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Transition Metal Free Chemoselective Reduction of α,β-Unsaturated Ketones to Saturated Ketones Using Tosyl Hydrazide as a Hydrogen Donor

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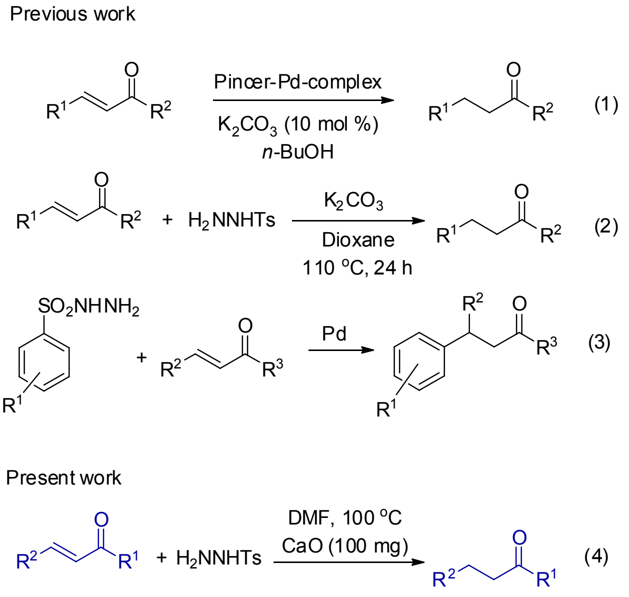
An efficient, inexpensive and simple method for the reduction of various *α*,*β*-unsaturated ketones to corresponding saturated ketones using tosyl hydrazide as a hydrogen donor in DMF using calcium oxide powder has been reported. A variety of enones underwent reduction without forming undesirable side products. High chemoselectivity, broad functional group tolerance and good yields are the noteworthy features of this protocol.

Keywords *α*,*β*-unsaturated carbonyl compounds, tosyl hydrazide, transition metal free, saturated ketones

Introduction

The chemoselective reduction of double bond of *α*,*β*-unsaturated carbonyl compounds is of great interest in organic synthesis.[1] Several research groups have been working on the development of an efficient, selective and inexpensive protocols for the reduction of *α*,*β*-unsaturated carbonyl compounds. In this direction, Satoshi *et al*.[2] have reported the iridium catalyzed reduction of chalcones to saturated ketones using alcohols as a hydrogen source. In addition, Pincer-Pd[3] (Scheme 1, reaction 1) complex and many other transition metals like rhodium,[4] ruthenium,[5] cobalt,[6] indium,[7] titanium[8] and few other catalysts[9] have been used for the reduction of isolated double bonds. Scrap automobile catalyst has been used to facilitate the conjugate reduction of isolated double bonds to saturated carbonyl compounds.[10] In further, Nandy and his group[11] reported reduction of isolated double bond by using ammonium formate as the hydrogen donor with catalytic amount of 10% Pd/C in methanol/THF at reflux temperature. In 2002, Kosal and his co-workers[12] have reported chemoselective reduction of *α*,*β*-unsaturated carbonyl compounds using Cp_2TiCl_2 derivative in the presence of Zn dust as a catalyst. Interestingly, reduction of *α*,*β*-unsaturated carbonyl compounds has been achieved using biocatalyst *Penicillium citrinum* CBMAI 1186.[13] In addition to above methods several research groups have showed different approaches for the synthesis of saturated ketones.[14]

Scheme 1 Synthesis of *α*,*β*-saturated ketones



However, all the literature reported methods have one or the other disadvantages like prolonged heating, low yields, using expensive noble metals and harsh reaction conditions, so there is an urgent need for the development of a new protocol which circumvents these difficulties. On the other hand, tosyl hydrazide has been used in various palladium catalyzed reactions to make a C—C bond.[15] Haukaas *et al*.[16] have reported enantioselective synthesis of 2-deoxy and 2,3-dideoxyhexoses

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using NSBH/Et_3N as a diimide precursor. Zhou and his co-workers[17] have reported synthesis of saturated ketones from chalcones using tosyl hydrazide as hydrogen donor in the presence of base at reflux temperature (Scheme 1, reaction 2), and Chen and his co-workers[18] reported conjugate addition of tosyl hydrazides to α,β-unsaturated ketones (Scheme 1, reaction 3).

All the literature reported methods require an additional hydrogen source for hydrogenation of unsaturated carbonyl compounds in the presence of inner transition metals. Since tosyl hydrazide could be used as a hydrogen source,[19] which is stable in air and can be prepared easily in one step from readily available tosyl chloride and hydrazine hydrate,[20] these qualities make this reagent as an alternate hydrogen source. Tosyl hydrazide has been tested on the α,β-unsaturated carbonyl system for the various transformations.[21] By keeping all these facts in mind, we tried tosyl hydrazide as a hydrogen source for the reduction of α,β-unsaturated ketones to saturated carbonyl compounds (Scheme 1, reaction 4). We have been engaged from the past few years in the development of novel synthetic protocols for the synthesis of various heterocycles using different catalysts.[22] As continuation of our research work, we herein report a simple, efficient, economical and effective method for the chemoselective reduction of α,β-unsaturated carbonyl compounds using tosyl hydrazide as hydrogen source.

Experimental

Reactions were monitored by TLC using precoated sheets of silica gel G/UV-254 of 0.25 mm thickness (Merck 60F254) using UV light for visualization. The melting points were determined on a Selaco melting point apparatus and uncorrected. ^1H and ^{13}C NMR spectra were recorded on an NMR spectrometer operating at 400 and 100 MHz, respectively, using the residual solvent peaks as reference relative to $SiMe_4$. Mass spectra were measured with Micromass Q-Tof (HRESI-MS). ATR-Fourier transform infrared (FTIR) spectra were recorded using a Thermo Nicolet FTIR spectrometer (Model 5700, Madison, WI) fitted with a single bounce attenuated total reflectance (ATR) accessory with a ZnSe crystal of range 400—4000 cm^{-1}

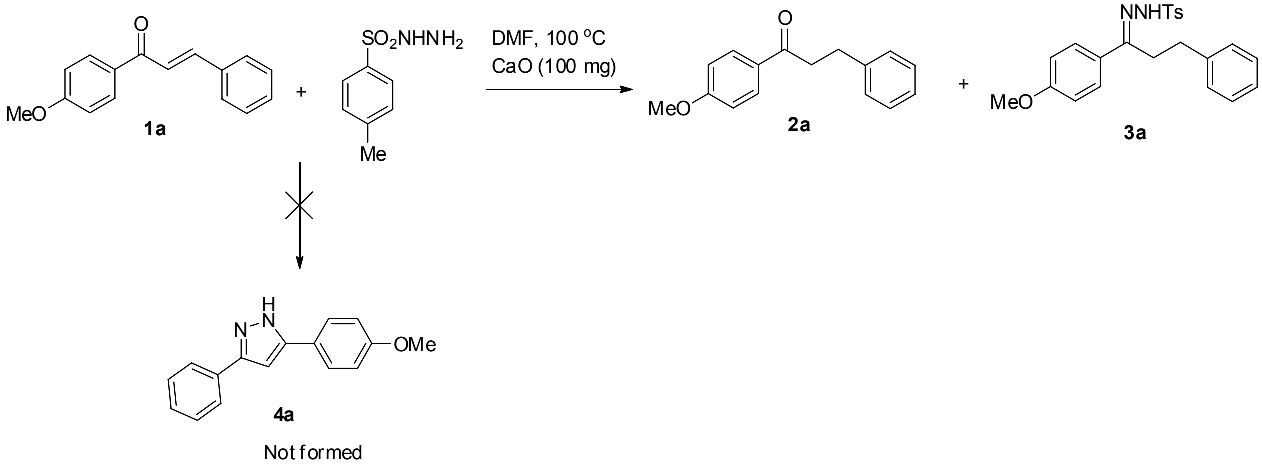
General procedure for the synthesis of saturated ketones (2a)

All reactions were performed on a 0.50 mmol scale relative to chalcones. (*E*)-1-(4-Methoxyphenyl)-3-phenylprop-2-en-1-one (**1a**) (1 mmol), 4-methylbenzenesulfonyl hydrazide (1.2 mmol), CaO (100 mg) and 3 mL of DMF were taken in a round bottom flask equipped with a stirrer. The reaction mixture was agitated at 100 ℃ for 0.45 h. Following, to the reaction mixture was added water (2 mL), and extracted with ethyl acetate (10 mL×3). The combined organic phases were washed with brine (5 mL×2), dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was subjected to column chromatography with hexanes/EtOAc (V∶V=5∶0.1) as eluent to obtain the desired **2k** (87% yields). The remaining substituted saturated carbonyl compounds were prepared in the similar manner.

Results and Discussion

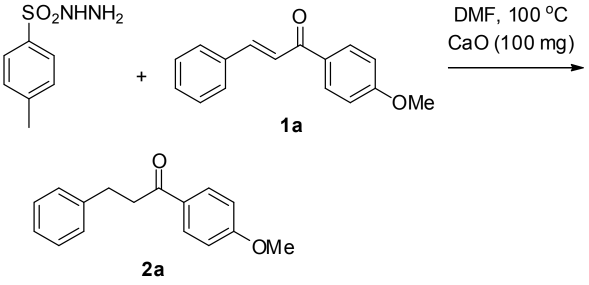
Initially we have selected (*E*)-1-(4-methoxyphenyl)-3-phenylprop-2-en-1-one (**1a**) as a model substrate for the synthesis of pyrazoles **4a**. Interestingly the reaction produced mixture of saturated ketone **2a** and saturated tosyl imine **3a** (Table 1, Entry 2) instead of pyrazole product **4a** (Scheme 2). By inspiring with these findings we went on to optimize the reaction conditions to get an exclusively saturated ketone product which looks interesting. For the optimization study, initially we examined a variety of inorganic bases. In the presence of strong bases such as NaOH and Cs_2CO_3, reaction yielded the product in low yields (Table 1, Entries 7, 9). Whereas the bases like Na_2CO_3, K_2CO_3 gave improved yields (Table 1, Entries 5, 6 and 8). In further, we screened the

Scheme 2 Synthesis of 1-(4-methoxyphenyl)-3-phenylprop-2-one (**2a**)



reaction using various acid and base catalysts under solvent and solvent free conditions, among which CaO was found to be very effective (Table 1, Entry 15) for the transformation of α,β-unsaturated carbonyl compounds to saturated ketones (Table 1, Entries 10—16).

Table 1 Optimization of conjugate reduction of chalcone **1a** with tosylhydrazine^a



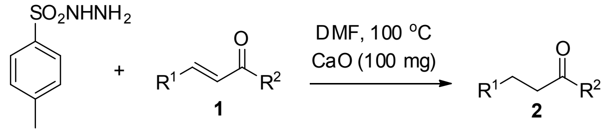
Entry	Solvent	Base	Time/h	Temp./℃	Yield^b/%	
					2a	**3a**
1	DCM	CaO	24	r.t	—	—
	EtOH	CaO	8	80	45	55
3	EtOH	$CaCO_3$	12	80	20	80
4	EtOH	—	24	80	trace	—
5	EtOH	K_2CO_3	1.5	80	87	—
6	MeOH	K_2CO_3	1.75	80	65	35
7	EtOH	NaOH	18	80	10	90
8	EtOH	Na_2CO_3	6	80	70	30
9	EtOH	Cs_2CO_3	3	80	30	70
10	EtOH	ZrO_2-Al_2O_3	6	80	65	35
11	DMF	ZrO_2-β-Cd	4	100	90	10
12	—	ZrO_2-β-Cd	4	80	60	40
13	—	ZrO_2-β-Cd	0.5	100		90
14	—	ZrO_2-Al_2O_3	3	100	40	50
15	**DMF**	**CaO**	**1**	**100**	**90**	—
16	DMF	ZrO_2-β-Cd	1	100	50	50
17	THF	CaO	0.75	80	60	30
18	EtOH	CaO	4	70	70	30

^{a} Reaction conditions: **1a** (1 mmol), $TsNHNH_2$ (1.2 mmol), CaO (100 mg) in DMF (3 mL), 100 ℃. ^{b} Isolated yields.

With the optimized reaction condition in hand, we next explored the generality of the protocol by using different funtionalized chalcones in the presence of tosyl hydrazide and CaO powder in DMF and the results are summarized in Table 2. Thus, α,β-unsaturated carbonyl compounds bearing electron-donating and electron-withdrawing substitutents on aromatic ring underwent reaction smoothly; producing the corresponding saturated ketones in good to excellent yields (Table 3, Entries 1—14). Interestingly, α,β-unsaturated carbonyl compounds bearing thiophene ring also gave the corresponding product in excellent yields (Table 3, Entries 8—14).

It was found that the methoxy group on the aromatic ring was survived throughout the reaction and gave the corresponding saturated ketones up to 83% yields (Table 2, Entries 1, 3, 8, 9). In addition, substrates with the halogen group proceeded smoothly to afford the desired product in moderate yields (Table 2, Entries 4—7). The reaction of substrates bearing thiophene ring underwent smoothly to afford the desired products in good yields (Table 2, Entries 8—14).

Table 2 Synthesis of different substituted saturated ketones from α,β-unsaturated carbonyl compounds^a



Entry	R^1	R^2	**2**	Time/h	Yield^b/%
1	4-OMeC_6H_4	C_6H_5	**2a**	1	95[23]
2	$4\text{-NH}_2C_6H_4$	$2,4\text{-Cl}_2C_6H_3$	**2b**	2.25	78
3	4-OMeC_6H_4	4-BrC_6H_4	**2c**	1.25	83[25]
4	C_6H_5	4-BrC_6H_4	**2d**	1.5	55[26]
5	4-OMeC_6H_4	$3,4\text{-(OMe)}_2C_6H_3$	**2e**	3	45
6	4-OMeC_6H_4	4-FC_6H_4	**2f**	2	65[27]
7	4-BrC_6H_4	4-BrC_6H_4	**2g**	1.75	60
8	2-Thiophenyl	$3,4\text{-(OMe)}_2C_6H_3$	**2h**	1.75	85
9	2-Thiophenyl	4-OMeC_6H_4	**2i**	2	82[28]
10	2-Thiophenyl	C_6H_5	**2j**	1.5	70[24]
11	2-Thiophenyl	4-MeC_6H_4	**2k**	1.75	78
12	2-Thiophenyl	4-FC_6H_4	**2l**	2	85
13	2-Thiophenyl	4-EtC_6H_4	**2m**	1.75	83
14	2-Thiophenyl	Benzo[1,3]dioxole	**2n**	4	90

^{a} Reaction conditions: **1** (1 mmol), tosyl hydrazide (1.2 mmol), CaO (100 mg) in DMF (3 mL), refluxed at 100 ℃ until completion of reaction. ^{b} Isolated yields.

Table 3 Catalyst recycle studies

Catalyst	Time/min	Yield/%
1	45	95
2	45	93
3	45	93
4	55	90
5	60	88

Recycling study of the catalyst

We also investigated reusability of catalyst under DMF using model chalcone **1a** with tosyl hydrazine in presence of 100 mg CaO powder. After completion of the reaction, the mixture was dissolved in ethyl acetate (10 mL) and the catalyst was filtered off. The powder CaO was treated with ethanol, acetone, and then washed with distilled water. It was then dried in an oven at 80 ℃ for 2 h and used for the next catalytic cycle. Powder CaO was found to be reusable up to five catalytic cycles without any significant loss in activity (Table 3).

Conclusions

In conclusion, we have developed a simple, efficient, inexpensive and excellent method for the conversion of different substituted *α*,*β*-unsaturated carbonyl compounds into corresponding saturated ketones in the presence of tosyl hydrazide and powder CaO in DMF. The present work does not demand harsh and prolonged reaction conditions. The reaction goes to completion in the absence of noble metal catalysts and easy workup procedure makes this process as a benign protocol.

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