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Synthesis of Pyrazine C-Ribosides via Direct Metalation

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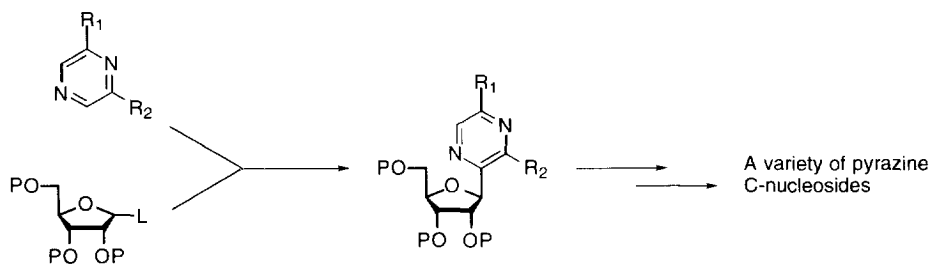
Abstract: A direct metalation method has been developed for the synthesis of novel pyrazine C-nucleosides. The regiochemistry was controlled by selecting different substituents on the pyrazine ring and excellent stereoselectivity was achieved via a hydride delivery strategy. The scope and limitations of this method were studied. The uniquely designed **4b** is a versatile synthon for the preparation of other pyrazine C-nucleosides. Copyright © 1996 Elsevier Science Ltd

The unique structure and properties of C-nucleosides have generated considerable interest in both their chemistry and biochemistry.[1] A substantial number of naturally occurring and synthetic C-nucleosides, many with interesting biological activities, have been prepared via a variety of approaches.[1a] Although pyrimidine-like nucleosides have been studied extensively, an entire class of compounds, the pyrazine C-nucleosides, were still missing from this array until recently. These pyrazine C-nucleosides, which are isosteres of pyrimidine nucleosides, have structural similarities to many of the naturally occurring nucleosides. Due to these similarities, these compounds have high potential as chemotherapeutic agents.

Scheme I



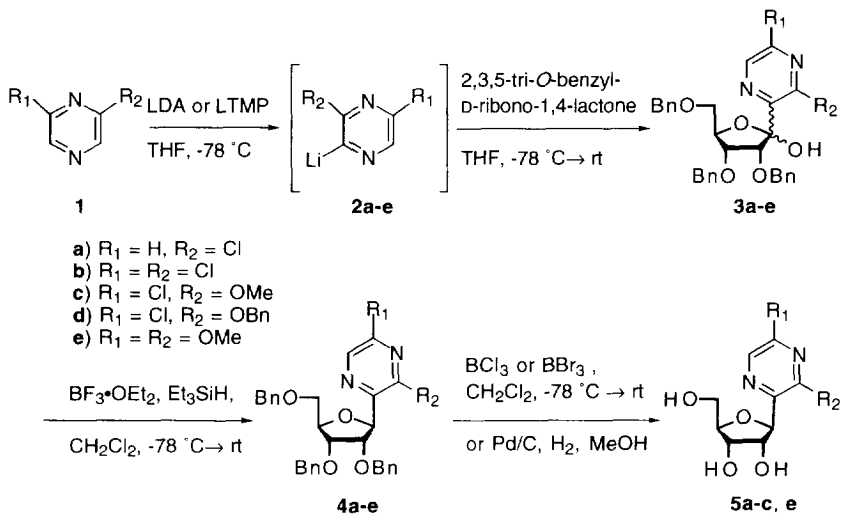
P= protecting groups
L= leaving groups
R_1, R_2= H, Cl, Alkoxy

While our studies were in progress, Benner and coworkers reported the preparation of a pyrazine C-nucleoside.[2] While effective, their stepwise construction of an isocytidine isostere is difficult to be adopted to our system. A more preferred method, as outlined in Scheme I, would be the direct condensation of a

carbohydrate moiety with a functionalized heterocycle from which a wider variety of analogs could be easily derived. Recently, we have published the synthesis of some 2'-deoxy pyrazine C-nucleosides via palladium-mediated cross-couplings.[3] We now wish to report on the development of a different approach, which leads to the synthesis of pyrazine C-ribosides, involving the condensation of a functionalized γ-lactone with a preformed lithiopyrazine moiety.

There have been a number of studies on the lithiation of pyrazines involving both the aromatic protons and the exocyclic protons on alkyl substituents.[4] The lithiating agents range from alkyl lithiums to lithium amides. According to the studies on pyrazine lithiation by Quéguiner and coworkers, lithium diisopropylamide (LDA) and lithium 2,2,6,6-tetramethylpiperidide (LTMP) have been found to give the best results.[5] Although lithiated pyrazines have been reported to react with strong electrophiles such as benzaldehyde and methyl iodide, we found that the less reactive 2,3,5-tri-*O*-benzyl-D-ribono-1,4-lactone[6] was also a good substrate under controlled conditions. Thus, substituted pyrazines **1a-e** were treated with LTMP or LDA at a low temperature to give the lithiopyrazine intermediates **2a-e**. The regiochemical outcomes were, as anticipated,[5] dictated by the directing effect of the ortho-groups. Treatment of **2a-e** with the lactone afforded, upon workup, the hemiacetals **3a-e**. The resultant hemiacetals were treated with triethylsilane in the presence of borontrifluoride diethyletherate to remove the hydroxyl groups[7] and gave the protected pyrazine C-nucleosides **4a-e** (Scheme II). Deprotection was accomplished either by Lewis acid catalyzed hydrolysis or palladium catalyzed hydrogenolysis, depending on the substituents.

Scheme II



A typical procedure is as follows: To a solution of *n*-butyl lithium (1.6 M solution in hexane, 9.38 mL, 15.0 mmol) in 50 mL of dry THF at -78 °C under argon was added 2,2,6,6-tetramethylpiperidine (2.45 mL, 15.0 mmol). The mixture was stirred at 0 °C for 30 minutes and the pale yellow solution was then cooled to -78 °C. A solution of 2,6-dichloropyrazine (**1b**, 2.23 g, 15.0 mmol) in 50 mL of dry THF was then added

dropwise and the mixture was stirred at -78 °C for 1 hour to give a dark red solution. 2,3,5-Tri-*O*-benzyl-D-ribono-1,4-lactone (7.53 g, 18.0 mmol) was dissolved in 50 mL of dry THF and then transferred dropwise into the lithiopyrazine solution at -78 °C. The mixture was stirred at -78 °C under argon for 3 hours, warmed to room temperature and then stirred for 10 hours. The reaction was quenched by the addition of a saturated ammonium chloride solution. The reaction mixture was extracted with diethyl ether (3 x 50 mL) and the combined organic phase was dried over magnesium sulfate. After filtration, the solvent was removed *in vacuo* and the resultant orange oil was applied to a silica gel column (5 x 20 cm) and eluted with 20% ethyl acetate in hexane to give **3b** as a clear oil (6.56 g, 77% yield). A portion of this oil (4.14 g, 7.0 mmol) was dissolved in 30 mL of dry dichloromethane. To this solution, at -78 °C under argon, borontriflouride diethyletherate (3.60 mL, 30.0 mmol) and triethylsilane (4.60 mL, 20.0 mmol) were added. The mixture was stirred at room temperature for 5 days, quenched with a saturated sodium bicarbonate solution and extracted with diethyl ether (3 x 30 mL). The combined organic extracts were dried over sodium sulfate, filtered, and evaporated *in vacuo*. The residue was applied to a silica gel column (4 x 13 cm) and eluted with 10% ethyl acetate in hexane to give 3.95 g (93% yield) of **4b**[8] as a clear oil. The results of other reactions are summarized in Table 1.

Table 1. Condensation of Pyrazines **1a-e**[a] and 2,3,5-Tri-*O*-benzyl-D-ribono-1,4-lactone

Entry	Compound	R_1	R_2	Lithiating agent	Yield[b]
1	**4a**	H	Cl	LTMP	65
2	**4b**	Cl	Cl	LTMP	72
3	**4c**	Cl	OCH_3	LDA	50
4	**4d**	Cl	OBn	LDA	70
5	**4e**	OCH_3	OCH_3	LTMP	44

a) **1a** is commercially available, **1b-e** were prepared according to literature procedures[9].
b) All yields are isolated yields of **4a-e** from **1a-e**.

It was found that the reaction temperature was the key factor in these condensation reactions, as higher reaction temperatures generally resulted in the decomposition of both the pyrazine and the lactone. The benzyl protecting groups on the carbohydrate moiety were chosen due to their stability towards both the lithiation and the deoxygenation conditions. Other protecting groups usually gave poor yields at the condensation step and decomposed in the presence of Lewis acids. The rates for the deoxygenation step were, to a large extent, dependent upon the substituents on the pyrazine. Electron-donating groups, such as a methoxy or a benzyloxy group, dramatically accelerated the reactions, while an electron-withdrawing group, such as a chlorine group, prolonged the reaction time and required higher reaction temperatures (data not shown). This phenomenon could be explained by the stability of the oxonium ions generated from the hemiacetals. A relatively electron rich pyrazine can stabilize the oxonium ion at the anomeric position, while an electron deficient pyrazine destabilizes it. In contrast to earlier studies on this type of reaction[10], it was found that solvents have virtually no effect on the stereochemistry. Thus, reactions in the more polar dichloromethane and the less polar toluene gave the same product in similar yields. The anomeric configurations were assigned based upon the 2',3'-*O*-acetonal analogs of the products, where the chemical shift difference between the two methyl groups in the proton NMR are

generally greater than 0.24 ppm, indicating the desired β anomers.[11] This result was presumably due to the coordination of triethylsilane to the 2'-oxygen followed by the delivery of a hydride ion from the α-face of the molecule.[12]

The synthesis of other pyrazine C-nucleosides derived from the above compounds is being pursued in our laboratory. The biological data of these compounds will be published elsewhere.

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8. **4b** ^{1}H-NMR ($CDCl_3$) δ 8.30 (s, 1H), 7.27 (m, 15H), 5.47(d, 1H, *J*=5.7 Hz), 4.67-4.46 (m, 6H), 4.39 (m, 2H), 4.13 (dd, 1H), 3.59 (d, 2H). ^{13}C-NMR ($CDCl_3$) δ 149.8, 147.6, 146.7, 142.2, 138.3, 137.9, 137.7, 128.6, 128.5, 128.4, 128.2, 128.1, 128.01, 127.97, 127.7, 82.6, 80.5, 79.2, 78.0, 77.6, 77.2, 76.9, 73.5, 72.7, 72.4, 70.4. Anal. Calcd. for $C_{30}H_{28}O_4N_2Cl_2$: C, 65.34; H, 5.12; N, 5.08. Found: C, 65.34; H, 5.32; N, 5.08.
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