

Departments of Chemistry, Long Island University  
and the Polytechnic Institute of Brooklyn

## The Preparation and Some Reactions of 3,6-Dimethyl-2-pyrazinylithium (Ia)

Albert Hirschberg (Ib), Alan Peterkofsky, and Paul E. Spoerri (Ic)

The widespread use of the halogen-metal interconversion reaction in the preparation of organolithium compounds, in which the metal is directly attached to a variety of heterocyclic ring systems is well documented (2). A survey of the literature reveals however, that no organometallic derivative of pyrazine, in which the metal is directly attached to the pyrazine nucleus has been prepared, although a number of attempts utilizing chloro and bromopyrazines have been reported (3,4,5). It has now been found that a pyrazinylithium derivative can be readily obtained by halogen-metal interconversion using a more reactive iodopyrazine derivative (6).

Addition of an ether solution of *n*-butyllithium to a solution of 2-iodo-3,6-dimethylpyrazine (I) in ether resulted in the formation of a reddish mixture. Carbonation of this mixture allowed the isolation of a solid which proved to be 3,6-dimethyl-2-pyrazinoic acid monohydrate (II), a compound previously prepared by Stoehr (7) by the selective oxidation of 2-ethyl-3,6-dimethylpyrazine (III).

A comparison sample of the acid was prepared by the hydrolysis of 2-cyano-3,6-dimethylpyrazine (IV), a new compound readily synthesized by treating 2-iodo-3,6-dimethylpyrazine (I) with cuprous cyanide in refluxing 3-picoline (8). Alkaline hydrolysis of the nitrile (IV) led to the isolation of an acid which proved to be identical with the acid isolated from the carbonation procedure as shown by mixture melting point and infrared examination of the two materials.

This evidence constituted unequivocal proof that the carbonation product was 3,6-dimethyl-2-pyrazinoic acid monohydrate (II) and that nuclear metalation had indeed occurred. These inter-relationships are summarized in the following chart.

Treatment of the dimethylpyrazinylithium reagent (V) with several aromatic aldehydes followed by hydrolysis gave the carbinols listed in Table I. In each case a compound was isolated which gave a positive nitrochromic acid test for alcohols (9) and whose infrared spectrum exhibited a broad peak in the region 3400-3200  $\text{cm}^{-1}$ , indicative of a bonded hydroxyl group (10). These data are also summarized in Table I.

Interest in the preparation of carbinols containing aliphatic sidechains led to several attempts involving the reaction of 3,6-dimethyl-2-pyrazinylithium (V) with acetaldehyde. These attempts, involving several different methods have thus far been unsuccessful.

Since the carbinols prepared in this work, contain the hydroxyl group alpha to the pyrazine nucleus and represent a new series of pyrazine derivatives (11) their synthetic utility seems worthy of further study and work along this line is being considered.

TABLE I  
Pyrazinyl-Phenyl Carbinols

Compound	R	$\nu$ max (KBr) $\text{cm}^{-1}$	Yield %
VI	H	3400-3350	57
VII	<i>p</i> -OCH <sub>3</sub>	3460-3200	58
VIII	<i>m</i> -NO <sub>2</sub>	3200-3170	47

### EXPERIMENTAL (12)

#### 2-Iodo-3,6-dimethylpyrazine (I).

This compound was prepared according to a procedure described by Hirschberg and Spoerri (6) in 48% yield, m.p. 61-62°.

Preparation of 3,6-dimethyl-2-pyrazinoic acid monohydrate (II) by carbonation.

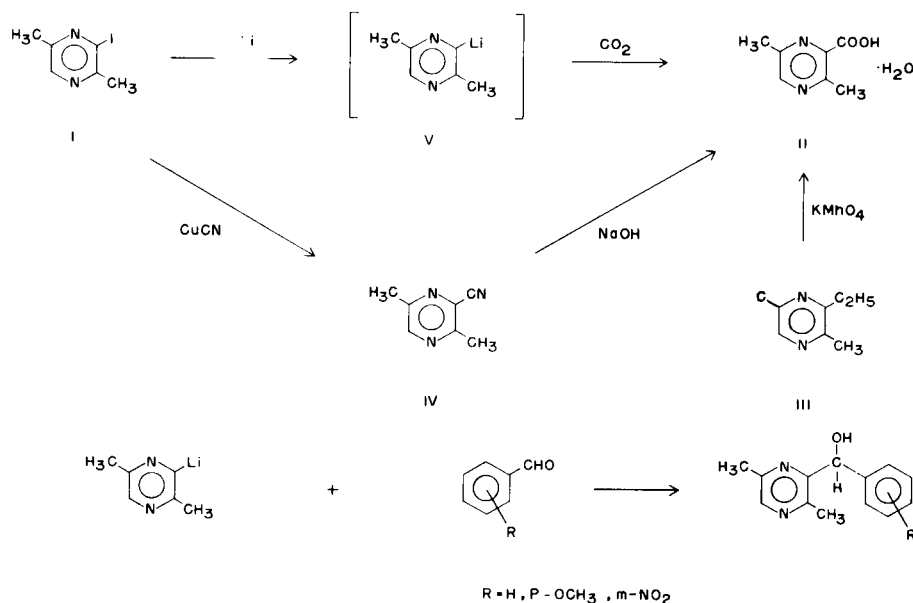
A solution of 0.052 mole of *n*-butyllithium in 100 ml. of ether was added rapidly to a solution of 10.1 g. (0.043 mole) of 2-iodo-3,6-dimethylpyrazine (I) in 50 ml. of anhydrous ether previously cooled to -50°. The resulting reddish mixture was stirred under nitrogen for 7 minutes and then poured over finely powdered carbon dioxide. After evaporation of the excess carbon dioxide, the mixture was extracted with five 50 ml. portions of 5% aqueous sodium hydroxide solution. The extract was adjusted to pH 7 with 10% nitric acid and evaporated under reduced pressure at room temperature to a volume of about 40 ml. This solution was then cooled to 10° and carefully acidified to pH 1 with 10% nitric acid. The solution was refrigerated for 24 hours and the needles of the monohydrate collected. Purification by sublimation yielded 2.94 g. (45.3%) of white crystals melting at 114-115° (lit., (7) m.p. 116-117°).

*Anal.* Calcd. for C<sub>7</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>·H<sub>2</sub>O: C, 49.40; H, 5.92; N, 16.46. Found: C, 49.53; H, 6.08; N, 16.53.

#### 2-Cyano-3,6-dimethylpyrazine (IV).

A mixture of 9.8 g. (0.042 mole) of 2-iodo-3,6-dimethylpyrazine (I) and 12.0 g. (0.134 mole) of cuprous cyanide in 40 ml. of anhydrous 3-picoline was allowed to reflux for three hours and poured while hot into a vigorously stirred mixture of 400 ml. of ice-cold 4*N* hydrochloric acid and 100 ml. of chloroform. After stirring for 30 minutes, the mixture was filtered and the residue washed with another 25 ml. of chloroform. The aqueous layer of the filtrate was further extracted with 100 ml. of chloroform and the extracts combined. After drying over magnesium sulfate, the chloroform solution was concentrated to a volume of 50 ml. by evaporation under reduced pressure at room temperature. The residue was then distilled under reduced pressure and a yellow liquid collected at 100-104° (22 mm.). The material solidified upon standing, and was purified by sublimation to give 3.9 g. (70.3%) of white crystals melting at 49-50°.

*Anal.* Calcd. for C<sub>7</sub>H<sub>7</sub>N<sub>3</sub>: C, 63.14; H, 5.30; N, 31.56. Found: C, 62.98; H, 4.81; N, 31.23.



## 2-(3,6-Dimethylpyrazinyl)phenylcarbinol (VI).

A solution of 0.025 mole of *n*-butyllithium in 75 ml. of anhydrous ether was added rapidly to a solution of 5.0 g. (0.021 mole) of 2-iodo-3,6-dimethylpyrazine (I) in 75 ml. of anhydrous ether previously cooled to  $-50^{\circ}$ . The reddish solution was stirred under nitrogen for 7 minutes and then a solution of 3.2 g. (0.030 mole) of benzaldehyde in 50 ml. of dry ether was added slowly. The mixture was allowed to warm up slowly and then refluxed for one hour after which, the mixture was poured into a liter of ice water saturated with ammonium chloride. The ether layer was separated and the aqueous layer extracted with four 50 ml. portions of ether. The combined ether extracts were dried over magnesium sulfate, treated with decolorizing carbon and filtered. Evaporation of the filtrate under reduced pressure at room temperature yielded a residual oil which was distilled to give 2.61 g. (56.7%) of a viscous yellow oil boiling at  $175-190^{\circ}$  (13 mm.). Further distillation gave an analytical sample whose boiling point was  $185-187^{\circ}$  (13 mm.).

*Anal.* Calcd. for C<sub>13</sub>H<sub>14</sub>N<sub>2</sub>O: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.63; H, 6.70; N, 12.69.

## 2-(3,6-Dimethylpyrazinyl)-4-methoxyphenylcarbinol (VII).

To a solution of the pyrazinyl lithium intermediate V, in ether at  $-50^{\circ}$ , prepared as described above, was added a solution of 4.1 g. (0.030 mole) of *p*-methoxybenzaldehyde in 50 ml. of anhydrous ether. The mixture was then allowed to warm up gradually and then refluxed for one hour. The tan reaction mixture was then poured into a liter of ice water saturated with ammonium chloride. The solid which formed was filtered and dried, while the ether layer was evaporated under reduced pressure at room temperature to a volume of 5 ml. and then refrigerated. After 24 hours, the solid which precipitated from the ether was filtered, dried and combined with the material originally obtained. The total weight of the solid isolated was 3.02 g. (57.9%). Four recrystallizations from petroleum ether (boiling range  $30-60^{\circ}$ ) afforded an analytical sample of white crystals melting at  $73-74^{\circ}$ .

*Anal.* Calcd. for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>: C, 68.84; H, 6.60; N, 11.47. Found: C, 69.17; H, 6.68; N, 11.15.

## 2-(3,6-Dimethylpyrazinyl)-3-nitrophenylcarbinol (VIII).

To a solution of the pyrazinyl lithium intermediate V, prepared as described previously, at  $-50^{\circ}$ , was added slowly a solution of 5.0 g. (0.033 mole) of *m*-nitrobenzaldehyde in 125 ml. of dry ether. The tannish yellow mixture was stirred for a period of 20 minutes while the bath temperature was allowed to rise to  $10^{\circ}$ . The nitrogen flow was stopped and 50 ml. of water was then added to the reaction mixture followed by 50 ml. of concentrated hydrochloric acid. The aqueous layer was separated and poured cautiously into a warm solution of potassium carbonate in 60 ml. of water. The dark oil which separated was taken up in 250 ml. of chloroform. Evaporation of the chloroform under reduced pressure at room temperature left an oily residue. The oil was chromatographed on alumina (Matheson, Coleman and Bell, 80-200 mesh) and elution with benzene gave 2.61 g. (46.5%) of white crystals melting at  $90-93^{\circ}$ . After three recrystallizations from water an analytical sample melting at  $99-100^{\circ}$  was obtained.

*Anal.* Calcd. for C<sub>13</sub>H<sub>13</sub>N<sub>2</sub>O<sub>3</sub>: C, 60.23; H, 5.05; N, 16.21. Found: C, 60.16; H, 5.13; N, 15.97.

Preparation of 3,6-dimethyl-2-pyrazinoic acid monohydrate (II) by hydrolysis of nitrile (IV).

A solution of 1.01 g. (0.0076 mole) of 2-cyano-3,6-dimethylpyrazine (IV) and 1.10 g. (0.0275 mole) of sodium hydroxide in 40 ml. of 70% ethanol was allowed to reflux until the evolution of ammonia ceased (about 4 hours). After removal of the solvent by evaporation, the residue was dissolved in 20 ml. of distilled water and filtered. The filtrate was cooled to  $10^{\circ}$  and carefully acidified to pH 1 with 10% nitric acid. The solution was refrigerated for 24 hours and the precipitate collected. Purification by sublimation gave 0.98 g. (85.5%) of white crystals melting at  $114-115^{\circ}$ , which proved to be identical with the acid prepared by the carbonation procedure described above.

## REFERENCES

- (1a) A portion of the thesis submitted by Alan Peterkofsky in partial fulfillment of the requirements for the M.S. degree, Long Island University, June, 1964. (b) To whom inquiries should be sent at Long Island University. (c) Polytechnic Institute of Brooklyn.
- (2) R. G. Jones and H. Gilman, in "Organic Reactions," Vol. VI, Roger Adams, Ed., John Wiley and Sons, Inc., New York, N. Y., 1951, p. 339.
- (3) B. Klein and P. E. Spoerri, *J. Am. Chem. Soc.*, **72**, 2949 (1951).
- (4) B. Klein, Doctoral Dissertation, Polytechnic Institute of Brooklyn, June, 1950.
- (5) A. E. Erickson, Doctoral Dissertation, Polytechnic Institute of Brooklyn, June, 1950.
- (6) A. Hirschberg and P. E. Spoerri, *J. Org. Chem.*, **26**, 1907 (1961).
- (7) C. Stoehr, *J. Prakt. Chem.*, (2) **47**, 480 (1893).
- (8) G. Karmas and P. E. Spoerri, *J. Am. Chem. Soc.*, **78**, 2141 (1956).
- (9) N. Cheronis and J. Entrikln, "Semimicro Qualitative Organic Analysis," Interscience, New York, N. Y., 1959, pp. 237-238.
- (10) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day Inc., San Francisco, 1962, pp. 30-32.
- (11) R. Levine and coworkers have reported the synthesis of a series of pyrazinylmethylcarbinols by means of the condensation of several aldehydes and ketones with pyrazinylmethylsodium. These compounds contain the hydroxyl group beta to the pyrazine ring. [J. Behun and R. Levine, *J. Am. Chem. Soc.*, **81**, 5666 (1959). M. Kamal and R. Levine, *J. Org. Chem.*, **27**, 1360 (1962).]
- (12) Infrared spectra were obtained using a Perkin-Elmer Infracord spectrophotometer, Model 137 D. Melting points were taken on a Mel-Temp apparatus and are uncorrected. Microanalyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y. The preparation of *n*-butyllithium was carried out as described by Jones and Gilman (2).

Received April 30, 1965

Brooklyn, New York