A Solvent-Free and One-Pot Strategy for Ecocompatible Synthesis of Substituted Benzofurans from Various Salicylaldehydes, Secondary Amines, and Nonactivated Alkynes Catalyzed by Copper(I) Oxide Nanoparticles

Hashem Sharghi,* Pezhman Shiri, Mahdi Aberi

Department of Chemistry, Shiraz University, Shiraz, 71454, Iran
Fax +98(711)2280926; E-mail: shashem@chem.susc.ac.ir

Received: 03.03.2014; Accepted after revision: 12.05.2014

Abstract: Copper(I) oxide nanoparticles (CONPs) catalyze multicomponent coupling/cycloisomerization reactions between various 2-hydroxybenzaldehydes, secondary amines, and nonactivated alkynes to give 2,3-disubstituted 1-benzofurans. All reactions are carried out under solvent- and ligand-free conditions at 100 °C in air. The combination of copper-catalyzed C–H activation and an O-annulation process is essential for this transformation. This methodology provides rapid access to substituted 1-benzofurans in good to excellent yields with high atom economy and high catalytic efficiency. This procedure eliminates the need for propargylamine derivatives, uncyclized intermediates that make purification difficult. The CONPs and tetrabutylammonium bromide were reused successfully for up to five times.

Key words: 1-benzofurans, copper(I) oxide nanoparticles, one-pot cascade reaction, solvent-free conditions, morpholine

The benzofuran scaffold has played a critical role in the discovery of bioactive molecules.[1] Structural and substitution modifications on this oxygen heterocyclic building block often lead to the identification of compounds with a wide variety of biological activity, such as anticancer,[2] anti-oxidative,[3] and anti-inflammatory[4] properties.

Over the past few years, transition-metal-catalyzed Mannich base cycloisomerization reactions have proved to be a very simple and efficient route for the synthesis of complex nitrogen/oxygen heterocyclic buildings.[5,6] However, there are a few reports of the one-pot multicomponent synthesis of 1-benzofurans using copper-catalyzed coupling/annulation reaction.[6] Thus in recent years, the development of methods for the synthesis of 1-benzofurans in a sustainable manner has been an active research topic in both academic and pharmaceutical research. One-pot and multicomponent conditions have emerged as powerful techniques to enhance the reaction rates of a variety of chemical transformations,[7,8] while reactions catalyzed by green catalysts such as copper are attractive in the growing field of green chemistry. Furthermore, this chemistry represents a rare example of a copper-catalyzed coupling/cycloisomerization reaction. The prominence of 1-benzofurans as a basic framework in biologically active compounds and natural products has promoted extensive experimental studies toward their synthesis and functionalization, a few examples are: cross-coupling of sodium (benzofuran-2-yl)dimethylsilanolate with aryl bromides or aryl chlorides using $(t\text{-}Bu_3P)_2Pd$,[9a] the addition of phenols to bromoalkynes and intramolecular cyclization of (*Z*)-2-bromovinyl phenyl ethers,[9b] copper(I) bromide catalyzed coupling of *N*-tosylhydrazones and terminal alkynes,[9c] palladium-catalyzed one-pot synthesis of 1-benzofurans from 2-chlorophenols and terminal alkynes,[9d] synthesis of either C2- or C3-substituted 1-benzofurans from 2-chloro-1-(2-hydroxyphenyl)ethanones,[9e] transformation of O-arylated products into substituted benzofurans,[9f] synthesis of 2,3-disubstituted benzofurans by platinum–olefin-catalyzed carboalkoxylation of *O*-alkynylphenyl acetals,[9g] palladium-catalyzed synthesis of benzofurans from 2-chloroaryl alkynes[9h] and a host of other methods.[9i–n]

While these methods enriched the approaches to 1-benzofuran derivatives, their utility and applicability are often compromised by the loss of catalyst, their use of expensive metals and ligands, the utilization of harsh reaction conditions, and their adverse environmental impact due to the use of volatile and toxic organic solvents.

In this respect, a newly emerged one-pot multicomponent reaction of a salicylaldehyde, activated or nonactivated alkynes, and a secondary amine is a reliable pathway towards 1-benzofurans. Initially, Li and Nguyen[6a] reported that [Cu]- or [Ag]-catalyzed coupling of salicylaldehydes, amines, and alkynes containing a heteroatom afforded 2,3-disubstituted 1-benzofurans with good efficiency. Then, Sakai and co-workers[6b] reported that this coupling/cycloisomerization reaction could be realized via Cu(I) and Cu(II) as a two metal catalytic system in the presence of 4-(dimethylamino)pyridine as the base. However, the alkynes employed therein were limited to those activated alkynes bearing a Csp–Si bond. Recently, Zhang and co-workers[6c] also presented an improved, more general procedure starting from nonactivated terminal alkynes in the presence of CuI/[bmim]OAc and $[bmim]PF_6$. However, these methods are still associated with one or more restrictions such as low reaction rate, utilization of harsh reaction conditions, non-reusability of the catalyst, the use of toxic and expensive solvents, and limited substrate scope. Herein, we report a novel modification of the work developed by Li and Nguyen and later by Sasaki and co-workers for the one-pot multicomponent synthesis of highly regioselective 2,3-disubstituted 1-ben-

SYNTHESIS 2014, 46, 2489–2498
Advanced online publication: 25.06.2014
DOI: 10.1055/s-0034-1378206; Art ID: ss-2014-z0156-op

zofurans using copper(I) oxide nanoparticles (CONPs)[10] as a reusable and efficient catalyst under solvent-free conditions. Moreover, the catalyst and tetrabutylammonium bromide can be used for five reaction cycles.

As part of our continuing interest in the development of greener catalysts and cleaner procedures for organic reactions used in the laboratory and industry,[11] herein we developed a new method for the synthesis of 2,3-disubstituted 1-benzofuran derivatives via a tandem alkyne–aldehyde–amine (A3) coupling followed by cyclization under mild conditions, very high reaction rate, and using an inexpensive and reusable catalyst.

In an attempt to carry out the multicomponent coupling/cycloisomerization reaction between 2-hydroxybenzaldehyde, morpholine, and phenylacetylene with CONPs as catalyst under solvent-free conditions at 100 °C, 2-[1-(morpholin-4-yl)-3-phenylprop-2-ynyl]phenol (**4**) was formed and the cyclization failed to take place. This may be due to the low nucleophilicity of the oxygen atom in 2-hydroxybenzaldehyde. Thus, potassium carbonate as a base and tetrabutylammonium bromide as an additive were added to the reaction mixture. It was found that the propargylic amine derivative **4** could be smoothly cyclized to afford 4-(2-benzyl-1-benzofuran-3-yl)morpholine (**5a**) as the desired product (Scheme 1).

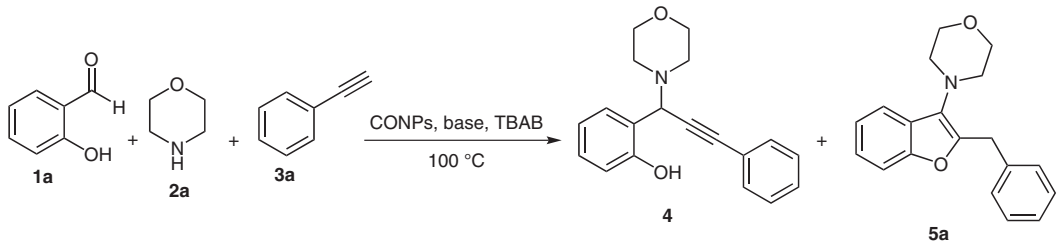
These results prompted us to investigate the further applicability of this reaction (Table 1). In order to establish the optimum reaction conditions, the three component reaction between salicylaldehyde, morpholine, and phenylacetylene (1:1.1:1) was studied varying the parameters such as the copper catalyst, solvent, and base.

Initially, the use of a series of copper sources [including $Cu(OAc)_2$, $CuBr_2$, $CuSO_4$, CuO powder, Cu_2O, CONPs] was examined in this reaction (Table 1, entries 1–5 and 12). Copper(I) oxide nanoparticles (CONPs) were found to be the most effective catalyst in terms of stability, reaction rate, and isolated yield of the product.

Table 1 Copper-Catalyzed Coupling/Cycloaddition Reaction of 2-Hydroxybenzaldehyde, Morpholine, and Phenylacetylene under Various Conditions[a]

Entry	Catalyst[b] (mol%)	Base	Solvent	Temp (°C)	Time (h)	Yield[c] (%)
1	$Cu(OAc)_2 \cdot H_2O$ (25)	K_2CO_3	–[d]	100	1.75	70
2	$CuSO_4$ (25)	K_2CO_3	–[d]	100	1.75	71
3	$CuBr_2$ (25)	K_2CO_3	–[d]	100	1.75	75
4	CuO powder (15)	K_2CO_3	–[d]	100	1.75	62
5	Cu_2O (20)	K_2CO_3	–[d]	100	1.75	83
6	CONPs (15)	K_2CO_3	toluene	100	1.75	89
7	CONPs (15)	K_2CO_3	1,4-dioxane	100	1.75	87
8	CONPs (15)	K_2CO_3	MeCN	reflux	1.75	23
9	CONPs (15)	K_2CO_3	PEG-300	130	1.75	13
10	CONPs (15)	K_2CO_3	H_2O	100	1.75	0
11	CONPs (15)	K_2CO_3	EtOH	reflux	1.75	0
12	CONPs (15)	K_2CO_3	–[d]	100	1.25	90
13	CONPs (10)	K_2CO_3	–[d]	100	1.75	83
14	CONPs (5)	K_2CO_3	–[d]	100	1.75	75
15	CONPs (20)	K_2CO_3	–[d]	100	1.75	91
16	CONPs (25)	K_2CO_3	–[d]	100	1.75	90
17	CONPs (20)	Et_3N	–[d]	100	3.00	25
18	CONPs (15)	Cs_2CO_3	–[d]	100	1.75	77
19	CONPs (15)	K_3PO_4	–[d]	100	4.00	0
20	CONPs (15)	NaOAc	–[d]	100	4.00	49
21	CONPs (15)	*i*-Pr_3N	–[d]	100	4.00	57
22	CONPs (15)	–	–[d]	100	3.00	0

[a] All reactions were carried out in the present of TBAB.
[b] CONPs = copper(I) oxide nanoparticles
[c] Isolated yield.
[d] Solvent-free reaction.



Scheme 1 The reaction between 2-hydroxybenzaldehyde, morpholine, and phenylacetylene as a model reaction

Recently, the acceleration of copper-catalyzed organic reactions by using ligated copper halides as the catalyst has attracted much attention, however because of the use of expensive and challenging synthetic routes to the ligands, these methods are not acceptable. Due to their inexpensive, simple preparation, and low sensitivity to light and air, CONPs were chosen for the further exploration of the scope and limitations of this three-component coupling reaction of salicylaldehydes, secondary amines, and nonactivated alkynes.[12]

In the next step, we found that the loading levels of the CONPs also have an effect on the yield. According to Table 1, entries 12–16, the optimal catalyst loading in the synthesis of **5a** is at a concentration of 15 mol%. When the amount of CONPs was reduced, the yield of **5a** decreased, whereas raising CONPs concentration did not lead to an appreciable increase in the yield. During our optimization studies, the effect of solvents was examined and among the solvents tested in Table 1, toluene and 1,4-dioxane were the most suitable reaction media for three-component coupling reactions of salicylaldehydes, secondary amines, and nonactivated alkynes followed by base-assisted O-annulation reaction (entries 6 and 7). Lower yields were observed for **5a** when using other solvents, such as acetonitrile and PEG-300 (entries 8 and 9). However, no desired product was detected when the reaction was performed in ethanol and water (entries 10 and 11). The absence of solvent increased the concentration of the reactants and was beneficial in accelerating the coupling/cycloisomerization reaction. As well, avoiding the use of toxic chemicals and reducing environmental pollution, all one-pot three-component reactions were performed under solvent-free conditions (entry 12 and Table 2). In the next step, the effect of various inorganic and organic bases was screened via this one-pot cascade reaction and the results showed that potassium carbonate was still the best choice (entries 12 and 17–22).

The scope and generality of this Mannich base O-annulation reaction catalyzed by CONPs was explored using a variety of substrates. In all cases, one-pot and three-component reactions proceeded well and afforded the desired products **5a**–**n** in excellent yields and high regioselectivities (Table 2).

Table 2 Solvent-Free and One-Pot Three-Component Synthesis of 2,3-Disubstituted 1-Benzofurans[a]

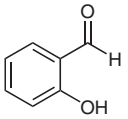
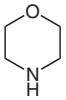
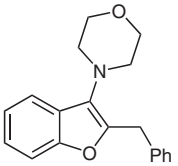
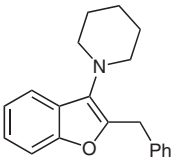
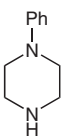
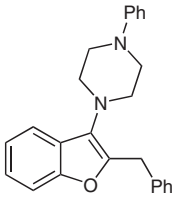
Entry	Aldehyde	Amine	Alkyne	Product	Time (h)	Yield[b] (%)
1	 **1a**	 **2a**	 **3a**	 **5a**	1.25	90 (79[c])
2	**1a**	 **2b**	**3a**	 **5b**	1.25	90 (75[c])
3	**1a**	 **2c**	**3a**	 **5c**	1.25	87

Table 2 Solvent-Free and One-Pot Three-Component Synthesis of 2,3-Disubstituted 1-Benzofurans[a] (continued)

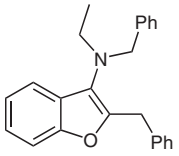
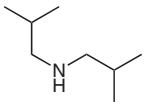
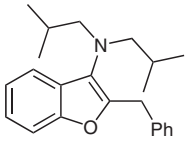
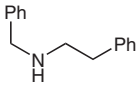
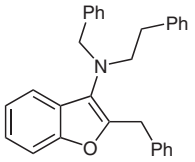
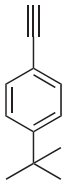
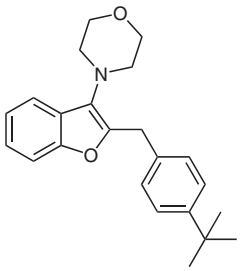
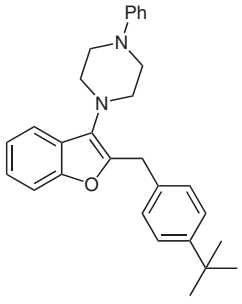
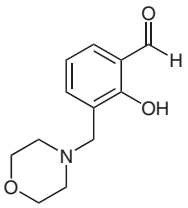
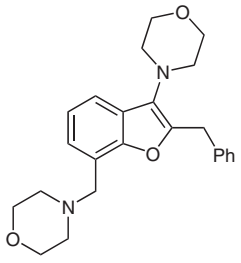
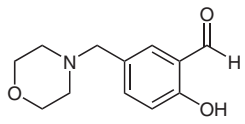
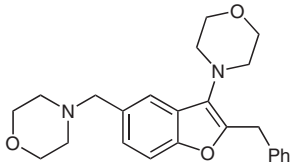
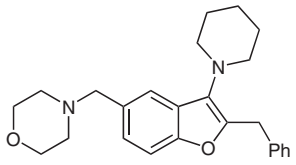
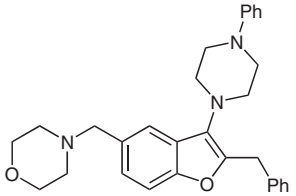
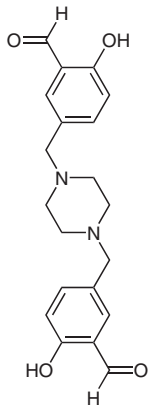
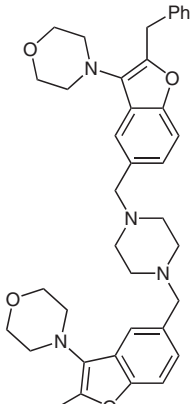
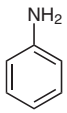
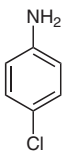
Entry	Aldehyde	Amine	Alkyne	Product	Time (h)	Yield[b] (%)
4	**1a**	 **2d**	**3a**	 **5d**	1.25	89
5	**1a**	 **2e5**	**3a**	 **5e**	1.50	85
6	**1a**	 **2f**	**3a**	 **5f**	1.50	88
7	**1a**	**2a**	 **3b**	 **5g**	1.25	89
8	**1a**	**2c**	**3b**	 **5h**	1.25	85
9	 **1b**	**2a**	**3a**	 **5i**	6.50	79

Table 2 Solvent-Free and One-Pot Three-Component Synthesis of 2,3-Disubstituted 1-Benzofurans[a] (continued)

Entry	Aldehyde	Amine	Alkyne	Product	Time (h)	Yield[b] (%)
10	 **1c**	**2a**	**3a**	 **5j**	1.50	88
11	**1c**	**2b**	**3a**	 **5k**	1.50	89
12	**1c**	**2c**	**3a**	 **5l**	1.50	89
13	 **1d**	**2a**	**3a**	 **5m**	3.25	80
14	**1a**	 **2g**	**3a**	–	1.50	0
15	**1a**	 **2h**	**3a**	–	1.50	0

[a] Conditions: salicylaldehyde (1.0 mmol), secondary amine (1.1 mmol), nonactivated alkyne (1.0 mmol), CONPs (15 mol%), TBAB (1.0 mmol), K_2CO_3 (1.0 mmol).
[b] Isolated yield.
[c] Reaction was performed on a 10-mmol scale.

Various cyclic and noncyclic secondary amines also reacted with salicylaldehyde and phenylacetylene to afford the desired products in good to excellent yields (Table 2). Unfortunately, aromatic amines, such as aniline and 4-chloroaniline, gave no reaction (entries 15 and 16).

Due to their wide range of pharmacological and biological activity, the synthesis of compounds bearing morpholine[13] is a current target. Working on the envisaged strategy, we discovered that we could successfully accomplish the synthesis of the desired 1-benzofurans containing morpholin-4-ylmethyl using a copper-catalyzed coupling/cycloisomerization process involving C–H activation without elaborate reaction conditions (entries 9–12). In addition, this methodology could then be extended to the synthesis of a bis(1-benzofuran) by the successive multicomponent coupling/cycloisomerization reactions in good yield (entry 13).

Considering that the literature focuses on the reusability of CONPs especially those methods that use CONPs and tetrabutylammonium bromide together, they were reused for five cycles of the reaction[10] (Table 3). After completion of the reaction, the mixture was extracted with diethyl ether. In order to reuse copper(I) oxide nanoparticles and tetrabutylammonium bromide together, they were solidified, evaporated in vacuo, cooled, and then subjected to a second run by charging with the same substrates (salicylaldehyde derivative, secondary amine, phenylacetylene, and K_2CO_3). The copper content in the product was determined through ICP. Results indicate that 7% of the copper content was leached during the five reaction cycles.

Table 3 Reusability of Copper(I) Oxide Nanoparticles and Tetrabutylammonium Bromide in the Synthesis of 2,3-Disubstituted 1-Benzofurans

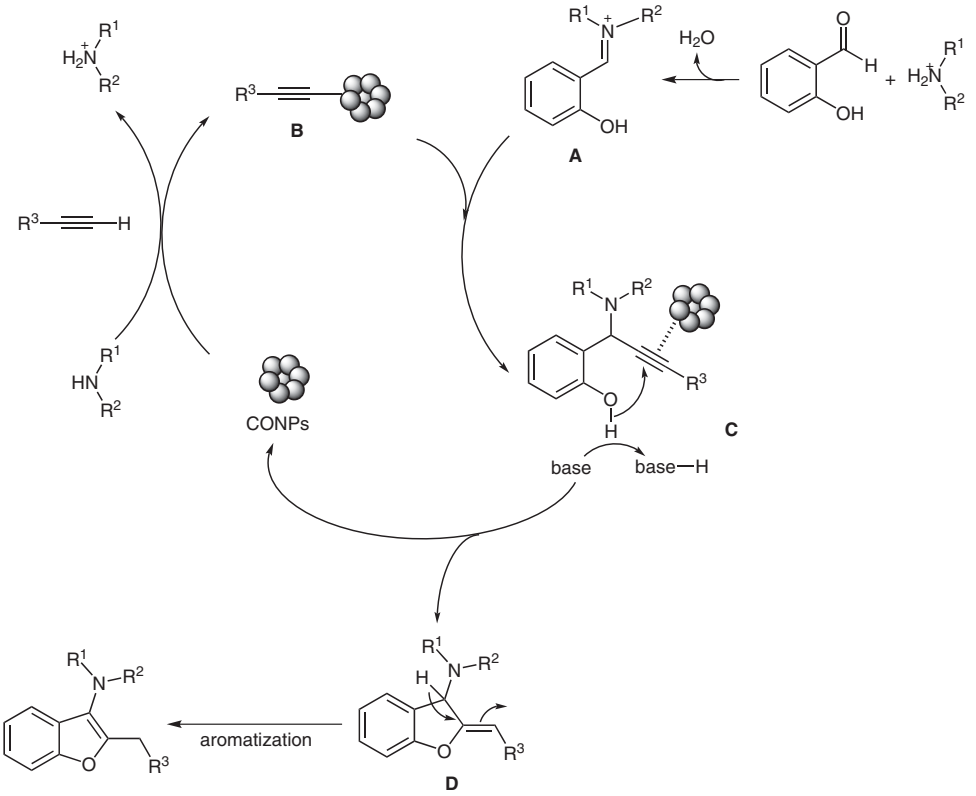
Reaction run	Time (h)	Yield[a] (%)
1	1.25	90
2	1.25	88
3	1.25	85
4	1.25	85
5	1.25	82

[a] Isolated yield.

Finally, to check the feasibility of this procedure on a preparative scale, we performed the coupling/cycloisomerization of salicylaldehyde, morpholine or piperidine and phenylacetylene on a 10-mmol scale in the present of the catalyst. As expected, the reaction proceeded similarly to the experiment on a smaller scale, except that a slightly longer reaction time was required (Table 2, entries 1 and 2).

Herein, we proposed a mechanism for the CONPs catalyzed preparation of 2,3-disubstituted 1-benzofurans (Scheme 2), which is in analogy to the established mechanism as reported in the literature.[14]

We believe that the synthesis of 2,3-disubstituted 1-benzofurans under these conditions follows through an iminium ion **A** by the reaction of salicylaldehyde and



Scheme 2 Proposed mechanism for the synthesis of 2,3-disubstituted 1-benzofurans in the presence of CONPs

secondary amine in the presence of catalyst by the elimination of a water molecule. The CONPs probably facilitates the formation of **A** by increasing the electrophilicity of the carbonyl group. The Cu–acetylide intermediate **B** generated in situ results in the activation of the C–H bond due to the reaction of acetylene and catalyst. Then **B** reacts with **A** to provide corresponding amine as intermediate **C**. At this stage, the potassium carbonate plays its role as a base to increase the nucleophilicity of the oxygen atom on the aryl ring to give intermediate **D**. It was expected that under the reaction conditions, a subsequent isomerization of **D** into the desired product would occur (Scheme 2).

In summary, we have developed and implemented a simple, green, efficient, and highly selective methodology for the one-pot and three-component tandem reaction of salicylaldehydes, secondary amines, and nonactivated alkynes under solvent-free conditions using CONPs as a catalyst. This procedure has several unique advantages, such as large-scale synthesis, high conversions, cleaner reaction profile, and cost efficiency. These advantages make it a green process for the highly regioselective synthesis of 2,3-disubstituted 1-benzofurans from a wide range of substrates. Hence, we believe that it will find wide application in organic synthesis as well as in industry.

All chemicals and solvents were obtained from Fluka, Aldrich, and Merck and used without further purification. The determination of purity of the substrates and reaction monitoring were accomplished by TLC on silica gel PolyGram SILG/UV 254 plates. Column chromatography was carried out using a short glass column of silica gel 60 (70–230 mesh). NMR spectra were recorded on a Bruker Avance DPX-250 (^{1}H NMR at 250 MHz and ^{13}C NMR at 62.9 MHz) spectrometer using TMS as an internal standard in pure deuterated solvents. Mass spectra were determined on a Shimadzu GCMS-QP 1000 EX instruments at 70 or 20 eV. IR spectra were obtained using a Shimadzu FT-IR 8300 spectrophotometer. Melting points were determined on a Buchi Melting Point B-545 electrical melting point apparatus. Cu_2O nanoparticles were prepared according to a previously reported procedure.[15]

Copper-Catalyzed Coupling/Cycloisomerization Reaction; General Procedure

CONPs (15 mol%) were added to a mixture of salicylaldehyde derivative (1.0 mmol), secondary amine (1.1 mmol), phenylacetylene (1.0 mmol), TBAB (1.0 mmol), and K_2CO_3 (1.0 mmol) at 100 °C, and the mixture was stirred for the time shown in Table 2 (TLC monitoring). After completion of the reaction, Et_2O was added to the mixture and the mixture was filtered and the solution was washed with water. The solvent was concentrated to afford the crude product, which after chromatography (silica gel 60, 70–230 mesh, hexane–EtOAc) gave the corresponding 2,3-disubstituted 1-benzofurans.

4-(2-Benzyl-1-benzofuran-3-yl)morpholine (5a)

Light yellow solid; yield: 264 mg (90%); mp 105–108 °C.

IR (KBr): 540 (w), 748 (s), 840 (w), 902 (w), 1033 (m), 1110 (s), 1211 (s), 1257 (s), 1380 (m), 1450 (s), 1496 (m), 2846 (w), 2962 cm^{-1} (m).

^{1}H NMR ($CDCl_3$): δ = 3.18 (t, *J* = 4.75 Hz, 4 H), 3.86 (t, *J* = 4.75 Hz, 4 H), 4.17 (s, 2 H), 7.14–7.40 (m, 8 H), 7.66–7.69 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 32.29, 52.61, 67.72, 111.72, 119.93, 122.11, 123.49, 126.09, 126.49, 128.56, 128.76, 138.19, 150.25, 153.50.

MS: *m*/*z* (%) = 296 (M^+ + 3, 3.0), 295 (M^+ + 2, 18.7), 294 (M^+ + 1, 79.2), 293 (M^+, 100.0), 234 (79.4), 218 (16.1), 178 (12.3), 158 (0.1), 121 (62.3), 91 (46.8), 73 (31.9), 57 (53.4).

Anal. Calcd for $C_{19}H_{19}NO_2$ (293.364): C, 77.79; H, 6.53; N, 10.91. Found: C, 77.83; H, 6.55; N, 10.90.

1-(2-Benzyl-1-benzofuran-3-yl)piperidine (5b)

Brown solid; yield: 262 mg (90%); mp 74–75 °C.

IR (KBr): 663 (w), 702 (w), 756 (s), 856 (w), 979 (w), 1026 (w), 1149 (w), 1218 (m), 1288 (w), 1380 (w), 1458 (m), 1612 (m), 1720 (w), 1797 (w), 2854 (w), 2939 (m), 3024 cm^{-1} (w).

^{1}H NMR ($CDCl_3$): δ = 1.35–1.43 (m, 2 H), 1.49–1.52 (m, 4 H), 2.91–2.96 (m, 4 H), 3.96 (s, 2 H), 6.94–7.16 (m, 8 H), 7.42–7.47 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 24.31, 26.79, 32.48, 53.80, 111.51, 120.16, 121.80, 123.22, 126.34, 128.49, 128.59, 134.43, 138.54, 148.92, 153.45.

MS: *m*/*z* (%) = 293 (M^+ + 2, 0.5), 292 (M^+ + 1, 2.0), 291 (M^+, 3.3), 238 (10.5), 216 (14.4), 121 (100.0), 91 (66.0), 65 (25.3).

Anal. Calcd for $C_{20}H_{21}NO$ (291.392): C, 82.44; H, 7.26; N, 4.81. Found: C, 82.46; H, 7.29; N, 7.22.

1-(2-Benzyl-1-benzofuran-3-yl)-4-phenylpiperazine (5c)

Brown solid; yield: 320 mg (87%); mp 115–120 °C.

IR (KBr): 694 (s), 756 (s), 933 (w), 1026 (s), 1126 (s), 1226 (s), 1326 (w), 1380 (w), 1450 (s), 1496 (s), 1596 (s), 1720 (w), 2831 (w), 2917 (w), 3055 cm^{-1} (w).

^{1}H NMR ($CDCl_3$): δ = 3.12 (s, 8 H), 3.97 (s, 2 H), 6.65–7.18 (m, 13 H), 7.46–7.49 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 32.38, 50.26, 52.37, 111.68, 116.44, 120.03, 122.09, 123.46, 126.23, 126.47, 128.51, 128.58, 128.82, 128.89, 129.20, 138.26, 150.01, 151.48, 153.49.

MS: *m*/*z* (%) = 370 (M^+ + 2, 1.1), 369 (M^+ + 1, 3.1), 368 (M^+, 6.0), 335 (22.1), 292 (100.0), 223 (13.3), 194 (10.1), 165 (12.6), 121 (24.0), 91 (48.6), 57 (18.8).

Anal. Calcd for $C_{25}H_{24}N_2O$ (368.477): C, 81.49; H, 6.56; N, 7.60. Found: C, 81.51; H, 6.55; N, 7.57.

***N*,2-Dibenzyl-*N*-ethyl-1-benzofuran-3-amine (5d)**

Brown oil; yield: 303 mg (89%).

IR (KBr): 663 (w), 756 (s), 833 (w), 1026 (w), 1118 (m), 1218 (m), 1365 (w), 1458 (s), 1612 (s), 1720 (m), 2862 (w), 2962 cm^{-1} (s).

^{1}H NMR ($CDCl_3$): δ = 1.05 (t, *J* = 7.25 Hz, 3 H), 3.21 (q, *J* = 7.25 Hz, 2 H), 4.05 (s, 2 H), 4.32 (s, 2 H), 7.14–7.41 (m, 13 H), 7.69–7.73 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 14.05, 31.78, 48.42, 59.82, 111.72, 120.05, 121.90, 123.22, 124.10, 124.83, 126.29, 126.99, 128.20, 128.39, 128.70, 128.84, 137.99, 139.47, 152.75, 153.68.

MS: *m*/*z* (%) = 343 (M^+ + 2, 1.1), 342 (M^+ + 1, 4.2), 341 (M^+, 4.4), 266 (9.3), 250 (3.9), 148 (3.9), 121 (32.2), 91 (100.0), 65 (13.2).

Anal. Calcd for $C_{24}H_{23}NO$ (341.451): C, 84.42; H, 6.76; N, 4.10. Found: C, 84.43; H, 6.74; N, 4.09.

2-Benzyl-*N*,*N*-diisobutyl-1-benzofuran-3-amine (5e)

Brown oil; yield: 284 mg (85%).

IR (KBr): 663 (w), 756 (s), 833 (w), 1026 (w), 1118 (m), 1218 (m), 1365 (w), 1458 (s), 1612 (s), 1720 (m), 2862 (w), 2962 cm^{-1} (s).

^{1}H NMR ($CDCl_3$): δ = 0.95 (d, *J* = 6.5 Hz, 12 H), 1.61–1.77 (m, 2 H), 2.90 (d, *J* = 7.25 Hz, 4 H), 4.22 (s, 2 H), 7.15–7.41 (m, 8 H), 7.64–7.69 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 20.88, 27.35, 32.05, 64.59, 111.72, 120.29, 121.82, 123.24, 126.40, 126.52, 128.44, 128.74, 138.02, 151.74, 153.86.

MS: *m*/*z* (%) = 337 (M^+ + 2, 8.0), 336 (M^+ + 1, 11.1), 335 (M^+, 16.7), 292 (100.0), 260 (26.3), 236 (12.1), 207 (23.5), 121 (49.6), 86 (38.2), 57 (62.4).

Anal. Calcd for $C_{23}H_{29}NO$ (335.488): C, 82.34; H, 8.71; N, 4.18. Found: C, 82.36; H, 8.72; N, 4.15.

_N_,2-Dibenzyl-_N_-(2-phenylethyl)-1-benzofuran-3-amine (5f)
Brown solid; yield: 367 mg (88%); mp 57–59 °C.

IR (KBr): 702 (s), 748 (s), 843 (w), 1026 (m), 918 (w), 1072 (w), 1126 (m), 1257 (m), 1365 (m), 1450 (s), 1496 (s), 1604 (m), 1797 (m), 1728 (s), 2846 (m), 2923 (m), 3031 cm^{-1} (s).

^{1}H NMR ($CDCl_3$): δ = 2.79 (t, *J* = 8 Hz, 2 H), 3.47 (t, *J* = 8 Hz, 2 H), 3.98 (s, 2 H), 4.35 (s, 2 H), 7.05–7.30 (m, 17 H), 7.41–7.45 (m, 1 H), 7.70–7.73 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 31.84, 35.31, 55.79, 60.19, 111.82, 120.01, 122.10, 123.39, 126.00, 126.36, 126.58, 126.65, 127.16, 128.28, 128.46, 128.72, 128.78, 128.98, 137.94, 139.11, 140.03, 152.65, 153.74.

MS: *m*/*z* (%) = 419 (M^+ + 2, 1.2), 418 (M^+ + 1, 3.1), 417 (M^+, 5.1), 326 (39.8), 234 (5.9), 121 (33.0), 91 (100.0).

Anal. Calcd for $C_{30}H_{27}NO$ (417.549): C, 86.30; H, 6.52; N, 3.35. Found: C, 86.27; H, 6.55; N, 3.39.

4-[2-(4-*tert*-Butylbenzyl)-1-benzofuran-3-yl]morpholine (5g)
Brown solid; yield: 310 mg (89%); mp 68–70 °C.

IR (KBr): 563 (w), 709 (w), 748 (s), 840 (w), 918 (w), 1026 (w), 1110 (s), 1203 (s), 1257 (s), 1365 (w), 1450 (s), 1512 (m), 1612 (s), 1728 (s), 2854 (w), 2965 cm^{-1} (s).

^{1}H NMR ($CDCl_3$): δ = 1.22 (s, 9 H), 3.11 (t, *J* = 4.5 Hz, 4 H), 3.78 (t, *J* = 4.5 Hz, 4 H), 4.06 (s, 2 H), 7.06–7.32 (m, 7 H), 7.55–7.61 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 30.30, 30.66, 51.54, 66.61, 110.60, 118.80, 120.98, 122.34, 124.40, 125.02, 127.13, 127.55, 134.00, 148.19, 149.34, 152.39.

MS: *m*/*z* (%) = 351 (M^+ + 2, 4.6), 350 (M^+ + 1, 11.2), 349 (M^+, 12.8), 234 (10.4), 218 (10.7), 147 (32.8), 121 (100.0), 91 (13.2), 73 (13.2), 57 (33.0).

Anal. Calcd for $C_{23}H_{27}NO_2$ (349.471): C, 79.05; H, 7.79; N, 4.01. Found: C, 79.07; H, 7.77; N, 4.05.

1-[2-(4-*tert*-Butylbenzyl)-1-benzofuran-3-yl]-4-phenylpiperazine (5h)
White solid; yield: 360 mg (85%); mp 128–131 °C.

IR (KBr): 524 (w), 563 (w), 694 (m), 756 (s), 810 (w), 840 (w), 894 (w), 933 (m), 1026 (s), 1134 (s), 1226 (s), 1265 (m), 1334 (w), 1373 (m), 1450 (s), 1496 (s), 1596 (s), 2815 (w), 2954 (m), 3031 cm^{-1} (w).

^{1}H NMR ($CDCl_3$): δ = 1.30 (s, 9 H), 3.36 (s, 8 H), 4.16 (s, 2 H), 6.91–7.41 (m, 12 H), 7.98–7.71 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 31.47, 31.90, 34.48, 50.27, 52.49, 111.74, 116.44, 120.02, 120.06, 122.12, 123.48, 125.56, 126.34, 128.31, 128.83, 129.26, 135.24, 149.33, 150.25, 151.63, 153.56.

MS: *m*/*z* (%) = 427 (M^+ + 2, 1.6), 426 (M^+ + 1, 4.0), 425 (M^+, 7.1), 291 (3.8), 234 (11.2), 161 (2.6), 132 (33.0), 105 (14.1), 83 (100.0), 57 (10.8).

Anal. Calcd for $C_{29}H_{32}N_2O$ (424.584): C, 82.04; H, 7.60; N, 6.60. Found: C, 82.09; H, 7.63; N, 6.57.

4-[2-Benzyl-7-(morpholin-4-ylmethyl)-1-benzofuran-3-yl]morpholine (5i)
Brown solid; yield: 309 mg (79%); mp 84–91 °C.

IR (KBr): 702 (w), 756 (w), 856 (w), 910 (w), 1110 (s), 1203 (s), 1265 (w), 1450 (m), 1643 (m), 2846 (w), 2954 cm^{-1} (w).

^{1}H NMR ($CDCl_3$): δ = 2.41 (t, *J* = 4.5 Hz, 4 H), 3.09 (t, *J* = 4.5 Hz, 4 H), 3.60 (t, *J* = 4.5 Hz, 4 H), 3.73 (s, 2 H), 3.77 (t, *J* = 4.5 Hz, 4 H), 4.10 (s, 2 H), 7.04–7.21 (m, 7 H), 7.50 (dd, J_1 = 7.5 Hz, J_2 = 1.25 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 32.31, 52.55, 53.24, 56.09, 66.90, 67.69, 118.95, 120.81, 122.10, 124.77, 125.93, 126.43, 128.47, 128.53, 128.82, 138.23, 150.03, 152.38.

MS: *m*/*z* (%) = 394 (M^+ + 2, 29.7), 393 (M^+ + 1, 70.5), 392 (M^+, 73.1), 307 (100.0), 276 (12.0), 249 (14.7), 221 (24.7), 149 (14.5), 133 (41.3), 105 (21.6), 86 (89.9), 57 (84.1).

Anal. Calcd for $C_{24}H_{28}N_2O_3$ (392.496): C, 73.44; H, 7.19; N, 7.14. Found: C, 73.47; H, 7.22; N, 7.17.

4-[2-Benzyl-5-(morpholin-4-ylmethyl)-1-benzofuran-3-yl]morpholine (5j)
White solid; yield: 348 mg (88%); mp 98–100 °C.

IR (KBr): 540 (w), 609 (w), 702 (m), 763 (w), 918 (w), 1033 (w), 1110 (s), 1203 (m), 1257 (m), 1326 (w), 1373 (w), 1458 (m), 2815 (m), 2962 cm^{-1} (w).

^{1}H NMR ($CDCl_3$): δ = 2.46–2.48 (m, 4 H), 3.16–3.20 (m, 4 H), 3.56 (s, 2 H), 3.70–3.73 (m, 4 H), 3.84–3.88 (m, 4 H), 3.16 (s, 2 H), 7.18–7.33 (m, 7 H), 7.59 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 32.35, 52.58, 53.62, 63.58, 67.04, 67.70, 111.33, 120.39, 124.87, 126.01, 126.48, 128.56, 128.67, 131.70, 138.18, 150.61, 152.90.

MS: *m*/*z* (%) = 394 (M^+ + 2, 32.8), 393 (M^+ + 1, 66.3), 392 (M^+, 81.2), 307 (95.8), 276 (11.3), 249 (21.8), 221 (29.0), 178 (10.6), 149 (17.9), 133 (43.3), 105 (24.5), 86 (100.0), 57 (95.3).

Anal. Calcd for $C_{24}H_{28}N_2O_3$ (392.496): C, 73.44; H, 7.19; N, 7.14. Found: C, 73.47; H, 7.15; N, 7.11.

4-{[2-Benzyl-3-(piperidin-1-yl)-1-benzofuran-5-yl]methyl}morpholine (5k)
Brown solid; yield: 347 mg (89%); mp 68–72 °C.

IR (KBr): 617 (w), 756 (w), 794 (w), 864 (m), 1010 (m), 1110 (s), 1211 (m), 1257 (m), 1380 (s), 1450 (s), 1627 (m), 2808 (w), 2854 (w), 2910 cm^{-1} (m).

^{1}H NMR ($CDCl_3$): δ = 1.52–1.54 (m, 2 H), 1.63–1.69 (m, 4 H), 2.36 (t, *J* = 4.5 Hz, 4 H), 3.05 (t, *J* = 5 Hz, 4 H), 3.48 (s, 2 H), 3.62–3.66 (m, 4 H), 4.07 (s, 2 H), 6.96–7.22 (m, 7 H), 7.46–7.49 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 24.29, 26.83, 32.54, 53.60, 53.75, 63.63, 67.04, 111.14, 120.63, 124.61, 126.32, 126.59, 128.47, 128.56, 130.14, 131.20, 138.54, 149.22, 152.84.

MS: *m*/*z* (%) = 393 (M^+ + 3, 11.1), 392 (M^+ + 2, 31.2), 391 (M^+ + 1, 50.5), 390 (M^+, 96.7), 339 (14.8), 305 (86.1), 292 (13.1), 231 (40.6), 178 (14.7), 149 (31.5), 133 (65.7), 112 (53.5), 86 (100.0), 57 (73.1).

Anal. Calcd for $C_{25}H_{30}N_2O_2$ (390.523): C, 76.89; H, 7.74; N, 7.17. Found: C, 76.92; H, 7.77; N, 7.15.

4-{[2-Benzyl-3-(4-phenylpiperazin-1-yl)-1-benzofuran-5-yl]methyl}morpholine (5l)
Brown oil; yield: 415 mg (89%).

IR (KBr): 524 (w), 694 (s), 756 (s), 864 (w), 1026 (m), 1118 (s), 1226 (s), 1257 (m), 1334 (m), 1380 (m), 1450 (s), 1496 (s), 1596 (s), 1643 (m), 2815 (m), 3031 cm^{-1} (w).

^{1}H NMR ($CDCl_3$): δ = 2.36–2.39 (m, 4 H), 3.27 (s, 8 H), 3.47 (s, 2 H), 3.63 (t, *J* = 4.75 Hz, 4 H), 4.1 (s, 2 H), 6.78–7.27 (m, 12 H), 7.54–7.55 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 32.40, 50.23, 52.42, 53.54, 63.55, 66.95, 111.32, 116.41, 116.57, 120.06, 120.63, 124.92, 126.16, 126.47, 126.91, 128.57, 129.20, 131.41, 138.23, 150.47, 151.53, 152.93.

MS: *m*/*z* (%) = 469 (M^+ + 1, 0.5), 468 (M^+, 2.8), 325 (2.3), 280 (19.1), 161 (17.8), 132 (100), 91 (47.0), 56 (51.8).

Anal. Calcd for $C_{30}H_{33}N_3O_2$ (467.609): C, 77.06; H, 7.11; N, 8.99. Found: C, 77.09; H, 7.10; N, 8.96.

4-{2-Benzyl-5-[(4-{[2-benzyl-3-(morpholin-4-yl)-1-benzofuran-5-yl]methyl}piperazin-1-yl)methyl]-1-benzofuran-3-yl}morpholine (5m)

Brown solid; yield: 416 mg (80%); mp 155–157 °C.

IR (KBr): 547 (w), 702 (s), 794 (w), 918 (w), 1010 (m), 1110 (s), 1211 (m), 1265 (m), 1373 (m), 1450 (s), 1612 (m), 2815 (m), 2954 cm^{-1} (m).

^1H NMR ($CDCl_3$): δ = 2.52 (s, 8 H), 3.16 (t, *J* = 4.5 Hz, 8 H), 3.59 (s, 4 H), 3.85 (t, *J* = 4.5 Hz, 8 H), 4.15 (s, 4 H), 7.16–7.31 (m, 14 H), 7.57 (s, 2 H).

^{13}C NMR ($CDCl_3$): δ = 32.33, 52.55, 52.90, 63.05, 6769, 111.25, 120.50, 125.01, 125.93, 126.45, 128.52, 128.69, 131.68, 138.17, 150.45, 152.85.

MS: *m*/*z* (%) = 698 (M^+ + 2, 0.8), 697 (M^+ + 1, 1.5), 696 (M^+, 4.9), 509 (12.1), 391 (45.3), 350 (10.1), 307 (98.6), 242 (60.6), 176 (15.4), 142 (80.2), 91 (83.3), 56 (100.0).

Anal. Calcd for $C_{44}H_{48}N_4O_4$ (696.886): C, 75.84; H, 6.94; N, 8.04. Found: C, 75.89; H, 6.97; N, 8.01.

Acknowledgment

We gratefully acknowledge the support of this work by the Shiraz University Research Council.

Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000084.

References

(1) (a) Moss, G. P. *Pure Appl. Chem.* **2000**, *72*, 1493. (b) Zareba, K. M. *Drugs Today* **2006**, *42*, 75. (c) Kumar, V.; Ackerman, J. H.; Alexander, M. D.; Bell, M. R.; Christiansen, R. G.; Dung, J. S.; Jaeger, E. P.; Herrmann, J. L. Jr.; Krolski, M. E.; McKloskey, P.; Batzold, F. H.; Juniewicz, P. E.; Reel, J.; Snyder, B. W.; Winneker, R. C. *J. Med. Chem.* **1994**, *37*, 4227. (d) Ohemeng, K. A.; Appollina, M. A.; Nguyen, V. N.; Schwender, C. F.; Singer, M.; Steber, M.; Ansell, J.; Argentieri, D.; Hageman, W. *J. Med. Chem.* **1994**, *37*, 3663. (e) Zacchino, S.; Rodriguez, G.; Pezzenati, G.; Orellana, G.; Enriz, R.; Gonzalez Sierra, M. *J. Nat. Prod.* **1997**, *60*, 659.

(2) (a) Flynn, B. L.; Hamel, E.; Jung, M. K. *J. Med. Chem.* **2002**, *45*, 2670. (b) Lambert, J. D.; Meyers, R. O.; Timmermann, B. N.; Dorr, R. T. *Cancer Lett.* **2001**, *171*, 47. (c) Thompson, L. U.; Rickard, S. E.; Orcheson, L. J.; Seidl, M. M. *Carcinogenesis* **1996**, *17*, 1373. (d) Navarro, E.; Alonso, S. J.; Trujillo, J.; Jorge, E.; Perez, C. *J. Nat. Prod.* **2001**, *64*, 134. (e) Gangjee, A.; Devraj, R.; McGuire, J. J.; Kisliuk, R. L. *J. Med. Chem.* **1995**, *38*, 3798.

(3) (a) Silva, D. H. S.; Pereira, F. C.; Zanoni, M. V. B.; Yoshida, M. *Phytochemistry* **2001**, *57*, 437. (b) Maeda, S.; Masuda, H.; Tokoroyama, T. *Chem. Pharm. Bull.* **1994**, *42*, 2500.

(4) (a) Borsato, M. L. C.; Grael, C. F. F.; Souza, G. E. P.; Lopes, N. P. *Phytochemistry* **2000**, *55*, 809. (b) Day, S. H.; Chiu, N. Y.; Tsao, L. T.; Wang, J. P.; Lin, C. N. *J. Nat. Prod.* **2000**, *63*, 1560.

(5) (a) Yan, B.; Liu, Y. *Org. Lett.* **2007**, *9*, 4323. (b) Bai, Y.; Zeng, J.; Ma, J.; Liu, W.; Gorityala, B. K.; Liu, X.-W. *J. Comb. Chem.* **2010**, *12*, 696. (c) Patil, S. S.; Patil, S. V.; Bobade, V. D. *Synlett* **2011**, 2379.

(6) (a) Nguyen, R. V.; Li, C.-J. *Synlett* **2008**, 1897. (b) Sakai, N.; Uchida, N.; Konakahara, T. *Tetrahedron Lett.* **2008**, *49*, 3437. (c) Zhang, X.; Li, D.; Jia, X.; Wang, J.; Fan, X. *Catal. Commun.* **2011**, *12*, 839.

(7) For a recent monograph, see: *Multicomponent Reactions*; Zhu, J.; Bienayme, H., Eds.; Wiley-VCH: Weinheim, **2005**.

(8) For reviews, see: (a) Sunderhaus, J. D.; Martin, S. F. *Chem. Eur. J.* **2009**, *15*, 1300. (b) Isambert, N.; Lavilla, R. *Chem. Eur. J.* **2008**, *14*, 8444. (c) Domling, A. *Chem. Rev.* **2006**, *106*, 17. (d) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471. (e) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321. (f) Domling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168. (g) Ugi, I.; Domling, A.; Werner, B. *J. Heterocycl. Chem.* **2000**, *37*, 647. (h) Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 366. (i) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123. (j) Ugi, I.; Domling, A.; Horl, W. *Endeavour* **1994**, *18*, 115. (k) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831. (l) Choudhury, L. H.; Parvin, T. *Tetrahedron* **2011**, *67*, 8213.

(9) (a) Denmark, S. E.; Smith, R. C.; Chang, W.-T. T.; Muhuhi, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 3104. (b) Wang, S.; Li, P.; Yu, L.; Wang, L. *Org. Lett.* **2011**, *13*, 5968. (c) Zhou, L.; Shi, Y.; Xiao, Q.; Liu, Y.; Ye, F.; Zhang, Y.; Wang, J. *Org. Lett.* **2011**, *13*, 968. (d) Wang, J.-R.; Manabe, K. *J. Org. Chem.* **2010**, *75*, 5340. (e) Pei, T.; Chen, C.-Y.; DiMichele, L.; Davies, I. W. *Org. Lett.* **2010**, *12*, 4972. (f) Maimone, T. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 9990. (g) Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022. (h) Anderson, K. W.; Ikawa, T.; Tundel, R. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 10694. (i) De Luca, L.; Giacomelli, G.; Nieddu, G. *J. Org. Chem.* **2007**, *72*, 3955. (j) Shibata, T.; Hashimoto, Y.-K.; Otsuka, M.; Tsuchikama, K.; Endo, K. *Synlett* **2011**, 2075. (k) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 10292. (l) Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 2395. (m) Duan, X.-F.; Shen, G.; Zhang, Z.-B. *Synthesis* **2010**, 2547. (n) Fiandanese, V.; Bottalico, D.; Marchese, G.; Punzi, A.; Quarta, M. R. *Synthesis* **2009**, 3853.

(10) (a) Tang, B.-X.; Wang, F.; Li, J.-H.; Xie, Y.-X.; Zhang, M.-B. *J. Org. Chem.* **2007**, *72*, 6294. (b) Li, J.-H.; Tang, B.-X.; Tao, L.-M.; Xie, Y.-X.; Liang, Y.; Zhang, M.-B. *J. Org. Chem.* **2006**, *71*, 7488. (c) Chanda, K.; Rej, S.; Huang, M. H. *Chem. Eur. J.* **2013**, *19*, 16036. (d) Sharghi, H.; Aberi, M. *Synlett* **2014**, *25*, 1111.

(11) (a) Sharghi, H.; Hosseini-Sarvari, M.; Moeini, F.; Khalifeh, R. *Helv. Chim. Acta* **2010**, *93*, 435. (b) Sharghi, H.; Hosseini-Sarvari, M.; Moeini, F. *Can. J. Chem.* **2008**, *86*, 1044. (c) Sharghi, H.; Khoshnood, A.; Khalifeh, R. *Iran. J. Sci. Technol.* **2012**, *A1*, 25. (d) Sharghi, H.; Khoshnood, A.; Doroodmand, M. M.; Khalifeh, R. *J. Iran. Chem. Soc.* **2012**, *9*, 231. (e) Sharghi, H.; Aberi, M.; Doroodmand, M. M. *J. Iran. Chem. Soc.* **2012**, *9*, 189. (f) Sharghi, H.; Khalifeh, R.; Mansouri, S. G.; Aberi, M.; Eskandari, M. M. *Catal. Lett.* **2011**, *141*, 1845. (g) Sharghi, H.; Khalifeh, R.; Moeini, F.; Beyzavi, M. H.; Salimi Beni, A.; Doroodmand, M. M. *J. Iran. Chem. Soc.* **2011**, *8*, S89. (h) Sharghi, H.; Jokar, M.; Doroodmand, M. M.; Khalifeh, R. *Adv. Synth. Catal.* **2010**, *352*, 3031. (i) Sharghi, H.; Khalifeh, R.; Salimi Beni, A. *J. Iran. Chem. Soc.* **2010**, *7*, 275. (j) Sharghi, H.; Beyzavi, M. H.; Safavi, A.; Doroodmand, M. M.; Khalifeh, R. *Adv. Synth. Catal.* **2009**, *351*, 2391. (k) Sharghi, H.; Khalifeh, R.; Doroodmand, M. M. *Adv. Synth. Catal.* **2009**, *351*, 207. (l) Sharghi, H.; Aberi, M.; Doroodmand, M. M. *Adv. Synth.*

Catal. **2008**, *350*, 2380. (m) Sharghi, H.; Khalifeh, R. *Can. J. Chem.* **2008**, *86*, 426. (n) Sharghi, H.; Asemani, O.; Khalifeh, R. *Synth. Commun.* **2008**, *38*, 1128. (o) Sharghi, H.; Khalifeh, R. *Heterocycles* **2007**, *71*, 1601. (p) Sharghi, H.; Salimi Beni, A. *Helv. Chim. Acta* **2007**, *90*, 1373.

(12) Shen, G.; Lv, X.; Qian, W.; Bao, W. *Tetrahedron Lett.* **2008**, *49*, 4556.

(13) (a) Sammons, M.; Jennings, S. M.; Herr, M.; Hulford, C. A.; Wei, L.; Hallissey, J. F.; Kiser, E. J.; Wright, S. W.; Piotrowski, D. W. *Org. Process Res. Dev.* **2013**, *17*, 934. (b) Zask, A.; Kaplan, J.; Verheijen, J. C.; Richard, D. J.; Curran, K.; Brooijmans, N.; Bennett, E. M.; Toral-Barza, L.; Hollander, I.; Ayral-Kaloustian, S.; Yu, K. *J. Med. Chem.* **2009**, *52*, 7942.

(14) (a) Ramu, E.; Varala, R.; Sreelatha, N.; Adapa, S. R. *Tetrahedron Lett.* **2007**, *48*, 7184. (b) Sreedhar, B.; Suresh Kumar, A.; Surendra Reddy, P. *Tetrahedron Lett.* **2010**, *51*, 1891. (c) Bhatte, K. D.; Sawant, D. N.; Deshmukh, K. M.; Bhanage, B. M. *Catal. Commun.* **2011**, *16*, 114. (d) Yoo, W.-J.; Zhao, L.; Li, C.-J. *Aldrichimica Acta* **2011**, *44*, 43. (e) Li, C.-J. *Acc. Chem. Res.* **2010**, *43*, 581.

(15) Kooti, M.; Matouri, L. *Sci. Iran.* **2010**, *17*, 73.

