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$C(\alpha)$,*O*-Dilithiooximes, $C(\alpha)$,*N*-dilithiophenylhydrazones, or $C(\alpha)$,*N*-dilithioacylhydrazones were prepared in an excess of lithium diisopropylamide (LDA) and condensed with a variety of esters followed by acid-cyclization to give substituted isoxazoles and pyrazoles.

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Introduction.

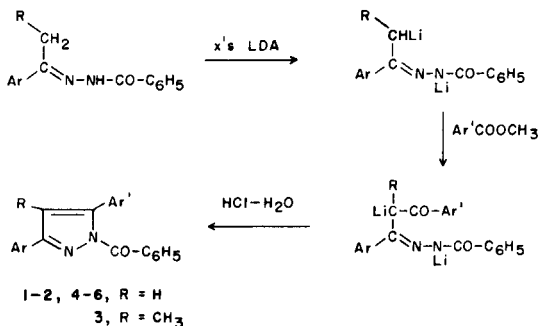
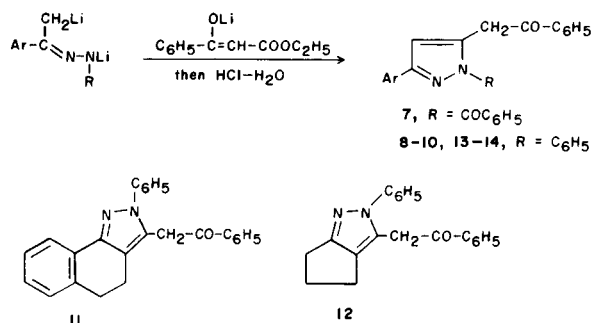
Recently we reported an improved synthesis of 3,5-disubstituted pyrazoles and isoxazoles from the 1,4-dianions of $C(\alpha)$ -phenylhydrazones and $C(\alpha)$ -oximes using excess lithium diisopropylamide (LDA) for metalation of entry compounds, $C(\alpha)$ -oximes and $C(\alpha)$ -phenylhydrazones [2]. A preliminary report from us [3] also dealt with the preparation of $C(\alpha)$,*N*-dilithioacylhydrazones, and the treatment of these lithiated intermediates with several electrophilic reagents such as ketones. Other preliminary and follow-up reports dealt with the condensation of $C(\alpha)$ -dianions with electrophilic-nucleophilic reagents, such as lithiated ethyl benzoylacetate [4-6].

N-Acylpyrazoles.

The initial efforts to metalate $C(\alpha)$,*N*-acylhydrazones with *n*-butyllithium in tetrahydrofuran (THF)/hexane followed by condensation with methyl benzoates and acid cyclization to *N*-acylpyrazoles were unsuccessful. Only hydrolysis products were isolated and identified [7]. During the current investigation, these acylhydrazones were metalated with lithium diisopropylamide (LDA) instead, condensed with methyl or ethyl benzoates (including methyl *p*-hydroxybenzoate and methyl salicylate), and resulting lithiated intermediates were acid-cyclized to *N*-acylpyrazoles **1-7** (Table).

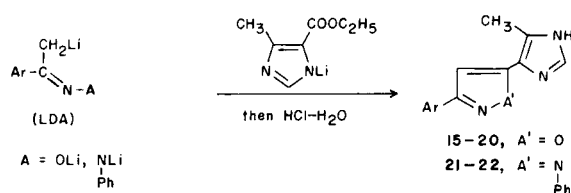
5-Phenacylpyrazoles.

Our initial attempts to prepare 5-phenacylisoxazoles were successful, and this new synthon resulted from the condensation of $C(\alpha)$ -dilithiooximes, prepared in an excess of LDA, with ethyl benzoylacetate followed by acid cyclization [6]. We are now able to prepare 5-phenacylpyrazoles **8-14** by the condensation of dilithioacylhydrazones or dilithiophenylhydrazones, prepared in an excess of LDA, with ethyl benzoylacetate. The main difference between the isoxazole and pyrazole studies is the condensation time (1 hour with oxime dianions; 2 hours with phenylhydrazine or acylhydrazone dianions) of the dianion with the presumably lithiated ethyl benzoylacetate to give other lithiated precyclization intermediates, which were acid-cyclized to the desired heterocyclic products **8-14** (See Table and Experimental).



Imidazolylisoxazoles and Imidazolypyrazoles.

The reaction of certain of the $C(\alpha)$ -dianions with electrophilic-nucleophilic reagents has been extended to the condensation of $C(\alpha)$ -dianions of oximes and phenylhydrazones (in excess LDA) with ethyl 4-methyl-5-imidazolecarboxylate to give new lithiated intermediates which were acid cyclized to imidazolylisoxazoles **15-20** and imidazolypyrazoles **21** and **22**.



Discussion.

All of the heterocyclic materials reported in this study appear to be new. Their structures were readily established by absorption spectra and supported by combustion analysis (Table). Proton magnetic resonance was utilized primarily to confirm the structure. Those substituted isoxazoles and pyrazoles possessing a C_4 -hydrogen atom usually displayed an easily identifiable singlet absorption from δ 6.7-7.2 ppm [8-9]. The nmr spectra of phenacylpyrazoles displayed methylene absorptions ($-\text{CH}_2\text{CO}-$) between δ 4 and 5 ppm, and the pmr spectra of imidazolypyrazoles and imidazolylisoxazoles displayed C_4 - CH_3 absorption of the imidazole moiety from δ 1.85-3.00 ppm. (See Table for absorptions of other materials from products.) The carbonyl absorption of phenacylpyrazoles was noted from 1680-1700 cm^{-1} , and the carbonyl of *N*-acylpyrazoles was noted from 1700-1735 cm^{-1} . Mass spectra of **2**, **3**, and **11**, readily displayed major fragmentations at m/e , 105 corresponding to $[\text{C}_6\text{H}_5\text{CO}]^+$, which was anticipated for *N*-benzoyl-**2** and phenacylpyrazoles **11** and **13**. Only **13** readily displayed a molecular ion M^+ (416/418 - 1/1 -bromine doublet).

The yields of the materials reported in the Table vary from 16 to 88%. In our experience, most of our strong-base procedures give products that fall into one of the three categories: low (I-*ca.* 20%), fair (II-*ca.* 50%) and

good (III-*ca.* 80%). If a particular compound is needed in a better yield than those of categories I or II, the parameters of condensation time and temperature can be adjusted, and this may result in improved yields. Although we have tried other cyclization procedures, we have not been able to improve upon simply quenching the strong-base condensation mixture with 100 ml of 3*N* hydrochloric acid, and heating the resulting two-phase mixture under reflux [10].

Other factors which may effect the yield of products may be a more difficult cyclization of keto-acylpyrazole intermediates to give *N*-acylpyrazoles or the somewhat sluggish condensation of $C(\alpha)$ -anions with electrophilic-nucleophilic reagents to give phenacylpyrazoles, imidazolylisoxazoles, or imidazolypyrazoles.

The obvious strong features of these syntheses are that the starting materials (oximes, phenylhydrazones, and acylhydrazones) are one easy synthetic step away from readily available and usually inexpensive $C(\alpha)$ -ketones, the synthetic procedures are readily reproducible by someone not necessarily familiar with strong-base synthesis techniques, and the heterocyclic materials are of unequivocal structure [11]. The products are easily purified by recrystallization from routine solvents, hence other purification procedures (*e.g.* chromatographic) are not necessary.

EXPERIMENTAL

Tetrahydrofuran (THF) was distilled from sodium (benzophenone) immediately before use. Oximes, phenylhydrazones and acylhydrazones were prepared by standard procedures [12-13], and they were dried in a vacuum desiccator or by refluxing in hexane and collecting water in a water trap [14]. Nuclear magnetic resonance spectra were obtained with a Varian Associates EM 360L NMR Spectrometer and absorptions are re-

Table
Pyrazoles and Isoxazoles

Compound No.	Name	Empirical Formula	Yield (%)	Mp (°C)	Elemental Analysis			NMR (δ ppm) [i]
					Calcd.	Found	Solvent	
1	1-benzoyl-3-phenyl-5-(4-tolyl)pyrazole	$\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}$	25	136-137 [b]	81.63	5.36	8.28	(deuteriochloroform): 2.42 (s, ArCH_3), 6.80 (s, C_4 -H) and 7.00-8.33 (m, ArH)
					81.36	5.47	8.01	
2	1-benzoyl-5-phenyl-3-(4-tolyl)pyrazole	$\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}$	46	156-158 [c]	81.63	5.36	8.28	(deuteriochloroform): 2.05 (s, ArCH_3), 6.78 (s, C_4 -H) and 7.08-8.22 (m, ArH)
					81.40	5.48	8.27	
3	1-benzoyl-4-methyl-5-phenyl-3-(4-tolyl)pyrazole	$\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}$	16	132-134 [c]	81.79	5.72	7.95	(deuteriochloroform): 2.18 (s, ArCH_3), 2.42 (s, C_4 - CH_3) and 7.21-8.30 (m, ArH)
					81.64	5.86	7.93	
4	1-benzoyl-5-(4-hydroxyphenyl)-3-phenylpyrazole	$\text{C}_{22}\text{H}_{16}\text{N}_2\text{O}_2$	16	159-160 [h]	77.63	4.74	8.23	(deuteriochloroform): 6.82 (s, C_4 -H), 7.30-8.30 (m, ArH) and 9.6 (s, ArOH)
					77.64	4.99	7.93	
5	1-benzoyl-5-(2-hydroxyphenyl)-3-(4-methoxyphenyl)pyrazole	$\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}_3$	30	169-171 [b]	74.58	4.90	7.56	(DMSO- d_6): 3.80 (s, ArOCH_3), 6.76 (s, C_4 -H) and 6.93-8.37 (m, ArH)
					74.29	4.94	7.60	

Table, continued

Compound No.	Name	Empirical Formula	Yield (%)	Mp (°C)	Elemental Analysis			NMR (δ ppm) [i] Solvent
					Calcd./Found	C	H	
6	1-benzoyl-5-(4-hydroxyphenyl)-3-(4-methoxyphenyl)pyrazole	C ₂₃ H ₁₈ N ₂ O ₃	31	168-169 [e]	74.58 74.31	4.90 5.18	7.56 7.35	(DMSO-d ₆): 3.83 (s, ArOCH ₃), 6.85-8.20 (m, ArH and C ₄ -H) and 9.90 (s, ArOH)
7	1-benzoyl-3-(4-methoxyphenyl)-5-phenacylpyrazole	C ₂₅ H ₂₀ N ₂ O ₃	18	156 [c]	75.74 75.51	5.08 5.35	7.07 7.01	(deuteriochloroform): 3.88 (s, ArOCH ₃), 4.92 (s, -CH ₂ CO-) and 6.80-8.28 (m, ArH and C ₄ -H)
8	1,3-diphenyl-5-phenacylpyrazole	C ₂₃ H ₁₈ N ₂ O	60	137-138 [d]	81.63 81.43	5.36 5.43	8.27 8.41	(deuteriochloroform): 4.36 (s, -CH ₂ CO-), 6.67 (s, C ₄ -H) and 6.93-8.03 (m, ArH)
9	5-phenacyl-1-phenyl-3-(4-tolyl)pyrazole	C ₂₄ H ₂₀ N ₂ O	64	148-149 [d]	81.79 81.58	5.72 5.81	7.95 8.01	(deuteriochloroform): 2.37 (s, ArCH ₃), 4.37 (s, -CH ₂ CO-), 6.63 (s, C ₄ -H) and 7.17-8.03 (m, ArH)
10	3-(4-methoxyphenyl)-5-phenyl-1-phenylpyrazole	C ₂₄ H ₂₀ N ₂ O ₂	14	117-119 [d]	78.24 78.01	5.47 5.53	7.60 7.63	(deuteriochloroform): 3.87 (s, ArOCH ₃), 4.40 (s, -CH ₂ CO-), 6.67 (s, C ₄ -H) and 6.93-8.10 (m, ArH)
11	4,5-dihydronaphtho[1,2-c]-3-phenacyl-4-phenylpyrazole	C ₂₅ H ₂₀ N ₂ O	88	128-130 [d]	82.39 82.47	5.53 5.70	7.63 7.83	(deuteriochloroform): 2.66-3.08 (m, -CH ₂ CH ₂ -), 4.37 (-CH ₂ CO-) and 7.23-8.30 (ArH)
12	4,5,6,7-tetrahydro-3-phenacyl-2-phenyl-2H-indazole [a]	C ₂₁ H ₂₀ N ₂ O	67	128-132 [h]	79.72 79.49	6.37 6.29	8.85 8.87	(deuteriochloroform): 1.63-2.91 (m, -CH ₂ CH ₂ CH ₂ -), 4.28 (s, -CH ₂ CO-) and 7.23-8.07 (m, ArH)
13	3-(4-bromophenyl)-5-phenacyl-1-phenylpyrazole	C ₂₃ H ₁₇ BrN ₂ O	34	123-125 [g]	66.20 66.14	4.11 4.31	6.71 7.00	(deuteriochloroform): 4.37 (s, -CH ₂ CO-), 6.68 (s, C ₄ -H) and 6.83-8.20 (m, ArH)
14	3-benzyl-5-phenacyl-1,4-diphenylpyrazole	C ₃₀ H ₂₄ N ₂ O	26	164-166 [g]	84.08 83.92	5.64 5.92	6.54 6.42	(deuteriochloroform): 3.98 (s, -CH ₂ -), 4.15 (s, CH ₂ CO-) and 7.23-7.90 (m, ArH)
15	5-(4-methylimidazolyl)-3-(4-tolyl)isoxazole [j]	C ₁₄ H ₁₃ N ₃ O	28	223-224 [b]	70.28 70.23	5.48 5.64	17.56 17.32	(deuteriochloroform/trifluoroacetic acid): 2.46 (ArCH ₃), 2.73 (ArCH ₃), 7.17 (C ₄ -H), 7.33-7.83 (m, ArH) and 8.83 (s, NH)
16	5-(4-methylimidazolyl)-3-(3,4-dimethoxyphenyl)isoxazole	C ₁₈ H ₁₄ N ₃ O ₃	16	269-271 [g]	63.37 63.21	4.96 5.23	14.78 14.67	(deuteriochloroform/trifluoroacetic acid): 2.63 (s, ArCH ₃), 3.87 (s, ArOCH ₃), 6.80-7.47 (m, C ₄ -H and ArH) and 8.70 (s, NH)
17	5-(4-methylimidazolyl)-3-(4-methoxyphenyl)isoxazole	C ₁₄ H ₁₃ N ₃ O ₂	31	212-213 [g]	65.87 66.15	5.13 5.28	16.46 16.21	(DMSO-d ₆ /trifluoroacetic acid): 2.57 (s, ArCH ₃), 3.85 (s, ArOCH ₃) and 7.06-8.10 (m, C ₄ -H, ArH and NH)
18	3-benzyl-5-(4-methylimidazolyl)-4-phenylisoxazole	C ₂₀ H ₁₇ N ₃ O	17	176-180 [b]	76.17 75.92	5.43 5.72	13.32 13.12	(DMSO-d ₆): 2.08 (s, ArCH ₃), 4.05 (s, -CH ₂ -) and 7.00-7.68 (m, ArH)
19	5-(4-methylimidazolyl)-3-(2-naphthyl)isoxazole	C ₁₇ H ₁₃ N ₃ O	50	235-237 [f]	74.17 73.96	4.76 4.89	15.26 15.01	(DMSO-d ₆ /trifluoroacetic acid): 2.73 (s, ArCH ₃), 7.27 (s, C ₄ -H) and 7.57-8.83 (m, ArH)
20	5-(4-methylimidazolyl)-3,4-diphenylisoxazole	C ₁₉ H ₁₅ N ₃ O	26	250-252 [b]	75.73 75.60	5.02 5.07	13.94 13.93	(DMSO-d ₆ /trifluoroacetic acid): 1.85 (s, ArCH ₃), 7.30-7.55 (m, ArH) and 9.27 (s, NH)
21	5-(4-methylimidazolyl)-1-phenyl-3-(<i>p</i> -tolyl)pyrazole	C ₂₀ H ₁₈ N ₄	20	216-218 [d]	76.41 76.12	5.77 6.08	17.82 17.57	(DMSO-d ₆): 2.03 (ArCH ₃), 2.37 (ArCH ₃), 7.00 (C ₄ -H) and 7.17-8.0 (ArH)
22	5-(4-methylimidazolyl)-1,3-diphenylpyrazole	C ₁₉ H ₁₅ N ₄	53	251-253 [g]	75.97 75.90	5.37 5.42	18.65 18.54	(deuteriochloroform/trifluoroacetic acid): 2.00 (ArCH ₃), 7.40-8.03 (C ₄ -H and ArH) and 8.73 (s, NH)

[a] Or 3,4-tetramethylene-5-phenacyl-1-phenylpyrazole. [b] Recrystallized from ethanol. [c] Recrystallized from ethanol/benzene. [d] Recrystallized from methanol. [e] Recrystallized from methanol/water. [f] Recrystallized from ethanol/water. [g] Recrystallized from methanol/ethanol. [h] Recrystallized from 1-propanol. [i] Infrared spectra were primarily utilized to differentiate starting materials from products: phenacyl functional groups (-CH₂CO₂H₂) were displayed at 1680-1700 cm⁻¹ and *N*-benzoyl functional groups were displayed at 1700-1735 cm⁻¹. [j] 4-Methylimidazolyl nomenclature utilized since condensation reagent is ethyl 4-methyl-5-imidazolecarboxylate. The methyl group could have alternatively been designated for the 5-position.

ported in δ ppm downfield from an internal tetramethylsilane (TMS) standard. Infrared spectra were obtained with a Perkin-Elmer 710B or 267 spectrometer. Melting points were obtained in a Mel-Temp melting point apparatus in open capillary tubes and are uncorrected. Combustion analysis were performed by Robertsons's Microanalytical Laboratory, 73 West End Avenue, Florham Park, NJ 07932. *n*-Butyllithium was purchased from the Lithium Corporation of America, Bessemer City, NC 28016.

Mass spectra were obtained in the Mass Spectral Laboratory, Department of Pharmacology, at the Medical University of South Carolina, Charleston, SC 29424 on Finnigan 3200 Mass Spectrometer, electron impact mode at 70 eV.

1-Benzoylpyrazoles.

A 0.033 mole sample (0.044 mole sample for **4**, **5**, and **6**) 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**, **5**, and **6**) 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 dried 0.010 mole sample of benzoylhydrazone dissolved in 40-50 ml of THF [15] during 5 minutes. The metalation time was 45-60 minutes. A 0.011 mole sample of ester dissolved in 30 ml of THF was then added during 5 minutes and the condensation was allowed to proceed with stirring at 0° for an additional 45-60 minutes. This was followed by the rapid addition of 100 ml of 3*N* hydrochloric acid, heating the stirred two-phase mixture under reflux for 60 minutes and cooling the mixture by letting it stand or pouring into a large flask (1 or 2 liter) containing ice. The mixture was neutralized with excess solid sodium bicarbonate [16]. The aqueous and organic layers were separated, and the aqueous layer was extracted with three 75 ml portions of ethyl ether. The ether extracts and organic phase were combined, dried (magnesium sulfate), filtered and concentrated (rotovaporator). The oil or solid that resulted was crystallized and recrystallized from solvent or solvents indicated in the footnote of the Table.

5-Phenacylpyrazoles.

A 0.044 mole sample of LDA was prepared in a manner similar to that described in the previous experiment. To this solution was added 0.010 mole of freshly prepared and dried phenylhydrazone [17] dissolved in 30 ml of THF. The metalation time was at least 60 minutes and this was followed by addition of 0.010 mole of ethyl benzoylacetate dissolved in 40 ml of THF. The condensation time was a minimum of 2 hours and the subsequent acid cyclization with 100 ml of 3*N* hydrochloric acid proceeded for 60 minutes. The workup was the same as that described for *N*-acylpyrazoles.

Methylimidazolylisoxazoles and Methylimidazolylpyrazoles.

A 0.044 mole sample of LDA was treated with 0.010 mole of oxime or phenylhydrazone dissolved in 30 ml of THF. After a 60 minute period of metalation, a THF slurry of ethyl 4-methyl-5-imidazolecarboxylate was added and condensation proceeded for at least 2½-3 hours. Cyclization with 3*N* hydrochloric acid proceeded for 1 hour. The workup was the same as that described for *N*-acylpyrazoles.

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- [1] Author to whom correspondence should be directed.
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- [15] If the benzoylhydrazone was not very soluble in THF, it was added as a slurry.
- [16] After neutralization, the mixture was still slightly acidic.
- [17] Phenylhydrazones will slowly decompose and should be used as soon as possible. We have been able to store them for a limited period of time in evacuated vials at 0°.