The Preparation of 5-Phenacylisoxazoles and 5-Hydroxyphenyl-isoxazoles and -pyrazoles by the Condensation of C(α)-Dianions with Ethyl Benzoylacetate and Methyl Salicylate

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C(α), *O*-Dilithiooximes and C(α), *N*-Dilithiophenylhydrazones were prepared in an excess of lithium diisopropylamide (LDA). The former was condensed with ethyl benzoylacetate and methyl salicylate, and the latter condensed with methyl salicylate. The resulting precyclization intermediates were then treated with aqueous acid, which was followed by cyclodehydration to give phenacylisoxazoles and hydroxyphenyl-isoxazoles and -pyrazoles.

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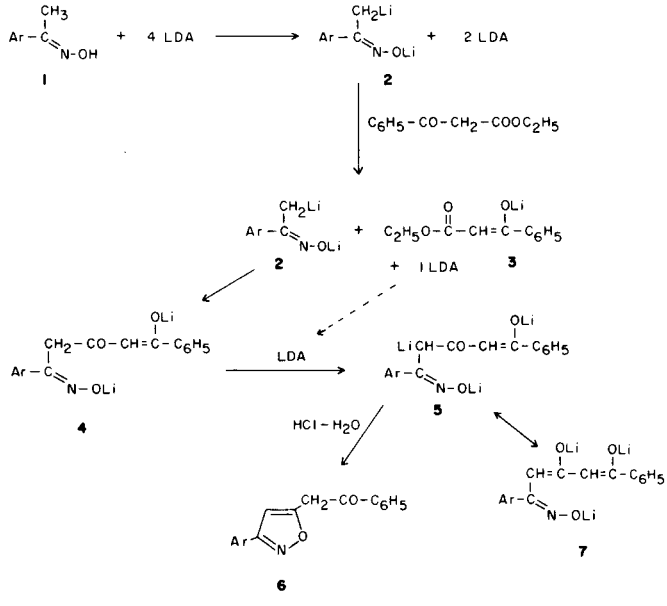
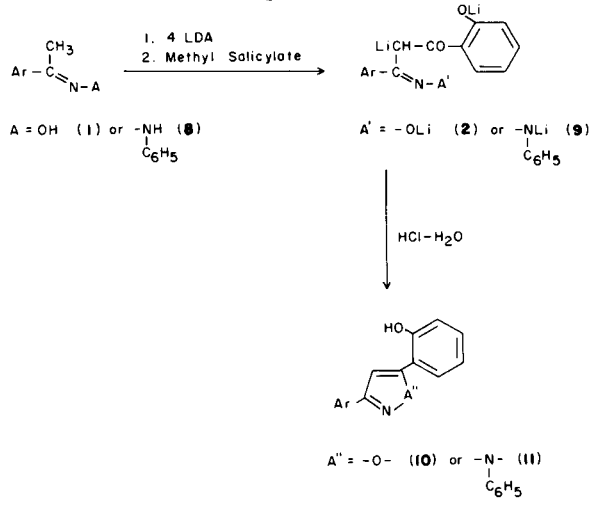
In connection with our recent investigations involving the condensation of C(α), *O*-dilithiooximes and C(α), *N*-dilithiophenylhydrazones with electrophilic reagents, such as aromatic esters (2), and electrophilic-nucleophilic reagents, such as methyl anthranilate and isatoic anhydride (3), it was desirable to condense these dilithiated intermediates with other electrophilic-nucleophilic reagents.

Interestingly, Harris (4) condensed dilithiated 1,3-diketones with ethyl sodiobenzoylacetate to give the expected products in fair-to-good, or even excellent yields. If dilithiooximes, or dilithiophenylhydrazones were to undergo similar condensations with ethyl lithiobenzoylacetate, the resulting intermediates could be cyclodehydrated to give 5-phenacylisoxazoles and 5-phenacylpyrazoles, respectively.

Our initial experimental procedure involved the addition of the oxime **1** (or phenylhydrazone) to a fourfold molar excess of lithium diisopropylamide. After metalation, the dilithiated intermediate **2** was presumed present with a twofold excess of base (LDA). This mixture was treated with ethyl benzoylacetate, which probably transformed the ester into ethyl lithiobenzoylacetate **3** (in an excess of LDA); **3** condensed with the dilithiated oxime **2** to give another intermediate **4**, and **4** reacted with the remaining base (LDA) to give the expected precyclization intermediate **5** (5). Neutralization of **5** with dilute acid (3*N* hydrochloric acid) was followed by cyclodehydration to give the 5-phenacylisoxazole **6**. Dilithiated phenylhydrazones, prepared under the same conditions, either did not readily condense with ethyl lithiobenzoylacetate, or the precyclization intermediate did not cyclize to give the desired product. In a single successful experiment, polylithiated dibenzylketone phenylhydrazone did condense with this ester, and after acid cyclization gave 3-benzyl-1,4-diphenyl-5-phenacylpyrazole in 51% yield. (Footnote (c) of Table and experimental section).



Lithiated methyl salicylate was found to readily undergo condensation with dilithiooximes and dilithiophenylhydrazones, and presumed precyclization intermediates readily



Table

Substituted Isoxazoles and Pyrazoles

Compound No.	Product Name	Empirical Formula	% Yield	mp °C		Combustion Analyses C	H	N	NMR Data (δ ppm) (d) (e)
6a	5-phenacyl-3-phenyl-isoxazole	$C_{17}H_{13}NO_2$	30	87 (a)	Calcd.			5.32	(deuteriochloroform), 4.45 (CH_2CO), 6.57 (C_4H), and 7.00-8.33 (ArH)
					Found			5.51	
6b	5-phenacyl-3-(4-tolyl)-isoxazole	$C_{18}H_{15}NO_2$	47	129-131	Calcd.	77.96	5.45	5.05	(deuteriochloroform + DMSO-d_6), 2.33 ($ArCH_3$), 4.57 (CH_2CO), 6.63 (C_4H) and 6.87-8.17 (ArH)
					Found	77.68	5.62	5.06	
6c	5-phenacyl-3-(4-methoxy-phenyl)isoxazole	$C_{18}H_{15}NO_3$	39	128	Calcd.	73.71	5.15	4.78	(deuteriochloroform), 3.77 (OCH_3), 4.40 (CH_2CO), 6.47 (C_4H), and 6.7-8.17 (ArH)
					Found	73.85	5.12	4.57	
6d	5-phenacyl-3-(4-chloro-phenyl)isoxazole (b,c)	$C_{17}H_{12}ClNO_2$	30	188-189	Calcd.	68.58	4.06	4.70	(trifluoroacetic acid), 4.73 (CH_2CO), 6.67 (C_4H), and 7.2-8.17 (ArH)
					Found	68.38	4.30	4.43	
10a	3-phenyl-5-(2-hydroxy-phenyl)isoxazole	$C_{15}H_{11}NO_2$	55	233-234	Calcd.	75.94	4.67	5.90	(trifluoroacetic acid), 6.7-8.17 (C_4H and ArH)
					Found	76.20	4.95	5.95	
10b	3-(4-tolyl)-5-(2-hydroxy-phenyl)isoxazole	$C_{16}H_{13}NO_2$	82	198-199	Calcd.	76.48	5.21	5.57	(deuteriochloroform + DMSO-d_6), 2.40 ($ArCH_3$), 6.63-8.07 (C_4H and ArH)
					Found	76.71	5.45	5.52	
10c	3-(4-chlorophenyl)-5-(2-hydroxyphenyl)isoxazole	$C_{15}H_{12}ClNO_2$	49	164-165	Calcd.	66.31	3.71	5.16	(trifluoroacetic acid), 6.90-8.20 (C_4H and ArH)
					Found	66.48	3.98	4.97	
10d	5-(2-hydroxyphenyl)-4-methyl-3-phenylisoxazole	$C_{16}H_{13}NO_2$	60	148-150	Calcd.	76.48	5.21	5.57	(deuteriochloroform + DMSO-d_6), 2.10 (CH_3), and 7.07-7.70 (ArH)
					Found	76.76	5.16	5.47	
10e	3-benzyl-5-(2-hyroxy-phenyl)-4-phenylisoxazole	$C_{22}H_{17}NO_2$	62	136-138	Calcd.	80.71	5.23	4.28	(deuteriochloroform + DMSO-d_6), 4.00 (CH_2), and 6.8-7.56 (ArH)
					Found	80.89	5.50	4.52	
10f	4,5-dihydro-3-(2-hydroxy-phenyl)napth[1,2-c]-isoxazole	$C_{17}H_{13}NO_2$	26	204-205	Calcd.	77.55	4.98	5.32	(deuteriochloroform + DMSO-d_6), 2.83 (CH_2CH_2) and 6.8-8.0 (ArH)
					Found	77.27	5.16	5.26	
10g	3-(4-fluorophenyl)-5-(4-hydroxyphenyl)isoxazole	$C_{15}H_{10}FNO_2$	22	208	Calcd.	70.58	3.95	5.49	(DMSO-d_6), 6.8-8.07 (C_4H and ArH)
					Found	70.39	4.22	5.52	
11a	1,3-diphenyl-5-(2-hydroxy-phenyl)pyrazole	$C_{21}H_{16}N_2O$	65	150-154	Calcd.	80.75	5.16	8.97	(deuteriochloroform + DMSO-d_6), 6.76 (C_4H) and 6.9-8.13 (ArH)
					Found	80.92	5.31	8.68	
11b	5-(2-hydroxyphenyl)-1,3,4-triphenylpyrazole	$C_{27}H_{20}N_2O$	92	234-235	Calcd.	83.48	5.19	7.21	(deuteriochloroform + DMSO-d_6), 6.73-7.67 (ArH)
					Found	83.59	5.24	6.98	
11c	3-(4-chlorophenyl)-5(2-hydroxyphenyl)-1-phenylpyrazole	$C_{21}H_{15}ClN_2O$	90	189-190	Calcd.	72.73	4.36	8.08	(trifluoroacetic acid), 6.83-7.83 (C_4H and ArH)
					Found	72.48	4.55	7.89	
11d	1,3-diphenyl-5-(4-hydroxy-phenyl)pyrazole	$C_{21}H_{16}NO_2$	31	232	Calcd.	80.75	5.16	8.97	(DMSO-d_6), 6.80-8.00 (C_4H and ArH)
					Found	80.77	5.40	9.10	

(a) Lit mp 90°, see references (6). (b) A precyclization intermediate, mp 170°, was isolated when *p*-fluoroacetophenone oxime was metalated in excess LDA and condensed with ethyl benzoylacetate. *Anal.* Calcd. for $C_{17}H_{14}FNO_3$: C, 68.19; H, 4.71; N, 4.68. Found: C, 68.23; H, 4.48; N, 4.41. (c) 3-Benzyl-1,4-diphenyl-5-phenacylpyrazole (51%); *Anal.* Calcd. for $C_{30}H_{24}N_2O$: C, 84.08; H, 5.65; N, 6.54. Found: C, 83.81; H, 5.57; N, 6.31. (d) A few hydroxyphenyl heterocyclic materials displayed ArOH *ca.*, δ 9.6 ppm which readily exchanged with deuterium oxide. This was attributed to intramolecular hydrogen bonding with C_4H. (e) Infrared spectra were primarily utilized to differentiate starting materials form products.

underwent neutralization and cyclodehydrations to give substituted hydroxyphenylisoxazoles and hydroxyphenylpyrazoles, respectively (Table). The procedure also involved adding the oxime **1** or phenylhydrazone **8** to an excess of lithium diisopropylamide (LDA) followed by condensation with methyl salicylate, neutralization and acid cyclization of presumed intermediates **2** and **9** (oxime or phenylhydrazone:LDA:salicylate-1:4:1:). As anticipated, methyl *p*-hydroxybenzoate underwent condensation with dilithiated oximes and phenylhydrazones. Similar cyclizations gave the expected products (Table).

(Products **10 d-f** and **11 b&d** from other oximes or phenylhydrazones, *e.g.*, propiophenone oxime, are listed in the Table. Ethyl *p*-hydroxybenzoate is the electrophilic-nucleophilic reagent used to prepare **10g** and **11d**.)

Phenacylisoxazole **6a** (Table) had a melting point that compared well with that reported for the same material prepared by another method (6). Infrared spectra of these materials contained carbonyl (C=O) absorptions at 1670-1680 cm^{-1}; the most convincing nuclear magnetic resonance spectra displayed C_4-H singlets at *ca* δ 6.6 ppm and sharp singlets ($CO-CH_2$) at *ca* δ 4.7 ppm.

Interestingly, dilithiated *p*-fluoroacetophenone oxime (excess LDA) condensed with ethyl benzoylacetate to give an isolatable uncyclized intermediate (footnote (b), Table). The *p*-fluoro atom probably diminished the nucleophilicity of the oxime oxygen and prevented cyclodehydration.

All of the hydroxyphenylisoxazoles and hydroxyphenylpyrazoles appeared to be new. Nmr spectra of these materials were more informative than infrared spectra,

and they contained C_4-H, methyl, methoxy where applicable, along with aromatic resonance absorptions (Table).

While one might expect that these Claisen-type condensations would not proceed well because they would involve the condensation of a carbanion nucleophile with a less reactive electrophile (one with a nucleophilic group in a position for resonance interaction with the electrophilic group), the fact that these reactions do proceed relatively well (30-92% yield) indicates that another factor, such as the stability of the lithiated condensation intermediates (*e.g.*, **7**), may have a direct influence on the overall success of this reaction.

In addition, this synthon has the advantage of using readily prepared starting materials, oximes and phenylhydrazones, and an experimental procedure that is readily reproduced by someone who is not very familiar with strong-base synthesis techniques.

EXPERIMENTAL

Tetrahydrofuran (THF) was distilled from sodium (benzophenone) immediately before use. Oximes and phenylhydrazones were prepared by standard procedures (7,8), and they were stored in a vacuum desiccator until needed. Nuclear magnetic resonance spectra were obtained with a Varian Associates, EM 300X nmr spectometer (TMS internal standard). Infrared spectra were obtained with a Perkin-Elmer 700 Infrared Spectrometer. Melting points were obtained in a Thomas-Hoover melting point apparatus in open capillary tubes and are uncorrected. Combustion analysis were performed by Dr. G. I. Robertson's Microanalytical Laboratory, 73 West End Avenue, Florham Park, NJ 07932. *n*-Butyllithium was purchased form Lithium Corporation of America, Bessemer City, NC.

Isoxazole and Pyrazole Synthesis.

A 0.044-mole sample of *n*-butyllithium was added to the round-bottomed flask with a syringe (dry nitrogen atmosphere). After cooling the flask in an ice-bath, a 0.044-mole sample of diisopropylamine dissolved in 25-30 ml of dry tetrahydrofuran (THF) was added at a fast dropwise rate to the stirred *n*-butyllithium. The lithium diisopropylamide (LDA) that formed was stirred for 20 minutes and a 0.01-mole sample of oxime dissolved in 25-30 ml of THF was added during 5 minutes to the LDA and stirred for 45 minutes. Then a 0.011-mole sample of methyl salicylate or ethyl benzoylacetate dissolved in 25-30 ml of THF was added during 5 minutes, and the mixture was stirred at 0° for an additional 30-35 minutes. The mixture was rapidly neutralized by adding 100 ml of 3 *N* hydrochloric acid, and the apparatus was disassembled, and the flask was placed in a heating mantle and fitted with a reflux condenser. The mixture was stirred and heated under reflux for 1 hour and cooled. Then it was poured into a large flask (1 or 2 liter) and carefully neutralized with solid sodium bicarbonate. The aqueous and organic layers were separated, and the aqueous layer was extracted with three 75-ml portions of ethyl ether; the ether extracts were added to the organic phase, dried (magnesium sulfate), filtered and concentrated (rotoevaporator). The oil or solid that resulted was crystallized and recrystallized from ethanol and water.

3-Benzyl-1,4-diphenyl-5-phenacylpyrazole (footnote (c), Table) was prepared by the same procedure.

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