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ortho-Formylation of oxygenated phenols

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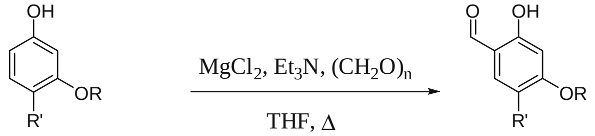
ABSTRACT

Oxygenated phenols are mono-formylated using a mixture of paraformaldehyde, $MgCl_2$, and Et_3N in THF. In all cases but one, only one regioisomer of the salicylaldehyde is obtained in good to high yield.

Formylation of aromatic compounds is an important reaction in synthetic organic chemistry, and numerous methods are available.[1] By directed *ortho*-metallation of an activated phenol, a formyl group can be introduced selectively,[2] but this methodology requires the introduction and removal of the activating group for the synthesis of salicylaldehydes. On the other hand, salicylaldehydes are accessible from the corresponding phenols by several classical formylation reactions. However, the yields are often only moderate and the lack of regioselectivity is problematic.[3] Moreover, the reaction conditions are quite harsh employing environmentally disagreeable reagents. The regioselectivity is even more of a problem for 1,3-dihydroxylated phenols (resorcinols). The recently reported regioselective *ortho*-formylation of substituted phenols using the $MgCl_2$–Et_3N base system and paraformaldehyde affords salicylaldehydes in excellent yields.[4] The salicylaldehydes obtained by this method have been employed by us and others for the preparation of useful products and intermediates.[5] We wanted to extend this methodology to substituted mono-protected resorcinols, a structural feature found in many natural products and biologically active substances.[6]

Reacting paraformaldehyde and 3-methoxyphenol in the presence of the $MgCl_2$–Et_3N base system yielded 4-methoxysalicylaldehyde (**1**) and 6-methoxysalicylaldehyde in 92% and 5% yield, respectively (Scheme 1).[7,8] Replacing the methoxy group with the larger benzyloxy group, afforded exclusively 4-benzyloxysalicylaldehyde (**2**) in 88% yield. The same encouraging results were obtained with either *tert*-butyldimethylsilyl or thexyldimethylsilyl protecting groups; salicylaldehydes **3** and **4** were obtained in 80% and 88% yields, respectively. Further substitution with either chlorine or bromine atoms at the 4-position afforded the mono-formylated salicylaldehydes **5**–**11** in good to high yields (Table 1). Formylation of 3-(*tert*-butyldimethylsilyloxy)-4-chlorophenol and 3-(*tert*-butyldimethylsilyloxy)-4-bromophenol was accompanied by minor unidentified byproducts. The structural assignments of the salicylaldehydes were based on spectral data and by comparison with authentic samples.[7,8]

Resorcinols mono-protected as acetate, pivalate, or *tert*-butoxycarbonyl derivatives were subjected to the same reaction conditions, but only low yields of the corresponding salicylaldehydes were obtained in all three cases. Furthermore, subjecting 2,3-dimethoxyphenol to the formylating reagents gave the corresponding salicylaldehyde **12** in only 11% yield. On the other hand, 2,3-(methylenedioxy)-phenol, a structural entity found in several highly oxygenated natural products[9] was cleanly converted into the desired salicylaldehyde **13** in almost quantitative yield using our formylation protocol. When 3,4-(methylenedioxy)-phenol was reacted



R = H, Me, Bn, TBS, TDS
R' = H, Cl, Br

Scheme 1.

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0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
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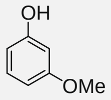
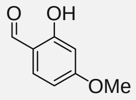
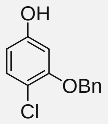
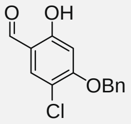
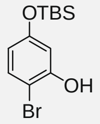
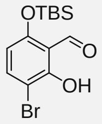
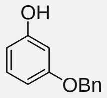
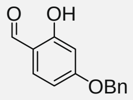
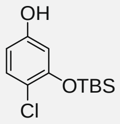
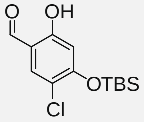
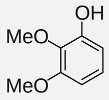
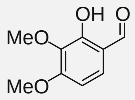
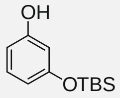
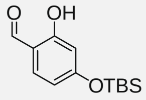
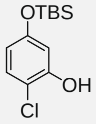
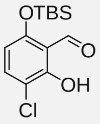
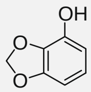
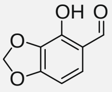
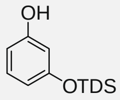
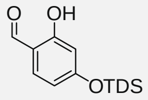
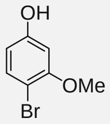
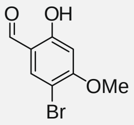
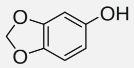
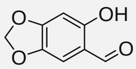
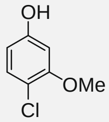
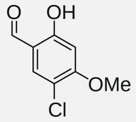
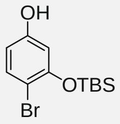
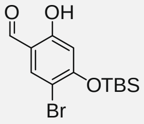
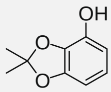
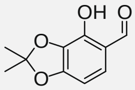
Table 1
ortho-Formylation of oxygenated phenols

Phenol	Aldehyde (yield %)	Phenol	Aldehyde (yield %)	Phenol	Aldehyde (yield %)
	 **1** (92)[a]		 **6** (85)		 **11** (85)
	 **2** (88)		 **7** (60)		 **12** (11)
	 **3** (80)		 **8** (73)		 **13** (97)
	 **4** (88)		 **9** (90)		 **14** (45)
	 **5** (94)		 **10** (73)		 **15** (82)

[a] 5% of 6-methoxysalicylaldehyde was also obtained.

under the same conditions, 2-hydroxy-4,5-(methylenedioxy)-benzaldehyde **14** was formed in 45% yield. Furthermore, salicylaldehyde **15** was obtained in 82% yield as the sole product when 2,3-(isopropylidenedioxy)-phenol was subjected to the *ortho*-formylation conditions. Again, complete regioselectivity was observed in all three cases.[7,8]

In conclusion, we have extended our simple and regioselective *ortho*-formylation protocol to mono-protected resorcinols and methylenedioxy- substituted phenols. The formylations occurred with high to excellent yields.

Acknowledgment

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7. *Typical experimental procedure*: To a dry THF solution (10 ml) of the phenol (1 mmol), anhydrous magnesium chloride (0.19 g, 2 mmol), triethylamine (0.20 g, 2 mmol) and paraformaldehyde (90 mg, 3 mmol) were added. The reaction mixture was heated to reflux under an argon atmosphere for 1–4 h, and monitored by TLC (hexane:ethyl acetate = 8:2). After complete consumption of the phenol, the reaction mixture was cooled and diluted with diethyl ether (20 ml). The organic layer was washed successively with HCl (1 M, 2 × 10 ml) and water (2 × 10 ml), and then dried ($MgSO_4$). In most cases the product was sufficiently pure for further use, or the product was purified by column chromatography using hexane:ethyl acetate (95:5 to 70:30). Spectral and physical data of new products: *4-(t-Butyldimethylsilyloxy)-2-hydroxybenzaldehyde* (**3**)[10]: pale brown oil (80% yield); $R_f = 0.39$ (9:1 hexane:EtOAc); IR (KBr, cm^{-1}) ν: 3567, 1646; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 11.31$ (s, 1H), 9.70 (s, 1H), 7.38 (d, $J = 8.5$ Hz, 1H), 6.45 (dd, $J = 8.5$, 2.2 Hz, 1H), 6.37 (d, $J = 2.2$ Hz, 1H), 0.96 (s, 9H), 0.23 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 194.50$, 164.06, 135.41, 115.80, 113.07, 107.62, 25.48, 18.21, −4.37. *4-[(2,3-*

Dimethylbutan-2-yl)-dimethylsilyloxy]-2-hydroxybenzaldehyde (**4**)[11]: colorless oil (88% yield); $R_f = 0.38$ (9:1 hexane:EtOAc); IR (KBr, cm^{-1}) ν: 3524, 1646, 1626; ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 11.31$ (s, 1H), 9.69 (s, 1H), 7.37 (d, $J = 8.5$ Hz, 1H), 6.44 (dd, $J = 2.2, 8.5$ Hz, 1H), 6.36 (d, $J = 2.1$ Hz, 1H), 1.75–1.62 (m, 1H), 0.91 (m, 12H), 0.27 (s, 6H); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 194.46$, 164.05, 163.60, 135.37, 115.75, 113.10, 107.65, 34.00, 25.12, 19.97, 18.46, −2.42. *5-Chloro-2-hydroxy-4-methoxybenzaldehyde* (**5**)[12]: white solid (94% yield); mp 106–107 °C; $R_f = 0.37$ (8:2 hexane:EtOAc); IR (KBr, cm^{-1}) ν: 3281, 1643, 1623; ^{1}H NMR (200 MHz, CDCl$_3$): $\delta = 11.38$ (s, 1H), 9.64 (s, 1H), 7.46 (s, 1H), 6.45 (s, 1H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 193.61$, 162.91, 161.64, 133.75, 114.75, 114.10, 100.32, 56.52. *4-(Benzyloxy)-5-chloro-2-hydroxybenzaldehyde* (**6**)[13]: white solid (85% yield); mp 105–106 °C; $R_f = 0.59$ (6:4 hexane:EtOAc); IR (KBr, cm^{-1}) ν: 3408, 1645, 1622; ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 11.42$ (s, 1H), 9.69 (s, 1H), 7.53 (s, 1H), 7.50–7.31 (m, 5H), 6.56 (s, 1H), 5.20 (s, 2H); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 193.68$, 162.81, 160.77, 135.01, 133.92, 128.71, 128.37, 127.05, 114.96, 114.67, 101.63, 70.99. *4-(t-Butyldimethylsilyloxy)-5-chloro-2-hydroxybenzaldehyde* (**7**): white solid (60% yield); mp 42–43 °C; $R_f = 0.57$ (8:2 hexane:EtOAc); IR (KBr, cm^{-1}) ν: 3425, 1651; ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 11.18$ (s, 1H), 9.56 (s, 1H), 7.47 (s, 1H), 6.42 (s, 1H), 1.00 (s, 9H), 0.27 (s, 6H); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 193.77$, 162.18, 159.12, 134.32, 117.60, 115.89, 108.08, 25.42, 18.29, -4.46; HRMS *m*/*z* calcd for $C_{13}H_{19}ClO_3Si$ (M$^+$): 286.0792; found: 286.0790. *6-(t-Butyldimethylsilyloxy)-3-chloro-2-hydroxybenzaldehyde* (**8**): yellow solid; (73% yield); mp 107–110 °C; $R_f = 0.53$ (8:2 hexane:EtOAc); IR (KBr, cm^{-1}) ν: 3373, 1645; ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 12.27$ (s, 1H), 10.26 (s, 1H), 7.38 (d, $J = 8.8$ Hz, 1H), 6.28 (d, $J = 8.8$ Hz, 1H), 0.98 (s, 9H), 0.27 (s, 6H); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 194.42$, 158.60, 158.13, 137.73, 113.84, 113.55, 109.77, 25.56, 18.30, −4.40; HRMS *m*/*z* calcd for $C_{13}H_{19}ClO_3Si$ (M$^+$): 286.0792, found: 286.0793. *5-Bromo-4-(t-butyldimethylsilyloxy)-2-hydroxybenzaldehyde* (**10**): yellow oil (73% yield); $R_f = 0.58$ (8:2 hexane:EtOAc); IR (KBr, cm^{-1}) ν: 3406, 1651, 1618; ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 11.19$ (s, 1H), 9.65 (d, $J = 0.4$ Hz, 1H), 7.64 (s, 1H), 6.41 (s, 1H), 1.02 (s, 9H), 0.29 (s, 6H); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 193.70$, 162.83, 160.01, 137.66, 116.56, 107.56, 106.06, 25.49, 18.32; HRMS *m*/*z* calcd for $C_{13}H_{19}BrO_3Si$ (M$^+$): 330.0287; found; 330.0284. *6-(t-Butyldimethylsilyloxy)-3-bromo-2-hydroxybenzaldehyde* (**11**): yellow solid (85% yield); mp 94–97 °C; $R_f = 0.60$ (8:2 hexane:EtOAc); IR (KBr, cm^{-1}) ν: 3418, 1645; ^{1}H NMR (200 MHz, CDCl$_3$): $\delta = 12.40$ (s, 1H), 10.23 (s, 1H), 7.53 (dd, $J = 0.3, 8.8$ Hz, 1H), 6.25 (d, $J = 8.8$ Hz, 1H), 0.98 (s, 9H), 0.27 (s, 6H); ^{13}C NMR (50 MHz, CDCl$_3$): $\delta = 194.23$, 159.57, 158.86, 140.71, 113.91, 110.52, 101.76, 25.56, 18.30, −4.39; HRMS *m*/*z* calcd for $C_{12}H_{19}BrO_3Si$ (M$^+$): 330.0287; found; 330.0281. *2-Hydroxy-3,4-(methylenedioxy)-benzaldehyde*: (**13**): white solid (97% yield); mp 113–115 °C (lit.[14] 115–116 °C); $R_f = 0.62$ (7:3 hexane:EtOAc); ^{1}H NMR (200 MHz, CDCl$_3$): $\delta = 10.97$ (s, 1H), 9.71 (s, 1H), 7.14 (d, $J = 8.2$ Hz, 1H), 6.56 (d, $J = 8.2$ Hz, 1H), 6.08 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 195.06$, 155.13, 145.49, 134.10, 130.43, 118.25, 102.80, 101.95. *2-Hydroxy-3,4-(isopropylidene-dioxy)benzaldehyde* (**15**): pale yellow solid (82% yield); mp 68–69 °C; IR (KBr, cm^{-1}) ν: 3382, 1663; $R_f = 0.34$ (8:2 hexane:EtOAc); ^{1}H NMR (200 MHz, CDCl$_3$): $\delta = 10.93$ (s, 1H), 9.67 (s, 1H), 7.08 (d, $J = 8.2$ Hz, 1H), 6.46 (d, $J = 8.2$ Hz, 1H), 1.71 (s, 6H); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 194.94$, 154.73, 145.31, 133.82, 129.84, 120.92, 117.81, 101.96, 25.87; HRMS *m*/*z* calcd for $C_{10}H_{10}O_4$ (M$^+$): 194.0579; found: 194.0579.

8. The regioisomeric ratio of salicylaldehydes was determined by ^{1}H NMR analyzes of the crude reaction mixtures and by comparison with authentic samples.
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