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Synthesis of Substrates for Aldolase-Catalysed Reactions: A Comparison of Methods for the Synthesis of Substituted Phenylacetaldehydes

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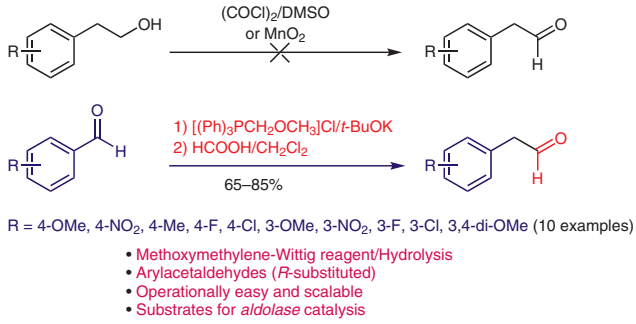

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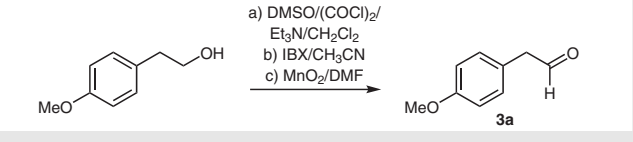
Abstract Methods for the synthesis of phenylacetaldehydes (oxidation, one-carbon chain extension) were compared by using the synthesis of 4-methoxyphenylacetaldehyde as a model example. Oxidations of 4-methoxyphenylethanol with activated DMSO (Swern oxidation) or manganese dioxide gave unsatisfactory results; whereas oxidation with 2-iodoxybenzoic acid (IBX) produced 4-methoxyphenylacetaldehyde in reasonable (75%) yield. However, Wittig-type one-carbon chain extension with methoxymethylene-triphenylphosphine followed by hydrolysis gave an excellent (81% overall) yield of 4-methoxyphenylacetaldehyde from 4-methoxybenzaldehyde (a cheap starting material). This approach was subsequently used to synthesise a set of 10 substituted phenylacetaldehydes in good to excellent yields.

Key words benzaldehyde, phenylacetaldehyde derivatives, homologation reaction

Aldolases are an important class of enzymes that take part in fundamental metabolic processes. In nature, they catalyse the stereoselective formation (or cleavage) of carbon–carbon bonds, and therefore they have also been considered for use in preparative organic synthesis.[1] For such applications, the properties (stereopecificity, substrate scope) of the native enzymes need to be changed or tuned; for example by the process of directed evolution.[2] For the characterization of *E. coli* fructose-6-phosphate aldolase[3] (FSA) variants produced by directed evolution we required a set of phenylacetaldehyde substrates with different ring substituents. All aldehydes had been synthesised before, often as intermediates in syntheses of biologically active compounds.[4a,5,6b,7–9] However, very few, if any, were commercially available and therefore all had to be chemically resynthesised. Generally speaking, the three most popular methods for the synthesis of aldehydes are: partial oxidation of the corresponding alcohols, carbon-chain extension of a lower-homolog aldehyde, or partial reduction of the corresponding carboxylic acids or -esters. In this paper, we present a comparison of the first two methods for the synthesis of a model phenylacetaldehyde (4-methoxyphenylacetaldehyde) and then application of the method that proved most suitable (Wittig-type one-carbon extension) to the synthesis of a set of 10 substituted phenylacetaldehydes. Partial reduction methods[10] were not investigated because of the reduction sensitivity of some of the required ring substituents (e.g. the nitro group).

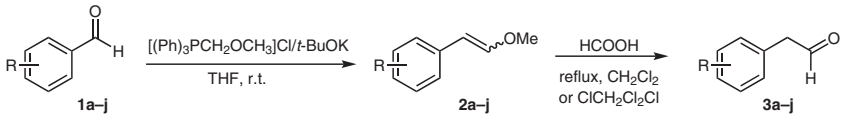
We considered oxidative methods based on activated DMSO,[11] hypervalent iodine,[6] and transition metal oxides.[12] These methods were applied to the model compound 4-methoxybenzyl alcohol and the results are summarised in Scheme 1. With DMSO/oxalyl chloride in dichloromethane (Swern oxidation), TLC and NMR spectroscopy indicated a multicomponent reaction mixture, and the desired 4-methoxyphenylacetaldehyde (**3a**) was isolated by column chromatography in only 20% yield. With the hypervalent iodine reagent IBX (2-iodoxybenzoic acid), the expected aldehyde **3a** was isolated in 75% yield after a tedious chromatographic purification. Revelant[6b] reports an 88% yield of **3a** (without chromatographic purification) for the same reaction. High phenylacetaldehyde yields have also been reported[7,14] for the oxidation of phenylethanols with Dess–Martin periodinane, another hypervalent iodine reagent.

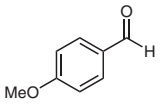
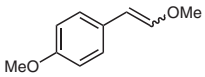
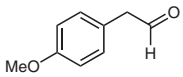
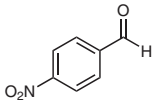
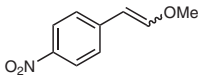
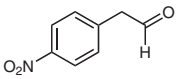
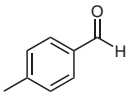
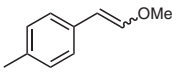
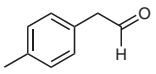
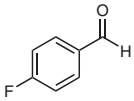
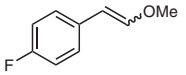
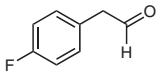
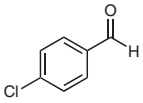
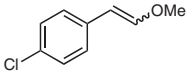
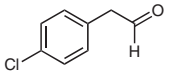
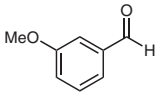
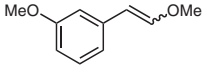
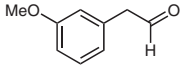
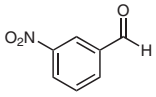
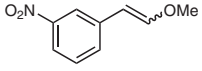
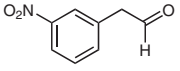
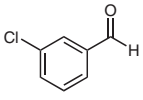
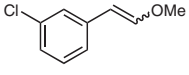
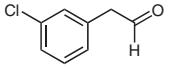
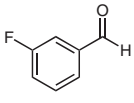
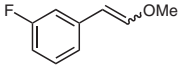
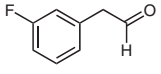
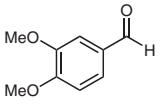
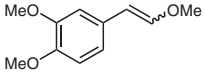
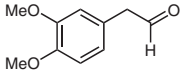


Scheme 1 Reaction of 4-methoxybenzyl alcohol with various oxidation reagents. (a) 25% yield, (b) 75% yield, (c) 0% yield (but 77% of 4-methoxybenzaldehyde)

Finally, with MnO_2 in THF an aldehyde product was isolated in 77% yield after chromatography. This product, however, turned out to be the next lower aldehyde homolog, 4-methoxybenzaldehyde. Obviously, the bond between the aldehyde carbonyl and the benzylic carbon atom had been cleaved under the reaction conditions. A similar result has

Table 1 Reaction of Substituted Benzaldehydes **1a–j** with Methoxymethylene-triphenylphosphine Followed by Hydrolysis of the Resulting Enol Ethers **2a–j** to Give Phenylacetaldehydes **3a–j**

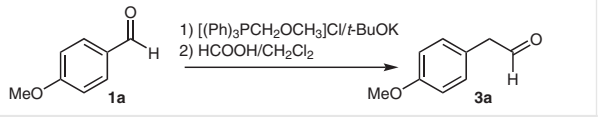


Entry	Starting aldehyde (**1**)	Wittig reaction time (h)	Enol ether (**2**)	Yield (%)	*E*/*Z*	Ref.	Hydrolysis time (h)	Product aldehyde (**3**)	Yield (%)	Ref.
a		16		95[a]	1/1	5,15,16	16		85	6b,8,16,17
b		16		97[a]	1/1	5,14	16		88	18,19
c		16		95[a]	1/1	5	16		80[a]	17,20
d		16		91[a]	1/1	15,21	16		70	22,24
e		16		93[a]	1/1	8	16		86	17,23
f		16		97[a]	1/1	5,16	24		79[a]	8,16
g		24		95[a]	1/1	5	36		68[a]	24
h		24		98[a]	1/1,5	8	3		73[a]	8,17,24
i		24		98[a]	1/1,5	14	4		65[a]	7,24
j		16		97[a]	1/1,3	16	3		81[a]	14,16

[a] Chromatographic purification

been reported for phenylethanol oxidations with pyridinium chlorochromate.[6b]

In view of the above results with oxidation reagents and in view of the fact that many of the required phenylethanols are not commercially available (most have to be prepared by reduction of the corresponding carboxylic acid derivatives) we decided to turn our attention to methods based on one-carbon chain extension of an existing aldehyde. We focused on a modification[4,5] of the original[13] Wittig-type reaction of an aldehyde with methoxymethylene-triphenylphosphine. A reaction of the phosphine reagent (prepared in situ from the corresponding phosphonium salt with potassium *tert*-butoxide in THF) was therefore performed with 4-methoxybenzaldehyde (**1a**, Scheme 2). The enol ether product (a 1:1 mixture of *E* and *Z* isomers, 95% yield) was hydrolysed (10% formic acid in dichloromethane) to give 4-methoxy phenylacetaldehyde (**3a**) in 81% overall yield. The high overall yield in this test reaction, the relative simplicity of the procedure, and the fact that a large variety of substituted benzaldehydes is commercially available encouraged us to choose this method for the synthesis of our desired set of substituted phenylacetaldehydes.



Scheme 2 Reaction of 4-methoxybenzaldehyde with methoxymethylene-triphenylphosphine followed by hydrolysis

We subjected a series of substituted benzaldehydes (Table 1) to the Wittig extension/hydrolysis reaction conditions. Substituents ranged from strongly electron-donating (methoxy) to electron-withdrawing (nitro) groups placed either in *para* or *meta* positions of the benzaldehydes. A *m*,*p*-dimethoxybenzaldehyde was also included in the set. The results (starting aldehydes, enol ethers and product aldehydes) are listed in Table 1, together with yields, enol ether *E*/*Z* ratios, reaction times, and references for known compounds. As can be seen in Table 1, the yields in both the Wittig extension and hydrolysis steps were high throughout. In particular, the Wittig reaction gave high yields (>90%) regardless of benzaldehyde substituents, even after chromatographic purification. The *E*/*Z* product ratios were close to unity except for entries 8–10; the reason for these minor discrepancies are unclear. Interestingly, the *E* products have been reported[5] to dominate in similar reactions employing a shorter reaction time and another base (LiHMDS). The rate and yield in the enol ether hydrolysis step were sensitive to structural variations, with yields being somewhat lower (by 5–20%) for *meta*- as compared to *para*-substituted phenylacetaldehydes. For most enol ethers, formic acid in dichloromethane heated to reflux and a reaction time of 24–36 hours was sufficient. However, for the *m*-chloro-, *m*-fluoro- and 3,4-dimethoxy-substituted derivatives dichloroethane heated to reflux and a reaction time of 3–4 hours was optimal, longer times led to product degradation/lower yields. Thus, the enol ether hydrolysis reaction conditions were critical, as has been noted previously by others.[9] The best results in our hands were obtained with 10% formic acid in dichloromethane. Interestingly, addition of extra water during hydrolysis resulted in more complex reaction mixtures, indicating the initial formation of an intermediate formic acid adduct. In many cases, the crude aldehyde products were sufficiently pure for further use without chromatographic purification. A general experimental procedure is given in the references[25] and further details of the experiments can be found in the Supporting Information.

In summary, methods to synthesise substituted phenylacetaldehydes (oxidation, one-carbon chain extension) have been compared. The Wittig-type carbon-chain extension protocol based on treatment of substituted benzaldehydes with methoxymethylene-triphenylphosphine followed by hydrolysis was found to be a very robust method and gave consistently high yields. It also allowed use of reagents and starting materials that are commercially available to a much greater extent than methods based on oxidation. The method was used to prepare a set of substituted phenylacetaldehydes that will be used as test substrates in aldolase-catalysed reactions.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591963.

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(25) **General Procedure for Benzaldehyde Homologation (Scheme 2)**

To a stirred suspension of $[(Ph)_3PCH_2OCH_3]Cl$ (6.70 g, 19.5 mmol, 1.2 equiv) in dry THF (12 mL) was added *t*-BuOK (2.40 g, 21.4 mmol, 1.3 equiv) at 0 °C. The reaction mixture was stirred for 20 min. Then, the benzaldehyde derivative (16.2 mmol, 1 equiv) was added, and the mixture was stirred for 16–24 h at r.t. (see Table 1). The reaction mixtures were monitored by TLC, and when the reactions were deemed complete they were quenched by the addition of water (30 mL) and extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent was evaporated. The crude enol ether products were purified by column chromatography (8:1 *n*-pentane/ethyl acetate); for yields and *E*/*Z* ratios, see Table 1. The purified enol ether product (*E*/*Z* mixture) was dissolved in dichloromethane (30 mL, entries 1–5) or dichloroethane (30 mL, entries 6–10). Then, formic acid (98%, 3 mL) was added, and the mixture was heated to reflux for 3–36 h (see Table 1). The reaction mixtures were monitored by TLC and when the reactions were deemed complete, the mixtures were cooled to r.t., diluted with dichloromethane, and washed with aq $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered, and the solvent was evaporated. In some cases (see Table 1) purification of the crude products on a short silica gel column (100:0 to 95:5 toluene/ethyl acetate gradient) was performed. For NMR spectroscopic data of the individual compounds, see Supporting Information.