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Regioselective synthesis of poly-substituted thiophenes from Baylis–Hillman adducts

Hyun Seung Lee, Se Hee Kim, Jae Nyoung Kim *

Department of Chemistry and Institute of Basic Science, Chonnam National University, Gwangju 500-757, Republic of Korea

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ABSTRACT

The reaction of Baylis–Hillman acetates and ethyl mercaptoacetate in the presence of DBU in DMF produced 2,3,4-trisubstituted tetrahydrothiophenes at room temperature as a diastereomeric mixture via the sequential S_N2' and Michael addition. Aromatization of tetrahydrothiophenes by DDQ oxidation produced 2,3,4-trisubstituted thiophenes in good yields.

Recently, various kinds of aromatic compounds have been synthesized from Baylis–Hillman adducts including benzenes, naphthalenes, pyridines, quinolines, pyrroles, and furans.[1,2] The synthesis of thiophene derivatives from the Baylis–Hillman adducts, however, has not been reported to the best of our knowledge.[3] Poly-substituted thiophenes have been used as important synthetic intermediates in organic synthesis,[4] and many thiophene moiety-containing compounds showed interesting biological activities.[4] In these respects, a development of an efficient synthetic method of poly-functionalized thiophenes is especially important.

During our continuous efforts on the synthesis of regioselectively substituted aromatic compounds from Baylis–Hillman adducts,[2] we decided to develop an efficient synthetic approach of thiophenes. Our synthetic strategy of 2,3,4-trisubstituted thiophenes is schematically depicted in Scheme 1: (i) synthesis of S_N2' product **I** from the reaction of Baylis–Hillman acetate **1a** and ethyl mercaptoacetate (**2a**), (ii) intramolecular Michael reaction[2f,2g] of **I** to a diastereomeric mixture of tetrahydrothiophene **III**, and (iii) dehydrogenative aromatization of **III** with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone)[5] to produce 2,3,4-trisubstituted thiophene **3a**.

Initially, we examined the reaction of **1a** and **2a** in the presence of K_2CO_3 in DMF and we could isolate the intermediate **I** (*E*/*Z* = 10:1) in 91%. ^{1}H NMR interpretation showed that **I** was contaminated with a trace amount of **II** (<5%). Treatment of this mixture (**I** and **II**) with DBU afforded a mixture of **III** and **IV** in 84% (rt, 40 min). When we run the reaction of **1a** and **2a** in the presence of DBU in DMF, we could isolate a mixture of **III** and **IV** in a slightly improved yield (overall 83%). Totally eight isomers of **III** and **IV** could be produced and thus we used them without further purification. Dehydrogenative oxidation of the mixture (**III** and **IV**) was carried out with DDQ in *o*-dichlorobenzene (110 °C, 3 h) to produce two thiophenes **3a** (92%)[6] and **4a** (5%),[6] and the separation of **3a** and **4a** was easy.

Encouraged by the successful results, we synthesized various thiophenes **3b–i** from the reactions of the Baylis–Hillman acetates **1a–g** and thiols **2a–c**, by using the same strategy and the results are summarized in Table 1. As in Table 1, thiophenes **3b–i** were obtained in good to moderate yields (55–89%) except **3g** (vide infra). The regioisomeric thiophenes **4a–i** were observed on TLC in most cases and we separated them in low yields (4–8%) in some cases. During the synthesis of compound **3g** (entry 7), however, many side products were formed when we run the DDQ oxidation with the corresponding tetrahydrothiophene intermediates. The reaction of **1a** and thioacetonitrile (**2b**)[7a] or phenacyl mercaptan (**2c**)[7b] showed similar results to produce **3h** and **3i** in moderate yields (entries 8 and 9).

As a next trial, we examined the reaction of acetyl derivative **1h** and **2a** as shown in Scheme 2. The reaction showed somewhat different results. At the initial stage of the reaction intermediate **VI** was the major component. However, the amount of intermediate **VII** was increased slowly. Actually, intermediate **VII** was isolated in 76% after 6 h,[8] whereas compounds **VI** and **VII** were isolated in 47% and 40%, respectively, when we quenched the reaction mixture after 15 min. As in our previous report on the synthesis of pyrrole derivatives,[2f,2g] aldol type product **VI** was generated rapidly via the S_N2' product **V**, however, this intermediate **VI** was

* Corresponding author. Tel.: +82 62 530 3381; fax: +82 62 530 3389.
E-mail address: kimjn@chonnam.ac.kr (J.N. Kim).

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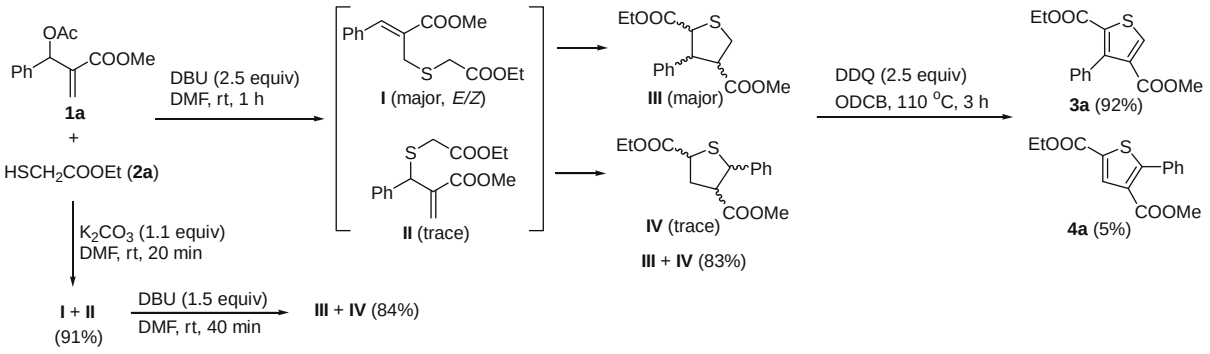
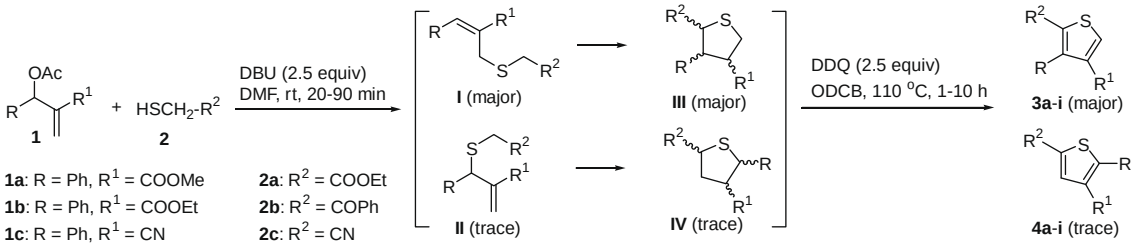


Scheme 1.

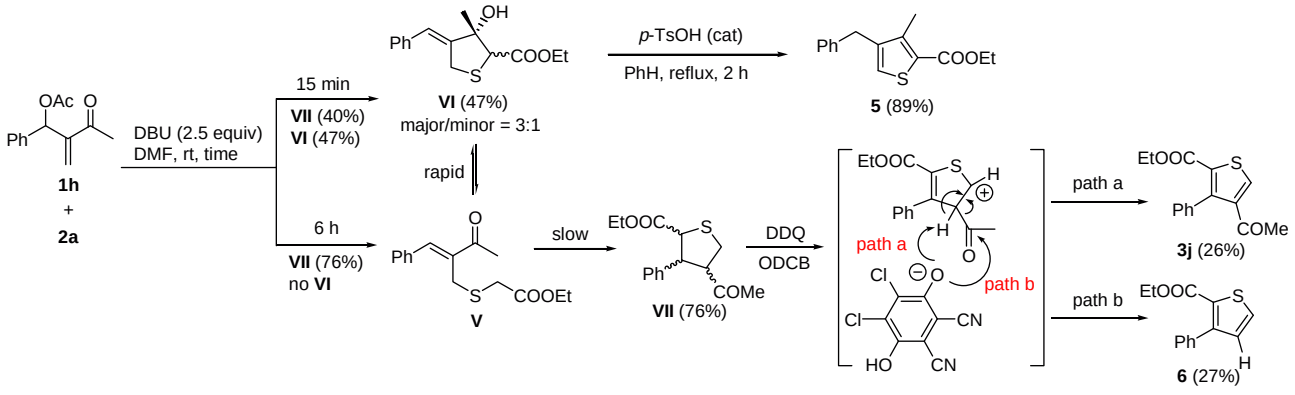
Table 1
Synthesis of 2,3,4-trisubstituted thiophenes



1a: R = Ph, R^1 = COOMe **2a**: R^2 = COOEt
1b: R = Ph, R^1 = COOEt **2b**: R^2 = COPh
1c: R = Ph, R^1 = CN **2c**: R^2 = CN
1d: R = 2-naphthyl, R^1 = COOMe
1e: R = 4-chlorophenyl, R^1 = COOMe
1f: R = 4-methylphenyl, R^1 = COOMe
1g: R = pentyl, R^1 = COOMe

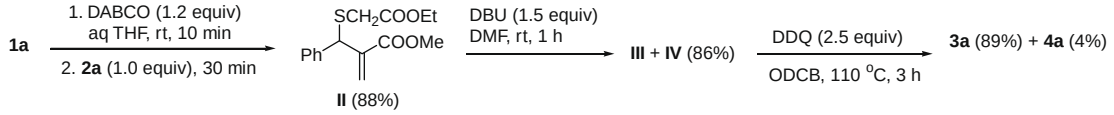
Entry	1 + 2	Condition (min)	III + IV[a] (%)	Conditions (h)	Product **3** (%)	Product **4** (%)
1	**1a** + **2a**	60	83	3	**3a** (92)	**4a** (5)
2	**1b** + **2a**	30	78	3	**3b** (87)	**4b** (nd)[c]
3	**1c** + **2a**	60	75	4	**3c** (82)	**4c** (nd)[c]
4	**1d** + **2a**	60	76	1	**3d** (85)	**4d** (6)
5	**1e** + **2a**	30	82	3	**3e** (89)	**4e** (5)
6	**1f** + **2a**	90	79	4	**3f** (55)	**4f** (4)
7	**1g** + **2a**	40	76	6	**3g** (20)[b]	**4g** (8)
8	**1a** + **2b**	20	76	10	**3h** (83)	**4h** (nd)[c]
9	**1a** + **2c**	20	71	3	**3i** (58)[b]	**4i** (nd)[c]

[a] Crude diastereomeric mixture of **III** and **IV**.
[b] Intractable side products were formed during DDQ oxidation.
[c] Trace amounts of compound **4** was observed on TLC, but we did not separate.

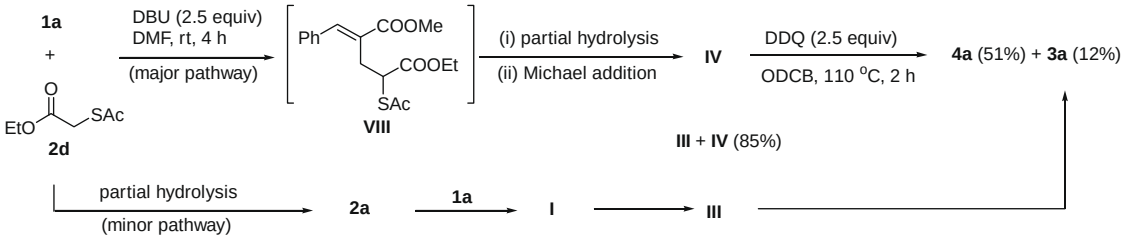


Scheme 2.

converted into Michael addition compound **VII** slowly (Scheme 2). The compound **VI** was isolated as a *syn/anti* mixture (3:1) and we prepared thiophene **5** in 89% by dehydration (*p*-TsOH, benzene, refluxing) and concomitant isomerization process. DDQ oxidation



Scheme 3.



Scheme 4.

of **VII** was carried out similarly, however, we obtained the desired thiophene **3j** in low yield (26%) along with unexpected thiophene **6** in 27%. The mechanism for the deacetylative aromatization to compound **6** could be explained as shown in Scheme 2.[5e–g] When the phenoxide of DDQ attacks the hydrogen atom (path a) **3j** could be formed whereas when the anion attacks the carbonyl group of the acetyl moiety (path b) compound **6** could be formed.[9]

In order to synthesize the minor product **4a** in an increased yield, we prepared **II** from **1a** via the corresponding DABCO salt as shown in Scheme 3.[3a,10] Compound **II** was prepared in good yield (88%). Treatment of **II** with DBU in DMF afforded a mixture of tetrahydrothiophene intermediates in 86%. However, subsequent DDQ oxidation produced **3a** (89%) as the major product again, unfortunately. Based on the experimental results, we could conclude that the secondary adduct **II** might be isomerized to the thermodynamically more stable primary adduct **I**, under the conditions of DBU/DMF, to produce **III** to a large extent.

Thus we examined another route for the synthesis of **4a** as shown in Scheme 4. The reaction of **1a** and **2d**, a protected form of **2a**, could produce **VIII** and the intermediate **VIII** could be transformed to **IV** through a partial hydrolysis of the thioacetate group[11] and intramolecular Michael reaction. Actually, we obtained a mixture of tetrahydrothiophenes in 85% yield. Treatment of this mixture with DDQ afforded **4a** in an increased yield (51%) in comparison with 5% (entry 1 in Table 1). However, compound **3a** was obtained together in low yield (12%) through the pathway comprising of a partial hydrolysis of **2d** to **2a** and the sequential processes involving the formation of **I** and **III**, as shown in Scheme 4.

In summary, we developed an efficient synthetic process of 2,3,4-trisubstituted thiophenes from Baylis–Hillman adducts via the sequential S_N2' reaction of thiols, intramolecular Michael addition, and DDQ oxidation. This is the first example for the synthesis of thiophenes from Baylis–Hillman adducts and the studies on the synthesis of differently substituted thiophenes are currently underway.

Acknowledgments

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6. *Typical procedure for the synthesis of compound* **3a**: To a stirred solution of **1a** (234 mg, 1.0 mmol) and **2a** (120 mg, 1.0 mmol) in DMF (2 mL) was added DBU (381 mg, 2.5 mmol) and the mixture was stirred at room temperature for 60 min. The reaction mixture was poured into dilute HCl solution and extracted with ether. Drying with $MgSO_4$, removal of solvent, and column chromatographic purification process (hexanes/ether, 10:1) afforded a crude mixture of **III** and **IV** as colorless oil, 244 mg (83%). To the crude tetrahydrothiophenes (**III** + **IV**, 176 mg, 0.6 mmol) in *o*-dichlorobenzene (0.5 mL) was added DDQ (341 mg, 1.5 mmol) and heated to 110 °C for 3 h. After removal of solvent under reduced pressure and column chromatographic purification process (hexanes/ether, 10:1) we obtained **3a** (160 mg, 92%) and **4a** (9 mg, 5%). Other thiophenes were synthesized similarly and the representative spectroscopic data of **3a**, **4a**, **3h**, **3i**, **5**, and **6** are as follows.

Compound **3a**: 92%; white solid, mp 45–47 °C; IR (KBr) 1732, 1699, 1240, 1221 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.10 (t, J = 7.2 Hz, 3H), 3.66 (s, 3H), 4.13 (q, J = 7.2 Hz, 2H), 7.20–7.26 (m, 2H), 7.35–7.41 (m, 3H), 8.27 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.72, 51.62, 61.05, 127.25, 127.52, 128.70, 131.05, 133.57, 135.14, 137.05, 147.97, 161.28, 162.30; ESIMS m/z 291 (M^++1). Anal. Calcd for $C_{15}H_{14}O_4S$: C, 62.05; H, 4.86. Found: C, 62.34; H, 4.91.

Compound **4a**: 5%; white solid, mp 53–55 °C; IR (KBr) 1716, 1249, 1201 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.39 (t, J = 7.2 Hz, 3H), 3.75 (s, 3H), 4.37 (q, J = 7.2 Hz, 2H), 7.37–7.52 (m, 5H), 8.16 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.26, 51.74, 61.48, 128.10 (2C), 129.34, 129.60, 131.95, 132.33, 135.51, 156.62, 161.51, 162.90; ESIMS m/z 291 (M^++1). Anal. Calcd for $C_{15}H_{14}O_4S$: C, 62.05; H, 4.86. Found: C, 61.87; H, 5.08.

Compound **3h**: 83%; white solid, mp 65–67 °C; IR (KBr) 1730, 1636, 1238, 1202 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.71 (s, 3H), 7.09–7.19 (m, 7H), 7.28–7.34 (m, 1H), 7.50–7.53 (m, 2H), 8.37 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.78, 127.31, 127.77 (2C), 129.37, 130.02, 132.36, 132.87, 134.18, 137.07, 137.13, 140.15, 145.77, 162.74, 190.06; ESIMS m/z 323 (M^++1). Anal. Calcd for $C_{19}H_{14}O_3S$: C, 70.79; H, 4.38. Found: C, 70.95; H, 4.64.

Compound **3i**: 58%; white solid, mp 78–80 °C; IR (KBr) 2219, 1732, 1445, 1273, 1207 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.72 (s, 3H), 7.36–7.47 (m, 5H), 8.32 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.99, 108.90, 113.31, 128.05, 129.00, 129.04, 132.01, 132.13, 138.58, 152.60, 161.59; ESIMS m/z 244 (M^++1). Anal. Calcd for $C_{13}H_9NO_2S$: C, 64.18; H, 3.73; N, 5.76. Found: C, 64.33; H, 3.98; N, 5.46.

Compound **5**: 89%; colorless oil; IR (film) 1707, 1258 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.36 (t, J = 7.2 Hz, 3H), 2.43 (s, 3H), 3.88 (s, 2H), 4.32 (q, J = 7.2 Hz, 2H), 6.98 (s, 1H), 7.12–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.86, 14.34, 35.47, 60.61, 126.30, 127.28, 127.72, 128.53, 128.65, 139.16, 142.46, 144.91, 162.96; ESIMS m/z 261 (M^++1). Anal. Calcd for $C_{15}H_{16}O_2S$: C, 69.20; H, 6.19. Found: C, 69.37; H, 6.32.

Compound **6**: 27%; colorless oil; IR (film) 1719, 1696, 1413, 1275, 1223 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.23 (t, J = 7.2 Hz, 3H), 4.23 (q, J = 7.2 Hz, 2H), 7.08 (d, J = 5.1 Hz, 1H), 7.35–7.47 (m, 5H), 7.49 (d, J = 5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.05, 60.91, 127.62, 127.73, 127.81, 129.23, 130.03, 131.50, 135.80, 148.34, 162.10; ESIMS m/z 233 (M^++1). Anal. Calcd for $C_{13}H_{12}O_2S$: C, 67.21; H, 5.21. Found: C, 67.47; H, 5.14.

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8. *Major component of* **VII** *was separated (>95% purity) and the spectroscopic data are as follows*: colorless oil; IR (film) 1732, 1711, 1454, 1360 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.18 (t, J = 7.0 Hz, 3H), 1.93 (s, 3H), 3.11 (dd, J = 11.0 and 10.5 Hz, 1H), 3.32 (dd, J = 11.0 and 10.5 Hz, 1H), 3.53–3.58 (m, 1H), 3.92 (dd, J = 11.0 and 9.5 Hz, 1H), 4.06 (d, J = 9.5 Hz, 1H), 4.05–4.16 (m, 2H), 7.25–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.92, 30.09, 34.10, 53.56, 54.45, 61.48, 63.10, 127.57, 127.66, 128.94, 138.66, 171.48, 206.33; ESIMS m/z 279 (M^++1). Anal. Calcd for $C_{15}H_{18}O_3S$: C, 64.72; H, 6.52. Found: C, 64.94; H, 6.66.
9. Debenzoylated thiophene was not observed for the benzoyl case (entry 8 in Table 1), and this may be due to the steric hindrance of the benzoyl moiety to be attacked by DDQ anion.
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