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Synthesis of 1,3-diaryl benzo[*c*]thiophenes

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Abstract—An array of 1,3-diarylbenzo[*c*]thiophenes has been synthesized via the ring opening of lactones followed by thionation using Lawesson's reagent.

The electronic properties of linear π-conjugated oligomers have acquired a growing importance in many areas of modern chemistry. In recent years, there has been tremendous interest in organic molecules that can be further elaborated into materials exhibiting promising electrochemical, optical and electronic effects that are desirable for the fabrication of electroluminescent devices.[1–3] Among these, the contribution of arylvinylenes and heteroarylvinylenes in the fabrication of electroluminescent devices is noteworthy.[4] In particular thiophene oligomers are frequently applied as semiconducting materials in molecular electronic devices[5] or optical devices.[6] The thiophene oligomers are the most widely investigated model compounds for electrically conducting polymers.[7]

The synthesis and characterization of a benzannelated terthiophene, namely 1,3-dithienylbenzo[*c*]thiophene **1**, has been reported independently by four groups.[8] Cava and co-workers reported a detailed synthesis of several 1,3-dithienylbenzo[*c*]thiophenes and their analogs.[9] A Vilsmeier formylation of 1,3-dithienylbenzo[*c*]thiophene followed by condensation with active methylene compounds led to the synthesis of several dithienylbenzo[*c*]thiophene based vinylenes. Oxidative oligomerization studies of 1,3-dithienylbenzo[*c*]thiophene have also been carried out. Roncali et al. reported the synthesis and electropolymerization studies of 1,3-(bis-3,4-ethylenedioxythienyl)benzo[*c*]thiophene.[10] The synthesis of a novel nucleoside analog replacing a DNA base with 1,3-dithienylbenzo[*c*]thiophene has also been reported.[11]

Keywords: Lactone; Grignard reagents; Thionation; Benzo[*c*]-thiophene.
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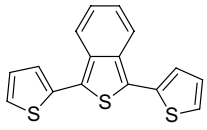
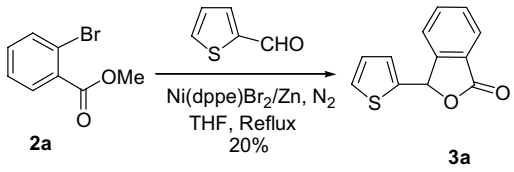
The nucleosides of this type are useful as potential probes for understanding the structure and dynamics of nucleic acids and can also be used as fluorescent labels. Finally, the enhanced photoluminescence behavior of a dithienylbenzo[*c*]thiophene derivative during a photobleaching process has been observed.[12]



1

The intriguing photophysical properties of thienyl oligomers prompted us to explore further the synthesis of benzo[*c*]thiophene derivatives. Our focus was centered on the synthesis of derivatives, which are reasonably stable and easily processable. Having targeted the synthesis of benzo[*c*]thiophenes, we turned our attention to the synthesis of the intermediate lactones.[13] Since the conventional Friedel–Crafts phthaloylation was successful only with thiophene, it was decided to explore other methods, which can deliver highly substituted lactones in reasonable yields.

A survey of the literature revealed that the synthesis of several phthalides could be easily achieved via a three-component coupling reaction using Ni(dppe)Br_2–Zn as the catalyst.[14] However, as a model study, the preparation of known lactone **3a** using this procedure was found to be sluggish and gave only a 20% yield, Scheme 1. Repetition of the experiment with other aldehydes such as anthracene-9-carboxaldehyde and veratraldehyde was found to be futile.

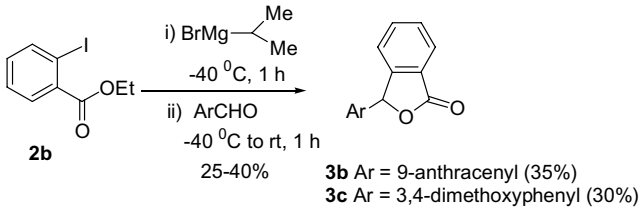


Scheme 1.

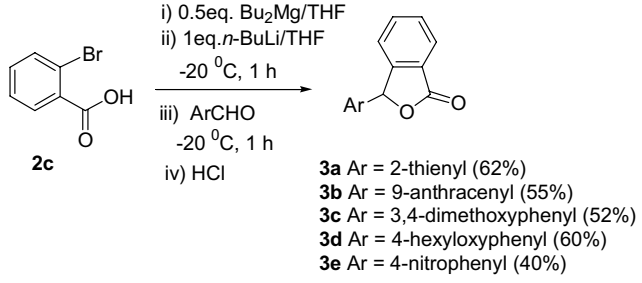
The preparation of lactones **3b**, **c** was achieved using an exchange reaction[15] of ethyl 2-iodobenzoate with isopropylmagnesium bromide, Scheme 2.

Next, the magnesio protocol published by Kato and coworkers was explored.[16] Notably, the synthesis of different types of lactone was achieved through metalation of 2-bromobenzoic acid using combinations of Bu_2Mg and *n*-BuLi under noncryogenic condition. By adopting this procedure, the synthesis of several multifunctional lactones **3a**–**e** was realized in relatively better yields, Scheme 3.

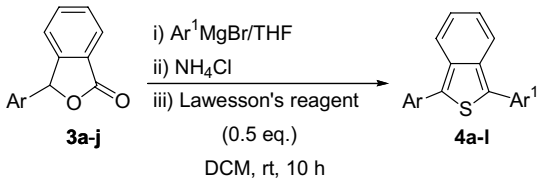
The synthesis of other lactones **3f**–**j** was achieved through the reaction of freshly prepared aryl Grignard reagents with 2-carboxybenzaldehyde,[17] Scheme 4. It is noteworthy that these lactones **3f**–**j** could not be prepared with the lithiation procedure mentioned above.



Scheme 2.



Scheme 3.



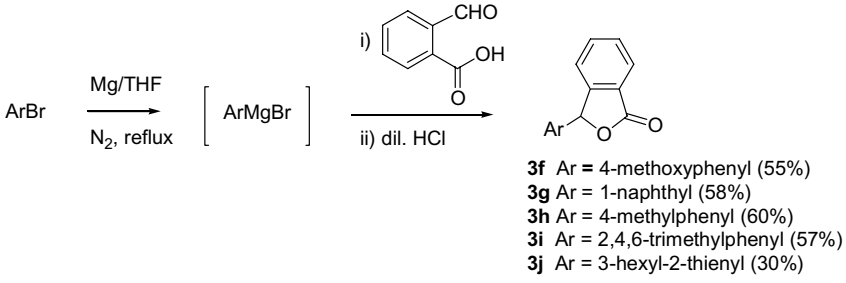
Scheme 5.

Having prepared lactones **3a**–**j** in reasonable yields, conversion of these lactones into the respective 1,3-diarylbenzo[*c*]thiophenes was undertaken. The ring opening of lactones **3a**–**j** with aryl Grignard reagents followed by thionation with 0.5 equiv of Lawesson's reagent and column chromatographic purification afforded several benzo[*c*]thiophene analogs, Scheme 5. Ring opening of the lactones followed by workup using aq NH_4Cl led to the intermediate keto-alcohols,[9] which on thionation followed by cyclization afforded respective products **4a**–**l**.

Details such as the nature of the lactones, Grignard reagents and the products along with their yields are summarized in Table 1. The reaction of various lactones with freshly prepared Grignard reagents and a subsequent thionation reaction led to the synthesis of 1,3-bisaryl benzo[*c*]thiophenes **4a**–**l** in 40–65% overall yields (entries 1–14). The structure of **4i** was confirmed by X-ray analysis[18] (Fig. 1).

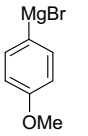
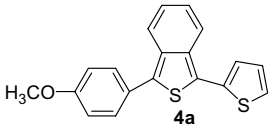
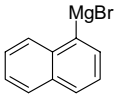
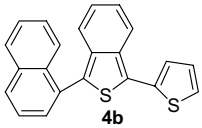
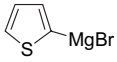
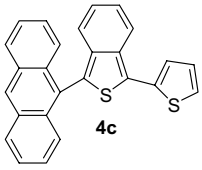
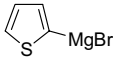
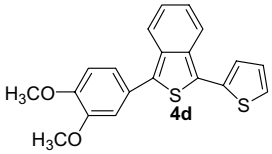
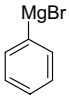
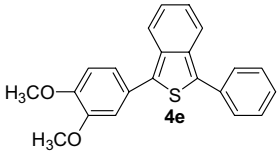
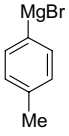
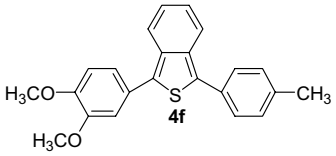
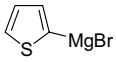
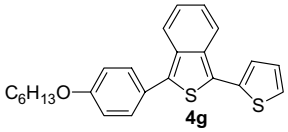
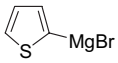
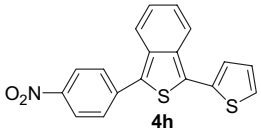
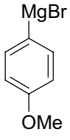
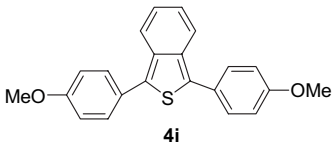
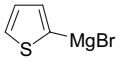
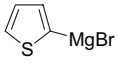
Most of these benzo[*c*]thiophenes have at least one position which can be used for further electrophilic substitution. Benzo[*c*]thiophene **4h** containing the electron-withdrawing NO_2 function was synthesized in 42% yield. The UV spectrum of benzo[*c*]thiophenes **4a**–**l** exhibited λ_{max} values between 412 and 470 nm, Table 2.

Finally, the attempted ring opening of lactone **3a** with commercially available ethynyl or propynyl Grignard reagents followed by thionation did not afford the expected products, only starting material was recovered, Scheme 6. The failure of the lactone ring opening in **3a** may be due to the basic character of acetylenic Grignards.



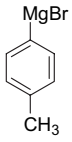
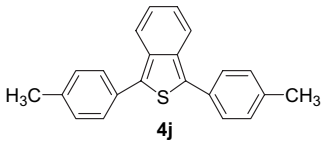
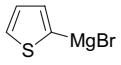
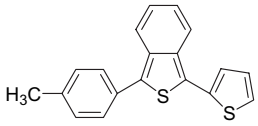
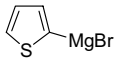
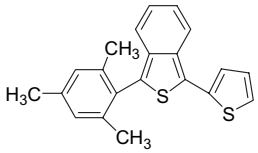
Scheme 4.

Table 1. Synthesis of benzo[*c*]thiophene analogs

Entry	Lactones	Ar^1MgBr[19]	Products[20]	Yield (%)[a] mp
1	**3a**		 **4a**	40 (170 °C)
2	**3a**		 **4b**	43 (Semi-solid)
3	**3b**		 **4c**	45 (170 °C)
4	**3c**		 **4d**	55 (85 °C)
5	**3c**		 **4e**	51 (88 °C)
6	**3c**		 **4f**	58 (138 °C)
7	**3d**		 **4g**	65 (80 °C)
8	**3e**		 **4h**	42 (116 °C)
9	**3f**		 **4i**	66 (122 °C)
10	**3f**		**4a**	62 (107 °C)
11	**3g**		**4b**	53 (Semi-solid)

(*continued on next page*)

Table 1 (*continued*)

Entry	Lactones	Ar^1MgBr[19]	Products[20]	Yield (%)[a] mp
12	**3h**		 **4j**	62 (118 °C)
13	**3h**		 **4k**	60 (106 °C)
14	**3i**		 **4l**	57 (Thick liquid)

[a] Isolated yield after column chromatography.

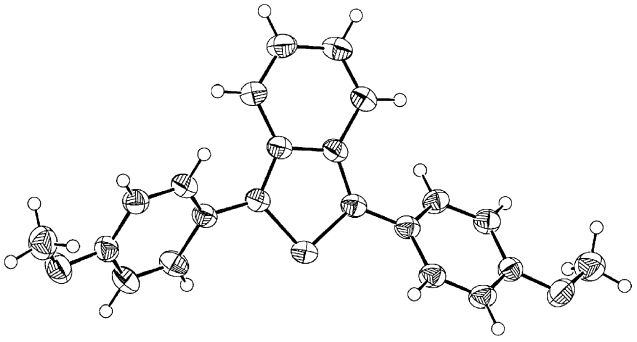
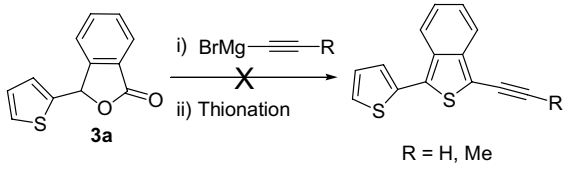


Figure 1. ORTEP style plot of compound **4i** in Thermal ellipsoids are drawn at the 50% probability level.



Scheme 6.

In summary, syntheses of several lactones have been achieved involving two methods. All the lactones were smoothly converted into benzo[*c*]thiophene analogs in two steps. The UV spectra of benzo[*c*]thiophene derivatives are presented. The highly fluorescent nature of these heterocycles may be suitable for the fabrication of LED devices. Further synthetic studies in this area are currently in progress.

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Table 2. UV spectral data for **4a–l**

	Products											
	4a	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**	**4h**	**4i**	**4j**	**4k**	**4l**
λ_{max} (nm) (DCM)	412	414	423	445	422	425	416	470	418	424	420	416

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18. X-ray data for the X-ray data for compound **4i**: X-ray data were collected at 293(2) K on a ENRAF NONIUS-CAD4 diffractometer with graphite monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å). The structure was solved by direct methods (SHELX-97). Refinement was done by full-matrix least-squares procedures on F^2 using SHELX-97. All non-hydrogen atoms were refined anisotropically. $C_{22}H_{18}O_2S$, MW = 346, yellow crystal of size: $0.30 \times 0.22 \times 0.28$ mm^3, crystal system: orthorhombic, space group: P_{cab}, cell parameters: $a = 7.508(6)$ Å, $b = 16.493(9)$ Å, $C = 27.952(9)$ Å, $V = 3461(4)$ Å^3, $Z = 8$, Dc = 1.330 mg/m^3, $T = 293(2)$ K, μ(Mo-Kα) = 0.199 mm^{-1}, $F_{000} = 1456$, total number of l.s. parameters = 228, $R_1 = 0.0580$ for 3579 $I > 2\sigma(I)$ and 0.0955 for all 5044 data. $WR_2 = 0.1716$, GOF = 1.043 for all data. Crystallographic data (excluding structure factors) for **4i** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 268130. Copies of the data may be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44(0)-1223-33603 or e-mail: deposit@ccdc.cam.ac.uk).
19. The aryl Grignards reagents were prepared from the corresponding bromo compounds by refluxing with magnesium in dry THF under N_2 atmosphere.
20. All benzo[*c*]thiophene analogs **4a**–**l** gave satisfactory spectral and analytical data.

A representative procedure for 4g: Freshly prepared thienyl magnesium bromide (from 2-bromothiophene, 2.89 g 1.71 mL, 17.72 mmol) and Mg (0.510 g, 21.27 mmol) were added to a solution of phthalide **3d** (5 g, 16.12 mmol) at 0 °C. After the addition was complete, the reaction mixture was poured into an ice-cooled NH_4Cl solution, and extracted with CH_2Cl_2 (100 mL) and dried (Na_2SO_4). The solution was treated with Lawesson's reagent (3.26 g, 8.05 mmol) and stirred at room temperature overnight. The solvent was removed and the residue was gently heated on a steam bath with ethanol. The crude product was purified by column chromatography (neutral alumina, hexane) to afford benzo[*c*]thiophene **4g** as a yellow solid (4.1 g, 65%).

Spectral data of some selected benzo[*c*]thiophenes: For **4a**: mp 107 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.91 (s, 3H), 7.03 (d, $J = 8.8$ Hz, 2H), 7.05–7.16 (m, 3H), 7.33–7.36 (m, 2H), 7.59 (d, $J = 8.8$ Hz, 2H), 7.74 (d, $J = 8.8$ Hz, 1H), 7.95 (d, $J = 8.76$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.64, 114.80, 121.54, 124.30, 124.79, 125.34, 125.42, 126.20, 128.04, 130.70, 132.21, 134.37, 135.15, 136.24, 159.63. MS(EI) *m*/*z* (%): 322(M$^+$, 100), 307(93), 279(32), 195(43), 161(45), 77(14). Elemental Anal. Calcd for $C_{19}H_{14}OS_2$: C, 70.77; H, 4.38; S, 19.89%. Found: C, 70.60; H, 4.36; S, 19.80%.

For **4c**: mp 170 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.92–7.01 (m, 3H), 7.12 (dd, $J = 3.68$ Hz, $J = 1.44$ Hz, 1H), 7.29 (d, $J = 3.88$ Hz, 1H), 7.42–7.56 (m, 5H), 7.85 (d, $J = 9.28$ Hz, 1H), 8.00 (d, $J = 8.8$ Hz, 2H), 8.06 (d, $J = 8.32$ Hz, 2H), 8.62 (s, 1H). MS(EI) *m*/*z* (%): 392(M$^+$, 5), 375(100), 351(26), 301(15), 264(29), 233(42), 154(27). Elemental Anal. Calcd for $C_{26}H_{16}S_2$: C, 79.55; H, 4.11; S, 16.34%. Found: C, 79.46; H, 4.18; S, 16.36%.

For **4g**: mp 80 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, $J = 6.1$ Hz, 3H), 1.32–1.51 (m, 6H), 1.77 (quin, $J = 7.1$ Hz, 2H), 3.94 (t, $J = 6.25$ Hz, 2H), 6.94–7.09 (m, 5H), 7.28 (d, $J = 4.04$ Hz, 2H), 7.52 (d, $J = 8.24$ Hz, 2H), 7.72 (d, $J = 8.45$ Hz, 1H), 7.92 (d, $J = 8.45$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.04, 22.58, 25.69, 29.18, 31.55, 68.05,114.98, 121.27, 123.93, 124.94, 125.01, 126.61, 127.01, 127.71, 130.30, 134.20, 135.15, 135.81, 136.24, 158. 87. MS(EI) *m*/*z* (%): 392 (M$^+$, 49), 346(14), 281(100), 239(55), 223(43), 137(62), 104(59). Elemental Anal. Calcd for $C_{24}H_{24}OS_2$: C, 73.43; H, 6.16; S, 16.34%. Found: C, 73.35; H, 6.14; S, 16.29%.

For **4h**: mp 116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17–7.24 (m, 4H), 7.40 (dd, $J = 2.44$ Hz, $J = 1.22$ Hz, 1H), 7.44 (d, $J = 4.88$ Hz, 1H), 7.83 (d, $J = 9.28$ Hz, 2H), 8.02 (d, $J = 2.44$ Hz, 1H), 8.34 (d, $J = 8.8$ Hz, 2H). MS(EI) *m*/*z* (%): 338 (M+1$^+$, 100), 292(69), 228(42), 123(36), 82(29). Elemental Anal. Calcd for $C_{18}H_{11}NO_2S_2$: C, 64.07; H, 3.29; N, 4.15; S, 19.01%. Found: C, 64.03; H, 3.33; N, 4.12; S, 18.95%.

For **4j**: mp 118 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 6H), 7.05 (dd, $J = 3.44$ Hz, $J = 3.4$ Hz, 2H), 7.29 (d, $J = 7.8$ Hz, 4H), 7.57 (d, $J = 7.8$ Hz, 4H), 7.80 (dd, $J = 3.92$ Hz, $J = 2.92$ Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.22, 121.20, 123.93, 129.08, 129.70, 131.46, 133.83, 134.99, 137.29. MS(EI) *m*/*z* (%): 314(M$^+$,100), 298(18), 283(20), 208(17), 157(35), 77(12). Elemental Anal. Calcd for $C_{22}H_{18}S$: C, 84.03; H, 5.77; S, 10.20%. Found: C, 83.83; H, 5.83; S, 10.34%.