Electrophilic Aromatic Formylation with Bis-phenylthionium Ions

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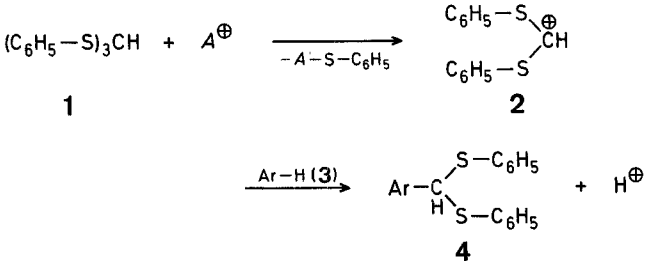
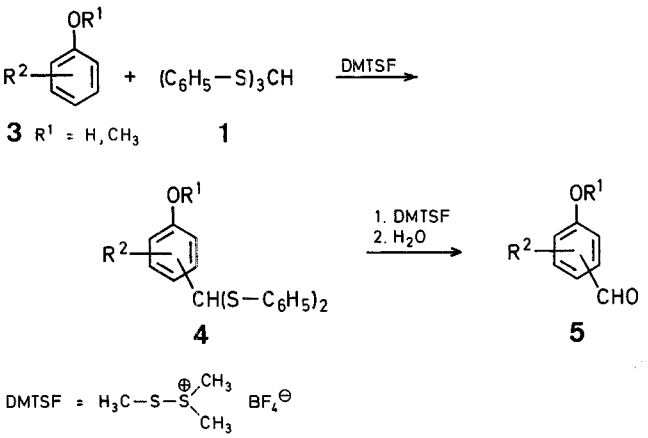
The introduction of a formyl group into an aromatic nucleus has been the subject of many investigations[1]; however, the presently available procedures still present limitations in terms of yield, general applicability, and the hazardous nature of some of the reagents. In a continuation of our interest[2] in the synthetic exploitation of the carbocationic species produced from the reaction between soft, thiophilic Lewis acids [$A^{\oplus}$] and tris[phenylthio]methane (**1**) and derivatives (i.e. bis-thionium ions[3]), we examined the reaction of **1** with $A^{\oplus}$ under aprotic conditions in the presence of nucleophilic aromatic substrates (**3**). The object of this work was to effect a C—C bond formation sequence via bis[phenylthio]-carbocation **2**:



$A^{\oplus}$ = thiophilic Lewis acid

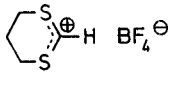
The use of copper(I) or silver(I) salts[2] as reaction initiator [$A^{\oplus}$] was unrewarding; however, with dimethyl-(methylthio)-sulfonium tetrafluoroborate (DMTSF)[4], ready reaction with oxygen-activated aromatic systems (**3**) was observed and the derived arenecarboxaldehyde bis-phenylthio acetals (**4**) could be obtained in good yield. Subsequently it was found that excess DMTSF promoted thioacetal hydrolysis, so the yields reported in the Table were estimated by isolation of the aldehydes (**5**) produced in the one-pot sequence:



This procedure provides an efficient, operationally simple formylation method provided the aromatic ring is activated. Aromatic substrates such as ferrocene, alkylthio-, trimethylsilylmethyl-, and alkylbenzenes were unreactive. The regioselectivity of the reaction is particularly noteworthy. Only one isomer was detected in each reaction and a *para* preference was noted, provided this position was not blocked. For example, formylation of 3-methylphenol (**3f**) gave 4-hydroxy-2-methylbenzaldehyde (**5f**) regioselectively in 51% yield which contrasts with literature yields of 12%[5] and 22%[6] of **5f** accompanied in both instances by regioisomers.

Reaction with nitrogen-substituted aromatics lead to quantitative recovery of reagent **1** together with substrate **3**. It appeared that DMTSF was reacting preferentially with the amino nitrogen rather than **1**. Nitrogen nucleophiles have been utilized with cationic species produced from DMTSF[7] although a recent report[8] on the rapid, amine-induced decomposition of DMTSF has appeared. Successful reaction with these substrates may require the stepwise formation of cation **2** followed by addition of the aromatic compound **3**.

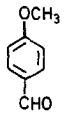
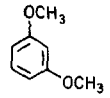
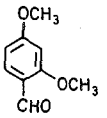
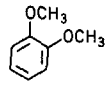
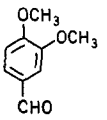
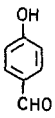
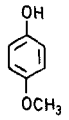
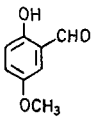
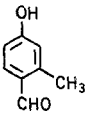
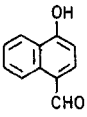
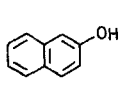
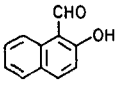
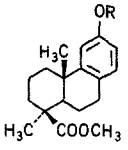
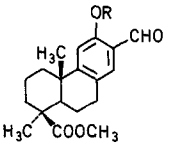
Reports of the reaction of 1,3-dithienium tetrafluoroborate (**6**) with nucleophilic alkenes have appeared[9] but, in our hands, reaction of **6** with some of the aromatic substrates listed in the Table were not promising.



This observed difference in reactivity may be related to the relative stability of **6** compared with **2**. As a measure of this effect it was noted that bis[phenylthio]methane gave no evidence for formation of **2** by hydride abstraction on exposure to triphenylmethyl tetrafluoroborate whereas this reaction serves to produce **6** from 1,3-dithiane in good yield[10]. The chemoselective preparation of reagent **2** using the thiophilic DMTSF combined with its attractive subsequent reactivity commends the procedure reported herein over a related process using the cyclic 1,3-dithiolenium ion generated using hard Lewis acids[6].

4-Hydroxynaphthalene-1-carboxaldehyde (5g); Typical Procedure: Dimethyl-(methylthio)-sulfonium tetrafluoroborate (DMTSF[11]; 0.587 g, 3 mmol) is added to a stirred solution of 1-naphthol (0.144 g, 1 mmol) and tris[phenylthio]methane (**1**; 0.340 g, 1 mmol) in dry dichloromethane (20 ml) at room temperature. After 2 h, analytical T.L.C. shows all naphthol has reacted and the crude product **5g** is isolated by dilution with water (50 ml) and ether extraction (3 × 20 ml). Preparative T.L.C. of the crude product obtained by evaporation of the organic solvents in vacuo affords aldehyde **5g**; yield: 0.120 g, 0.7 mmol (70%); m.p. 180–181°C (Ref.[5], m.p. 181°C).

Table. Aromatic Aldehydes (**5**) from Hydroxy- or Methoxyarenes (**3**) and Dimethyl-(methylthio)-sulfonium Tetrafluoroborate (DMTSF)

Educt **3**	Product **5**	Reaction Time [h]	Yield [%]	m.p. [°C]	m.p. [°C] reported or Molecular Formula
a 		15	35	oil	$C_8H_8O_2$ (1362)[a]
b 		1.5	70	70–71°	71°[12,a]
c 		15	45	oil	$C_9H_{10}O_3$ (166.2)[a]
d 		1	57	114°	116°[12,a]
e 		2	60	oil	$C_8H_8O_3$ (152.1)[b]
f 		1	51	105°	110°[5,c]
g 		2	70	180–181°	181°[5,a]
h 		2	87	82°	82°[12,a]
i, j 					
i R = H		1	63	129–130°	$C_{19}H_{24}O_4$ (316.4)
j R = CH_3		15	60	124–126°	123.5–125.5°[14]

[a] Identified by comparison (T.L.C., I.R., ^{1}H-N.M.R.) with an authentic sample.

[b] ^{1}H-N.M.R. (60 MHz, $CDCl_3$/TMS_{int}): $\delta = 10.56$ (s, OH); 9.76 (s, 1 H); 7.3–6.7 (m, 3 H); 3.78 ppm (s, 3 H).

[c] ^{1}H-N.M.R. (90 MHz, CD_2Cl_2/TMS_{int}): $\delta = 10.02$ (s, 1 H); 7.68 (d, 1 H, $J = 8$ Hz); 6.77 (dd, 1 H, $J = 8, 2$ Hz); 6.72 (d, 1 H, $J = 2$ Hz); 2.60 ppm (s, 3 H).

^{1}H-N.M.R. (90 MHz, acetonitrile-d_3/TMS_{int}): $\delta = 10.10$ (s, 1 H); 8.85 (br. s, OH); 6.8–9.3 ppm (m, 6 H).

2,4-Dimethoxybenzaldehyde (5b); Typical Procedure:

Dimethyl-(methylthio)-sulfonium tetrafluoroborate (DMTSF[11]; 0.704 g, 3.6 mmol) is added to a stirred solution of 1,3-dimethoxybenzene (0.166 g, 1.2 mmol) and tris[phenylthio]methane (0.408 g, 1.2 mmol) in dry dichloromethane (25 ml) at room temperature. The mixture is stirred for 1.5 h and the crude product then isolated by dilution with water (50 ml) and ether extraction (3 × 20 ml). The solvents are evaporated in vacuo and the residual crude product is flash-chromatographed with dichloromethane/ether (1/1) to give crystalline **5b**; yield: 0.14 g (0.84 mmol, 70%); m.p. 71–72°C (sublimation) (Ref.[12], m.p. 69–72°C).

^{1}H-N.M.R. (60 MHz, $CDCl_3$/TMS_{int}): $\delta = 10.23$ (s, 1 H); 7.76 (d, 1 H, $J_{AB} = 8$ Hz, 6-H); 6.50 (dd, 1 H, $J_{AB} = 8$ Hz, 5-H); 6.43 (d, 1 H, $J = 1$ Hz, 3-H); 3.83 (s, 3 H, OCH_3); 3.80 ppm (s, 3 H, OCH_3).

2-Hydroxy-5-methoxybenzaldehyde (5e); Typical Procedure:

Dimethyl-(methylthio)-sulfonium tetrafluoroborate (DMTSF[11]; 0.587 g, 3 mmol) is added to a stirred solution of 4-methoxyphenol (0.124 g, 1 mmol) and tris[phenylthio]methane (0.34 g, 1 mmol) in dry dichloromethane (20 ml) at room temperature. After 2 h, T.L.C. shows that all starting materials have reacted and the crude product is isolated by dilution with water (50 ml) and ether extraction (3 × 20 ml). The solvents are evaporated in vacuo and the residual crude product is flash-chromatographed on silica gel with dichloromethane to give product **5e**; yield: 0.091 g (0.6 mmol, 60%); oil.

^{1}H-N.M.R. (60 MHz, $CDCl_3$/TMS_{int}): $\delta = 10.56$ (s, OH); 9.76 (s, 1 H); 6.8–7.3 (m, 3 H); 3.78 ppm (s, 3 H).

Methyl 13-Formyl-12-methoxypodocarpa-8,11,13-trien-19-oate (5j):

Dimethyl-(methylthio)-sulfonium tetrafluoroborate (DMTSF[11]; 0.587 g, 3 mmol) is added to a stirred solution of methyl 12-methoxypodocarpa-8,11,13-trien-19-oate (0.302 g, 1 mmol) and tris[phenylthio]me-

thane (0.340 g, 1 mmol) in dry dichloromethane (20 ml) at room temperature. The mixture is stirred for 15 h and the crude product then isolated by dilution with water (50 ml) and ether extraction (3 × 20 ml). After evaporation of the solvents in vacuo, the crude product is separated by column chromatography to give product **5j**; yield: 0.2 g (0.6 mmol, 60%); m.p. 124–126°C (aqueous ethanol) (Ref.[14]; m.p. 123.5–125.5°C).

^{1}H-N.M.R. (60 MHz, $CDCl_3/TMS_{int}$): $\delta = 10.32$ (s, 1 H); 7.48 (s, 1 H); 6.83 (s, 1 H); 3.85 (s, 3 H); 3.65 (s, 3 H); 3.0–1.0 (m, 11 H); 1.27 (s, 3 H); 1.03 ppm (s, 3 H).

Methyl 13-Formyl-12-hydroxypodocarpa-8,11,13-trien-19-oate (5i): This compound is prepared in the same manner as **5j**; yield of **5i**: 0.20 g (63%); m.p. 129–130°C.

$C_{19}H_{24}O_4$	calc.	C 72.12	H 7.65
(316.4)	found	71.88	7.49

I.R. (CCl_4): $\nu = 3400$ (br); 1720 (s); 1650 (s) cm^{-1}.

^{1}H-N.M.R. (60 MHz, $CDCl_3/TMS_{int}$): $\delta = 10.50$ (s, OH); 9.70 (s, 1 H); 7.18 (s, 1 H); 6.86 (s, 1 H); 3.62 (s, 3 H); 3.0–0.8 (m, 11 H); 1.23 (s, 3 H); 0.98 ppm (s, 3 H).

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