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Highly Selective Synthesis of β-Amino Carbonyl Compounds over ZSM-5-SO_3H under Solvent-free Conditions

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ZSM-5-SO_3H efficiently catalyzed the one-pot three-component Mannich reaction of aldehydes, anilines, and ketones. β-Aminocarbonyl compounds were obtained in reasonable yields and excellent stereoselectivities when the reaction was carried out at room temperature under solvent-free conditions. Simple experimental conditions and product isolation procedure makes this protocol potential for the development of clean and environment-friendly strategy for the synthesis of β-amino-ketones. The catalyst was recovered and reused for subsequent runs.

Key Words : Mannich-reaction, β-Amino carbonyl compound, ZSM-5-SO_3H, Solvent-free

Introduction

β-Amino carbonyl compounds are the extremely important precursors for synthesis of pharmaceuticals and natural products including β-amino alcohols, β-amino acids and β-lactams.[1] Various methods have been reported in the literature to synthesis these compounds employing a variety of catalysts. Mannich reaction is the most straightforward and atom-economic route to β-amino carbonyl compounds. The first Mannich reaction was a two-component system, where the imine as electrophile is pre-formed and then reacted with nucleophiles such as enolates, enol ethers, and enamines.[2] However, the drastic reaction conditions for the classical intermolecular Mannich reaction limit its synthetic usefulness. Therefore, numerous modifications of this reaction have been developed to overcome the drawbacks. A more appropriate version of Mannich reaction involved the one-pot three-component approach that allowed a wide range of structural variations in the reactants-aldehydes, anilines, and ketones to give β-amino carbonyl compounds using an appropriate catalyst. Conventional catalysts for classical Mannich reaction involve mainly Lewis acids,[3] sulfamic acid (SA),[4] silica supported perchloric acid,[5] silica supported solfuric acid (SSA)[6] and boric acid.[7] Trogers,[8] organocatalic,[9] ionic liquids,[10] $Fe(Cp)_2PF_6$,[11] Cu-nanoparticles[12] and $NbCl_5$,[13] have also been found to catalyze this reaction. However, they often suffer from drawbacks of long reaction times, harsh reaction conditions, toxicity of solvents and catalysts and difficulty in product separation, which limit their use in the synthesis of complex molecules. Hence, development of a synthetic protocol that is nature friendly, simple, efficient and cost effective remains an ever challenging objective.

Using reusable heterogeneous solid acid catalysts have also received much attention because of their special advantages such as, stability (toward air and moisture), lack of corrosion, ease of handling, recovery, low waste generation and environmental friendliness, such as, zeolites, clays and hetropolyacids.[14,15] Among zeolites, ZSM-5 is an alumino silicate zeolite and is composed of several pentasil units linked together by oxygen bridges to form pentasil chain. ZSM-5 has high silicon to aluminum ratio, whenever an Al^{3+} cation replaces a Si^{4+} cation, an addition of positive charge is required to keep the material charge-natural with proton as the cation, the material become very acidic. The very regular 3-D structure and the acidity of ZSM-5 can be utilized for acid-catalyzed reactions.

In addition, there is current research and general interest in solvent-free systems because of their importance in industry and in developing technologies due to their simplicity in processing and handling.[16]

Recently, as a part of our studies on the synthesis and application of solid acid catalyst,[17] ZSM-5-SO_3H was synthesized for the first time in our group.[18] Herein, we wish to report, three-component diastereo-controlled Mannich reaction catalyzed by a ZSM-5-SO_3H under solvent-free conditions.

Experimental Section

General. All chemicals were purchased from Merck and Fluka chemical companies. Infrared spectra were recorded on Nicolet (impact 400D model) FTIR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker DRX 500 Avance spectrophotometer in $CDCl_3$ as the solvent and TMS as internal standard. The products were characterized by comparison of their spectral and physical data with those of authentic samples. All yields refer to isolated yield.

Synthesis of Catalyst. Zeolite ZSM-5 was prepared under the hydrothermal conditions with $SiO_2/Al_2O_3 = 80$. Sodium chloride (2.50 g) and Aluminum Sulfate (0.59 g) were

dissolved at room temperature in distilled water (10.12 g) then 1.89 g tetra propyl ammonium bromide (TPA), distilled water (7.12 g) and sulfuric acid (1.09 g) were added to this solution and stirred to dissolve completely. At the end 15.00 g sodium silicate was added and the synthesis was carried out by stirring at room temperature for 1 h or more to obtain a milk homogeneous mixture. Then the mixture was moved to the reactor and kept at 110 ºC for 2 h and 230 ºC for 5.5 h. The solution was filtered and washed with distilled water. Template removal was performed by calcinations in 550 ºC for 6 h. ZSM-5-SO_3H was synthesized following the procedure previously reported by Zolfigol for the synthesis of silicasulfuric acid.[24]

Typical Procedure for the Synthesis of β-Amino Carbonyl Compounds 4. To a vigorously stirred mixture of benzaldehyde (0.265 g, 2.5 mmol), aniline (0.232 g, 2.5 mmol) and ZSM-5-SO_3H (0.01 g,) cyclohexanone (0.49 g, 5 mmol) was added at room temperature under solvent-free conditions. The progress of the reaction was monitored by TLC. After completion of the reaction, ethyl acetate (20 mL) was added and the catalyst removed by filtration. After evaporation of the solvent, the crude product was purified by recrystallization in ethyl acetate:*n*-hexane mixed solvent or ethanol.

Characterization of Compounds 4a-4j.

(*S*)-2-((*R*)-Phenyl(phenylamino)methyl)cyclohexanone (4a): White Solid, mp 128-129 ºC; IR (KBr, cm^{-1}) 1497, 1510, 1602 (C=C, aromatic), 1700 (C=O, carbonyl), 3322 (NH, second amine); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.72 (m, 2H), 1.88 (m, 4H), 1.94 (m, 1H), 1.97 (m, 1H), 2.3 (m, 1H), 4.68 (d, 1H, *J* = 7.0 Hz), 4.77 (s, 1H, br), 6.58 (d, 2H , *J* = 8.5 Hz), 6.67 (t, 1H, *J* = 7.5 Hz), 7.1 (t, 2H, *J* = 7.5 Hz), 7.2 (t, 1H, *J* = 7.5 Hz), 7.34 (t, 2H, *J* = 7.5 Hz), 7.41 (2H, d, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.1, 28.3, 31.7, 42.2, 51.2, 57.9, 58.4 114.1, 118.0, 127.6, 127.7, 128.9, 129.5, 142.1, 147.6, 213.3.

(*S*)-2-((*R*)-(2-Chlorophenyl)(phenylamino)methyl)cyclohexanone (4b): White Solid, mp 136-137 ºC; IR (KBr, cm^{-1}) 1447, 1514, 1594, (C=C, aromatic), 1701 (C=O, carbonyl), 3328 (NH, second amine); ^{1}H NMR (500 MHZ, $CDCl_3$) δ 1.71-2.19 (m, 6H), 2.32-2.45 (m, 2H), 2.94 (m, 1H), 4.95 (d, 1H, *J* = 5.0 Hz), 5.04 (s, 1H, br), 6.56 (d, 2H, *J* = 8.0 Hz), 6.69 (t, 1H, *J* = 7.5 Hz), 7.10-7.25 (m, 4H), 7.38 (m, 1H), 7.60 (m, 1H).

(*S*)-2-((*R*)-(2-Chlorophenylamino)(phenyl)methyl)cyclohexanone (4c): White Solid, mp 136-137ºC; IR (KBr, cm^{-1}) 1445, 1500, 1597 (C=C, aromatic), 1695 (C=O, carbonyl), 3379 (NH, second amine); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.74 (m, 2H), 1.83 (m, 1H), 1.92 (m, 2H), 2.2 (m, 1H), 2.3 (m, 1H), 2.5 (m, 1H), 2.94 (m, 1H), 4.75 (d, 1H, *J* = 6.5 Hz), 5.4 (s, 1H, br), 6.52-6.59 (m, 2H), 6.96 (m, 1H), 7.3-7.42 (m, 6H).

(*S*)-2-((*R*)-(4-Chlorophenyl)(4-methoxyphenylamino)-methyl)cyclohexanone (4d): White Solid, mp 131-132 ºC; IR (KBr, cm^{-1}) 1436, 1514, 1597, (C=C, aromatic), 1702 (C=O, carbonyl), 3381 (NH, second amine); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.72-1.98 (m, 6H), 2.37-2.42 (m, 2H), 2.73 (m, 1H), 3.8 (s , 3H), 4.53 (d, 1H, *J* = 7.5 Hz), 4. 82 (s, 1H, br), 6.48 (d, 2H, *J* = 10.5 Hz), 6.87 (d, 2H, *J* = 10.0 Hz), 7.02 (d, 2H, *J* = 10.5 Hz), 7.28 (d, 2H, *J* = 10.0 Hz).

(*S*)-2-((*R*)-(4-Bromophenyl)(4-methoxyphenylamino)-methyl)cyclohexanone (4e): White Solid, mp 132-133 ºC; IR (KBr, cm^{-1}) 1436, 1519, 1610, (C=C, aromatic), 1708 (C=O, carbonyl), 3395 (NH, second amine); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.71-1.92 (m, 6H), 2.32-2.46 (m, 2H), 2.70 (m, 1H), 3.8 (s, 3H), 4.53 (d, 1H, *J* = 7.0 Hz), 4.59 (s, 1H, br), 6.43 (d, 2H, *J* = 7.5 Hz), 6.87 (d, 2H, *J* = 8.5 Hz), 7.16 (d, 2H, *J* = 8.0 Hz), 7.28 (d, 2H, *J* = 8.5 Hz).

(*S*)-2-((*R*)-(4-Bromophenylamino)(4-nitrophenyl)methyl)cyclohexanone (4f): Yellow Solid, mp 134-135 ºC; IR (KBr, cm^{-1}) 1452, 1495,1593, (C=C, aromatic), 1705 (C=O, carbonyl), 3390 (NH, second amine); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.77-2.04 (m, 6H), 2.36-2.48 (m, 2H), 2.87 (m, 1H), 4.72 (d, 1H, *J* = 5.5 Hz), 4.85 (s, 1H, br), 6.45 (d, 2H, *J* = 8.5 Hz), 6.92 (d, 2H, *J* = 8.5 Hz), 7.59 (d, 2H, *J* = 10.0 Hz), 8.17 (d, 2H, *J* = 10.0 Hz).

2-((4-Chlorophenylamino)(phenyl)methyl)cyclohexanone (4g): White Solid, mp 136-137 ºC. IR (KBr, cm^{-1}) 1443, 1513, 1597 (C=C, aromatic), 1701 (C=O, carbonyl), 3386 (NH, second amine); ^{1}H NMR (500 MHz, $CDCl_3$, (*anti*/*syn* = 55/45)) δ 1.69-1.96 (m, 6H), 2.05 (m, 1H), 2.32 (m, 1H), 2.36 (m, 1H), 4.57 (d, 0.55H, *J* = 6.5 Hz, for anti), 4.77 (d, 0.45 H, *J* = 4.5 Hz, for *syn*), 4.78 (s, 1H, br), 6.45 (m, 2H), 7.18 (m, 2H), 7.25 (m, 1H), 7.33 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) for *anti* and *syn*: δ 23.9, 24.4, 27.5, 27.9, 28.8, 31.5, 41.9, 42.2, 55.6, 56.7, 57.1, 57.3, 115.2, 115.3, 119.9, 127.4, 127.7, 127.9, 128.4, 128.9, 129.0, 129.1, 142.7, 143.5, 147.7, 148.1, 210.4, 211.7.

2-((2-Methoxyphenylamino)(phenyl)methyl)cyclohexanone (4h): White Solid, mp 136-137 ºC: IR (KBr, cm^{-1}) 1448, 1518, 1602, (C=C, aromatic), 1707 (C=O, carbonyl), 3419 (NH, second amine); ^{1}H NMR (500 MHz, $CDCl_3$, (*anti*/*syn* = 56/44)) δ 1.71-1.93 (m, 6H), 2.43-2.63 (m, 2H), 2.87 (m, 1H), 3.9 (s, 3H), 4.75 (d, 0.56H, *J* = 7.0 Hz, for anti), 4.92 (d, 0.44H, *J* = 5.5, for *syn*), 5.1 (s, 1H, br), 6.45-6.77 (m, 4H), 7.24-7.43 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) for *anti* and *syn*: δ 24.0, 24.5, 27.9, 28.8, 29.5, 32.1, 42.1, 42.4, 56.1, 56.3, 56.4, 56.8, 57.0, 57.1, 110.6, 110.7, 111.4, 116.7, 116.8, 121.6, 121.7, 127.4, 127.6, 128.2, 128.3, 128.8, 129.0, 137.9, 138.0, 143.1, 143.4, 147.4, 147.5, 211.5, 212.5.

2-((3-Chlorophenylamino)(phenyl)methyl)cyclohexanone (4i): White Solid, mp 122-123 ºC: IR (KBr, cm^{-1}) 1483, 1526, 1597, (C=C, aromatic), 1703 (C=O, carbonyl), 3341 (NH, second amine); ^{1}H NMR (500 MHz, $CDCl_3$, (*anti*/*syn* = 56/44)) δ 1.91 (m, 5H), 2.06 (m, 1H), 2.08 (m, 1H), 2.35 (m, 1H), 2.45 (m, 1H), 4.59 (d, 0.5H, *J* = 5.5 Hz, for anti), 4.80 (d, 0.5H, *J* = 4.0 Hz, for *syn*), 4.90 (s, 1H, br), 6.43-6.65 (m, 3H), 6.96 (m, 1H), 7.26-7.34 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) for *anti* and *syn*: δ 24.3, 25.2, 27.3, 28.4, 29.1, 32.1, 42.4, 42.8, 56.7, 57.6, 57.7, 58.4, 112.3, 112.6, 113.7, 114.2, 117.8, 118.0, 127.6, 127.7, 127.8, 127.9, 128.9, 129.0, 130.4, 130.5, 135.1, 135.2, 141.3, 141.6, 148.9, 149.1, 211.7, 213.2.

Typical Procedure for the Synthesis of β-Amino Carbonyl Compounds 6. To a vigorously stirred mixture of benzaldehyde (0.212 g, 2 mmol), aniline (0.186 g, 2 mmol) and ZSM-5-SO_3H (0.05 g,) acetophenone (0.188 g, 2.4 mmol) was added at 60 ºC under solvent-free conditions. The progress of the reaction was monitored by TLC. After completion of the reaction, ethyl acetate (20 mL) was added and the catalyst removed by filtration. After evaporation of the solvent, the crude product was purified by recrystallization in ethyl acetate:n-hexane mixed solvent.

Characterization of Compounds 6a-6h.

1,3-Diphenyl-3-(phenylamino)propan-1-one (6a): White Solid, mp 168-169 ºC; IR (KBr, cm^{-1}) 1442, 1509, 1596, (C=C, aromatic), 1670 (C=O, carbonyl), 3385 (NH, second amine); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.46 (dd, 1H, J_1 = 16.1, J_2 = 7.5 Hz), 3.54 (dd, 1H, J_1 = 16.1, J_2 = 7.5 Hz), 5.06 (dd, 1H, J_1 = 7.5, J_2 = 5.5 Hz), 6.61 (d, 2H , J = 5.5 Hz), 6.71 (t, 1H, J = 7.5 Hz), 7.28 (t, 2H, J = 7.5 Hz), 7.35 (t, 1H, J = 7.5 Hz), 7.43-7.64 (m, 7H), 8.06 (d, 2H, J = 5.5 Hz).

3-(4-Cholorophenylamino)-1,3-diphenylpropan-1-one (6b): White Solid, mp 171-172 ºC; IR (KBr, cm^{-1}) 1454, 1498, 1597, (C=C, aromatic), 1669 (C=O, carbonyl), 3386 (NH, second amine); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.44 (dd, 1H, J_1 = 16.1, J_2 = 7.5 Hz), 3.53 (dd, 1H, J_1 = 16.1, J_2 = 7.5 Hz), 4.95 (dd, 1H, J_1 = 7.5, J_2 = 5.5 Hz), 6.52 (d, 2H, J = 10.0 Hz), 7.05 (d, 2H, J = 10.0 Hz), 7.25-7.49 (m, 7H), 7.61 (m, 1H), 7.93 (d, 2H, J = 10.0 Hz).

1,3-Diphenyl-3-(*p*-tolylamino)propan-1-one (6d): White Solid, mp 171-172 ºC; IR (KBr, cm^{-1}) 1449, 1490, 1626 (C=C, aromatic), 1664 (C=O, carbonyl), 3371 (NH, second amine); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.26 (s, 3H), 3.46 (dd, 1H, J_1 = 16.1, J_2 = 7.5 Hz), 3.55 (dd, 1H, J_1 = 16.1, J_2 = 7.5 Hz), 5.02 (dd, 1H, J_1 = 7.5, J_2 = 5.5 Hz), 6.53 (d, 2H, J = 10.0 Hz), 6.94 (d, 2H, J = 10.0 Hz), 7.28-7.58 (m, 8H), 7.94 (d, 2H, J = 10.0 Hz).

3-(3-Chlorophenylamino)-1,3-diphenylpropan-1-one (6f): White Solid, mp 132-134 ºC; IR (KBr, cm^{-1}) 1449, 1511, 1598 (C=C, aromatic), 1664 (C=O, carbonyl), 3362 (NH, second amine.); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.46 (dd, 1H, J_1 = 16.1, J_2 = 7.5 Hz), 3.54 (dd, 1H, J_1 = 16.1, J_2 = 7.5 Hz), 5.02 (dd, 1H, J_1 = 7.5, J_2 = 5.5 Hz), 6.47-6.67 (m, 3H), 7.03 (t, 1H, J =7.5 Hz), 7.31-7.53 (m, 7H), 7.61 (t, 1H, J = 7.5 Hz), 7.94 (d, 2H, J = 7.5 Hz).

3-(4-Chlorophenyl)-1-phenyl-3-(phenylamino)propan-1-one (6g): White Solid, mp 119-120 ºC; IR (KBr, cm^{-1}) 1449, 1488, 1600, (C=C, aromatic), 1667 (C=O, carbonyl), 3391 (NH, second amine.); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.47 (dd, 1H, J_1 = 16.1, J_2 = 7.5 Hz), 3.52 (dd, 1H, J_1 = 16.1, J_2 = 7.5 Hz), 5.03 (dd, 1H, J_1 = 7.5, J_2 = 5.5 Hz), 6.59 (d, 2H, J = 9.5 Hz), 6.73 (t, 1H, J =7.5 Hz), 7.14 (t, 2H, J =7.5 Hz), 7.34-7.57 (m, 7H), 8.06 (d, 2H , J = 9.5 Hz).

3-(4-Chlorophenyl)-3-(4-chlorophenylamino)-1-phenylpropan-1-one (6h): White Solid, mp 131-132 ºC; IR (KBr, cm^{-1}) 1443, 1513, 1597 (C=C, aromatic), 1667 (C=O, carbonyl), 3381 (NH, second amine.); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.45 (dd, 1H, J_1 = 16.1, J_2 = 7.5 Hz), 3.51 (dd, 1H, J_1 = 16.1, J_2 = 7.5 Hz), 4.96 (dd, 1H, J_1 = 7.5, J_2 = 5.5 Hz), 6.50 (d, 2H, J = 9.5 Hz), 7.07 (d, 2H, J = 9.5 Hz), 7.48 (d, 2H, J = 9.5 Hz), 7.50 (d, 2H, J = 9.5 Hz), 7.54-7.65 (m, 3H), 7.92 (d, 2H, J = 9.5 Hz).

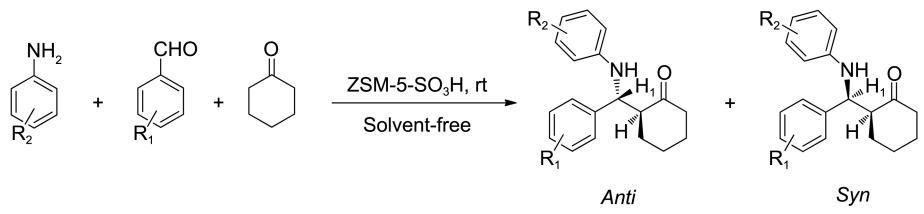
Results and Discussion

Recently, it has been observed that ZSM-5-SO_3H showed very good activity and selectivity and low catalytic deactivation for the synthesis and deprotection of 1,1-diacetates. This catalyst has been characterized by SEM, XRD, FTIR and BET techniques.[18] In this work, one-pot three-component Mannich reaction of aldehydes, anilines, and ketones over ZSM-5-SO_3H as catalyst, has been studied. The effect of different parameters on the synthesis of various β-aminocarbonyl compounds was investigated. In order to optimize the reaction conditions, we chose the reaction of aniline (2.5 mmol), and benzaldehyde (2.5 mmol), with cyclohexanone (5 mmol) as a reaction model (Scheme 1). To start with, the reaction was screened in different solvents such as CH_3CN, CH_2Cl_2 and EtOH as well as solvent-free conditions at room temperature (Table 1, entries 1-4). Ethanol and acetonitrile provided excellent yields and proved to be the solvent of choice, whereas dichloromethane afforded lower yields. On the other hand, comparison between the results obtained in solutions and solvent-free conditions showed that the reac-

Table 1. Mannich reactions of benzaldehyde (2.5 mmol), aniline (2.5 mmol), and cyclohexanone (5 mmol) under different conditions

Entry	Solvent	ZSM-5-SO_3H	Time (min)	Yield (%)[a]
1	EtOH	0.01 g	110	90
2	CH_3CN	0.01 g	180	87
3	CH_2Cl_2	0.01 g	240	77
4	Solvent-free	0.015 g	60	94
5	Solvent-free	0.01 g	60	97
6	Solvent-free	0.008 g	75	93
7	Solvent-free	0.005 g	80	90
8	Solvent-free	–		0

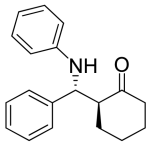
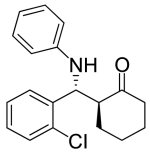
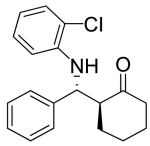
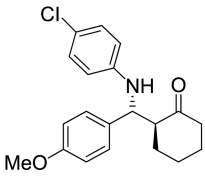
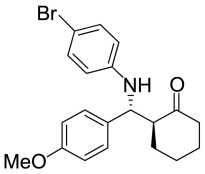
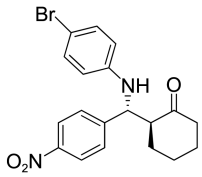
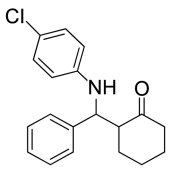
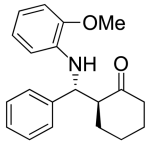
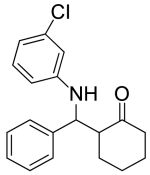
[a]Isolated yield



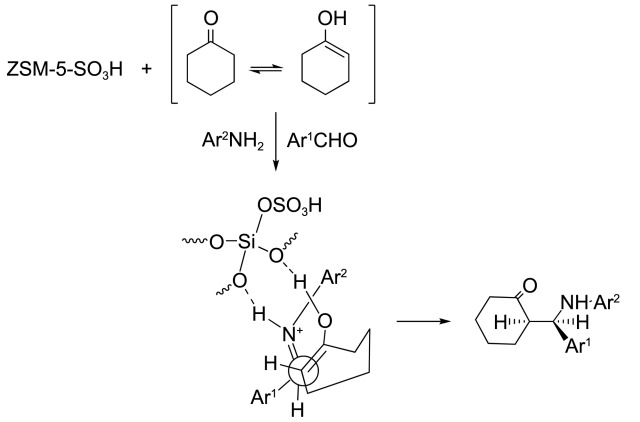
Scheme 1. Direct Mannich reactions of aromatic aldehydes, anilines, and cyclohexanone.

tion proceeds faster in solvent-free conditions and the product obtained in higher yield. Thereafter, the effect of amount of catalyst on the reaction was also investigated. Generally, there was no reaction in the absence of catalyst (Table 1, entry 8), indicating that this was indeed a ZSM-5-SO_3H catalyzed reaction and the yield were increased over the amount of catalyst. The optimum amount of catalyst (0.01 g) was determined from experiments corresponding to entries 4-7 of Table 1. No improvement in the yield was found with further increase of the catalyst. Hence, the

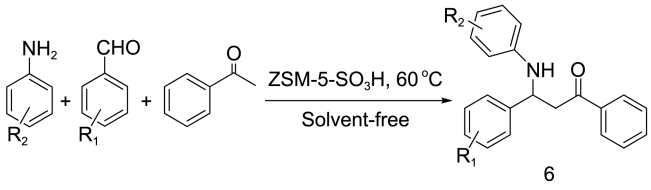
Table 2. Solvent-free Mannich reactions for the synthesis of **4**[a]

Entry	R^1	R^2	Product	Time (min)	Yield %[b]	mp/°C (Lit)	*Anti*/*Syn*[c]
4a	H	H		60	97	128-129 (129[8])	100:0
4b	2-Cl	H		80	66	136-137 (139[22])	100:0
4c	H	2-Cl		110	90	136-137 (138[8])	100:0
4d	4-OMe	4-Cl		75	90	131-132 (131[14])	100:0
4e	4-OMe	4-Br		75	95	132-133 (131[3e])	100:0
4f	4-NO_2	4-Br		65	78	134-135	100:0
4g	H	4-Cl		85	87	137-138 (137[14])	55:45
4h	H	2-OMe		110	78	136-137 (137[3e])	52:48
4i	H	3-Cl		130	78	122-123 (121[21])	50:50

[a]R^1PhCOH (2.5 equiv.), R^2PhNH_2 (2.5 equiv.), Cyclohexanone (5 equiv.) and Cat 0.01 g, room temperature. [b]Isolated yield. [c]According to ^{1}H NMR



Scheme 2. Possible transition states.



Scheme 3. Direct Mannich reactions of aromatic aldehydes, anilines, and acetophenone.

optimal amount of catalyst was chosen as 0.01 g based on 2.5 mmol of benzaldehyde for further study.

In order to show the generality and scope of the new protocol, the reactions of different aromatic aldehydes, anilines and cyclohexanone were carried out at room temperature under solvent-free conditions (Table 2). The results show that the β-amino ketones are obtained in good to high yields with excellent diastereoselectivity. The annotations indicate that both electron-donating and electron-withdrawing substituents on aldehydes and amines undergo the reaction with good to excellent yields and the anti-products were always formed as only or in a major scale, independent of the nature of substituents on the aldehyde or amine as depicted in Table 2.

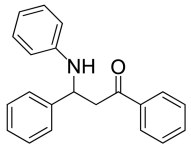
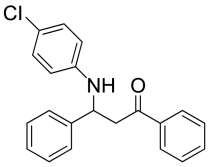
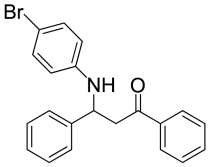
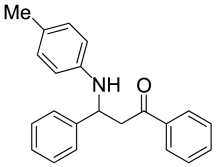
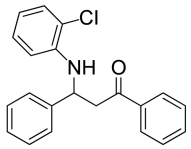
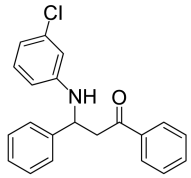
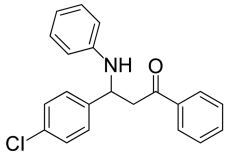
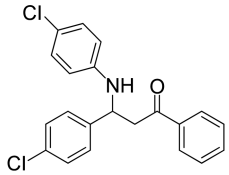
The anti and syn isomers were identied by the coupling constants (*J*) of the vicinal protons adjacent to C=O and NH in their ^{1}H NMR spectra.[19] *J* signal of anti isomer is higher than that of the syn one. The anti/syn ratio was determined by ^{1}H NMR judged by the intensity of the H_1 (Scheme 1).

The possible transition states are proposed in Scheme 2. If hydrogen bonds are formed among ZSM-5-SO_3H, the imine and the enol form of cyclohexanone, the aryl groups of aldimine would be anti to each other and there should be less steric repulsion on it, between the methylene groups of cyclohexanone and aryl group on the carbon atom, as well as ZSM-5-SO_3H and H_1. So the most stable transition state would produce the anti isomer.[6]

This encouraging result prompted us to test acetophenone as ketone in the Manich reaction (Scheme 3). As acetophenone was less reactive than cyclohexanone, more catalyst and longer reaction time were necessary to afford the desired products. The best result was obtained when the ratio of aniline, benzaldehyde and acetophenone was 1.0:1.0:1.2. Also, we found that 0.05 g of catalyst was necessary and the reaction should be done at 60 °C. Table 3 demonstrates that excellent yields of β-amino ketones are obtained across the selected aldehydes and amines including those that bear an electron-withdrawing or electron-donating group.

The recycling performance of the ZSM-5-SO_3H in the Mannich reaction was also investigated. After the reaction,

Table 3. Solvent-free Mannich reactions for the synthesis of **6**[a]

Entry	R^1	R^2	Product	Time (h)	Yield %[b]	mp/°C (Lit)
6a	H	H		5	98	168-169 (169[20])
6b	H	4-Cl		7	97	171-172 (171[20])
6c	H	4-Br		7	97	178-180 (178[8])
6d	H	4-Me		6	97	171-172 (171[20])
6e	H	2-Cl		8	92	115-116 (116[23])
6f	H	3-Cl		9	92	132-134 (132[21])
6g	2-Cl	H		8	92	119-120 (119[14])
6h	4-Cl	4-Cl		6	96	131-132 (155-157[14])

[a]R^1PhCOH (2.0 equiv.), R^2PhNH_2 (2.0 equiv.), Acetophenone (2.4 equiv.) and Cat 0.05 g, 60 °C. [b]Isolated yield.

ethyl acetate was added and the catalyst was isolated from the reaction mixture by filtration and calcinated at 550 ºC for 5.5 hours. The catalyst was reused in the next run without further purication. The catalyst can be reused at least three times without appreciable decrease in yield and reaction rate.

Conclusion

In summary, we have developed a new method for the Mannich reaction in the presence of ZSM-5-SO_3H for the preparation of anti β-amino carbonyl compounds under solvent-free conditions. This procedure offers several advantages for the Mannich reaction such as low loading of catalyst, mild conditions, high yields, clean reactions, which make it a useful and attractive methodology for organic synthesis. Quite a number of products are solid and insoluble in water, which can be obtained by filtration and recrystallization. This simple work-up procedure is also beneficial to this method. In addition recyclability of this protocol is attractive and useful. Further applications of this catalyst to other transformations are currently under investigation.

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