The Reaction of Alkylpyrazine Anions with Some Electrophiles. Synthesis of 1,2-*bis*(2-pyrazyl)ethanes

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The reaction of alkylpyrazine anions with iodine, 1,2-dibromoethylene or oxygen gives 1,2-*bis*-(2-pyrazyl)ethanes.

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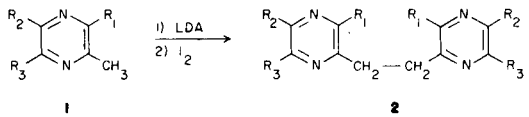
As part of a program to prepare novel pyrazine derivatives, we became interested in the synthesis of 1,2-*bis*-(2-pyrazyl)ethanes. Alkylpyrazines were chosen as starting materials since they can be easily converted to their anions which in turn can participate in coupling reactions. Indeed, treatment of the anions of several alkylpyrazines (**1a-d**) with iodine, a reported coupling reagent for carbanions (1), gave the desired products as shown in Scheme 1. The reactions, except for the case of **1d** proceeded smoothly giving only the products and unreacted starting

Scheme 1



1

1a, $R_1=R_2=R_3=CH_3$
1b, $R_1=R_2=H, R_3=CH_3$
1c, $R_1=CH_3, R_2=R_3=H$
1d, $R_1=R_2=R_3=H$

2

2a, $R_1=R_2=R_3=CH_3$
2b, $R_1=R_2=H, R_3=CH_3$
2c, $R_1=CH_3, R_2=R_3=H$
2d, $R_1=R_2=R_3=H$

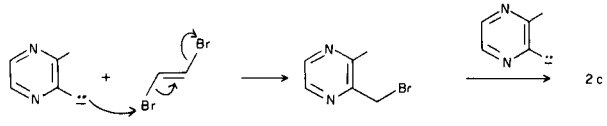
materials. The low yield (4%) of **2d** obtained from **1d** is due to addition of the anion to the pyrazine ring as shown by the isolation of a mixture of two products identified by nmr as pyrazyl-6-methyl-2-pyrazylmethane (**3**) and

3 **4**

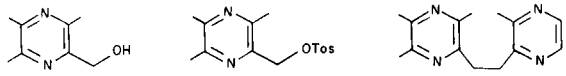
pyrazyl-5-methyl-2-pyrazylmethane (**4**). The observation that the stoichiometry of the reaction is one mole of anion to 0.5 mole of iodine suggests that the reaction proceeds by nucleophilic attack of the anion on an iodine molecule to form iodomethylpyrazine which in turn reacts rapidly with a second anion molecule *via* an S_N2 type reaction to yield the product.

An alternative useful synthetic route to 1,2-*bis*-(2-pyrazyl)ethanes is demonstrated for the case of **2c**. Treatment of the anion of 2,3-dimethylpyrazine (**1c**) with 1,2-dibromoethylene gave **2c** in 55% yield. This result can best be rationalized as shown in Scheme 2. The observation that 1,2-dibromoethylene can lead to the coupling of anions has previously been noted (2).

Scheme 2



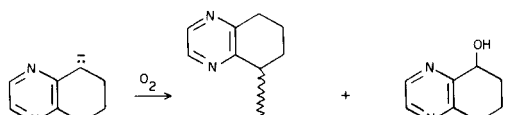
Preparation of 1,2-*bis*(2-pyrazyl)ethanes *via* the iodine or the 1,2-dibromoethylene mediated coupling of alkylpyrazine anions is useful only when the parent pyrazines can give a single anion. Moreover, the above methods cannot be used for the preparation of nonsymmetrical compounds. We have however, developed a two step synthesis which overcomes these difficulties. Treatment of the anion of **1a** with molecular oxygen gave the hydroxylmethyl derivative **5**. Reaction of **5** with LDA followed by the addition of tosyl chloride gave the corresponding tosylate **6**. The latter was reacted with the anion of **1c** to yield 1-(3-methyl-2-pyrazyl)-2-(3,5,6-trimethyl-2-pyrazyl)ethane (**7**).



5 **6** **7**

Quite interestingly, the reaction of **1a** with oxygen gave also a major by-product (12%), identified as **2a**. The generality of this rather unusual reaction was demonstrated by an additional example: Treatment of the anion of 5,6,7,8-tetrahydroquinoxaline (**8**) with oxygen resulted in the formation of a significant amount (10%) of a mixture of *meso*- and *d,l*-5,5'-*bis*(5,6,7,8-tetrahydroquinoxalyl) (**9**), in addition to the expected major product, 5-hydroxy-5,6,7,8-tetrahydroquinoxaline (**10**) (Scheme 3). A similar dimerization of alkylaromatic (3) and alkylheteroaromatic (4) anions in the presence of oxygen has been reported and is assumed to proceed *via* a radical mechanism.

Scheme 3



8 **9** **10**

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EXPERIMENTAL

All reactions involving organometallic reagents were carried out under a nitrogen atmosphere. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Ir spectra were recorded with a Perkin-Elmer 621 spectrophotometer. Nmr spectra were recorded with a Varian XL-100 or a Brucker WP80 spectrometer, and the chemical shifts are given in δ units downfield from internal TMS. Mass spectra were recorded with a CEC 21-104 spectrometer. Elemental analyses were performed by Galbraith Laboratories Inc., Knoxville, Tennessee. Both qualitative and preparative tlc were carried out on silica gel GF plates using hexane containing 15-40% acetone as the eluent. Column chromatography was conducted on silica gel 60 mesh using hexane containing 5-30% acetone as the eluent.

1,2-*Bis*(3,5,6-trimethyl-2-pyrazyl)ethane (**2a**).

To a solution of lithium diisopropylamide (0.05 mole) in dry ether (100 ml.) and hexane (20 ml.) was added at 0° a solution of tetramethylpyrazine (**1a**) (6.8 g., 0.05 mole) in dry ether (40 ml.). The mixture was stirred at room temperature for one hour and cooled to 0°. To the cooled solution was slowly added a solution of iodine (6.35 g., 0.025 mole) in dry ether (80 ml.), and the mixture was stirred at 0° for 30 minutes. Water was added, and the ether layer was separated, washed with water, and dried (magnesium sulfate). Evaporation of the solvent gave an oil (7.3 g.) from which 2.1 g. (31%) of **2a** was isolated by column chromatography. Recrystallization of **2a** from hexane gave plates, m.p. 117-119°; ir (nujol): 1450, 1410 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.44 (s, 18H, $6CH_3$), 3.20 (s, 4H, $2CH_2$); ms: (m/e) 270 (M^+, 56), 255 (32), 241 (21), 149 (100), 136 (22), 135 (20), 53 (70).

Anal. Calcd. for $C_{16}H_{22}N_4$: C, 71.07; H, 8.20; N, 20.73. Found: C, 71.17; H, 8.34; N, 20.75.

1,2-*Bis*(6-methyl-2-pyrazyl)ethane (**2b**).

The synthesis of **2b** was carried out as described for **2a** using 5.4 g. (0.05 mole) of 2,6-dimethylpyrazine (**1b**). The crude product (5.3 g.) was subjected to column chromatography to give 1.9 g. (36%) of pure **2b**. Recrystallization from hexane gave plates, m.p. 99-101°; ir (nujol): 1540, 1460, 1430 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.55 (s, 6H, $2CH_3$), 3.24 (s, 4H, $2CH_2$), 8.21 (s, 2H, pyrazine), 8.26 (s, 2H, pyrazine); ms: (m/e) 214 (M^+, 29), 213 (40), 146 (13), 145 (14), 121 (100), 66 (31), 53 (16), 52 (12), 42 (22), 41 (14), 40 (20), 39 (86).

Anal. Calcd. for $C_{12}H_{14}N_4$: C, 67.25; H, 6.59; N, 26.15. Found: C, 67.11; H, 6.73; N, 25.89.

1,2-*Bis*(3-methyl-2-pyrazyl)ethane (**2c**).

Method A.

The synthesis of **2c** was carried out as described for **2a** using 5.4 g. (0.05 mole) of 2,3-dimethylpyrazine (**1c**). Evaporation of the ether solution gave only 2.8 g. of crude product; consequently, the aqueous layer was extracted with methylene chloride, and the methylene chloride extracts yielded an additional 2.0 g. of crude product which was identical in composition to the original product. Pure **2c** (2.3 g., 43%) was obtained by preparative tlc. Recrystallization from hexane gave plates, m.p. 94-96°; ^1H nmr (deuteriochloroform): δ 2.60 (s, 6H, $2CH_3$), 3.33 (s, 4H, $2CH_2$), 8.29 (q, 4H, pyrazine); ms: (m/e), 214 (M^+, 24), 199 (26), 185 (16), 121 (100), 119 (13), 108 (13), 107 (13), 93 (16), 80 (10), 67 (26), 66 (18), 53 (21), 52 (20).

Anal. Calcd. for $C_{12}H_{14}N_4$: C, 67.26; H, 6.59; N, 26.15. Found: C, 67.28; H, 6.70; N, 26.03.

Method B.

To a stirred suspension of the anion of **1c** (0.1 mole) in ether (200 ml.) at 0°, prepared as described for **1a**, was added with stirring a solution of 1,2-dibromoethylene (9.3 g., 0.05 mole) in ether (40 ml.). The mixture was left stirring at 0° for 40 minutes. Work-up as above afforded an oil (21.0 g.). A portion of the crude mixture (1 g.) was subjected to preparative tlc to give 280 mg. (55%) of **2c**, m.p. 94-96 (from hexane). The product was identical with authentic **2c** (Method A), by mixed m.p., tlc, ir and nmr.

1,2-*Bis*(2-pyrazyl)ethane (**2d**).

The synthesis of **2d** was carried out as described for **2a** using 4.8 g. (0.05 mole) of 2-methylpyrazine (**1d**). Evaporation of the etheral fraction gave 0.8 g. of crude product, and an additional 4.0 g. of crude product was obtained from the aqueous phase by methylene chloride extraction. Column chromatography of the combined crude product gave 0.5 g. of a material which was identified as a mixture of **2d**, pyrazyl-6-methyl-2-pyrazylmethane (**3**) and pyrazyl-5-methyl-2-pyrazylmethane (**4**) on the basis of the mixture's nmr spectrum. The amount of **2d** constituted 35% of the mixture which represents a 4% yield. Isolation of pure **2d** was accomplished by repeated (5 times) preparative tlc of the mixture, followed by recrystallization from hexane to give needles (5.0 mg.), 69-72°; ^1H nmr (deuteriochloroform): δ 3.32 (s, 4H, CH_2), 8.33-8.59 (m, 6H, pyrazine); ms: (m/e) 186 (M^+, 34), 185 (68), 171 (10), 158 (12), 132 (18), 131 (21), 118 (12), 107 (100), 93 (10), 80 (22), 79 (24), 66 (25), 53 (36), 52 (45), 51 (16).

Anal. Calcd. for $C_{10}H_{10}N_4$: C, 64.50; H, 5.41; N, 30.09. Found: C, 64.16; H, 5.62; N, 29.68.

3,5,6-Trimethylpyrazine-2-methanol (**5**).

To a solution of lithium diisopropylamide (0.05 mole) in ether (100 ml.) and hexane (20 ml.) maintained at 0° was added a solution of tetramethylpyrazine (6.8 g., 0.05 mole) in dry ether (40 ml.). The mixture was stirred at room temperature for one hour, cooled to 0°, and treated with oxygen until the red color changed into yellow (about one hour). Water was added, and the mixture was treated with a large excess of sodium sulfite. The ether layer was separated and the aqueous layer was extracted with methylene chloride. The organic layers were combined, dried (magnesium sulfate), and the solvent was evaporated to give 6.5 g. of an oil. The oil was subjected to thin layer chromatography to give 1.40 g. (21%) of **5**. An analytical sample was obtained by subliming the product isolated from tlc, m.p. 67-69°; ir (nujol): 3240, 1418, 1450; ^1H nmr (deuteriochloroform): δ 2.42 (s, 3H, CH_3), 2.48 (s, 6H, $2CH_3$), 4.67 (s, 2H, CH_2); ms: (m/e) 152 (M^+, 100), 151 (76), 134 (53), 133 (10), 124 (19), 123 (94), 122 (20), 121 (40), 93 (14), 82 (12), 80 (20), 70 (12), 69 (41), 55 (10), 54 (30), 53 (40), 52 (46), 51 (10), 42 (65), 41 (20).

Anal. Calcd. for $C_9H_{12}N_2O$: C, 63.13; H, 7.95; N, 18.41. Found: C, 63.37; H, 8.08; N, 18.67.

Also isolated was 0.86 g. (12%) of **2a**, identical in all respects to **2a** prepared by the iodine mediated coupling of the anion of tetramethylpyrazine.

1-(3-Methyl-2-pyrazyl)-2-(3,5,6-trimethyl-2-pyrazyl)ethane (**7**).

A solution of **5** (0.83 g., 0.0055 mole) in dry ether (40 ml.) was added to a solution of lithium diisopropylamide (0.0055 mole) in dry ether (50 ml.), and the mixture was stirred at room temperature for 90 minutes. To the above solution was added a solution of tosyl chloride (1.05 g., 0.0055 mole) in dry ether (40 ml.) and the mixture was stirred for 90 minutes. To the solution of the tosylate thus prepared was added, with stirring, a suspension of the anion of 2,3-dimethylpyrazine (**1c**) (0.594 g., 0.0055 mole) in dry ether (100 ml.). The mixture was stirred at room temperature for 2 hours. Water was added, and the ether layer was separated, washed with water, and dried (magnesium sulfate). Evaporation of the solvent gave an oil which was purified by preparative tlc to give 0.65 g. (49%) of **7**. An analytical sample was obtained by sublimation, m.p. 42-44°; ^1H nmr (deuteriochloroform): δ 2.44 (s, 6H, $2CH_3$), 2.46 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 3.25 (s, 4H, CH_2), 8.21 (ABq, 2H, pyrazine).

Anal. Calcd. for $C_{14}H_{18}N_4$: C, 59.39; H, 7.49; N, 23.12. Found: C, 59.11; H, 7.68; N, 22.99.

Reaction of the Anion of 5,6,7,8-Tetrahydroquinoxaline with Oxygen.

A solution of 5,6,7,8-tetrahydroquinoxaline (2.68 g., 0.01 mole) in dry ether (30 ml.) was added to a solution of lithium diisopropylamide (0.01 mole) in dry ether (100 ml.) at 0°. The resulting red mixture was stirred at 0° for 15 minutes after which oxygen was passed through it with vigorous stirring until the solution was yellow (about 30 minutes). To the cold solution was added 30 ml. of 1.67*M* hydrochloric acid, followed by

addition of a large excess of sodium sulfite, and the mixture was stirred until a negative peroxide test was obtained. The mixture was basified to *p*H 9 using sodium carbonate, the ether layer was separated, washed with water, and dried (magnesium sulfate). Evaporation of the ether gave an oil (1.1 g.). Preparative thin layer chromatography of the oil gave 260 mg. (10%) of a mixture of *d,l*- and *meso* 5,5'-*bis*(5,6,7,8-tetrahydroquinoxalyl) (**9**); ^{1}H nmr (deuteriochloroform): δ 1.85 (m, 8H, 6,6',7,7'-CH_2), 2.98 (m, 4H, 8,8'-CH_2), 3.88 (br t, C-5,5'-CH, minor isomer), 4.22 (br t, C-5,5'-CH, major isomer), 8.18 (ABq, pyrazine, minor isomer), 8.34 (ABq, pyrazine, major isomer). Recrystallization of the mixture from hexane gave a small amount of needles, m.p. 110-114°, which was a single isomer of **9** of undetermined stereochemistry; ir (nujol): 1457, 1435, 1408, 1402 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.22-2.25 (m, 8H, 6,6',7,7'-CH_2), 2.98 (m, 4H, 8,8'-CH_2), 4.22 (br, t, 2H, 5,5'-CH), 8.34 (ABq, 4H, pyrazine); ms: (m/e) 266, (M^+ 100), 238 (13), 237 (13), 223 (15), 134 (100), 133 (100), 41 (29), 39 (28).

Anal. Calcd. for $C_{16}H_{18}N_4$: C, 72.15; H, 6.81; N, 21.04. Found: C, 72.30; H, 6.90; N, 21.03.

The aqueous layer was extracted with methylene chloride (5 × 100 ml.) and the methylene chloride solution was dried over magnesium sulfate. Evaporation of the solvent gave 1.6 g. of an oil which was subjected to preparative thin layer chromatography to give 5-hydroxy-5,6,7,8-tetrahydroquinoxaline (**10**) as an oil. Sublimation at 80-90°C (0.05 mm Hg) gave 600 mg. (20%) of crystals, m.p. 53-55°; ir (nujol): 3380, 1460, 1430, 1400, 1072 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.65-2.56 (m, 4H, 6,7-CH_2), 3.00 (m, 2H, 8-CH_2), 4.81 (br t, 1H, CH), 8.39 (ABq, 2H, pyrazine); ms: (m/e) 150 (80), 131 (7), 122 (55), 107 (6), 95 (12), 94 (100), 93 (23), 68 (11), 67 (9), 66 (7), 65 (7), 52 (16).

Anal. Calcd. for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.92; H, 6.88; N, 18.68.

REFERENCES AND NOTES

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(3) D. H. R. Barton and D. W. Jones, *J. Chem. Soc.*, 3563 (1965).

(4) E. C. Taylor and J. S. Driscoll, *J. Org. Chem.*, **26**, 3796 (1961).