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

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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 hydrosulfide 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.

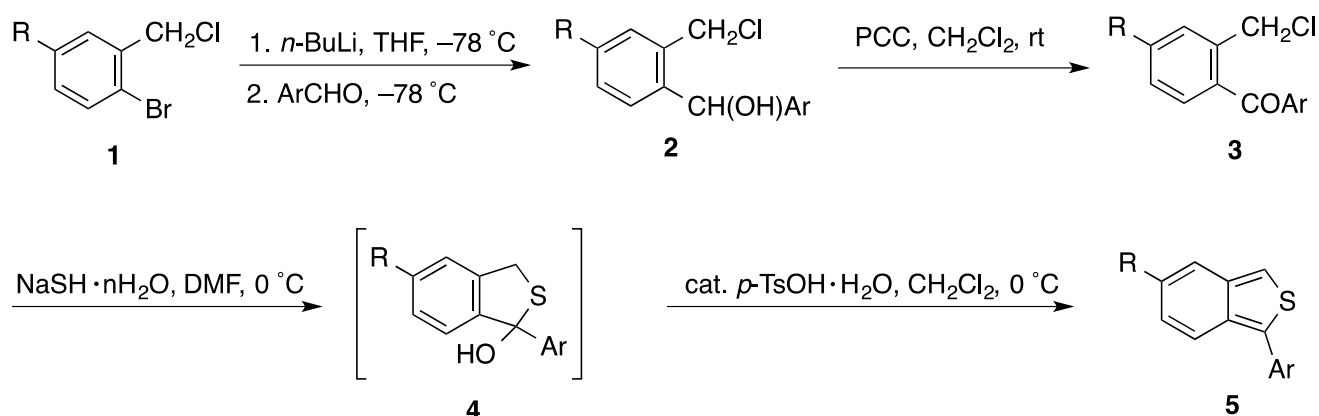
INTRODUCTION

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 P₄S₁₀⁴ or Lawesson's reagent⁵ 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 P₄S₁₀ and Na₂S-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 $-78\text{ }^{\circ}\text{C}$,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 hydrosulfide smoothly in DMF at $0\text{ }^{\circ}\text{C}$ 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 ^1H 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 $0\text{ }^{\circ}\text{C}$ 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

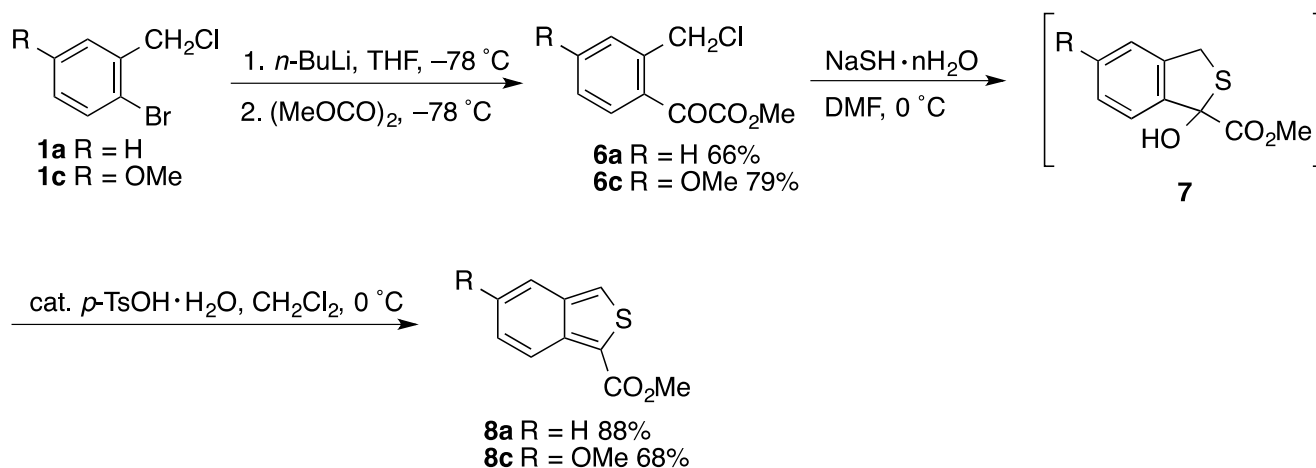
satisfactorily pure form for spectral analyses (Entry 4). TLC analyses during the reaction revealed the production of **5d** in a respectable extent. However, the product appeared to decompose during workup and/or purification (column chromatography on silica gel) probably due to its instability to air 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 ₆ H ₄	2b	56	3b	72	5b	54
3	1a	H	3,4-Cl ₂ C ₆ H ₃	2c	75	3c	72	5c	63
4	1a	H	4-MeOC ₆ H ₄	2d	76	3d	83	5d	b
5	1a	H	4-NCC ₆ H ₄	2e	68	3e	67	5e	71
6	1b	Cl	Ph	2f	73	3f	80	5f	52
7	1b	Cl	3,4-Cl ₂ C ₆ H ₃	2g	60	3g	82	5g	67
8	1b	Cl	4-NCC ₆ H ₄	2h	70	3h	75	5h	74
9	1c	OMe	Ph	2i	72	3i	82	5i	15
10	1c	OMe	4-NCC ₆ H ₄	2j	68	3j	83	5j	37

^a Yields of isolated products. ^b Too unstable on SiO₂ 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 hydrosulfide 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. ¹H NMR and ¹³C NMR spectra were recorded in CDCl₃ 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 PF₂₅₄. 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)methanol⁹ 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)methanol⁸ 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 NH₄Cl (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 (Na₂SO₄), and concentrated by evaporation. The residue was purified by column chromatography on SiO₂ (AcOEt/hexane 1:7) to afford **2a** (0.30 g, 73%); a white solid; mp 65–66 °C (hexane/CH₂Cl₂); IR (KBr) 3349 cm⁻¹; ¹H 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); ¹³C 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 C₁₄H₁₃ClO: 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/CH₂Cl₂); 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); ¹³C 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 C₁₄H₁₂Cl₂O: 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); ¹³C 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 C₁₄H₁₁Cl₃O (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); ¹³C 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 C₁₅H₁₅ClO₂ (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); ¹³C 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 C₁₅H₁₂ClNO (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); ¹³C 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 C₁₄H₁₂Cl₂O (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 $\text{C}_{14}\text{H}_{10}\text{Cl}_4\text{O}$ (M): 333.9486. Found: m/z 333.9476.

4-{[4-Chloro-2-(chloromethyl)phenyl](hydroxy)methyl}benzotrile (2h): a pale-yellow oil; R_f 0.37 (Et₂O/hexane 1:1); IR (neat) 3428, 2228, 1610 cm^{-1} ; ^1H 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 $\text{C}_{15}\text{H}_{11}\text{Cl}_2\text{NO}$ (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} ; ^1H 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 $\text{C}_{15}\text{H}_{15}\text{ClO}_2$ (M): 262.0761. Found: m/z 262.0753.

4-{[2-(Chloromethyl)-4-methoxyphenyl](hydroxy)methyl}benzotrile (2j): a colorless oil; R_f 0.24 (AcOEt/hexane 1:3); IR (neat) 3458, 2228, 1609 cm^{-1} ; ^1H 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 $\text{C}_{16}\text{H}_{14}\text{ClNO}_2$ (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} ; ^1H 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} ; ^1H 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 $\text{C}_{14}\text{H}_{10}\text{Cl}_2\text{O}$ (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); ¹³C 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 C₁₄H₉Cl₃O: 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/CH₂Cl₂); 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); ¹³C 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 C₁₅H₁₃ClO₂: 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/CH₂Cl₂); 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); ¹³C 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 C₁₅H₁₀ClNO: 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); ¹³C 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 C₁₄H₁₀Cl₂O (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); ¹³C 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 C₁₄H₈Cl₄O (M): 331.9329. Found: *m/z* 331.9328.

4-[4-Chloro-2-(chloromethyl)benzoyl]benzonitrile (3h): a white solid; mp 129–131 °C (hexane/CH₂Cl₂); 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); ¹³C 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 C₁₅H₉Cl₂NO: 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 $\text{C}_{15}\text{H}_{14}\text{ClO}_2$ (M+H): 261.0683. Found: m/z 261.0677.

4-[2-(Chloromethyl)-4-methoxybenzoyl]benzotrile (3j): a colorless needles; mp 131–133 °C (hexane); IR (KBr) 2234, 1654, 1607 cm^{-1} ; ^1H 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 $\text{C}_{16}\text{H}_{12}\text{ClNO}_2$: 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 $\text{NaSH}\cdot n\text{H}_2\text{O}$ (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 $\cdot\text{H}_2\text{O}$ (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 ($\text{Et}_2\text{O}/\text{hexane}$ 1:5); IR (neat) 1689, 1661 cm^{-1} ; ^1H 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 $\text{C}_{14}\text{H}_{10}\text{S}$ (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} ; ^1H 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 $\text{C}_{14}\text{H}_9\text{ClS}$ (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} ; ^1H 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 $\text{C}_{14}\text{H}_8\text{Cl}_2\text{S}$ (M): 277.9724. Found: m/z 277.9713.

4-(Benzo[*c*]thiophen-1-yl)benzotrile (5e): a yellow solid; mp 76–79 °C (hexane/ CH_2Cl_2); IR (KBr) 2222, 1687, 1662 cm^{-1} ; ^1H 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 $\text{C}_{15}\text{H}_9\text{NS}$ (M): 235.0456. Found: m/z 235.0462. Anal. Calcd for $\text{C}_{15}\text{H}_9\text{NS}$: 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} ; ^1H 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 $\text{C}_{14}\text{H}_9\text{ClS}$ (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} ; ^1H 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 $\text{C}_{14}\text{H}_7\text{Cl}_3\text{S}$ (M): 311.9334. Found: m/z 311.9325.

4-(5-Chlorobenzo[*c*]thiophen-1-yl)benzotrile (5h): a yellow solid; mp 129–133 °C (decomp) (hexane/ Et_2O); IR (KBr) 2228, 1667, 1601 cm^{-1} ; ^1H 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 $\text{C}_{15}\text{H}_8\text{ClNS}$ (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} ; ^1H 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 $\text{C}_{15}\text{H}_{12}\text{OS}$ (M): 240.0609. Found: m/z 240.0609.

4-(5-Methoxybenzo[*c*]thiophen-1-yl)benzotrile (5j): a yellow needles; mp 121–133 °C (hexane/ CH_2Cl_2); IR (KBr) 2228, 1624, 1600 cm^{-1} ; ^1H 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 C₁₆H₁₁NOS (M): 265.0561. Found: *m/z* 265.0552. Anal. Calcd for C₁₆H₁₁NOS: 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 SiO₂ 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, CDCl₃) 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/CH₂Cl₂); 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); ¹³C 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 C₁₁H₁₂ClO₄ (M+H): 243.0424. Found: *m/z* 243.0426.

Methyl Benzo[*c*]thiophene-1-carboxylate (8a): a yellow solid; mp 38–39 °C (hexane/CH₂Cl₂); 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); ¹³C 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 C₁₀H₈O₂S (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); ¹³C 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 C₁₁H₁₀O₃S (M): 222.0351. Found: *m/z* 222.0354. Anal. Calcd for C₁₁H₁₀O₃S: C, 59.44; H, 4.54. Found: C, 59.14; H, 4.61.

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