JOC*Note*

Regioselective Copper-Catalyzed Amination of Bromobenzoic Acids Using Aliphatic and Aromatic Amines

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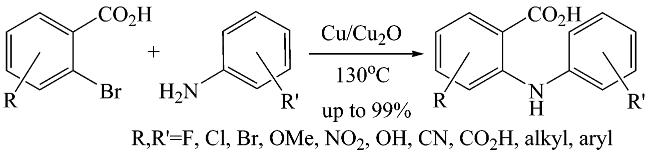

A chemo- and regioselective copper-catalyzed cross-coupling procedure for amination of 2-bromobenzoic acids is described. The method eliminates the need for acid protection and produces *N*-aryl and *N*-alkyl anthranilic acid derivatives in up to 99% yield. *N*-(1-Pyrene)anthranilic acid has been employed in metal ion-selective fluorosensing. Titration experiments showed that this pyrene-derived amino acid forms an equimolar complex with Hg(II) in water resulting in selective fluorescence quenching even in the presence of other metal ions such as Zn(II) and Cd(II).

The synthesis of *N*-aryl anthranilic acids such as flufenamic and mefenamic acid has received considerable attention during recent years because they are important nonsteroidal antiinflammatory drugs and candidates for the therapy of neurodegenerative and amyloid diseases.[1] *N*-Aryl anthranilic acids are also synthetic precursors of acridines, which have been utilized as antimalarial and anticancer drugs.[2] Because of their excellent solubility in water, intriguing stereodynamic properties in peptide chains, and potential use in drug development, *N*-aryl anthranilic acids and other nonnatural achiral amino acids have found various biomedical applications.[3] Achiral amino acids have been incorporated into biologically active peptides to alter secondary protein structures and biochemical properties or to investigate the stereochemical control of peptide folding.[4] Recently, helicity of achiral peptide chains has been induced through asymmetric noncovalent domino effects using an external chiral stimulus.[5]

The first direct synthesis of *N*-aryl anthranilic acids from 2-chlorobenzoic acid was accomplished by Ullmann.[6] Since then, various copper-catalyzed amination procedures suitable to *ortho*-chlorobenzoic acids have been described by us and others.[7] Palladium-catalyzed amination of aryl halides exhibiting free carboxylic acid groups in the meta or para position has also been explored.[8] *N*-Aryl anthranilic acids are usually prepared from 2-chlorobenzoic acids or via coupling of anthranilic acid and aryl halides,[9] although a wide range of 2-bromobenzoic acid derivatives are readily available, for example, through oxidation of 2-alkyl-1-bromobenzenes[10] or lithiation of dibromobenzenes and subsequent treatment with carbon dioxide.[11] Common drawbacks of cross-coupling procedures using bromobenzoic acids are limited tolerance of functional groups due to very high reaction temperatures and low yields with sterically hindered arylamines.[12] We therefore wish to report a highly regioselective synthetic procedure providing convenient access to a range of *N*-aryl and *N*-alkyl anthranilic acids exhibiting various functional groups through Cu-catalyzed amination of 2-bromobenzoic acids. The use of water-soluble *N*-(1-pyrene)anthranilic acid for metal-ion-selective fluorosensing has also been investigated.

Initially, we employed CuI, Cu_2O, or Cu and combinations thereof as catalysts in the reaction of 2-bromobenzoic acid, **1**, and aniline, **2**, using *n*-butanol, 2-ethoxyethanol, and ethylene glycol as solvent. Further screening of bases (Na_2CO_3, Cs_2CO_3, K_3PO_4, NaOAc, *tert*-BuOK, and 2,2,6,6-tetramethylpiperidine)

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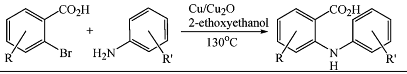
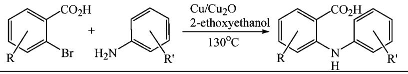
TABLE 1. . Amination of Bromobenzoic Acids with Aryl Amines[a]





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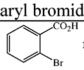
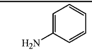
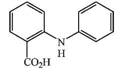
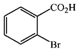
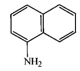
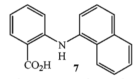
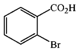
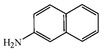
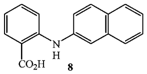
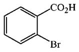
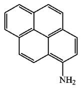
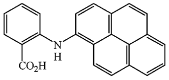
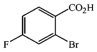
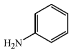
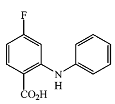
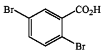
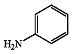
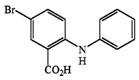
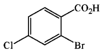
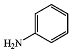
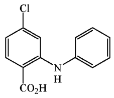
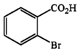
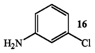
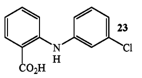
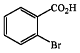
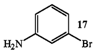
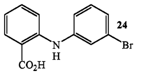
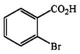
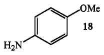
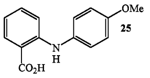
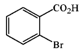
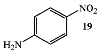
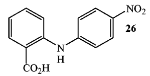
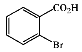
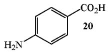
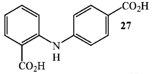
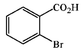
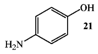
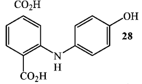
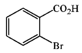
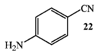
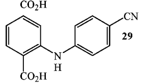
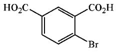
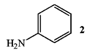
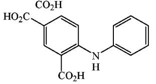
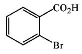
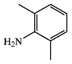
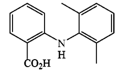
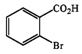
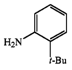
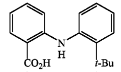
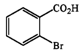
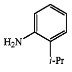
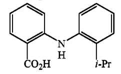
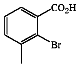
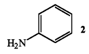
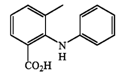
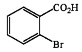
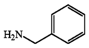
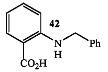
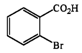
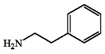
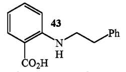
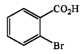
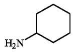
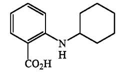
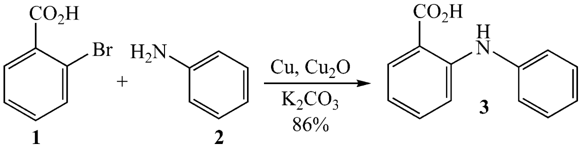
1	 1	 2	 3	86
2	 1	 4	 7	97
3	 1	 5	 8	90
4	 1	 6	 9	55
5	 10	 2	 13	82
6	 11	 2	 14	84
7	 12	 2	 15	94
8	 1	 16	 23	84
9	 1	 17	 24	81
10	 1	 18	 25	88
11	 1	 19	 26	53
12	 1	 20	 27	80[c]
13	 1	 21	 28	63[c]
14	 1	 22	 29	71
15	 26	 2	 30	99[c]
16	 1	 31	 34	68
17	 1	 32	 35	53
18	 1	 33	 36	78
19	 37	 2	 38	58
20	 1	 39	 42	82[d]
21	 1	 40	 43	91[d]
22	 1	 41	 44	65[d]

[a] Reaction conditions: A mixture of 2-bromobenzoic acid (8.8 mmol), 1.05 equiv of aniline derivative, 1.0 equiv of K_2CO_3, 9 mol % of Cu, and 4 mol % of Cu_2O was heated in 3 mL of 2-ethoxyethanol to 130 °C for 24 h. [b] Isolated yields. [c] 2 equiv of K_2CO_3 was used. [d] 2 equiv of the amine was used.

SCHEME 1. Copper-Catalyzed Amination of 2-Bromobenzoic Acid



showed that the best results for the synthesis of *N*-phenylanthranilic acid, **3**, are obtained in the presence of potassium carbonate and catalytic amounts of Cu powder and copper(I) oxide in 2-ethoxyethanol at 130 °C (Scheme 1).

The optimized amination procedure was then applied to a variety of aryl- and alkylamines and bromobenzoic acids to evaluate the synthetic potential of this method (Table 1). Reaction of bromobenzoic acid **1** with 1-aminonaphthalene, **4**, 2-aminonaphthalene, **5**, or 1-aminopyrene, **6**, gave the corresponding *N*-aryl anthranilic acids **7**−**9** in 55−97% yields (entries 2−4). Importantly, the copper-catalyzed amination proceeds with remarkable chemo- and regioselectivity because only the bromide adjacent to the carboxylic acid moiety is replaced. Amination of 2-bromo-4-fluorobenzoic acid, **10**, 2,5-dibromobenzoic acid, **11**, and 2-bromo-4-chlorobenzoic acid, **12**, with aniline yielded *N*-phenyl-4-fluoroanthranilic acid, *N*-phenyl-5-bromoanthranilic acid, and *N*-phenyl-4-chloroanthranilic acid **13**−**15**, in 82−94% yields (entries 5−7). Aryl halide bonds located in the aniline ring are also not affected. *N*-(3-Chlorophenyl)- and *N*-(3-bromophenyl)anthranilic acids, **23** and **24**, were obtained through cross-coupling of **1** with anilines **16** and **17**, respectively, in 81 to 84% yields (entries 8 and 9). Comparison of the results obtained with 4-substituted anilines **18**−**22** reveals that incorporation of electron-donating groups facilitates the amination reaction (entries 10−14). In particular, formation of *N*-(4-nitrophenyl)anthranilic acid, **26**, proved to be slow and substantial amounts of starting materials were recovered after 24 h. By contrast, coupling of 4-bromoisophthalic acid, **26**, and aniline gave anthranilic acid **30** in quantitative amounts (entry 15). The amination protocol is also suitable to the synthesis of sterically crowded anthranilic acids such as **34**−**36**, which were obtained in 53−78% yields from 2,6-dimethylaniline, **31**, 2-*tert*-butylaniline, **32**, and 2-isopropylaniline, **33**, respectively (entries 16−18). Coupling of aniline and 2-bromo-3-methylbenzoic acid, **37**, gave *N*-phenyl-3-methylanthranilic acid, **38**, in 58% yield (entry 19). Noteworthy is that the formation of **35** in only 24% yield by copper(II) acetate-promoted amination of 2-bromobenzoic acid has been reported.[12] The amination protocol can also be applied to aliphatic amines. Employing 2 equiv of primary and secondary aliphatic amines **39**, **40**, and **41** in the reaction with 2-bromobenzoic acid, we obtained the corresponding anthranilic acids

42, **43**, and **44** in 65−91% yield (entries 20−22). The results show that our amination procedure provides convenient access to a wide range of *N*-aryl and *N*-alkyl anthranilic acids from readily available, unprotected 2-bromobenzoic acids and aniline derivatives or primary aliphatic amines. The reaction tolerates various functionalities and proceeds with remarkable regioselectivity, which is probably due to the accelerating effect of *ortho*-carboxylate groups in homogeneous copper-catalyzed exchange reactions.[13]

Because *N*-(1-pyrene)anthranilic acid, **9**, has a metal binding site in close proximity to the fluorescent pyrene ring, we decided to study its use as a metal ion sensor in aqueous solution. The increasing demand for new strategies that can be employed in real-time analysis of alkali, alkaline earth, and transition metals in aqueous solutions has led to the development of numerous chemo- and biosensors.[14] We have recently reported the use of highly constrained 1,8-diacridylnaphthalenes for selective fluorosensing of Cu(II), Fe(II), and Fe(III).[15] Although the construction of molecular sensors exhibiting a fluorophore in close proximity to a metal-chelating site has resulted in a variety of useful fluorosensors, high selectivity toward one metal ion in water has rarely been accomplished. Chang and co-workers have developed an 8-hydroxyquinoline sensor bearing an ionophoric boron-dipyrrolemethene group that proved to be highly selective for Hg(II) in dioxane−water solutions.[16] A water-soluble fluorescent naphthalimide PET sensor exhibiting an iminodiacetate receptor with high selectivity for Zn(II) and an azobenzene-derived sensor for naked-eye detection of Cu(II) in water have recently been reported by Gunnlaugsson et al.[17] MerR-type metal-regulating proteins have been used to construct metal-ion sensitive biosensors for selective detection of Hg(II) or Cu(I), Ag(I), and Au(I).[18] Spectrophotometric detection of Hg(II) in aqueous solution has also been accomplished using an optically transparent, mesoporous nanocrystalline TiO_2 film sensitized with a ruthenium dye.[19]

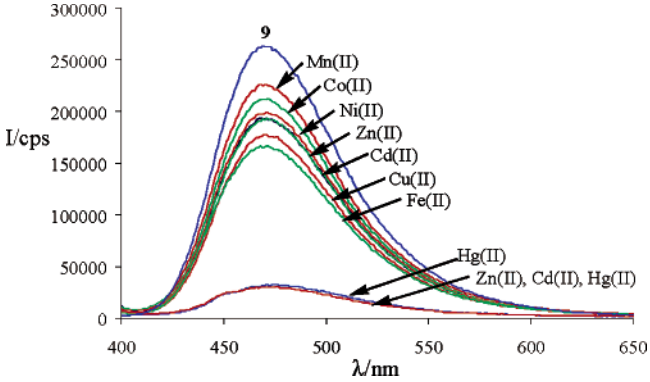


FIGURE 1. Fluorescence spectra of **9** in the absence and presence of various transition-metal ions in aqueous 3×10^{-4} M K_3PO_4 solution (pH = 8.0). The concentration of **9** was 2.5×10^{-5} M, and the metal ion concentration was 1.0×10^{-4} M. Excitation wavelength = 390 nm.

Investigation of the fluorescence properties of pyrene-derived anthranilic acid **9** revealed one maximum at approximately 470 nm and a quantum yield of 0.12. Fluorescence studies using 25 μM of **9** were performed in aqueous 3×10^{-4} M K_3PO_4 solution at pH = 8.0. The screening of the fluorescence of **9** in the presence of 10^{-4} M main group and transition-metal chlorides showed selective fluorescence quenching but no shift of the emission maximum (Figure 1). No quenching was observed in the presence of main group metal ions such as Na^+, K^+, Mg^{2+}, and Al^{3+}, whereas addition of some transition metals results in a considerable decrease of the fluorescence response of **9**. Increasing the metal ion concentrations above 10^{-4} M did not result in any further quenching. Most importantly, only Hg(II) exhibits a strong quenching effect which is not diminished in the presence of equimolar amounts of Zn(II) and Cd(II). The sensor can thus be employed for selective detection of Hg(II) in water.

Mercury and its ionic forms are highly toxic environmental pollutants that can be introduced into the food chain by bacterial methylation and subsequent bioaccumulation. Mercury salts and Hg-derived organometallic compounds have serious neurotoxic effects and cause disruption of the central nervous system, e.g. Minamata disease. Because mercury ions are often accompanied by Zn(II) and Cd(II), it is crucial to develop Hg(II)-selective sensors that are not compromised by the presence of these transition-metal ions.[20] The remarkable fluorescent response of water-soluble *N*-(1-pyrene)anthranilic acid, **9**, to mercury chloride in the presence of both Zn(II) and Cd(II) may open new entries for a fast quantitative and qualitative analysis of Hg(II) ions in aqueous samples (Figure 2).

We attempted to grow single crystals of **9** for X-ray analysis and conducted fluorescence titration experiments to reveal the three-dimensional structure of the sensor and the stoichiometry and stability of the corresponding Hg(II) complex. We were able to grow colorless triclinic crystals of **9** belonging to the $P\bar{1}$ space group from a DMF solution (Figure 3 and Table 2).

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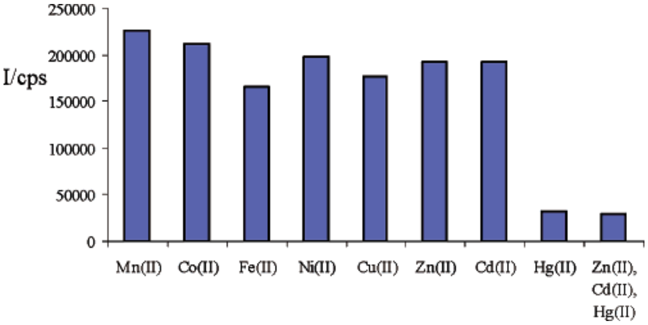

FIGURE 2. Fluorescence of **9** in aqueous 3×10^{-4} M K_3PO_4 solution (pH = 8.0) in the presence of Mn(II), Co(II), Fe(II), Ni(II), Cu(II), Zn(II), Cd(II), and Hg(II) chlorides. The concentration of **9** was 2.5×10^{-5} M. The metal ion concentration was 1.0×10^{-4} M. Excitation wavelength = 390 nm. Emission wavelength = 470 nm.

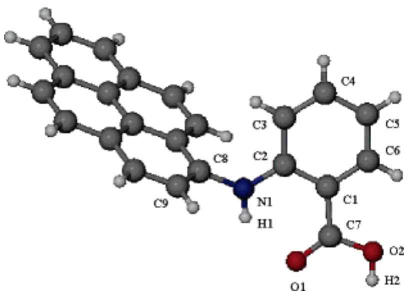

FIGURE 3. Single-crystal structure of **9**.

TABLE 2. Selected Crystallographic Data of 9-DMF

empirical formula	$C_{26}H_{22}N_2O_3$
formula weight	410.46
crystal system	triclinic
space group	$P\bar{1}$
unit cell dimensions	$a = 8.367(5)$ Å
	$b = 11.281(7)$ Å
	$c = 13.200(5)$ Å
	$\alpha = 65.18(4)°$
	$\beta = 79.23(4)°$
	$\gamma = 69.25(4)°$
volume	1056.5(10) Å^3
Z	4
density (calcd)	1.290 g cm^{-3}
crystal size	0.4 × 0.4 × 0.2 mm

Crystallographic analysis shows that the sensor does not undergo intramolecular proton transfer to form a zwitterionic structure which can be attributed to the low basicity of the diarylamine moiety. However, the amino function participates in intramolecular hydrogen bonding with the coplanar carboxylic acid group. The O1···H1–N1 hydrogen bond length is 1.975 Å, and the angle (C2–N1–C8–C9) between the pyrene and the anthranilic plane was determined to be 72.3°.[21]

The X-ray structure and low basicity of the secondary diarylamino function suggest that only the carboxylate group of deprotonated **9** participates in the coordination to Hg(II) in aqueous solution. Job analysis of Hg(II) chloride and **9** at a total concentration of 8.0×10^{-5} M revealed the existence of one maximum at a molar ratio of 0.5 which suggests the formation of an equimolar complex (see Supporting Information).[22] Addition of 2.5×10^{-5} to 1.25×10^{-4} M of Hg(II) to a 25 μM solution of **9** in 3×10^{-4} M K_3PO_4 (pH = 8.0) results in fluorescence quenching following the Benesi–Hildebrand equation derived for a 1:1 complex.[23] Benesi–Hildebrand plotting gave an association constant for Hg(II)–**9** of 1262 M^{-1} (see Supporting Information).

In summary, we have developed a Cu/Cu_2O-catalyzed cross-coupling procedure that allows highly regioselective amination of 2-bromobenzoic acids. The reaction complements existing methods, tolerates various functional groups, and gives *N*-aryl and *N*-alkyl anthranilic acids in good to high yields. Pyrene-derived anthranilic acid **9** was used for fluorimetric metal-ion detection in water and showed strong fluorescence quenching in the presence of Hg(II), whereas other metal ions exhibit considerably smaller effects on the fluorescence intensity. The Hg(II)-sensing ability of this nonnatural amino acid is not compromised in the presence of Zn(II) and Cd(II).

Experimental Section

Typical Amination Procedure. A mixture of 1-aminopyrene (2.0 g, 9.3 mmol), 2-bromobenzoic acid (1.75 g, 8.8 mmol), K_2CO_3 (8.8 mmol), Cu powder (0.2–0.3 μm, 0.8 mmol), Cu_2O (<5 μm, 0.4 mmol), and 3 mL of 2-ethoxyethanol was refluxed at 130 °C for 24 h under nitrogen. The cooled reaction mixture was poured into 30 mL of water to which decolorized charcoal was added. The mixture was filtrated through Celite. The crude product was obtained by precipitation upon acidification of the filtrate with diluted HCl. The residue was dissolved in 100 mL of 5% aqueous Na_2CO_3. The solution was filtered through Celite, and *N*-(1-pyrenyl)anthranilic acid **9** (1.65 g, 4.9 mmol) was obtained in 55% yield as an off-white solid by precipitation as described above. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.94 (dd, *J* = 7.4 Hz, 7.4 Hz, 1H), 7.14 (d, *J* = 8.3 Hz, 1H), 7.43 (dd, *J* = 8.0 Hz, 7.4 Hz, 1H), 8.09–8.41 (m, 10H), 10.7 (bs, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 114.2, 118.1, 122.0, 122.1, 124.8, 124.9, 125.4, 125.7, 125.8, 126.4, 126.7, 127.2, 128.0, 128.2, 131.4, 131.7, 133.6, 134.6, 135.2, 148.8, 172.7. Anal. Calcd for $C_{23}H_{15}NO_2$: C, 81.88; H, 4.48; N, 4.15. Found: C, 81.63; H, 4.74; N, 4.32.

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Supporting Information Available: Synthetic procedures, UV, fluorescence, and single-crystal analysis data of anthranilic acid **9**, and NMR spectra of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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[21] O1 and H2 undergo intermolecular hydrogen bonding to cocrystallizing DMF (not shown). O1···H–C(DMF) = 2.331 Å, H2···O–C(DMF) = 1.818 Å.

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