A New Synthesis of Substituted Pyrazoles from 1,4-Dianions of Phenylhydrazones Having an α-Hydrogen.

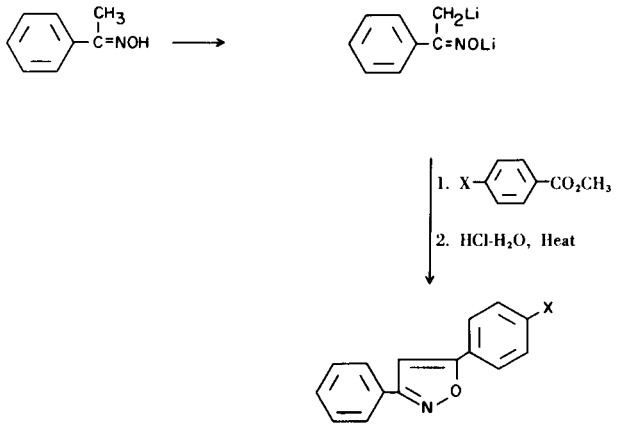
Robert S. Foote, Charles F. Beam and Charles R. Hauser (1)

Paul M. Gross Chemical Laboratory, Duke University

The 1,4-dianions of acetophenone, *para*-substituted acetophenones, deoxybenzoin and dibenzyl ketone phenylhydrazone were prepared by treatment of the respective phenylhydrazone with two molecular equivalents of *n*-butyllithium in tetrahydrofuran-hexane at 0° and condensed with a variety of aromatic esters, followed by acid cyclization to give the substituted pyrazole in good yield. The synthesis procedure appears to be a convenient and unequivocal method for preparing a particular pyrazole isomer without interfering side reactions. The 1,4-dianion of *N,N*-diphenylsemicarbazone was also prepared, and the condensation-cyclization gave the pyrazole in somewhat lower yield.

Recently, a new unequivocal method was developed in this laboratory for the synthesis of unsymmetrical isoxazoles (2). This involved the conversion of an oxime, such as acetophenone oxime, to its 1,4-dilithio salt by means of two molecular equivalents of *n*-butyllithium and aroylating the methyl carbon of this salt with an aromatic ester and cyclizing the intermediate aroyl derivative with acid (Scheme I).

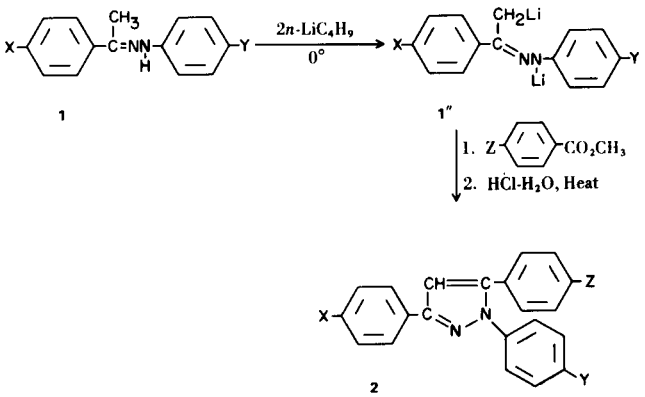
SCHEME I



During the present investigation, this method was extended to phenylhydrazones, such as acetophenone phenylhydrazone, and was shown to be applicable to the synthesis of other unsymmetrical pyrazoles starting with the appropriate phenylhydrazone, or a *N,N*-diphenyl semicarbazone.

A series of 1,3,5-trisubstituted pyrazoles (**2a-i**) was prepared in good yield from the 1,4-dianions of acetophenone phenylhydrazone or a *para*-substituted acetophenone phenylhydrazone. These dianions were formed at 0° instead of -80° (3) in tetrahydrofuran-hexane by the reaction of two moles of *n*-butyllithium per mole of phenylhydrazone to give 1,4-dianion **1″**, followed by the aroylation with methyl benzoate or methyl *para*-substituted benzoates. Similar 1,4-dianions had been previously formed by the reaction of two moles of potassium amide in liquid ammonia per mole of phenylhydrazone (4). The intermediate ketophenylhydrazone was not isolated but was cyclized directly, under acid conditions, to give the desired pyrazole (Scheme II).

SCHEME II

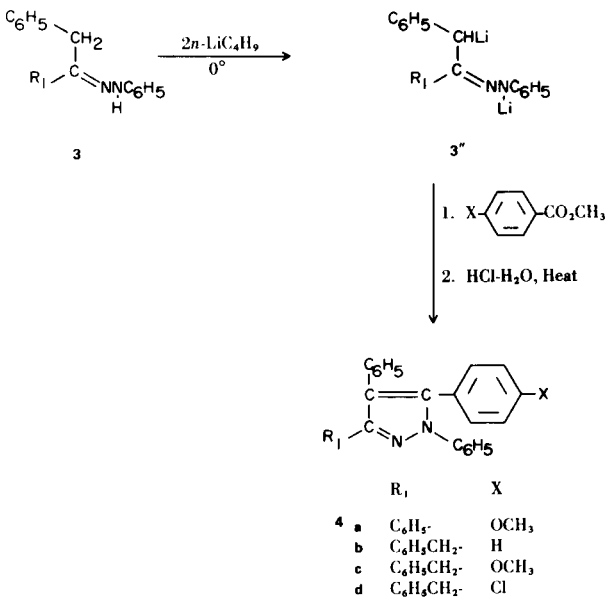


	X	Y	Z
a	H	H	H
b	H	H	Cl
c	Cl	H	H
d	Cl	H	Cl
e	H	Cl	Cl
f	Cl	H	OCH_3
g	H	Cl	OCH_3
h	OCH_3	H	Cl
i	H	H	OCH_3

That the integrity of the carbon-nitrogen double-bond is maintained was indicated by the preparation of individual isomers **2b** and **2c** and isomers **2f** and **2h** from different phenylhydrazone dianions. In each case only one isomer was isolated.

Several 1,3,4,5-tetrasubstituted pyrazoles (**4a-d**) were also prepared in good yield from the condensation-cyclization of the 1,4-dianion of deoxybenzoin phenylhydrazone and dibenzyl ketone phenylhydrazone, respectively (Scheme III).

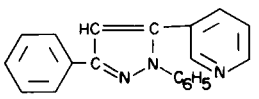
SCHEME III



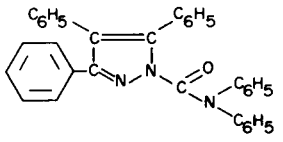
Interestingly, the preparation of pyrazoles **4b-d** indicate that the method is also adaptable to the synthesis of alkyl substituted pyrazoles as well. The high yields obtained for these pyrazoles (85-95%) indicated that the dianions formed were primarily 1,4- and not 1,3-dianions, (which may have resulted from ionization of each of the methylene hydrogens).

Since precursory nicotinyl β-diketones for **5** appear not to be known, the condensation-cyclization of the 1,4-dianion of acetophenone phenylhydrazone with ethyl nicotinate provided a convenient synthesis of this new type of 5-substituted pyrazole.

The semicarbazone of acetophenone failed to give a cyclized product after treatment with two and three moles of *n*-butyllithium per mole of semicarbazone followed by the acid cyclization procedure; however, the *N,N*-diphenylsemicarbazone of deoxybenzoin when treated with two moles of *n*-butyllithium per mole of semicarbazone followed by condensation with methyl benzoate and subsequent acid cyclization gave pyrazole **6** in 19% yield.



5



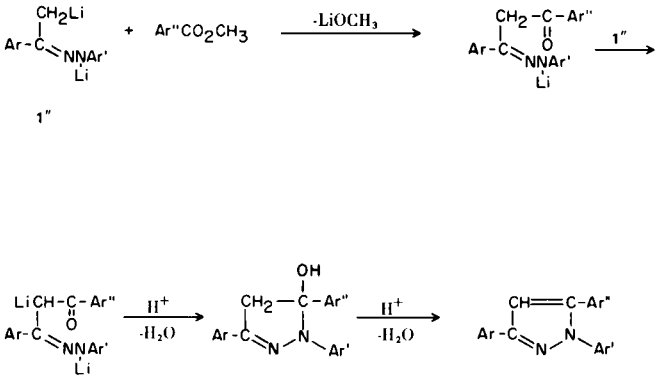
6

The structure of each of the pyrazoles prepared was supported by infrared spectra. Particular attention was given to the carbon-nitrogen double bond absorption which was noted (Table I) at 6.24-6.29 μ. With the exception of pyrazole **6**, characteristic carbonyl absorptions were absent, and in all instances hydroxyl absorptions were also absent. The other absorptions noted were in agreement with those previously reported for substituted pyrazoles (5). In addition, the structures of pyrazoles **2b-i**, **4a-d**, **5**, and **6** were supported by elemental analysis (Table I).

Discussion.

This synthesis of substituted pyrazoles appears to be an unequivocal method for the preparation of a particular pyrazole isomer. It has the advantage of an efficient and rapid experimental procedure and usually requires the use of readily available starting materials. The starting phenylhydrazones were prepared by a standard procedure (6) and must be used immediately.

The molar ratio of reactants (2 base:1 phenylhydrazone: 1/2 ester) is consistent with a modified Claisen aroylation (7) and is outlined as follows:



An alternate procedure requiring another molar ratio of reactants (3 base:1 phenylhydrazone:1 ester) was not considered since the extra equivalent of *n*-butyllithium would preferentially react with the ester and not the monanion (8).

TABLE I

Number	Name of Pyrazole	% Yield	M.p. °C	Formula	Anal.	C	H	N	ir (microns)
2a	1,3,5-Triphenylpyrazole	80	139-140 (a) (b)	$C_{21}H_{16}N_2$		---	---	---	6.27 (h)
2b	5-(*p*-Chlorophenyl)-1,3-diphenylpyrazole	82	114-115 (b)	$C_{21}H_{15}ClN_2$	Calcd.	76.25	4.57	8.47	6.26 (h)
					Found	76.42	4.65	8.54	
2c	3-(*p*-Chlorophenyl)-1,5-diphenylpyrazole	76	145-146 (b)	$C_{21}H_{15}ClN_2$	Calcd.	76.25	4.57	8.47	6.27 (h)
					Found	76.32	4.47	8.35	
2d	3,5-Di(*p*-chlorophenyl)-1-phenylpyrazole	80	140-141 (b)	$C_{21}H_{14}Cl_2N_2$	Calcd.	69.06	3.86	7.67	6.26 (h)
					Found	69.09	3.87	7.65	
2e	1,5-Di(*p*-chlorophenyl)-3-phenylpyrazole	85	143-145 (b)	$C_{21}H_{14}Cl_2N_2$	Calcd.	69.06	3.86	7.67	6.29 (h)
					Found	69.16	3.60	7.59	
2f	3-(*p*-Chlorophenyl)-5-(*p*-methoxyphenyl)-1-phenylpyrazole	83	111-112 (c)	$C_{22}H_{17}ClN_2O$	Calcd.	73.23	4.75	7.76	6.26 (h)
					Found	73.37	4.60	7.63	
2g	1-(*p*-Chlorophenyl)-5-(*p*-methoxyphenyl)-3-phenylpyrazole	70	104-106 (d)	$C_{22}H_{17}ClN_2O$	Calcd.	73.23	4.75	7.76	6.29 (h)
					Found	73.15	4.72	7.75	
2h	5-(*p*-Chlorophenyl)-3-(*p*-methoxyphenyl)-1-phenylpyrazole	86	143-144 (b)	$C_{22}H_{17}ClN_2O$	Calcd.	73.23	4.75	7.76	6.27 (h)
					Found	73.50	4.69	7.90	
2i	1,3-Diphenyl-5-(*p*-methoxyphenyl)-pyrazole	37	78-80 (e)	$C_{22}H_{18}N_2O$	Calcd.	80.96	5.56	8.58	6.27 (h)
					Found	80.79	5.76	8.55	
4a	5-(*p*-Methoxyphenyl)-1,3,4-triphenyl-pyrazole	93	198-200 (b)	$C_{28}H_{22}N_2O$	Calcd.	83.55	5.51	6.96	6.24 (i)
					Found	83.58	5.56	6.87	
4b	3-Benzyl-1,4,5-triphenylpyrazole	89	162-163 (b)	$C_{28}H_{22}N_2$	Calcd.	87.01	5.74	7.25	6.28 (i)
					Found	86.96	5.82	7.23	
4c	3-Benzyl-1,4-diphenyl-5-(*p*-methoxyphenyl)pyrazole	86	153-154 (b)	$C_{29}H_{24}N_2O$	Calcd.	83.62	5.81	6.73	6.28 (i)
					Found	83.80	5.76	6.69	
4d	3-Benzyl-5-(*p*-chlorophenyl)-1,4-diphenylpyrazole	85	157-158 (b)	$C_{28}H_{21}ClN_2$	Calcd.	79.90	5.03	6.66	6.26 (h)
					Found	80.14	5.26	6.59	
5	1,3-Diphenyl-5-(3-pyridyl)-pyrazole	29	112-113 (f)	$C_{20}H_{15}N_3$	Calcd.	80.78	5.09	14.13	6.29 (h)
					Found	81.03	5.17	13.93	
6	1-(*N*,*N*-Diphenylcarboxamido)-3,4,5-triphenylpyrazole	19	240-241 (g)	$C_{34}H_{25}N_3O$	Calcd.	83.07	5.12	8.54	6.29 (h)
					Found	83.04	5.11	8.64	

(a) Reported m.p. 140-140.5°, see reference (9). (b) Recrystallized from 95% ethanol. (c) Recrystallized from ethyl ether or pentane. (d) Recrystallized from methanol. (e) Recrystallized from pentane. (f) Recrystallized from ethanol-water or hexane. (g) Recrystallized from acetone. (h) Potassium bromide pellet. (i) Chloroform solution.

EXPERIMENTAL

All analyses were performed by M-H-W Laboratories, Garden City, Michigan. Infrared spectra were obtained on Perkin-Elmer 137 and 237 Spectrometers. Melting points were taken 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 phenylhydrazones (5) were recrystallized from 95% ethanol, dried by suction filtration, and used immediately.

General Procedure for Conversion of a Phenylhydrazone to its Dilithio Salt.

To a stirred solution of 0.025 mole of phenylhydrazone in 100 ml. of THF, which was cooled to 0° and blanketed with a nitrogen atmosphere, was added during 5 minutes, 22.5 ml. (0.05 mole) of 2.25 *M* *n*-butyllithium. After 30 minutes, the solution was assumed to contain 0.025 mole of dilithio salt, which was condensed with an ester as described below.

General Procedure for Aroylation of Dilithio Salt Followed by Acid.

Cyclization to Form the Pyrazole.

A 0.0125-mole sample of ester dissolved in 25 ml. of THF was added during 5 minutes to a solution containing 0.025 mole of dilithio salt (prepared as described above). After stirring at 0° for 15 minutes, the mixture was neutralized with 100 ml. of 3 N hydrochloric acid. The mixture was then heated under reflux for 1 hour, cooled, and the layers separated. The aqueous layer was neutralized with sodium bicarbonate and extracted with three 50-ml. portions of ether. The combined ether extracts were concentrated (drying not necessary) and the residue was washed with 10 ml. of cold (0°) methanol and filtered. If a solid did not immediately crystallize, 5-10 ml. of methanol was added and crystallization usually occurred upon refrigeration of the mixture. Recrystallization solvents are indicated in Table I.

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