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An Easy Photochemical Approach to the Synthesis of the Food-Borne Carcinogen 2-Amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine

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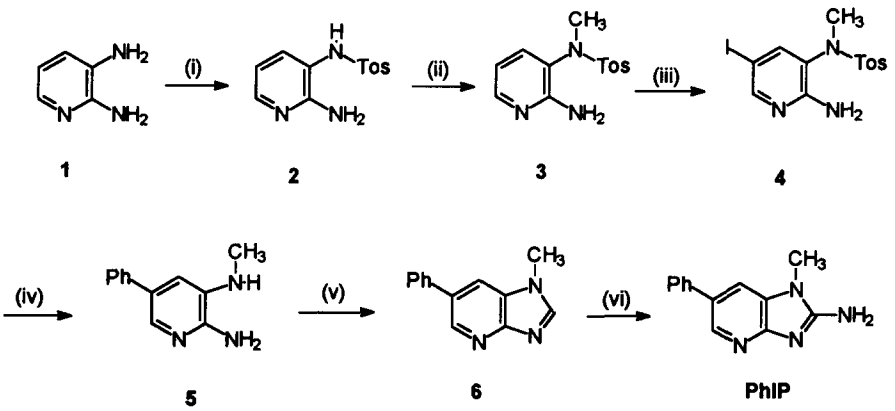
Abstract: Mutations induced by substances formed during food cooking are a field of growing interest; for a better comprehension of the mechanism of action of these carcinogens, simple routes to their synthesis are needed. In this letter we describe an easy method for 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) synthesis, starting from the commercially available 2,3-diaminopyridine **1** via the 2-amino-3-methylamino-5-phenylpyridine **5** formation. The key step of this approach is the one pot synthesis of **5** performed by photolysis of 2-amino-5-iodo-3-(*N*-methyl-*N*-tosylamino)pyridine **4** to obtain simultaneous phenylation and tosyl group removal. Compound **5** was then used as an intermediate to obtain the 1-methyl-6-phenylimidazo[4,5-*b*]pyridine **6** which was aminated to afford PhIP in good overall yields.

2-Amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) was found to be one of the most important mutagenic compound formed during cooking beef meat[1]. PhIP has also been identified in cigarette smoke condensate[2] and it was found the major mutagenic agent present in the urine of cigarette smokers.[3] These findings suggest that this compound might play an important role in the aetiology of human cancers. In this context it has also been shown that PhIP induces DNA damage via metabolic activation.[4]

Methods of synthesis are already present in the literature but the complex synthetic procedures and the low yields reported are the main drawbacks. The synthesis proposed by Knize and Felton[5] starts from 3-phenilpyridine and affords PhIP through the imidazole ring formation performed by pyridine ring aminations and final cyclization with cyanogen bromide. This procedure involves reactions performed in drastic conditions (e.g high pressure) and low overall yields are obtained. Choshi T. *et al.* report[6] a synthesis of PhIP trough pyridine ring formation starting from the not commercially available 1-methyl-

2,4,5-tribromoimidazole[7] to synthesise 1-methyl-6-phenylimidazo[4,5-*b*]pyridine. The final treatment of this compound with $NaNH_2$ afforded PhIP in high yields. This synthetic procedure involves many steps and the extreme temperature conditions required (–78°C) as well as the low global yields obtained are the main limitations.

In order to enhance toxicological and pharmacological studies and better elucidate the role of PhIP and related substances in the aetiology of human cancers, new methods for the synthesis of these compounds are required. We synthesised PhIP by imidazole ring formation starting from commercially available 2,3-diaminopyridine **1** to obtain 1-methyl-6-phenylimidazo[4,5-*b*]pyridine **6** as reported in the **Scheme**. The key step of this approach is the one pot synthesis of 2-amino-3-methylamino-5-phenylpyridine **5** by photolysis of 2-amino-5-iodo-3-(*N*-methyl-*N*-tosylamino)pyridine **4** to obtain the simultaneous phenyl substitution of the iodine in position 5 and the tosyl group removal.



Scheme of synthesis of PhIP. *Reagents*: (i) *p*-Tosylchloride, (ii) CH_3I, K_2CO_3, (iii) I_2, (iv) hv, benzene, CF_3COOH, (v) HCOOH, (vi) $NaNH_2$

Compound **4** was obtained from **1** by selective tosylation with *p*-tosyl chloride in anhydrous pyridine under reflux and subsequent methylation of the obtained 2-amino-3-tosylaminopyridine **2**[8], performed with methyliodide and K_2CO_3 in acetone at room temperature, to afford 2-amino-3-(*N*-methyl-*N*-tosylamino)pyridine **3**[9] in 63% overall yield. The reaction of **3** with iodine in H_2O/acetic acid at 80°C allows compound **4**[10] to be obtained in 68% yield.

The photolysis of **4** was performed in benzene/CF_3COOH at 313 nm using Pyrex test tubes, to obtain compound **5** in 45% yield.[11] Product **5** was then refluxed in formic acid (99%) to afford **6** in quantitative yield. The final amination of **6** was carried out with sodium amide following the procedure described by Choshi[6] to give PhIP in 80% yield. Analytical data correspond to those reported.

In this letter we have proposed a new approach to the synthesis of PhIP in good yield starting from the commercially available **1** according to the **Scheme.** This procedure seems simpler than those previous reported in the literature[5,6] because it involves fewer steps and less drastic conditions. The possibility to perform the photochemical phenylation at C-5 of 1,2 substituted pyridines by photolysis of 5-iodo derivatives provides an alternative way to the synthesis of these compounds. The results reported make this approach appropriate to obtain this class of compounds in high quantities for toxicological and pharmacological studies to better investigate the role of PhIP and related substances in the aetiology of human cancers.

The photochemical phenylation to obtain compound **5** may be considered the most complex reaction to be optimised in order to synthesise the desired product in higher yield. However, the possibility to perform the phenylation of substituted pyridine allows PhIP to be obtained using commercially available products as starting material and reduces the synthetic steps required. Moreover the use of trifluoroacetic acid in the reaction medium allows the simultaneous removal of the tosyl group improving the performance of this photochemical step. Experimental and analytical data as well as the synthesis of related compounds will be published elsewhere.

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8. ^{1}H NMR δ ($CDCl_3$) 2.42 (3H, s), 3.02 (2H, br s), 5.26 (1H, br s), 6.50 (1H, dd, *J* =5, 7.5 Hz), 6.92 (1H, dd, *J*=2, 7.5Hz), 7.28 (2H, d, *J*=8.8Hz), 7.65 (2H, d, *J*=8.8Hz), 7.88 (1H, dd, *J*=2, 5Hz). MS *m/z* 262 (M^+-1). Mp 195-200°C.
9. ^{1}H NMR δ ($CDCl_3$) 2.46 (3H, s), 3.11 (3H, s), 5.01 (2H, s), 6.48 (1H, dd, *J*=5.7, 10.3Hz), 6.62 (1H, d, *J*=10.3Hz), 7.32 (2H, d, *J*=8.5Hz), 7.61 (2H, d, *J*=8.5Hz), 8.01 (1H, d, *J*=5.7Hz). MS *m/z* 277 (M^+). Mp 135-137°C.
10. ^{1}H NMR δ ($CDCl_3$) 2.49 (3H, s), 3.07 (3H, s), 5.07 (2H, s), 6.74 (1H, d, *J*=2.85Hz), 7.38 (2H, d, *J*=6.27Hz), 7.59 (2H, d, *J*=6.27Hz), 8.15 (1H, d, *J*=2.85Hz). MS *m/z* 403 (M^+). Mp 171-172°C.
11. Compound **4** (1.6 g, 3.97 mmol) was dissolved in benzene (400 mL) and trifluoroacetic acid (3.5 mL). The solution was apportioned in 8 Pyrex test tube and irradiated at 313 nm for 2 h. The irradiated solution were repeatedly washed with 10% KOH (350 mL total volume), the benzene solution was dried, the solvent removed under *vacuum* and the residue chromatographed with ethyl acetate-methanol (85:15) to give **5** in 45% yield. ^{1}H NMR δ ($CDCl_3$) 2.92 (3H, s), 3.74 (1H, br s), 4.70 (2H, br s), 6.99 (1H, d, *J*=2Hz), 7.29-7.38 (1H, m), 7.39-7.47 (2H, m), 7.50-7.58 (2H, m), 7.76 (1H, d, *J*=2Hz). MS *m/z* 199 (M^+). Mp 118-122°C.

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