Tetrahedron Letters 50 (2009) 3588–3592

Contents lists available at ScienceDirect

Tetrahedron Letters

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

p-Toluenesulfonic acid-mediated cyclization of *o*-(1-alkynyl)anisoles or thioanisoles: synthesis of 2-arylsubstituted benzofurans and benzothiophenes

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ARTICLE INFO

Article history:
Received 15 January 2009
Revised 5 March 2009
Accepted 10 March 2009
Available online 16 March 2009

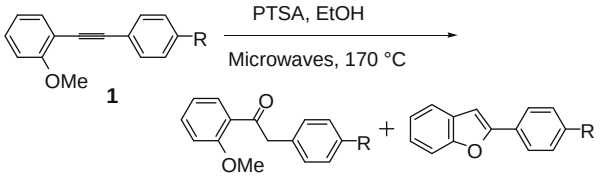
Keywords:
Benzofurans
Benzothiophenes
Isocoumarins
Alkynes
Electrophilic cyclization
Microwave irradiation
p-Toluenesulfonic acid

ABSTRACT

A variety of 2-arylbenzo[*b*]furans are readily prepared in good to excellent yields from the cyclization of *o*-(1-alkynyl)anisole derivatives under mild reaction conditions using an alcoholic media, *p*-toluenesulfonic acid under microwave irradiation. Starting from the corresponding *o*-(1-alkynyl)thioanisole derivatives, this friendly and environmentally free-metal procedure has been successfully extended to the synthesis of benzo[*b*]thiophenes. Relative to the electronic nature of the substituents, the selectivity of the cyclization reaction from differently *o*,*o*′-substituted diarylalkynes is also discussed.

Conversions of alkynes to their corresponding carbonyl compounds are very important and essential in functional group transformation.[1] As part of a research program directed toward a selective functionalization of a carbon–carbon triple bond,[2] we previously reported the hydration of internal alkynes, in water or alcoholic media under a catalytic amount of *p*-toluenesulfonic acid (PTSA).[3] Under this environmentally friendly procedure, aliphatic arylalkynes were regioselectively converted into their corresponding carbonyl compounds according to Markovnikov's rules. Interestingly, we next demonstrated that under similar conditions, diarylalkynes bearing in the *ortho* position of the aromatic nucleus an electron-withdrawing group such as an ester, an acid, or an amide group afforded 3-arylsubstituted isocoumarins in high yields.[4] Additionally, under microwave irradiation diarylalkynes having an *ortho* electron-donating methoxy group also reacted successfully but at higher temperatures (170 °C). However, and contrary to our expectations, the reaction did not afford exclusively the carbonyl product **2** but also allowed the formation of the cyclized product 2-arylbenzo[*b*]furans **3** (Scheme 1).[3b] One can note that the electronic nature of the *para* R substituent on alkyne **1** influences the distribution of compounds **2** and **3**, since the major product is the carbonyl compound **2a** when R = H, whereas benzofuran **3b** predominated when R = Me.

The most common route to heterocycles of type **3** is undoubtedly the cyclization of *o*-(1-alkynyl)phenol compounds through a transition metal-catalyzed activation of the triple bond.[5] In order to develop a rapid and metal-free access to 2-arylsubstituted benzo[*b*]furans **3**, according to the green chemical philosophy,[6] we set out to carefully examine the transformation of **1** to **3**, since benzofurans are ubiquitous structural motifs in both natural products and synthetic pharmaceuticals.[7] Additionally, in spite of efficient procedures for the preparation of benzofurans from internal alkynes having an *ortho* phenolic-free function are well known,[5] to the best of our knowledge there is no report on their synthesis from the corresponding anisole derivatives. We speculate that, replacing the R substituent (H or Me) on alkyne **1** by a variety of strong electron-donating groups would increase the reactivity of the triple bond and, at least the yields of **3**.



	2	3
a: R = H	58%	39%
b: R = Me	14%	63%

Scheme 1.

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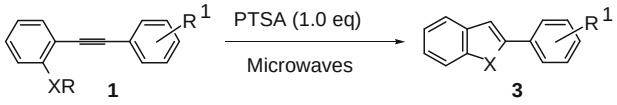
0040-4039/$ - see front matter © 2009 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2009.03.087

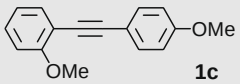
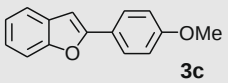
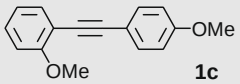
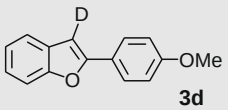
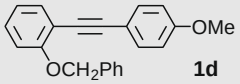
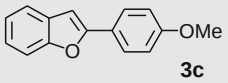
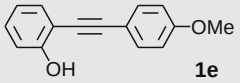
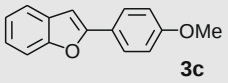
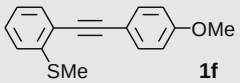
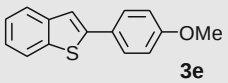
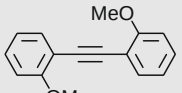
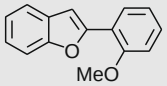
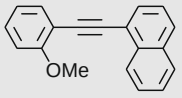
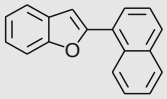
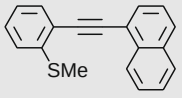
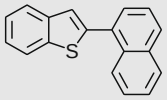
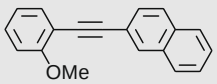
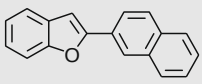
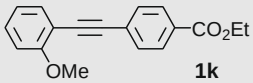
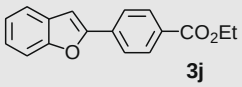
Interestingly, starting from *o*-(1-alkynyl)thioanisoles this new and environmentally friendly procedure could also be extended to the synthesis of 2-aryl-substituted benzo[*b*]thiophene derivatives[8] which are prevalent in many compounds of biological interest.[9,7b] Herein, we report the results of this study and how the electronic nature of *ortho* substituents on diarylalkynes influences the regiochemical course of this cyclization.

Initially, we studied the reaction with alkyne **1c** bearing on aromatic rings an *ortho* and a *para* methoxy group both useful for the cyclization and for the activation of the triple bond, respectively. The best conditions required the use of PTSA (1.0 equiv) in EtOH or MeOH under microwave irradiation at 130 °C within 1 h. Accordingly, the expected benzofuran **3c** was obtained in satisfactory yields and no trace of the hydration product was detected (Table 1, entries 1 and 2). Carrying out the reaction in CD_3OD formed **3d** with no signal at 6.88 ppm in ^1H NMR spectrum, clearly indicating a deuteration on the 3-position of the benzofuran ring (entry 3).

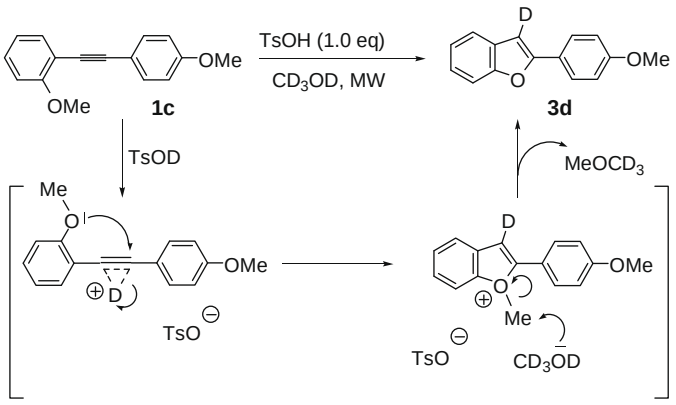
The formation of **3d** is believed to proceed initially through a deuterium exchange between CD_3OD and PTSA followed by acidic deuterium activation of the triple bond (Scheme 2). Subsequent regioselective 5-*endo*-dig-cyclization with the *ortho* methoxy sub-

Table 1
Reaction of *ortho*-substituted arylalkynes **1** with PTSA in EtOH: synthesis of 2-arylbenzo[*b*]furans and 2-arylbenzo[*b*]thiophenes



Entry	Alkyne **1**	*T* (°C)	Time (h)	Solvent	Product	Yield[a] (%)
1	 **1c**	130	1	EtOH	 **3c**	76
2		130	1	MeOH		74
3	 **1c**	130	1	CD_3OD	 **3d**	80
4	 **1d**	130	1	EtOH	 **3c**	62[b]
5	 **1e**	130	1	EtOH	 **3c**	79
6	 **1f**	130	1	EtOH	 **3e**	94
7	 **1g**	160	2	EtOH	 **3f**	83
8	 **1h**	160	2	EtOH	 **3g**	92
9	 **1i**	160	2	EtOH	 **3h**	93
10	 **1j**	160	2	EtOH	 **3i**	44[c]
11	 **1k**	160	2	EtOH	 **3j**	0[d]

[a] Isolated yield.
[b] Ethylbenzylether was also observed in the crude reaction mixture.
[c] A 32% of hydration product was isolated where the carbonyl function is proximal to the *o*-methoxyphenyl ring.
[d] A 47% of hydration product was isolated where the carbonyl function is proximal to the *o*-methoxyphenyl ring. No starting material was left.



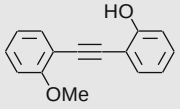
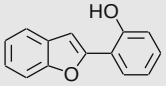
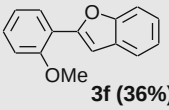
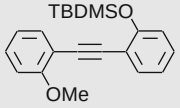
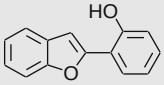
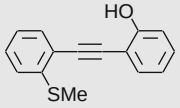
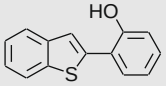
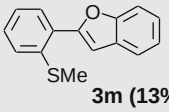
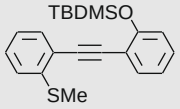
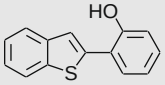
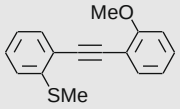
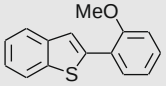
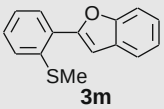
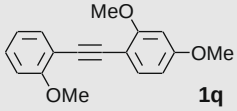
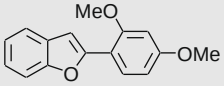
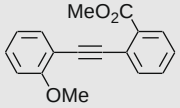
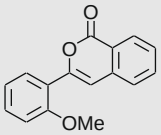
Scheme 2. A plausible mechanistic formation of **3d**.

stituent would lead to an oxonium species. The latter would be cleaved by the nucleophilic solvent to form the C3 deuterated benzofuran **3d**.

To support this hypothesis, an attempt was achieved with alkyne **1d** having an *ortho* benzyloxy substituent. As expected, in EtOH the reaction provided the benzofuran **3c** together with ethylbenzylether resulting from the oxonium cleavage (entry 4).[10] It should be noted that **1e** with an *ortho* hydroxyl-free substituent also underwent the cyclization reaction to afford **3c** in a similar yield as it was observed from **1c** (entry 5).

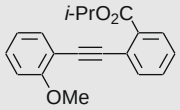
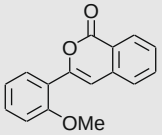
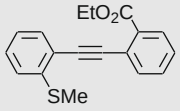
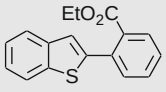
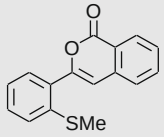
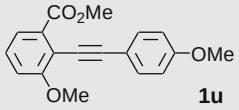
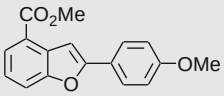
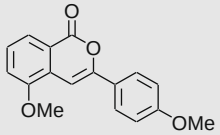
Keeping in mind our initial goal to extend this reaction to the synthesis of benzothiophene derivatives, we next examined the cyclization of thioanisole **1f**. We were pleased to observe the formation of the corresponding benzothiophene **3e** in excellent yield (94%, entry 6). By utilizing these experimental conditions, we carried out the cyclization with the symmetrical substrate **1g** having two *ortho* methoxy groups on aromatic rings. At 130 °C within 1 h, the reaction took place smoothly to provide the desired compound **3f** together with starting material **1g**. Increasing the temperature to 160 °C, the reaction went to completion and **3f** was isolated in a 83% isolated yield (entry 7). The scope of this reaction was successfully demonstrated when switching the 2-methoxyphenyl by the 1-naphthyl group. In both examples depicted in

Table 2
Selectivity in heterocycle formation from *o,o′*-disubstituted diarylalkynes **1**[a]

Entry	Alkyne **1**	*T* (°C)	Product (yield (%))[b]	Ratio
1	 **1l**	160	 **3k (60%)**  **3f (36%)**	62:38
2	 **1m**	160	 **3k (61%)**	–
3	 **1n**	160	 **3l (71%)**  **3m (13%)**	85:15
4	 **1o**	160	 **3l (88%)**	–
5	 **1p**	130	 **3n**  **3m**	82:18[c]
6	 **1q**	160	 **3o (65%)**	–[d]
7	 **1r**	130	 **3p (95%)**	–

(*continued on next page*)

Table 2 (*continued*)

Entry	Alkyne **1**	*T* (°C)	Product (yield (%))[b]	Ratio
8	 **1s**	160	 **3p (88%)**	–
9	 **1t**	160	 **3q (21%)**  **3r (42%)**	33:67
10	 **1u**	160	 **3s (57%)**  **3t (25%)**	70:30[e]

[a] All reactions were performed according to general procedure; see: Ref. 11.
[b] Isolated yield.
[c] Obtained as an inseparable mixture.
[d] A 26% of hydration product was isolated where the carbonyl function is proximal to the *o,p*-dimethoxyphenyl ring.
[e] The reaction was performed in MeOH.

entries 8 and 9, benzofuran **3g** and benzothiophene **3h** were obtained in 92% and 93% isolated yield, respectively. However, with substrate **1j** containing a 2-naphthyl substituent, the reaction proceeded to give **3i** in 44% yield (entry 10) together with a notable amount of the hydration product (32%) where the carbonyl function is proximal to the *ortho* methoxyphenyl ring. These results clearly suggest that the 1-naphthyl substituent acts as a better electron-donating group than its 2-isomer for the activation of the triple bond. Finally, introducing a *para* ethoxycarbonyl group on the aromatic nucleus totally deactivates the carbon–carbon triple bond and, as expected no cyclization occurred. In this case, the reaction provided exclusively in a moderate yield (47%, entry 11) the hydration product where the carbonyl function is proximal to the *ortho* methoxyphenyl ring.

Overall, this new process offered an efficient method for the preparation of benzofuran and benzothiophene derivatives[11] from easily accessible *ortho* methoxy and thiomethoxy diarylalkynes.[12]

We continued to demonstrate the high potency of this friendly methodology, this time in terms of regioselectivity of the cyclization reaction, when using differently *o,o′*-disubstituted diarylalkynes and the results are summarized in Table 2. Initially, we examined the reaction with substrates having two *o,o′*-electron-donating substituents (Table 2, entries 1–6). Depending on the nature of substituents on the aromatic rings, a regioisomeric heterocyclic mixture to a single product, resulting from *ortho* and/or *ortho′* substituent attack was observed. Alkyne **1l** with an *ortho* methoxy and *ortho′*-hydroxyl substituent can undergo cyclization at both the OMe and OH oxygen atoms to give **3k** and **3f** in 60% and 36% yield, respectively, (**3k**:**3f** 62:38, entry 1). However a total selectivity was observed when replacing the *ortho* hydroxyl group with a *tert*-butyldimethylsilyloxy substituent. Under these conditions, the cyclization was followed by a deprotection reaction leading to benzofuran **3k** in 61% isolated yield (entry 2). A similar trend in selectivity was also observed with alkynes **1n** and **1o** having an *ortho* methylthio substituent as **1o** gives exclusively benzothiophene **3l** (entry 4) whereas, **1n** leads to a mixture of easily separable **3l** (71%) and **3m** (13%) (entry 3). This selectivity (**3n**:**3m** 82:18, entry 5) was also observed with alkyne **1p** clearly indicating that the methylthio substituent is a better nucleophile than the methoxy or the hydroxy one. Interestingly, starting from *o,o′,p*-trimethoxyalkyne **1q**, a single cyclization product **3o**[13] (65%, entry 6) was formed together with a small amount of the hydration compound (26%) where the carbonyl function is proximal to the *o,p*-dimethoxyphenyl nucleus.

Once the selective cyclization with alkynes having two *o,o′*-electron-donating substituents was studied, we sought to examine the reaction with substrates **1r–u** bearing both an *ortho* electron-donating and an electron-withdrawing substituents (Table 2, entries 7–10). Using our protocol with alkyne **1r**, the 6-*endo* cyclization proceeded exclusively with the *ortho* ethoxycarbonyl function rather than OMe group and provides isocoumarin **3p** in an excellent yield (95%, entry 7). This selectivity for the isocoumarin **3p** could not be reversed in favor of the benzofuran skeleton upon cyclization of substrate **1s** containing a bulkier *ortho* isopropyloxycarbonyl substituent (entry 8). When replacing in **1r** the *ortho* methoxy substituent by a more nucleophilic methylthio one, the cyclization from **1t** was less selective, producing predominantly the six-membered-ring lactone **3r** together with a notable amount (21%) of the benzothiophene **3q** (entry 9). Finally, an attempt was made with alkyne **1u** containing both an *ortho* electron-donating and electron-withdrawing substituents on the same nucleus. In this case the cyclization occurred preferentially at the oxygen atom of the methoxy rather than the methoxycarbonyl substituent to give the benzofuran **3s** and the isocoumarin **3t** in 57% and 25% yield, respectively, (entry 10).

In conclusion, a useful synthesis of 2-arylbenzo[*b*]furans and 2-arylbenzo[*b*]thiophenes has been achieved using in alcoholic media *p*-toluenesulfonic acid under microwave irradiation. This metal-free procedure which proceeds under environmentally friendly conditions utilizes readily available *o*-(1-alkynyl)anisole and *o*-(1-alkynyl)-thioanisole derivatives. From *o,o′*-substituted diarylalkyne substrates we demonstrated that the cyclization selectivity is strongly dependent on the electronic nature of the *ortho* substituents and in some cases it may allow a selective synthesis of the

above heterocycles or isocoumarins. Further application of this process to generate benzofuran or benzothiophene-based chemical libraries of potential pharmacological interest is currently underway.

Acknowledgments

The CNRS is gratefully acknowledged for financial support of this research and MRES for a doctoral fellowship to M.J. Thanks also to Estelle Morvan for NMR studies.

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11. *Typical procedure*: To an Emrys Optimizer 0.5–2 mL pyrex reaction vessel were added alkyne (0.2 mmol) and PTSA.H_2O (38 mg; 0.2 mmol) in EtOH (1 mL). The reaction vessel was then placed in the Emrys Optimizer and exposed to microwave irradiation according to the following specifications: temperature, 130 °C or 160 °C (see Table 2); time (1 h); fixed hold time: on; sample absorption: high; pre-stirring: 60 s. After cooling to room temperature, H_2O (3 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 2 mL). Organic layers were dried, concentrated, and the crude was purified by column chromatography on silica gel. Data for all new products are described in entries 2, 3, 6, 9, and 10 in Table 2.
Entry 2. Compound **3k** (61%). R_f 0.22 (cyclohexane:EtOAc, 9:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.72–6.78 (m, 2H), 6.84 (s, 1H), 6.91 (s, 1H), 6.99–7.09 (m, 3H), 7.28 (m, 1H), 7.35 (m, 1H), 7.46 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 103.5, 111.2, 116.2, 117.5, 120.9, 121.1, 123.6, 124.6, 127.3, 128.6, 130.4, 153.5, 154.1, 154.4. IR (ν cm^{-1}): 3451, 3352, 1590, 1446, 1212, 1017, 743. MS (APCI+) *m/z* 211.0 (M+H)$^+$.
Entry 3. Compound **3l** (71%). R_f 0.21 (cyclohexane:EtOAc, 95:5). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.63 (s, 1H), 6.99–7.05 (m, 2H), 7.27–7.43 (m, 3H), 7.40 (dd, *J* = 7.6 Hz, *J* = 1.6 Hz, 1H), 7.56 (s, 1H), 7.81–7.89 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 116.5, 121.0, 121.2, 122.3, 123.0, 123.8, 124.7, 124.8, 130.0, 130.4, 139.4, 140.0, 140.4, 152.9. IR (ν cm^{-1}): 3511, 3054, 1481, 1449, 1432, 1333, 1290, 1173, 747. MS (APCI+) *m/z* 227.0 (M+H)$^+$. Compound **3m** (13%). R_f 0.61 (cyclohexane:EtOAc, 9:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.54 (s, 3H), 7.22–7.31 (m, 3H), 7.34–7.36 (m, 3H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.63 (dt, *J* = 7.6 Hz, J = 0.7 Hz, 1H), 7.91 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.3, 106.9, 111.2, 121.4, 123.0; 124.7, 125.0, 126.0, 128.9, 129.1, 129.3, 137.1, 153.6, 154.4. IR (ν cm^{-1}): 2922, 1454, 1260, 1017, 804, 747. MS (APCI+) *m/z* 241.0 (M+H)$^+$.
Entry 6. Compound **3o** (65%). R_f 0.30 (cyclohexane:EtOAc, 9:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.90 (s, 3H), 4.01 (s, 3H), 6.61–6.68 (m, 2H), 7.22–7.32 (m, 3H), 7.54 (dt, *J* = 6.6 Hz, *J* = 1.1 Hz, 1H), 7.62 (m, 1H), 8.03 (d, *J* = 8,6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.6 (2), 98.9, 104.4, 105.0, 110.7, 112.9, 120.8, 122.7, 123.7, 128.1, 130.2, 152.6, 153.8, 157.9, 161.1. IR (ν cm^{-1}): 2937, 2836, 1610, 1502, 1252, 1208, 1158, 1029, 796, 740. MS (APCI+) *m/z* 255.0 (M+H)$^+$.
Entry 9. Compound **3q** (21%). R_f 0.27 (cyclohexane:EtOAc, 6:4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.04 (t, *J* = 7.1 Hz, 3H), 4.18 (q, *J* = 7.1 Hz, 2H), 7.24 (s, 1H), 7.31–7.39 (m, 2H), 7.45 (dd, *J* = 7.3, *J* = 1.6 Hz, 1H), 7.51–7.57 (m, 2H), 7.76–7.81 (m, 2H), 7.84 (d, *J* = 7,7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.9, 61.4, 122.2, 123.1, 123.7, 124.4, 124.6, 128.5, 129.7, 131.1, 131.5, 132.5, 134.4, 140.2, 140.5, 142.6, 168.6. IR (ν cm^{-1}): 2982, 1720, 1289, 1257, 1127, 1084, 726. MS (APCI-) *m/z* 209.0 (M−CO_2Et)$^-$. Compound **3r** (42%). R_f 0.12 (cyclohexane:CH_2Cl_2, 6:4). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.48 (s, 3H, SCH_3), 6.85 (s, 1H), 7.20–7.26 (m, 1H), 7.32 (dd, *J* = 8.0 Hz, *J* = 1.1 Hz, 1H), 7.37–7.43 (m, 1H), 7.48–7.60 (m, 3H), 7.73 (td, *J* = 7.6 Hz, *J* = 1.3 Hz, 1H), 8.30 (dt, *J* = 7.9 Hz, *J* = 0.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.5, 107.2, 120.7, 124.9, 126.1, 126.2, 128.5, 129.7, 129.8, 130.2, 131.9, 134.9, 137.3, 138.2, 153.1, 162.6. IR (ν cm^{-1}): 2939, 1669, 1596, 1510, 1485, 1251, 1168, 1025, 841, 749. MS (APCI+) *m/z* 269.0 (M+H)$^+$.
Entry 10. Compound **3s** (57%). R_f 0.51 (cyclohexane:CH_2Cl_2, 6:4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.87 (s, 3H), 4.00 (s, 3H), 7.00 (d, *J* = 8.7 Hz, 2H), 7.28 (t, *J* = 8.1 Hz, 1H), 7.51 (s, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.86 (d, *J* = 8.7 Hz, 2H), 7.95 (d, *J* = 7.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 52.1, 55.5, 101.0, 114.5 (2C), 115.4, 122.1, 123.0, 123.1, 125.6, 127.0 (2C), 130.5, 155.3, 158.1, 160.6, 167.3. IR (ν cm^{-1}): 2952, 1712, 1503, 1247, 1175, 1137, 1042, 751. MS (APCI+) *m/z* 283.0 (M+H)$^+$. Compound **3t** (25%). R_f 0.22 (cyclohexane:CH_2Cl_2, 6:4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.96 (s, 3H), 7.00 (d, *J* = 8.3 Hz, 2H), 7.07 (t, *J* = 8.0 Hz, 1H), 7.36–7.40 (m, 2H), 7.45–7.51 (m, 2H), 7.70 (t, *J* = 8.3 Hz, 1H), 7.97 (dd, *J* = 7.9 Hz, *J* = 1.7 Hz, 1H), 8.30 (d, *J* = 7.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.8, 107.1, 111.5, 120.8, 120.9, 121.0, 126.4, 128.1, 129.0, 129.5, 130.9, 134.8, 138.2, 150.6, 157.4, 162.8. IR (ν cm^{-1}): 1724, 1625, 1493, 1225, 1021, 754. MS (APCI+) *m/z* 253.0 (M+H)$^+$. Benzofurans and benzothiophenes **3c–i** described in Table 1 are known compounds.
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13. The structure of benzofuran **3o** was assigned based on NOE experiments.