Synthesis of Symmetric Diallyl Disulfides from Baylis-Hillman Acetates

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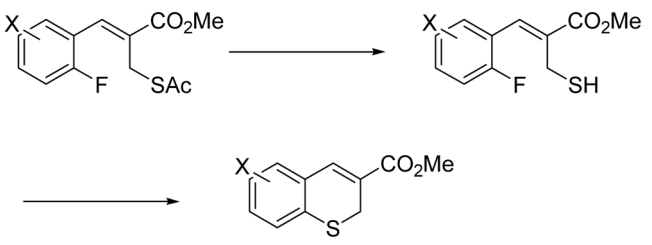
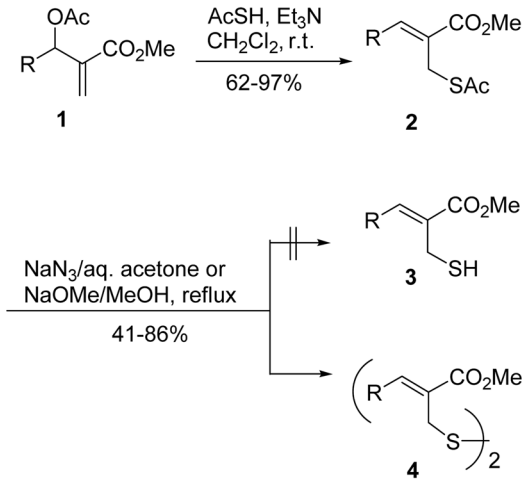
During the past decade, the Baylis-Hillman (BH) reaction has been extensively studied and is now one of the most efficient carbon-carbon bond forming reaction.[1] Much attention has recently been focused on the S_N2' nucleophilic substitution of the BH adducts with a variety of nucleophiles[2] and many heterocycles have been synthesizied including quinolines,[3] dihydroquinolines,[4] quinolones,[5] pyrrolidines,[6] coumarins[2] and indoles.[7] It was reported that 2,2'-dithiodibenzaldehyde could be used as a masked thiosalicyl aldehyde in the BH reaction with suitably activated alkenes in the presence of DBU to give thiochromenes.[8] However, the most obvious drawback is that the starting dithiodibenzaldehyde is not available commercially. As part of our continuing studies towards development of the BH chemistry,[9] we desired to have the thiol group at the allylic position of 3-aryl-2-propenoates. To the best of our knowledge, there are only limited number of reports in the literature[10] for the conversion of the BH adducts into the corresponding 2-acetylthiomethyl-2-propenoates in acidic conditions using thiolacetic acid, but the thiolacetylation of the BH acetates is not known. In principle, such acetylthiomethyl compounds after hydrolysis of thiolester group might be extended further toward the building of thiochromene derivatives *via* an intramolecular nucleophilic aromatic substitution reaction as shown in Scheme 1.

The readily available BH acetates **1a-h**[2,11] provided a convenient starting point for the synthesis of 2-acetylthiomethyl-2-propenoates **2a-h.** Treatment of the BH acetates **1a-h** with thiolacetic acid in the presence of triethylamine at room temperature gave the 2-acetylthiomethyl-2-propenoates **2a-h** in good to excellent yields as shown in Table 1 (Scheme 2).

The stereochemistry of the products was established by compairing ^{1}H NMR values of olefinic proton with literature values of similar compounds.[12] In all cases, the stereoselectivity was found to be 100% (*E*)-selectivity. In order to prepare the unknown thiol derivative **3**, we carried out the



Scheme 1



Scheme 2

Table 1. Methyl (*E*)-3-Aryl-2-acetylthiomethyl-2-propenoates **2**

Reactant	R	Product	Yield (%)	Time
1a	2,4,5-$F_3C_6H_2$	**2a**	62	2 h
1b	2-Cl-5-$NO_2C_6H_3$	**2b**	75	10 min
1c	2,3-$Cl_2C_6H_3$	**2c**	68	1 h
1d	C_6H_5	**2d**	92	1.5 h
1e	2-FC_6H_4	**2e**	89	2.5 h
1f	2-BrC_6H_4	**2f**	97	10 min
1g	4-ClC_6H_4	**2g**	75	10 min
1h	4-$MeOC_6H_4$	**2h**	87	0.5 h

hydrolysis of thioacetyl derivative **2a** with weakly basic NaN_3 in aqueous acetone[13] at reflux temperature. The desired allyl thiol **3a** was not obtained. Instead, symmetric diallyl disufides **4a** produced in 71% yield. This result led us to transform the representative acetylthiomethyl derivatives **2b-h** into diallyl disufides **4b-h** under the similar reaction conditions. We then examined the effect of the base. In the case of using NaOMe in methanol the same reaction occurred rapidly, but the yields of disulfides are generally low. The results and reaction conditions were summarized in Table 2.

The interconversion of thiols and disulfides is a fundamental transformation in organosulfur chemistry and such switching plays important role in biological system.[14]

The easy oxidation of thiols on exposure to air is well known.[15] It is also known that autooxidation of thiols is accelerated by bases.[16] Literatures reveal the availability of a

Table 2. Diallyl Disufides **4**

Ractant	R	Product	Method[a]	Yield (%)	Time (h)
2a	2,4,5-$F_3C_6H_2$	**4a**	A	71	7
2b	2-Cl-5-$NO_2C_6H_3$	**4b**	A	67	20
			B	61	5
2c	2,3-$Cl_2C_6H_3$	**4c**	A	70	10
2d	C_6H_5	**4d**	A	86	18
			B	65	0.5
2e	2-FC_6H_4	**4e**	A	60	15
2f	2-BrC_6H_4	**4f**	A	86	25
			B	44	4
2g	4-ClC_6H_4	**4g**	A	82	16
			B	41	0.5
2h	4-$MeOC_6H_4$	**4h**	A	83	20
			B	51	1

[a]Method A: NaN_3 in 50% aqueous acetone. Method B: NaOMe in MeOH

variety of techniques for preparing both symmetric and unsymmetric disulfides, many of which are based upon the reaction of a thiol with a sulfenylating agent such as sulfenyl halides,[17] sulfenamides,[18] sulfenimides,[19] sulfenylhydrazides,[20] and disulfides.[21]

In summary, we have demonstrated an efficient synthesis of symmetric diallyl disulfides by treatment of the Baylis-Hillman acetates with thiolacetic acid followed by hydrolysis with sodium azide. Further studies on their use in various chemical transformations including thiochromene synthesis are now in progress.

Experimental Section

Silica gel 60 (70-230 mesh ASTM) used for column chromatography was supplied by E. Merck. Analytical TLC analysis was carried out on a Merck silica gel 60 F_{254} TLC plates. Melting points were taken using an Electrothermal melting point apparatus and are uncorrected. Electron impact (EI) mass spectra were obtained using a Jeol SX102 mass spectrometer. IR spectra were recorded on a Nicolet Magna 550 FTIR spectrometer. The ^{1}H and ^{13}**C** NMR spectra were measured on a Gemini 300 spectrometer using $CDCl_3$. All chemical shifts are reported in ppm relative to TMS and coupling constants (J) are expressed in Hz.

All the required Baylis-Hillman acetates **1a-h** were prepared by the reaction of the corresponding aldehydes with methyl acrylate in the presence of DABCO followed by acetylation with acetic anhydride according to the literature procedures.[2,11]

Methyl (*E*)-3-Aryl-2-acetylthiomethyl-2-propenoates 2a-h; General Procedure: To a stirred solution of **1** (2 mmol) in CH_2Cl_2 (5 mL) was added CH_3COSH (0.17 g, 2.2 mmol) and Et_3N (0.24 g, 2.4 mmol) at r.t. After stirring at the same temperature for the time indicated in Table 1, the reaction mixture was diluted with water (5 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was evaporated *in vacuo*. The reaction mixture was chromatographed on silica gel eluting with hexane/EtOAc (5 : 1) to afford pure **2.**

The physical and spectral data of **2a-h** prepared by this general method are as follows.

2a: 62%, white solid, mp 59-59.5 °C; IR (KBr) 1706, 1680, 1631, 1505, 1431, 1335 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 3.95 (s, 2H, CH_2), 6.97-7.05 (m, 1H, Ar), 7.23-7.31 (m, 1H, Ar), 7.68 (s, 1H, CH).

2b: 75%, yellow solid, mp 68-69 °C; IR (KBr) 1711, 1696, 1607, 1523, 1441, 1347 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3H, CH_3), 3.87 (s, 2H, CH_2), 3.88 (s, 3H, OCH_3), 7.63 (d, J = 8.9 Hz, 1H, Ar), 7.79 (s, 1H, CH), 8.17-8.23 (m, 2H, Ar).

2c: 68%, white solid, mp 82 °C; IR (KBr) 1707, 1690, 1451, 1437, 1419, 1361, 1286 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 3.89 (s, 2H, CH_2), 7.21-7.29 (m, 2H, Ar), 7.47-7.50 (m, 1H, Ar), 7.82 (s, 1H, CH).

2d: 92%, oil; IR (CH_2Cl_2) 1715, 1693, 1630, 1435, 1267 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.04 (s, 2H, CH_2), 7.31-7.38 (m, 5H, Ar), 7.78 (s, 1H, CH).

2e: 89%, white solid, mp 50-51 °C; IR (KBr) 1715, 1685, 1633, 1610, 1483, 1435, 1309, 1260 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.00 (s, 2H, CH_2), 7.09-7.22 (m, 2H, Ar), 7.34-7.41 (m, 2H, Ar), 7.84 (s, 1H, CH).

2f: 97%, white solid, mp 69 °C; IR (KBr) 1704, 1466, 1437, 1419, 1361, 1286 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 3.91 (s, 2H, CH_2), 7.21-7.39 (m, 3H, Ar), 7.63 (d, J = 7.9 Hz, 1H, Ar), 7.81 (s, 1H, CH).

2g: 75%, white solid, mp 70-71 °C; IR (KBr) 1718, 1686, 1623, 1591, 1491, 1422, 1269 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 4.03 (s, 2H, CH_2), 7.33 (d, J = 8.8 Hz, 2H, Ar), 7.40 (d, J = 8.3 Hz, 2H, Ar), 7.75 (s, 1H, CH).

2h: 87%, oil; IR (CH_2Cl_2) 1709, 1690, 1604, 1512, 1436, 1259 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.11 (s, 2H, CH_2), 6.94 (d, J = 8.8 Hz, 2H, Ar), 7.39 (d, J = 8.8 Hz, 2H, Ar), 7.76 (s, 1H, CH).

Diallyl Disulfides 4a-h; General Procedure: Method A: To a solution of **2a-h** (2 mmol) in 50% aqueous acetone (10 mL) was added NaN_3 (0.19 g, 3 mmol) and stirred at reflux temperature for the time indicated in Table 2. The reaction mixture was concentrated under reduced pressure and the residue was extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were dried over anhydrous $MgSO_4$ and the solvent was evaporated *in vacuo*. The reaction mixture was chromatographed on silica gel eluting with hexane/EtOAc (10 : 1) to afford pure **4a-h**.

The physical and spectral data of **4a-h** prepared by this general method are as follows.

4a: 71%, white solid, mp 102-103 °C; IR (KBr) 1720, 1635, 1619, 1503, 1427, 1332, 1295, 1260 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.66 (s, 4H, CH_2), 3.87 (s, 6H, OCH_3), 6.94-7.03 (m, 2H, Ar), 7.50-7.59 (m, 2H, Ar), 7.69 (s, 2H, CH); ^{13}C NMR ($CDCl_3$) δ 30.1, 52.6, 105.9, 118.0, 131.4, 145.1, 148.7, 152.3, 154.2, 157.6, 166.7; MS: m/z (%) = 522 (2) [M^+], 491 (24), 459 (17), 261 (60), 229 (100), 169 (35).

4b: 67%, yellow solid, mp 151-152 °C; IR (KBr) 1708,

1639, 1598, 1562, 1515, 1437, 1338, 1280 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.83 (s, 4H, CH_2), 3.88 (s, 6H, OCH_3), 7.40 (d, J = 8.5 Hz, 2H, Ar) 7.58 (s, 2H, CH), 8.02-8.09 (m, 4H, Ar); ^{13}C NMR ($CDCl_3$) δ 24.0, 52.6, 124.4, 124.5, 124.8, 127.3, 131.5, 135.5, 143.5, 145.6, 165.5; MS: m/z (%) = No M^+, 251 (40), 236 (100), 192 (26), 190 (43), 146 (39), 102 (22).

4c: 70%, white solid, mp 85-86 °C; IR (KBr) 1702, 1630, 1580, 1557, 1451, 1435, 1410, 1284, 1254 cm^{-1}; ^1H NMR ($CDCl_3$) δ3.51 (s, 4H, CH_2), 3.85 (s, 6H, OCH_3), 7.23-7.48 (m, 6H, Ar), 7.75 (s, 2H, CH); ^{13}C NMR ($CDCl_3$) δ 30.1, 52.4, 127.3, 128.5, 130.6, 131.3, 133.5, 135.5, 137.5, 138.2, 166.9; MS: m/z (%) = 550 (3) [M^+], 483 (17), 275 (10), 243 (100), 183 (75), 149 (82).

4d: 86%, oil; IR (CH_2Cl_2) 1716, 1627, 1493, 1447, 1434, 1266 cm^{-1}; ^1H NMR ($CDCl_3$) δ3.74 (s, 4H, CH_2), 3.84 (s, 6H, OCH_3), 7.30-7.52 (m, 10H, Ar), 7.76 (s, 2H, CH); ^{13}C NMR ($CDCl_3$) δ 30.1, 52.2, 128.6, 128.9, 129.0, 129.7, 134.9, 141.1, 167.8; MS: m/z (%) = 414 (2) [M^+], 207 (11), 175 (80), 115 (100), 91 (20).

4e: 60%, white solid, mp 87.5-88.5 °C; IR (KBr) 1711, 1630, 1608, 1482, 1455, 1436, 1309, 1265 cm^{-1}; ^1H NMR ($CDCl_3$) δ3.66 (s, 4H, CH_2), 3.84 (s, 6H, OCH_3), 7.05-7.38 (m, 6H, Ar), 7.57-7.62 (m, 2H, Ar), 7.79 (s, 2H, CH); ^{13}C NMR ($CDCl_3$) δ 30.3, 52.3, 115.6, 122.8, 124.2, 130.7, 133.4, 134.5, 158.8, 162.1, 167.2; MS: m/z (%) = 450 (6) [M^+], 419 (20), 387 (25), 225 (32), 193 (100), 133 (47).

4f: 86%, white solid, mp 84.5 °C; IR (KBr) 1709, 1623, 1584, 1464, 1432, 1295, 1253 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.53 (s, 4H, CH_2), 3.84 (s, 6H, OCH_3), 7.18-7.60 (m, 8H, Ar), 7.73 (s, 2H, CH); ^{13}C NMR ($CDCl_3$) δ 30.1, 52.3, 124.3, 127.4, 130.1, 130.5, 132.8, 135.3, 139.9, 141.0, 167.2; MS: m/z (%) = No M^+, 461 (18), 459 (18), 334 (8), 332 (7), 320 (13), 318 (12), 293 (58), 255 (40), 253 (50), 205 (42), 174 (88), 147 (40), 115 (100).

4g: 82%, oil; IR (CH_2Cl_2) 1715, 1627, 1591, 1490, 1434, 1264 cm^{-1}; ^1H NMR ($CDCl_3$) δ3.71 (s, 4H, CH_2), 3.85 (s, 6H, OCH_3), 7.38 (d, J = 8.5 Hz, 4H, Ar), 7.43 (d, J = 8.5 Hz, 4H, Ar), 7.70 (s, 2H, CH); ^{13}C NMR ($CDCl_3$) δ30.1, 52.3, 128.9, 129.3, 131.0, 133.2, 135.1, 139.8, 167.5; MS: m/z (%) = 482 (1) [M^+], 243 (34), 241 (92), 211 (36), 209 (100), 181 (21), 149 (71), 115 (53).

4h: 83%, white solid, mp 68-69 °C; IR (KBr) 1709, 1604, 1571, 1511, 1435, 1305, 1259 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.80 (s, 4H, CH_2), 3.84 (s, 6H, OCH_3), 6.92 (d, J = 8.8 Hz, 4H, Ar), 7.52 (d, J = 8.8 Hz, 4H, Ar), 7.72 (s, 2H, CH); ^{13}C NMR ($CDCl_3$) δ30.2, 52.1, 55.3, 114.1, 126.4, 127.4, 131.8, 141.0, 160.4, 168.1; MS: m/z (%) = No M^+, 237 (86), 205 (79), 177 (24), 145 (100).

Method B: To a solution of the appropriate **2** (2 mmol) in CH_3OH (5 mL) was added $NaOCH_3$ (0.12 g, 2.2 mmol) and stirred at reflux temperature for the time indicated in Table 2. The work-up procedure was the same as described above to afford the corresponding **4**.

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