Efficient Synthesis of Novel 3-(Het)arylanthranilic Acids via a Suzuki Cross-Coupling Reaction of 7-Iodoisatin with (Het)arylboronic Acids in Water

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In contrast with anthranilic acid derivatives, which have been extensively used as building blocks in medicinal chemistry, few studies have addressed their biphenyl analogues. In looking for novel and versatile scaffolds, of use in combinatorial chemistry, we focused on the synthesis of 3-arylanthranilic acids of type **2**. An in depth survey of the literature shows only one description of 3-phenylanthranilic acid itself (**2**, R = H) obtained as a byproduct of ammonolysis of phenyloxazepinone,[1] one recent synthesis of **2** (R = H) via isatin **3** (R = H),[2] and one palladium-catalyzed cross-coupling of monoorganozinc halides with 3-iodoanthranilonitriles.[3] This situation prompted us to investigate a general method to prepare compounds of type **2** based on the development of Suzuki-type cross-coupling reactions.[4]

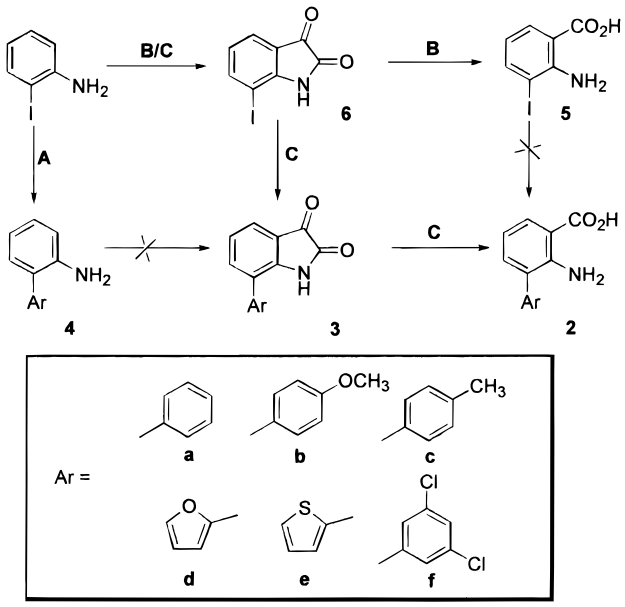
Results and Discussion

At the initiation of this project, three routes were envisaged starting from 2-iodoaniline, as depicted in Scheme 1.

The first, route A, was a cross-coupling reaction of *o*-iodoaniline with various boronic acids, followed by cyclization of isatin and oxidative cleavage of this latter according to the method previously described by Marvel and Hiers.[5] This route was unsatisfactory. Although the first step gave reasonable results, the second failed totally, and in our hands, no cyclization of isatin occurred with substituted biphenylamine **4**.

The second, route B, was the synthesis of 3-iodoanthranilic acid **5**, via 7-iodoisatin **6**, and a cross-coupling reaction at the final step. While the hitherto unknown **5** was prepared with a reasonable yield (30% from 2-iodoaniline), the cross-coupling reaction was completely ineffective; the unprotected amino acid was always recovered unchanged at the end of the reaction. On the basis of the above and considering 7-iodoisatin **6** as a biprotected precursor of anthranilic acid, we investigated the route C (the most improbable as a result of the fragility of isatins), the cross-coupling reaction of **6** with

Scheme 1



boronic acids. Unexpectedly our first results indicated clearly that the cross-coupling was gradually effective, but as might have been anticipated, it was concomitant with the cleavage of the isatin ring, leading to an unworkable mixture at the end of the reaction.

These observations prompted us to study in depth the experimental conditions of this cross-coupling reaction. A long-lasting reaction (more than 40 h at reflux temperature in DME) was the major deleterious fact; we tried to shorten this reaction time by modifying the nature of the base ($NaHCO_3$, TEA, NaOH), as well as the type and the quantity of Pd(0) catalyst (5−20%), but none of these modifications was efficient. To improve the reactivity of the partners, we increased the solubility by adding more water, until a highly diluted and homogeneous reaction mixture was obtained.[6] These modifications allowed a rapid coupling reaction without cleavage of the iodoisatin **6**, and finally, the optimal conditions were found to be **6**, 1 mmol; $ArB(OH)_2$, 1.1 equiv; $NaHCO_3$, 2 equiv; $Pd(PPh_3)_4$, 0.05 equiv; DME/H_2O v/v, 60 mL; 85 °C; 5 h to give arylisatins **3a**−**f** with 55−70% yield. Oxidative cleavage of **3** was then readily performed in an alkaline medium in the presence of hydrogen peroxide to give the desired anthranilic acid **2a**−**f** in a 70−75% yield.[7]

In conclusion, the methodology we have developed allows the chemistry of arylisatins and arylanthranilic acids. The presence of an aromatic substitution fails to alter the reactivity of the anthranilic moiety, and for example, reactive species such as 8-arylisatoic anhydrides or 3-aryl-2-aminophénylglyoxylic acids were readily obtained following standard methods[8] and will be published elsewhere.

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Experimental Section

7-Iodoisatin (6). In a 250 mL flask is placed chloral hydrate (1.81 g, 0.011 mol) in H_2O (24 mL). To this solution are then added, in order, crystallized sodium sulfate (25.56 g, 0.18 mol), 2-iodoaniline (2.19 g, 0.01 mol) in H_2O (36 mL), hydrochloric acid (1.35 mL, 0.03 mol), and finally, a solution of hydroxylamine hydrochloride (2.1 g, 0.03 mol) in H_2O (10 mL). The mixture is stirred and heated to 80 °C for 1 h and then cooled to room temperature. The precipitate corresponding to 2-iodohydroxyiminoacetanilide is filtered and dried under vacuum to give a white solid (2.19 g, 76%): mp 157−158 °C; ^{1}H NMR ($CDCl_3$) δ 8.98 (br s, 1H), 8.77 (s, 1H), 8.29 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 9.5 Hz, 1H), 7.60 (s, 1H), 7.37 (m, 1H), 6.87 (m, 1H); IR(KBr)$_{\lambda max}$ 3434 (OH), 3309 (NH), 1660 (CO). Anal. Calcd for $C_8H_7N_2O_2I$: C, 33.12; H, 2.43; N, 9.65. Found: C, 33.38; H, 2.59; N, 9.87. Then, concentrated sulfuric acid (15 mL) is warmed to 50 °C in a 100 mL flask fitted with an efficient stirrer, and to this is added dry 2-iodohydroxyiminoacetanilide (2.19 g, 7.5 mmol) at the rate necessary to keep the temperature between 60−70 °C. After the addition of the isonitroso compound is finished, the solution is heated to 80 °C and kept at this temperature for about 15 min to complete the reaction. Then the reaction mixture is cooled to room temperature and poured into cracked ice with continual stirring. After 1 h, the 7-iodoisatin **6** is filtered, washed several times with cold water, and then dried under vacuum to give a crude red product (1.02 g, 50%) **6**: mp 208 °C; ^{1}H NMR ($CDCl_3$) δ 8.26 (s, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 6.95 (dd, J = 8.4 Hz, J = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 183.16, 158.4, 151.3, 146.6, 125.6, 125.2, 119.5, 77.9; IR(KBr)$_{\lambda max}$ 3410 (NH), 1740 (CO). Anal. Calcd for $C_8H_4NO_2I$: C, 35.19; H, 1.47; N, 5.13. Found: C, 35.46; H, 1.68; N, 5.38.

7-Arylisatins (3). General Procedure. To a mixture of 7-iodoisatin **6** (272.9 mg, 1 mmol) and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) in DME (30 mL) is added the corresponding arylboronic acid (1.1 mmol), followed by the addition of sodium hydrogen carbonate (168 mg, 2.0 mmol) in H_2O (30 mL). The reaction mixture is refluxed with vigorous stirring, and the rate of the reaction is followed by TLC. After the starting aryl halide was consumed (5 h), the organic solvent is removed under reduced pressure. The residue, partially soluble in H_2O, is extracted with CH_2Cl_2 (30 mL), and then the organic layer is dried ($CaCl_2$) and evaporated. The crude products are purified by column chromatography (CH_2Cl_2/MeOH, 97.5/2.5).

7-Phenylisatin (3a): orange solid, 55%, mp 185−186 °C; ^{1}H NMR ($CDCl_3$) δ 7.83 (br s, 1H), 7.51 (m, 7H), 7.21 (m, 1H); IR(KBr)$_{\lambda max}$ 3406 (NH), 1745 (CO), 1741 (CO). Anal. Calcd for $C_{14}H_9N_1O_2$: C, 75.32; H, 4.06; N, 6.27. Found: C, 75.52; H, 4.28; N, 6.48.

7-(4-Methoxyphenyl)isatin (3b): orange solid, 70%, mp >200 °C; ^{1}H NMR ($CDCl_3$) δ 7.80 (br s, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.33 (d, J = 8.6 Hz, 2H), 7.20 (m, 1H), 7.04 (d, J = 8.6 Hz, 2H), 3.87 (s, 3H); IR(KBr)$_{\lambda max}$ 3448 (NH), 1742 (CO), 1730 (CO). Anal. Calcd for $C_{15}H_8N_1O_3$: C, 71.99; H, 3.22; N, 5.59. Found: C, 72.27; H, 3.33; N, 5.72.

7-(4-Methylphenyl)isatin (3c): orange solid, 55%, mp 178 °C; ^{1}H NMR ($CDCl_3$) δ 7.79 (br s, 1H), 7.60 (d, J = 7.4 Hz, 1H), 7.56 (d, J = 7.4 Hz, 1H), 7.35−7.28 (m, 4H), 7.19 (m, 1H), 2.43 (s, 3H); IR(KBr)$_{\lambda max}$ 3448 (NH), 1740 (CO). Anal. Calcd for $C_{15}H_8N_1O_2$: C, 76.91; H, 3.44; N, 5.97. Found: C, 77.15; H, 3.68; N, 6.18.

7-(Fur-2-yl)isatin (3d): red solid, 65%, mp 220 °C; ^{1}H NMR ($CDCl_3$) δ 8.88 (br s, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.59 (s, 1H), 7.55 (d, J = 7.2 Hz, 1H), 7.15 (m, 1H), 6.77 (m, 1H), 6.58 (m, 1H); IR (KBr)$_{\lambda max}$ 3246 (NH), 1741 (CO), 1739 (CO). Anal. Calcd for $C_{12}H_7N_1O_3$: C, 67.60; H, 3.30; N, 6.57. Found: C, 67.42; H, 3.11; N, 6.35.

7-(Thien-2-yl)isatin (3e): orange solid, 65%, mp 170−171 °C; ^{1}H NMR ($CDCl_3$) δ 8.13 (br s, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.61 (d, J = 7.3 Hz, 1H), 7.47 (m, 1H), 7.20−7.18 (m, 3H); IR-(KBr)$_{\lambda max}$ 3276 (NH), 1739 (CO). Anal. Calcd for $C_{12}H_7N_1O_2S_1$: C, 62.87; H, 3.07; N, 6.10. Found: C, 62.42; H, 3.03; N, 5.92.

7-(3,5-Dichlorophenyl)isatin (3f): red solid, 60%, mp >220 °C; ^{1}H NMR ($CDCl_3$) δ 9.66 (br s, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.51 (m, 1H), 7.47 (m, 1H), 7.41 (br s, 1H), 7.34 (br s, 2H), 7.16 (m, 1H); IR(KBr)$_{\lambda max}$ 3442 (NH), 1739 (CO). Anal. Calcd for $C_{14}H_7N_1O_2Cl_2$: C, 57.56; H, 2.41; N, 4.79. Found: C, 57.32; H, 2.33; N, 4.61.

3-Arylanthranilic Acids (2). General Procedure. To a stirred suspension of 7-arylisatin **3** (1 mmol) in 5% sodium hydroxide (5 mL) is added 30% hydrogen peroxide (5 mL) dropwise. The reaction mixture is stirred at 50 °C for 30 min and then allowed to reach room temperature. The filtered solution is acidified to pH 4 with 1 M hydrochloric acid, and the solid product **2** is collected by filtration.

3-Phenylanthranilic acid (2a): beige solid, 72%, mp 146 °C (lit 148−149 °C); ^{1}H NMR (DMSO) δ 7.84 (m, 1H), 7.54−7.45 (m, 5H), 7.22 (m, 1H), 6.70 (m, 1H); IR(KBr)$_{\lambda max}$ 3488, 3367 (NH_2), 1661 (CO). Anal. Calcd for $C_{13}H_{11}N_1O_2$: C, 73.22; H, 5.20; N, 6.57. Found: C, 72.95; H, 5.03; N, 6.66.

3-(4-Methoxyphenyl)anthranilic acid (2b): white solid, 70%, mp 158 °C;^{1}H NMR ($CDCl_3$) δ 7.94 (d, J = 7.7 Hz, 1H), 7.34 (d, J = 8.3 Hz, 2H), 7.25 (d, J = 7.9 Hz, 1H), 7.00 (d, J = 8.3 Hz, 2H), 6.71 (m, 1H), 3.86 (s, 3H); IR(KBr)$_{\lambda max}$ 3470, 3362 (NH_2), 1655 (CO). Anal. Calcd for $C_{14}H_{13}N_1O_3$: C, 69.12; H, 5.38; N, 5.75. Found: C, 68.97; H, 5.13; N, 5.59.

3-(4-Methylphenyl)anthranilic acid (2c): beige solid, 75%, mp 160 °C; ^{1}H NMR (DMSO) δ 10.24 (br s, 1H), 7.74 (m, 1H), 7.60 (m, 1H), 7.25−7.11 (m, 4H), 6.61 (m, 1H); IR(KBr)$_{\lambda max}$ 3492, 3376 (NH_2), 1653 (CO). Anal. Calcd for $C_{14}H_{13}N_1O_2$: C, 73.99; H, 5.76; N, 6.16. Found: C, 73.78; H, 5.53; N, 5.91.

3-(Fur-2-yl)anthranilic acid (2d): salmon solid, 82%, mp 137 °C; ^{1}H NMR ($CDCl_3$) δ 7.97 (m, 1H), 7.57 (m, 2H), 6.61 (m, 3H); IR(KBr)$_{\lambda max}$ 3488, 3371 (NH_2), 1671 (CO). Anal. Calcd for $C_{11}H_9N_1O_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.12; H, 4.51; N, 6.71.

3-(Thien-2-yl)anthranilic acid (2e): beige solid, 77%, mp 138 °C; ^{1}H NMR ($CDCl_3$) δ 7.98 (d, J = 7.9 Hz, 1H), 7.40 (m, 2H), 7.19 (m, 1H), 7.15 (m, 1H), 6.70 (m, 1H), 6.29 (br s, 2H); IR(KBr)$_{\lambda max}$ 3459, 3350 (NH_2), 1667 (CO). Anal. Calcd for $C_{11}H_9N_1O_2S_1$: C, 60.25; H, 4.13; N, 6.38. Found: C, 59.95; H, 3.97; N, 6.21.

3-(3,5-Dichlorophenyl)anthranilic acid (2f): white solid, 76%, mp 196−198 °C; ^{1}H NMR ($CDCl_3$) δ 8.00 (d, J = 7.1 Hz, 1H), 7.40 (br s, 1H), 7.33 (br s, 2H), 7.22 (d, J = 7.1 Hz, 1H), 6.74 (m, 1H); IR(KBr)$_{\lambda max}$ 3489, 3362 (NH_2), 1666 (CO). Anal. Calcd for $C_{13}H_9N_1O_2Cl_2$: C, 55.34; H, 3.22; N, 4.96. Found: C, 55.47; H, 3.18; N, 4.72.

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