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Catalyst-Free Reduction of Aldimines with Hantzsch Esters

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An efficient catalyst-free reduction of aldimines is reported. In the absence of any additional catalysts, a series of *N*-aromatic aldimines were reduced with Hantzsch esters as the hydrogenation source. Moderate to excellent isolated yields (up to 99 %) were obtained under mild conditions.

Key Words: Catalyst-free, Reduction, Aldimines, Hantzsch esters.

INTRODUCTION

The NADH-like Hantzsch esters was an inexpensive, readily available, non-toxic organoreductants, which has been successfully used in the reduction of olefins, ketones and imines[1-10]. In addition, the Hantzsch esters were also demonstrated suitable for the direct reductive amination in the presence of Brønsted acids and Lewis acids such as phosphoric acid, thiourea, Mg(II), $Sc(OTf)_3$, $ZnCl_2$ and so on[11-14]. In all these reported reductive reaction with Hantzsch esters, catalyst acids are absolutely necessary. The absence of acids lead to sluggish reaction or no products. However, the existence of acids made disadvantages of corrosivity and hard work-up. To the best of our knowledge, there is no report about catalyst-free reductive reaction with Hantzsch esters as hydrogen source.

Schreiner and co-workers[9] reported that the derivative of thiourea can catalyze reduction of aldimines with Hantzsch esters in a mild reaction conditions. According to the report, the aldimine was reduced in the absence of catalyst with trace products at room temperature. Considering the effects of substrate reactivity and reaction conditions, it is assumed that the protocol could be realized without the catalyst through optimizing reaction conditions. Herein, the catalyst-free reduction of aldimines with Hantzsch esters is reported.

EXPERIMENTAL

All starting materials were of the commercially available (analytical grade) and used without further purification. All solvents used in the reactions were distilled from appropriate drying agents prior to use. Reactions were monitored by thin layer chromatography using silica gel HSGF254 plates. Flash chromatography was performed using silica gel HG/T2354-92 or alumina. Melting poits were measured with SGW X-4 melting point apparatus. ^{1}H NMR (300 or 600 MHz) spectra were recorded in $CDCl_3$. ^{1}H NMR chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal st andard ($CDCl_3$, δ 7.26 ppm).

General procedure for the synthesis of aldimines: A mixture of $NaHCO_3$ (50 mmol), amine (10 mmol), aldehyde (10 mmol) and activated molecular 4Å sieves (8.0 g) in anhydrous toluene (50 mL) was heated at 80 ºC for 12 h under an 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 through column chromatography on alumina.

General procedure for the catalyst-free reduction of aldimines with Hantzsch esters: The aldimine 1 (1.0 mmol) and Hantzsch esters (1.1 eq) were stirred in toulene (8 mL) at 70 ºC under nitrogen atmosphere. After 24 h, the solvent was removed under reduced pressure and the residue purified through column chromatography on silica gel (hexane/EtOAc) to gave pure amine [2].

RESULTS AND DISCUSSION

Firstly, higher active aldimine **1b** was used to react with the Hantzsch esters at the same conditions. As expected, the better reactivity of the aldimine the higher yield was. The desired amine with 30 % yield is obtained (Table-1, entry 2) after 24 h, at the room temperature. Then, the reaction between aldimine **1b** and Hantzsch esters is carried out without catalyst at enhanced temperature. Much to our surprise, we got 88 % yield (Table-1, entry 3) after 24 h. Therefore, it is

TABLE-1
EFFECTS OF REACTION CONDITIONS ON THE REDUCTION OF ALDIMINE[a]

Entry	Aldimine	Solvent	Temperature (ºC)	Yield (%)[b]
1	**1a**	CH_2Cl_2	Room temperature	Trace
2	**1b**	CH_2Cl_2	Room temperature	30
3	**1b**	CH_2Cl_2	40	88
4	**1b**	EtOAc	40	42
5	**1b**	MeCN	40	48
6	**1b**	THF	40	20
7	**1b**	DMF	40	Trace
8	**1b**	Toluene	40	53
9	**1b**	Toluene	70	98

[a]Unless specified otherwise, the reaction was performed at 1.0 mmol scale with 1.1 equiv of Hantzsch esters for 24 h.
[b]Isolated yield based on the imine.

concluded that the aldimine can be reduced with Hantzsch esters in the absence of any additional catalysts.

To futher improve the yield, we screened various common solvents. As shown in Table-1, the yield was generally low when ethylacetate, acetonitrile, tetrahydrofuran, *N*,*N*-dimethyl formamide and toluene as solvents (entries 4-8, Table -1) at 40 ºC. However, the yield was increased to 98 % when the reaction was carried out at 70 ºC with the toluene as solvent (entry 9, Table-1).

In order to evaluate the generality of this protocol, various *N*-aryl aldimine (**1a-j**) were employed under optimal conditions. The results were summarized in Table-2. Generally, aldimines (**1b-e**) with PMP groups in R_1 reacted well to give excellent yields (95-99 %, entries 2-5, Table-2), including electron-rich, electron-deficient substituted aryl aldehydes. Aliphatic and heterocyclic aldimines can also be reduced with high yields (97 % and 85 %, entries 6-7, Table-2). Additionally, for the *N*-Ph and *N*-4-MePh aldimines, the amine products were obtained in very good yields (90 % and 98 %,entries 1 and 8, Table-2). But for the *N*-4-ClPh and *N*-Naph aldimines, the yields were moderate (71 % and 50 %, entries 9-10, Table-2). *N*-Bn ketimines was also investigated with this protocol, unfortunately, no product was obtained.

TABLE-2
CATALYST-FREE REDUCTION OF ALDIMINES[a]

Entry	Aldimine	R_1	R_2	Yield (%)[b]
1	**1a**	C_6H_5	C_6H_5	90
2	**1b**	PMP	C_6H_5	98
3	**1c**	PMP	4-Br-C_6H_4	99
4	**1d**	PMP	4-NO_2-C_6H_4	98
5	**1e**	PMP	4-MeO-C_6H_4	95
6	**1f**	PMP	2-furanyl	97
7	**1g**	PMP	*n*-C_4H_9	85
8	**1h**	4-Me-C_6H_4	C_6H_5	98
9[c]	**1i**	4-Cl-C_6H_4	C_6H_5	71
10[c]	**1j**	1-Naph	C_6H_5	50

[a]Unless specified otherwise, the reaction was performed at 1.0 mmol scale with 1.1 equiv. of Hantzsch esters in toluene (8 mL) for 24 h.
[b]Isolated yield based on the imine.
[c]40 h reaction time.

Spectral data of the synthesized compounds

***N*-Benzylbenzenamine (2a):** Yellowish liquid, 90 % yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.28 (s, 2H), 6.62-7.44 (m, 10H).

***N*-Benzyl-4-methoxybenzenamine (2b):** Yellowish liquid, 98 % yield; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.72 (s, 3H), 4.27 (s, 2H), 6.58-6.60 (m, 2H), 6.75-6.78 (m, 2H), 7.25 (t, *J* = 7.14 Hz, 1H), 7.31-7.36 (m, 4H).

***N*-(4-Bromobenzyl)-4-methoxybenzenamine (2c):** Yellowish solid, 99 % yield; m.p. 48-51 ºC; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.73 (s, 3H), 4.24 (s, 2H), 6.55-6.57 (m, 2H), 6.75-6.77 (m, 2H), 7.24 (d, *J* = 8.22 Hz, 2H), 7.44 (d, *J* = 8.22 Hz, 2H).

***N*-(4-Nitrobenzyl)-4-methoxybenzenamine (2d):** Red solid, 98 % yield; m.p. 92-94 ºC; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.73 (s, 3H), 4.42 (s, 2H), 6.53-6.56 (m, 2H), 6.75-6.78 (m, 2H), 7.53 (d, *J* = 8.82 Hz, 2H), 8.18 (d, *J* = 8.64 Hz, 2H).

***N*-(4-Methoxybenzyl)-4-methoxybenzenamine (2e)**: Yellowish solid, 95 % yield; m.p. 92-93 ºC; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.74 (s, 3H), 3.80 (s, 3H), 4.21 (s, 2H), 6.59-6.62 (m, 2H), 6.76-6.79 (m, 2H), 6.86-6.88 (m, 2H), 7.28 (d, *J* = 8.58 Hz, 2H).

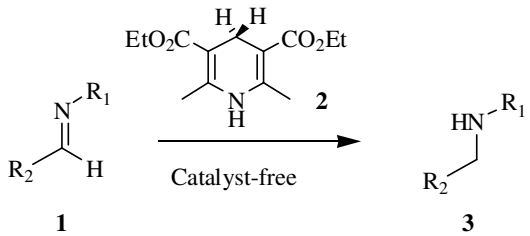
***N*-(Furan-2-ylmethyl)-4-methoxybenzenamine (2f):** Yellowish solid, 99 % yield; m.p. 44-45 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.75 (s, 3H), 4.27 (s, 3H), 6.22 (d, *J* = 3.12 Hz, 1H), 6.31 (d, *J* = 2.99 Hz, 1H), 6.64 (d, *J* = 8.85 Hz, 2H), 6.77 (d, *J* = 8.88 Hz, 2H), 7.36 (s, 1H).

***N*-Butyl-4-methoxybenzenamine (2g):** Yellowish liquid, 85 % yield; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.32 Hz, 3H), 1.39-1.45 (m, 2H), 1.56 - 1.61 (m, 2H), 3.06 (t, *J* = 7.38 Hz, 2H), 6.58 (d, *J* = 8.82 Hz, 2H), 6.77 (d, *J* = 8.82 Hz, 2H).

***N*-Benzyl-4-methylbenzenamine (2h):** Yellowish liquid, 98 % yield; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.16 (s, 3H), 4.23 (s, 2H), 6.49 (d, *J* = 8.34 Hz, 2H), 6.90 (d, *J* = 8.16 Hz, 2H), 7.12-7.29 (m, 5H).

***N*-Benzyl-4-chlorobenzenamine (2i):** Yellowish solid, 71 % yield; m.p. 42-43 ºC; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.22 (s, 2H), 6.48 (d, *J* = 8.82 Hz, 2H), 7.03 (d, *J* = 8.82 Hz, 2H), 7.18-7.27 (m, 5H).

***N*-Benzylnaphthalen-1-amine (2j)**: Yellowish solid, 99 % yield; mp 66-68 ºC; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.43 (s, 2H), 6.59 (d, *J* = 7.20 Hz, 1H), 7.17-7.77 (m, 11H).



1a R_1 = Ph, R_2 = Ph
1b R_1 = PMP, R_2 = Ph

Fig. 1. Reduction of aldimine

Conclusion

In summary, a highly efficient catalyst-free method for the reduction of aldimines with Hantzsch esters as hydrogen source is developed . With this protocol, a set of N-aromatic aldimines can be reduced with moderate to excellent yields in absence of any additional catalyst. Further investigations aimed

at direct reductive amination of aldehydes with Hantzsch esters without catalysts are in progress.

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