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Innovative Approaches to the Imidazo[4,5-*b*]pyridine Ring System. Development of an Efficient Process for Industrial-Scale Production of a Key Intermediate for Potent Angiotensin II Receptor Antagonists

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Abstract. Two syntheses of 2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine (**3**), an important intermediate for the synthesis of several potent angiotensin II antagonists, have been investigated. The first route involves conversion of 1,1-bis(methylthio)-2-nitroethene (**17**) to 2-amino-4,6-dimethyl-3-nitropyridine (**6**); catalytic hydrogenation of **6** in propionic acid gave **3** in high yield. In the second synthesis, propionitrile is converted to imidate hydrochloride **15**·HCl which is neutralised and reacted with aminoacetonitrile in the presence of acetylacetone to give **3** in 55% overall yield. The propionitrile route was scaled up to produce **3** in the pilot plant.

Introduction

In view of its importance in blood-pressure regulation, the renin-angiotensin system (RAS) has been a prime target for the treatment of cardiovascular disease. One therapeutic approach which has undergone intensive recent investigation is the attempt to block the action of angiotensin II (AII), the biologically active octapeptide of the RAS, at the level of its receptor; the first AII antagonist to reach the market as a treatment for hypertension was *Merck*'s Losartan potassium (*Cozaar*®, **1**). Several AII antagonists based on the imidazo[4,5-*b*]pyridine ring system have been described, one example being L-159,282 (**2**) which was reported to be significantly more potent *in vivo* than Losartan [1]. The conventional approach to the synthesis of **2** has been *via* *N*(3)-alkylation of 2-ethyl-5,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridine (**3**), which is thus of interest as a general precursor to the group of potent AII antagonists exemplified by **2**.

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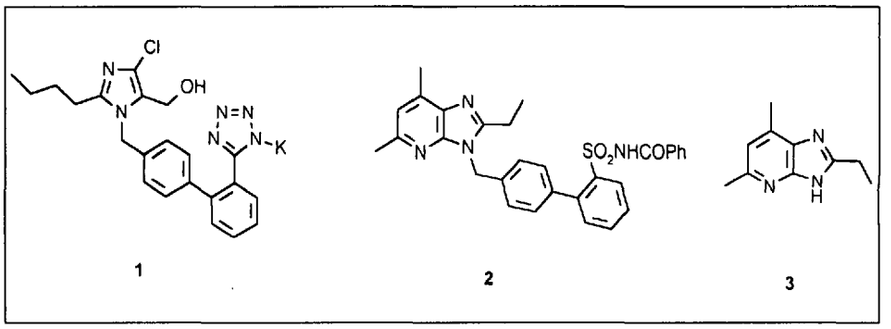
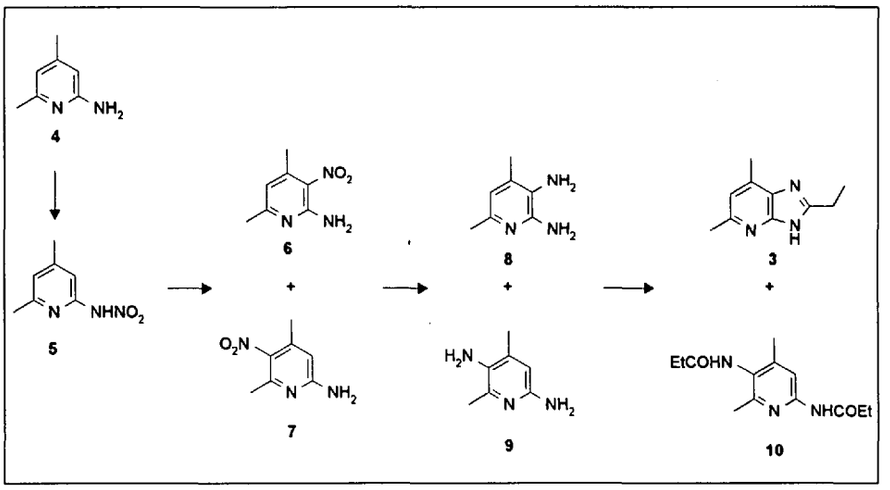
Published Syntheses of 3

In the first published synthesis [2] of **3**, 2-(*N*-nitramino)pyridine **5** was prepared by nitration (HNO_3/H_2SO_4) of aminopyridine **4** at *ca.* –10° (*Scheme 1*). Treatment of **5** with conc. H_2SO_4 at 0° gave a mixture of **6** and **7** (55:45) which was subjected directly to catalytic hydrogenation (10% Pd/C in MeOH). Treatment of the resulting mixture of diaminopyridines **8** and **9** with propionic acid in polyphosphoric acid gave a mixture of **3** and **10**. Disadvantages of this route to **3** are the lack of regioselectivity in the nitration step and the resultant requirement for chromatographic separation of **3** and **10**.

In an alternative synthesis [3] of **3** (*Scheme 2*), condensation of acetylacetone with amidine hydrochloride **11** gave 2-aminonicotinamide **12** in 92% yield. *Hofmann* rearrangement of **12** using $PhI(OAc)_2$ (or more conveniently NBS/KOH [4]) gave a high yield of the urea derivative **13**, which was converted to **3** by treatment with a mixture of propionic acid and propionic anhydride in the presence of $MgCl_2$. Hydrochloride **11** can be prepared in two steps from cyanoacetic ester; this synthesis of **3** thus requires five steps from commercially available starting materials.



Scheme 1



In view of its importance as an intermediate and the disadvantages associated with the two syntheses described above, we decided to seek a more efficient approach to **3**.

Retrosynthetic Analysis

Two routes for construction of the imidazo[4,5-*b*]pyridine ring system were investigated (*Scheme 3*). The first makes use of 1,1-bis(methylthio)-2-nitroethen (**17**) as starting material for an alternative approach to diaminopyridine **8**, the second relies on condensation of acetylacetone with aminoimidazole **14**; the planned synthesis of **14** foresaw reaction of aminoacetonitrile with imidate **15**.

Synthesis of 3 *via* Diaminopyridine 8

Two regioselective syntheses of **8** were investigated (*Scheme 4*). The first was based on a published synthesis [5] of 2-amino-4,6-dimethyl-3-nitropyridine and involved condensation of enamine **16** (prepared by reaction of acetylacetone with ammonia) with **17**, an intermediate previously used in an industrial synthesis of the antiulcer agent ranitidine [6]. This reaction gave only moderate yield of pyridine **6**, apparently due to the lack of reactivity between **16** and **17**. Our planned alternative synthesis of **6** had in fact been described shortly before we began this work; the reported yields [7] for the conversions of **17** to **18** and **18** to **6** were 45% and 52%, respectively. After careful optimisation, we discovered that treatment of **17** with NH_3 under pressure and at lower temperature than that previously reported gave **18** in an improved yield of 77%, and that carrying out the reaction between **18** and excess acetylacetone (which could be recycled) in 2-methoxyethanol gave **6** in 93% yield. The purity of **6**, which could thus be isolated in 72% yield based on **17**, was such that it could be subjected to catalytic hydrogenation without prior purification.

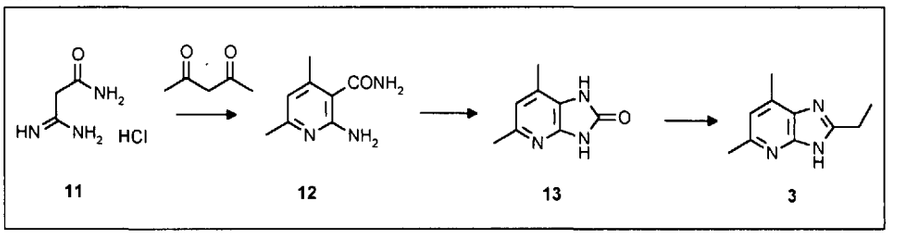
Hydrogenation of **6** to diaminopyridine **8** has been described [8] using 28 wt.-% of 10% Pd/C in methanol. In an attempt to convert **6** directly to **3** we first investigated its hydrogenation using propionitrile as solvent. This reaction proceeded smoothly using 3 wt.-% of 10% Pd/C to give **8** which crystallised directly from propionitrile in excellent yield (98%) and purity (> 99%). We then turned to the hydrogenation of **6** in propionic acid; this reaction proceeded smoothly at elevated temperature (120–130°) and gave a mixture of **8** and **3**. This result provided the basis of a practical and efficient one-pot process for the direct conversion of **6** to **3** in 76% yield by means of hydrogenation in propionic acid with a catalytic amount of H_2SO_4 to accelerate the conversion of **8** to **3** (*Scheme* 5).

In summary, imidazo[4,5-*b*]pyridine **3** was prepared in 55–60% overall yield from **17** *via* a combination of previously reported transformations, all of which were improved considerably. The main drawback of this synthesis is the relatively high cost of key intermediate **18**.

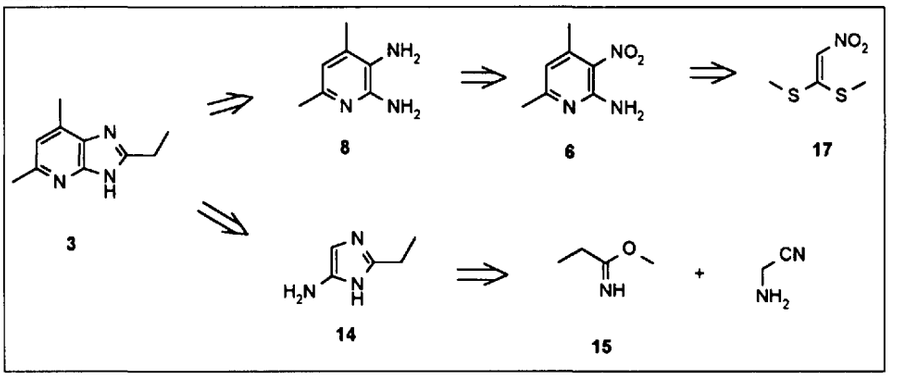
The Propionitrile Route to 3

Our alternative approach to **3** (*Scheme 3*) foresaw preparation of **14** *via* reaction of aminoacetonitrile with imidate **15**; we

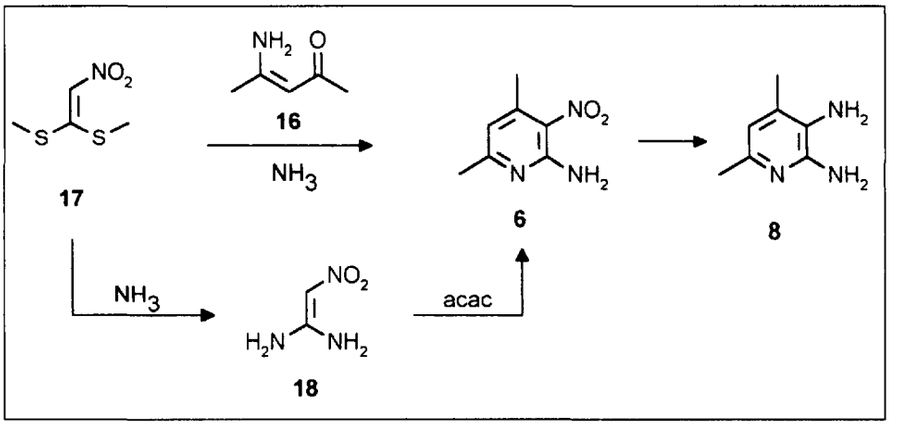
Scheme 2



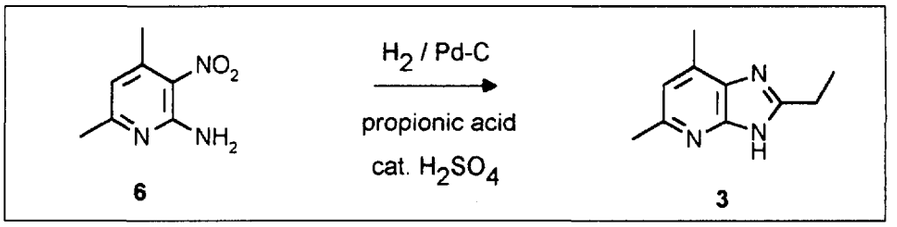
Scheme 3



Scheme 4



Scheme 5



anticipated that the open-chain intermediate **19** would cyclise spontaneously (*Scheme 6*).

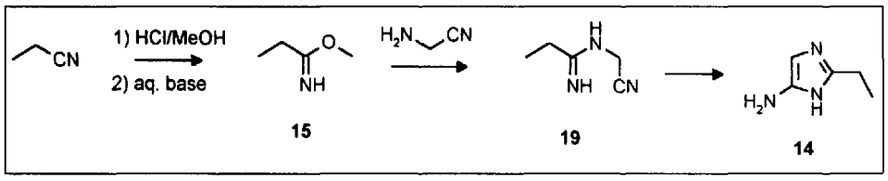
Pinner reaction of propionitrile with HCl in dry methanol at 15° gave the hydrochloride of **15** which could be neutralised with aqueous base to give **15**. During the neutralisation step, the maintenance of the pH in the range 9–10 was critical: at higher pH, **15** suffered reconversion to propionitrile, at lower pH, rapid hydrolysis of **15** to methyl propionate was the predominant reaction. Initial attempts to prepare **19** or **14** by reaction of **15** with aminoacetonitrile gave complex mixtures. Spectroscopic analysis indicated that **14** had been formed but had decomposed to give mainly polymeric material. One literature report [9] indicated that 5-unsubstituted 4-aminoimidazoles are not stable enough to be isolated but can be trapped by electrophiles. With this in mind, we decided to carry out the reaction of aminoacetonitrile with **15** in the presence of 1 equiv. of acetylacetone. To our delight, we were able to isolate **3**, albeit in moderate yield (*ca.* 25%; *Scheme 7*); the main by-products appeared to be polymeric. By using 2–5 equiv. of acetylacetone, we were able to reduce the extent of polymer formation and increase the yield of **3** to 55–60%. The excess acetylacetone could be recycled.

The procedure was simplified and improved by development of an alternative method to prepare **15**, namely by addition of a suspension of its hydrochloride in methanol to a slurry of the sodium enolate of acetylacetone in methanol. The advantages of this method were: *1.* The losses of **15** due to its solubility in water were eliminated. *2.* The ideal basicity of the enolate of acetylacetone meant that the losses of **15** due to the side reactions (see above) which occurred in aqueous milieu were eliminated. *3.* The acetylacetone formed during the liberation of **15** can be converted directly to **3**. After considerable optimisation of reaction parameters, a process was developed in which the liberation of **15** and the subsequent sequence of reactions which lead to formation of **3** could be carried out in one pot (*Scheme 8*).

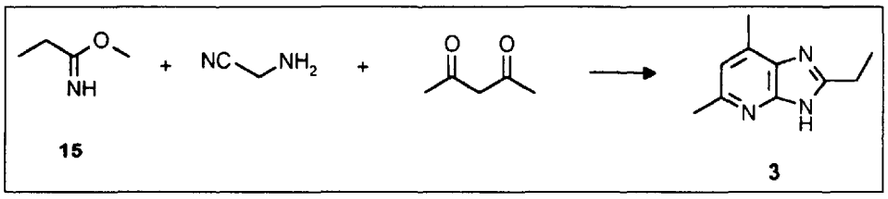
Conclusion

A novel and elegant process which affords **3** in *ca.* 55% yield based on propionitrile and requires no isolation of intermediates was developed in the laboratory and scaled up to produce **3** in the pilot plant. Particular advantages of the process developed are its brevity, its high overall yield, and the limited amounts of waste which are generated.

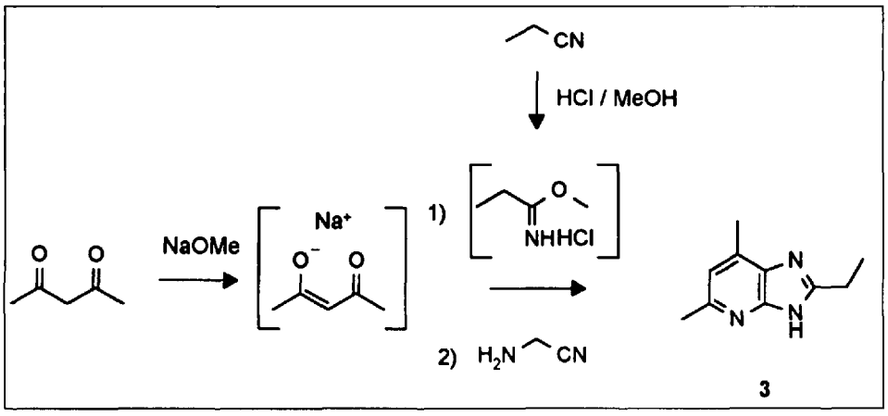
Scheme 6



Scheme 7



Scheme 8



Experimental Part

Preparation of **15** · HCl. Gaseous HCl (323 g, 9 mol) was bubbled into a soln. of propionitrile (248 g, 4.5 mol) in CH_3OH (288 g, 9.0 mol) at such a rate that the temperature could be maintained at 0–5°. The suspension was stirred for further 2 h at 5° and stored at 0° until use.

Preparation of aminoacetonitrile. To a soln. of NaOH (121 g, 3 mol) in CH_3OH (750 ml) aminoacetonitrile hydrochloride (278 g, 3 mol) was added as a solid over 5 min at 0°. The resulting suspension was stirred at 0° until use.

Synthesis of **3**. To acetylacetone (991 g, 9.9 mol) at 0° was added 30% sodium methoxide (1620 g, 9.0 mol). The resulting suspension was stirred at 0° before addition of the suspension of **15** · HCl. The mixture was stirred at 0° for 30 min before addition of the suspension of aminoacetonitrile. The mixture was heated at reflux (*ca.* 65°) for 16 h before distillation of solvent until the temperature reached 85°. Toluene (2 l) and H_2O (2 l) were added, and the distillation was continued until the temperature reached 90°. The pH was adjusted to 8 by addition of conc. HCl (10 ml) and the phases were separated at 80°. The organic layer was cooled to r.t. and diluted with water (1.8 l). The pH of the stirred emulsion was adjusted to 2 by addition of conc. HCl (300 ml) and the phases were separated. The aq. layer was adjusted to pH 7.5 by addition of 30% aq. NaOH (300 ml) and stirred at 0°. After 2 h, the white precipitate was filtered, washed with H_2O (2 × 1.5 l) and dried at 45° under reduced pressure to give 285.0 g of **3** as an off-white solid (99.3 GC wt.-%, 54 % yield based on aminoacetonitrile).

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