An efficient and facile synthesis of 2-bromo-5-methylpyrazine

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Received: 26th May, 2009 ; Accepted: 5th June, 2009

ABSTRACT
A facile and efficient synthesis of 2-bromo-5-methyl pyrazine is described. The synthetic scheme involves the conversion of 5-methylpyrazine-2-carboxylic acid to the corresponding amide which on Hofmann degradation gives the amine compound. This amine compound on diazotization followed by in-situ bromination produces the targeted 2-bromo-5-methyl pyrazine.

INTRODUCTION
The emergence of drug-resistant pathogenic strains in recent years, e.g. Streptococcus pneumoniae, Staphylococcus aureus, Enterococcus faecium, Pseudomonas aeruginosa, Stenotrophomonas maltophilia, Salmonella typhi, has been of major concern[1-4]. Among other infectious diseases, tuberculosis, caused by Mycobacterium tuberculosis, seems to be the most invasive, and the multidrug resistance (MDR) phenomenon makes it the world’s number one killer especially for immunosuppressed AIDS patients[5]. Because of this, there is a great need for antibacterial and antituberculous drugs with improved properties such as enhanced activity against MDR strains and reduced toxicity.

Pyrazines (1) represent an important class of heterocyclic compounds[6]. As several bio synthetic paths allow the conversion of an amino acid into a pyrazine, this structural unit is found in many natural products. They are important flavor ingredients in food[7], and have shown interesting anticancer[8] as well as antituberculosis[9] activities. Pyrazines have been used widely as agrochemicals as well[10]. Substituted pyrazines have also gained increased attention in recent years due to their usefulness as important constituents either of biologically active compounds[11] or functional materials[12].

Pyrazinamide (2) is one of the most effective antituberculous drugs. Various pyrazine derivatives and pyrazinamide analogs also exhibit high antibacterial activity such as esters of pyrazinoic acid[13], pyrazine thiocarboxamide and N-hydroxy methylpyrazine thiocarboxamide[14] and ring substituted pyrazinylchalcones[15]. Microbiological evaluation of the 2-bromo-5-methylpyrazine (3) was performed by determining the antituberculous activity on Mycobacterium tuberculosis, M. avinum, M. kansasii and M. fortutium in vitro in comparison with the effect of pyrazinamide[16] (Figure 1).

KEYWORDS
5-methylpyrazine-2-carboxylic acid; Hofmann degradation; Diazotization; 2-bromo-5-methylpyrazine.
RESULTS AND DISCUSSION

Irrespective of the importance of 2-bromo-5-methylpyrazine (3), an efficient synthetic route to this key 2-bromo-5-methylpyrazine (3) intermediate has thus far not been fully developed. Only one report is available as on date for the preparation of 2-bromo-5-methylpyrazine (3)\textsuperscript{16}, direct condensation of aminoacetamide chloride with methylglyoxal gave 5-methyl pyrazine-2-ol which being treated with phosphoryl bromide resulted the title compound. However, poor yields reduce the efficiency of this approach.

For these reasons, the aim of this study is to develop an efficient and improved route to synthesize the 2-bromo-5-methylpyrazine (3) by using 5-methylpyrazine-2-carboxylic acid (7). The preparation of 5-methyl pyrazine-2-carboxylic acid\textsuperscript{17} involves the free radical chlorination of 2,5-dimethylpyrazine (4) with N-chlorosuccinimide in the presence of benzoyl peroxide as initiator afforded 2-chloromethyl-5-methylpyrazine (5) which was refluxed with anhydrous NaOAc in absolute ethanol under argon gave acetoxymethyl derivative. Hydrolysis of the obtained acetoxymethyl derivative with NaOH gave alcohol (6) which on oxidation with KMnO\textsubscript{4} produces the desired acid (7) in 50% overall yield (Scheme I).

We have utilized 5-methylpyrazine-2-carboxylic acid (7) as a key starting material for the preparation of title compound (Scheme II). 5-Methylpyrazine-2-carboxylic acid (7) which is well available commercially and is converted to the methyl ester (8) using H\textsubscript{2}SO\textsubscript{4} in methanol followed by the reaction with ammonia in methanol produces the corresponding amide (9). This amide on Hofmann degradation produces the 2-amino-5-methylpyrazine (10). For this reaction, literature\textsuperscript{18} reveals the usage of potassium hypochlorite which is prepared in-situ by using chlorine in aqueous potassium hydroxide. To avoid the usage of chlorine gas, we have utilized the potassium hypochlorite in the reaction directly. However, upon direct usage of potassium hypochlorite results the run away reaction. Finally, it has been identified a commercial viable Hofmann degradation reaction conditions by using Br\textsubscript{2} in aqueous KOH to prepare 2-amino-5-methylpyrazine, (10).

\textbf{Scheme I}

\textbf{Scheme II}

2-Amino-5-methylpyrazine, (10) on diazotization with NaNO\textsubscript{2}/HBr followed by displacement with molecular bromine (Sandmeyer type reaction) produces the 2-bromo-5-methyl pyrazine, (3). Initially, this reaction proceeded with only 5-7% yield. To improve the yield, conditions for the formation of diazonium salt, stability and reactivity of the obtained diazonium salt at different reaction temperatures was studied. Complete absence of amine compound (10) was observed with NaNO\textsubscript{2}/HBr at 0°C, and target compound formation was not observed with NaBr or CuBr at the same temperature. However, 25-30% product (3) formation was observed with molecular bromine as a brominating agent instead of NaBr or CuBr at 0°C. The unmanageable exothermicity of this reaction intended us to examine the feasibility of this reaction at further low temperatures and found that -45°C is the optimum temperature to control exothermic nature of the reaction. At -15 to -10°C, we have observed only 10% product formation with NaBr or CuBr and 20% product formation with...
molecular bromine. Yield was not much improved even at further low temperatures.

It was started suspecting about the stability of the corresponding diazonium salt. To prove this, bromine was added to the reaction prior to the formation of diazonium salt which gave > 60% of product formation even at -45°C. After these results, the reasons for the low yield could be the obtained diazonium salt is highly unstable at above -20°C and not reactive towards the NaBr and CuBr at below -20°C. The immediate availability of the bromine radical after the formation of diazonium salt gives the more product formation.

As a conclusion, an efficient and facile synthesis of 2-bromo-5-methylpyrazine (3) is described by conversion of 5-methylpyrazine-2-carboxylic acid to the corresponding amide which on Hofmann degradation gave the amine compound. This amine compound on diazotization followed by in-situ bromination yielded the targeted 2-bromo-5-methylpyrazine. Based on this process 2 Kg of title compound was prepared.

**EXPERIMENTAL SECTION**

Melting points were determined on a Buchi 540 melting point apparatus and are uncorrected. ¹H and ¹³C NMR (proton decoupled) spectra were recorded on Varian 400 MHz spectrometer using DMSO-d₆ and CDCl₃ as solvent, and tetramethyl silane (TMS) as internal standard. Mass spectra were recorded on Agilent triple quadrupole mass spectrometer equipped with turboion spray interface at 375°C. Unless otherwise mentioned, all the solvents and reagents used were of commercial grade. TLC was performed on pre coated silica-gel plates, which were visualized using UV light.

**Preparation of methyl 5-methylpyrazine-2-carboxylate (8)**

To a cooled solution of methanol (300 mL) and 5-methylpyrazine-2-carboxylic acid (100 g, 0.724 mole), conc. sulphuric acid (8.0 mL) was added drop wise at 0-5°C. The reaction mixture was heated to 65°C and maintained at this temperature for over night. After completion of the reaction, cool the reaction mass to RT and distill off the solvent under vacuum at below 30°C. The obtained residue was partitioned between water (300 mL) and toluene (500 mL). Both the layers were separated and the aqueous layer was extracted with toluene (2’ 400 mL). Combined organic layer was washed with 2% aqueous sodium hydroxide solution (100 mL), dried over sodium sulfate, filtered and the solvent was removed by evaporation under vacuum at below 45°C to give the compound 2 as a light brown colored solid; 91% yield; mp 92-5 °C; ¹H NMR (CDCl₃): δ 2.6 (s, 3H), 3.95 (s, 3H), 8.75 (s, 1H), 9.05 (s, 1H); MS: m/z (M⁺+1) 153.1;

**Preparation of 5-methylpyrazine-2-carboxamide, (9)**

To a cooled solution of methanol (800 mL) and crude compound 2 (100.0 g, 0.657 mole), ammonia gas was purged at 0-5°C for 4 hr. Completion of the reaction was monitored by TLC. After completion of the reaction, filtered the reaction mass and the obtained solid was washed with pre-cooled methanol (80 mL) to give compound 3 as a light brown colored powder; 82% yield; mp 206-207°C; ¹H NMR (CDCl₃): δ 2.7 (s, 3H), 5.85 (bs, 1H, D₂O exchangeable), 7.60 (bs, 1H, D₂O exchangeable), 8.40 (s, 1H), 9.3 (s, 1H); MS: m/z (M⁺+1) 138.0.

**Preparation of 5-methylpyrazin-2-amine, (10)**

To a cooled solution of water (80 mL) and potassium hydroxide (18.0 g, 0.321 mole), bromine was added drop wise at 0-5°C. Compound 3 (10.0 g, 0.073 mole) was added to the reaction mass at 0-5°C and the reaction mass was maintained at same temperature for 1 hr. Another lot of potassium hydroxide (4.09g, 0.073 mole) was charged at 0-5°C. The reaction mass was heated to 85-90°C for 2 hr. Completion of the reaction was monitored by TLC. After completion of the reaction, compound was extracted with dichloromethane (3’ 100 mL). Combined organic layer was washed with water, dried over sodium sulfate and evaporation of the solvent under reduced pressure to give residue. The residue was triturated with n-hexane and the obtained solid was filtered to give compound 4 as a yellow colored powder; 75% yield; mp 113-15°C; ¹H NMR (CDCl₃): δ 2.4 (s, 3H), 4.4 (bs, 2H, D₂O exchangeable), 7.85 (s, 1H), 7.95 (s, 1H); MS: m/z (M⁺+1) 110.

**Preparation of 2-bromo-5-methylpyrazine, (3)**

Powdered 5-methylpyrazin-2-amine, 4 (100.0 g, 0.916 mole) was added with vigorous stirring in por-
tions to 48% aq. hydrobromic acid (1000 mL) at 25-30°C. After the entire compound was dissolved, the reaction mixture was cooled to -55 to -50°C. To this suspension, cooled bromine (132.0 mL) was added dropwise over 1 hr, maintaining the temperature at -50°C and was stirred for 90 min at this temperature. Then sodium nitrite (168.0 g, 2.435 mole) in water (340 mL) was added dropwise at -50°C. The reaction mixture was cooled to -55 to -50°C and was stirred for 90 min at this temperature. After completion of the reaction, reaction mass was basified with aqueous sodium hydroxide (pH > 9) at below 20°C and the compound was extracted with n-hexane (3’500 mL). Distill off the solvent under reduced pressure at below 30°C until the reaction mass volume becomes 300 mL. The residue was cooled to -15°C and maintained the temperature at below 30°C and the compound was extracted with n-hexane suspensio, cooled bromine (132.0 mL) was added dropwise over 1 hr, maintaining the temperature at -50°C. After the entire compound was dissolved, the reaction mixture was cooled to -55 to -50°C and was stirred for 90 min at this temperature.

The authors thank Inogent Laboratories Private Limited (A GVK BIO Company) for the financial support and encouragement.

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