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o-Formylation of electron-rich phenols with dichloromethyl methyl ether and $TiCl_4$

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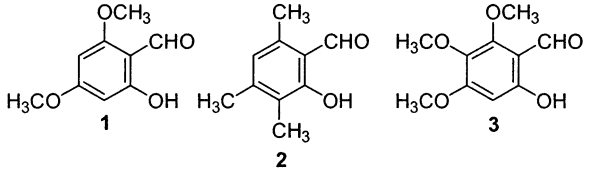
Abstract—*o*-Formylation of electron-rich phenols is accomplished with dichloromethyl methyl ether and $TiCl_4$. The reaction gives excellent yields, good regioselectivity, and does not leading to diformylation.

1. Introduction

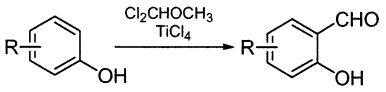
In solid-phase chemistry,[1] the lability of most of the acid-labile handles can be fine-tuned by the introduction of electron-donating substituents into a phenyl ring.[2] The way that these building blocks are functionalized is usually through an aldehyde function, which can undergo reduction or aminative reduction to afford the corresponding alcohol or amine functions. The handles are bifunctional spacer molecules and so a phenol function can serve as an anchor to the solid support. Furthermore, formyl-substituted phenols bearing electron-donating substituents are important compounds and/or interesting intermediates in other fields of organic chemistry.[3] A number of methods have been described in the literature for the formylation of phenols, but most of these give only low yields, leading to diformylation, and/or lack regioselectivity.

In one of our current programmes, we became interested in preparing 2-formyl-3,5-dimethoxyphenol (**1**) from 3,5-dimethoxyphenol, 2-formyl-3,5,6-trimethylphenol (**2**) from 2,3,5-trimethylphenol, and 2-formyl-3,4,5-trimethoxyphenol (**3**) from 3,4,5-trimethoxyphenol. The formyl derivatives are useful in their own right as direct handle precursors (e.g. **1** is the precursor of the *o*-backbond amide linker (BAL) handle[4]) or intermediates for benzopyran- or benzofuran-based handles.

The application of one of the most common formylation methods, the Vilsmeier–Haack reaction (DMF, $POCl_3$), and the Duff reaction (hexamethylenetetramine in strong acid medium) in attempts to obtain **2** did not afford the desired product with good purity or regioselectivity. This result was consistent with one of our earlier findings, when Vilsmeier–Haack conditions were applied to 3,5-dimethoxyphenol gave a mixture of the 2- and 4-formyl derivatives together with a small amount of the 2,4-diformyl derivative.[5] Moreover, the Vilsmeier–Haack reaction employs harsh conditions and the outcome strongly depends on the stirring conditions, with efficient mechanical stirring giving the best results.



Given the problems outlined above, it was decided to investigate formylation with dichloromethyl methyl ether in the presence of titanium(IV) chloride—a method first described by Gross et al.[6] and further developed by Cresp et al. [7]An assessment of this reaction when applied to polysubstituted aromatic rings is presented.



Keywords: benzofuran; benzopyran; handle; linker; protecting group; solid phase.

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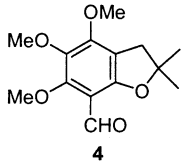
2. Results and discussion

As mentioned in the introduction, the Vilsmeier–Haack conditions applied to 3,5-dimethoxyphenol to obtain **1** led to a mixture of 4-formyl-3,5-dimethoxyphenol (52%), 2-formyl-3,5-dimethoxyphenol (**1**) (11%), and 2,4-diformyl-3,5-dimethoxyphenol (1%).[5] More recently, Landi and Ramig described the lithiation of 3,5-dimethoxyphenol with triisopropylsilyl chloride and *n*-butyllithium, followed by reaction with DMF to afford regioselectively the 4-formyl derivative (74%).[8] Reaction of 3,5-dimethoxyphenol with $TiCl_4$ (2.2 equiv.) followed by addition of dichloromethylmethyl ether led regioselectively to the 2-formyl (**1**) in preference over the 4-formyl derivative (91:9 at −60°C, 75% yield; 82:18 at 0°C, 94% yield, and 80:20 at 25°C). The pure 2-formyl-3,5-dimethoxyphenol (**1**) was obtained with an overall yield of 65% from the crude obtained at 0°C after column chromatography.

When similar conditions were applied to 2,3,5-trimethylphenol a mixture of 2- and 4-formyl-3,5,6-trimethylphenol (7:3, at 0°C, 93% yield) was obtained. Separation of the two isomers was easily achieved by crystallization from ethanol/water (2-formyl derivative (**2**), 71% overall yield; 4-formyl derivative, 15% overall yield). Application of the same conditions to 3,4,5-trimethoxyphenol led exclusively to the 2-formyl-3,4,5-trimethoxyphenol (**3**) in high yield; the 2,6-diformyl derivative was not detected as in the previous cases.

The regioselectivity of this reaction can be interpreted in terms of coordination of the Ti with oxygen atoms from both the phenol and the ether. Such coordination would favour the regioselectivity and should also increase the electrophilicity of the dichloromethyl methyl ether and therefore the reaction rate.[9] The higher regioselectivity of the reaction of 3,5-dimethoxyphenol to give **1** when compared to 2,3,5-trimethylphenol to give **2** can be explained by the fact that the $TiCl_4$ will also coordinate with a methoxy group at position 3 or 5, thus partially blocking susbstitution at position 4.

This hypothesis is supported by the fact that when similar conditions (2.2 equiv. of $TiCl_4$) were applied to 2,3-dihydro-2,2-dimethyl-4,5,6-trimethoxybenzofuran to give **4**, more than 25% of the starting compound remained unreacted. However, almost quantitative yields (73% after column chromatography purification) were obtained when 5 equiv. of $TiCl_4$ and 4 equiv. of dichloromethyl methyl ether were used. The need for the larger amounts of reagents can be explained by coordination of the $TiCl_4$ with two contiguous methoxy groups.[10] Similar large excesses have to be used for the formylation of other methoxy-rich aromatic systems such as (3,4-dihydro-2-methyl-5,6,7-trimethoxy-2*H*-1-benzopyran-2-yl)acetic acid to give **5** (81% yield after column chromatography purification).[11]



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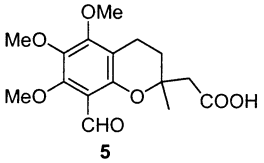

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3. Experimental protocols

3.1. General procedure for the formylation reaction

Reagents were used as received without further purification. Dichloromethane (DCM) was passed through an alumina column, stored over CaH_2 under an Ar atmosphere, and protected from the light.

A solution of the appropriate phenol (20–150 mmol) in DCM (1.5 mL/g phenol) was purged with N_2, cooled with an ice bath, and $TiCl_4$ (2.2 equiv. to obtain **1** and **2** and 5 equiv. to obtain **3**–**5**) was added dropwise over 15–30 min. The reaction mixture was left to react for 30–60 min. Dichloromethyl methyl ether (1 equiv.) was added over 15 min and the mixture left to react for a further 1–2 h. The reaction was quenched by the addition of saturated NH_4Cl solution and the mixture was left to stand for 1 h. The organic phase was separated and washed with 0.1 N HCl, saturated $NaHCO_3$ solution, and brine. The solution was dried over $MgSO_4$, filtered, and the solvent evaporated under reduced pressure. The purified products were homogeneous by HPLC (Nucleosil C_{18}, 250×40 mm, 10 μm; linear gradient of CH_3CN (+0.036% TFA) into H_2O (+0.045% TFA) at 1.0 mL/min flow rate; 220 nm), and were characterised using different physical techniques.

3.2. Physical data

3.2.1. 2-Formyl-3,5-dimethoxyphenol (1). From 3,5-dimethoxyphenol: mp: 63–66°C; IR (KBr): 2977, 1615, 1505, 1458, 1225, 1159, 1115, 1048 cm^{-1}; MS (CI, NH_3): $m/e=183$ (M^++1, 100%); ^1H NMR (300 MHz, $CDCl_3$): $\delta=3.81$ and 3.83 (2s, 6H, 2×OCH_3), 5.88 (d, $J=2.25$, 1H, arom.), 5.99 (d, $J=2.25$, 1H, arom.), 10.07 (s, 1H, CHO), 12.49 (s, OH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=55.60$ and 55.63 (2×CH_3, OCH_3), 90.48 and 92.88 (2×CH, arom.), 105.97 (C2, arom.), 163.50, 166.27 and 168.07 (C1, C3, C5, arom.), 191.74 (CHO) ppm; HPLC: 13.2 min (from 3:7 to 1:0 over 30 min).

3.2.2. 2-Formyl-3,5,6-trimethylphenol (2). From 2,3,5-trimethylphenol: mp: 75–76°C; IR (KBr): 2963, 1636, 1445, 1400, 1345, 1308, 1262, 1099, 1022 cm^{-1}; MS (CI, NH_3): $m/e=165$ (M^++1, 100%), 182 (M^++18, 37%), 199 (M^++35, 10%); ^1H NMR (300 MHz, $CDCl_3$): $\delta=2.11$, 2.25 and 2.50 (3s, 3×3H, 3×CH_3), 6.51 (s, 1H, arom.), 10.20 (s, 1H, CHO), 12.28 (s, OH) ppm; ^1H NMR (200 MHz, CD_3OD): $\delta=1.85$, 2.02 and 2.29 (3s, 3×3H, 3×CH_3), 6.34 (s, 1H, arom.), 10.0 (s, 1H, CHO) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=10.35$ (CH_3-*C6*), 17.59 and 20.61 (2×CH_3, CH_3-*C3* and CH_3-*C5*), 116.27 (C2, arom.), 122.82 (CH, arom.), 123.38 (C6, arom.), 138.42 (C3, arom.), 147.26 (C5, arom.), 161.37 (C1, arom.), 194.63 (CHO) ppm; HPLC: 19.27 min (from 3:7 to 1:0 over 30 min).

3.2.3. 4-Formyl-3,5,6-trimethylphenol. From 2,3,5-trimethylphenol: mp: 123–125°C; IR (KBr): 2925, 1650, 1565, 1499, 1428, 1306, 1264, 1103, 1034 cm^{-1}; MS (CI, NH_3): $m/e=165$ (M^++1, 35%), 182 (M^++18, 100%); ^1H NMR (300 MHz, $CDCl_3$): $\delta=2.19$, 2.53 and 2.54 (3s, 3×3H, 3×CH_3), 6.05 (s, 1H, OH), 6.54 (s, 1H, arom.), 10.49 (s, 1H, CHO) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=11.16$ (CH_3-*C2*), 15.80 (CH_3-*C3*), 20.79 (CH_3-*C5*), 115.85 (CH, arom.), 121.69 (C2, arom.), 126.50 (C4, arom.), 141.30 and 142.93 (2×C5, C3 and C1, arom.), 151.71 (C1, arom.), 192.96 (CHO) ppm; HPLC: 10.89 min (from 3:7 to 1:0 over 30 min).

3.2.4. 2-Formyl-3,4,5-trimethoxyphenol (3). From 3,4,5-trimethoxyphenol: mp: 55–57°C; IR (KBr): 1638, 1490, 1368, 1299, 1248, 1204, 1150, 1106 cm^{-1}; MS (CI, NH_3): $m/e=213$ (M^++1, 100%); ^1H NMR (300 MHz, $CDCl_3$): $\delta=3.77$, 3.88 and 4.02 (3s, 9H, 3×OCH_3), 6.17 (s, 1H, arom.), 10.02 (s, 1H, CHO), 12.08 (s, OH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=56.18$, 61.12 and 61.99 (3×CH_3, OCH_3), 95.18 (CH, arom.), 108.35 (C2, arom.), 133.81 (C4, arom.), 155.43 (C3, arom.), 161.06 and 162.02 (C1 and C5, arom.), 192.60 (CHO) ppm; HPLC: 11.85 min (from 0:1 to 1:0 over 30 min).

3.2.5. 2,3-Dihydro-2,2-dimethyl-4,5,6-trimethoxybenzofuran-7-carbaldehyde (4). From 2,3-dihydro-2,2-dimethyl-4,5,6-trimethoxybenzofuran: mp: 64–65°C; IR (KBr): 2975, 2939, 1684, 1594, 1457, 1416, 1358, 1200, 1047 cm^{-1}; MS (CI, NH_3): $m/e=267$ (M^++1, 100%); ^1H NMR (300 MHz, $CDCl_3$): $\delta=1.52$ (s, 6H, 2×CH_3), 3.02 (s, 2H, CH_2), 3.80, 3.94 and 4.03 (3s, 3×3H, 3×OCH_3), 10.17 (s, 1H, CHO) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=28.19$ (2×CH_3), 40.33 (CH_2), 59.65, 61.25 and 62.13 (3×CH_3, 3×OCH_3), 89.39 (C2, arom.), 109.93 (C7, arom.), 112.77 (C4′, arom.), 138.10 (C5, arom.), 154.10 (C6, arom.), 155.84 (C7′, arom.), 157.01 (C4, arom.), 189.90 (CHO) ppm; HPLC: 11.77 min (from 3:7 to 1:0 over 30 min).

3.2.6. (8-Formyl-3,4-dihydro-2-methyl-5,6,7-trimethoxy-2*H*-1-benzopyran-2-yl)acetic acid (5). From (3,4-dihydro-2-methyl-5,6,7-trimethoxy-2*H*-1-benzopyran-2-yl)-acetic acid: oil; IR (KBr): 3280, 2942, 1739, 1683, 1586, 1464, 1399, 1283 cm^{-1}; MS (CI, NH_3): $m/e=$ 325 (M^++1, 9%). ^1H NMR (300 MHz, $CDCl_3$): $\delta=$ 1.42 (s, 3H, CH_3), 1.83–1.97 (m, 2H, CH_2-*C3*), 2.60–2.81 (m, 4H, CH_2), 3.85, 4.01 and 4.07 (3s, 9H, 3×OCH_3), 10.23 (CHO) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=16.33$ (CH_2, C4), 21.77 (CH_3), 30.58 (CH_2, C3), 47.82 (CH_2-C2), 60.77, 61.11 and 62.44 (3×CH_3, OCH_3), 75.43 (C2, arom.), 110.05 (C8, arom.), 113.48 (C5′, arom.), 138.47 (C6, arom.), 149.52, 152.30 and 157.69 (3×Cq, C7, C8′ and C5, arom.), 170.50 (COOH), 188.96 (CHO) ppm; HPLC: 9.34 min (from 3:7 to 1:0 over 30 min).

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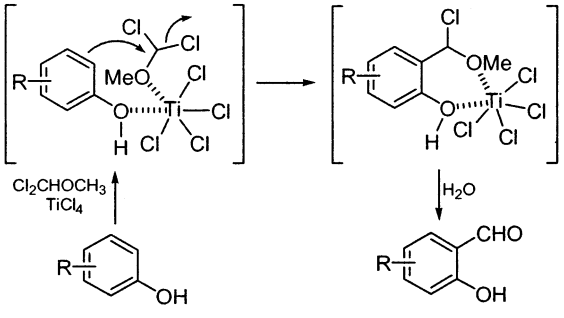
9. The reaction could take place through the following mechanism:



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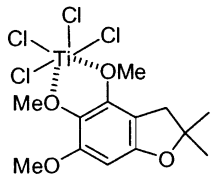

11. Solladié et al. have also reported excellent yields for the formylation of pentamethylchromans, systems similar to **5** (see Ref. 3).