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$HClO_4$–SiO_2 catalyzed stereoselective synthesis of β-amino ketones via a direct Mannich-type reaction

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Abstract—The $HClO_4$–SiO_2 catalyzed three-component, one-pot Mannich reaction of ketones, aromatic aldehydes and aromatic amines is carried out in ethanol to afford the corresponding β-amino ketones in good yields and high stereoselectivities in favor of the *anti*-isomer. Three new compounds are reported.

1. Introduction

Solid supported reagents are unique acid catalysts that have become popular over the last two decades. The activity and selectivity of a reagent dispersed on the surface of a support are improved as the effective surface area of the reagent is increased significantly, and hence they are expected to perform more effectively than the individual reagents.[1]

Low toxicity, moisture resistance, air tolerance and low prices are other common features that make the use of solid supported reagents as attractive alternatives to conventional Lewis acids or metal triflates.

Silica supported perchloric acid ($HClO_4$–SiO_2) has received considerable attention as an inexpensive, nontoxic and recyclable catalyst for numerous organic transformations, affording the corresponding products in excellent yields and with high selectivity.[2] To the best of our knowledge, there has been no report on the use of $HClO_4$–SiO_2 as a catalyst in the Mannich reaction.

The Mannich reaction is an important carbon–carbon bond forming reaction in organic synthesis.[3] It is used for the synthesis of β-amino carbonyl compounds, which are important synthetic intermediates for various pharmaceuticals and natural products.[4] Mannich reactions using electrophiles, such as imines and stable nucleophiles, such as enolates, enol ethers and enamines, have been reported in the literature.[5] A more desirable version of the Mannich reaction involves the use of a one-pot, three-component strategy that allows for a wide range of structural variations. In this context, recent developments in asymmetric synthesis, using a three-component protocol, have made the Mannich reaction very valuable.[6]

In this work we have found $HClO_4$–SiO_2 to be an efficient catalyst in EtOH at room temperature for the synthesis of β-amino carbonyl compounds through a one-pot, three-component reaction of aldehydes, amines and ketones.

Initially, the three-component Mannich reaction of benzaldehyde (2.5 mmol), aniline (2.5 mmol) and cyclohexanone (3 mmol) was examined. To optimize the reaction conditions, solvents such as CH_3CN, 1,4-dioxane, Et_2O, THF, toluene and EtOH were examined. Ethanol was found to be the best solvent as far as yields and reaction times were concerned. All the products precipitate in ethanol. Further experimentation revealed that the optimum amount of catalyst was 2 mol %, (Scheme 1).

The reaction of different aromatic aldehydes, anilines and cyclohexanone gave product **4** in good to high yields with excellent *anti* selectivity. The results are summarized in Table 1. 4-Nitrobenzaldehyde and 4-nitroaniline possessing strong electron-withdrawing groups did not react. 4-Bromoaniline showed the reverse selectivity in favor of the *syn*-isomer (entry 3).

Keywords: Mannich reaction; β-Amino ketones; Silica perchloric acid; Stereoselective.
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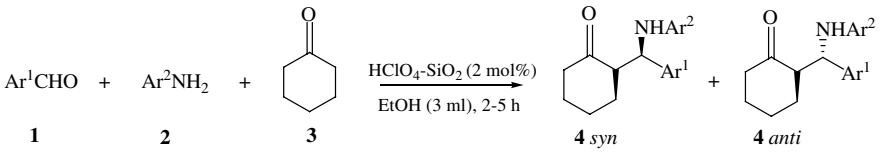


Scheme 1. One-pot, three-component Mannich reaction.

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

Entry	R^1	R^2	Time (h)	Yield[b] (%)	*anti*/*syn*[c]
1	Ph	Ph	2	98	99:1
2	Ph	4-MeC_6H_4	2	90	98:2
3	Ph	4-BrC_6H_4	3	75	28:72
4	4-MeC_6H_4	Ph	2	80	87:23
5	4-ClC_6H_4	Ph	3	85	95:5
6	1-Naphthyl	Ph	5	90	99:1
7	1-Naphthyl	4-MeC_6H_4	4	92	94:6
8	4-BrC_6H_4	Ph	4	83	98:2
9	4-ClC_6H_4	4-MeC_6H_4	3.5	80	97:3
10	4-$NO_2C_6H_4$	Ph	12	nr[d]	—
11	Ph	4-$NO_2C_6H_4$	12	nr	—

[a] Reaction conditions: aromatic aldehyde (2.5 mmol), aromatic amine (2.5 mmol), cyclohexanone (3 mmol), and $HClO_4$–SiO_2 (2 mol %).
[b] Isolated yields, products were confirmed by ^1H NMR.
[c] *Anti*/*syn* ratio was determined by ^1H NMR.
[d] No reaction.

The isomers were identified from the values of the coupling constants between the vicinal protons α- and β- to C=O. It has been reported that the *J* value of *anti* isomers (ca. 7.5 Hz) is higher than those of *syn* isomers (ca. 4.5 Hz) in these types of systems.[7] The *anti*/*syn* ratio was determined by the relative areas under the absorption peaks for H_β.

As shown in Table 1, the *anti*-isomer predominated over the *syn*-isomer with the exception of entry 3. A possible transition state is proposed in which hydrogen bonds form between $HClO_4$–SiO_2, the imine and the enol form of cyclohexanone (Scheme 2).[8] Transition state I provides more space for the aryl groups of the aldimine and less steric repulsion between the aryl groups and the catalyst in the *anti*-isomer, that is, the most stable transition state produces the *anti*-isomer.

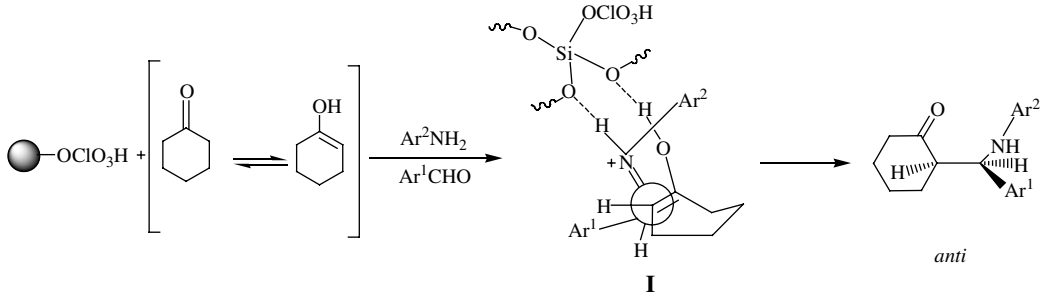
The one-pot, three-component Mannich reaction using acetophenone was also studied (Scheme 3). It was found that the corresponding β-amino carbonyl compounds were formed in good to moderate yields. The results are summarized in Table 2. Acetophenone was less reactive than cyclohexanone and required a greater quantity of catalyst (4 mol %) and longer reaction times to afford the desired products.

In summary, good stereoselectivity, high yields, nontoxic solvents, very easy work-up, low catalyst loading and no formation of by-products are the merits of this procedure.

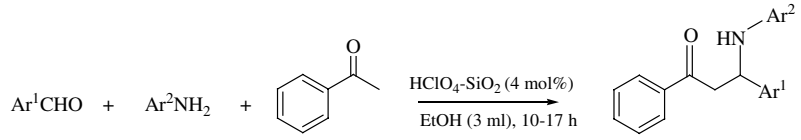
2. Experimental

2.1. A: general procedure for the synthesis of β-aminocarbonyl compounds using cyclohexanone

A mixture of benzaldehyde (2.5 mmol), aniline (2.5 mmol), cyclohexanone (3 mmol) and $HClO_4$–SiO_2 (0.01 g, 2 mol %) was stirred in EtOH (3 ml) at room temperature for 2–5 h. The reaction was monitored by TLC. After completion of the reaction, ethyl acetate



Scheme 2. Possible transition states leading to the *anti*-product.



Scheme 3. Mannich-type reaction of aromatic aldehydes, anilines and acetophenone.

Table 2. Mannich-type reactions of aromatic aldehydes, anilines and acetophenone[a]

Entry	R^1	R^2	Time (h)	Yield[b] (%)	Mp (°C)
1	Ph	Ph	12	95	168–170[9]
2	4-ClC_6H_4	Ph	15	80	131–132[10]
3	4-MeC_6H_4	Ph	15	85	128–130[9]
4	1-Naphthyl	Ph	36	Nr[c]	—
5	4-BrC_6H_4	Ph	17	75	130–131[8]
6	4-$MeOC_6H_4$	Ph	12	89	147–149[8]
7	Ph	4-$NO_2C_6H_4$	12	90	177–178[9]
8	Ph	4-MeC_6H_4	10	90	165–167[9]

[a] Reaction conditions: aldehyde (2.5 mmol), amine (2.5 mmol), acetophenone (2.5 mmol) and $HClO_4$–SiO_2 (4 mol %).
[b] Isolated yield, products were confirmed by ^1H NMR.
[c] No reaction.

was added and catalyst was removed by filtration. The filtrate was washed with $NaHCO_3$ (aq) and brine and was dried over $MgSO_4$. The solvent was removed under reduced pressure. Pure β-amino ketone was recrystallized from EtOH. In some cases, trituration in petroleum ether was necessary.

2.2. B: general procedure for the synthesis of β-aminocarbonyl compounds from acetophenone

A mixture of benzaldehyde (2.5 mmol), aniline (2.5 mmol), acetophenone (2.5 mmol) and $HClO_4$–SiO_2 (0.02 g, 4 mol %) was stirred in EtOH (3 ml) at room temperature for 10–17 h. The reaction was monitored by TLC. The products precipitated from the reaction mixture. The precipitate was filtered off, 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%).

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

3. Preparation and recycling of $HClO_4$–SiO_2

$HClO_4$–SiO_2 was prepared according to Asit K. Chakraborti's procedure.[2a] The catalyst was separated from the reaction mixture and washed with EtOH and dried at 100 °C for 24 h to give recycled $HClO_4$–SiO_2. The reaction of benzaldehyde, aniline and cyclohexanone was repeated with recycled catalyst and the yields were found to remain in the range of 90% for five recycles.

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

4.1. 2-((*p*-Toluidino)(1-naphthyl)methyl)cyclohexanone (Table 1, entry 7)

Mp 137–139 °C, IR (KBr): ν_{max}/cm^{-1} 3392, 1697, 1520, 1290, 784; ^1H NMR (300 MHz; $CDCl_3$; Me_4Si): δ 8.0 (d, 1H, $J = 8.33$ Hz), 7.9 (t, 2H, $J = 8.3$ Hz), 7.73 (d, 1H, $J = 8.1$ Hz), 7.42–7.56 (m, 3H), 6.83 (d, 2H, $J = 8.24$ Hz), 6.56 (d, 2H, $J = 8$ Hz), 5.42 (d, 0.06H, *syn*, $J = 4.1$ Hz), 5.3 (d, 0.94H, *anti*, $J = 5.72$ Hz), 3.2 (t, 1H, $J = 4.9$ Hz), 2.15–2.39 (m, 1H), 1.9–2.15 (m, 2H), 2.13 (s, 3H), 1.68–1.9 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.33, 25.06, 28.14, 33.16, 43.05, 55.09, 56.50, 113.79, 114.44, 122.09, 125.01, 125.23, 125.81, 126.18, 126.88, 127.52, 129.46, 129.60, 131.36, 133.91, 137.09, 144.92, 213.19; Anal. Calcd for $C_{24}H_{25}NO$: C, 83.93; H, 7.28; N, 4.08. Found: 83.99; H, 7.65; N, 4.07.

4.2. 2-((4-Bromophenyl)(phenylamino)methyl)cylohexanone (Table 1, entry 8)

Mp 110–112 °C, IR (KBr): ν_{max}/cm^{-1} 3393, 1713, 1600, 1493, 1275, 1011, 753; ^1H NMR (300 MHz; $CDCl_3$; Me_4Si): δ 7.4–7.44 (dd, 2H, $J = 7.4$Hz and $J = 2.4$ Hz), 7.28 (t, 2H, $J = 5.4$ Hz), 7.03–7.13 (m, 3H), 6.71 (t, 1H, $J = 6.9$ Hz), 6.58 (d, 2H, $J = 8.1$ Hz), 4.72 (d, 0.02H, *syn*, $J = 4.41$ Hz), 4.57(d, 0.98H, *anti*, $J = 6.72$ Hz), 2.86 (s, 1H), 2.34–2.43 (m, 2H), 1.6–1.9 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of diastereoisomers): δ 24.01, 24.89, 27.03, 27.85, 28.89, 31.53, 42.06, 42.45, 56.35, 56.96, 57.17, 57.62, 113.70, 114.08, 117.87, 117.95, 120.90, 129.11, 129.14, 129.28, 129.46, 131.45, 131.55, 131.66, 131.77, 131.83, 140.79, 146.84, 212.46; Anal. Calcd for $C_{19}H_{20}ONBr$: C, 63.70; H, 5.58; N, 3.91. Found: C, 63.69; H, 5.62, N, 4.01.

4.3. 2-((*p*-Toluidino)(4-chlorophenyl)methyl)cyclohexanone (Table 1, entry 9)

Mp 119–121 °C, IR (KBr): ν_{max}/cm^{-1} 3379, 1701, 1523, 1493, 1289, 813; ^1H NMR (300 MHz; $CDCl_3$; Me_4Si): δ 7.42 (d, 2H, $J = 8.27$ Hz), 7.28–7.31 (m, 2H), 7.09–7.12 (m, 1H), 6.9 (d, 2H, $J = 8.17$ Hz), 6.78 (d, 2H, $J = 7.6$ Hz), 4.6 (d, 0.03H, *syn*, $J = 5.5$ Hz), 4.5 (d, 0.97H, *anti*, $J = 8.22$ Hz), 2.36–2.5 (m, 2H), 2.3 (s, 1H), 2.22 (s, 3H), 1.66–1.83 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.39, 23.94, 27.81, 31.41, 41.98, 56.88, 58.48, 114.47, 127.35, 127.87, 128.64, 128.89, 129.0, 129.66, 129.94, 131.59, 132.91, 139.66, 143.65, 212.71; Anal. Calcd for $C_{20}H_{22}NOCl$: C, 73.28; H, 6.71; N, 4.27. Found: C, 73.38; H, 6.99, N, 4.25.

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