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Highly Stereoselective Synthesis of β-Amino Ketones via a Mannich Reaction Catalyzed by Cellulose Sulfuric Acid as a Biodegradable, Efficient, and Recyclable Heterogeneous Catalyst

Firouzeh Nemati [a], Amir Soheyl Fakhaei [a], Ali Amoozadeh [a] & Yaser Saeidi Hayeniaz [b]

[a] Department of Chemistry, Faculty of Science, Semnan University, Semnan, Iran

[b] Faculty of Chemistry, Tarbiat Moallem University, Tehran, Iran

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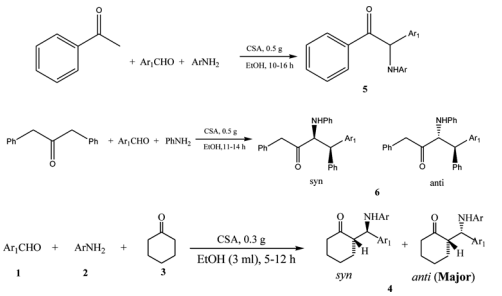
HIGHLY STEREOSELECTIVE SYNTHESIS OF β-AMINO KETONES VIA A MANNICH REACTION CATALYZED BY CELLULOSE SULFURIC ACID AS A BIODEGRADABLE, EFFICIENT, AND RECYCLABLE HETEROGENEOUS CATALYST

Firouzeh Nemati,[1] Amir Soheyl Fakhaei,[1] Ali Amoozadeh,[1] and Yaser Saeidi Hayeniaz[2]

[1]*Department of Chemistry, Faculty of Science, Semnan University, Semnan, Iran*
[2]*Faculty of Chemistry, Tarbiat Moallem University, Tehran, Iran*

GRAPHICAL ABSTRACT



Abstract *The efficient use of cellulose sulfuric acid as a heterogeneous catalyst promotes three-component, one-pot Mannich reaction of various ketones, aromatic aldehydes, and aromatic amines in ethanol to make the corresponding β-amino ketones with high stereoselectivity in favor of the anti-isomer. This protocol has several advantages such as good yield, mild reaction conditions, no environmental hazards, and simple workup procedure.*

Keywords β-Amino ketones; cellulose sulfuric acid; Mannich reaction; stereoselective

INTRODUCTION

In recent years, a large number of articles have been devoted to the introduction and applications of valuable ecofriendly catalysts.[1] One of the most simple and useful strategies for the preparation of such catalysts is the attachment of organic or inorganic materials to different solid supports. Low toxicity, moisture resistance, air tolerance, greater selectivity, easier handling, and low cost are some of the

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Address correspondence to Firouzeh Nemati, Department of Chemistry, Faculty of Science, Semnan University, Semnan, Iran. E-mail: fnemati_1350@yahoo.com; fnemati@semnan.ac.ir

beneficial features of this method that make it a viable alternative to noncatalytic methods. The use of biopolymers and especially cellulose for support of sulfuric acid, as an example of newly investigated solid acid catalysts, is worthy of note.[2,3]

The Mannich reaction is an important carbon–carbon bond-forming reaction in organic synthesis.[2] It is used for the synthesis of β-amino carbonyl compounds, which are significant synthetic intermediates for various pharmaceuticals and natural products.[4] In addition, recent developments in using a three-component protocol made the Mannich reaction even more valuable in asymmetric synthesis.[5–13]

In his work, we report that cellulose sulfuric acid (CSA) is an efficient catalyst for the synthesis of β-amino carbonyl compounds in EtOH at room temperature through a one-pot, three-component reaction of aldehydes, amines, and ketones.

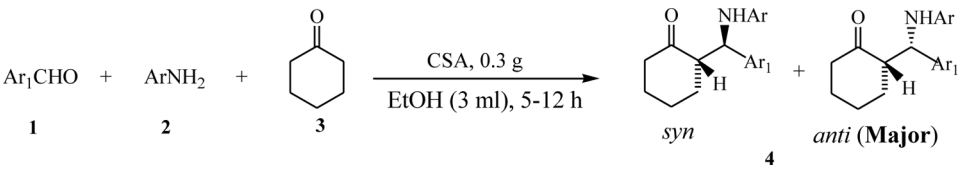
RESULTS AND DISCUSSION

In continuation of our investigation of Mannich reactions,[14,15] we now introduce CSA as an effective and highly stereoselective catalyst for the one-pot synthesis of β-amino carbonyl compounds via a multicomponent reaction of aryl aldehydes, anilines, and cyclohexanone (Scheme 1).

To establish the optimum conditions for this reaction, initially, the three-component Mannich reaction of benzaldehyde (2 mmol), aniline (2 mmol), and cyclohexanone (3 mmol) was examined, and various solvents such as tetrahydrofuran (THF), H_2O, EtOH, CH_2Cl_2, and CH_3CN were chosen. Ethanol was found to be the best solvent as far as yield, reaction rate, cost, and environmental acceptability were concerned. In addition, some of the products precipitate in ethanol. Further experiments revealed the optimum amount of catalyst to be 0.3 g.

To show the generality and scope of this new protocol, we used different aromatic aldehydes and aromatic amines bearing electron-withdrawing and electron-donating groups in addition to cyclohexanone in the presence of 0.3 g CSA in EtOH. The reaction gave the corresponding products (**4**) in good to excellent yields (Scheme 1). The results are summarized in Table 1.

An important feature of this procedure was that strong-withdrawing substituents such as the nitro group on aromatic aldehyde and electron-donating group on aromatic amines (Table 1, entries 4, 8, and 15) result in good yield. This is because the electron-withdrawing substituents on benzaldehyde and electron-donating substituents on aniline have a great impact on the rate of the formation of the compound ArCH=NPh derived from the aryl aldehydes and aryl amines. According to this explanation, benzaldehyde with strong electron-donating groups and arylamine with electron-withdrawing groups would not work well (Table 1, entries 11,



1 2 3 4

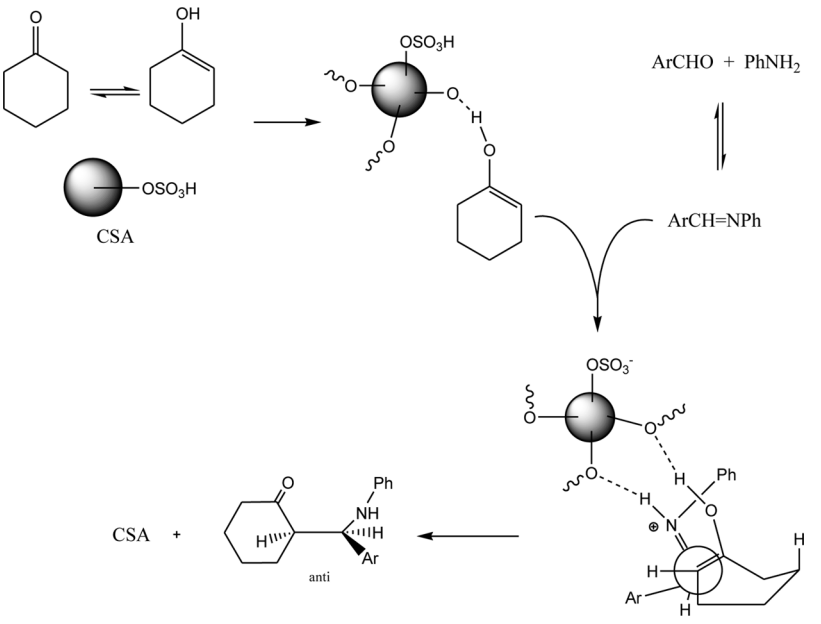
Scheme 1. One-pot three-component direct Mannich reaction.

Table 1. Mannich-type reaction of aromatic aldehydes, anilines, and cyclohexanone[a] in EtOH

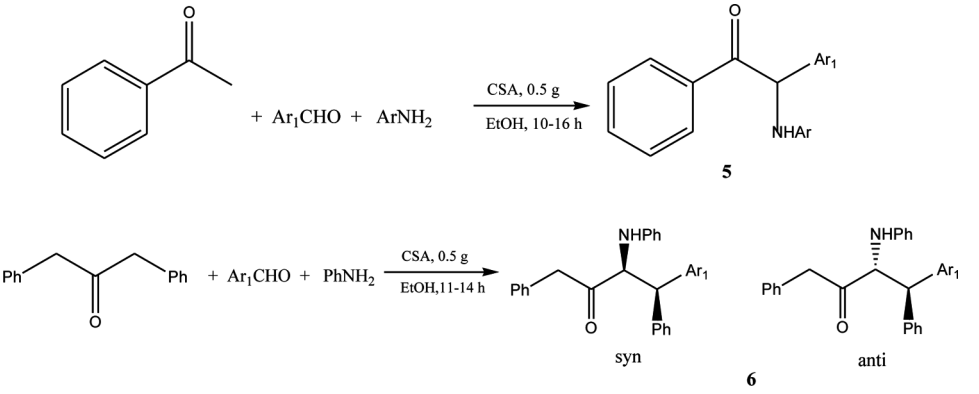
Entry	Ar_1	Ar	Time (h)	Yield (%)[b]	*anti*/*syn*[c]	M.P. °C
1	C_6H_5	Ph	6	80	99/1	138–140[14]
2	2-ClC_6H_4	Ph	6	80	99/1	150–151[15]
3	4-MeC_6H_4	Ph	12	75	99/1	120–121[14]
4	2-$NO_2C_6H_4$	Ph	5	80	33/67	159–160[16]
5	2-Naphthyl	Ph	7	75	99/1	129–131[14]
6	4-ClC_6H_4	Ph	6	75	99/1	69–70[14]
7	4-BrC_6H_4	Ph	5	75	70/30	110–112[14]
8	4-$NO_2C_6H_4$	Ph	5	80	99/1	123–125
11	4-OHC_6H_4	Ph	12	Trace	—	—
12	4-$MeOC_6H_4$	Ph	12	Trace	—	—
13	C_6H_5	4-BrC_6H_4	7	75	99/1	98–99[17]
14	C_6H_5	4-$NO_2C_6H_4$	12	No reaction	—	—
15	C_6H_5	4-MeC_6H_4	8	75	98/2	118–119[18]

[a]Reaction conditions: Aromatic aldehyde (2 mmol), aniline (2 mmol), cyclohexanone (3 mmol), CSA (0.3 g).
[b]Isolated yields, products were confirmed by ^{1}H NMR.
[c]*Anti*/*syn* ratio was determined by ^{1}H NMR.

12, and 14). Interestingly, the results in Table 1 show that the *anti*- isomer is much more favored than *syn*- one with an exception of entry 4 in Table 1. The *anti*- and *syn*- isomers were identified by measurements of the coupling constants (*J*) of the adjacent vicinal protons to C=O and NH in ^{1}H NMR spectra. The coupling



Scheme 2. Possible mechanism.



Scheme 3. Mannich-type reaction of aromatic aldehydes, anilines with acetophenone, and 1,3-diphenylpropan-2-one.

constants for the *anti-* isomers are reported to be larger than those of the *syn-*isomers.[19,20]

The observed *anti-* selectivity may be rationalized based on previously reports.[14,15,19] We propose that the in situ–generated enolate attacks the in situ–generated aldimine as shown in Scheme 2.[10] If hydrogen bonding occurs among cellulose, aldimine, and enolate, the aryl and phenyl groups would be *anti-* to each other, so there is minimum steric repulsion between the methylene group in cyclohexanone and aryl group, as well as cellulose and H. Therefore, this transition state leads to an *anti-* isomer. In summary, we propose that powerful hydrogen bonding exists in cellulose, imine, and enol form of cyclohexanone (Scheme 2) because of the observed excellent *anti-* selectivity of the reaction.

Table 2. Mannich-type reaction of aromatic aldehydes, anilines, and acetophenone or 1,3-diphenylpropan-2-one[a] in EtOH

Entry	Ketone	Ar_1	Ar	Time (h)	Yield (%)[b]	*anti/syn*	M.P °C
1	Acetophenone	C_6H_5	Ph	14	95	–	168–169[14]
2	Acetophenone	4-OMe C_6H_4	Ph	16	74	–	148–149[14]
3	Acetophenone	4-MeC_6H_4	Ph	14	80	–	135–137[14]
4	Acetophenone	4-ClC_6H_4	Ph	12	75	–	131–133[14]
5	Acetophenone	4-BrC_6H_4	Ph	11	75	–	130–132[14]
6	Acetophenone	4-$NO_2C_6H_5$	Ph	10	65	–	104–105[21]
7	Acetophenone	C_6H_5	4-ClC_6H_4	12	75	–	164–166[16]
8	Acetophenone	C_6H_5	4-MeC_6H_4	10	85	–	165–167[14]
9	Acetophenone	C_6H_5	4-$NO_2C_6H_4$	24	–	–	–
10	1,3-diphenylpropan-2-one	C_6H_5	Ph	14	90	99/1	168–170
11	1,3-diphenylpropan-2-one	4-FC_6H_4	Ph	11	80	88/12	148–150
12	1,3-diphenylpropan-2-one	4-MeO C_6H_4	Ph	14	83	99/1	132–133

[a]Reaction conditions: Aldehyde (2 mmol), aromatic aniline (2 mmol), acetophenone (2 mmol) or 1,3-diphenylpropan-2-one (2 mmol) and CSA (0.5 g).

[b]Isolated yield, products were confirmed by ^{1}H NMR.

[c]No reaction.

These encouraging results prompted us to test other ketones such as 1,3-diphenylpropan-2-one (dibenzylketone) and acetophenone (Scheme 3). Corresponding β-amino carbonyl compounds were formed in good yields (Table 2). Acetophenone and 1,3-diphenylpropan-2-one are less reactive than cyclohexanone and required a larger quantity of catalyst (0.5 g) and longer reaction time to yield the desired products. High *anti*-selectivity was also observed for product **6** (Table 2, entries 10–12). The highly electron-deficient 4-nitroaniline did not work (Table 2, entry 9). High electron-withdrawing groups such as NO_2 decrease the activity of the amine to produce the aldimine and result in a very poor yield.

In summary, three-component Mannich-type reactions of aryl aldehydes, aromatic amines, and ketones are efficiently catalyzed by CSA in EtOH. The reaction works well with a wide range of structural variations in all the three components. The most important advantages of this methodology are the mild conditions, good yield, and high stereoselectivity. In addition, our process involves an environmentally benign, cheap, and recyclable catalyst.

EXPERIMENTAL

Chemicals were purchased from the Fluka, Merck, and Aldrich chemical companies. Melting points were determined by an Electrothermal 9100 and are not corrected. Thin-layer chromatography (TLC) on commercial aluminum-backed plates of silica gel 60 F254 was used to monitor the progress of reactions. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 300-MHz spectrometers with 7–10 mM solutions in $CDCl_3$ in the presence of tetramethylsilane as internal standard. Infrared (IR) spectra were recorded using a Perkin-Elmer 843 spectrometer with KBr plates. Elemental analyses were performed by Perkin-Elmer CHN analyzer, 2400 series II.

Preparation and Recycling of Cellulose Sulfuric Acid

CSA was prepared according to Shaabani et al.'s procedure.[2] The catalyst was separated from the reaction mixture, washed thoroughly with chloroform and EtOH, and dried at 80 °C for 24 h to give recycled CSA. The reaction of benzaldehyde, aniline, and cyclohexanone was repeated with recycled catalyst, and the yields remained in the range of 70% for three runs.

General Procedure for the Synthesis of β-Aminocarbonyl Compounds Using Cyclohexanone

A mixture of arylaldehyde (2 mmol), aniline (2 mmol), cyclohexanone (3 mmol), and CSA (0.3 g) was stirred in EtOH (3 mL) at room temperature for 5–12 h. The reaction was monitored by TLC. The products precipitated from the reaction mixture. The precipitate was filtered off and dissolved in hot EtOH, and the catalyst was removed by hot filtration.

The filtrate was kept at room temperature, and the resulting crystallized product was collected by filtration and washed with EtOH (95%). Some products were separated and purified by dry flash column chromatography.

General Procedure for the Synthesis of β-Aminocarbonyl Compounds Using Acetophenone or 1,3-Diphenylpropan-2-one

A mixture of arylaldehyde (2 mmol), aniline (2 mmol), acetophenone or 1,3-diphenylpropan-2-one (2 mmol), and CSA (0.5 g) was stirred in EtOH (5 mL) at room temperature for 10–16 h. The reaction was monitored by TLC. The products were precipitated from the reaction mixtures, filtered off, dissolved in hot EtOH, and left to crystallize at room temperature. The resulting crystallized product was collected by filtration and washed with EtOH (95%). The β-aminocarbonyl compounds from 1,3-diphenylpropan-2-one were separated and purified by dry flash chromatography.

All products were characterized by IR, ^{1}H NMR, and ^{13}C NMR and were identified by comparison of the spectral data and melting points with those reported in literature.

Spectral (IR, ^{1}H NMR, and ^{13}C NMR) and analytical data of new compounds are given.

Selected Data

2-[(Phenylamino)(4-nitrophenyl)methyl]cyclohexanone (Table 1, Entry 8). mp 123–125 °C, IR (KBr): ν max/cm^{-1}: 3405, 1700, 1575, 1550, 1350; ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si): δ 8.16 (d, $J = 8.77$ Hz, 2H), 7.59 (d, $J = 8.68$ Hz, 2H), 7.13–7.08 (m, 2H), 6.70 (t, $J = 7.32$ Hz, 1H), 6.53 (d, $J = 7.92$ Hz, 2H), 4.72 (d, $J = 5.35$ Hz, *anti*, 1H), 2.92–2.87 (m, 1H), 2.45–2.30 (m, 2H), 2.06–1.91 (m, 3H), 1.84–1.74 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.5, 25.0, 27.0, 27.8, 29.1, 32.0, 42.4, 56.9, 58.1, 113.8, 114.1, 118.5, 123.7, 128.3, 128.6, 129.2, 129.3, 146.3, 147.1, 149.5, 211.9. Anal. calc. for $C_{19}H_{20}N_2O_3$: C, 70.37; H, 6.17; N, 8.64%; Found: C, 70.25; H, 6.01; N, 8.54%.

1,3,4-Triphenyl-4-(phenylamino)butan-2-one (Table 2, Entry 10). mp 168–170 °C; IR (KBr): ν max/cm^{-1}: 3405, 1710, 1601, 1320, 667; ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si): δ 7.42–7.39 (m, 2H), 7.34–7.25 (m, 8H), 7.19–7.13 m, 3H), 6.99–6.93 (m, 2H), 6.71 (dd, $J = 7.19$, $J = 1.77$ Hz, 2H), 6.58 (t, $J = 7.3$ Hz, 1H), 6.34 (dd, $J = 8.13$, $J = 1$ Hz, 2H), 4.98 (d, *anti*, $J = 10.15$ Hz, 1H), 4.14 (d, $J = 10.15$ Hz, 1H), 3.31 (dd, $J = 20$, $J = 16$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 50.7, 59.8, 64.7, 113.9, 117.8, 126.8, 127.4, 127.6, 128.3, 128.5, 128.6, 128.8, 129.1, 129.2, 129.5, 133.0, 134.7, 142.0, 147.2, 205.4; Anal. calc. for $C_{28}H_{25}NO$; C, 85.93; H, 6.39; N, 3.58%; Found: 85.83; H, 6.28; N, 3.45%.

4-(4-Fluorophenyl)-1,3-diphenyl-4-(phenylamino)butan-2-one (Table 2, Entry 11). mp 148–150 °C; IR (KBr): ν max/cm^{-1} 3428, 1700, 1600, 1508, 750, 700; ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si): δ 7.38–7.30 (m, 7H), 7.2–7.15 (m, 3H), 7.0–6.9 (m, 4H), 6.72–6.7 (m, 2H), 6.62–6.57 (m, 1H), 6.30 (dd, $J = 8.5$, $J = 1$ Hz, 2H), 4.97 (d, *anti,* $J = 10.17$ Hz, 0.88H), 4.87 (d, *syn,* $J = 4.73$ Hz, 0.12H), 4.15 (d, *syn,* $J = 7.59$ Hz, 0.12H), 4.10 (d, *anti,* $J = 10.17$ Hz, 0.88H), 3.74 (s, 1H), 3.37 (dd, $J = 16.8$, $J = 15.66$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 50.5, 58.8, 64.6, 113.6, 113.9, 115.2, 115.5, 118.0, 126.9, 128.4, 128.6, 128.8, 129.0, 129.1, 129.2, 129.3,

129.4, 129.6, 132.7, 134.4, 137.6, 146.9, 163.6, 205.1. Anal. calc. for $C_{28}H_{24}NOF$: C, 82.15; H, 5.86; N, 3.42%. Found: C, 82.02; H, 5.79, N, 3.30%.

4-(4-Methoxyphenyl)-1,3-diphenyl-4-(phenylamino)butan-2-one (Table 2, Entry 12). mp 132–133 °C, IR (KBr): ν max/cm^{-1} 3409, 1714, 1605, 1516, 760; ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si): δ 7.35–7.26 (m, 7H), 7.19–7.15 (m, 3H), 6.99–6.94 (m, 2H), 6.84–6.80 (m, 2H), 6.71 (dd, $J = 6.71$, $J = 1.77$ Hz, 2H), 6.58 (t, $J = 7.3$ Hz, 1H), 6.33 (dd, $J = 8.13$, $J = 1$ Hz, 2H), 4.98 (d, *anti,* $J = 10.15$ Hz, 1H), 4.14 (d, *anti,* $J = 10.15$ Hz, 1H), 3.81 (s, 3H), 3.7 (s, br, 1H), 3.33 (dd, $J = 20$, $J = 16$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 50.7, 59.8, 64.7, 113.9, 117.8, 126.9, 127.5, 127.6, 128.3, 128.5, 128.6, 128.8, 129.1, 129.2, 129.5, 133.0, 134.7, 142.1, 147.1, 205.4. Anal. calc. for $C_{29}H_{27}NO_2$: C, 82.66; H, 6.41; N, 3.32%; Found C, 82.55; H, 6.29, N, 3.25%.

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