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Magnesium-Assisted Imidazole Formation from Unreactive Ureas

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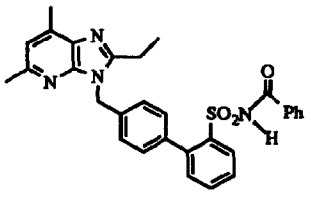
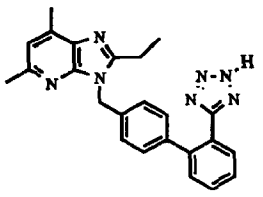
Abstract: *Novel and facile synthesis of imidazopyridine derivatives 1 from highly stable ureas 5 is described.*

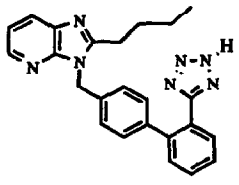
There has been significant interest in derivatives of imidazopyridine due to their varied biological activity toward several diseases.[1] More recently the heterocycle has become a prominent feature in the class of nonpeptide AII receptor antagonists,[2] as exemplified by the potential anti-hypertensives MK-996[3a], L-158,809[3b] and EMD 60218.[4] Generally, syntheses of the imidazopyridine heterocycle have relied upon the preparation of a 2,3-diaminopyridine precursor using classical chemistry[5a,b] followed by condensation of the diamine with the appropriate carboxylic acid to form the imidazole.[5c] These approaches are often inefficient and lack regio-control. Our strategy focused on the preparation of an appropriate pyridinoimidazolone intermediate **5**: condensation of a 1,3-dicarbonyl derivative with malonamamidine and subsequent Hofmann rearrangement provided the desired urea derivative of 2,3-diaminopyridine. Conversion of the ureas **5** to the desired imidazoles **1**, however, posed a significant challenge due to the ***stability*** and ***unreactivity*** of the carbonyl group.[6] To the best of our knowledge no method currently exists for the direct conversion of a urea to a 2-alkyl or aryl substituted-imidazole. Disclosed herein is an efficient protocol for the preparation of imidazopyridines via a magnesium-catalyzed activation of the urea carbonyl toward solvolysis and condensation with carboxylic acids to provide 2-substituted-imidazoles (Scheme 1).



MK-996



L-158, 809



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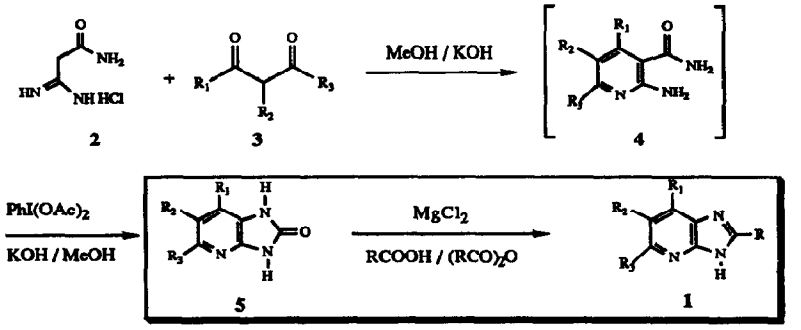
The imidazolutidine **1b** is a key component of the AII antagonist L-158,809. In our study, a highly efficient, two-step synthesis of the urea precursor **5b** (Scheme 1) was developed: Malonamamidine hydrochloride (**2**) was condensed with 2,4-pentanedione (**3b**) in the presence of 1.1 equivalents of KOH in MeOH at room temperature to afford 2-amino-4,6-dimethylnicotinamide (**4b**) in 92% yield.[6b] The product crystallized directly from the reaction mixture. The reaction generally required >20 h to reach completion; higher temperatures shortened the reaction time, but did not yield as pure a product. Recently, Moriarty[7] reported the Hofmann rearrangement of nicotinamide to 3-aminopyridine with iodobenzene diacetate. Treatment of **4b** with 1.0 equivalent of iodobenzene diacetate in the presence of 2.5 equivalents of KOH in MeOH at -5 °C gave rearrangement to the isocyanate, which was trapped intramolecularly to form the urea derivative **5b** of 2,3-

diaminolutidine in > 95% yield;[8] no detectable formation of the methyl carbamate via quenching of the isocyanate with the solvent was observed. The condensation and Hofmann rearrangement can also be conducted as a single-vessel procedure: Malonamamidine hydrochloride was first condensed with *1.0 equivalent of 2,4-pentanedione*[9] in KOH/MeOH. Once the reaction was complete, iodobenzene diacetate was simply added to affect the Hofmann rearrangement. Product **5b** crystallized from the reaction mixture and was isolated directly by filtration in 80% overall yield.

Scheme 1

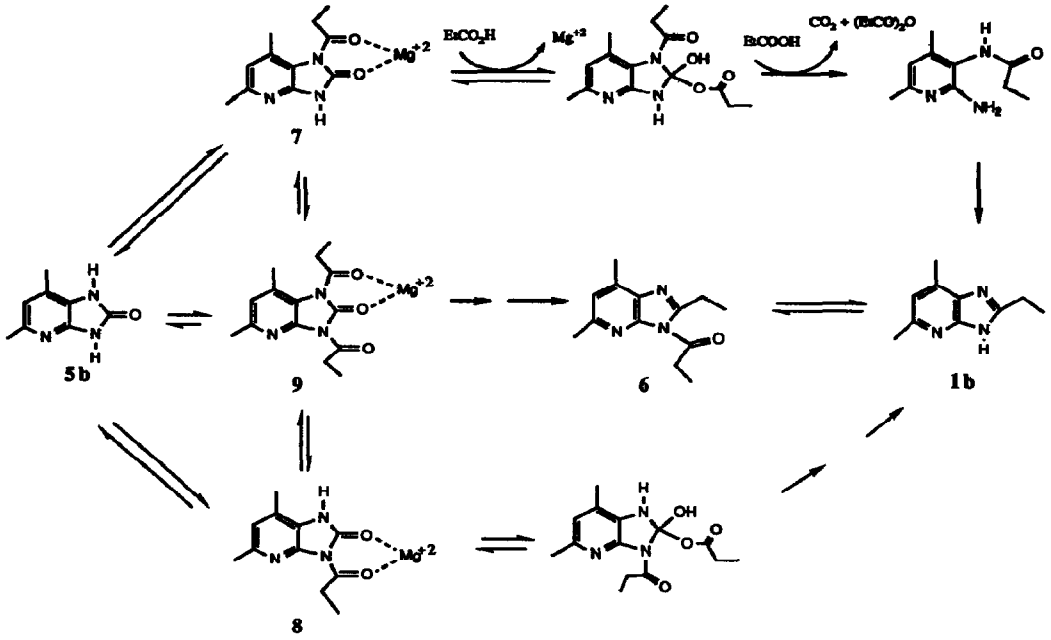


Our initial approach for conversion of the urea of **5b** to the imidazole ring was to hydrolyze the urea to the corresponding diaminopyridine then condense the diamine with propionic acid.[5c] The urea, however, proved to be extremely inert to hydrolysis under both acidic and basic conditions, transamination with ethylenediamine or analogues in conjunction with titanium isopropoxide, or addition of EtMgBr. Activation of the urea by acylation of one or both of the nitrogens with propionic anhydride facilitated the cleavage of the urea. By heating the urea in neat propionic anhydride at 180 °C in a sealed tube for 18 h a mixture of **7**, **8** and **9** was obtained. None of the desired **1b** was produced until propionic acid was included in the reaction mixture: heating the urea in a 1:1 mixture of propionic acid/propionic anhydride at 160 °C in a sealed tube for 18 h yielded 32% of the desired imidazolutidine **1b**, 10% of the starting urea, and four by-products. Interestingly, when only propionic acid was used, no reaction occurred. Evidently, the combination is needed to convert the urea directly to the imidazolutidine. After refluxing the urea in a 1:1 mixture of propionic acid/propionic anhydride at 149 °C for more than 5 days, 15% of **1b** and 75% of *N*-propionyl imidazolutidine **6** were obtained (Scheme 2); upon treatment with aqueous NH_4OH, water or MeOH at 60 °C the labile propionyl group of **6** was cleaved to provide the desired imidazolutidine **1b**.

In order to achieve a more efficient conversion of **5** to **1** activation of the urea carbonyl was explored. Interestingly, the rate of the reaction increased tremendously with the addition of a Mg salt; Mg^{2+} is very effective at chelating oxygen. When one equivalent of $MgCl_2$ was added to the reaction mixture, the reaction time ***decreased >17-fold*** from >5 days to 7 hours. $MgCl_2$ permitted rapid conversion of the urea to the imidazolutidine in propionic anhydride/propionic acid with quantitative conversion by HPLC.

Scheme 2

Reaction Pathway for the Formation of Imidazolutidine



The proposed reaction pathway for the activation of the urea carbonyl of intermediates **7**, **8**, or **9** with $MgCl_2$ is through chelation of the carbonyls, thereby facilitating the nucleophilic attack of propionic acid. These intermediates were individually subjected to $MgCl_2$ in propionic acid to provide a mixture of compounds **5b**, **1b** and **6**. The evolution of the CO_2 was detected with a Drager Polymeter. The propionic anhydride plays the dual role of an acylating and dehydrating agent. Although schematically only 1.0 equivalent of anhydride is necessary, an excess is required; for example, 1.0 and 2.0 equivalents of propionic anhydride gave only 33% and 62% conversion, respectively. Four equivalents of propionic anhydride resulted in a quantitative conversion to imidazolutidine. The $MgCl_2$ acts as a catalyst: decreasing the number of equivalents of $MgCl_2$ from 3 to 1 gave a quantitative conversion to imidazolutidine, without affecting the reaction time. Further lowering the charge to 0.25 or 0.5 equivalents gave complete conversion of the urea to the desired imidazolutidine, with a 3-fold decrease in the rate.

Due to the success and simplicity of the synthesis of imidazolutidine **1b**, the generality of the method was investigated (see Table 1). In all cases, the conversion of the urea to the imidazole was >95% by HPLC with isolated yields varying somewhat. The effect of the reaction temperature on the rate was evidenced with acetic anhydride/acetic acid (entry c); the lower reflux temperature extended the reaction time to 48 h. This was confirmed when a control experiment of urea **5b** heated at 116 °C required two days to complete versus seven hours.

Table 1. Conversion of Urea 5 to Imidazolutidine 1

Urea 5[a]	R_1	R_2	R_3	R	Temperature (°C)	Reaction time(h)	Isolated yield (%) of 1[e]
a	H	H	H	Bu	150	8	78[b,c]
b	Me	H	Me	Et	145	7	85[b]
c	Me	H	Me	Me	116	48	80[b]
d	Me	H	Me	Bu	150	9	90[b]
e	H	Et	Me	Pr	150	8	75[b,c]
f	Me	Me	Me	Ph	150	10	70[d]

a) The appropriate urea 5 has been synthesized according to Scheme 1. b) Isolated directly after addition of MeOH at 50 °C followed by distillation of solvents and then adjusting the pH to 8.5. c) Purified by chromatography. d) Directly isolated by adding MeOH and refluxing for 4 h followed by distillation of solvents. The solvent switch to ether produced product which was filtered. (e) The reaction was monitored by HPLC using Zorbax RX-C-8, CH_3CN / H_2O with 0.1% H_3PO_4 in each; gradient elution 30:70 to 60:40 for 15 min, 60:40 15min; Flow 1.0 mL/ min. The yield was not optimized.

The use of a magnesium salt for promoting urea cleavage clearly offers a practical method in the chemistry of 1,2-diamino systems. Besides the one-step conversion of a urea to an imidazole several other interesting opportunities are presented. For example, the highly stable urea derivative can be utilized either as a protecting group for diamines or as precursors for C-C bond formation processes at the urea carbonyl carbon center. Further work in this area is currently in progress.

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(6) (a) Ureas are often used as solvents because of their stability and unreactivity at the carbonyl center. Barker, J. B.; Rosenfarb, J.; Caruso, J. A. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 503. (b) Conversions of ureas to imidazoles are normally accomplished via 2-chloroimidazole followed by hydrogenation. See Dornow, A.; Hahmann, O. *Arch. Pharmaz. Ber. Dtsch. pharmaz.Ges.* **1957**, *290*, 20. (c) Alkyl-functionalization of C-2 position of an imidazole is complicated by C-2 and C-5 selectivity; therefore, the C-5 position must be protected at an earlier stage before functionalizing C-2. The functionalization of C-2 is achieved by metal assisted coupling of allyl substrates with N-SEM-2-iodo imidazoles; see Knapp, S.; Albaneze, J.; Schugar, H.J. *J. Org. Chem.* **1993**, *58*, 997.
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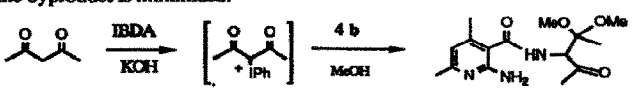
(8) Original synthesis of urea 5b was accomplished via aminonicotinmide 4b with Br_2 / KOH at high temperature. An attempt to effect this Hofmann rearrangement only provided a low yield (see ref.6b).
(9) A side reaction of iodobenzene diacetate with excess pentanedione in the one-vessel sequence produced compound 1. With only one equivalent of 2,4-pentanedione the byproduct is minimized.



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