Synthesis of Aromatic Aldehydes by Oxidative Hydroxymethylation

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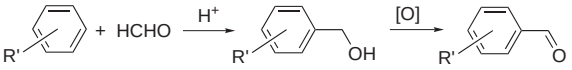
Abstract: A new high yield method for the synthesis of aromatic aldehydes has been developed. The procedure is based on an acid catalyzed hydroxymethylation of an arene substrate by paraformaldehyde with concurrent selective oxidation of the intermediate aromatic carbinol by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to the aldehyde product.

Key words: aldehydes, arenes, electrophilic aromatic substitutions, oxidations, quinones

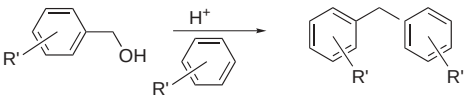
The discovery of new methods for the preparation of chemicals is an important goal in the development of modern methods for chemical synthesis. Of special significance are the use procedures that minimize amounts of waste and by-products. In this context, the preparation of rather simple aromatic aldehydes presents a surprisingly difficult challenge. Perusal of basic organic textbooks will show that many different approaches can be taken towards the synthesis of aromatic aldehydes including: (a) direct oxidation of methylaromatic substrates to aromatic aldehydes using stoichiometric reagents such as silver(II) oxide, ceric ammonium nitrate, selenium dioxide, manganese dioxide, chromyl chloride and periodic acid;[1] (b) chlorination/bromination of methylaromatic substrates in the presence of peroxides and/or light as radical chain initiators followed by hydrolysis to the required aldehyde; (c) oxidation of the methylaromatic substrates to the corresponding carboxylic acids with oxidants such as nitric acid, chromic acid and derivatives and potassium permanganate[1] followed by halogenation to acyl halides and catalytic hydrogenation to the corresponding aromatic aldehydes using palladium-based catalysts;[2] (d) halogenation of arenes to the corresponding haloarenes followed by carbonylation with carbon monoxide in the presence of noble metal based catalysts (usually palladium) to yield aromatic aldehydes;[3] (e) formylation of arenes with various reagents notably (i) aluminum chloride/gaseous hydrogen chloride/carbon monoxide (Gatterman–Koch reaction),[4] (ii) zinc cyanide/hydrogen chloride (Gatterman reaction),[5] (iii) phosphorous oxychloride disubstituted formamides (Vilsmeier–Haack reaction),[6] (iv) chloroform/sodium hydroxide (Reimer–Tiemann reaction),[7] (v) dichloromethyl methyl ether/aluminum chloride,[8] and (vi) formylfluoride/boron trifluoride.[9] All these methods are either multistage procedures, or use bromine/chlorine with the associated halide waste or use often reagents with formation of hazardous (in)organic waste.

An alternative method for the preparation of aryl aldehydes would be to hydroxymethylate an arene with formaldehyde to yield an intermediate arylmethanol with in situ oxidation of the arylmethanol by any number of methods, Scheme 1.



Scheme 1 Oxidative hydroxymethylation for synthesis of aryl aldehydes

A major problem with this concept is the fact that normally the hydroxymethylation step requires the use of a Brønsted acid catalyst such as sulfuric acid. Under these conditions the intermediate arylmethanol reacts with the arene substrate to yield condensation products, Scheme 2. In the limited case of phenol and some of its alkylated derivatives, the concept delineated in Scheme 1 has been realized, mostly in the patent literature, since no Brønsted acid is reportedly needed for the hydroxymethylation reaction. Thus, salicylaldehyde products may be obtained using for the arylmethanol oxidation step tin chlorides,[10] chromium salts,[11] peroxides and manganese compounds,[12] titanium or zirconium compounds,[13] or clays modified with trialkylamines[14] as catalysts.



Scheme 2 Formation of diarylmethanes under hydroxymethylation conditions

Beyond the aforementioned case of oxidative hydroxymethylation for certain phenolic substrates there exists no general method for preparation of aryl aldehydes from arenes by the reaction pathway as delineated in Scheme 1. Notably, in the one case where such a possibility has been mentioned in the literature for the oxidative hydroxylation of anisole the reaction yield is low, <25%, and required high temperatures, ca. 350 °C.[15]

A high yield procedure for oxidative hydroxymethylation would be an advantageous alternative to the classic methods described above.[1–9] Such a preliminary procedure is now described as outlined in Scheme 3, wherein 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) is used as the oxidant for the intermediate aryl methanol.[16] The 2,3-

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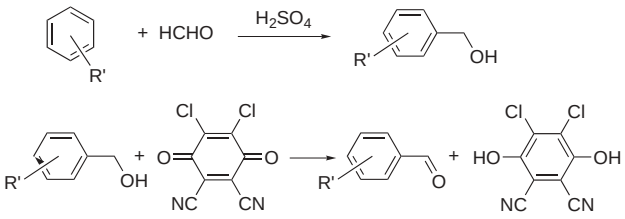
Table 1 Oxidative Hydroxymethylation of Arenes to Aryl Aldehydes[a]

Substrate	Isolated yield (%)	Product (purity, %)
1,2-Dimethoxybenzene	92	3,4-Dimethoxybenzaldehyde (95)
1,4-Dimethoxybenzene	89	2,5-Dimethoxybenzaldehyde (99)
Methoxybenzene	87	2- and 4-Methoxybenzaldehyde (99)[b]
Ethoxybenzene	94	2- and 4-Ethoxybenzaldehyde (99)[c]
4-Methoxynaphthalene	74	4-Methoxy-1-naphthaldehyde (99)
1,3-Benzodioxole	63	Piperonal (98)
Thiophene	91	Thiophene-2-carboxyaldehyde (98)
Benzothiophene	95	Benzothiophene-2-carboxyaldehyde (93)[d]

[a] Reaction conditions: 10 mmol arene, 100 mmol paraformaldehyde, 0.0025 mmol H_2SO_4, 20 mmol DDQ, 10 mL MeCN, 5 h, 80 °C.
[b] 75% 4-Methoxybenzaldehyde, 25% 2-methoxybenzaldehyde.
[c] 78% 4-Ethoxybenzaldehyde, 22% 2-ethoxybenzaldehyde.
[d] Ca. 7% benzothiophene-3-carboxyaldehyde.



Scheme 3 Synthesis of aryl aldehydes by oxidative hydroxymethylation with DDQ as oxidant

dichloro-5,6-dicyanohydroquinone (DDHQ) formed in the reaction can be recovered and re-oxidized to DDQ with nitric acid.[17]

In a typical procedure 10 mmol arene, 3 g (100 mmol) paraformaldehyde, 0.25 mg (0.0025 mmol) H_2SO_4 and 4.54 g (20 mmol) DDQ were stirred in 10 mL acetonitrile for 5 hours at 80 °C. The reaction mixture was cooled to room temperature. The precipitate formed was filtered and washed twice with EtOAc. The product from the filtrate and wash was purified by flash chromatography. The results for some exemplary substrates are presented in Table 1.

The method presented, although conceptually novel and quite effective for arylethers and thiophenes still has two limitations related to substrate scope. First, less reactive arenes such as benzene require larger amounts of acid for the hydroxymethylation reaction. Under such conditions the in situ oxidation to the aryl aldehyde is less rate competitive and mostly coupling products (Scheme 2) are still formed. Second, for methylated substrates such as 4-methoxytoluene, there is a competitive parallel oxidation of the methyl moiety to aldehyde that reduces the reaction yield. It should be noted that the procedure also requires a disadvantageous excess of paraformaldehyde as a reagent.

In a typical oxidative hydroxymethylation procedure (Table 1) 10 mmol arene substrate, 3 g (100 mmol) paraformaldehyde, 0.25 mg (0.0025 mmol) H_2SO_4 and 4.54 g (20 mmol) DDQ were stirred in 10 mL MeCN for 5 h at 80 °C. The reaction mixtures were then cooled and the precipitate containing the DDHQ product was filtered and washed twice with EtOAc. The filtrate containing the aryl aldehyde products was purified by flash chromatography and the product was analyzed by ^{1}H NMR and GC. The GLC were carried out with both FID and MS detectors using a Restek Rtx-5MS column (5% phenymethylsilicone, 30 m, 0.32 mm ID, 0.25 µm coating). The determination of the regioselectivity of the reactions and the confirmation of the GC analysis was carried out by ^{1}H NMR.

Acknowledgment

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