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Synthesis of 4-(2,2-dibromovinyl)phenol and its one-pot esterification

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Abstract In situ treatment of 4-(2,2-dibromovinyl)phenol, which was prepared from 4-hydroxybenzaldehyde and carbon tetrabromide in CH_2Cl_2 under Corey–Fuchs conditions, with a diverse range of acids in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) gave the corresponding esters in high yields.

Keywords *gem*-Dibromoalkene · Corey–Fuchs condition · One-pot · Synthesis · Esterification

Introduction

gem-Dibromoalkenes are versatile organic intermediates in organic synthesis. They have found wide applications in the synthesis of trisubstituted alkenes of defined stereochemistry by transition-metal-catalyzed site-selective monoarylation and monoalkylation reactions. The cross-coupling reaction of *gem*-dibromoalkenes with alkynes and organometallic reagents such as Grignard reagents, organozinc reagents, organostannanes, boronic acids, and derivatives can be stopped at the monosubstituted stage, giving the *trans*-configured main products [1, 2]. *gem*-Dibromoalkenes have also been widely used for the synthesis of alkynes [3, 4]. Besides, allylsilanes, one of the most useful functional groups for carbon–carbon bond forming reactions, can also be achieved by tandem cross-coupling of *gem*-dibromoalkenes with trimethysilylmethyl Grignard reagent and selective

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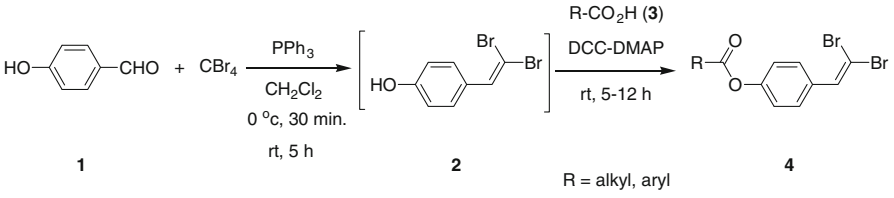
protodesilylation of the corresponding intermediates [5]. Direct coupling of 1,1-dibromoethenes with 2-aminophenols was proven to be useful method under mild reaction conditions for the synthesis of benzoxazoles, an important class of heterocyclic compounds due to their wide spectrum of biological and photochromatic activities [6]. Recently, a novel method for the iron-catalyzed ketonization of 2-aryl-1,1-dibromoalkenes with KOAc was reported achieving a series of α-acetoxy aryl ketones [7]. In addition, reduction of *gem*-dibromoalkenes provides an important method for the stereoselective synthesis of (E)-vinyl bromides [8], another kind of important cross-coupling reagent.

Condensation of aromatic aldehydes with CBr_4, known as Corey–Fuchs reaction, is an important method for the synthesis of *gem*-dibromoalkenes [9, 10]. However, the preparation of 4-(2,2-dibromovinyl)phenol, a kind of *gem*-dibromoalkene containing phenol fragment that shows some important properties in organic chemistry, was seldom reported. Our research on the synthesis of 4-(2,2-dibromovinyl)phenol showed that the reaction of 4-hydroxybenzaldehyde with carbon tetrabromide under an improved Corey–Fuchs condition could proceed smoothly although the expected product 4-(2,2-dibromovinyl)phenol is instable. According to Corey–Fuchs' procedure, dibromoolefins were formed by the addition of the aldehyde (1 equiv.) to a mixture of triphenylphoephine (4 equiv.) and carbon tetrabromide (2 equiv.) in methylene chloride at 0 °C with a reaction time of 5 min. In our procedure, a triphenylphoephine (4 equiv.) solution of methylene chloride was added dropwise to a stirred methylene chloride solution of 4-hydroxybenzaldehyde and carbon tetrabromide (2 equiv.) at 0 °C. The reaction system was stirred for 30 min at 0 °C and 5 h at room temperature. The product turns from a light-yellow solid to a vicious and brownish black solid when separated from the reaction system and exposed to the air for 5 days or stored in refrigerator at 4 °C for 20 days. In this paper, we wish to report the synthesis and tandem esterification of 4-(2,2-dibromovinyl)phenol, which may provide more stable derivatives of the synthetic intermediate (Scheme 1).

Results and discussion

4-(2,2-Dibromovinyl)phenol **2** was obtained in a yield of 90% by the reaction of 4-hydroxybenzaldehyde **1** and CBr_4 according to an improved procedure of Corey–Fuchs reaction [9, 10]. One-pot esterification of the intermediate **2** with various



Scheme 1 Synthesis and one-pot esterification of 4-(2,2-dibromovinyl)phenol

acids, without isolation from the condensation system, was achieved in high yields at room temperature. The results are summarized in Table 1.

This tandem esterification proved to be applicable not only for aliphatic acids such as formic acid, acetic acid, butyric acid, and ferrocenylformic acid, affording the corresponding esters **4a–d** in 84–91% yields (Table 1, entries 1–4), but also for aromatic acids such as benzoic acid, 4-methylbenzoic acid and 4-chlorolbenzoic acid, giving **4e–g** in 84–86% yields (Table 1, entries 5–7). In the case of α,β-unsaturated acids including cinnamic acid, (*E*)-3-(4-bromophenyl)acrylic acid and 3-ferrocenyl acrylic acid, the corresponding 3-acrylates **4 h–j** were also isolated in yields of 80–83% (Table 1, entries 8–10). The structures of **4a–j** were characterized by IR, ^{1}H NMR, ^{13}C NMR and elementary analysis.

Experimental

Melting points were recorded using WRS-1B digital melting point apparatus and were uncorrected. IR spectra were obtained on a Perkin-Elmer FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker DPX-400 spectrometer with $SiMe_4$ as an internal standard. Elemental analyses were performed with a Perkin-Elmer 2,400 CHNS elemental analyzer. All reactions were monitored by TLC with HuanghaiGF$_{254}$ silica gel-coated plates. Column chromatography was carried out using 300–400 mesh silica gel at medium pressure.

Synthesis of 4-(2,2-dibromovinyl)phenol

To a stirred CH_2Cl_2 solution (10 mL) of 4-hydroxybenzaldehyde **1** (122 mg, 1 mmol) and CBr_4 (663 mg, 2 mmol) was added dropwise PPh_3 (1,049 mg, 4 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction system was stirred for 30 min at 0 °C and 5 h at room temperature. After the completion of the reaction monitored by TLC, the reaction mixture was filtered through silicon gel. The filtrate was extracted with 10% NaOH (30 × 3 mL). To the combined aqueous layer was added 10% HCl under stirring to a pH of 5. The precipitate was filtered, washed with water, and dried over vacuum desiccator. Purification by column chromatography (silica gel, EtOAc-petroleum ether) afforded **2** as a light-yellow solid. Mp: 105.3–107.3 °C. IR (KBr): 3410, 1605, 1507, 1438, 1232, 873, 819 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.83 (2H, d, $J = 8.8$ Hz), 7.39 (1H, s), 7.43 (2H, d, $J = 8.8$ Hz), 7.55–7.67 (1H, br). ^{13}C NMR (100 MHz, $CDCl_3$): δ 87.19, 115.41, 127.80, 130.08, 136.33, 156.06. Anal. Calcd for $C_8H_6Br_2O$: C, 34.57; H, 2.18; Br, 57.50. Found: C, 34.51; H, 2.21; Br, 57.54.

One-pot esterification of 4-(2,2-dibromovinyl)phenol

To the reaction system for the synthesis of 4-(2,2-dibromovinyl)phenol was added acids **3** (1 mmol), DCC (231 mg, 1.1 mmol), and DMAP (12 mg, 0.1 mmol). The reaction system was stirred for 5–12 h at room temperature. After the completion of the esterification screened by TLC, the reaction mixture was filtered through silicon

Table 1 One-pot esterification of 4-(2,2-dibromovinyl)phenol

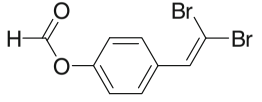
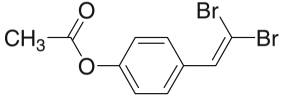
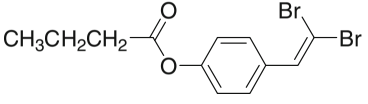
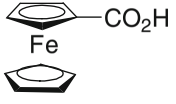
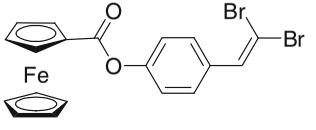
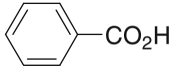
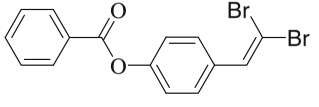
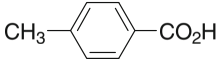
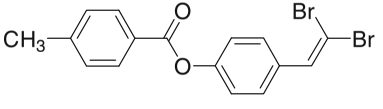
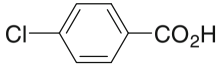
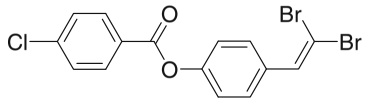
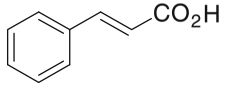
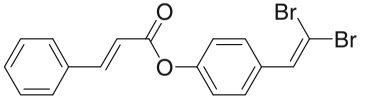
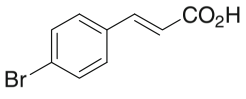
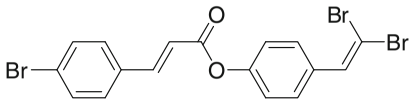
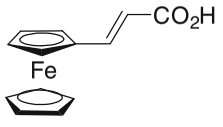
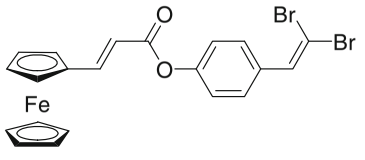
Entry	Acids **3**	Products **4**[a]	Time (h)	Yields of **4**[b] (%)
1	HCO_2H		5	91 (**4a**)
2	CH_3CO_2H		5	87 (**4b**)
3	$CH_3CH_2CH_2CO_2H$		8	85 (**4c**)
4			12	84 (**4d**)
5			12	86 (**4e**)
6			12	84 (**4f**)

Table 1 continued

Entry	Acids **3**	Products **4**[a]	Time (h)	Yields of **4**[b] (%)
7			12	85 (**4 g**)
8			12	82 (**4 h**)
9			12	83 (**4i**)
10			12	80 (**4j**)

[a] Reaction conditions: To the reaction system for the synthesis of 4-hydroxybenzaldehyde was added: acids **2**, 1 mmol; DCC, 1.1 mmol; DMAP, 10 (mol) %; rt, 5–12 h

[b] Isolated yields based on 4-hydroxybenzaldehyde **1**

gel. The filtrate was washed with saturated brine (20 × 2 mL) and water (20 mL). The organic layer was dried over Na_2SO_4, concentrated under reduced pressure, and dried in high vacuum. Purification of the residue by column chromatography (silica gel, EtOAc-petroleum ether) afforded **4**.

4-(2,2-Dibromovinyl)phenyl formate ***4a***

Mp: 99.3–99.8 °C. IR (KBr): 3006, 1604, 1506, 1231, 1180, 873, 819 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.11 (1H, s), 6.82 (2H, d, $J = 8.8$ Hz), 7.39 (1H, s), 7.46 (2H, d, $J = 8.8$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 87.50, 115.31, 128.11, 130.09, 130.12, 136.20, 155.66. Anal. Calcd for $C_9H_6Br_2O_2$: C, 35.33; H, 1.98; Br, 52.23. Found: C, 35.35; H, 1.97; Br, 52.27.

4-(2,2-Dibromovinyl)phenyl acetate ***4b***

Vicious light-yellow liquid. IR (KBr): 2926, 1763, 1603, 1504, 1206, 1169, 913 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.31 (3H, s), 7.10 (2H, d, $J = 8.8$ Hz), 7.46 (1H, s), 7.55 (2H, d, $J = 8.8$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.09, 89.82, 121.58, 129.54, 132.87, 135.88, 150.49, 169.09. Anal. Calcd for $C_{10}H_8Br_2O_2$: C, 37.54; H, 2.52; Br, 49.94. Found: C, 37.59; H, 2.50; Br, 49.91.

4-(2,2-Dibromovinyl)phenyl butyrate ***4c***

Mp: 44.8–45.8 °C. IR (KBr): 3015, 2963, 1750, 1598, 1505, 1209, 1174, 1147, 836 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.04 (3H, t, $J = 7.2$ Hz), 1.74–1.83 (2H, m), 2.54 (2H, t, $J = 7.2$ Hz), 7.09 (2H, d, $J = 8.8$ Hz), 7.45 (1H, s), 7.55 (2H, d, $J = 8.8$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.64, 18.44, 36.24, 89.80, 121.65, 129.57, 132.81, 135.98, 150.64, 171.85. Anal. Calcd for $C_{12}H_{12}Br_2O_2$: C, 41.41; H, 3.48; Br, 45.92. Found: C, 41.46; H, 3.49; Br, 45.85.

4-(2,2-Dibromovinyl)phenyl benzoate ***4d***

Mp: 104.9–106.7 °C. IR (KBr): 1738, 1595, 1504, 1450, 1263, 1204, 1171, 1059, 707 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.24 (2H, d, $J = 8.8$ Hz), 7.49 (1H, s), 7.52–7.67 (5H, m), 8.20 (2H, d, $J = 8.8$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 98.93, 121.79, 128.64, 129.33, 129.66, 130.22, 133.00, 133.76, 135.97, 150.83, 164.91. Anal. Calcd for $C_{15}H_{10}Br_2O_2$: C, 47.16; H, 2.64; Br, 41.83. Found: C, 47.25; H, 2.69; Br, 41.75.

4-(2,2-Dibromovinyl)phenyl 4-methylbenzoate ***4e***

Mp: 110.9–111.5 °C. IR (KBr): 1736, 1609, 1508, 1278, 1218, 1077 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 2.43 (3H, s), 7.34 (2H, d, $J = 8.4$ Hz), 7.42 (2H, d, $J = 8.0$ Hz), 7.70 (2H, d, $J = 8.0$ Hz), 7.82 (1H, s), 8.03 (2H, d, $J = 8.4$ Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.42, 89.53, 122.25, 126.14, 129.70, 129.73,

130.03, 132.89, 136.38, 144.81, 150.70, 164.51. Anal. Calcd for $C_{16}H_{12}Br_2O_2$: C, 48.52; H, 3.05; Br, 40.35. Found: C, 48.58; H, 3.03; Br, 40.32.

4-(2,2-Dibromovinyl)phenyl 4-chlorobenzoate ***4f***

Mp: 127.4–127.9 °C. IR (KBr): 1733, 1590, 1504, 1278, 1210, 1167, 1081 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 7.37 (2H, d, $J = 8.4$ Hz), 7.69 (2H, d, $J = 5.2$ Hz), 7.71 (2H, d, $J = 5.2$ Hz), 7.83 (1H, s), 8.13 (2H, d, $J = 8.4$ Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 89.66, 122.18, 127.81, 129.33, 129.76, 131.84, 133.09, 136.35, 139.25, 150.51, 163.74. Anal. Calcd for $C_{15}H_9Br_2ClO_2$: C, 43.26; H, 2.18; Br, 38.37. Found: C, 43.21; H, 2.15; Br, 38.45.

4-(2,2-Dibromovinyl)phenyl ferrocenylcarboxylate ***4 g***

Mp: 77.0–78.7 °C. IR (KBr): 1731, 1598, 1506, 1451, 1266, 1204, 1099, 817 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 4.36 (5H, s), 4.62 (2H, s), 4.93 (2H, s), 7.29 (2H, d, $J = 8.4$ Hz), 7.69 (2H, d, $J = 8.4$ Hz), 7.82 (1H, s). ^{13}C NMR (100 MHz, DMSO-d_6): δ 69.35, 70.03, 70.45, 72.37, 89.40, 122.28, 129.73, 132.65, 136.43, 150.61, 169.62. Anal. Calcd for $C_{19}H_{14}Br_2FeO_2$: C, 46.58; H, 2.88; Br, 32.62. Found: C, 46.65; H, 2.85; Br, 32.53.

4-(2,2-Dibromovinyl)phenyl cinnamate ***4 h***

Mp: 117.3–118.3 °C. IR (KBr): 1743, 1634, 1600, 1576, 1505, 1310, 1220, 1138, 767 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 6.89 (1H, d, $J = 15.6$ Hz), 7.28 (2H, d, $J = 8.8$ Hz), 7.44–7.48 (3H, m), 7.68 (2H, d, $J = 8.8$ Hz), 7.80–7.83 (3H, m), 7.88 (1H, d, $J = 15.6$ Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 89.47, 117.16, 122.15, 128.85, 129.17, 129.72, 131.11, 132.79, 133.97, 136.38, 146.87, 150.54, 164.88. Anal. Calcd for $C_{17}H_{12}Br_2O_2$: C, 50.03; H, 2.96; Br, 39.16. Found: C, 50.10; H, 2.99; Br, 39.07.

(E)-4-(2,2-Dibromovinyl)phenyl 3-(4-bromophenyl)acrylate ***4i***

Mp: 147.1–148.4 °C. IR (KBr): 3089, 2947, 1741, 1635, 1505, 1220, 1145, 1071, 820 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 6.94 (1H, d, $J = 16.0$ Hz), 7.28 (2H, d, $J = 8.8$ Hz), 7.66 (2H, d, $J = 6.0$ Hz), 7.68 (2H, d, $J = 6.0$ Hz), 7.78 (1H, d, $J = 8.8$ Hz), 7.81 (1H, s), 7.86 (1H, d, $J = 16.0$ Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 89.50, 118.07, 122.12, 124.55, 129.73, 130.76, 132.15, 132.83, 133.28, 136.37, 145.52, 150.49, 164.74. Anal. Calcd for $C_{17}H_{11}Br_3O_2$: C, 41.93; H, 2.28; Br, 49.22. Found: C, 41.96; H, 2.24; Br, 49.27.

4-(2,2-Dibromovinyl)phenyl 3-ferrocenyl acrylate ***4j***

Mp: 138.7–139.9 °C. IR (KBr): 1716, 1624, 1598, 1505, 1208, 1170, 1143, 876 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 4.23 (5H, s), 4.54 (2H, s), 4.80 (2H, s), 6.37 (1H, d, $J = 15.6$ Hz), 7.26 (2H, d, $J = 8.4$ Hz), 7.67 (2H, d, $J = 8.4$ Hz),

7.75 (1H, d, $J = 15.6$ Hz), 7.81 (1H, s). ^{13}C NMR (100 MHz, DMSO-d_6): δ 69.27, 69.75, 71.48, 78.14, 89.31, 113.18, 122.18, 129.64, 132.54, 136.41, 148.98, 150.73, 164.81. Anal. Calcd for $C_{21}H_{16}Br_2FeO_2$: C, 48.88; H, 3.13; Br, 30.97. Found: C, 48.94; H, 3.10; Br, 30.91.

Conclusions

In conclusion, we developed a facile method for the synthesis of 4-(2,2-dibromovinyl)phenol and its tandem esterification catalyzed by DCC-DMAP under mild conditions in high yields. The synthetic applications of these *gem*-dibromoalkene compounds in metal-catalyzed cross-coupling reaction were in progress in our laboratory.

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