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Short Communication

MANDELIC ACID: ORGANOCATALYST FOR EFFICIENT SYNTHESIS OF SECONDARY AMINES FROM ALDEHYDES AND PRIMARY AMINES

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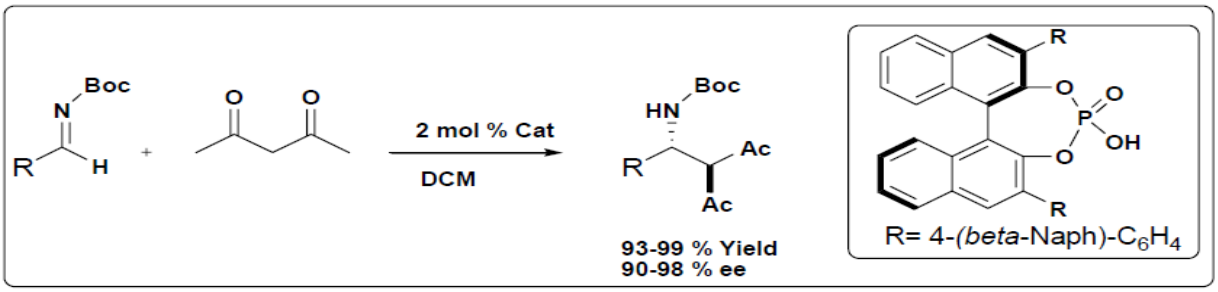
ABSTRACT

Mandelic acid was found to be gentle and efficient organocatalyst for the synthesis of diversified secondary amines from aldehydes primary amines via imine using Hantzsch DHP ester which act as a hydrogen source in one-pot manner under mild conditions. The green and inexpensive process described herein requires only catalytic amount of mandelic acid and provides quick access to the structurally diverse amines in high yields under mild conditions.

Keywords: Mandelic acid, Organocatalyst, Aldehydes, Primary amines.

1. INTRODUCTION

Since the rediscovery of asymmetric organocatalysis at the dawn of the new millennium, an exponential number of papers on this subject appeared throughout the years [1]. It generated several excellent reviews and books where various aspects of this field have been dissected [2, 3]. Broadly specking the organocatalysts can be classified into four main categories, viz. Lewis Base, Lewis Acid, Bronsted, Base, and Bronsted Acid Catalyst. The organocatalyst and organocatalysis has become recently one of the most powerful paradigms due to its wide substrate scope, good to excellent yield, excellent distereoselectivity, low cost and ready access etc. Bronsted acidic organocatalysis is another versatile type of organocatalysis. Several important organic reactions [4-6] such as Mannich, Michael, Aldol condensation and cycloaddition reactions have been successfully accomplished in good to excellent yield and stereos-electivity. For example, Terada et al. [7] reported an efficient and mild protocol for Mannich reaction and reductive amination reaction catalysed by organo-phosphoric acid [8] (scheme-1).



Scheme 1

Reductive amination of aldehydes and ketones, in which a mixture of a carbonyl compound and an amine is treated with a reductant in a "one-pot" fashion, is one of the most useful methods for the preparation of secondary or tertiary amines and related functional compounds [9]. The amines are structural element in a multitude of biologically active natural products and pharmaceuticals and therefore their synthesis has become an objective of high priority from the perspective of medicinal chemistry and organic synthesis [10]. The most commonly employed procedures for reductive aminations of carbonyls utilizes metal hydrides such as $NaBH_3CN$, $NaBH_4$ as reducing agents [11] and rely on Bronsted or Lewis acids for selective activation of imine in the presence of carbonyls. However these methods suffer from the limitations such as

incompatibility with acid labile functionalities, use of dangerous and or expensive catalysts, difficulties in handling and excess use of amines. To avoid these drawbacks, one of the best alternatives is to apply organoreductant that possesses excellent reproducibility. In recent years, the natural product enzyme cofactor NAD(P) and NAD(P)H have been a motivation for the investigation of use of Hantzsch ester and other 1,4-dihydropyridine derivatives as attractive biomimetic reducing agent for the applications in synthetic and physical organic chemistry [12]. This theoretical design of biochemical hydride reduction, wherein an enzyme and cofactor are replaced by catalysts and dihydropyridine analogues respectively, has been employed in chemical reduction of many double bond containing compounds [13-15].

The Hantzsch esters has been reported to be efficient biomimitic reducing agent for the reductive amination of aldehydes and ketones in the presence of Lewis acids such as Mg (II) [16], SiO_2 [17], Al_2O_3 [18] and $Sc(OTf)_3$ [19] also in presence of molecular iodine [20]. In addition, Bronsted acid has also reported to be effective catalyst for this transformation. Menche *et al*. reported the use of Hantzsch ester and thiourea as novel reagent-catalyst combination for a mild and selective reductive amination of aldehydes [21] and ketones [22, 23].

2. PRESENT WORK

A plethora of methods are available in the literature for reductive amination process and many of them offer a simple access to the structurally diverse amines in high yields under mild conditions. But, some of these methods involve the use of costly metal triflate or hazardous Lewis or protic acid catalysts and other require extreme use of one or more reagents and heating for longer time. In view of the inexpensive and environmental concern in modern organic and medicinal chemistry research, there is still need to increase further milder, efficient, economical and environmentally benign practice for the reductive amination of aldehydes. The organic acids such as mandelic acid are inexpensive, easily available and environmentally benign in nature. Till date, the potential of mandelic acid as mild organocatalyst has not been tested very much in organic synthesis. We thought it is valuable to discover the potential of mandelic acid for the development of mild and environmentally benign protocol for the reductive amination of aldehydes leading to the highly important secondary amines. The present work deals with development of an efficient and mild reductive amination of structurally diverse aldehydes using DHP ester as a biomimetic hydride transfer agent.

3. RESULTS AND DISCUSSION

We started our investigation with the reductive amination of benzaldehyde and p-toluidine as a model reaction. The reaction was carried out using equimolecular amount of aldehyde, amine and Hantzsch ester in the presence of varying amount of mandelic acid catalysts in THF at room temperature, (scheme 1). The results are summarized in table 1. In the absence of catalyst, the reaction hardly proceed which obviously justifies the requirement of the catalyst to carry out of the reaction further. However, using catalytic amount of mandelic acid the reaction proceeds smoothly and best result was obtained using 15 mol % of catalyst.

Table 1: Reductive amination of benzaldehyde and p-toluidine catalysed by mandelicacid[a]

Entry	Mandelic acid (mol%)	Time (h)	Yield (%)[b]
1	None	24	Trace
2	2.5	12	72
3	5	12	78
4	10	10	85
5	15	10	92
6	**15**	**10**	**95[c]**
7	15	10	86[d]

[a] Reaction conditions: Benzaldehyde (1.0 mmol), p-toluidine (1.0 mmol) and Hantzsch ester (1.0 mmol) in the presence of mandelic acid in THF at room temperature. [b] Isolated yields.[c] Hantzsch ester (1.1mmol), [d]4-Phenyl-1,4-Dihydropyridine ester was used as a reducing agent.

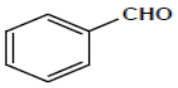
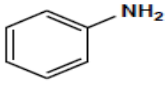
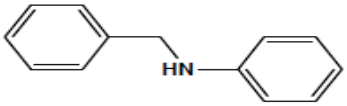
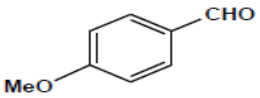
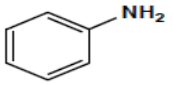
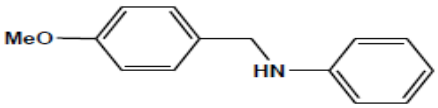
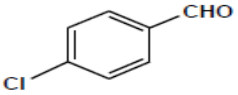
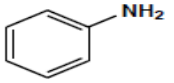
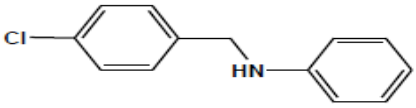
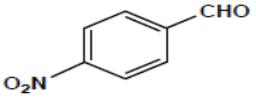
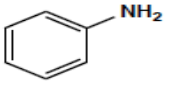
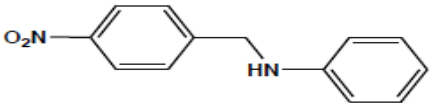
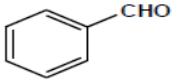
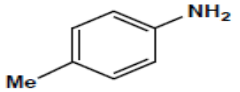
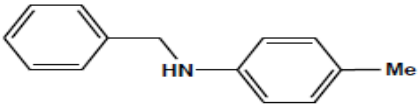
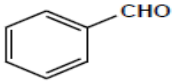
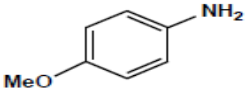
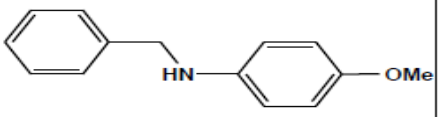
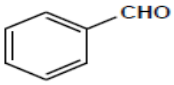
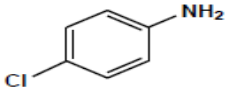
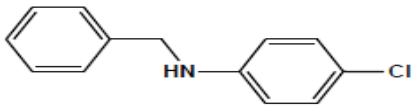
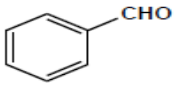
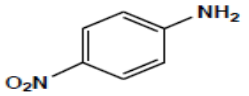
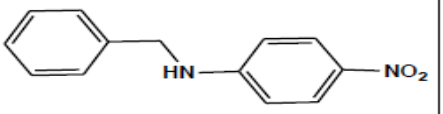
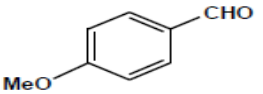
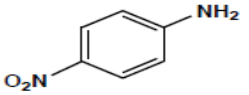
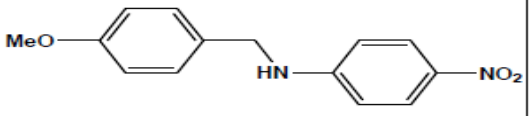
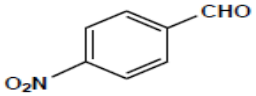
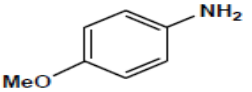
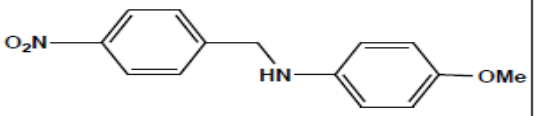
As an alternate reducing system, another dihydropyridine ester, 4-phenyl 1,4-dihydropyridine (table 1, entry 7) was investigated but it was found to be less effective and provided the product in considerably lower yield than with parent ester.

Thus the present study revealed that the best reaction conditions were 1 equiv of aldehyde, 1 equiv of amine and 1.1 equiv of Hantzsch ester in the presence of 15 mol % of mandelic acid in THF at room temperature for 10h. In order to explore the scope and generality of

the present reaction conditions, structurally diverse aldehydes and amines were employed to reductive amination using our optimized reaction conditions, (scheme 2).

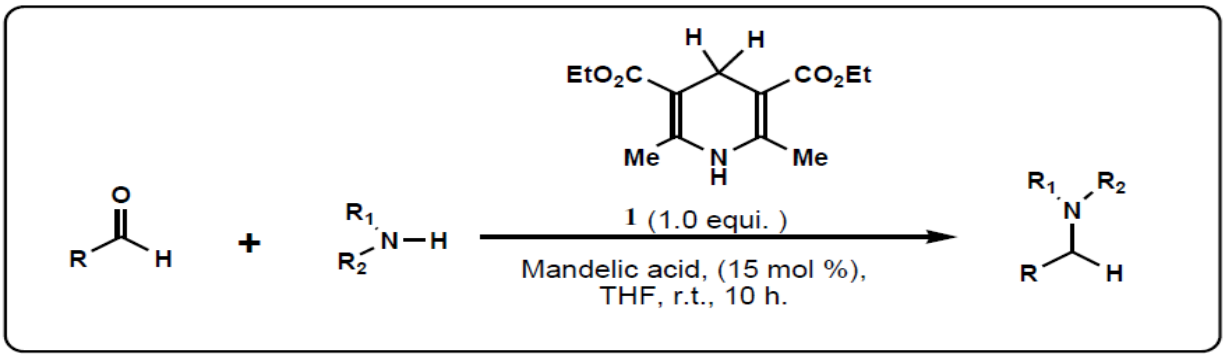
The results are summarized in table 2. In all example studied, the desired amines were obtained in high to excellent yields in acceptable reaction time. Aromatic aldehydes bearing both electron releasing (table 2, entry 2) as well as electron withdrawing group (table 2 entry 4) participated successfully in the reductive amination. Structurally diverse aromatic amines were investigated under present reaction conditions. Electron rich (table 2 entries 5 & 6) as well as electron deficient amines (table 2 entry 8) reacted efficiently under present reaction conditions to give good to high yields of the products. Methoxybenzaldehyde and nitroaniline gives high yield (table 2 entry 09) also, nitrobenzaldehyde and methoxyaniline gave high yield as mention (table 2 entry 10). Thus the present procedure has broad scope and diversity extension through structural variation can be achieved in one-pot manner.

Table 2: Scope of various aldehydes and amines in reductive amination catalysed by Mandelic acid[a]

Entry	Aldehyde	Amine	Product	Yield(%)[b]
01				85
02				90
03				88
04				80
05				95
06				96
07				89
08				84
09				80
10				84

[a] *Reaction conditions: 1.0 mol of aldehyde, 1.0 mol of amines and 1.1 mol of DHP ester in the presence of 15 mol% Mandelic acid in THF at room temperature for 10h.* [b] *Isolated yields*

The mild reaction conditions described herein are evident by the fact that acid sensitive functionalities such as nitro, halides, and alkoxy group both on aldehydes as well as amines were well tolerated. It is important to note thatmandelic acid is readily available, green and cheap catalyst and requires in low catalytic amount. The 1,4-Dihydropyridine esters **1**, can be synthesized at a great ease on large scale by Hantzsch condensation reaction [24].



Scheme 2

4. EXPERIMENTAL

4.1. General consideration

All the solvents were redistilled before used. Analytical TLCs were performed on Merck silica gel 60F254 plates. The amines, aldehydes and other chemicals were purchased from SD Fine Chemicals Ltd.

4.2. General procedure

To a mixture of aldehyde (1.0 mmol), amine (1.0 mmol) and Hantzsch dihydropyridine ester **1** (1.1 mmol) in THF 10 ml was added mandelic acid (15 mol %) and resulting mixture was stirred at room temperature for 10h. After completion of reaction (TLC), the mixture was washed with $NaHCO_3$ and brine and finally with water. After drying over anhydrous $NaSO_4$, solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel using petroleum ether-ethyl acetate as eluent to give analytically pure products in 80-96% yields.

4.3. Spectral data

4.3.1. N-(4-chlorobenzyl)-aniline

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.087 (br, 1H), 4.33 (s, 2H), 6.63-6.65 (d, 2H), 6.74-6.78 (t, 1H), 7.19-7.27 (t, 2H), 7.33(s, 4H)

4.3.2. N-(p-Nitrobenzyl)-p-anisidine

^{1}H NMR (400 MHz, $CDCl_3$) δ= 3.74 (s, 3H), 4.41 (s, 2H), 6.56(d, 2H), 6.75 (d, 2H) 7.54 (d, 2H), 8.20 (d, 2H).

5. CONCLUSION

In conclusion, we have developed a mild, high yielding and green protocol for the direct reductive amination of aldehydes using readily available Hantzsch ester as a biomemitic reducing agent in the presence of catalytic amount of mandelic acid. Though currently we have investigated the reductive amination of aldehydes only, the detail investigation as regard to applicability of the reaction conditions for ketones would be undertaken in our laboratory.

Conflict of interest

None declared

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