The Convergent Syntheses of Pyrazinyl and Quinoxalinyl Phenylmethanones from 2-Lithio Pyrazines and Quinoxalines

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Pyrazines and quinoxalines bearing 2-substituents that direct *ortho* metalation reacted with lithium 2,2,6,6-tetramethylpiperidide to produce 2-substituted-3-lithiopyrazines and quinoxalines. These lithio reagents reacted with *N*-methoxy-*N*-methylbenzamide to give good to moderate yields of 3-substituted pyrazinyl or quinoxalinylphenylmethanones. The 3-methylthio substituents of some ketone products were oxidized to methylsulfonyl groups that were susceptible to nucleophilic displacement.

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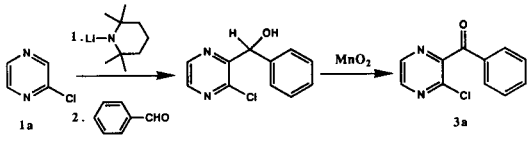
Pyrazinyl ketones and alcohols find use as odor and flavoring agents [1,2], intermediates in the syntheses of pyridines [3], plant fungicides [4], and aromatase inhibitors [5]. We have been particularly interested in the development of convergent synthetic methods for the production of those (pyrazinyl)phenylmethanones that are intermediates in the syntheses of the fungicides and aromatase inhibitors.

Among the methods previously developed for synthesizing pyrazinylmethanones from pyrazines is the homolytic substitution of pyrazines by aroyl and acyl radicals [6,7]. However, these approaches do not generally produce high yields and often, with substituted pyrazines, give mixtures of isomeric acylation products.

A recent electrophilic approach to pyrazinylmethanones that controls regiospecificity and produces good yields has been developed by Turck, *et al.*, (Scheme 1). This route

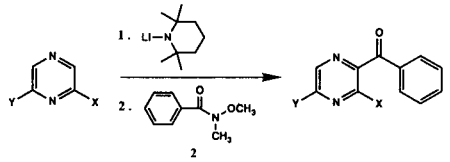
Scheme 1



uses the low temperature lithiation of 2-chloropyrazine with lithium 2,2,6,6-tetramethylpiperidide (LiTMP), reaction of the 3-chloro-2-lithiopyrazine with an aldehyde, and subsequent oxidation of the pyrazinyl alcohol to the ketone [8]. While this two step reaction sequence produces good yields of the (3-chloropyrazinyl)phenylmethanone **3a**, a general single step method that avoided the potentially complicating oxidation step was desired. We now report the development of such a method using the ketone synthesis developed by Nahm and Weinreb [9]. In addition, we show how this procedure can be applied to other 2-substituted pyrazines and quinoxalines.

When a tetrahydrofuran solution of 3-chloro-2-lithiopyrazine was treated with *N*-methoxy-*N*-methylbenzamide **2** at -78°, **3a** was isolated in 51% yield (Scheme 2). This yield was somewhat less than the 76% overall yield reported by Turck, *et al.*, for their two step process, but an additional reaction step was avoided [8].

Scheme 2



	X	Y
1 a	Cl	H
b	OCH_3	H
c	SCH_3	H
d	Cl	Cl
e	OCH_3	OCH_3

	X	Y	% Yield
3 a	Cl	H	51
b	OCH_3	H	63
c	SCH_3	H	76
d	Cl	Cl	59
e	OCH_3	OCH_3	45

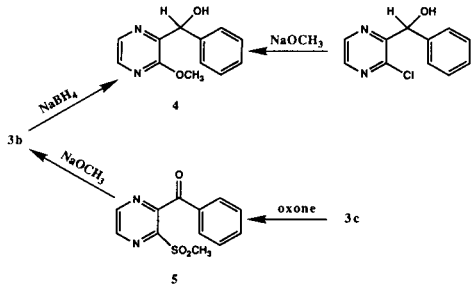
In addition to chloro substituents, alkoxy and thioalkyl groups have been used to direct *ortho* lithiation in aryl and heteroaryl compounds, but their use in stabilizing lithiopyrazines has not been investigated [10]. We found that when 2-methoxypyrazine was added to an excess of LiTMP at -78° and the reaction mixture subsequently treated with **2**, (2-methoxypyrazinyl)phenylmethanone **3b** (63% yield) was obtained. Similarly, 2-(thiomethyl)pyrazine under these conditions gave 3-(methylthio)pyrazinyl]-phenylmethanone **3c** (76% yield). The increased yields obtained in going from 2-chloro- to 2-methoxy- and 2-(methylthio)pyrazine may be an indication of the relative stability of the respective lithiopyrazines. The reaction employing 2-chloropyrazine produced some uncharacterized, highly colored, insoluble material, while reactions using the other two substrates were relatively clean.

The 2-lithiopyrazines bearing more than one stabilizing group could also be produced by this procedure. When either 2,6-dichloropyrazine or 2,6-dimethoxypyrazine was added to LiTMP at -78° and the reaction mixture treated with **2**, the respective trisubstituted pyrazines **3d** (59% yield) and **3e** (45% yield) were obtained.

The proposed regiochemistry of the (2-methoxypyrazinyl)phenylmethanone was confirmed by reducing **3b** with sodium borohydride to give the same alcohol, **4**, that was

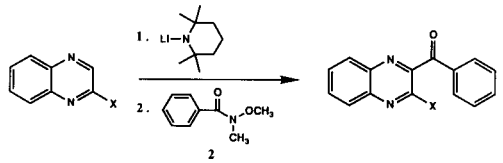
produced by heating (3-chloropyrazinyl)phenylmethanol [8] with sodium methoxide (Scheme 3). The regiochemistry of **3c** was determined by oxidizing the compound to the sulfone **5** and displacing the methylsulfonyl group with sodium methoxide to produce **3b**.

Scheme 3



To our knowledge, there are no examples of 2-lithioquinoxalines, *i.e.*, 'lithiobenzopyrazines,' being used to synthesize substituted quinoxalines. We attempted to generate the 2-lithio-3-chloroquinoxaline by adding 2-chloroquinoxaline to LiTMP at -78°, but this gave a highly colored reaction mixture that, upon treatment with **2**, did not yield the desired ketone **7a** (Scheme 4). Only highly

Scheme 4



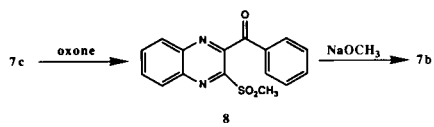
	X
6 a	Cl
b	OCH_3
c	SCH_3

	X	% Yield
7 a	Cl	0
b	OCH_3	43
c	SCH_3	42

colored insoluble materials and 2-chloroquinoxaline were obtained. However, similar treatment of 2-methoxy- or 2-(methylthio)quinoxaline produced the respective ketones **7b** (43% yield) and **7c** (42% yield). These reactions were also accompanied by highly colored solids that were easily separable from the desired ketones. This new method of synthesizing quinoxalinylphenylmethanones complements the homolytic substitution of quinoxaline developed by Gardini and Minisci [11] as it provides direct access to 2,3-disubstituted quinoxalines of this class.

Although failure to obtain chloroquinoxaline **7a** denied us an easily displaceable group that could be used to synthesize other 3-substituted quinoxalines, this problem was circumvented by oxidizing **7c** to the reactive sulfone **8** with potassium peroxymonosulfate (oxone) [12] (Scheme 5). The methylsulfonyl group of **8** was rapidly displaced with sodium methoxide at ambient temperature to give **7b** demonstrating that **8** is a valuable alternate intermediate in the syntheses of other 3-substituted quinoxalines.

Scheme 5



These syntheses of pyrazinyl- and (quinoxalinyl)phenylmethanones from pyrazines and quinoxalines containing substituents that direct *ortho* metalation provide new convergent methods of producing these compounds in moderate to good yields. The use of this method to synthesize acyl pyrazines and quinoxalines and their corresponding ketone reduction products, many of which may serve as odor and flavoring agents, is under active investigation. The further elaboration of sulfonylquinoxaline **8** by nucleophilic displacement of the sulfonyl group is also being pursued.

EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus and are uncorrected. A Waters PrepLC/500A using PrepPAK-500 silica gel cartridges, with the solvents specified, were used for hplc separations. A Harrison Research Chromatotron model 7924T using Analtech precast silica gel rotors, with the solvents specified, were used for radial chromatography. Merck F254 silica gel plates were used for tlc. All reactions, exclusive of extraction procedures, were conducted under an argon atmosphere. A QE300 was employed for nmr measurements using the solvents described. No particular attempt was made to optimize reaction conditions for most of the reactions described.

General Synthesis of Pyrazinylmethanones **3** and Quinoxalinylmethanones **7**.

A solution of 4 ml (0.024 mole) of 2,2,6,6-tetramethylpiperidine in 125 ml of tetrahydrofuran was cooled to -8° as 14 ml (0.022 mole) of 1.6 *M* *n*-buyllithium in hexane was added dropwise with vigorous stirring. After 10 minutes, the solution was cooled to -78° and (0.022 mole) of the 2-substituted pyrazine or quinoxaline in 10 ml of tetrahydrofuran was added dropwise. After 20 minutes, 3.0 g (0.018 mole) of benzamide **2** in 10 ml of tetrahydrofuran was added dropwise. The reaction was stirred 1.5 hours followed by addition of 20 ml of 1 *N* hydrochloric acid. The cooling was removed and when the internal temperature reached 0° the volatile organics were evaporated. The residue was suspended in an additional 50 ml of water and the mixture extracted 3x with 50 ml of dichloromethane. The combined extracts were washed with brine, dried, and the solvent evaporated to give crude material that was purified as described in the specific examples.

(3-Chloropyrazinyl)phenylmethanone (**3a**).

From 7.2 ml (0.043 mole) of 2,2,6,6-tetramethylpiperidine, 300 ml of tetrahydrofuran, 25 ml (0.04 mole) of 1.6*M* *n*-butyllithium in hexane, 4.49 g (0.039 mole) of 2-chloropyrazine, and 6 g (0.036 mole) **2** was obtained 4.05 g of white solid **3a** (51% yield) after purification by hplc eluting with an 8 liter gradient starting with hexane and going to 40% ethyl acetate. Solid could be recrystallized from hexane to give floculant white crystals, mp 80-81°, lit mp 82° [8]; pmr (deuteriochloroform): ppm 7.50 (2H, t), 7.68 (1H, t), 7.84 (2H, d), 8.57 (1H, d), 8.60 (1H, d).

Anal. Calcd. for $C_{11}H_7ClN_2O$: C, 60.43; H, 3.23; N, 12.81. Found: C, 60.35; H, 3.17; N, 13.13.

(2-Methoxypyrazinyl)phenylmethanone (**3b**).

From 4 ml (0.024 mole) of 2,2,6,6-tetramethylpiperidine, 125 ml of tetrahydrofuran, 14 ml (0.022 mole) of 1.6*M* *n*-butyllithium in hexane, 2.42 g (0.022 mole) of 2-methoxypyrazine, and 3.3 (0.020 mole) of **2** was obtained 2.7 g of **3b** (63% yield) as a straw colored liquid after purification by hplc eluting with an 8 liter gradient starting with hexane and going to 30% ethyl acetate; pmr (deuteriochloroform): ppm 4.02 (3H, s), 7.50 (2H, t), 7.65 (1H, t), 7.88 (2H, d), 8.24 (1H, d), 8.28 (1H, d).

Anal. Calcd. for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.70; N, 13.08. Found: C, 67.26; H, 4.72; N, 12.96.

[3-(Methylthio)pyrazinyl]phenylmethanone (**3c**).

From 4 ml (0.024 mole) of 2,2,6,6-tetramethylpiperidine, 125 ml of tetrahydrofuran, 14 ml (0.022 mole) of 1.6*M* *n*-butyllithium in hexane, 2.77 g (0.022 mole) of 2-(methylthio)pyrazine, and 3.0 g (0.018 mole) of **2** was obtained 3.14 g of **3c** after recrystallization from ether (76% yield), mp 103-104°; pmr (deuteriochloroform): ppm 2.575 (3H, s), 7.50 (2H, t), 7.62 (1H, t), 7.97 (2H, d), 8.33 (1H, d), 8.57 (1H, d).

Anal. Calcd. for $C_{12}H_{10}N_2OS$: C, 62.59; H, 4.38; N, 12.16. Found: C, 62.32; H, 4.37; N, 12.08.

(3,5-Dichloropyrazinyl)phenylmethanone (**3d**).

From 4 ml (0.024 mole) of 2,2,6,6-tetramethylpiperidine, 125 ml of tetrahydrofuran, 14 ml (0.022 mole) of 1.6*M* *n*-butyllithium in hexane, 3.0 g (0.020 mole) of 2,6-dichloropyrazine, and 3.0 g (0.018 mole) of **2** was obtained 2.67 g of **3d** as tan crystals after recrystallization from hexane (59% yield), mp 89-90°; pmr (deuteriochlooform): ppm 7.50 (2H, t), 7.68 (1H, t), 7.84 (2H, d), 8.60 (1H, s).

Anal. Calcd. for $C_{11}H_6Cl_2N_2O$: C, 52.20; H, 2.39; N, 11.07. Found: C, 51.98; H, 2.42; N, 10.94.

(3,5-Dimethoxypyrazinyl)phenylmethanone (**3e**).

From 3.5 ml (0.021 mole) of 2,2,6,6-tetramethylpiperidine, 125 ml of tetrahydrofuran, 13 ml (0.021 mole) of 1.6*M* *n*-butyllithium in hexane, 2.42 g (0.017 mole) of 2,6-dimethoxypyrazine, and 2.6 g (0.016 mole) of **2** was obtained 1.75 g of **3e** after purification by radial chromatography on silica gel eluting with 20% ethyl acetate/hexane (45% yield), mp 66.5-67.5°; pmr (deuteriochloroform): ppm 4.06 (3H, s), 4.07 (3H, s), 7.47 (2H, t), 7.57 (1H, t), 7.88-7.91 (3H, m).

Anal. Calcd. for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.47. Found: C, 63.92; H, 5.10; N, 11.41.

(2-Methoxy-3-quinoxalinyl)phenylmethanone (**7b**).

From 4 ml (0.024 mole) of 2,2,6,6-tetramethylpiperidine, 125 ml of tetrahydrofuran, 14 ml (0.022 mole) of 1.6*M* *n*-butyllithium in hexane, 3.5 g (0.022 mole) of 2-methoxyquinoxaline, and 3 g (0.018) of **2** was obtained 2.05 g of **7b** as colorless crystals after recrystallization from ether (43% yield), mp 160-161°; pmr (deuteriochloroform): ppm 4.10 (3H, s), 7.50 (2H, t), 7.65 (2H, m), 7.78 (1H, t), 7.99 (3H, m), 8.07 (1H, d).

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.44; H, 4.51; N, 10.82.

[3-(Methylthio)-2-quinoxalinyl]phenylmethanone (**7c**).

From 4 ml (0.024 mole) of 2,2,6,6-tetramethylpiperidine, 125 ml of tetrahydrofuran, 14 ml (0.022 mole) of 1.6*M* *n*-butyllithium in hexane, 3.6 g (0.020 mole) of 2-(methylthio)quinoxaline, and 3 g (0.018 mole) of **2** was obtained 2.1 g of **7c** as bright yellow needles after recrystallization from ethyl acetate (42% yield), mp 113-114°; pmr (deuteriochloroform): ppm 2.70 (3H, s), 7.50 (2H, t), 7.68 (2H, m), 7.82 (1H, t), 8.05 (4H, m).

Anal. Calcd. for $C_{16}H_{12}N_2OS$: C, 68.55; H, 4.31; N, 9.99. Found: C, 68.26; H, 4.28; N, 9.76.

(2-Methoxypyrazinyl)phenylmethanol (**4**).

To a sodium methoxide solution prepared from 0.4 g (0.0174 mole) of sodium and 25 ml of methanol was added 0.35 g (0.00158 mole) of (3-chloropyrazinyl)phenylmethanol [8]. The reaction was heated to reflux for 1 hour, the solvent evaporated, and the residue treated with 15 ml of ice-water. The resulting solid was collected, dried, and recrystallized from hexane to give 0.165 g of **4** as white needles (48% yield), mp 102.5-103.5°; pmr (deuteriochloroform): ppm 3.94 (3H, s), 4.93 (1H, d), 5.92 (1H, d), 7.26-7.41 (5H, m), 8.065 (1H, d), 8.135 (1H, d).

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.79; H, 5.65; N, 12.95.

Preparation of **4** from **3b**.

To a solution of 1.0 g (0.0053 mole) of **3b** in 20 ml of 2-propanol was added with stirring 0.2 g (0.0053 mole) of sodium borohydride. After 45 minutes, 1 ml of water was carefully added to destroy excess reducing agent. The solvent was evaporated, residue suspended in 20 ml of water, and the mixture extracted 2x with 75 ml of ether. The extracts were dried, the solvent evaporated, and the residue was recrystallized from ether to give 0.66 g (66% yield) of a white solid whose pmr was identical to that of **4** produced by the previously described method.

[3-(Methylsulfonyl)pyrazinyl]phenylmethanone (**5**).

A mixture of 0.5 g (0.0022 mole) of **3c** and 30 ml of methanol was vigorously stirred as 3 g (0.0043 mole) of oxone in 15 ml of water was added dropwise. After 3 days, the methanol was evaporated and the aqueous residue was treated with 0.4 g sodium bisulfite in 5 ml of water. The mixture was extracted 3x with 25 ml of ethyl acetate, the extracts dried, and the solvent evaporated to give a white solid. Recrystallization of the solid from ether gave 0.43 g of **5** as floculant white needles (75% yield), mp 141-143°; pmr (deuteriochloroform): ppm 3.35 (3H, s), 7.52 (2H, t), 7.67 (1H, t), 7.865 (2H, d), 8.90 (2H, m).

Anal. Calcd. for $C_{12}H_{10}N_2O_3S$: C, 54.95; H, 3.84; N, 10.68. Found: C, 54.66; H, 3.80; N, 10.57.

Preparation of **3b** from **5**.

To a sodium methoxide solution prepared from 0.1 g (0.0043 mole) of sodium and 10 ml of methanol was added 0.15 g (0.00057 mole) of **5**. After 3 hours, 3 ml of 1*N* hydrochloric acid was added and the methanol was evaporated. The residue was diluted with 10 ml of water and extracted 3x with 15 ml of ether, the extracts dried, and the solvent evaporated to give 0.053 g of yellowish liquid (43% yield). The pmr of this material was identical to that of **3b**.

[3-(Methylsulfonyl)-2-quinoxalinyl]phenylmethanone (**8**).

A mixture of 0.5 g (0.00179 mole) of **7c** and 50 ml of methanol was vigorously stirred as 2.2 g (0.0036 mole) of oxone in 12 ml of water was added dropwise. After 3 days, the methanol was evaporated and the aqueous residue treated with 0.4 g of sodium bi-

sulfite in 5 ml of water. The mixture was extracted 3x with 25 ml of ethyl acetate, the extracts dried, and the solvent evaporated. The yellowish solid residue was recrystallized from ether to give 0.41 g of **8** as colorless crystals (73% yield), mp 187-188.5°; pmr (deuteriochloroform): ppm 3.45 (3H, s), 7.54 (2H, t), 7.68 (1H, t), 8.03 (4H, m), 8.25 (1H, m), 8.39 (1H, m).

Anal. Calcd. for $C_{16}H_{12}N_2O_3S$: C, 61.53; H, 3.87; N, 8.97. Found: C, 61.41; H, 3.91; N, 8.70.

Preparation of **7b** from **8**.

To a sodium methoxide solution prepared from 0.1 g (0.0043 mole) of sodium and 10 ml of methanol was added 0.15 g (0.00048 mole) of **8**. After 1 hour, 3 ml of 1*N* hydrochloric acid was added and the methanol was evaporated. The residue was diluted with 10 ml of water and extracted 2x with 15 ml of ether, the extracts dried, and the solvent evaporated to give 0.1 g of a floculant white solid (79% yield). The pmr of the material was identical to that of authentic **7b**.

Acknowledgement.

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