

Department of Chemistry, University of Pittsburgh

The Chemistry of Pyrazine and its Derivatives. X.

The Mono- and Diacylation of Tetramethylpyrazine

Sujit K. Chakrabartty (1) and Robert Levine

By the use of sodium amide in liquid ammonia or phenyllithium in ether as the condensing agent it has been possible to synthesize a series of ketones containing the pyrazine ring with the structure, $\text{RCOCH}_2\text{C}_4\text{N}_2(\text{CH}_3)_3$ where R is alkyl, aryl or heterocyclic. Also, under appropriate conditions, tetramethylpyrazine has been diacylated to give three diketones of the type $(2\text{-RCOCH}_2)\text{-}(6\text{-R}'\text{COCH}_2)\text{C}_4\text{N}_2(\text{CH}_3)_2\text{-}3, 5$.

In earlier papers in this series the prototropic reactions of methylpyrazine (2-5) and 2,6-dimethylpyrazine (6-9) were described. The present report is concerned with the acylation of tetramethylpyrazine. While earlier (3) we found that methylpyrazine is metalated at its methyl group by phenyllithium in only very low yield probably due to azomethine addition of the phenyllithium to the pyrazine ring, sodium amide is a very effective metalating agent. We have now found that both sodium amide in liquid ammonia and phenyllithium in ether can be used to effect the lateral metalation of tetramethylpyrazine (I) since I cannot undergo azomethine addition with phenyllithium.

The over-all reaction to give the ketones (II) is shown in the accompanying chart of equations. The stoichiometry which is required to give the highest yields (Table I) of acylmethyltrimethylpyrazines is 2:2:1, *i. e.*, two equivalents of sodium amide or phenyllithium to two equivalents of I to one equivalent of ester. These results agree with the scheme proposed earlier for the acylation of methylpyrazine (4) and 2,6-dimethylpyrazine (6). While only the monoacylation product was obtained (*e. g.* II, R is C_6H_5) using phenyllithium as the condensing agent, mixtures of II (R is C_6H_5) and the diacylated product, 2,6-diphenacyl-3,5-dimethylpyrazine (VI) were obtained when sodium amide was the condensing agent.

It can be seen (Tables I and II) that higher yields of ketones are obtained when phenyllithium is used as the condensing agent than when the reactions are effected by sodium amide. This could be explained by postulating that phenyllithium would be expected to coordinate with a pyrazine nitrogen atom more effectively than sodium amide to give a quasi six-membered ring compound (III) in which the potential phenyl anion is located in a very favorable position to abstract a proton from the adjacent methyl group to give IV which then rearranges to V. The results of these acylations appear in Table II.

It was also of interest to see whether, as has been done previously with 2,6-dimethylpyrazine (9), it would be possible to diacylate I using phenyllithium

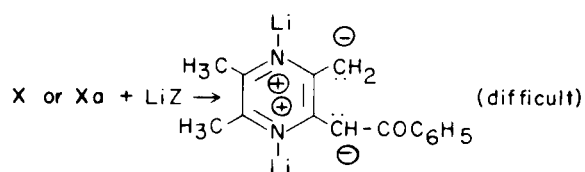
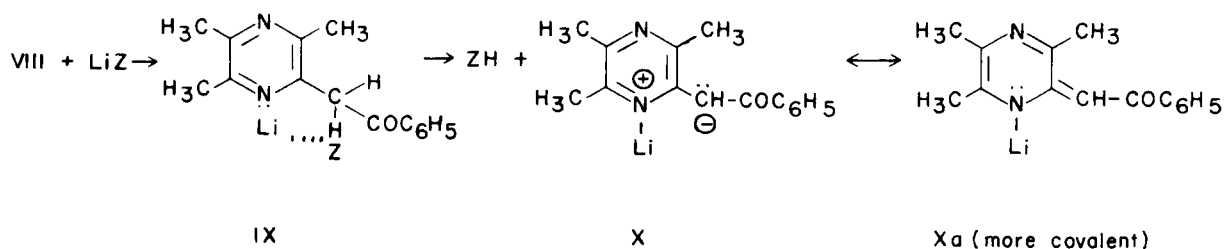
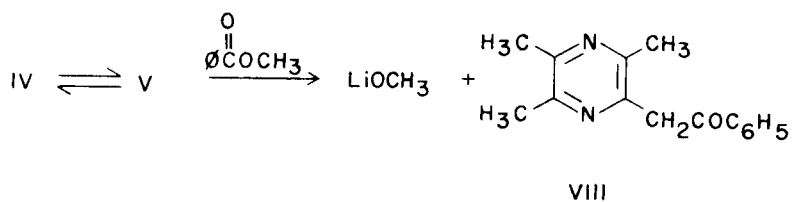
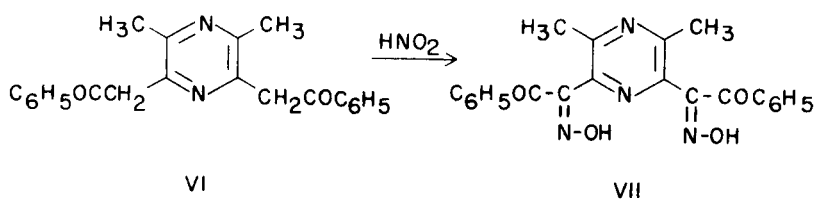
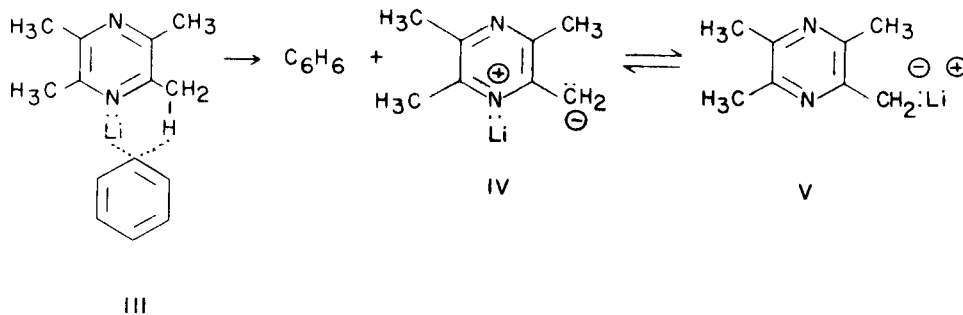
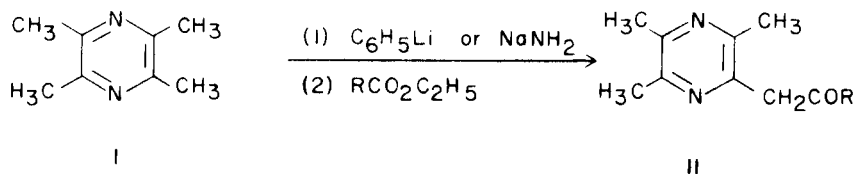
and sodium amide as condensing agents. It can be seen (Table I) that the best yield (32.8%) of the diacylated product was obtained using a 6:1:1 molar ratio of sodium amide to I to ethyl benzoate. It can also be seen (Table II) that some diacylated material was obtained when I was acylated with ethyl anisate and ethyl isobutyrate as well as with ethyl benzoate using a 2:2:1 molar ratio of reactants.

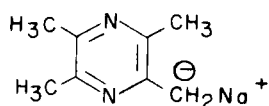
There is little doubt about the structure of the diacylated products. Thus, the dibenzoylated compound was shown to be 2,6-diphenacyl-3,5-dimethylpyrazine (VI) by: (1) comparing its ultraviolet spectrum with that of an authentic sample of 2,6-dimethylpyrazine and (2) by nitrosating a sample of it to give 2,6-bis-(1-oximinophenacyl)-3,5-dimethylpyrazine (VII). The nitrosation reaction shows that both benzoyl groups are not on the same carbon atom, while the ultraviolet spectrum indicates that these groups are on the two and six methyl carbon atoms. Similar results were obtained with 2,6-di-(*p*-methoxyphenacyl)-3,5-dimethylpyrazine.

In order to further verify the structure of VI, the benzylation of phenacyltrimethylpyrazine was studied. Using sodium amide in liquid ammonia a good yield (67.8%) of 2,6-diphenacyl-3,5-dimethylpyrazine was obtained. However, when phenyllithium was used as the condensing agent, 80-90% of the starting materials were recovered and less than 5% of a red-colored solid, m. p. 123-127° from 60-70° petroleum ether, was obtained. The elemental analysis of this material showed that it is probably a dimethyldiphenacylpyrazine. However, it is not VI as shown by a mixed melting point determination. Spectral studies on this compound have not yet been made since it was obtained in such a low yield. It might well be 2,3-diphenacyl-5,6-dimethylpyrazine.

The results of the last two experiments may also explain why a considerable amount of the diacylated product (VI) is obtained during the acylation of I when sodium amide is used as the condensing agent and no diketone is obtained when phenyllithium is used to effect the reaction.

It is believed that the ketone VIII (II, R is C_6H_5)





XI

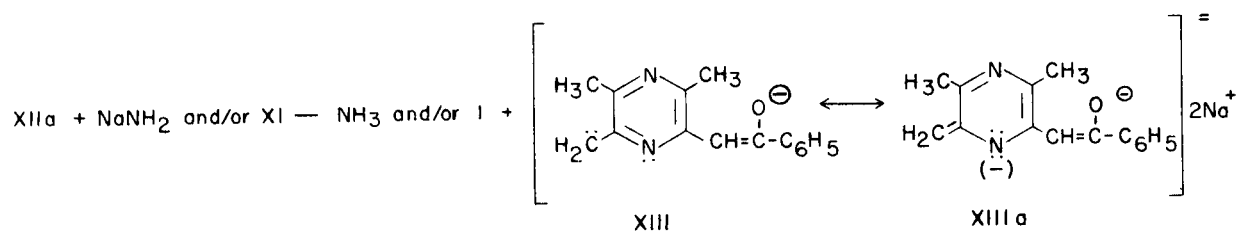
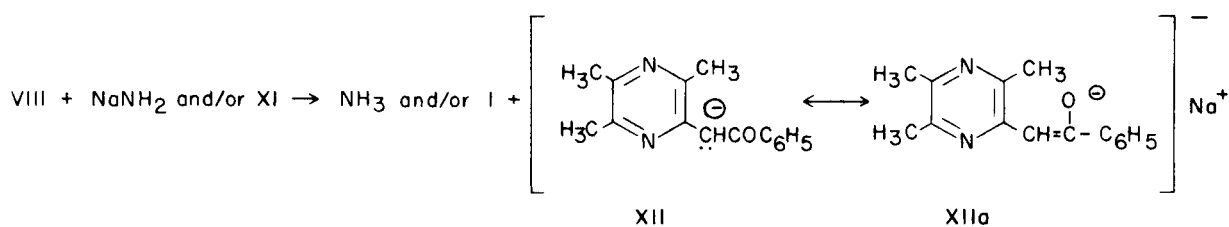
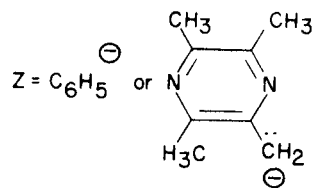
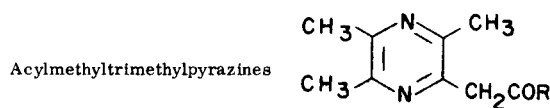


TABLE I
The Benzoylation of Tetramethylpyrazine (TMP)

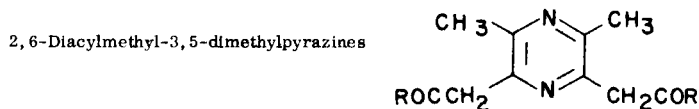
Base	Molar Ratio of Reactants Base:TMP:Ester	Anion-Formation Time, Hrs.	% Yield		% Recovery of Reactants		
			Monoketone	Diketone	TMP	Ester	
C ₆ H ₅ Li	1:1:1	24	3.3	0	45.8	57.2	
NaNH ₂	2:1:1	0.5	13.3	0	40.0	30.0	
	2:1:1	2.0	44.8	21.8	30.0	10.0	
	2:2:1	0.5	32.1	8.0	57.0	0	
	2:2:1	2.0	49.5	16.5	43.0	12.0	
	2:2:1	3.0	66.7	0	58.8	17	
C ₆ H ₅ Li	2:2:1	24	68.1	0	54.2	15	
	NaNH ₂	4:1:4	0.5	27.6 (a)	8.7 (a)	27.8	52.4
		6:1:1	2.0	0	32.8	35.2	0

(a) Yield based on TMP.

TABLE II



and



Compound	R	R'	Yield, %		M. p. or b. p. (mm.)	Formula	Carbon, %		Hydrogen, %	
			NaNH ₂	C ₆ H ₅ Li			Calcd.	Found	Calcd.	Found
1	C ₆ H ₅ (a)	--	49.5	66.7	64-66	C ₁₆ H ₁₆ N ₂ O	74.99	74.70	6.71	6.85
2	C ₆ H ₅	C ₆ H ₅	16.5	0	114-116	C ₂₂ H ₂₀ N ₂ O ₂	76.70	76.36	5.83	5.95
3	<i>p</i> -CH ₃ OC ₆ H ₄	--	38.4	48.2	93-94	C ₁₈ H ₁₈ N ₂ O ₂	71.09	71.29	6.77	6.95
4	<i>p</i> -CH ₃ OC ₆ H ₄	<i>p</i> -CH ₃ OC ₆ H ₄	16.8	0	134-136	C ₂₄ H ₂₄ N ₂ O ₄	71.27	71.38	5.98	6.13
5	<i>p</i> -ClC ₆ H ₄ (a)	--	29.2	36.0	131-132	C ₁₅ H ₁₅ ClN ₂ O	65.57	65.74	5.50	5.63
6	3-C ₅ H ₄ N	--	47.5	60.0	112.8-114.2	C ₁₄ H ₁₅ N ₃ O	69.68	69.34	6.26	6.19
7	<i>n</i> -C ₃ H ₇	--	31.2	42.1	130-134 (2) 61-63	C ₁₂ H ₁₈ N ₂ O	69.87	69.62	8.79	9.02
8	<i>i</i> -C ₃ H ₇	--	44.6	58.0	50-50.5	C ₁₂ H ₁₈ N ₂ O	69.87	69.85	8.79	8.64
9	<i>i</i> -C ₃ H ₇	<i>i</i> -C ₃ H ₇	11.2	0	101-104	C ₁₆ H ₂₄ N ₂ O ₂	69.53	69.63	8.74	8.84
10	<i>t</i> -C ₄ H ₉	--	33.5	54.6	66-70	C ₁₃ H ₂₀ N ₂ O	70.87	70.82	9.15	9.17
Monopicrates										
1a					142-144	C ₂₁ H ₁₉ N ₅ O ₈	53.80	54.01	4.08	3.98
2a					188-190	C ₂₈ H ₂₃ N ₆ O ₉	58.64	58.80	4.04	4.36
3a					131-132.8	C ₂₂ H ₂₁ N ₆ O ₉	52.90	53.11	4.24	4.50
4a					164-165	C ₃₀ H ₂₇ N ₆ O ₁₁	56.87	56.75	4.30	4.51
5a					193-194.7	C ₂₁ H ₁₈ ClN ₆ O ₈	50.06	50.08	3.60	3.63
6a					230 (dec.)	C ₂₀ H ₁₈ N ₆ O ₈	51.06	51.21	3.86	4.06
7a					98-102	C ₁₈ H ₂₁ N ₆ O ₈	49.65	49.52	4.86	4.87
8a					87-94 (softens then melts)	C ₁₈ H ₂₁ N ₆ O ₈	49.65	49.73	4.86	4.84
9a					164-172 (softens then melts) (b)	C ₂₈ H ₃₀ N ₆ O ₁₈	45.77	45.83	4.12	3.86
10a					142-143 (c)	C ₁₃ H ₂₁ N ₃ O	66.35	66.33	9.00	9.02

(a) Methyl ester was used. In all other cases ethyl esters were used. (b) This is a dipicrate. (c) This is a monooxime.

is formed by the reaction of methyl benzoate with IV \rightleftharpoons V. It is further suggested that VIII is converted to its anion at the methylene group by reaction with phenyllithium and/or IV by the initial condensation of the phenyllithium and/or IV with the nitrogen atom of VIII to give IX which loses ZH to give X, the monoanion of VIII with the lithium coordinated on the nitrogen atom. While X is resonance stabilized by structure Xa, the dianion which would be formed by removing a proton from the methyl group in the number 6 position is not resonance stabilized and hence would not be expected to form to an appreciable extent. While the dianion which would be formed by removing a proton from

the methyl group of the number 3 carbon atom of X would indeed be resonance stabilized, it is believed that this anion is not formed to a large extent because of steric reasons.

With sodium amide, however, the situation appears to be quite different. The monoketone (VIII) may react with sodium amide and/or XI (the metal is now associated with carbon rather than with nitrogen) to give XII-XIIa. Now, the dianion (XIII), which would be formed by removing a proton from the methyl group of the number 6 carbon atom, would be resonance stabilized with XIIIa making an important contribution.

EXPERIMENTAL

A. Synthesis of Phenacyltrimethylpyrazine Using Phenyllithium as the Condensing Agent.

Phenyllithium (0.1 mole) was prepared from lithium ribbon (0.2 mole, 1.4 g.) in 200 ml. of anhydrous ether. To the cooled (ice bath) solution of phenyllithium, tetramethylpyrazine (0.1 mole, 13.6 g. in 25 ml. of ether) was added over a period of 15 min. to give a blood-red suspension of the lithium derivative of tetramethylpyrazine. The reaction mixture was stirred for 3 hrs. with refluxing for the last hr. Methyl benzoate (0.05 mole, 6.9 g. in an equal volume of ether) was added dropwise and stirring continued for two more hrs. at which time the mixture was yellow-orange in color. The mixture was poured onto ice, made slightly acidic (pH 6-6.5) with concentrated hydrochloric acid and extracted with several portions of chloroform. The ether and the chloroform extracts were dried over anhydrous sodium sulfate and the solvents removed at atmospheric pressure. Vacuum distillation of the combined residues gave first a sublimate (tetramethylpyrazine, 8.0 g.), followed by methyl benzoate (1.4 g.) and finally phenacyltrimethylpyrazine (8.0 g., 66.7%), b.p. 168-175° at 2 mm., m.p. 64-66° when recrystallized from petroleum ether (30-60° B.P.).

B. Synthesis of 2,6-Diphenacyl-3,5-dimethylpyrazine (I) from Tetramethylpyrazine Using Sodium Amide as the Condensing Agent.

1. To a freshly prepared suspension of sodium amide (from 0.6 mole, 13.8 g. of sodium in 500 ml. of liquid ammonia) tetramethylpyrazine (0.1 mole, 13.6 g. in 25 ml. of anhydrous ether) was added. The deep red mixture was stirred for 3 hrs. at the reflux temperature of liquid ammonia and then methyl benzoate (0.1 mole, 13.6 g. in an equal volume of anhydrous ether) was added dropwise. Stirring was continued for another 3 hrs. and then the reaction was quenched by the addition of solid ammonium chloride (30.0 g.). The ammonia was replaced by 200 ml. of ether by warming the reaction mixture on a steam bath. When the liquid ammonia was completely displaced, as was indicated by the refluxing of the ether, the mixture was poured onto ice, neutralized by concentrated hydrochloric acid and extracted with several portions of chloroform. The combined chloroform extracts were dried over anhydrous sodium sulfate, the solvent removed at atmospheric pressure and the residue fractionated under reduced pressure. There were isolated: 4.8 g. of tetramethylpyrazine, 3.0 g. of benzamide, m.p. 127-130° and 11.3 g. (32.8%) of 2,6-diphenacyl-3,5-dimethylpyrazine, b.p. 230-255° at 0.3 mm., m.p. 114-116° when recrystallized from petroleum ether (60-70° B.P.).

2. From phenacyltrimethylpyrazine using sodium amide as the condensing agent. Phenacyltrimethylpyrazine (0.1 mole, 24 g., R is C₆H₅), sodium amide (0.1 mole) and methyl benzoate (0.1 mole, 13.6 g.) were allowed to react as described for the last experiment to give 18.2 g. (76%) of unreacted II (R is C₆H₅), 11.4 g. (82%) of unreacted methyl benzoate and 4.2 g. (67.8% based on the ester consumed) of 2,6-diphenacyl-3,5-dimethylpyrazine (VI).

C. Conversion of VI to 2,6-Bis-(1-oximinophenacyl)-3,5-dimethylpyrazine, (VII).

Sodium nitrite (2.0 g. in 25 ml. of water) was added slowly (30 min.) to a stirred solution of the diketone (VI) (2.0 g. in 25 ml. of glacial acetic acid). The mixture was stirred for 3 hrs. at room temperature. The deep yellow color of the mixture slowly faded to light yellow and a solid began to separate. Water (250 ml.) was added and the solid filtered to give 2.3 g. of crude VI, m.p. 177-183°. This material was recrystallized from ethanol-water to give 1.2 g. of white, crystalline VI, m.p. 209.5-210.3.

Anal. Calcd. for C₂₂H₁₈O₄N₄: C, 65.63; H, 4.51. Found: C, 65.88; H, 4.70.

Similar results were obtained on the nitrosation of 2,6-bis (*p*-methoxyphenacyl)-3,5-dimethylpyrazine which gave a dioxime, m.p. 187-189°.

Anal. Calcd. for C₂₄H₂₂N₄O₈: C, 62.33; H, 4.80. Found: C, 62.34; H, 5.08.

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- (1) This work is based on part of the thesis to be presented by S. K. C. to the Graduate Faculty of the University of Pittsburgh in partial fulfillment of the requirements for the Ph.D. degree. Part of this work was done under Contract No. AT(30-1)-670 between the U. S. Atomic Energy Commission and the University of Pittsburgh.
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Pittsburgh, Pennsylvania 15213