Lewis Acid Catalyzed One-Pot Selective Synthesis of Aminobenzofurans and *N*-Alkyl-2-aryl-2-(arylimino)acetamides: Product Dependence on the Nature of the Aniline

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Abstract: An efficient one-pot reaction between isocyanides, anilines, and salicylaldehydes (2-hydroxybenzaldehydes) in the presence of a Lewis acid proceeds smoothly at room temperature within a short time interval to afford aminobenzofurans and *N*-alkyl-2-aryl-2-(arylimino)acetamide derivatives in high yields depending on the electron density of the aniline component.

Key words: multicomponent reaction, Lewis acids, substituent effects, cyclization, Schiff bases

Multicomponent reactions (MCRs)[1] have a significant importance due to their exceptional synthetic efficiency. They allow the incorporation of more than two building blocks giving rise to complex structures in a one-pot reaction. MCRs also tend to be ecofriendly by reducing the number of synthetic steps, time consumption, and waste production. Isocyanide-based MCRs,[2] for example the Passerini[1e,3] and Ugi reactions,[4] are especially important for the construction of diverse chemical libraries of interesting heterocyclic scaffolds. They are able to deliver a wide variety of peptide analogues and heterocyclic compounds for study in drug discovery programmes. The high reactivity of isocyanides towards C(sp^2 or sp) electrophilic centers[5] makes them useful reactants in organic synthesis, especially in one-pot reactions.

A few methods have been reported for the synthesis of heterocycles utilizing isocyanides, amines, and aldehydes in the presence of an acid catalyst,[2e–h] but these either require long reaction times or high temperatures to complete the reaction. Garcia–Gonzalez et al.[2f] reported that MCRs involving an aryl isocyanide, a salicylaldehyde (2-hydroxybenzaldehyde), and 2-aminophenol in refluxing toluene containing ammonium chloride as proton source gave benzoxazine derivatives via cyclization involving the *o*-hydroxy group of the aniline component; the alternative benzofuran derivative was not formed. With 4-nitroaniline on the other hand, benzoxazine formation is not possible and the final product is derived via elimination of the aniline component. Ramazani et al.[2g] used salicylaldehyde derivatives and a secondary amine in the presence of silica gel and observed the formation of iminobenzofuran derivatives taking 24 hours. This prompted us to develop such a methodology that would preferably require room temperature and shorter reaction times. We believe that the use of an appropriate Lewis acid catalyst can improve the reaction conditions. Hence we have investigated different Lewis acid catalysts for the synthesis of the heterocyclic molecule.

In this article, we observed that the use of primary aromatic amines bearing a strong electron-withdrawing group (R^2 = 2-CO_2H, 3-NO_2, or 4-NO_2) with a salicylaldehyde derivative and an alkyl isocyanide in ethanol containing cerium(IV) ammonium nitrate[6] as a Lewis acid catalyst affords aminobenzofuran derivatives in high yield (79–85%), whereas for aniline derivatives lacking a strong EWG the reaction takes a different course and *N*-alkyl-2-aryl-2-aryliminoacetamide derivatives are obtained in good yield (65–76%) via an oxidation step. It may be pointed out that though many natural products[7] containing benzofuran moieties are biologically active,[8,9] there are few reports[2g–i,10,11] on the synthesis of benzofuran derivatives. To the best of our knowledge, this is the first one-pot synthesis of aminobenzofuran derivatives using a Lewis acid catalyst at low temperatures within a short reaction time. Our method also offers an ecofriendly approach to benzofuran derivatives with varying substitution patterns.

In our initial experiments, salicylaldehyde, 4-nitroaniline, and *tert*-butyl isocyanide were employed to optimize the reaction conditions. As shown in Table 1, a series of Lewis acid catalysts were screened and cerium(IV) ammonium nitrate seemed to be the best choice. Using the optimized reaction conditions, salicylaldehydes **1**, aniline derivatives containing strong electron-withdrawing substituents **2**, and isocyanides **3** were reacted to produce benzofuran derivatives **7** (Table 2). We selected 4-nitroaniline, 3-nitroaniline, and anthranilic acid as strong electron-deficient anilines. In the presence of the carboxylic acid group of anthranilic acid, the desired aminobenzofuran derivatives **7b–d** (entries 2–4,) were formed in good yield (82–85%) after column chromatography. The reactions were complete within 35–45 minutes in the presence of cerium(IV) ammonium nitrate (based on TLC monitoring), whereas without cerium(IV) ammonium nitrate, or any Lewis acid, reactions were very slow.

Interestingly, when reactions were carried out with 2-chloroaniline, 2-bromoaniline, 2-iodoaniline, and 4-bromoaniline **2**, isocyanides **3**, and salicylaldehydes **1**, we

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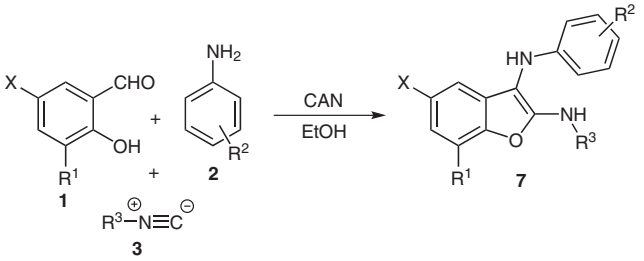
Table 1 Optimization of Reaction Conditions[a]

Entry	Catalyst	Time (h)	Yield[b] (%)
1	$FeCl_3$	24	45
2	$Cu(OAc)_2$	24	n.r.[c]
3	$Ce(NH_4)_2(NO_3)_6$ (CAN)	2	83
4	$Zn(OAc)_2$	24	n.r.[c]
5	$Yb(OTf)_3$	2	68
6	$Er(OTf)_3$	2	65
7	$In(OTf)_3$	2	68
8	$Sm(OTf)_3$	2	75
9	$Y(OTf)_3$	2	60
10	$CuBr_2$	24	n.r.[c]
11	$CeCl_3 \cdot 7\ H_2O$	2	48

[a] Reaction conditions: salicylaldehyde, 4-nitroaniline, *tert*-butyl isocyanide, catalyst (5 mol%), EtOH (5 mL), r.t.
[b] Isolated yield.
[c] No reaction.

Table 2 Efficient Synthesis of Benzofuran Derivatives[a]



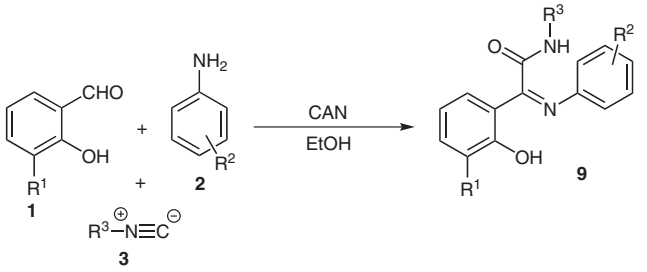
Entry	R^1	X	R^2	R^3	Product	Yield[b] (%)
1	H	H	4-NO_2	*t*-Bu	**7a**	83
2	H	H	2-CO_2H	*t*-Bu	**7b**	84
3	H	H	2-CO_2H	*i*-Pr	**7c**	82
4	H	NO_2	2-CO_2H	*t*-Bu	**7d**	85
5	OMe	H	3-NO_2	*t*-Bu	**7e**	79

[a] Reaction conditions: salicylaldehyde (1 mmol), electron-deficient aniline (1 mmol), isocyanide (1 mmol), CAN (5 mol%), EtOH (5 mL), r.t., 2 h.
[b] Isolated yield.

obtained the unusual adducts, *N*-alkyl-2-aryl-2-(arylimino)acetamide derivatives **9** (Table 3). In the presence of electron-releasing group (OMe) in the salicylaldehyde component using 2-bromoaniline, 4-bromoaniline, compounds **9e** and **9f** were isolated in 75% and 76% yields, respectively (entries 5 and 6).

When the reaction with salicylaldehyde, aniline, and *tert*-butyl isocyanide was carried out under the same conditions, the unusual adduct **9d** (entry 4) was formed in 65% yield. Reaction with cyclohexyl isocyanide, 2-iodoaniline, and salicylaldehyde produced **9c** in 68% yield (entry 3), and using *tert*-butyl isocyanide gave **9b** in 72% yield (entry 2). Next we planned to carry out one reaction in the presence of electron-rich salicylaldehyde and electron-deficient aniline; the reaction of *o*-vanillin, 3-nitroaniline, and *tert*-butyl isocyanide in presence of cerium(IV) ammonium nitrate gave benzofuran derivative **7e** (entry 5) in good (79%) yield.

Table 3 Synthesis of *N*-Alkyl-2-aryl-2-(arylimino)acetamide Derivatives[a]



Entry	R^1	R^2	R^3	Product	Yield[b] (%)
1	H	2-Cl	*t*-Bu	**9a**	73
2	H	2-I	*t*-Bu	**9b**	72
3	H	2-I	Cy	**9c**	68
4	H	H	*t*-Bu	**9d**	65
5	OMe	2-Br	*t*-Bu	**9e**	75
6	OMe	4-Br	*t*-Bu	**9f**	76

[a] Reaction conditions: salicylaldehyde (1 mmol), halogenated aniline (1 mmol), isocyanide (1 mmol), CAN (5 mol%), EtOH (5 mL), r.t., 2 h.
[b] Isolated yield.

In all of the above cases the reactions were quite clean. It should be noted that the attempted reactions with benzylamine furnished only the corresponding imine with salicylaldehyde and *tert*-butyl isocyanide; *p*-anisidine and *p*-toluidine resulted in intractable mixtures of products.

Compounds **7a–e** were characterized on the basis of their IR, ^1H and ^{13}C NMR, and mass spectra and elemental analysis. The ^1H NMR spectrum of **7a** consisted of one singlet for the *tert*-butyl group (δ = 1.32, CMe_3), deuterium oxide exchangeable signals for amine hydrogen atoms (δ = 5.71 and 8.37) along with appropriate chemical shifts for the eight hydrogen atoms of the two aromatic moieties. The ^{13}C NMR spectrum of **7a** showed 18 distinct resonances, in agreement with the adduct structure. The mass spectrum of **7a** displayed a peak at *m/z* 348 attributed to the $[M + Na]^+$ ion. The ^1H and ^{13}C NMR spectra of compounds **7b–e** were broadly similar to those of **7a**, except for the signals for the aromatic moieties and the alkyl groups which exhibited the expected changes in signal patterns.

For compounds **9a–f**, the ^1H NMR spectrum of **9a** consisted of one singlet for the *tert*-butyl group (δ = 1.12, CMe_3),

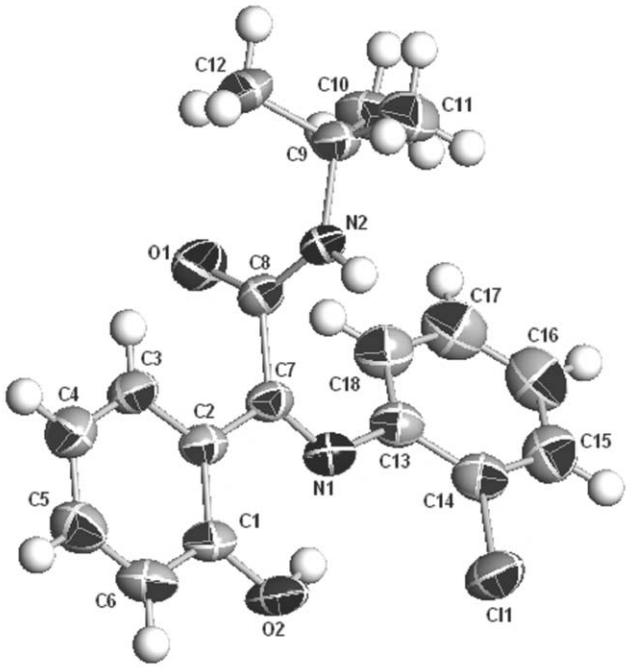
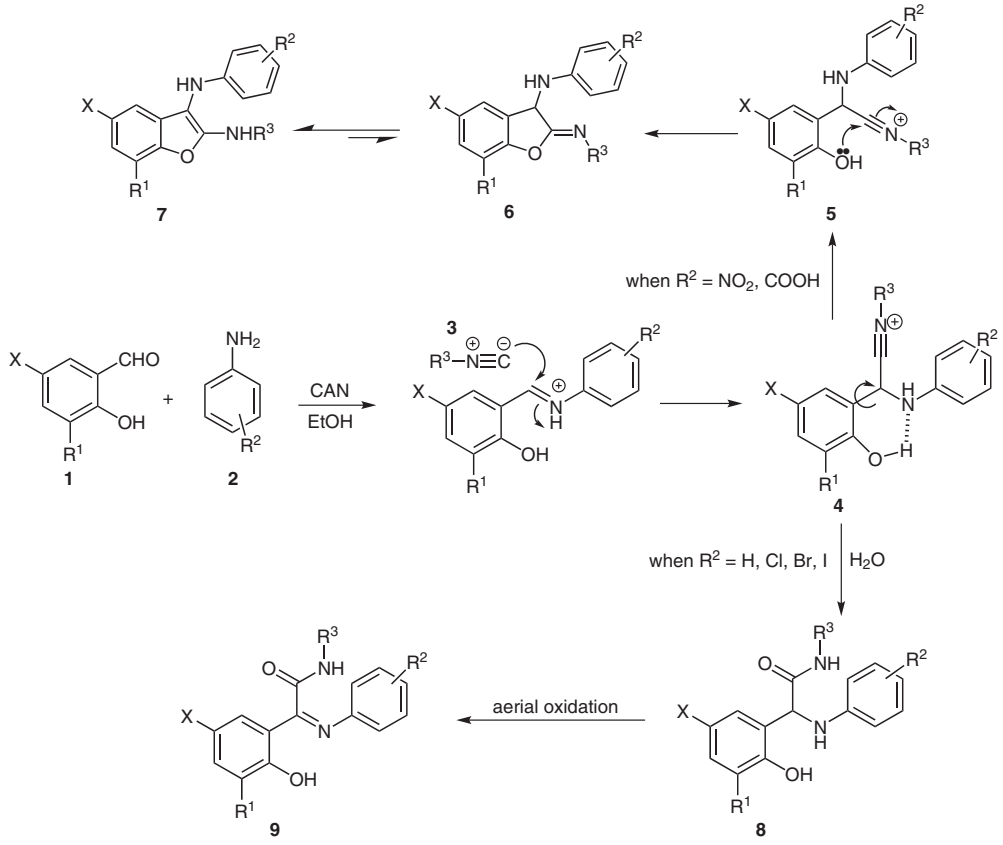


Figure 1 ORTEP diagram of compound **9a**

one amide proton signal (δ = 5.48) and one sharp singlet at δ = 12.79 which indicate the presence of the chelated phenolic OH group. Signals for eight hydrogen atoms with appropriate chemical shifts (δ = 6.90 to 7.55) and coupling constants indicated the presence of two aromatic rings. The ^{13}C NMR spectrum of **9a** showed 18 distinct peaks and the mass spectrum displayed the molecular ion peak $[M]^+$ at *m*/*z* 330. Finally single crystal X ray analysis[12] of **9a** conclusively confirmed its structure (Figure 1).

The data shows that the bond distance for C7–N1 is 1.286 Å, in agreement with the values reported for a C=N bond.[2f] It is of considerable importance that the crystal structure of **9a** shows one intramolecular interaction between O2–H2···N1 with distance 1.79 Å.[2f] This proximity is fully consistent with the strong deshielding of H2 (δ = 12.79) found in the ^{1}H NMR spectrum of **9a**. The ^{1}H and ^{13}C NMR spectra of compounds **9b–f** were similar to those of **9a**.

Although the mechanism of the above reactions has not been established, a possible one is outlined in Scheme 1.[2e] Initially the carbonyl group of **1** is activated by coordination of the oxygen atom with cerium(IV) ammonium nitrate facilitating the formation of the 2-(arylimino)phenol, which is also activated by cerium(IV) ammonium nitrate. Thereafter, nucleophilic addition of isocyanides **3** produces the intermediate **4** which is stabilized and conformationally locked by intramolecular hydrogen bonding, unless electron density around the aromatic amine nitrogen atom is reduced by a strong deactivating substituent (NO_2, CO_2H). In the conformation **4**, the adjacent hydroxy group cannot participate in intramolecular cyclization. As a consequence, addition of water[13] could result in adduct



Scheme 1 Proposed mechanism for the synthesis of benzofurans and *N*-alkyl-2-aryl-2-(arylimino)acetamide derivatives

8 and this produces the final product **9** upon aerial oxidation.

When R^2 = 2-CO_2H, 3-NO_2, 4-NO_2, i.e. in the presence of a strong electron-withdrawing substituent, poor electron density around aromatic amine nitrogen atom discourages the formation of an intramolecular hydrogen bond. Thus C–C bond rotation (as shown in **4**, Scheme 1) could result, leading to conformer **5**, which would generate **6** through intramolecular cyclization. Subsequent tautomerization could then lead to final product **7**.

In conclusion, we have developed an efficient, one-pot synthesis of benzofurans and the unusual *N*-alkyl-2-aryl-2-(arylimino)acetamide derivatives from readily available isocyanides **3**, salicylaldehyde or substituted analogues **1**, and substituted anilines **2** in the presence of a Lewis acid at room temperature.

The ease of purification, fairly short reaction times and good yields of the products make this procedure a useful addition to modern organic synthesis. Our methodologies also offer more opportunities for further functionalization.

Reaction at r.t. generally implies a temperature of 25 °C. Some reagents were obtained from commercial sources and used without purification. The solvents used were of technical grade, and freshly distilled prior to use. All melting points were obtained on a laboratory devices melting point bath and are uncorrected. ^{1}H (300 MHz, 600 MHz) and ^{13}C (75 MHz, 150 MHz) NMR spectra were recorded using $CDCl_3$ and DMSO-d_6 with TMS as internal standard on Bruker DPX 300 MHz and Bruker DRX 600 MHz NMR instruments at r.t. IR spectra were recorded on a Jasco-FTIR Model-410, using KBr pellets. Mass spectra were measured in ESIMS (+), EIMS, FAB-MS, and HRMS mode. DI-EIMS were recorded on a GCMS-Shimadzu-QP5050A and ESIMS were done on a Waters Micromass Q-TOF micro™ Mass Spectrometer. X-ray crystallographic data of single crystals were collected on Bruker Kappa Apex II with Mo-Kα radiation (λ = 0.71073 Å). TLC was performed on pre-coated plates (0.25 nm, silica gel 60 F_{254}). PE = petroleum ether.

2-(*tert*-Butylamino)-3-(nitrophenylamino)benzofurans 7a and 7e; General Procedure

To a stirred soln of salicylaldehyde or *o*-vanillin **1** (1 mmol) and nitroaniline **2** (1 mmol) in EtOH (5 mL) was added CAN (5 mol%) immediately followed by isocyanide **3** (1 mmol). The mixture was stirred at r.t. for 2 h and a yellow solid precipitated; this was filtered and washed with the minimum amount of EtOH. The filtrate was evaporated in vacuo and the solid was triturated (CH_2Cl_2 and hexane) to give a solid product which was combined with the previous yellow solid residue.

2-(*tert*-Butylamino)-3-(4-nitrophenylamino)benzofuran (7a)

Yellow powder; mp 162–165 °C; R_f = 0.62 (PE–EtOAc, 4:1).

IR (KBr): 3290, 2968, 1597, 1492, 1337, 1190, 1109, 835, 740 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.32 (s, 9 H), 5.71 (s, 1 H), 6.64 (d, *J* = 8.7 Hz, 2 H), 6.92 (d, *J* = 6.9 Hz, 1 H), 7.00–7.11 (m, 2 H), 7.39 (d, *J* = 7.5 Hz, 1 H), 8.04 (d, *J* = 9.0 Hz, 2 H), 8.37 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.4 (3 CH_3), 53.6 (C), 96.3 (C), 110.5 (CH), 112.4 (2 CH), 116.0 (CH), 120.9 (CH), 123.0 (CH), 126.2 (2 CH), 127.0 (C), 139.1 (C), 149.2 (C), 152.8 (C), 155.0 (C).

MS (ESI): *m*/*z* = 348 [M + Na]$^+$.

Anal. Calcd for $C_{18}H_{19}N_3O_3$: C, 66.45; H, 5.89; N, 12.91. Found: C, 66.27; H, 6.11; N, 13.12.

2-(*tert*-Butylamino)-7-methoxy-3-(3-nitrophenylamino)benzofuran (7e)

Yellow powder; mp 163–166 °C; R_f = 0.67 (PE–EtOAc, 4:1).

IR (KBr): 3316, 2967, 1625, 1527, 1475, 1348, 1303, 1203, 1087, 730 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.29 (s, 9 H), 3.93 (s, 3 H), 5.48 (s, 1 H), 6.56 (d, *J* = 7.5 Hz, 1 H), 6.71 (d, *J* = 7.8 Hz, 1 H), 6.96–7.02 (m, 2 H), 7.32–7.45 (m, 3 H), 7.67 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 30.1 (3 CH_3), 52.7 (C), 55.8 (CH), 98.7 (C), 104.5 (CH), 106.6 (CH), 108.9 (CH), 111.1 (CH), 119.4 (CH), 123.4 (CH), 129.2 (C), 130.0 (CH), 137.0 (C), 144.1 (C), 148.7 (C), 149.0 (C), 153.9 (C).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{21}N_3O_4$: 378.1430; found: 378.1469.

Anal. Calcd for $C_{19}H_{21}N_3O_4$: C, 64.21; H, 5.96; N, 11.82. Found: C, 64.09; H, 6.09; N, 11.64.

(Benzofuran-3-ylamino)benzoic Acids 7b–d; General Procedure

To a soln of salicylaldehyde **1** (1 mmol) and anthranilic acid **2** (1 mmol) in EtOH (5 mL) was added CAN (5 mol%) immediately followed by isocyanide **3** (1 mmol). The mixture was stirred at r.t. for 1 h. The solvent was removed via rotary evaporation. To the mixture was added H_2O (10 mL) and then it was extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The crude residue was purified via column chromatography (silica gel, 100–200 mesh) to give **7b–d**.

2-[2-(*tert*-Butylamino)benzofuran-3-ylamino]benzoic Acid (7b)

Brown powder; mp 178–181 °C; R_f = 0.27 (PE–EtOAc, 4:1).

IR (KBr): 3337, 2967, 1665, 1455, 1387, 1260, 744 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.29 (s, 9 H), 5.62 (s, 1 H), 6.46 (d, *J* = 6.6 Hz, 1 H), 6.67 (br s, 1 H), 6.90–6.91 (d-like, 1 H), 7.04 (s, 2 H), 7.27 (br s, 1 H), 7.37–7.39 (d-like, 1 H), 7.88 (br s, 1 H), 8.83 (br s, 1 H), 12.84 (br s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 30.2 (3 CH_3), 52.8 (C), 98.4 (C), 110.2 (CH), 113.4 (CH), 115.8 (CH), 116.2 (CH), 120.6 (CH), 122.6 (CH), 127.6 (C), 131.6 (CH), 134.0 (CH), 148.7 (C), 150.2 (C), 154.1 (C), 170.2 (C).

MS (EI): *m*/*z* = 324.

Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.54; H, 6.43; N, 8.55.

2-[2-(Isopropylamino)benzofuran-3-ylamino]benzoic Acid (7c)

Yellow amorphous solid; mp 163–166 °C; R_f = 0.29 (PE–EtOAc, 4:1).

IR (KBr): 3338, 2968, 1671, 1645, 1575, 1455, 1260, 742 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.13 (d, *J* = 6.3 Hz, 6 H), 3.79–3.86 (m, 1 H), 6.42 (dd, *J* = 8.7, 13.2 Hz, 1 H), 6.64 (t, *J* = 7.3 Hz, 1 H), 6.82 (d, *J* = 7.2 Hz, 1 H), 6.90–6.95 (t-like, 1 H), 6.99–7.04 (t-like, 1 H), 7.27 (dd, *J* = 7.8, 14.7 Hz, 2 H), 7.86 (d, *J* = 7.5 Hz, 1 H), 8.74 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.9 (2 CH_3), 45.8 (CH), 93.5 (C), 109.6 (C), 110.0 (CH), 113.9 (CH), 115.9 (CH), 116.4 (CH), 120.1 (CH), 122.9 (CH), 128.8 (C), 132.4 (CH), 135.7 (CH), 149.0 (C), 151.5 (C), 154.2 (C), 173.8 (C).

MS (EI): *m*/*z* = 310.

Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.50; H, 5.98; N, 8.87.

2-[2-(*tert*-Butylamino)-5-nitrobenzofuran-3-ylamino]benzoic Acid (7d)

Brown amorphous solid; mp 205–208 °C; R_f = 0.16 (PE–EtOAc, 4:1),

IR (KBr): 3368, 2973, 1650, 1516, 1340, 1255, 749 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.36 (s, 9 H), 6.43–6.48 (m, 2 H), 6.73 (br s, 1 H), 7.28–7.30 (m, 1 H), 7.59–7.62 (m, 2 H), 7.89 (dd, *J* = 2.1, 8.7 Hz, 2 H), 8.83 (br s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 30.2 (3 CH_3), 52.9 (C), 95.0 (C), 110.1 (CH), 110.5 (CH), 113.1 (CH), 115.7 (CH), 116.2 (CH), 129.2 (C), 131.8 (CH), 134.2 (CH), 143.7 (C), 149.9 (C), 151.7 (C), 157.6 (C), 170.1 (C).

MS (FAB+): *m*/*z* = 369.

Anal. Calcd for $C_{19}H_{19}N_3O_5$: C, 61.78; H, 5.18; N, 11.38. Found: C, 62.05; H, 4.93; N, 11.12.

(Phenylimino)acetamides 9a–f; General Procedure

To a soln of salicylaldehyde **1** (1 mmol) and aniline **2** (1 mmol) in EtOH (5 mL) was added CAN (5 mol%) immediately followed by isocyanide **3** (1 mmol). The mixture was stirred at r.t. for 3–4 h. The solvent was removed via rotary evaporation and the crude product was crystallized (CH_2Cl_2–hexane) to give **9a–f**.

***N*-*tert*-Butyl-2-(2-chlorophenylimino)-2-(2-hydroxyphenyl)acetamide (9a)**

Yellow solid; mp 155–158 °C; R_f = 0.57 (PE–EtOAc, 4:1).

IR (KBr): 3290, 3059, 2978, 1663, 1601, 1552, 1449, 1208, 883, 758 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.12 (s, 9 H), 5.48 (s, 1 H), 6.94 (t, *J* = 7.7 Hz, 1 H), 7.05 (d, *J* = 8.4 Hz, 1 H), 7.12–7.19 (m, 2 H), 7.28–7.30 (m, 1 H), 7.44 (t, *J* = 7.7 Hz, 2 H), 7.54 (d, *J* = 7.8 Hz, 1 H), 12.79 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.2 (3 CH_3), 52.4 (C), 115.8 (C), 118.2 (CH), 119.1 (CH), 122.8 (CH), 125.6 (C), 126.6 (CH), 127.7 (CH), 129.3 (CH), 131.0 (CH), 134.4 (CH), 144.4 (C), 161.6 (C), 162.2 (C), 169.5 (C).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{19}ClN_2NaO_2$: 353.1033; found: 353.1068.

Anal. Calcd for $C_{18}H_{19}ClN_2O_2$: C, 65.35; H, 5.79; N, 8.47. Found: C, 65.12; H, 5.98; N, 8.25.

***N*-*tert*-Butyl-2-(2-hydroxyphenyl)-2-(2-iodophenylimino)acetamide (9b)**

Off-white solid; mp 164–168 °C; R_f = 0.57 (PE–EtOAc, 4:1).

IR (KBr): 3264, 3069, 2965, 1633, 1605, 1554, 1454, 1195, 753 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.11 (s, 9 H), 5.43 (s, 1 H), 6.94 (t, *J* = 7.2 Hz, 2 H), 7.08 (dd, *J* = 8.1, 14.1 Hz, 2 H), 7.36 (t, *J* = 7.7 Hz, 1 H), 7.44 (t, *J* = 7.7 Hz, 1 H), 7.56 (d, *J* = 7.8 Hz, 1 H), 7.88 (d, *J* = 7.8 Hz, 1 H), 12.69 (s, 1 H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 28.2 (3 CH_3), 52.5 (C), 91.2 (C), 115.6 (C), 118.2 (CH), 119.2 (CH), 121.8 (CH), 127.0 (CH), 129.3 (CH), 131.1 (CH), 134.4 (CH), 138.4 (CH), 149.0 (C), 161.5 (C), 162.2 (C), 169.0 (C).

MS (EI): *m*/*z* = 422.

Anal. Calcd for $C_{18}H_{19}IN_2O_2$: C, 51.20; H, 4.54; N, 6.63. Found: C, 50.98; H, 4.36; N, 6.42.

***N*-Cyclohexyl-2-(2-hydroxyphenyl)-2-(2-iodophenylimino)acetamide (9c)**

Yellow solid; mp 170–173 °C; R_f = 0.55, (PE–EtOAc, 4:1).

IR (KBr): 3229, 3069, 2930, 2853, 1631, 1194, 754 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.79–0.90 (m, 2 H), 1.06–1.13 (m, 1 H), 1.19–1.30 (m, 2 H), 1.51 (d, *J* = 8.7 Hz, 4 H), 1.59 (s, 1 H), 3.74 (dd, *J* = 9.9, 18.9 Hz, 1 H), 5.47 (d, *J* = 8.1 Hz, 1 H), 6.93 (t, *J* = 7.7 Hz, 2 H), 7.08 (t, *J* = 8.3 Hz, 2 H), 7.36 (t, *J* = 7.4 Hz, 1 H), 7.44 (t, *J* = 7.5 Hz, 1 H), 7.54 (d, *J* = 7.8 Hz, 1 H), 7.86 (d, *J* = 8.1 Hz, 1 H), 12.72 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.3 (CH_2), 25.1 (2 CH_2), 32.2 (2 CH_2), 48.0 (CH), 91.5 (C), 115.6 (C), 118.2 (CH), 119.2 (CH), 121.4 (CH), 127.2 (CH), 129.4 (CH), 131.1 (CH), 134.4 (CH), 138.5 (CH), 148.9 (C), 161.2 (C), 162.2 (C), 168.9 (C).

MS (FAB+): *m*/*z* = 449.

Anal. Calcd for $C_{20}H_{21}IN_2O_2$: C, 53.58; H, 4.72; N, 6.25. Found: C, 53.36; H, 4.89; N, 6.03.

***N*-*tert*-Butyl-2-(2-hydroxyphenyl)-2-(phenylimino)acetamide (9d)**

Grey solid; mp 169–172 °C; R_f = 0.53 (PE–EtOAc, 4:1),

IR (KBr): 3286, 1644, 1603, 1567, 1226, 1192, 754 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.16 (s, 9 H), 5.21 (s, 1 H), 6.91 (t, *J* = 7.3 Hz, 1 H), 7.02 (d, *J* = 8.4 Hz, 1 H), 7.13 (d, *J* = 7.5 Hz, 2 H), 7.22 (t-like, 1 H), 7.37 (t-like, 3 H), 7.52 (d, *J* = 7.8 Hz, 1 H), 13.29 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.2 (3 CH_3), 52.3 (C), 116.2 (C), 117.8 (CH), 118.9 (CH), 121.3 (2 CH), 125.8 (CH), 128.9 (2 CH), 130.6 (CH), 133.7 (CH), 146.4 (C), 161.9 (C), 162.3 (C), 168.1 (C).

MS (EI): *m*/*z* = 296.

Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 73.19; H, 6.56; N, 9.22.

2-(2-Bromophenylimino)-*N*-*tert*-butyl-2-(2-hydroxy-3-methoxyphenyl)acetamide (9e)

Yellow solid; mp 170–173 °C; R_f = 0.36 (PE–EtOAc, 4:1),

IR (KBr): 3320, 3064, 2969, 1671, 1602, 1538, 1460, 1258, 1205, 1024, 855, 742 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.12 (s, 9 H), 3.94 (s, 3 H), 5.47 (s, 1 H), 6.88 (d, *J* = 7.8 Hz, 1 H), 7.03–7.18 (m, 4 H), 7.33 (t-like, 1 H), 7.63 (d, *J* = 7.8 Hz, 1 H), 13.12 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.0 (3 CH_3), 52.4 (C), 56.0 (CH_3), 115.3 (CH), 115.5 (C), 115.7 (C), 118.4 (CH), 122.2 (CH), 122.5 (CH), 126.8 (CH), 128.1 (CH), 132.2 (CH), 145.4 (C), 148.6 (C), 152.3 (C), 161.5 (C), 169.2 (C).

MS (EI): *m*/*z* = 404, 406.

Anal. Calcd for $C_{19}H_{21}BrN_2O_3$: C, 56.31; H, 5.22; N, 6.91. Found: C, 56.57; H, 5.48; N, 7.07.

2-(4-Bromophenylimino)-*N*-*tert*-butyl-2-(2-hydroxy-3-methoxyphenyl)acetamide (9f)

Light yellow solid; mp 173–176 °C; R_f = 0.30 (PE–EtOAc, 2:1).

IR (KBr): 3318, 3070, 2958, 1670, 1588, 1530, 1458, 1250, 1196, 1022, 854, 740 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.23 (s, 9 H), 3.89 (s, 3 H), 5.52 (s, 1 H), 6.85 (d-like, 1 H), 6.96–7.12 (m, 4 H), 7.48 (d, *J* = 8.1 Hz, 1 H), 13.56 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.0 (3 CH_3), 51.3 (C), 56.0 (CH_3), 115.9 (CH), 116.3 (C), 118.0 (C), 118.4 (CH), 121.9 (CH), 123.8 (2 CH), 131.5 (2 CH), 145.6 (C), 148.5 (C), 151.8 (C), 161.4 (C), 169.3 (C).

MS (ESI$^+$): *m*/*z* = 404, 406, 427 [M + Na]$^+$.

Anal. Calcd for $C_{19}H_{21}BrN_2O_3$: C, 56.31; H, 5.22; N, 6.91. Found: C, 56.06; H, 4.99; N, 7.10.

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References

(1) (a) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321. (b) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, *24*, 4957. (c) *Multicomponent Reactions*; Zhu, J.; Bienaymé, H., Eds.; Wiley-VCH: Weinheim, **2005**. (d) Liang, B.; Wang, X.; Wang, J.-X.; Du, Z. *Tetrahedron* **2007**, *63*, 1981. (e) Syamala, M. *Org. Prep. Proced. Int.* **2009**, *41*, 1. (f) Sun, J.; Xia, E.-Y.; Zhang, l.-L.; Yan, C.-G. *Eur. J. Org. Chem.* **2009**, 5247. (g) Karmakar, B.; Banerji, J. *Tetrahedron Lett.* **2010**, *51*, 2748. (h) Gérard, S.; Renzetti, A.; Lefevre, B.; Fontana, A.; de Maria, P.; Sapi, J. *Tetrahedron* **2010**, *66*, 3065. (i) Song, W.; Lu, W.; Wang, J.; Lu, P.; Wang, Y. *J. Org. Chem.* **2010**, *75*, 3481.

(2) (a) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168. (b) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899. (c) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (d) Teimouri, M. B.; Mansouri, F. *J. Comb. Chem.* **2008**, *10*, 507. (e) Li, J.; Liu, Y.; Li, C.; Jia, X. *Tetrahedron Lett.* **2009**, *50*, 6502. (f) García-González, M. C.; González-Zamora, E.; Santillan, R.; Domínguez, O.; Méndez-Stivalet, J. M.; Farfán, N. *Tetrahedron* **2009**, *65*, 5337. (g) Ramazani, A.; Mahyari, A. T.; Rouhani, M.; Rezaei, A. *Tetrahedron Lett.* **2009**, *50*, 5625. (h) Adib, M.; Mahdavi, M.; Bagherzadeh, S.; Zhu, L.-G.; Rahimi-Nasrabadi, M. *Tetrahedron Lett.* **2010**, *51*, 27. (i) Kobayashi, K.; Shirai, Y.; Fukamachi, S.; Konishi, H. *Synthesis* **2010**, 666.

(3) (a) Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 126. (b) Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 181.

(4) (a) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrückner, C. *Angew. Chem.* **1959**, *71*, 386. (b) Ugi, I.; Steinbrückner, C. *Angew. Chem.* **1960**, *72*, 267. (c) Ugi, I.; Steinbrückner, C. *Chem. Ber.* **1961**, *94*, 2802. (d) Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 810. (e) Ugi, I.; Lohberger, S.; Karl, R. In *Comprehensive Organic Synthesis*, Vol. 2; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, **1993**, Chap. 4.6, 1083. (f) De Silva, R. A.; Santra, S.; Andreana, P. R. *Org. Lett.* **2008**, *10*, 4541. (g) Faggi, C.; García-Valverde, M.; Marcaccini, S.; Menchi, G. *Org. Lett.* **2010**, *12*, 788.

(5) (a) Ugi, I. *Isonitrile Chemistry*; Academic Press: London, **1971**. (b) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168. (c) Dömling, A. *Chem. Rev.* **2006**, *106*, 17.

(6) (a) Varala, R.; Nuvula, S.; Adapa, S. R. *Synlett* **2006**, 1549. (b) More, S. V.; Sastry, M. N. V.; Yao, C. F. *Green Chem.* **2006**, *8*, 91. (c) Varala, R.; Enugala, R.; Nuvula, S.; Adapa, S. R. *Synlett* **2006**, 1009. (d) Nair, V.; Deepthi, A. *Chem. Rev.* **2007**, *107*, 1862. (e) Nair, V.; Deepthi, A. *Tetrahedron* **2009**, *65*, 10745. (f) Casey, B. M.; Eakin, C. A.; Jiao, J.; Sadasivam, D. V.; Flowers, R. A. *Tetrahedron* **2009**, *65*, 10762. (g) Kidwai, M.; Bhatnagar, D. *Tetrahedron Lett.* **2010**, *51*, 2700. (h) Alcaide, B.; Almendros, P.; Carrascosa, R.; Rosario Torres, M. *Eur. J. Org. Chem.* **2010**, 823. (i) Sridharan, V.; Menéndez, J. C. *Chem. Rev.* **2010**, *110*, 3805.

(7) (a) Kamthong, B.; Robertson, A. *J. Chem. Soc.* **1939**, 925. (b) Emerson, O. H.; Bickoff, E. M. *J. Am. Chem. Soc.* **1958**, *80*, 4381. (c) DeGraw, J.; Bonner, W. A. *J. Org. Chem.* **1962**, *27*, 3917. (d) Stevenson, P. C.; Veitch, N. C. *Phytochemistry* **1998**, *48*, 947. (e) Okamoto, Y.; Ojika, M.; Sakagami, Y. *Tetrahedron Lett.* **1999**, *40*, 507. (f) Ito, J.; Takaya, Y.; Oshima, Y.; Niwa, M. *Tetrahedron* **1999**, *55*, 2529. (g) Wang, Y.; Zhang, A. *Tetrahedron* **2009**, *65*, 6986. (h) Rao, M. L. N.; Awasthi, D. K.; Banerjee, D. *Tetrahedron Lett.* **2010**, *51*, 1979.

(8) (a) Chen, Y.; Chen, S.; Lu, X.; Cheng, H.; Ou, Y.; Cheng, H.; Zhou, G.-C. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1851. (b) Asoh, K.; Kohchi, M.; Hyoudoh, I.; Ohtsuka, T.; Masubuchi, M.; Kawasaki, K.; Ebiike, H.; Shiratori, Y.; Fukami, T. A.; Kondoh, O.; Tsukaguchi, T.; Ishii, N.; Aoki, Y.; Shimma, N.; Sakaitani, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1753. (c) Galal, S. A.; Abd El-All, A. S.; Abdallah, M. M.; El-Diwani, H. I. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2420. (d) Abdel-Wahab, B. F.; Abdel-Aziz, H. A.; Ahmed, E. M. *Eur. J. Med. Chem.* **2009**, *44*, 2632. (e) Bursavich, M. G.; Brooijmans, N.; Feldberg, L.; Hollander, I.; Kim, S.; Lombardi, S.; Park, K.; Mallon, R.; Gilbert, A. M. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2586.

(9) (a) Koca, M.; Servi, S.; Kirilmis, C.; Ahmedzade, M.; Kazaz, C.; Özbek, B.; Ötük, G. *Eur. J. Med. Chem.* **2005**, *40*, 1351. (b) Schultz, D. M.; Prescher, J. A.; Kidd, S.; Marona-Lewicka, D.; Nichols, D. E.; Monte, A. *Bioorg. Med. Chem.* **2008**, *16*, 6242. (c) Ettaoussi, M.; Péres, B.; Klupsch, F.; Delagrange, P.; Boutin, J.-A.; Renard, P.; Caignard, D.-H.; Chavatte, P.; Berthelot, P.; Lesieur, D.; Yous, S. *Bioorg. Med. Chem.* **2008**, *16*, 4954. (d) Ando, K.; Kawamura, Y.; Akai, Y.; Kunitomo, J.; Yokomizo, T.; Yamashita, M.; Ohta, S.; Ohishi, T.; Ohishi, Y. *Org. Biomol. Chem.* **2008**, *6*, 296. (e) Kirilmis, C.; Ahmedzade, M.; Servi, S.; Koca, M.; Kizirgil, A.; Kazaz, C. *Eur. J. Med. Chem.* **2008**, *43*, 300.

(10) (a) Eidamshaus, C.; Burch, J. D. *Org. Lett.* **2008**, *10*, 4211. (b) Gill, G. S.; Grobelny, D. W.; Chaplin, J. H.; Flynn, B. L. *J. Org. Chem.* **2008**, *73*, 1131. (c) Rao Lingam, V. S. P.; Vinodkumar, R.; Mukkanti, K.; Thomas, A.; Gopalan, B. *Tetrahedron Lett.* **2008**, *49*, 4260. (d) Csékei, M.; Novák, Z.; Kotschy, A. *Tetrahedron* **2008**, *64*, 8992. (e) Isono, N.; Lautens, M. *Org. Lett.* **2009**, *11*, 1329. (f) Martinez, C.; Alvarez, R.; Aurrecoechea, J. M. *Org. Lett.* **2009**, *11*, 1083. (g) Majumdar, K. C.; Chattopadhyay, B.; Maji, P. K.; Chattopadhyay, S. K.; Samanta, S. *Heterocycles* **2010**, *81*, 517; and references cited therein.

(11) (a) Shen, Z.; Dong, V. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 784. (b) Murai, M.; Miki, K.; Ohe, K. *Chem. Commun.* **2009**, 3466. (c) Miyata, O.; Takeda, N.; Naito, T. *Heterocycles* **2009**, *78*, 843. (d) János, F.; András, K. *Synthesis* **2009**, 85. (e) Hung, N. T.; Hussain, M.; Malik, I.; Villinger, A.; Langer, P. *Tetrahedron Lett.* **2010**, *51*, 2420. (f) Kokubo, K.; Harada, K.; Mochizuki, E.; Oshima, T. *Tetrahedron Lett.* **2010**, *51*, 955. (g) Bochicchio, A.; Chiummiento, L.; Funicello, M.; Lopardo, M. T.; Lupattelli, P. *Tetrahedron Lett.* **2010**, *51*, 2824. (h) Barange, D. K.; Raju, B. R.; Kavala, V.; Kuo, C.-W.; Tu, Y.-C.; Yao, C.-F. *Tetrahedron* **2010**, *66*, 3754. (i) Jaseer, E. A.; Prasad, D. J. C.; Sekar, G. *Tetrahedron* **2010**, *66*, 2077.

(12) *Crystal data of compound* **10a**: $C_{18}H_{19}ClN_2O_2$, FW = 330.80, monoclinic, space group *P*21/*c*, *a* = 12.0348 (13) Å, *b* = 18.050 (2) Å, *c* = 7.9752 (9) Å, β = 102.269 (5)°, *V* = 1692.9 (3) Å^3, *Z* = 4, *T* = 296 (2) K, d_{calcd} = 1.298 g cm^{-3}, *F*(000) = 696. Diffraction data were measured with MoKα

(λ = 0.71073 Å) radiation at 296 K using a Bruker Kappa Apex 2 CCD system. A total of 2404 unique reflections were measured (θ_{max} = 25.00°). Data analyses were carried out with the Fast Fourier Transform program. The structures were solved by direct methods using the SHELXS-97[14] program. Refinements were carried out with a full matrix least squares method against $F2$ using SHELXL-97.[15] Non-hydrogen atoms were refined with anisotropic thermal parameters. The final R value was $R1$ = 0.0375 and $wR2$ = 0.1202 with $I > 2\sigma(I)$. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre with reference number CCDC 773605.

(13) Yavari, I.; Djahaniani, H. *Tetrahedron Lett.* **2006**, *47*, 1477.
(14) (a) Program for solution of crystal structures: Sheldrick, G. M. *SHELXS-97*; University of Göttingen: Germany, **1997**. (b) Sheldrick, G. M. *Acta Crystallogr., Sect. A* **1990**, *46*, 467.
(15) Program for refinement of crystal structures: Sheldrick, G. M. *SHELXL-97*; University of Göttingen: Germany, **1997**.