A simple and environmentally friendly method for the synthesis of *N*-phenylanthranilic acid derivatives

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A simple, efficient and environmentally friendly method for the synthesis of *N*-phenylanthranilic acid derivatives by the copper acetate catalysed reaction of *o*-halobenzoic acid with anilines using sodium acetate as base and water as media is described.

Keywords: *N*-phenylanthranilic acid, *o*-halobenzoic acid, anilines, copper acetate, sodium acetate and water

The substituted *N*-phenylanthranilic acid is a common intermediate in the synthesis of a number of pharmaceutically important molecules. *e.g.*, the widely used antimalarials,[1-2] anti-inflammatory[3] and antineoplastics.[4] The synthesis of this intermediate usually involve the condensation of functionalised anilines and *o*-halobenzoic acid derivatives resulting in the desired *N*-phenylanthranilic acid by either Ullmann–Goldberg coupling/Jourdan–Ullmann coupling,[5-6] palladium catalysed C–N coupling reaction,[7-8] ultrasonic irradiation[9-10] or nucleophilic substitution of diphenyliodinium-2-carboxylate (DPIC) with anilines.[11]

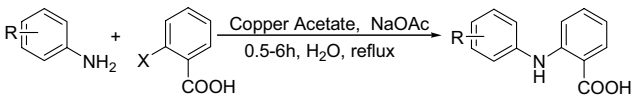
The drawbacks of palladium catalysed C–N coupling methodology include the cost of the reagents, the removal of the trace palladium from late stage synthetic intermediates, difficulty of coupling electron-rich or *o*-substituted aryl halides further the limitations in terms of generality and sensitivity of catalysts to air and moisture have lessened the utility of the method.[12] Nucleophilic substitution of diphenyliodinium-2-carboxylate (DPIC) with anilines is an excellent reagent for the preparation of *o*-substituted benzoic acids.[13-14] This method is laborious, tedious and time consuming.

Traditional copper catalysed Ullmann–Goldberg coupling or Jourdan–Ullmann coupling protocols necessitate the use of higher reaction time and temperature, stochiometric amounts of anilines and copper reagents, which on scale, leads to problems of waste disposal and they have been plagued by poor substrate scope.[15] Recent developments of the reaction utilise *o*-halobenzoic acids and anilines, or other amino aryls, together with a base and a source of copper.[16,17] These reactions can be carried out under mild conditions than the classical Ullmann condensation by using appropriate ligands.[18] The reaction can be provoked by sonication.[6] Recently developed the reaction for a broader range of substrates has seen the use of copper complexes.[19] Alternatively other methods using aryl boronic acids, arylbismuth compounds, or organolead compounds[20] have been developed for *N*-arylation. However, copper-mediated coupling is still the reaction of choice for its greater functional group compatibilities, commercial availability of a wide variety of substrates, stability with air/moisture and feasibility to large and industrial-scale production.

The use of water as a solvent has generated considerable interest from the economical, environmental and the regulatory constraints faced in the chemical and pharmaceutical industries. Development of environmentally benign organic reactions has become a crucial and demanding research area in modern organic chemical research.[21] Organic synthesis in water not only represents a new technology with minimum waste problems, but also a new methodology since the properties of water can be used to manipulate the reactivity of organic compounds. Replacing organic solvents with water offers economic advantages, improves safety and minimises waste disposal and great opportunities for green chemistry.[22] In this concern, we report a simple, convenient, efficient, economic and environmentally friendly method for the synthesis of *N*-phenylanthranilic acid derivatives by the copper acetate catalysed reaction of *o*-halobenzoic acid with anilines in the presence of sodium acetate as base and water as media (Scheme 1).

The reactivity of *o*-halobenzoic acid varies in the order I > Br > Cl. The reaction goes smoothly with *o*-iodobenzoic acid as a reactant with higher yields of *N*-phenylanthranilic acid in shorter duration (Table 1). However, the reaction also goes well with the bromo and chlorobenzoic acid with little more time. The results are summarised in Table 1. Since the *N*-arylation of anilines is maximum with *o*-iodobenzoic acid, we have selected the *o*-iodobenzoic acid as reactant to synthesise the *N*-phenylanthranilic acid derivatives.

The yield of the *N*-phenylanthranilic acid was dramatically increased within shorter time, when we have used copper acetate than the other copper salts like copper oxide, copper chloride in the above condition. The condensation goes well with good yield in shorter duration by using *o*-halobenzoic acid with 2.0 equiv. of anilines by using 1.2 equiv. of sodium acetate and 5 % weight of copper acetate (with respect to *o*-iodobenzoic acid) in water (Table 2). The same condition also goes well, when DMF used as solvent but the method suffers in ease of product isolation.



Where R=H, CH_3, OCH_3, Cl, NO_2, COOH, NH_2.
X=Cl, Br, I

Scheme 1

Table 1 Effect of *o*-halobenzoic acid on *N*-phenylanthranilic acid yield with aniline, copper acetate and sodium acetate in aqueous media

Entry	*o*-Halobenzoic acid	Anilines	Time/h	Product	Yield/%
1	*o*-Iodobenzoic acid	Aniline	0.5	*N*-Phenylanthranilic acid	97
2	*o*-Bromobenzoic acid	Aniline	2.5	*N*-Phenylanthranilic acid	94
3	*o*-Chlorobenzoic acid	Aniline	4.0	*N*-Phenylanthranilic acid	91

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Table 2 The effect of copper salts on the yield of *N*-phenylanthranilic acid with iodobenzoic acid, aniline and sodium acetate in aqueous media

Time/h	0.5	1.0	1.5	2.0	3.0	4.0
Copper acetate	97	97	97	97	97	92
Copper oxide	38	43	53	61	68	68
Copper chloride	41	49	54	59	62	63

Table 3 The effect of base on the yield of *N*-phenylanthranilic acid with iodobenzoic acid, aniline and copper acetate in aqueous media

Equivalent used	1.0	1.2	1.4	1.6	1.8	2.0
Sodium acetate, yield/%	74	97	97	96	92	90
Potassium carbonate, yield/%	55	63	71	72	71	68

We have tried the condensation of *o*-halobenzoic acid with anilines in different solvents like dimethylformamide, isopropyl alcohol, *n*-butanol, water, using 1.0–2.0 equiv. of potassium carbonate, potassium hydroxide, sodium hydroxide, sodium acetate as base and 4–15 % weight (with respect to *o*-halobenzoic acid) of different copper salts like copper oxide, copper chloride and copper acetate. We have observed that, a green dye was formed, when we have used potassium hydroxide or sodium hydroxide as base in different solvents with different copper salts. The yields were low, when we have used potassium carbonate and the yields were good with sodium acetate as base in different solvent with different copper salts (Table 3).

A variety of substituted *N*-phenylanthranilic acid has been synthesised by condensation of *o*-iodobenzoic acid and substituted anilines by copper acetate using sodium acetate in aqueous media. The overview of this methodology was examined using different solvent media, different bases, and other functionally and sterically hindered anilines. The presence of electron withdrawing groups like chloro, nitro and carboxylic groups in anilines slow down the reaction. Where as the electron releasing group facilitates the process. It can be seen that *o*-substituted compounds give comparatively less yields as compared to *p*-substituted compounds, which may be attributed to steric hindrance. The *N*-phenylanthranilic acid derivatives synthesised were characterised by TLC, melting points, GCMS, ^{13}C and ^{1}H NMR spectra. In this method, we have not observed the formation of double substitution at nitrogen atom. We have run the parallel experiment with the diphenylamine and *o*-halobenzoic acid to confirm the possibility of forming tertiary amine. In addition, we did not observe the homo coupling of *o*-halobenzoic acid and confirmed with GCMS of *N*-phenylanthranilic acid.

In summary, we have developed a convenient, high yield procedure for the synthesis of *N*-phenylanthranilic acid derivatives, which are the key intermediates in the synthesis of acridines and this method can be used for the synthesis of anti-inflammatory drug mefanamic acid with good yield. The obvious advantages of the proposed method are its simple operation, compatibility not only for laboratory scale but also for larger scale synthesis, commercial availability of the reagents, milder reaction conditions and absence of unwanted by-products. The complete absence of organic solvents should lead to an easy work-up in larger scale preparations. The catalyst is stable, inexpensive, commercially available and water soluble in nature. The present method offers an economical, safe and environmentally friendly alternative to available procedures.

Experimental

Melting points were determined on a Selcon apparatus and are uncorrected. Thin layer chromatography (TLC) was accomplished using plates precoated with silica gel 60 F-254 (Merck). Mass spectra were recorded by GCMS at Indian Institute of Science, Bangalore, India. All ^{13}C and ^{1}H NMR spectra were recorded on a AMX-300 MHz spectrometer instrument. Chemical shifts are reported as delta values (ppm) downfield from internal standard Me_4Si in DMSO-d_6. Elemental analysis was performed on a model Vario EL III elemental analyser.

General procedure

A two-necked round bottom flask was charged with copper acetate 5 % wt (with respect to iodobenzoic acid), iodobenzoic acid (1 mmol), anilines (2 mmol), sodium acetate (1.2 mmol) and water (15 ml). The mixture was refluxed for 1–6 h in an oil bath under vigorous magnetic stirring until the TLC shows the disappearance of starting material. The reaction mixture was cooled to room temperature, acidified with dil HCl to pH 2 and stirred for overnight. The crystals/solids were filtered, washed with dil HCl followed by water.

2-(phenylamino)benzoic acid: Greenish-cream solid; m.p. 181–183 °C (lit.[23] 182–184 °C); reaction time, 30 mins; yield, 95 %. ^{1}H NMR: δ = 6.76–7.90(m, 9H, ArH), 9.6(s, 1H, NH), 13.01(s, 1H, COOH), ^{13}C NMR: δ113.63 (C1), δ117.21 (C5), δ118.93 (C4a), δ119.87 (C3), δ121.67 (C2a), δ129.29 (C6a), δ130.19 (C3a), δ131.87 (C5a), δ135.37 (C6), δ140.57 (C4), δ142.14 (C1a), δ146.33 (C2), δ170.041 (COOH). *m/z* = 213 M^+, 195 (loss of water due to *ortho* effect, 100 %). Anal. Calcd. For $C_{13}H_{11}NO_2$: C, 73.23; H, 5.20; N, 6.57. Found C, 73.25; H, 5.16; N, 6.53.

2-(o-Tolylamino)benzoic acid: Brownish shiny solid: m.p. 183–185 °C (lit.[24] 185 °C); reaction time, 1 h; yield, 92 %. ^{1}H NMR: δ = 2.31 (s, 3H, CH_3), 6.72–7.80(m, 8H, ArH), 9.50(s, 1H, NH), 13.06(s, 1H, COOH). ^{13}C NMR: δ16.27 (CH_3), δ116.15 (C1), δ119.51 (C5), δ119.93 (C4a), δ120.87 (C3), δ121.02 (C6a), δ129.29 (C5a), δ131.19 (C3a), δ131.87 (C6), δ132.23 (C2a), δ135.37 (C4), δ139.57 (C1a), δ145.14 (C2), δ170.041 (COOH). Anal. Calcd. For $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found C, 73.94; H, 5.73; N, 6.15.

2-(p-Tolylamino)benzoic acid: Greenish-white solid; m.p. 196 °C (lit.[25] 195–196 °C); reaction time, 1 h; yield, 94 %. ^{1}H NMR: δ = 2.31(s, 3H, CH_3), 6.72–7.85(m, 8H, ArH), 9.6(s, 1H, NH), 13.01(s, 1H, COOH). ^{13}C NMR: δ26.72 (CH_3), δ115.18 (C1), δ119.86 (C5), δ119.42 (C3), δ119.87 (C2a), δ120.56 (C6a), δ128.38 (C4a), δ131.63 (C5a), δ132.56 (C3a), δ132.81 (C6), δ135.57 (C4), δ138.57 (C1a), δ144.17 (C2), δ170.041 (COOH). Anal. Calcd. For $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found C, 73.95; H, 5.75; N, 6.13.

2-(2,3-Dimethylphenylamino)benzoic acid: Yellowish-white solid; m.p. 228–230 °C (lit.[26] 195–196 °C); reaction time, 1.5 h; yield, 93 %. ^{1}H NMR: δ = 2.31(s, 3H, CH_3), 2.22(s, 3H, CH_3) 6.84–7.75 (m, 7H, ArH), 9.4(s, 1H, NH), 13.01(s, 1H, COOH). ^{13}C NMR: δ24.75 (CH_3), δ25.82 (CH_3), δ115.18 (C1), δ118.85 (C5), δ118.42 (C6a), δ120.87 (C4a), δ120.56 (C6), δ127.38 (C5), δ130.63 (C6), δ131.56 (C3a), δ132.81 (C2a), δ134.57 (C4), δ138.57 (C1a), δ144.17 (C2), δ170.041 (COOH). Anal. Calcd. For $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81. Found C, 74.61; H, 6.22; N, 5.77.

2-(2-Methoxyphenylamino)benzoic acid: Greenish–yellow solid; m.p. 173–174 °C; reaction time, 1.5 h; yield, 88 %. ^{1}H NMR: δ = 3.82(S, 3H, OCH_3), 6.75–7.90(m, 8H, ArH), 9.6(s, 1H, NH), 13.10(s, 1H, COOH). ^{13}C NMR: δ55.58 (OCH_3), δ113.62 (C1), δ117.06 (C3a), δ119.04 (C5), δ120.04 (C3), δ120.56 (C4a), δ123.38 (C6a), δ129.43 (C5a), δ130.23 (C1a), δ131.81 (C6), δ135.48 (C4), δ146.77 (C2), δ150.98 (C2a), δ171.99 (COOH). Anal. Calcd. For $C_{14}H_{13}NO_3$: C, 69.13; H, 5.39; N, 5.76. Found C, 69.16; H, 5.37; N, 5.77.

2-(4-Methoxyphenylamino)benzoic acid: Light green solid; m.p. 180–182 °C (lit.[27] 181 °C); reaction time, 1.5 h; yield, 92 %.

^{1}H NMR: δ = 3.89(S, 3H, OCH_3), 6.75–7.85(m, 8H, ArH), 9.45 (s, 1H, NH), 12.95(s, 1H, COOH). ^{13}C NMR: δ56.54 (OCH_3), δ113.81 (C1), δ116.36 (C3a), δ117.04 (C5a), δ119.72 (C5), δ120.56 (C3), δ122.38 (C6a), δ123.43 (C2a), δ132.23 (C6), δ132.81(C1a), δ136.48 (C4), δ145.81 (C2), δ152.90 (C4a), δ170.59 (COOH). Anal. Calcd. For $C_{14}H_{13}NO_3$: C, 69.13; H, 5.39; N, 5.76. Found C, 69.11; H, 5.37; N, 5.72.

2-(2-Aminophenylamino)benzoic acid: After reaction completion, the reaction mixture was washed with chloroform to remove excess unreacted *o*-phenylendiamine and then it was acidified to pH 6–6.5 with acetic acid and kept for overnight stirring. The crystals were filtered and dried. Light green solid; m.p. 128–130 °C; reaction time, 1 h; yield, 91 %.

^{1}H NMR: δ = 5.8(S, 2H, NH_2), 6.52–7.85(m, 8H, ArH), 9.45(s, 1H, NH), 13.01(s, 1H, COOH). ^{13}C NMR: δ113.62 (C1), δ118.45 (C3a), δ118.63 (C5), δ119.72 (C3), δ120.26 (C5a), δ121.38 (C4a), δ122.63 (C6a), δ132.63 (C6), δ135.63 (C4), δ139.63 (C1a), δ142.81 (C2a), δ145.90 (C2), δ170.59 (COOH). Anal. Calcd. For $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found C, 68.42; H, 5.31; N, 12.29.

2-(2-Chlorophenylamino)benzoic acid: Yellow crystal: m.p. 171–172 °C; reaction time, 2 h; yield, 81 %. ^{1}H NMR: δ = 6.85–7.95(m, 8H, ArH), 9.85(s, 1H, NH), 13.15(s, 1H, COOH). ^{13}C NMR: δ114.41 (C1), δ115.1 (C5), δ119.293 (C3), δ121.95 (C4a), δ124.66 (C6a), δ125.77 (C5a), δ128.73 (C2a), δ130.87 (C3a), δ132.62 (C6), δ134.97 (C1a), δ138.21 (C4), δ146.33 (C2), δ170.58 (COOH). Anal. Calcd. For $C_{13}H_{10}NO_2Cl$: C, 63.04; H, 4.07; N, 5.66. Found C, 62.98; H, 4.01; N, 5.52.

2-(4-Chlorophenylamino)benzoic acid: Yellow crystal; m.p. 176–178 °C (lit.[28] 177 °C); reaction time, 2 h; yield, 83 %. ^{1}H NMR: δ = 6.82-7.95(m, 8H, ArH), 9.65(s, 1H, NH), 13.05(s, 1H, COOH). ^{13}C NMR: δ114.7 (C1), δ116.9 (C5), δ119.79 (C3), δ121.57 (C2a), δ122.27 (C6a), δ125.27 (C4a), δ129.72 (C5a), δ130.72 (C3a), δ133.62 (C6), δ135.97 (C4), δ138.99 (C1a), δ146.63 (C2), δ171.82 (COOH). Anal. Calcd. For $C_{13}H_{10}NO_2Cl$: C, 63.04; H, 4.07; N, 5.66. Found C, 63.05; H, 4.06; N, 5.59.

2-(2-Nitrophenylamino)benzoic acid: Yellow crystal; m.p. 217–218 °C (lit.[29] 219 °C); reaction time, >6 h; yield, 10 %. ^{1}H NMR: δ = 6.65–7.95(m, 8H, ArH), 9.75(s, 1H, NH), 13.15(s, 1H, COOH). ^{13}C NMR: δ114.7 (C1), δ119.9 (C5), δ120.79 (C3), δ121.57 (C4a), δ122.63 (C6a), δ124.27 (C3a), δ132.72 (C6), δ135.72 (C4), δ136.62 (C5a), δ138.27 (C2a), δ138.99 (C1a), δ145.63 (C2), δ171.27 (COOH). Anal. Calcd. For $C_{13}H_{10}N_2O_4$: C, 60.47; H, 3.90; N, 10.85. Found C, 60.49; H, 3.89; N, 10.81.

2-(3-Nitrophenylamino)benzoic acid: Yellow solid; m.p. 216–218 °C (lit [30] 218 °C); reaction time, >6 h; yield, 15 %. ^{1}H NMR: δ = 6.72–7.95(m, 8H, ArH), 9.85(s, 1H, NH), 13.05(s, 1H, COOH). ^{13}C NMR: δ114.4 (C1), δ118.9 (C5), δ120.27 (C3), δ121.09(C2a), δ121.90 (C6a), δ123.27 (C3a), δ124.72 (C5a), δ132.72 (C6), δ136.36 (C4), δ138.54 (C4a), δ144.18 (C2), δ146.63 (C1a), δ171.54 (COOH). Anal. Calcd. For $C_{13}H_{10}N_2O_4$: C, 60.47; H, 3.90; N, 10.85. Found C, 60.44; H, 4.91, N, 10.86.

2-(4-Carboxyphenylamino)benzoic acid: White solid; m.p. 288–289 °C (lit.[31] 290 °C); reaction time, 3 h; yield, 59 %. ^{1}H NMR: 6.8–8.0(m, 8H, ArH), 9.65(s, 1H, NH), 13.15(s, 2H, 2COOH). ^{13}C NMR: δ117.31 (C1), δ121.77 (C5), δ122.94 (C2a), δ128.05 (C6a), δ129.39 (C3), δ129.93 (C4a), δ131.77 (C5a), 132.33 (C6), 134.08 (C3a), δ136.78 (C4), δ140.38 (C2), δ146.87 (C1a), δ168.04 (COOH), δ169.85 (COOHa). Anal. Calcd. For $C_{14}H_{11}NO_4$: C, 65.37; H, 4.31; N, 5.46.Found C, 65.36; H, 4.30; N, 5.45.

2-(2-Chloro-6-methylphenylamino)benzoic acid: White solid; m.p. 199–200 °C; reaction time, 4 h; yield, 48 %. ^{1}H NMR: δ = 2.1 (S, 3H, CH_3), 6.15–7.9(m, 7H, ArH), 9.35(s, 1H, NH), 13.10 (s, 1H, COOH). ^{13}C NMR: δ18.16 (CH_3), δ117.31 (C1), δ120.77 (C5), δ122.04 (C3), δ122.65 (C4a), δ129.39 (C3a), δ127.77 (C2a), δ129.72 (C5a), δ133.38 (C6), δ136.87 (C6a), 137.05 (C4), 146.05 (C2), 147.45(C1a), δ169.09 (COOH). Anal. Calcd. For $C_{14}H_{12}NO_2Cl_1$: C, 64.24; H, 4.62; N, 5.35. Found C, 64.25; H, 4.63; N, 5.36.

2-(Naphthalene-7-ylamino)benzoic acid: Brown crystal, m.p. 188–189 °C; reaction time, 3 h; yield, 67 %. ^{1}H NMR: δ = 6.85–7.85(m, 11H, ArH), 9.85(s, 1H, NH), 13.10(s, 1H, COOH). ^{13}C NMR: δ112.24 (C1a), δ117.31 (C1), δ119.77 (C3a), δ120.04 (C5), δ121.65 (C3), δ123.34 (C6a), δ127.72 (C8a), δ128.09 (C7a), δ129.38 (C5a), δ131.07 (C9a), 132.05 (C4a), 132.81 (C6), 136.45(C10a), δ137.09 (C4), δ145.54 (C2a), 147.36 (C2), 171.07(COOH). Anal. Calcd. For $C_{17}H_{13}NO_2$: C, 77.55; H, 4.97; N, 5.32. Found C, 77.56; H, 4.98; N, 5.33.

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