Synthesis of Diaminothiazoloyl-N-methylbenzimidazoles

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ABSTRACT

Natural products especially from marine sources exhibit excellent biological activity. They exhibit a variety of bioactivity such us antibiotic, anticancer, antiinflammatory, antitumor, antiviral, antibacterial and antifungicidal activites. The chemical compounds, which are separated from marine sources usually consists of nitrogen containing heterocyclic rings. Many of these may be classified as marine alkaloids due to this fact. Alkaloids have long claimed the attention of humans due to their significant bioactivity. Thus several alkaloids have found a place in western as well as in eastern systems of medicine. In fact phytochemicals such as alkaloids have been in use from time immemorial for the treatment of illness.

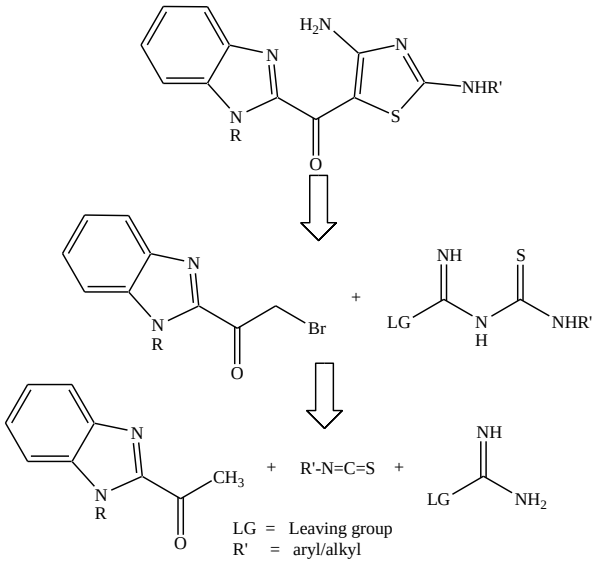
A. INTRODUCTION

Benzimidazole shares several structural features with indole. In addition, benzimidazoles exhibits several significant biological activities just as indoles. The literature survey given below shows several examples of compounds having a benzimidazole ring which exhibit remarkable bioactivity. Thus the simple benzimidazole derivative possesses antitumor activity and also acts as an antihistaminic.

The 2-phenylbenzimidazole derivative possesses antiinflammatory activity and antimicrobial activity. Another 2-phenylbenzimidazole derivative is useful in the treatment of inflammation and immune disorders such as arthritis and transplant rejection. The 5,6-dimethylbenzimidazole derivative shows antiischemic, antihypoxic and antiarrhythmic activities.The nitrobenzimidazole derivative shows antiviral activity, whereas the benzimidazolylphenylhydrazide shows antimicrobial activity and antitubercular activity and the nitrostyrylbenzimidazole shows antimicrobial activity.

RESULTS AND DISCUSSIONS

1. Synthetic Planning In order to achieve the above objectives, the following retrosynthetic approach appeared feasible.



The retrosynthetic approach shows that this type of dendrodoine analogs could be synthesised by using the precursors 2-(2-bromoacetyl)benzimidazole and amidinothioureas. On the basis of a literature search based on Beilstein database it appears that no satisfactory method for 2-(2-bromoacetyl)benzimidazole has been so for reported. We attemped to prepare 2-(2-bromoacetyl)benzimidazole by a variety of brominating agents including copper(II) bromide. The thin layer chromatogram of the product obtained in such bromination invariably showed several spots indicating that the reaction was complicated. We had also tried to brominate 2-acetylbenzimidazole by radical bromination. Under this condition, we observed that a fair amount of 2- acetylbenzimidazole hydrobromide gets deposited. After the above unsuccessful attempts, we decided to turn our attention to 2-acetyl-N-methylbenzimidazole. A retrosynthetic analysis for the synthesis of the targeted analogs of dendrodoine can be written as follows.

2. Synthesis of diaminothiazoloyl-N-methylbenzimidazoles

a. Synthesis of precursors

i. 2-(2-Bromoacetyl)-N-methylbenzimidazole

The preparation of 2-(2-bromoacetyl-N-methylbenzimidazole consisted of four steps. The first is the preparation of 2-(1-hydroxyethyl)benzimidazole starting from 2-phenelenediamine and lactic acid. The 2-(1-hydroxyethyl)benzimidazole is next oxidized to 2-acetylbenzimidazole. The third step, involved the N-methylation of 2-acetylbenzimidazole and the last step was the conversion of

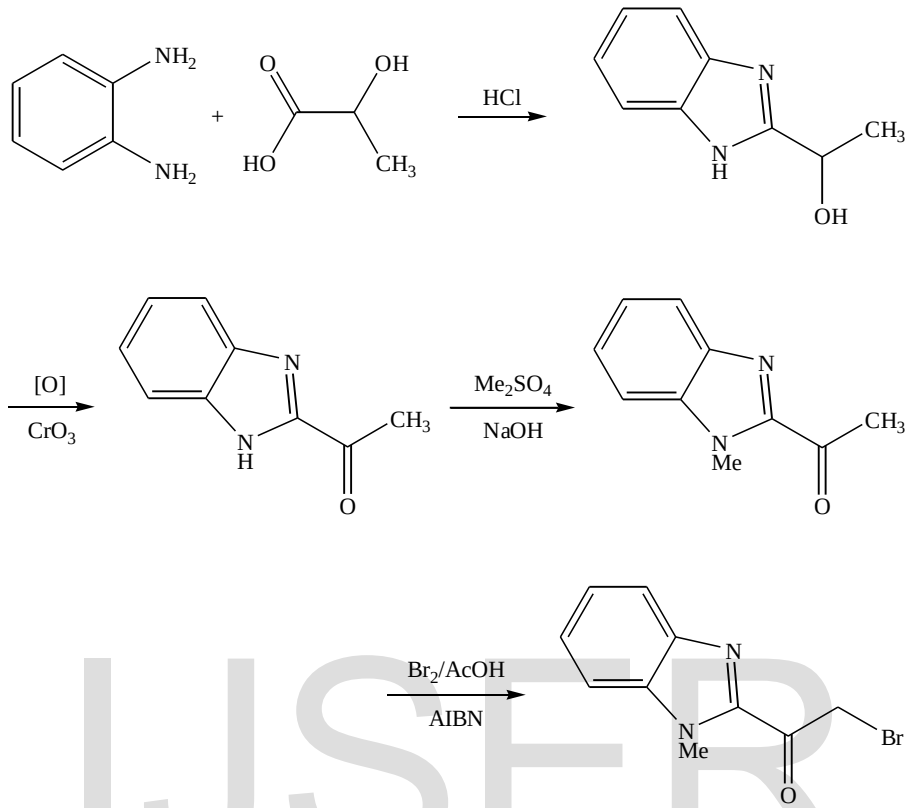
2-(2-bromoacetyl)-N-methylbenzimidazole into 2-(2-bromoacetyl)-N-benzimidazole.

Firstly, 2-(1-hydroxyethyl)benzimidazole was prepared from 1.2-diaminobenzene and lactic acid.[154] Next it was oxidized by chromium(III) oxide to 2-acetylbenzimidazole.[155] Its ^{1}H NMR (300 MHz, $CDCl_3$) spectrum shows a three-hydrogen singlet at δ 2.84 due to the methyl group. The multiplet at δ 7.21-7.67 has been assigned to the H-5, H-6 and H-7 of the benzimidazole ring. The H-4 of the benzimidazole gives rise to a one-hydrogen doublet at δ 7.90. The downfield singlet if one-hydrogen at δ 10.50 is assignable to the NH hydrogen of the benzimidazole ring. In the next step 2-acetyl-N-methylbenzimidazole was converted to 2-acetyl-N-methylbenzimidazole. In this step 2-acetylbenzimidazole was treated with dimethyl sulphate in sodium hydroxide solution to afford 2-acetyl-N-methylbenzimidazole.[155] In the IR (KBr) spectrum the shift of carbonyl stretching frequency from 1681cm^{-1} to 1688cm^{-1} confirmed this conversion. The ^{1}H NMR spectrum (300 MHz, $CDCl_3$) consists of three-hydrogen singlet at δ 2.84, which can be assignable to the methyl group attached to carbonyl group. The methyl group attached to nitrogen of benzimidazole ring appears as a three-hydrogen singlet at δ 4.15.The H-5, H-6 and H-7 of the benzimidazole ring gives rise to a multiplet at δ 7.30-7.49. The downfield doublet of one-hydrogen is ascribed to the H-4 of the benzimidazole ring.

In 1978, Prakash et al. effected the bromination of 2-acetyl-N-methylbenzimidazole using bromine in dry chloroform and heating under reflux for 1h gave 2-(2-bromoacetyl)-N-methylbenzimidazole hydrobromide. The neutralisation of this salt afforded 2-(2-bromoacetyl)-N-methylbenzimidazole in 78% yield. We have now modified this radical bromination step by using bromine in glacial acetic acid and AIBN as a radical initiator. The reaction yielded 2-(2-bromoacetyl)-N-methylbenzimidazole hydrobromide. The free base was released using sodium bicarbonate to afford 2-(2-bromoacetyl)-N-methylbenzimidazole in 89% yield. The shift in υC=O from 1688cm^{-1} (–$COCH_3$) to 1707cm^{-1} (–$COCH_2Br$) confirms the bromination.

The ^{1}H NMR spectrum (300 MHz, $CDCl_3$) shows a three-hydrogen singlet at δ 4.17, which has been assignable to the methyl group attached to nitrogen of the benzimidazole ring. The two-hydrogen singlet at δ 4.88 is due to the two hydrogens of –$COCH_2Br$ group. The multiplet of three-hydrogen at δ 7.33-7.51 is ascribed to the H-5, H-6 and H-7 of the benzimidazole ring. The H-4 of the benzimidazole ring gives rise to a one-hydrogen doublet at

δ 7.87. The reaction sequence adopted for the preparation of 2-(2-bromoacetyl)-1-methylbenzimidazole is shown below.



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