Regioselective Copper-Catalyzed C–N and C–S Bond Formation Using Amines, Thiols and Halobenzoic Acids

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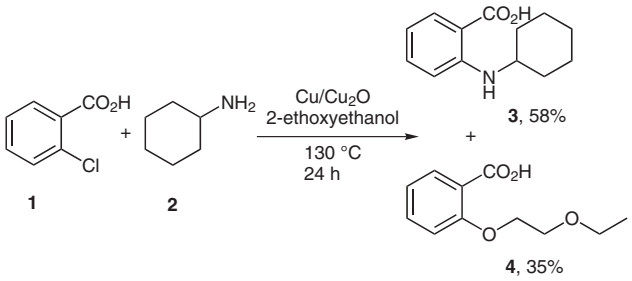
Abstract: A regioselective method for highly efficient C–N and C–S bond formation with 2-halobenzoic acids is described. The Cu/Cu_2O-catalyzed reaction is carried out in 2-ethoxyethanol or ethylene glycol diethyl ether and does not require the use of strong base or other additives. This procedure eliminates the need for acid protection, tolerates a wide range of functional groups and provides aromatic and aliphatic amines and sulfides in 81–99% yield.

Key words: amines, thiols, halobenzoic acids, carbon–heteroatom bond formation

The synthesis of flufenamic, mefenamic and other anthranilic acids has received increasing attention due to important biomedical applications.[1] Some aromatic amino acids possess anti-inflammatory properties and have been identified as promising candidates for the therapy of neurodegenerative disorders and amyloid diseases.[2] Incorporation of achiral amino acids into peptides has become a widespread tool to modify secondary protein structures and biochemical properties and to investigate peptide folding and chiral amplification.[3] The synthesis of anthranilic acids from unprotected 2-chlorobenzoic acid was first reported by Ullmann.[4] Since then, copper-catalyzed amination of a range of 2-halobenzoic acids has been accomplished[5] and a few cases of palladium-catalyzed amination of aryl halides bearing free carboxylic acid groups in *meta* and *para* positions have been identified.[5a,6] To date, anthranilic acids have mostly been prepared either by Ullmann–Jourdan coupling, which suffers from poor substrate scope and often involves high temperatures and stoichiometric amounts of copper reagents, or by Buchwald–Hartwig amination with alkyl 2-halobenzoates and subsequent ester cleavage.[7] Despite the significance of arylthiobenzoic acids to the pharmaceutical industry,[8] few examples of catalytic C–S bond formation with free benzoic acids are known.[9] Copper-catalyzed coupling of thiophenols with 2-halobenzamides[10] and chlorobenzoic acids[11] has been described. Recently, our laboratory decided to reinvestigate the scope of copper-catalyzed C–N bond formation using unprotected 2-halobenzoic acid and aniline derivatives.[12] We now wish to report a general approach to N-alkyl anthranilic acids and C–S bond formation with aliphatic and aromatic thiols.



Scheme 1 Copper-catalyzed amination of **1** using **2** in ethoxyethanol

In previous studies we learned that amination of 2-halobenzoic acids with aromatic amines, in the presence of catalytic amounts of copper and copper(I) oxide, proceeds with high yields when ethoxyethanol is used as solvent, whereas formation of *N*-alkyl anthranilic acids proved more difficult. For example, 2-chlorobenzoic acid (**1**), and aminocyclohexane (**2**), gave *N*-cyclohexyl anthranilic acid (**3**) in only 58% yield (Scheme 1). Chromatographic separation and NMR spectroscopic analysis of by-products revealed that 35% of ether **4** was formed; similar results were obtained when 2-bromobenzoic acid (**5**) was employed in the same reaction. In order to extend the copper-catalyzed amination procedure to aliphatic amines, we decided to replace 2-ethoxyethanol with ethylene glycol diethyl ether and optimized the catalyst amount and composition as well as temperature and reaction time. The best results were obtained when a solution of benzoic acid **1** and two equivalents of aliphatic amine **2** was heated to 130 °C for 24 hours in the presence of 4 mol% of copper(I) oxide, 9 mol% of copper powder and stoichiometric amounts of potassium carbonate. Under these conditions, anthranilic acid **3** was obtained in 93% yield (Table 1). The reaction could also be conducted at lower temperatures although longer reaction times were required. We found that the starting materials were not fully consumed after 24 hours when the Cu/Cu_2O-catalyzed coupling of **1** and **2** was carried out at 80 °C but **3** was still isolated in a remarkable 85% yield (entry 1). Reaction of acid **1** with other aliphatic amines furnished anthranilic acids **7**, **9** and **11** in 85–99% yield (entries 2–4). Incorporation of electron-deficient and electron-rich substituents into 2-chlorobenzoic acid did not significantly affect the results (entries 5–10); 3-chloro-4-nitrobenzoic acid (**14**) and 3,4-dimethoxy-2-chlorobenzoic acid (**16**), afford the corresponding amino acids **15** and **17** in 86% and 84% yield, respectively. The copper-catalyzed C–N bond formation

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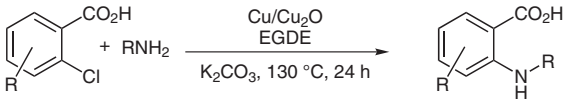
proceeded with excellent regioselectivity. We found that only the chloride adjacent to the carboxylate group was replaced, while halides located in *meta* and *para* positions did not react (entries 5, 8 and 10). This is consistent with previous reports from our laboratories and others.[12,13] While excellent results were obtained with primary amines, we obtained only moderate yields when secondary amines were employed in the same reaction. For example, coupling of 2-chlorobenzoic acid with *N*-methyl benzylamine and piperidine gave the corresponding tertiary amines in only 40% and 45% yield, respectively.[14]

Table 1 Copper-Catalyzed C–N Bond Formation with 2-Chlorobenzoic Acids[a]



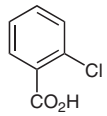
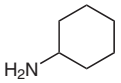
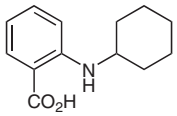
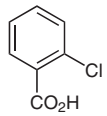
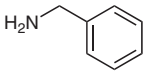
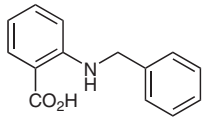
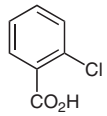
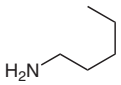
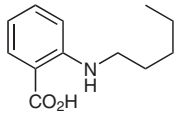
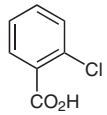
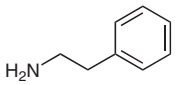
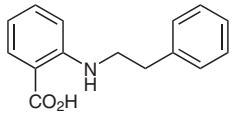
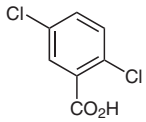
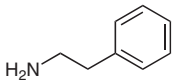
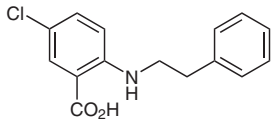
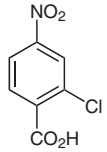
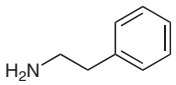
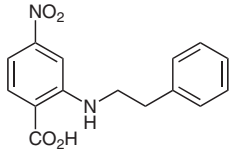
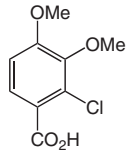
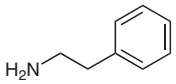
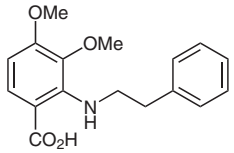
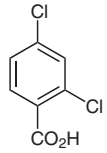
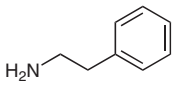
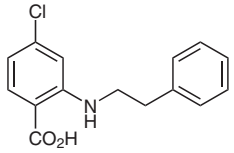
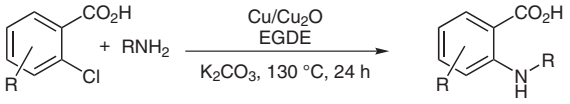
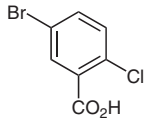
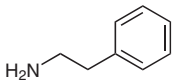
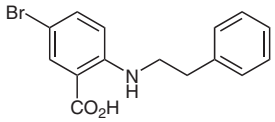
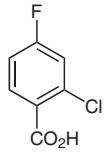
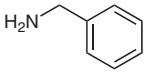
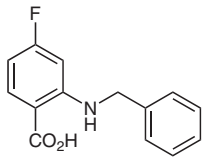
Entry	Aryl chloride	Amine	Product	Yield (%)
1	 **1**	 **2**	 **3**	93 (85)[b]
2	 **1**	 **6**	 **7**	>99
3	 **1**	 **8**	 **9**	85
4	 **1**	 **10**	 **11**	91
5	 **12**	 **10**	 **13**	94
6	 **14**	 **10**	 **15**	86
7	 **16**	 **10**	 **17**	84[c]
8	 **18**	 **10**	 **19**	82

Table 1 Copper-Catalyzed C–N Bond Formation with 2-Chlorobenzoic Acids[a] (continued)

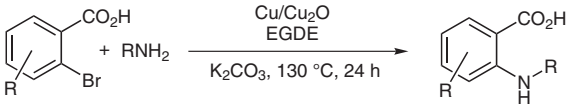


Entry	Aryl chloride	Amine	Product	Yield (%)
9	 **20**	 **10**	 **21**	84
10	 **22**	 **6**	 **23**	92

[a] Reaction conditions: 2-chlorobenzoic acid (8.8 mmol), amine (17.6 mmol), K_2CO_3 (8.8 mmol), Cu (0.8 mmol), Cu_2O (0.4 mmol), ethylene glycol diethyl ether (EGDE) (3 mL), 130 °C, 24 h.
[b] At 80 °C.
[c] For 12 h.

The same conditions were successfully applied to the reaction of bromobenzoic acids. As discussed above for the formation of *N*-alkyl anthranilic acids from chlorobenzoic acids, the amination was found to proceed with high regioselectivity and proved insensitive to the presence of electron-donating and electron-withdrawing groups in the aromatic ring (Table 2, entries 4, 6, 8 and 9). Our method affords significantly higher yields than other amination protocols. For example, anthranilic acid **7** can be prepared in quantitative amounts within 24 hours from both **1** and **5** (entry 2 in Table 1 and Table 2), which compares favorably with a previously reported CuI-catalyzed procedure providing **7** from 2-chloro- and 2-bromobenzoic acid in only 48% and 53% yield, respectively, after 48 to 72 hours.[5a]

Table 2 Copper-Catalyzed C–N Bond Formation with 2-Bromobenzoic Acids[a]



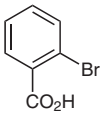
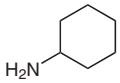
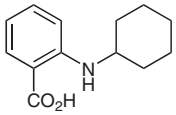
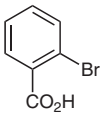
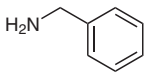
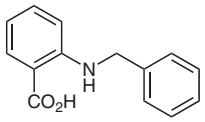
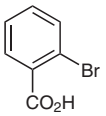
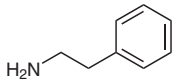
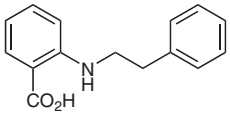
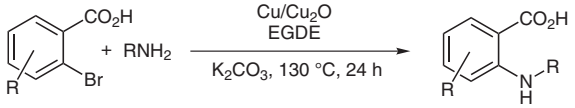
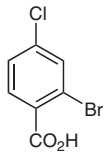
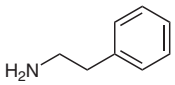
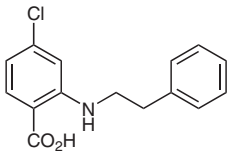
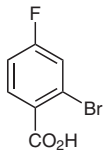
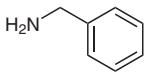
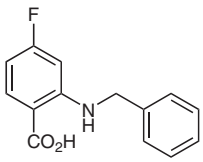
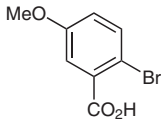
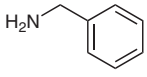
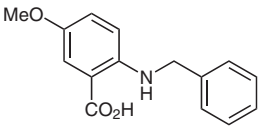
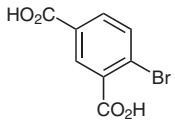
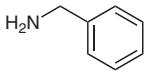
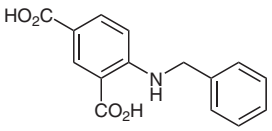
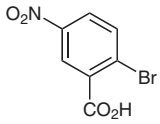
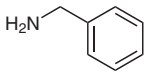
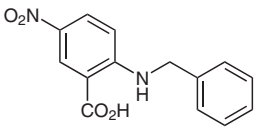
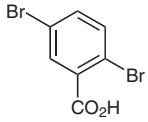
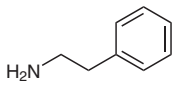
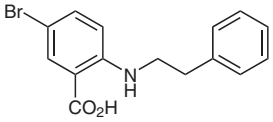
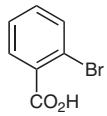
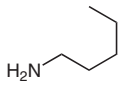
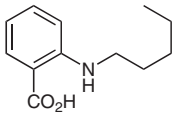
Entry	Aryl bromide	Amine	Product	Yield (%)
1	 **5**	 **2**	 **3**	82
2	 **5**	 **6**	 **7**	95
3	 **5**	 **10**	 **11**	91

Table 2 Copper-Catalyzed C–N Bond Formation with 2-Bromobenzoic Acids[a] (continued)

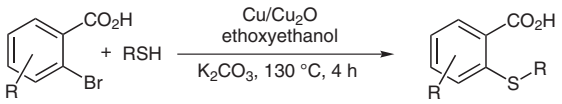


Entry	Aryl bromide	Amine	Product	Yield (%)
4	 **24**	 **10**	 **19**	94
5	 **25**	 **6**	 **23**	90
6	 **26**	 **6**	 **27**	85
7	 **28**	 **6**	 **29**	91
8	 **30**	 **6**	 **31**	81
9	 **32**	 **10**	 **21**	88
10	 **5**	 **8**	 **9**	97

[a] Reaction conditions: 2-bromobenzoic acid (8.8 mmol), amine (17.6 mmol), K_2CO_3 (8.8 mmol), Cu (0.8 mmol), Cu_2O (0.4 mmol), EGDE (3 mL), 130 °C, 24 h.

The same catalytic system is suitable for construction of C–S bonds with both aliphatic and aromatic thiols. We found that Cu/Cu_2O-catalyzed coupling of 2-bromobenzoic acids with thiols was considerably faster than C–N and C–O bond formation and aryl ether by-products such as **4** were not observed when the reaction was carried out in 2-ethoxyethanol. Product purification could be conveniently accomplished by precipitation from aqueous solution when 2-ethoxyethanol is used as solvent, whereas chromatographic purification was usually required when the coupling reaction was conducted in ethylene glycol diethyl ether. Although aliphatic thiols reacted more slowly than thiophenols, both diaryl and alkyl aryl sulfides were obtained in more than 90% yields (Table 3).[15] It is noteworthy that coupling products **34**, **38**, **44** and **50** were isolated in quantitative amounts (entries 1, 3, 6 and 9), which underscores the point that our procedure provides a valuable alternative to methods based on alkylation and arylation of thiosalicylic acid.[16]

Table 3 Copper-Catalyzed C–S Bond Formation with 2-Bromobenzoic Acids[a]



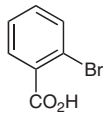
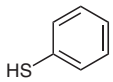
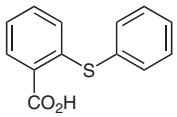
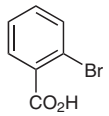
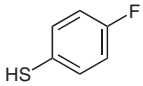
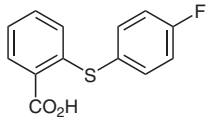
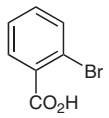
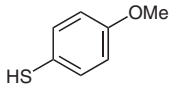
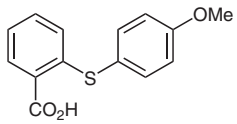
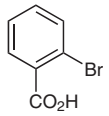
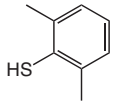
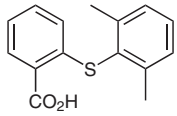
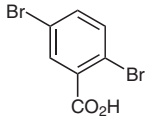
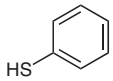
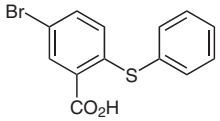
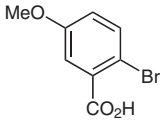
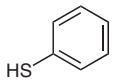
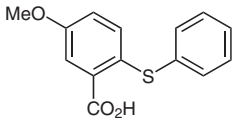
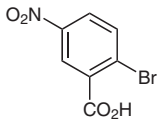
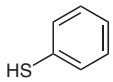
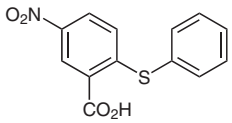
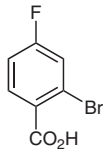
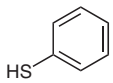
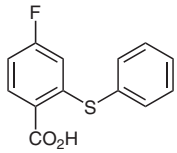
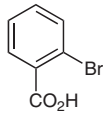
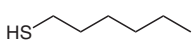
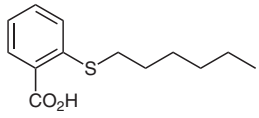
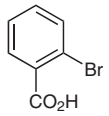
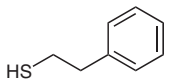
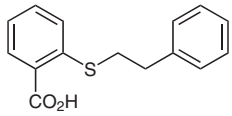
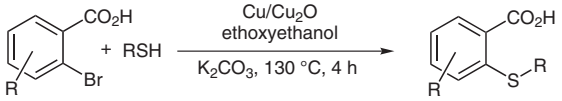
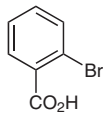
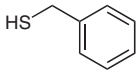
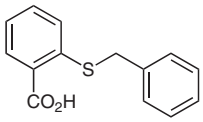
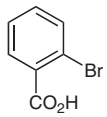
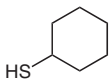
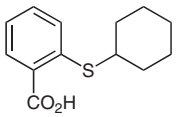
Entry	Aryl bromide	Thiol	Product	Yield (%)
1	 **5**	 **33**	 **34**	99
2	 **5**	 **35**	 **36**	92
3	 **5**	 **37**	 **38**	>99
4	 **5**	 **39**	 **40**	94[b]
5	 **41**	 **33**	 **42**	92
6	 **43**	 **33**	 **44**	>99
7	 **45**	 **33**	 **46**	92
8	 **47**	 **33**	 **48**	90
9	 **5**	 **49**	 **50**	>99[c]
10	 **5**	 **51**	 **52**	95[c]

Table 3 Copper-Catalyzed C–S Bond Formation with 2-Bromobenzoic Acids[a] (continued)



Entry	Aryl bromide	Thiol	Product	Yield (%)
11	 **5**	 **53**	 **54**	97[c]
12	 **5**	 **55**	 **56**	92[c]

[a] Reaction conditions: 2-bromobenzoic acid (8.8 mmol), thiol (8.8 mmol), K_2CO_3 (8.8 mmol), Cu (0.8 mmol), Cu_2O (0.4 mmol), ethoxyethanol (3 mL), 130 °C, 4 h.
[b] Reaction performed for 6 h.
[c] Reaction performed for 12 h.

In summary, we have developed a method for highly efficient Cu/Cu_2O-catalyzed C–N and C–S bond formation with 2-halobenzoic acids. The reaction tolerates a wide range of functional groups and provides aromatic and aliphatic amines and sulfides in 81–99% yield. The remarkable regioselectivity, experimental simplicity and the low cost of the catalytic system are attractive features of this procedure, which may prove useful for the synthesis of pharmaceutically relevant anthranilic acids and benzoic acid derived sulfides.

All chemicals were of reagent grade and were purchased from Aldrich. All reactions were carried out under nitrogen atmosphere under anhydrous conditions. Flash chromatography was performed on silica gel (Merck Kieselgel 60, particle size 0.032–0.063 mm). NMR spectra were obtained at 300 MHz (^{1}H NMR) and 75 MHz (^{13}C NMR) on a Varian FT-NMR spectrometer using $CDCl_3$ as solvent unless noted otherwise. Chemical shifts are reported in ppm relative to TMS. Combustion analysis was performed on a 2400 Perkin Elmer CHN elemental analyzer.

Coupling with Amines; General Procedure

A mixture of amine (17.6 mmol), 2-halobenzoic acid (8.8 mmol), K_2CO_3 (1.21 g, 8.8 mmol), Cu powder (51 mg, 0.8 mmol), Cu_2O (38 mg, 0.4 mmol) and ethylene glycol diethyl ether (3 mL) was heated to 130 °C for 24 h under nitrogen. The reaction was cooled to r.t. and the solvent was removed under reduced pressure. The residue was poured into H_2O (30 mL), treated with charcoal and the mixture was filtrated through celite. Acidification of the filtrate (pH 5) with dilute HCl gave a precipitate, which was dissolved in aq Na_2CO_3 (5%, 100 mL) and the solution was filtered through Celite and subjected to precipitation as described above. Flash chromatography (EtOAc–hexane, 30%) afforded the desired *N*-alkyl anthranilic acids.

***N*-Cyclohexylanthranilic Acid (3)[12b]**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28–1.44 (m, 5 H), 1.62–1.65 (m, 1 H), 1.76–1.80 (m, 2 H), 2.02–2.05 (m, 2 H), 3.35–3.43 (m, 1 H), 6.56 (ddd, *J* = 8.6, 8.1, 1.0 Hz, 1 H), 6.71 (d, *J* = 8.6 Hz, 1 H), 7.34 (ddd, *J* = 8.6, 8.1, 1.7 Hz, 1 H), 7.98 (dd, *J* = 8.1, 1.7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.0, 26.1, 33.2, 50.9, 108.6, 112.1, 114.4, 133.2, 135.8, 151.3, 174.7.

***N*-Benzylanthranilic Acid (7)[12b]**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.48 (s, 2 H), 6.18 (dd, *J* = 8.3, 8.3 Hz, 2 H), 7.26–7.35 (m, 6 H), 7.98 (dd, *J* = 7.8, 1.2 Hz, 1 H), 8.05 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 46.9, 109.0, 111.9, 115.1, 126.9, 127.2, 128.7, 132.6, 135.6, 138.7, 151.6, 173.5.

***N*-Pentylanthranilic Acid (9)[17]**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 5.4 Hz, 3 H), 1.37–1.41 (m, 4 H), 1.66–1.72 (m, 2 H), 3.19 (t, *J* = 7.1 Hz, 2 H), 6.58 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1 H), 6.68 (d, *J* = 8.1 Hz, 1 H), 7.48 (ddd, *J* = 8.1, 6.8, 1.7 Hz, 1 H), 7.98 (dd, *J* = 8.1, 1.7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.7, 23.1, 29.5, 30.0, 43.5, 109.1, 112.0, 115.0, 133.4, 136.3, 152.6, 175.0.

***N*-Phenethylanthranilic Acid (11)[12b]**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.98 (t, *J* = 7.1, 2 H), 3.47 (t, *J* = 7.1 Hz, 2 H), 6.60 (ddd, *J* = 9.5 Hz, 7.1 Hz, 1.0 Hz, 1 H), 6.71 (d, *J* = 8.6 Hz, 1 H), 7.22–7.42 (m, 6 H), 8.00 (dd, *J* = 1.7 Hz, 8.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.9, 44.8, 109.1, 111.7, 115.1, 126.9, 129.0, 129.2, 133.1, 136.0, 139.4, 151.9, 174.7.

5-Chloro-*N*-phenethylanthranilic Acid (13)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.95 (t, *J* = 6.8 Hz, 2 H), 3.40 (t, *J* = 6.8 Hz, 2 H), 6.64 (d, *J* = 9.0 Hz, 1 H), 7.19–7.35 (m, 6 H), 7.90 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.0, 45.1, 110.1, 113.5, 119.9, 127.3, 129.3, 129.4, 132.3, 136.2, 139.4, 150.7, 173.9.

Anal. Calcd for $C_{15}H_{14}ClNO_2$: C, 65.34; H, 5.12; N, 5.08. Found: C, 65.28; H, 5.21; N, 5.02.

4-Nitro-*N*-phenethylanthranilic Acid (15)[18]

^{1}H NMR (300 MHz, CD_3OD): δ = 3.16 (t, *J* = 6.8 Hz, 2 H), 3.54 (s, 1 H), 3.72 (t, *J* = 6.8 Hz, 2 H), 7.38 (m, 1 H), 7.44–7.48 (m, 5 H), 7.66 (d, *J* = 2.2 Hz, 1 H), 8.23 (d, *J* = 8.8 Hz, 1 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 35.1, 44.2, 105.3, 107.8, 114.9, 126.4, 128.5, 128.7, 133.5, 139.2, 151.5, 152.0, 169.2.

3,4-Dimethoxy-*N*-phenethylanthranilic Acid (17)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.90 (t, *J* = 7.3 Hz, 2 H), 3.67 (t, *J* = 7.3 Hz, 2 H), 3.72 (s, 3 H), 3.90 (s, 3 H), 6.43 (d, *J* = 9.0 Hz, 1 H), 7.19–7.30 (m, 5 H), 7.84 (d, *J* = 9.0 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.7, 49.0, 56.5, 60.7, 103.3, 109.6, 126.9, 129.1, 129.5, 129.8, 138.8, 139.9, 146.4, 158.6, 173.0.

Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.43; H, 6.67; N, 4.60.

4-Chloro-*N*-phenethylanthranilic Acid (19)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.98 (t, *J* = 7.1 Hz, 2 H), 3.44 (t, *J* = 7.1 Hz, 2 H), 6.58 (dd, *J* = 8.6, 2.0 Hz, 1 H), 6.68 (d, *J* = 2.0 Hz, 1 H), 7.22–7.28 (m, 3 H), 7.31–7.37 (m, 2 H), 7.73 (br s, 1 H), 7.88 (d, *J* = 8.8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.0, 45.1, 107.9, 111.8, 115.9, 127.4, 129.4, 129.5, 134.6, 139.3, 142.7, 152.8, 173.9.

Anal. Calcd for $C_{15}H_{14}ClNO_2$: C, 65.34; H, 5.12; N, 5.08. Found: C, 65.01; H, 5.50; N, 5.00.

5-Bromo-*N*-phenethylanthranilic Acid (21)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.99 (t, *J* = 7.3 Hz, 2 H), 3.48 (t, *J* = 7.3 Hz, 2 H), 6.60 (ddd, *J* = 7.3, 7.1, 1.0 Hz, 1 H), 6.72 (d, *J* = 8.3 Hz, 1 H), 7.20–7.43 (m, 5 H), 7.99 (dd, *J* = 8.1, 1.7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.1, 45.0, 109.4, 112.0, 115.4, 127.2, 129.3, 129.5, 133.3, 136.3, 139.7, 152.2, 175.0.

Anal. Calcd for $C_{15}H_{14}BrNO_2$: C, 56.27; H, 4.41; N, 4.37. Found: C, 56.10; H, 4.80; N, 4.05.

4-Fluoro-*N*-benzylanthranilic Acid (23)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.44 (d, *J* = 4.6 Hz, 2 H), 6.27–6.36 (m 2 H), 7.29–7.37 (m, 5 H), 8.00 (dd, *J* = 9.0, 6.8 Hz, 1 H), 8.11 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 47.7, 98.8 (d, $J_{C–F}$ = 25.7 Hz), 103.9 (d, $J_{C–F}$ = 22.7 Hz), 106.4 (d, $J_{C–F}$ = 1.5 Hz), 127.6, 128.1, 129.5, 136.1 (d, $J_{C–F}$ = 11.8 Hz), 138.6, 154.4 (d, $J_{C–F}$ = 12.8 Hz), 168.6 (d, $J_{C–F}$ = 253.1 Hz), 174.0.

Anal. Calcd for $C_{14}H_{12}FNO_2$: C, 68.56; H, 4.93; N, 5.71. Found: C, 68.11; H, 4.92; N, 5.98.

5-Methoxy-*N*-benzylanthranilic Acid (27)

^{1}H NMR (300 MHz, CD_3OD): δ = 3.75 (s, 3 H), 4.51 (s, 2 H), 6.73 (d, *J* = 9.3 Hz, 1 H), 7.09 (dd, *J* = 9.0, 3.2 Hz, 1 H), 7.33 (m, 1 H), 7.36–7.40 (m, 4 H), 7.48 (d, *J* = 3.2 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 46.3, 55.4, 110.4, 113.2, 114.6, 122.5, 126.9, 127.0, 128.5, 139.7, 145.7, 148.9, 169.7.

Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.88; H, 6.01; N, 5.47.

5-Carboxy-*N*-benzylanthranilic Acid (29)

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.63 (s, 2 H), 6.83 (d, *J* = 8.8 Hz, 1 H), 7.35–7.44 (m, 5 H), 7.90 (d, *J* = 8.8 Hz, 1 H), 8.54 (s, 1 H), 8.89 (br s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 45.7, 110.1, 111.4, 116.3, 127.1, 128.6, 134.1, 134.9, 138.7, 153.4, 166.8, 169.6.

Anal. Calcd for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.13; H, 4.96; N, 5.02.

5-Nitro-*N*-benzylanthranilic Acid (31)[19]

^{1}H NMR (300 MHz, CD_3OD): δ = 4.77 (s, 2 H), 6.99 (d, *J* = 9.3 Hz, 1 H), 7.46–7.55 (m, 5 H), 8.28 (d, *J* = 9.0 Hz, 1 H), 8.99 (br s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 45.8, 112.0, 127.0, 127.2, 128.6, 129.1, 135.2, 137.9, 154.5.

Coupling with Thiols; General Procedure

A mixture of thiol (11.4 mmol), 2-bromobenzoic acid (8.8 mmol), K_2CO_3 (1.21 g, 8.8 mmol), Cu powder (51 mg, 0.8 mmol), Cu_2O (38 mg, 0.4 mmol) and 2-ethoxyethanol (3 mL) was heated to 130 °C for 4 h. The reaction was cooled to r.t. and the solvent was removed under reduced pressure. The residue was poured into H_2O (30 mL), treated with charcoal and the mixture was filtrated through Celite. Acidification of the filtrate with diluted HCl (pH 5) gave a precipitate, which was dissolved in aq Na_2CO_3 (5%, 100 mL) and the solution was filtrated through Celite and subjected to precipitation as described above. Precipitation upon acidification gave pure sulfides.

2-(Phenylthio)benzoic Acid (34)[20]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.84 (d, *J* = 8.1 Hz, 1 H), 7.18 (dd, *J* = 7.7, 7.7 Hz, 1 H), 7.31 (ddd, *J* = 7.3, 7.3, 1.5 Hz, 1 H), 7.45–7.49 (m, 3 H), 7.59–7.65 (m, 2 H), 8.17 (dd, *J* = 7.7, 1.2 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 124.9, 125.9, 127.8, 130.0, 130.5, 132.7, 132.9, 133.9, 136.5, 145.4, 172.7.

2-(4-Fluorophenylthio)benzoic Acid (36)

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.78 (dd, *J* = 8.3, 1.0 Hz, 1 H), 7.30 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1 H), 7.40–7.50 (m, 3 H), 7.65–7.72 (m, 2 H), 8.02 (dd, *J* = 7.8, 1.5 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 117.2 (d, $J_{C–F}$ = 21.7 Hz), 124.6, 126.4, 127.3, 127.7 (d, $J_{C–F}$ = 3.0 Hz), 130.9, 132.5, 137.9 (d, $J_{C–F}$ = 8.6 Hz),142.0, 163.2 (d, $J_{C–F}$ = 247.8 Hz), 167.3.

Anal. Calcd for $C_{13}H_9FO_2S$: C, 62.89; H, 3.65. Found: C, 62.78; H, 3.81.

2-(4-Methoxyphenylthio)benzoic Acid (38)[21]

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.91 (s, 3 H), 6.74 (d, *J* = 8.1 Hz, 1 H), 7.16 (d, *J* = 8.5 Hz, 2 H), 7.25 (dd, *J* = 7.3, 7.3 Hz, 1 H), 7.43 (dd, *J* = 7.3, 7.3 Hz, 1 H), 7.56 (d, *J* = 8.5 Hz, 2 H), 8.01 (d, *J* = 7.6 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 55.4, 115.7, 122.0, 124.1, 125.9, 126.8, 130.9, 132.3, 137.4, 143.4, 160.3, 167.3.

2-(2,6-Dimethylphenylthio)benzoic Acid (40)

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.40 (s, 6 H), 6.49 (d, *J* = 8.1 Hz, 1 H), 7.26 (dd, *J* = 7.3, 7.3 Hz, 1 H), 7.36–7.44 (m, 4 H), 8.04 (dd, *J* = 7.6, 1.2 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.1, 124.0, 124.2, 127.7, 128.7, 129.7, 130.4, 131.3, 132.4, 140.8, 143.3, 167.5.

Anal. Calcd for $C_{15}H_{14}SO_2$: C, 69.74; H, 5.46. Found: C, 69.57; H, 5.66.

5-Bromo-2-(phenylthio)benzoic Acid (42)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.67 (d, *J* = 8.8 Hz, 1 H), 7.37 (dd, *J* = 8.8, 2.2 Hz, 1 H), 7.44–7.50 (m, 3 H), 7.54–7.60 (m, 2 H), 8.25 (d, *J* = 2.4 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 118.3, 127.2, 129.5, 130.3, 130.7, 132.1, 135.3, 136.5, 136.7, 144.8, 171.2.

Anal. Calcd for $C_{13}H_9BrO_2S$: C, 50.50; H, 2.93. Found: C, 50.12; H, 3.21.

2-(Phenylthio)-5-methoxybenzoic Acid (44)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.85 (s, 3 H), 6.93 (dd, *J* = 13.4, 9.0 Hz, 2 H), 7.41–7.53 (m, 3 H), 7.54–7.56 (m, 2 H), 7.69 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.2, 116.6, 121.1, 128.1, 129.3, 130.3, 131.0, 134.2, 134.5, 135.2, 157.9, 171.9.

Anal. Calcd for $C_{14}H_{12}O_3S$: C, 64.60; H, 4.65. Found: C, 64.48; H, 4.88.

2-(Phenylthio)-5-nitrobenzoic Acid (46)[22]

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.96 (d, J = 9.0 Hz, 1 H), 7.68–7.74 (m, 5 H), 8.27 (d, J = 8.8 Hz, 1 H), 8.75 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 125.7, 126.5, 127.0, 127.1, 130.1, 130.4, 130.5, 135.6, 143.8, 151.8, 165.8.

2-(Phenylthio)-4-fluorobenzoic Acid (48)

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.38 (dd, J = 10.5, 2.4 Hz, 1 H), 7.13 (ddd, J = 8.1, 8.1, 2.7 Hz, 1 H), 7.63–7.71 (m, 5 H), 8.12 (dd, J = 8.8, 6.1 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 111.8 (d, J_{C-F} = 21.7 Hz), 112.8 (d, J_{C-F} = 25.7 Hz), 130.0, 130.3, 131.3, 135.6, 147.0, 164.2 (d, J_{C-F} = 251.8 Hz).

Anal. Calcd for $C_{13}H_9O_2S$: C, 62.89; H, 3.65. Found: C, 62.63; H, 3.99.

2-(Hexylthio)benzoic Acid (50)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, J = 6.8 Hz, 3 H), 1.29–1.35 (m, 4 H), 1.44–1.53 (m, 2 H), 1.69–1.80 (m, 2 H), 2.93 (t, J = 7.3 Hz, 2 H), 7.18 (ddd, J = 7.7, 7.3, 1.2 Hz, 1 H), 7.33 (d, J = 7.7 Hz, 1 H), 7.48 (ddd, J = 8.1, 7.3, 1.5 Hz, 1 H), 8.13 (dd, J = 8.1, 1.7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.1, 23.6, 29.2, 30.0, 32.5, 33.3, 124.8, 126.7, 127.3, 133.7, 134.2, 144.4, 172.9.

Anal. Calcd for $C_{13}H_{18}O_2S$: C, 65.51; H, 7.61. Found: C, 65.22; H, 7.92.

2-(Phenethylthio)benzoic Acid (52)[23]

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.01 (t, J = 7.1 Hz, 2 H), 3.28 (t, J = 7.1 Hz, 2 H), 7.28–7.34 (m, 2 H), 7.37–7.41 (m, 4 H), 7.55 (d, J = 7.8 Hz, 1 H), 7.61 (ddd, J = 6.8, 6.8, 1.5 Hz, 1 H), 7.98 (dd, J = 7.8, 1.5 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 32.3, 33.9, 123.8, 125.6, 126.3, 128.4, 130.9, 132.3, 139.8, 140.2, 140.6, 167.5.

2-(Benzylthio)benzoic Acid (54)[16d]

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.30 (s, 2 H), 7.31 (m, 1 H), 7.37 (d, J = 7.1 Hz, 1 H), 7.43 (dd, J = 7.3, 7.3 Hz, 2 H), 7.51–7.60 (m, 4 H), 8.01 (d, J = 8.1 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 35.5, 123.7, 125.4, 126.9, 127.4, 128.2, 128.9, 130.7, 132.1, 136.3, 141.0, 167.2.

2-(Cyclohexylthio)benzoic Acid (56)

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.33–1.51 (m, 5 H), 1.69 (m, 1 H), 1.79–1.83 (m, 2 H), 2.03–2.07 (m, 2 H), 3.44 (m, 1 H), 7.29 (ddd, J = 2.4, 6.1, 8.1 Hz, 1 H), 7.53–7.60 (m, 2 H), 7.87 (d, J = 7.3 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 25.3, 25.4, 32.4, 42.6, 124.2, 127.3, 130.4, 131.7, 138.4, 167.7.

Anal. Calcd for $C_{13}H_{16}O_2S$: C, 66.07; H, 6.82. Found: C, 65.99; H, 7.02.

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