HETEROCYCLES, Vol. 94, No. 9, 2017, pp. 1707 - 1717. © 2017 The Japan Institute of Heterocyclic Chemistry
Received, 16th June, 2017, Accepted, 20th July, 2017, Published online, 28th July, 2017
DOI: 10.3987/COM-17-13767

# AN EFFICIENT SYNTHESIS OF 1-ARYLBENZO[*c*]THIOPHENES *VIA* THE REACTION OF 2-(CHLOROMETHYL)PHENYLLITHIUMS WITH AROMATIC ALDEHYDES

**Kazuhiro Kobayashi,* Yuuya Honda, and Yuuho Shigemura**

Applied Chemistry Field, Chemistry and Biotechnology Course, Department of Engineering, Graduate School of Sustainability Science, Tottori University, 4-101 Koyama-minami, Tottori 680-8552, Japan; E-mail: kkoba@chem.tottori-u.ac.jp

**Abstract** – A simple and efficient sequence for the preparation of 1-arylbenzo[*c*]thiophenes has been developed. Thus, 2-(chloromethyl)-phenyllithiums, generated by treating 2-(chloromethyl)phenyl bromides with butyllithium, are allowed to react with aromatic aldehydes to afford the corresponding diarylmethanol derivatives. These alcohols are oxidized with pyridinium chlorochromate (PCC) to give aryl[(2-chloromethyl)phenyl]-methanones, of which treatment with sodium hydrogensulfide gives 1-aryl-1,3-dihydrobenzo[*c*]thiophen-1-ols. Dehydration of these crude alcohols to the desired products can be accomplished by the treatment with a catalytic amount of *p*-toluenesulfonic acid.

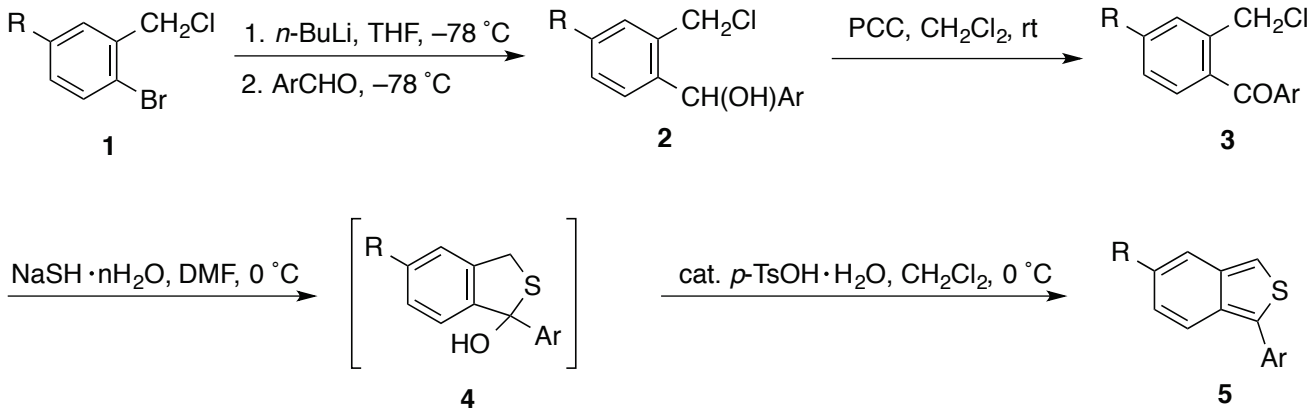
## INTRODUCTION

Compounds with the benzo[*c*]thiophene core are an important class of molecules because of their interesting biological,[1] electronic,[2] and photophysical properties.[3] Although reactions of 1,2-diacylbenzenes with $P_4S_{10}$[4] or Lawesson's reagent[5] have emerged as the method to access 1,3-disubstituted benzo[*c*]thiophenes, development of new methods continues to be of synthetic interest. Therefore, several efficient methodologies for the synthesis of benzo[*c*]thiophene derivatives have recently been developed,[6] such as $P_4S_{10}$ and $Na_2S$-mediated annulation 3-(2-formylphenyl)acrylate,[6b] gold superacid-catalyzed migratory cycloisomerization of a diallyl dithioacetal[6c] or rhodium(III)-catalyzed dehydrogenative annulation of thiophene-2-carboxamides with two equivalents of alkynes.[6d] We were interested in developing a simple synthetic methods of benzo[*c*]thiophene derivatives and wish to report the results our investigation which offer a new and efficient approach to 1-arylbenzo[*c*]thiophenes (**5**)

using an operational simple four-step sequence commencing from readily available 2-(chloromethyl)phenyl bromides (**1**).

## RESULTS AND DISCUSSION

Transformation of **1** into **5** was conducted as illustrated in Scheme 1. Compounds (**1**) were easily prepared from the respective commercially available starting materials following the literature procedures.[7-9] The reaction of 2-(chloromethyl)phenyllithiums, generated by the bromine/lithium exchange between **1** and butyllithium in THF at –78 ˚C,[10] with aromatic aldehydes is the first step of the present sequence. It afforded aryl[2-(chloromethyl)phenyl]methanols (**2**) in relatively good yields as compiled in Table 1. Oxidation of **2** with pyridinium chlorochromate (PCC) in dichloromethane at room temperature gave aryl[2-(chloromethyl)phenyl]methanones (**3**) in generally good yields, which reacted with sodium hydrogensulfide smoothly in DMF at 0 ˚C to afford 1-aryl-1,3-dihydrobenzo[*c*]thiophen-1-ols (**4**). These compounds proved to exist as mixtures with the respective tautomeric sulfanyl ketone derivatives on the basis of $^1$H NMR spectroscopy of the crude reaction mixtures and were used in the next step without purification. Dehydration of **4** by the treatment with a catalytic amount of *p*-toluenesulfonic acid monohydrate in dichloromethane at 0 ˚C proceeded immediately to provide, after isolation by column chromatography on silica gel or recrystallization, the desired products (**5**).




**Scheme 1**

The results are summarized in Table 1 as well. The yields obtained by using precursors (**3a**-**e**), derived from 2-(chloromethyl)phenyl bromide (**1a**) and five aromatic aldehydes, were dependent upon substituent(s) on the 1-aryl groups. Substitution of electron-withdrawing group(s) increased the yields of the products (Entries 2, 3, and 5). Conversely, substitution of an electron-donating methoxy group gave a disappointing result. Under the standard reaction and isolation conditions, [2-(chloromethyl)phenyl](4-methoxyphenyl)methanone (**3d**) did not give the desired 1-(4-methoxyphenyl)benzo[*c*]thiophene (**5d**) in a

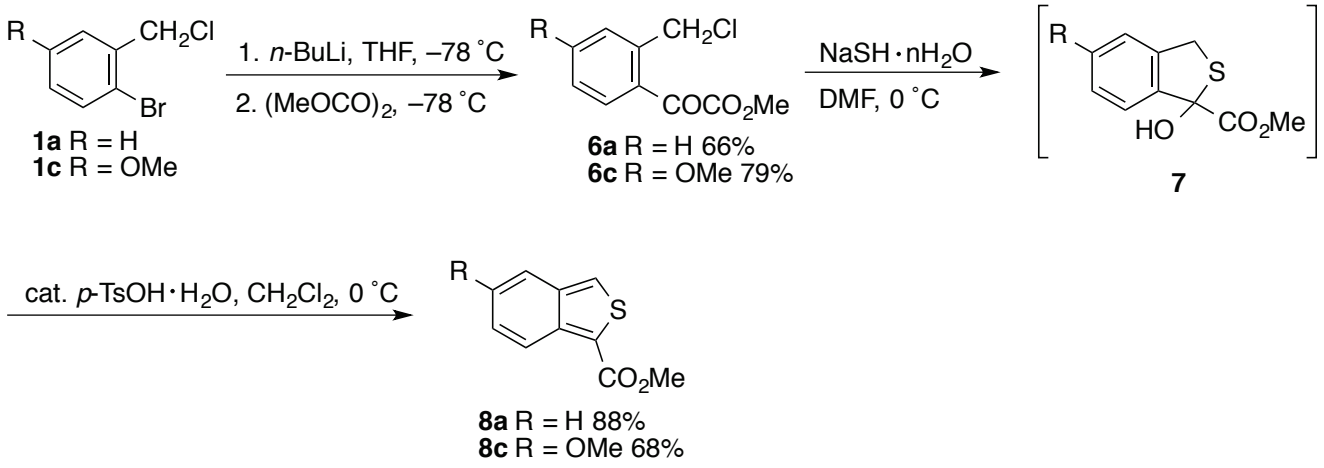
satisfactorily pure form for spectral analyses (Entry 4). TLC analyses during the reaction revealed the production of **5d** in a respectable extent. However, the product appeared to decompose during workup and/or purification (column chromatography on silica gel) probably due to its instability to air and/or acid. The products carrying an electro-withdrawing chloro substituent at the 5-position (**5f**-**h**) were obtained in moderate to fair yields (Entries 6-8). Conversely, substitution with an electron-donating methoxy group led to the isolation of the desired products (**5i**) and (**5j**) in lower yields (Entries 9 and 10).

**Table 1.** Preparation of 1-arylbenzo[*c*]thiophenes (**5**)

| Entry | **1** | R | Ar in ArCHO | **2** | Yield/%[a] | **3** | Yield/%[a] | **5** | Yield/%[a] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | H | Ph | **2a** | 73 | **3a** | 89 | **5a** | 45 |
| 2 | **1a** | H | 3-$ClC_6H_4$ | **2b** | 56 | **3b** | 72 | **5b** | 54 |
| 3 | **1a** | H | 3,4-$Cl_2C_6H_3$ | **2c** | 75 | **3c** | 72 | **5c** | 63 |
| 4 | **1a** | H | 4-$MeOC_6H_4$ | **2d** | 76 | **3d** | 83 | **5d** | b |
| 5 | **1a** | H | 4-$NCC_6H_4$ | **2e** | 68 | **3e** | 67 | **5e** | 71 |
| 6 | **1b** | Cl | Ph | **2f** | 73 | **3f** | 80 | **5f** | 52 |
| 7 | **1b** | Cl | 3,4-$Cl_2C_6H_3$ | **2g** | 60 | **3g** | 82 | **5g** | 67 |
| 8 | **1b** | Cl | 4-$NCC_6H_4$ | **2h** | 70 | **3h** | 75 | **5h** | 74 |
| 9 | **1c** | OMe | Ph | **2i** | 72 | **3i** | 82 | **5i** | 15 |
| 10 | **1c** | OMe | 4-$NCC_6H_4$ | **2j** | 68 | **3j** | 83 | **5j** | 37 |

[a] Yields of isolated products. [b] Too unstable on $SiO_2$ to be isolated.

Subsequently, the preparation of benzo[*c*]thiophene-1-carboxylates (**8**) was attempted. We are pleased to find that 2-(chloromethyl)phenyllithiums reacted successfully with dimethyl oxalate to afford methyl [2-(chloromethyl)benzoyl]formates **6** in fair-to-good yields. Treatment of these α-keto esters with sodium hydrogensulfide to give the corresponding 1,3-dihydrobenzo[c]thiophen-1-ol derivatives (**7**), which underwent smooth dehydration under the same condition as described for the preparation of **5** to furnish **8** in good overall yields from **6**. These results are illustrated in Scheme 2.




**Scheme 2**

In conclusion, we have developed an expedient synthetic route to 1-substituted benzo[*c*]thiophene derivatives utilizing the reaction of *o*-(chloromethyl)phenyllithiums with aromatic aldehydes or dimethyl oxalate. Since the present procedure can be carried out under mild conditions with readily available starting materials, it may find some value in organic synthesis. Studies on the utilization of these lithium compounds for the preparation of other useful heterocycles are under investigation in our laboratory.

## EXPERIMENTAL

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were recorded with a Perkin–Elmer Spectrum 65 FTIR spectrophotometer. $^{1}$H NMR and $^{13}$C NMR spectra were recorded in $CDCl_3$ using TMS as an internal reference with a Bruker Biospin AVANCE II 600 spectrometer operating at 600 MHz and 150 MHz, respectively, or a JEOL ECP500 FT NMR spectrometer operating at 500 and 125 MHz, respectively. High-resolution MS spectra were measured by a JEOL JMS-T100GCV (EI or FI, TOF; 70 eV or 2100 V, respectively) or a Thermo Scientific Exactive (ESI, positive) spectrometer. Elemental analyses were performed with an Elementar Vario EL II instrument. TLC was carried out on Merck Kieselgel 60 $PF_{254}$. Column chromatography was performed using WAKO GEL C-200E. All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

**Starting Materials.** 1-Bromo-2-(chloromethyl)benzene (**1a**),[7] (2-bromo-5-chlorophenyl)methanol,[8] and (2-bromo-5-methoxyphenyl)methanol[9] were prepared according to the reported procedures. Butyllithium was supplied by Asia Lithium Corporation. All other chemicals used in this study were commercially available.

**1-Bromo-2-(chloromethyl)benzenes (1b)[9] and (1c).**[11] These compounds were prepared from (2-bromo-5-chlorophenyl)methanol[8] and (2-bromo-5-methoxyphenyl)methanol,[12] respectively, according to the procedure described for the preparation of **1a** in 69% and 64% yields.

**Typical Procedure for the Preparation of Aryl[(2-chloromethyl)phenyl]methanols (2). [2-(Chloromethyl)phenyl]phenylmethanol (2a).** To a stirred solution of **1a** (0.37 g, 1.8 mmol) in THF (10 mL) at –78 ˚C was added *n*-BuLi (1.6 M in hexane, 1.8 mmol) dropwise. After 15 min, PhCHO (0.19 g, 1.8 mmol) was added and stirring was continued for 30 min at the same temperature before addition of saturated aqueous $NH_4Cl$ (20 mL). The mixture was warmed to room temperature and extracted with AcOEt (3 × 15 mL). The combined extracts were washed with brine (15 mL), dried ($Na_2SO_4$), and concentrated by evaporation. The residue was purified by column chromatography on $SiO_2$ (AcOEt/hexane 1:7) to afford **2a** (0.30 g, 73%); a white solid; mp 65–66 ˚C (hexane/$CH_2Cl_2$); IR (KBr) 3349 cm$^{-1}$; $^{1}$H NMR (500 MHz) δ 2.37 (d, *J* = 4.0 Hz, 1H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 6.23 (d, *J* = 4.0 Hz, 1H), 7.27–7.37 (m, 8H), 7.47 (d, *J* = 7.4 Hz, 1H); $^{13}$C NMR (125 MHz) δ 43.9,

72.5, 126.8, 127.77, 127.83, 128.2, 128.6, 129.2, 130.6, 134.9, 141.9, 142.5. Anal. Calcd for $C_{14}H_{13}ClO$: C, 72.26; H, 5.63. Found: C, 72.16; H, 5.69.

**[2-(Chloromethyl)phenyl](3-chlorophenyl)methanol (2b):** a white solid; mp 48–51 °C (hexane/$CH_2Cl_2$); IR (KBr) 3205 $cm^{-1}$; $^1H$ NMR (500 MHz) δ 2.44 (br s, 1H), 4.59 (d, $J$ = 11.5 Hz, 1H), 4.67 (d, $J$ = 11.5 Hz, 1H), 6.20 (s, 1H), 7.22–7.39 (m, 8H); $^{13}C$ NMR (125 MHz,) δ 43.8, 71.8, 124.9, 126.8, 127.8, 128.1, 128.6, 129.4, 129.8, 130.8, 134.5, 135.0, 141.4, 144.6. Anal. Calcd for $C_{14}H_{12}Cl_2O$: C, 62.94; H, 4.53. Found: C, 63.12; H, 3.68.

**[2(-Chloromethyl)phenyl](3,4-dichlorophenyl)methanol (2c):** a colorless oil; $R_f$ 0.54 (AcOEt/hexane 1:3); IR (neat) 3314 $cm^{-1}$; $^1H$ NMR (500 MHz) δ 2.51 (d, $J$ = 4.0 Hz, 1H), 4.60 (d, $J$ = 12.0 Hz, 1H), 4.68 (d, $J$ = 12.0 Hz, 1H), 6.17 (d, $J$ = 4.0 Hz, 1H), 7.18 (dd, $J$ = 8.0, 1.7 Hz, 1H), 7.31–7.41 (m, 5H), 7.49 (d, $J$ = 1.7 Hz, 1H); $^{13}C$ NMR (125 MHz) δ 43.8, 71.3, 126.1, 128.2, 128.6, 128.8, 129.5, 130.4, 130.9, 131.6, 132.6, 135.0, 141.1, 142.8. HR-MS (EI). Calcd for $C_{14}H_{11}Cl_3O$ (M): 299.9875. Found: $m/z$ 299.9880.

**[2-(Chloromethyl)phenyl](4-methoxyphenyl)methanol (2d):** a colorless oil; $R_f$ 0.33 (AcOEt/hexane 1:5); IR (neat) 3403, 1611 $cm^{-1}$; $^1H$ NMR (500 MHz) δ 2.32 (d, $J$ = 4.0 Hz, 1H), 3.79 (s, 3H), 4.54 (d, $J$ = 11.5 Hz, 1H), 4.59 (d, $J$ = 11.5 Hz, 1H), 6.19 (d, $J$ = 4.0 Hz, 1H), 6.86 (d, $J$ = 8.6 Hz, 2H), 7.25 (d, $J$ = 8.6 Hz, 2H), 7.30 (td, $J$ = 7.4, 1.1 Hz, 1H), 7.31–7.39 (m, 2H), 7.54 (d, $J$ = 8.4 Hz, 1H); $^{13}C$ NMR (125 MHz) δ 43.9, 55.3, 72.1, 113.9, 127.4, 128.0, 128.2, 129.1, 130.6, 134.6, 134.8, 142.1, 159.2. HR-MS (FI). Calcd for $C_{15}H_{15}ClO_2$ (M): 262.0761. Found: $m/z$ 262.0760.

**4-{[2-(Chloromethyl)phenyl](hydroxy)methyl}benzonitrile (2e):** a yellow oil; $R_f$ 0.18 (AcOEt/hexane 1:5); IR (neat) 3439, 2230, 1608 $cm^{-1}$; $^1H$ NMR (500 MHz) δ 2.68 (d, $J$ = 2.9 Hz, 1H), 4.62 (d, $J$ = 11.5 Hz, 1H), 4.72 (d, $J$ = 11.5 Hz, 1H), 6.26 (s, 1H), 7.26 (dd, $J$ = 6.9, 2.9 Hz, 1H), 7.32–7.37 (m, 2H), 7.40 (dd, $J$ = 6.9, 2.9 Hz, 1H), 7.51 (d, $J$ = 8.0 Hz, 2H), 7.63 (d, $J$ = 8.0 Hz, 2H); $^{13}C$ NMR (125 MHz) δ 43.7, 71.7, 111.2, 118.7, 127.3, 128.5, 128.9, 129.5, 131.0, 132.2, 135.2, 141.1, 147.9. HR-MS (EI). Calcd for $C_{15}H_{12}ClNO$ (M): 257.0607. Found: $m/z$ 257.0601.

**[4-Chloro-2-(chloromethyl)phenyl]phenylmethanol (2f):** a colorless oil; $R_f$ 0.28 (AcOEt/hexane 1:8); IR (neat) 3355 $cm^{-1}$; $^1H$ NMR (500 MHz) δ 2.35 (s, 1H), 4.50 (d, $J$ = 12.0 Hz, 1H), 4.55 (d, $J$ = 12.0 Hz, 1H), 6.17 (s, 1H), 7.29–7.37 (m, 7H), 7.45 (d, $J$ = 8.0 Hz, 1H); $^{13}C$ NMR (125 MHz) δ 43.0, 72.1, 126.8, 128.1, 128.7, 129.0, 129.2, 130.4, 133.7, 136.5, 140.2, 142.0. HR-MS (EI). Calcd for $C_{14}H_{12}Cl_2O$ (M): 266.0265. Found: $m/z$ 266.0278.

**[4-Chloro-2-(chloromethyl)phenyl](3,4-dichlorophenyl)methanol (2g):** a pale-yellow oil; $R_f$ 0.29 (AcOEt/hexane 1:10); IR (neat) 3324 $cm^{-1}$; $^1H$ NMR (600 MHz) δ 2.42 (d, $J$ = 3.8 Hz, 1H), 4.52 (d, $J$ = 10.9 Hz, 1H), 4.61 (d, $J$ = 10.9 Hz, 1H), 6.13 (d, $J$ = 3.8 Hz, 1H), 7.16 (ddd, $J$ = 8.3, 2.2, 1.1 Hz, 1H), 7.31 (d, $J$ = 8.3 Hz, 1H), 7.34 (dd, $J$ = 8.3, 2.0 Hz, 1H), 7.40 (d, $J$ = 2.0 Hz, 1H), 7.42 (d, $J$ = 8.3 Hz, 1H),

7.46 (d, *J* = 2.2 Hz, 1H); $^{13}$C NMR (150 MHz) δ 42.9, 71.0, 126.0, 128.7, 129.5, 129.7, 130.6, 130.7, 132.0, 132.9, 134.4, 136.8, 139.5, 142.3. HR-MS (EI). Calcd for $C_{14}H_{10}Cl_4O$ (M): 333.9486. Found: *m*/*z* 333.9476.

**4-{[4-Chloro-2-(chloromethyl)phenyl](hydroxy)methyl}benzonitrile (2h):** a pale-yellow oil; $R_f$ 0.37 ($Et_2O$/hexane 1:1); IR (neat) 3428, 2228, 1610 cm$^{-1}$; $^1$H NMR (600 MHz) δ 2.57 (d, *J* = 3.4 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 6.21 (d, *J* = 3.4 Hz, 1H), 7.24 (d, *J* = 8.3 Hz, 1H), 7.32 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.41 (d, *J* = 2.2 Hz, 1H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.65 (d, *J* = 8.1 Hz, 2H); $^{13}$C NMR (150 MHz) δ 42.8, 71.4, 111.7, 118.6, 127.3, 129.5, 130.0, 130.8, 132.4, 134.6, 137.0, 139.5, 147.3. HR-MS (FI). Calcd for $C_{15}H_{11}Cl_2NO$ (M): 291.0218. Found: *m*/*z* 291.0232.

**[2-(Chloromethyl)-4-methoxyphenyl]phenylmethanol (2i):** a colorless oil; $R_f$ 0.29 (AcOEt/hexane 1:5); IR (neat) 3402, 1610 cm$^{-1}$; $^1$H NMR (600 MHz) δ 2.33 (d, *J* = 2.9 Hz, 1H), 3.80 (s, 3H), 4.55 (d, *J* = 11.5 Hz, 1H), 4.64 (d, *J* = 11.5 Hz, 1H), 6.16 (d, *J* = 2.9 Hz, 1H), 6.85 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.92 (d, *J* = 2.2 Hz, 1H), 7.28–7.35 (m, 6H); $^{13}$C NMR (150 MHz) δ 43.9, 55.3, 72.1, 114.2, 116.0, 126.6, 127.6, 128.5, 129.5, 134.1, 136.3, 142.9, 159.1. HR-MS (EI). Calcd for $C_{15}H_{15}ClO_2$ (M): 262.0761. Found: *m*/*z* 262.0753.

**4-{[2-(Chloromethyl)-4-methoxyphenyl](hydroxy)methyl}benzonitrile (2j):** a colorless oil; $R_f$ 0.24 (AcOEt/hexane 1:3); IR (neat) 3458, 2228, 1609 cm$^{-1}$; $^1$H NMR (500 MHz) δ 2.53 (d, *J* = 3.4 Hz, 1H), 3.81 (s, 3H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.70 (d, *J* = 12.0 Hz, 1H), 6.19 (d, *J* = 3.4 Hz, 1H), 6.85 (dd, *J* = 8.67, 2.3 Hz, 1H), 6.93 (d, *J* = 2.3 Hz, 1H), 7.12 (d, *J* = 8.6 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H); $^{13}$C NMR (125 MHz) δ 43.7, 55.4, 71.4, 111.1, 114.6, 116.2, 118.8, 127.1, 130.1, 132.2, 133.2, 136.7, 148.3, 159.6. MR-MS (EI). Calcd for $C_{16}H_{14}ClNO_2$ (M): 287.0713. Found: *m*/*z* 287.0706.

**Typical Procedure for the Preparation of Aryl[2-(chloromethyl)phenyl]methanones (3). [2-(Chloromethyl)phenyl]phenylmethanone (3a).**[13] A mixture of **2a** (0.19 g, 0.80 mmol) and PCC (0.34 g, 1.6 mmol) in $CH_2Cl_2$ (10 mL) containing Celite 545 (0.8 g) was stirred at rt for 10 min. After the mixture was filtered under reduced pressure, the filtrate was concentrated by evaporation and subjected to column chromatography on $SiO_2$ to give **3a** (0.16 g, 89%); a yellow oil; $R_f$ 0.39 (AcOEt/hexane 1:10); IR (neat) 1663 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 4.79 (s, 2H), 7.36–7.42 (m, 2H), 7.46–7.53 (m, 3H), 7.57–7.63 (m, 2H), 7.83 (dd, *J* = 7.4, 1.1 Hz, 2H).

**[2-(Chloromethyl)phenyl](3-chlorophenyl)methanone (3b):** a yellow oil; $R_f$ 0.53 (AcOEt/hexane 1:10); IR (neat) 1668 cm$^{-1}$; $^1$H NMR (500 MHz) δ 4.78 (s, 2H), 7.36 (d, *J* = 7.4 Hz, 1H), 7.39–7.43 (m, 2H), 7.52 (td, *J* = 7.4, 1.1 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.68 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.82 (s, 1H); $^{13}$C NMR (125 MHz) δ 43.2, 127.9, 128.5, 129.5, 129.8, 130.1, 130.7, 131.2, 133.3, 134.8, 137.3 (2C), 139.0, 196.0. HR-MS (FI). Calcd for $C_{14}H_{10}Cl_2O$ (M): 264.0109. Found: *m*/*z* 264.0098.

**[2-(Chloromethyl)phenyl](3,4-dichlorophenyl)methanone (3c):** a white solid; mp 68–70 ˚C (hexane); IR (KBr) 1668 $cm^{-1}$; $^1H$ NMR (500 MHz) δ 4.77 (s, 2H), 7.34 (d, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.52–7.58 (m, 3H), 7.64 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.92 (d, *J* = 1.7 Hz, 1H); $^{13}C$ NMR (125 MHz) δ 43.2, 128.0, 129.3, 129.4, 130.6, 130.8, 131.4, 132.0, 133.2, 136.98, 137.04, 137.4, 138.1, 195.0. Anal. Calcd for $C_{14}H_9Cl_3O$: C, 56.13; H, 3.03. Found: C, 55.99; H, 3.09.

**[2-(Chloromethyl)phenyl](4-methoxyphenyl)methanone (3d):** a white solid; mp 87–89 ˚C (hexane/$CH_2Cl_2$); IR (KBr) 1647 $cm^{-1}$; $^1H$ NMR (500 MHz) δ 3.88 (s, 3H), 4.74 (s, 2H), 6.94 (d, *J* = 9.2 Hz, 2H), 7.34–7.39 (m, 2H), 7.49 (td, *J* = 7.4, 1.1 Hz, 1H), 7.56 (d, *J* = 7.4 Hz, 1H), 7.82 (d, *J* = 9.2 Hz, 2H); $^{13}C$ NMR (125 MHz) δ 43.3, 55.5, 113.7, 127.7, 128.9, 130.2, 130.4, 130.5, 132.8, 136.6, 138.8, 163.9, 196.0. Anal. Calcd for $C_{15}H_{13}ClO_2$: C, 69.10; H, 5.03. Found: C, 68.93; H, 5.12.

**4-[2-(Chloromethyl)benzoyl]benzonitrile (3e):** a white solid; mp 104–105 ˚C (hexane/$CH_2Cl_2$); IR (KBr) 2231, 1668, 1605 $cm^{-1}$; $^1H$ NMR (500 MHz) δ 4.80 (s, 2H), 7.33 (d, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.59 (d, *J* = 7.4 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.91 (d, *J* = 8.0 Hz, 2H); $^{13}C$ NMR (125 MHz) δ 43.2, 116.5, 117.9, 128.0, 129.6, 130.6, 130.9, 131.6, 132.3, 136.8, 137.9, 140.7, 195.9. Anal. Calcd for $C_{15}H_{10}ClNO$: C, 70.46; H, 3.94; N, 5.48. Found: C, 70.08; H, 3.97; N, 5.46.

**[4-Chloro-2-(chloromethyl)phenyl]phenylmethanone (3f):** a colorless oil; $R_f$ 0.47 (AcOEt/hexane 1:10); IR (neat) 1664 $cm^{-1}$; $^1H$ NMR (500 MHz) δ 4.74 (s, 2H), 7.33 (d, *J* = 8.6 Hz, 1H), 7.36 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.49 (dd, *J* = 8.0, 7.4 Hz, 2H), 7.60–7.64 (m, 2H), 7.80 (dd, *J* = 8.0, 1.1 Hz, 2H); $^{13}C$ NMR (125 MHz) δ 42.6, 127.8, 128.6, 130.3, 130.6, 130.9, 133.6, 136.2, 136.9, 137.1, 139.2, 196.4. HR-MS (EI). Calcd for $C_{14}H_{10}Cl_2O$ (M): 264.0109. Found: *m*/*z* 264.0111.

**[4-Chloro-2-(chloromethyl)phenyl](3,4-dichlorophenyl)methanone (3g):** a colorless oil; $R_f$ 0.38 (AcOEt/hexane 1:5); IR (neat) 1668 $cm^{-1}$; $^1H$ NMR (600 MHz) δ 4.73 (s, 2H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.39 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.57 (d, *J* = 8.3 Hz, 1H), 7.60 (d, *J* = 2.0 Hz, 1H), 7.61 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.89 (d, *J* = 2.0 Hz, 1H); $^{13}C$ NMR (150 MHz) δ 42.5, 128.1, 129.2, 130.7, 131.0, 131.9, 133.4, 135.2, 136.7, 137.5 (2C), 138.4, 139.5, 194.0. HR-MS (FI). Calcd for $C_{14}H_8Cl_4O$ (M): 331.9329. Found: *m*/*z* 331.9328.

**4-[4-Chloro-2-(chloromethyl)benzoyl]benzonitrile (3h):** a white solid; mp 129–131 ˚C (hexane/$CH_2Cl_2$); IR (KBr) 2228, 1664, 1604 $cm^{-1}$; $^1H$ NMR (600 MHz) δ 4.69 (s, 2H), 7.20 (d, *J* = 8.2 Hz, 1H), 7.32 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.54 (d, *J* = 2.0 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.81 (d, *J* = 8.4 Hz, 2H); $^{13}C$ NMR (150 MHz) δ 42.5, 116.8, 117.8, 128.1, 130.5, 131.0, 131.1, 132.4, 134.9, 137.9, 139.9, 140.4, 194.9. Anal. Calcd for $C_{15}H_9Cl_2NO$: C, 62.10; H, 3.13; N, 4.83. Found: C, 62.09; H, 3.31; N, 4.66.

**[2-(Chloromethyl)-4-methoxyphenyl]phenylmethanone (3i):** a colorless oil; $R_f$ 0.37 (AcOEt/hexane 1:10); IR (neat) 1659, 1603 $cm^{-1}$; $^1H$ NMR (600 MHz) δ 3.87 (s, 3H), 4.85 (s, 2H), 6.83 (dd, *J* = 8.6, 2.3

Hz, 1H), 7.13 (d, *J* = 2.3 Hz, 1H), 7.36 (d, *J* = 8.6 Hz, 1H), 7.44 (dd, *J* = 8.0, 7.4 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.76 (dd, *J* = 8.0, 1.1 Hz, 2H); $^{13}$C NMR (150 MHz) δ 43.7, 55.5, 112.3, 116.3, 128.3, 129.9, 130.2, 132.79, 132.83, 138.3, 140.3, 161.6, 196.8. HR-MS (ESI). Calcd for $C_{15}H_{14}ClO_2$ (M+H): 261.0683. Found: *m*/*z* 261.0677.

**4-[2-(Chloromethyl)-4-methoxybenzoyl]benzonitrile (3j):** a colorless needles; mp 131–133 ˚C (hexane); IR (KBr) 2234, 1654, 1607 cm$^{-1}$; $^1$H NMR (500 MHz) δ 3.91 (s, 3H), 4.89 (s, 2H), 6.86 (d, *J* = 8.6 Hz, 1H), 7.16 (s, 1H), 7.33 (d, *J* = 8.6 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.86 (d, *J* = 8.0 Hz, 2H); $^{13}$C NMR (125 MHz) δ 43.7, 55.6, 112.4, 115.9, 116.9, 118.0, 128.4, 130.4, 132.2, 133.2, 141.0, 141.9, 162.3, 195.0. Anal. Calcd for $C_{16}H_{12}ClNO_2$: C, 67.26; H, 4.23; N, 4.90. Found: C, 67.09; H, 4.33; N, 4.84.

**Typical Procedure for the Preparation of Benzo[*c*]thiophenes (5) and (8). 1-Phenylbenzo[*c*]thiophene (5a).**[14] To a stirred solution of NaSH·n$H_2O$ (70% as NaSH; 33 mg, 0.42 mmol) in DMF (2 mL) at 0 ˚C was added a solution of **3a** (96 mg, 0.42 mmol) in DMF (2 mL) dropwise. After consumption of **3a** had been confirmed by TLC analyses on $SiO_2$ (about 3 h), the mixture was diluted by adding AcOEt (10 mL) and was treated with saturated aqueous $NH_4Cl$ (15 mL). The layers were separated and the aqueous layer was extracted with AcOEt (2 × 10 mL). The combined organic layers were washed with $H_2O$ (2 × 10 mL) and brine (10 mL), dried ($Na_2SO_4$), and concentrated by evaporation. The residue was dissolved in $CH_2Cl_2$ (3 mL) and *p*-TsOH·$H_2O$ (7.9 mg, 0.042 mmol) was added at 0 ˚C under stirring. Stirring was continue for 15 min before the mixture was diluted with $CH_2Cl_2$ (20 mL) and adding anhydrous $K_2CO_3$ (0.20 g). After 15 min stirring, the mixture was filtered by reduced pressure and the filtrate was concentrated by evaporation. The residue was purified by column chromatography on $SiO_2$ to give **5a** (40 mg, 45%); a reddish-yellow oil; $R_f$ 0.79 ($Et_2O$/hexane 1:5); IR (neat) 1689, 1661 cm$^{-1}$; $^1$H NMR (500 MHz) δ 6.96–6.99 (m, 2H), 7.27 (t, *J* = 7.4 Hz, 1H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.48 (dd, *J* = 9.2, 2.2 Hz, 1H), 7.55 (s, 1H), 7.57 (d, *J* = 7.4 Hz, 2H), 7.72 (d, *J* = 9.2 Hz, 1H); $^{13}$C NMR (150 MHz) δ 115.8, 120.7, 122.4, 122.5, 123.9, 127.4, 128.9, 129.2, 133.8, 134.5, 134.9, 139.5. HR-MS (EI). Calcd for $C_{14}H_{10}S$ (M): 210.0503. Found: *m*/*z* 210.0502.

**1-(3-Chlorophenyl)benzo[*c*]thiophene (5b):** a yellow oil; $R_f$ 0.83 (AcOEt/hexane 1:10); IR (neat) 1696, 1668 cm$^{-1}$; $^1$H NMR (500 MHz) δ 7.06–7.12 (m, 2H), 7.33 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.40 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.65 (dd, *J* = 2.3, 1.7 Hz, 1H), 7.69 (s, 1H), 7.79 (d, *J* = 9.2 Hz, 1H); $^{13}$C NMR (125 MHz) δ 116.7, 120.4, 122.5, 123.7, 124.5, 127.26, 127.33, 128.9, 130.2, 132.9, 134.1, 134.8, 136.3, 139.6. HR-MS (EI). Calcd for $C_{14}H_9ClS$ (M): 244.0113. Found: *m*/*z* 244.0111.

**1-(3,4-Dichlorophenyl)benzo[*c*]thiophene (5c):** a yellow oil; $R_f$ 0.76 (AcOEt/hexane 1:10); IR (neat) 1696, 1671 cm$^{-1}$; $^1$H NMR (500 MHz) δ 6.99–7.06 (m, 2H), 7.39 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.45 (d, *J* =

8.0 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 1H), 7.62 (s, 1H), 7.65–7.67 (m, 2H); $^{13}$C NMR (125 MHz) δ 117.1, 120.1, 122.6, 123.8, 124.8, 128.2, 130.5, 130.9, 131.3, 131.6, 133.0, 134.3, 134.5, 139.6. HR-MS (EI). Calcd for $C_{14}H_8Cl_2S$ (M): 277.9724. Found: *m*/*z* 277.9713.

**4-(Benzo[*c*]thiophen-1-yl)benzonitrile (5e):** a yellow solid; mp 76–79 °C (hexane/$CH_2Cl_2$); IR (KBr) 2222, 1687, 1662 cm$^{-1}$; $^1$H NMR (500 MHz) δ 7.11 (t, *J* = 8.6, 6.9 Hz, 1H), 7.16 (dd, *J* = 8.6, 6.9 Hz, 1H), 7.62 (d, *J* = 8.6 Hz, 1H), 7.74 (d, *J* = 8.6 Hz, 2H), 7.76 (d, *J* = 8.6 Hz, 2H), 7.80 (s, 1H), 7.81 (d, *J* = 8.0 Hz, 1H); $^{13}$C NMR (125 MHz) δ 110.3, 118.6, 118.9, 120.0, 122.7, 124.0, 125.3, 129.2, 132.1, 132.7, 134.6, 139.3, 139.9. HR-MS (EI). Calcd for $C_{15}H_9NS$ (M): 235.0456. Found: *m*/*z* 235.0462. Anal. Calcd for $C_{15}H_9NS$: C, 76.57; H, 3.86; N, 5.95. Found: C, 76.31; H, 3.85; N, 5.90.

**5-Chloro-1-phenylbenzo[*c*]thiophene (5f):** a yellow solid; mp 91–93 °C (hexane/$CH_2Cl_2$); IR (KBr) 1662, 1608 cm$^{-1}$; $^1$H NMR (500 MHz) δ 6.99 (d, *J* = 9.2 Hz, 1H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.4 Hz, 2H), 7.56 (s, 2H), 7.62 (d, *J* = 7.4 Hz, 2H), 7.72 (d, *J* = 9.2 Hz, 1H); $^{13}$C NMR (125 MHz) δ 115.0, 120.6, 122.0, 125.3, 127.8, 129.1, 129.2, 130.2, 132.0, 133.9, 136.3, 139.3. HR-MS (EI). Calcd for $C_{14}H_9ClS$ (M): 244.0113. Found: *m*/*z* 244.0111.

**5-Chloro-1-(3,4-dichlorophenyl)benzo[*c*]thiophene (5g):** a yellow solid; mp 97–99 °C (decomp) (hexane/$Et_2O$); IR (KBr) 1664 cm$^{-1}$; $^1$H NMR (500 MHz) δ 7.05 (dd, *J* = 9.2, 1.7 Hz, 1H), 7.45 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.58 (s, 1H), 7.63 (s, 1H), 7.65 (d, *J* = 9.2 Hz, 1H), 7.70 (d, *J* = 1.7 Hz, 1H); $^{13}$C NMR (125 MHz) δ 116.3, 120.8, 121.3, 126.1, 128.2, 130.4, 130.5, 131.0, 131.9, 132.5, 133.0, 133.2, 133.9, 139.4. HR-MS (EI). Calcd for $C_{14}H_7Cl_3S$ (M): 311.9334. Found: *m*/*z* 311.9325.

**4-(5-Chlorobenzo[*c*]thiophen-1-yl)benzonitrile (5h):** a yellow solid; mp 129–133 °C (decomp) (hexane/$Et_2O$); IR (KBr) 2228, 1667, 1601 cm$^{-1}$; $^1$H NMR (600 MHz) δ 7.09 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.61 (s, 1H), 7.71–7.76 (m, 6H); $^{13}$C NMR (150 MHz) δ 111.0, 117.7, 118.7, 121.0, 121.2, 126.6, 129.3, 130.6, 132.8, 132.9, 133.4, 138.7, 139.7. HR-MS (EI). Calcd for $C_{15}H_8ClNS$ (M): 269.0066. Found: *m*/*z* 269.0073.

**5-Methoxy-1-phenylbenzo[*c*]thiophene (5i):** a brown oil; $R_f$ 0.67 (AcOEt/hexane 1:1); IR (neat) 1623 cm$^{-1}$; $^1$H NMR (600 MHz) δ 3.76 (s, 3H), 6.70 (d, *J* = 2.3 Hz, 1H), 6.72 (dd, *J* = 9.2, 2.3 Hz, 1H), 7.27 (t, *J* = 7.4 Hz, 1H), 7.29 (s, 1H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.55 (dd, *J* = 7.4, 1.1 Hz, 2H), 7.60 (d, *J* = 9.2 Hz, 1H); $^{13}$C NMR (150 MHz) δ 55.0, 97.7, 112.1, 120.0, 121.8, 127.4, 128.9, 129.1, 130.8, 134.5, 135.4, 139.9, 156.5. HR-MS (EI). Calcd for $C_{15}H_{12}OS$ (M): 240.0609. Found: *m*/*z* 240.0609.

**4-(5-Methoxybenzo[*c*]thiophen-1-yl)benzonitrile (5j):** a yellow needles; mp 121–133 °C (hexane/$CH_2Cl_2$); IR (KBr) 2228, 1624, 1600 cm$^{-1}$; $^1$H NMR (500 MHz) δ 3.86 (s, 3H), 6.82 (d, *J* = 1.7 Hz, 1H), 6.89 (dd, *J* = 9.7, 1.7 Hz, 1H), 7.51 (s, 1H), 7.67 (d, *J* = 9.7 Hz, 1H), 7.73 (s, 4H); $^{13}$C NMR (125 MHz) δ 55.1, 98.1, 110.4, 114.8, 118.9, 121.0, 121.3, 129.1, 131.5, 132.5, 132.7, 139.3, 140.4, 156.7.

MR-MS (EI). Calcd for $C_{16}H_{11}NOS$ (M): 265.0561. Found: *m/z* 265.0552. Anal. Calcd for $C_{16}H_{11}NOS$: C, 72.43; H, 4.18; N, 5.28. Found: C, 72.26; H, 4.21; N, 5.21.

**Methyl [2-(Chloromethyl)benzoyl]formate (6a).**[15] To a stirred solution of 1-(chloromethyl)-2-lithiobenzene, generated from **1a** (1.0 g, 5.1 mmol) as described for the preparation of **2a**, in THF (20 mL) at –78 ˚C was added a solution of $(MeOCO)_2$ (0.60 g, 5.1 mmol) in THF (5 mL) as fast as possible. After 5 min, the mixture was worked up as described for the preparation of **2a** and the crude product was purified by column chromatography on $SiO_2$ to give **6** (0.72 g, 66%); a pale-yellow oil; $R_f$ 0.36 (AcOEt/hexane 1:5); IR (neat) 1740, 1689, 1600 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 3.98 (s, 3H), 5.01 (s, 2H), 7.48 (dd, *J* = 7.4, 6.9 Hz, 1H), 7.64 (dd, *J* = 7.4, 6.9 Hz, 1H), 7.68 (d, *J* = 7.4 Hz, 1H), 7.76 (d, *J* = 7.4 Hz, 1H).

**Methyl [2-(Chloromethyl)-4-methoxybenzoyl]formate (6c):** a pale-yellow solid; mp 45–46 ˚C (hexane/$CH_2Cl_2$); IR (KBr) 1728, 1671, 1609 $cm^{-1}$; $^1H$ NMR (500 MHz) δ 3.92 (s, 3H), 3.97 (s, 3H), 5.06 (s, 2H), 6.92 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.25 (d, *J* = 2.3 Hz, 1H), 7.76 (d, *J* = 8.6 Hz, 1H); $^{13}C$ NMR (125 MHz) δ 44.6, 52.8, 55.7, 112.7, 117.0, 122.5, 136.1, 142.9, 164.2, 164.6, 186.3. HR-MS (ESI). Calcd for $C_{11}H_{12}ClO_4$ (M+H): 243.0424. Found: *m/z* 243.0426.

**Methyl Benzo[*c*]thiophene-1-carboxylate (8a):** a yellow solid; mp 38–39 ˚C (hexane/$CH_2Cl_2$); IR (KBr) 1697, 1615 $cm^{-1}$; $^1H$ NMR (500 MHz) δ 3.97 (s, 3H), 7.16 (dd, *J* = 8.6, 6.9 Hz, 1H), 7.33 (dd, *J* = 8.6, 6.9 Hz, 1H), 7.63 (d, *J* = 8.6 Hz, 1H), 7.96 (s, 1H), 8.43 (d, *J* = 8.6 Hz, 1H); $^{13}C$ NMR (150 MHz) δ 51.8, 121.0, 122.1, 122.4, 124.2, 125.6, 127.3, 139.3, 140.1, 163.3. HR-MS (EI). Calcd for $C_{10}H_8O_2S$ (M): 192.0245. Found: *m/z* 192.0241.

**Methyl 5-Methoxybenzo[*c*]thiophene-1-carboxylate (8c):** a pale-yellow solid; mp 72–74 ˚C (hexane); IR (KBr) 1698, 1623 $cm^{-1}$; $^1H$ NMR (500 MHz) δ 3.85 (s, 3H), 3.96 (s, 3H), 6.84 (d, *J* = 1.7 Hz, 1H), 7.05 (dd, *J* = 9.7, 1.7 Hz, 1H), 7.69 (s, 1H), 8.31 (d, *J* = 9.7 Hz, 1H); $^{13}C$ NMR (150 MHz) δ 51.8, 55.1, 98.0, 121.2, 121.7, 122.85, 122.91, 136.9, 139.9, 156.7, 163.3. HR-MS (EI). Calcd for $C_{11}H_{10}O_3S$ (M): 222.0351. Found: *m/z* 222.0354. Anal. Calcd for $C_{11}H_{10}O_3S$: C, 59.44; H, 4.54. Found: C, 59.14; H, 4.61.

## ACKNOWLEDGEMENTS

We are grateful to Mrs. Miyuki Tanmatsu of this university for recording mass spectra and performing combustion analyses.

## REFERENCES AND NOTES

1. (a) J. E. Campbell, U. Campbell, T. G. Hanania, and L. Shao, *PCT Int. Appl.*, 2013, WO 2013119895 (*Chem. Abstr.*, 2013, **159**, 371127); (b) Y. Huang and F. Zheng, *PCT Int. Appl.*, 2017, WO 201704599 (*Chem. Abstr.*, 2017, **166**, 350470).

2. K. Isobe, K. Onaka, and T. Ishikawa, *US Pat. Appl. Publ.*, 2013, US 20130056074 (*Chem. Abstr.*, 2013, **158**, 423609).
3. M. Nandakumar, E. Sankar, and A. K. Mohanakrishnan, *Synth. Commun.*, 2016, **46**, 1810.
4. Y. Cohen, J. Klein, and M. Rabinovitz, *J. Chem. Soc., Chem. Commun.*, 1987, 1538.
5. S. Ogawa, H. Muraoka, K. Kikuta, F. Saito, and R. Sato, *J. Organomet. Chem.*, 2007, **692**, 60.
6. (a) A. K. Mohanakrishnan and P. Amaladass, *Tetrahedron Lett.*, 2005, **46**, 4225; (b) N. Yasmin, M. Ghosh, and J. K. Ray, *RSC Adv.*, 2014, **38**, 19932; (c) W. Bebrouwer, R. A. J. Seigneur, T. S. A. Heugebaert, and C. V. Stevens, *Chem. Commun.*, 2015, **51**, 729; (d) K. Fukuzumi, Y. Unoh, Y. Nishii, T. Satoh, K. Hirano, and M. Miura, *J. Org. Chem.*, 2016, **81**, 2474.
7. Y. Zhang, D. Stephenes, G. Hemandez, R. Mendoza, and O. V. Larionov, *Chem. Eur. J.*, 2012, **18**, 16612.
8. I. Kers, I. Macsari, G. Csjernyik, M. Nylöf, K. Skogholm, L. Sandberg, A. Minidis, T. Bueters, J. Malmborg, A. B. Eriksson, P.-E. Lund, E. Venyike, L. Luo, J.-E. Nyström, and Y. Besidski, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 6108.
9. E. Shimpukada, B. D. Hudson, C. K. Hovgaardm G. Milligan, and T. Ulven, *J. Med. Chem.*, 2012, **55**, 4511.
10. The bromine/lithium exchange between 2-(chloromethyl)phenyl bromide and butyllithium was carried out at –100 ˚C: (a) W. E. Parham, L. D. Jones, and Y. A. Sayed, *J. Org. Chem.*, 1976, **41**, 1184; (b) J. Farrokh, T. Craven, and D. A. Hunt, *Tetrahedron Lett.*, 2017, **58**, 1900.
11. J. H. Gardner and T. F. McDonnell, *J. Am. Chem. Soc.*, 1941, **63**, 2279.
12. R. Mancuso, S. Mehta, B. Gabriele, G. Salemo, W. S. Jenks, and R. C. Larock, *J. Org. Chem.*, 2010, **75**, 897.
13. T. P. Ivanov and A. Draganov, *Monatsh. Chem.*, 1968, **99**, 1990.
14. J. O'Brochta and A. Lowy, *J. Am. Chem. Soc.*, 1939, **61**, 2765.
15. C. Lu, J. Liu, and X. Du, *Nongyao*, 2011, **50**, 187 (*Chem. Abstr.*, 2011, **156**, 151193).