

Highly Efficient One-Pot Three-Component Mannich Reaction Under Solvent-Free Conditions

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Abstract. A mild and practically-convenient one-pot procedure for the direct Mannich reaction has been developed using a condensation of amines, aldehydes and unmodified ketones under solvent free conditions in the presence of ZnI_2 with good to excellent yields. The present methodology offers several advantages, such as excellent yields, simple procedures, short reaction times and milder conditions with very small amounts of catalyst. Furthermore, it is the first time that the catalytic activity of several catalysts under solvent free conditions has been studied. It was found that both the diastereoselectivity and the rate of reaction were improved with various Lewis acids and metal oxides. However, the chiral catalysts, such as L-cystine, (-)-cinchonidine and L-proline, did not work well in terms of yield and diastereoselectivity under this condition.

Keywords: Amine; Aldehyde; Catalyst; Mannich reaction; Solvent-free.

INTRODUCTION

The development of solvent-free organic synthetic methods has become an important research area, aiming to make the syntheses simpler, to save energy and to prevent hazardous solvent waste and toxicity in chemical processes. Many organic solvents are ecologically harmful and their use should, therefore, be minimized as far as possible or even avoided altogether [1,2].

Mannich type reactions are among the most important carbon-carbon bond forming reactions in organic synthesis [3]. They provide β -amino carbonyl compounds which are important synthetic intermediates for various pharmaceuticals and natural products [4]. The increasing popularity of the Mannich reaction has been fueled by the ubiquitous nature of nitrogen containing compounds in drugs and natural products [5]. There are several elegant reports on the use of organocatalysis in the asymmetric Mannich reaction of aldehydes with unmodified ketones and

amine in one-pot [6-9]. However, by using known Lewis acid and organocatalysis in the Mannich reaction in an organic solvent [10-15] or water [16-25], the yields obtained were only moderate, even with high catalyst loadings. Surprisingly, there are no reports on solvent-free Mannich reactions in the literature. Thus, expanding the scope of a Lewis acid catalysis under solvent-free conditions in an unmodified Mannich reaction is a useful and challenging objective.

RESULTS AND DISCUSSION

In continuation of our research interest in developing a green organic chemistry, by using water as the reaction medium [22,26] or by performing organic transformations under solvent-free conditions [27-31], we herein report an efficient, environmentally benign direct Mannich reaction under mild conditions. In this report, the Mannich reaction was carried out under a cleaner reaction condition in the presence of a small amount of ZnI_2 at room temperature; reducing the amount of waste by omitting any solvent, with good yields and a relatively high diastereoselectivity, with a very simple workup procedure (Scheme 1).

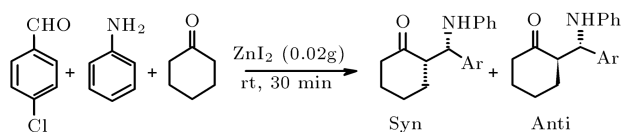
Initially, the three-component Mannich reaction of 4-chlorobenzaldehyde (3.0 mmol), aniline (3 mmol), and cyclohexanone (5 mmol) was examined. As a

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Scheme 1. ZnI_2 catalyzed Mannich reaction.

preliminary study, several Lewis acids were screened in the model reaction. The results of an extensive Lewis acid screening study and the optimization of several reaction conditions at room temperature are shown in Table 1. It was found that both the diastereoselectivity and the rate of the reaction were improved when various Lewis acids, such as $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, CsCl , CsBr , MgClO_4 , LiClO_4 , SbF_3 , ZrCl_4 , $\text{RuCl}_3 \cdot 7\text{H}_2\text{O}$, MgF_2 , $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ and $\text{MnCl}_2 \cdot 2\text{H}_2\text{O}$, were used at ambient temperature (Table 1). Furthermore, a slight improvement in diastereoselectivity and yield were

observed when the reaction was carried out in the presence of heteropoly acids, such as $\text{H}_3\text{PMo}_{12}\text{O}_{40}$ and $\text{H}_3\text{PW}_{12}\text{O}_{40}$, and metal oxides, such as Nd_2O_3 , La_2O_3 , SiO_2 and Al_2O_3 , under solvent-free conditions at room temperature. An interesting observation was that chiral catalysts, such as L-cystine, (-)-cinchonidine and L-proline, did not work well in terms of yield and diastereoselectivity under this condition. The diastereoselectivity of the reaction was determined by ^1H NMR analysis of the crude products and by comparison with those reported in the literature. In general, anti selectivity was observed for all of Lewis acids, the chiral catalyst and the metal oxide under solvent-free conditions. After a survey of different reaction conditions, the best results obtained for the Mannich reaction were in the presence of ZnI_2 (0.02 g) at room temperature with relatively good diastereoselectivity.

The scope and generality of the present method were investigated by performing Mannich reactions with various aldehydes and aromatic amines under optimum conditions. The three-component Mannich reactions proceeded smoothly in the presence of 2 mol% of ZnI_2 at room temperature, to give the corresponding products a good yield (Table 2). Various aromatic aldehydes bearing different substitutes, such as OMe, Cl and NO_2 , on the benzene ring and thiophene carbaldehyde were suitable for this reaction. Aromatic amines bearing Me, Cl, Br, isopropyl and n-butyl on the benzene ring were favorable to this reaction. However, it was observed that the ZnI_2 had no catalytic activity for the Mannich reaction when aliphatic aldehydes, such as isobutyraldehyde, and aliphatic amines, such as benzylamine, were used as substrates.

Table 1. The results of using different promoter in solvent-free Mannich reaction.

Entry	Catalyst (0.02 g) ^a	Yields	Syn: Anti ^b
1	-	45	40:60
2	-	78 ^c	42:58
3	$\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$	82	35:65
4	$\text{CeCl}_3 \cdot 7\text{H}_2\text{O}/\text{NaI}$	85	35:65
5	CSCl	80	30:70
6	CSBr	85	22:78
7	MgF_2	64	28:72
8	MgClO_4	80	23:77
9	LiClO_4	68	25:75
10	LiClO_4	64 ^d	37:63
11	SbF_3	55	32:68
12	Nd_2O_3	72	32:68
13	La_2O_3	60	26:74
14	SiO_2	75	28:72
15	Al_2O_3	78	29:71
16	$\text{MnCl}_2 \cdot 2\text{H}_2\text{O}$	72	32:68
17	$\text{RuCl}_3 \cdot 7\text{H}_2\text{O}$	70	28:72
18	$\text{H}_3\text{PW}_{12}\text{O}_{40}$	88	32:68
19	$\text{H}_3\text{PMo}_{12}\text{O}_{40}$	84	30:70
20	$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$	82	39:61
21	$(\text{Cp})_2\text{TiCl}_2$	78	32:68
22	L-Cystine	80	26:74
23	(-)-Cinchonidine	60	28:72
24	L-Proline	58	36:64
25	ZrCl_4	90	66:34
26	ZnI_2	95	36:64

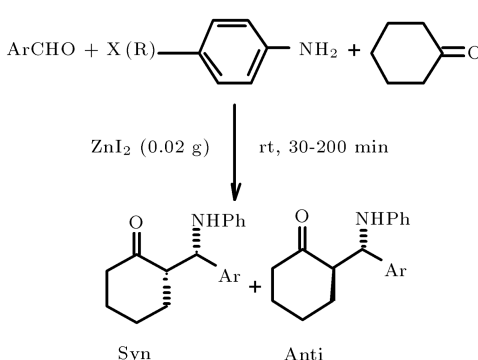
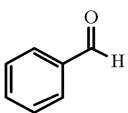
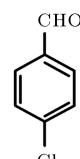
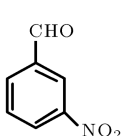
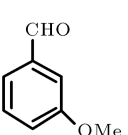
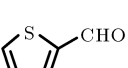
a: For 3 mmol scale reaction; b: Based on ^1H NMR;
c: Reaction run at 70°C; d: 0.1 g LiClO_4 was used.

CONCLUSION

A one-pot three-component strategy combined with a high-throughput screening of a catalyst has been successfully applied to practical simple catalysts for a directed Mannich reaction. The present catalytic system provides an attractive protocol for various biologically active β -aminoketones in terms of the following features:

- (i) The chemicals are all inexpensive and readily available;
- (ii) The reaction shows enhanced diastereoselectivity and yields when the amount of catalyst is reduced;
- (iii) The reaction is environmentally benign and energy-saving because of solvent-free and room-temperature reaction conditions;
- (iv) Exceptionally low catalyst loading (0.02 g) is sufficient to achieve high product yields.

Table 2. One-pot Mannich reaction under solvent-free conditions.

Entry	Aldehydes	Amines	Syn:Anti	Yields
				
1		X=Cl	35:65	80
2		X=Br	28:62	85
3		R=H	40:60	90
4		R=CH ₃	42:58	90
5		R=n-Bu	38:62	88
6		R=Iso-propyle	45:55	85
7		R=OMe	42:58	82
8		X=Cl	40:60	75
9		X=Br	30:70	78
10		R=H	42:58	86
11		R=CH ₃	44:66	80
12		R=n-Bu	36:64	82
13				
14		X=Cl	45:55	90
15		R=H	40:60	96
16		R=CH ₃	48:62	94
17		X=Cl	42:58	70
18		R=H	28:62	84
19		R=CH ₃	30:70	72
20		X=Cl	42:58	78
21		R=H	40:60	82

EXPERIMENTAL SECTION

General

All chemicals were obtained from commercial suppliers and used without further purification. Anhydrous conditions are not required for the reaction. NMR spectra were recorded on a Bruker

ACF 500, using CDCl₃/CCl₄ or CDCl₃/DMSO-d₆ as the solvent. Column chromatography was performed on silica gel, Merck grade 60. Ethyl acetate, petroleum ether and water were distilled before use. The reactions were carried out at room temperature and all aldehydes, ketones, amines and catalysts employed are commercially available.

Preparation of Catalyst

All catalysts are commercially available, purchased from commercial suppliers and used without further purification.

Effect of Catalyst

The effect of different catalysts on the yield of the Mannich reaction is given in Table 1. As shown in the table, both reactivity and selectivity were strongly influenced by the catalyst. Reactions without a catalyst give very low yields and, furthermore, in the organic solvent, a large excess of catalyst (20 mol%) was needed to present the desired products after a long reaction time. When the reactions were carried out under solvent free conditions, a very small amount of catalyst was needed for completion after a short reaction time.

General Procedure

A catalyst (0.02 g) was added to the mixture of cyclohexanone (5 mmol), aldehyde (3 mmol) and aromatic amine (3 mmol) in a test tube. The mixture was stirred at room temperature for an appropriate time until the reaction mixture was solidified. The resulting mixture was washed with water to recover the catalyst, and the crude product was presented. The crude product was purified via recrystallization or chromatography to give the corresponding compounds. All compounds were characterized on the basis of their spectroscopic data (IR, NMR, MS) and by comparison with those reported in the literature.

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