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Tetrahedron Letters 49 (2008) 2519–2522
Tetrahedron Letters

Synthesis of pyrazine acetals by the biased reaction of symmetric 2,5-bis(chloromethyl) or 2,3,5,6-tetrakis(chloromethyl) substituents on pyrazine ring with sodium alkoxides

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Received 8 January 2008; revised 17 February 2008; accepted 22 February 2008
Available online 4 March 2008

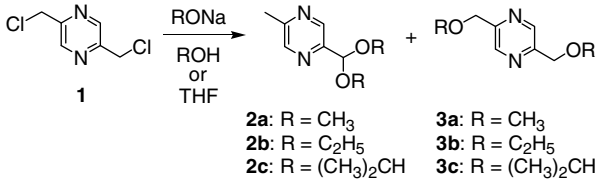
Abstract

2,5-Bis(chloromethyl)pyrazine reacted with sodium alkoxide to give unexpected 2-dialkoxymethyl-5-methylpyrazine along with normal substitution product, 2,5-bis(alkoxymethyl)pyrazine. The reaction of 2,3,5,6-tetrakis(chloromethyl)pyrazine with sodium alkoxide afforded similar results to yield 2,6-bis(dialkoxymethyl)-3,5-dimethylpyrazine along with other alkoxymethylpyrazines. The ratio of products depended on the solvent and alkoxide used. A general discussion of the mechanism of such a pyrazine acetal synthesis in the basic conditions is given.

Keywords: Pyrazine; Biased reaction; 1,6-Elimination; Quinodimethane; Pd(II) complex

Pyrazine derivatives have been widely used in the fields of medicinal chemistry for the skeleton of biologically active sites[1] and in metal coordination chemistry as *N*,*N*′-bidentate ligands;[2] thus, synthetic methods of substituted pyrazines have been developed.[3] During our studies related to the functionalization of pyrazines, we conducted preliminary studies on the introduction of alkoxy groups into chloromethylpyrazines with sodium alkoxides in order to define the reaction parameters. When 2,5-bis(chloromethyl)pyrazine (**1**) was treated with sodium methoxide, 2-dimethoxymethyl-5-methylpyrazine (**2a**) was isolated along with desired 2,5-bis(methoxymethyl)pyrazine (**3a**). Such a formation of acetal carrying *gem*-dimethoxy group was an unexpected reaction since nucleophilic substitution of alkoxide to haloalkane easily occurs; thus, syntheses of alkoxymethylpyrazines have been reported in the literature and substitution in dichloromethyl group with alkoxides leading to the corresponding acetals has been known for some pyrazine derivatives.[4] Herein, we describe the acetal synthesis by the biased reaction of *trans*-bis(chloromethyl) groups substituted in pyrazine with sodium alkoxides. The mechanism of the reaction is also discussed.

Substrate **1** was prepared by the chlorination of 2,5-dimethylpyrazine with *N*-chlorosuccinimide according to the previously reported procedure.[5] The reaction of **1** with sodium methoxide in methanol gave a mixture of **2a** and **3a** (Scheme 1).[6] In the reaction of **1** with sodium ethoxide in ethanol, the ratio of products (**2b** and **3b**) dramatically changed (Table 1). In the case of 2-propoxylation, acetal **2c** was predominantly prepared. The product ratios of **2**



Scheme 1. Reaction of **1** with sodium alkoxide.

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doi:10.1016/j.tetlet.2008.02.119

Table 1
Isolated yields of **2** and **3** from the reaction of **1** with sodium alkoxide[6]

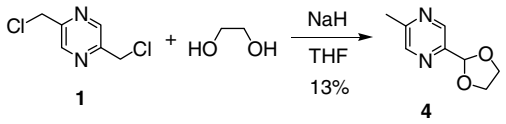
R	Solvent	Yield (%)		Solvent	Yield (%)	
		2	**3**		**2**	**3**
CH_3	CH_3OH	11	63	THF	46	7.3
C_2H_5	C_2H_5OH	31	39	THF	41	5.7
$(CH_3)_2CH$	$(CH_3)_2CHOH$	43	9.4	THF	27	0

and **3** were dependent on reaction solvent as well as alkoxide employed. In the reaction in THF, ratios of acetals **2** increased, although total yield of alkoxylated products decreased. On reacting **1** with an excess of methoxide or ethoxide in THF, **2a** or **2b** was predominantly produced along with **3a** or **3b** as a minor product, respectively. By the reaction of **1** with sodium 2-propoxide in THF, **2c** was the only product bearing alkoxy group; the residue was a mixture of decomposition products of pyrazine rings. In these reactions, unreacted substrate **1** was not detected. Reaction of **1** with disodium ethylene glycolate gave the corresponding acetal **4** although in low yield (Scheme 2). When *tert*-butoxide was used in the reaction, no alkoxylated product was detected and the pyrazine ring was supposed to be decomposed or incorporated into some polymeric structures.

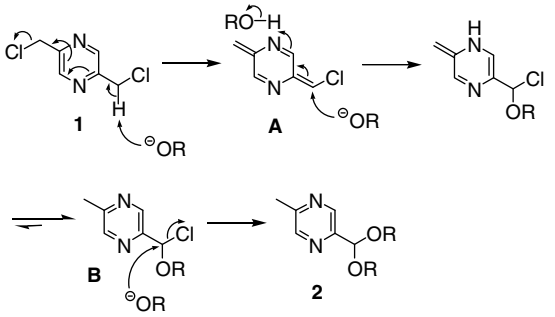
As stated above, total yields of alkoxylated products were not high even in alcohols. It has been reported by Matsuura et al. in 1975 that 3,6-diethoxy-2,5-bis(chloromethyl)pyrazine reacted with sodium alkoxides but the yield of 3,6-diethoxy-2,5-bis(alkoxymethyl)pyrazine was very low and a structure-unknown substance was produced as the main product.[7] Thus, selective introduction of substituents to pyrazine ring by S_N2 substitution reaction did not proceed smoothly in term of yield and by-products as compared to other aromatic compounds.[4,7]

The structure of pyrazine acetals **2** and 2,5-bis(alkoxymethyl) pyrazines **3** was determined by ^1H NMR, IR, and elemental analyses.[8] The formation of pyrazine acetal (**2**) was confirmed by converting it to pyrazine aldehyde (δ 10.13 ppm for the formyl group) by acid-catalyzed hydrolysis.

Reaction mechanism of acetal formation by the reaction of **1** with alkoxide is proposed as shown in Scheme 3. Deprotonation from methylene on chloromethyl group of **1** by alkoxide causes 1,6-elimination of HCl to produce *p*-quinodimethane derivative **A** at the first process.[9] Subsequent addition of alkoxide to **A** would give 2-(alkoxychloromethyl)-5-methylpyrazine (**B**). Equilibrium of tautomeric structure would be near the product. Then the nucleophilic substitution reaction of chloride with alkoxide affords pyrazine acetal **2**. When solvent molecules act as nucleophilic reagents, 2,5-bis(alkoxymethyl)pyrazine (**3**) is formed preferentially. The result that the reaction with sodium 2-propoxide gave a higher formation ratio of acetal can be explained by the high basicity and low nucleophilicity of 2-propoxide.



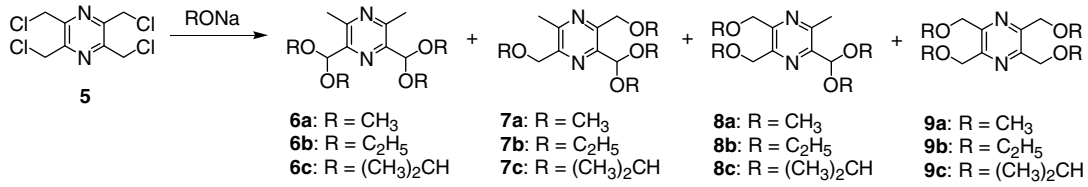
Scheme 2. Reaction of **1** with disodium ethylene glycolate.



Scheme 3. Plausible mechanism for acetal formation of **1** with alkoxide.

For a further understanding of parameters of this acetal synthesis, 2,3,5,6-tetrakis(chloromethyl)pyrazine (**5**) was then prepared by the chlorination of 2,3,5,6-tetramethylpyrazine according to the literature.[5] Reaction of **5** with sodium alkoxide in corresponding alcohol resulted in the formation of a mixture of di-acetal **6**, mono-acetals **7** and **8**, and tetrakis(alkoxymethyl) compound **9** as shown in Scheme 4. The use of THF as the reaction solvent resulted in the formation of an insoluble black solid, and neither acetal nor alkoxymethylpyrazine derivative was isolated. Similar result had been reported in 1976 by Taylor et al., who obtained only extremely insoluble black solid by the reaction of 2-amino-3-cyano-5-bromomethylpyrazine with 2-lithio-1,3-dithiane in THF at −25 °C. They surmised that the strongly basic dithiane anion initiated the dehydrobromination of 2-amino-3-cyano-5-bromomethylpyrazine by the deprotonation of amino group, and that the resulting quinoid-like pyrazine intermediate subsequently polymerized.[10] Although a quinoid-like pyrazine intermediate formed in the reaction of **5** with alkoxide at the first step, intermolecular reaction might occur to yield insoluble polymeric material instead of the ether produced by the addition of alkoxide or alcohol because of low concentration of alcohol species. On the other hand, the solubility of **5** in alcohols was not high for the reaction at room temperature. Therefore, mixtures of corresponding alcohols and THF were employed for the reaction at room temperature. The results are summarized in Table 2.

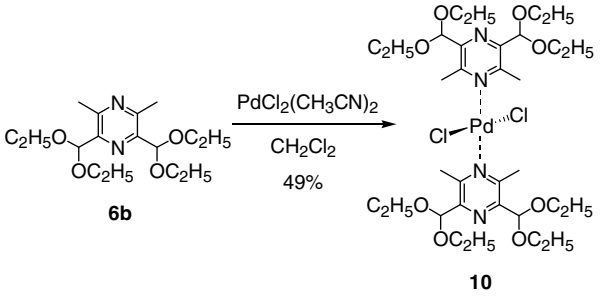
Reaction of **5** with sodium methoxide in refluxing methanol gave a mixture of 2,3,5,6-tetrakis(methoxymethyl)-pyrazine (**9a**) and 2-dimethoxymethyl-3,6-bis(methoxymethyl)-5-methylpyrazine (**7a**) along with half molar amounts of di-acetal **6a** and mono-acetal **8a**. On the other hand, the reaction of **5** with sodium ethoxide in refluxing ethanol gave di-acetal **6b** as a major product and 2,3,5,6-tetrakis(ethoxymethyl) derivative **9b** as a minor product as in the reaction of **1**. By the reaction of **5** with 2-propoxide in refluxing 2-propanol was obtained only di-acetal **6c**.



Scheme 4. Reaction of **5** with sodium alkoxide.

Table 2
Isolated yields of alkoxy compounds **6**–**9** from the reaction of **5** with sodium alkoxide

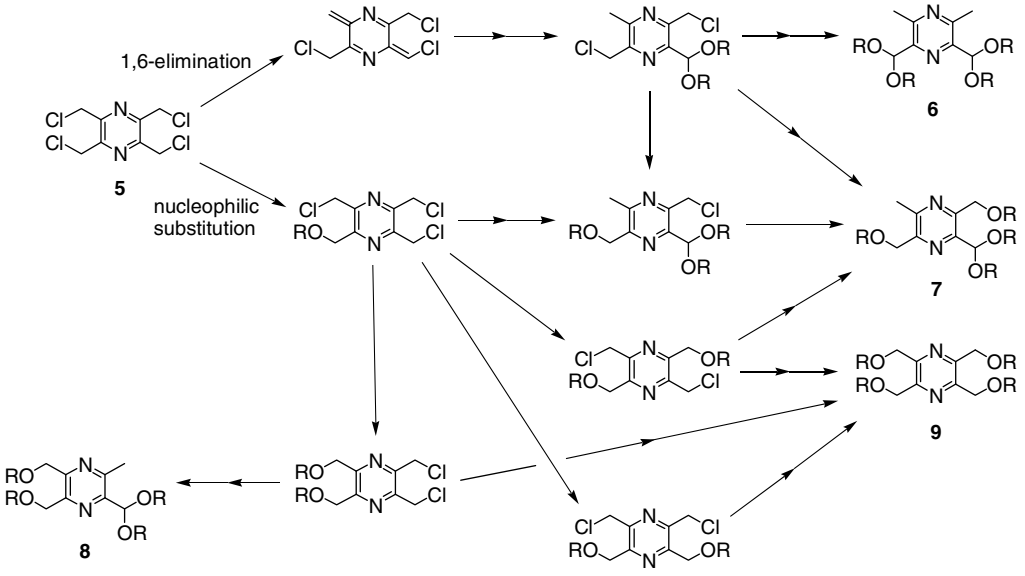
Entry	R	Solvent	Alkoxide/**5** (equiv)	Temp	Time (h)	Yield (%)			
						6	**7**	**8**	**9**
1	CH_3	CH_3OH	5.5	Reflux	24	11	22	10	28
2	C_2H_5	C_2H_5OH	5.6	Reflux	24	26	17	8.1	1.4
3	C_2H_5	C_2H_5OH	21	Reflux	24	38	30	8.6	2.7
4	$(CH_3)_2CH$	$(CH_3)_2CHOH$	6.4	Reflux	24	17	0	0	0
5	CH_3	CH_3OH/THF (5:1)	5.3	rt	45	9.9	16	8.3	21
6	C_2H_5	C_2H_5OH/THF (5:1)	6.3	rt	15.5	20	17	6.1	2.9
7	C_2H_5	C_2H_5OH/THF (40:3)	8.0	rt	18	33	29	9.6	5.6
8	$(CH_3)_2CH$	$(CH_3)_2CHOH$/THF (5:1)	5.6	rt	24	10	0	0	0



Scheme 5. Synthesis of Pd(II) complex **10**.

The reaction of **5** with alkoxide in a mixed solvent of corresponding alcohol and THF (5:1 v/v) at room temperature gave similar formation ratios of products as those obtained for the reaction in refluxing alcohol. The best yield of acetal **6** was obtained by the reactions in refluxing ethanol with excess amount of sodium ethoxide.

In analogy with **2** and **3**, all the structures of these products were determined by elemental analyses and ^{1}H NMR data (see Supplementary data). Diacetal **6** was also converted to 3,5-dimethylpyrazine-2,6-dicarbalaldehyde by the treatment with *p*-toluenesulfonic acid in THF. In order to decide the structure of di-acetal **6**, the complexation of **6b** with Pd(II) ion was achieved according to the previously reported procedure.[11] By stirring a solution of **6b** and 1/2 molar amount of $[PdCl_2(CH_3CN)_2]$ was prepared



Scheme 6. Plausible reaction pathways for alkoxylation of **5**.

trans-[$PdCl_2$(**6b**)$_2$] complex (**10**) (Scheme 5). The geometrical structure of **10** was confirmed by a single Cl–Pd–Cl IR band (362 cm^{-1}) due to the anti-symmetric stretching mode for *trans*-$PdCl_2$ configuration along with the absence of a symmetric Cl–Pd–Cl stretching band for a *cis*-$PdCl_2$ configuration.[12] ^{1}H NMR spectrum of **10** exhibited singlet peaks for the methine groups and the methyl groups attached directly to pyrazine ring, suggesting clearly that these substituents were at the magnetically equivalent positions, respectively. Comparison of the ^{1}H NMR peaks of **10** with those of **6b** revealed remarkably downfield shift ($\Delta\delta =$ 1.14 ppm) for the methyl peak on complexation, while the peak for methine hydrogens was scarcely shifted ($\Delta\delta = -0.02$ ppm). Therefore, two pyrazine ligands adopted C_2 symmetry and coordinated to a Pd(II) ion at the nitrogen whose neighboring carbons were connected to less hindered methyl groups.

Proper reaction pathways for the preparation of di-acetal **6**, mono-acetals **7** and **8**, and tetrakis(alkoxymethyl) derivative **9** are shown in Scheme 6. 2,3-Diacetal derivatives were not detected in these reactions; thus, deprotonation from 3-chloromethyl group in 2-dialkoxymethyl-3,6-bis(chloromethyl)-5-methylpyrazine was inhibited due to steric and/or electronic effect of 2-acetal group. Preferential acetal formation in the reaction of *trans*-bis(chloromethyl)pyrazine with sodium alkoxide is an unexpected reaction; however, the mechanistic course appears to be obscured due to the potentially tautomeric methylpyrazine. Product ratios of such alkoxylation were dependent on the reaction solvent as well as alkoxide used. Synthesis of new pyrazine derivatives having different circumstances around two nitrogen atoms is expected by taking advantage of this biased reaction.

Acknowledgment

The present work was supported by a Grant-in-Aid for Priority Areas (417, No. 17029049) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan.

Supplementary data

Supplementary data (experimental procedures and spectroscopic data for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.02.119.

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6. *General procedure*: A solution of **1** (100 mg, 0.56 mmol) in absolute methanol (9 ml) was slowly added under nitrogen to a solution of sodium methoxide (6.7 mmol: 155 mg for sodium) in absolute methanol (15 ml) and then the mixture was refluxed for 24 h. After the removal of sodium salts, the residue was chromatographed on silica gel, eluting with ethyl acetate/cyclohexane (3:2 v/v), to afford **2a** (10.3 mg, 11%) and **3a** (59.3 mg, 63%).
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8. In the ^{1}H NMR spectrum of **2**, a set of signals attributed to alkoxy groups (e.g., δ 3.42 ppm for **2a**) and singlet peak due to methyl protons (δ 2.59 ppm for **2a**), methine proton (δ 5.44 ppm for **2a**), and two nonequivalent pyrazine protons (δ 8.46 and 8.69 ppm for **2a**) were observed, respectively. In the case of **3**, ^{1}H NMR peaks due to a pair of alkoxymethyl groups (e.g., δ 3.50, and 4.63 ppm for **3a**) and a singlet peak due to two equivalent pyrazine protons (δ 8.64 ppm for **3a**) appeared.
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