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Microwave assisted $Pd(OAc)_2$-catalyzed chemoselective reduction of aryl α,β-unsaturated esters with triethylsilane

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ABSTRACT

In this communication, we have reported that the $Pd(OAc)_2$–Et_3SiH-DMF system promotes the microwave-assisted chemoselective reduction of aryl α,β-unsaturated esters in good yields. The protocol affords a convenient reduction of aryl-conjugated double bonds even in presence of other functional groups like esters, phenols, and ethers.

Keywords: *Chemoselective; Microwave; Palladium; Reduction; Triethylsilane.*

1. Introduction

In recent years microwave assisted reactions have emerged as an increasingly popular field in organic chemistry [1]. This non-conventional heating approach uses the electromagnetic radiation ranging from 1 meter to 1 mm, with frequencies between 0.3 and 300 GHz. Microwave heating provides a straightforward and inexpensive reaction condition for carrying out a variety of organic transformations. Other advantages of this method include homogenized heating leading to accelerated reactions and better yields.

Palladium catalyzed reduction of carbon-carbon multiple bonds forms an important organic transformation relevant to both academic and industrial research [2]. Although Pd/C is known to be the most ubiquitous catalyst for hydrogenation, its reaction often proceeding in good yields but the use of elevated pressure along with poor selectivity makes this approach unappealing. Other literature known procedure for the reduction of carbon-carbon multiple bonds include the use of expensive catalyst or pyrophoric hydrides [3]. For instance, Zhou *et. al.* demonstrated the application of a nickel catalyst supported by Me-DuPhos, a chiral bisphopshine in combination with DMF for chemo- and stereoselective reduction of α,β-unsaturated esters [3l]. Andersson's group reported a iridium-catalyzed asymmetric 1,4-hydrogenation of conjugated esters [3m]. Very recently, Sawamura's group developed a novel enantioselective conjugate reduction reaction utilizing chiral phenol–NHC/copper catalyst systems [3n]. Using a similar protocol Teichert's group had earlier reported a catalytic reduction of α,β-unsaturated esters with a NHC-Cu(I)-H_2 combination [3o]. Most of these methods use one or more expensive reagents which are not very selective.

In the past Pd/Et_3SiH has been used for the reduction of alkyl halides and functionalities like azide, imine, conversion of aromatic carbonyls and benzyl alcohols to corresponding methylenes and alcohols [4]. Previously, Mirza-Aghayan's group have reported the use of $PdCl_2$/Et_3SiH/EtOH system for reduction of alkenes to alkanes [5], isomerization of alkenes [6] and chemoselective reduction of α,β-unsaturated ketones to corresponding saturated ketones [7]. Even though

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abundance of reducing reagents are available for this transformation, new reagents, especially the catalytic chemoselective variety, are still highly desirable.

Previously, we had reported a highly chemoselective $Pd(OAc)_2/Et_3SiH/DMF$ system for conversion of aromatic aldehydes and Ketones to corresponding silyl protected alcohols [8]. In continuation of our work, we wish to report, in this communication a modified microwave assisted chemoselective 1,4 reduction of aromatic α,β-unsaturated esters using $Pd(OAc)_2/Et_3SiH/DMF$ system.

2. Experimental

2.1. General

Commercially available reagents (Aldrich, Strem and Fluka) were used as received. The NMR spectra were recorded on Bruker Avance 400MHz spectrometer. All measurements were performed at 22°C in $CDCl_3$ unless stated otherwise. CEM discover microwave synthesizer was used to carry out the chemoselective reduction.

2.2. General procedure

To a 35 mL microwave reaction vial with a magnetic stir bar was added $Pd(OAc)_2$ (0.5 mol%) in DMF (2.0 mL). To this was added aromatic α,β-unsaturated esters (1.0 mmol) followed by triethylsilane (2 mmol). The resulting solution was stirred for 30 minutes under microwave conditions (150 W). After completion of the reaction, it was quenched by the addition of water and the mixture extracted with EtOAc. The organic layer was further washed with brine (5 x 10 mL), dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure to give the crude product, which was purified by column chromatography (petroleum ether/EtOAc as eluent) to afford the pure product **2a-e**.

Spectral data

*Ethyl 3-phenylpropanoate (**2a**):*

Yield: 85%. ^{1}HNMR ($CDCl_3$): δ = 1.20 (t, *J* = 7.2 Hz , 3H), 2.57 (t, *J* = 7.2 Hz , 2H), 2.92 (t, *J* = 7.2 Hz , 3H), 4.04 (q, *J* = 7.2 Hz, 2H), 7.15-7.29 (m, 5H). ^{13}CNMR ($CDCl_3$): δ = 14.1, 30.8, 35.7, 60.1, 126.1, 128.2, 128.3, 140.4, 172.5.

*Ethyl 3-(2-hydroxyphenyl)propanoate (**2b**):*

Yield: 78%. ^{1}HNMR ($CDCl_3$): δ = 1.22 (t, *J* = 7.1 Hz, 3H), 2.68 (t, *J* = 6.9 Hz , 2H), 2.90 (t, *J* = 6.9 Hz , 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 6.77-6.84 (m, 2H), 7.02-7.09 (m, 2H), 7.45 (br s, 1H). ^{13}CNMR ($CDCl_3$): δ = 14.1, 25.2, 34.9, 61.1, 116.6, 120.5, 127.1, 127.8, 130.0, 154.4, 175.2.

Ethyl 3-p-tolylpropanoate (2c):

Yield: 83%. ^{1}HNMR ($CDCl_3$): δ = 1.23 (t, *J* = 7.1 Hz, 3H), 2.31 (s, 3H), 2.54 (t, *J* = 7.1 Hz , 2H), 2.92 (t, *J* = 7.1 Hz , 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 7.09 (s, 4H). ^{13}CNMR ($CDCl_3$): δ = 14.3, 19.2, 28.3, 34.7, 60.3, 126.1, 126.4, 128.5, 130.3, 135.8, 138.6, 172.8.

*Ethyl 3-(4-hydroxy-3-methoxyphenyl)propanoate (**2d**):*

Yield: 80%. ^{1}HNMR ($CDCl_3$): δ = 1.25 (t, *J* = 7.2 Hz, 3H), 2.56 (t, *J* = 7.5 Hz, 2H), 2.86 (t, *J* = 7.5 Hz, 2H), 3.82 (s, 3H), 4.13 (q, *J* = 7.2 Hz, 2H), 5.76 (br s, 1H), 6.62-6.81 (m, 3H). ^{13}CNMR ($CDCl_3$): δ = 14.1, 30.6, 36.2, 55.6, 60.2, 110.8, 114.4, 120.7, 132.2, 144.0, 146.3, 172.7.

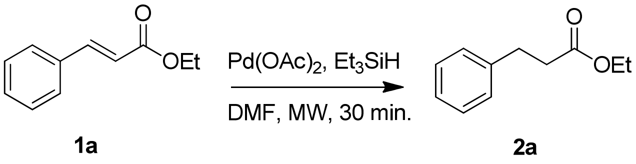
*Ethyl 3-phenylbutanoate (**2e**):*

Yield: 83%. ^{1}HNMR ($CDCl_3$): δ = 1.16 (t, *J* = 7.2 Hz, 3H), 1.27 (d, *J* = 6.8 Hz, 3H), 2.56 (m, 2H), 3.24 (m, 1H), 4.03 (q, *J* = 7.2 Hz, 2H), 7.15-7.30 (m, 5H). ^{13}CNMR ($CDCl_3$): δ = 14.2, 21.9, 36.5, 43.0, 60.1, 126.4, 126.7, 128.5, 145.7, 172.1.

3. Results and discussion

As a model substrate, ethylcinnamate **1a** was subjected to 1,4-reduction using DMF as solvent, in the presence of $Pd(OAc)_2$ (0.5 mol%) as catalyst with Et_3SiH (1.2 equiv) as hydride source. The desired product, ethyl hydrocinnamate **2a** was obtained in 24% yield in 8 h (Entry 1,Table 1). When the reaction was carried out with 2 equivalent Et_3SiH at 25 °C, **2a** was obtained in 39% yield (Entry 2, Table 1). On the other hand when the reaction was subjected to microwave irradiation (150 W), ethyl hydrocinnamate **2a** was furnished in 73% yield in 15 minutes (Entry 3, Table 1). Extending the reaction to 30 minutes improved the yield further (Entry 5, Table 1). Increasing the catalyst loading, reaction time and temperature of the reaction had no significant effect on the product yields.

In order to improve the yield further, we performed several experiments to identify the most effective and suitable conditions, such as variation of catalyst, solvents and time. For instance, a combination of 10% Pd/C gave only moderate yields of the desired saturated product **2a** (30 minutes, 2 mmol Et_3SiH, MW, Entry 11, Table 1).



Scheme 1. Pd-catalyzed chemoselective 1,4-reduction of aromatic α,β-unsaturated esters.

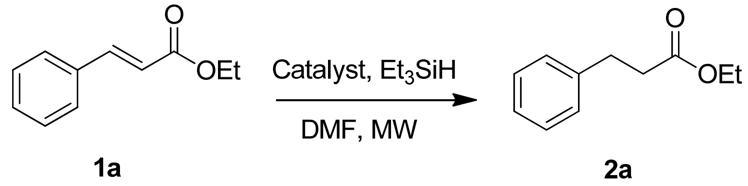
On the other hand, $Pd(Ph_3P)_4$ in combination with 2 mmol Et_3SiH under similar microwave conditions gave only 20% yield of **2a** (Entry 10, Table 1). Several other Pd-catalysts were also screened and the results of such a study are shown in Table 1.

Next, the optimization for solvent system and hydride source was done, the results of which are presented in Table 2. A number of different solvents such as DMF, H_2O, CH_2Cl_2 and CH_3CN were screened. During the screening of variety of solvents, it was found that DMF when used with 0.5 mol% $Pd(OAc)_2$ and 2 equiv. of Et_3SiH gave the best yield of the saturated product **2a** (85%) in 30 minutes (Entry 4, Table 2). When other hydrosilanes such as Ph_3SiH and Me_2PhSiH were used as a hydride source with DMF as solvent, we observed that the yield of the product was miserably low (16% and 23% respectively). Among several other solvents, the formation of product **2a** was noticed (24% yield) with only CH_3CN (Entry 2, Table 2). Although, water is a high dielectric solvent suitable for carrying out a variety of microwave assisted reactions, in our case desired product was not detected under the standard reaction conditions when water was used as a solvent (Entry 7, Table 2).

The chemoselective reduction was investigated at the same molar ratio of ethyl cinnamate **1a** and triethylsilane at various powers and time of microwave irradiation as well. From Fig. 1, it is clear that the %yields for chemoselective reduction increases with rise in power level. The highest yield of the compound (2a) was observed at 30 minutes when the microwave power level was 150W. To our surprise, when the time of reaction was increased to 60 minutes at 150 W, there was no change in yield. On the other hand, we were not able to isolate the compounds at higher power levels, probably because of decomposition of compound at higher power levels.

In order to view the validity of this process, we turned our attention to briefly investigate the scope of the reaction by subjecting a wide range of functionalized aromatic α,β-unsaturated esters (Table 3). Indeed, the protocol gave excellent yields of the respective reduced products. The method has shown high tolerance for other sensitive functional groups such as ester, hydroxyl and ether.

Table 1. Pd-catalyzed reduction of ethylcinnamate **1a**: Effect of catalysts.[a]



Entry	Catalyst	Et_3SiH	Time	Yield of 2a (%)[b]
1	$Pd(OAc)_2$	1.2 equiv.	8 h	24[c]
2	$Pd(OAc)_2$	2 equiv.	8 h	39[d]
3	$Pd(OAc)_2$	2 equiv.	15 min.	73
4	$Pd(OAc)_2$	2 equiv.	20 min.	76
5	$Pd(OAc)_2$	2 equiv.	30 min.	85
6	$Pd(OAc)_2$	2 equiv.	1 h	84
7	$PdCl_2$	2 equiv.	30 min.	43
8	$Pd(PhCN)_2Cl_2$	2 equiv.	30 min.	64
9	$Pd(dba)_2$	2 equiv.	30 min.	34
10	$Pd(Ph_3P)_4$	2 equiv.	30 min.	20
11	10% Pd/C	2 equiv.	30 min.	53

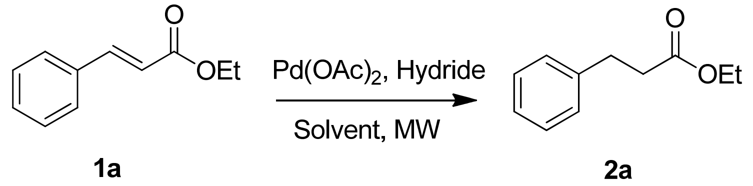
[a] Reaction conditions: Ethylcinnamate (1 mmol), Pd-catalyst (0.5 mol%), Et_3SiH, DMF (2 ml), MW (150 W).

[b] Isolated yield.

[c] Pd-catalyst (0.5 mol%), Et_3SiH (1.2 mmol), DMF (2 ml), 8 h.

[d] Pd-catalyst (0.5 mol%), Et_3SiH (2 mmol), DMF (2 ml), 25 °C, 8 h.

Table 2. Pd(OAc)$_2$-catalyzed reduction of ethylcinnamate **1a**: Effect of solvents.[a]



Entry	Solvent	Hydride Source	Yield of 2a (%)[b]
1	CH_2Cl_2	Et_3SiH	No reaction
2	CH_3CN	Et_3SiH	24
3	Toluene	Et_3SiH	No reaction
4	DMF	Et_3SiH	85
5	DMF	Ph_3SiH	16[c]
6	DMF	Me_2PhSiH	23[d]
7	H_2O	Et_3SiH	No reaction

[a] Reaction condition: Ethylcinnamate (1 mmol), Pd(OAc)$_2$ (0.5 mol%), Et_3SiH (2 mmol), solvent (2 ml), MW (150 W).

[b] Isolated yield.

[c] Ph_3SiH (2 mmol).

[d] Me_2PhSiH (2 mmol).

However, the reaction failed in the case of aliphatic α,β-unsaturated esters (Table 3, Entry 6). Thus, this catalytic system can be unique in selectively reducing aromatic α,β-unsaturated esters in preference to aliphatic ones. The reason for chemoselectivity towards aromatic substrate may be due to extended conjugation which is possible only in the presence of adjacent aromatic rings (Fig. 2).

During the reaction Pd(OAc)$_2$ in presence of triethyl silane converts into a black mass probably due to the reduction of Pd(+2) into Pd(0) species. Unfortunately, the fine black powder, possibly the active catalyst system could not be recovered. Therefore, in order to check the reusability our catalyst system in such reactions, we carried out a second batch of reaction in the same vessel by adding an additional 1 mmol of unsaturated ester **1a** along with 2 mmol of Et_3SiH after the first batch of reaction was over. The second batch of reaction subjected to the optimized condition gave only 27% yield of the desired product. The third cycle with same substrate **1a** under similar reaction conditions could furnish only 5% yield of the desired product **2a**. The mechanism and the subsequent decrease in the catalytic activity of our Pd/silane system is currently being investigated.

4. Conclusions

We have shown that microwave assisted Pd(OAc)$_2$ – Et_3SiH – DMF combination is a highly effective system for chemoselective reduction of aromatic α,β-unsaturated esters. The catalyst system is not sensitive towards other functional groups and affords the reduced product is excellent yields. Other advantages of our catalyst system include short reaction time, higher yields, easy to handle and commercially viable reagents.

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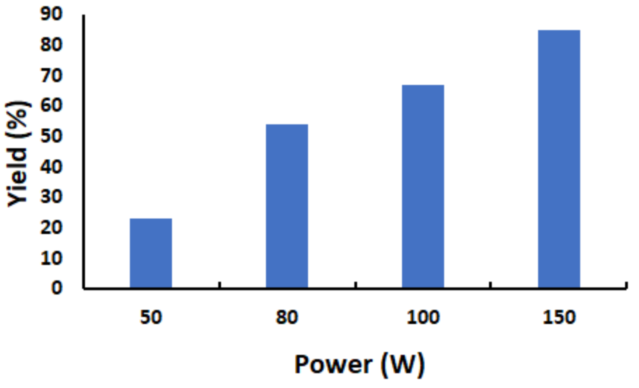
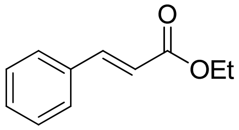
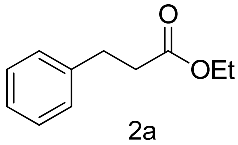
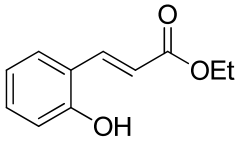
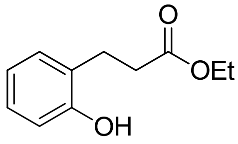
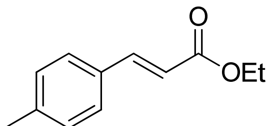
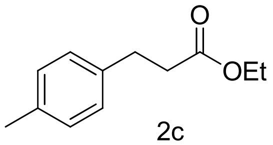
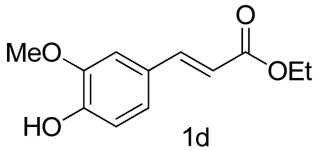
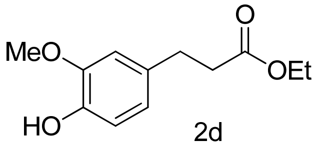
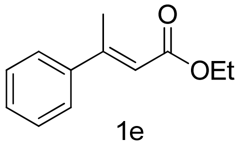
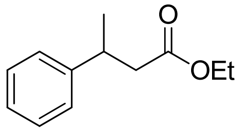
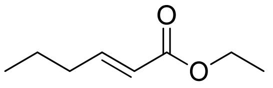


Fig. 1. Power level versus % yield for the preparation hydrocinnamate **2a**.

Table 3. Pd-catalyzed reduction of aryl α,β-unsaturated esters: Substrate Scope.[a]

Entry	Substrates 1(a-f)	Product 2 (a-f)	Yield (%)[b]
1	 1a	 2a	85
2	 1b	 2b	78
3	 1c	 2c	83
4	 1d	 2d	80
5	 1e	 2e	83
6	 1f	-	N.R.

[a]Reaction condition: α,β-unsaturated esters (1 mmol), $Pd(OAc)_2$ (0.5 mol%), Et_3SiH (2 mmol), dry DMF (2 ml), MW (150 W), 30 min.
[b]Isolated yield.

I

II, R = Alkyl

Fig. 2. Plausible α,β-complex for aromatic (I) and alkyl system (II).

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