Synthesis of 5-Arylthio-3-hydroxyphthalates by the First [4+2] Cycloadditions of 3-Arylthio-1-silyloxy-1,3-butadienes with Dimethyl Acetylenedicarboxylate

Inam Iqbal,[a] Muhammad Imran,[a] Peter Langer*[a,b]

[a] Institut für Chemie, Universität Rostock, Albert Einstein Str. 3a, 18059 Rostock, Germany
E-mail: peter.langer@uni-rostock.de

[b] Leibniz-Institut für Katalyse an der Universität Rostock e.V., Albert Einstein Str. 29a, 18059 Rostock, Germany

Received 2 January 2009; revised 26 March 2009

Abstract: A variety of 5-arylthio-3-hydroxyphthalates were prepared by [4+2] cycloadditions of 3-arylthio-1-trimethylsilyloxy-1,3-butadienes with dimethyl acetylenedicarboxylate.

Key words: arenes, cyclizations, diaryl sulfides, regioselectivity, silyl enol ethers

Diaryl sulfides are of pharmacological importance and are found in many natural products. Such compounds include, for example, the lissoclibadins, dibenzothiophenes, cyclic sulfides, varacins (lissoclinotoxins), and related natural products.[1] Diaryl sulfides are available by reaction of arenes with sulfur[2] or sulfur dichloride,[3] by condensation of organometallic reagents with chlorophenylsulfides[4] or by base-mediated reactions of thiophenols with chloroarenes.[5] However, competing formation of polysulfides and (in several cases) the low regioselectivities of the reactions are severe drawbacks of these classic synthetic approaches. In recent years, a number of transition-metal catalyzed[6] and metal-free,[7] carbon–sulfur coupling reactions have been developed which allow the formation of diaryl sulfides under mild conditions. However, reactions of sterically encumbered substrates are often difficult or not possible at all. In addition, the synthesis of the starting materials – substituted aryl halides or triflates – can be a difficult and tedious task.

An alternative approach to the synthesis of diaryl sulfides is based on the use of sulfur-containing building blocks in cyclization reactions. Hilt and co-workers reported a convenient approach to diaryl sulfides by cobalt(I)-catalyzed [4+2] cycloaddition of alkynyl sulfides with 1,3-butadienes.[8] Recently, we have studied[9] the synthesis of 3- and 5-(arylthio)salicylates by titanium tetrachloride-mediated formal [3+3] cyclizations[10] of 1,3-bis(silyloxy)-1,3-butadienes[11] with 3-silyloxy-2-en-1-ones.[12] Chan et al. reported the synthesis of 2-(phenylthio)benzoates by $TiCl_4$-mediated [3+3] cyclization of 3-silyloxy-2-en-1-ones with 1-methoxy-3-phenylthio-1-trimethylsilyloxy-1,3-butadiene.[13] We have recently reported the synthesis of 5-chloroethyl-2-(arylthio)benzoates by $TiCl_4$-mediated domino '[3+3] cyclization / homo-Michael' reaction of 3-arylthio-1-trimethylsilyloxy-1,3-butadienes with 1,1-diacylcyclopropanes.[14]

Herein, we report on the [4+2] cycloaddition reactions of 3-arylthio-1-trimethylsilyloxy-1,3-butadienes with dimethyl acetylenedicarboxylate (DMAD). This method provides a convenient and general approach to a wide range of novel 5-arylthio-3-hydroxyphthalates which are not readily available by other methods. In contrast to the C–S coupling reactions outlined above, the method reported herein relies on the assembly of one of the two arene moieties.

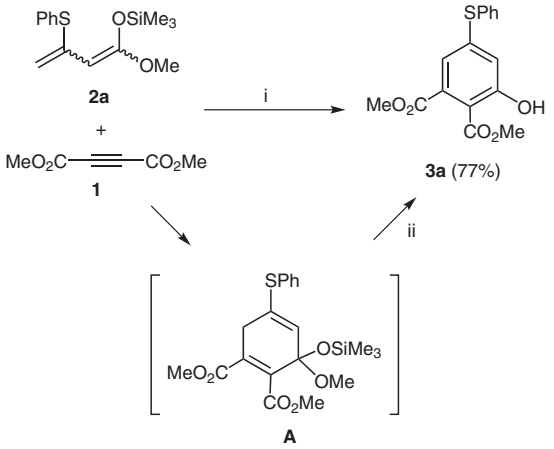
The known 3-arylthio-1-trimethylsilyloxy-1,3-butadienes **2a–j** were prepared from either methyl acetoacetate or methyl 3-oxopentanoate and from the corresponding thiophenols in two steps.[13,15,16]

The [4+2] cycloaddition of DMAD (**1**) with 3-phenylthio-1-trimethylsilyloxy-1,3-butadiene (**2a**) resulted in formation of the 5-phenylthio-3-hydroxyphthalate (**3a**) in up to 77% yield (Scheme 1). The best yields were obtained when a **2a/1** ratio of ~1:2 was used, when the reaction was carried out without solvent (neat), when the temperature was allowed to slowly rise from –78 °C to 20 °C, and when an aqueous solution of ammonium chloride was used for the work-up (to induce the aromatization). An inseparable 1:2 mixture of **3a** and 5-phenylthio-3-methoxyphthalate was reported to be obtained when a benzene solution of the starting materials was stirred at –10 °C for 16 hours and when the reaction was quenched by addition of tetrahydrofuran and hydrochloric acid (5%).[13] The reaction presumably proceeds by cycloaddition to give intermediate **A** (Scheme 1). Subsequently, cleavage of the silyl ether under the acidic work-up conditions and elimination of methanol from the intermediary hemiacetal, afforded the product **3a**.

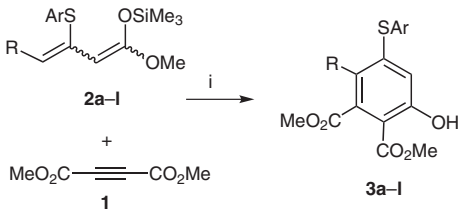
The cyclization of DMAD with 3-arylthio-1-trimethylsilyloxy-1,3-butadienes **2a–l** afforded the novel 5-arylthio-3-hydroxyphthalates **3a–l** in moderate to good yields (Scheme 2, Table 1). A wide range of products could be successfully prepared. The best yields were obtained for products derived from dienes containing an electron-rich aryl group. The yield of product **3h**, containing a bulky naphthyl group, was lower than the yield of **3a**, which contains a phenyl group. The yields dropped slightly using dienes containing a C-4 methyl group.

SYNTHESIS 2009, No. 14, pp 2430–2434
Advanced online publication: 27.05.2009
DOI: 10.1055/s-0029-1216828; Art ID: T00109SS
© Georg Thieme Verlag Stuttgart · New York

Downloaded by: Collections and Technical Services Department. Copyrighted material.



Scheme 1 Possible mechanism for the formation of arene **3a**. *Reagents and conditions*: (i) (a) neat, –78 to 20 °C, 20 h; (b) NH_4Cl, H_2O; (ii) NH_4Cl, H_2O.



Scheme 2 Synthesis of arenes **3a–l**. *Reagents and conditions*: (i) (a) neat, –78 to 20 °C, 20 h; (b) NH_4Cl, H_2O.

Table 1 Synthesis of Arenes **3a–l**

2,**3**	R	Ar	Yield of **3** (%)[a]
a	H	Ph	77
b	H	4-MeC_6H_4	69
c	H	4-ClC_6H_4	64
d	H	4-FC_6H_4	51
e	Me	4-EtC_6H_4	64
f	H	4-EtC_6H_4	69
g	H	3-MeC_6H_4	67
h	H	2-Naphthyl	54
i	H	3-ClC_6H_4	60
j	Me	4-MeC_6H_4	59
k	Me	4-ClC_6H_4	55
l	Me	4-FC_6H_4	53

[a] Yield of isolated products.

In conclusion, we have reported a convenient synthesis of a variety of 5-arylthio-3-hydroxyphthalates by the first [4+2] cycloadditions of 3-arylthio-1-trimethylsilyloxy-1,3-butadienes with dimethyl acetylenedicarboxylate. The scope and applications of this methodology are currently under study in our laboratory.

All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For ^1H and ^{13}C NMR spectra, the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, H_2O) or electrospray ionization (ESI). IR spectra were recorded using the indicated techniques. For preparative scale chromatography, silica gel (60–200 mesh) was used. Melting points are uncorrected. Dienes 2a–l were prepared according to the literature.[13,15,16]

General Procedure

To neat **2a–l** (1.5 mmol), was added **1** (2.25 mmol) at –78 °C. The solution was allowed to warm to 20 °C during 20 h with stirring. To the solution was added aq NH_4Cl (10%, 25 mL) and CH_2Cl_2 (20 mL). The organic and the aqueous layers were separated and the latter was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo to give a residue which was purified by chromatography (EtOAc–heptanes, 1:9).

Dimethyl 3-Hydroxy-5-phenylsulfanylphthalate (3a)

Starting with **2a** (420 mg, 1.5 mmol) and **1** (319 mg, 2.25 mmol), **3a** was isolated.

Yield: 367 mg (77%); highly viscous oil.

IR (KBr): 3057 (w), 3000 (w), 2950 (w), 2845 (w), 1732 (s), 1668 (s), 1596 (s), 1556 (m), 1474 (m), 1437 (s), 1329 (s), 1265 (s), 1197 (s), 1167 (s), 1120 (s), 1068 (m), 1016 (s), 933 (m), 852 (m), 802 (m), 774 (m), 744 (s), 689 (s), 562 (m) cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 3.65 (s, 3 H, OCH_3), 3.69 (s, 3 H, OCH_3), 6.48–7.32 (m, 7 H_{arom}), 10.57 (s, 1 H, OH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 52.6 (OCH_3), 52.8 (OCH_3), 106.6 (C), 116.2, 117.1, 129.5 (CH_{arom}), 129.9 (2 × CH_{Ar}), 130.0 (C), 134.8 (2 × CH_{arom}), 135.7, 148.3, 161.7, 168.9, 169.0 (C).

MS (EI, 70 eV): *m*/*z* (%) = 319 (18), 318 (100) [M^+], 287 (34), 285 (55), 270 (11), 269 (65), 253 (16), 228 (20), 226 (10), 200 (27), 198 (11), 171 (25).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{16}H_{14}O_5S$: 318.05565; found: 318.055736.

Dimethyl 3-Hydroxy-5-(4-methylphenylsulfanyl)phthalate (3b)

Starting with **2b** (441 mg, 1.5 mmol) and **1** (319 mg, 2.25 mmol), **3b** was isolated.

Yield: 344 mg (69%); highly viscous oil.

IR (KBr): 3022 (w), 2998 (w), 2950 (w), 2921 (w), 2847 (w), 1733 (s), 1668 (s), 1595 (s), 1555 (m), 1491 (m), 1433 (s), 1331 (s), 1266 (s), 1196 (s), 1164 (s), 1120 (s), 1016 (s), 934 (m), 852 (m), 802 (s), 773 (m), 744 (m), 703 (m), 636 (m), 586 (m), 567 (m) cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 2.32 (s, 3 H, CH_3), 3.77 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 6.54–6.60 (dd, *J* = 1.8 Hz, 2 H_{arom}), 7.17 (d, *J* = 8.2 Hz, 2 H_{arom}), 7.35 (d, *J* = 8.2 Hz, 2 H_{arom}), 10.69 (s, 1 H, OH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 21.3 (CH_3), 52.6 (OCH_3), 52.7 (OCH_3), 106.3 (C), 115.6, 116.7 (CH_{arom}), 126.0, 130.6 (C), 130.7 (2 × CH_{arom}), 135.1 (2 × CH_{arom}), 140.0, 149.1, 161.5, 169.0, 169.1 (C).

MS (EI, 70 eV): *m*/*z* (%) = 333 (17), 332 (100) [M^+], 301 (22), 299 (34), 285 (15), 283 (47), 267 (12), 242 (11), 214 (15).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{17}H_{16}O_5S$: 332.07130; found: 332.071408.

Dimethyl 3-Hydroxy-5-(4-chlorophenylsulfanyl)phthalate (3c)

Starting with **2c** (471mg, 1.5 mmol) and **1** (319 mg, 2.25 mmol), **3c** was isolated.

Downloaded by: Collections and Technical Services Department. Copyrighted material.

Yield: 338 mg (64%); highly viscous oil.

IR (KBr): 3079 (w), 3044 (w), 3006 (w), 2955 (w), 2853 (w), 1727 (s), 1673 (s), 1594 (s), 1557 (s), 1475 (m), 1440 (s), 1434 (s), 1406 (m), 1388 (m), 1328 (s), 1265 (s), 1199 (s), 1164 (s), 1120 (s), 1016 (s), 934 (m), 852 (m), 802 (s), 773 (m), 744 (m), 703 (m), 636 (m), 586 (m), 567 (m) cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 3.70 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 6.52–7.31 (m, 6 H_{arom}), 10.62 (s, 1 H, OH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 52.7 (OCH_3), 52.8 (OCH_3), 107.0 (C), 116.4, 117.2 (CH_{arom}), 126.9, 128.7 (C), 130.1 (2 × CH_{arom}), 135.9 (2 × CH_{arom}), 147.3, 149.1, 161.5, 168.8, 168.9 (C).

MS (EI, 70 eV): *m*/*z* (%) = 354 (35) [M^+], 353 (16), 352 (100) [M^+], 323 (12), 322 (12), 321 (48), 320 (20), 319 (42), 305 (19), 303 (44), 287 (13), 264 (13), 262 (36), 260 (12), 234 (24), 171 (11).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{16}H_{13}O_5SCl$: 352.01667; found: 352.016164.

Dimethyl 3-Hydroxy-5-(4-fluorophenylsulfanyl)phthalate (3d)
Starting with **2d** (447 mg, 1.5 mmol) and **1** (319 mg, 2.25 mmol), **3d** was isolated.

Yield: 257 mg (51%); highly viscous oil.

IR (KBr): 3094 (w), 3067 (w), 2999 (w), 2951 (w), 2847 (w), 1732 (s), 1669 (s), 1588 (s), 1555 (m), 1488 (s), 1435 (m), 14397 (m), 1332 (s), 1268 (s), 1218 (s), 1198 (s), 1169 (s), 1155 (s), 1121 (s), 1089 (m), 1014 (s), 934 (m), 832 (s), 802 (s), 702 (m), 638 (m), 567 (m) cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 3.69 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 6.45–7.33 (m, 6 H_{arom}), 10.62 (s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.7 (OCH_3), 52.8 (OCH_3), 106.0 (C), 115.8, 116.7, 117.0, 117.3 (CH_{arom}), 135.8, (C), 137.2, 137.3 (CH_{arom}), 148.3, 161.5, 161.9, 165.3, 168.9, 169.0 (C).

MS (EI, 70 eV): *m*/*z* (%) = 337 (16), 336 (100) [M^+], 305 (36), 304 (24), 303 (39), 287 (38), 271 (12), 246 (42), 244 (11), 218 (25), 216 (10), 189 (16).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{16}H_{13}O_5SF$: 336.04622; found: 336.045809.

Dimethyl 3-Hydroxy-6-(4-ethylphenylsulfanyl)-4-methylphthalate (3e)
Starting with **2e** (483 mg, 1.5 mmol) and **1** (319 mg, 2.25 mmol), **3e** was isolated.

Yield: 345 mg (64%); highly viscous oil.

IR (KBr): 3071 (w), 3021 (w), 2951 (w), 2873 (w), 1735 (s), 1667 (s), 1590 (s), 1562 (s), 1492 (m), 1430 (s), 1331 (s), 1278 (m), 1217 (s), 1125 (s), 1042 (s), 1004 (m), 939 (s), 827 (s), 802 (s), 743 (s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.09 (t, *J* = 7.6 Hz, 3 H, CH_3), 2.03 (s, 3 H, CH_3), 2.51 (q, *J* = 7.6 Hz, 2 H, CH_2), 3.70 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 6.19 (s, 1 H_{arom}), 7.08 (d, *J* = 8.2 Hz, 2 H_{arom}), 7.23 (d, *J* = 8.2 Hz, 2 H_{arom}), 10.68 (s, 1 H, OH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 15.2 (CH_2CH_3), 15.8 (CH_3), 28.6 (CH_2), 52.4 (OCH_3), 52.8 (OCH_3), 105.0 (C), 114.8 (CH_{arom}), 122.3, 126.2 (C), 129.6 (2 × CH_{arom}), 134.7 (C), 135.5 (2 × CH_{arom}), 146.3, 150.2, 159.8, 169.2, 169.4 (C).

MS (EI, 70 eV): *m*/*z* (%) = 361 (22), 360 (100) [M^+], 329 (27), 326 (26), 313 (17), 312 (12), 311 (56), 299 (29), 296 (39), 270 (10), 268 (10), 267 (26), 240 (12).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{19}H_{20}O_5S$: 360.10260; found: 360.101772.

Dimethyl 3-Hydroxy-5-(4-ethylphenylsulfanyl)phthalate (3f)
Starting with **2f** (462 mg, 1.5 mmol) and **1** (319 mg, 2.25 mmol), **3f** was isolated.

Yield: 358 mg (69%); highly viscous oil.

IR (KBr): 3094 (w), 3067 (w), 2999 (w), 2951 (w), 2847 (w), 1732 (s), 1669 (s), 1588 (s), 1555 (m), 1488 (s), 1435 (m), 14397 (m), 1332 (s), 1268 (s), 1218 (s), 1198 (s), 1169 (s), 1155 (s), 1121(s), 1089 (m), 1014 (s), 934 (m), 832 (s), 802 (s), 702 (m), 638 (m), 566 (m) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, *J* = 7.6 Hz, 3 H, CH_3), 2.61 (q, *J* = 7.6 Hz, 2 H, CH_2), 3.76 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 6.17–6.21 (dd, *J* = 8.2, 1.8 Hz, 2 H_{arom}), 7.06 (d, *J* = 8.2 Hz, 2 H_{arom}), 7.23 (d, *J* = 8.2 Hz, 2 H_{arom}), 10.69 (s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.2 (CH_3), 28.6 (CH_2), 52.6 (OCH_3), 52.7 (OCH_3), 106.4 (C), 115.7, 116.8 (CH_{arom}), 126.3 (C), 129.5, 135.1 (2 × CH_{arom}), 135.7, 146.2, 149.1, 161.5, 169.0, 169.1 (C).

MS (EI, 70 eV): *m*/*z* (%) = 347 (21), 346 (100) [M^+], 315 (24), 313 (35), 299 (12), 298 (11), 297 (53), 285 (33), 281 (14), 228 (10), 227 (10), 226 (10) cm^{-1}.

HRMS (EI): *m*/*z* [M^+] calcd for $C_{18}H_{18}O_5S$: 346.08695; found: 346.086443.

Dimethyl 3-Hydroxy-5-(4-methylphenylsulfanyl)phthalate (3g)
Starting with **2g** (441 mg, 1.5 mmol) and **1** (319 mg, 2.25 mmol), **3g** was isolated.

Yield: 333 mg (67%); highly viscous oil.

IR (KBr): 3022 (w), 2998 (w), 2950 (w), 2921 (w), 2847 (w), 1733 (s), 1668 (s), 1595 (s), 1555 (m), 1491 (m), 1433 (s), 1331 (s), 1266 (s), 1196 (s), 1164 (s), 1120 (s), 1016 (s), 934 (m), 852 (m), 802 (s), 773 (m), 744 (m), 703 (m), 636 (m), 586 (m), 567 (m) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.28 (s, 3 H, CH_3), 3.77 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 6.58–7.24 (m, 6 H_{arom}), 10.68 (s, 1 H, OH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 21.2 (CH_3), 52.6 (OCH_3), 52.7 (OCH_3), 106.5 (C), 116.1, 117.0 (CH_{arom}), 129.5 (C), 129.7, 130.4, 131.9, 135.4 (CH_{arom}), 135.7, 139.8, 148.6, 161.5, 169.0, 169 (C).

MS (EI, 70 eV): *m*/*z* (%) = 333 (17), 332 (100) [M^+], 301 (22), 299 (34), 285 (15), 283 (47), 267 (12), 242 (11), 214 (15).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{17}H_{16}O_5S$: 332.07130; found: 332.071173.

Dimethyl 3-Hydroxy-5-(2-naphthyl)sulfanylphthalate (3h)
Starting with **2h** (496 mg, 1.5 mmol) and **1** (319 mg, 2.25 mmol), **3h** was isolated.

Yield: 298 mg (54%); highly viscous oil.

IR (KBr): 3052 (w), 2999 (w), 2949 (w), 2840 (w), 1731 (s), 1666 (s), 1595 (s), 1555 (s), 1497 (m), 1434 (s), 1400 (m), 1330 (s), 1264 (s), 1196 (s), 1167 (s), 1119 (s), 1016 (s), 934 (s), 850 (s), 802 (s), 742 (s), 646 (m) cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 3.68 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 6.56–7.92 (m, 8 H_{arom}), 10.60 (s, 1 H, OH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 52.6 (OCH_3), 52.8 (OCH_3), 106.6 (C), 116.4, 117.2 (CH_{Ar}), 127.2 (C), 127.3, 127.8, 127.9, 129.7, 130.9 (CH_{arom}), 133.3, 133.8 (C), 134.7, 134.9 (CH_{arom}), 135.8, 148.1, 161.5, 168.9, 169.0 (C).

MS (EI, 70 eV): *m*/*z* (%) = 369 (19), 368 (100) [M^+], 337 (11), 335 (17), 319 (24), 303 (18), 250 (19), 248 (10), 221 (12).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{20}H_{16}O_5S$: 368.07130; found: 368.071809.

Downloaded by: Collections and Technical Services Department. Copyrighted material.

Dimethyl 3-Hydroxy-5-(3-chlorophenylsulfanyl)phthalate (3i)
Starting with **2i** (471 mg, 1.5 mmol) and **1** (319 mg, 2.25 mmol), **3i** was isolated.

Yield: 317 mg (60%); highly viscous oil.

IR (KBr): 3079 (w), 3044 (w), 3006 (w), 2955 (w), 2853 (w), 1727 (s), 1673 (s), 1594 (s), 1557 (s), 1475 (m), 1440 (s), 1434 (s), 1406 (m), 1388 (m), 1328 (s), 1265 (s), 1199 (s), 1164 (s), 1120 (s), 1016 (s), 934 (m), 852 (m), 802 (s), 773 (m), 744 (m), 703 (m), 636 (m), 586 (m), 567 (m) cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 3.78 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 6.64–7.30 (m, 6 H_{arom}), 10.69 (s, 1 H, OH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 52.7 (OCH_3), 52.8 (OCH_3), 107.0 (C), 117.1, 117.8, 129.5, 130.8, 132.3 (CH_{arom}), 132.5 (C), 133.9 (CH_{arom}), 135.4, 136.0, 146.5, 161.5, 168.7, 168.9 (C).

MS (EI, 70 eV): *m/z* (%) = 354 (35) [M^+], 353 (16), 352 (100) [M^+], 323 (12), 322 (12), 321 (48), 320 (20), 319 (42), 305 (19), 303 (44), 287 (13), 264 (13), 262 (36), 260 (12), 234 (24), 171 (11).

HRMS (EI): *m/z* [M^+] calcd for $C_{16}H_{13}O_5SCl$: 352.01667; found: 352.016166.

Dimethyl 3-Hydroxy-6-(4-methylphenylsulfanyl)-4-methylphthalate (3j)
Starting with **2j** (462 mg, 1.5 mmol) and **1** (319 mg, 2.25 mmol), **3j** was isolated.

Yield: 306 mg (59%); highly viscous oil.

IR (KBr): 3071 (w), 3021 (w), 2951 (w), 2873 (w), 1735 (s), 1667 (s), 1590 (s), 1562 (s), 1492 (m), 1430 (s), 1331 (s), 1278 (m), 1217 (s), 1125 (s), 1042 (s), 1004 (m), 939 (s), 827 (s), 802 (s), 743 (s) cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 2.14 (s, 3 H, CH_3), 2.33 (s, 3 H, CH_3), 3.81 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 6.27 (s, 1 H_{arom}), 7.18 (d, *J* = 8.2 Hz, 2 H_{arom}), 7.36 (d, *J* = 8.2 Hz, 2 H_{arom}), 10.78 (s, 1 H, OH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 14.8 (CH_3), 20.3 (CH_3), 51.4 (OCH_3), 51.8 (OCH_3), 104.6 (C), 113.9 (CH_{arom}), 121.3, 125.1 (C), 129.6, 129.8, 134.4, 134.5 (CH_{arom}), 139.1, 149.2, 158.8, 168.1, 168.3 (C).

MS (EI, 70 eV): *m/z* (%) = 347 (22), 346 (100) [M^+], 329 (27), 326 (26), 313 (17), 312 (12), 311 (56), 299 (29), 296 (39), 270 (10), 268 (10), 267 (26), 240 (12).

HRMS (EI): *m/z* [M^+] calcd for $C_{18}H_{18}O_5S$: 346.08695; found: 346.086893.

Dimethyl 3-Hydroxy-6-(4-chlorophenylsulfanyl)-4-methylphthalate (3k)
Starting with **2k** (492 mg, 1.5 mmol) and **1** (319 mg, 2.25 mmol), **3k** was isolated.

Yield: 302 mg (55%); highly viscous oil.

IR (KBr): 3073 (w), 3025 (w), 2951 (w), 2873 (w), 1735 (s), 1667 (s), 1590 (s), 1562 (s), 1492 (m), 1430 (s), 1331 (s), 1278 (m), 1217 (s), 1128 (s), 1046 (s), 1004 (m), 945 (s), 827 (s), 802 (s), 747 (s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.16 (s, 3 H, CH_3), 3.85 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 6.36–7.42 (m, 5 H_{arom}), 10.81 (s, 1 H, OH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 17.2 (CH_3), 53.8 (OCH_3), 54.0 (OCH_3), 106.6 (C), 117.0 (CH_{arom}), 124.1, 130.3, 130.5, 131.2 (C), 131.4, 137.3 (2 × CH_{arom}), 149.5, 161.0, 170.2, 170.4 (C).

MS (EI, 70 eV): *m/z* (%) = 368 (39) [M^+], 367 (19), 366 (100) [M^+], 328 (17), 326 (26), 313 (17), 312 (12), 311 (56), 299 (29), 296 (39), 270 (10), 268 (10), 267 (26), 240 (13).

HRMS (EI): *m/z* [M^+] calcd for $C_{17}H_{15}O_5SCl$: 366.03232; found: 366.031813.

Dimethyl 3-Hydroxy-6-(4-fluorophenylsulfanyl)-4-methylphthalate (3l)
Starting with **2l** (468 mg, 1.5 mmol) and **1** (319 mg, 2.25 mmol), **3l** was isolated.

Yield: 378 mg (53%); highly viscous oil.

IR (KBr): 3075 (w), 3025 (w), 2951 (w), 2871 (w), 1736 (s), 1667 (s), 1591 (s), 1562 (s), 1492 (m), 1432 (s), 1331 (s), 1278 (m), 1217 (s), 1128 (s), 1046 (s), 1004 (m), 945 (s), 827 (s), 802 (s), 747 (s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.06 (s, 3 H, CH_3), 3.73 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 6.16–7.33 (m, 5 H_{arom}), 10.71 (s, 1 H, OH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 15.7 (CH_3), 52.4 (OCH_3), 52.8 (OCH_3), 105.9 (C), 115.0, 117.1, 117.5 (CH_{arom}), 122.4, 125.1 (C), 137.4, 137.6 (CH_{arom}), 137.8, 137.9, 149.3, 159.8, 169.0, 169.2 (C).

MS (EI, 70 eV): *m/z* (%) = 351 (19), 350 (100) [M^+], 327 (17), 326 (26), 313 (17), 312 (12), 311 (56), 299 (29), 296 (39), 270 (10), 268 (10), 267 (26), 240 (13).

HRMS (EI): *m/z* [M^+] calcd for $C_{17}H_{15}O_5SF$: 350.04622; found: 350.04731.

Acknowledgment

Financial support by the State of Pakistan (HEC scholarship for I. I.) and by the State of Mecklenburg-Vorpommern (scholarship for M. I.) is gratefully acknowledged.

References

(1) (a) Behar, V.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 7017. (b) Toste, F. D.; Still, I. W. J. *J. Am. Chem. Soc.* **1995**, *117*, 7261. (c) Davidson, B. S.; Molinski, T. F.; Barrows, L. R.; Ireland, C. M. *J. Am. Chem. Soc.* **1991**, *113*, 4709. (d) Mori, Y.; Taneda, S.; Hayashi, H.; Sakushima, A.; Kamata, K.; Suzuki, A. K.; Yoshino, S.; Sakata, M.; Sagai, M.; Seki, K.-i. *Biol. Pharm. Bull.* **2002**, *25*, 145. (e) Davis, R. A.; Sandoval, I. T.; Concepcion, G. P.; Moreira da Rocha, R.; Ireland, C. M. *Tetrahedron* **2003**, *59*, 2855. (f) Liu, H.; Fujiwara, T.; Nishikawa, T.; Mishima, Y.; Nagai, H.; Shida, T.; Tachibana, K.; Kobayashi, H.; Mangindaan, R. E. P.; Namikoshi, M. *Tetrahedron* **2005**, *61*, 8611. (g) Kaplan, M. L.; Reents, W. D. *Tetrahedron Lett.* **1982**, *23*, 373. (h) Hosoya, Y.; Adachi, H.; Nakamura, H.; Nishimura, Y.; Naganawa, H. *Tetrahedron Lett.* **1996**, *37*, 9227.

(2) See for example: (a) Glass, H. B.; Reid, E. E. *J. Am. Chem. Soc.* **1929**, *51*, 3428. (b) Dougherty, G.; Hammond, P. D. *J. Am. Chem. Soc.* **1935**, *57*, 117. (c) For the trifluoromethanesulfonic acid-catalyzed sulfurization of cycloalkanes, see: Olah, G. A.; Wang, Q.; Prakash, G. K. S. *J. Am. Chem. Soc.* **1990**, *112*, 3697.

(3) Kemp, D. S.; Carey, R. I.; Dewan, J. C.; Galakatos, N. G.; Kerkman, D.; Leung, S.-L. *J. Org. Chem.* **1989**, *54*, 1589; and references cited therein.

(4) Chua, M.; Hoyer, H. *Z. Naturforsch., B* **1965**, *20*, 416.

(5) (a) Baxter, I.; Ben-Haida, A.; Colquhoun, H. M.; Hodge, P.; Kohnke, F. H.; Williams, D. J. *Chem. Eur. J.* **2000**, *6*, 4285; and references cited therein. (b) Campbell, J. R. *J. Org. Chem.* **1964**, *29*, 1830.

Downloaded by: Collections and Technical Services Department. Copyrighted material.

(6) (a) Taniguchi, N. *J. Org. Chem.* **2007**, *72*, 1241. (b) Fernández-Rodríguez, M. A.; Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 2180. (c) Murata, M.; Buchwald, S. L. *Tetrahedron* **2004**, *60*, 7397.
(7) (a) Gendre, F.; Yang, M.; Diaz, P. *Org. Lett.* **2005**, *7*, 2719. (b) Bates, C. G.; Gujadhur, R. K.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 2803. (c) Rábai, J. *Synthesis* **1989**, 523.
(8) (a) Hilt, G.; Lüers, S. *Synthesis* **2003**, 1784. (b) Hilt, G.; Lüers, S.; Harms, K. *J. Org. Chem.* **2004**, *69*, 624.
(9) (a) Rashid, M. A.; Reinke, H.; Langer, P. *Tetrahedron Lett.* **2007**, *48*, 2321. (b) Rashid, M. A.; Rasool, N.; Adeel, M.; Reinke, H.; Fischer, C.; Langer, P. *Tetrahedron* **2008**, *64*, 3782.
(10) For a review of [3+3] cyclizations, see: Feist, H.; Langer, P. *Synthesis* **2007**, 327.
(11) For a review of 1,3-bis(silyloxy)-1,3-butadienes, see: Langer, P. *Synthesis* **2002**, 441.
(12) (a) Chan, T.-H.; Brownbridge, P. *J. Am. Chem. Soc.* **1980**, *102*, 3534. (b) Brownbridge, P.; Chan, T.-H.; Brook, M. A.; Kang, G. J. *Can. J. Chem.* **1983**, *61*, 688.
(13) (a) Chan, T. H.; Prasad, C. V. C. *J. Org. Chem.* **1986**, *51*, 3012. (b) Chan, T. H.; Prasad, C. V. C. *J. Org. Chem.* **1987**, *52*, 110.
(14) Rashid, M. A.; Rasool, N.; Iqbal, I.; Imran, M.; Langer, P. *Tetrahedron Lett.* **2008**, *49*, 2466.
(15) (a) Wilson, B. D. *Synthesis* **1992**, 283. (b) Heilbron, I.; Jones, E. R. H.; Julia, M. *J. Chem. Soc.* **1949**, 1434. (c) Searles, S.; Sanchez, R. A.; Soulen, R. L.; Kundinger, D. G. *J. Org. Chem.* **1967**, *32*, 2655. (d) Banville, J.; Brassard, P. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1852. (e) Barker, D.; Brimble, M. A.; Do, P.; Turner, P. *Tetrahedron* **2003**, *59*, 2441.
(16) Iqbal, I.; Imran, M.; Villinger, A.; Langer, P. *Synthesis* **2009**, 297.

Downloaded by: Collections and Technical Services Department. Copyrighted material.