With compliments of the Author
A Convenient Synthesis of Tri- and Tetramethylbenzaldehydes from Readily Available Phenols

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Abstract: This letter describes a convenient synthesis of the six isomeric tri- and tetramethylbenzaldehydes, which are not readily available from major chemical suppliers. Formylation of readily available phenols via electrophilic aromatic substitution provides compounds containing the correct aromatic substitution pattern. Suzuki cross-coupling of the corresponding trifluoromethanesulfonates with methylboronic acid then provides the benzaldehydes as single isomers.

Key words: aldehydes, palladium, Suzuki, aromatic compounds, formylation

Substituted benzaldehydes are important starting materials for use in a variety of chemical processes and they are frequently employed in medicinal chemistry to introduce substituted aryl groups into potential drug molecules. The introduction of multiple methyl groups onto the benzene ring can serve to alter the preferred three-dimensional conformation of the aryl unit in the molecule, leading to subtle changes in chemical and biological properties.1 There are 19 different benzaldehydes incorporating one or more methyl substituents on the aromatic ring and 13 of these compounds are available commercially in gram quantities from major suppliers.2 The remaining compounds 1a–f (Figure 1) are not available from major commercial suppliers, so typically they must be synthesized from more readily available aryl precursors. Aldehydes 1a–f have previously been synthesized by a variety of different routes including direct formylation of polymethylated benzenes,3 side-chain oxidation of polymethylated benzenes,4 Grignard reaction of an aryl bromide with a suitable electrophile,5 partial reduction of carboxylic acid derivatives,6 or degradation of bicyclic systems.7 In the latter three cases the starting materials used are often as complex to prepare as the target aldehyde itself. Whilst direct formylation of a polymethylated benzene potentially offers a very direct route, polymethyl benzenes are prone to acid-catalyzed isomerization processes during the harsh conditions often needed for electrophilic aromatic substitution reactions.8 This can lead to complex mixtures of regiosomeric products which can be extremely difficult to separate.

As part of an ongoing medicinal chemistry project, we required access to all of the 19 methylated benzaldehyde isomers to explore a complex structure–activity relationship. In order to prepare all of the six isomers shown in Figure 1, we have developed a new synthetic route to enable all of these compounds to be prepared from cheap, commercially available phenols.

We envisaged that the desired aldehydes could potentially be synthesized by formylation of a phenol in an electrophilic aromatic substitution reaction, followed by cross-coupling of the phenol-derived sulfonate ester with methylboronic acid (Scheme 1). The phenol group would serve to activate the aromatic ring towards electrophilic aromatic substitution, preventing competing isomerization processes, and direct the substitution reaction to provide the desired product isomer. After isolation of the desired regioisomer, the phenol can then be converted into a methyl group via the corresponding trifluoromethanesulfonate ester. The phenols 2a–e required for the synthesis of aldehydes 1a–e are all commercially available. In the case of aldehyde 1f, a suitable dihydroquinone precursor 2f containing the required substitution pattern is commercially available (vide infra).

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The formylation of phenols 2a–e was carried out using dichloromethyl methyl ether and aluminium trichloride at room temperature (Scheme 2). Phenol 2a underwent formylation in good yield to give aldehyde 3, which was converted into triflate 4 under standard conditions. The formylation of phenol 2b under similar conditions gave a mixture of isomeric aldehydes where the major product was the undesired para-substitution product. Nevertheless, the isomers could readily be separated by chromatography, and aldehyde 5 was subsequently converted into aryl trifluoromethanesulfonate 6. Phenol 2c underwent formylation in good yield to give aldehyde 7 which was in turn converted into triflate 8. The formylation of phenol 2d gave a mixture of isomeric aldehydes 9 and 10 which was converted into a mixture of the two corresponding triflates 11 and 12. This mixture of isomers is inconsequential as both triflates 11 and 12 will ultimately be converted into the same aldehyde 1d upon Suzuki coupling with methyboronic acid. Phenol 2e provides no regioselectivity issues in the aromatic substitution reaction, and aldehyde 13 and triflate 14 were synthesized without difficulty.

With the desired triflates in hand, we then turned our attention to the proposed Suzuki cross-coupling with methyboronic acid (Scheme 3 and Table 1). The cross-coupling of methyboronic acid with aryl triflates has previously been reported under a variety of conditions. We evaluated several protocols for the conversion of triflate 4 into aldehyde 1a. With Pd(PPh3)4 as the catalyst, negligible conversion into the desired product was observed using either K2CO3 or K3PO4 as the base. Upon switching to PdCl2(dpff), however, excellent conversion into the desired product 1a was observed. With optimized conditions for the Suzuki cross-coupling in hand we went on to complete the synthesis of the aldehydes 1a–e (Table 1).

Scheme 2  Forymylation of starting phenols and subsequent conversion into the corresponding aryl trifluoromethanesulfonates. *Reagents and conditions:* a) Cl2CHOMe, AICl3, CH2Cl2, r.t., 65% (3), 15% (5), 71% (7), 44% (9 and 10), 60% (13); b) Tf2O, Et3N, CH2Cl2, 64% (4), 34% (6), 53% (8), 95% (11 and 12), 46% (14).

Scheme 3  Suzuki cross-coupling of trifluoromethanesulfonates with methyboronic acid

Table 1  Suzuki Cross-Coupling Reactions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Trifluoromethanesulfonate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>1a</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>1b</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>1c</td>
<td>61</td>
</tr>
<tr>
<td>4</td>
<td>11 and 12</td>
<td>1d</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td>1e</td>
<td>80</td>
</tr>
</tbody>
</table>

The remaining aldehyde 1f was synthesized from commercially available dihydroquinone 2f via trifluoromethanesulfonate formation and cross-coupling to give ester 15 (Scheme 4). An unoptimized reduction–oxidation sequence then provided aldehyde 1fa in moderate yield.

Scheme 4  Reagents and conditions: a) Tf2O, Et3N, CH2Cl2, 98%; b) MeB(OH)2, K2CO3, PdCl2(dpff), THF–H2O (10:1) reflux, 87%; c) DIBAL-H, PhMe–Et2O, 63%; d) DMSO, COCl2, then Et3N, CH2Cl2, 18%.

In conclusion, we have developed a general synthetic route to tri- or tetramethylbenzaldehydes from readily available phenols. Electrophilic aromatic formylation of a phenol provides access to compounds with the required substitution pattern as single isomers. Conversion into the
corresponding triflate and Suzuki cross-coupling with methylboronic acid furnishes the target tri- and tetramethylbenzaldehydes as single isomers.

Acknowledgment

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Supporting Information

for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are experimental procedures and 1H and 13C NMR spectra for all compounds.

References and Notes


(2) All three methlybenzaldehydes and all six dimethylbenzaldehydes can be purchased from major commercial suppliers; 2,4,5-trimethylbenzaldehyde, 2,3,6-trimethylbenzaldehyde, 2,3,5,6-tetramethylbenzaldehyde, and pentamethylbenzaldehyde are also readily available.


(10) General Procedure for Formylation

Aluminium trichloride (4.82 g, 36 mmol) was added to a solution of phenol (33 mmol) in anhydrous CH2Cl2 (50 mL) under argon, and the solution stirred for 10 min. Dichloromethyl methyl ether (3.3 mL, 36 mmol) was added dropwise via a syringe pump (7.7 mL/h). The reaction was left to stir for a further 10 min before cold H2O (200 mL) was added slowly. After stirring for a further 10 min, the organic layer was separated and washed with brine (100 mL) and H2O (150 mL), dried over MgSO4, filtered, and concentrated to give the aldehyde which was purified by column chromatography.

2-Hydroxy-3,5-dimethylbenzaldehyde (3)

Brown viscous oil; Rf = 0.97 (EtOAc–PE, 1:1). IR: νmax = 3201, 2921, 1646, 1467, 1260 cm–1. 1H NMR (600 MHz, CDCl3): δ = 10.19 (s, 1 H, CHO), 7.62 (d, 1 H, J = 2.0 Hz ArH), 2.42 (s, 3 H, Me), 2.38 (s, 3 H, Me). 13C NMR (150 MHz, CDCl3): δ = 196.8 (CH), 150.0 (CH2), 131.9 (CH), 128.6 (C6), 126.6 (C7), 119.9 (C8), 20.3 (CH3), 15.1 (CH2). HRMS (EI): m/z calc for C9H10O2 [M]+: 150.0680; found: 150.0681.

General Procedure for Suzuki Cross-Coupling

Triethylamine (4.04 g, 40 mmol) was added to a solution of phenol (13 mmol) in anhydrous CH2Cl2 (13 mL) at −78 °C under argon, and the solution stirred for 30 min. Trifluoromethanesulfonic anhydride (2.5 mL, 15 mmol, 1.1 equiv) was added dropwise via a syringe pump (7.7 mL/h). The reaction was left to stir for a further 2 h. The reaction mixture was diluted with CH2Cl2 (15 mL) and washed with sat. NaHCO3 (20 mL), brine (20 mL), and H2O (20 mL), dried (MgSO4), filtered, and concentrated to give the trifluoromethanesulfonate which was purified by column chromatography.

2-Formyl-4,6-dimethylphenyl trifluoromethanesulfonate (4)

Yellow viscous oil; Rf = 0.91 (EtOAc–PE, 1:1). IR: νmax = 2883, 1701, 1598, 1407, 1207, 1136 cm–1. 1H NMR (600 MHz, CDCl3): δ = 10.19 (s, 1 H, CHO), 7.62 (d, 1 H, J = 2.0 Hz, ArH), 7.38 (d, 1 H, J = 3.4 Hz ArH), 2.42 (s, 3 H, Me), 2.38 (s, 3 H, Me). 13C NMR (150 MHz, CDCl3): δ = 187.4 (CH), 145.9 (C7), 139.1 (C6), 138.8 (CH2), 132.5 (C5), 129.2 (C4), 128.5 (CH), 118.4 (q, J = 321 Hz, C3), 20.9 (CH3), 16.5 (CH2). HRMS (EI): m/z calc for C9H8O2F3S [M]+: 282.0174; found: 282.0174.

General Procedure for Suzuki Cross-Coupling

K2CO3 (397 mg, 3 mmol) and PdCl2(dppf)·CH2Cl2 (116 mg, 10 mol%) were added to a solution of aryl trifluoromethanesulfonate (1 mmol) in THF (25 mL) which was left to stir for 5 min. H2O (HPLC grade, 1.25 mL) was added, followed by methylboronic acid (255 mg, 4 mmol). The reaction was heated at reflux overnight. EtOAc (7 mL) was added, and the
organic layer was separated and washed with H₂O (2 × 10 mL), dried over MgSO₄, filtered, and concentrated to give
the aldehyde which was purified by column chromatography.

**2,3,5-Trimethylbenzaldehyde (1a)**

Brown oil; Rₚ = 0.82 (EtOAc–PE, 1:1). IR: νₓmax = 2923, 1692, 1478 cm⁻¹. ¹H NMR (600 MHz, CDCl₃): δ = 10.28 (s, 1 H, CHO), 7.46 (s, 1 H, ArH), 7.20 (s, 1 H, ArH), 2.52 (s, 3 H, Me), 2.33 (s, 3 H, Me), 2.30 (s, 3 H, Me). ¹³C NMR (150 MHz, CDCl₃): δ = 193.5 (CH), 138.3 (Cₗ), 136.4 (CH), 136.3 (Cₗ), 135.4 (Cₗ), 134.3 (Cₗ), 130.1 (CH), 21.2 (CH₃), 20.2 (CH₃), 14.3 (CH₃). HRMS (EI): m/z calcd for C₁₀H₁₂O [M]+: 148.0888; found: 148.0876.