Reactivity of Pyrazolo[4,3-*c*][1,2,5]oxadiazin-3(5*H*)-ones toward *C*-Nucleophiles: Synthesis of Pyrazolo[3,4-*b*]pyrazines

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The reaction of pyrazolo[4,3-*c*][1,2,5]oxadiazin-3(5*H*)-ones **1** with carbanions prepared *in situ* from compounds containing an activated methylene group afforded pyrazolo[3,4-*b*]pyrazines **4-13** in good yields. The possible reaction mechanism is proposed and discussed.

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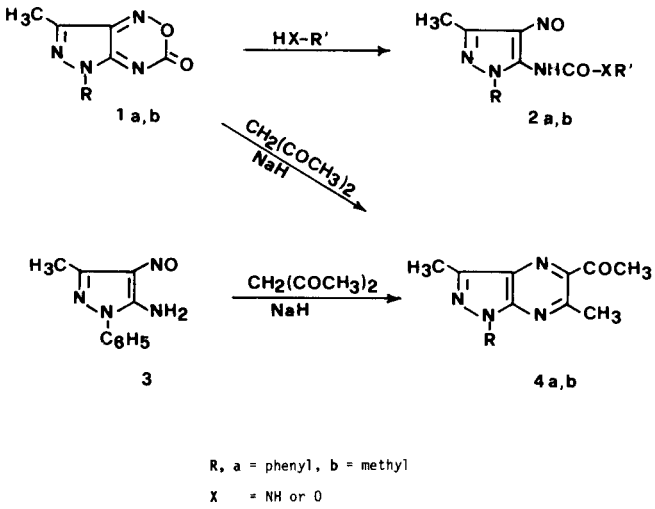
During our search for biologically active heterocyclic compounds, we found that pyrazolo[4,3-*c*][1,2,5]oxadiazin-3-(5H)-ones **1** readily react with amines and alcohols [1-4] to give the ring opened products **2** (Scheme 1). Since **1** showed high reactivity toward these nucleophiles, it seemed interesting to investigate the behaviour of **1** toward *C*-nucleophiles, in particular carbanions derived from compounds containing an activated methylene group. As a first exploratory investigation, a solution of **1a** in anhydrous tetrahydrofuran was treated with acetylacetone in the presence of sodium hydride. Within 15 minutes the red color of the starting material **1a** disappeared; at the same time carbon dioxide evolved from the reaction mixture. The resulting precipitate was characterized as 1-phenyl-3,6-dimethyl-5-acetylpyrazolo[3,4-*b*]pyrazine **4a**. The structure of **4a** was inferred from correct elemental analysis and spectral data; moreover a low yield of **4a** was obtained by an alternative synthesis, based on the condensation of 1-phenyl-3-methyl-4-nitroso-5-aminopyrazole **3** [5] with acetylacetone. Pyrazolooxadiazinone **1b** reacted with acetylacetone under the same conditions giving the analogous 5-acetylpyrazolopyrazine **4b**.

Scheme 1



R, a = phenyl, b = methyl

X = NH or O

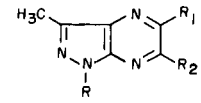
These results prompted us to investigate the reactivity of **1** toward a series of carbanions, that were directly prepared *in situ* by the action of sodium hydride on β-diketones, β-diesters, malononitrile, β-ketoamides and β-ketoesters. In all cases the first findings were confirmed and pyrazolopyrazines **4-13** were recovered in good to excellent yields (Tables 1,2). In particular, a single reaction product was recovered in the reaction of **1** with β-diketones, that afforded 5-acylpyrazolopyrazines **4,5**; with β-diesters that gave 5-alkoxycarbonyl-6-hydroxpyrazolopyrazines **6,7**; with malononitrile that led to 5-cyano-6-aminopyrazolopyrazines **8** and with β-ketoamides that produced 5-*N*-substituted-carboxamidopyrazolopyrazines **9,10**. Two reaction products were recovered with ketoesters: methyl acetoacetate gave a mixture of 5-methoxycarbonyl-6-methylpyrazolopyrazine **11** and 5-acetyl-6-hydroxypyrazolopyrazine **13**; ethylacetoacetate yielded an analogous mixture of 5-ethoxycarbonyl-6-methylpyrazolopyrazine **12** and of compound **13**.

The possible mechanism explaining the formation of pyrazolopyrazines is speculated as follows (Scheme 2). The carbanion attacks the 1-nitrogen atom of pyrazolooxadiazinone **1** with cleavage of the N-O bond and formation of the unstable ring opened intermediate **14**. The successive intramolecular nucleophilic attack by nitrogen of carboxyimine function at carbonyl group leads to cyclic **4**, with loss of carbon dioxide. As a general rule, when the carbanion is symmetrical, a single reaction product must be expected, as found for β-diketones, β-diesters and malononitrile. When the carbanion is unsymmetrical the attack of nitrogen is directed toward the more electrophilic carbon. Thus β-ketoamides, containing a more electrophilic keto group afforded a single reaction product while β-ketoesters containing two competitive electrophilic carbons gave two kinds of products, one deriving from the attack at keto group (compounds **11,12**), the second (compounds **13**) from the attack at ester function with displacement of alkoxy group.

The yield of **13** was lower to that of **11** and **12**, due to the prevalent attack at more electrophilic carbonyl carbon. In all the experiments performed, the reaction rate was too

Table 1

Pyrazolo[3,4-*b*]pyrazines **4-13a,b**



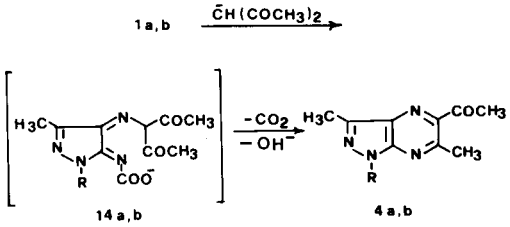
Compound	[a]	R	R_1	R_2	Yield %	Mp °C [b]	Analysis % Calcd./Found C	H	N
4a	A	C_6H_5	$COCH_3$	CH_3	96	135-136	67.64	5.30	21.04
							67.40	5.33	21.05
4b	A	CH_3	$COCH_3$	CH_3	93	137-138	58.80	5.92	27.43
							58.78	5.91	27.37
5a	B	C_6H_5	COC_6H_5	C_6H_5	96	201-202	76.90	4.65	14.35
							76.93	4.60	14.44
5b	B	CH_3	COC_6H_5	C_6H_5	85	175-176	73.17	4.91	17.06
							73.02	4.87	16.99
6a	C	C_6H_5	$COOCH_3$	OH	88	196-197	59.15	4.25	19.70
							58.80	4.18	19.91
6b	C	CH_3	$COOCH_3$	OH	81	195-196	48.64	4.53	25.21
							48.36	4.49	25.06
7a	D	C_6H_5	$COOC_2H_5$	OH	86	153-154	60.39	4.73	18.78
							60.08	4.64	18.79
7b	D	CH_3	$COOC_2H_5$	OH	80	165-166	50.84	5.12	23.71
							50.56	5.05	23.90
8a	E	C_6H_5	CN	NH_2	98	230-231	62.39	4.02	33.58
							62.10	3.99	33.42
8b	E	CH_3	CN	NH_2	87	243-244	51.05	4.30	44.65
							51.38	4.33	44.85
9a	F	C_6H_5	$CONHC_6H_5$	CH_3	97	197-198	69.95	4.99	20.40
							69.79	5.07	20.64
9b	F	CH_3	$CONHC_6H_5$	CH_3	98	137-138	64.04	5.37	24.89
							64.06	5.40	25.07
10a	G	C_6H_5	$CONHCH_2C_6H_5$	CH_3	80	159-160	70.55	5.36	19.59
							70.52	5.40	19.65
10b	G	CH_3	$CONHCH_2C_6H_5$	CH_3	80	127-128	65.06	5.80	23.71
							65.35	5.85	23.60
11a	H	C_6H_5	$COOCH_3$	CH_3	61	119-120	63.82	4.99	19.84
							63.91	5.01	19.82
11b	H	CH_3	$COOCH_3$	CH_3	54	127-128	54.50	5.49	25.44
							54.52	5.48	25.47
12a	I	C_6H_5	$COOC_2H_5$	CH_3	62	104-106	64.85	5.44	18.90
							64.56	5.35	19.03
12b	I	CH_3	$COOC_2H_5$	CH_3	57	110-111	56.39	6.02	23.91
							56.35	5.98	23.82
13a	H or I	C_6H_5	$COCH_3$	OH	32	178-179	62.67	4.51	20.88
							62.48	4.50	20.80
13b	H or I	CH_3	$COCH_3$	OH	28	149-150	52.41	4.85	27.17
							52.08	4.79	26.93

[a] Activated methylene derivatives reacted with **1a,b**: A = acetylacetone; B = dibenzoylmethane; C = dimethyl malonate; D = diethyl malonate; E = malononitrile; F = acetoacetanilide; G = *N*-benzylacetoacetamide; H = methyl acetoacetate; I = ethyl acetoacetate. [b] Crystallisation solvent = ethanol.

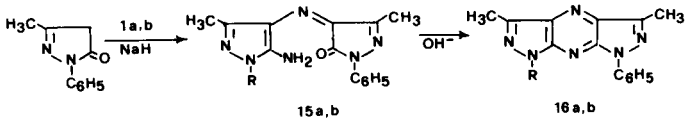
fast to allow the isolation of any intermediate; however when **1** was reacted with 1-phenyl-3-methyl-5-pyrazolone under the usual conditions, the relative intermediates **15a,b** could be isolated as red stable products (Scheme 3).

Compounds **15**, when refluxed in sodium hydroxide, yielded quantitatively the known dipyrazolo[3,4-*b*:4′,3′-*e*]-pyrazines **16** [6]. The structure of **15** is responsible for the initial attack of 5-pyrazolone carbanion at 1-nitrogen of pyrazolooxadiazinone.

Scheme 2



Scheme 3



In conclusion, the pyrazolooxadiazinone system **1** is very reactive toward nucleophiles, according to the reported literature on polyheteroatom six-membered rings [7]. "Hard" nucleophiles such as amines and alcohols preferentially attack the carbonyl sp^2 carbon to give pyrazole derivatives **2** while "soft" nucleophiles attack 1-nitrogen and lead to pyrazolo[3,4-*b*]pyrazines. In these latter reactions the 1-nitrogen atom, bonded to oxygen, exhibits the typical reactivity of a dipolar nitroso function and it becomes the preferential site of attack by the negative charged carbanion. The present method for preparing pyrazolo[3,4-*b*]pyrazines 5/6 functionalized appears of convenient applicability and involves the use of easily available starting materials **1**, that are obtained by reacting the pertinent 4-nitroso-5-aminopyrazoles with trichloromethyl chloroformate.

Table 2

IR, ^{1}H-NMR Spectral Data of Compounds **4-13**

Compound	IR (cm^{-1}) [a]	^{1}H-NMR (δ) [b]
4a	1690, 1600, 1545, 1515	2.73 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 2.98 (s, 3H, CH_3), 7.3-7.7 (m, 3H, ArH) 8.25-8.35 (m, 2H, ArH)
4b	1690, 1570, 1540, 1520	2.65 (s, 3H, CH_3), 2.75 (s, 3H, CH_3), 2.98 (s, 3H, CH_3), 4.05 (s, 3H, CH_3N)
5a	1675, 1600, 1540, 1505	2.75 (s, 3H, CH_3), 7.3-8.0 (m, 13H, ArH), 8.4-8.5 (m, 2H, ArH)
5b	1665, 1595, 1560, 1540	2.67 (s, 3H, CH_3), 4.17 (s, 3H, CH_3N), 7.3-8.0 (m, 10H, ArH)
6a	3050 (br), 1675, 1560, 1490	2.71 (s, 3H, CH_3), 4.12 (s, 3H, CH_3O), 7.2-7.6 (m, 3H, ArH), 8.2-8.3 (m, 2H, ArH), 12.00 (br, 1H, OH, deuterium oxide exchangeable)
6b	3050 (br), 1675, 1580, 1500	2.65 (s, 3H, CH_3), 4.0 (s, 3H, CH_3N), 4.12 (s, 3H, CH_3O), 11.9 (s, 1H, OH, deuterium oxide exchangeable)
7a	3130 (br), 1685, 1570, 1500	1.52 (t, J = 8 Hz, 3H, CH_3), 2.72 (s, 3H, CH_3), 4.52 (q, J = 8 Hz, CH_2), 7.35-7.60 (m, 3H, ArH), 8.2-8.3 (m, 2H, ArH), 12.1 (s, 1H, OH, deuterium oxide exchangeable)
7b	3100 (br), 1670, 1590, 1460	1.55 (t, J = 8 Hz, 3H, CH_3), 2.65 (s, 3H, CH_3), 3.98 (s, 3H, CH_3N), 4.62 (q, J = 8 Hz, 2H, CH_2), 12.1 (br, 1H, OH, deuterium oxide exchangeable)
8a	3460, 3360, 3240, 2240, 1640, 1550, 1520	(hexadeuteriodimethylsulfoxide) 2.55 (s, 3H, CH_3), 7.0 (br, 2H, NH_2, deuterium oxide exchangeable), 7.6-7.3 (m, 3H, ArH), 8.1-8.2 (m, 2H, ArH)
8b	3410, 3320, 3160, 2240, 1660, 1580, 1540	(hexadeuteriodimethylsulfoxide) 2.47 (s, 3H, CH_3), 3.82 (s, 3H, CH_3N),7.10 (br, 2H, NH_2, deuterium oxide exchangeable)
9a	3340, 1690, 1530, 1510	2.74 (s, 3H, CH_3), 3.17 (s, 3H, CH_3), 7.3-7.8 (m, 8H, ArH), 8.2-8.4 (m, 2H, ArH), 9.75 (br, 1H, NH, deuterium oxide exchangeable)
9b	3340, 1680, 1525 (br), 1430	2.68 (s, 3H, CH_3), 3.15 (s, 3H, CH_3), 4.10 (s, 3H, CH_3N), 7.2-7.8 (m, 5H, ArH), 9.8 (br, 1H, NH, deuterium oxide exchangeable)
10a	3400, 1665, 1555, 1520	2.68 (s, 3H, CH_3), 3.16 (s, 3H, CH_3), 4.62 (d, J = 6 Hz, 2H, CH_2), 7.3-7.6 (m, 8H, ArH), 8.15-8.30 (m, 2H, ArH), 8.3 (br, 1H, NH, deuterium oxide exchangeable)
10b	3360, 1655, 1520 (v.br)	2.62 (s, 3H, CH_3), 3.15 (s, 3H, CH_3), 4.09 (s, 3H, CH_3N), 4.72 (d, J = 6 Hz, 2H, CH_2), 7.3-7.6 (m, 5H, ArH), 8.3 (br, 1H, NH, deuterium oxide exchangeable)
11a	1730, 1550, 1515	2.75 (s, 3H, CH_3), 2.98 (s, 3H, CH_3), 4.03 (s, 3H, CH_3O), 7.3-7.6 (m, 3H, ArH), 8.2-8.4 (m, 2H, ArH)
11b	1725, 1575, 1550	2.65 (s, 3H, CH_3), 2.90 (s, 3H, CH_3), 4.0 (s, 3H, CH_3N), 4.05 (s, 3H, CH_3O)
12a	1715, 1550, 1515	1.48 (t, J = 8 Hz, 3H, CH_3), 2.75 (s, 3H, CH_3), 2.95 (s, 3H, CH_3), 4.52 (q, J = 8 Hz, 2H, CH_2), 7.3-7.6 (m, 3H, ArH), 8.2-8.35 (m, 2H, ArH)
12b	1720, 1575, 1550, 1520	1.48 (t, J = 8 Hz, 3H CH_3), 2.68 (s, 3H, CH_3), 2.90 (s, 3H, CH_3), 4.07 (s, 3H, CH_3), 4,54 (q, J = 8 Hz, 2H, CH_2)
13a	1660, 1595, 1560, 1520, 1500	2.68 (s, 3H, CH_3), 2.85 (s, 3H, CH_3), 7.3-7.7 (m, 3H, ArH), 8.2-8.35 (m, 2H, ArH), 12.9 (br, 1H, OH, deuterium oxide exchangeable)
13b	1655, 1590, 1385, 1200	2.62 (s, 3H, CH_3), 2.85 (s, 3H, CH_3), 4.0 (s, 3H, CH_3N), 12.9 (s, 1H, OH, deuterium oxide exchangeable)

[a] Potassium bromide. [b] Deuteriochloroform was used as the solvent, unless otherwise noted.

EXPERIMENTAL

Melting points were determined with a Büchi capillary apparatus and are uncorrected. The ir spectra were recorded with a Hitachi-Perkin 157 G spectrometer using potassium bromide pellets. The ^{1}H-nmr spectra were recorded on a Perkin-Elmer spectrometer R 32 (90 MHz); chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane as the internal standard.

5-Phenyl-7-methylpyrazolo[4,3-*c*][1,2,5]oxadiazin-3(5*H*)-one (**1a**).

Trichloromethyl chloroformate (1.32 ml, 11 mmoles) was added to a suspension of 1-phenyl-3-methyl-4-nitroso-5-aminopyrazole (2.02 g, 10 mmoles) [5] in anhydrous tetrahydrofuran (100 ml). After being stirred for 30 minutes at room temperature, the solution was evaporated to dryness and the red residue was crystallized from chloroform-light petroleum to give 2.14 g (94%) of **1a**, mp 161-162°, lit [3] 160-162°; ir (potassium bromide): 1780, 1640, 1600, 1500, 1450 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.6 (s, CH_3, 3H), 7.4-8.1 (m, aromatic, 5H).

5,7-Dimethylpyrazolo[4,3-*c*][1,2,5]oxadiazin-3(5*H*)-one (**1b**).

This compound was prepared as above, starting from 1,3-dimethyl-4-nitroso-5-aminopyrazole [8], yield 96%, mp 167-169°, lit [2] 167-170°; ir (potassium bromide): 1760, 1640, 1620, 1510, 1440 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.4 (s, CH_3, 3H), 3.1 (s, CH_3, 3H).

General Procedure for Pyrazolo[3,4-*b*]pyrazines **4-13**.

A solution of **1** (10 mmoles) and of the pertinent reagent (11 mmoles) in anhydrous tetrahydrofuran (70 ml), kept under stirring at room temperature, was treated with a 55% sodium hydride dispersion (0.5 g, 11 mmoles). After the reaction was completed (within 15-30 minutes, as ascertained by tlc), the solvent was evaporated. The residue was treated with water (50 ml) and acidified with hydrochloric acid. The resulting precipitate was collected and washed with water; it appeared to be pure by tlc. Analytical and spectral data are recorded in Tables 1,2.

Reaction of **1** with Ketoesters: **1a** with Methyl Acetoacetate.

A 55% sodium hydride dispersion (0.5 g, 11 mmoles) was added to a solution of **1a** (2.28 g, 10 mmoles) and methyl acetoacetate (1.18 ml, 11 mmoles) in anhydrous tetrahydrofuran (50 ml). After being stirred for 30 minutes, the suspension was acidified with acetic acid and the solvents were evaporated. The residue was submitted to column flash chromatography [9] (liquid phase: dichloromethane) giving two peaks. The fractions corresponding to the less polar peak were evaporated and the residue was characterized as 1-phenyl-3-methyl-5-acetyl-6-hydroxypyrazolo-[3,4-*b*]pyrazine **13a**, yield 0.86 g, (32%), mp 178-179° (ethanol); ir (potassium bromide): 1665, 1595, 1560 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.68 (s, CH_3, 3H), 2.85 (s, CH_3, 3H), 7.3-7.7 (m, aromatic, 3H), 8.2-8.35 (m, aromatric, 2H), 12.9 (OH, 1H, deuterium oxide exchangeable).

The fractions corresponding to the more polar peak were evaporated and the residue was characterized as 1-phenyl-3,6-dimethyl-5-methoxycarbonylpyrazolo[3,4-*b*]pyrazine **11a**, yield 1.72 g, (61%), mp 119-120° (ethanol); ir (potassium bromide): 1730, 1600, 1550, 1435, 1240 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.75 (s, CH_3, 3H), 2.98 (s, CH_3, 3H), 4.03 (s, CH_3, 3H), 7.3-7.6 (m, aromatic, 3H), 8.2-8.35 (m, aromatic, 2H).

Following the above described procedure, the pairs of products **11b-13b**, **12a-13a** and **12b-13b** were prepared and separated (Tables 1, 2).

Reaction of **1** with 1-Phenyl-3-methyl-5-pyrazolone: Synthesis of Compounds **15**.

A 55% sodium hydride dispersion (0.32 g, 7 mmoles) was added to a solution of **1a** (1.14 g, 5 mmoles) and of 1-phenyl-3-methyl-5-pyrazolone (1.32 g, 6 mmoles) in anhydrous tetrahydrofuran (40 ml).

After being stirred for 60 minutes, the suspension was acidified with hydrochloric acid and the resulting red precipitate was collected and washed with water. It was dried *in vacuo* over phosphorus pentoxide and crystallized from ligroin, yield 1.64 g, (88%), mp 156-158°; ir (potassium bromide): 3490, 1720, 1690, 1560, 1520. 1490 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.22 (s, CH_3, 3H), 2.8 (s, CH_3, 3H), 7.15-8.1 (m, aromatic, 10H), 7.5 (s, NH_2, 2H, deuterium oxide exchangeable).

Anal. Calcd. for $C_{20}H_{18}N_6O$: C, 67.04; H, 5.06 ; N, 23.44. Found: C, 67.20; H, 5.06; N, 23.32.

Compound **15b** was prepared as above, starting from **1b**, yield 1.33 g (92%), mp 210-212° (ligroin); ir (potassium bromide): 3280, 1650, 1610, 1590, 1500 cm^{-1}; ^{1}H-nmr (hexadeuteriodimethylsulfoxide): δ 2.2 (s, CH_3, 3H), 2.8 (s, CH_3, 3H), 7.4-8.1 (m, aromatic, 5H); 8.6 (s, NH_2, 2H, deuterium oxide exchangeable).

Anal. Calcd. for $C_{15}H_{16}N_6O$: C, 60.79; H, 5.44;N, 28.35. Found C, 60.65; H, 5.53; N, 28.17.

Synthesis of Compounds **16**.

1,7-Diphenyl-3,5-dimethyldipyrazolo[3,4-*b*:4',3'-*e*]pyrazine (**16a**).

A suspension of **15a** (1.17 g, 5 mmoles) in 0.4% sodium hydroxide (50 ml) was heated under reflux for 20 minutes. The color of the mixture changed from dark red to dark orange. Chilling of the reaction mixture in ice caused the complete separation of a precipitate that was collected and washed with water, yield 1.68 g (99%), mp 206° (ethanol); the product was identical with a sample of **16a** prepared by the reported methods [6].

Compound **16b** was prepared following the above described procedure, starting from **15b**, yield 99%, mp 224-225° (ethanol). The product was identical with a sample of **16b** prepared by the known methods [6].

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