Tetrahedron 67 (2011) 9291–9297

Contents lists available at SciVerse ScienceDirect

Tetrahedron

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

tert-BuOK-mediated carbanion–yne intramolecular cyclization: synthesis of 2-substituted 3-benzylbenzofurans

Po-Yuan Chen [a], Tzu-Pin Wang [a], Keng-Shiang Huang [b], Chai-Lin Kao [a], Jui-Chi Tsai [a], Eng-Chi Wang [a,*]

[a] Department of Medicinal & Applied Chemistry, Kaohsiung Medical University, Kaohsiung 807, Taiwan
[b] School of Chinese Medicine for Post-Baccalaureate, I-Shou University, Kaohsiung 82445, Taiwan

ARTICLE INFO

Article history:
Received 22 February 2011
Received in revised form 29 September 2011
Accepted 30 September 2011
Available online 6 October 2011

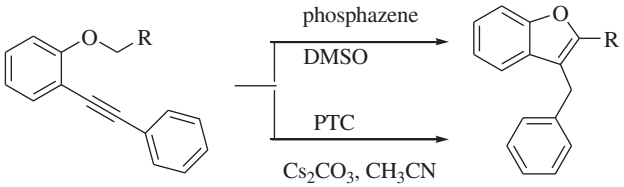
Keywords:
o-Iodophenol
Sonogashira reaction
Carbanion–yne intramolecular cyclization
5-*exo*-*dig* Cyclization
2-Substituted 3-benzylbenzofurans

ABSTRACT

A mild, efficient, and regioselective carbanion–yne intramolecular cyclization mediated by *t*-BuOK for the synthesis of 2-substituted 3-benzylbenzofurans is developed. It was started from *o*-iodophenol (**1**), based on O-alkylation, and the Sonogashira reaction in sequence to produce 2-(2-phenylethynylphenoxy)-1-arylalkanones (**5**). An intramolecular carbanion–yne 5-*exo*-*dig* cyclization reaction of **5**, which was mediated by *t*-BuOK, yielded title benzofurans in good yields.

1. Introduction

The carbon–carbon bond formation, an important synthetic strategy for constructing various benzocarbocyclic and benzoheterocyclic compounds, has been well documented in literatures. For instance, strategies for intramolecular carbon–carbon bond formation which mainly reported were the intramolecular Heck reaction for medium-sized oxa-heterocycles,[1] for including coumarins,[2] tetrahydroanthracenes,[3] as well as others.[4] Because benzofurans exhibited diverse biological activities, such as antibacterial and antifungal,[5] antitumor and antiviral,[6] anticonvulsant and anti-inflammatory,[7] and antileishmanial activity,[8] the development of a mild, diverse, efficient, and practical route for the synthesis of benzofuranoides is requisite and significant from the view-points of synthetic and medicinal chemistry. Up to present various approaches for the synthesis of benzofuran, such as palladium-catalyzed enolate arylation with *o*-bromophenols,[9] palladium-catalyzed reactions of propargylic carbonates with nucleophiles,[10] a one-pot sequential Sonogashira coupling,[11] and ring-closing metathesis[12] have been disclosed. Recently, Terada, et al.[13a] developed an excellent method using phosphazene base-catalyzed an intramolecular carbon–carbon bond cyclization in DMSO (dimethyl sulfoxide) for the synthesis of 2-substitued 3-benzylbenzofurans and Hu et al.[13b] also reported the similar strategy for benzofurans using phase-transfer-catalyzed methodology (Scheme 1).

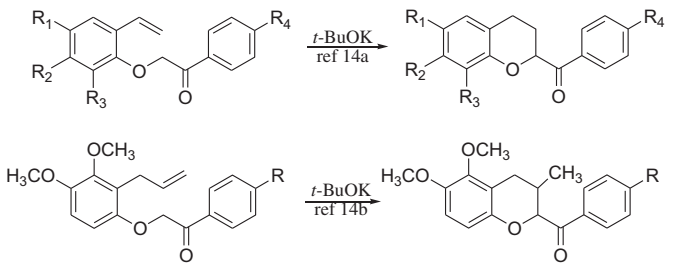


Scheme 1. Intramolecular cyclization of *o*-alkynylphenyl ether mediated by phosphazene[13a] or PTC/cesium carbonate[13b] to generate benzofuran.

However, those methods described above have encountered some disadvantages. Such as, phosphazene used by Terada's method as reaction base is complicated in structure and very expensive in price and DMSO utilized as reaction solvent is a high boiling point solvent and is difficult to remove. Moreover, the selected PTC (phase transfer catalyst) and base for cyclization reported by Hu et al. to yield benzofurans, which is variable with reaction condition and lacking of straightforward, are disadvantages. Moreover those reported methods to prepare benzofurans with limited substituents and insufficient investigation for insight into this carbanion–yne cyclization are drawbacks. Recently we have successfully reported a carbanion–olefin cyclization which mediated by potassium *tert*-butoxide for diverse chroman derivatives (Scheme 2).[14]

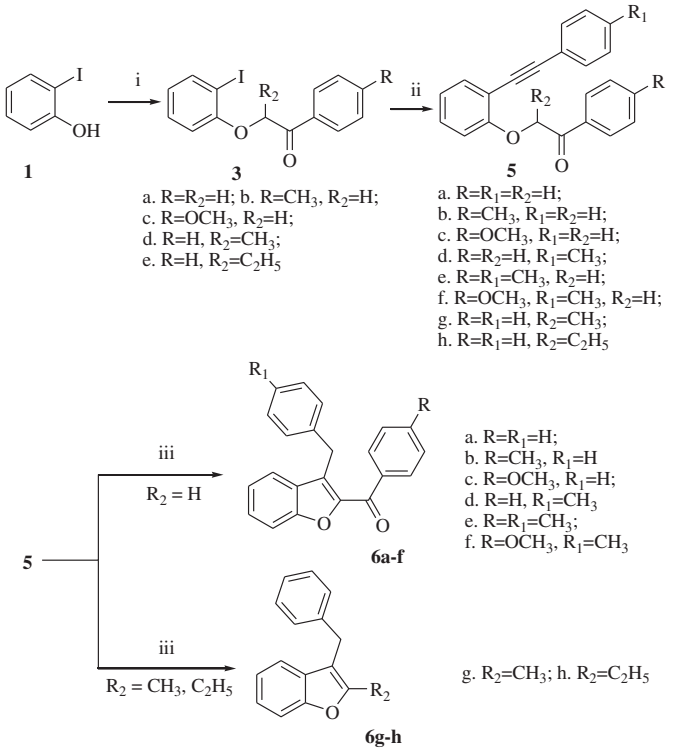
* Corresponding author. E-mail address: enchwa@kmu.edu.tw (E.-C. Wang).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.09.144



Scheme 2. Carbanion–olefin cyclization mediated by potassium *tert*-butoxide to yield chroman derivatives.

In these studies we found both 2-phenylvinylphenoxy and 2-phenylallylphenoxy intermediates could be, respectively, mediated by potassium *tert*-butoxide to undergo carbanion–olefin intramolecular 6-*endo*-*trig* cyclization with regiospecificity to yield chroman derivatives. Thus, we would like to extend our previous studies to investigate the cyclization of carbanion–yne mediated by potassium *tert*-butoxide. Herein, we report the result to build up various 2-substituted 3-benzylbenzofurans from intramolecular carbanion–yne 5-*exo*-*dig* cyclization by two different pathways, which briefly mediated by potassium *tert*-butoxide (Scheme 3).

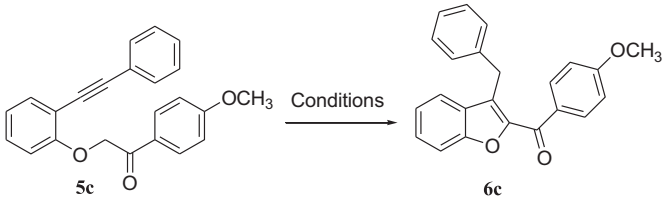


Scheme 3. Intramolecular carbanion–yne 5-*exo*-*dig* type cyclization reaction mediated by *t*-BuOK to generate 2-aroyl-3-benzylbenzofurans. Reagents and reaction condition: (i) 2-bromoacetophenones (**2a**–**e**), K_2CO_3, acetone, reflux 2–3 h, 87–91%; (ii) $Pd(PPh_3)_2Cl_2$, CuI, phenylacetylene (**4a**), *p*-methylphenylacetylene (**4b**), $(^iPr)_2NH$, THF, reflux 3 h, 76–84%; (iii) *t*-BuOK, THF, reflux 0.5 h, 80–88%.

2. Results and discussion

As a general procedure, the reaction of *o*-iodophenol (**1**) with 2-bromoacetophenones (**2a**–**e**) in the presence of K_2CO_3 afforded 2-(2-iodophenoxy)arylethanones (**3a**–**e**) in yields of 87–91%. The typical absorption of IR at 1673–1698 cm^{-1} exhibited the presence of C=O group in the molecules of **3a**–**e**, and the methylene protons with singlet signals at δ 5.24–5.32 in ^1H NMR were commonly found in the structure **3a**–**c**. The elucidation of structures **3d**–**e** are as follows. In ^1H-NMR spectrum, a doublet methyl signal with coupling constant J=6.8 Hz at δ 1.80 and a quartet one-proton signal with coupling constant J=6.8 Hz at δ 5.39 indicating the presence of $-CH(CH_3)CO-$ group were found in **3d**. A triplet methyl signal with coupling constant J=8.0 Hz at δ 1.20, a multiplet two-protons signal at δ 2.17, and a double doublet one-proton signal with coupling constant J=8.0, 4.8 Hz at δ 5.16 indicating the presence of $-CH(CH_2CH_3)CO-$ group were found in **3e**. The selected ^1H NMR spectral data described above are consistent with the data required for **3a**–**e**. Other spectral data including IR, ^1H NMR, ^{13}C NMR, EIMS, and EA are all equally matched with the data needed for **3a**–**e**. Then, compound **3** was, respectively, allowed to react with phenylacetylene (**4a**), and *p*-methylphenylacetylene (**4b**), in the presence of CuI, $Pd(PPh_3)_2Cl_2$, and diisopropylamine to undergo the Sonogashira reaction[15] to give 2-(2-phenylethynylphenoxy)-1-arylethanones (**5a**–**h**) in 76–84% yields. The appearance of C–C triple bond at 2216–2218 cm^{-1} and carbonyl group at 1692–1703 cm^{-1} in the spectra of IR in **5a**–**h** indicated the successful work of the Sonogashira reaction. Spectral data, such as ^1H NMR, ^{13}C NMR, EIMS, HRMS, and EA are all consistent with the data required for **5a**–**h**. In order to figure out the optimized reaction of base-mediated the carbanion–yne cyclization, compound **5c** was utilized as model to react with various bases and under various conditions. The results obtained were depicted in Table 1.

Table 1
Treatment of **5c** with various bases (1.2 equiv), solvents (10 mL), and temperature to examine the yield of **6c**



5c 6c

Entry	Base	Solvent	Temp (°C)	Time[a] (h)	Yield[b] (%)
1	*t*-BuOK	THF	rt	1.5	80
2	*t*-BuOK	THF	Reflux	0.5	88
3	*t*-BuOK	CH_2Cl_2	Reflux	1.5	76
4	*t*-BuOK	*t*-BuOH	Reflux	1	82
5	NaOEt	EtOH	rt	3	33[c]
6	NaOEt	THF	rt	4	47[c]
7	$NaNH_2$	THF	rt	4	51

[a] Determined by monitoring the consumption of starting material with TLC.
[b] Isolated by column chromatography.
[c] Recovery of starting material.

From the experimental results obtained at Table 1, we found that compound **5c** can be briefly and efficiently cyclized using *t*-BuOK in refluxing THF (entry 2) to yield benzofurans with regioselectivity and in high yields (80–88%), via an intramolecular 5-*exo*-*dig* carbanion–yne cyclization. In monitoring by TLC, we found when sodium amide was used as base to give not only the desired product but also other unidentified by-products in this cyclization. When sodium ethoxide was used as base, the longer reaction time and lower yield than that of *t*-BuOK were found (entries 5 and 6). Thus, in this cyclization, the trend of base in the reactivity in THF is potassium *tert*-butoxide>sodium amide>sodium ethoxide (entries 1, 6, and 7). Meanwhile the trend of solvent for this cyclization is THF>*t*-BuOH>CH_2Cl_2 (entries 2, 3, and 4). Therefore, the cyclization of 2-(2-phenylethynylphenoxy)-1-arylethanones (**5a**–**f**) to yield a series of 2-aroyl-3-benzylbenzofurans (**6a**–**f**) is achieved using the optimum condition (*t*-BuOK in refluxing THF), which obtained from our experimental results. The chemical structures of

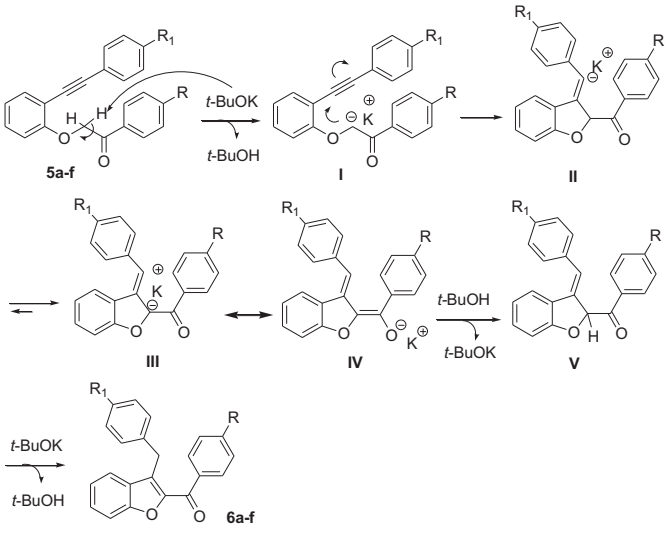
compounds **6a**–**f** are fully supported by their spectral data, such as ^{1}H NMR, ^{13}C NMR, EIMS, HRMS, and EA. The % yields, selected physical and spectral data of 2-aroyl-3-benzylbenzofurans (**6a**–**f**) are summarized in Table 2.

Table 2
Selected physical and spectral data of 2-aroyl-3-benzylbenzofurans (**6a**–**f**)

Compd	Yield (%)	Mp (°C)	IR (cm^{-1})	HRMS[a]	EA[a] (C%; H%)
6a	80	94–95 (96–98)[13a]	1644	Calcd 312.1150 Found 312.1152	Calcd 84.59: 5.16 Found 84.39; 5.18
6b	83	119–120	1638	Calcd 326.1307 Found 326.1306	Calcd 84.64; 5.56 Found 84.67; 5.56
6c	88	98–99	1637	Calcd 342.1256 Found 342.1257	Calcd 80.68; 5.30 Found 80.51; 5.28
6d	83	118–119	1644	Calcd 326.1307 Found 326.1310	Calcd 84.64; 5.56 Found 84.56; 5.55
6e	85	111–112	1642	Calcd 340.1363 Found 340.1363	Calcd 84.68; 5.92 Found 84.55; 5.96
6f	87	120–121	1638	Calcd 356.1412 Found 356.1414	Calcd 80.88; 5.66 Found 80.56; 5.63

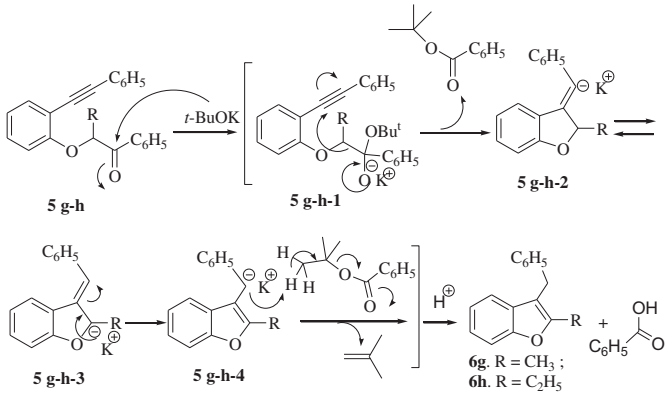
[a] Data measured from Southern Precious Instrumental Center of NSC, Taiwan.

Based on the obtained results, the reaction mechanism of this type of 5-*exo*-*dig* carbanion–yne cyclization could be rationally proposed as follows (Scheme 4).



Scheme 4. The mechanism of an intramolecular carbanion–yne 5-*exo*-*dig* cyclization for 2-aroyl-3-benzylbenzofurans.

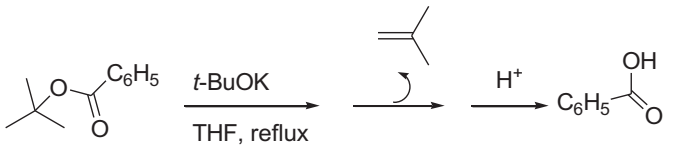
One of the hydrogen, which is nearby the carbonyl group was abstracted by *t*-BuOK to yield a carbanion (**I**), and followed by undergoing intramolecular carbanion–yne *5-exo-dig* cyclization reaction to generate carbanion **II**. The unstable transient anion **II** is subsequently converted into anion **III**, which is stabilized by an enolate **IV** via a protonation–deprotonation process mediated by *t*-BuOH and *t*-BuOK. Then, the C-2 in **IV** picked up a proton from *t*-BuOH to generate **V**. The transient **V** further undergoes a process of deprotonation–protonation mediated by *t*-BuOK and *t*-BuOH to yield the stable aromatic benzofuran ring. According to the proposed mechanism, the overall reaction, 1 equiv *t*-BuOK is required for this cyclization which matches with the requirement (1.2 equiv) of base in experiments. On the other hand, 2-(2-(2-phenylethynyl) phenoxy)-1-phenylpropan-1-one (**5g**) and (2-(2-phenylethynyl) phenoxy)-1-phenylbutan-1-one (**5h**), which bearing a methyl group and ethyl group at the α-position of the carbonyl group were allowed to react with *tert*-BuOK at the same reaction condition. After quenching with dilute HCl, 3-benzyl-2-methylbenzofuran (**6g**) and 3-benzyl-2-ethylbenzofuran (**6h**) were obtained in 86 and 85% yields, together with benzoic acid, which was isolated in yields of 82–80%. Apparently, the benzofurans (**6g**,**h**), which were obtained underwent the different reaction pathway than that of **6a**–**f**. Thus, it can be developed as a new strategy for the synthesis of 2-alkyl-3-benzylbenzofurans. The structural elucidation of 3-benzyl-2-methylbenzofuran (**6g**), as an example, was determined by its spectral data. For instances, no carbonyl absorption and no C–C triple bond were found in IR spectrum. Furthermore, one singlet signal with three protons at δ 2.4 indicating the presence of methyl group, and one singlet signal with two protons at δ 4.0 exhibiting the presence of benzylic protons, and another nine aromatic protons with multiplet at δ 7.1–7.4 were found in the ^{1}H NMR spectrum. Two sp^3 carbons, one at δ 12.0 and the other one at δ 29.6, and twelve sp^2 carbons were observed in ^{13}C NMR spectrum. In addition, molecular ion *m*/*z* 222 found in EIMS and *m*/*z* 222.1042 found in HRMS further verified the correctness of compound **6g**. The structure of **6h** is elucidated as the same procedures as for **6g**. In the previous study,[18] 3-benzyl-2-ethylbenzofuran (**6h**), prepared from 2-ethylbenzofuran via benzoylation, reduction, and deoxygenation, was found to be an essential building block for benzofuranyloxadiazolidine-3,5-diones, which played an important role as PAI-1 inhibitor (plasminogen activator inhibitor-1) for treatment of disorders related to fibrinolytic system impairment. However, methods for preparing 2-ethylbenzofuran reported were not readily accessible.[19] Therefore our method for 3-benzyl-2-ethylbenzofuran (**6h**) has great advantages over the existing protocol described above. Thus, in this study, we have successfully established a novel strategy not only for **6g**,**h** but also could be applied for other 2-alkyl-3-benzylbenzofurans. The elucidation of by-product benzoic acid is confirmed simply by comparing with commercial available authentic sample. The result shown is consistent with IR spectrum and correctness in melting-point [mp for benzoic acid: 121–124 °C, found: 123–124 °C]. The interpretation of reaction mechanism of formation **6g**,**h** from **5g**,**h** could be rationally illustrated as follows (Scheme 5). Initially, (i) the bulky base *t*-BuOK due to steric hindrance could not abstract the proton nearby the carbonyl group but underwent the nucleophilic addition by attacking the carbonyl group of **5g**,**h** to give transient **5g**,**h**-**1**, (ii) because of much hindrance in **5g**,**h**-**1**, *tert*-butyl benzoate was eliminated and generated a carbanion which spontaneously underwent 5-*exo*-*dig* cyclization to yield transient **5g**,**h**-**2**, (iii) after protonation and deprotonation process, the resulting **5g**,**h**-**3** was aromatized to construct the stable benzofuran ring to generate transient benzylic anion **5g**,**h**-**4**, (iv) the forming benzylic anion



Scheme 5. The proposed mechanism for the formation of **6g** and **6h** from **5g** and **5h**, respectively.

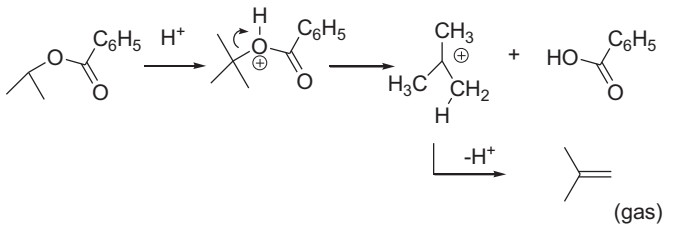
which is bulky and strong base, immediately attacked one of the proton of *tert*-butyl group in *tert*-butyl benzoate to cause elimination and to yield potassium benzoate and isobutene, and (v) after quenching with dilute HCl solution, 2-alkyl-3-benzylbenzofuran (**6g**,**h**) and benzoic acid were produced, but isobutene [bp=−6.9 °C] was lost in the reaction for the lower boiling point.

In order to illustrate the rationality of the proposed mechanism, *tert*-butyl benzoate prepared from known procedure,[20] was allowed to react with potassium *tert*-butoxide in refluxing THF. After monitoring by TLC to make sure the consumption of starting material (it took 20 min), the reaction mixture was quenched with dilute HCl. Benzoic acid was obtained in 88% yield (Scheme 6).



Scheme 6. Reaction of *tert*-butyl benzoate with *t*-BuOK, and workup in acidic condition to yield benzoic acid.

Based on experimental result obtained above, *tert*-butyl benzoate reacted with bulky base to undergo elimination to yield benzoic acid could be confirmed. In contrast, *tert*-butyl benzoate treated with acid to yield benzoic acid and isobutylene via elimination has been previously reported,[21] and can be interpreted as follows (Scheme 7).



Scheme 7. Reaction of *tert*-butyl benzoate with acid to yield benzoic acid.

Thus, our proposed mechanism for yielding 2-alkyl-3-benzylbenzofurans (**6g**,**h**) from **5g**,**h** also could be rationally illustrated, even could not capture isobutylene gas. Both for the synthesis of 2-aroyl-3-benzylbenzofurans and for 2-alkyl-3-benzylbenzofurans, were briefly established which is different from previous studies by Terada,[13a] Liu,[13b] and Liang,[17] with different bases or catalyst.

3. Conclusion

In this study we have established two concise and efficient synthetic routes, one for 2-aroyl-3-benzylbenzofurans and the other for 2-alkyl-3-benzylbenzofurans. It started from *o*-iodophenol to prepare 2-phenylethynylphenoxy derivatives as key intermediates by the Sonogashira coupling. The key intermediates (**5a**–**f**) were mediated by *t*-BuOK to go through an intramolecular carbanion–yne 5-*exo*-*dig* cyclization to give 2-aroyl-3-benzylbenzofurans (**6a**–**f**) in good yields and with regiospecificity. On the other hand, the intermediates (**5g**,**h**), which have an alkyl group at the α-position were cyclized by *t*-BuOK to undergo another intramolecular carbanion–yne 5-*exo*-*dig* cyclization with stereoselectivity to yield 2-alkyl-3-benzylbenzofurans (**6g**,**h**) by going through another mechanism, i.e., addition–elimination–cyclization processes. In conclusion, we found that *t*-BuOK can be diversely and efficiently applied for not only carbanion–olefin but also carbanion–yne cyclization. Moreover, we also found that *t*-BuOK-mediated carbanion–olefin to undergo 6-*endo*-*trig* cyclization to yield chroman derivatives but carbanion–yne to undergo 5-*exo*-*dig* cyclization to yield benzofuran derivatives.

4. Experimental

4.1. General

Melting points (Yanaco micro melting-point apparatus) were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian Unity plus 400 Spectrometer. Chemical shifts were measured in parts per million with respect to TMS. IR spectra were run on a Perkin–Elmer spectrometer. Elemental analyses were recorded on a Heraeus CHN–O Rapid analyzer. Mass spectra were recorded on a Chem/hp/middle spectrometer connected to a Hewlett Packard series II model gas–liquid chromatography. HRMS spectra were performed on a JEOL JMS SX/SX 102A instrument. Silica gel (230–400 mesh) for column chromatography and precoated silica gel plates (60 F_{254}) for TLC were purchased from E. Merck Co. UV light (254 nm) was used to detect spots on TLC plates after development.

4.2. General procedure for the preparation of 2-(2-iodophenoxy)-1-arylethanone (3a–e)

2-Iodophenol (**1**) (2.2 g, 10 mmol) dissolved in acetone (40 mL) was added with 2-bromoacetophenones (**2a**–**e**) (12 mmol) and anhydrous K_2CO_3 (2.07 g, 15 mmol). The resulting mixture was stirred and refluxed for 2–3 h, then cooled to room temperature, and filter. The filtrate was concentrated in vacuo to give crude product. After purification with column chromatography (ethyl acetate/*n*-hexane=1:15), pure of 2-(2-iodophenoxy)-1-arylethanones **3a**–**e** were yielded.

*4.2.1. 2-(2-Iodophenoxy)-1-phenylethanone (**3a**).* Compound **3a** (2.94 g, 87%) was obtained as colorless crystals; mp 123–124 °C (lit.[16] mp 123 °C), R_f=0.43 (ethyl acetate/*n*-hexane=1:4); IR_{max} (neat) cm^{-1}: 1685 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.32 (s, 2H, $ArOCH_2CO$–), 6.74 (dd, *J*=8.4, 1.2 Hz, 2H, ArH), 7.25 (td, *J*=8.4, 1.6 Hz, 1H, ArH), 7.50 (td, *J*=6.8, 1.6 Hz, 2H, ArH), 7.62 (ddt, *J*=8.4, 6.8, 1.2 Hz, 1H, ArH), 7.79 (dd, *J*=8.0, 1.6 Hz, 1H, ArH), 8.04 (dd, *J*=8.4, 1.2 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 72.0, 86.4, 112.6, 123.5, 128.4, 128.8, 129.4, 134.0, 134.4, 139.8, 156.8, 194.1; EIMS (70 eV) *m*/*z* (rel intensity, %) 338 (M^+, 2), 212 (19), 211 (100), 106 (6), 105 (42), 91 (6), 77 (25); HRMS calcd for $C_{14}H_{11}IO_2$: 337.9804. Found: 337.9804. Anal. Calcd for $C_{14}H_{11}IO_2$: C, 49.73; H, 3.28. Found: C, 49.77; H, 3.24.

*4.2.2. 2-(2-Iodophenoxy)-1-p-tolylethanone (**3b**).* Compound **3b** (3.20 g, 91%) was obtained as colorless crystals; mp 132–133 °C, R_f=0.46 (ethyl acetate/*n*-hexane=1:4); IR_{max} (neat) cm^{-1}: 1698 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.43 (s, 3H, $ArCH_3$), 5.29 (s, 2H, $ArOCH_2CO$–), 6.73 (dd, *J*=8.4, 1.2 Hz, 2H, ArH), 7.23 (td, *J*=7.6, 1.6 Hz, 1H, ArH), 7.29 (dd, *J*=8.4, 0.4 Hz, 1H, ArH), 7.79 (dd, *J*=7.6, 1.6 Hz, 1H, ArH), 7.94 (dd, *J*=8.4, 1.6 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.8, 72.0, 86.39, 112.6, 123.4, 128.5, 129.4, 129.5, 131.9, 139.8, 145.0, 156.8, 193.7; EIMS (70 eV) *m*/*z* (rel intensity, %) 352 (M^+, 1), 226 (17), 225 (100), 120 (8), 119 (46), 91 (23), 65 (7); HRMS calcd for $C_{15}H_{13}IO_2$: 351.9960. Found: 351.9961. Anal. Calcd for $C_{15}H_{13}IO_2$: C, 51.16; H, 3.72. Found: C, 51.07; H, 3.76.

*4.2.3. 2-(2-Iodophenoxy)-1-(4-methoxyphenyl)ethanone (**3c**).* Compound **3c** (3.31 g, 90%) was obtained as colorless crystals; mp 108–109 °C (lit.,[16] no mp data), R_f=0.45 (ethyl acetate/*n*-hexane=1:4); IR_{max} (neat) cm^{-1}: 1673 cm^{-1} (C=O); ^{1}H NMR

($CDCl_3$, 400 MHz) δ 3.87 (s, 3H, $ArOCH_3$), 5.24 (s, 2H, $ArOCH_2CO-$), 6.75 (dd, J=8.4, 1.2 Hz, 2H, ArH), 6.96 (dd, J=7.2, 2.0 Hz, 2H, ArH), 7.24 (td, J=8.0, 1.6 Hz, 1H, ArH), 7.77 (dd, J=8.0, 1.6 Hz, 1H, ArH), 8.04 (dd, J=8.8, 2.0 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.5, 71.9, 86.3, 112.5, 114.0, 123.3, 127.4, 129.4, 130.8, 139.7, 156.8, 164.1.8, 192.7; EIMS (70 eV) m/z (rel intensity, %) 368 (M^+, 0.2), 242 (16), 241 (100), 137 (22), 135 (81), 121 (14), 77 (15); HRMS calcd for $C_{15}H_{13}IO_3$: 367.9909. Found: 367.9911. Anal. Calcd for $C_{15}H_{13}IO_3$: C, 48.93; H, 3.56. Found: C, 48.72; H, 3.50.

*4.2.4. 2-(2-Iodophenoxy)-1-phenylpropan-1-one (**3d**).* Compound **3d** (3.13 g, 89%) was obtained as colorless crystals; mp 115–116 °C (lit.,[16] no mp data), R_f=0.45 (ethyl acetate/*n*-hexane=1:4); IR_{max} (neat) cm^{-1}: 1677 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.80 (d, J=6.8 Hz, 3H, $ArOCHCH_3COAr$), 5.39 (q, J=6.8 Hz, 1H, $ArOCHCH_3-COAr$), 6.67 (m, 2H, ArH), 7.17 (ddd, J=8.0, 7.2, 1.6 Hz, 1H, ArH), 7.46 (td, J=8.8, 2.0 Hz, 2H, ArH), 7.57 (ddd, J=8.8, 7.2, 1.6 Hz, 1H, ArH), 7.75 (dd, J=8.0, 1.6 Hz, 1H, ArH), 8.13 (dd, J=8.4, 1.6 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.0, 78.8, 86.9, 113.0, 123.2, 128.7, 129.1, 129.4, 133.7, 136.8, 139.8, 156.2, 198.6; EIMS (70 eV) m/z (rel intensity, %) 352 (M^+, 11), 247 (64), 226 (20), 225 (100), 121 (38), 106 (23), 78 (18).

*4.2.5. 2-(2-Iodophenoxy)-1-phenylbutan-1-one (**3e**).* Compound **3e** (3.18 g, 87%) was obtained as colorless crystals; mp 128–129 °C, R_f=0.43 (ethyl acetate/*n*-hexane=1:4); IR_{max} (neat) cm^{-1}: 1693 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.20 (t, J=7.6 Hz, 3H, $ArOCH(CH_2CH_3)COAr$), 2.17 (m, 2H, $ArOCH(CH_2CH_3)COAr$), 5.16 (dd, J=8.0, 4.8 Hz, 1H, $ArOCH(CH_2CH_3)COAr$), 6.59 (dd, J=8.4, 1.2 Hz, 1H, ArH), 6.65 (td, J=8.0, 1.6 Hz, 1H, ArH), 7.14 (ddd, J=8.8, 7.2, 1.6 Hz, 1H, ArH), 7.46 (td, J=8.8, 1.6 Hz, 2H, ArH), 7.57 (ddd, J=8.4, 6.8, 1.2 Hz, 1H, ArH), 7.75 (dd, J=8.0, 1.6 Hz, 1H, ArH), 8.14 (dd, J=8.4, 1.2 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 10.4, 26.9, 84.1, 86.5, 112.4, 123.0, 128.7, 129.1, 129.4, 133.7, 134.0, 139.7, 156.2, 198.5; EIMS (70 eV) m/z (rel intensity, %) 366 (M^+, 15), 261(100), 241(31), 134(55), 109(18), 105(18), 78(20); HRMS calcd for $C_{16}H_{15}IO_2$: 366.0117. Found: 366.0120. Anal. Calcd for $C_{16}H_{15}IO_2$: C, 52.48; H, 4.13. Found: C, 52.45; H, 4.07.

4.3. General procedure for the preparation of 5a–h

Bis(triphenylphosphine)palladium(II) chloride (0.14 g, 0.2 mmol), CuI (0.05 g, 0.26 mmol), and diisopropylamine (1.27 mL, 9 mmol) in THF (25 mL) was stirred and added **3a–e** (5 mmol) and arylacetylenes (**4a**,**b**) (7.5 mmol) in drops. The reaction mixture was stirred and heated to reflux for 3 h. After cooling, the solution was quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2 (5×20 mL). The combined organic layers were washed with brine (20 mL), and dried over $MgSO_4$ and was filtered, concentrated in vacuo in sequences. The obtained residue was purified from flash column chromatography (ethyl acetate/*n*-hexane=1:5) to afford the desired compound **5a–h**.

*4.3.1. 1-Phenyl-2-(2-phenylethynylphenoxy)ethanone (**5a**).* Compound **5a** (1.19 g, 76%) was obtained as brown crystals; mp 95–96 °C (lit.[13a] mp 90–92 °C); R_f=0.53 (ethyl acetate/*n*-hexane=1:3); IR_{max} (neat) cm^{-1}: 1702 cm^{-1} (C=O), 2217 cm^{-1} (C≡C); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.32 (s, 2H, OCH_2COAr), 6.84 (dd, J=8.4, 0.8 Hz, 1H, ArH), 6.97 (td, J=8.4, 0.8 Hz, 1H, ArH), 7.24 (m, 1H, ArH), 7.30 (m, 3H, ArH), 7.44 (m, 4H, ArH), 7.50 (dd, J=7.6, 1.6 Hz, 1H, ArH), 7.55 (tt, J=8.8, 1.2 Hz, 1H, ArH), 8.05 (dd, J=8.0, 1.6 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 71.9, 86.5, 93.9, 112.8, 113.3, 121.6, 123.4, 128.1, 128.2, 128.4, 128.7, 129.6, 131.5, 133.5, 133.7, 134.5, 158.4, 194.5; EIMS (70 eV) m/z (rel intensity, %) 312 (M^+, 57), 208 (18), 207 (100), 179 (21), 178 (32), 106 (68), 78 (34); HRMS calcd for $C_{22}H_{16}O_2$: 312.1150. Found: 312.1152. Anal. Calcd for $C_{22}H_{16}O_2$: C, 84.59; H, 5.16. Found: C, 84.36; H, 5.24.

*4.3.2. 2-(2-Phenylethynylphenoxy)-1-p-tolylethanone (**5b**)*[17]. Compound **5b** (1.30 g, 80%) was obtained as brown liquid (lit.[17]); R_f=0.56 (ethyl acetate/*n*-hexane=1:3); IR_{max} (neat) cm^{-1}: 1698 cm^{-1} (C=O), 2217 cm^{-1} (C≡C); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.36 (s, 3H, $ArCH_3$), 5.29 (s, 2H, OCH_2COAr), 6.84 (dd, J=8.4, 0.8 Hz, 1H, ArH), 6.96 (td, J=8.4, 0.8 Hz, 1H, ArH), 7.23 (m, 1H, ArH), 7.29 (m, 3H, ArH), 7.44 (m, 2H, ArH), 7.50 (dd, J=7.6, 1.6 Hz, 1H, ArH), 7.96 (dd, J=8.0, 1.6 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6, 71.9, 85.5, 93.9, 112.8, 113.3, 121.5, 123.4, 128.0, 128.1, 128.6, 129.4, 129.6, 131.5, 132.1, 133.5, 144.7, 158.5, 194.2; EIMS (70 eV) m/z (rel intensity, %) 326 (M^+, 100), 311 (18), 221 (16), 207 (42), 178 (15), 119 (95), 91 (36); HRMS calcd for $C_{23}H_{18}O_2$: 326.1307. Found: 326.1309.

*4.3.3. 1-(4-Methoxyphenyl)-2-(2-phenylethynylphenoxy)-ethanone (**5c**).* Compound **5c** (1.42 g, 83%) was obtained as colorless crystals; mp 100–101 °C; R_f=0.49 (ethyl acetate/*n*-hexane=1:3); IR_{max} (neat) cm^{-1}: 1692 cm^{-1} (C=O), 2216 cm^{-1} (C≡C); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.81 (s, 3H, OCH_3), 5.27 (s, 2H, OCH_2COAr), 6.90 (dd, J=8.8, 0.8 Hz, 1H, ArH), 6.98 (td, J=8.4, 0.8 Hz, 1H, ArH), 7.26 (td, J=8.4, 1.6 Hz, 1H, ArH), 7.31 (m, 3H, ArH), 7.45 (m, 2H, ArH), 7.51 (dd, J=7.6, 1.6 Hz, 1H, ArH), 8.10 (dd, J=8.8, 2.0 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.4, 72.1, 85.6, 93.87, 112.8, 113.3, 113.9, 121.6, 123.5, 127.8, 128.1, 128.2, 129.6, 131.1, 131.6, 133.5, 158.6, 164.0, 193.3; EIMS (70 eV) m/z (rel intensity, %) 342 (M^+, 53), 311 (8), 237 (24), 165 (8), 136 (10), 135 (100), 77 (13); HRMS calcd for $C_{23}H_{18}O_3$: 342.1256. Found: 342.1256. Anal. Calcd for $C_{23}H_{18}O_3$: C, 80.68; H, 5.30. Found: C, 80.70; H, 5.36.

*4.3.4. 1-Phenyl-2-(2-p-tolylethynylphenoxy)ethanone (**5d**).* Compound **5d** (1.28 g, 79%) was obtained as brown crystals; mp 97–98 °C; R_f=0.55 (ethyl acetate/*n*-hexane=1:3); IR_{max} (neat) cm^{-1}: 1699 cm^{-1} (C=O), 2218 cm^{-1} (C≡C); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.35 (s, 3H, $ArCH_3$), 5.34 (s, 2H, OCH_2COAr), 6.85 (d, J=8.4 Hz, 1H, ArH), 6.97 (td, J=8.4, 0.8 Hz, 1H, ArH), 7.11 (d, J=8.0 Hz, 1H, ArH), 7.24 (td, J=8.0, 1.6 Hz, 1H, ArH), 7.46 (m, 2H, ArH), 7.50 (dd, J=7.6, 2.0 Hz, 2H, ArH), 7.57 (tt, J=8.4, 0.8 Hz, 1H, ArH), 8.07 (dd, J=8.4, 1.6 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.5, 72.1, 84.8, 94.2, 113.0, 113.7, 120.3, 121.7, 128.5, 128.7, 129.0, 129.4, 131.5, 133.5, 133.7, 134.6, 138.2, 158.4, 194.7; EIMS (70 eV) m/z (rel intensity, %) 326 (M^+, 41), 222 (18), 221 (100), 179 (15), 178 (40), 105 (29), 77 (16); HRMS calcd for $C_{23}H_{18}O_2$: 326.130. Found: 326.1307. Anal. Calcd for $C_{23}H_{18}O_2$: C, 84.64; H, 5.56. Found: C, 84.38; H, 5.53.

*4.3.5. 1-p-Tolyl-2-(2-p-tolylethynylphenoxy)ethanone (**5e**).* Compound **5e** (1.41 g, 83%) was obtained as colorless crystals; mp 116–117 °C; R_f=0.53 (ethyl acetate/*n*-hexane=1:3); 1693 cm^{-1} (C=O), 2217 cm^{-1} (C≡C); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.36 (s, 3H, $ArCH_3$), 2.38 (s, 3H, $ArCH_3$), 5.31 (s, 2H, OCH_2COAr), 6.85 (d, J=8.4 Hz, 1H, ArH), 6.97 (td, J=8.4, 0.8 Hz, 1H, ArH), 7.12 (d, J=8.0 Hz, 1H, ArH), 7.24 (m, 3H, ArH), 7.34 (dd, J=8.0, 1.6 Hz, 2H, ArH), 7.49 (dd, J=7.6, 1.6 Hz, 1H, ArH), 7.97 (dd, J=8.0, 1.6 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.5, 21.7, 72.1, 84.8, 94.1, 112.9, 113.6, 120.4, 121.6, 128.7, 129.0, 129.4, 131.5, 132.2, 133.5, 138.2, 144.7, 158.5, 194.4; EIMS (70 eV) m/z (rel intensity, %) 340 (M^+, 32), 221 (78), 205 (15), 178 (37), 119 (100), 91 (52), 65 (15); HRMS calcd for $C_{24}H_{20}O_2$: 340.1463. Found: 340.1465. Anal. Calcd for $C_{24}H_{20}O_2$: C, 84.68; H, 5.92. Found: C, 84.32; H, 5.98.

*4.3.6. 1-(4-Methoxyphenyl)-2-(2-p-tolylethynylphenoxy)-ethanone (**5f**).* Compound **5f** (1.50 g, 84%) was obtained as colorless crystals; mp 125–126 °C; R_f=0.53 (ethyl acetate/*n*-hexane=1:3); IR_{max} (neat) cm^{-1}: 1703 cm^{-1} (C=O), 2216 cm^{-1} (C≡C); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.35 (s, 3H, $ArCH_3$), 3.80 (s, 3H, OCH_3), 5.25 (s, 2H,

OCH_2COAr), 6.86 (d, J=8.4 Hz, 1H, ArH), 6.89 (dd, J=8.8, 2.0 Hz, 2H, ArH), 6.96 (td, J=8.4, 0.8 Hz, 1H, ArH), 7.11 (d, J=7.6 Hz, 2H, ArH), 7.24 (m, 1H, ArH), 7.35 (dd, J=8.0, 1.6 Hz, 2H, ArH), 7.49 (dd, J=8.0, 2.0 Hz, 1H, ArH), 8.09 (dd, J=8.8, 2.0 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.5, 55.4, 72.1, 84.9, 94.1, 112.8, 113.5, 113.9, 120.4, 121.5, 127.7, 129.0, 129.4, 131.0, 131.5, 133.4, 138.2, 158.5, 163.9, 193.3; EIMS (70 eV) m/z (rel intensity, %) 356 (M^+, 28), 237 (10), 221 (22), 178 (15), 136 (9), 135 (100), 77 (13); HRMS calcd for $C_{24}H_{20}O_3$: 356.1412. Found: 356.1409. Anal. Calcd for $C_{24}H_{20}O_3$: C, 80.88; H, 5.66. Found: C, 80.80; H, 5.67.

*4.3.7. 1-Phenyl-2-(2-phenylethynylphenoxy)propan-1-one (**5g**).* Compound **5g** (1.27 g, 78%) was obtained as pale yellow solid; mp 96–97 °C (lit.,[17] mp 94.9–96.7 °C), R_f=0.53 (ethyl acetate/*n*-hexane=1:3); IR_{max} (neat) cm^{-1}: 1695 cm^{-1} (C=O), 2216 cm^{-1} (C≡C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.80 (d, J=6.8 Hz, 3H, $-CH(CH_3)CO-$), 5.51 (q, J=6.8 Hz, 1H, $-CH(CH_3)CO-$), 6.83 (d, J=8.4 Hz, 1H, ArH), 6.94 (td, J=8.4, 0.8 Hz, 1H, ArH), 7.19 (ddd, J=8.4, 7.6, 1.6 Hz, 1H, ArH), 7.34 (m, 3H, ArH), 7.40 (m, 2H, ArH), 7.50 (m, 4H, ArH), 8.17 (dd, J=8.4, 1.2 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.94 78.84, 85.78, 93.81, 113.9, 114.3, 121.7, 123.6, 128.1, 128.3, 128.6, 129.2, 129.6, 131.5, 133.6, 134.0, 137.1, 158.0, 198.9; EIMS (70 eV) m/z (rel intensity, %) 326 (M^+, 92), 283 (24), 221 (100), 178 (24), 165 (20), 105 (23), 103 (20).

*4.3.8. 1-Phenyl-2-(2-phenylethynylphenoxy)butan-1-one (**5h**).* Compound **5h** (1.34 g, 79%) was obtained as yellow liquid, R_f=0.52 (ethyl acetate/*n*-hexane=1:3); IR_{max} (neat) cm^{-1}: 1698 cm^{-1} (C=O), 2217 cm^{-1} (C≡C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.19 (t, J=7.6 Hz, 3H, $ArOCH(CH_2CH_3)COAr$), 2.18 (m, 2H, $ArOCH(CH_2CH_3)COAr$), 5.26 (dd, J=7.6, 5.2 Hz, 1H, $ArOCH(CH_2CH_3)COAr$), 6.75 (d, J=8.4 Hz, 1H, ArH), 6.91 (td, J=8.4, 1.2 Hz, 1H, ArH), 7.16 (ddd, J=8.0, 7.6, 2.0 Hz, 1H, ArH), 7.32 (m, 3H, ArH), 7.42 (m, 2H, ArH), 7.47 (dd, J=8.0, 2.0 Hz, 1H, ArH), 7.54 (m, 3H, ArH), 8.18 (dd, J=8.8, 1.2 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 22.6, 26.9, 31.6, 84.0, 93.7, 113.5, 121.3, 128.1, 128.3, 128.6, 128.7, 129.1, 129.6, 131.5, 133.5, 133.6, 134.3, 158.3, 198.9; EIMS (70 eV) m/z (rel intensity, %) 340 (M^+, 100), 325 (44), 311 (39), 235 (56), 165 (26), 132 (31), 131 (95); HRMS calcd for $C_{24}H_{20}O_2$: 340.1463. Found: 340.1460.

4.4. General procedure for the preparation of 2-aroyl-3-arylbenzofuran (6a–f)

To a stirred solution of compounds **5a**–**f** (1 mmol) in anhydrous THF (10 mL) was added potassium *tert*-butoxide (1.2 mmol), and the mixture were stirred and refluxed for 30 min. After cooling, the solution was quenched with saturated NH_4Cl solution, and extracted with CH_2Cl_2 (5×20 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$ was filtered, evaporated, and the residue was purified by column chromatography (ethyl acetate/*n*-hexane=1:20) to give **6a**–**f**.

*4.4.1. 2-Benzoyl-3-benzylbenzofuran (**6a**).* Compound **6a** (0.25 g, 80%) was obtained as yellow crystals; mp 94–95 °C (lit.[13a] mp 96–98 °C); R_f=0.46 (ethyl acetate/*n*-hexane=1:5); IR_{max} (neat) cm^{-1}: 1644 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.54 (s, 2H, $ArCH_2$), 7.21 (m, 4H, ArH), 7.40 (m, 4H, ArH), 7.54 (m, 4H, ArH), 8.10 (dd, J=8.4, 1.2 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.4, 112.2, 122.1, 123.4, 126.3, 128.0, 128.3, 128.5, 128.6, 128.7, 129.1, 129.8, 132.7, 137.7, 139.1, 148.3, 154.4, 185.8; EIMS (70 eV) m/z (rel intensity, %) 312 (M^+, 100), 311 (65), 297 (15), 296 (15), 235 (11), 178 (14), 77 (12); HRMS calcd for $C_{22}H_{16}O_2$: 312.1150. Found: 312.1152. Anal. Calcd for $C_{22}H_{16}O_2$: C, 84.59; H, 5.16. Found: C, 84.38; H, 5.18.

*4.4.2. 3-Benzyl-2-(4-methylbenzoyl)-benzofuran (**6b**).* Compound **6b** (0.27 g, 83%) was obtained as a colorless crystals; mp 119–120 °C; R_f=0.45 (ethyl acetate/*n*-hexane=1: 5); IR_{max} (neat) cm^{-1}: 1638 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.46 (s, 3H, $ArCH_3$), 4.54 (s, 2H, $ArCH_2$), 7.22 (m, 4H, ArH), 7.36 (dd, J=8.8, 0.8 Hz, 2H, ArH), 7.37 (dd, J=8.4, 0.8 Hz, 2H, ArH), 7.45 (td, J=8.4, 1.2 Hz, 1H, ArH), 7.55 (td, J=8.8, 1.2 Hz, 2H, ArH), 8.04 (dd, J=8.0, 1.6 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.7, 30.5, 112.3, 122.1, 123.4, 126.3, 127.9, 128.5, 128.7, 129.1, 130.0, 135.1, 139.2, 143.6, 148.6, 154.4, 185.5; EIMS (70 eV) m/z (rel intensity, %) 326 (M^+, 23), 325 (9), 312 (23), 311 (100), 310 (6), 233 (6), 205 (8); HRMS calcd for $C_{23}H_{18}O_2$: 326.1307. Found: 326.1306. Anal. Calcd for $C_{23}H_{18}O_2$: C, 84.64; H, 5.56. Found: C, 84.67; H, 5.56.

*4.4.3. 3-Benzyl-2-(4-methoxybenzoyl)benzofuran (**6c**).* Compound **6c** (0.30 g, 88%) was obtained as colorless crystals; mp 98–99 °C; R_f=0.45 (ethyl acetate/*n*-hexane=1:5); IR_{max} (neat) cm^{-1}: 1637 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.90 (s, 3H, OCH_3), 4.54 (s, 2H, $ArCH_2$), 7.01 (dd, J=8.8, 2.0 Hz, 2H, ArH), 7.22 (m, 4H, ArH), 7.37 (d, J=8.8 Hz, 2H, ArH), 7.44 (td, J=8.4, 1.2 Hz, 1H, ArH), 7.55 (m, 2H, ArH), 8.18 (dd, J=9.2, 1.6 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.5, 55.5, 112.2, 113.6, 122.0, 123.4, 126.3, 127.8, 128.4, 128.5, 128.7, 130.4, 132.4, 139.2, 148.7, 154.3, 163.4, 184.2; EIMS (70 eV) m/z (rel intensity, %) 342 (M^+, 40), 341 (17), 327 (19), 325 (12), 312 (28), 311 (100), 265 (9); HRMS calcd for $C_{23}H_{18}O_3$: 342.1256. Found: 342.1257. Anal. Calcd for $C_{23}H_{18}O_3$: C, 80.68; H, 5.30. Found: C, 80.51; H, 5.28.

*4.4.4. 2-Benzoyl-3-(4-methylbenzyl)benzofuran (**6d**).* Compound **6d** (0.27 g, 83%) was obtained as colorless crystals; mp 118–119 °C; R_f=0.45 (ethyl acetate/*n*-hexane=1:5); IR_{max} (neat) cm^{-1}: 1644 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.28 (s, 3H, $ArCH_3$), 4.50 (s, 2H, $ArCH_2$), 7.07(d, J=7.6 Hz, 2H, ArH), 7.25 (td, J=8.0, 1.2 Hz, 4H, ArH), 7.44 (td, J=8.4, 1.2 Hz, 2H, ArH), 7.51 (m, 2H, ArH), 7.59 (m, 2H, ArH), 8.10 (dd, J=8.4, 1.2 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.0, 30.0, 112.2, 122.1, 123.4, 128.0, 128.3, 128.4, 128.6, 129.2, 129.4, 129.8, 132.7, 135.8, 136.0, 137.7, 148.2, 154.4, 185.9; EIMS (70 eV) m/z (rel intensity, %) 326 (M^+, 100), 325 (55), 311 (26), 309 (14), 234 (14), 205 (14), 178 (12); HRMS calcd for $C_{23}H_{18}O_2$: 326.1307. Found: 326.1310. Anal. Calcd for $C_{23}H_{18}O_2$: C, 84.64; H, 5.56. Found: C, 84.56; H, 5.55.

*4.4.5. 2-(4-Methylbenzoyl)-3-(4-methylbenzyl)benzofuran (**6e**).* Compound **6e** (0.29 g, 85%) was obtained as colorless crystals; mp 111–112 °C; R_f=0.42 (ethyl acetate/*n*-hexane=1:5); IR_{max} (neat) cm^{-1}: 1642 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.28 (s, 3H, $ArCH_3$), 2.46 (s, 3H, $ArCH_3$), 4.49 (s, 2H, $ArCH_2$), 7.07 (d, J=8.0 Hz, 2H, ArH), 7.24 (dd, J=8.0, 0.8 Hz, 3H, ArH), 7.32 (d, J=8.0 Hz, 2H, ArH), 7.44 (td, J=8.4, 1.2 Hz, 1H, ArH), 7.53 (dd, J=8.4 Hz, 1H, ArH), 7.57 (dd, J=8.0, 0.8 Hz, 1H, ArH), 8.03 (d, J=8.0 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.0, 21.7, 30.0, 112.2, 122.1, 123.4, 127.9, 128.5, 128.6, 129.0, 129.2, 130.0, 135.1, 135.8, 136.1, 143.6, 148.4, 154.3, 185.5; EIMS (70 eV) m/z (rel intensity, %) 340 (M^+, 23), 326 (25), 325 (100), 233 (12), 205 (21), 189 (11), 91 (23); HRMS calcd for $C_{24}H_{20}O_2$: 340.1463. Found: 340.1463. Anal. Calcd for $C_{24}H_{20}O_2$: C, 84.68; H, 5.92. Found: C, 84.55; H, 5.96.

*4.4.6. 2-(4-Methoxybenzoyl)-3-(4-methylbenzyl)benzofuran (**6f**).* Compound **6f** (0.31 g, 87%) was obtained as colorless crystals; mp 120–121 °C; R_f=0.43 (ethyl acetate/*n*-hexane=1:5); IR_{max} (neat) cm^{-1}: 1638 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.29 (s, 3H, $ArCH_3$), 3.91 (s, 3H, OCH_3), 4.50 (s, 2H, $ArCH_2$), 7.01 (dd, J=9.2, 2.0 Hz, 2H, ArH), 7.07 (d, J=8.0 Hz, 2H, ArH), 7.25 (m, 3H, ArH), 7.44 (td, J=8.4, 1.2 Hz, 1H, ArH), 7.55 (m, 2H, ArH), 8.17 (dd, J=8.8, 2.0 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.0, 30.0, 55.5, 112.2, 113.6, 113.9, 122.1, 123.3, 127.7, 128.5, 128.6, 128.7, 129.2, 130.5, 132.4, 135.8, 136.2, 154.3, 163.4, 184.2; EIMS (70 eV) m/z (rel intensity, %) 356 (M^+, 43), 341 (19), 326 (28), 325 (100), 221 (15), 205 (21), 77

(22); HRMS calcd for $C_{24}H_{20}O_3$: 356.1412. Found: 356.1414. Anal. Calcd for $C_{24}H_{20}O_3$: C, 80.88; H, 5.66. Found: C, 80.56; H, 5.63.

4.5. General procedure for the preparation of 2-alkyl-3-benzylbenzofuran (6g,h) from 5g,h

The reaction procedure is the same for preparation of **6a**–**f**, which described above. At the end of reaction (it took 30 min), which was monitored by TLC analysis, the reaction mixture was cooled to room temperature and acidified by 2% HCl until the color change of Congo red paper from red to blue. The resulting mixture was extracted with dichloromethane (20 mL×3). The organic layers were combined and washed with brine, dried with anhydrous magnesium sulfate, filtered, and concentrated in vacuo, in sequences. The resulting residue was purified by silica gel column chromatography. Eluted with *n*-hexane/ethyl acetate (5:1) to give 2-alkyl-3-benzyl-benzofurans (**6g**,**h**), and eluted with *n*-hexane/ethanol (5:1) to yield benzoic acid (82–80%).

*4.5.1. 3-Benzyl-2-methylbenzofuran (**6g**).* Compound **6g** (0.19 g, 86%) was obtained as a yellow liquid; R_f=0.49 (ethyl acetate/*n*-hexane=1:5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.40 (s, 3H, CH_3), 3.95 (s, 2H, $ArCH_2$), 7.09 (m, 1H, ArH), 7.16 (m, 3H, ArH), 7.23 (m, 4H, ArH), 7.37 (d, J=8.0 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.01, 29.60, 110.5, 119.1, 122.1, 123.1, 126.1, 128.3, 128.4, 129.4, 129.6, 139.8, 151.5, 154.0; EIMS (70 eV) *m*/*z* (rel intensity, %) 222 (M^+, 100), 221 (16), 208 (24), 207 (72), 179 (14), 179 (13), 145 (15), HRMS calcd for $C_{16}H_{14}O$: 222.1045. Found: 222.1042.

*4.5.2. 3-Benzyl-2-ethylbenzofuran (**6h**)*[18]. Compound **6h** (0.20 g, 85%) was obtained as a yellow liquid; R_f=0.46 (ethyl acetate/*n*-hexane=1:5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (t, J=7.6 Hz, 3H, $-CH_2CH_3$), 2.78 (q, J=7.6 Hz, 2H, $-CH_2CH_3$), 3.98 (s, 2H, $CH_2C_6H_5$), 7.09 (m, 1H, ArH), 7.17 (m, 3H, ArH), 7.24 (m, 4H, ArH), 7.39 (d, J=8.0 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.9, 19.9, 29.5, 110.6, 112.1, 119.3, 122.6, 123.1, 126.1, 128.2, 128.4, 129.6, 139.9, 154.0, 156.5; EIMS (70 eV) *m*/*z* (rel intensity, %) 236 (M^+, 100), 221 (14), 208 (12), 207 (30), 193 (22), 178 (14), 115 (9), HRMS calcd for $C_{17}H_{16}O$: 236.1201. Found: 236.1204.

Acknowledgements

The research grants from the National Science Council of Taiwan (NSC-99-2113-M-037-007) are grateful. We also thank the anonymous reviewers for their valuable comments to improve the quality of this work.

References and notes

1. Majumdar, K. C.; Chattopadhyay, B.; Ray, K. *Tetrahedron Lett.* **2007**, *48*, 7633–7636.
2. Chang, C. P.; Pradiuldi, S. V.; Hong, F. E. *Inorg. Chem. Commun.* **2009**, *12*, 596–598.
3. Sengupta, S.; Mukhopadhyay, R.; Achari, B.; Banerjee, A. K. *Tetrahedron Lett.* **2005**, *46*, 1515–1519.
4. (a) Ray, D.; Paul, S.; Brahma, S.; Ray, J. K. *Tetrahedron Lett.* **2007**, *48*, 8005–8008; (b) Sant'Ana, D. P.; Pinho, V. D.; Maior, MC. L. S.; Costa, P. R. R. *Tetrahedron Lett.* **2009**, *50*, 3753–3755; (c) Mehta, G.; Harish, M.; Shinde, H. M. *Tetrahedron Lett.* **2003**, *44*, 7049–7053; (d) Ferreira, B. R. V.; Pirovani, R. V.; Souza-Filho, L. G.; Coelho, F. *Tetrahedron* **2009**, *65*, 7712–7717; (e) Donaldson, L. R.; Haigh, D.; Hulme, A. N. *Tetrahedron* **2008**, *64*, 4468–4477.
5. (a) Abdel-Aziz, H. A.; Mekawey, A. A. I. *Eur. J. Med. Chem.* **2009**, *44*, 4985–4997; (b) Aslam, S. N.; Stevenson, P. C.; Kokubun, T.; Hall, D. R. *Microbiol. Res.* **2009**, *164*, 191–195.
6. Galal, S. A.; Abd El-All, A. S.; Abdallah, M. M.; El-Diwani, H. I. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2420–2428.
7. Dawood, K. M.; Abdel-Gawad, H.; Rageb, E. A.; Ellithey, M.; Mohamed, H. A. *Bioorg. Med. Chem.* **2006**, *14*, 3672–3680.
8. Miert, S. V.; Dyck, S. V.; Schmidt, T. J.; Brun, R.; Vlietinck, A.; Lemiere, g.; Pieters, L. *Bioorg. Med. Chem.* **2005**, *13*, 661–669.
9. Eidamshaus, C.; Burch, J. D. *Org. Lett.* **2008**, *10*, 4211–4214.
10. Yoshida, M.; Morishita, Y.; Fujita, M.; Ihara, M. *Tetrahedron Lett.* **2004**, *45*, 1861–1864.
11. Csekei, M.; Novak, Z.; Kotschy, A. *Tetrahedron* **2008**, *64*, 8992–8996.
12. Tsai, T. W.; Wang, E. C.; Huang, K. S.; Li, S. R.; Wang, Y. F.; Lin, Y. L.; Chen, Y. H. *Heterocycles* **2004**, *63*, 1771–1781.
13. (a) Kanazawa, C.; Goto, K.; Terada, M. *Chem. Commun.* **2009**, 5248–5250; (b) Hu, J.; Wu, L. Y.; Wang, X. C.; Hu, Y. Y.; Niu, Y. N.; Liu, X. Y.; Yang, S.; Liang, Y. M. *Adv. Synth. Catal.* **2010**, *352*, 351–356.
14. (a) Chen, L.-Y.; Li, S.-R.; Chen, P. Y.; Tsai, I.-L.; Hsu, C. L.; Lin, H. P.; Wang, T. P.; Wang, E.-C. *Tetrahedron Lett.* **2009**, *50*, 5748–5750; (b) Li, S.-R.; Shu, C.-J.; Chen, L.-Y.; Chen, H.-M.; Chen, P. Y.; Wang, E.-C. *Tetrahedron* **2009**, *65*, 8702–8707.
15. Songashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470.
16. Kraus, G. A.; Schroeder, J. D. *Synlett* **2005**, 2504–2506.
17. Wang, Z. Q.; Liang, Y.; Lei, Y.; Zhou, M. B.; Li, J. H. *Chem. Commun.* **2009**, 5232–5244.
18. Mahmoud, E. H.; Malamas, M. S. U.S. Pat. Appl. Publ. US 20050070585 A1, 2005.
19. He, Z.; Yudin, A. K. *Org. Lett.* **2006**, *8*, 5829–5832.
20. Wright, S. W.; Hageman, D. L.; Wright, A. S.; McClure, L. D. *Tetrahedron Lett.* **1997**, *38*, 7345–7348.
21. Altschul, R.; Herbert, J. *J. Am. Chem. Soc.* **1948**, *70*, 351–354.