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Original Research Article

Organocatalytic enantioselective one-pot synthesis of *β*-aminoketones *via* Mannich reaction

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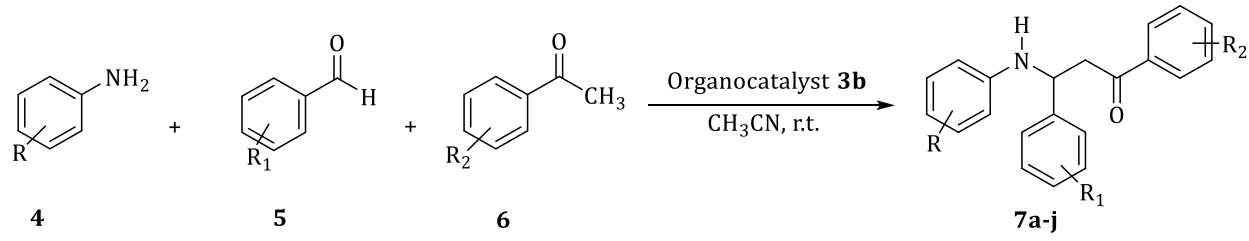
ABSTRACT

An effective protocol for the asymmetric synthesis of *β*-amino carbonyl compounds using pyrrolidine based organocatalyst has been developed *via* one-pot three-component Mannich reaction. The organocatalyst (S)-*N*-(2,4-dinitrophenyl) pyrrolidine-2-carboxamide **3b** confirmed to be the superior organocatalyst in solvent acetonitrile to obtain corresponding products in up to 89% yield and with excellent *ee* (90%). This organocatalytic reaction reveals productive result with a range of other aldehydes. Aromatic aldehydes having electron withdrawing substituent show the best results. Excellent yields, high enantioselectivity, mild reaction condition, and simple experimental work-up procedure are some of the advantages of this method.

Graphical Abstract



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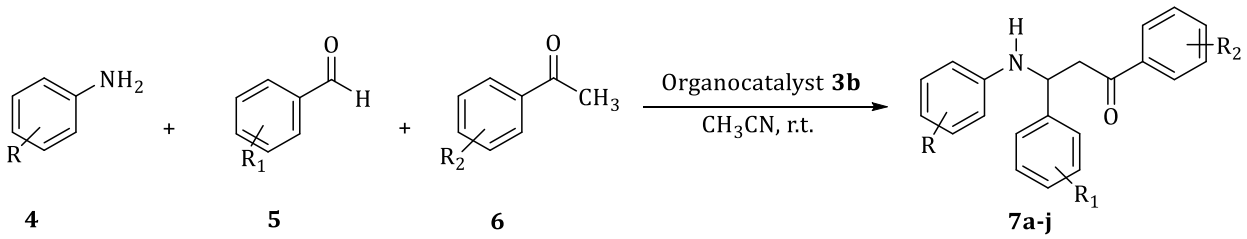
Introduction

Mannich reaction is one of the most important reactions in synthetic organic chemistry [1] which forms the carbon-carbon bond. Mannich reaction is usual method for the synthesis of *β*-amino carbonyl compounds, which are key intermediates in the production of several nitrogen containing natural products and pharmaceuticals [2]. Enantioenriched *β*-amino carbonyl compounds, which are extremely useful chiral building blocks and intermediates in organic synthesis [3–5] are efficiently prepared by the catalytic asymmetric Mannich reaction. Direct three-component Mannich reaction do not need the tedious preparation of enolates or imines as like in the indirect asymmetric two-component Mannich reaction; as an outcome they have received increasing interest. Although huge development has been made in direct three-component Mannich reactions in controlling stereoselectivity by using chiral organometallic [6–9] and organocatalysts [10–14]. Various approaches were developed for the synthesis of *β*-aminoketones *via* Mannich reaction [15–22]. Thus, there is still need for the enhancement of an effective method for the asymmetric Mannich reaction.

Therefore, in continuation of our work in enantioselective organocatalytic synthesis [23–25], herein we describe an efficient method for highly enantioselective Mannich reaction using a chiral pyrrolidine based organocatalyst under ambient temperature condition (Scheme 1).



Scheme 1.

Experimental

Materials and methods

All solvents were employed as commercial anhydrous grade without further purification. The column chromatography was carried out over silica gel (100-120 mesh). Melting points were determined in open capillary tube and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz spectrometer in $CDCl_3$ solvent. Mass spectra were taken on Polaris-Q Thermo scintific GC-MS. Enantiomeric purity is determined on waters alliance 2695 separation module HPLC systems.

General procedure for synthesis of β-amino carbonyl compounds via Mannich reaction

In a round-bottom flask, aromatic aldehydes (1 mmol), and aromatic amines (1 mmol) in acetonitrile (15 mL) were mixed and stirred for half an hour at room temperature in presence of organocatalyst (10 mol%). Then acetophenone (1 mmol) was added to the reaction mixture and stirred at room temperature for appropriate time. After reaction completion indicated by TLC, the reaction mixture was diluted with 50 mL of water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, concentrated, and the resulting residue was purified by column chromatography using silica gel mesh 80-120 to offer pure product.

3-(4-chlorophenylamino)-1-(4-chlorophenyl)-3-(4-hydroxyphenyl)propan-1-one (7c)

IR (KBr) (ν_{max}/ cm^{-1}): 785.2, 840.4, 1290.1, 1385.6, 1680.7, 2919.1, and 3423.32. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86-7.82 (m, 4H), 7.41-7.30 (m, 4H), 6.98-6.94 (m, 4H), 5.48 (s, 1H, OH), 4.90 (d, 1H, J = 5.6 Hz), 4.35 (s, 1H, NH), 3.40 (d, 2H, J = 6.8 Hz,). ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.6, 155.8, 146.2, 140.2, 138.0, 135.2, 131.5, 129.0, 127.8, 126.9, 120.6, 114.9, 112.4, 71.8, 55.8. MS: m/z 380.6 (M^+) obtain; expected 385.06; HPLC: 88% *ee*. [Determined by chiral HPLC using chiral cel OD-H, *n*-hexane: ethanol: diethylamine (95:5:0.1), flow rate 1.0 mL/min, λ= 288 nm; tR (minor) = 4.50 min, tR (major) = 5.20 min].

3-(4-chlorophenylamino)-1-(4-chlorophenyl)-3-(4-hydroxy-3-methoxyphenyl)propan-1-one (7d)

IR (KBr) (ν_{max}/ cm^{-1}): 747.6, 828.5, 1277.7, 1385.6, 1624.1, 2850, 2919.1, and 3423.7. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (m, 2H), 7.41 (m, 2H), 7.36-7.30 (m, 4H), 7.19-7.15 (m, 3H), 5.25 (s, 1H, OH), 4.72 (s, 1H), 4.35 (s, 1H, NH), 4.04 (s, 3H, OCH_3), 3.35 (d, 2H, J = 6.6 Hz,). ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.8, 153.2, 148.0, 144.8, 140.2, 138.3, 135.6, 130.8, 129.0, 127.8, 123.4, 121.0, 117.2, 115.0, 111.4, 70.8, 57.2, 52.8. MS: m/z 410.1 (M^+) obtain; expected 415.07 (M^+); HPLC: 86% *ee*. [Determined by chiral HPLC using chiral cel OD-H, *n*-hexane: ethanol: diethylamine (95:5:0.1), flow rate 1.0 mL/min, λ= 288 nm; tR (minor) = 4.50 min, tR (major) = 5.20 min].

Results and Discussion

The procedures for preparing pyrrolidine based chiral organocatalysts **3a–c** were outlined in Scheme 2. First, commercially available Boc-*L*-proline reacted with cyanuric chloride in ethyl acetate solvent and then amine was added and the mixture was left stirring for at least an additional 60 min. The solid was then filtered and rinsed with small amount of ethyl acetate. The filtrate was wash with 20 mL of 1 M NaOH. The bottom organic layer is extracted with distilled water. The resulting product

Scheme 2. Reagent and conditions: a) cyanuric chloride, ethyl acetate, Et_3N, R_1-NH_2, r.t.; b) TFA, DCM, 0 °C

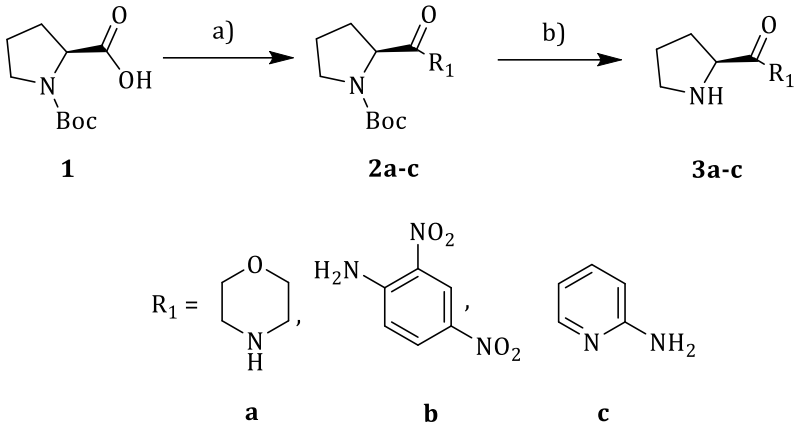


Table 1. Effect of catalysts and solvents on Mannich reaction

Entry	Organocatalyst	Solvent	Mol%	Time (h)	Yield[a] (%)	*ee*[b]
1	**3a**	DCM	10	48	40	38
2	**3b**	DCM	10	32	62	60
3	**3c**	DCM	10	38	45	44
4	**3b**	Toluene	10	30	58	48
5	**3b**	MeCN	10	20	89	90
6	**3b**	THF	10	36	59	52
7	**3b**	Neat	10	40	42	40
8	**3b**	MeCN	12	20	88	90
9	**3b**	MeCN	15	20	86	88
10	**3b**	MeCN	-	48	38	35

[a] Isolated yields

[b] Determined by chiral HPLC

was then digested in ether. After, the *N*-Boc protecting group was removed to get pyrrolidine based chiral organocatalysts **3a–c**.

Initially a set of experiments were performed by the model reaction of *p*-methyl aniline, *p*-nitrobenzaldehyde and *p*-chloroacetophenone using several solvent in the presence of 10 mol% of organocatalysts (**3a–3c**) to offer the corresponding product **7a**. The results obtained are listed in Table 1. In presence of organocatalyst **3a**, the reaction completed in 48 h with 38% yield in solvent DCM (Table 1, entry 1). The model reaction with organocatalyst **3b** in solvent DCM afforded 52% yield and 50% *ee* in 32 h (Table 1, entry 2). When the reaction was performed in solvent DCM with organocatalyst **3c**, we got desired product in 38 h with 48% yield (Table 1, entry 3). Further the model reaction is carried out in solvent toluene with organocatalyst **3b** which offered 48% yield and 48% *ee* (Table 1, entry 4). However, the superior result was observed when the reaction was

performed in solvent acetonitrile using organocatalyst **3b**; 89% product yield was obtained with 90% *ee* in 20 h (Table 1, entry 5). Again we perform the same reaction with organocatalyst **3b** in solvent THF which offer 59% yield in 36 h (Table 1, entry 6) and without solvent the reaction afforded poor results (Table 1, entry 7).

From this study, we have decided to perform next optimization in solvent acetonitrile with organocatalyst **3b**. So considering acetonitrile as best solvent, the effect of catalytic amount was studied. There was no considerable effect of increase in amount of catalyst, for 12 mol% and 15 mol%, the reaction gave almost similar results as compared with 10 mol% (Table 1, entries 8 and 9). In absence of catalyst, the reaction gave low product yield with extended reaction time (Table 1, entry 10).

Optimistic by these results, we screened a variety of aromatic aldehydes with substituted aniline and substituted acetophenone and in each case we observed good to excellent yields as well as enantioselectivity. The results are shown in Table 2.

Table 2. One-pot three component Mannich reaction[c]

Entry	R	R_1	R_2	Time (h)	Products	M.P. (°C)	Yield[a] (%)	*ee*[b]
1	4-Me	4- NO_2	4-Cl	20	**7a**	193-194	89	90
2	H	H	4-Cl	22	**7b**	118-120[19]	86	87
3	4-Cl	4-OH	4-Cl	20	**7c**	178-180	88	88
4	4-Cl	3-OMe,4-OH	4-Cl	23	**7d**	172-174	90	86
5	4-OMe	H	H	22	**7e**	160-162[15]	84	88
6	H	H	H	19	**7f**	166-167[15]	82	87
7	4-NO_2	H	H	20	**7g**	182-183[19]	84	85
8	H	4-Cl	H	22	**7h**	115-116[16]	85	89
9	H	H	4-NO_2	21	**7i**	144-145[19]	89	86
10	H	H	4-Me	23	**7j**	135-136[19]	83	89

[a] Isolated yields

[b] Determined by chiral HPLC

[c] Progress of reaction was determined by thin layer chromatography

Conclusions

In conclusion, we have developed a new efficient protocol for the asymmetric synthesis of *β*-amino carbonyl compounds *via* Mannich reaction. Several organocatalysts (**3a–3c**) were used to study the Mannich reaction. The organocatalyst (S)-*N*-(2,4-dinitrophenyl) pyrrolidine-2-carboxamide **3b**

confirmed to be the superior organocatalyst in solvent acetonitrile to obtain corresponding product **7a** in up to 89% yield and with excellent *ee* (90%). This organocatalytic reaction reveals productive result with a range of other aldehydes. Aromatic aldehydes having electron withdrawing substituent show the best results. Mild reaction conditions and high yields with excellent enantioselectivity with a wide range of substrates are some striking features of the reaction.

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Disclosure Statement

No potential conflict of interest was reported by the authors.

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