The Preparation of *N*-Carboalkoxypyrazoles and *N*-Phenylpyrazoles from C(α)-Dianions of Carboalkoxyhydrazones and Phenylhydrazones

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The 1,4-dianions of C(α),*N*-carboalkoxyhydrazones and C(α),*N*-phenylhydrazones were prepared in an excess of lithium diisopropylamide (LDA). These dilithiated intermediates resulted from metalation of substituted hydrazones of several all-aliphatic cyclic ketones, aliphatic-aromatic cyclic ketones phenylacetaldehyde, and several substituted propiophenones or acetophenones. The esters utilized for Claisen-type condensations of these dianion intermediates included methyl salicylate, methyl *p*-hydroxybenzoate, methyl nicotinate and related materials. The condensations were followed by acid-cyclizations to give a variety of *N*-phenylpyrazoles and *N*-carboalkoxypyrazoles, most of which are new.

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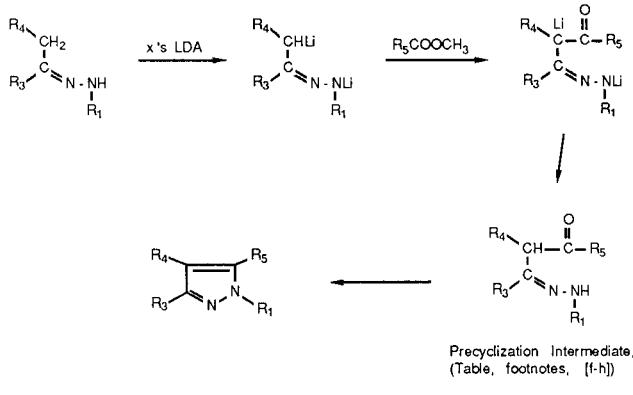
Introduction.

One of our recent major research endeavors has dealt with the preparation and reactions of polylithiated intermediates such as substituted C(α),*N*-dilithiohydrazones [1-8] (metalation - condensation - cyclization). These preliminary [1,2] and follow up investigations [3-7] have resulted in new preparations of pyrazoles utilizing *n*-butyllithium for metalation of entry compounds (*e.g.*, C(α)-phenylhydrazones) [3], the improved syntheses of these 1,4-dianions and products utilizing excess lithium diisopropylamide (LDA) for metalation instead [4], and the condensation of these reactive polylithiated intermediates with aromatic (and salicylate) esters, acid chlorides, and other electrophilic reagents [5-8]. In many instances the lithiated condensation intermediates could be neutralized and cyclodehydrated to unsymmetrical pyrazoles (usually 3,5-disubstituted) of unequivocal structure. Other well-documented preparative methods, such as the condensation of unsymmetrical ß-diketones with hydrazides, usually affords mixtures of isomers, and often requires additional separation techniques [9-12].

There is current interest in pyrazoles because of their potential for biological activity [13]. Traditional and new synthetic methods are used to prepare new materials for medicinal [14], agricultural [15], and other studies. Usually, most unsymmetrical pyrazoles that are targeted, prepared and reported by us are new [16].

This paper will deal with the following situations not previously explored by us in former strong-base investigations involving polylithiated hydrazone intermediates: (1) utilization of more all-aliphatic ketones for preparation of entry compounds, substituted hydrazones; (2) development of syntheses of *N*-carboalkoxyhydrazones beyond the preliminary report [2]; (3) more condensations of dianions with methyl lithium *p*-hydroxybenzoate; (4) the preparation and Claisen-type condensations of dilithiated phenylacetaldehyde hydrazones; and (5) reporting additional examples of the preparation of substituted pyrazoles containing another heterocyclic pendant group (*e.g.*, 3-pyridyl).



R_1 = $COOCH_3$ or $COOC_2H_5$, **1-24**; R_1 = C_6H_5, **25-40**
R_3 = H, **19-25**; R_3, other = substituted aromatic, heteroaromatic or aliphatic substituent
R_4 = H, **1-5** and **26**; R_4 = CH_3, **6-8**; R_4, other = substituted aromatic or aliphatic substituent
R_5 = substituted aromatic or heteroaromatic substituent, **1-40**

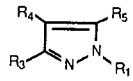
N-Carboalkoxypyrazoles (R_1 = $COOCH_3$ or $COOC_2H_5$).

N-Carboalkoxypyrazoles **1-24** (Table) were prepared in 11-85% yield from the condensation-cyclization of C(α)-dilithiocarboalkoxyhydrazones and a variety of esters. They were characterized by absorption spectra with support from combustion analyses (for C,H,N-Table). Proton magnetic resonance for pyrazoles **1-5** (R_4 = H) displayed a C_4-H absorption between δ 6.63-7.2 ppm [17], and pyrazoles **6-8** (R_4 = CH_3), which were prepared from propiophenone carboalkoxyhydrazones, displayed a C_4-CH_3 absorption between δ 2.04-2.15 ppm. Pyrazoles **9-11** (R_3 and R_4 = $(-CH_2-)_n$, n = 6 or 10) resulted from all-aliphatic ketone carboalkoxyhydrazones of cyclooctanone or cyclodo-

decanone, and pyrazoles **12-18** resulted from aliphatic-aromatic ketone carboalkoxyhydrazones - (*e.g.* from α-tetralone) (Table). Interestingly, precyclization intermediates for **14**, **16**, or **17**, α-acylcarboalkocyhydrazones (Table and Scheme - footnotes [f-h]), could be isolated. They were independently cyclodehydrated to the desired pyrazole utilizing tetrahydrofuran solvent and methanesulfonic acid catalyst (this cyclization). It was usually more desirable to avoid isolation of these intermediates, and this could be accomplished by adding additional solvent-grade tetrahydrofuran to the newly acidified (with hydrochloric acid-regular cyclization), two-phased reaction mixture. This was especially important if considerable solid material resulted upon addition of the hydrochloric acid to quench the mul-

Table

N-Carboalkoxypyrazoles and *N*-Phenylpyrazoles



Compound No.	R_1	R_3	R_4	R_5	Empirical Formula	Yield (%)	Mp (°C)	Elemental Analysis Calcd./Found C	H	N	NMR (δ ppm) (solvent)/ IR (cm^{-1}) (Nujol)
1	$COOCH_3$	4-FC_6H_4	H	4-$H_2NC_6H_4$	$C_{17}H_{14}FN_3O_2$	11 [a]	137-139	65.59 65.81	4.53 4.80	13.50 13.28	(deuteriochloroform/trifluoroacetic acid): 3.80 (s, -NH_2), 3.98 (s, -OCH_3), 6.76 (s, C_4-H), 7.45-8.18 (m, ArH) / 1740 (C=O), 3360 and 3450 (NH_2)
2	$COOCH_3$	4-ClC_6H_4	H	2-ClC_6H_4	$C_{17}H_{12}Cl_2N_3O_2$	46 [b]	150-153	58.81 58.79	3.48 3.64	8.07 7.92	(deuteriochloroform): 4.00 (s, -OCH_3), 6.63 (s, C_4-H), and 7.24-7.51 (m, ArH) / 1695 (C=O)
3	$COOCH_3$	C_6H_5	H	4-$H_2NC_6H_4$	$C_{17}H_{15}N_3O_2$	44 [c]	126-127	69.61 69.55	5.15 5.20	14.33 14.15	(deuteriochloroform/trifluoroacetic acid): 3.90-4.00 (s, $ArNH_2$), 4.00 (s, -OCH_3), 6.70 (s, C_4-H), 6.80-8.10 (m, Ar-H) / 1750 (C=O), 3360 and 3500 (NH_2)
4	$COOCH_3$	3-pyridyl	H	4-HOC_6H_4	$C_{16}H_{13}N_3O_3$	67 [c]	145 [i]	65.08 64.79	4.44 4.40	14.23 13.96	(deuteriochloroform/trifluoroacetic acid): 4.00 (s, -OCH_3), 6.85-9.50 (m, C_4-H and Ar-H) / 1750 and 1770 (C=O)
5	$COOCH_3$	3-pyridyl	H	4-ClC_6H_4	$C_{16}H_{12}ClN_3O_2$	85 [a]	151-153	61.25 61.26	3.86 3.85	13.39 13.38	(DMSO-d_6/trifluoroacetic acid): 4.00 (s, -OCH_3), 7.16-7.35 (s, C_4-H and ArH), 7.36-9.65 (m, Ar-H) / 1775 (C=O)
6	$COOCH_3$	4-BrC_6H_4	CH_3	4-$CH_3OC_6H_4$	$C_{19}H_{17}BrN_2O_3$	33 [b]	131-133	56.88 56.95	4.27 4.36	6.98 6.96	(deuteriochloroform): 2.05 (s, C_4-CH_3), 3.80-4.13 (s-broad, $ArOCH_3$ and -OCH_3), and 6.93-8.01 (m, ArH) / 1765 (C=O)
7	$COOCH_3$	4-$CH_3C_6H_4$	CH_3	4-HOC_6H_4	$C_{19}H_{18}N_2O_3$	26 [a]	206-208	70.79 70.56	5.65 5.73	8.69 8.64	(deuteriochloroform/trifluoroacetic acid): 2.15 (s, C_4-CH_3), 2.45 (s, $ArCH_3$), 4.03 (s, -OCH_3), 7.10-7.59 (m, ArH) / 1760 (C=O)
8	$COOCH_3$	4-$CH_3OC_6H_4$	CH_3	4-ClC_6H_4	$C_{19}H_{17}ClN_2O_3$	32 [a]	127-128	63.96 63.74	4.80 4.85	7.85 7.71	(deuteriochloroform): 2.04 (s, C_4-CH_3), 3.90 (s, -OCH_3), 3.99 (s, -OCH_3), 7.00-7.88 (m, ArH) / 1740 (C=O)
9	$COOCH_3$	— $(CH_2)_{10}$ —		4-HOC_6H_4	$C_{21}H_{28}N_2O_3$	31 [a]	194-197	70.76 70.74	7.92 8.16	7.85 8.15	(deuteriochloroform/trifluoroacetic acid): 1.36 (s-broad, $(CH_2)_{10}$), 3.93 (s, -OCH_3), 7.17-7.34 (m, ArH) / 1770 (C=O)
10	$COOCH_3$	— $(CH_2)_6$ —		4-ClC_6H_4	$C_{17}H_{19}ClN_2O_2$	31 [c]	122-124	64.05 63.95	6.01 6.12	8.79 8.68	(deuteriochloroform/trifluoroacetic acid): 1.54 (s-broad, $(CH_2)_6$), 3.87 (s, -OCH_3), 7.21-7.60 (m, ArH) / 1760 (C=O)
11	$COOCH_3$	— $(CH_2)_6$ —		4-HOC_6H_4	$C_{17}H_{20}N_2O_3$	44 [c]	180-183	67.98 67.90	6.71 6.98	9.33 9.24	(deuteriochloroform/trifluoroacetic acid): 1.60 (s-broad, $(-CH_2)_6$), 4.00 (s, -OCH_3), 7.00-7.48 (m, ArH) / 1745 (C=O)
12	$COOCH_3$	1,2,3,4-tetrahydro-1,2-naphthyl		4-$H_2NC_6H_4$	$C_{19}H_{17}N_3O_2$	42 [c]	195-197	71.46 71.61	5.37 5.39	13.16 13.00	(deuteriochloroform/trifluoroacetic acid): 2.70-3.30 (m, $-CH_2CH_2-$), 4.00 (-OCH_3), 7.17-8.55 (m, ArH and NH_2) / 1760 (C=O), 3390 and 3490 (NH_2) [l]
13	$COOCH_3$	1,2,3,4-tetrahydro-1,2-naphthyl		3-ClC_6H_4	$C_{19}H_{15}ClN_2O_2$	51 [c]	182-183	67.36 67.29	4.46 4.60	8.27 7.99	(deuteriochloroform): 2.40-2.70 (m, $-CH_2CH_2-$), 3.80 (s, -OCH_3), and 7.0-7.30 (m, ArH) / 1735 (C=O) [l]
14	$COOC_2H_5$	1,2,3,4-tetrahydro-1,2-naphthyl		4-ClC_6H_4	$C_{20}H_{17}ClN_2O_2$ [f]	83 [a]	173-175	68.09 68.30	4.86 5.02	7.94 7.94	(deuteriochloroform): 1.30 (t, -CH_3), 2.8 (s-broad, $-CH_2CH_2-$), 4.40 (q, -OCH_2), and 7.20-7.50 (m, ArH) / 1760 (C=O) [l]
15	$COOCH_3$	5,7-dimethyl-1,2,3,4-tetrahydro-1,2-naphthyl		4-$H_2NC_6H_4$	$C_{21}H_{21}N_3O_2$	27 [c]	215-216	72.60 72.54	6.09 6.29	12.10 11.92	(deuteriochloroform/trifluoroacetic acid): 2.30 (s, Ar-CH_3), 2.80 (s-broad, $-CH_2CH_2-$), 4.00 (s, -OCH_3), 7.30-7.85 (m, ArH) / 1760 (C=O), 3390 and 3475 (NH_2) [m]
16	$COOC_2H_5$	1,2,3,4-tetrahydro-1,2-naphthyl		3-ClC_6H_4	$C_{20}H_{17}ClN_2O_2$ [g]	42 [a]	132-134	68.09 68.20	4.86 5.03	7.94 8.09	(deuteriochloroform): 1.30 (t, -CH_3), 2.58-3.28 (m, $-CH_2CH_2-$), 4.42 (q, OCH_2), and 7.30-7.72 (m, ArH) / 1755 (C=O) [l]
17	$COOCH_3$	1,2,3,4-tetrahydro-1,2-naphthyl		4-ClC_6H_4	$C_{19}H_{15}ClN_2O_2$ [h]	54 [d]	189-190	67.36 67.40	4.46 4.54	8.27 8.10	(deuteriochloroform/trifluoroacetic acid): 1.98-3.01 (m, $-CH_2CH_2-$), 3.95 (s, -OCH_3), and 7.07-7.43 (1, Ar-H) / 1750 (C=O) [l]
18	$COOCH_3$	6,7,8,9-tetrahydro-5,6-5*H*-benzocycloheptenyl		3,4,5-trimethoxyphenyl	$C_{23}H_{24}N_2O_5$	65 [a]	159-161	67.63 67.50	5.92 6.00	6.86 6.74	(deuteriochloroform): 2.10-3.00 (m, $(-CH_2-)_3$), 3.90 (s, OCH_3), 4.0 (s, -OCH_3), 6.75 (s, ArH), 7.29-7.77 (m, ArH) / 1760 (C=O) [n]
19	$COOC_2H_5$	H	C_6H_5	3,4,5-trimethoxyphenyl	$C_{21}H_{22}N_2O_5$	57 [a]	183	65.96 65.97	5.80 5.64	7.32 7.14	(deuteriochloroform/trifluoroacetic acid): 1.30 (t, -CH_3), 3.70-4.00 (m, OCH_3), 4.25 (q, -OCH_2-), 6.60-7.50 (m, Ar H) and 8.35 (s, C_3-H) / 1760 (C=O)
20	$COOC_2H_5$	H	C_6H_5	4-ClC_6H_4	$C_{18}H_{15}ClN_2O_2$	41 [a]	150-152	66.16 66.22	4.63 4.78	8.57 8.30	(deuteriochloroform): 1.29 (t, -CH_3), 4.40 (q, -OCH_2-), 7.27-7.51 (m, ArH), and 8.01 (s, C_3-H) / 1780 (C=O)

Table (continued)

Compound No.	R_1	R_3	R_4	R_5	Empirical Formula	Yield (%)	Mp (°C)	Elemental Analysis Calcd./Found C	H	N	NMR (δ ppm) (solvent)/ IR (cm^{-1}) (Nujol)
21	$COOC_2H_5$	H	C_6H_5	4-$CH_3OC_6H_4$	$C_{19}H_{18}N_2O_3$	62 [a]	164-166	70.79 70.98	5.63 5.90	8.69 8.44	(deuteriochloroform): 1.30 (t, $-CH_3$), 3.87 (s, $ArOCH_3$), 4.38 (q, $-OCH_2-$), 6.90-7.37 (m, ArH), and 8.03 (s, C_3-H) / 1750 (C=O)
22	$COOCH_3$	H	C_6H_5	4-ClC_6H_4	$C_{17}H_{13}ClN_2O_2$	33 [c]	153-154	65.28 65.38	4.19 4.50	8.96 8.71	(deuteriochloroform/trifluoroacetic acid): 4.00 (s, $-OCH_3$) and 7.20-7.60 (m, Ar-H), and 8.30 (s, C_3-H), / 1760 (C=O)
23	$COOCH_3$	H	C_6H_5	3-ClC_6H_4	$C_{17}H_{13}ClN_2O_2$	48 [a]	125-127	65.29 65.45	4.19 4.44	8.96 8.78	(deuteriochloroform/trifluoroacetic acid): 3.90 (s, $-OCH_3$), 7.24-7.45 (m, ArH), 8.03 (s, C_3-H) / 1760 (C=O)
24	$COOCH_3$	H	C_6H_5	4-HOC_6H_4	$C_{17}H_{14}N_2O_3$ $\cdot CH_3OH$	45 [c]	248-250	66.24 65.99	5.55 5.79	8.58 8.25	(deuteriochloroform/trifluoroacetic acid): 3.87 (s, $-OCH_3$), 6.72-6.90 (m, ArH), 8.33 (s, C_3-H) / 1780 (C=O)
25	C_6H_5	H	C_6H_5	4-ClC_6H_4	$C_{21}H_{15}ClN_2$	72 [d]	194-197 [j]			8.47 8.17	(deuteriochloroform): 6.90-7.20 (m, ArH) and 8.00 (s, C_3-H)
26	C_6H_5	4-BrC_6H_4	H	4-HOC_6H_4	$C_{21}H_{15}BrN_2O$	35 [a]	246-249	64.47 64.32	3.86 4.09	7.16 7.07	(deuteriochloroform/trifluoroacetic acid): 6.95-7.85 (m, ArH and C_4-H)
27	C_6H_5	$-(CH_2)_{10}-$		2-HOC_6H_4	$C_{25}H_{30}N_2O$	27 [a]	180-182	80.17 79.87	8.07 7.93	7.48 7.44	(deuteriochloroform/trifluoroacetic acid): 1.43 (s-broad, $(CH_2)_{10}$), and 6.87-7.44 (m, ArH) [n]
28	C_6H_5	$-(CH_2)_{10}-$		4-HOC_6H_4	$C_{25}H_{30}N_2O$	67 [a]	210-212	80.17 80.08	8.07 8.18	7.48 7.33	(deuteriochloroform/trifluoroacetic acid): 1.44 (s-broad, $(CH_2)_{10}$), and 6.78-7.84 (m, ArH)
29	C_6H_5	$-(CH_2)_{10}-$		3,4,5-trimethoxyphenyl	$C_{28}H_{36}N_2O_3$	33 [a]	105-107	74.97 74.96	8.09 8.34	6.24 6.02	(deuteriochloroform): 1.27 (s, $(CH_2)_{10}$), 3.93 (s, $ArOCH_3$), and 6.85-7.45 (m, ArH)
30	C_6H_5	$-(CH_2)_5-$		4-HOC_6H_4	$C_{18}H_{16}N_2O$	85 [d]	250-252	78.24 78.35	5.84 5.95	10.14 9.98	(deuteriochloroform/trifluoroacetic acid): 2.90 (s-broad, $(CH_2)_5$), and 6.80-7.80 (m, Ar-H)
31	C_6H_5	$-(CH_2)_4-$		4-HOC_6H_4	$C_{19}H_{18}N_2O$	77 [d]	257-258	78.59 78.74	6.25 6.18	9.65 9.52	(deuteriochloroform/trifluoroacetic acid): 2.20-3.00 (m, $(-CH_2-)_4$) and 6.70-7.80 (m, Ar-H)
32	C_6H_5	$-(CH_2)_4-$		2-HOC_6H_4	$C_{19}H_{18}N_2O$	74 [d]	221-222	78.59 78.33	6.25 6.37	9.65 9.51	(deuteriochloroform/trifluoroacetic acid): 1.90 (s-broad, $-(CH_2-)_4$) and 6.80-7.60 (m, Ar-H)
33	C_6H_5	C_6H_5	C_6H_5	4-HOC_6H_4	$C_{27}H_{20}N_2O$	65 [d]	262-263	83.48 83.28	5.19 5.29	7.21 7.26	(deuteriochloroform/trifluoroacetic acid): 7.20-7.77 (m, ArH)
34	C_6H_5	$C_6H_5CH_2$	C_6H_5	2-HOC_6H_4	$C_{28}H_{22}N_2O$	32 [c]	166-168	83.56 83.34	5.51 5.80	6.96 6.67	(deuteriochloroform/trifluoroacetic acid): 4.30 (s, $-CH_2-$) and 6.70-7.45 (m, Ar-H)
35	C_6H_5	$C_6H_5CH_2$	C_6H_5	4-HOC_6H_4	$C_{28}H_{22}N_2O$ $\cdot C_2H_5OH$	64 [a]	237-239	80.33 80.38	6.29 6.14	6.25 6.23	(deuteriochloroform/trifluoroacetic acid: 1.22 (t, CH_3), 3.72 (q, $-CH_2O-$), 4.25 (s, $-CH_2-$) and 6.70-7.60 (m, ArH)
36	C_6H_5	4-BrC_6H_4	H	2-HOC_6H_4	$C_{21}H_{15}BrN_2O$	27 [a]	191-193	64.46 64.53	3.86 4.03	7.16 7.29	(deuteriochloroform/trifluoroacetic acid): 6.78-7.69 (m, C_4-H and ArH)
37	C_6H_5	2,3-dihydro-1,2-1*H*-indenyl		4-HOC_6H_4	$C_{22}H_{16}N_2O$	53 [e]	287-288	81.46 81.63	4.97 5.11	8.65 8.45	(deuteriochloroform/trifluoroacetic acid): 3.98 (s, $-CH_2-$) and 6.70-8.03 (m, ArH) [o]
38	C_6H_5	1,2,3,4-tetrahydro-1,2-naphthyl		4-HOC_6H_4	$C_{23}H_{18}N_2O$	62 [d]	215-219	81.63 81.70	5.36 5.56	8.28 8.24	(deuteriochloroform/trifluoroacetic acid): 2.87-3.33 (m, $-CH_2CH_2-$), and 6.87-7.90 (m, ArH) [l]
39	C_6H_5	1,2,3,4-tetrahydro-1,2-naphthyl		3-pyridyl	$C_{22}H_{17}N_3$	10 [d]	158-161	72.60 72.54	6.09 6.29	12.10 11.92	(deuteriochloroform): 2.63-3.00 (m, $-CH_2CH_2-$) and 7.10-9.00 (m, ArH) [l]
40	C_6H_5	C_6H_5	C_6H_5	3-pyridyl	$C_{26}H_{19}N_3$	54 [d]	232-234	83.62 83.67	5.13 5.18	11.25 11.02	(deuteriochloroform/trifluoroacetic acid): 7.10-9.20 (m, ArH)

[a] Recrystallized from ethanol. [b] Recrystallized from methanol/water. [c] Recrystallized from methanol. [d] Recrystallized from ethanol/benzene. [e] Recrystallized from xylene/dimethylformamide. [f] Precyclization intermediate, acylcarboethoxyhydrazone for **14**, (58%) mp 203-205° (ethanol/benzene). *Anal.* Calcd. for $C_{20}H_{19}ClN_2O_3$: C, 64.78; H, 5.16; N, 7.55. Found: C, 64.90; H, 5.42; N, 7.40. [g] Precyclization intermediate, acylcarboethoxyhydrazone, for **16** (39%), mp 174-176° (ethanol). *Anal.* Calcd. for $C_{20}H_{19}ClN_2O_3$: C, 64.78; H, 5.16; N, 7.55. Found: C, 65.09; H, 5.23; N, 7.52. [h] Precyclization intermediate, acylcarbomethoxyhydrazone, for **17** (49%), mp 193-195° (ethanol). *Anal.* Calcd. for $C_{20}H_{17}ClN_2O_3$: C, 63.96; H, 4.81; N, 7.85. Found: C, 63.61; H, 5.02; N, 7.79. [i] Sublimes at this temperature. [j] Lit. mp 194.9-195.3°, see reference [19c]. [k] Infrared spectra for compounds **25-40** mainly distinguished products from phenylhydrazones. 2-Hydroxyphenyl and 4-hydroxyphenyl absorptions for other pyrazoles (where applicable) were sometimes ambiguous, but were usually displayed *ca.* 3100-3400 cm^{-1}. Hydroxyphenyl and other absorptions were displayed *ca.* 1410-1260 cm^{-1}. [l] 1-Tetralone was used to make the entry hydrazone for this product. [m] 5,7-Dimethyl-1-tetralone was used to make the entry hydrazone for this product. [n] Benzo-1-suberone was used to make the entry hydrazone for this product. [o] 1-Indanone was used to make the entry hydrazone for this product.

tiple anion condensation intermediates (see experimental). Pyrazoles **19-24** (R_3 = H and R_4 = C_6H_5) resulted from dilithiated carboalkoxyhydrazone derivatives of phenylacetaldehyde, and their proton nmr spectra displayed a C_3-H absorption from δ 8.00 -8.35 ppm [18].

N-Phenylpyrazoles (R_1 = C_6H_5).

N-Phenylpyrazoles **25-40** were prepared in 10-85% yield from the condensations of C(α)-dilithiophenylhydrazones with a variety of aromatic or heteroaromatic esters. A noteworthy feature of these pyrazole preparations involved utilizing phenylhydrazone entry compounds prepared from a variety of starting materials such as phenylacetaldehyde (for pyrazole **25**), all-aliphatic cyclic ketones (for pyrazoles **27-32**), α-indanone (for fused-ring pyrazole **37**), and α-tetralone (for fused-ring pyrazoles **38** and **39**). These C(α)-dianions were condensed with methyl 4-aminobenzoate, methyl 4-hydroxybenzoate (probably as a

lithiated phenoxide), methyl nicotinate, or other esters, to give intermediates that were also acid-cyclized to pyrazoles (see Table). The characterization of these new materials utilized absorption spectra, with support from combustion analyses (see Table).

Discussion.

N-Carboalkoxypyrazoles **1-24** resulted from cyclodehydration of acyl-carboalkoxyhydrazone precyclization intermediates without detectable and/or extensive hydrolysis of the carboalkoxyhydrazones (to give a ß-diketone) or *N*-Carboalkoxypyrazoles (to give the N-H pyrazole after decarboxylation of the N-COOH pendant group). Condensation-cyclization of 1,4-dianions with lithiated salicylates or *p*-hydroxybenzoates and *p*-aminobenzoates (electrophilic-nucleophilic reagents) proceeded reasonably well. Condensation-cyclization of the hydrazone 1,4-dianions gave products that would be more difficult to prepare by other methods [19].

The strong features of these syntheses are as follows: the starting materials can be readily prepared by an easy, one-step procedure utilizing a variety of available C(α)-aldehydes and C(α)-ketones; the heterocyclic products are of unequivocal structure since all of the atoms making up the five-membered ring are in place prior to the cyclization step; purification of products usually involves straight-forward recrystallization from routine solvents (chromatographic separations not needed); and someone not very familiar with strong-base synthesis procedures can be successful with the overall preparations.

EXPERIMENTAL

Tetrahydrofuran (THF) was distilled from sodium (benzophenone) immediately before use. Phenylhydrazones [20] and carboalkoxyhydrazones [21] were prepared by the condensation of equimolar amounts of aldehyde or ketone and substituted hydrazine (phenyl- or carboalkoxy-), and they were dried in a vaccum desiccator immediately before use [22]. Nuclear magnetic resonance spectra were obtained with a Varian Associates EM 360L NMR Spectrometer, and absorptions are reported in δ ppm downfield from an internal tetramethylsilane (TMS) standard. Infrared spectra were obtained with a Perkin-Elmer 710 B Spectrometer. Melting points were obtained in a Mel-Temp melting point apparatus in open capillary tubes and are uncorrected. Combustion analyses (C, H, N) were performed by Robertson's Microanalytical Laboratory, 73 West End Avenue, Florham Park, NJ 07932. *n*-Butyllithium (1.6 M/hexane) was purchased from the Lithium Corporation of America, Bessemer City, NC 28016.

1-Phenylpyrazoles or 1-Carboalkoxypyrazoles.

A 0.033-mole sample (0.044-mole sample for **4**, **7**, **9**, **11**, **24**, **26-28**, **30-38**) of *n*-butyllithium was added to a round-bottomed flask with a syringe (dry nitrogen atmosphere). After cooling the flask in an ice-bath, a 0.033-mole sample (0.044 mole sample for **4**, **7**, **9**, **11**, **24**, **26-28**, **30-38**) of diisopropylamine dissolved in 30 ml of dry tetrahydrofuran (THF) was added at a fast dropwise rate to the stirred *n*-butyllithium. The resulting lithium diisopropylamide (LDA) was stirred at 0° for an additional 20-30 minutes before adding a 0.010-mole sample of hydrazone dissolved in 40-50 ml of dry THF [23] during 5 minutes. The metalation time at 0° was 60 minutes. A 0.011-mole sample of ester dissolved in 100 ml [24] of dry THF was added during 5 minutes, and the condensation was allowed to proceed with stirring at 0° for an additional 1.5-2 hours. This was followed by the rapid addition of 100 ml of 3*N* hydrochloric acid, heating the well-stirred, two-phase mixture under reflux for 60 minutes, and cooling the mixture by pouring it into a large flask (1 or 2 liter) containing ice. The mixture was neutralized with excess solid sodium bicarbonate. At this point, it was usually advantageous to add solvent-grade ether or THF (*ca.* 100 ml). The aqueous and organic layers were separated, and the aqueous layer was extracted with three, 75-ml portions of ethyl ether [25]. The ether extracts and organic phase were combined, dried (magnesium sulfate), filtered, and concentrated (roto-evaporator). The oil or solid that resulted was crystallized and recrystallized from solvent or solvents indicated in the footnote of the Table.

1-Carboalkoxypyrazoles from Acyl-Carboalkoxyhydrazones.

A 1.0 g-sample of acyl-carboalkoxyhydrazone (see footnotes [f, g, and h] Table) was dissolved in 60 ml of solvent grade THF and added to 10 ml of 3*N* methanesulfonic acid. The mixture was stirred and heated under reflux for 1 hour. After cooling, the mixture was extracted with ether, and organic extracts were combined, dried (magnesium sulfate), and concentrated (roto-evaporator). The oil or solid material that resulted was taken up in ethanol (*ca.* 10 ml) (footnote f and g - Table) or methanol (*ca.* 10 ml) (footnote h Table) and crystallization occurred upon cooling. The yields of 1-carboalkoxypyrazoles **14**, **16** and **17** were 60-83%.

Isolation of these noncyclized intermediates could be avoided by addition of excess solvent grade THF (*ca.* 100 ml) to those reactions, which after addition of the 3*N* hydrochloric acid (quenching of condensation intermediates), contained solid residue. Good stirring of the heated two-phase mixture was necessary to complete cyclization.

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[22] Dry carboalkoxypyrazoles are stable materials; however, phenylhydrazones are usually unstable, and they were used immediately. They could be stored, if desired, in refrigerated and evacuated (vacuum) serum vials.

[23] If the substituted hydrazone was insoluble in THF, it was added as a slurry.

[24] Esters were generally more soluble in THF, and we did not hesitate to add additional THF, as necessary, to ensure complete solution.

[25] Solvent grade THF was substituted for those residues less soluble in ethyl ether.