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Friedländer Synthesis of the Food Carcinogen 2-Amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine

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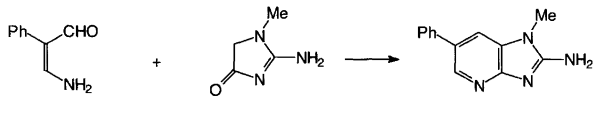
2-Amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine has been prepared in 26% yield from 3-amino-2-phenylpropenal and creatinine which were heated with *N,O*-bis(trimethylsilyl)acetamide at 120°C for 2 h. Under certain other conditions, the main product was a pyrimidine derivative.

The reported syntheses of the title compound (PhIP) involve multi-step routes, generally starting from a pyridine derivative and ending with the formation of the imidazole ring through cyclization of a diamine with cyanogen bromide.[1,2] By contrast, a recent PhIP synthesis starts from an imidazole derivative, the pyridine ring being formed through an electrocyclic reaction in one of the eight steps.[3] However, a much simpler approach has been suggested.[4] It is shown in Scheme 1, where one of the starting materials is the imidazole derivative creatinine (**2**), believed to be the common precursor of PhIP and other aminoimidazoaza-arenes during frying.[5] In Scheme 1, PhIP is formed in a single reaction from **2** and the known[6,7] amino aldehyde (*Z*-form shown) through a Friedländer synthesis.[8] In practice, however, this required more than one step, and the total yield of PhIP was only about 1%.

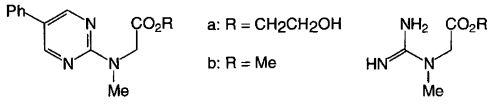


1 **2** PhIP

Scheme 1.

Results and discussion

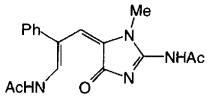
The common substrates in the Friedländer synthesis are an aromatic *o*-amino-aldehyde or -ketone and a carbonyl compound, with a reactive α-methylene group. Occasionally, an acyclic analogue of **1**, *viz.*, 3-aminopropenal or its 2-methyl homologue, has been used as the amino component.[9] Recently, Ronne *et al.*[10] performed some typical Friedländer syntheses with creatinine (**2**) as the methylene component, simply by heating the reactants in ethylene glycol. However, heating **1** and **2** in this way did not yield PhIP but the pyrimidine **3a**. Presumably, **2** had undergone alcoholytic ring opening to the creatine ester **4a**, with subsequent pyrimidine ring formation through reaction with **1**. In a pressure vessel with methanol instead of ethylene glycol, the methyl ester **3b** was obtained, presumably via **4b**. Recently, Ronne[11] obtained an analogue of **3a** from 2-aminobenzo[*b*]furan-3-carboxaldehyde, **2** and ethylene glycol.



3 **4**

The Friedländer synthesis consists of a Perkin reaction[12] and the formation of a Schiff base. The mutual order of the reaction steps may depend on the reaction conditions.[8] In the first attempts to prepare PhIP according to Scheme 1, typical Perkin reaction conditions were used, and the intermediate **5** was isolated as a mixture of geometric isomers[4] (one isomer shown). Since **5** must have formed via enolization of **2** or its *N*-acetyl derivative,[13] the latter was treated with *N,O*-bis(trimethylsilyl)-acetamide (BSA)[14] in chloroform, in order to obtain the enolic silyl ether **6**.[15] When the silylation mixture, presumably containing **6** (and/or its *N*-trimethylsilyl derivative), was treated with the *N*-acetyl derivative of **1** and polyphosphoric acid (PPA) or its trimethylsilyl ester,[16] PhIP was indeed formed, but the yield was low and variable (1–17%).[15]

These results were now confirmed, but 2-methyl-5-phenylpyrimidine (**7**)[17] was also identified in the reaction mixtures. Since **7** was also obtained from unacetylated **1** and in the absence of **2**, it was probably formed from **1** and BSA. Previously,[17] **7** has been prepared from a derivative of **1** and acetamidine. Finally, reproducible and some-



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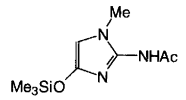

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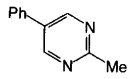

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what higher yields of PhIP were obtained by omitting the PPA, the solvent chloroform and the acetylation of the reactants. Thus, PhIP was conveniently prepared by simple heating of **1**, **2** and BSA at 120°C for 2 h. After chromatography and recrystallization, the yield was 26%. This is higher than the overall yields of PhIP obtained by previously published multistep procedures.[1–3]

Compound **1** was first reported[6,7] as the enol-imine tautomer and not as the enamine tautomer shown. However the ^{1}H NMR spectrum clearly proved the amino aldehyde structure. Compound **1** was obtained and used as a mixture of the geometric isomers, with the undesired *E*-form predominating. However, the isomers should be rapidly interconverted under the reaction conditions. Thus, gradual interconversion was observed in several organic solvents, as previously[18] reported for similar compounds.

The present method might also be used for preparation of PhIP analogues from acyclic analogues of **1**,[19] or from derivatives of **1**, substituted in the benzene ring.[20]

Experimental

Melting points (uncorrected) were determined with a Mettler FP5 instrument. The ^{1}H NMR spectra were recorded at 400 MHz and 20°C on a Varian VXR-400 spectrometer and referenced to the solvent [δ($CHCl_3$) 7.26; δ(Me_2SO) 2.49]. The coupling constants *J* are given in Hz without sign. The mass spectra were recorded at 70 eV (electron impact, direct insertion) on a JMS-SX/SX 102A instrument. Perfluorokerosene was used as the standard for the high resolution mass spectra (HR-MS). Flash liquid chromatography (FC) was performed on silica gel (230–400 mesh ASTM, Merck). All reactions and purifications were monitored by TLC (UV detection) on aluminium sheets coated with silica gel 60 F_{254} (Merck). Solvents were mixed on a volume basis. Petroleum refers to petroleum ether boiling at 40–60°C.

3-Amino-2-phenylpropenal (**1**) was prepared in 55% yield by hydrogenation of 3-hydroxy-2-phenylacrylonitrile[21] in the presence of Raney nickel.[6] Higher temperatures resulted in faster reaction[7] but lower yield. After preliminary melting and resolidification at ca. 85°C, pure **1** melted at 96–97°C (Lit.[6] 110°C). Whether polymorphism and/or isomerization is involved is not known. MS, *m/z* (rel. int.): 147 (100, *M*). ^{1}H NMR ($CDCl_3$), (*E*)-**1**: δ 9.17 (1-H, s), 7.2–7.5 (Ph, m), 7.08 (3-H, t, *J* 6.8), ca. 5.1 (NH_2, br s). (*Z*)-**1**: δ 9.62 (1-H, d, *J* 3.8), 7.2–7.5 (3-H and Ph, m), ca. 5.5 (NH_2, br s).

N-(5-Phenyl-2-pyrimidinyl)sarcosine 2-hydroxyethyl ester (**3a**). 3-Amino-2-phenylpropenal (**1**, 1.00 g, 6.8 mmol) and creatinine (**2**, 1.50 g, 13.6 mmol) were dissolved in 1,2-ethanediol (25 ml). The solution was heated on an oil bath at 160°C for 4 h. After cooling, water (75 ml) was added, and the dark mixture was extracted with chloroform (3 × 75 ml). The extract was washed with water (10 ml) and saturated aq. NaCl (10 ml) and dried (Na_2SO_4). The solvent was evaporated off and the resulting product was purified twice by FC ($CHCl_3$–MeOH 6:1 and EtOAc–petroleum 2:1). Recrystallization (petroleum–$CHCl_3$) yielded **3a** (0.50 g, 25%). M.p. 94–95°C. HR-MS, *m/z* Found: 287.1295. Calc. for $C_{15}H_{17}N_3O_3$: 287.1270 (*M*). ^{1}H NMR [$(CD_3)_2SO$]: δ 8.71 (4-H and 6-H, br s), 7.35–7.65 (Ph, m), 4.83 (OH, t, *J* 5.4), 4.45 (NCH_2, s), 4.08 (CO_2CH_2, t, *J* 5.4), 3.57 (CH_2OH, q, *J* 5.4), 3.21 (Me, s).

N-(5-Phenyl-2-pyrimidinyl)sarcosine methyl ester (**3b**). A solution of 3-amino-2-phenylpropenal (**1**, 190 mg, 1.29 mmol) and creatinine (**2**, 580 mg, 5.2 mmol) in methanol (10 ml) was heated at 160°C for 4 h in a Teflon-lined pressure vessel. After cooling, water (25 ml) was added and the mixture was extracted with ethyl acetate (3 × 50 ml). The extract was washed with water (10 ml) and saturated aq. NaCl (10 ml) and dried (Na_2SO_4). The solvent was evaporated off and the resulting product was purified by FC (petroleum–EtOAc 6:1). Recrystallization (petroleum) yielded **3b** (66 mg, 20%), m.p. 99–100°C. HR-MS, *m/z* Found: 257.1188. Calc. for $C_{14}H_{15}N_3O_2$: 257.1164 (*M*). ^{1}H NMR ($CDCl_3$): δ 8.57 (4-H and 6-H, br s), 7.3–7.5 (Ph, m), 4.44 (CH_2, s), 3.76 (OMe, s), 3.31 (NMe, s).

2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine PhIP. Creatinine (**2**, 0.80 g, 7.1 mmol) and 3-amino-2-phenylpropenal (**1**, 0.40 g, 2.7 mmol) were heated in BSA (3.0 g, 14.7 mmol) at 120°C for 2 h under dry nitrogen. After cooling, 1 M hydrochloric acid (25 ml) was added. The mixture was stirred for 5 min, then basified with saturated aq. NaOH to pH > 11 and extracted with 1-butanol (3 × 25 ml). The extract was washed with water (10 ml) and saturated aq. NaCl (10 ml) and dried (Na_2SO_4). The solvent was evaporated off and the resulting product purified by FC ($CHCl_3$–MeOH 5:1). Recrystallization (PhMe–BuOH–DMF) yielded PhIP (160 mg, 26%), identical (TLC, ^{1}H NMR, MS) with a sample prepared from 3-bromo-5-methoxypyridine.[2]

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