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A New and Efficient Synthesis of 4-Functionalized Benzo[*b*]furans from 2,3-Dihalophenols

Roberto Sanz,*,† M. Pilar Castroviejo,† Yolanda Fernández,† and Francisco J. Fañanás‡

Departamento de Química, Área de Química Orgánica, Facultad de Ciencias, Universidad de Burgos, Pza. Missael Bañuelos s/n, 09001-Burgos, Spain, and Instituto Universitario de Química Organometálica "Enrique Moles", Universidad de Oviedo, C/Julián Clavería, 8, 33006-Oviedo, Spain

rsd@ubu.es

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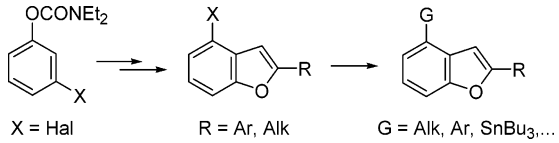

Tandem Sonogashira coupling/5-*endo-dig* cyclization reactions on 2,3-dihalophenols suppose a straightforward entry to 4-halobenzo[*b*]furans, which can be easily transformed into 4-functionalized benzo[*b*]furans, that are difficult to synthesize by other procedures. On the other hand, the starting 2,3-dihalophenols are efficiently prepared from commercially available 3-halophenols, via their *N,N*-diethyl carbamates by selective lithiation at the 2-positions by treatment with *s*-BuLi/TMEDA or LDA at low temperature and reaction with halogen electrophilic reagents.

Molecules containing the benzo[*b*]furan scaffold show a wide range of biological activities,[1] and there is a growing interest in the developing of general and versatile synthetic methods for the synthesis of this kind of compounds.[2] We have recently reported a new route to 4-functionalized indole derivatives based on an anionic cyclization via benzyne intermediates.[3] When we tried to extend this methodology to the synthesis of the corresponding oxygenated analogues (i.e., 4-functionalized benzo[*b*]furans), we found that the reaction failed due to a favored β-elimination process in the 2-lithioallyl ether intermediate.[3b] We envisaged that another entry to this interesting class of compounds could involve the functionalization of 4-halobenzo[*b*]furan derivatives via halogen−lithium exchange, Pd-catalyzed couplings, and so on. However, whereas 5- and 7-halobenzo[*b*]furans can be prepared by the cyclization reaction of *p*- and *o*-halophenol derivatives,[4] respectively, the cyclization of the analogous *m*-halophenols does not selectively lead to the corresponding 4-halobenzo[*b*]furans. Among the few methods reported, both the CsF-mediated or thermal [3,3] Claisen rearrangement of 3-halophenyl propargyl ethers,[5] and the cyclization under acidic conditions of *m*-halo *O*-aryloximes[6] or 1-halo-3-(2,2,diethoxy-ethoxy)-benzene,[7] afford mixtures of 4- and 6-halobenzo[*b*]furans which are usually difficult to separate. In a different approach, Watanabe et al. have recently described the first synthesis of 4-chlorobenzo[*b*]furan via selective mono-*tert*-butoxylation of 2,6-dichlorophenylacetaldehyde dimethyl acetal.[8] In this context, we reasoned that if we were able to prepare 2-iodo-3-halophenols, the subsequent tandem Sonogashira coupling/5-*endo-dig* cyclization reactions[9] would provide us the corresponding 4-halobenzo[*b*]furans (Scheme 1).

However, the main problem we found when we initiated this study was the very scarce number of available 2,3-dihalophenols. To the best of our knowledge, 2,3-dichlorophenol is the only commercially available 2,3-dihalophenol. 3-Fluoro-2-halophenols[10] and 2-halo-3-iodophenols have not been described before and other 2,3-dihalophenols are only accessible via multistep and tedious procedures based on traditional electrophilic aromatic substitution.[11]

On the other hand, it has been shown that phenols can be easily functionalized by the selective lithiation of the

* To whom correspondence should be addressed. Fax: +34 947258831.
† Universidad de Burgos.
‡ Universidad de Oviedo.

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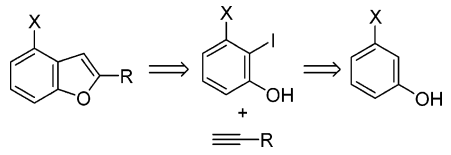
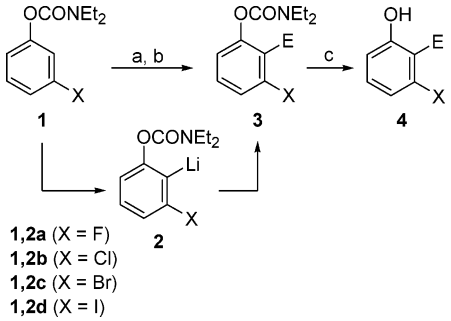
SCHEME 1. Retrosynthetic Analysis of 4-Halobenzo[*b*]furans



SCHEME 2. Synthesis of *O*-2,3-Dihalophenyl Carbamates 3 and 2,3-Dihalophenols 4[a]



[a] Reagents and conditions: (a) *s*-BuLi/TMEDA (1.2 equiv), THF, −78 °C, 2 h, for **1a,b** or LDA (1.1 equiv), THF, −78 °C, 30 min for **1c**,**d**; (b) E^+ (I_2, $C_2H_4Br_2$, $C_2Cl_4Br_2$, C_2Cl_6), −78 to +20 °C; (c) NaOH (10 equiv), EtOH, reflux, 5−8 h.

corresponding carbamate and subsequent reaction with electrophiles.[12] Herein, we want to report a new and efficient preparation of several 2,3-dihalophenols using the *O*-carbamate-directed metalation methodology and the application of these useful building blocks to the synthesis of 4-functionalized benzo[*b*]furans.

The starting *O*-carbamates **1a**−**d** were prepared from the corresponding commercially available 3-halophenol in near quantitative yield by their treatment with NaH[13] or *n*-BuLi and further reaction with *N*,*N*-diethylcarbamoyl chloride.[14] The directed *ortho* metalation (D*o*M) reactions of aryl *O*-carbamates **1a**[15] and **1b**[16] have been described by Snieckus et al. by using *s*-BuLi/TMEDA in THF at −78 °C. The *ortho* lithiation was complete for these carbamates in 1.5−2 h under these conditions, and it took place only at the sterically disfavored 2-position rather than at the 6-position probably due to the cooperative effect of the halide and the carbamate. Efficient trapping of the intermediate anions **2a** and **2b** was carried out by addition of the corresponding electrophile (iodine, hexachloroethane, 1,2-dibromo-1,1,2,2-tetrachloroethane, or 1,2-dibromoethane) at −78 °C to afford *O*-3-fluoro-2-halophenyl carbamates **3a**−**c** and *O*-3-chloro-2-halophenyl carbamates **3d**,**e** in good yields (Scheme 2 and Table 1). The reaction of **2b** proceeded more efficiently with iodine than with either of the bromine-based electrophiles: the use of 1,2-dibromo-1,1,2,2-tetrachloroethane gave rise to a small amount of 2,3-dichlorophenyl *N*,*N*-diethylcarbamate which resulted to be inseparable from the desired **3e**; on the other hand, the use of 1,2-dibromoethane as electrophile led to a competitive protonation of intermediate **2b**. The steric hindrance in intermediate **2** could be the responsible for the competitive reaction of this organolithium with smaller electrophiles (chloro vs bromo in $C_2Br_2Cl_4$ and hydrogen vs bromo in $C_2H_4Br_2$).

TABLE 1. Synthesis of *O*-2,3-Dihalophenyl Carbamates 3

entry	product	X	E^+	E	yield[a] (%)
1	**3a**	F	I_2	I	88
2	**3b**	F	$C_2Br_2Cl_4$	Br	84
3	**3c**	F	C_2Cl_6	Cl	83
4	**3d**	Cl	I_2	I	86
5	**3e**	Cl	$C_2H_4Br_2$	Br	64[b]
6	**3f**	Br	I_2	I	84
7	**3g**	Br	$C_2H_4Br_2$	Br	71[c]
8	**3h**	Br	C_2Cl_6	Cl	92
9	**3i**	I	I_2	I	74
10	**3j**	I	$C_2H_4Br_2$	Br	60[d]
11	**3k**	I	C_2Cl_6	Cl	70

[a] Isolated yield based on the starting carbamate **1**. [b] **1b** was also formed in 21% yield. [c] **1c** was also formed in 22% yield. [d] **1d** was also formed in 24% yield.

Although there are many examples in the literature describing *ortho* lithiations of fluoro- and chlorobenzene derivatives, there are fewer examples of *ortho* lithiation of the corresponding bromo-[17] and iodobenzene derivatives.[18] As far as we know, no reports on the D*o*M of *O*-carbamates **1c** and **1d**, bearing *m*-bromo and *m*-iodo substituents, have been reported. Not surprisingly, when we tried the standard metalation conditions (*s*-BuLi/TMEDA), a mixture of products were obtained, probably due to competing halogen−lithium exchange. Therefore, we carried out a brief study of bases which would be able to *ortho*-lithiate without affecting the halide at the *meta*-position. After several experiments, we observed that the deprotonation of **1c** exclusively occurs at the C-2 position by treatment with LDA at −78 °C. Subsequent quenching of the resulting aryllithium **2c** with the corresponding halogenated electrophile proceeded to give the expected carbamates **3f**−**h** in good yields (Table 1). Even iodocarbamate **1d** could be *ortho*-lithiated with LDA (1.1 equiv) under the same reaction conditions; however, complete metalation was not achieved, giving rise to lower yields of carbamates **3i**−**k**. Longer reaction times or an increase in the amount of base led to competitive lithiation at the 4-position. As before, when 1,2-dibromoethane was used as electrophile, competitive protonation of the 2-lithiated intermediates **2c** and **2d** resulted in slightly lower yields of **3g** and **3j**. Finally, application of the LDA methodology to the *ortho*-lithiation of carbamates **1a** and **1b** gave rise to carbamates **3a**−**e** with slightly lower yields than those obtained by the *s*-BuLi/TMEDA procedure.

Alkaline hydrolysis[19] of carbamates **3** with 10 equiv of NaOH in refluxing ethanol for 5−8 h gave 2,3-dihalophe-

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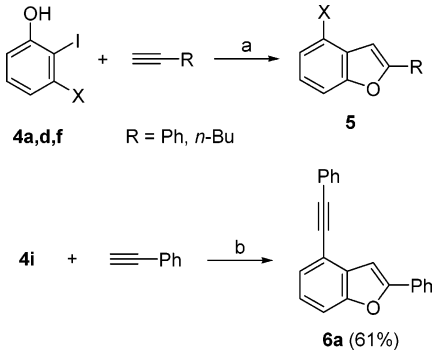
TABLE 2. Synthesis of 2,3-Dihalophenols 4 by Hydrolysis of Carbamates 3

entry	Product	X	E	*t* (h)	yield[a] (%)
1	**4a**	F	I	8	66
2	**4b**	F	Br	5.5	75
3	**4c**	F	Cl	6	45[b]
4	**4d**	Cl	I	8	88
5	**4e**	Cl	Br	6.5	82
6	**4f**	Br	I	5	89
7	**4g**	Br	Br	5	94
8	**4h**	Br	Cl	6.5	82
9	**4i**	I	I	8	82
10	**4j**	I	Br	5	70
11	**4k**	I	Cl	5.5	85

[a] Isolated yield based on the starting carbamate **3**. [b] Lower yield probably due to its high volatility.

SCHEME 3. Synthesis of 4-Halobenzo[*b*]furans 5 and 4-Alkynylbenzo[*b*]furan 6a[a]



[a] Reagents and conditions: (a) [$Pd(OAc)_2(PPh_3)_2$] (2 mol %), CuI (4 mol %), alkyne (1.2 equiv), DMF, piperidine (1 equiv), 60 °C, 5 h; (b) [$Pd(OAc)_2(PPh_3)_2$] (4 mol %), CuI (8 mol %), alkyne (2.4 equiv), DMF, piperidine (2 equiv), 60 °C, 5 h.

TABLE 3. Synthesis of 4-Halobenzo[*b*]furans 5

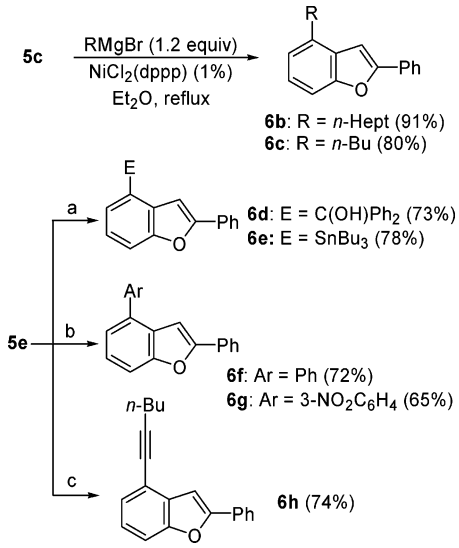
entry	product	X	R	yield[a] (%)
1	**5a**	F	Ph	79
2	**5b**	F	*n*-Bu	60
3	**5c**	Cl	Ph	61
4	**5d**	Cl	*n*-Bu	73
5	**5e**	Br	Ph	72
6	**5f**	Br	*n*-Bu	62

[a] Isolated yield based on the starting phenol **4**.

nols **4** in good yields (Scheme 2 and Table 2). It is interesting to note that all *O*-2,3-dihalophenylcarbamates **3** and several of the dihalophenols **4** have been prepared for the first time.

Once we had found an easy method for the preparation of 2,3-dihalophenols **4**, we decided to investigate the transformation of these compounds into the corresponding 4-halobenzo[*b*]furans. Thus, reaction of the 2-iodo-3-halophenol derivatives **4a**,**d** and **f** with two different terminal alkynes (phenylacetylene and 1-hexyne) under copper−palladium-catalyzed conditions for the tandem Sonogashira coupling/5-*endo-dig* cyclization[9a] gave the expected 4-halobenzo[*b*]furans **5** in moderate to good yields (Scheme 3 and Table 3). However, when 2,3-diiodophenol **4i** was treated with phenylacetylene under the same reaction conditions, 2-phenyl-4-phenylethynylbenzo[*b*]furan **6a** was exclusively obtained in low yield. Its formation arises from a subsequent Sonogashira coupling between the phenylacetylene and the 4-iodobenzo[*b*]furan intermediate. Decreasing the amount of the alkyne did not avoid the formation of **6a**, and only lower yields of this compound were obtained. The addition of an excess of the alkyne is required for obtaining **6a** in a useful yield (Scheme 3).

SCHEME 4. Synthesis of 4-Functionalized Benzo[*b*]furans 6b−h[a]



[a] Reagents and conditions: (a) (1) *t*-BuLi (2 equiv), Et_2O, −78 °C, 30 min; (2) E^+ [Ph_2CO, $SnBu_3Cl$, (1.1 equiv)], −78 to +20 °C (b) $ArB(OH)_2$ (1.5 equiv), [$Pd(PPh_3)_4$] (4 mol %), Na_2CO_3 (1.5 equiv), DME−H_2O (2.5:1), 80 °C, 48 h; (c) [$PdCl_2(PPh_3)_2$] (10 mol %), CuI (20 mol %), PPh_3 (10 mol %), 1-hexyne (3 equiv), Et_3N−DMF (2:1), 70 °C, 96 h.

Finally, we decided to check the usefulness of these 4-halobenzo[*b*]furans **5** as precursors of 4-functionalized benzo[*b*]furans.[20] For example, the 4-chloro derivative **5c** was subjected to nickel-catalyzed Kumada coupling[21] with Grignard reagents, affording 4-alkyl-substituted benzo[*b*]furans **6b**,**c** in good yields (Scheme 4). In another attempt, under treatment with *t*-BuLi in diethyl ether at −78 °C, the 4-bromo derivative **5e** underwent bromine−lithium exchange and the corresponding 4-lithium derivative further reacted with electrophiles (benzophenone or tributyltin chloride) at temperatures between −78 and +20 °C affording benzofuran derivatives **6d**,**e** in good yield (Scheme 4). Moreover, bromide **5e** proved to be a useful starting material for several Pd-catalyzed couplings. Thus, 4-arylbenzo[*b*]furans **6f**,**g** are readily accessible from 4-bromobenzo[*b*]furan **5e** by a Suzuki cross-coupling reaction with arylboronic acids under Pd catalysis following a procedure recently described for indole derivatives (Scheme 4).[22] Finally, though 4-alkynylbenzo[*b*]furans can be prepared in a straightway manner from 2,3-diiodophenol **4i** and 2 equiv of alkyne as indicated

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(20) Recently new benzo[*b*]furans functionalized at C4 and C7-positions have been synthesized and developed as blue-light emitting materials: Hwu, J. R.; Chuang, K.-S.; Chuang, S. H.; Tsay, S.-C. *Org. Lett.* **2005**, *7*, 1545−1548.

(21) Kumada, M. *Pure Appl. Chem.* **1980**, *52*, 669−679.

(22) Witulski, B.; Azcon, J. R.; Alayrac, C.; Arnautu, A.; Collot, V.; Rault, S. *Synthesis* **2005**, 771−780.

for **6a** in Scheme 3, it would be desirable that different alkynes could be coupled at the C4-position of the benzofuran. So, coupling of **5e** with 1-hexyne in the presence of $PdCl_2(PPh_3)_2$ and CuI as catalysts[22] afforded 4-alkynylbenzo[*b*]furan **6h** in good yield (Scheme 4).

In summary, we have presented a practical and efficient route to 4-halo and 4-functionalized benzo[*b*]furans from readily available starting materials, 3-halophenols, and reagents, based on a tandem Sonogashira coupling/5-*endo-dig* cyclization of 3-halo-2-iodophenols with alkynes. Moreover, we have also developed an easy preparation of 2,3-dihalophenols and current work in our laboratory is focused on extending the synthetic scope of these compounds.

Experimental Section

General Procedure for the Synthesis of *O*-3-Chloro- and *O*-3-Fluoro-2-halophenyl *N,N*-Diethylcarbamates 3a−e. Synthesis of 3-Chloro-2-iodophenyl *N,N*-Diethylcarbamate (3d; Table 1, Entry 4). To a well-stirred solution of *s*-BuLi (9.23 mL of a 1.3 M solution in cyclohexane/hexane, 12 mmol) and TMEDA (1.81 mL, 12 mmol) in dry THF (40 mL) kept at −78 °C under N_2 atmosphere was added carbamate **1b** (2.28 g, 10 mmol), and the mixture was stirred at −78 °C for 2 h. Then, iodine (3.05 g, 12 mmol) was added and stirring continued at low temperature for further 30 min. The reaction mixture was then allowed to warm to room temperature, quenched with aqueous $Na_2S_2O_3$, and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The crude was purified by column chromatography (eluent: hexane/EtOAc, 10/1) on silica gel to afford **3d** (3.04 g, 86%): white solid; mp 69−71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.25 (m, 2H), 7.06 (dd, J = 7.3, 2.2 Hz, 1H), 3.54 (q, J = 7.2 Hz, 2H), 3.41 (q, J = 7.2 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 153.4, 152.7, 139.5, 129.5, 126.1, 121.3, 96.8, 42.4, 42.1, 14.4, 13.3; EI-LRMS *m/z* 353 (M^+, 0.1), 100 (100); IR (KBr) 1707, 1415, 1237, 1153, 1041, 964 cm^{-1}. Anal. Calcd for $C_{11}H_{13}ClINO_2$: C, 37.37; H, 3.71; N, 3.96. Found: C, 37.49; H, 3.85; N, 3.89.

General Procedure for the Synthesis of *O*-3-Bromo- and *O*-3-Iodo-2-halophenyl *N,N*-Diethylcarbamates 3f−k. Synthesis of 3-Bromo-2-chlorophenyl *N,N*-Diethylcarbamate (3h; Table 1, Entry 8). *n*-BuLi (4.4 mL of a 2.5 M solution in hexane, 11 mmol) was added to a solution of *i*-Pr_2NH (1.54 mL, 11 mmol) in THF (30 mL) at 0 °C. After 30 min at 0 °C, the LDA solution was cooled at −78 °C and carbamate **1c** (2.72 g, 10 mmol) was added. The resulting solution was stirred for 30 min at −78 °C, and then hexachloroethane (2.84 g, 12 mmol) was added. After 30 min at low temperature, the reaction mixture was allowed to warm to room temperature and quenched with H_2O, and THF was evaporated under reduced pressure. The aqueous phase was extracted with EtOAc (3 × 25 mL), and the combined organic layers were washed with HCl 1 M, dried over anhyd Na_2SO_4, and evaporated under reduced pressure. The crude was purified by column chromatography (eluent: hexane/EtOAc, 5/1) on silica gel to afford **3h** (2.82 g, 92%): white solid; mp 40−42 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, J = 8, 1.7 Hz, 1H), 7.20 (dd, J = 8.0, 1.7 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 3.49 (q, J = 7.1 Hz, 2H), 3.40 (q, J = 7.1 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H);^{13}C NMR (100.6 MHz, $CDCl_3$) δ 152.9, 148.9, 130.5, 128.6, 127.8, 123.4, 123.2, 42.6, 42.2, 14.3, 13.4; EI-LRMS *m/z* 270 (M^+-Cl, 4), 100 (100); IR (KBr) 1716, 1415, 1243, 1156, 960 cm^{-1}. Anal. Calcd for $C_{11}H_{13}BrClNO_2$: C, 43.09; H, 4.27; N, 4.57. Found: C, 43.21; H, 4.24; N, 4.45.

General Procedure for the Deprotection of *O*-2,3-Dihalophenyl *N,N*-Diethylcarbamates 3. Synthesis of 3-Chloro-2-iodophenol (4d; Table 2, Entry 4). To a solution of the carbamate **3d** (1.76 g, 5 mmol) in EtOH (50 mL) was added a large excess of NaOH (2 g, 0.05 mol). The mixture was refluxed for 8 h (completion of the hydrolysis was monitored by GC−MS). After the mixture was cooled to room temperature, most of the EtOH was evaporated under reduced pressure, the residue was diluted with Et_2O, and the excess of NaOH was neutralized at 0 °C using a solution of 1 M HCl. The aqueous solution was extracted with Et_2O (3 × 20 mL), and the combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The crude was purified by column chromatography (eluent: hexane/EtOAc, 5/1) on silica gel to afford **4d** (1.12 g, 88%): brownish solid; mp 54−56 °C (lit.[11] mp 56 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (t, J = 8.2 Hz, 1H), 7.03 (dd, J = 8.2, 1.5 Hz, 1H), 6.88 (dd, J = 8.2, 1.5 Hz, 1H), 5.55 (br s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.6, 136.6, 130.3, 121.6, 111.9, 91.3; EI-LRMS *m/z* 256 (M^+ + 2, 31), 254 (M^+, 100); IR (KBr) 3275, 1568, 1435, 1272, 896, 767 cm^{-1}. Anal. Calcd for C_6H_4ClIO: C, 28.32; H, 1.58. Found: C, 28.30; H, 1.55.

General Procedure for the Synthesis of 4-Halobenzo[*b*]furans 5. Synthesis of 4-Bromo-2-phenylbenzo[*b*]furan (5e; Table 3, Entry 5). To a stirred solution of phenol **4f** (0.299 g, 1 mmol) and piperidine (0.085 g, 1 mmol) in DMF (1 mL) under N_2 atmosphere were added phenylacetylene (0.123 g, 1.2 mmol), $Pd(OAc)_2(PPh_3)_2$ (0.015 g, 0.02 mmol), and CuI (0.008 g, 0.04 mmol). The mixture was heated at 60 °C for 5 h, and then it was cooled to room temperature and diluted with H_2O (15 mL). The aqueous solution was extracted with Et_2O (3 × 20 mL), and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The crude was purified by column chromatography (eluent: hexane) on silica gel to afford **5e** (0.197 g, 72%): white solid; mp 66−68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91−7.87 (m, 2H), 7.58−7.45 (m, 3H), 7.44−7.38 (m, 2H), 7.16 (t, J = 8.1 Hz, 1H), 7.07 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.5, 154.5, 130.8, 129.9, 129.1, 128.9, 126.0, 125.1, 113.9, 110.3, 102.3, 101.4; EI-LRMS *m/z* 274 (M^+ + 2, 96), 272 (M^+, 100); IR (KBr) 1423, 1268, 1248, 1160, 1022, 908, 751, 685 cm^{-1}; HRMS calcd for $C_{14}H_9BrO$ 271.9837, found 271.9878. Anal. Calcd for $C_{14}H_9BrO$: C, 61.57; H, 3.32. Found: C, 61.49; H, 3.28.

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Supporting Information Available: Typical experimental procedures and spectroscopic details for all compounds not listed in the text and a copy of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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