A Highly Efficient Copper-Catalyzed Method for the Synthesis of 2-Hydroxybenzamides in Water

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Received: 19.12.2011; Accepted after revision: 19.03.2012

Abstract: An efficient copper-catalyzed synthetic method for the preparation of 2-hydroxybenzamides is described for the first time from 2-chlorobenzamide substrates using copper iodide/1,10-phenanthroline and a base, potassium hydroxide, in neat water. By using this reaction, a series of 2-hydroxybenzamides with functional groups such as fluoro, chloro, iodo, methoxy, amide, and alcohol have been obtained in 33–96% yield. Other aromatic 2-chloroarylamides such as naphthalene, pyridine, and thiophene are found to be equally compatible to the reaction. It is proposed that the reaction proceed via formation of copper-amide complex, which may facilitate the hydroxylation in water. Overall, the first report on copper-catalyzed hydroxylation reaction in water and first catalytic route for the synthesis of 2-hydroxybenzamides is presented. Simple purification procedure and convenience of employing low-cost reagents in neat water make this method practical and economical for the synthesis of 2-hydroxybenzamides.

Key words: copper, 2-hydroxybenzamides, hydroxylation, catalysis in water, C–O coupling

2-Hydroxybenzamides have numerous applications such as anion binding, sensors, as well as a ligand for various metal complex formations.[1] Also, 2-hydroxybenzamides have been used as precursors for the synthesis of other ligands such as 2-(2′-hydroxyphenyl)-2-oxazoline.[2] Furthermore, a wide range of pharmacological activities namely antibacterial, antifungal, and anti-inflammatory have been well documented.[3] Recently, 2-hydroxybenzamides have also attracted considerable interest due to their cancer, psoriasis, and restenosis related activities.[4]

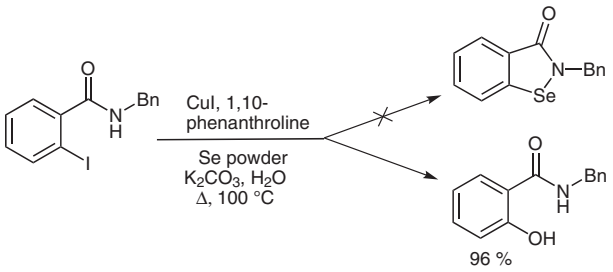
Present methods for the synthesis of 2-hydroxybenzamides depend on salicylic acid, which is obtained by the reaction of sodium phenolate with carbon dioxide at high pressure (100 atm) and high temperature (390 K) on commercial scale, a process known as Kolbe–Schmitt reaction. Moreover, synthesis of some of the substituted salicylic acids requires multiple steps.[5] Therefore, it would be worth developing an economical and environmentally benign method for the synthesis of 2-hydroxybenzamides from readily available and economical substrates under mild reaction conditions. Copper-catalyzed carbon–heteroatom (N, O, S, and Se) coupling reactions have emerged as a new strategy for the synthesis of heteroatom containing organic molecules.[6–11] Among these coupling reactions, copper-catalyzed hydroxylation of aryl halides has attracted considerable interest in recent time.[8–11] The pioneering work of Taillefer et al.[8] and You et al.[9a] on copper-catalyzed hydroxylation reaction led to study this reaction for the synthesis of useful organic molecules and also to search improvised reaction conditions. Water compatible ligands, 8-hydroxyquinolin-*N*-oxide and lithium pipecolinate have been utilized to exploit various aryl halides in copper-catalyzed hydroxylation reaction.[9b,g] Similarly, D-glucose is employed as a green ligand by Sekar et al. to further improvise the copper-catalyzed hydroxylation reaction conditions.[9f] Arylboronic acid substrates have been utilized for copper-catalyzed hydroxylation reaction in neat water at room temperature.[9e,h] Although the reaction shows broad functional group tolerance under normal reaction conditions, arylboronic acid substrates are required for hydroxylation reaction. Recently, phase-transfer reagent such as tetrabutylammonium hydroxide or tetrabutylammonium bromide has been employed to carry out copper-catalyzed hydroxylation reaction in neat water on aryl halide substrates.[9c,10] It is now well established that neat water as a solvent is not effective for copper-catalyzed hydroxylation reaction of aryl halides, unless phase-transfer catalyst or organic solvent is employed. In this context, development of a copper-catalyzed hydroxylation reaction in neat water using simple reagents would not only be cost effective, environmentally benign but also expected with greater chemoselectivity.[12,13]

To the best of our knowledge, copper-catalyzed hydroxylation reaction of aryl halides in neat water has not been described till today. Also, copper-catalyzed hydroxylation of 2-halobenzamides has not been reported in the literature. Here in this study, for the first time, we report an efficient and practical copper-catalyzed hydroxylation reaction for the synthesis of 2-hydoxybenzamides in neat water.

Recently, our group has developed a copper-catalyzed carbon–selenium–nitrogen bond-forming reaction from 2-halobenzamides and selenium powder in an organic solvent, DMF.[14] When the same reaction was performed in water, the reaction does not proceed to form Se–N heterocycles, however, the reaction afforded 2-hydroxybenzamide in excellent yield (96%) in 15 minutes (Scheme 1).

The excellent yield of 2-hydroxybenzamide **1** under benign reaction conditions in neat water encouraged us to develop a simple reaction protocol for the synthesis of 2-hydroxybenzamide from 2-chlorobenzoyl chloride in one

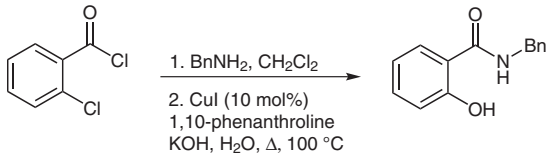
SYNTHESIS 2012, 44, 1417–1426
Advanced online publication: 12.04.2012
DOI: 10.1055/s-0031-1289755; Art ID: SS-2011-N1148-OP



Scheme 1 Copper-catalyzed synthesis of 2-hydroxybenzamide from 2-iodobenzamide. [a] Isolated yield. [b] Monitored by TLC and confirmed by NMR and mass spectrometry.

pot. The practical advantages of choosing 2-chloroaroyl chloride/2-chlorobenzamide as substrates are as follows: a) although, reaction time is generally longer for chloro substrates than the corresponding bromo and iodo substrates, the chloro substrates are very cheap; b) a diversely substituted 2-chlorobenzoyl chloride with methoxy, chloro, fluoro, nitro, etc. groups and most importantly 2-chloroaroyl chloride for naphthalene, pyridine, and thiophene are readily available, which could be valuable for the synthesis of a diverse series of 2-hydroxyarylamide under one set of reaction conditions. We chose 2-chloro-*N*-benzylbenzamide substrate (prepared in situ from 2-chlorobenzoyl chloride and benzylamine) to optimize the reaction conditions in neat water (Table 1). Initially, various bases were screened to achieve complete conversion of 2-chloro-*N*-benzylbenzamide into 2-hydroxybenzamide. Weak bases such as potassium and sodium carbonate were not effective for the complete conversion of 2-chlorobenzamide (Table 1, entries 1 and 2). Strong bases such as KOH and NaOH were found to be effective for the complete conversion of the substrate.

Table 1 Optimization of Reaction Conditions for 2-Chlorobenzoyl Chloride



Entry	CuI/L (mol%)	Base (equiv)	Time (h)	Conversion (%)[a]	Yield (%)[b]
1	10	K_2CO_3 (10)	14	86	80
2	10	Na_2CO_3 (10)	14	74	66[c]
3	10	NaOH (8)	10	100	95
4	**10**	**KOH (8)**	**10**	**100**	**96**
5	10	KOH (1)	10	30	nd[d]
6	10	KOH (3)	10	40	nd
7	10	KOH (5)	10	70	64
8	15	KOH (8)	7	100	94
9	25	KOH (8)	1	100	97
10	25[e]	KOH (8)	14	10	nd

[a] Based on substrate recovered from the reaction mixture.
[b] Isolated yield.
[c] Formation of side product was also observed as monitored by TLC.
[d] nd = not determined.
[e] No ligand was used.

We chose KOH for further optimization of reaction conditions. In the next set of experiments, the concentration of KOH was varied in the presence of 10 mol% of CuI/L and product formation was observed for 10 hours (Figure 1).

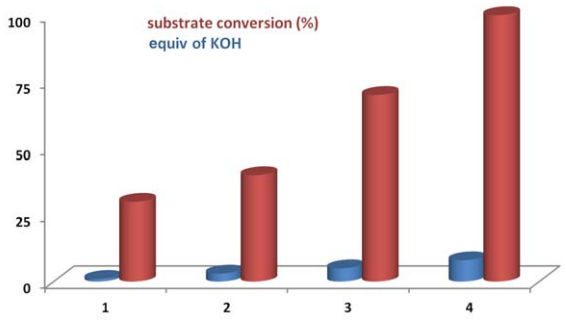


Figure 1 Effect of KOH on the CuI-catalyzed hydroxylation reaction. X-axis represents four set of experiments: 1 (1 equiv of KOH), 2 (3 equiv of KOH), 3 (5 equiv of KOH), and 4.0 (8 equiv of KOH) and Y-axis represents percentage conversion of substrate. Reaction was carried out on a 1 mmol scale, progress of reaction was monitored for 10 h, and each experiment was repeated twice.

It is apparent from Figure 1 that eight equivalents of KOH is necessary for the complete conversion of substrate in 10 hours. Further increase in KOH did not produce any effect on reaction time. Excess of KOH (8–12 equiv) and prolonged heating did not lead to any side product and also yield of hydroxylated product remained nearly the same. It is worth noting that the yield of **1** obtained from 2-chloro-*N*-benzylbenzamide is the same as obtained from the corresponding 2-iodo-*N*-benzylbenzamide substrate in our reaction system (96% yield of **1** from chloro and iodo substrates). Next, catalyst loading versus reaction time is studied using three concentration sets of CuI and ligand (10, 15, and 25 mol%) using eight equivalents of KOH at 100 °C. When catalyst concentration was lowered from 25 to 10 mol%, considerable increase in reaction time was observed. Since product obtained under reaction conditions using 10 mol% of CuI/L and eight equivalents of base require only minimum purification (for purity of crude product **1**, see: ^1H and ^{13}C NMR in the Supporting Information, Figure S1 and S2), 10 mol% CuI and 1,10-phenanthroline was used for further investigation. Having optimized conditions in hand, diversely substituted 2-hydroxybenzamides **1**–**22** were synthesized from 2-chloro substrates (Tables 2–4).

2-Chlorobenzamide substrates were prepared from the respective benzoyl chlorides and primary amines in dichloromethane. The resulting crude 2-chlorobenzamides were

subjected to copper-catalyzed hydroxylation without further purification (for details, please see experimental procedure). Next, fluorinated 2-hydroxybenzamides **3**–**5** were obtained in 72–87% yield from readily accessible 2-chlorobenzoyl chloride substrates in one pot (Table 2, entries 3–5). 4-Fluoro and 2-chloro-3,4-difluorobenzamides reacted completely to give respective 2-hydroxybenzamides **4** and **5** in 8 and 10 hours, respectively; however, substitution at 5-position increases the reaction time (16 h) considerably (Table 2, entry 3). By following the copper-catalyzed hydroxylation protocol, nitro-substituted 2-hydroxybenzamides **6** and **7** were also obtained in 85 and 87% yield, respectively. Electron-rich methoxy-substituted 2-chlorobenzamide substrates underwent hydroxylation reaction successfully (Table 2, entries 8 and 9). However, 3-methoxy-substituted 2-hydroxybenzamide **9** was obtained in 44% yield, and 40% of unreacted substrate was recovered.

Table 2 Copper-Catalyzed Synthesis of Substituted 2-Hydroxybenzamides by Hydroxylation of in situ Prepared 2-Chlorobenzamides in Water at 100 °C[a]

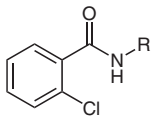
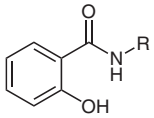
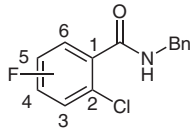
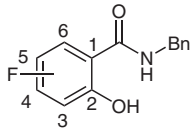
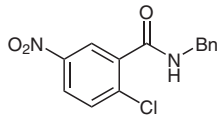
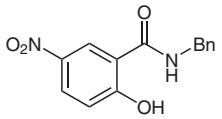
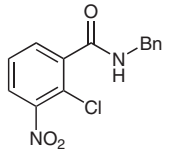
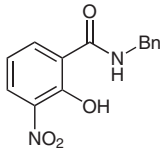
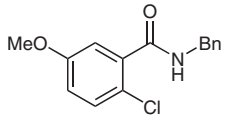
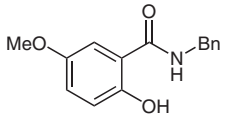
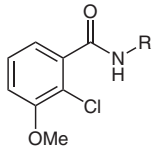
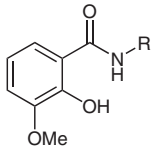
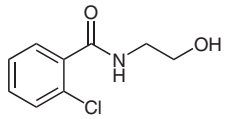
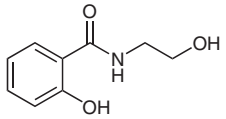
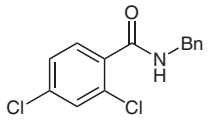
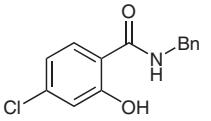
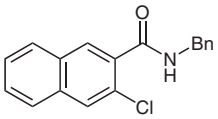
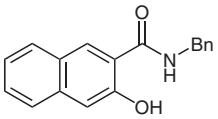
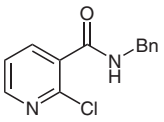
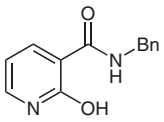
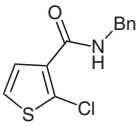
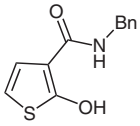
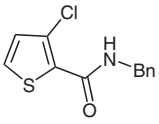
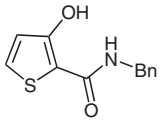
Entry	Substrate	Product		Yield (%)[b]
				
1	R = Bn	R = Bn	**1**	96
2	R = Ph	R = Ph	**2**	94
				
3	5-F	5-F	**3**	72
4	4-F	4-F	**4**	83
5	4,5-difluoro	4,5-difluoro	**5**	87
6			**6**	85
7			**7**	87
8			**8**	61
9			**9**	44
	R = 1-(naphthalen-1-yl)ethyl			
10			**10**	64

Table 2 Copper-Catalyzed Synthesis of Substituted 2-Hydroxybenzamides by Hydroxylation of in situ Prepared 2-Chlorobenzamides in Water at 100 °C[a] (continued)

Entry	Substrate	Product		Yield (%)[b]
11			**11**	91
12			**12**	90
13			**13**	62
14			**14**	33
15			**15**	57

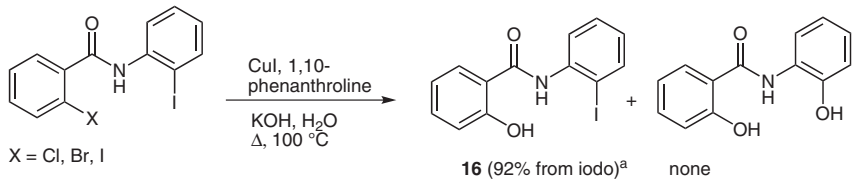
[a] Reaction conditions: 1. 2-chlorobenzoyl chloride (1.0 equiv), primary amine (1.5 equiv), CH_2Cl_2 (solvent), 0 °C to r.t., 3–6 h; 2. CuI (10 mol%), 1,10-phenanthroline (10 mol%), KOH (8.0 equiv), H_2O (solvent), 100 °C, unless otherwise stated.
[b] Isolated yield.

Next, the generality of hydroxylation reaction on 2-chloro-*N*-(2-hydroxyethyl)benzamide having an additional acidic proton was studied (Table 2, entry 10; for more substrates with an additional acidic proton, see Table 3). 2-Hydroxy-*N*-(2-hydroxyethyl)benzamide (**10**), a precursor for the synthesis of naturally occurring 2-(2′-hydroxyphenyl)-2-oxazoline ligand,[2] was obtained in 84% yield in one pot from 2-chlorobenzoyl chloride.

After studying amenability of copper-catalyzed hydroxylation reaction to the substrates containing additional acidic proton, our attention turned to chlorine, bromine, and iodine substituted substrates (Table 2, entry 11, and Scheme 2). *N*-Benzyl-2,4-dichlorobenzamide having an additional chloro substituent at the 3-position reacted chemoselectively to give 4-chloro-2-hydroxybenzamide **11** in 91% yield.

Similarly, when the copper-catalyzed reaction was performed on 2-chloro-, 2-bromo-, and 2-iodo-*N*-(2-iodophenyl)benzamides (Scheme 2), hydroxylation occurred chemoselectively at 2-position and iodine substituent remained unaffected. From this study, it is observed that hydroxylation occurred selectively at ortho position (ortho to benzamide functionality) and other halogen (chlorine and iodine) substituent remains unaffected under the reaction conditions. This excellent selectivity could be due to anchimeric effect of ortho amide functionality.

Other aromatics such as naphthyl, pyridyl, and thiophenyl also showed compatibility in copper-catalyzed hydroxylation reaction and the yield of the reaction seems invariable with respect to heteroaryl amides. 3-Hydroxy-2-naphthamide has been proven to be effective precursor for the sterioselective synthesis of 1,10-bi-2-naphthol



16 (92% from iodo)[a] none
16 (89% from bromo)[a] none
16 (86% from chloro)[a] trace[b]

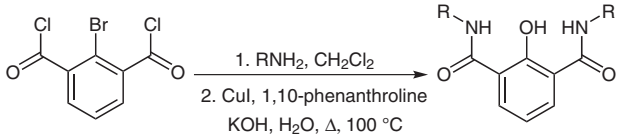
Scheme 2 Chemoselective copper-catalyzed hydroxylation. [a] Isolated yield. [b] Monitored by TLC and confirmed by NMR and mass spectrometry.

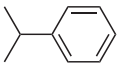
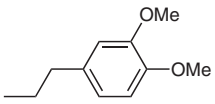
(BINOL), which is a well-known chiral ligand.[15] Here, 3-hydroxy-2-naphthamide **12** was obtained in 90% yield from 3-chloronaphthoyl chloride in one pot using copper-catalyzed hydroxylation reaction in neat water.

Synthesis of 2-hydroxynicotinamides has not been well explored[16] compared to 2-hydroxybenzamides presumably due to sluggish reaction between 2-hydroxynicotinoyl chloride and primary amine. 2-Hydroxynicotinamide **13** was readily obtained from easily available 2-chloronicotinic acid in 62% yield in one pot. Similar to pyridine, synthesis of thiophene-based hydroxy amide is also not well documented because of scarce availability of 3-hydroxythiophene-2-carboxylic acid. Moreover, synthesis of 2-hydroxythiophenamide and its related substrate 2-hydroxythiophene-3-carboxylic acid has not been described in the literature. Copper-catalyzed reaction in neat water can be exploited not only for the synthesis of 3-hydroxythiophenamide **15** but also for the synthesis of new 2-hydroxythiophenamide **14**.

The generality of copper-catalyzed hydroxylation reaction of 2-bromo-N^1,N^3- diphenylethylisophthalamide substrates having an additional amide functionality was also studied (Table 3). 2-Bromoisophthaloyl dichloride, which was readily available to us, was used for amidation followed by copper-catalyzed hydroxylation reaction. 2-Hydroxy-bis-benzamides **17** and **18** were obtained for the first time in 84 and 80% yield using copper-catalyzed reaction in neat water.

Table 3 Copper-Catalyzed Synthesis of 2-Hydroxy-N^1,N^3-diphenylethylisophthalamides in Water[a]



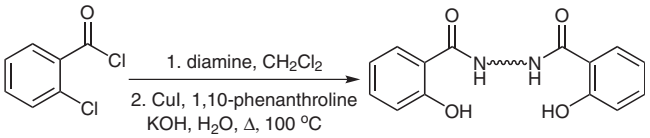
Entry	R		Yield (%)[b]
1		**17**	84
2		**18**	80

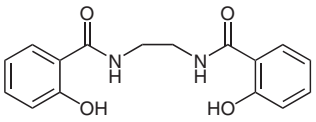
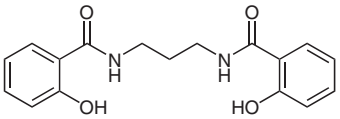
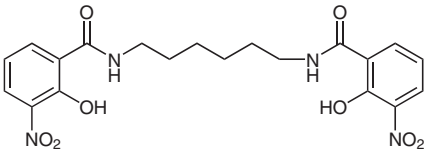
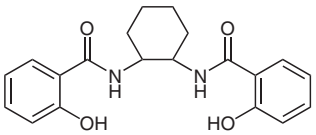
[a] Reaction conditions: 1. 2-bromoisophthaloyl dichloride (1.0 equiv), primary amine (2.4 equiv), CH_2Cl_2 (solvent), 0 °C to r.t., 5 h; 2. CuI/1,10-phenanthroline (10 mol%), KOH (8.0 equiv), H_2O (solvent), 100 °C.
[b] Isolated yield.

After studying the synthesis of 2-hydroxybenzamides, we explored the synthesis of bis(2-hydroxybenzamide) compounds (Table 4), which have been used as a ligand for metal complexation reaction.[17]

For this purpose, 2-chlorobenzoyl chloride was treated with diamines such as ethylenediamine, propylenediamine, and 1,2-diaminocyclohexane. Copper-catalyzed hydroxylation reaction on resulted diamide substrates gave bis-hydroxybenzamides in one pot (Table 4, entries 1–4).

Table 4 Copper-Catalyzed Synthesis of Bis(2-hydroxybenzamide) Compounds in Water[a]

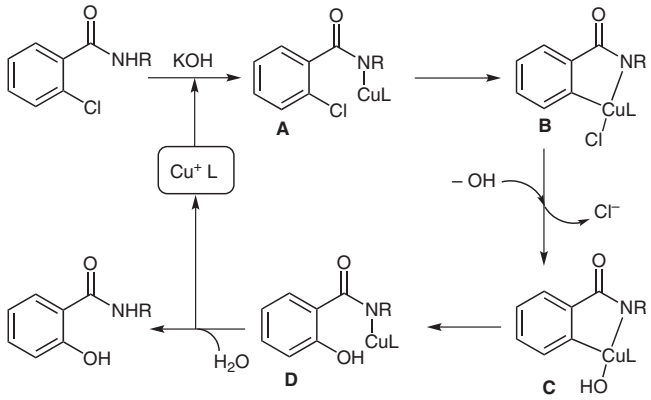


Entry	Product		Yield (%)[b]
1		**19**	77
2		**20**	72
3		**21**	63
4		**22**	74

[a] Reaction conditions: 1. 2-chlorobenzoyl chloride (1.0 equiv), primary amine (0.5 equiv), CH_2Cl_2 (solvent), 0 °C to r.t., 6 h; 2. CuI/1,10-phenanthroline (20 mol%), KOH (8.0 equiv), H_2O (solvent), 100 °C.
[b] Isolated yield.

The plausible catalytic cycle is presented in Scheme 3 for the copper-catalyzed hydroxylation of 2-chlorobenzamides under basic conditions in neat water. Copper(I) may react with the amide in the presence of a base and forms LCu(I)amide complex **A**. After this, oxidative addition of Cu into the C–Cl bond would lead to the formation of a Cu(III) intermediate **B**, which may undergo substitution reaction with OH^- leading hydroxocopper intermediate **C**. Reductive elimination would produce 2-hydroxybenzamide and concomitant release of LCu(I) complex. Although, other copper complex species may be present in the reaction mixture, concentration of LCu(I)amide **A** would be much higher as reported earlier.[18] Furthermore, oxidative addition of aryl chloride to LCu(I)amide is expected to be more favorable due to intramolecular nature of reaction.

2-Chloro-*N*,*N*-diethylbenzamide substrate lacking acidic proton was subjected to hydroxylation reaction under identical reaction conditions to gain further insight into the mechanism. Interestingly, formation of hydroxylated product was not observed as monitored by TLC and mass spectrometry. Similarly simple iodo- and chlorobenzene



Scheme 3 Proposed reaction mechanism for copper-catalyzed hydroxylation of 2-chlorobenzamide

failed to yield phenol under our reaction conditions in neat water. Chlorobenzene was recovered 90% from the reaction mixture after heating for 24 hours and iodobenzene was converted into a side product. 2-Chlorobenzoic acid substrate having CO_2H coordinating group also failed to give 2-hydroxybenzoic acid under our reaction conditions on heating for 48 hours.[19] It is worth citing that copper-catalyzed hydroxylation in 2-chlorobenzoic acid, similar substrate to 2-chlorobenzamide, has been studied. However, the reaction requires longer time and phase-transfer reagent to achieve 2-hydroxybenzoic acid in 66% yield.[9c] These control experiments and related reported study suggest that the presence of amidic proton (NH) in the substrate is crucial for hydroxylation in neat water.

In summary, we have developed a simple and efficient copper-catalyzed method for the synthesis of substituted 2-hydroxybenzamides from 2-chloroaroyl chloride in one pot. The reaction system requires readily available substrates and reagents such as 2-chloroaroyl chlorides, primary amines, copper iodide, 1,10-phenanthroline, potassium hydroxide, and eco-friendly solvent water. Furthermore, mild reaction conditions and simple purification procedure make this method highly practical. We have also achieved the synthesis of some important 2-hydroxybenzamides, which are not accessible by other methods. Overall, broader substrate scope, excellent selectivity, and mild reaction conditions will be useful for the synthesis of substituted 2-hydroxybenzamides on smaller to larger scale. Further investigation to broaden the substrate scope of this copper-catalyzed hydroxylation reaction in neat water is currently ongoing in our laboratory.

All NMR experiments were carried out on 400 or 500 MHz spectrometers in DMSO-d_6 or $CDCl_3$ and NMR chemical shifts are reported in ppm referenced to the solvent peaks of $CDCl_3$ [7.26 ppm for ^{1}H and 77.1 (± 0.1) ppm for ^{13}C, respectively] or DMSO-d_6 (2.50 ppm for ^{1}H and 39.5 ppm for ^{13}C, respectively). Mass analysis is performed on quadruple-time of flight (Q-TOF) mass spectrometer equipped with an ESI source (+ve or –ve). Melting points are uncorrected. CuI and 1,10-phenanthroline were used as received from Aldrich. Silica gel (60 mesh size) was used for column chromatography. TLC analysis of reaction mixtures was performed using silica gel plates. Substituted benzoyl chlorides were prepared from respective benzoic acids by refluxing with excess $SOCl_2$. Excess of $SOCl_2$ was removed under vacuo and the resulting residue was used for amide preparation without further purification.

_N_-Benzyl-2-hydroxybenzamide (1); Typical Procedure

In a 50 mL capacity single-necked round-bottomed flask, 2-chlorobenzoyl chloride (0.425 g, 2.4 mmol) was dissolved in anhyd CH_2Cl_2 (15 mL) and cooled to 0 °C. To this cold solution was slowly added benzylamine (0.385 g, 3.6 mmol) in CH_2Cl_2 (10 mL) from a dropping funnel. The resulting reaction mixture was stirred for 1 h at 0 °C and 2 h at r.t. Then, CH_2Cl_2 was evaporated under reduced pressure at 40 °C. The residue was washed with H_2O (15 mL) and the aqueous layer was decanted. To the crude 2-chloro-*N*-benzylbenzamide were added H_2O (8 mL), CuI (46 mg, 0.24 mmol), and 1,10-phenanthroline (44 mg, 0.24 mmol), and the mixture was stirred at r.t. for 10 min. Then, KOH (1.4 g, 24.4 mmol) was added. After this, the reaction flask was fitted with a reflux condenser and the mixture was heated at reflux in an oil bath at 100 °C for 10 h. Progress of the reaction was monitored by TLC (eluent: hexane–EtOAc, 8:2). The reaction mixture was acidified with 10% aq HCl and extracted with EtOAc (3 × 30 mL). The combined EtOAc layers were dried (Na_2SO_4) and evaporated under reduced pressure at 40 °C. The crude product was of almost pure quality (see NMR data in Supporting Information for crude product) and was purified by column chromatography [silica gel, EtOAc–hexane (1:4)]; yield: 0.53 g (96%); colorless crystals; mp 134–136 °C (Lit.[20] mp 134–137 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.34 (s, 1 H), 7.44–7.36 (m, 7 H), 7.02 (dd, *J* = 8.4, 1.0 Hz, 1 H), 6.85 (m, 1 H), 6.65 (s, 1 H), 4.66 (d, *J* = 5.7 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 161.6, 137.4, 134.4, 128.9, 127.92, 127.91, 125.4, 118.70, 118.69, 114.1, 43.7.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{14}NO_2$: 226.0862; found: 226.0869.

2-Hydroxy-_N_-phenylbenzamide (2)

Column chromatography [silica gel, EtOAc–hexane (1:4)]; yield: 0.60 g (94%); colorless crystals; mp 129 °C (Lit.[21] mp 129–131 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.0 (s, 1 H), 8.0 (s, 1 H), 7.62–7.54 (m, 3 H), 7.49–7.38 (m, 3 H), 7.23 (m, 1 H), 7.05 (dd, *J* = 8.4, 1.0 Hz, 1 H), 6.94 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4, 161.8, 136.6, 134.7, 129.2, 125.5, 125.4, 121.3, 119.0, 118.9, 114.6.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{12}NO_2$: 212.0706; found: 212.0702.

_N_-Benzyl-5-fluoro-2-hydroxybenzamide (3)

Column chromatography [silica gel, EtOAc–hexane (1:4)]; yield: 0.20 g (72%); colorless crystals; mp 150–152 °C.

IR (KBr): 3365, 3055, 2930, 1643, 1601, 1555, 1505, 1455, 1420, 1367, 1265, 1236, 1164, 1142, 1106, 739, 703 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.0 (s, 1 H), 7.42–7.34 (m, 6 H), 7.15 (m, 1 H), 7.06 (dd, *J* = 8.8, 3.0 Hz, 1 H), 7.0 (m, 1 H), 6.5 (br s, 1 H), 4.64 (d, *J* = 5.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 167.5, 164.9, 163.9, 163.8, 137.2, 129.0, 128.0, 127.9, 127.3, 127.2, 110.82, 110.79, 106.7, 106.5, 105.4, 105.2, 43.7.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{12}FNO_2$ + Na: 268.0744; found: 268.0741.

_N_-Benzyl-4-fluoro-2-hydroxybenzamide (4)

Column chromatography [silica gel, EtOAc–hexane (1:4)]; yield: 0.155 g (83%); colorless crystals; mp 86 °C.

IR (KBr): 3359, 2923, 1647, 1605, 1551, 1501, 1355, 1238, 831 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.0 (s, 1 H), 7.43–7.32 (m, 5 H), 7.18–7.13 (m, 1 H), 7.06 (dd, *J* = 8.8, 3.0 Hz, 1 H), 7.0–6.97 (m, 1 H), 6.53 (s, 1 H), 4.65 (d, *J* = 5.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.91, 168.88, 157.76, 157.74, 156.1, 153.7, 137.1, 128.9, 128.0, 127.9, 121.5, 119.9, 119.8, 113.96, 113.90, 111.2, 110.9, 43.9.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{12}FNO_2$ + Na: 268.0744; found: 268.0786.

_N_-Benzyl-4,5-difluoro-2-hydroxybenzamide (5)
Column chromatography [silica gel, EtOAc–hexane (1:4)]; yield: 0.24 g (87%); colorless crystals; mp 118 °C.

IR (KBr): 3374, 2921, 1598, 1558, 1515, 1371, 1270, 1199, 1156, 860, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.4 (s, 1 H), 7.43–7.35 (m, 5 H), 7. 19 (t, *J* = 9.4 Hz, 1 H), 6.81 (m, 1 H), 6.44 (s, 1 H), 4.64 (d, *J* = 5.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 159.1, 159.0, 155.3, 155.2, 152.8, 152.6, 144.6, 144.5, 142.2, 142.1, 137.0, 129.011, 128.1, 128.0, 113.33, 113.3, 113.14, 113.12, 109.5, 107.3, 107.1, 43.9.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{11}F_2NO_2$ + Na: 286.0648; found: 286.0650.

_N_-Benzyl-2-hydroxy-5-nitrobenzamide (6)
Column chromatography [silica gel, EtOAc–hexane (1:4)]; yield: 0.24 g (85%); yellow crystals; mp 221–223 °C (Lit.[22] mp 221–223 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.3 (s, 1 H), 8.51 (dd, *J* = 7.8, 1.8 Hz, 1 H), 8.27 (dd, *J* = 8.4, 1.7 Hz, 1 H), 8.11 (br s, 1 H), 7.40–7.33 (m, 5 H), 7.12 (t, *J* = 7.8 Hz, 1 H), 4.71 (d, *J* = 5.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.6, 152.4, 138.4, 136.7, 133.7, 127.69, 127.66, 126.6, 126.5, 121.6, 118.8, 43.0.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{12}FNO_2$ + Na: 268.0744; found: 268.0786.

_N_-Benzyl-2-hydroxy-3-nitrobenzamide (7)
Column chromatography [silica gel, EtOAc–hexane (1:4)]; yield: 0.32 g (87%); yellow crystals; mp 122 °C (Lit.[23] mp 122 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.34 (s, 1 H), 8.50 (dd, *J* = 7.7, 1.8 Hz, 1 H), 8.27 (dd, *J* = 8.4, 1.8 Hz, 1 H), 8.12 (br s, 1 H), 7.40–7.33 (m, 5 H), 7.12 (t, *J* = 8.1 Hz, 1 H), 4.71 (d, *J* = 5.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.8, 153.5, 139.5, 137.8, 134.8, 128.81, 128.78, 127.72, 127.6, 122.6, 119.9, 44.1.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{12}N_2O_4$ + Na: 295.0689; found: 295.0689.

_N_-Benzyl-2-hydroxy-5-methoxybenzamide (8)
Column chromatography [silica gel, EtOAc–hexane (1:4)], yield: 0.28 g (61%); colorless crystals; mp 90–92 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.8 (s, 1 H), 7.39–7.33 (m, 5 H), 7.03 (dd, *J* = 9.0, 2.9 Hz, 1 H), 6.95 (d, *J* = 9.0 Hz, 1 H), 6.87 (d, *J* = 2.9 Hz, 1 H), 6.71 (s, 1 H), 4.64 (d, *J* = 5.7 Hz, 2 H), 3.76 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.6, 155.6, 151.8, 137.4, 128.9, 127.91, 127.87, 121.1, 119.3, 114.0, 109.9, 56.1, 43.7.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{15}NO_3$ + Na: 280.0944; found: 280.0919.

2-Hydroxy-3-methoxy-_N_-[1-(naphthalen-1-yl)ethyl]benzamide (9)
Column chromatography [silica gel, EtOAc–hexane (1:3)]; yield: 0.08 g (44%); colorless crystals; mp 176–180 °C.

IR (KBr): 3360, 3054, 2925, 2847, 1638, 1585, 1539, 1462, 1375, 1249, 1061, 777, 739 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.90 (s, 1 H), 8.14 (d, *J* = 8.3 Hz, 1 H), 7.90 (dd, *J* = 7.9, 1.7 Hz, 1 H), 7.85 (d, *J* = 8.2 Hz, 1 H), 7.62–7.49 (m, 4 H), 7.02 (dd, *J* = 8.2, 1.3 Hz, 1 H), 6.96 (dd, *J* = 8.1, 1.2 Hz, 1 H), 6.85 (br d, *J* = 7.5 Hz, 1 H), 6.75 (t, *J* = 8.0 Hz, 1 H), 6.12 (quint, *J* = 7.0 Hz, 1 H), 3.90 (s, 3 H), 1.80 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4, 151.1, 148.9, 137.7, 134.0, 131.0, 128.9, 128.6, 126.8, 126.0, 125.2, 123.1, 122.7, 118.2, 117.6, 114.8, 114.7, 56.1, 45.2, 20.8.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{19}NO_3$ + Na: 344.1257; found: 344.1260.

2-Hydroxy-_N_-(2-hydroxyethyl)benzamide (10)
Column chromatography [silica gel, EtOAc–hexane (2:3)]; yield: 0.23 g (64%); colorless crystals; mp 113–114 °C (Lit.[24] mp 113–114 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.2 (s, 1 H), 7.46 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.36 (t, *J* = 7.8 Hz, 1 H), 6.94 (d, *J* = 8.3 Hz, 1 H), 6.81 (t, *J* = 7.6 Hz, 1 H), 3.80 (t, *J* = 5.0 Hz, 2 H), 3.57 (q, *J* = 5.3 Hz, 2 H), 3.07 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 160.9, 134.3, 126.0, 119.0, 118.3, 114.3, 42.1, 29.7.

HRMS (ESI): *m*/*z* $[M – H]^+$ calcd for $C_9H_{10}NO_3$: 180.0655; found: 180.0708.

_N_-Benzyl-4-chloro-2-hydroxybenzamide (11)
Column chromatography [silica gel, EtOAc–hexane (1:4)]; yield: 0.29 g (91%); colorless crystals; mp 124 °C (Lit.[25] mp 123–127 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.40 (s, 1 H), 7.33–7.18 (m, 6 H), 6.93 (d, *J* = 2.1 Hz, 1 H), 6.73 (dd, *J* = 8.6, 2.1 Hz, 1 H), 6.47 (br s, 1 H),), 4.55 (d, *J* = 5.7 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.5, 160.7, 138.3, 135.5, 127.3, 126.35, 126.3, 124.6, 117.5, 117.1, 111.0, 42.1.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{12}ClNO_2$ + Na: 284.0449; found: 284.0437.

_N_-Benzyl-3-hydroxy-2-naphthamide (12)
Column chromatography [silica gel, EtOAc–hexane (1:4)]; yield: 0.12 g (90%); colorless crystals; mp 164 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.75 (s, 1 H), 7.78–7.67 (m, 2 H), 7.48–7.28 (m, 8 H), 6.88 (br s, 1 H), 4.72 (d, *J* = 5.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.6, 156.7, 137.3, 137.1, 129.0, 128.6, 128.5, 128.05, 128.0, 126.8, 126.8, 126.3, 123.9, 116.9, 112.4, 44.0.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{15}NO_2$ + Na: 300.0995; found: 300.0977.

_N_-Benzyl-2-hydroxynicotinamide (13)
Column chromatography [silica gel, EtOAc–hexane (1:4)]; yield: 111 mg (62%); pale yellow powder; mp 190–192 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.85 (s, 1 H), 9.99 (br t, *J* = 5.4 Hz, 1 H), 8.68 (dd, *J* = 7.2, 2.2 Hz, 1 H), 7.47 (dd, *J* = 6.3, 2.2 Hz, 1 H), 7.41–7.37 (m, 5 H), 6.54 (dd, *J* = 7.2, 6.3 Hz, 1 H), 4.71 (d, *J* = 5.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.0, 163.8, 145.5, 138.6, 137.7, 128.6, 127.5, 127.2, 121.4, 108.0, 43.4.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{12}N_2O_2$ + Na: 251.0791; found: 251.0781.

_N_-Benzyl-2-hydroxythiophene-3-carboxamide (14)
Column chromatography [silica gel, EtOAc–hexane (1:4)]; yield: 29 mg (33%); colorless crystals; mp 78–80 °C.

IR (KBr): 3313, 3091, 2925, 2852, 1633, 1550, 1453, 1421, 1293, 1057, 827, 720, 696 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.9 (dd, *J* = 3.0, 1.3 Hz, 1 H), 7.41 (dd, *J* = 5.1, 1.3 Hz, 1 H), 7.39–7.31 (m, 6 H), 6.33 (br s, 1 H), 4.60 (d, *J* = 5.7 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.9, 138.2, 137.3, 128.8, 128.4, 127.9, 127.7, 126.6, 126.0, 43.9.

HRMS (ESI): *m*/*z* $[M - H]^+$ calcd for $C_{12}H_{10}NO_2S$: 232.0427; found: 232.0434.

_N_-Benzyl-3-hydroxythiophene-2-carboxamide (15)
Column chromatography [silica gel, EtOAc–hexane (1:4)]; yield: 0.157 g (57%); colorless crystals; mp 114–116 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.20 (s, 1 H), 7.36 (m, 5 H), 7.25 (d, *J* = 5.4 Hz, 1 H), 6.80 (d, *J* = 5.4 Hz, 1 H), 6.00 (s, 1 H), 4.60 (d, *J* = 5.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.0, 163.9, 137.7, 127.85, 127.80, 127.78, 127.3, 120.2, 104.9, 43.4.

HRMS (ESI): *m*/*z* $[M - H]^+$ calcd for $C_{12}H_{10}NO_2S$: 232.0427; found: 232.0426.

2-Hydroxy-_N_-(2-iodophenyl)benzamide (16) from 2-Halo-_N_-(2-iodophenyl)benzamide
Column chromatography [silica gel, EtOAc–hexane (1:4)]; yield starting from 2-iodo-*N*-(2-iodophenyl)benzamide: 0.345 g (92%), from 2-bromo-*N*-(2-iodophenyl)benzamide: 0.30 g (89%), from 2-chloro-*N*-(2-iodophenyl)benzamide: 0.57 g (86%) (Scheme 2); colorless crystals; mp 137–139 °C.

IR (KBr): 3420, 2922, 1667, 1614, 1436, 1288, 1247, 1212, 1158, 910, 748, 657 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.80 (s, 1 H), 8.3 (s, 1 H), 8.23 (dd, *J* = 8.3, 1.5 Hz, 1 H), 7.78 (dd, *J* = 8.0, 1.4 Hz, 1 H), 7.60 (dd, *J* = 8.0, 1.4 Hz, 1 H),7.40 (m, 1 H) 7.35 (m, 1 H), 6.99 (dd, *J* = 8.4, 1.0 Hz, 1 H), 6.93 (m, 2 H).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{10}INO_2$: 360.9576; found: 360.3246.

2-Hydroxy-N^1,N^3-bis(1-phenylethyl)isophthalamide (17)
Column chromatography [silica gel, EtOAc–hexane (2:3)]; yield: 0.230 g (84%); colorless crystals; mp 168–170 °C.

IR (KBr): 3311, 3064, 2977, 2930, 1650, 1597, 1580, 1538, 1435, 1365, 1276, 1210, 757, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.5 (s, 1 H), 7.95 (d, *J* = 7.8 Hz, 2 H), 7.41–7.26 (m, 12 H), 6.90 (t, *J* = 7.8 Hz, 1 H), 5.33 (quint, *J* = 7.0 Hz, 2 H), 1.60 (d, *J* = 7.0 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.9, 160.6, 143.2, 133.1, 128.7, 127.4, 126.1, 118.5, 118.0, 49.4, 22.1.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{24}N_2O_3$ + Na: 389.1860; found: 389.1906.

N^1,N^3-Bis(3,4-dimethoxyphenethyl)-2-hydroxyisophthalamide (18)
Column chromatography [silica gel, EtOAc–hexane (1:1)]; yield: 0.240 g (80%); colorless crystals; mp 138 °C.

IR (KBr): 3368, 2928, 1651, 1590, 1515, 1438, 1261, 1233, 1156, 1028, 806, 761 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.91 (s, 1 H), 8.81 (br t, 2 H), 8.02 (d, *J* = 7.8 Hz, 2 H), 7.01 (t, *J* = 7.7 Hz, 1 H), 6.88 (d, *J* = 9.3 Hz, 4 H), 6.77 (d, *J* = 7.8 Hz, 2 H), 3.72 (s, 12 H), 3.54 (q, *J* = 7.9 Hz, 4 H), 2.80 (t, *J* = 7.0 Hz, 4 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.4, 160.1, 149.0, 147.7, 133.1, 132.1, 121.0, 118.7, 113.0, 112.3, 55.9, 55.8, 41.3, 34.8.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{28}H_{32}N_2O_7$ + Na: 531.2102; found: 531.2073.

***N*,*N*′-(Ethane-1,2-diyl)bis(2-hydroxybenzamide) (19)**
Column chromatography [silica gel, EtOAc–hexane (1:1)]; yield: 0.27 g (77%); colorless crystals; mp 110 °C (Lit.[26] mp 111–113 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.95 (br t, 2 H), 7.82 (d, *J* = 8.0 Hz, 2 H), 7.38 (dt, *J* = 7.7, 1.6 Hz, 2 H), 6.9 (m, 4 H), 3.49 (t, *J* = 2.6 Hz, 4 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 174.6, 165.3, 138.9, 132.9, 123.7, 122.6, 120.4, 43.8.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{16}N_2O_4$ + Na: 323.1002; found: 323.1027.

***N*,*N*′-(Propane-1,3-diyl)bis(2-hydroxybenzamide) (20)**
Column chromatography [silica gel, EtOAc–hexane (1:1)]; yield: 0.32 g (72%); colorless crystals; mp 181 °C (Lit.[26] mp 181–182 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.60 (s, 2 H), 8.87 (t, *J* = 5.4 Hz, 2 H), 7.84 (dd, *J* = 7.8, 1.2 Hz, 2 H), 7.38 (t, *J* = 7.7 Hz, 2 H), 6.90 (t, *J* = 8.3 Hz, 4 H), 3.4 (t, *J* = 6.4 Hz, 4 H), 1.84 (quint, *J* = 7.0 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.5, 160.5, 134.1, 128.1, 119.0, 117.8, 115.7, 37.2, 29.3.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{17}H_{18}N_2O_4$ + Na: 337.1159; found: 337.1192.

***N*,*N*′-(Hexane-1,6-diyl)bis(2-hydroxy-3-nitrobenzamide) (21)**
Column chromatography [silica gel, EtOAc–hexane (3:2)]; yield: 0.14 g (63%); pale yellow crystals; mp 170–172 °C.

IR (KBr): 3304, 2929, 2853, 1644, 1581, 1524, 1434, 1367, 1285, 741 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.60 (s, 2 H), 9.25 (t, *J* = 5.4 Hz, 2 H), 8.18 (dd, *J* = 8.0, 1.5 Hz, 2 H), 8.10 (dd, *J* = 8.0, 1.5 Hz, 2 H), 7.06 (t, *J* = 8.0 Hz, 2 H), 3.33 (q, *J* = 6.8 Hz, 4 H) (merged with H_2O), 1.60 (m, 4 H), 1.40 (m, 4 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.1, 155.4, 139.0, 132.7, 129.6, 118.1, 117.6, 39.7, 28.9, 26.5.

HRMS (ESI): *m*/*z* $[M - H]^+$ calcd for $C_{20}H_{21}N_4O_8$: 445.1354; found: 445.1356.

***N*,*N*′-(Cyclohexane-1,2-diyl)bis(2-hydroxybenzamide) (22)**
Column chromatography [silica gel, EtOAc–hexane (3:2)]; yield: 0.23 g (74%); colorless crystals; mp 235 °C (Lit.[27] mp 238–239 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.39 (s, 2 H), 8.64 (d, *J* = 7.4 Hz, 2 H), 7.77 (d, *J* = 7.8 Hz, 2 H), 7.34 (dt, *J* = 7.6, 1.5 Hz, 2 H), 6.84 (m, *J* = 10.9 Hz, 4 H), 4.03 (m, 2 H), 1.97 (m, 2 H), 1.76 (m, 2 H), 1.52 (m, 2 H), 1.33 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.9, 160.2, 134.0, 128.4, 118.9, 117.6, 115.8, 52.6, 32.0, 25.0.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{22}N_2O_4$ + Na: 377.1472; found: 377.1471.

Acknowledgment

Dr. S.K. thanks Department of Science and Technology (DST), New Delhi and Board of Research in Nuclear Science (BRNS), Department of Atomic Energy, Bombay for funding. Central Instrument facility at IISER Bhopal is thanked for NMR and Mass data collection. S.J.B. is thankful to IISER Bhopal and University Grant Commission, New Delhi for a fellowship. S.K. kindly acknowledges one of the reviewers for constructive suggestions.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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