: (m/z) 475 (M+H); ir (potassium bromide): 1734, cm^{-1}; 1516 ^1H nmr (deuteriochloroform): δ 1.14 (3H, t, J = 7 Hz), 2.31 (3H, s), 2.99 (1H, dd, J = 8 Hz, JAB = 15 Hz), 3.30 (1H, dd, J = 8 Hz, JAB = 15 Hz), 3.80 (3H, s), 4.08 (2H, q, J = 7 Hz), 4.62 (1H, dd, J = 8 Hz), 6.15 (1H, s), 6.83-7.35 (12H, m).

General Synthesis of Ethyl 3-(1,5-diphenyl-3-pyrazolyl)-2-arylpropanoates **10**.

Sodium hydride (0.1 mole, 60% suspension in mineral oil) was suspended in anhydrous dimethylformamide (200 ml). The suspension was cooled to 0° under a nitrogen atmosphere. The ethyl arylacetate (0.1 mole) in dimethylformamide (200 ml) was added dropwise and the resulting solution was stirred for 1 hour. The 3-bromomethyl-1,5-diphenylpyrazole (0.03 mole) in dimethylformamide (200 ml) was added dropwise and the resulting solution was allowed to warm to room temperature. The solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate (250 ml). The ethyl acetate solution was washed four times with 100 ml portions of water, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using hexane/20% ethyl acetate as the mobile phase. These compound are usually isolated as oils or glasses.

Ethyl 3-[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-2-(4-chlorophenyl)propanoate **10c**.

The above procedure was followed and **10c** was isolated as a clear colorless oil (72%); ms: (m/z) 495 (M+H); IR (KBr) ir (potassium bromide): 1731, 1513 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.28 (3H, t, J = 8 Hz), 3.15 (1H, dd, J = 8 Hz), 3.15 (1H, dd, J = 8 Hz, JAB = 15 Hz), 3.30-3.62 (2H, m), 3.82 (3H, s), 4.15 (2H, q, J = 7 Hz), 6.17 (1H, s), 6.83 (2H, d, J = 8 Hz), 7.02-7.32 (10H, m).

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[9] This procedure is also used to generate the aldehydes **3**.

[10] Florosil is a registered trademark of the Floridin Company.

[11] Dedicated to Professor Francis Johnson on his sixtieth birthday.