Reactions of Dilithiooximes, Dilithiophenylhydrazones and Trilithiohydrazones with Nitriles. Acid-Cyclization to Isoxazoles or Pyrazoles.

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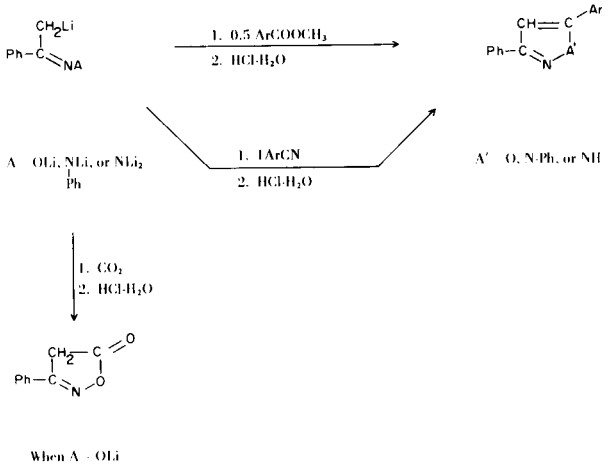
Certain *C(α)O*-dilithiooximes, *C(α)N*-dilithiophenylhydrazones, and *C(α)N,N*-trilithiohydrazones were treated with a variety of nitriles. The intermediates were not isolated, but cyclized with acid to give isoxazoles or pyrazoles.

We have recently developed methods for the aroylation-cyclization of *C(α)O*-dilithiooximes (3), *C(α)N*-dilithiophenylhydrazones (4), and *C(α)N,N*-trilithiohydrazones (5) to give isoxazoles and pyrazoles. This involved the conversion of oximes, phenylhydrazones, and hydrazones of ketones containing an α-hydrogen atom, such as acetophenone, to their multilithio intermediates by treatment with two or three molecular equivalents of *n*-butyllithium. These intermediates were aroylated at the α-carbanionic centers with a variety of esters followed by acid-cyclization to give the respective heterocyclic compound (Scheme I). The synthetic utility of the *C(α)O*-dilithiooximes was further extended by a carboxylation-cyclization procedure, which afforded a new preparative method for 2-isoxazolin-5-ones (6).

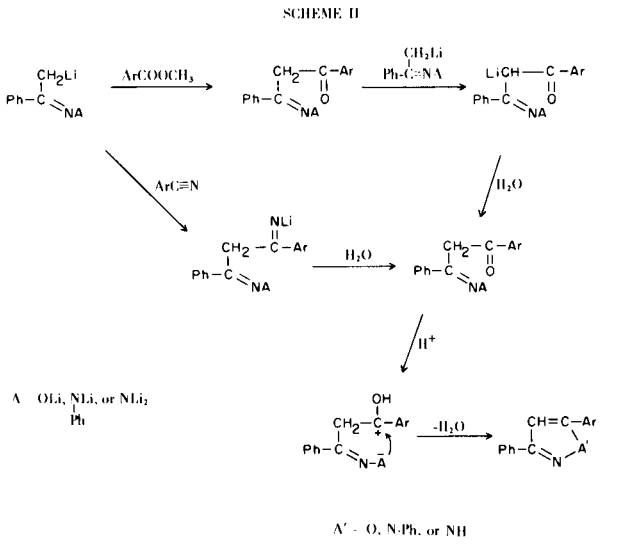
SCHEME I



The treatment of these multilithio intermediates with a variety of nitriles (7) promised to be of additional interest, since the assumed imine intermediate (8) could be hydrolyzed to the ketone and cyclodehydrated to give isoxazoles and pyrazoles, and would be an alternate synthetic route to these compounds.

During the present investigation this synthetic procedure using nitriles was developed, and a variety of isoxazoles and pyrazoles were prepared 1-15 (see Table). The principle advantage of the new procedure over the previous procedures (3,4,5) is that the resulting heterocyclic compound can be prepared in greater quantities. With the new procedure, the ratio of compound with the α-hydrogen atom to nitrile is 1:1, and the yield is based upon the nitrile; with the previous procedure, this ratio (α-hydrogen atom compound: ester) is 1:0.5 (9) and the yield is based upon the ester (see Scheme II). In addition, unsymmetrical 3,5-, *N*-phenylpyrazoles and isoxazoles can also be prepared by this synthetic procedure, since the structural position of the 3- and 5-substituents has been established prior to the cyclodehydration.

SCHEME II



TABLE

Isoxazoles and Pyrazoles

Compound Number	Name	Yield (%)	M.p., °C	Empirical Formula		Elemental Analyses (h) C	H	N
1	3,5-Diphenylisoxazole	73	139-141 (a)	$C_{15}H_{11}NO$		----	---	---
2	3-(*p*-Chlorophenyl)-5-phenylisoxazole	65	172 (b)	$C_{15}H_{10}ClNO$		----	---	---
3	5-(*p*-Chlorophenyl)-3-phenylisoxazole	45	176-178 (c)	$C_{15}H_{10}ClNO$		----	---	---
4	5-(*p*-Methoxyphenyl)-3-(*p*-tolylphenyl)isoxazole	55	128-130	$C_{17}H_{15}NO_2$	Calcd.	76.96	5.70	5.28
					Found	76.84	5.48	5.13
5	3-(*p*-Fluorophenyl)-5-phenylisoxazole	62	169-170	$C_{15}H_{10}FNO$	Calcd.	75.30	4.21	5.85
					Found	75.48	4.14	5.92
6	3-(*p*-Fluorophenyl)-5-(*p*-methoxyphenyl)isoxazole	49	125-128	$C_{16}H_{12}FNO_2$	Calcd.	71.37	4.49	5.20
					Found	71.58	4.44	4.97
7	1,3,5-Triphenylpyrazole	68	138-139 (d)	$C_{21}H_{16}N_2$		----	---	---
8	3,5-Di-(*p*-chlorophenyl)-1-phenylpyrazole	30	139-141 (e)	$C_{21}H_{14}Cl_2N_2$		----	---	---
9	1,5-Diphenyl-3-(*p*-fluorophenyl)-pyrazole	50	85- 87	$C_{21}H_{15}FN_2$	Calcd.	80.23	4.81	8.91
					Found	80.04	4.76	8.70
10	3-(*p*-Fluorophenyl-5-(*p*-methoxyphenyl)pyrazole	71	100-102	$C_{22}H_{17}FN_2O$	Calcd.	76.73	4.98	8.13
					Found	76.45	4.91	7.97
11	1,3-Diphenyl-5-(*p*-tolylphenyl)-pyrazole	74	116-117	$C_{22}H_{18}N_2$	Calcd.	85.12	5.85	9.03
					Found	85.06	5.83	9.03
12	3,5-Diphenylpyrazole	59	200-201 (f)	$C_{15}H_{12}N_2$		----	---	---
13	3(5)-(*p*-Chlorophenyl)-3(5)phenylpyrazole	61	216-217 (g)	$C_{15}H_{10}ClN_2$		----	---	---
14	3(5)-(*p*-Tolylphenyl)-3(5)phenylpyrazole	65	179-180	$C_{16}H_{14}N_2$	Calcd.	82.02	6.02	11.96
					Found	82.25	6.02	12.04
15	3(5)-(*m*-Tolylphenyl)-3(5)phenylpyrazole	52	145-147	$C_{16}H_{14}N_2$	Calcd.	82.02	6.02	11.96
					Found	82.12	6.09	12.05

(a) 141°, see C. Goldschmidt, *Ber.*, **28**, 2540 (1895). (b) 175°, see G. Bianchetti, D. Pocar and P. D. Croce, *Gazz. Chem. Ital.*, **93**, 1714 (1963). (c) 178-179°, see P. Grunanger, *ibid.*, **89**, 1771 (1959). (d) 140-140.5°, see L. Knorr and H. Laubmann, *Ber.*, **21**, 1206 (1888). (e) 140-141°, see reference 4. (f) 200°, see T. Posner, *Ber.*, **34**, (1901): W. Wislicenus, *Ann. Chem.*, **308**, 254 (1899). (g) 216-217°, see reference 5. (h) The nmr spectra of all heterocyclic compounds reported were in agreement with the assigned structures.

The structure of the isoxazoles and pyrazoles were established by melting point comparisons or elemental analysis (compounds **4**, **5**, **6**, **9**, **10**, **11**, **14**, and **15**) and nmr spectra. Each heterocyclic compound had an absorption signal in the region of δ 6.8-7.3 ppm, which was assigned to the proton at the 4-position of the heterocyclic ring (3,4,5,10). Other resonance absorptions were consistent with the assigned structures.

The presumed imine intermediates (Scheme II) were not isolated but were hydrolyzed and cyclized directly to the isoxazole or pyrazole. In addition, we have observed that the best yields were obtained when the materials obtained from the acid-cyclization were immediately recrystallized from 95% ethanol. The overall importance of the acid-cyclization procedure, especially in the case of the pyrazole preparations, and the isolation of intermediates prior to cyclization may be of interest for other investigations.

The synthesis described in the present work provides an alternate method for the preparation of isoxazoles and pyrazoles and is compatible with a variety of substituent groups, requires readily available starting materials, and has a short, simple experimental procedure.

EXPERIMENTAL

All analyses were performed by M-H-W Laboratories, Garden City, Michigan. Nmr spectra were obtained in trifluoroacetic acid with a Varian Associates A-60 Spectrometer and chemical shifts are reported in parts per million downfield (δ) from an internal tetramethylsilane (TMS) standard. Melting points were

obtained in a Thomas-Hoover melting point apparatus in open tubes and are uncorrected. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride immediately before use. The *n*-butyllithium was obtained from Alfa Inorganics, Inc., Beverly, Massachusetts, and was used as supplied. The oximes were prepared by the method of Shriner, Fuson and Curtin (11); the phenylhydrazones were prepared by a standard method and (12) were recrystallized from 95% ethanol, dried by suction filtration, and used immediately; the hydrazones were prepared by standard methods (13,14,15).

Isoxazole and Pyrazole Synthesis.

To a stirred solution of 0.025 mole of oxime, phenylhydrazone, or hydrazone in 100 ml. of THF, which was cooled to 0°, and under nitrogen, *n*-butyllithium (0.075 mole to the hydrazone, or 0.050 mole to the oxime or phenylhydrazone) was added during 5 minutes. After 30 minutes (or 2-3 hours in the case of the hydrazones), 0.025 mole of nitrile in 100 ml. of THF was added during 5 minutes. The mixture was stirred at 0° for 1 hour, then neutralized with 100 ml. of 3 *N* hydrochloric acid, heated under reflux for 1 hour and cooled. The aqueous layer was neutralized with sodium bicarbonate and extracted with three 50-ml. portions of ether. The combined organic layers were concentrated (Rotovac) and recrystallized from 95% ethanol.

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