

Preparation of 5,6,11,12-Tetrahydrocycloocta[1,2-*b*:5,6-*b'*]dipyrazine

Yoram Houminer\* and David L. Williams

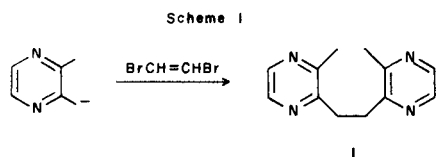
Philip Morris Research Center, P. O. Box 26583,  
Richmond, Virginia 23261  
Received August 13, 1984

The reaction of 1,2-bis(3-methyl-2-pyrazyl)ethane (**1**) with two equivalents of LDA followed by 1,2-dibromoethylene gave a mixture of two intramolecular ring closure products, **2** and **3**, in low yields. A dimer **4** resulting from an intermolecular coupling reaction was also isolated.

*J. Heterocyclic Chem.*, **22**, 373 (1985).

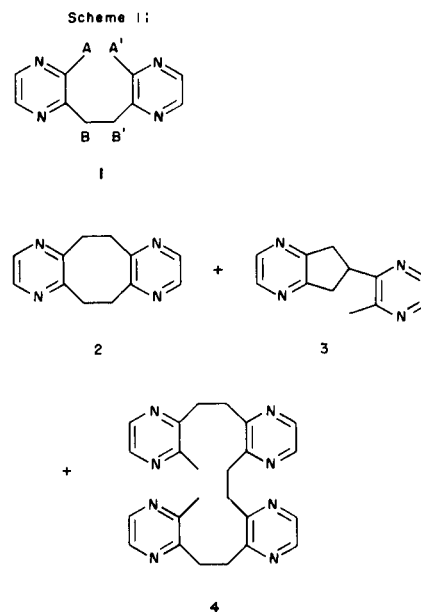
Alkylpyrazines are an important class of compounds due mainly to their unique flavor properties [1]. They are found in nature in a large variety of consumer products such as food and tobacco [2,3]. Among the most common pyrazines are a large variety of alkylpyrazines. These are often used as starting materials in the synthesis of other pyrazine derivatives. Thus, they are easily metalated by lithium amides such as lithium diisopropylamide (LDA) and the resulting anions can be reacted with a wide spectrum of electrophiles to give different pyrazine derivatives [3].

We have recently reported [4] that alkylpyrazine anions react with electrophiles which are capable of promoting coupling reactions to form the corresponding 1,2-bis(alkylpyrazine)ethanes. An example of such a reaction is shown in Scheme I for the case of 2,3-dimethylpyrazine and 1,2-dibromoethylene.



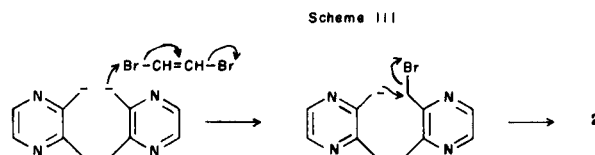
The investigation reported in this paper is an extension of this study to other coupling reactions, in particular to intramolecular coupling reactions involving dianions derived from systems such as **1**.

When **1** is treated with two equivalents of LDA, four possible dianions can be formed (AA', AB', BB', AB, where A, A', B, B' designate the location of the negative charge). The formation of BB' is very unlikely, since in this dianion the two negative charges are located on two adjacent carbons. The formation of AB is also unlikely because in this case the two negative charges are stabilized by the same pyrazine ring. Indeed, when **1** was treated with two equivalents of LDA followed by one equivalent of 1,2-dibromoethylene, two products, **2** and **3**, resulting from intramolecular ring closure (intramolecular coupling) reactions, were isolated (Scheme II). A dimer (**4**) resulting from an intermolecular coupling reaction was also isolated.



The structures of the three products were established from their ms and <sup>1</sup>H-nmr spectra. The <sup>1</sup>H-nmr spectrum of **2** shows a singlet in the methylene region at δ 3.48 (8H) and a singlet in the aromatic region at δ 8.24 (4H). The ms of **2** shows a molecular ion at 212. The <sup>1</sup>H-nmr spectrum of **3** shows a singlet at δ 2.73 (3H), two AA'BB'X multiplets at δ 3.52 (4H) and 4.18 (1H), and two singlets in the aromatic region at δ 8.40 and 8.43 (4H). The ms of **3** also indicates a molecular ion at 212 but its fragmentation pattern is different from that of **2**. The <sup>1</sup>H-nmr spectrum of **4** shows a singlet at δ 2.61 (6H), two singlets at δ 3.38 and 3.43 (12H) and two singlets at δ 8.32 and 8.34 (8H). The ms of **4** indicates a molecular ion at 426 and a fragmentation pattern characteristic of 1,2-bis(pyrazine)ethanes [4].

The formation of **2** and **3** proceeds most likely *via* a two step reaction as illustrated in Scheme III for the case of **2**.



It should be noted that when two equivalents of LDA are used in the reaction, there is a possibility that **1** is partially converted into a mixture of its monoanions. The formation of **4** could indeed proceed *via* a monoanion reaction, similar to the coupling of 2,3-dimethylpyrazine to form **1** (Scheme I). However, it is very unlikely that **2** and **3** are formed through the monoanions of **1**.

The yields from a typical reaction in ether at 0° are summarized in the Table. We have made several attempts to increase the yield of **2** and **3** by carrying out the reaction under different conditions; changing temperatures, solvents, reagents and concentrations. However, no significant improvement was obtained in this reaction and in some cases the yields were even lower.

Table

Reactions of **1** in Ether at 0° with LDA Followed by BrCH = CHBr

Product	<b>2</b>	<b>3</b>	<b>4</b>	Recovered <b>1</b>
Yield % [a]	0.7	2.5	3.6	11.7

[a] Tlc purified and crystallized.

In all cases studied the yields of **2** and **3** are low, with most of the starting material being converted into tar. The major product in the reaction is **4**, a compound resulting from an intermolecular coupling reaction. We also have some indication that the tar which is formed in the above reaction is in part a mixture of higher homologues of the intermolecular coupling process. Thus, intermolecular couplings either through dianions or monoanions compete with the formation of **2** and **3** and therefore are responsible for their low yield. However, since dilution experiments did not increase the yield of **2** and **3**, other factors should be considered as well. We have recently reported [4] that alkylpyrazine anions can add to a pyrazine ring to form dimeric and higher oligomeric products. This is a side reaction that takes place in most of the alkylpyrazine anion reactions resulting in the formation of tar. We now find that the amount of LDA used in the preparation of alkylpyrazine anions also can affect the yields of these reactions. For example, we have tested 2,3-dimethylpyrazine as a model compound and found that when treated at 0° in ether with one equivalent of LDA, about 80% of the starting materials was recovered when the mixture was quenched with water. No significant difference was found when the same reaction mixture was left overnight at room temperature prior to quenching. However, when 2,3-dimethylpyrazine was treated with 2.5 equivalents of LDA at 0° in ether and quenched with water after 30 minutes, not even trace amounts of the starting material could be recovered. This observation may further explain the low yields of products obtained in the reaction of **1** treated with two equi-

valents of LDA.

In summary, this investigation led to the preparation of several new pyrazine derivatives. It should be noted that compound **2** is a new ring system which to the best of our knowledge has not yet been reported in the literature. This study has also generated additional information about the chemistry of alkylpyrazine anions and dianions, and has demonstrated the synthetic potential of these and similar intermediates.

## 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. The nmr spectra were recorded with a Bruker WP80 spectrometer and the chemical shifts are given in  $\delta$  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% acetone as the eluent.

Reaction of 1,2-bis(3-Methyl-2-pyrazyl)ethane (**1**) with 1,2-Dibromoethylene.

To a stirred solution of lithium diisopropylamide (0.022 mole) in dry ether (200 ml) and hexane (9.5 ml) was added at 0° a solution of **1** (2.14 g, 0.01 mole) in dry ether (80 ml) over a period of 5 minutes. The dark brown suspension was stirred at 0° for 15 minutes. 1,2-Dibromoethylene (1.86 g, 0.01 mole) in dry ether (80 ml) was added over a 10 minute period and the resulting dark purple solution was stirred for 70 minutes at 0-10°. Water (150 ml) was added and the ether layer was separated. The aqueous layer was extracted with ether and the combined ether layers were washed with water, dried (sodium sulfate) and evaporated under reduced pressure to give 2.5 g of a brown oil. Repeated (2 times) preparative tlc afforded pure 5,6,11,12-tetrahydrocycloocta[1,2-*b*:5,6-*b'*]dipyrazine (**2**). Recrystallization from hexane gave 14 mg (0.7%) of white needles, mp 158-160°; <sup>1</sup>H-nmr (deuteriochloroform):  $\delta$  3.48 (s, 8H, 4CH<sub>2</sub>), 8.24 (s, 4H, pyrazine); ms: (m/e), 212 (M<sup>+</sup>, 85), 211 (30), 197 (100), 119 (24), 78 (9).

Anal. Calcd. for C<sub>12</sub>H<sub>12</sub>N<sub>4</sub>: C, 67.90; H, 5.79; N, 26.40. Found: C, 67.75; H, 5.72; N, 26.32.

The tlc also afforded pure 6-(3-methyl-2-pyrazyl)-6,7-dihydro-5*H*-cyclopentapyrazine (**3**). Recrystallization from hexane gave 54 mg (2.5%) of white needles, mp 98-99°; <sup>1</sup>H-nmr (deuteriochloroform):  $\delta$  2.73 (s, 3H, CH<sub>3</sub>), 3.52 (part of an AA'BB'X m, 4H, 2CH<sub>2</sub>), 4.18 (part of an AA'BB'X m, 1H, CH), 8.40 (s, 2H, pyrazine), 8.43 (s, 2H, pyrazine); ms: (m/e), 212 (M<sup>+</sup>, 95), 211 (40), 197 (19), 119 (100), 78 (10).

Anal. Calcd. for C<sub>12</sub>H<sub>12</sub>N<sub>4</sub>: C, 67.90; H, 5.70; N, 26.40. Found: C, 67.87; H, 5.75; N, 26.29.

Also separated was pure **4**. Recrystallization from hexane-methylene chloride gave 76 mg (3.6%) of white needles, mp 153-155°; <sup>1</sup>H-nmr (deuteriochloroform):  $\delta$  2.61 (s, 6H, 2CH<sub>3</sub>), 3.38 (s, 6H, 3CH<sub>2</sub>), 3.43 (s, 6H, 3CH<sub>2</sub>), 8.32 (s, 4H, pyrazine), 8.34 (s, 4H, pyrazine); ms: (m/e), 426 (M<sup>+</sup>, 100), 411 (4), 369 (7), 319 (47), 305 (32), 215 (27), 213 (39), 211 (30), 199 (34), 197 (28), 134 (12), 121 (19), 119 (30), 109 (61), 108 (22), 107 (12).

Several modifications of the above reaction were carried out:

a) The reaction was carried out in tetrahydrofuran at -78° [5]. LDA was allowed to react with **1** for 10 minutes and the resulting mixture was reacted with 1,2-dibromoethylene for 20 minutes. A small amount of **4** was formed but neither **2** nor **3** could be detected by tlc.

b) The reaction was carried out in ether at 0° using all reactants at one half of the above concentration. The addition of **1** to lithium diisopropylamide was done slowly (30 minutes) and the mixture was allowed to react with 1,2-dibromoethylene for 40 minutes. No improvement in yields was noted.

c) The reaction was carried out at 0° in tetrahydrofuran using all reactants at one half of the above concentration. The anions mixture was reacted with 1,2-dibromoethylene for 20 minutes. A small amount of **4** was formed along with trace amount of **3**. However, **2** could not be detected in the crude mixture.

d) The reaction was carried out in ether at 0° using methyl lithium instead of lithium diisopropylamide. Only a trace amount of **4** was formed but neither **2** nor **3** could be detected by tlc.

e) The reaction was carried out in ether at 0° using lithium 2,2,6,6-tetramethylpiperidide. Only **4** was formed but neither **2** nor **3** were detected by tlc.

## REFERENCES AND NOTES

- [1] G. Ohloff and I. Flament, *Prog. Chem. Org. Nat. Prod.*, **6**, 231 (1979).
- [2] G. Ohloff and I. Flament, *Heterocycles*, **11**, 663 (1978).
- [3] G. W. H. Cheeseman and E. S. G. Werstiuk, *Adv. Heterocyclic Chem.*, **14**, 99 (1972).
- [4] Y. Houminer and E. B. Sanders, *J. Heterocyclic Chem.*, **17**, 647 (1980).
- [5] The solubility of **1** in ether at -78° is very low.