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A New Synthetic Approach toward Ring-Expanded ("Fat") Purine Nucleobases: Synthesis and Use of 5-Dichloromethyl-1-*p*-methoxybenzyl-4-nitroimidazole as a Versatile Intermediate

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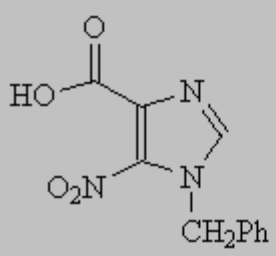
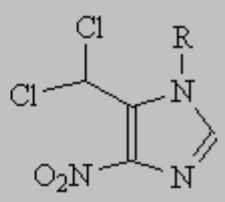
INTRODUCTION

Ring expanded ("fat") purine nucleosides are of chemical, biochemical, biophysical, and medicinal interest.[1-12] The majority of "fat" nucleosides reported from this laboratory in recent yeas were synthesized using the common imidazole precursor, namely 1-benzyl-5-nitro-imidazole- 4-carboxylic acid (**I**).[5-11] However, the synthesis of **I** suffered from a number of drawbacks, including multi-step procedures, prolonged reaction periods (sometimes days), poor yields, tedious work-ups, and the necessity of separation of regioisomers, all of which contributed to the difficulty in preparing **I** on a reasonably large scale. We present here an efficient, convenient, and a versatile alternative for **I** in 5-dichloromethyl-1-*p*-methoxybenzyl -4-nitroimidazole (**II**). The latter has a number of novel features which will potentially not only enable the efficient resynthesis of the previously reported "fat" nucleosides from this laboratory, but will also open new ways for the synthesis of a wide variety of novel "fat" nucleosides that would otherwise be difficult to prepare using **I**. The novel features of **II** include (a) the presence of a versatile, highly reactive dichloromethyl functional group which can serve as the site of both nucleophilic and electrophilic attacks for further annulation of the appropriate side chain , (b) the potentially facile conversion of the above dichloromethyl group into a wide variety of other reactive functional groups including, but not limited to, a carboxylic acid, a carboxaldehyde, or an iminomethylene functionality, and (c) the attachment of the more conveniently removable *p*-methoxybenzyl protecting group at the 1-position as compared to the unsubstituted benzyl group of **I**. In addition, the synthesis of **II** is brief, convenient, reasonably good-yielding, and can be prepared on a reasonably large scale from readily available and inexpensive starting materials.



I



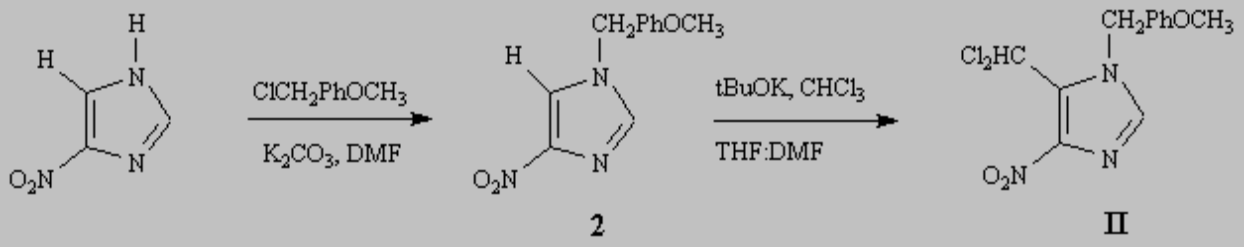
II

RESULTS AND DISCUSSION

The synthesis of **II** exploits the principle of nucleophilic substitution on an activated heterocycle. The method is generally referred to as Vicarious Nucleophilic Substitution or the VNS method.[13] The latter is a novel way of introducing an -functionalized alkyl chain onto activated aromatic rings.[13] Although electron-rich 5-membered nitrogen heterocycles such as imidazoles do not normally undergo nucleophilic substitution reactions, the introduction of strong electron- withdrawing groups such as a nitro functionality can render them vulnerable to such reactions.

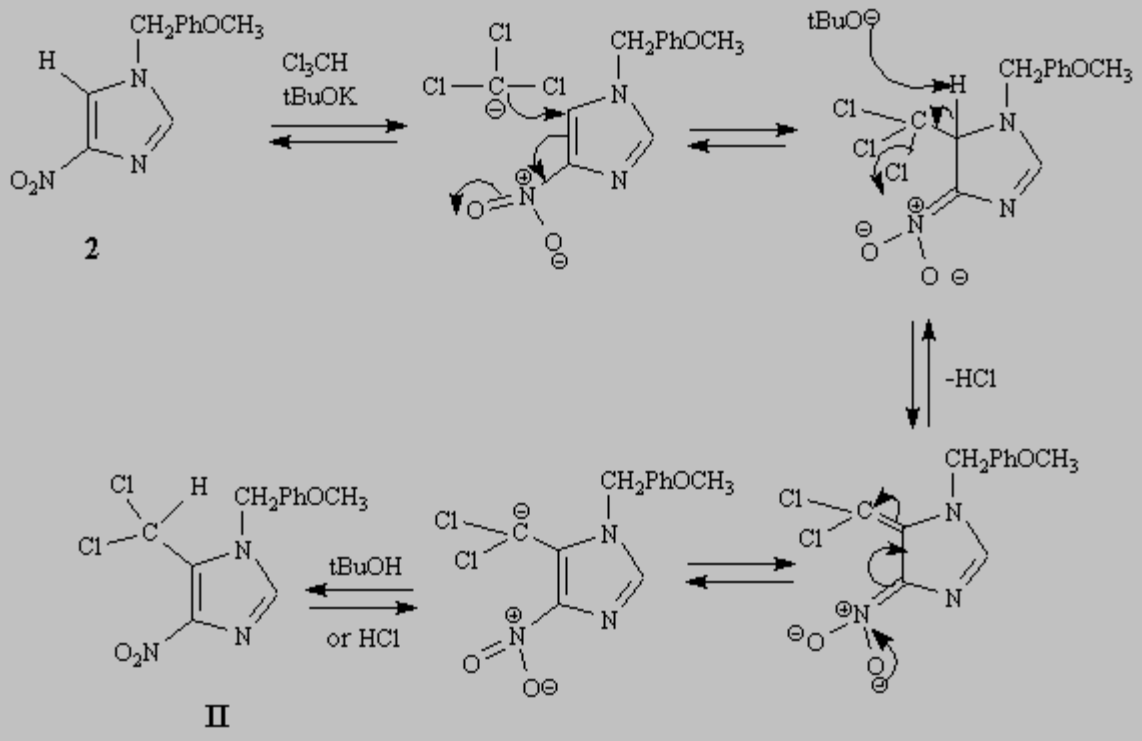
The synthesis started with 4-nitroimidazole (**Scheme 1**), and the first step was to protect the *N*-H of imidazole with a benzyl group; in this case, *para*-methoxybenzyl chloride was employed for

Scheme 1



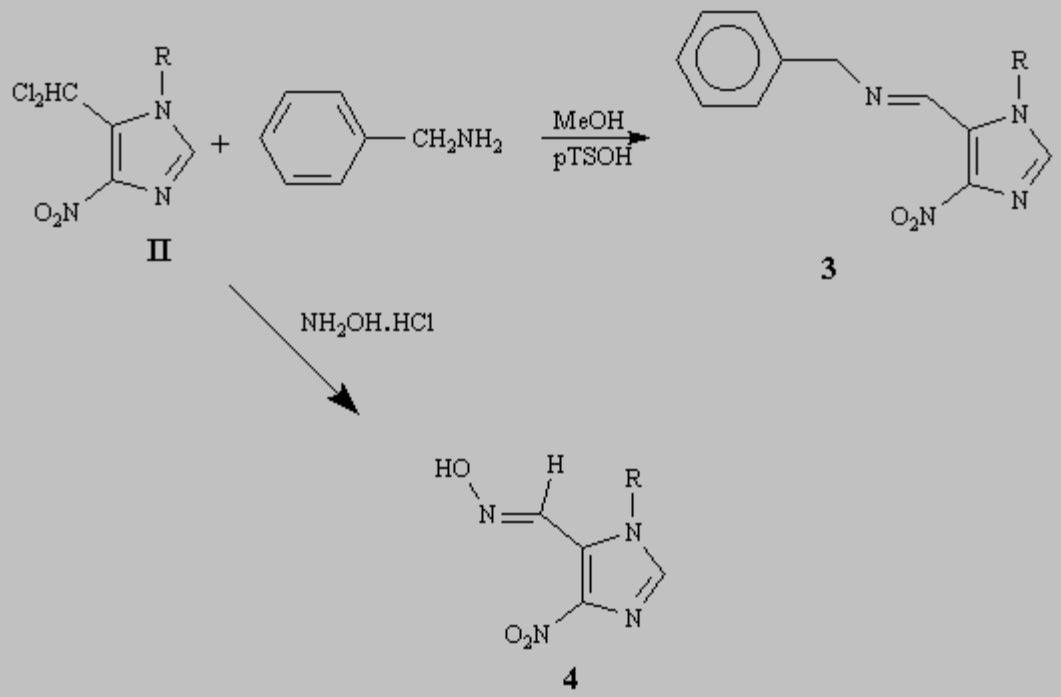
reasons described under Introduction above. Treatment of 4-nitroimidazole with *para*-methoxybenzyl chloride and potassium carbonate in DMF yielded 1-*p*-methoxybenzyl-4- nitroimidazole (**2**) as a colorless crystalline solid in 90% yield. Compound **2** was subjected to VNS using chloroform and potassium *t*-butoxide in DMF to yield the target 5-dichloromethyl-1- *p*-methoxybenzyl-4-nitroimidazole (**II**) in 60% yield. The ^{1}H-NMR of **II** in deuterated dimethyl sulfoxide revealed the proton of 5-dichloromethyl group as a singlet at 7.96, and the imidazole ring proton at 8.01 also as a singlet. The elemental microanalysis was consistent and the mass spectrum showed the correct MH^{+} ion at m/z 316. A mechanism for the formation of **II** from **2** by the VNS method is outlined in **Scheme 2**. The first step, most likely the rate determining, involves the nucleophilic attack of the carbanion formed from chloroform onto position 5 of the imidazole ring. The subsequent base-catalyzed elimination of hydrogen chloride, followed by reprotonation of the dichloromethylene carbon atom and the ring aromatization produces **II**. The presence of a nitro group on the imidazole ring is apparently critical for the VNS method to succeed.

Scheme 2



Compound **II** was reacted with two representative amine nuclephiles, including benzylamine and *N*-hydroxylamine (**Scheme 3**). The products **3** and **4**, obtained in 44% and 63% yields, respectively, were fully characterized by spectroscopic and microanalytical data.

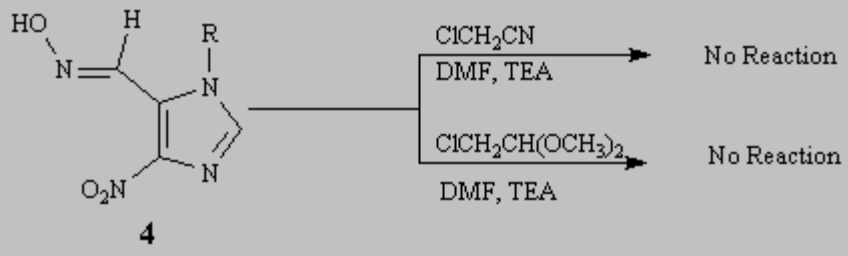
Scheme 3



Our final goal was to demonstrate the feasibility of employing **II** for the synthesis of "fat" nucleosides. To this end, we decided to further explore the reactivity of **4** with alkylating agents, which, if reacted successfully, would yield product with the appropriate carbon fragment attached that would afford the 5:7 heterocyclic ring system upon ring closure.

However, the reaction of **4** with either chloroacetonitrile or chloroacetaldehyde dimethyl acetal, even under forcing conditions, failed to proceed (**Scheme 4**). The reason for the failure is believed to be the inactivation of the oxime nitrogen atom because of conjugation with the electron-withdrawing nitro group attached at the 4-position of the imidazole ring. In order to alleviate this problem, we then decided to reduce the nitro group into an amino group before carrying out the necessary alkylation or acylation reactions.

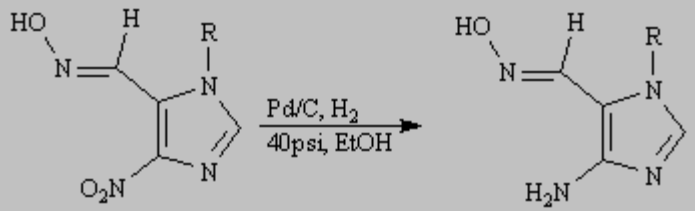
Scheme 4



4

The reduction of **4** was carried out in a Parr hydrogenation apparatus, using 10% Palladium and charcoal in ethanol at 40 psi of hydrogen gas to afford the desired amine **5** in 71% yield (**Scheme 5**). Compound **5** was reacted with dichloroacetyl chloride to obtain 4-(2,2-dichloroacetyl)amino- 5-(*N*-hydroxyiminomethylene)-1-*p*-methoxybenzylimidazole (**6**) as a crystalline solid in 74%

Scheme 5



4 **5**

yield. The ^{1}H NMR of **6** exhibited the presence of D_2O-exchangeable amide NH as well as the *N*-OH functionalities integrating for a proton each at 11.24 and 10.54 , respectively, suggesting that the reaction had taken place at the 4-amino function intead of the oxime nitrogen atom. Compound **6** was a suitable precursor for the synthesis of a representative "fat" nucleobase Indeed, the ring-closure of **6** with sodium methoxide in methanol produced the novel, 5:7-fused heterocycle **III**, albeit in somewhat low (34%) yield. The reason for the relatively poor yield of this reaction is not yet clear, although optimum reaction conditions for this last synthetic step are yet to be worked out. It is also not obvious as to when the methanolysis of the halide group(s) takes place, whether before or after the ring-closure. In any case, compound **III**, with its interesting *N*-oxide structure, bears a broad scope for further chemical, biochemical, biological, as well as chemotherapeutic explorations Because of their intriguing physicochemical properties, coupled with their unique biological behavior, the heterocyclic *N*-oxides have earned the separate classification as an independent, unique family of organic compounds.[66-73]

Conclusion and Future Work

The synthesis of the target imidazole derivative, 5-dichloromethyl-1-*p*-methoxybenzyl- 4-nitroimidazole (**II**), has been accomplished. Compound **II** is a key imidazole precursor for the synthesis of a wide variety of old as well as new "fat" nucleobases and nucleosides. The synthesis of **II** is short, convenient, reasonably good-yielding, and can be prepared on a large scale from readily available and inexpensive starting materials. Furthermore, the dichloromethyl

functionality of **II** is anticipated to be amenable for easy conversion into a number of other reactive functional groups including, but not limited to, a carboxaldehyde, a carboxylic acid, aor an iminomethylene group. We have further demonstrated the use of **II** in future "fat" nucleoside syntheses by successfully synthesizing a representative "fat" nucleobase **III**.

Acknowledgment

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