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$FeCl_3 \cdot 6H_2O$-catalyzed selective conjugate reduction of alkylidene-β-keto esters and alkylidene-1,3-diketones

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ABSTRACT

$FeCl_3 \cdot 6H_2O$/triethylsilane composite catalyst system is successfully developed for the selective conjugate reduction of carbon-carbon double bond of Michael acceptor-alkylidene-β-keto esters and alkylidene-1,3-diketones under mild reaction conditions to afford the corresponding saturated β-keto esters and 1,3-diketones. The process involves the iron-catalyzed hydrosilylation, followed by in situ hydrolysis of silyl enol ether. The optimal reaction conditions include 20 mol% of $FeCl_3 \cdot 6H_2O$ and triethylsilane in dichloromethane at room temperature. A broad range of substrates undergoes the reduction in 1, 4-selective manner to afford the corresponding saturated compounds in excellent yields.

Introduction

Composite reducing systems comprising of hydrosilanes and transition metal catalysts have been highly successful reduction strategies in organic synthesis [1]. The chemoselective reduction of one functionality over another without any side reactions is always a challenge in both chemical and pharmaceutical industries. However, organosilanes, unlike organometallic reagents are usually unreactive and inert towards various organic substrates [2]. Trialkylsilanes are known to be poor reducing agents and these organosilanes can be activated by appropriate Lewis acids in order to explore their effective use in organic synthesis [2,3]. Alternatively, transmetallation has also been explored to activate the less reactive organosilanes to carry out organic transformations [4]. Nowadays, the selective conjugate reduction of α, β-unsaturated ketones has become one of the important functional group transformations for the synthesis of natural products and biologically active compounds under environmentally friendly conditions. It's known in the literature that Et_3SiH/$EtMe_2SiH$ coupled with the suitable transition metal reagents lead to the conjugate reduction of α, β-unsaturated ketones and esters [5]. Metals such as Ir, Rh, Pd and other metal complexes have been explored for the hydrosilylation reaction for achieving the conjugate reduction [6,7]. Likewise, the hydrosilylation methods for the reduction of α, β-unsaturated ketones and esters have also been achieved by exploring the use of first-row transition elements [8] such as Ti, Zn, Cu, Fe, Ni and the early transition element such as Mo [9]. Hydrosilylation strategy has been successfully explored for the reduction of olefins, carbonyls and imines [6–9]. The conjugate reduction of α, β-unsaturated ketones and esters are complex and commonly suffers from the competitive 1, 2-reduction. Usually, it can lead to multiple reduction products via 1, 2-reduction, 1, 4-reduction and complete competitive reductions. The chemoselective conjugate reduction is an important and challenging task in organic synthesis [10]. The chemoselective reduction of a particular functional group without reducing other sensitive moieties is desirable and demanding.

Interestingly, most of the work on hydrosilylation has been focused on the reduction of ketones or α, β-unsaturated ketones [8b–8d,11]. Also, most of the hydrosilylation methods require the use of base or acid for the final hydrolysis of silylated intermediates [8d]. Surprisingly, there are no reports on the selective reduction/hydrosilylation reaction on the alkylidene β-keto esters. It would be interesting to explore the novel catalyst system comprising of simple and commercially available metal catalyst. It is also desirable to develop a protocol without the need for any ligands and additives/co-catalysts. Among the transition metal catalysts, iron is believed to be ideal in many ways, as it is environmentally benign, easily available and less expensive. Herein, we report the versatility of $FeCl_3 \cdot 6H_2O$/Et_3SiH system for the selective conjugate reduction of the carbon-carbon double bond of alkylidene-β-keto esters, alkylidene-1,3-diketones and –Meldrum's adducts under mild reaction conditions.

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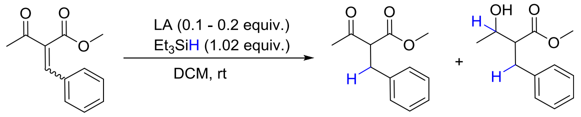
Results and discussion

At the outset, we commenced our work with a model reaction of benzylidene methylacetoacetate **1a** with various Lewis acids in presence of triethylsilane in DCM at room temperature. Compound **1a** did not react with Et_3SiH (1 equiv.) in presence of different Lewis acids (entry 1–6 and 8, Table 1). Surprisingly, metal salts which are known to catalyze hydrosilylation of enones did not catalyze effectively the reduction of alkylidene β-keto ester **1a**. It is interesting and unusual that the alkylidene β-keto esters did not react under the reaction conditions even though they are more reactive than enones. The reaction of compound **1a** with anhydrous $FeCl_3$ and Et_3SiH in DCM at room temperature led to multiple products (entry 9, Table 1). Interestingly, catalytic amount of $FeCl_3{\cdot}6H_2O$ (10 mol%) under the reaction condition afforded the desired product **2a** (64%) along with corresponding alcohol **3a** (1, 2-reduction product) in 13% yield (entry 10, Table 1). Gratifyingly, $FeCl_3{\cdot}6H_2O$ (20 mol%, 0.2 equiv.) reacted smoothly under the reaction conditions to afford the conjugate reduction product **2a** in 85% yield along with a significantly lower amount of alcohol **3a** in 6% yield (entry 11, Table 1).

The treatment of compound **1a** with $FeCl_2{\cdot}4H_2O$ (entry 12, Table 1) under the reaction conditions led to just a trace amount of desired product **2a**. Likewise, compound **1a** did not react with Et_3SiH (1.02 equiv.) in presence of other Lewis acids (entry 13–18, Table 1). The reaction did not work in the absence of any catalyst (entry 20, Table 1).

Encouraged by this initial success, we screened various solvents for optimizing the reaction conditions. Non-polar solvents such as chloroform, benzene and toluene afforded the conjugate reduction product **2a** in poor yield (entry 2–4, Table 2). While solvents such as ethyl acetate and acetone afforded the product **2a** in trace amounts. The protic solvent such as methanol afforded the mixture of **2a** and **3a**. While aprotic polar solvents proved to be disadvantageous. DCM proved to be the optimum solvent for the desired transformation (entry 1, Table 2).

Table 1
Screening of Lewis acid (LA) catalysts for optimizing the reaction conditions.[a]

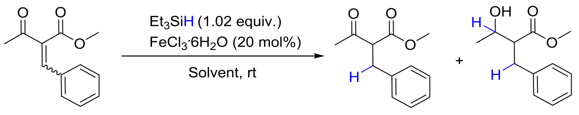


1a **2a** **3a**

Entry	LA (Catalyst)[a]	Time (h)	Yield[c] (%)
1	$CuCl_2{\cdot}2H_2O$	24	Trace
2	$MnCl_2{\cdot}6H_2O$	24	NR
3	$NiCl_2{\cdot}6H_2O$	24	NR
4	$Cu(OAc)_2$	24	NR
5	$Zn(OAc)_2$	24	NR
6	$CuSO_4{\cdot}5H_2O$	24	NR
7	Cu(I)Br	24	27 + 12[d]
8	$CoCl_2{\cdot}6H_2O$	24	NR
9	$FeCl_3$	4	Multiple products
10	$FeCl_3{\cdot}6H_2O$	12	64 + 13[d]
11	**$FeCl_3{\cdot}6H_2O$**[b]	**8**	**85 + 6**[d]
12	$FeCl_2{\cdot}4H_2O$	24	Trace
13	$CeCl_3{\cdot}7H_2O$	24	NR
14	$SnCl_2{\cdot}2H_2O$	24	15
15	$MgBr_2{\cdot}6H_2O$	24	NR
16	$Cu(NO_3)_2{\cdot}3H_2O$	24	NR
17	$Ni(acac)_2$	24	NR
18	$Fe(acac)_3$	24	NR
19	$Fe(ClO_4)_3XH_2O$	24	Trace
20	No Catalyst	24	NR

[a] Reactions were performed with 0.1 equiv. (10 mol%) of Lewis acids (LA) and Et_3SiH (1.02 equiv.) in DCM.
[b] 20 mol% of catalyst was used.
[c] Isolated yield of the product after column chromatography.
[d] Yield of alcohol **3a**. NR = No Reaction.

Table 2
Screening of solvents for optimizing the reaction.[a]



1a **2a** **3a**

Entry	Solvent	Time (h)	Yield[b] (%)
1	**DCM**	**8**	**85 + 6**[c]
2	$CHCl_3$	12	54 + 11
3	Toluene	12	28 + 8
4	Benzene	12	25 + 6
5	EtOAc	24	Trace
6	MeOH	12	30 + 15[c]
7	Acetone	24	Trace
8	THF	24	NR
9	ACN	24	NR
10	DMF	24	NR
11	DMSO	24	NR

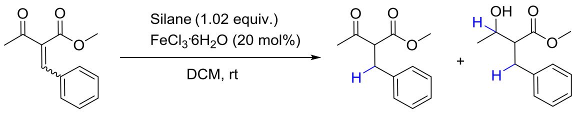
[a] Reactions were screened on **1a** (1 mmol) with Et_3SiH (1.02 equiv.) and $FeCl_3{\cdot}6H_2O$ (20 mol%) in various solvents.
[b] Isolated yield after column chromatography.
[c] Yield of alcohol **3a** after column chromatography NR = No Reaction.

In order to explore the most suitable and optimum silyl reducing agent, we screened the reaction with triethoxysilane and triphenylsilane in presence of $FeCl_3{\cdot}6H_2O$ (see Table 3). The reaction of benzylidene methylacetoacetate **1a** with triethoxylsilane (1.02 equiv.) in DCM, $FeCl_3{\cdot}6H_2O$ (20 mol%) led to an inseparable mixture of products (entry 2, Table 3). While, the triphenylsilane afforded the mixture of **2a** and **3a** (see entry 3, Table 3).

Triethylsilane proved to be the most suitable reducing agent by affording the corresponding conjugate reduction product **2a** in 85% yield. Based on different screening experiments $FeCl_3{\cdot}6H_2O$ (20 mol%), Et_3SiH (1.02 equiv.) in DCM at room temperature proved to be the optimum reaction condition.

Having optimum reaction conditions in hand, we planned to explore the substrate scope for the generality of the method. Various alkylidene methyl acetoacetates (**1b-1l**) under the optimum reaction conditions afforded the corresponding 1, 4-conjugate reduction products (**2b-2l**) in good to excellent yields (see Scheme 1). This method proved to be highly chemoselective as it afforded selectively 1, 4-conjugate addition products and we observed only a trace amount of 1, 2-addition products (alcohol). The substrate containing both electron-donating and weak

Table 3
Screening of silane reducing agents for optimizing the reduction reaction.[a]



1a **2a** **3a**

Entry	Silane	Time (h)	Yield[b] (%)
1	Et_3SiH	8	85 + 6[c]
2	$(EtO)_3SiH$	12	Inseparable Mixture
3	Ph_3SiH	8	66 + 15[c]

[a] Reactions were screened on **1a** (1 mmol) with silane (1.02 equiv.) and $FeCl_3{\cdot}6H_2O$ (20 mol%) in DCM.
[b] Isolated yield.
[c] Yield of alcohol **3a**.

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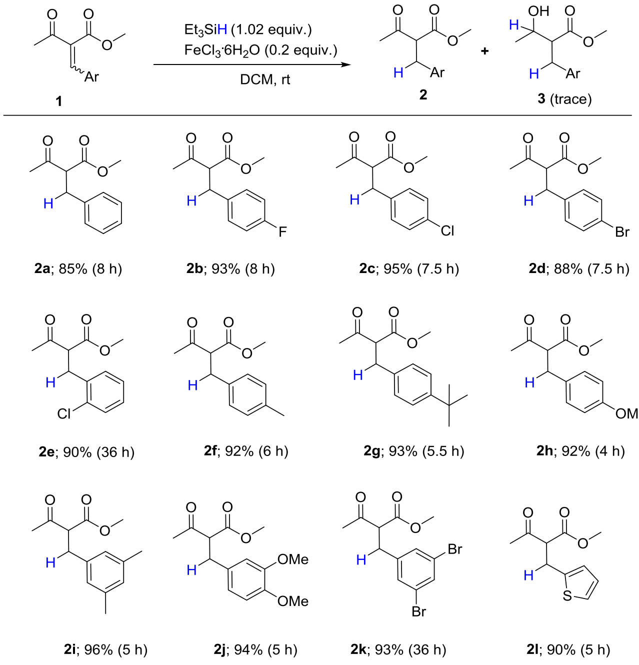
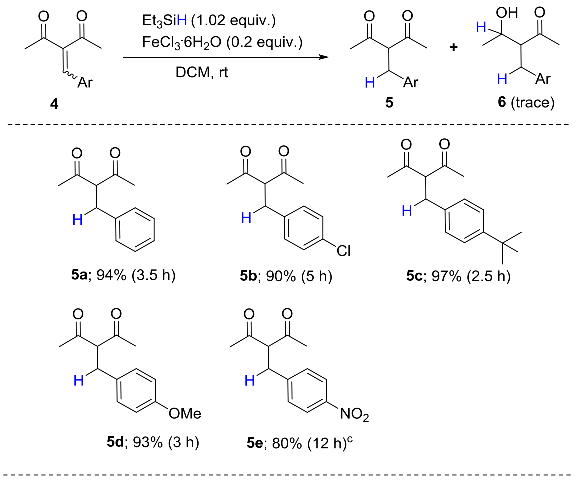


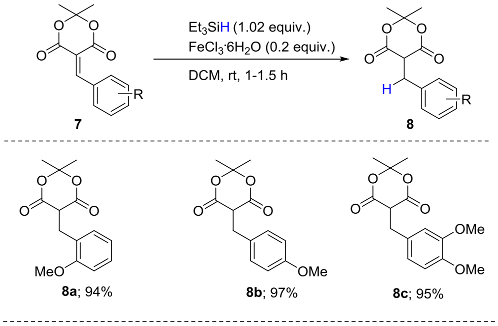
Scheme 1. Substrate scope of alkylidene β-ketoesters for reduction under optimized reaction conditions^{a,b}. ^{a}Reactions were performed on **1a-1l** (1 mmol, 1 equiv.) with $FeCl_3\cdot 6H_2O$ (20 mol%) and Et_3SiH (1.02 equiv.) in DCM at rt. ^{b}Isolated yield.

electron withdrawing groups, and heteroaryl derived substrate reacted smoothly under the reaction conditions. Substrates with strong electron withdrawing groups (*p*-CN- and *p*-NO_2-Phenyl) did not react under the reaction conditions. Also attempts towards the reduction of α, β-unsaturated ketones such as cyclohexenone and benzylidene acetone were unsuccessful as reactions led to the mixture of products (1,2- and 1,4-reduction and complete reduction products).

Later, we turned our attention towards acetyl acetone derivatives. The alkylidene acetylacetone derivatives (**4a–4e**) under optimum reaction conditions afforded the corresponding 1, 4-conjugate reduction products (**5a–5e**) chemoselectively in good to excellent yields (See Scheme 2).



Scheme 2. Substrate scope of alkylidene β-diketones for reduction under optimized reaction conditions^{a,b}. ^{a}Reactions were performed on **4a–4e** (1 mmol) with $FeCl_3\cdot 6H_2O$ (20 mol%) and Et_3SiH (1.02 equiv.) in DCM at rt. ^{b}Isolated yield. ^{c}Compound **6e** was isolated in 9% yield.



Scheme 3. Substrate scope of Meldrum's adducts for reduction under optimized reaction conditions^{a,b}. ^{a}Reactions were performed on **7a–7c** (1 mmol, 1 equiv.) with $FeCl_3\cdot 6H_2O$ (20 mnol%) and Et_3SiH (1 equiv.) in DCM at rt. ^{b}Isolated yield after column chromatography.

However, substrates with electron withdrawing group **4e** afforded the desired product **5e** along with 1, 2-addition product **6e** in a smaller quantity (Scheme 2).

To expand the scope of the methodology further we synthesized a few alkylidene Meldrum's acid derivatives (**7a**–**7c**). These compounds under the optimum reaction conditions afforded the corresponding 1, 4-conjugate addition products (**8a**–**8c**) exclusively in almost quantitative yields (Scheme 3). The method proved to be highly selective for the 1,4-conjugate reduction.

Conclusions

In conclusion, a novel reducing system comprising of $FeCl_3\cdot 6H_2O$/triethylsilane is successfully developed for the highly selective conjugate reduction of the carbon-carbon double bond of alkylidene β-keto esters and alkylidene 1,3-diketones under the mild reaction conditions. The chemoselective reduction afforded exclusively 1, 4-conjugate reduction products as major products and the method did not require the use of any base/acid for the desilylation. A broad range of alkylidene derivatives underwent smooth reduction under practical reaction conditions.

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