Asian Journal of Chemistry; Vol. 23, No. 7 (2011), 3101-3103

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in

Trifluoromethanesulfonic Acid as an Efficient Catalyst in the Reduction of Ketimines

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(*Received*: 21 September 2010; *Accepted*: 14 March 2011) AJC-9737

Trifluoromethanesulfonic acid was found to be highly efficient catalyst in the reduction of ketimines with Hantzsh esters as the hydrogen source. The catalyst loading could be decreased to 1 mol %. Moderate to excellent isolated yields (up to 99 %) were obtained under mild conditions.

Key Words: Trifluoromethanesulfonic acid, Reduction, Ketimines, Hantzsh esters.

INTRODUCTION

Trifluoromethanesulfonic acid (TfOH) is a versatile strong acid[1]. It was used in different organic transformations such as Friedel Crafts acylation, alkene coupling, [3+2] cycloaddition, benzylation of aromatics, Ritter reactions, *etc.*[2-9].

Imines reduction is one of the most straightforward way for the preparation of amines, an important building blocks for biologically molecules and drugs. In the past decades, remarkable progress has been made in the field. Various hydride reagents have been employed such as H_2, $NaBH_4$, $NaBH_3CN$, $NaBH(OAc)_3$, Cl_3SiH, $PhSiH_3$, *etc.*[10]. However, the utility of these hydride reagents suffer from drawbacks such as harsh experimental conditions, poor chemoselectivity and environmental problems.

Recently, the NADH-like Hantzsch esters have been reported as an inexpensive, readily available, non-toxic, practicable and versatile hydrogen source in organic synthesis[11]. They have been successfully used in the reduction of olefins, ketones as well as imines. In the field of imines reduction, several groups such as Rueping, List, MacMillan, Antilla, You and Du have made significant progresses[12-17]. However, to the best of our knowledge, there is no report about using trifluoromethanesulfonic acid as catalyst in the reduction of ketimines. Herein, we reported that the trifluoromethanesulfonic acid served as an efficient catalyst for the reduction of ketimines with Hantzsch esters as hydrogen source.

EXPERIMENTAL

General procedure for the synthesis of imines: A mixture of $NaHCO_3$ (50 mmol), amine (10 mmol), ketone (10 mmol) and activated molecular 4 Å sieves (8.0 g) in anhydrous toluene (50 mL) was heated at 80 ºC for 12 h in argon atmosphere. The mixture was filtered through celite. The filtrate was then evaporated *in vacuo* and the product was crystallized from appropriate solvents or purified by distillation to give pure imine.

General procedure for the catalytic reduction of imines: In an argon atmosphere, the imine **1** (0.20 mmol), Hantzsch dihydropyridine (0.28 mmol, 1.4 eq), TfOH (0.002 mmol, 0.01 eq) and toluene (4 mL) were stirred at 70 ºC for 16 h. Then sodium hydroxide solution (0.1 mol/L, 1 mL) was added to neutralize the acid. The mixture was extracted with ethyl acetate (3 × 15 mL). The organic phase was separated and concentrated *in vacuo*. The combined extracts was washed with brine, dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The residue was purified through column chromatography on silica gel (silica gel, hexane/EtOAc) to gave pure amine **2**.

Spectral data of the products

N-(4-Methoxyphenyl)-[1-phenyl-ethyl] amine (2a): ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.50 (d, *J* = 6.66 Hz, 3H), 3.68 (s, 3H), 4.40 (q, *J* = 6.66 Hz, 1H), 6.47 (d, *J* = 8.88 Hz, 2H), 6.69 (d, *J* = 8.88 Hz, 2H), 7.20 - 7.23 (m, 1H), 7.31 (t, *J* = 7.38 Hz, 2H), 7.36 (d, *J* = 7.2 Hz, 2H).

N-Phenyl-(1-phenyl-ethyl) amine (2b): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.54 (d, *J* = 6.72 Hz, 3H), 4.05 (brs, 1H), 4.51 (q, *J* = 6.72 Hz, 1H), 6.53 (m, 2H), 6.66 (m, 1H), 7.08-7.14 (m, 2H), 7.26 - 7.40 (m, 5H).

N-(4-Methoxyphenyl)-[1-(naphthalen-2-yl)-ethyl] amine (2c): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.60 (d, *J* = 6.71 Hz, 3H), 3.68 (s, 3H), 4.58 (q, *J* = 6.67 Hz, 1H), 6.56 (d, *J* = 8.96 Hz, 2H), 6.68 (d, *J* = 6.57 Hz, 2H), 7.43 - 7.53 (m, 3H), 7.78-7.83 (m, 4H).

N-Phenyl-[1-(naphthalen-2-yl)-ethyl] amine (2d): ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.65 (d, *J* = 6.72 Hz, 3H), 4.19 (brs, 1H), 4.71 (q, *J* = 6.54 Hz, 1H), 6.63 (d, *J* = 8.32 Hz, 2H), 6.72 (t, *J* = 7.14 Hz, 1H), 7.16 (t, *J* = 8.12 Hz, 2H), 7.49-7.54 (m, 2H), 7.57 (d, *J* = 8.46 Hz, 1H), 7.96-7.89 (m, 4H).

N-(4-Methoxyphenyl)-[1-(4-methoxy)phenyl-ethyl] amine (2e): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.52 (d, *J* = 6.69 Hz, 3H), 3.69 (s, 3H), 3.78 (s, 3H), 4.37 (q, *J* = 6.77 Hz, 1H), 6.55 (d, *J* = 8.83 Hz, 2H), 6.68 (d, *J* = 8.94 Hz, 2H), 6.83 (d, *J* = 8.64 Hz, 2H), 7.27 (d, *J* = 9.10 Hz, 2H).

N-Phenyl-[1-(4-methoxy)phenyl-ethyl] amine (2f): ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.56 (d, *J* = 6.72 Hz, 3H), 3.84 (s, 3H), 4.07 (brs, 1H), 4.52 (q, *J* = 6.72 Hz, 3H), 6.59 (d, *J* = 8.44 Hz, 2H), 6.72 (t, *J* = 7.32 Hz, 1H), 6.93 (d, *J* = 8.64 Hz, 2H), 7.17 (t, *J* = 8.04 Hz, 2H), 7.35 (d, *J* = 8.58 Hz, 2H).

N-(4-Methoxyphenyl)-[1-(4- bromo)phenyl -ethyl] amine (2g): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49 (d, *J* = 6.73 Hz, 3H), 3.70 (s, 3H), 4.36 (q, *J* = 6.73 Hz, 1H), 6.47 (d, *J* = 8.92 Hz, 2H), 6.70 (d, *J* = 8.94 Hz, 2H), 7.24 (d, *J* = 8.24 Hz, 2H), 7.43 (d, *J* = 8.89 Hz, 2H).

N-Phenyl-[1-(4- bromo)phenyl-ethyl] amine (2h): ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.48 (d, *J* = 6.82 Hz, 3H), 4.00 (brs, 1H), 4.42 (q, *J* = 6.84 Hz, 1H), 6.46 (d, *J* = 7.50 Hz, 2H), 6.65 (t, *J* = 7.30 Hz, 1H), 7.09 (t, *J* = 8.52 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 8.32 Hz, 2H).

N-(4-Methoxyphenyl)-[1-(4- chloro)phenyl-ethyl] amine (2i): ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.41 (d, *J* = 6.72 Hz, 3H), 3.62 (s, 3H), 4.30 (q, *J* = 6.72 Hz, 1H), 6.39 (d, *J* = 8.8 Hz, 2H), 6.61 (d, *J* = 8.94 Hz, 2H), 7.17 - 7.26 (m, 4H).

N-(4-Methoxyphenyl)-[1- phenyl-propyl] amine (2j): ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 7.38 Hz, 3H), 1.71-1.79 (m, 2H), 3.60 (s, 3H), 4.07-4.08 (m, 1H), 6.41 (d, *J* = 8.70 Hz, 2H), 6.60 (d, *J* = 8.82 Hz, 2H), 7.12-7.25 (m, 5H).

N-(4-Methoxyphenyl)-[3-methylbutan-2-yl] amine (2k): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.78 Hz, 3H), 0.96 (d, *J* = 6.88 Hz, 3H), 1.07 (d, *J* = 6.49 Hz, 3H), 1.78-1.88 (m, 1H), 3.22-3.30 (m, 1H), 3.74 (s, 3H), 6.53-6.58 (m, 2H), 6.75-6.80 (m, 2H).

N-Benzyl-(1-phenyl-ethyl) amine (2l): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (d, *J* = 6.50 Hz, 3H), 3.60 (d, *J* = 13.0 Hz, 1H), 3.67 (d, *J* = 13.00 Hz, 1H), 3.82 (q, *J* = 6.50 Hz, 1H), 7.08-7.38 (m, 10H).

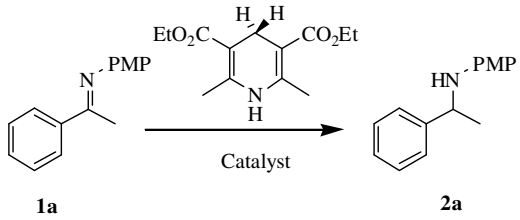
RESULTS AND DISCUSSION

The reduction of **1a** was used as a model reaction to test the efficiency of different sulfonic acids. Methanesulfonic acid and 4-nitrobenzenesulfonic acid catalyzed the transformation with the yield of 34 and 58 %, respectively. In comparison, trifluoromethanesulfonic acid gave much higher yield (73 %, entry 3, Table-1) under identical conditions. So trifluoromethanesulfonic acid was considered to be the best catalyst among them. To improve the yield, a serial reaction conditions sunch as solvent, temperature and catalyst loading were examined. As shown in Table-1, the solvents showed dramatic effect on the reaction (entries 3-6). Low yields were obtained (19 and 33 %, entries 4 and 5) when ether or acetonitrile was used. Toluene gave much higher yield (83 %, entry 6). The reaction temperature was also found to affect the reactivity greatly when the reaction was carried out in the toluene. Higher temperature could result in higher yield (entries 6-10). At 70 ºC, the best reactivity was obtained (98 %, entry 10). The lowest effective catalyst loading was found to be 1 mol %. Further lowering the catalyst loading to 0.5 mol % caused unacceptable loss of the reactivity (41 %, entry 13).

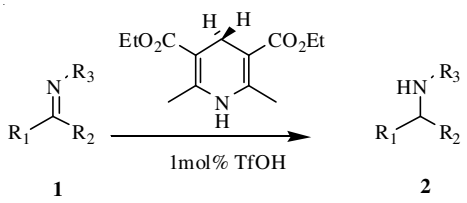
TABLE-1
EFFECTS OF DIFFERENT REACTION CONDITIONS ON THE REDUCTION OF KETIMINE **1a***

Entry	Catalyst	Catalyst loading (%)	Solvent	Temp. (ºC)	Yield (%)**
1	CH_3SO_3H	10	CH_2Cl_2	40	34
2	4-$NO_2C_6H_4SO_3H$	10	CH_2Cl_2	40	58
3	CF_3SO_3H	10	CH_2Cl_2	40	73
4	CF_3SO_3H	10	Et_2O	Reflux	19
5	CF_3SO_3H	10	CH_3CN	40	33
6	CF_3SO_3H	10	Toluene	40	83
7	CF_3SO_3H	10	Toluene	0	trace
8	CF_3SO_3H	10	Toluene	25	39
9	CF_3SO_3H	10	Toluene	60	90
10	CF_3SO_3H	10	Toluene	70	98
11	CF_3SO_3H	5	Toluene	70	98
12	CF_3SO_3H	1	Toluene	70	95
13	CF_3SO_3H	0.5	Toluene	70	41

*Unless specified otherwise, the reaction was performed at 0.2 mmol scale with 1.4 equiv. of Hantzsch esters and 10 mol % of the catalyst for 16 h. **Isolated yield based on the imine.



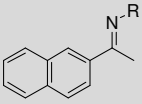
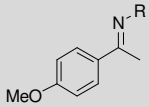
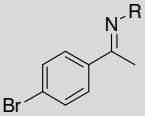
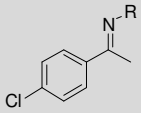
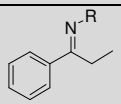
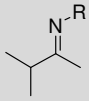
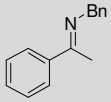
Structure of reductions of ketimine **1a**



Structure of reductions of ketimine **1**

Base on the optimal conditions, the generality of TfOH was explored. A series of ketimines (**1a-l**) including electron-rich and electron-deficient aromatic ketimines as well as the aliphatic ketimines were reduced with Hantzsch esters. As illustrated in Table-2, the desired products were obtained with moderate to excellent yields (67-99 %, Table-2) catalyzed by 1 mol % of TfOH at 70 ºC in toluene for 16 h. Especially, imines **1a**, **1c**, **1e**, **1g**, **1j**, **1k** with PMP groups in R^3 reacted well to give excellent yields (92-99 %, entries 1, 3, 5, 7, 10, 11, Table-2). Generally, the substrates with N-PMP group could be reduced with higher yield than those with N-phenyl group. In addition, the N-benzyl ketimines and with bulky group ketimine were also proven to be suitable substrates for the catalyst (69 and 99 %, entries 10 and 12, Table-2).

TABLE-2
REDUCTION OF KETIMINES **1** WITH TfOH*

Entry	Ketimines		Yield** (%)
1		**1a** R = PMP	95
2		**1b** R = Ph	93
3		**1c** R = PMP	93
4		**1d** R = Ph	85
5		**1e** R = PMP	92
6		**1f** R = Ph	89
7		**1g** R = PMP	95
8		**1h** R = Ph	85
9***		**1i** R = PMP	67
10		**1j** R = PMP	99
11		**1k** R = PMP	93
12***		**1l**	69

*Unless specified otherwise, the reaction was performed at 0.2 mmol scale with 1.4 equiv. of Hantzsch esters and 1 mol % of the catalyst for 16 h. **Isolated yield based on the imine. ***72 h reaction time.

Conclusion

In summary, a highly efficient catalyst is developed for the reduction of ketimines with Hantzsch ester for transfer hydrogenation. The catalyst loading can be decreased to 1 mol % and the yield was up to 99 %. The results extend the application of trifluoromethanesulfonic acid and provide a new efficient catalyst for reduction of ketimines.

ACKNOWLEDGEMENTS

The authors are grateful for the financial supports from the Youth Founds of Sichuan Province (2010JQ0048), Sichuan Education Department Project (09ZA110), Cultivating Talents Project of Xihua University (R0720523) and the Key Laboratory of Natural Medicine Research and Engineering, Xihua University (XZD0821-09-1).

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