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C(α),N-Carboalkoxyhydrazones were metalated with an excess of lithium diisopropylamide (LDA), and the resulting dianions were condensed with methyl iodide, an unsubstituted ketone, a benzoate ester, salicylates, a benzoylacetate, or ethyl chloroformate.

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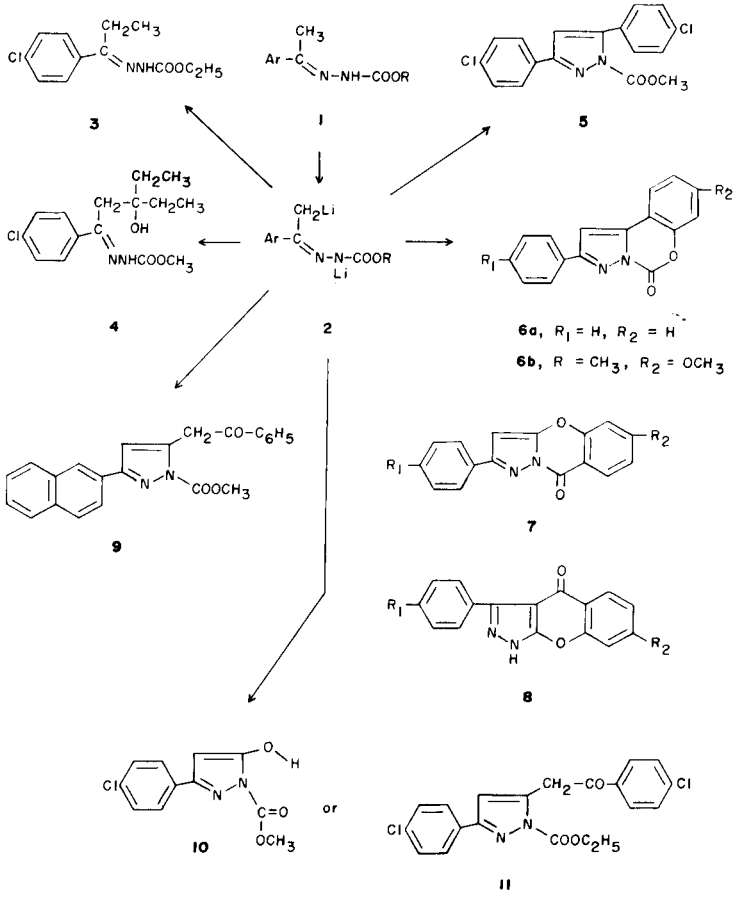
We are reporting our initial results on the preparation of *C*(α),*N*-dilithiocarboalkoxyhydrazones **2**, and the condensation of these dianions with a variety of electrophilic and electrophilic-nucleophilic reagents to give new products, which includes pyrazoles, benzopyanopyrazoles, hydroxypyrazoles and phenacylpyrazoles.

Our initial experiments involved the preparation of dianion **2** by treatment of carboalkoxyhydrazone **1** (in THF) [1] with an excess of lithium diisopropylamide (LDA) at 0°. After metalation (45 minutes), dianion **2** was treated with traditional electrophilic reagents such as methyl iodide, diethylketone, or methyl *p*-chlorobenzoate. Only *C*-alkylated product **3** (mp 116-117°, ethanol) was isolated in 64% yield. Its structure was established by proton magnetic resonance spectra [2] [δ 1.18 and 1.37 (t, CH_3), 2.67 (q, $-CH_2-$), 4.38 (q, $-CH_2O-$), 7.15-7.95 (m, ArH), and 8.35 ppm (s, NH)] and supported by combustion analysis [3].

Anal. Calcd. for $C_{12}H_{15}ClN_2O_2$: C, 56.59; H, 5.94; N, 11.00. Found: C, 56.72; H, 6.06 N, 10.96.

The *N*-alkylated product was not isolated even though an excess of methyl iodide was used [4]. The aldol-type condensation product **4** (mp 128-129°, methanol) was isolated in 35% yield, and its structure was also established by proton magnetic resonance spectra [δ 0.83 (t, $-CH_3$), 1.52 (q, $-CH_2-$), 2.92 (s, $-CH_2-$), 3.87 (s, $-OCH_3$), and 6.98-7.83 ppm (m, ArH)] and supported by combustion



analysis.

Anal. Calcd. for $C_{15}H_{21}ClN_2O_3$: C, 57.60; H, 6.77; N, 8.96. Found: C, 57.60: H, 7.03; N, 8.80.

The Claisen-type condensation-cyclization product, pyrazole **5**, (mp 136-139°, methanol) was isolated in 40% yield [pmr: δ 4.05 (s, $-OCH_3$), 6.98 (s, C_4-H), and 7.38-8.21 ppm (m, ArH)]. Apparently, the acid cyclization product, resulting from condensation of **2** with methyl *p*-chlorobenzoate, did not extensively hydrolyze the *N*-carbomethoxy ester to the acid (N-COOH), which would have decarboxylated to give another pyrazole (N-H) [5].

Anal. Calcd. for $C_{17}H_{12}Cl_2N_2O_2$: C, 58.81; H, 3.48; N, 8.06. Found: C, 58.86; H, 3.71; N, 8.04.

When dianion **2**, prepared with an excess of LDA, was treated with methyl salicylates, the resulting intermediates were quenched with 3*N* hydrochloric acid and acid-cyclized to give benzopyanopyrazoles **6a-b** in 35% and 55% yields, respectively. Two other isomers, **7** [6] and **8** [7] were also initially suspected as candidates for the single isolated product. Proton nmr spectra of **6a-b** contained C_4-H resonance absorptions at δ 7.30 (**6a**) and 7.20 (**6b**) ppm, which ruled out isomer **8**. The infrared spectra displayed carboxyl absorptions at 1775 (**6a**) and 1760 (**6b**) cm^{-1}, which also ruled out isomers **7** and **8**. No NH absorption was noted, which also ruled out **8**. We could assign mass spectra fragmentations [8] for ions resulting from benzopyranopyrazoles **6a-b**, and we also noted a small ion fragment appearing to be M-44 (CO_2), which would not have resulted from isomers **7** and **8**. The C-13 nmr spectra [9] for benzopyranopyrazoles **6a-b** provided most convincing evidence of structure with chemical shifts at δ 158.1 (**6a**) and 158.0 (**6b**) ppm, which were assigned to the urethane-type carbonyl carbon. Isomers **7** and **8** would have had carbonyl carbon absorptions greater than δ 165 ppm. The spectra had no absorptions in this region.

2-Phenylbenzopyrano[3,4-*b*]pyrazole (**6a**).

This compound had mp 198-202°, xylene.

Anal. Calcd. for $C_{16}H_{10}N_2O_3$: C, 73.27; H, 3.84; N, 10.68. Found: C, 73.19; H, 3.79; N, 10.71.

2-(4-Methylphenyl)-8-methoxybenzopyrano[3,4-*b*]pyrazole (**6b**).

This compound had mp 195-197°, xylene.

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15. Found: C, 70.61; H, 4.76; N, 9.14.

When dianion **2**, (excess LDA, carboalkoxyhydrazone: LDA, 1:4), was treated with ethyl benzoylacetate, the presumed enolate of this ester condensed with **2**, which was followed by acid-cyclization to give phenacylpyrazole **9** (mp 172-173°, methanol), in 25% yield. Proton nmr spectra [δ 4.03 (s, $-OCH_3$), 4.77 (s, $-CH_2$-), and 7.22-8.47 ppm (m, naphthyl),] clearly established that **9** was the product, and that no further cyclization had occurred to give a product analogous to benzopyranopyrazole **6**.

Anal. Calcd. for $C_{23}H_{18}N_2O_3$: C, 74.58; H, 4.90; N, 7.56. Found: C, 74.74; H, 5.09; N, 7.43.

Dianion **2** was treated with ethyl chloroformate to give lithiated intermediates, whose structure appears to depend upon condensation time. When a short condensation time (30 minutes) was used, subsequent quenching and acid-cyclization with 3*N* hydrochloric acid gave 5-hydroxypyrazole **10** (mp 195-198°, methanol/ethanol) in 34% yield. The proton nmr spectra clearly established the predominant 5-hydroxypyrazole (enol) structure [δ 4.25 (s, $-OCH_3$), 6.30 (s, C_4-H), and 7.45-7.83 ppm (m, ArH)].

Anal. Calcd. for $C_{11}H_9ClN_2O_3$: C, 52.29; H, 3.59; N, 11.09. Found: C, 52.01; H, 3.73; N, 10.84.

The acid-cyclized hydrolysis from an intermediate resulting from a longer condensation time (90 minutes) was a 5-phenacylpyrazole **11** (mp 140-142°, methanol/ethanol), which was isolated in 16% yield, [pmr spectra: δ 1.33 (t, $-CH_3$), 4.40 (q, $-OCH_2$-), 4.70 (s, $-OCH_3$), 6.63 (s, C_4-H), and 7.03-8.15 (m, ArH)].

Anal. Calcd. for $C_{20}H_{16}Cl_2N_2O_3$: C, 59.57; H, 4.00; N, 6.95. Found: C, 59.54; H, 4.28; N, 6.77.

Phenacylpyrazole **11** probably resulted from the condensation of two molecules of dianion **2** (carbanion centers) with ethyl chloroformate, which was followed by cyclization to give the pyrazole and hydrolysis of the pendant carboethoxyhydrazone to the ketone.

The preparation of dilithiocarboalkoxyhydrazones **2**, and their reactions with electrophilic, nucleophilic-electrophilic reagents, and other reactants has suitable potential for development of new synthons beyond the preliminaries described here. Our work with other *C*(α)-anions (*e.g.* oximes, phenylhydrazones, *etc.*) during the past few years has only begun to show us the synthetic potential of these multiple-anion systems. The parallel for reaction of different but analogous *C*(α)-dianions with electrophilic reagents is not always there. For example, dilithiooximes can be prepared by treatment of oximes with *n*-butyllithium and carboxylated (CO_2) to give intermediates that can be acid-cyclized to 2-isoxazolin-5-ones [10]. 2-Pyrazolin-5-ones are prepared from phenylhydrazones by treatment with excess LDA, condensation with diethyl carbonate, and followed by acid-cyclization [11]. Phenylhydrazones metalated with excess LDA, condensed with salicylate esters, and followed by acid-cyclization resulted in *o*-hydroxyphenylpyrazoles [12], while carboalkoxyphenylhydrazones metalated with excess LDA, condensed with salicylate esters, and followed by acid cyclization lead to benzopyranopyrazoles.

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REFERENCES AND NOTES

[1] R. Braun and W. Dittmar, *Cancer Res.*, **38**, 3512 (1978).

[2] Varian Associates EM 360 L Nuclear Magnetic Resonance Spectrometer. Chemical shifts are reported in δ ppm downfield from an internal tetramethylsilane (TMS) standard.

[3] Robertson's Microanalytical Laboratory, 73 West End Avenue, Florham Park, New Jersey 07932.

[4] F. E. Henoch and C. R. Hauser, *Can. J. Chem.*, **47**, 157 (1969).

[5] C. F. Beam, R. S. Foote and C. R. Hauser, *J. Chem. Soc., C*, 1658 (1971).

[6] Isomer **7** may have resulted from an intramolecular cyclization of **2** to give an *N*-anion of a 5-pyrazoline. The *N*-anion may have been *N*-acylated by the carbomethoxy group of the salicylate, and the resulting intermediate, if formed, could have been cyclized to **7**. We have no evidence for such a reaction occurring under these conditions on related systems, and the mechanistic pathway does not seem very probable.

[7] Isomer **8** may have resulted for a Claisen-type *C*-acylation of the carbanion of **2** with the salicylate ester, which may have been followed by metalation of the resulting *C*(α)-methylene with excess LDA. This new intermediate may have undergone an intramolecular condensation with the carbomethoxy group and followed by subsequent cyclization to **8**. This mechanistic pathway also appears unlikely.

[8] Finnigan 3200 Mass Spectrometer, electron impact mode at 70 eV (Medical University of South Carolina).

[9] IBN-NR 80 multi-probe spectrometer (USC-Columbia).

[10] J. S. Griffiths, C. F. Beam and C. R. Hauser, *J. Chem. Soc., C*, 974 (1971).

[11] J. D. Wilson, T. D. Fulmer, L. P. Dasher and C. F. Beam, *J. Heterocyclic Chem.*, **17**, 389 (1980).

[12] M. J. Livingston, M. F. Chick, E. O. Shealy and C. F. Beam, *J. Heterocyclic Chem.*, **19**, 215 (1982).