The Preparation of Selected Benzopyrano[3,4-*b*]pyrazoles by the Condensation of *C*(α),*N*-Dilithiocarboalkoxyhydrazones and Salicylate Esters

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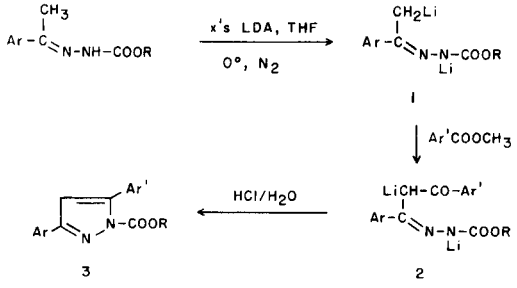
Received December 24, 1985

Selected *C*(α),*N*-dilithiocarboalkoxyhydrazones were prepared in an excess of lithium diisopropylamide (LDA) and condensed with a variety of salicylate esters to give intermediates that were acid-cyclized to benzopyrano[3,4-*b*]pyrazoles (coumarin-pyrazoles).

J. Heterocyclic Chem., **23**, 1343 (1986).

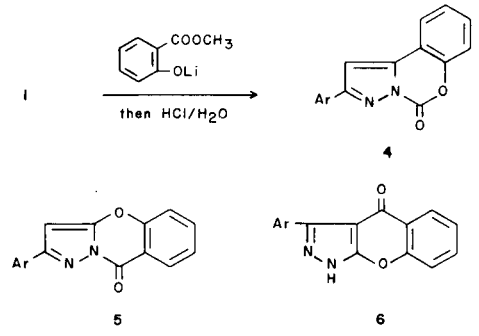
Introduction.

Recently, we reported a preliminary study dealing with the preparation and reactions of *C*(α),*N*-dilithiocarboalkoxyhydrazones **1** [1]. These dilithiated intermediates **1** were subsequently condensed regiospecifically with a variety of electrophilic compounds at the carbanion center. For example, **1**, prepared in an excess of lithium diisopropylamide (LDA), was condensed with aromatic esters to give presumed lithiated precyclization intermediates **2**, which could be easily cyclodehydrated with hydrochloric acid to *N*-carboalkoxypyrazoles **3** without extensive hydrolysis of the *N*-carboalkoxy pendant group [2].

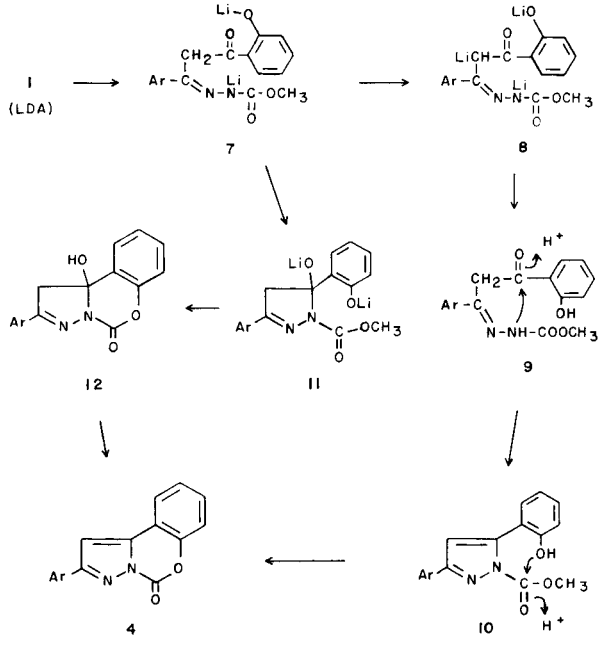


Results and Discussion.

Interestingly, **1**, also prepared in an excess of LDA, condensed with salicylate esters to give intermediates that cyclized to benzopyrano[3,4-*b*]pyrazoles, **4**, instead of unsymmetrical 3,5-disubstituted pyrazole, **3** (Ar' = *o*-HOC_6H_4-) [3]. The structure of **4** was established on the basis of absorption spectra and supported by combustion analysis and an acceptable mechanistic pathway, which together ruled out isomers **5** and **6** [1]. The main features of this assignment were the infrared absorption of the urethane-type carbonyl (> 1750 cm^{-1}), mass spectra: small ion fragments appearing to be loss of CO_2(M-44) for **4a** and **4c**, and most convincing C-13 nmr spectra for selected benzopyrano[3,4-*b*]pyrazoles **4a** and **4c** with chemical shifts at δ 158.1 and 158.0 ppm [4], which were assigned to the carbonyl urethane-type carbon (see footnote of Table).

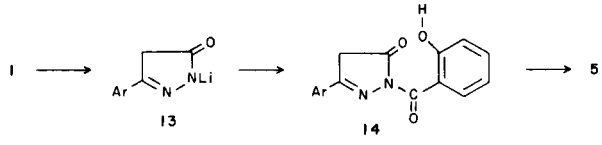


The mechanistic pathway can be illustrated by the following sequence of steps. Dilithiated carboalkoxyhydrazone **1**, in an excess of LDA, was treated with a methyl salicylate, which probably transformed this electrophilic reagent into a phenoxide (lithiated methyl salicylate) prior to condensation with the C(α)-anion. This condensation (Claisen-type) probably resulted in intermediate **7**, which

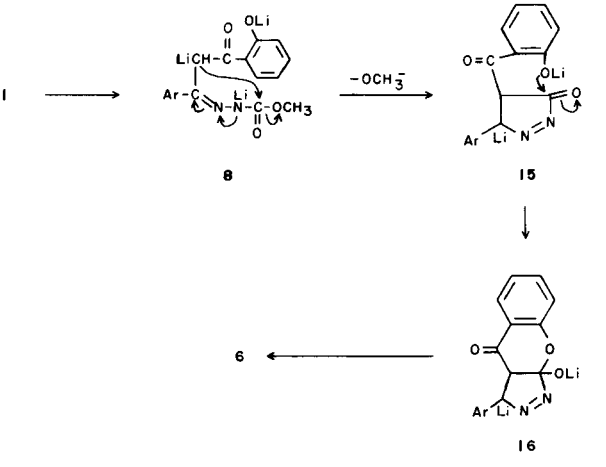


could react with excess LDA to give **8** [5]; **8**, upon treatment with aqueous acid could give **9**, which could cyclize to pyrazole **10**. Then, **10** could undergo cyclization to give product **4**; or the nitrogen anion of **7** could condense with the ketone to give alkoxy-pyrazoline **11**. Alternatively, **11** may have acid-cyclized to **12**, which upon linear dehydration would give benzopyranopyrazole **4**.

Isomer **5** would have resulted from an intramolecular cyclization of **1** to give an *N*-anion of 2-pyrazolin-5-one **13**; **13** would have been *N*-acylated by the carbomethoxy group of the salicylate, and the resulting intermediate **14**, if formed, could have been cyclized to **5**. We have no evidence for such reaction occurring under these conditions on related systems [6], and this mechanistic pathway does not seem very probable.



Isomer **6** would have resulted from a Claisen-type, *C*-acylation of the carbanion of **1** with the salicylate ester to intermediate **7**, which may have been followed by metalation of the resulting *C*(α)-methylene with excess LDA to intermediate **8**. This new intermediate, **8**, would have undergone an intramolecular condensation with the carbomethoxy group to give cyclized intermediate **15**, cyclization again of **15** to **16**, and linear dehydration of **16** to **6**. This mechanistic pathway also appears unlikely [7].



All of the fused-ring heterocyclic materials **4a-t** reported in this study are new. The yield of these compounds reported here varies from 8 to 90%. If a particular benzopyranopyrazole **4** is needed in a better yield, the parameters of condensation time and temperature can be adjusted, and this may result in improved yields [8].

The obvious strong feature of this synthesis is that carboalkoxyhydrazones are one easy synthetic step away from readily available and usually inexpensive *C*(α)-ketones [9], the synthetic procedure is readily reproducible by someone not necessarily familiar with strong-base synthesis techniques, and the fused-ring products are easily purified by recrystallization from routine solvents, hence other purification procedures (*e.g.*, vacuum sublimation, chromatography) are not necessary. While every benzopyranopyrazole **4a-t** reported in this study appears to be new, the basic three fused-rings (**4q-s** five fused-rings), for benzopyrano[3,4-*b*]pyrazoles also have not been reported earlier than our preliminary study [1]. Other investigators have recently developed synthons, or studied isomeric or similar benzopyranopyrazoles (*e.g.*, benzo[4,3-*c*]pyrazoles) or related fused-ring heterocyclic molecules [10-19].

EXPERIMENTAL

Tetrahydrofuran (THF) was distilled from sodium (benzophenone) immediately before use. Carboalkoxyhydrazones were prepared by simple modification of standard procedure [9] which involved heating an alcohol solution of equimolar quantities of *C*(α)-ketone and methyl (or ethyl) carbazate plus a small amount of glacial acetic acid. These materials could be readily recrystallized from methanol (or ethanol for ethyl esters), air dried, and subsequently dried in a vacuum desiccator. Nuclear magnetic resonance spectra were obtained with a Varian Associates EM 360L NMR Spectrometer, and absorptions were reported in δ ppm downfield from an internal tetramethylsilane (TMS) standard. Infrared spectra were obtained with a Perkin-Elmer 710 B or 267 Spectrometer. Melting points were obtained in a Mel-Temp melting point apparatus in open capillary tubes and are uncorrected. Combustion analyses were performed by Robertson's Microanalytical Laboratory, 73 West End Avenue, Florham Park, NJ 07932. *n*-Butyllithium was purchased from the Lithium Corporation of America, Bessemer City, NC 28016.

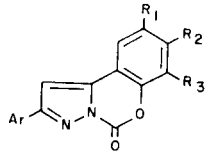
Mass spectra were obtained in the Mass Spectral Laboratory, Department of Pharmacology, at the Medical University of South Carolina (MUSC), Charleston, SC 29425, on a Finnigan 3200 Mass Spectrometer, electron impact mode at 70 eV. Carbon-13 nmr spectra were obtained at the University of South Carolina - Columbia on an IBN-NR 80 multiprobe spectrometer.

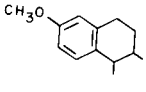
Benzopyrano[3,4-*b*]pyrazoles.

A 0.044-mole sample of *n*-butyllithium (*ca.* 1.6 *M*) was added to an oven dried three-necked (or two-necked) 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 35-40 ml of dry tetrahydrofuran (THF) was added at fast dropwise rate to the stirred *n*-butyllithium solution. The resulting lithium diisopropylamide (LDA) was stirred at 0° for an additional 20-30 minutes before adding, during 5-7 minutes, a 0.010-mole sample of *C*(α)-carboalkoxyhydrazone dissolved in 50 ml of THF [20]. The metalation was continued for *ca.* 60 minutes at 0°. A 0.011-mole sample of salicylate ester dissolved in 30-40 ml of THF was then added during 5 minutes, and the condensation was allowed to proceed with stirring at 0° for an additional 2 hr. If precipitation occurred after ester addition, an additional 80-100 ml of dry THF was added, and the stirring was extended an additional 30 min. Neutralization was accomplished by directly adding 100 ml of 3*N* hydrochloric acid at room temperature, which was followed by heating the stirred two-phase mixture under reflux for 60 minutes. If precipitation occurred after adding acid, and additional 100 ml of solvent grade THF was added to the mixture prior to heating. At the end of the reflux period, the mixture was cooled and poured into a large flask (1 or 2 liter) containing ice. The mix-

Table

Benzopyrano[3,4-*b*]pyrazoles and Related Materials



Compound No.	Ar	R_1	R_2	R_3	Empirical Formula	Yield (%)	Melting Point (°C)	Elemental Analysis Calcd./(Found) C	H	N	Infrared (C=O) cm^{-1}	NMR (δ ppm) (Solvent)
4a	C_6H_5	H	H	H	$C_{16}H_{10}N_2O_2$	35	198-202 [b]	73.27 (73.19)	3.84 (3.79)	10.68 (10.71)	1775 [j]	(deuteriochloroform/trifluoroacetic acid): 7.30-8.22 (m, ArH and C_4-H) [f] [h]
4b	4-ClC_6H_4	H	H	H	$C_{16}H_9ClN_2O_2$	46	257-259 [c]	64.77 (64.90)	3.05 (3.41)	9.44 (9.57)	1805 [j]	(trifluoroacetic acid): 7.50-8.23 (m, ArH and C_4-H)
4c	4-$CH_3C_6H_4$	H	OCH_3	H	$C_{18}H_{14}N_2O_3$	55	195-197 [b]	70.58 (70.61)	4.61 (4.76)	9.15 (9.14)	1750 [j]	(trifluoroacetic acid): 2.48 (s, $ArCH_3$), 4.07 (s, $ArOCH_3$), 7.13-8.17 (m, ArH, and C_4-H) [g] [i] [4]
4d	4-$CH_3OC_6H_4$	H	H	H	$C_{17}H_{12}N_2O_3$	55	220-223 [d]	69.86 (69.82)	4.14 (4.04)	9.58 (9.36)	1760 [k]	(deuteriochloroform/trifluoroacetic acid): 4.03 (s, $ArOCH_3$) and 7.10-8.25 (m, ArH and C_4-H)
4e	C_6H_5	H	OCH_3	H	$C_{17}H_{12}N_2O_3$	30	169-170 [b]	69.86 (69.73)	4.14 (4.31)	9.58 (9.42)	1760 [j]	(deuteriochloroform/trifluoroacetic acid): 4.08 (s, $ArOCH_3$), and 7.20-8.05 (m, ArH and C_4-H)
4f	2-ClC_6H_4	H	OCH_3	H	$C_{17}H_{11}ClN_2O_3$	37	177-179 [c]	62.49 (62.48)	3.39 (3.35)	8.57 (8.75)	1792 [k]	(trifluoroacetic acid): 4.03 (s, $ArOCH_3$), 7.07-8.05 (m, ArH and C_4-H)
4g	4-BrC_6H_4	H	OCH_3	H	$C_{17}H_{11}BrNO_3$	32	214-215 [c]	55.01 (54.87)	2.99 (2.84)	7.55 (7.80)	1780 [k]	(deuteriochloroform): 4.08 (s, $ArOCH_3$), 7.12-8.13 (m, ArH and C_4-H)
4h	2-HOC_6H_4	H	OCH_3	H	$C_{17}H_{12}N_2O_4$	36	240-244 [c]	66.23 (66.53)	3.92 (4.03)	9.09 (8.99)	1760 [k]	(trifluoroacetic acid): 4.00 (s, $ArOCH_3$), 7.02-8.02 (m, ArH and C_4-H)
4i	2,3-di-(CH_3O)-C_6H_3	H	H	H	$C_{18}H_{13}N_2O_4$	56	230-232 [c]	60.60 (60.88)	3.67 (3.76)	7.85 (7.75)	1780 [k]	(trifluoroacetic acid): 4.02 (s, $ArOCH_3$), 7.03-7.97 (m, ArH and C_4-H)
4j	2-$CH_3OC_6H_4$	H	H	H	$C_{17}H_{12}N_2O_3$	30	214-216 [c]	69.86 (70.03)	4.14 (4.12)	9.58 (9.57)	1770 [k]	(trifluoroacetic acid): 4.20 (s, $ArOCH_3$), 7.15-8.27 (m, ArH and C_4-H)
4k	2-naphthyl	H	H	H	$C_{20}H_{12}N_2O_2$	40	258-261 [c]	76.91 (77.11)	3.87 (3.93)	8.97 (8.83)	1790 [k]	(trifluoroacetic acid): 6.67-8.07 (naphthyl, ArH and C_4-H)
4l	4-$CH_3OC_6H_4$	H [CH_3-C_4(pyrazole)]	H	H	$C_{18}H_{14}N_2O_3$	21	211-213 [b]	70.58 (70.29)	4.61 (4.44)	9.15 (9.21)	1760 [k]	(trifluoroacetic acid): 2.73 (s, C_4-CH_3), 4.03 (s, $ArOCH_3$), and 7.17-8.47 (m, ArH)
4m	4-ClC_6H_4	Br	H	H	$C_{16}H_8BrClN_2O_2$	19	278-281 [c]	51.16 (51.04)	2.15 (2.16)	7.46 (7.21)	1770 [k]	(deuteriochloroform/trifluoroacetic acid): 7.33-8.17 (m, ArH and C_4-H)
4n	4-FC_6H_4	H	H	H	$C_{16}H_9FN_2O_2$	35	194-197 [b]	68.57 (68.49)	3.24 (3.41)	10.00 (9.88)	1795 [k]	(deuteriochloroform/trifluoroacetic acid): 7.08-8.25 (m, ArH and C_4-H (7.13))
4o	4-CH_3CH_2-C_6H_4-	H	H	H	$C_{18}H_{14}N_2O_2$	86	160-162 [b]	74.47 (74.38)	4.86 (4.95)	9.65 (9.78)	1780 [k]	(deuteriochloroform): 1.32 (t, CH_3), 2.65 (q, CH_2), and 6.97-8.03 (m, ArH and C_4-H)
4p	4-CH_3CH_2-C_6H_4	H	OCH_3	H	$C_{19}H_{16}N_2O_3$	8	168-170 [d]	71.24 (70.99)	5.03 (4.92)	8.74 (8.74)	1765 [k]	(deuteriochloroform): 1.25 (t, CH_3), 2.67 (q, CH_2), 3.87 (s, $ArOCH_3$), 6.73-8.03 (m, ArH and C_4-H)
4	 [a]	H	CH_3	H	$C_{19}H_{14}N_2O_2$	83	269-271 [c]	75.48 (75.19)	4.67 (4.66)	9.27 (9.23)	1750 [k]	(trifluoroacetic acid): 2.63 (s, $ArCH_3$), 3.40 (s, -CH_2CH_2-[l]), and 7.36-7.83/7.93-8.40 (m, ArH)
4r	 [a]	H	H	H	$C_{19}H_{14}N_2O_3$	61	308-312 [e]	71.69 (71.66)	4.43 (4.66)	8.80 (8.82)	1767 [k]	(deuteriochloroform/trifluoroacetic acid): 3.33 (m, -CH_2CH_2-[l]), 4.00 (s, $ArOCH_3$), and 6.97-7.33/7.50-8.33 (m, ArH)
4s	 [a]	H	H	H	$C_{18}H_{12}N_2O_2$	90	303-305 [c]	74.99 (74.97)	4.20 (4.35)	9.72 (9.62)	1780 [j]	(trifluoroacetic acid): 3.40 (s, -CH_2CH_2-[l]), and 7.37-8.40 (m, ArH)
4t	Aliphatic 3,4-pyrazole -$(CH_2)_{10}$-[a]	H	H	H	$C_{20}H_{24}N_2O_2$	26	211-213 [c]	74.04 (74.22)	7.46 (7.53)	8.63 (8.60)	1770 [k]	(deuteriochloroform/trifluoroacetic acid): 1.00-2.42 and 3.17-3.33 (m, -$(CH_2)_{10}$) and 7.53-8.43 (m, ArH)

[a] Entry compounds are the carbomethoxyhydrazones of 1-tetralone (for **4q** and **4s**) and 6-methoxy-1-tetralone (for **4r**) and cyclodecanone (for **4t**). [b] Recrystallized from xylenes. [c] Recrystallized from xylenes/dimethylformamide. [d] Recrystallized from benzene/dimethylformamide. [e] Recrystallized from methanol/dimethylformamide. [f] C-13 nmr, benzopyranopyrazole **4a**, (deuteriochloroform): 158.0 (0-CO-N), 148.8, 142.0, 140.7, 131.3, 130.7, 129.8, 128.7, 126.8, 125.8, 123.8, 117.0, 112.5 and 99.8 ppm. [g] C-13 nmr, benzopyranopyrazole **4c** (deuteriochloroform): 162.1, 158.1 (O-CO-N), 150.2, 142.3, 140.8, 139.9, 129.4, 128.1, 126.7, 124.7, 113.4, 105.5, 101.2, 98.2, 55.8, and 21.3 ppm [h] ms: for **4a**, m/e (% relative intensity) 262 M (19), 218 (M - CO_2), 205 (< 1), 189 (22), 176 (4), 163 (13), 159 (79), 151 (12), 150 (11), 139 (12), 131 (23), 115 (68), 109 (30), 103 (85), 94 (65), 88 (38), 77 (100), 63 (58), and 51 (78). [i] ms: for **4c** 306 M (100), 291 (4), 263 (9), 262 (M - CO_2), 233 (30), 219 (20), 203 (8), 189 (64), 176 (25), 174 (28), 165 (13), 163 (14), 153 (18), 145 (15), 139 (12), 133 (11), 130 (32), 116 (21), 115 (21), 106 (38), 102 (24), 91 (98), 75 (25), 65 (32), 63 (30), and 51 (21). [j] Potassium bromide pellet. [k] Nujol mull. [l] Isochronous absorption.

ture was neutralized with excess solid sodium bicarbonate, and the aqueous and organic layers separated. The aqueous layer was extracted with three, 75-ml portions of ethyl ether, or 50 ml of THF if there was any insoluble organic material present. The ether extracts and organic phase were combined, dried with anhydrous magnesium sulfate (drying omitted if solid material still present) and concentrated (rotoevaporator). The oil or solid residue was crystallized and recrystallized from solvent or solvents indicated in the footnote of the Table.

Acknowledgements.

This project was supported at the College of Charleston (in part) by a grant from the Donors of the Petroleum Research Fund, administered by the American Chemical Society, (in part) by a grant awarded by the Cottrell Science Program of the Research Corporation, and (in part) by a grant awarded by the American Heart Association-South Carolina Affiliate.

We are indebted to Dr. J. James Vrbanac for mass spectra. We are also indebted to Ms. Tammy Fulmer, a graduate student in the Department of Chemistry, USC-Columbia, for C-13 nmr spectra. Ms. Rebecca Tummons, a medical student at MUSC, participated in the preliminary investigation [1].

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[2] Hydrolysis of the *N*-carboalkoxy group would result in the *N*-carboxylic acid which would decarboxylate to the N-H pyrazole. See: C. F. Beam, R. S. Foote, and C. R. Hauser, *J. Chem. Soc.*, C, 1658 (1971).

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[4] The chemical shift, δ 162.1 ppm (footnote [g] of Table) was assigned to the 8-methoxyphenyl carbon (C-OCH_3). The carbonyl carbon absorptions for isomers **5** and **6** would probably appear at chemical shifts greater than δ 165 ppm.

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[7] While diacylations cannot be entirely ruled out, the nucleophilicity of this lithiated *N*-carbomethoxy group would be diminished. Also, our experience has shown us that diacylations proceed better with stronger electrophiles, such as carboxylic acid chlorides. See: C. F. Beam, D. C. Reames, C. E. Harris, L. W. Dasher, W. M. Hollinger, N. L. Shealy, R. M. Sandifer, M. Perkins, and C. R. Hauser, *J. Org. Chem.*, **40**, 514 (1975).

[8] Most of our strong-base procedures give products that fall into one of three categories: low (I - *ca.* 20%), fair (II - *ca.* 50%) and good (III -*ca.* 80%). If a particular compound is needed in a better yield than those of categories I or II, the parameters of condensation time (usually longer than 2 hours at 0°) and temperature can be adjusted (from Dry Ice-acetone to room temperature), and this may result in improved yields.

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[20] Less soluble carboalkoxyhydrazones were added directly to the stirred mixture in addition to 50 ml of dry THF.