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Synthesis of a new isomer of creatinine and its use in the preparation of the food mutagen 2-amino-1-methyl-6-phenyl-1*H*-imidazo[4,5-*b*]pyridine (PHIP)

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ABSTRACT

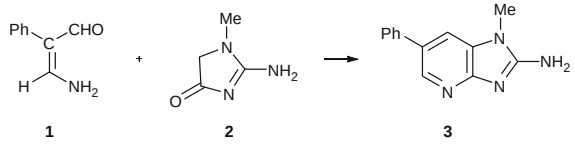
Base-induced cyclization of *N*′-cyanomethyl-*N*′-methylurea gives 1-methyl-4-amino-imidazol-2-one, this in turn is condensed with 3-hydroxy-2-phenylacrolein to yield an imidazo[4,5-*b*]pyridine which is converted into 2-amino-1-methyl-6-phenyl-1*H*-imidazo[4,5-*b*]pyridine (PHIP).

2-Amino-1-methyl-6-phenyl-1*H*-imidazo[4,5-*b*]pyridine (PHIP) **3** was identified in fried ground beef[1,2] as a food mutagen by Felton et al. in 1986. Since then, a large number of studies on this abundant food contaminant have been published. Not surprisingly, several synthetic procedures for **3** have been developed.[3–6] Most of these start from pyridine derivatives (typically 5-bromo-2,3-diaminopyridine) which are subsequently elaborated via a number of difficult steps (e.g., Chichibabin aminations) ending with formation of the fused imidazole ring by cyclization involving cyanogen bromide. However, a much simpler procedure (Scheme 1) starting with creatinine **2** was developed by Lindström[7] in 1995.

Unfortunately, the yield was disappointingly low (1%), although it could be improved to 24% by running the reaction (on a modest scale) in *N*,*O*-bis-trimethylsilylacetamide (BSA).[7] Facile ring-opening of creatinine was identified as a major problem since in a similar experiment (Scheme 2) in our laboratory, the pyrimidine derivative **4** was obtained as the product in high yield. A similar cleavage was previously observed by Ronne et al.[8] who heated a mixture of **1** and **2** in ethylene glycol and obtained the ethylene glycol monoester of **4**. The structure was proved by an independent synthesis starting from the known[9,10] pyrimidine derivative **6**. The starting 'dialdehyde' **5** was prepared by reacting phenylacetic acid[11,12] with the Vilsmeier reagent.

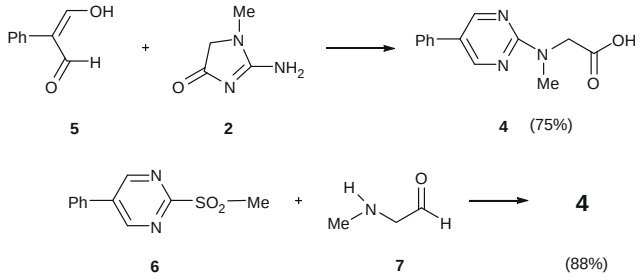
At this point an hitherto unknown isomer of creatinine, namely **8** was considered as a starting material for making **3**, and it was easily synthesized by cyclization of the known nitrile **9** (Scheme 3).[13,14] The parent des-methyl derivative of **8** had earlier been similarly prepared and described in the patent literature.[15]

Although the imidazole derivative **8** was readily hydrolyzed to *N*-methylhydantoin under acidic conditions (H_2O, HCl, rt) it was found to be much more robust than its isomer **2** and condensation of **5** and **8** gave the known 1*H*-imidazo[4,5-*b*]pyridine derivative **10** (Scheme 4) in excellent yield (92%) and the NMR data agreed nicely with those in the literature.[5]



1 2 3

Scheme 1.



5 2 4 (75%)

6 7 4 (88%)

Scheme 2.

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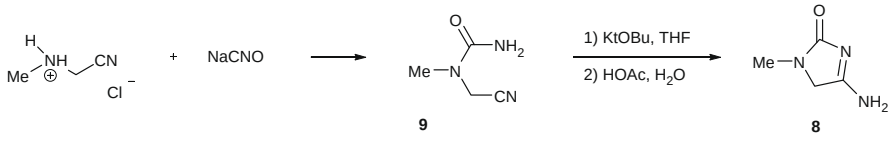
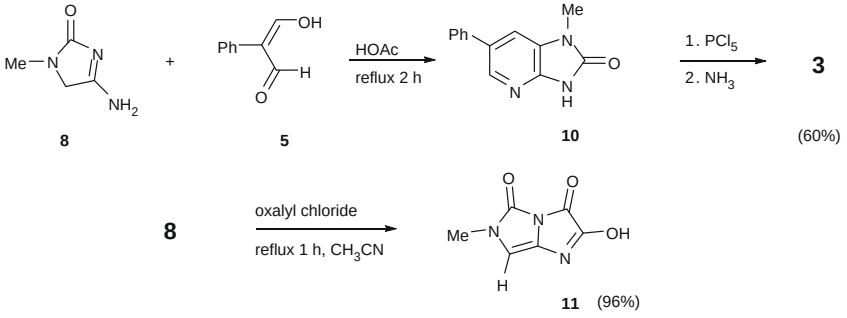


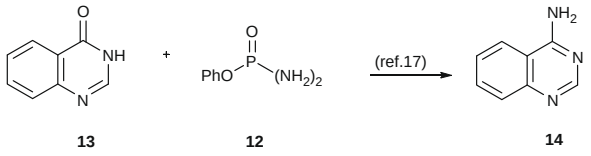
Scheme 3.



Scheme 4.

The bidentate electrophile had obviously condensed in C,N-fashion and not in N,N-fashion. However, when oxalyl chloride was used as the electrophile, condensation involved the two available nitrogens and the yellow-coloured product **11** was isolated.[16] This fused imidazolone of low solubility featured a diagnostic CH signal at 95.2 ppm in the ^{13}C NMR spectrum.

The fused imidazolone **10** could be converted into PHIP **3** by a known technique (treatment with PCl_5 followed by NH_3 in a pressure bottle) in 60% yield. This procedure is somewhat cumbersome so we considered direct amination with the phosphorus-based reagent **12**, which had been used for the amination of, for example, **13** to give **14**.[17] Unfortunately, the carbonyl group in **10** is much less reactive and the envisaged transformation failed.



The new procedure described herein will improve the availability of PHIP, for example, for labeling work.

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16. Compound **11**, gave the following ^{13}C NMR data (75 MHz, DMSO-d_6): δ 29.6 (q), 95.2 (d), 119.4 (s), 145.1 (s), 151.4 (s), 157.7 (s).
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