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A Chemoselective Hydrogenation of the Olefinic Bond of α,β-Unsaturated Carbonyl Compounds in Aqueous Medium under Microwave Irradiation†

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Abstract: A microwave-assisted mild and ecofriendly catalytic transfer hydrogenation process was developed to reduce various α,β-unsaturated carbonyl compounds into the corresponding saturated carbonyl compounds in the presence of silica-supported palladium chloride as catalyst and a combination of MeOH/HCOOH/H_2O (1:2:3) as hydrogen source within 22–55 minutes in moderate to excellent yields with 100% chemoselectivity.

Keywords: chemoselectivity; hydrogenation; microwave heating; α,β-unsaturated carbonyl compounds, water

Introduction

Chemoselective reduction[1] of α,β-unsaturated carbonyl compounds has remained an attractive area of organic synthesis due to the wide range of applications of the resulting saturated carbonyl compounds as food sweeteners and in the flavour, perfumery, and pharmaceutical industries.[2] For example, phloretin, a pharmaceutically important dihydrochalcone, is known to inhibit the growth of Molt-4 human leukemic cells[3a] besides its application as a percutaneous enhancer for topical drugs.[3b] Similarly, 3,4-dihydroxy-substituted hydrocinnamate is reported to significantly lower the plasma total cholesterol concentration in comparison to a lovastatin-treated group.[3c]

In addition, these saturated carbonyl compounds are also used as intermediates for the synthesis of various biologically active compounds,[4] including the synthesis of HIV-I protease inhibitors.[4c] Among the various available reduction protocols[5] for the synthesis of these important dihydro compounds,[2–4] catalytic transfer hydrogenation (CTH)[6] has emerged as the most viable, mainly due to the non-involvement of highly flammable and explosive molecular hydrogen or metal hydride donors. Moreover, CTH processes generally involve easy handling and recovery of products, recycling of catalyst and minimization of undesired toxic wastes. Although CTH of the carbonyl group in the presence of olefinic bonds is often achieved with relative ease,[7] reports of the chemoselective transformation of the olefinic bonds in the presence of carbonyl groups remain limited. Some of the CTH methods for chemoselective hydrogenation of olefinic bond include catalysts such as $[Ir(cod)Cl]_2$/dppp/Cs_2CO_3/isopropyl alcohol,[8] Cp_2TiCl/MeOH,[9] proline/Pd/Al_2O_3,[10] PdMCM-41/ammonium formate,[11] $Pd(PPh_3)_4$/tetraethylene glycol/$Si(OMe)_4$[12] under conventional conditions.

Of late, there has been a growing interest in the use of ultrasonics[11,13] and microwave irradiation[14] for CTH reactions as tools of "green" chemistry.[15] Reports on microwave-assisted chemoselective manipulation of double bonds have utilized various organic hydrogen donors[8,16] including the commonly used inexpensive formate salt[17] and resin supported formate.[18] However, all these methods are somewhat limited by expensive catalysts, maintenance of anhydrous conditions, poor chemoselectivity and, above all, requirement of sealed tubes[17,18] under microwave irradiation. In this context, we now report a microwave-assisted, chemoselective hydrogenation of α,β-unsaturated carbonyl compounds in the presence of silica-supported palladium chloride as catalyst and a 1:2:3 mixture of MeOH/HCOOH/H_2O proceeding with 100% chemoselectivity.

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Results and Discussion

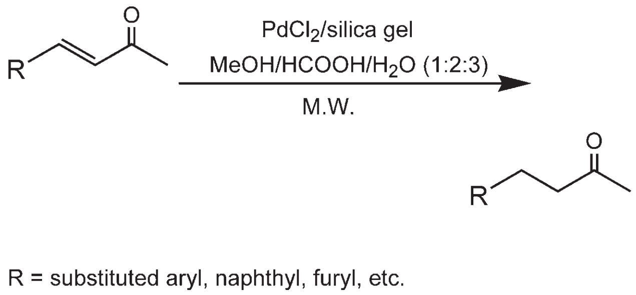
In our ongoing interest in green chemistry[15] with microwave-assisted reactions,[19] we decided to perform the reduction of the olefinic bond of 4-(4′-hydroxyphenyl)-3-buten-2-one (**1b**) for its hydrogenation into raspberry ketone[20] (**1a**), a well known FEMA GRAS (No. 2588) approved flavouring agent, using HCOOH[21] as a hydrogen source in combination of $PdCl_2$/NaOH[22] under microwave irradiation. However, the above method produced only 20% of product **1a** even after 70 min of irradiation (960 Watts) of **1b**. Addition of isopropyl alcohol[23] or a high-boiling ethylene glycol[17c,24] to the above combination also did not improve the yield of product **1a**.

After several variants in the above reaction, a hydrogenating mixture comprising $PdCl_2$/HCOOH in methanol was found to be most suitable and **1a** was obtained in up to 43% yield. Prompted by reports on water-methanol-assisted yield enhancement in organic reactions,[25] we decided to utilize a combination of methanol and water in our case also. A 1:2 ratio of methanol and water with HCOOH, and catalytic amounts of $PdCl_2$, under microwave irradiation for 37 min, increased the yield of **1a** to 53%. After a lot of experiments, a 1:2:3 mixture of MeOH:HCOOH:H_2O with catalytic amounts of $PdCl_2$ in 30 min under microwave irradiation proved to be optimum and provided a 71% yield of **1a**. The use of water[26] results in the rapid release of hydrogen gas from HCOOH which brings about a faster reaction and a better yield. During the reaction, we realized that there was some evaporation of the product inside the microwave oven, as there was no starting material or side product in spite of the moderate yield of **1a**. Consequently, the reaction was either conducted under varied levels of microwave power (300–700 Watts) or in an ice bath, but all to no avail. Ultimately, we decided to perform the above reaction under heterogeneous conditions by first adsorbing the catalyst, substrate and the reagent mixture on silica gel,[27] followed by microwave irradiation, which remarkably increased the yield of **1a** up to 84% within 22 min with 100% chemoselectivity (Scheme 1). As expected, addition of silica gel not only checked evaporation of the reagents and product but also provided a suitable matrix for the reaction growth.

The plausible reason behind the 100% chemoselectivity attained in the above reaction comprises partial protonation of the carbonyl group by formic acid which may lower the energy[28] of the HOMO and LUMO of the enone thereby speeding up hydrogenation at the olefinic site (Fig. 1). Moreover, during the hydrogenation cycle, the complex conjugate[29] formed by the palladium cation and formate ions is probably stabilized by protonation at the carbonyl group (Scheme 2).

The protonation of the carbonyl group and formation of palladium complex at the olefinic site take place simultaneously and prevent palladium from attacking the carbonyl site. Hence, it is the protonation of carbonyl group, or indirectly formic acid, which induces the 100% chemoselectivity and the catalyst has hardly any role in determining the site of action. To further strengthen this observation, in a test reaction, formic acid was replaced by another hydrogen transferring agent, i.e., ammonium formate (10 equivs.) with all other conditions remaining the same and the result showed 65% of **1a** along with the dihydrocinnamoyl alcohol. The formation of the alcohol in this case can be easily explained as there was no prior protonation of the carbonyl group paving the way for hydrogenation to occur at both the prospective positions. This finding of non-selectivity with ammonium formate is well documented.[17d]

Of late, some alarms have been raised on the reproducibility of the domestic microwave ovens due to unevenness of the microwave energy inside.[15b] We, however, repeated the above conversion of **1b** into **1a** thrice and the yields in every case were reproducible (84 ± 1%). Moreover, the above conversion of **1b** into **1a** with silica-supported palladium chloride as catalyst and the combination of MeOH/HCOOH/H_2O (1:2:3) was also performed under a monomode[15b] microwave system (CEM Discover® System, 300 Watts, temperature 100–120 °C) for 26 min. The result of the above reaction under monomode microwave conditions showed a similar yield of 83% in comparison to a multimode domestic



R = substituted aryl, naphthyl, furyl, etc.

Scheme 1.

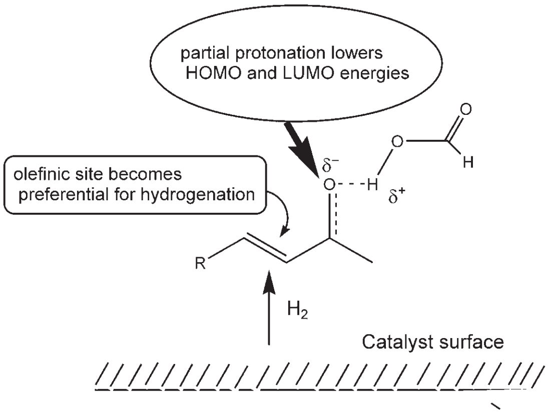
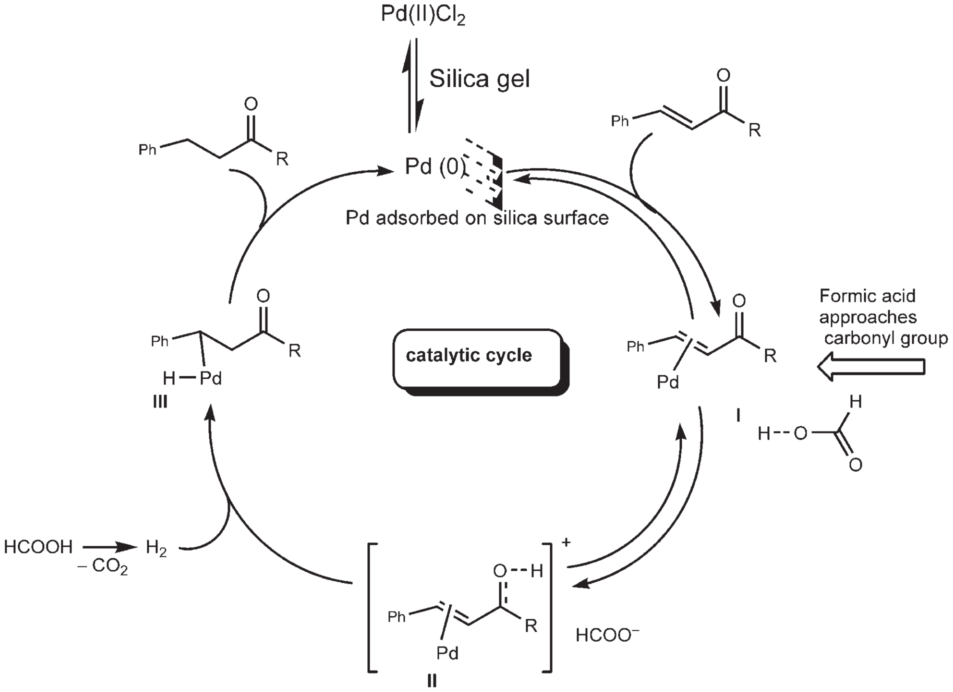


Figure 1.



Scheme 2.

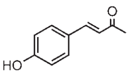
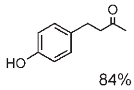
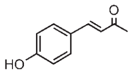
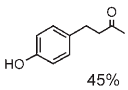
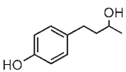
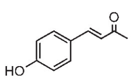
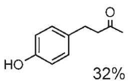
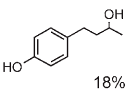
microwave (84% yield), which implied that our method worked efficiently in both multimode and monomode microwave conditions.

The same methodology, when applied in conventional as well as ultrasound conditions, produced both **1a** and its corresponding alcohol (Table 1). Such an effect of microwaves on inducing chemoselectivity in the reaction is due to the rapidity in the achievement of a polar transition state due to superheating[15b] which shifted the kinetics more towards the required product. Overall, the above combination of reagents in aqueous medium facilitated easy recovery of the product after mere washing of the mixture with the solvent. After reaction, the remaining silica-supported palladium chloride was reused and found to be active even after five cycles of reuse with a mere 5% loss in the activity.

To further evaluate the effect of the carbonyl group on the hydrogenation reaction, the above method was tested on 1-(4′-hydroxyphenyl)-1-butene, a simple olefinic compound without a carbonyl group. The result, as clearly mentioned in Table 2, showed that olefinic compounds successfully provided the corresponding reduced product, albeit in low yield as compared to its α,β-unsaturated analogue **1a**. The above experiment clearly showed that the reduction of the double bond occurred with or without conjugation of the carbonyl function. However, the low yield in the above case may be due to the easy evaporation of the more volatile product inside the microwave reactor as, in spite of the low yield, there were no starting or the side products detected (Table 2).

Based on the above encouraging results, the method was successfully applied to various other α,β-unsaturated aryl carbonyl groups (**2b**–**15b**) to provide the corresponding commercially important hydrogenated products (**2a**–**15a**) in good to excellent yields (Table 3). The spectral data of these products matched with the reported values. In all the cases, the reaction showed good reproducibility and reflected remarkable discrimination between olefins on one side and all other reducible

Table 1. Comparative studies of the CTH of **1b** under microwave, conventional and ultrasound conditions.

Substrate (**1b**)	Reaction method	Reaction time (in minutes)	Conversion	
	microwave	22[a]	 84%	
	conventional	720[b]	 45%	 25%
	ultrasound	300[c]	 32%	 18%

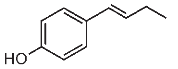
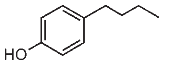
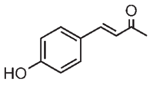
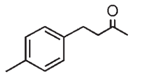
Reaction conditions: reagents: silica gel (2 g), $PdCl_2$ (0.012 g), **1b** (0.0025 mol) and 2 mL of reagent mixture $MeOH:HCOOH:H_2O$ (1:2:3)

[a] Irradiated at 960 W.

[b] Refluxed continuously.

[c] Sonicated with 75% duty, pulse length 9 sec, pause of 30 sec after every 10 min for 300 min.

Table 2. CTH of 1-(4′-hydroxyphenyl)-1-butene and **1b** with $PdCl_2$/silica gel/HCOOH/MeOH/H_2O under microwave irradiation.[a]

Substrate	Product	Irradiation time (in minutes)	Yield [%]	Conversion [%]
		22	65[b]	100
		22	84	100

Reaction conditions: reagents: silica gel (2 g), $PdCl_2$ (0.012 g), substrate (0.0025 mol) and 2 mL of reagent mixture MeOH:HCOOH:H_2O (1:2:3).

[a] Irradiated at 960 W.

[b] The reaction is performed at 450 W as an increase in either power level or irradiation time reduces the product yield due to its rapid evaporation.

groups like carbonyls, nitro (entry 7) and halogen (entry 9) on the other. However, dehalogenation[30] of aromatic halides has been observed under previously reported CTH methods. Under the same conditions, even an unsaturated ester (entry 10) produced the normal saturated ester without affecting the ester group. Similarly, this method worked well on aliphatic α,β-unsaturated carbonyl compounds (entry 11) but only moderate yields of the compounds (**10a** and **11a**) were obtained with 100% chemoselectivity. The moderate yield of the compounds in this case was due to the easy evaporation of the low-boiling products under microwave irradiation. Surprisingly, cinnamaldehyde (entry 13), under the above conditions, provided dihydrocinnamyl alcohol and 4-methoxyphenylpropane[31] besides forming the expected dihydrocinnamaldehyde. Similarly, furan (entry 14) and coumarin (entry 15) produced tetrahydrofuran and phenylpropionic acid, respectively, along with the expected dihydro products. Such unexpected products during hydrogenation reactions are documented,[13b,32] although scarcely. Overall, it was realized that in hydroxyl-substituted α,β-unsaturated aromatic carbonyl compounds (entries 1 and 2), the reaction was accomplished in a shorter reaction time than in the case of other substituents (Table 3).

Conclusion

In conclusion, we have devised an environmentally benign, effective, mild and chemoselective hydrogenating protocol for α,β-unsaturated aryl carbonyl systems, wherein microwave irradiation seems to attenuate the reactivity of the present reagent system and plays an important role in imparting selectivity to the reaction. The ecofriendly advantage of this protocol ensues a remarkable reduction of solvents, the use of heterogeneous media and simplicity in the experimental aspects, thus preventing pollution "at source." Further work is in progress aiming for a reduction in the reaction period.

Experimental Section

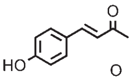
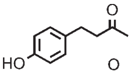
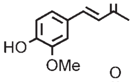
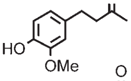
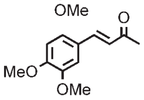
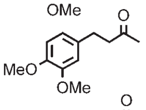
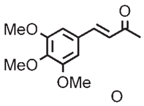
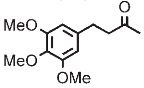
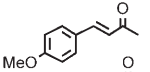
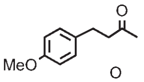
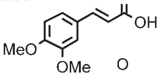
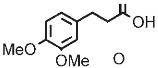
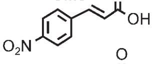
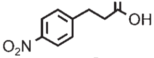
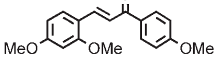
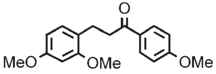
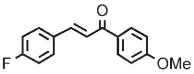
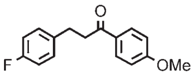
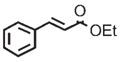
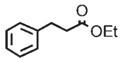
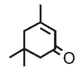
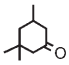
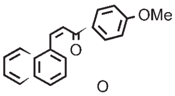
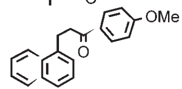
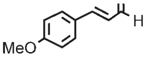
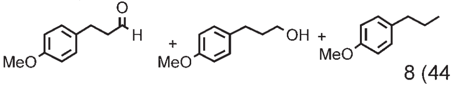
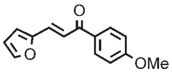
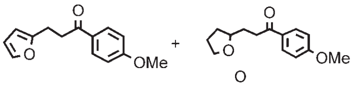
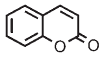
General Remarks

Melting points were determined with a Mettler FP80 micromelting point apparatus and are uncorrected. Column chromatography was performed on silica gel (60–120 mesh size). ^1H (300 MHz) and ^{13}C NMR (75.4 MHz) NMR spectra was recorded in $CDCl_3$ on a Bruker Avance 300 spectrometer. A Kenstar domestic microwave oven (2450 MHz, 960 Watts) was used for the reactions.

General Procedure for the Chemoselective Hydrogenation of α,β-Unsaturated Carbonyl Compounds (1b–15b) into their Dihydro Products (1a–15a) in a Domestic Microwave Oven

In a typical experiment, a homogeneous mixture containing silica gel (2 g) and $PdCl_2$ (0.010–0.015 g) was prepared by completely mixing both in a mortar. In an Erlenmeyer flask, this powdered mixture, the α,β-unsaturated ketone **1b**–**15b** (0.0025 mol) and 2–4 mL of reagent mixture MeOH:HCOOH:H_2O (1:2:3) were charged. The mixture was then irradiated in the microwave oven with addition of 1 mL of the reagent mixture after every 10 min. Progress of the reaction was monitored by TLC and UV spectra. After completion of the reaction, the mixture was loaded on a silica gel column and eluted with EtOAc (3 × 10 mL). The combined organic solvents were washed with water (3 × 10 mL) and dried over Na_2SO_4. The crude product, thus obtained was, in most of the cases, found to be pure enough on NMR and others were purified further in a silica gel column with a 1:4 mixture of EtOAc and hexane. The spectral data and mp of obtained products **1a**–**15a** agreed well with the reported values.[20,33,34]

Table 3. Chemoselective reduction of α,β-unsaturated carbonyl compounds (**b**) into their dihydro products (**a**).

Entry	Substrate (**b**)	Reaction time (in minutes)	Product (**a**)	Yield [%]
1		22		84
2		24		80
3		49		88
4		45		95
5		45		85
6		30		74
7		40		72
8		50		84
9		52		80
10		46		74
11		29		67
12		35		96
13		54		8 (44, 36)[a]
14		40		50 (39)[a]
15		55		55(14)[a]

[a] Numbers in the parenthesis indicate yields of the side products in the same order.

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