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# Regioselective double Boekelheide reaction: first synthesis of 3,6-dialkylpyrazine-2,5-dicarboxaldehydes from DL-alanine

Sajal Kumar Das *, Joseph Frey *

*Department of Chemistry and Institute for Nanotechnology and Advanced Materials, Bar Ilan University, Ramat Gan 52900, Israel*

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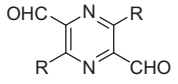
ABSTRACT

Pyrazine-2,5-dicarboxaldehyde was synthesized on a multi-gram scale by $MnO_2$ oxidation of 2,5-bis(hydroxymethyl)pyrazine, which in turn was obtained from 2,5-dimethylpyrazine employing double Boekelheide reaction as a key step as reported previously. This reaction was subsequently utilized in a regioselective fashion as a key step to synthesize efficiently, for the first time, 3,6-di(long-chain)alkylpyrazine-2,5-dicarboxaldehydes starting from DL-alanine. These monomers are certain to have importance as electron deficient and chemically versatile components for new materials development.



Aromatic or heteroaromatic dialdehydes have been at the forefront of material science research due to the broad synthetic scope of aldehyde chemistry. Specifically, these bifunctional intermediates can serve as key precursors for making conjugated oligo- and polymers utilizing Wittig or Horner–Wadsworth–Emmons olefination, Knoevenagel condensation, Corey–Fuchs alkynation, and imine formation reaction.[1] Also, their use in the syntheses of conjugated systems containing benzimidazole, benzoxazole, and benzothiazole are well documented in the literature.[2] They have also recently been used to prepare non-conjugated poly(benzoins).[3] While these applications are diverse, the majority of dialdehydes constitute only limited range of families. Classic examples include the extensively studied and widely used benzene-1,4-dialdehydes[4] and thiophene-2,5-dialdehydes.[5] To the best of our knowledge, there is no research involved in the design, synthesis, and applications of 3,6-di(long-chain)alkylpyrazine-2,5-carboxaldehydes.[6] On the other hand, the presence of an electron deficient azaheterocycle ring like pyrazine in a conjugated backbone can significantly change the polymer property.[7] However, due to the difficulty in preparing functionalized pyrazine monomers, materials containing pyrazine in the conjugated chain have been scarcely reported.[8] In this Letter, we report the synthesis of pyrazine-2,5-dicarboxaldehydes **1** and **20a–c** (Fig. 1) which is certain to have importance as electron deficient and chemically versatile components for materials development.




R = H (**1**), *n*-hexyl (**20a**), *n*-octyl (**20b**) and 2-ethylhexyl (**20c**)

**Figure 1.** Pyrazine-2,5-dicarboxaldehydes **1** and **20a–c**.

We first focused on the synthesis of the known dialdehyde, that is, pyrazine-2,5-dicarboxaldehyde **1**. The synthesis of **1** has been accomplished by two different routes; one was by the vapor phase catalytic oxidation of 2,5-dimethylpyrazine[9] and the other method utilized ozonolysis of 2,5-distyrylpyrazine (Scheme 1).[10] However, both these methods are difficult to conduct at a laboratory viable level particularly on large scale. Additional disadvantages of these two methods are unwanted formation of 5-methylpyrazine-2-carboxaldehyde, commercial unavailability and instability of 2,5-distyrylpyrazine, and more importantly, the tedious isolation of highly water soluble **1** from aqueous solution.

Our initial attempts to obtain **1** by LAH or DIBAL reduction of diester **4** or diamide **5** were unsuccessful (Scheme 1).

A possible explanation might be that a highly electron deficient pyrazine ring is normally susceptible to nucleophilic attack. This effect is even more pronounced in the presence of the two electron withdrawing groups, resulting in the formation of mainly by-products with reduced pyrazine ring or the decomposition of starting materials. Consequently, we chose to synthesize 2,5-bis(hydroxymethyl)pyrazine **6** (Scheme 2) which could be oxidized to **1**. Synthesis of compound **6** was reported more than 50 years ago[11] but

* Tel.: +972 3 531 7682; fax: +972 3 738 4053.
*E-mail addresses:* sajalkdas@gmail.com (S.K. Das), Joseph.Frey@biu.ac.il (J. Frey).

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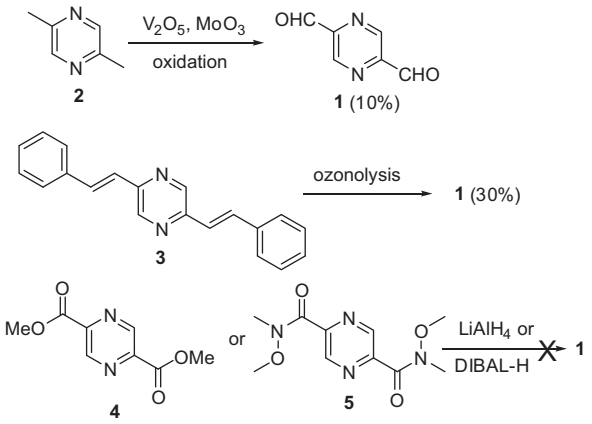



**Scheme 1.** Literature synthetic routes and our initial unsuccessful attempts to **1**.

surprisingly, to the best of our knowledge, there is no precedence for the synthesis of **1** by using this approach.

The synthesis starts from the commercially available 2,5-dimethylpyrazine **2** which we treated with *m*-CPBA in ethyl acetate to furnish corresponding *N*,*N*-dioxide derivative **6** in 90% yield. Isolation of the pure product by mere filtration of the reaction mixture prompted us to choose *m*-CPBA over the literature known $H_2O_2$–AcOH system in this reaction. Next, heating a suspension of **6** in acetic anhydride at 158 °C for 7 h resulted in a diacetate derivative **7** in 20% yield. The reaction was run for a longer time to minimize the formation of the monoacetate product in this double Boekelheide reaction,[12] and by a modified work-up of the crude product, the yield of the reaction was improved slightly. The low product yield in this reaction was due to the formation of large amount of black polymeric materials.[12] Nevertheless, the reaction on large scale could provide multi-gram quantities of **7**.

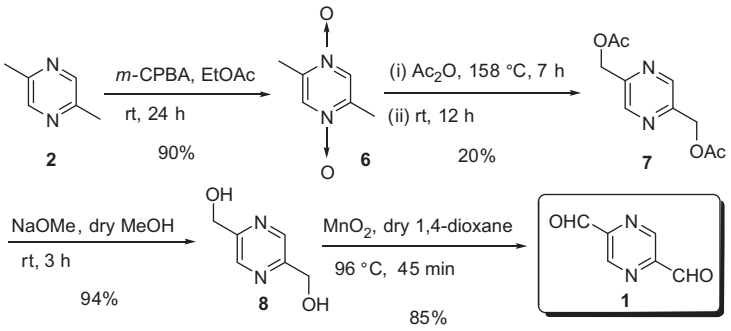
Next, deacetylation of **7** by NaOMe in dry methanol afforded compound **8** in high yield. This compound is highly polar and insoluble at low or room temperature in all the organic solvents which are generally used for alcohol to aldehyde oxidation reactions. However, activated $MnO_2$ could effectively oxidize compound **8** into **1** in dry 1,4-dioxane at 96 °C. This reaction was high yielding (85%) and did not produce any side product; thus enabling the isolation of the pure product just by filtration of the reaction mixture.

Although, the synthesis of dialdehyde **1** from **2** is a four-step reaction sequence with an overall yield of 8%, it has several noticeable advantages. First, all the steps were operationally very simple, reproducible and could be performed on a large scale and multigram quantities of dialdehyde **1** were easily accessible from a single batch. Second, two of the synthetic steps produced pure reaction products which did not require column chromatography. And most importantly, water soluble **1** was isolated very easily under anhydrous condition.

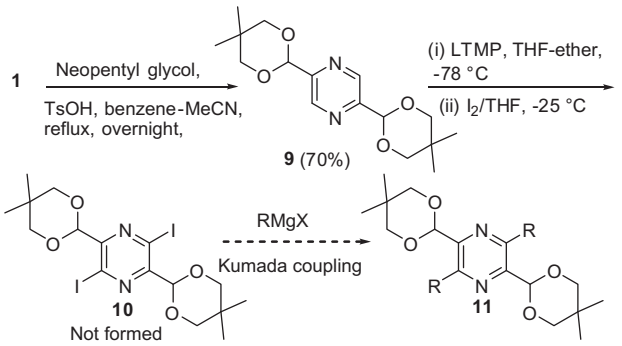
It is a well known fact that for better solubility of oligomers and polymers in common organic solvents, the monomer must contain long-chain alkyl groups. Commonly used alkyl groups are *n*-hexyl, *n*-octyl, 2-ethylhexyl etc. So, we then turned our attention to synthesize 3,6-di(long-chain)alkylpyrazine-2,5-dicarboxaldehydes. In 1999, Zhang and Tour synthesized 3,6-diodopyrazine-2,5-diketals by neopentylketal-directed lithiation of pyrazine ring.[13] In this context, we were very much interested to synthesize a similar compound, namely, 3,6-diodopyrazine-2,5-di(neopentyl)acetal **10** (Scheme 3) as the subsequent introduction of two long chain alkyl groups on the pyrazine ring was planned to achieve by Kumada coupling strategy. Toward that objective, dialdehyde **1** was first treated with neopentyl glycol in a refluxing benzene–acetonitrile solvent system in the presence of a catalytic amount of TsOH to furnish diacetal **9** in good yield. Unfortunately, crystalline compound **9** was completely insoluble in THF and ether at low temperature and hence, Tour's reaction condition of diodination of pyrazine nucleus by LTMP mediated lithiation did not work in our case. We could recover almost all the unreacted starting material and running the reaction from 0 °C to rt resulted in complete decomposition of **9**.

As the above route for the synthesis of 3,6-di(long-chain)alkylpyrazine-2,5-carboxaldehydes was unsuccessful, we then turned our attention again to the double Boekelheide reaction strategy for which synthesis of 3,6-dimethyl-2,5-di(long-chain)alkylpyrazines was essential. Toward that objective, DL-alanine **12** was converted into the corresponding Weinreb amide **14** following a reported two-step reaction sequence (Scheme 4).[14] Next, addition of freshly prepared *n*-hexylmagnesium bromide to **14** at 15–20 °C in dry THF provided ketone **15a** in high yield. It is very important to mention that there was no reaction at −78 °C and negligible conversion took place at 0 °C. Ketones **15b,c** were similarly synthesized. When ketones **15a,b** were subjected to standard hydrogenation reaction using hydrogen balloon and 10% Pd-C, the products were surprisingly the corresponding pyrazine derivatives **16a–b** rather than simple α-amino-ketone derivatives. The reactions were very clean and we could not detect any intermediate compounds despite close monitoring by TLC. However, hydrogenation of ketone **15c** provided mainly the corresponding α-amino-ketone derivative which was then kept in open flask for 12 h to get pyrazine **16c** in moderate yield. In this case, the presence of ethyl side group might have put some difficulty in the auto-condensation reaction. Pyrazines **16a–c** were then converted to corresponding *N*,*N*-dioxide derivatives **17a–c** by treating with *m*-CPBA in high yields.

With compound **17a–c** in hand, the stage was then set for double Boekelheide reaction. It is well known that acetoxylation in the Boekelheide rearrangement of N-oxides of pyridine or pyrazine derivatives can take place both at methyl and methylene carbons attached to the heterocyclic rings. Thus, tetraalkylpyrazine-N,N-dioxides **17a–c** have four Boekelheide rearrangement sites which




**Scheme 2.** Synthesis of pyrazine-2,5-carboxaldehyde **1**.



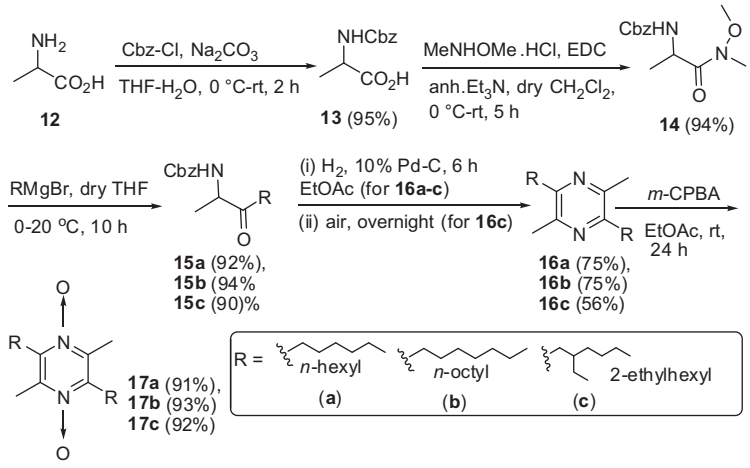

**Scheme 3.** Attempted synthesis of diacetal **10**.

raise the issue of regioselectivity (Scheme 5). For example, compound **17a** on heating with acetic anhydride might produce four possible products. In order to obtain **18a**, Boekelheide rearrangement of **17a** must occur regioselectively on two methyl groups.

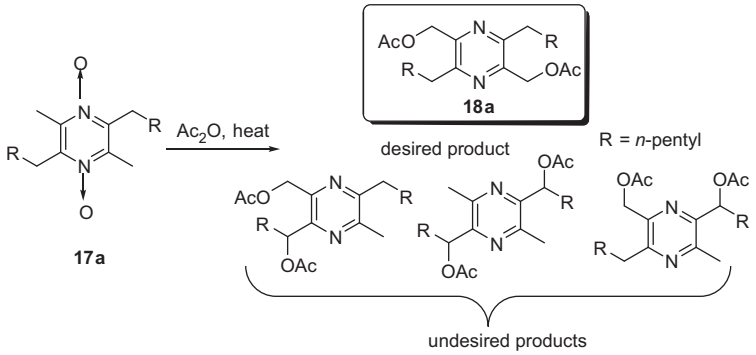
To know the outcome, compound **17a** was heated at 158 °C for 7 h in acetic anhydride and we were delighted to see that the reaction led to the formation of the desired product **18a** in 45% yield (Scheme 6). The product was easily isolated by column chromatography and recrystallization. The absence of any signal corresponding to methyl groups on the pyrazine ring in the $^1$H NMR of the crude product confirmed the formation of **18a** as the sole Boekelheide rearrangement product. Although, there was formation of a significant amount of brown colored polymeric material in this case also, we note the substantial contribution of the alkyl chains to the successful outcome of this synthetic step as we consider the limiting low reaction yield in the corresponding reaction of the parent pyrazine system **6**. Similarly, compound **17b–c** furnished the corresponding diacetates **18b–c** without the formation of undesired isomeric products. Next, 3,6-di(long-chain)alkylpyrazine-2,5-dicarboxaldehydes **20a–c** was obtained by deacetylation of **18a–c** and $MnO_2$ oxidation of the resulting alcohols **19a–c**. Dialdehydes **20a–c** could be synthesized on gram scale from a single batch and stored for long time without decomposition in the freezer in $N_2$ flushed container.

Next, we were very much interested to explore the reactivity of dialdehydes **20a–c** in Wittig olefination as we were very much curious about the tolerance of the highly electron deficient pyrazine ring to strong basic and nucleophilic reaction conditions present in the Wittig reaction. Toward this direction, phosphonium salt[15] **21** (4.0 equiv) was treated with potassium tert-butoxide (3.0 equiv) in dry THF at 0 °C to generate the corresponding ylide which was subsequently reacted with aldehyde **20a** (Scheme 7). We were pleased to see that the reaction led to the formation of the desired diolefin compound **22** in moderate yield.

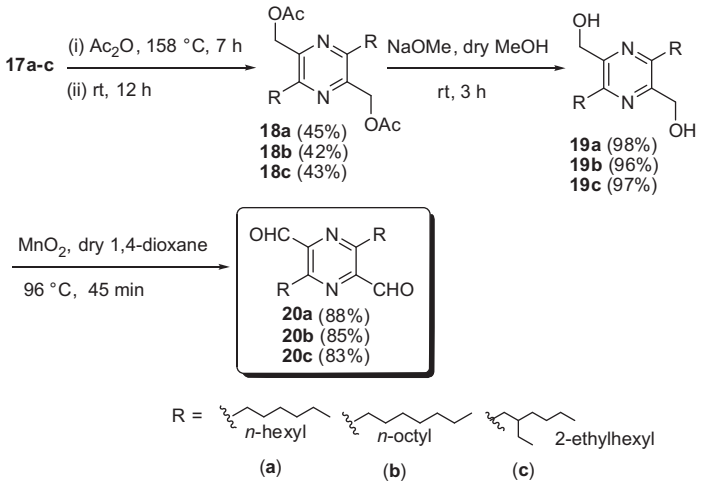
It is very important to mention that the phosphonium salt was taken in excess to ensure the complete consumption of base. We observed that the presence of excess base resulted in lower yield of **22** possibly due to cleavage of the pyrazine ring. Compound **22**, related diene compounds, and other triblock monomers which could be synthesized easily from **20a–c** should be useful in the synthesis of several donor–acceptor copolymers incorporating pyrazine acceptor and well-known donors like thiophene,



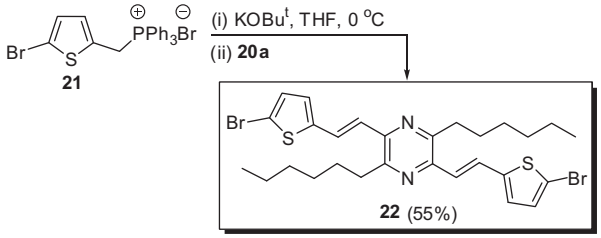

**Scheme 4.** Synthesis of 3,6-dimethyl-2,5-di(longchain)alkylpyrazine-N,N-dioxides **17a–c**.




**Scheme 5.** Probable products in the Boekelheide rearrangement of **17a**.




**Scheme 6.** Synthesis of 3,6-di(long-chain)alkylpyrazine-2,5-carboxaldehydes **20a–c**.




**Scheme 7.** Wittig olefination of **20a** leading to **22**.

ethylenedioxythiophene, dialkoxylphenylene, carbazole, phenothiazine etc. utilizing Suzuki and Sonogashira coupling reactions. In this communication while we describe the first synthesis of 3,6-dialkyl-2,5-pyrazinedicarboxaldehydes and monomer **22**, our future efforts will be in the applications of **22** and related molecules in organic materials.

In summary, we have synthesized pyrazine-2,5-dicarboxaldehyde on a multi-gram scale by $MnO_2$ oxidation of 2,5-bis(hydroxymethyl)pyrazine, which in turn was obtained from 2,5-dimethylpyrazine employing double Boekelheide rearrangement as a key step as reported previously. Subsequently, 3,6-di(long-chain)alkylpyrazine-2,5-dicarboxaldehydes were synthesized starting from DL-alanine by utilizing the Boekelheide reaction in a regioselective fashion. Special features of the synthetic route are the ease of the reaction sequence and the cheap commercial availability of the starting materials. Despite having attractive symmetry in 2,5-disubstituted pyrazines, they have been somewhat neglected in polymer science due to the difficulty in preparing functionalized pyrazines. It is anticipated that this new family of monomers will find applications as electron deficient and chemically versatile components for new materials development. Work in this direction is currently in progress and will be published in the future. In addition, functionalized diazinyl heterocycles have been widely used to synthesize a large number of biologically important molecules; therefore, the new synthetic strategies described here would likely have applications far beyond the scope of material science.

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## Supplementary data

Supplementary data (experimental procedures, copies of $^1H$ and $^{13}C$ NMR spectra of all new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.057.

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