Efficient copper-catalyzed N-arylations of nitrogen-containing heterocycles and aliphatic amines in water†

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A simple and efficient copper-catalyzed method has been developed for N-arylations of nitrogen-containing heterocycles and aliphatic amines in water. The protocol uses (1*E*,2*E*)-oxalaldehyde dioxime (OADO) as the ligand, and water as the solvent, and shows good tolerance towards various functional groups.

Introduction

The formation of transition metal catalyzed carbon–nitrogen bonds *via* cross-coupling reactions plays an important role in the preparation of numerous important products in biological, pharmaceutical and material sciences.[1] The copper-catalyzed Ullmann-type reaction[2] is a traditional method to assemble these compounds. For a long time, high reaction temperatures, stoichiometric amounts of copper reagents and low tolerance of functional groups prevented further development of these methods.[4a] However, significant achievements in the palladium-catalyzed N-arylation of amines have been made under mild conditions.[3] Considering the readily availability and low toxicity of copper catalysts and their ligands, the development of a cheaper copper-catalyzed system enabling N-arylation of amines has become an important goal. In the past decade, great progress in the copper-catalyzed Ullmann-type reaction has been made, which has relied on the utilization of certain bidentate additives.[4]

Water is the most economical and environmentally friendly solvent possible,[5] and the wide applications of N-arylated compounds in many fields have stimulated researches into the development of new strategies for their synthesis in water. However, synthesis of organic molecules in water entails the additional challenges of water tolerance for the catalyst/ligand systems and the associated problems of substrate solubility and reactivity.[6] Recently, Zhou and co-workers reported copper-catalyzed N-arylation of imidazoles in water, but the ligands were not readily available, and scope of substrates was limited.[7] In continuation of our endeavors to develop copper-catalyzed cross couplings in organic solvents[8] and in aqueous media,[9] herein we report a simple, practical and efficient copper-catalyzed N-arylation of nitrogen-containing heterocycles and aliphatic amines using readily available (1*E*,2*E*)-oxalaldehyde dioxime (OADO) as the ligand, and environmentally benign water as the solvent.

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† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra of compounds **3a–p** and **3a′–o′**. See DOI: 10.1039/c002172e

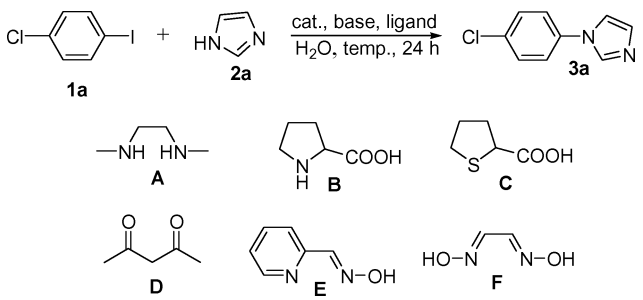
Results and discussion

Copper-catalyzed N-arylations of nitrogen-containing heterocycles in water

As shown in Table 1, 1-chloro-4-iodobenzene and 1*H*-imidazole were chosen as the model substrates to optimize reaction conditions including catalysts, ligands and bases under a nitrogen atmosphere. Six ligands were tested using 10 mol% of CuBr as the catalyst, 10 mol% of tetrabutylammonium bromide as the phase transfer catalyst (PTC) and 2 equiv of NaOH as the base (relative to the amount of 1-chloro-4-iodobenzene) in water at 100 °C (entries 1–6), ligand (1*E*,2*E*)-oxalaldehyde dioxime (OADO) providing the highest yield (entry 6). No target product was observed in the absence of ligand (entry 7). Other bases, KOH (entry 8), CsOH (entry 9) and K_3PO_4 (entry 10), were investigated, and NaOH showed better activity (compare entries 6 and 8–10). Lower reaction temperatures led to lower yields (entries 11 and 12). Copper salts were screened (compare entries 6 and 13–17), and CuCl was found be the best (entry 14). The ratio of catalyst, ligand and phase transfer catalyst was varied, and the catalyst system using 5 mol% CuCl, 10 mol% OADO, 10 mol% tetrabutylammonium bromide and 2 equiv NaOH found to be optimal at 100 °C.

As shown in Table 2, we attempted the coupling reactions of various aryl halides with nitrogen-containing heterocycles in water under our standard conditions, and the examined substrates provided the corresponding target products in good to excellent yields. For aryl halides, substrates containing electron-withdrawing groups showed higher activity than those containing electron-donating groups, and the reactivity order of the aryl halides was iodides > bromides > chlorides. For example, the coupling reaction of 1-bromo-3-iodobenzene with 1*H*-pyrrole yielded the target product (**3d**) containing bromine on the benzene ring (entry 4). The aryl chloride showed low reactivity; however, addition of KI promoted the reaction. For example, cross-coupling of 1-chloro-3-nitrobenzene (**1n**) with

Table 1 Copper-catalyzed coupling of 1-chloro-4-iodobenzene with 1*H*-imidazole: optimization of conditions[a]



Entry	Catalyst (mol%)	Ligand (mol%)	$^{n}Bu_4NBr$ (mol%)	Base	Temp. (°C)	Yield (%)[b]
1	CuBr (10)	A (20)	10	NaOH	100	51
2	CuBr (10)	B (20)	10	NaOH	100	32
3	CuBr (10)	C (20)	10	NaOH	100	21
4	CuBr (10)	D (20)	10	NaOH	100	78
5	CuBr (10)	E (20)	10	NaOH	100	70
6	CuBr (10)	F (20)	10	NaOH	100	89
7	CuBr (10)	—	10	NaOH	100	0
8	CuBr (10)	F (20)	10	KOH	100	82
9	CuBr (10)	F (20)	10	CsOH	100	81
10	CuBr (10)	F (20)	10	K_3PO_4	100	77
11	CuBr (10)	F (20)	10	NaOH	25	0
12	CuBr (10)	F (20)	10	NaOH	60	43
13	CuI (10)	F (20)	10	NaOH	100	89
14	CuCl (10)	F (20)	10	NaOH	100	92
15	$CuSO_4$ (10)	F (20)	10	NaOH	100	73
16	$Cu(OAc)_2$ (10)	F (20)	10	NaOH	100	64
17	Cu_2O (2.5)	F (10)	10	NaOH	100	59
18	CuCl (10)	F (20)	—	NaOH	100	0
19	CuCl (10)	F (20)	5	NaOH	100	91
20	**CuCl (5)**	**F (10)**	**10**	**NaOH**	**100**	**92**

[a] Reaction conditions: 1-chloro-4-iodobenzene (1 mmol), 1*H*-imidazole (1.2 mmol), catalyst (0.1 mmol), base (2 mmol), water (1.5 mL), nitrogen atmosphere, 24 h. [b] Isolated yield.

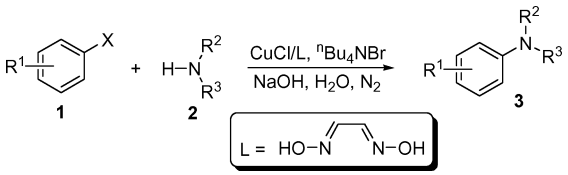
1*H*-imidazole (**2a**) provided 1-(3-nitrophenyl)-1*H*-imidazole (**3p**) in 66% yield in the presence of 1 equiv of KI (entry 16). 2-Bromobenzoic acid (**1m**) exhibited high activity (97% yield) (entry 15), and the results showed an *ortho*-substituent effect of the carboxyl group.[8r] The N-arylations above tolerated various functional groups, including C–Cl bonds (entries 1 and 2), a C–F bond (entry 3), C–Br bonds (entries 4 and 13), nitro groups (entries 8–10 and 16), a carbonyl (entry 11), a carboxyl (entry 15) and ether groups (entries 8 and 13).

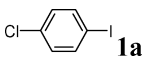
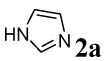
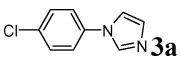
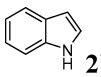
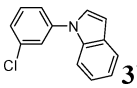
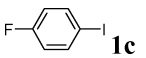
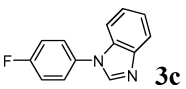
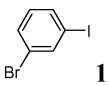
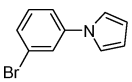
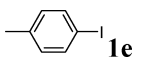
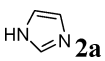
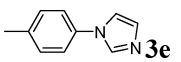
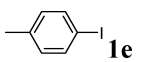
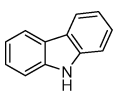
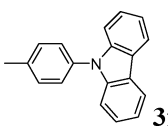
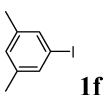
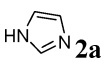
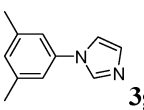
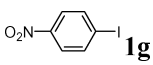
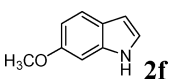
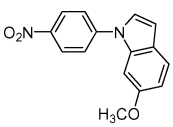
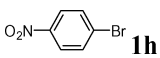
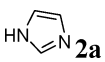
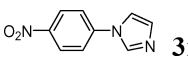
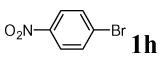
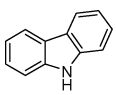
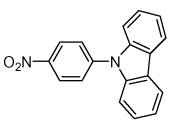
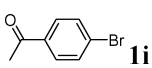
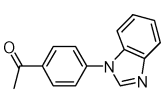
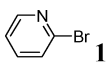
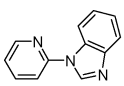
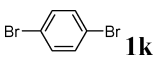
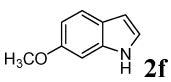
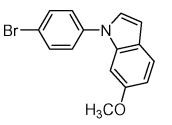
Copper-catalyzed N-arylations of aliphatic amines in water

A similar optimization process was performed for copper-catalyzed N-arylations of aliphatic amines in water. 1-Chloro-4-iodobenzene and 3-aminopropanol were applied as the model substrates to optimize reaction conditions including catalysts, ligands and bases under nitrogen atmosphere. Four copper salts (Cu_2O, CuI, CuBr and CuCl) were investigated (entries 1–4), and CuBr was the most effective (entry 3). The other ligands (D and F) were tested (entries 5 and 6), with OADO displaying the highest activity (entry 6). Several bases were compared (entries 6–9), and NaOH was found to be the best choice (entry 6). Therefore, the optimal conditions for copper-catalyzed N-arylations of aliphatic amines in water are as follows: 5 mol% of CuBr as the catalyst, 10 mol% of OADO as the ligand, 10 mol% of tetrabutylammonium bromide as the phase transfer catalyst, and 2 equiv of NaOH as the base at 100 °C.

The scope of the reaction was investigated under our optimized conditions. As shown in Table 4, most of the substrates examined provided good to excellent yields at 100 °C. For the aryl halides, the substrates containing electron-withdrawing groups showed higher reactivity than those containing electron-donating groups, and the reactivity order of the aryl halides was iodides > bromides > chlorides. Aryl halides, even aryl chlorides with a carboxyl group *ortho* to the halogen, all provided higher yields (entries 12–15). In fact, aryl chlorides were previously found to be poor substrates for copper-catalyzed Ullmann-type couplings,[4] and the results showed an *ortho*-substituent effect[8r] of the carboxyl group during N-arylation, as shown in Scheme 1. Coordination of 2-chlorobenzoic acid (**1s**) with CuBr first forms **I** in the presence of base (NaOH). Oxidation addition of **I** provides complex **II**, and exchange of amine with Br in **II** gives **III**. Reduction–elimination of **III** leads to **IV**, treatment of **IV** with NaOH gives **V** with release of the copper catalyst, and acidification of **V** affords the target product (**3n′**). The N-arylations above tolerated various functional groups, including C–Cl bonds (entries 1–4), a C–F bond (entry 5), a C–Br bond (entry 10), an ether (entry 8), nitro groups (entries 11 and 12) and carboxyl groups (entries 12–15) in the aryl halides, and hydroxy (entries 2, 6, 12 and 15), and carboxyl groups (entries 4 and 7) in the amines.

Table 2 Copper-catalyzed N-arylation of nitrogen-containing heterocycles in water[a]



Entry	1	2	Product	Yield (%)[b]
1	 1a	 2a	 3a	92
2	 1b	 2b	 3b	93
3	 1c	 2c	 3c	83
4	 1d	 2d	 3d	75
5	 1e	 2a	 3e	88
6	 1e	 2e	 3f	89
7	 1f	 2a	 3g	87
8	 1g	 2f	 3h	96
9	 1h	 2a	 3i	85
10	 1h	 2e	 3j	85
11	 1i	 2c	 3k	62
12	 1j	 2c	 3l	87
13	 1k	 2f	 3m	79

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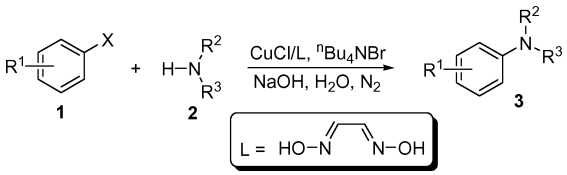
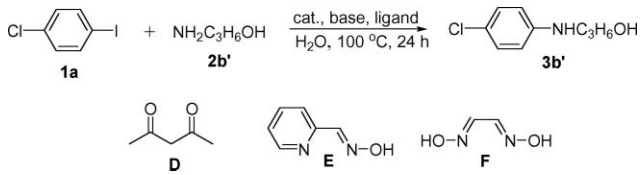


Entry	1	2	Product	Yield (%)[b]
14	1l	2d	3n	69
15	1m	2a	3o	97
16	1n	2a	3p	66[c]

[a] Reaction conditions: **1** (1 mmol), **2** (1.2 mmol), CuCl (0.05 mmol), $^{n}Bu_4NBr$ (0.1 mmol), ligand (0.1 mmol), NaOH (3 mmol for entry 15; 2 mmol for others), water (1.5 mL), 100 °C, nitrogen atmosphere, 24 h. [b] Isolated yield. [c] Addition of KI (1 mmol).

Table 3 Copper-catalyzed coupling of 1-chloro-4-iodobenzene with 3-aminopropanol: optimization of conditions[a]

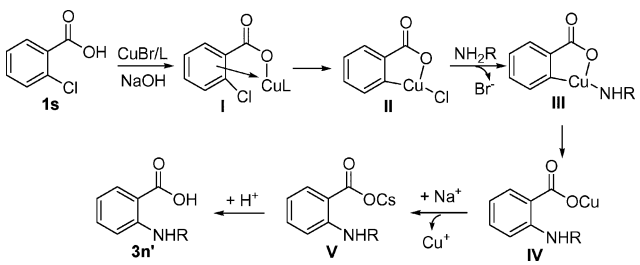


Entry	Catalyst (mol%)	Ligand	Base	Yield [%][b]
1	Cu_2O (2.5)	E	NaOH	77
2	CuI (5)	E	NaOH	78
3	CuBr (5)	E	NaOH	83
4	CuCl (5)	E	NaOH	61
5	CuBr (5)	D	NaOH	61
6	**CuBr (5)**	**F**	**NaOH**	**85**
7	CuBr (5)	F	KOH	71
8	CuBr (5)	F	CsOH	73
9	CuBr (5)	F	K_3PO_4	76

[a] Reaction conditions: 1-chloro-4-iodobenzene (1 mmol), 3-aminopropanol (1.2 mmol), catalyst (0.025 mmol for Cu_2O; 0.05 mmol for other copper salts), ligand (0.1 mmol), $^{n}Bu_4NBr$ (0.1 mmol), base (2 mmol), water (1.5 mL), nitrogen atmosphere, 24 h. [b] Isolated yield.

Conclusion

We have developed a simple and efficient copper-catalyzed method for N-arylation of nitrogen-containing heterocycles and aliphatic amines in water. The protocol uses (1*E*,2*E*)-oxalaldehyde dioxime (OADO) as the ligand of copper-catalyst, environmentally friendly water as the solvent, and the cross-couplings performed well at 100 °C. The method has good tolerance towards various functional groups in the substrates, and we hope that it will attract attention from industrial and academic researchers.



Scheme 1 Possible mechanism for amination of 2-chlorobenzoic acid (**1s**).

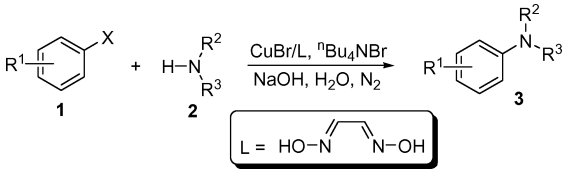
Experimental

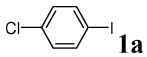
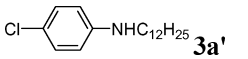
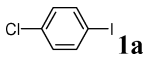
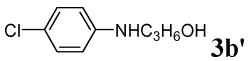
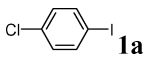
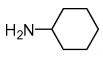
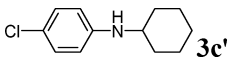
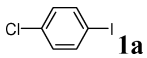
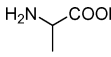
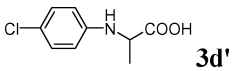
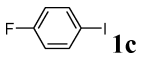
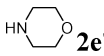
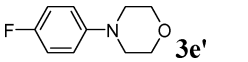
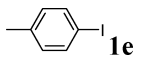
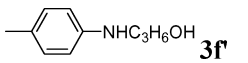
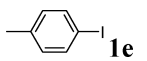
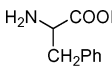
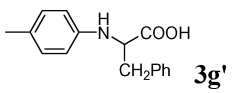
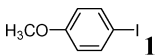
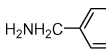
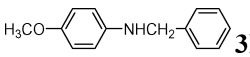
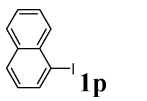
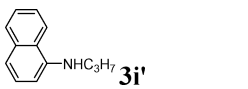
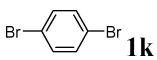
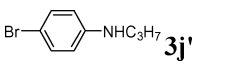
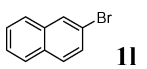
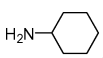
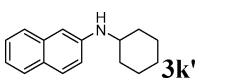
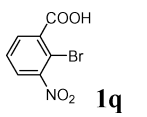
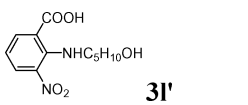
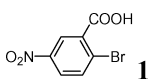
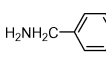
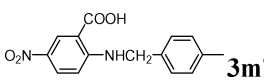
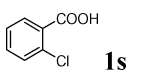
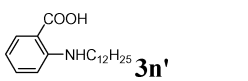
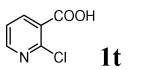
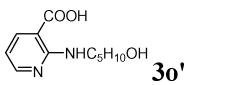
All reagents and solvents were obtained from commercial suppliers and used without further purification. CuCl and CuBr were purchased from Alfa Aesar. All reagents were weighed and handled in air at room temperature. Column chromatography was performed on silica gel (200–300 mesh). Proton and carbon magnetic resonance spectra (^1H NMR and ^{13}C NMR) were recorded using either tetramethylsilane (TMS) as the internal standard in $CDCl_3$ (^1H NMR: TMS at 0.00 ppm, $CHCl_3$ at 7.24 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm) or tetramethylsilane (TMS) as the internal standard in DMSO-d_6 (^1H NMR: TMS at 0.00 ppm, DMSO at 2.50 ppm; ^{13}C NMR: DMSO at 40.0 ppm).

General procedure for synthesis of compounds 3a–p and 3a′–o′

A 10 mL Schlenk tube equipped with a magnetic stirring bar was charged with CuCl (0.05 mmol, 5.0 mg) (see Table 1 and Table 2) or CuBr (0.05 mmol, 7.3 mg) (see Table 3 and Table 4), NaOH (2 mmol, 80 mg), (1*E*,2*E*)-oxalaldehyde dioxime (0.1 mmol, 9 mg), tetrabutylammonium bromide (0.1 mmol, 33 mg), and aryl halide (1.2 mmol), if it was a solid. The tube was evacuated and back-filled with nitrogen, and this procedure was repeated three times. If the aryl halide (1.2 mmol) was liquid, then it

Table 4 Copper-catalyzed N-arylation of aliphatic amines in water[a]



Entry	1	3	Product	Yield (%)[b]
1	 **1a**	$H_2NC_{12}H_{25}$ **2a′**	 **3a'**	78
2	 **1a**	$H_2NC_3H_6OH$ **2b′**	 **3b'**	85
3	 **1a**	 **2c'**	 **3c'**	80
4	 **1a**	 **2d'**	 **3d'**	91
5	 **1c**	 **2e'**	 **3e'**	86
6	 **1e**	$H_2NC_3H_6OH$ **2b′**	 **3f'**	82
7	 **1e**	 **2f'**	 **3g'**	89
8	 **1o**	 **2g'**	 **3h'**	74
9	 **1p**	$H_2NC_3H_7$ **2h′**	 **3i'**	83
10	 **1k**	$H_2NC_3H_7$ **2h′**	 **3j'**	81
11	 **1l**	 **2c'**	 **3k'**	72
12	 **1q**	$H_2NC_5H_{10}OH$ **2i′**	 **3l'**	91
13	 **1r**	 **2j'**	 **3m'**	83
14	 **1s**	$H_2NC_{12}H_{25}$ **2a′**	 **3n'**	87
15	 **1t**	$H_2NC_5H_{10}OH$ **2i′**	 **3o'**	89

[a] Reaction conditions: **1** (1 mmol), **2** (1.2 mmol), CuBr (0.05 mmol), $^nBu_4NBr$ (0.1 mmol), ligand (0.1 mmol), NaOH (3 mmol for entries 4, 7 and 12–15; 2 mmol for others), water (1.5 mL), 100 °C, nitrogen atmosphere, 24 h. [b] Isolated yield.

was added at this point, followed by water (1.5 mL) at room temperature under a stream of nitrogen, and the tube was sealed and put into a pre-heated oil bath at 100 °C for 24 h under a positive pressure of nitrogen. After the resulting solution had cooled to room temperature, it was extracted with ethyl acetate (3 × 3 mL). The combined organic phase was concentrated, and the remaining residue was purified by column chromatography on silica gel to provide the desired product.

1-(4-Chlorophenyl)-1*H*-imidazole (3a)[10]

Eluent petroleum–ethyl acetate (1 : 2). Yield 164 mg (92%). White solid, m.p. 98–99 °C (lit.[10] 85–87 °C). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.85 (s, 1H), 7.46 (d, J = 8.91 Hz, 2H), 7.34 (d, J = 8.91 Hz, 2H), 7.25 (s, 1H), 7.21 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 135.9, 135.6, 133.2, 130.7, 130.1, 122.7, 118.2. ESI-MS m/z 179.1, 181.0 $[M + H]^+$.

1-(3-Chlorophenyl)-1*H*-indole (3b)[11]

Eluent petroleum–ethyl acetate (25 : 1). Yield 212 mg (93%). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.65 (d, J = 7.57 Hz, 1H), 7.52 (d, J = 7.89 Hz, 1H), 7.46 (s, 1H), 7.38-7.31 (m, 2H), 7.23-7.13 (m, 4H), 6.65 (d, J = 3.10 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 141.1, 135.7, 135.3, 130.7, 129.6, 127.7, 126.6, 124.5, 122.9, 122.4, 121.4, 120.9, 110.5, 104.5. ESI-MS m/z 228.1 $[M + H]^+$.

1-(4-Fluorophenyl)-1*H*-benzo[*d*]imidazole (3c)[12]

Eluent petroleum–ethyl acetate (1 : 2). Yield 176 mg (83%). White solid, m.p. 122–124 °C (lit.[12] 118.5–119.5 °C). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.06 (s, 1H), 7.87 (t, J = 4.47 Hz, 1H), 7.47-7.43 (m, 3H), 7.32 (t, J = 4.13 Hz, 2H), 7.24 (t, J = 8.42 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$, ppm) δ 162.0 (d, J = 248.53 Hz), 143.9, 142.3, 133.9, 132.4, 126.1 (d, J = 8.67 Hz), 123.9, 122.9, 120.7, 117.1 (d, J = 23.12 Hz), 110.27. ESI-MS m/z 213.2 $[M + H]^+$.

1-(3-Bromophenyl)-1*H*-pyrrole (3d)

Eluent petroleum–ethyl acetate (50 : 1). Yield 165 mg (75%). White solid, m.p. 81–83 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.54 (s, 1H), 7.37-7.24 (m, 3H), 7.05 (t, J = 2.07 Hz, 2H), 6.35 (t, J = 2.07 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 141.9, 130.9, 128.6, 123.6, 123.2, 119.3, 119.0, 111.1. ESI-MS m/z 244.2, 246.4 $[M + Na]^+$. HR-MS $[M + H]^+$ m/z Calcd for $C_{10}H_9BrN$: 221.9918. Found: 221.9921.

1-*p*-Tolyl-1*H*-imidazole (3e)[13]

Eluent petroleum–ethyl acetate (1 : 2). Yield 139 mg (88%). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.82 (s, 1H), 7.26 (s, 5H), 7.19 (s, 1H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 137.5, 135.6, 135.0, 130.4, 130.2, 121.5, 118.4, 21.0. ESI-MS m/z 159.1 $[M + H]^+$.

9-*p*-Tolyl-9*H*-carbazole (3f)[14]

Eluent petroleum–ethyl acetate (15 : 1). Yield 229 mg (89%). White solid, m.p. 112–113 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.13 (d, J = 7.90 Hz, 2H), 7.43-7.35 (m, 8H), 7.28–7.20 (m, 2H), 2.46 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 141.1, 137.4, 135.1, 130.5, 127.1, 125.9, 123.3, 120.3, 119.8, 109.9, 21.3. ESI-MS m/z 258.1 $[M + H]^+$.

1-(3,5-Dimethylphenyl)-1*H*-imidazole (3g)[15]

Eluent petroleum–ethyl acetate (1 : 2). Yield 150 mg (87%). Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.83 (s, 1H), 7.19 (s, 2H), 6.97 (s, 3H), 2.35 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 139.8, 137.3, 135.6, 130.2, 129.1, 119.2, 118.4, 21.3. ESI-MS m/z 173.1 $[M + H]^+$.

6-Methoxy-1-(4-nitrophenyl)-1*H*-indole (3h)

Eluent petroleum–ethyl acetate (15 : 1). Yield 257 mg (96%). Brown solid. m.p. 163–164 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.38 (d, J = 8.94 Hz, 2H), 7.66 (d, J = 8.94 Hz, 2H), 7.56 (d, J = 8.94 Hz, 1H), 7.25 (d, J = 3.10 Hz, 1H), 7.11 (s, 1H), 6.89 (d, 8.60 Hz, 1H), 6.68 (d, J = 3.10 Hz, 1H), 3.84 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 157.4, 145.4, 145.0, 136.1, 126.2, 125.6, 124.2, 123.3, 122.2, 110.9, 106.1, 94.7, 55.9. HR-MS $[M + H]^+$ m/z Calcd for $C_{15}H_{13}N_2O_3$: 269.0926. Found: 269.0931.

1-(4-Nitrophenyl)-1*H*-imidazole (3i)[16]

Eluent petroleum–ethyl acetate (1 : 2). Yield 161 mg (85%). Yellow solid. m.p. 208–209 °C (lit.[16] 203–205 °C). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.38 (d, J = 8.94 Hz, 2H), 7.99 (s, 1H), 7.59 (d, J = 8.60 Hz, 2H), 7.38 (d, 1H), 7.28 (d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 146.3, 142.0, 135.4, 131.8, 125.8, 121.1, 117.7. ESI-MS m/z 190.1 $[M + H]^+$.

9-(4-Nitrophenyl)-9*H*-carbazole (3j)[17]

Eluent petroleum–ethyl acetate (50 : 1). Yield 254 mg (85%). Yellow solid. m.p. 169-171 °C (lit.[17] 209–211 °C). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.49 (d, J = 8.49 Hz, 2H), 8.15 (d, J = 7.57 Hz, 2H), 7.81 (d, J = 8.26 Hz, 2H), 7.52-7.43 (m, 4H), 7.35 (t, J = 7.40 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 145.8, 143.9, 139.9, 126.8, 126.5, 125.6, 124.2, 121.3, 120.7, 109.7. ESI-MS$m/z$ 311.7 $[M + Na]^+$.

1-(4-(1*H*-Benzo[*d*]imidazol-1-yl)phenyl)ethanone (3k)[18]

Eluent petroleum–ethyl acetate (1 : 2). Yield 146 mg (62%). Yellow solid. m.p. 134–136 °C (lit.[18] 136–138 °C). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.20 (s, 2H), 8.17 (s, 1H), 7.91-7.88 (m, 1H), 7.65 (d, J = 7.91 Hz, 2H), 7.62–7.59 (m, 1H), 7.39–7.36 (m, 2H), 2.68 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$, ppm) δ 196.6, 144.2, 141.8, 140.2, 136.2, 133.2, 130.4, 124.3, 123.4, 120.9, 110.5, 26.7. ESI-MS m/z 237.2 $[M + H]^+$.

1-(Pyridin-2-yl)-1*H*-benzo[*d*]imidazole (3l)[19]

Eluent petroleum–ethyl acetate (1 : 2). Yield 170 mg (87%). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.58 (d, J = 6.54 Hz, 2H), 8.07-8.04 (m, 1H), 7.88-7.84 (m, 2H), 7.54 (d, J = 8.26 Hz, 1H), 7.40-7.32 (m, 2H), 7.27 (t, J = 6.19 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 149.9, 149.5, 144.7, 141.4, 139.0, 132.2, 124.3, 123.3, 121.9, 120.7, 114.4, 112.7. ESI-MS m/z 196.1 $[M + H]^+$.

1-(4-Bromophenyl)-6-methoxy-1*H*-indole (3m)

Eluent petroleum–ethyl acetate (50 : 1). Yield 239 mg (79%). Red solid. m.p. 73-74 °C. ^{1}H NMR (600 MHz, $CDCl_3$, ppm) δ 7.64 (d, J = 8.94 Hz, 2H), 7.55 (d, J = 8.94 Hz, 1H), 7.38 (d, J = 8.25 Hz, 2H), 7.17 (d, J = 3.44 Hz, 1H), 6.99 (s, 1H), 6.85 (dd, J = 8.94 Hz, 2.06 Hz, 1H), 6.61 (d, J = 2.75 Hz, 1H), 3.82 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$, ppm) δ 156.9, 139.0, 136.4, 132.8, 126.7, 125.8, 123.5, 121.8, 119.7, 110.4, 104.0, 93.9, 55.8. HR-MS $[M + H]^+$ m/z Calcd for $C_{15}H_{13}BrNO$: 302.0186. Found: 302.0189.

1-(Naphthalen-2-yl)-1*H*-pyrrole (3n)[20]

Eluent petroleum. Yield 133 mg (69%). White solid, m.p. 111–112 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.90 (d, J = 8.60 Hz, 1H), 7.84 (d, J = 7.91 Hz, 2H), 7.78 (s, 1H), 7.58 (d, J = 8.60 Hz, 1H), 7.54-7.43 (m, 2H), 7.21 (d, J = 2.06 Hz, 2H), 6.39 (d, J = 2.06 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$, ppm) δ 138.2, 133.9, 131.5, 129.6, 127.8, 127.7, 127.0, 125.6, 120.2, 119.6, 117.5, 110.7. ESI-MS m/z 194.2 $[M + H]^+$.

2-(1*H*-Imidazol-1-yl)benzoic acid (3o)[21]

After completion of the reaction, the resulting solution was adjusted to pH = 6 ~ 7 with HCl (1M), and the following work-up was performed according to general procedure. Eluent petroleum–ethyl acetate (3 : 1). Yield 182 mg (97%). White solid, m.p. 113-115 °C. ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 7.85 (s, 1H), 7.60 (d, J = 7.57 Hz, 1H), 7.54–7.39 (m, 3H), 7.33 (d, J = 7.22 Hz, 1H), 6.98 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6, ppm) δ 169.6, 137.3, 135.6, 130.9, 130.8, 130.3, 130.1, 127.3, 121.8. ESI-MS m/z 189.1 $[M + H]^+$, m/z 211.1 $[M + Na]^+$.

1-(3-Nitrophenyl)-1*H*-imidazole (3p)[12]

Eluent petroleum–ethyl acetate (1 : 2). Yield 125 mg (66%). Brown solid. m.p. 118–120 °C (lit.[12] 109–110 °C). ^{1}H NMR (600 MHz, $CDCl_3$, ppm) δ 8.30 (s,1H), 8.25 (d, J = 8.25 Hz, 1H), 8.09 (s, 1H), 7.78 (d, J = 8.25 Hz, 1H), 7.72 (t, J = 7.91 Hz, 1H), 7.51 (s, 1H), 7.41 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 147.9, 138.0, 131.0, 128.9, 128.6, 125.5, 121.1, 115.7, 113.5. ESI-MS m/z 190.1 $[M + H]^+$.

4-Chloro-*N*-dodecylaniline (3a′)[8c]

Eluent petroleum–ethyl acetate (10 : 1). Yield 231 mg (78%). Pale yellow solid. m.p. 46–47 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.09 (d, J = 8.60 Hz, 2H), 6.50 (d, J = 8.60 Hz, 2H), 3.57 (s, br, 1H), 3.05 (t, J = 7.05 Hz, 2H), 1.61–1.56 (m, 2H), 1.36–1.26 (m, 18H), 0.88 (t, J = 6.53 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 147.1, 129.0, 121.6, 113.8, 44.2, 32.0, 29.7, 29.6, 29.5, 29.4, 27.2, 22.7, 14.2. ESI-MS m/z 297.3 $[M + H]^+$.

3-(4-Chlorophenylamino)propan-1-ol (3b′)

Eluent petroleum–ethyl acetate (5 : 1). Yield 158 mg (85%). Brown oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.11 (d, J = 8.94 Hz, 2H), 6.54 (d, J = 8.60 Hz, 2H), 3.79 (t, J = 8.58 Hz, 2H), 3.23 (t, J = 6.53 Hz, 2H), 2.85 (s, br, 2H), 1.90–1.81 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 146.9, 129.1, 122.2, 114.2, 61.6, 42.1, 31.7. HR-MS $[M + H]^+$ m/z Calcd for $C_9H_{13}ClNO$: 186.0686. Found: 186.0683.

4-Chloro-*N*-cyclohexylaniline (3c′)[8c]

Eluent petroleum–ethyl acetate (5 : 1). Yield 168 mg (80%). Gray solid. m.p. 44–45 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.07 (d, J = 8.60 Hz, 2H), 6.48 (d, J = 8.60 Hz, 2H), 3.43 (s, br, 1H), 3.23-3.15 (m, 1H), 2.01 (d, J = 12.73 Hz, 2H), 1.76–1.72 (m, 2H), 1.66–1.62 (d, J = 12.38 Hz, 1H), 1.41–1.05 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 145.9, 129.1, 121.3, 114.3, 51.9, 33.3, 25.9, 25.0. ESI-MS m/z 210.3 $[M + H]^+$.

2-(4-Chlorophenylamino)propanoic acid (3d′)[22]

After completion of the reaction, the resulting solution was adjusted to pH = 6–7 with HCl (1 M), and the following work-up was performed according to the general procedure. Eluent petroleum–ethyl acetate (5 : 1). Yield 182 mg (91%). Brown solid. m.p. 143–145 °C. ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 12.56 (s, br, 1H), 7.10 (t, J = 8.60 Hz, 2H), 7.65 (t, J = 8.60 Hz, 2H), 6.18 (s, br, 1H), 3.94 (t, J = 7.57 Hz, 1H), 1.38 (t, J = 7.74 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ 176.1, 147.3, 129.0, 119.9, 114.2, 51.5, 18.5. ESI-MS m/z 199.1 $[M - H]^-$.

4-(4-Fluorophenyl)morpholine (3e′)[23]

Eluent petroleum–ethyl acetate (5 : 1). Yield 156 mg (86%). Brown oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 6.97–6.94 (m, 2H), 6.85–6.83 (m, 2H), 3.83 (s, 4H), 3.05 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 157.3 (d, J = 239.86 Hz), 147.9, 117.5 (d, J = 7.22 Hz), 115.7 (d, J = 22.40 Hz), 66.9, 50.3. ESI-MS m/z 182.1 $[M + H]^+$.

3-(*p*-Tolylamino)propan-1-ol (3f′)[24]

Eluent petroleum–ethyl acetate (5 : 1). Yield 135 mg (82%). Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 6.99 (d, J = 7.91 Hz, 2H), 6.57 (d, J = 7.22 Hz, 2H), 3.79 (t, J = 5.51 Hz, 2H), 2.25 (t, J = 6.02 Hz, 2H), 2.81 (s, br, 2H), 2.23 (s, 3H), 1.89–1.81 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 146.0, 129.8, 127.1, 113.5, 61.9, 42.6, 32.0, 20.5. ESI-MS m/z 166.2 $[M + H]^+$, m/z 188.1 $[M + Na]^+$.

3-Phenyl-2-(*p*-tolylamino)propanoic acid (3g′)[24]

After completion of the reaction, the resulting solution was adjusted to pH = 6–7 with HCl (1 M), and the following work-up was performed according to the general procedure. Eluent petroleum–ethyl acetate (10 : 1). Yield 227 mg (89%). Yellow solid. m.p. 154–155 °C. ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 12.52 (s, br, 1H), 7.28-7.18 (m, 5H), 6.86 (d, J = 7.91 Hz, 2H), 6.48 (d, J = 8.26 Hz, 2H), 5.73 (s, br, 1H), 4.07 (t, J = 6.88 Hz, 1H), 3.07-2.91 (m, 2H), 2.12 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ 175.2, 145.9 138.4, 129.8, 129.7, 128.6, 126.8, 125.3, 113.2, 58.25, 38.3, 20.5. ESI-MS m/z 154.1 $[M - H]^-$.

***N*-Benzyl-4-methoxyaniline (3h′)[24]**

Eluent petroleum–ethyl acetate (25 : 1). Yield 158 mg (74%). White solid, m.p. 52–53 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.37–7.22 (m, 5H), 6.76 (d, J = 8.94 Hz, 2H), 6.59

(d, J = 8.94 Hz, 2H), 4.26 (s, 2H), 3.72 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 152.3, 142.4, 139.7, 128.7, 127.6, 127.2, 115.0, 114.2, 55.9, 49.3. ESI-MS m/z 214.2 $[M + H]^+$.

N-Propylnaphthalen-1-amine (3i′)[25]

Eluent petroleum–ethyl acetate (5 : 1). Yield 154 mg (83%). Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.76 (d, J = 6.54 Hz, 2H), 7.41–7.38 (m, 2H), 7.33 (t, J = 7.91 Hz, 1H), 7.20 (d, J = 7.91 Hz, 1H), 7.58 (d, J = 7.57 Hz, 1H), 4.29 (s, br, 1H), 3.20 (t, J = 7.05 Hz, 2H), 1.79–1.71 (m, 2H), 1.07–1.02 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 143.7, 134.4, 128.8, 126.8, 125.8, 124.7, 123.4, 119.9, 117.2, 104.3, 46.1, 22.7, 12.0. ESI-MS m/z 186.1 $[M + H]^+$.

4-Bromo-*N*-propylaniline (3j′)

Eluent petroleum–ethyl acetate (10 : 1). Yield 173 mg (81%). White oil. ^{1}H NMR (600 MHz, $CDCl_3$, ppm) δ 7.22 (d, J = 8.94 Hz, 2H), 6.45 (d, J = 8.94 Hz, 2H), 3.65 (s, br, 1H), 3.01 (t, J = 6.88 Hz, 2H), 1.63–1.57 (m, 2H), 0.97 (t, J = 7.22 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$, ppm) δ 147.5, 131.9, 114.3, 108.5, 45.8, 22.6, 11.7. HR-MS $[M + H]^+$ m/z Calcd for $C_9H_{13}BrN$: 214.0231. Found: 214.0235.

N-Cyclohexylnaphthalen-2-amine (3k′)[26]

Eluent petroleum–ethyl acetate (3 : 1). Yield 162 mg (72%). White solid, m.p. 183-185 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.65–7.57 (m, 3H), 7.33 (t, J = 7.40 Hz, 1H), 7.15 (t, J = 7.23 Hz, 1H), 6.84-6.79 (m, 2H), 3.74 (s, br, 1H), 3.41–3.38 (m, 1H), 2.11 (d, J = 12.38 Hz, 2H), 1.81–1.64 (m, 3H), 1.47–1.12 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 144.9, 135.3, 129.0, 127.7, 127.3, 126.3, 125.8, 121.8, 118.3, 104.9, 51.8, 33.3, 26.0, 25.1. ESI-MS m/z 226.2 $[M + H]^+$.

2-(5-Hydroxypentylamino)-3-nitrobenzoic acid (3l′)

After completion of the reaction, the resulting solution was adjusted to pH = 6–7 with HCl (1 M), and the following work-up was performed according to the general procedure. Eluent petroleum–ethyl acetate (2 : 1). Yield 244 mg (91%). Yellow solid. m.p. 138–140 °C. ^{1}H NMR (600 MHz, DMSO-d_6, ppm) δ 13.45 (s, br, 1H), 8.58 (s, br, 1H), 8.08 (d, J = 6.19 Hz, 1H), 7.97 (d, J = 8.25 Hz, 1H), 6.75 (t, J = 7.91 Hz, 1H), 4.36 (s, br, 1H), 3.36 (t, J = 6.53 Hz, 2H), 2.83 (t, J = 6.88 Hz, 2H), 1.59–1.55 (m, 2H), 1.42–1.37 (m, 2H), 1.34–1.29 (m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6, ppm) δ 169.5, 145.7, 137.3, 137.2, 131.7, 117.1, 114.9, 61.0, 46.3, 32.5, 29.8, 23.3. HR-MS $[M + H]^+$ m/z Calcd for $C_{12}H_{17}N_2O_5$: 269.1137. Found: 269.1142.

2-(4-Methylbenzylamino)-5-nitrobenzoic acid (3m′)

After completion of the reaction, the resulting solution was adjusted to pH = 6–7 with HCl (1 M), and the following work-up was performed according to the general procedure. Eluent petroleum–ethyl acetate (3 : 1). Yield 237 mg (83%). Yellow solid. m.p. 253–254 °C. ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 13.54 (s, br, 1H), 9.15 (t, br, J = 5.68 Hz, 1H), 8.65 (d, J = 2.27 Hz, 1H), 8.13 (dd, J = 9.29 Hz, 2.75 Hz, 1H), 7.25–7.15 (m, 4H), 6.82 (d, J = 9.63 Hz, 1H), 4.57 (d, J = 5.85 Hz, 2H), 2.28 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6, ppm) δ 169.1, 155.0, 136.9, 135.4, 135.3, 129.7, 129.0, 127.6, 112.5, 110.1, 46.2, 21.1. HR-MS $[M + H]^+$ m/z Calcd for $C_{15}H_{15}N_2O_4$: 287.1032. Found: 287.1036.

2-(Dodecylamino)benzoic acid (3n′)[27]

After completion of the reaction, the resulting solution was adjusted to pH = 6–7 with HCl (1 M), and the following work-up was performed according to the general procedure. Eluent petroleum–ethyl acetate (25 : 1). Yield 265 mg (87%). White solid, m.p. 77–78 °C (lit.[27] 80–81 °C). ^{1}H NMR (600 MHz, DMSO-d_6, ppm) δ 12.37 (s, br, 1H), 7.77 (d, J = 8.25 Hz, 1H), 7.33 (t, J = 7.91 Hz, 1H), 6.69 (d, J = 8.25 Hz, 1H), 6.53 (t, J = 7.56 Hz, 1H), 3.14 (t, J = 6.88 Hz, 2H), 1.57 (t, J = 7.22 Hz, 2H), 1.35 (s, 2H), 1.23 (s, 16H), 0.85 (t, J = 6.88 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6, ppm) δ 170.5, 151.5, 134.9, 132.2, 114.4, 111.5, 110.2, 42.5, 31.8, 29.5, 29.2, 29.1, 27.0, 22.6, 14.4. ESI-MS m/z 306.4 $[M + H]^+$, m/z 328.4 $[M + Na]^+$.

2-(5-Hydroxypentylamino)nicotinic acid (3o′)

After completion of the reaction, the resulting solution was adjusted to pH = 6–7 with HCl (1 M), and the following work-up was performed according to the general procedure. Eluent petroleum–ethyl acetate (5 : 1). Yield 199 mg (89%). White solid, m.p. 91–92 °C. ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 12.99 (s, br, 1H), 8.24 (d, J = 3.10 Hz, 1H), 8.11 (s, br, 1H), 8.05 (d, J = 7.91 Hz, 1H), 6.57 (dd, J = 7.74 Hz, 4.65 Hz, 1H), 4.37 (s, br, 1H), 3.45-3.37 (m, 4H), 1.61–1.54 (m, 2H), 1.48–1.43 (m, 2H), 1.37–1.32 (m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6, ppm) δ 169.4, 158.8, 153.8, 140.6, 111.2, 106.2, 61.1, 40.7, 32.8, 29.5, 23.6. HR-MS $[M + H]^+$ m/z Calcd for $C_{11}H_{17}N_2O_3$: 225.1239. Found: 225.1237.

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References

1 M. Negwer, in *Organic-Chemical Drugs and their Synonyms: An International Survey*, 7th edn, Akademie Verlag: Berlin, 1994.
2 *N*-Arylation of anilines: (*a*) F. Ullmann, *Ber. Dtsch. Chem. Ges.*, 1903, **36**, 2382; (*b*) S. Gauthier and J. M. J. Fréchet, *Synthesis*, 1987, 383; (*c*) A. J. Paine, *J. Am. Chem. Soc.*, 1987, **109**, 1496; (*d*) R. Gujadhur, D. Venkataraman and J. T. Kintigh, *Tetrahedron Lett.*, 2001, **42**, 4791. *N*-Arylation of alkylamines: (*e*) D. Ma, Y. Zhang, J. Yao, S. Wu and F. Tao, *J. Am. Chem. Soc.*, 1998, **120**, 12459; (*f*) J. B. Arterburn, M. Pannala and A. M. Gonzalez, *Tetrahedron Lett.*, 2001, **42**, 1475. Arylation of ammonia: (*g*) F. Lang, D. Zewge, I. N. Houpis and R. P. Volante, *Tetrahedron Lett.*, 2001, **42**, 3251.
3 For reviews, see: (*a*) J. F. Hartwig, *Angew. Chem., Int. Ed.*, 1998, **37**, 2046; (*b*) J. P. Wolfe, S. Wagaw, J.-F. Marcoux and S. L. Buchwald, *Acc. Chem. Res.*, 1998, **31**, 805; (*c*) A. R. Muci and S. L. Buchwald, *Topics in Current Chemistry*, Springer-Verlag: Germany, 2002, vol. 219, ch. 5; (*d*) B. H. Yang and S. L. Buchwald, *J. Organomet. Chem.*, 1999, **576**, 125; (*e*) J. F. Hartwig, *Acc. Chem. Res.*, 1998, **31**, 852.

4 For recent reviews on copper-catalyzed cross couplings, see: (*a*) A. Klapars, J. C. Antilla, X. Huang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2001, **123**, 7727; (*b*) D. Ma and Q. Cai, *Acc. Chem. Res.*, 2008, **41**, 1450; (*c*) K. Kunz, U. Scholz and D. Ganzer, *Synlett*, 2003, 2428; (*d*) S. V. Ley and A. W. Thomas, *Angew. Chem., Int. Ed.*, 2003, **42**, 5400; (*e*) I. P. Beletskaya and A. V. Cheprakov, *Coord. Chem. Rev.*, 2004, **248**, 2337; (*f*) G. Evano, N. Blanchard and M. Toumi, *Chem. Rev.*, 2008, **108**, 3054; (*g*) F. Monnier and M. Taillefer, *Angew. Chem., Int. Ed.*, 2009, **48**, 6954 and references cited therein.

5 (*a*) *Organic Synthesis in Water*, ed. P. A. Grieco, Blackie A & P: London, 1998; (*b*) M. Siskin and A. R. Katritzky, *Chem. Rev.*, 2001, **101**, 825; (*c*) U. M. Lindström, *Chem. Rev.*, 2002, **102**, 2751; (*d*) S. Kobayashi and K. Manabe, *Acc. Chem. Res.*, 2002, **35**, 209; (*e*) N. Akiya and P. E. Savage, *Chem. Rev.*, 2002, **102**, 2725; (*f*) J. M. DeSimone, *Science*, 2002, **297**, 799; (*g*) M. Poliakoff, J. M. Fitzpatrick, T. R. Farren and P. T. Anastas, *Science*, 2002, **297**, 807; (*h*) C.-J. Li, *Chem. Rev.*, 2005, **105**, 3095; (*i*) D. G. Blackmond, A. Armstrong, V. Coomber and A. Wells, *Angew. Chem., Int. Ed.*, 2007, **46**, 3798; (*j*) S. Minakata and M. Komatsu, *Chem. Rev.*, 2008, **101**, 825; (*k*) Y.-C. Teo and G.-L. Chua, *Chem. Eur. J.*, 2009, **15**, 3072; (*l*) Y.-C. Teo, *Adv. Synth. Catal.*, 2009, **351**, 720; (*m*) X. Zhu, Y. Ma, L. Su, H. Song, G. Chen, D. Liang and Y. Wan, *Synthesis*, 2006, 3955; (*n*) M. Carril, R. SanMartin and E. Domínguez, *Chem. Soc. Rev.*, 2008, **37**, 639 and references cited therein.

6 D. Sinou, *Adv. Synth. Catal.*, 2002, **344**, 221.

7 (*a*) Y. Wang, Z. Wu, L. Wang, Z. Li and X. Zhou, *Chem. Eur. J.*, 2009, **15**, 8971; (*b*) L. Liang, Z. Li and X. Zhou, *Org. Lett.*, 2009, **11**, 3294.

8 Selected papers for copper-catalyzed cross couplings in organic solvents, see: (*a*) H. Rao, H. Fu, Y. Jiang and Y. Zhao, *J. Org. Chem.*, 2005, **70**, 8107; (*b*) H. Rao, Y. Jin, H. Fu, Y. Jiang and Y. Zhao, *Chem. Eur. J.*, 2006, **12**, 3636; (*c*) D. Jiang, H. Fu, Y. Jiang and Y. Zhao, *J. Org. Chem.*, 2007, **72**, 672; (*d*) X. Guo, H. Rao, H. Fu, Y. Jiang and Y. Zhao, *Adv. Synth. Catal.*, 2006, **348**, 2197; (*e*) L. Zeng, H. Fu, R. Qiao, Y. Jiang and Y. Zhao, *Adv. Synth. Catal.*, 2009, **351**, 1671; (*f*) X. Gao, H. Fu, R. Qiao, Y. Jiang and Y. Zhao, *J. Org. Chem.*, 2008, **73**, 6864; (*g*) C. Huang, X. Tang, H. Fu, Y. Jiang and Y. Zhao, *J. Org. Chem.*, 2006, **71**, 5020; (*h*) C. Huang, Y. Fu, H. Fu, Y. Jiang and Y. Zhao, *Chem. Commun.*, 2008, 6333; (*i*) D. Yang, H. Fu, L. Hu, Y. Jiang and Y. Zhao, *J. Org. Chem.*, 2008, **73**, 7841; (*j*) F. Wang, H. Liu, H. Fu, Y. Jiang and Y. Zhao, *Org. Lett.*, 2009, **11**, 2469; (*k*) D. Yang, H. Liu, H. Yang, H. Fu, L. Hu, Y. Jiang and Y. Zhao, *Adv. Synth. Catal.*, 2009, **351**, 1999; (*l*) L. Wang, H. Fu, Y. Jiang and Y. Zhao, *Chem. Eur. J.*, 2008, **14**, 10722; (*m*) X. Liu, Y. Zhang, L. Wang, H. Fu, Y. Jiang and Y. Zhao, *J. Org. Chem.*, 2008, **73**, 6207; (*n*) M. Niu, Z. Yin, H. Fu, Y. Jiang and Y. Zhao, *J. Org. Chem.*, 2008, **73**, 3813; (*o*) Y. Zhang, H. Fu, Y. Jiang and Y. Zhao, *Org. Lett.*, 2007, **9**, 3813; (*p*) M. Niu, H. Fu, Y. Jiang and Y. Zhao, *Chem. Commun.*, 2007, 272; (*q*) H. Rao, H. Fu, Y. Jiang and Y. Zhao, *Angew. Chem., Int. Ed.*, 2009, **48**, 1114; (*r*) X. Liu, H. Fu, Y. Jiang and Y. Zhao, *Angew. Chem., Int. Ed.*, 2009, **48**, 348.

9 For copper-catalyzed cross couplings in neatly aqueous medium, see: (*a*) F. Wang, H. Fu, Y. Jiang and Y. Zhao, *Green Chem.*, 2008, **10**, 452; (*b*) F. Wang, H. Fu, Y. Jiang and Y. Zhao, *Adv. Synth. Catal.*, 2008, **350**, 1830.

10 P. Franchetti, M. Grifantini, S. Martelli and M. L. Stein, *J. Med. Chem.*, 1974, **17**, 18.

11 R. Sarges, H. R. Howard, B. K. Koe and A. Weissman, *J. Med. Chem.*, 1989, **32**, 437.

12 R. A. Altman, E. D. Koval and S. L. Buchwald, *J. Org. Chem.*, 2007, **72**, 6190.

13 K. Swapna, A. V. Kumar, V. P. Reddy and K. R. Rao, *J. Org. Chem.*, 2009, **74**, 7514.

14 Z. Zhao, X. Xu, X. Chen, X. Wang, P. Lu, G. Yu and Y. Liu, *Tetrahedron*, 2008, **64**, 2658.

15 L. Liu, M. Frohn, N. Xi, C. Dominguez, R. Hungate and P. J. Reider, *J. Org. Chem.*, 2005, **70**, 10135.

16 X. Lv, Z. Wang and W. Bao, *Tetrahedron*, 2006, **62**, 4756.

17 F. Bellina, C. Calandri, S. Cauteruccio and R. Rossi, *Eur. J. Org. Chem.*, 2007, 2147.

18 H. Zhang, Q. Cai and D. Ma, *J. Org. Chem.*, 2005, **70**, 5164.

19 H.-G. Lee, J.-E. Won, M.-J. Kim, S.-E. Park, K.-J. Jung, B. R. Kim, S.-G. Lee and Y.-J. Yoon, *J. Org. Chem.*, 2009, **74**, 5675.

20 E. Paredes, R. Brasca, M. Kneeteman and P. M. E. Mancini, *Tetrahedron*, 2007, **63**, 3790.

21 B. Sreedhar, R. Arundhathi, P. L. Reddy, M. A. Reddy and M. L. Kantam, *Synthesis*, 2009, 2517.

22 S. A. Al-Awadi, M. R. Abdallah, M. A. Hasan and N. A. Al-Awadi, *Tetrahedron*, 2004, **60**, 3045.

23 M. G. Organ, M. Abdel-Hadi, St. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, M. Sayah and C. Valente, *Chem. Eur. J.*, 2008, **14**, 2443.

24 D. Wang and K. Ding, *Chem. Commun.*, 2009, 1891.

25 C. M. A. Alves, S. Naik, P. J. G. Coutinho and M. S. T. Gonçalves, *Tetrahedron Lett.*, 2009, **50**, 4470.

26 M. Kwit and J. Gawronski, *Tetrahedron*, 2008, **64**, 2658.

27 M. L. Docampo, R. F. Pellón, A. Estevez-Braun and A. G. Ravelo, *Eur. J. Org. Chem.*, 2007, 4111.