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Reaction of 2,3-Dialkylpyrazines and Methyllithium. Indirect Evidence for Ring Metalation

George P. Rizzi

The Procter & Gamble Company, Winton Hill Technical Center, Cincinnati, Ohio 45224

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The widespread occurrence of simple alkylpyrazines in roasted or browned foodstuffs,[1] *e.g.*, coffee, cocoa, peanuts, etc., has prompted considerable interest in the chemistry of these compounds. Certain of the trialkylpyrazines, *e.g.*, 2,5-dimethyl-3-ethylpyrazine are commonly synthesized by adding organolithiums to more readily available 2,5-dialkylpyrazines.[2] With 2,3-dialkylpyrazines and methyllithium, nuclear addition does not readily occur, instead side-chain and ring metalation take place.[2,3] In view of the contemporary importance of these compounds, we decided to examine the metalation of 2,3-dialkylpyrazines under various conditions.

The extent of 2,3-dimethylpyrazine (1) metalation was estimated by reaction with methyllithium in ether (diethyl ether) followed by D_2O quenching and high resolution mass spectrographic analysis of the deuterated products, Table I. The mass fragmentation pattern did not permit a distinction to be made between ring or chain metalated species. The absence of a *m/e* 95 fragment ion (predictable *via* normal methyl loss from $C_6H_6N_2D_2$) excluded the possibilities of CHD_2-containing species, ring dimetalation, or ring plus methyl dimetalation. Previously, both monomethyl metalated and vicinally dimethyl metalated 1 were shown to be present by alkylation with dimethyl sulfate.[3] No evidence for ring alkylation was found with dimethyl sulfate obviating ring metalation under these conditions.

Table I
Deuterated Species from D_2O Quenching of Metalated 2,3-Dimethylpyrazine

Reaction conditions[a]	Relative %[b]			
	$C_6H_8N_2$	$C_6H_7N_2D$	$C_6H_6N_2D_2$	$C_6H_5N_2D_3$
1.1, 0.5, 0	39	54	6.8	0.9
1.7, 0.5, 0	3.2	83	12	1.3
m/e calcd	108.069	109.075	110.080	111.087
m/e obsd[c]	108.067	109.073	110.078	111.083

[a] Mole ratio of MeLi/1, time in hr, temp (°C). [b] Values corrected for ^{13}C and ^{15}N content. [c] Precision *ca.* ±0.003 amu.

Evidence for pyrazine ring metalation was sought by quenching reaction products of 2-ethyl-3-methylpyrazine (2) and MeLi with D_2O, Table II. Pmr was used to determine the extent of metalation/deuteration of more acidic hydrogens relative to the presumably unmetalated terminal methyl in the ethyl side chain. Conditions which led to 54% monometalation of 1 produced 30% methyl metalation and a maximum of 1.1% ring metalation in **2**. Treatment of **2** with a sixteenfold excess of MeLi at 25° for 24 hr gave 50% methyl metalation apparently resulting in a mixture of CH_2D and CHD_2 species. Under the more forcing conditions, 15% of available ring positions also underwent metalation. In accord with reported hydrocarbon metalation data,[4] less metalation occurred at the methyl substituted ring CH_2 (31%) than at the ring CH_3 (50%) of **2**.

Table II
Metalation and D_2O Quenching of 2-Ethyl-3-methylpyrazine

Reaction conditions			Per cent substitution of D for H[a]		
MeLi/2 ratio	°C	hr	Ring H's	Ring CH_2	Ring CH_3
1.0	0	1.0	1.0	1.0	30
16	25	24	15	31	50

[a] Determined by pmr using ethyl group methyl (3.00 H) as internal standard, precision *ca.* ±10% of values shown.

A similar effect led to apparent retardation of methyl substitution in the metalation/methylation of methylpyrazine with sodamide and methyl iodide in liquid ammonia, Table III. The yields of isopropylpyrazine and *tert*-butylpyrazine were low relative to ethylpyrazine even in the presence of excess alkylating reagents. The lowered total alkylpyrazine yields in experiments designed to flavor *tert*-butylpyrazine formation possibly resulted from competitive N methylation and loss of quaternary salts during work-up. Since no ring methylated pyrazines were detected, we concluded that ring metalation by sodamide either did not occur or that it was slow relative to isopropylpyrazine side-chain metalation.

Table III
Methylation of Methylpyrazine in Liquid Ammonia

Mol of $NaNH_2$ and CH_3I/mol of methylpyrazine	Pyrazine yield, %[a]			
	Methyl	Ethyl	Isopropyl	*tert*-Butyl
1.0	4.9	77.6	2.6	trace
2.0	3.6	31.8	42.0	4.3
4.0	0.5	2.4	9.9	24.6

[a] Absolute yields based on 1 equiv of methylpyrazine as determined by glc on vacuum distilled products; no other products were detected.

Experimental Section[5]

Metalation/Deuteration of 1. To a stirred mixture of ether (5 ml) and 3.5 ml of 1.6 *M* MeLi in ether (5.6 mmol) at 0° was added

0.528 ml (5.0 mmol) of redistilled **1**. After 30 min, 5.0 ml of D_2O was added and the mixture was saturated with NaCl at 25°. The ether layer was dried ($MgSO_4$) and concentrated under vacuum to yield 0.416 g of purified by preparative glc on a 5 ft × 0.25 in. column containing 15% SF-96 on 30/60 mesh support. One peak was observed corresponding to the retention time (R_T) of undeuterated **1**. Metalation of **1** with excess MeLi involved adding 0.503 g (4.7 mmol) of **1** in 3 ml of ether to a mixture of ether (10 ml) and 5 ml of 1.6 *M* MeLi in ether at 0°. Quenching with D_2O followed by ether extraction gave 0.463 g of crude **1**. Glc analysis indicated complete absence of by-products and provided pure samples for mass spectral analysis.

Metalation/Deuteration of 2. A solution of **2** (0.9994 g, 8.19 mmol) in 5 ml of ether was added dropwise at 0° to 5.0 ml of 1.6 *M* MeLi in ether, stirred for 1 hr, and at 0° 2 ml of D_2O was added followed by 30 ml of saturated brine. Rapid ether extraction (3×), drying ($MgSO_4$), and concentration under vacuum gave crude deuterated **2** which was purified by glc on a 20 ft × 0.25 in. column packed with 18% diethylene glycol succinate on 60/80 mesh support to provide a sample for pmr analysis. No peaks other than **2** were observed. Similarly addition of **2** (0.127 g) to ether (10 ml) and 10 ml of 1.6 *M* MeLi at 25° gave, after 24-hr reaction and work-up, 0.1184 g of deuterated **2**. Pmr of undeuterated **2**: δ 1.23 [t, J = 8 Hz, 3 H, CH_2CH_3], 2.43 [s, 3 H, ring CH_3], 2.72 [q, J = 8 Hz, 2 H, CH_2CH_3], 8.10 [d, J = 2.0 Hz (not completely resolved), ring H] and 8.15 [d, J = 3.0 Hz, ring H] ppm. The aromatic region of deuterated **2** exhibited two broad lines of approximately equal area centered at δ 8.12 and 8.14 ppm. The question of which ring hydrogen has the greater chemical shift remains to be resolved.

Methylation of Methylpyrazine with $NaNH_2/CH_3I$. To 100 ml of liquid NH_3 containing 2.34 g (0.060 mol) of sodamide was added 2.82 g (0.030 mol) of methylpyrazine. After 15 minutes, 3.9 ml (0.030 mol) of methyl iodide was added and stirring was continued until the initial intense red color faded. Excess NH_3 was evaporated and the residue was continuously extracted with ether for 24 hr. The ether was removed, and the residue was distilled to afford 2.84 g of oil, bp 58–69° (15 mm). Glc analysis on a 10 ft × 0.25 in. column containing 15% SF-96 on 30/60 mesh support at 135° resolved the following alkylpyrazines (% yield): methyl- (3.6), ethyl- (31.8), isopropyl- (42), and *tert*-butyl- (4.3). Similar experiments in which only the amounts of sodamide and methyl iodide were varied led to the data in Table III. Pyrazines were isolated by preparative glc technique for characterization. Methyl- and ethylpyrazine were identified by comparison of R_T and ir spectral data with those of authentic samples. Isopropylpyrazine was an oil at 25°: pmr δ 1.30 [d, J = 7 Hz, 6 H, $(CH_3)_2CH$], 3.03 [m, J = 7 Hz, 1 H, $(CH_3)_2CH$], 8.30 and 8.38 ppm (br s, total of 3 H, ring hydrogens).

Anal. Calcd for $C_8H_{12}N_2$: C, 70.6 H, 8.8, N, 20.6. Found: C, 70.11; H, 9.01; N, 21.02.

tert-Butylpyrazine was an oil at 25°: pmr δ 1.34 [s, 9 H, $(CH_3)_3C$] and 8.20–8.56 ppm (unresolved group of peaks, 3 H, ring hydrogens).

Anal. Calcd for $C_8H_{12}N_2$: C, 70.6 H, 8.8, N, 20.6. Found: C, 70.11; H, 9.01; N, 21.02.

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Registry No.—**1**, 5910-89-4; **2**, 15707-23-0; methylpyrazine, 109-08-0; isopropylpyrazine, 29460-90-0; *tert*-butylpyrazine, 32741-11-0; methyllithium, 917-54-4.

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A Convenient Synthesis of 2,3-Dihydroimidazo[1,2-*c*]quinazolines

Goetz E. Hardtmann* and Hans Ott

Sandoz, Inc., Pharmaceutical Division, East Hanover, New Jersey 07936

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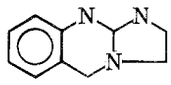
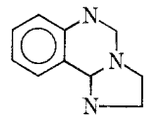
Recently several publications[1,2] have dealt with the preparation of the [2,1-*b*]imidazoquinazoline system (A). The isomeric [1,2-*c*] system (B) is known,[3,4] but no convenient synthetic approaches are available. We now wish to report a simple synthesis of this system utilizing the iodide-catalyzed rearrangement of aziridines originally used by Heine and coworkers[5] for the preparation of oxazolines.[6]

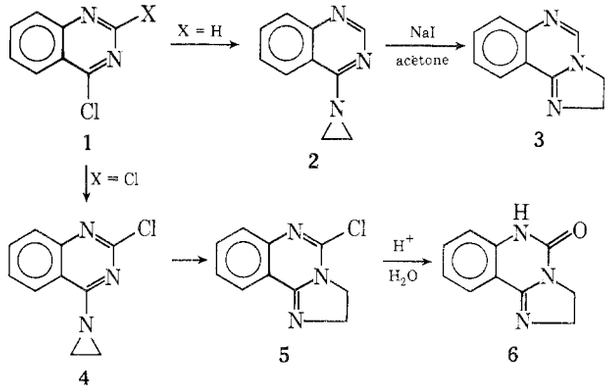


A [2,1-*b*]



B [1,2-*c*]

When 4-chloroquinazoline (1) was allowed to react at room temperature with an excess of ethylenimine, the expected aziridine **2** was formed. This product, when dissolved in acetone and stirred at room temperature in the presence of NaI, underwent rearrangement to the imidazo[1,2-*c*]quinazoline **3**.[3a] Similarly, 2,4-dichloroquinazoline reacted with ethylenimine, but only the 4-chloro substituent was replaced yielding **4**. Attempts to also replace the 2-chloro substituent by using elevated temperatures failed, resulting in the formation of ethylenimine polymers. The monosubstitution product **4** could be rearranged to **5** in the usual manner; treatment of **5** with acid gave the quinazolinone **6**.[4] Analogously 4-chloro- and 2,4-dichloro-6,7-dimethoxyquinazoline could be reacted with aziridines and the products rearranged to the corresponding imidazoquinazolines.



1 2 3 4 5 6

Experimental Section

The spectral data obtained from all products are in accordance with the assigned structure; nmr spectra were measured on a Varian A-60 instrument and the ir spectra with a Perkin-Elmer 137 spectrophotometer.

4-Aziridinoquinazoline (2). To a cooled solution of 4-chloroquinazoline (5 g, 0.03 mol) in methylene chloride (60 ml) ethylenimine (22 ml, 0.5 mol) dissolved in methylene chloride (50 ml) was added dropwise over a period of 30 min. The mixture was stirred at