Tetrahedron 68 (2012) 3942–3947

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

New synthetic method for benzofurans from 2-(cyanomethyl)phenyl derivatives

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ARTICLE INFO

Article history:
Received 10 December 2011
Received in revised form 19 March 2012
Accepted 21 March 2012
Available online 30 March 2012

Keywords:
Benzofuran
C2-substituted benzofuran
C3-carboxylated benzofuran
Benzyl cyanide
Intramolecular cyclization

ABSTRACT

A convenient and mild synthetic method of synthesizing benzofuran from various 2-(cyanomethyl) phenyl carbonyl compounds under reduced oxygen conditions is reported. Nine C-2 substituted benzofurans were synthesized at 52–89%.

1. Introduction

Active natural and synthetic benzofurans have been attracted because of their pharmaceutical utilities.[1,2] Accordingly, several synthetic strategies, such as acid-catalyzed cyclization of carbonyl containing compounds by dehydration (**A** type),[2] palladium[3] or platinum[4]-catalyzed cyclization (**B** type),[1c] ring closure via an intramolecular Wittig reaction[5] or *o*-(acyloxy)benzyl anions[6] (**C** type), Dieckmann condensation of activated methylene[1d,7] or ketene intermediate involved cyclization[8] (**D** type), acid-catalyzed ring formation of α-aryloxycarbonyls[9] or intramolecular Friedel–Crafts reaction[10] (**E** type), photolytic cyclization of α-phenylketones[11] (**F** type), and gold(III)-catalyzed tandem reaction of *O*-arylhydroxylamines with 1,3-dicarbonyl compounds[12] (**G** type) have been developed to produce benzofurans (Fig. 1). In addition, Youn reported one-pot procedures for the conversion of allyl aryl ethers to 2-methylbenzofurans (via sequential Claisen rearrangement and oxidative cyclization).[13] Ohe also reported the synthesis of 3-acyl-2-aminobenzofurans from 2-(cycanomethyl)phenyl esters using catalytic amount of $Pd(OAc)_2$, PCy_3, and Zn.[14]

Most strategies devised to synthesize benzofurans resemble the well known indole reactions, such as, those utilized during Leimgruber–Batcho, Reissert, Madelung, Bischler, and Fisher indole synthesis.[15] Of these, Wittig-type ring formation,[5a] which is used to produce benzofurans, is required to benzylidene phosphonium salts. During a pyrolysis study of *O*-(2-cyanomethylphenyl)-*N*,*N*-dimethyl thiocarbamate (**1**), a couple of benzofuran derivatives were isolated. Here, we describe a novel method of synthesizing benzofuran and provide a plausible mechanism.

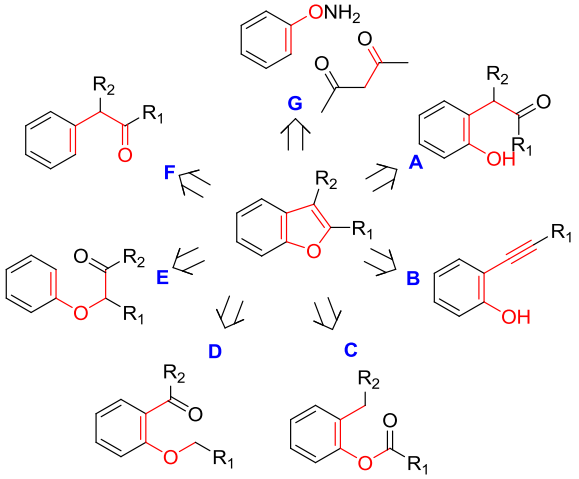

Fig. 1. Synthetic strategies used to synthesize benzofuran.

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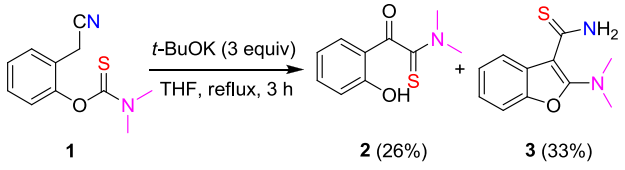
doi:10.1016/j.tet.2012.03.088

2. Results and discussion

As shown in Scheme 1, a cyano functionality at the benzyl carbon was selected because not only this allowed the straightforward preparation of the starting material, but also the doubly activated hydrogen at benzylic position by cyano and phenyl groups would easily be deprotonated. Thiocarbamate **1**, synthesized from 2-hydroxybenzyl cyanide and dimethylamino thiocarbamoyl chloride, was treated with *t*-BuOK under THF reflux for 3 h. Subsequently, 2-(2-hydroxyphenyl)-*N*,*N*-dimethyl-2-oxoethanethioamide (**2**) and 2-dimethylamino-3-thoicarbamoylbenzofuran (**3**) were isolated as major products.



Scheme 1.

2-Oxothioacetamide **2** could be generated by the oxidative decyanation of benzyl cyanide in a manner similar to that reported by Kulp and Rabjohn et al.[16] after rearrangement of thiocarbamoyl group as shown in Fig. 2. To proceed with the research, we changed the starting material to carbamate **4** from thiocarbamate **1** due to high viscosity of the latter.

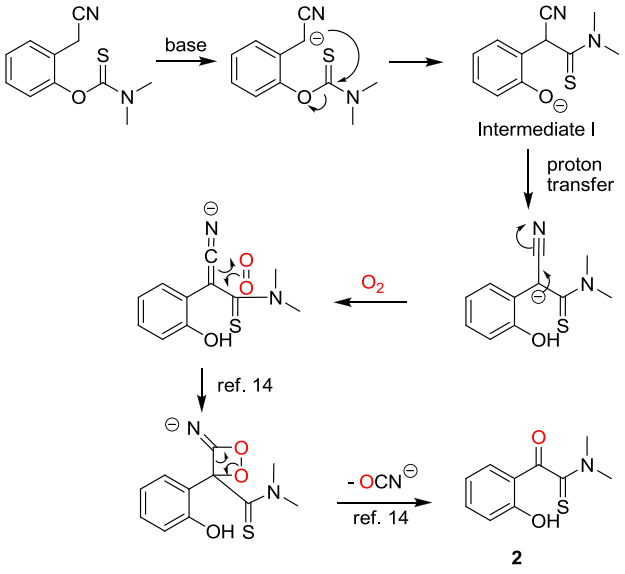
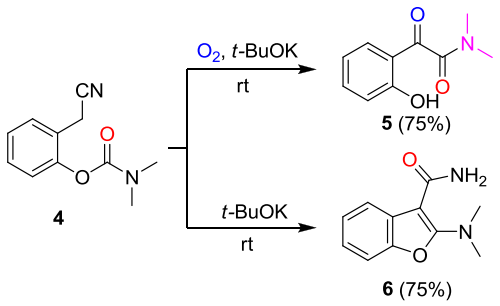


Fig. 2. Oxidative decyanation mechanism after rearrangement of thiocarbamoyl group.

To produce **5** and **6**, carbamate **4** was treated with *t*-BuOK under two different conditions: (i) with air bubbled through the reaction mixture, and (ii) under oxygen-free conditions (achieved using a Schlenk flask connected to vacuum and an Ar gas blanket to exclude oxygen-involving side reactions (Scheme 2)). As was expected, while the former condition produced 2-(2-hydroxyphenyl)-*N*,*N*-dimethyl-2-oxoacetamide (**5**) at a yield of 75% within 1 h at room temperature, under oxygen depleted free conditions 2-dimethylamino-3-amidobenzofuran (**6**) was produced at a yield of 75%. This marked difference was presumed to have been caused by the presence of singlet oxygen. Thus, we considered that the formation of benzofuran **6** might proceed via a mechanism unlike that of oxidative decyanation.



Scheme 2.

Two-dimensional TLC[17] and NMR of crude mixtures showed that the phenolic intermediate **4a** was present in the reaction mixture. When we developed the mixture of **4a** and **6** on silica gel TLC plate, compound **4a** appeared as the more polar spot. When this TLC gel plate was developed again after 90° rotation, the low spot of **4a** was split into two spots, which are corresponding to **6** and **4a**. Such evidence means that compound **4a** can be transformed to the desired benzofuran **6** on silica gel.

In particular, we noticed that acidic work up processing and silica gel chromatography improved the conversion of intermediate **4a** to 2-dimethylaminobenzofuran **6**. From a mechanistic point of view, we believe that intermediates II was converted to benzofuran **6** via by deprotonation in the presence of base. Furthermore, we believe that intermediate II could form several intermediates, which were observed in reaction mixtures to varying extents, and that these intermediates loose the benzylic proton to form the respective benzofurans (Fig. 3). Thus compound **4a** is probably a reaction intermediate, which can become the product under acidic conditions like on silica gel.

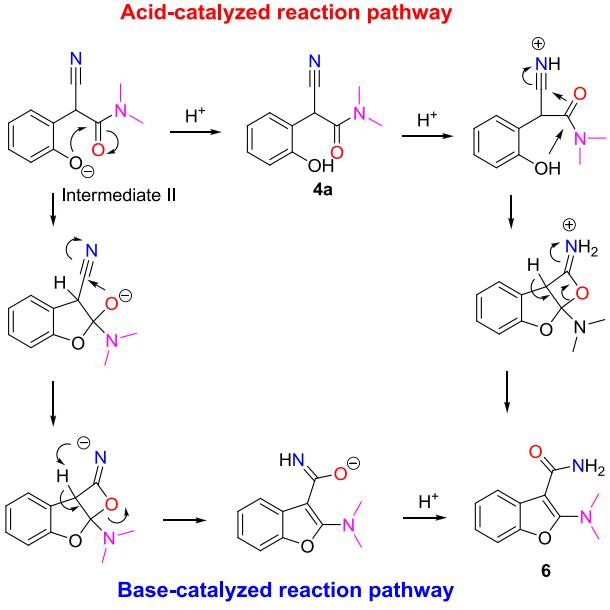
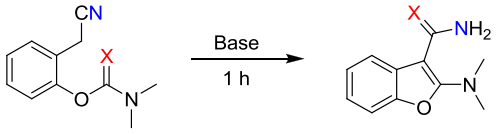


Fig. 3. Plausible mechanism from compound **4**.

To optimize conditions, the reaction was performed under various temperature using various solvents and bases (Table 1). First, the reaction mixture was treated with from 1 to 3 equiv of *t*-BuOK at room temperature for 1 h. 1 equiv of base gave only 11% of the 3-carboxyamidobenzofuran **6**, but 2 or 3 equiv increased the yield to 60 and 75%, respectively. However, when the reaction was performed using 3 equiv of base at −78 °C, the desired product was obtained at a yield of only 10% after 1 h. Further optimization was

Table 1
Optimization of the reaction[a]



1, X = S
4, X = O

3, X = S
6, X = O

Entry	X	Base	Equiv	Solvent	Temp (°C)	Yield[b] (%)
1	O	*t*-BuOK	1	THF	rt	11
2	O	*t*-BuOK	2	THF	rt	60
3	O	*t*-BuOK	3	THF	rt	75
4	O	*t*-BuOK	3	THF	−78	10
5	O	*t*-BuOK	3	DMF	rt	66
6	O	*t*-BuOK	3	Dioxane	rt	65
7	O	NaH	3	THF	rt	50
8	O	NaOMe	3	MeOH	rt	—
9	S	*t*-BuOK	3	THF	rt	75

[a] All reactions were carried out at the 1.0 mmol scale in 15 mL of solvent under argon.
[b] Isolated yields.

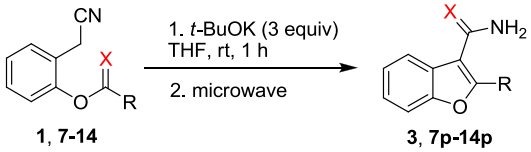
performed using several solvents and bases (Table 1, entries 5 and 6). Reactions containing 3 equiv of *t*-BuOK in DMF or dioxane were complete within 1 h at room temperature, yielding 66% and 65% of product **6**, respectively. The optimal reaction condition required for the synthesis of benzofuran was practically unaffected by solvent changes. Treatment with sodium hydride in THF produced benzofuran **6** at a yield of 50%, but reaction with sodium methoxide in MeOH failed to produce **6**. The use of thiocarbamate **1** as a substrate also successfully provided the thioamide **3** as the major product at a yield of 75% (Table 1, entry 9).

A comparison of our method of producing benzofurans with the well known acid-catalyzed cyclization (**A** type in Fig. 1) and with intramolecular Wittig ring closure (**C** type in Fig. 1), suggests that our synthetic method is more convenient for producing diverse benzofurans when the two main molecular building blocks, that is, 2-hydroxybenzyl cyanide and acid chloride or anhydride, are used as starting materials.

Synthesis of benzofuran from carbamate **7** (Fig. 3) using our optimized condition (the same condition at entry 3, Table 1) produced only a mixture of benzofuran **7p** and intermediate **7a** (structurally similar to intermediate **4a**), which could not be isolated in pure form. However, our aim was to produce benzofurans using a straightforward method. As we mentioned two-dimensional TLC results, compound **7a** was transformed to the desired benzofuran **7p** on silica gel TLC plate. The extracted organic layer of reaction mixture (0.5 mmol reaction scale) was washed with brine (5 mL×3) and dried over sodium sulfate. Silica gel (2.0 g) was poured into solution and solvent was evaporated under reduced pressure. Silica gel was dried in a high vacuum for 30 min and the residue was irradiated under microwave (30 s×3, 620 W). After the silica gel was suspended in EtOAc, silica gel was filtered the solvent was removed under reduced pressure to obtain **7p** (80 mg, 69%) as yellow solid.

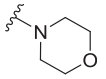
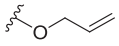
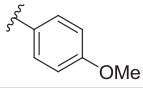
Using this microwave technique, several carbonyl starting compounds (thiocarbamate (**1**), carbamates (**7**–**11**), carbonates (**12** and **13**), and the ester (**14**)) were used to produce benzofurans (Table 2). Nine starting molecules were readily prepared by simply acylating 2-hydroxybenzyl cyanide with corresponding carbonyl chlorides at yields of 70–99%. Carbamates (**7**–**11**) produced the 2-aminobenzofurans (**7p**–**11p**) in yields ranging from 66 to 81%. In the case of carbonates, methyl **12** and allyl carbonate **13** afforded 2-methoxybenzofuran **12p** at 52% and 2-allyloxy benzofuran **13p** at 54%, respectively. In addition, the benzoate **14** with a *para*-methoxy group produced 2-(4-methoxy)phenyl benzofuran **14p** at a yield of 70%.

Table 2
Synthesis of various C2-substituted benzofurans[a]



1, **7-14**

3, **7p-14p**

Reactant	X	R	Product	Yield[b] (%)
1	S		**3**	89
7	O		**7p**	69
8	O		**8p**	81
9	O		**9p**	66
10	O		**10p**	67
11	O		**11p**	79
12	O		**12p**	52
13	O		**13p**	54
14	O		**14p**	70

[a] All reactions were carried out in 0.5 mmol scale at the condition of entry 3 of Table 1 (see Supplementary data for detail procedure).
[b] Isolated yields.

In conclusion, we described a convenient means of synthesizing C2-substituted benzofurans. In situ two-step reactions using *t*-BuOK in the absence of oxygen and microwave/silica gel treatment provided several C2-derivatize benzofurans in yields of 52–89%. Furthermore, straightforward purification of final product by filtration from silica gel eliminated the need for column chromatography. This described method is quite convenient as shown at Fig. 1, because various starting compounds could be easily prepared from commercially available carbonyl chlorides, such as, carbamoyl chloride, thiocarbamoyl chloride, chloroformate, and acid chloride, and because further derivatization of benzofurans at the C3 position can be used to search biologically active benzofurans.

3. Experimental section

3.1. 2-Hydroxybenzyl cyanide

2-Hydroxybenzylalcohol (5.0 g, 40.3 mmol) and potassium cyanide (3.0 g, 61.2 mmol) were dissolved in DMF (80 mL) and the solution was heated to 130 °C with stirring. After 8 h, the mixture was quenched with saturated aqueous NH_4Cl (200 mL), which was extracted with EtOAc (100 mL×3). The combined organic layer was washed with saturated aqueous NH_4Cl (50 mL×3), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (40% EtOAc/*n*-hexane) to obtain 2-hydroxybenzyl cyanide (2.5 g, 47%) as brown solid: mp

113–114 °C (116–118 °C in literature[18]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 2H), 5.54 (s, 1H, OH), 6.80 (dd, J=8.0, 0.8 Hz, 1H), 6.95 (td, J=7.2, 0.8 Hz, 1H), 7.20 (td, J=8.0, 1.6 Hz, 1H), 7.34 (dd, J=7.2, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5, 115.3, 116.8, 118.0, 121.2, 129.48, 129.57, 153.1; MS (EI) m/z 133 (M^+, 100). Registry No.: 14714-50-2.

3.2. General procedure for carbamate

*3.2.1. O-(2-Cyanomethylphenyl)-N,N-dimethyl thiocarbamate (**1**).* To a THF solution (5 mL) of 2-hydroxybenzyl cyanide (400 mg, 3.0 mmol) was added *t*-BuOK (500 mg, 4.5 mmol) THF solution (10 mL) at 0 °C. After stirring for 5 min, dimethylthiocarbamoyl chloride (3.6 mmol) was added and stirred at 90 °C. After 2 h, the reaction was quenched with water (30 mL), and then organic phase was extracted with EtOAc (20 mL×3). The combined organic layer was washed with brine (10 mL×3) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by flash column chromatography (30% EtOAc/*n*-hexane) to obtain **1** (463 mg, 70%) as yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.40 (s, 3H), 3.45 (s, 3H), 7.06 (d, J=8.0 Hz, 1H), 7.29 (t, J=7.6 Hz, 1H), 7.39 (t, J=8.0 Hz, 1H), 7.43 (d, J=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 38.8, 43.4, 117.1, 126.7, 123.7, 126.7, 129.40, 129.43, 151.7, 185.9; FT-IR (KBr) 750, 960, 1096, 1151, 1217, 1273, 1417, 1713 cm^{-1}; MS (EI) m/z 220 (M^+), 133, 88 (100), 72. HRMS (EI) calcd for $C_{11}H_{12}N_2OS$, 220.0670; found, 220.0670.

*3.2.2. O-(2-Cyanomethylphenyl)-N,N-dimethyl carbamate (**4**).* Dimethylcarbamoyl chloride (303 μL, 3.3 mmol) was used and desired product **4** (557 mg, 91%) was obtained as pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.01 (s, 3H), 3.14 (s, 3H), 7.17 (d, J=8.0 Hz, 1H), 7.22 (t, J=7.6 Hz, 1H), 7.34 (t, J=8.0 Hz, 1H), 7.39 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 36.4, 36.7, 117.1, 122.67, 122.77, 125.9, 129.26, 129.32, 149.2, 153.7; FT-IR (KBr) 753, 1163, 1225, 1391, 1489, 1686, 1725 cm^{-1}; MS (EI) m/z 204 (M^+), 72 (100). HRMS (EI) calcd for $C_{11}H_{12}N_2O_2$, 204.0899; found, 204.0895.

*3.2.3. O-(2-Cyanomethylphenyl)-N,N-diethyl carbamate (**7**).* Diethylcarbamoyl chloride (418 μL, 3.3 mmol) was used and desired product **7** (550 mg, 79%) was obtained as yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, J=7.2 Hz, 3H), 1.28 (t, J=7.2 Hz, 3H), 3.39 (q, J=7.2 Hz, 2H), 3.49 (q, J=7.2 Hz, 2H), 3.67 (s, 2H), 7.16 (dd, J=8.0, 0.8 Hz, 1H), 7.21 (td, J=7.6, 0.8 Hz, 1H), 7.34 (td, J=7.6, 1.2 Hz, 1H), 7.41 (d, J=7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 14.3, 19.2, 42.0, 42.3, 117.0, 122.61, 122.73, 125.7, 129.15, 129.19, 149.1, 152.9; MS (EI) m/z 232 (M^+), 100 (100), 72, 61. HRMS (EI) calcd for $C_{13}H_{16}N_2O_2$, 232.1212; found, 232.1215.

*3.2.4. O-(2-Cyanomethylphenyl)-N,N-diphenyl carbamate (**8**).* Diphenylcarbamoyl chloride (765 mg, 3.3 mmol) was used and desired product **8** (807 mg, 82%) was obtained as off-white solid: mp 98–100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.45 (s, 2H), 7.16 (td, J=7.2, 1.6 Hz, 1H), 7.25 (br s, 2H), 7.31 (br s, 1H), 7.33 (d, J=1.2 Hz, 2H), 7.351–7.402 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 116.9, 122.2, 125.9, 126.7, 129.02, 129.11, 129.13, 141.6, 148.7, 151.6; FT-IR (KBr) 835, 1032, 1147, 1255, 1464, 1510, 1701 cm^{-1}; MS (EI) m/z 328 (M^+), 196 (100), 168, 77. HRMS (EI) calcd for $C_{21}H_{16}N_2O_2$, 328.1212; found, 328.1209.

*3.2.5. 2-(Cyanomethyl)phenyl 1-piperidinecarboxylate (**9**).* 1-Piperidinecarbonyl chloride (413 μL, 3.3 mmol) was used and desired product **9** (671 mg, 91%) was obtained as off-white solid: mp 68–69 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65 (br s, 6H), 3.51 (br s, 2H), 3.66 (br s, 4H), 7.15 (dd, J=8.0, 1.2 Hz, 1H), 7.21 (td, J=7.6, 1.2 Hz, 1H), 7.34 (td, J=7.6, 2.0 Hz, 1H), 7.39 (dd, J=7.6, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 24.1, 25.4, 25.9, 45.2, 45.6, 117.0, 122.7, 125.7, 129.12, 129.18, 149.1, 152.3; FT-IR (KBr) 747, 1023, 1130, 1220, 1264, 1408, 1702 cm^{-1}; MS (EI) m/z 244 (M^+), 133, 112 (100), 69. HRMS (EI) calcd for $C_{14}H_{16}N_2O_2$, 244.1212; found, 244.1216.

*3.2.6. 2-(Cyanomethyl)phenyl 1-pyrrolidinecarboxylate (**10**).* 1-Pyrrolidinecarbonyl chloride (370 μL, 3.3 mmol) was used and desired product **10** (511 mg, 74%) was obtained as pale yellow solid: mp 74–75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89–2.02 (m, 4H), 3.48 (t, J=6.4 Hz, 2H), 3.61 (t, J=6.4 Hz, 2H), 3.69 (s, 2H), 7.20 (td, J=7.4, 1.6 Hz, 1H), 7.22 (d, J=7.8 Hz, 1H), 7.34 (td, J=7.8, 1.6 Hz, 1H), 7.39 (dd. J=8.4, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 24.8, 25.7, 46.38, 46.51, 117.0, 122.48, 122.62, 125.6, 129.10, 129.13, 149.0, 151.7; FT-IR (KBr) 770, 1065, 1096, 1168, 1220, 1399, 1707 cm^{-1}; MS (EI) m/z 230 (M^+), 98 (100), 55. HRMS (EI) calcd for $C_{13}H_{14}O_2N_2$, 230.1055; found, 230.1058.

*3.2.7. 2-(Cyanomethyl)phenyl 4-morpholinecarboxylate (**11**).* 4-Morpholinecarbonyl chloride (380 μL, 3.3 mmol) was used and desired product **11** (700 mg, 94%) was obtained as yellow solid: mp 88–89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.58 (br s, 4H), 3.65 (s, 2H), 3.77 (br s, 4H), 7.18 (dd, J=8.0, 1.2 Hz, 1H), 7.23 (td, J=7.6, 1.2 Hz, 1H), 7.36 (td, J=8.0, 1.6 Hz, 1H), 7.38 (d, J=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 44.2, 44.9, 66.3, 66.4, 116.9, 122.6, 122.7, 126.0, 129.35, 129.40, 148.9, 152.3; MS (EI) m/z 246 (M^+), 114 (100), 70. HRMS (EI) calcd for $C_{13}H_{14}N_2O_3$, 246.1004; found, 246.1003.

3.3. General procedure for carbonate

*3.3.1. 2-(Cyanomethyl)phenyl methyl carbonate (**12**).* To a solution of 2-hydroxybenzyl cyanide (400 mg, 3.0 mmol) and methyl chloroformate (254 μL, 3.3 mmol) in CH_2Cl_2 (10 mL) was added triethylamine (460 μL, 3.3 mmol) at 0 °C. After 5 min, removed the ice bath and stirred at room temperature. After 1 h, the mixture was quenched with water (30 mL), and then organic phase was extracted with CH_2Cl_2 (20 mL×3). The combined organic layer was washed with brine (20 mL×3) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by flash column chromatography (20% EtOAc/*n*-hexane) to obtain **12** (520 mg, 91%) as yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (s, 2H), 3.91 (s, 3H), 7.24 (dd, J=8.0, 1.2 Hz, 1H), 7.27 (td, J=8.0, 1.2 Hz, 1H), 7.37 (td, J=8.0, 1.6 Hz, 1H), 7.46 (dd, J=7.6, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5, 55.5, 116.6, 121.8, 122.1, 126.4, 129.18, 129.21, 148.4, 153.0; MS (EI) m/z 191 (M^+), 147, 132 (100), 104, 77. HRMS (EI) calcd for $C_{10}H_9NO_3$, 191.0582; found, 191.0585.

*3.3.2. Allyl 2-(cyanomethyl)phenyl carbonate (**13**).* Allyl chloroformate (360 μL, 3.3 mmol) was used and desired product **13** (654 mg, 99%) was obtained as yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (s, 2H), 4.75 (dt, J=6.0, 1.2 Hz, 2H), 5.34 (dd, J=10.6, 1.2 Hz, 1H), 5.43 (dd, J=17.6, 1.2 Hz, 1H), 5.94–6.04 (m, 1H), 7.25 (dd, J=8.0, 1.2 Hz, 1H), 7.27 (td, J=7.6, 1.2 Hz, 1H), 7.37 (td, J=8.0, 1.6 Hz, 1H), 7.46 (dd, J=7.6, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 69.5, 116.6, 119.7, 121.97, 122.13, 126.6, 129.31. 129.40, 130.6, 148.5, 152.4; MS (FAB) m/z 218 (M^+, 100), 154, 137, 107. HRMS (FAB) calcd for $C_{12}H_{12}NO_3$ ($[M+H]^+$), 218.0812; found, 218.0820.

*3.3.3. 2-(Cyanomethyl)phenyl 4-methoxybenzoate (**14**).* 4-Methoxybenzoyl chloride (563 mg, 3.3 mmol) was used and desired product **14** (603 mg, 75%) was obtained as light yellow solid: mp 94–95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (s, 2H), 3.91 (s, 3H), 7.01 (d, J=8.0 Hz, 2H), 7.26 (d, J=8.0 Hz, 1H), 7.31 (t, J=7.6 Hz, 1H), 7.43 (t, J=8.0 Hz, 1H), 7.51 (d, J=8.0 Hz, 1H), 8.18 (d, J=8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 55.6, 114.1, 117.0, 120.8, 122.76, 122.93, 126.6, 129.51,

129.60, 132.5, 148.8, 164.13, 164.27; MS (EI) *m/z* 267 (M^+), 135 (100), 107, 92, 77. HRMS (EI) calcd for $C_{16}H_{13}O_3N$, 267.0895; found, 267.0899.

3.4. Procedure of Scheme 1

To a THF solution (5 mL) of compound **1** (220 mg, 1.0 mmol) were added NaH (120 mg, 3.0 mmol), THF solution (5 mL) and stirred at 90 °C. After 3 h, reaction was quenched with saturated aqueous NH_4Cl (20 mL), and then organic phase was extracted with EtOAc (10 mL×3). The combined organic layer was washed with brine (5 mL×3) and dried over Na_2SO_4. After removal of the solvent, the residue was purified by flash column chromatography (5% EtOAc/45% DCM/*n*-hexane) to obtain **2** and **3**, respectively.

*3.4.1. 2-(2-Hydroxyphenyl)-N,N-dimethyl-2-oxoethanethioamide (**2**).* Yellow gum: ^1H NMR (400 MHz, $CDCl_3$) δ 3.25 (s, 3H), 3.54 (s, 3H), 6.88 (td, *J*=8.0, 0.8 Hz, 1H), 7.00 (dd, *J*=8.4, 0.8 Hz, 1H), 7.50 (dt, *J*=7.6, 0.8 Hz, 1H), 7.52 (dd, *J*=8.0, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.3, 42.5, 116.1, 118.6, 119.5, 131.9, 137.4, 163.5, 193.3, 193.5; MS (EI) *m/z* 209 (M^+), 176, 121, 88 (100). HRMS (FAB^+) calcd for $C_{10}H_{12}NO_2S$ ($[M+H]^+$), 210.0583; found, 210.0587.

*3.4.2. 2-Dimethylamino-3-thiocarboxamidobenzofuran (**3**).* Yield 98 mg (89%) yellow solid: mp 135–136 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.40 (s, 6H), 6.15 (br s, 2H, NH_2), 7.04 (t, *J*=8.0 Hz, 1H), 7.07 (d, *J*=8.0 Hz, 1H), 7.17 (t, *J*=8.0 Hz, 1H), 7.23 (d, *J*=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.7, 95.0, 109.8, 118.6, 121.0, 123.4, 126.3, 147.9, 162.8, 192.4; FT-IR (KBr) 750, 972, 1125, 1385, 1454, 1605 cm^{-1}; MS (EI) *m/z* 220 (M^+, 100), 176, 144, 115. HRMS (EI) calcd for $C_{11}H_{12}N_2OS$, 220.0670; found, 220.0672.

3.5. Procedure of Scheme 2

*3.5.1. 2-(2-Hydroxyphenyl)-N,N-dimethyl-2-oxoacetamide (**5**).* To a THF (5 mL) solution of SM (204 mg, 1.0 mmol) and *t*-BuOK (336 mg, 3.0 mmol) was bubbled air and stirred at room temperature. After 1 h, the reaction was quenched with saturated aqueous NH_4Cl (20 mL), and then organic phase was extracted with EtOAc (10 mL×3). The combined organic layer was washed with brine (5 mL×3) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by flash column chromatography (40% EtOAc/*n*-hexane) to obtain **5** (145 mg, 75%) as yellow viscose liquid: ^1H NMR (400 MHz, $CDCl_3$) δ 2.98 (s, 3H), 3.12 (s, 3H), 6.94 (t, *J*=8.0 Hz, 1H), 7.24 (d, *J*=8.4 Hz, 1H), 7.52 (t, *J*=8.0 Hz, 1H), 7.55 (d, *J*=8.2 Hz, 1H), 11.32 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.0, 37.1, 116.6, 118.5, 119.8, 132.0, 137.9, 163.2, 165.0, 196.7; MS (EI) *m/z* 193 (M^+), 121 (100), 72. HRMS (FAB^+) calcd for $C_{10}H_{12}NO_3$ ($[M+H]^+$), 194.0812; found, 194.0817.

*3.5.2. 3-Carboxamido-2-dimethylaminobenzofuran (**6**).* Compound **4** (204 mg, 1.0 mmol) and *t*-BuOK (336 mg, 3.0 mmol) were dried under high vacuum for 30 min and then purged with argon gas. After 5 min, freshly distilled THF (15 mL) under nitrogen was added and the reaction mixture was stirred for 1 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl (20 mL), and then organic phase was extracted with EtOAc (15 mL×3). The combined organic layer was washed with brine (5 mL×3) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by flash column chromatography (40% EtOAc/CH_2Cl_2) to obtain **6** (77 mg, 75%) as off-white solid: mp 112–113 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.09 (s, 6H), 5.66 (br s, 2H, NH_2), 7.04 (t, *J*=8.0 Hz, 1H), 7.17 (t, *J*=7.6 Hz, 1H), 7.23 (d, *J*=7.8 Hz, 1H), 7.24 (d, *J*=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.5, 87.3, 109.9, 118.6, 120.6, 123.4, 127.2, 148.7, 163.3, 168.6; FT-IR (KBr) 744, 1033, 1242, 1385, 1455, 1502, 1595, 1629 cm^{-1}; MS (EI) *m/z* 204 (M^+), 160 (100), 133, 104. HRMS (EI) calcd for $C_{11}H_{12}O_2N_2$, 204.0899; found, 204.0896.

3.6. General procedure for Table 2

*3.6.1. 3-Carboxamido-2-diethylaminobenzofuran (**7p**).* Compound **7** (116 mg, 0.5 mmol) and *t*-BuOK (170 mg, 1.5 mmol) were dried under high vacuum for 30 min and charged with argon gas. After 5 min, freshly distilled THF (10 mL) under nitrogen was added and stirred at room temperature for 1 h. The reaction was quenched by saturated aqueous NH_4Cl (20 mL), and then organic phase was extracted with EtOAc (15 mL×3). The combined organic layer was washed with brine (5 mL×3) and dried over Na_2SO_4. Silica gel (2.0 g) was poured into solution and solvent was evaporated under reduced pressure. Silica gel was dried in a high vacuum for 30 min and the residue was irradiated under Microwave (30 s×3, 620 W). After the silica gel was suspended in EtOAc, silica gel was filtered the solvent was removed under reduced pressure to obtain **7p** (80 mg, 69%) as yellow solid: mp 115–117 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, *J*=7.2 Hz, 6H), 3.56 (q, *J*=7.2 Hz, 4H), 5.58 (br s, 2H, NH), 7.04 (t, *J*=6.8 Hz, 1H), 7.15 (d, *J*=8.0 Hz, 1H), 7.18 (t, *J*=6.8 Hz, 1H), 7.23 (d, *J*=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 40.5, 88.1, 109.9, 118.0, 120.6, 123.3, 127.4, 148.6, 163.0, 167.7; MS (EI) *m/z* 232 (M^+), 160 (100), 133, 104, 72. HRMS (EI) calcd for $C_{13}H_{16}O_2N_2$, 232.1212; found, 232.1215.

*3.6.2. 3-Carboxamido-2-diphenylaminobenzofuran (**8p**).* Compound **8** (164 mg, 0.5 mmol) was used and desired product was obtained **8p** (133 mg, 81%) as pale yellow solid: mp 163–165 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 6.27 (d, *J*=8.0 Hz, 1H), 6.28 (br s, 2H, NH_2), 6.71 (td, *J*=7.8, 1.2 Hz, 1H), 6.88 (td, *J*=7.8, 1.2 Hz, 1H), 7.13 (d, *J*=7.6 Hz, 1H), 7.16 (td, *J*=7.6, 1.6 Hz, 2H), 7.20 (dd, *J*=7.2, 1.2 Hz, 4H), 7.29 (t, *J*=7.6 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 88.0, 109.2, 118.9, 120.7, 122.9, 125.3, 125.6, 126.8, 129.0, 144.1, 148.4, 166.0, 168.0; FT-IR (KBr) 693, 704, 745, 1017, 1249, 1350, 1409, 1493, 1627 cm^{-1}; MS (EI) *m/z* 328 (M^+), 169 (100). HRMS (FAB^+) calcd for $C_{21}H_{17}N_2O_2$, 329.1285; found, 329.1290.

*3.6.3. 3-Carboxamido-2-(piperidin-1-yl)benzofuran (**9p**).* Compound **9** (122 mg, 0.5 mmol) was used and desired product was obtained **9p** (80 mg, 66%) as yellow solid: mp 157–159 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.61–1.70 (m, 6H), 3.51–3.61 (m, 4H), 5.73 (br s, 2H, NH_2), 7.03 (td, *J*=7.8, 1.2 Hz, 1H), 7.16 (td, *J*=7.6, 0.8 Hz, 1H), 7.21 (dd, *J*=7.6, 1.6 Hz, 1H), 7.23 (d, *J*=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 26.4, 46.3, 87.4, 109.8, 118.1, 120.6, 123.3, 127.2, 148.5, 163.6, 167.6; FT-IR (KBr) 753, 993, 1187, 1242, 1486, 1518, 1591, 1637 cm^{-1}; MS (EI) *m/z* 244 (M^+, 100), 160, 133, 104, 84. HRMS (EI) calcd for $C_{14}H_{16}N_2O_2$, 244.1212; found, 244.1208.

*3.6.4. 3-Carboxamido-2-(pyrrolidin-1-yl)benzofuran (**10p**).* Compound **10** (115 mg, 0.5 mmol) was used and desired product was obtained **10p** (77 mg, 67%) as yellow solid: mp 122–124 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.91 (br s, 4H), 3.63 (br s, 4H), 5.74 (br s, 2H, NH_2), 7.03 (t, *J*=7.6 Hz, 1H), 7.16 (t, *J*=7.6 Hz, 1H), 7.37 (t, *J*=8.4 Hz, 1H), 7.26 (d, *J*=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4, 47.4, 88.5, 109.9, 118.8, 120.5, 123.2, 127.1, 148.9, 162.8, 166.8; FT-IR (KBr) 753, 1024, 1177, 1389, 1438, 1582, 1633 cm^{-1}; MS (EI) *m/z* 230 (M^+), 160 (100), 133, 104, 70. HRMS (EI) calcd for $C_{13}H_{14}N_2O_2$, 230.1055; found, 230.1055.

*3.6.5. 3-Carboxamido-2-(morpholin-4-yl)benzofuran (**11p**).* Compound **11** (123 mg, 0.5 mmol) was used and desired product was obtained **11** (97 mg, 79%) as yellow solid: mp 172–174 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.64 (t, *J*=4.8 Hz, 2H), 3.77 (t, *J*=4.8 Hz, 2H), 5.82 (br s, 2H, NH_2), 7.05 (t, *J*=7.2 Hz, 1H), 7.17 (d, *J*=5.2 Hz, 1H), 7.19 (t, *J*=6.8 Hz, 1H), 7.24 (d, *J*=8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 45.9, 67.1, 86.6, 110.0, 118.0, 121.0, 123.6, 126.6,

148.6, 164.2, 168.1; MS (EI) *m/z* 246 (M^+), 160 (100), 132, 104, 86. HRMS (EI) calcd for $C_{13}H_{14}N_2O_3$, 246.1004; found, 246.1000.

*3.6.6. 3-Carboxamido-2-methoxybenzofuran (**12p**).* Compound **12** (96 mg, 0.5 mmol) was used and desired product was obtained **12p** (50 mg, 52%) as yellow solid: mp 56–57 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (s, 3H), 5.98 (br s, 2H, NH_2), 7.07 (td, *J*=8.0, 1.2 Hz, 1H), 7.20 (td, *J*=7.6, 1.2 Hz, 1H), 7.22 (d, *J*=7.6 Hz, 1H), 7.65 (d, *J*=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.0, 84.6, 109.6. 115.2, 119.3, 121.5, 124.0, 126.6, 149.0, 164.4; MS (EI) *m/z* 191 (M^+), 159 (100), 131, 103. HRMS (EI) calcd for $C_{10}H_9NO_3$, 191.0582; found, 191.0582.

*3.6.7. 2-Allyloxy-3-carboxamidobenzofuran (**13p**).* Compound **13** (109 mg, 0.5 mmol) was used and desired product was obtained **13p** (59 mg, 54%) as yellow solid: mp 134–135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 (dt, *J*=5.6, 1.6 Hz, 2H), 5.28 (dd, *J*=10.6, 1.6 Hz, 1H), 5.42 (dd, *J*=17.2, 1.6 Hz, 1H), 6.02 (br s, 2H, NH_2), 6.020–6.117 (m, 1H), 7.06 (td, *J*=7.8, 1.6 Hz, 1H), 7.20 (td, *J*=7.6, 1.2 Hz, 1H), 7.21 (dd, *J*=7.6, 1.2 Hz, 1H), 7.67 (d, *J*=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.3, 84.4, 109.6, 117.6, 119.3, 121.4, 124.0, 126.6, 132.7, 149.0, 164.5; MS (FAB) *m/z* 217 (M^+, 100), 159, 132, 104. HRMS (EI) calcd for $C_{12}H_{11}NO_3$, 217.0739; found, 217.0741.

*3.6.8. 3-Carboxamido-2-(4-methoxyphenyl)benzofuran (**14p**).* Compound **14** (133 mg, 0.5 mmol) was used and desired product was obtained **14p** (93 mg, 70%) as yellow solid: mp 113–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H), 6.98 (d, *J*=8.8 Hz, 2H), 7.02 (br s, 2H, NH_2), 7.020–7.073 (m, 3H), 7.217–7.241 (m, 1H), 7.74 (d, *J*=8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 94.2, 109.9, 113.4, 119.0, 121.6, 123.5, 126.4, 129.7, 133.2, 149.0, 161.8, 166.3, 189.8; MS (EI) *m/z* 267 (M^+, 100), 266, 159, 135. HRMS (EI) calcd for $C_{16}H_{13}NO_3$, 267.0895; found, 267.0894.

Acknowledgements

This research was supported by the Converging Research Program (2011K00705) through the Ministry of Education, Science and Technology.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2012.03.088. These data include MOL files and InChIKeys of the most important compounds described in this article.

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