The Synthesis of Heteroaromatic Nitro Compounds from 3-Nitrochromone

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3-Nitrochromone (**1**) reacts with a series of nucleophiles by Michael addition followed by intramolecular condensation to yield pyrrolyl (**2**), phenyl (**3**), pyridyl (**4**), pyrido (**5,6**), pyrimidyl (**7**) and pyrazolyl (**8**) nitro derivatives. The reactions proceed under basic catalysis in 39-78% yields. Conversion of **4** to 3,4-dihydrobenzofuro[3,2-*b*]quinol-1-(2H)one (**12**) is also described. Carbon-13 data for **2, 5, 6** and **8** are discussed. The one bond C,H coupling constants in the nitropyridines are also reported and used as an analytical tool.

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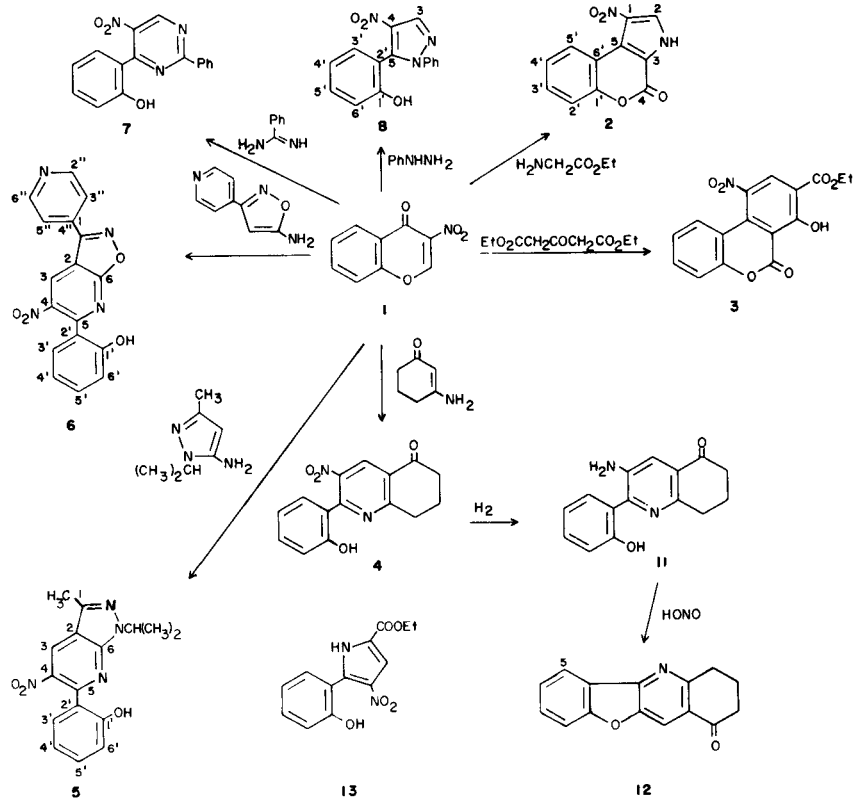
Although 3-nitrochromone **1** is readily accessible (1), its chemistry has not been extensively investigated. Our interest in chromones as substrates for the synthesis of potential antiallergic, antiinflammatory or antibacterial agents led us to study some chemistry of **1**. Herein we report the preparation for a variety of aromatic nitro compounds starting with **1** in which the electrophilic sites at positions 2 and 4 are utilized for aromatic ring formation.

As summarized in Scheme 1, pyrrolyl, phenyl, pyridyl, pyrido, pyrimidyl and pyrazolyl nitro derivatives are available from **1**. A general rationale for the formation of these products is outlined in Scheme 2 (2). 3-Nitrochromone **1** acts as an efficient Michael acceptor at position 2 for nucleophiles such as amines, enamines and stabilized enolates. This reaction leads to intermediates of general structure A. With proper selection of the nucleophile, an additional condensation between ZH_2 and the carbonyl is possible and this results in ring formation to give the final product, represented by structure B.

The reaction conditions used for the preparation of

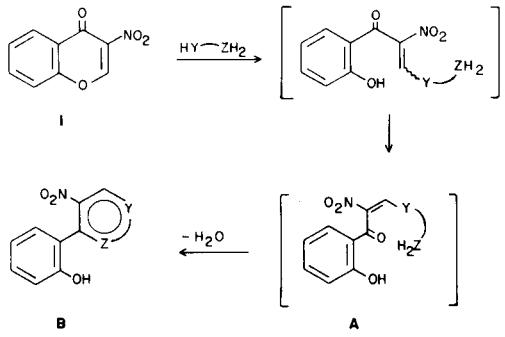
Scheme 1

Formation of Nitroaromatics from 3-Nitrochromone (**1**)



0022-152X/81/030619-04$02.25

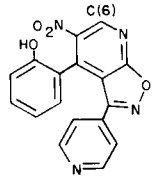
Scheme 2
General Mechanism of Ring Formation



these nitro compounds are listed in Table 1. Under basic catalysis, the products were isolated in 39-78% yield. The structures are supported by nmr, ir and mass spectral data. Lactones **2** and **3** presumably formed via the intermediate phenolic esters. For **2**, the formation of a lactone serves to verify the orientation of the addition of glycine ethyl ester to **1**, since addition in the reverse sense would yield a pyrrolecarboxylic acid **13** that could not cyclize to a lactone. For products **3** and **7**, isomeric aromatic structures are not possible due to symmetry of the nucleophiles.

Carbon-13 nmr spectra were obtained for products **2, 5, 6** and **8** and the chemical shift data are summarized in Table 2. The chemical shifts were assigned with the aid of the proton coupled spectra and by comparison with model compounds (3,4,5,6).

The carbon-13 spectra corroborated the assignment of the structures. Considering **6** as an example, the most likely alternative isomeric structure is **9**, which would arise from addition of 3-(4-pyridyl)isoxazol-5-amine to **1** in the reverse manner. Structures **6** and **9** can be differentiated on the basis of the carbon-13 nmr data of the proton carrying pyridine carbon. Its chemical shift (130.9 ppm) is incompatible with a carbon atom in the ortho position to the pyridine nitrogen [149.8 ppm in pyridine itself, *cf.*, also (3,7)]. The chemical shift is rather high for a carbon in the para position. This is due to the nitro group in the α-position (8) and the anellation by the five-membered ring (9). The one bond C,H coupling constant (J = 177 Hz) is large compared with pyridine (7). A systematic study of nitrated pyridines was therefore undertaken (see Table 3), which showed that the nitro group is responsible for this increase of J [similar to the benzene case (8)]. The data showed, furthermore, that the value of 177 Hz is in agreement with structure **6** if the increment caused by the oxygen in the 6 position (10, 11) is taken into account, and



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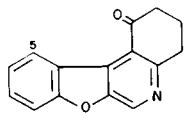

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Table 1
Nitroaromatics from 3-Nitrochromone **1**

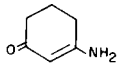
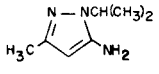
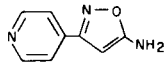
Compound No.	$\overset{\frown}{HYZH_2}$	Catalyst	Yield (%)	M.p. (°C)
2	$H_2NCH_2CO_2Et$	sodium ethoxide	39	285 dec.
3	$EtO_2CCH_2COCH_2CO_2Et$	pyridine	40	166-167
4		pyridine	68	192-194
5		pyridine	67	168-168.5
6		pyridine	68	255-256
7		triethylamine	42	158-159
8	$PhNHNH_2$	pyridine	70	166-168

Table 2
Carbon-13 Chemical Shifts of **2**, **5**, **6** and **8** in DMSO-d_6

Compound No.	Chemical Shifts (ppm) (b)															
	1	2	3	4	5	6	1′	2′	3′	4′	5′	6′	1′′	2′′,6′′	3′′,5′′	4′′
2	132.5	131.6 [198]	117.5	153.3	114.7		151.2	117.0	129.6	124.3 (a)	126.1 (a)	120.3				
5	142.7	112.4	127.6 [172]	141.9	150.3	149.0	154.8	125.9	130.5	119.4	130.5	115.2				
6	156.6	109.5	130.9 [177]	145.0	153.0	169.0	155.0	123.5	130.6 (a)	119.6	131.9 (a)	115.3		150.8	121.8	134.1
8			137.0	134.2	139.0		155.7	113.9	131.1 (a)	119.0	131.6 (a)	115.8	138.6	124.8	128.9	128.7

(a) Assignments may be interchanged.
(b) $^1J_{C,H}$ values (Hz) are given in [ ] below the appropriate chemical shift value.

Table 3
$^1J_{CH}$ in the Mononitropyridines (12) (a)

	Carbon Atom				
	2	3	4	5	6
2-Nitropyridine		174	169	167	184
3-Nitropyridine	190		170	168	182
4-Nitropyridine	183	172		172	183
Pyridine (7)	178	163	162	163	178
2-Chloro-5-nitropyridine (b)		180	178		194

(a) In deuteriochloroform, digital resolution 2-3 data points/Hz.
(b) In DMSO-d_6.

that a value on the order of 190 Hz would be expected for J of C(6) in **9**. Structure **9** can, therefore, also be ruled out on the basis of J. The argument for **4** and **5** is analogous. The J value of C(3) in **5** is very similar to that of C(4) in 3-nitropyridine. The J value of C(3) in **4** was extracted from the proton spectrum and amounts to 169 Hz, in complete agreement with the proposed structure.

The structure of **8** also follows from the carbon-13 nmr spectra. The isomeric structure formed by the inverse addition of phenylhydrazine can be excluded on the basis of the chemical shifts of the *N*-phenyl ring carbons, which require a substituent in the 5-position (6). The chemical shift of the proton carrying pyrazole carbon is, furthermore, only compatible with C(3) and not with C(5) (5,6).

The potential for further elaboration of these nitro derivatives is illustrated with **4**, in which nitro group reduction to give **11** followed by diazotization and intramolecular phenolic coupling led to **12**. The proton spectrum of **12** further corroborates structure **4**, since the proton H-C(5) (see Scheme 1) would absorb at much lower field than 8.28 ppm in the alternate structure **10**.

In conclusion, the use of 3-nitrochromone **1** provides a general entry into a wide variety of aromatic and heteroaromatic nitro derivatives which would not be readily available by other means.

EXPERIMENTAL

Melting points were taken on a Büchi melting point apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 157 spectrometer. ^{1}H-Nmr spectra were determined on a Varian HA 100 or T 60. Chemical shifts are given in ppm relative to tetramethylsilane as internal standard. Splitting patterns are designated s, singlet; d, doublet; t, triplet; q, quartet; qt, quintet; m, multiplet; b, broad. Coupling constants are given in Hz. ^{13}C-Nmr were determined on a Varian XL 100 using DMSO-d_6 as solvent and tetramethylsilane as reference. Column chromatography was performed on Merck silica gel 60, mesh size 70-238. Mass spectra were taken on a Varian CH-7 mass spectrometer.

1-Nitropyrrolo[2,3-*c*][1]benzopyran-4-one (**2**).

Sodium (0.70 g., 30.0 mmoles) was added portionwise to 50 ml. of ethanol. After complete reaction, 3-nitrochromone (1.9 g., 1.07 mmoles) followed by glycine ethyl ester hydrochloride (2.0 g., 1.43 mmoles) were added and the reaction was refluxed 5 hours. The reaction was cooled to room temperature and rotary evaporated. The residue was slurried in 2*N* aqueous hydrochloric acid. The proudct was filtered, washed with water and recrystallized from ethanol to give a tan crystalline product (0.90 g., 39%), m.p. 285°; nmr (DMSO-d_6): 13.9 (1H, bs), 8.73 (1H, m), 8.55 (1H, s), 7.3-7.7 (3H, m); ir (nujol): 3220, 2860, 1700, 1630 cm^{-1}; ms: m/e 230 (M$^+$), 200.

Anal. Calcd. for $C_{11}H_6N_2O_4$: C, 57.40; H, 2.60; N, 12.10. Found: C, 57.30; H, 2.70; N, 12.20.

Ethyl 7-Hydroxy-10-nitro-6-oxodibenzo[*b*,*d*]pyran-8-carboxylate (**3**).

A solution of 3-nitrochromone (32 g., 0.17 mole) and acetonedicarboxylic acid diethyl ester (50.0 g., 0.24 mole) in 200 ml. of pyridine was refluxed for 2 hours. The reaction was concentrated *in vacuo*. The residue was slurried in 200 ml. of 3*N* hydrochloric acid and then concentrated *in vacuo*. The residue was slurried in 200 ml. of ethanol and filtered to give beige crystals (21.9 g., 40%), m.p. 166-167°; nmr (deuteriochloroform): 13.18 (1H, bs, OH), 8.52 (1H, s), 7.25-7.78 (4H, m), 4.46 (2H, q, J = 7), 1.47 (3H, t, J = 7); ir (dichloromethane): 2960, 1735, 1705, 1680, 1610 cm^{-1}; ms: m/e 329 (M$^+$), 284, 253.

Anal. Calcd. for $C_{16}H_{11}NO_7$: C, 58.37; H, 3.37; N, 4.26. Found: C, 58.09; H, 3.41; N, 4.39.

7,8-Dihydro-2-(2-hydroxyphenyl)-3-nitroquinol-5-(6*H*)one (**4**).

To 3-nitrochromone (3.82 g., 20.0 mmoles) in 40 ml. of pyridine at room temperature was added 3-amino-2-cyclohexen-1-one (13) (2.3 g., 20 mmoles). The reaction was refluxed 4 hours, cooled to room temperature and rotary evaporated. The residue in 300 ml. of methylene chloride was extracted with 100 ml. of 2*N* hydrochloric acid and 100 ml. of water. The organic layer was dried (sodium sulfate) and rotary evaporated. The residue was recrystallized from ethyl acetate to give a yellow crystalline

product (3.9 g., 78%), m.p. 192-194°; nmr (deuteriochloroform + DMSO-d_6): 9.82 (1H, s, OH), 8.63 (1H, s), 7.72 (1H, dd, J = 8, 2), 7.35 (1H, m), 6.92 (2H, m), 3.27 (2H, t, J = 6), 2.73 (2H, t, J = 6), 2.22 (2H, qt, J = 6); ir (dichloromethane): 3220, 2900, 1710, 1605, 1540, 1345, 815 cm^{-1}.

Anal. Calcd. for $C_{15}H_{12}N_2O_4$: C, 63.38; H, 4.26; N, 9.86. Found: C, 63.39; H, 4.23; N, 9.94.

6-(2-Hydroxyphenyl)-3-methyl-1-(1-methylethyl)-5-nitropyrazolo[3,4-*b*]-pyridine (**5**).

A solution of 3-nitrochromone (19.2 g., 0.10 mole) and 3-amino-2-isopropyl-5-methylpyrazole (**14**) (14.1 g., 0.10 mole) in 300 ml. of pyridine was refluxed 4 hours. The solvent was removed by rotary evaporation. The residue was dissolved in 1*N* aqueous sodium hydroxide, cooled with ice and acidified with concentrated hydrochloric acid, producing yellow-brown crystals. The product was recrystallized from ethanol-water to give 17 g., m.p. 168-168.5°. From the mother liquor an additional 4.0 g. was obtained for a total yield of 21.0 g. (67%); nmr (deuteriochloroform + DMSO-d_6): 9.58 (1H, s, OH), 8.62 (1H, s), 7.65 (1H, dd, J = 7, 2), 7.29 (1H, dt, J = 7, 2), 7.01 (1H, dt, J = 7, 2), 6.90 (1H, d, J = 7), 5.29 (1H, heptet, J = 7), 2.62 (3H, s), 1.56 (6H, d, J = 7); ir (dichloromethane): 2940, 1610, 1525, 1340 cm^{-1}; ms: m/e 312 (M^+), 297, 266, 224.

Anal. Calcd. for $C_{16}H_{16}N_4O_3$: C, 61.53; H, 5.17; N, 17.94. Found: C, 61.57; H, 5.24; N, 17.81.

6-(2-Hydroxyphenyl)-5-nitro-3-(4-pyridyl)-isoxazolo[5,4-*b*]pyridine (**6**).

A suspension of 3-nitrochromone (13.5 g., 70.7 mmoles) and 5-amino-3-(4-pyridyl)isoxazole (**15**) (10.3 g., 64.0 mmoles) in 150 ml. of pyridine was refluxed 4 hours. During this period the reaction became a homogeneous solution. The reaction was rotary evaporated. The residue was recrystallized from ethanol to give yellow-brown crystals (14.6 g., 68%), m.p. 255-256°; nmr (DMSO-d_6): 10.30 (1H, s, OH), 9.34 (1H, s), 9.06-8.40 (2H, m), 8.25-8.00 (2H, m), 7.64 (1H, dd, J = 7, 2), 7.48 (1H, dt, J = 7, 2), 7.02 (1H, dt, J = 7, 1), 6.92 (1H, dd, J = 7, 1); ir (nujol): 3350, 2800, 2580, 1620 cm^{-1}.

Anal. Calcd. for $C_{17}H_{10}N_4O_4$: C, 61.08; H, 3.02; N, 16.76. Found: C, 60.92; H, 3.23; N, 16.46.

6-(2-Hydroxyphenyl)-5-nitro-2-phenylpyrimidine (**7**).

To 3-nitrochromone (9.5 g., 50.0 mmoles) in 90 ml. of ethanol at room temperature was added benzamidine (6.0 g., 50.0 mmoles) followed by triethylamine (5.0 g., 50.0 mmoles). The reaction was refluxed 1.5 hours, cooled to room temperature and rotary evaporated. The residue in 100 ml. of 2*N* aqueous hydrochloric acid was extracted with 3 x 100 ml. of methylene chloride. The combined organic portions were washed with 100 ml. of water, dried (sodium sulfate) and rotary evaporated to give a yellow oil (16 g.). Silica gel column chromatography using methylene chloride as eluent gave a yellow crystalline product (6.3 g., 42%), m.p. 158-159°; nmr (deuteriochloroform): 10.4 (1H, s, OH), 9.18 (1H, s), 8.40 (2H, m), 7.30-7.65 (5H, m), 6.85-7.15 (2H, m); ir (dichloromethane): 3560, 3080, 1650, 1595, 1570, 1415, 1350, 880, 800 cm^{-1}.

Anal. Calcd. for $C_{16}H_{11}N_3O_3$: C, 65.53; H, 3.78; N, 14.33. Found: C, 65.60; H, 4.05; N, 14.29.

5-(2-Hydroxyphenyl)-4-nitro-1-phenylpyrazole (**8**).

To 3-nitrochromone (9.5 g., 50.0 mmoles) in 50 ml. of pyridine at room temperature was added phenylhydrazine (5.5 g., 51.0 mmoles). The reaction was refluxed for 1 hour, cooled to room temperature and rotary evaporated. The residue was dissolved in 300 ml. of methylene chloride and extracted with 100 ml. of 2*N* hydrochloric acid and 100 ml. of water. The organic layer was dried (sodium sulfate) and rotary evaporated to give an orange oil (14.2 g.). Silica gel column chromatography using methylene chloride as eluent gave a yellow crystalline product (9.8 g., 70%), m.p. 166-168°; nmr (deuteriochloroform + DMSO-d_6): 9.51 (1H, s, OH), 8.38 (1H, s), 7.20-7.41 (6H, m), 6.70-7.05 (3H, m); ir (dichloromethane) 3580, 1625, 1605, 1565, 1520, 1395, 1330, 836, 823 cm^{-1}.

Anal. Calcd. for $C_{15}H_{11}N_3O_3$: C, 64.12; H, 3.95; N, 14.95. Found: C, 64.08; H, 4.18; N, 14.93.

3-Amino-7,8-dihydro-2-(2-hydroxyphenyl)quinol-5-(6*H*)one (**11**).

Compound **4** (14.1 g., 50.0 mmoles) in 140 ml. of dioxane was hydrogenated at 3 atmospheres pressure in the presence of Raney nickel (2.0 g.). After uptake, the catalyst was removed by filtration and the filtrate was rotary evaporated to give a yellow solid. Recrystallization (methylene chloride-ether-petroleum ether) gave yellow crystals (9.5 g., 75%), m.p. 183-185°. Nmr (deuteriochloroform + DMSO-d_6): 11.85 (1H, bs, OH), 7.89 (1H, dd, J = 9, 1), 7.75 (1H, s), 7.30 (1H, m), 6.95 (2H, m), 4.55 (2H, bs, NH_2), 3.03 (2H, t, J = 6), 2.67 (2H, t, J = 6), 2.18 (2H, p, J = 6); ir (dichloromethane): 3320, 2950, 1680, 1615, 1345, 827 cm^{-1}.

Anal. Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.88; H, 5.67; N, 11.20.

3,4-Dihydrobenzofuro[3,2-*b*]quinol-1-(2*H*)one (**12**).

To the above amine (4.3 g., 16.8 mmoles) in 30 ml. of 4*N* aqueous hydrochloric acid at 0° was added dropwise sodium nitrite (1.2 g., 16.5 mmoles) in 5 ml. of water. After addition the reaction was stirred at room temperature 10 minutes and then at 45° for 15 minutes. The reaction was cooled to 15° and filtered to give brown crystals (5.0 g.). Silica gel column chromatography using methylene chloride as eluent gave a yellow crystalline product (2.0 g., 50%), m.p. 175-178°; nmr (deuteriochloroform): 8.40 (1H, s), 8.28 (1H, dd, J = 8.2), 7.30-7.75 (3H, m), 3.34 (2H, t, J = 6), 2.78 (2H, t, J = 6), 2.27 (2H, p, J = 6); ir (dichloromethane): 2980, 1680, 1640, 1465, 1395, 1355, 1202, 850 cm^{-1}.

Anal. Calcd. for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.91. Found: C, 75.64; H, 4.67; N, 5.70.

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