NEW APPROACH TO THE IMIDAZOLUTIDINE MOIETY OF MK-996

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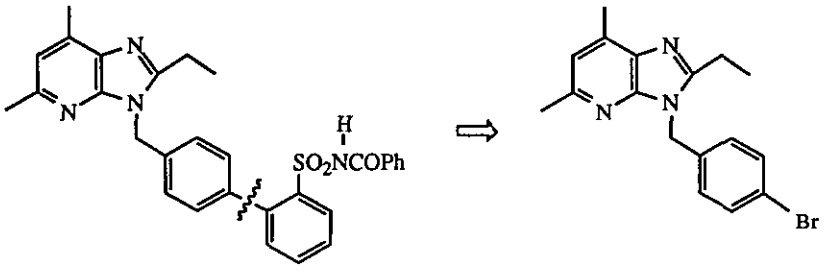
Abstract - A highly effective, regio-selective synthesis of imidazolutidine (**1**) is described starting from readily available malonamamidine hydrochloride and 2,4-pentanedione.

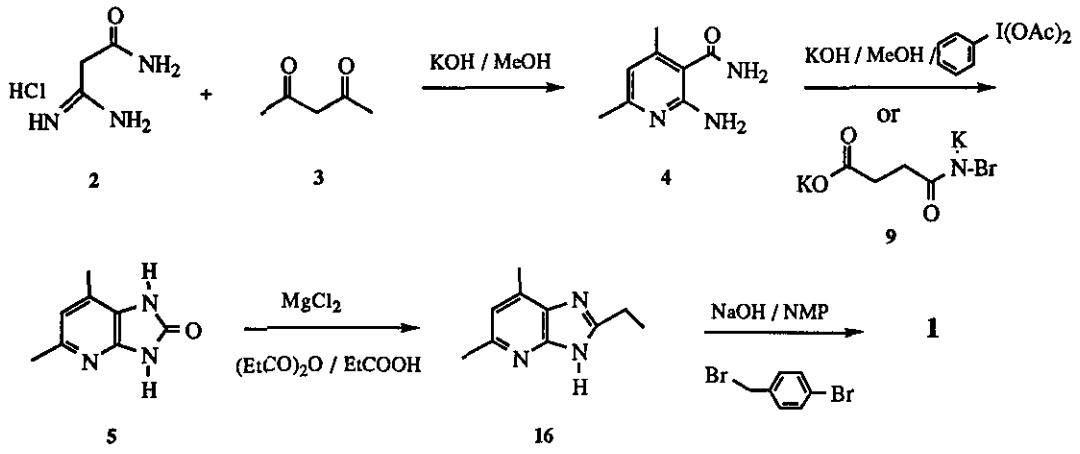
The renin-angiotensin system (RAS) is a crucial mechanism that regulate blood pressure in normal and pathophysiological states.[1] This cascade consists of two enzymes, renin and angiotensin-converting enzyme (ACE), that convert angiotensinogen to angiotensin II (AII).[2] AII is a powerful arterial vasoconstrictor that exerts its action by interacting with specific receptors (AT_1) that are present on cell membranes. One possible mode of controlling hypertension is antagonisim of the angiotensin II receptor.[3] Recently, MK-996[4] was discovered to be a potent, nonpeptidic, orally active AT_1-selective AII antagonist.



MK-996 **1**

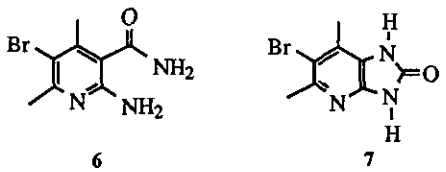
Using biaryl coupling methodology for the synthesis of MK-0996 the key intermediate of the synthesis was the benzylated imidazolutidine (**1**). Although syntheses of the imidazolutidine ring have been reported in the literature these are often inefficient and lack regio-control. Generally, these have 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 ring.[5c] Our strategy focused on the preparation of lutidinoimidazolone intermediate (**5**) by condensation of a malonamamidine (**2**) with 2,4-pentanedione (**3**) and subsequent Hofmann rearrangement[6] to afford the desired urea derivative of 2,3-diaminolutidine (Scheme 1). By using the symmetric substrate (**3**) regiochemistry was not an issue. Conversion of the urea (**5**) to the imidazole (**16**),[7] followed by regioselective benzylation of the N-3 nitrogen provided **1**. Herein, we report a new synthetic route for the preparation of imidazolutidine (**1**) with an overall yield of 64% from readily available malonamamidine hydrochloride.

Scheme 1



In our initial study a two-step synthesis of the urea precursor (**5**) (Scheme 1) was developed: Malonamamidine hydrochloride (**2**) was condensed with 2,4-pentanedione (**3**) in the presence of 1.1 equivalents of KOH in MeOH at room temperature to afford 2-amino-4,6-dimethylnicotinamide (**4**) in 92% yield.[7,8] The product crystallized directly from the reaction mixture. The reaction required >20 h to reach completion; higher temperatures shortened the reaction time, but did not yield as pure a product. Recently, Moriarity[9] reported the Hofmann rearrangement of nicotinamide to 3-aminopyridine with iodobenzene diacetate. Treatment of **4** 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 (**5**) of 2,3-diaminolutidine in >95% yield. 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 in KOH/MeOH. Once the reaction was complete, iodobenzene diacetate was added to effect the Hofmann rearrangement. Product (**5**) crystallized from the reaction mixture and was isolated directly by filtration in 80% overall yield.

This process for preparing the urea had a major drawback, however, Iodobenzene diacetate has limited applicability due to environmental hazards and the chemical instability in a large-scale operation. Alternatively, *N*-bromosuccinimide (NBS) would be a much more practical reagent for this conversion. Unfortunately, the Hofmann rearrangement of **4** with NBS-KOH in MeOH at -5 °C only provided a 60% yield of urea (**5**) along with a 30% recovery of the starting material and a mixture of the brominated by-products (**6**) and (**7**). The potential benefits of NBS were overshadowed by its dual nature as a brominating and oxidizing agent and its failure to oxidize the substrate completely. In order to develop a successful process, better control of the reaction was necessary.



First, the effect of the base on the rearrangement with NBS was examined. Experiments were run with 1 equivalent of solid NBS. In the absence of KOH in MeOH, **6** was obtained exclusively; no urea was observed. As the amount of base was increased by 0.25 equivalent increments, decreasing amounts of **6** and increasing amounts of urea (**5**) were obtained. The maximum conversion reached 60% with 2.5 equivalents of KOH. Apparently, ring bromination was favored under non-basic conditions, whereas the Hofmann rearrangement was favored under more basic conditions. In the presence of excess base, ring bromination still occurred and the reaction did not reach completion, indicating that a more complex system was involved.

Low-temperature nmr studies of KOH and NBS in solution clarified this confusing reaction. KOH was dissolved in D_2O and the resulting solution was cooled to -5 °C. NBS was then added and the solution was stirred at -5 °C until the NBS dissolved. The ^1H and ^{13}C nmr spectra of the resulting yellow solution were taken periodically at -5 °C. Immediately after dissolution, no NBS remained; two new species, one major (85%) and one minor (15%), were generated (Scheme 2). The major and minor species were identified as *N*-bromosuccinamic acid dipotassium salt (**9**) and potassium succinimide (**8**) respectively. Over time, NBS in equilibrium with the succinimide salt (**8**) irreversibly converted to species (**9**) (Table 1): After 5.5 hours, **9** had grown to 95.5% with only 4.5% of **8** remaining. After 16 hours at -5 °C **9** had grown to 96.0%, the succinimide salt had decreased to 2.5% and 1.5% of a new species (**11**) had been generated. Compound (**11**) was characterized as the β-alanine derivative, the Hofmann rearrangement product of the *N*-bromo species (**9**).[10] Stability studies of the reagent in aqueous media were also carried out by nmr. In D_2O at -5 °C **9** remained fairly stable; even after 9 days, 78% remained. Some decomposition to potassium succinamate (**10**) and rearrangement to the carbamate (**11**) were observed. After an aged solution was allowed to warm to room temperature, approximately half of the solution had decomposed to **10** within 30 minutes. Over 2 hours virtually all of **9** had decomposed to **10** (70%) and to four Hofmann rearrangement products; (**11**), (**12**) and two unidentified species (30%).[11]

The true oxidizing agent in the Hofmann rearrangement with NBS in aqueous KOH is *N*-bromosuccinamic acid dipotassium salt (**9**). These findings alleviated the bromination side reactions and provided an understanding as to why the reaction had failed to go to completion. Previously, the KOH/NBS solution was added to the substrate after 5 min; in this time frame only 85% of the desired reagent had been generated (Table 1), leaving unreacted NBS as the brominating agent and provided brominated products (**6**) and (**7**). A longer age of the KOH/NBS solution effectively converted the succinimide salt (**8**)/NBS mixture to the oxidizing species (**9**) (Scheme 2): After 16 hours at -5 °C, 96% conversion to **9** was assayed by nmr. Addition of this mixture to the nicotinamide at -20 °C increased the conversion of the amide (**4**) to the urea (**5**) from 60 to 95%. The rapid decomposition of the NBS-KOH mixture at room temperature also explains why previously the Hofmann reaction did not complete. As the reagent was syringed into the reaction flask, decomposition had already occurred. The instability of the reagent at room temperature was demonstrated; the NBS-KOH mixture was aged at -5 °C for 16 hours and then at room temperature for 2 hours. This reagent mixture only gave a 17 W%-yield of the urea with 82.5 W% of the

nicotinamide recovered. This is consistent with the decomposition observed by nmr at room temperature. It is crucial to maintain the reagent at -5 °C during the addition.

Scheme 2

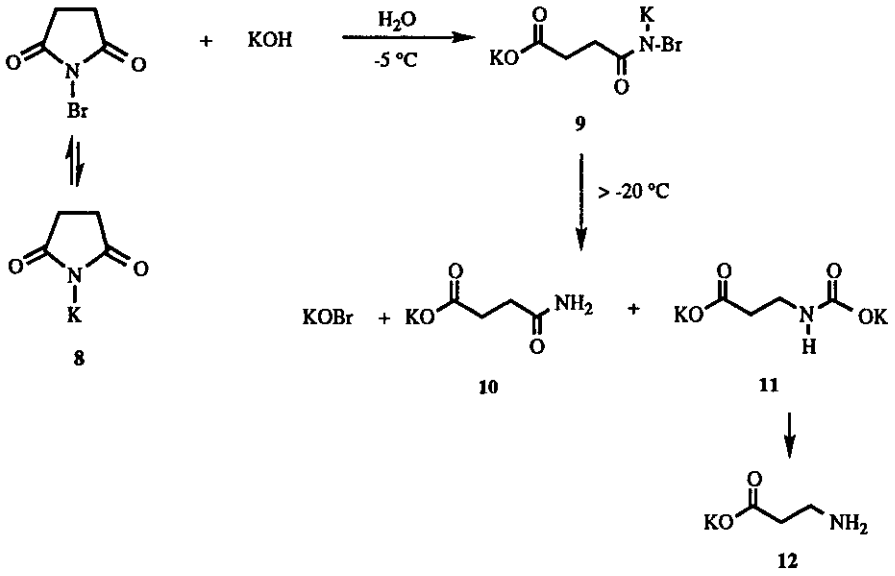


Table 1: The behavior of NBS in aqueous KOH at -5 °C

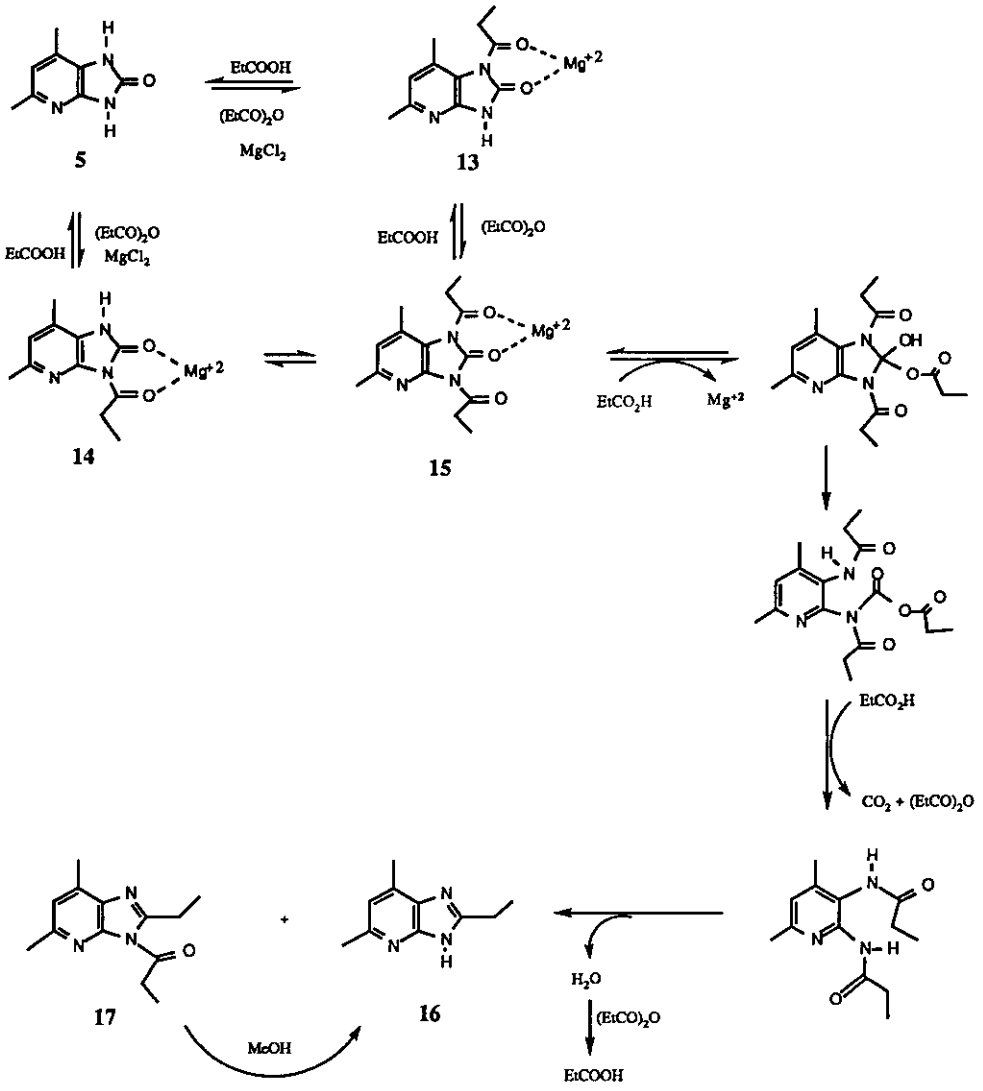
Time	8 (%)	9 (%)	10 (%)	11 (%)
5 min	15	85		
5.5 h	4.5	95.5		
16 h	2.5	96.0		1.5
9 d	0.5	78	16.5	5

A necessary aspect of success of this imidazolutidine synthesis was the conversion of urea (**5**) to the imidazole. However, this was difficult due to the stability and unreactivity of the carbonyl group.[6] Our initial approach 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. Interestingly, 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 hours a mixture of **13**, **14** and **15** was obtained. None of the desired **16** 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 hours yielded 32% of the desired imidazolutidine (**16**), 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 **16** and 75% of *N*-

propionylimidazolutidine (**17**) were obtained (Scheme 3). Upon treatment with aqueous NH_4OH, water, or MeOH at 60 °C the labile propionyl group of **17** was cleaved to provide the desired imidazolutidine (**16**).

Scheme 3

Mechanism for the Formation of Imidazolutidine



In order to achieve a more efficient conversion of **5** to **16** 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 1 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 relatively rapid conversion of the urea to the imidazolutidine in propionic anhydride/propionic acid with quantitative conversion by hplc; the isolated yield was 85%. The reaction pathway for the activation of the urea carbonyl of

intermediate (**15**) with $MgCl_2$ was proposed to involve chelation of the carbonyl, thereby facilitating the nucleophilic attack of propionic acid as shown in Scheme 3.[12]

After successfully synthesizing imidazolutine (**16**), completion of the synthesis of **1** by regioselective benzylation of the N-3 nitrogen was developed. Interestingly, reaction of compound (**16**) with 4-bromobenzyl bromide in the absence of base in *N*-methylpyrrolidinone (NMP)[13] provided the undesired isomer (**18**) as the major product. However, introduction of 1 equivalent of base, such as NaOH, provided the desired regioisomer as the major product. Evidently, the neutral form of **16** is more likely to be alkylated on the pyridine nitrogen; whereas, the anion form of **16** alkylates on the imidazole ring preferentially.

Table 2. Effect of Base on Regioselectivity

Bases	Solvent	Ratio of 1 and 18
NaOH (50% aqueous)	NMP	82:18
NaOH (50% aqueous)	TMU	82:18
NaOH (50% aqueous)	DMI	82:18
NaOH (powder)	NMP	87:13
LiOH(50% aqueous)	NMP	76:24
KOH(50% aqueous)	NMP	78:22
CsOH(50% aqueous)	NMP	80:20
NaH	NMP	88:12
K_2CO_3	DMAC	56:44
LiHMDSi	NMP	89:11
NaHMDSi (in THF)	NMP	89:11
KHMDSi (solid)	NMP	90:10
KHMDSi (in toluene)	NMP	90:10

Base is required to achieve the desired regioselectivity in the alkylation (Table 2). With 50% NaOH an 82:18 ratio of **1/18** was obtained. Interestingly, *t*-BuOK provided the highest ratio (92:8); however, the isolated yield was only 73%. Increasing the basicity further with an amide base, such as NaHMDSi enhanced the ratio as compared to 50% NaOH. Actually, the source of the increase in regioselectivity

was from the anhydrous conditions used with the alkoxide or amide bases. In fact, powdered NaOH (anhydrous form) increased the regioselectivity from 82:18 with the aqueous base to 87:13.

After understanding the benzylation reaction a practical process was developed for compound (**1**). Imidazolutidine was benzylated in NMP with 4-bromobenzyl bromide in the presence of 2 equivalents of powdered sodium hydroxide at 0 °C to afford a 79% yield of the bromobenzyl imidazolutidine (**1**). The desired product crystallized from the reaction mixture free of the regioisomer (**18**) upon the addition of water.

In summary, a practical and high-yielding synthesis for compound (**1**), the key building block of MK-996, was developed. By understanding the true nature of NBS in solution an effective Hofmann rearrangement was achieved to provide the diaminolutidine precursor. With the useful application of magnesium chloride as a Lewis acid in the activation of the urea a direct conversion to the imidazolutidine was possible. Finally, the discovery of the importance of the anhydrous conditions in the benzylation increased the regioselectivity of the reaction.

EXPERIMENTAL

^{1}H and ^{13}C nmr were recorded on a Bruker AM-300 spectrometer. Mass spectra were obtained at 70 eV with Finnigan-4500 spectrometer. The progress of the reactions were followed by High Performance Liquid Chromatography (hplc) with reversed-phase hplc assays on a Zorbax® RX-C8 column; 4.6 mm x 25 cm; 280 nm; mobil phase, acetonitrile/water with 0.1% H_3PO_4 in each; gradient elution, 30:70 to 60:40 over 15 min maintained at 60:40 over 15 min; maintained 60:40 to 30:70 over 2 min. All the solvents were purchased from Fisher Scientific Co., (except where noted). 2,4-Pentanedione, malonamamidene hydrocloride, iodobenzene diacetate, *N*-bromosuccinimide, anhydrous magnesium cloride, propionic anhydride, propionic acid, 4-bromobenzyl bromide and *N*-methylpyrrolidinone were purchased from Aldrich Chemical Co., Inc.

Method 1: Condensation and Hofmann Rearrangement with Iodobenzene Diacetate.

2-Oxo-5,7-dimethylimidazolo(5',4':2,3)pyridine (5): Under a nitrogen atmosphere malonamamidine hydrochloride (200 g, 1.45 mol) was added as a solid to a solution of potassium hydroxide (98.14 g, 1.75 mol) in methanol (5.15 l) at 23 °C over 10 min. Neat 2,4-pentanedione (149.3 ml, 1.45 mol) was then added dropwise to the milky-white suspension over 15 min. The reaction mixture was aged at room temperature for 24 h. Methanol (3.35 l) was added to the reaction mixture followed by a solution of potassium hydroxide (203.5 g, 3.63 mol) in methanol (1 l) at room temperature over 15 min. This mixture was stirred for 30 min and was then cooled to -5 °C. Iodobenzene diacetate (491.7 g, 1.45 mol) was added as a solid over 30 min at < -5 °C. The resulting slurry was warmed to room temperature over 3 h and aged for 12 h. The solid was filtered, washed with methanol (7.5 l) and vacuum dried to afford 254.7 g of **5** as a white solid in 79% yield (corrected for 74 weight % purity). The product was recrystallized from water: mp 361-363 °C, ^{1}H nmr (DMSO-d_6/CF_3COOH) δ 2.35 (s, 3 H), 2.25 (s, 3 H),

6.65 (s, 1 H), 10.7-10.85 (br s, 1 H), 10.95-11.1 (br s, 1 H); ^{13}C nmr (DMSO-*d6* / CF_3COOH) δ 11, 23.5, 117.5, 120.5, 126, 144, 148, 155. Mass spectrum, m/z (%) (M^+, 163), 148, 153, 120, 93, 66, 39, 36. Anal. Calcd for $C_8H_9N_3O$: C; 58.89, H; 5.56, N; 25.76 Found: C; 58.30, H; 5.16, N; 25.91.

Method 2: Hofmann Rearrangement of Amide (4) to Urea (5) with *N*-Bromosuccinamic Acid Dipotassium Salt.

***N*-Bromosuccinamic acid dipotassium Salt (9).** A solution of potassium hydroxide (2.53 g, 0.045 mol) in water (18 ml) was cooled to 0 °C and *N*-bromosuccinimide (3.22 g, 0.018 mol) was added as a solid over 5 min under a nitrogen atmosphere. The mixture was stirred at 0 °C until all the solid had dissolved giving a clear-yellow solution. The solution was aged at -5 °C in a glycol-water bath for 16 h. The assay yield was 96.5% by ^{1}H nmr.

^{1}H Nmr (400.1 MHz-D_2O) δ 2.48 (m , 2 H), 2.40 (m, 2 H); ^{13}C nmr (100.4 MHz-D_2O) δ 184.7, 181.0, 37.8, 34.6.

2-Oxo-5,7-dimethylimidazolo(5',4':2,3)pyridine (5): A solution of 2-amino-4,6-dimethylnicotinamide (**4**) (3.0 g, 0.018 mol) in methanol (42 ml) was cooled to -20 °C. A previously prepared solution of **9** [0.018 mol of *N*-bromosuccinimide and 0.045 mol of potassium hydroxide in water (18 ml) aged for 16 h at <-5°C] was added to the clear, colorless solution of **4** at -20 °C *via* a double-tipped needle under a nitrogen atmosphere. The resulting mixture was stirred at -20 °C for 5 h. The solid was filtered, washed with water (10 ml) and vacuum dried to afford 2.39 g of **5** as a white solid in 81% yield.

2-Ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine (16): The crude imidazolinone-lutidine from method 1 (247 g, 1.5 mol) was mixed with propionic acid (2.146 l, 28.77 mol) and propionic anhydride (2.146 l, 16.74 mol). After the mixture was stirred at room temperature under a nitrogen atmosphere for 5 min, magnesium chloride (143.4 g, 1.5 mol) was added. The mixture was then heated at reflux (145 °C) for 7-8 h. The reaction mixture was cooled to 60 °C and methanol (2.5 l) was added. This mixture was concentrated by distillation *in vacuo*, removing methanol, propionic acid, and methyl propionate. The distillation was monitored by ^{13}C nmr of the distillate, to ensure that methanol, methyl propionate and propionic anhydride were completely removed. Water (550 ml) was added to the concentrate and the final reaction volume was adjusted to 300 ml. Propionic acid formed a favorable azeotrope with water (83% water, 17% acid) at 99 °C. The solution was cooled to 40 °C and the pH was adjusted to 8.7 by addition of concentrated ammonium hydroxide (175 ml) maintaining the temperature at below 50 °C. The resulting slurry was cooled to -5 °C and aged for 1.5 h. The solid was filtered, washed with cold water (0 °C, 3.3 l), and dried in a vacuum oven at 50 °C with a nitrogen sweep for 48 h. The isolated yield of imidazolutidine (**16**) was 165.5 g (81% yield): mp 147-148 °C (water), ^{1}H nmr (DMSO-*d6* /CF_3COOH) δ 1.35 (t , J = 7.5 Hz, 3 H), 2.53 (s, 3 H), 2.57 (s, 3 H), 2.92 (q, J = 7.5 Hz, 2 H), 6.78 (s, 1 H); ^{13}C nmr (DMSO-*d6* /CF_3COOH) δ 12.98, 16.57, 23.73, 118.75, 132.91, 137.92, 148.97, 150.88,

156.73.Mass spectrum, EI, m/z 175, 169, 132, 90. Anal. Calcd for $C_{10}H_{13}N_3$: C, 68.54; H, 7.48; N, 23.98. Found: C, 68.04; H, 7.49; N, 24.10.

2-Ethyl-5,7-dimethyl-3-(4-bromobenzyl)imidazo[4,5-*b*]pyridine (1): Imidazolutidine (**16**) (5.30 g, 0.028 mol) was dissolved in *N*-methylpyrrolidinone (20 ml). Under a nitrogen atmosphere freshly ground sodium hydroxide (2.35 g, 0.057 mol) in *N*-methylpyrrolidinone (5 ml) was added to the solution of **1** at room temperature over 5 min. The addition of the NaOH solution was exothermic. Controlled addition only led to a 2 °C exotherm. The solution was aged at room temperature under a nitrogen atmosphere for 1 h. The reaction mixture was cooled to 0 °C and a solution of 4-bromobenzyl bromide (7.42 g, 0.029 mol) in *N*-methylpyrrolidinone (5 ml) was added dropwise over 5 min. The reaction mixture was warmed to room temperature directly after the addition and aged for 2 h. The reaction mixture was cooled to 0 °C and water (90 ml) was added dropwise over 15 min. Once the addition was complete, the reaction mixture was warmed to room temperature and aged for 1 h. The solid was filtered, washed with *N*-methylpyrrollidinone/water (1:3, 20 ml) and water (2 X 50 ml), and dried to afford 8.08 g of **1** as a tan solid in 79% yield: mp 107-108 °C (acetone/water), ^{1}H nmr (DMSO-*d6*) δ 1.21 (t, *J* = 7.1 Hz, 3 H), 2.49 (s, 3 H), 2.50 (s, 3 H), 2.75 (q, *J* = 7.0 Hz, 2 H), 5.4 (s, 2 H), 6.9 (s, 1 H), 7.06 (d, *J* = 7.7 Hz, 2 H), 7.50 (d, *J* = 7.8 Hz, 2 H); ^{13}C nmr (DMSO-*d6*) δ 11.1, 15.8, 20.5, 23.8, 43.6, 118.5, 120.5, 128.8, 131.5, 131.8, 136.6, 137.2, 147.2, 151.3, 155.2. Mass spectrum, EI, m/z 343, 328, 316, 264. Anal. Calcd for $C_{17}H_{18}N_3Br$: C, 59.31; H, 5.27; N, 12.21. Found: C, 59.77; H, 5.15; N, 11.59.

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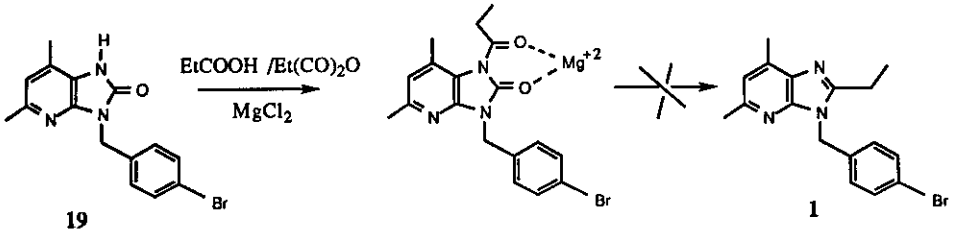
12 The proposed mechanism involves an equilibrium of the intermediates (**13**, **14** and **15**). The intermediate (**15**) is key to the ring opening process with propionic acid. If the N-3 nitrogen is blocked as the benzyl group (**19**) the reaction does not proceed.



19 **1**

13 Different solvents were examined in the benzylation of the imidazolutidine. The amide solvents proved to be the optimal for the desired regioselectivity.

Received, 2nd August, 1995