Rapid and Regioselective Hydrogenation of α,β-Unsaturated Ketones and Alkylidene Malonic Diesters Using Hantzsch Ester Catalyzed by Titanium Tetrachloride

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Abstract: A regioselective hydrogenation of α,β-unsaturated ketones and alkylidene malonic diesters using Hantzsch ester as the reducing agent and titanium tetrachloride as a catalyst is described. The short reaction times and mild reaction conditions are the advantages of this method.

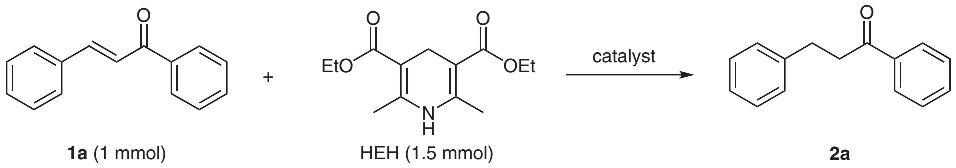
Key words: hydrogen transfer, reduction, α,β-unsaturated ketone, alkylidene malonic diester, titanium tetrachloride

Hydrogenation is one of the most important transformations both in biological organisms and chemistry. In biochemical reductions, this is commonly achieved by enzymes and hydride reduction cofactors such as dihydropyridine-based nucleotides NADH (reduced nicotinamide adenine dinucleotide) and NADPH (reduced nicotinamide adenine dinucleotide phosphate) whilst in chemical hydrogenations, the reaction has generally relied on metal catalysts,[1] metal hydrides,[2] or the Hantzsch 1,4-dihydropyridine (HEH) systems.[3]

The advantage of using HEH lies in the mildness of its reducing ability thus enabling selective reduction of a particular functional group. Thus there has been much interest in finding applications for HEH as a biomimetic reducing agent and various catalysts have been developed to accomplish these transformations.[4] In our continuing efforts to develop HEH-based synthetic methods,[5] we have recently explored the development of an alternative acid catalyst for the conjugate reduction of α,β-unsaturated ketones **1** and herein report our findings. To our knowledge, various catalysts for this reaction have already been reported but the reactions still require both heating and long reaction times.[4b–4f,6] Herein we report that $TiCl_4$ is an active catalyst for a mild and expeditious transfer hydrogenation of a variety of α,β-unsaturated ketones **1** with HEH to give saturated ketones **2** in good yields.

To search for an alternative catalyst for the regioselective reduction of α,β-unsaturated ketones with HEH, various acids and Lewis acids were examined. With 1,3-diphenylpropenone (**1a**), the best result was observed with $TiCl_4$ (entry 10, Table 1). To optimize the reaction, we screened various solvents and found the reaction to be dependent on both solvent and the amount of catalyst used (Table 2). Amongst the solvents screened, THF was the best solvent as the reaction gave the highest yield and was completed within one hour (entry 2, Table 2).

Table 1 Reduction of Compound **1a**



Entry	Catalyst (equiv)	Reaction conditions	Yield (%)[a]
1	TCA (2)	toluene, reflux, 24 h	30
2	TCA (2)	MeCN, MW, 110 °C, 30 min	trace
3	AcOH (2)	toluene, reflux, 24 h	32
4	TFA (2)	toluene, reflux, 24 h	30
5	TFA (2)	MeCN, MW, 110 °C, 30 min	trace
6	HCl–H_2O (2)	toluene, reflux, 24 h	NR[b]

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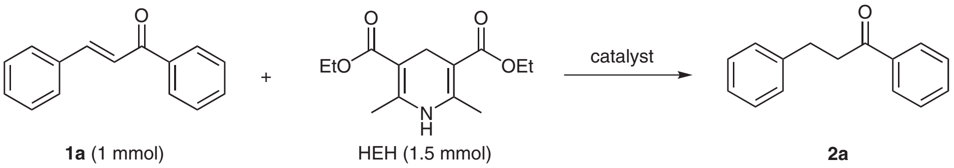
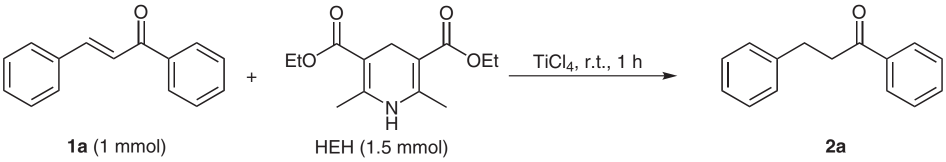
Table 1 Reduction of Compound **1a** (continued)



Entry	Catalyst (equiv)	Reaction conditions	Yield (%)[a]
7	proline (2)	toluene, reflux, 20 h	trace
8	$TsOH\cdot H_2O$ (2)	toluene, r.t., 4 h	trace
9	$TiCl_4$ (1.2)	toluene, r.t., 1 h	90
10	$TiCl_4$ (1.2)	THF, r.t., 1 h	95
11	$AlCl_3$ (1.2)	toluene, r.t., 1 h	58
12	$AlCl_3$ (2)	toluene, r.t., 1 h	72
13	$AlCl_3$ (1.2)	THF, r.t., 1 h	75
14	$FeCl_3$ (2)	toluene, r.t., 4 h	53
15	$ZnCl_2$ (2)	toluene, r.t., 4 h	42

[a] Isolated yield.
[b] NR means no apparent reaction.

Table 2 Optimization of the Reduction of **1a**



Entry	Equiv of $TiCl_4$	Solvent	Yield (%)[a]
1	0.2	THF	52
2	1.2	THF	95
3	2.2	THF	86
4	1.2	CH_2Cl_2	60
5	1.2	$CHCl_3$	62
6	1.2	MeCN	70
7	1.2	toluene	90

[a] Isolated yield.

We next explored the use of $TiCl_4$ in the reduction of a variety of α,β-unsaturated ketones with HEH under the optimized conditions. The reaction proceeded selectively and gave very good yields in all cases (Table 3). This demonstrates the versatility of $TiCl_4$ as a catalyst for the regioselective reduction of α,β-unsaturated ketones. A plausible mechanism for this reaction is shown in Scheme 1.

Table 3 Library of Compound **2**

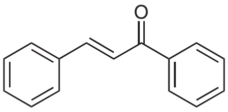
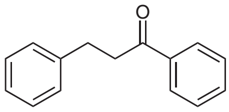
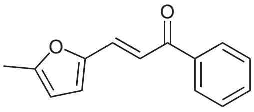
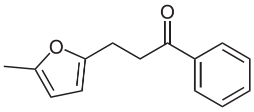
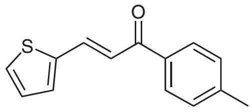
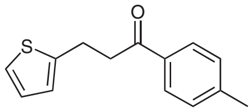
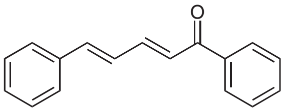
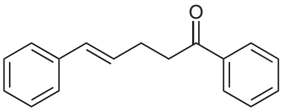
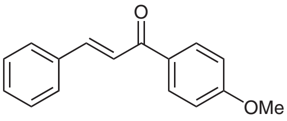
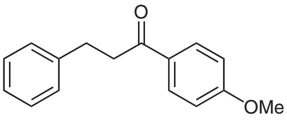
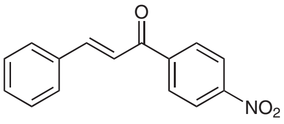
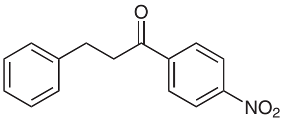
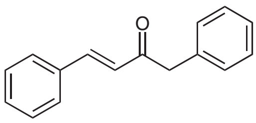
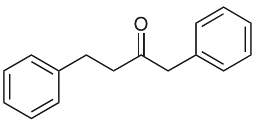
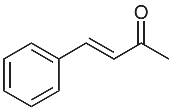
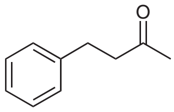
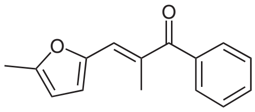
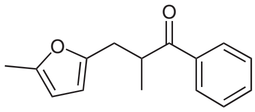
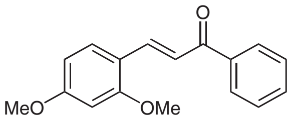
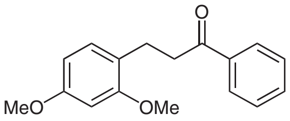
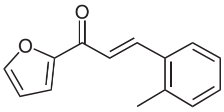
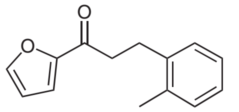
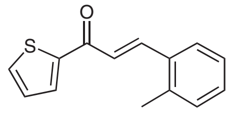
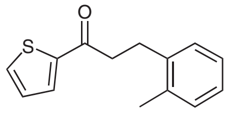
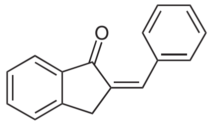
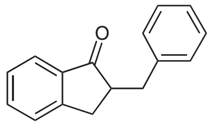
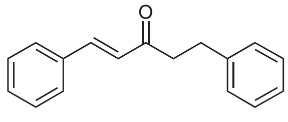
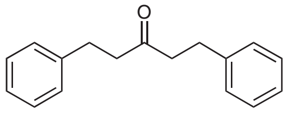
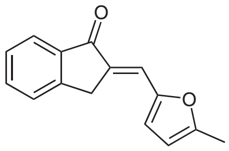
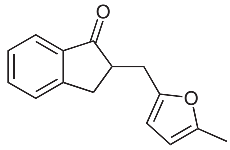
Entry	Substrate	Product	Yield (%)[a]
1	 **1a**	 **2a**	95 (96,[b] 94[c])
2	 **1b**	 **2b**	90
3	 **1c**	 **2c**	95
4	 **1d**	 **2d**	95
5	 **1e**	 **2e**	90
6	 **1f**	 **2f**	90
7	 **1g**	 **2g**	85
8	 **1h**	 **2h**	82 (54[d])
9	 **1i**	 **2i**	85
10	 **1j**	 **2j**	92
11	 **1k**	 **2k**	93

Table 3 Library of Compound **2** (continued)

Entry	Substrate	Product	Yield (%)[a]
12	 **1l**	 **2l**	99
13	 **1m**	 **2m**	82
14	 **1n**	 **2n**	88
15	 **1o**	 **2o**	94

[a] Isolated yield.

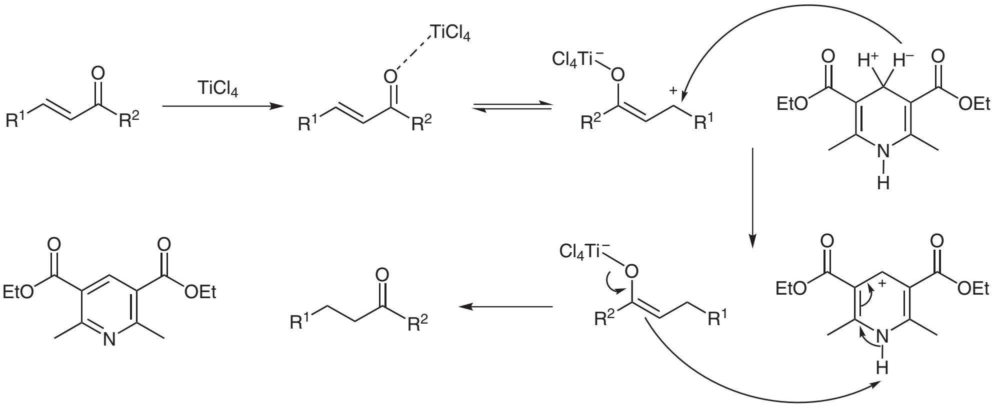
[b] Reaction was carried out with HEH, Pd/C in refluxing EtOH for 8 h.[4c]

[c] Reaction was carried out with HEH in the presence of silica gel in benzene at 80 °C for 17 h.[4d]

[d] Reaction was carried out with HEH–AcOH in toluene at 100 °C for 15 h.[4f]

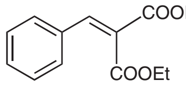
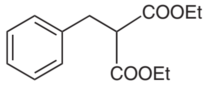
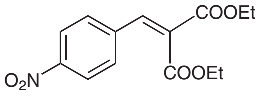
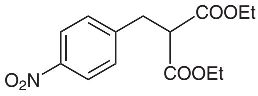
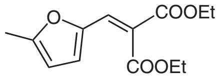
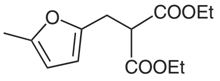
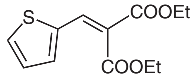
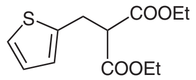
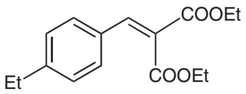
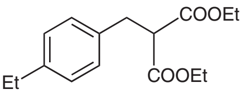
Encouraged by these results, we extended our study to alkylidene malonic diesters. Earlier studies have shown that benzylidene malonic diethyl ester **3a** was unreactive towards HEH even under reflux conditions.[3d,7] However, in the presence of $Mg(ClO_4)_2$ in acetonitrile or acetonitrile–methanol mixture and 2–6.5 hours of reflux, the carbon–carbon double bond of **3a** and 4-nitrobenzylidene malonic diethyl ester (**3b**) were shown to be selectively reduced with HEH or *N*-benzyl-1,4-dihydronicotinamide, a NADH model, to provide **4a** and **4b**, respectively, in ca. 97% yields.[7,8] For our initial study, **3a** was treated with HEH and $TiCl_4$ in THF at room temperature for one hour. This gave the corresponding carbon–carbon double-bond-reduced product **4a** in quantitative yield. With this success, the scope of this protocol was extended to other alkylidene malonic diesters and the results obtained show that the procedure affords a very efficient approach for a selective reduction of these compounds (Table 4).

In summary, we have shown that the $TiCl_4$-catalyzed HEH reduction of α,β-unsaturated ketones and alkylidene malonic diesters is a rapid and experimentally simple procedure for the preparation of saturated ketones and alkyl malonic diesters. The reaction expends the application of HEH as a biomimetic reducing agent in synthetic organic transformations.



Scheme 1 Proposed mechanism for the $TiCl_4$-Hantzsch ester reduction of α,β-unsaturated ketones

Table 4 Library of Compound **4**

Entry	Substrate	Product	Yield (%)[a]
1	 **3a**	 **4a**	99 (96[b])
2	 **3b**	 **4b**	93 (97[c])
3	 **3c**	 **4c**	99
4	 **3d**	 **4d**	99
5	 **3e**	 **4e**	90

[a] Isolated yield.

[b] Reaction was carried out with *N*-benzyl-1,4-dihydronicotinamide, $Mg(ClO_4)_2$ in refluxing MeCN for 2 h.[7]

[c] Reaction was carried out with HEH, $Mg(ClO_4)_2$ in refluxing MeCN–MeOH for 6.5 h.[8]

General Procedure for the Reduction of α,β-Unsaturated Ketones

To the respective α,β-unsaturated ketone (1 mmol) in THF (5.0 mL) was added HEH (0.38g, 1.5mmol) and $TiCl_4$ (1.2 mL of 1 M $TiCl_4$ in CH_2Cl_2, 1.2 mmol). The reaction mixture was stirred at r.t. for 60 min. Thereafter, the reaction mixture was concentrated and purified by flash column chromatography (Merck silica gel 60, F254).

General Procedure for the Synthesis of Alkylidene Malonic Diesters

Compound **3a** was synthesized according to a procedure which was reported earlier.[3d] Compounds **3b–e** were synthesized as follows: To a solution of the respective aldehyde (5 mmol), AcOH (0.0601 g, 1 mmol), and piperidine (0.0852 g, 1 mmol) in toluene (25 mL) was added diethyl malonate (0.8009 g, 5 mmol). The reaction mixture was refluxed for 12 h during which the H_2O produced was removed with a Dean–Stark trap. Thereafter, the reaction mixture was concentrated under reduced pressure and the residue obtained was dissolved in EtOAc (20 mL), washed with H_2O, concentrated, and purified by flash column chromatography (Merck silica gel 60, F254) to give compounds **3b–e**.

General Procedure for the Reduction of Alkylidene Malonic Diesters

To the alkylidene malonic diester (0.5 mmol) in THF (2.0 mL) was added Hantzsch ester (0.1898 g, 0.75 mmol) and $TiCl_4$ (0.6 mL of 1 M $TiCl_4$ in CH_2Cl_2, 0.6 mmol). The reaction mixture was stirred at r.t. for 60 min, concentrated, and then purified by flash column chromatography (Merck silica gel 60, F254) to give compound **4**.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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