

Organolithium Reactions of Iodopyrazines. II.  
Reactions of 3,6-Dimethyl-2-pyrazinylithium and of 2-Pyrazinylithium.

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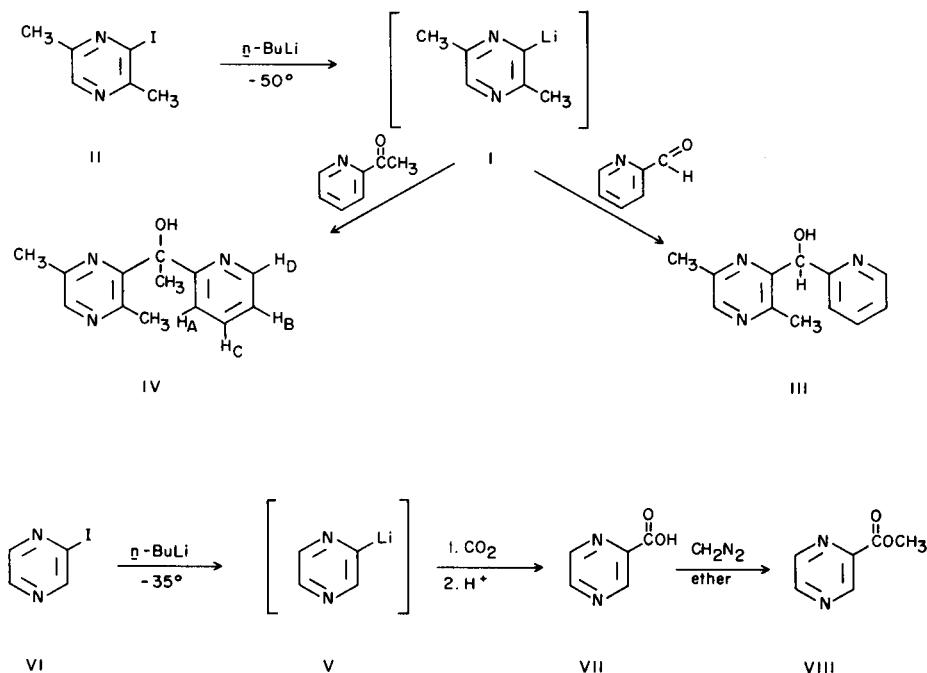
In 1965, Hirschberg, Peterkofsky and Spoerri, reported the preparation of the first organometallic derivative of a pyrazine in which the metal is directly attached to the heterocyclic ring (2). By means of a halogen-metal interconversion reaction the reactive 3,6-dimethyl-2-pyrazinyl-lithium intermediate (I) was prepared from 2-iodo-3,6-dimethylpyrazine (II), using *n*-butyllithium as the metallating agent. The lithium intermediate (I) was carbonated to form 3,6-dimethyl-2-pyrazinoic acid and it was condensed with several substituted benzaldehydes to form the corresponding substituted pyrazinylphenylcarbinols.

In the present study the 3,6-dimethyl-2-pyrazinyl-lithium intermediate (I) was condensed with a heterocyclic aldehyde, 2-pyridinecarboxaldehyde, to form (3,6-dimethyl-2-pyrazinyl)-2-pyridylcarbinol (III).

In addition, the 3,6-dimethyl-2-pyrazinyl-lithium intermediate (I) was condensed with a heterocyclic ketone, 2-acetylpyridine, to form (3,6-dimethyl-2-pyrazinyl)-2-pyridylmethylecarbinol (IV).

Unsubstituted 2-pyrazinyl-lithium (V) has been prepared from 2-iodopyrazine (VI) by means of a halogen-metal interconversion reaction at  $-35^{\circ}$ , using *n*-butyllithium as the metallating agent. This lithium intermediate (V) was carbonated to form an impure sample of 2-pyrazinoic acid (VII), a compound previously synthesized by Stoehr (3) by the oxidation of 2-methylpyrazine. The acid (VII) was esterified with an ether solution of diazomethane to form methyl-2-pyrazinoate (VIII).

These reactions are summarized below.



## EXPERIMENTAL (4)

## 2-Iodopyrazines (II, VI).

These compounds were prepared according to a procedure described by Hirschberg and Spoerri (5).

## (3,6-Dimethyl-2-pyrazinyl)-2-pyridylcarbinol (III).

A solution of 0.020 mole of *n*-butyllithium in 60 ml. of anhydrous ether was added rapidly to a solution of 4.0 g. (0.017 mole) of 2-iodo-3,6-dimethylpyrazine in 60 ml. of anhydrous ether previously cooled to  $-50^{\circ}$ . The reddish solution was stirred under nitrogen for seven minutes and then a solution of 2.66 g. (0.025 mole) of 2-pyridinecarboxaldehyde in 40 ml. of dry ether was added slowly. The mixture was allowed to warm up to room temperature and then refluxed for two hours, after which the mixture was poured into 800 ml. of ice water saturated with ammonium chloride. The ether layer was separated and the aqueous layer was extracted with four 50 ml. portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate, treated with decolorizing carbon and filtered. The filtrate was concentrated under reduced pressure and upon standing overnight a solid precipitated. The yellow solid was collected by filtration and washed with cold hexane to yield 0.6 g. (16.5%) of the carbinol (III). Three recrystallizations from hexane afforded an analytical sample of white crystals with a melting point of  $108-109.5^{\circ}$ .

The infrared spectrum (carbon tetrachloride) showed a hydroxyl peak at  $3380\text{ cm}^{-1}$ . The nmr spectrum (6, 7) (carbon tetrachloride) showed a six proton methyl singlet at  $\tau$  7.50, a doublet for the alcohol proton at  $\tau$  5.03, a methine proton doublet at  $\tau$  4.17, a complex envelope from  $\tau$  3.06 to  $\tau$  2.17 for the pyridine ring protons, H<sub>A</sub>, H<sub>B</sub>, H<sub>C</sub>, a singlet at  $\tau$  1.83 for the pyrazine ring proton and a multiplet at  $\tau$  1.58 for the pyridine ring proton, H<sub>D</sub>. The coupling constant for the methine proton and alcohol proton, J<sub>EF</sub>, was 6 Hz.

*Anal.* Calcd. for C<sub>12</sub>H<sub>13</sub>N<sub>3</sub>O: C, 66.96; H, 6.09; N, 19.52. Found: C, 67.18; H, 6.08; N, 19.52.

## (3,6-Dimethyl-2-pyrazinyl)-2-pyridylmethylcarbinol (IV).

A solution of 0.040 mole of *n*-butyllithium in 120 ml. of anhydrous ether was added rapidly to a solution of 8.0 g. (0.034 mole) of 2-iodo-3,6-dimethylpyrazine in 60 ml. of anhydrous ether previously cooled to  $-50^{\circ}$ . The reddish solution was stirred under nitrogen for seven minutes and then a solution of 6.06 g. (0.050 mole) of 2-acetylpyridine in 80 ml. of dry ether was added slowly. The mixture was allowed to warm up to room temperature and then refluxed for one hour, after which the mixture was poured into 800 ml. of ice water saturated with ammonium chloride. The ether layer was separated and the aqueous layer was extracted with four 100 ml. portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate, treated with decolorizing carbon and filtered. The filtrate was concentrated under reduced pressure and the residual oil was fractionally distilled at 35 mm. The residue in the still pot which failed to distill at  $175^{\circ}$  was dissolved in 100 ml. of ether, treated with decolorizing carbon and then filtered. The filtrate was concentrated under reduced pressure. Sublimation of the residual oil at  $64^{\circ}$  and 0.5 mm. yielded a colorless viscous oil which on scratching gave compound IV as a white solid, m.p.  $69-71^{\circ}$ . Three recrystallizations from methanol-water yielded 2.2 g. (28.2%) of white crystals with a melting point of  $73-73.5^{\circ}$ .

The infrared spectrum of the alcohol showed a broad hydroxyl peak at  $3340\text{ cm}^{-1}$ . The nmr spectrum (carbon tetrachloride)

showed three 3 proton singlets at  $\tau$  8.15, 7.82 and 7.50 corresponding to the three methyl groups. A one proton singlet at  $\tau$  4.15 corresponded to the alcohol proton. A complex envelope at  $\tau$  2.86 corresponded to the two pyridine ring protons, H<sub>A</sub> and H<sub>B</sub>. Another complex envelope at  $\tau$  2.50 corresponded to the pyridine ring proton, H<sub>C</sub>. There was a 1 proton singlet at  $\tau$  1.87 for the pyrazine ring proton and an envelope at  $\tau$  1.52 for the pyridine ring proton, H<sub>D</sub>.

*Anal.* Calcd. for C<sub>13</sub>H<sub>15</sub>N<sub>3</sub>O $\cdot$  $\frac{1}{2}$ H<sub>2</sub>O: C, 65.49; H, 6.77; N, 17.63. Found: C, 66.29; H, 6.78; N, 17.35.

## 2-Pyrazinoic Acid (VII).

A solution of 0.01 mole of *n*-butyllithium in 10 ml. of ether was added slowly to a solution of 2.00 g. (0.01 mole) of 2-iodopyrazine in 20 ml. of anhydrous ether previously cooled to  $-35^{\circ}$ . The resulting red-brown slurry was stirred under nitrogen for seven minutes and then poured over finely powdered dry ice. After evaporation of the excess carbon dioxide the mixture was extracted with five 50 ml. portions of 5% aqueous sodium hydroxide solution. The combined extracts were adjusted to pH 7 with 10% hydrochloric acid and evaporated under reduced pressure at  $40^{\circ}$  to a volume of about 250 ml. The solid which precipitated during the concentration was removed by filtration. The filtrate was cooled to  $10^{\circ}$  and carefully acidified to pH 1 with 10% hydrochloric acid. The solution was exhaustively extracted with ether using a continuous liquid-liquid extraction apparatus. The extract was dried over anhydrous magnesium sulfate, treated with decolorizing carbon and filtered. Evaporation of the filtrate under reduced pressure yielded a wet solid which was dried by washing with pentane. The yield of VII as a tan solid was 0.37 g. (29.9%), m.p.  $210-215^{\circ}$  dec. Attempts at further purification were unsuccessful.

The infrared spectrum (nujol) was identical with that of the pure acid.

## Methyl 2-pyrazinoate (VIII).

2-Pyrazinoic acid (0.2 g., 0.00161 mole) was suspended in ether. A diazomethane solution in ether was added dropwise until nitrogen was no longer evolved and the solution remained yellow in color. The solution was stirred for one half hour and was then concentrated under reduced pressure to yield a brown solid. The product was dissolved in ether, dried over anhydrous magnesium sulfate, treated with decolorizing carbon and the solution was filtered. Upon evaporation of the filtrate to dryness under reduced pressure compound VIII was obtained as a yellow solid. Sublimation of the ester at 0.3 mm. and  $60^{\circ}$  gave 0.11 g. (51%) of white crystals with a melting point of  $60-60.5^{\circ}$  (lit. (8)  $59.5-60.5^{\circ}$ ).

The infrared spectrum (chloroform) was identical with that of the authentic ester.

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Point Apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 137 sodium chloride spectrophotometer. Nuclear magnetic resonance spectra were determined on a Varian Associates A-60 spectrometer, using tetramethylsilane at  $\tau$  10 as an internal standard. All microanalyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

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