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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 polylmethylated 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 regioisomeric products which can be extremely difficult to separate.

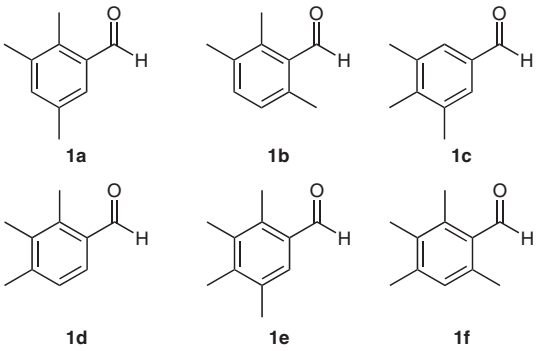
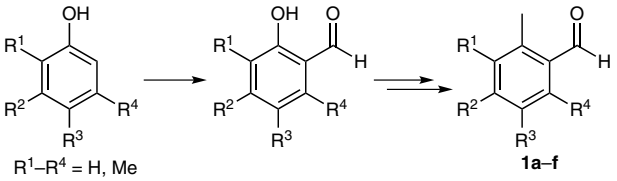


Figure 1 Tri- and tetramethylbenzaldehydes that are not readily available commercially



Scheme 1 Proposed synthetic route to tri- and tetramethylbenzaldehydes

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 trifluormethanesulfonate 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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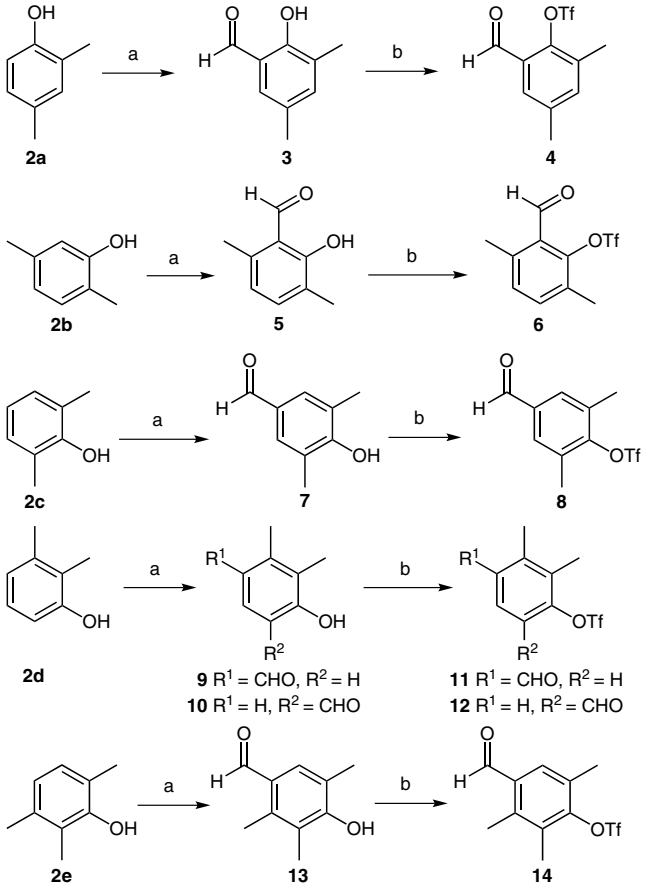
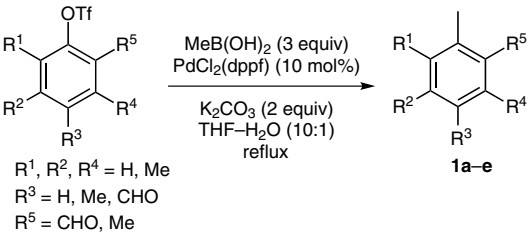
The formylation of phenols **2a**–**e** was carried out using dichloromethyl methyl ether and aluminium trichloride at room temperature (Scheme 2).[9] Phenol **2a** underwent formylation in good yield to give aldehyde **3**, which was converted into triflate **4** under standard conditions. The formylation 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**[9] was subsequently converted into aryl trifluoromethanesulfonate **6**.[10] Phenol **2c** underwent formylation in good yield to give aldehyde **7**[11] which was in turn converted into triflate **8**.[12] The formylation of phenol **2d** gave a mixture of isomeric aldehydes **9**[13] and **10**[14] which was converted into a mixture of the two corresponding triflates **11**[13] and **12**.[14] 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 methylboronic acid. Phenol **2e** provides no regioselectivity issues in the aromatic substitution reaction, and aldehyde **13**[15] and triflate **14** were synthesized without difficulty.



Scheme 2 Forymlation of starting phenols and subsequent conversion into the corresponding aryl trifluoromethanesulfonates. *Reagents and conditions*: a) Cl_2CHOMe, $AlCl_3$, CH_2Cl_2, r.t., 65% (**3**), 15% (**5**), 71% (**7**), 44% (**9** and **10**), 60% (**13**); b) Tf_2O, Et_3N, CH_2Cl_2, 64% (**4**), 34% (**6**), 53% (**8**), 95% (**11** and **12**), 46% (**14**).

With the desired triflates in hand, we then turned our attention to the proposed Suzuki cross-coupling with methylboronic acid (Scheme 3 and Table 1). The cross-coupling of methylboronic 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**.[16] With $Pd(PPh_3)_4$ as the catalyst, negligible conversion into the desired product was observed using either K_2CO_3 or K_3PO_4 as the base. Upon switching to $PdCl_2$(dppf), however, excellent conversion into the desired product **1a** was observed.[16d] With optimized conditions for the Suzuki cross-coupling in hand we went on to complete the synthesis of the aldehydes **1a**–**e** (Table 1).

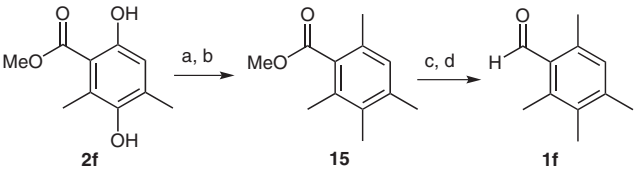


Scheme 3 Suzuki cross-coupling of trifluoromethanesulfonates with methylboronic acid

Table 1 Suzuki Cross-Coupling Reactions

Entry	Trifluoromethanesulfonate	Product	Yield (%)
1	**4**	**1a**[17]	99
2	**6**	**1b**[18]	99
3	**8**	**1c**[6a]	61
4	**11** and **12**	**1d**[19]	97
5	**14**	**1e**[3c]	80

The remaining aldehyde **1f** was synthesized from commercially available dihydroquinone **2f** via trifluoromethanesulfonate formation and cross-coupling to give ester **15** (Scheme 4).[20] An unoptimized reduction–oxidation sequence then provided aldehyde **1f**[3a] in moderate yield.



Scheme 4 *Reagents and conditions*: a) Tf_2O, Et_3N, CH_2Cl_2, 98%; b) $MeB(OH)_2$, K_2CO_3, $PdCl_2$(dppf), THF–H_2O, reflux, 87%; c) DIBAL-H, PhMe–Et_2O, 63%; d) DMSO, $COCl_2$, then Et_3N, CH_2Cl_2, 18%.

In conclusion, we have developed a general synthetic route to tri- or tetramethylbenzaldehydes from readily available phenols. Electrophilic aromatic formylation[21] of a phenol provides access to compounds with the required substitution pattern as single isomers. Conversion into the

corresponding triflate[22] and Suzuki cross-coupling with methylboronic acid[23] 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 ^{1}H and ^{13}C NMR spectra for all compounds.

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(21) **General Procedure for Formylation**
Aluminium trichloride (4.82 g, 36 mmol) was added to a solution of phenol (33 mmol) in anhydrous CH_2Cl_2 (50 mL) under argon, and the solution was 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 H_2O (200 mL) was added slowly. After stirring for a further 10 min, the organic layer was separated and washed with brine (100 mL) and H_2O (150 mL), dried over $MgSO_4$, filtered, and concentrated to give the aldehyde which was purified by column chromatography.
2-Hydroxy-3,5-dimethylbenzaldehyde (3)
Brown viscous oil; R_f = 0.97 (EtOAc–PE, 1:1). IR: ν_{max} = 3201, 2921, 1646, 1467, 1260 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 11.09 (s, 1 H, OH), 9.81 (s, 1 H, CHO), 7.20 (br s, 1 H, ArH), 7.15 (s, 1 H, ArH), 2.29 (s, 3 H, Me), 2.23 (s, 3 H, Me). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 196.8 (CH), 158.0 (C_q), 139.1 (CH), 131.0 (CH), 128.6 (C_q), 126.6 (C_q), 119.9 (C_q), 20.3 (CH_3), 15.1 (CH_3). HRMS (EI): *m/z* calcd for $C_9H_{10}O_2$ [M]$^+$: 150.0680; found: 150.0681.

(22) **General Procedure for Trifluoromethanesulfonate Synthesis**
Triethylamine (4.04 g, 40 mmol) was added to a solution of phenol (13 mmol) in anhydrous CH_2Cl_2 (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 CH_2Cl_2 (15 mL) and washed with sat. $NaHCO_3$ (20 mL), brine (20 mL), and H_2O (20 mL), dried ($MgSO_4$), filtered, and concentrated to give the trifluoromethanesulfonate which was purified by column chromatography.
2-Formyl-4,6-dimethylphenyl trifluoromethanesulfonate (4)
Yellow viscous oil; R_f = 0.91 (EtOAc–PE, 1:1). IR: ν_{max} = 2883, 1701, 1598, 1407, 1207, 1136 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.19 (s, 1 H, CHO), 7.62 (d, 1 H, *J* = 2.0 Hz, ArH), 7.38 (d, 1 H, *J* = 2.0 Hz ArH), 2.42 (s, 3 H, Me), 2.40 (s, 3 H, Me). ^{13}C NMR (150 MHz, $CDCl_3$: δ = 187.4 (CH), 145.9 (C_q), 139.1 (C_q), 138.8 (CH), 132.5 (C_q), 129.2 (C_q), 128.5 (CH), 118.4 (q, *J* = 321 Hz, C_q), 20.9 (CH_3), 16.5 (CH_3). HRMS (EI): *m/z* calcd for $C_{10}H_9F_3O_4S$ [M]$^+$: 282.0174; found: 282.0174.

(23) **General Procedure for Suzuki Cross-Coupling**
K_2CO_3 (397 mg, 3 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (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. H_2O (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 H_2O (2 × 10 mL), dried over $MgSO_4$, filtered, and concentrated to give the aldehyde which was purified by column chromatography.

2,3,5-Trimethylbenzaldehyde (1a)

Brown oil; R_f = 0.82 (EtOAc–PE, 1:1). IR: ν_{max} = 2923, 1692, 1478 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): 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). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 193.5 (CH), 138.3 (C_q), 136.4 (CH), 136.3 (C_q), 135.4 (C_q), 134.3 (C_q), 130.1 (CH), 21.2 (CH_3), 20.2 (CH_3), 14.3 (CH_3). HRMS (EI): *m/z* calcd for $C_{10}H_{12}O$ $[M]^+$: 148.0888; found: 148.0876.

