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A solvent-controlled highly efficient Pd–C catalyzed hydrogenolysis of benzaldehydes to methylbenzenes via a novel 'acetal pathway'

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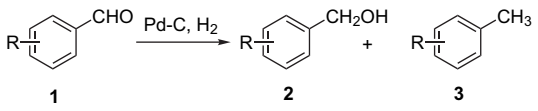
Abstract—Pd–C catalyzed hydrogenolysis of benzaldehydes to methylbenzenes has been described to proceed via a 'benzenemethanol pathway'. In this article, a novel 'acetal pathway' was first revealed by a systematic study when lower alcohols were used as solvents and a solvent-controlled highly efficient procedure was established.

1. Introduction

Palladium on carbon (Pd–C) is the most often used palladium-based catalyst featured with commercially available, cheap price, and easy regeneration. Pd–C catalyzed hydrogenation has been widely employed in numerous organic transformations in both academic and industry. Pd–C catalyzed hydrogenation of benzaldehyde (**1**) is a fundamental transformation to yield benzenemethanol (**2**) and methylbenzene (**3**) (Scheme 1). The active benzaldehyde (**1**) prefers to carry out a hydrogenolysis to give methylbenzene (**3**) as a major product.[1]



Scheme 1.

Since alkoxyl-substituted benzaldehydes (**1**) are economic and readily available starting materials, Pd–C catalyzed hydrogenolysis of them has afforded a practical method for preparation of alkoxyl-substituted methylbenzenes (**3**).[2–5] This transformation has been ambiguously described to proceed via a 'benzenemethanol pathway' because benzenemethanol (**2**) was often isolated as an intermediate or as a major by-product.[1,4b] Since no systematic work has been done, which makes possible a prediction of satisfactory conditions, quite different conditions were used in the literature. For example, MeOH, EtOH, EtOAc or HOAc was randomly used as a solvent. The acid catalyst was or was not employed without purpose. High pressure,[2] a large amount of catalyst,[3] or prolonged reaction time[4] was often used to overcome the low efficiency and minimize the residual intermediate.

Therefore, there is a great need to make a systematic study on this transformation, by which the function of each reactant could be well recognized and a highly efficient method could be established. In this article, we have made endeavors to accomplish this goal.

2. Results and discussion

Several hundred tons per year of 1,2,3-trimethoxy-5-methylbenzene (**3a**) were consumed as a precursor for the synthesis of coenzyme Q_{10}.[6,7] So far, **3a** was prepared mainly by reductive deoxygenation of 3,4,5-trimethoxy-benzaldehyde (**1a**).[2,7,8] Surprisingly, only one protocol using Pd–C catalyzed hydrogenolysis was reported in the literature, in which **3a** was obtained in 97% yield in acetic acid under 40 atmospheric hydrogen pressure for 3 days.[2]

During the study for an efficient preparation of **3a** by reductive deoxygenation of **1a**, we observed that the products of Pd–C catalyzed hydrogenation of **1a** strongly relied upon the reaction solvents (Table 1). The desired **3a** was obtained in 98% yield in MeOH or EtOH (entries 1 and 2). In other solvents, Pd–C catalyst was remarkably retarded with uptake

Keywords: Solvent-controlled; Pd–C catalyst; Hydrogenolysis; Benzaldehydes.
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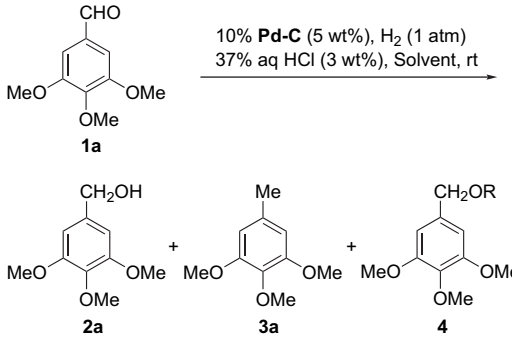
Table 1. Effect of solvent on the hydrogenation of **1a**[a]



Entry	Solvent	Time (h)	**2a**[c] (%)	**3a**[c] (%)	**4**[c] (%)
1	MeOH	1.5	0	98	0 (**4a**, R=Me)
2	EtOH	2	0	98	0 (**4b**, R=Et)
3	*i*-PrOH	7[b]	16	75	6 (**4c**, R=*i*-Pr)
4	*t*-BuOH	5[b]	26	70	0 (**4d**, R=*t*-Bu)
5	EtOAc	5.5[b]	30	66	0
6	THF	3.5[b]	34	63	0

[a] Pd–C catalyst: Aldrich 520888, palladium, 10 wt % on carbon powder, dry, Engelhard code C3645.
[b] At that time the absorption of hydrogen ceased due to the reason that Pd–C catalyst lost activity completely.
[c] 100% conversion of **1a** was observed and isolated yields were obtained.

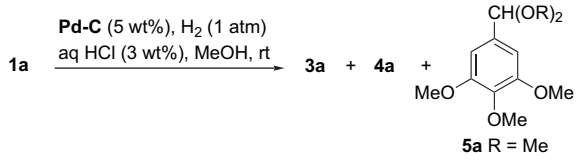
of 1.0 mol of hydrogen (entries 3–6). As a result, the hydrogenolysis was prevented from reaching completion to give a mixture of 3,4,5-trimethoxy-benzenemethanol (**2a**) and **3a**. 3,4,5-Trimethoxybenzyl isopropyl ether (**4c**) was also isolated in entry 3.

To understand those phenomena, two types of control experiments were performed. (a) After 1.0 mol of hydrogen was consumed in the hydrogenation of **1a**, compound **2a** was isolated as a major intermediate in entry 3 or a unique intermediate in entries 4–6. (b) The intermediate **2a** was hydrogenolyzed to give **3a** with same efficiency (2 h, 95–98%) in either MeOH or *t*-BuOH.

Thus, three conclusions can be deduced: (a) benzenemethanol **2a** was a common intermediate for the hydrogenations in entries 3–6, and its formation caused remarkable loss of activity of Pd–C catalyst (for unclear reasons);[9] (b) hydrogenolysis of **2a** was not affected by solvents; (c) the highly efficient hydrogenolysis of **1a** to **3a** in entries 1 and 2 must be mediated by an 'unknown intermediate' instead of benzenemethanol (**2a**).

To find the possible 'unknown intermediate', the hydrogenolysis of **1a** in MeOH was monitored. As shown in Table 2, two samples obtained from the first 5 and 8 min in the hydrogenolysis were tested. The former one showed that **1a** has been already exhausted and 3,4,5-trimethoxybenzaldehyde dimethyl acetal (**5a**) was isolated besides expected products **3a** and **4a** (entry 1). The latter one showed that **5a** disappeared completely and the proportion of **3a** increased largely (entry 2). Thus, dimethyl acetal (**5a**) is the 'unknown intermediate'. This hypothesis was confirmed when **5a** was used as a substrate under the same conditions, in which **4a** was detected as an intermediate and **3a** was obtained in 98% yield within 1.5 h.

Table 2. The intermediates in the hydrogenation of **1a**



Entry	Time (min)	Conversion of **1a** (%)	**3a** (%)	**4a** (%)	**5a** (%)
1	5	100	5	65	27
2	8	100	50	48	0
3	90	100	98	0	0

Next, the acetalizations of **1a** with different alcohols were tested. As shown in Table 3, dimethyl acetal **5a** was obtained in 95% yield in MeOH within 30 min (entry 1), while **5b** and **5c** (entries 2 and 3) were obtained in lower yields in EtOH and *i*-PrOH. No **5d** was detected at all when *t*-BuOH was used as a solvent (entry 4). These results strongly suggested that the selectivity for two intermediates in the hydrogenolysis of **1a** simply determined by the steric hindrance of the alcohol.

In addition, we also observed that Pd–C alone did not catalyze the acetalization of **1a** (entry 5). However, when it was used together with aq HCl, the yield of diethyl acetal (**5b**) doubled (entry 6). This may result from the fact that Pd–H intermediate was formed in the presence of aq HCl, which has proved to be a strong catalyst for the acetalization of carbonyl compounds.[10] Thus, the smallest size and doubly catalyzed acetalization (HCl and Pd–C) provided a reasonable explanation why **1a** was completely converted into **5a** within less than 5 min in MeOH.

Since the acetalization is a key step for the efficient hydrogenolysis of **1a** due to it prevents from the formation of **2a**, the effects of acid catalyst on the acetalization of **1a** were tested. As shown in Table 4, **3a** was obtained in excellent chemoselectivity and yield in the presence of a catalytic amount of strong acid, such as aq HCl, HCl or CF_3CO_2H (entries 2–4). However, when the reaction proceeded without acid catalyst (entry 1) or with weak acid HOAc (entry 5), a mixture with **2a** as a major product was obtained. Thus, a strong acid catalyst is essential for an efficient hydrogenolysis of **1a** because it catalyzes an efficient acetalization of **1a**.

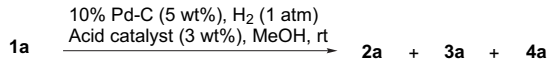
So far, we believe that a novel 'acetal pathway' for Pd–C catalyzed hydrogenolysis of **1a** to **3a** was revealed and

Table 3. Effect of alcohol structure on the acetalization of **1a**

Entry	ROH	Catalyst[a]	Time (min)	**5**[c] (%)
1	MeOH	aq HCl	30	95 (**5a**, R=Me)
2	EtOH	aq HCl	60	33 (**5b**, R=Et)
3	*i*-PrOH	aq HCl	60	8 (**5c**, R=*i*-Pr)
4	*t*-BuOH	aq HCl	60	0 (**5d**, R=*t*-Bu)
5	EtOH	Pd–C[b]	60	0
6	EtOH	aq HCl+Pd–C[b]	60	68 (**5b**, R=Et)
7	*t*-BuOH	aq HCl+Pd–C[b]	60	0

[a] 37% aq HCl was used.
[b] 5% w/w of Pd–C was used.
[c] Isolated yields were obtained.

Table 4. Effect of acid catalyst on the hydrogenolysis of **1a**



Entry	Acid catalyst	Conversion of **1a** (%)	Time (h)	**2a**[b] (%)	**3a**[b] (%)	**4a**[b] (%)
1	None	100	2.0	90	10	0
2	aq HCl (37 wt %)	100	1.5	0	100	0
3	HCl	100	2.5	0	100	0
4	CF_3CO_2H	100	5.0	0	100	0
5	CH_3CO_2H	100	2.0[a]	75	7	13

[a] At that time the absorption of hydrogen ceased due to the reason that Pd–C catalyst lost reactivity completely.
[b] Isolated yield was obtained.

a three-stage process was proposed as shown in Scheme 2. In the first stage, an efficient acetalization of **1a** in MeOH was doubly catalyzed by aq HCl and Pd–C to yield **5a** (within 5 min). Then, a Pd–C catalyzed 'fast C–O hydrogenolysis' was carried out to give **4a** (within 8 min). Finally, **4a** underwent a Pd–C catalyzed 'slow C–O hydrogenolysis' to give **3a** (within 1.5 h).

Based on the above analyses, the results in Table 1 can be well explained. By using MeOH or EtOH as a solvent, acetal **5a** or **5b** was produced as an intermediate through an 'acetal pathway'. Then, **5a** or **5b** underwent a double hydrogenolysis of C–O bonds to give **3a** with high efficiency, since benzaldehyde acetal and benzyl ether are extremely labile to hydrogenolysis. Since **1a** cannot be acetalized in *t*-BuOH or other non-alcoholic solvents, it was hydrogenated to give **2a** as an intermediate by a 'benzenemethanol pathway', which causes remarkable loss of the activity of Pd–C. Therefore, the hydrogenation in these solvents associated with low efficiency and was contaminated by residual intermediate **2a**. The hydrogenation in *i*-PrOH went through both pathways because *i*-PrOH has an intermediate steric hindrance. Actually, the 'acetal pathway' afforded a solvent-controlled highly efficient Pd–C catalyzed hydrogenolysis of **1a** to **3a**.

To generalize the application of 'acetal pathway', the hydrogenolysis of different benzaldehydes (**1a–j**) was tested. As shown in Table 5, they all gave the corresponding **3a–j** in excellent results. Under our standard conditions, *o*- and *p*-substitutents benefited the reaction efficiency (entries 2–7), while *m*-substitutents gave negative effects (entries 1, 8, and 9). In the case of **1i**, double amount of Pd–C catalyst (10 wt %) has to be used, otherwise the hydrogenation could not go to completion within 20 h (entry 9). Benzo-fused ring also reduced the reactivity of substrate and prolonged reaction time was required. The control experiments in entries 4, 5 and 9 clearly showed that 'acetal pathway' has greater advantages than 'benzylmethanol pathway'. For example, the substrate **1e** was converted into **3e** in 98% yield within 45 min in MeOH. However, at least 15 h were required for the same reaction with 96% conversion in EtOAc in Ref. 4b. So far, this method cannot be applied to the inactive benzaldehydes. For example, when fluorene-2-carboxaldehyde was used as a substrate, a mixture of 2-methylfluorene (43%) and (fluoren-2-yl)methanol (57%) was obtained.

3. Conclusion

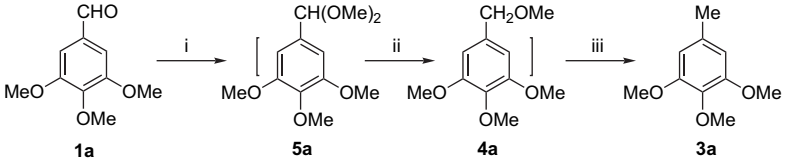
In summary, Pd–C catalyzed hydrogenolysis of active benzaldehydes to methylbenzenes was systemically studied. We observed that a benzylaldehyde acetal intermediate was produced when hydrogenolysis proceeded in lower alcohol solvent (MeOH or EtOH) instead of benzylmethanol intermediate recorded in the literature. Thus, a three-stage 'acetal pathway' was proposed, by which the functions of each reaction component were well recognized. As a result, a solvent-controlled highly efficient Pd–C catalyzed hydrogenolysis of benzaldehydes to methylbenzenes was established. By using this new procedure, the low efficiency occurring in the existing procedures was overcome completely.

4. Experimental

4.1. A typical procedure of Pd–C catalyzed hydrogenation of 3,4,5-trimethoxybenzaldehyde (1a) to 1,2,3-trimethoxy-5-methylbenzene (3a)

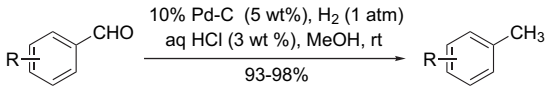
A suspension of 3,4,5-trimethoxybenzylaldehyde (**1a**, 491 mg, 2.5 mmol), Pd–C catalyst (24.5 mg), and aq HCl (37%, 40 mg) in MeOH (30 mL) was hydrogenated under room temperature and atmospheric pressure until the absorption of hydrogen ceased completely (it was carried out on an atmospheric pressure hydrogenator). Then the catalyst was filtrated off and the solvent was evaporated. The residue was diluted with CH_2Cl_2 (30 mL) and washed with brine and dried over Na_2SO_4. Removal of the solvent yielded product **3a** (446 mg, 98%), which is pure enough for satisfactory analyses. Mp 35–37 °C (lit.[2] 35–37 °C); IR: ν 2994, 2939, 2836, 1589, 1507, 1465, 1414, 1331, 1238, 1182, 1127, 1011, 968, 812, 778 cm^{-1}; ^1H NMR: δ 6.39 (2H, s), 3.84 (6H, s), 3.82 (3H, s), 2.31 (3H, s); ^{13}C NMR: δ 152.8, 135.5, 133.4, 105.7, 60.6, 55.7, 21.6.

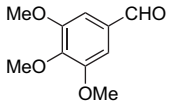
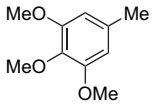
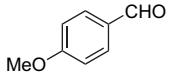
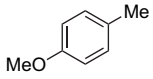
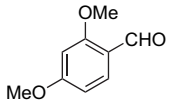
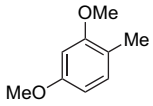
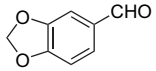
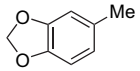
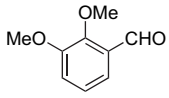
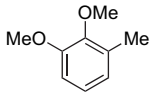
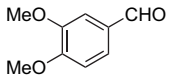
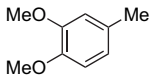
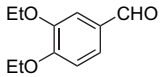
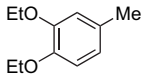
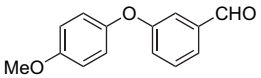
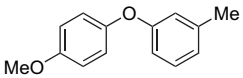
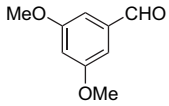
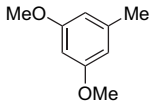
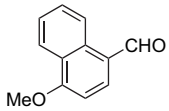
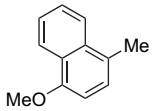
Similar procedure was used to convert the substrates **1b–j** efficiently to the corresponding products **3b–j**. Products **3a–j** are all known compounds and their characterization data and ^1H NMR and ^{13}C NMR spectra are reported in Supplementary data.



Scheme 2. Reagents and conditions: (i) acid and Pd–C catalyzed acetalization; (ii) Pd–C catalyzed fast C–O hydrogenolysis; (iii) Pd–C catalyzed slow C–O hydrogenolysis.

Table 5. Chemoselective hydrogenation of **1a–j** to **3a–j**[a]



Entry (no.)	1	3	Solvent	Pd–C (wt %)	Time (min)	Yield[b] (%)
1 (**a**)			MeOH	5	90	98
2 (**b**)			MeOH	5	30	96
3 (**c**)			MeOH	5	30	97
4 (**d**)			MeOH EtOAc EtOAc	5 5 20	30 225 40	93 94 93
5 (**e**)			MeOH EtOAc EtOAc	5 5 5	45 270 900	98 87[c] 96[d]
6 (**f**)			MeOH	5	45	96
7 (**g**)			MeOH	5	30	93
8 (**h**)			MeOH	5	90	95
9 (**i**)			MeOH MeOH EtOAc EtOAc	5 10 5 20	1200 120 240 380	19[e] 96 0[f] 96
10 (**j**)			MeOH	5	300	97

[a] 37% aq HCl was used.
[b] Isolated yields were obtained.
[c] A mixture with 10% of 2,3-dimethoxyphenylmethanol.
[d] See Ref. 4b, the hydrogenation without aq HCl.
[e] A mixture with 80% of 3,5-dimethoxybenzyl methyl ether.
[f] No absorption of hydrogen was observed.

Acknowledgements

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Supplementary data

Experimental procedures, characterization data, and ^{1}H NMR and ^{13}C NMR spectra for products **3a–j** are provided in the supplementary data. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.06.105.

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9. An interruption has been observed during the hydrogenation of benzaldehyde to benzenemethanol without any explanation in early references (see Ref. 1b). Recently, a detail study on Pd–C catalyzed hydrogenation of 2,3-dimethoxybenzaldehyde (**1e**) in EtOAc also showed that the conversion of **1e** to 2,3-dimethoxybenzenemethanol (**2e**) caused Pd–C catalyst to significantly lose its reactivity for unknown reasons (see Ref. 4b).
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