An Improved Synthesis of 3,5-Disubstituted Isoxazoles and Pyrazoles from *C(α),O*-Dilithiooximes and *C(α),N*-Dilithiophenylhydrazones

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C(α),O-Dilithiooximes and *C(α),N*-dilithiophenylhydrazones were prepared using an excess of lithium diisopropylamide (1:3). Condensation with esters followed by acid cyclization gave isoxazoles and pyrazoles.

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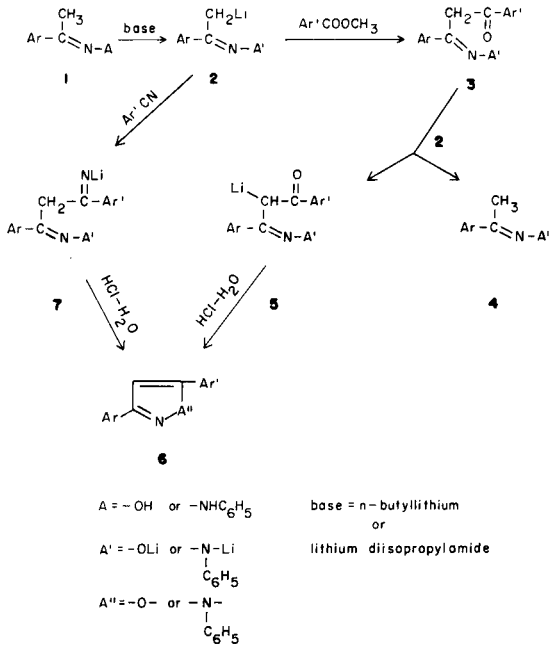
Recently, we reported the unequivocal synthesis of 3,5-disubstituted isoxazoles and pyrazoles (1-3) from the dianions of oximes and phenylhydrazones. In each instance the oxime or phenylhydrazone was treated with two equivalents of *n*-butyllithium in tetrahydrofuran/hexane. These reactive dilithiated intermediates were condensed with one-half equivalent of ester and then cyclized by acid to give the desired heterocyclic material. The yield was based upon the ester (oxime or phenylhydrazone:base:ester 1:2:0.5).

The reaction path (Scheme I) is envisioned as the dilithiation of **1** to **2**, which undergoes a Claisen-type condensation with an ester to give **3**; **3**, containing an acidic methylene proton, will react with **2** to give **4** (which consumes half of the dianion and **5**, which upon acidification, will undergo cyclodehydration to give desired heterocycle **6**. If **2** were treated with a nitrile instead of an ester, one-half of **2** would not be consumed since **2** would not abstract a proton from **7**; **7** would give **6** directly after acid hydrolysis and cyclodehydration (4). In order to condense **2** with an ester more effectively, a base is needed to react preferentially with **3** to give **5** (instead of competing with **2**). *n*-Butyllithium would not be a good choice, since it is a good enough nucleophile to react with the ester instead of with **3**. However, lithium diisopropylamide has the potential of being both a good base and a poor nucleophile.

When *C(α),O*-oximes and *C(α),N*-phenylhydrazones were treated with three equivalents of lithium diisopropylamide (oxime or phenylhydrazone 1:3) and condensed with esters, followed by acid cyclization, good to excellent yields of isoxazoles and pyrazoles were isolated (Table). Each heterocyclic compound was easily characterized by ^{1}H nmr spectra, since the C_4-hydrogen atoms when present were usually displayed at δ 6.7-7.2 ppm and discernible from other aromatic absorptions. Other pendant group resonance absorptions (*e.g.*, methoxy) and combustion analyses for new compounds also supported the structures. Interestingly, dilithiophenylhydrazones would readily condense with methyl isonicotinate and then undergo acid cyclization to the pyrazoles; dilithiooximes would condense with this ester but cyclodehydration after treatment with acid did not occur.

Scheme I



Another report described the preparation of isoxazoles by the condensation of *C(α),O*-dilithiooximes with dimethyl amides followed by an acid cyclodehydration (5). However, the greater availability of esters over nitriles (4) and amides plus the use of lithium diisopropylamide offers an improved synthetic procedure.

EXPERIMENTAL

Tetrahydrofuran was distilled from sodium (benzophenone). Nuclear magnetic resonance spectra were obtained on a Varian Associates EM 300X nmr spectrometer (TMS standard). Combustion analyses were performed by Robertson's Laboratory, 73 West End Ave., Florham Park, NJ. *n*-Butyllithium was purchased from the Lithium Corporation of America.

Preparation of Isoxazoles and Pyrazoles.

A 0.066 mole sample of *n*-butyllithium (in tetrahydrofuran/hexane) was cooled to 0° and blanketed with nitrogen. A 0.066 mole sample of diisopropylamine dissolved in 30 ml. of THF was added dropwise during 5 minutes, and the solution was stirred for 20-30 minutes. Then, 0.02 mole of oxime or phenylhydrazone dissolved in 30-40 ml. of THF was added

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Table

Isoxazoles and Pyrazoles

Compound No.	Name	Empirical Formula	Yield (%)	Melting Point (a) (°C)	Elemental Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Nuclear Magnetic Resonance δ (ppm)
1	3-(*p*-methoxyphenyl)-5-(*p*-tolyl)isoxazole	$C_{17}H_{15}NO_2$	100	146-148 (b)	—	—	—	—	—	—	2.40 ($ArCH_3$), 3.83 ($ArOCH_3$), 6.67-8.03 (C_4H and ArH) (e)
2	5-(*m*-chlorophenyl)-3-(*p*-tolyl)isoxazole	$C_{16}H_{12}ClNO$	88	127-129	71.25	4.48	5.19	71.52	4.48	5.08	2.37 ($ArCH_3$), 6.70 (C_4H), 6.93-8.0 (ArH) (f)
3	5-(*m*-chlorophenyl)-3-(*p*-methoxyphenyl)isoxazole	$C_{16}H_{12}ClNO_2$	76	128-130	67.26	4.23	4.90	67.52	4.26	4.83	3.77 ($ArOCH_3$), 6.73 (C_4H), 6.83-8.03 (ArH) (g)
4	5-(*p*-aminophenyl)-3,4-trimethyleneisoxazole	$C_{12}H_{12}N_2O$	100	175	71.98	6.04	13.99	71.69	5.93	13.88	2.33-2.90 ($-CH_2-)_3$, 4.90 (NH_2, exchangeable with deuterium oxide), 6.50-7.50 (ArH) (e)
5	5-(*o*-chlorophenyl)-3-(*p*-methoxyphenyl)isoxazole	$C_{16}H_{12}ClNO_2$	44	86	67.26	4.23	4.90	67.18	4.39	4.63	3.77 ($ArOCH_3$), 6.73 (C_4H), 6.90-8.03 (ArH) (f)
6	1,3,5-triphenylpyrazole	$C_{21}H_{16}N_2$	100	137 (c)	—	—	—	—	—	—	6.76 (C_4H), 7.10-8.10 (ArH) (f)
7	3-benzyl-1,4-diphenyl-5-isonicotinylpyrazole	$C_{27}H_{21}N_3$	87	187	83.69	5.46	10.84	83.42	5.58	10.60	4.0 ($-CH_2Ar$), 6.70-7.47 and 8.13-8.50 (ArH) (f)
8	5-isonicotinyl-3-(*p*-methoxyphenyl)-1-phenylpyrazole	$C_{21}H_{17}N_{30}$	67	181	77.04	5.23	12.83	77.18	5.18	12.72	3.80 ($ArOCH_3$), 6.73-7.93 and 8.40-8.63 (C_4H and ArH) (f)
9	1,3-diphenyl-5-isonicotinylpyrazole	$C_{20}H_{15}N_2$	60	150 (d)			14.13			14.22	6.83 (C_4H), 6.93-8.10 and 8.33-8.63 (ArH) (f)
10	3-(*p*-fluorophenyl)-5-isonicotinyl-1-phenylpyrazole	$C_{20}H_{14}FN_3$	40	129-131	76.18	4.47	13.32	76.37	4.66	13.13	6.80 (C_4H), 6.98-8.03 and 8.31-8.63 (ArH) (f)

(a) Melting points were taken in a Thomas Hoover Melting Point apparatus in open capillary tubes and are uncorrected. (b) Lit. (6) m.p. 148°. (c) Lit. (3) m.p. 139-140°. (d) Lit. (7) m.p. 153-155°. (e) Deuteriochloroform-DMSO-d_6 as solvent. (f) Deuteriochloroform as solvent. (g) DMSO-d_6 as solvent.

during 5 minutes, and the solution was stirred for 45 minutes. A 0.022 mole sample of ester was dissolved in 30 ml. of THF and added to the dilithiooxime or dilithiophenylhydrazone during 5 minutes, and the entire mixture was stirred for 30 minutes and treated with 100 ml. of 3*N* hydrochloric acid. The two-phase mixture was then heated under reflux for 1 hour, cooled, and poured into a large flask. It was desirable to add 100 ml. of ether and then carefully neutralize the mixture with sodium bicarbonate. The organic phase was separated and concentrated (Rotovac). If crystallization occurred at any point, the mixture was filtered and washed with water to remove any bicarbonate. The heterocyclic materials were recrystallized from ethanol or ethanol and water.

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