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One-pot synthesis of β -amino carbonyl compounds catalyzed silica supported phenylphosphinic acid

Abstract: A simple and facile synthesis of β -amino carbonyl compounds was developed by the one-pot condensation of cyclohexanone, aromatic aldehydes and anilines at 25°C in the presence of silica supported phenylphosphinic acid. β -Amino carbonyl compounds were obtained in moderate to good yields and reasonable diastereoselectivities. This method has the advantages of short reaction time, mild reaction conditions, reusable catalyst, cost efficiency and environment friendly. In addition, acetophenone and aliphatic ketones as reactants were investigated.

Keywords: β -amino carbonyl compounds; Mannich reaction; silica supported phenylphosphinic acid; synthesis.

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1 Introduction

β -Amino carbonyl compounds are valuable synthetic intermediates for various pharmaceuticals and natural products [1–3]. The Mannich-type reactions are classical methods for the synthesis of β -amino carbonyl compounds due to their atom-economy advantages and application in biologically active molecule syntheses. The reported Mannich reactions have been catalyzed by various catalysts such as $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ [4], NbCl_5 [5], BiCl_3 [6], CAN [7], $\text{Bi}(\text{OTf})_3$ [8], $\text{Zn}(\text{OTf})_2$ [9], $\text{HClO}_4 \cdot \text{SiO}_2$ [10], sulfated MCM-41 [11], ZSM-5- SO_3H [12], PEG- SO_3H [13], ionic liquid [14–17], sulphamic acid [18, 19], Cu-nanoparticles [20], $[\text{RE}(\text{PFO})_3]$

[21], silica based tin(II) catalyst [22], carbon based solid acid [23], polyaniline/ SiO_2 [24], lipase [25], saccharose [26], (bromodimethyl)sulfonium bromide [27], heteropolyacid salts [28], iodine-alumina under microwave irradiation [29], $\text{SO}_4^{2-}/\text{Ce}_x\text{Zr}_{1-x}\text{O}_2$ [30], 2-hydroxypyridine [31], ZnCl_2 [32]. However, these methods have certain drawbacks such as harsh reaction conditions, toxicity, difficulty in product separation, longer reaction time, and the use of an excess of expensive reagents/catalysts. Besides, acetophenone was adopted as reactant in the most current reports, whereas cyclohexanone was relatively less used. Therefore, there is still scope for an improved method which can avoid the above drawbacks and allow a wider range of structural variations of β -amino carbonyl compounds.

Herein β -amino carbonyl compounds were synthesized by one-pot three-component Mannich reaction of aromatic aldehydes, aromatic amines and cyclohexanone catalyzed silica supported phenylphosphinic acid ($\text{C}_6\text{H}_5\text{PO}_2\text{H}_2/\text{SiO}_2$, PPA/ SiO_2) which was rarely employed as catalyst in organic synthesis (Scheme 1).

2 Materials and methods

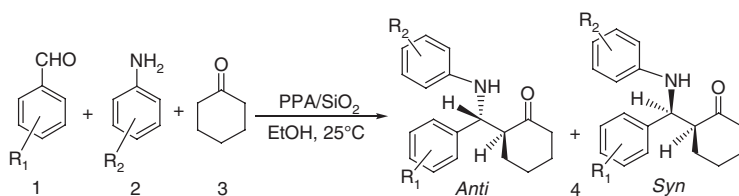
All reagents were of analytical grade and purchased from Sinopharm Chemical Reagent Co., Ltd., Shanghai, P.R. China, and were used without further purification.

2.1 Preparation of the catalyst

The catalyst is prepared by incipient-wetness impregnation method. First, the water adsorption of silica gel (230–325 mesh) is determined [33], the value is 1.05. Then a water solution of phenylphosphinic acid (PPA) (15%) is prepared, the solution (10.5 g) is added dropwise into silica gel (10.0 g) at room temperature with ultrasonic aid in an ultrasonic bath. After adding the solution, the mixture is kept in the ultrasonic bath for 2 h at room temperature in order to ensure the solution is fully absorbed. The mixture is then dried in vacuum at 100°C overnight. The drying temperature is maintained below the decomposition temperatures of the salts. The content of PPA in the catalyst determined by X-ray fluorescence (XRF) spectrometer is 0.89 mmol/g.

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

2.2 General procedure for the synthesis of β -amino carbonyl compounds

To a mixture of ketones (10 mmol), aromatic aldehydes (10 mmol) and anilines (10 mmol) in (5 ml) ethanol (EtOH), PPA/SiO₂ (5 mol%, 0.52 g) was added. The mixture was stirred at 25°C for the appropriate time. After completion of the reaction (TLC check), ethanol was added to the reaction mixture and heated up to boiling to dissolve the product and the catalyst was recovered by filtration. The product was collected from the filtrate after cooling to room temperature and recrystallized from ethanol or acetone/ethanol (2:3) to obtain the pure products.

2.3 Spectral data of products

Melting points were determined in X-6 micro melting point apparatus without further correction. IR spectra were recorded on a Perkin Elmer FTIR spectrometer in KBr. ¹H NMR spectra were obtained from solution in DMSO-*d*₆ or CDCl₃ using a Bruker AVANCE III 500 MHz spectrometer. Elemental analyses were performed using elemental Vario EL III CHNS/O Element analyzer.

All the products are known compounds. The desired pure products were characterized by spectral (IR, ¹H NMR) and analytical data, and by comparison of their physical and spectral data with those of authentic samples.

2-[Phenyl(phenylamino)methyl]cyclohexanone (4a): White Solid, m.p., 113–116°C; IR (KBr, cm⁻¹): 3325, 1704, 1604, 1498; ¹H NMR (500 MHz, CDCl₃): δ = 7.37–7.18 (m, 5H), 7.09–7.03 (m, 2H), 6.63–6.61 (m, 1H), 6.55–6.53 (m, 2H), 4.80 (s, 0.12H), 4.69 (s, 0.88H), 4.63 (br, s, J = 7.1 Hz, 1H), 2.76–2.74 (m, 1H), 2.44–2.30 (m, 2H), 1.98–1.84 (m, 4H), 1.73–1.62 (m, 2H); Anal. Calcd for C₁₉H₂₁NO: C 81.68, H, 7.58, N 5.01. Found: C 81.62, H 7.54, N 5.06.

2-[(Phenyl)(4-chlorophenylamino)methyl]cyclohexanone (4b): White Solid, m.p., 136–138°C; IR (KBr, cm⁻¹): 3388, 1704, 1599, 1512, 1445; ¹H NMR (500 MHz, CDCl₃): δ = 7.36–7.35 (m, 1H), 7.30–7.22 (m, 4H), 7.04–6.98 (m, 2H), 6.51–6.47 (m, 2H), 4.75 (d, 0.35H, J = 4.5 Hz), 4.56 (d, 0.65H, J = 7.5 Hz), 2.89–2.83 (m, 1H), 2.45–2.40 (m, 2H), 2.03–2.00 (m, 2H), 1.89–1.87 (m, 2H), 1.69–1.59 (m, 2H); Anal. Calcd for C₁₉H₂₀ClNO: C 72.71, H 6.42, N 4.46. Found: C 72.66, H 6.48, N 4.44.

2-[(4-Bromophenylamino)(phenyl)methyl]cyclohexanone (4c): White Solid, m.p., 99–100°C; IR (KBr, cm⁻¹): 3396, 1702, 1591, 1492, 1312; ¹H NMR (500 MHz, CDCl₃): δ = 7.32–7.28 (m, 4H), 7.22–7.20 (m, 1H), 7.12–7.10 (m, 2H), 4.77 (s, 0.22H), 4.72 (s, 0.78H), 4.57 (s, 0.22H), 4.52 (d, J = 6.9 Hz, 0.78H), 2.79–2.73 (m, 1H), 2.42–2.28 (m, 2H),

2.03–2.00 (m, 1H), 1.89–1.84 (m, 2H), 1.71–1.56 (m, 3H); Anal. Calcd for C₁₉H₂₀BrNO: C 63.70, H 5.63, N 3.91. Found: C 63.65, H 5.67, N 3.95.

2-[(2-Chlorophenyl)(phenylamino)methyl]cyclohexanone (4d): White Solid, m.p., 134–136°C; IR (KBr, cm⁻¹): 3330, 1702, 1592, 1512, 1446; ¹H NMR (500 MHz, CDCl₃): δ = 7.62 (m, 1H), 7.39 (m, 1H), 7.28–7.11 (m, 4H), 6.58 (d, 2H, J = 8.0 Hz), 6.69 (t, 1H, J = 7.5 Hz), 5.06 (s, 1H, br), 4.96 (d, 1H, J = 5.0 Hz), 2.95 (m, 1H), 2.48–2.34 (m, 2H), 2.22–1.70 (m, 6H); Anal. Calcd for C₁₉H₂₀ClNO: C 72.71, H 6.42, N 4.46. Found: C 72.74, H 6.43, N 4.48.

2-[(4-Chlorophenylamino)(4-methoxyphenyl)-methyl]cyclohexanone (4e): White Solid, m.p., 132–133°C; IR (KBr, cm⁻¹): 3377, 1704, 1600, 1513, 1490; ¹H NMR (500 MHz, CDCl₃): δ = 7.26 (d, J = 9.0 Hz, 2H), 7.00 (d, J = 9.2 Hz, 2H), 6.86 (d, J = 9.0 Hz, 2H), 6.46 (d, J = 9.0 Hz, 2H), 4.73 (s, 1H), 4.51 (d, J = 7.0 Hz, 1H), 3.78 (s, 3H), 2.69–2.68 (m, 1H), 2.42–2.34 (m, 2H), 1.93–1.66 (m, 6H); Anal. Calcd for C₂₀H₂₂ClNO₂: C 69.86, H 6.45, N 4.07. Found: C 69.96, H 6.38, N 4.04.

2-[(4-Bromophenylamino)(4-methoxyphenyl)-methyl]cyclohexanone (4f): White Solid; m.p., 131–133°C; IR (KBr, cm⁻¹): 3390, 1705, 1601, 1513, 1483, 1242; ¹H NMR (500 MHz, CDCl₃): δ = 7.26 (d, J = 8.6 Hz, 2H), 7.15 (d, J = 8.9 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 6.40 (d, J = 8.4 Hz, 2H), 4.70 (s, 0.91H), 4.66 (s, 0.09H), 4.51 (d, J = 7.0 Hz, 0.91H), 4.50 (s, 0.09H), 3.79 (s, 3H), eth 2.71–2.69 (m, 1H), 2.44–2.40 (m, 1H), 2.35–2.33 (m, 1H), 1.94–1.66 (m, 6H); Anal. Calcd for C₂₀H₂₂BrNO: C 61.86, H 5.71, N 3.61. Found: C 61.84, H 5.72, N 3.65.

2-[(4-Chlorophenyl)(4-chlorophenylamino)-methyl]cyclohexanone (4g): White Solid; m.p., 97–98°C; IR (KBr, cm⁻¹): 3401, 1703, 1602, 1504, 1319; ¹H NMR (500 MHz, CDCl₃): δ = 7.29–7.27 (m, 4H), 7.00 (d, J = 8.5 Hz, 2H), 6.40 (d, J = 8.3 Hz, 2H), 4.70 (s, 0.95H), 4.65 (s, 0.05H), 4.60 (s, 0.05H), 4.50 (d, J = 5.4 Hz, 0.95H), 2.71–2.69 (m, 1H), 2.40–2.32 (m, 1H), 2.31–2.27 (m, 1H), 2.00–1.96 (m, 1H), 1.89–1.88 (m, 2H), 1.84–1.60 (m, 3H); Anal. Calcd for C₁₉H₁₉Cl₂NO: C 65.53, H 5.50, N 4.02. Found: C 65.56, H 5.44, N 4.04.

2-[(3-Chlorophenylamino)(phenyl)methyl]cyclohexanone (4h): White Solid; m.p., 122–124°C; IR (KBr, cm⁻¹): 3336, 1701, 1598, 1520, 1481; ¹H NMR (500 MHz, CDCl₃): δ = 7.37–7.24 (m, 5H), 6.98–6.95 (m, 1H), 6.64–6.53 (m, 3H), 4.77 (d, 0.5H, J = 3.5 Hz), 4.55 (d, 0.5H, J = 5.0 Hz), 2.87–2.80 (m, 1H), 2.44–2.40 (m, 2H), 2.07–2.03 (m, 2H), 1.89–1.57 (m, 4H); Anal. Calcd for C₁₉H₂₀ClNO: C 72.71, H 6.42, N 4.46. Found: C 72.76, H 6.35, N 4.46.

3 Results and discussion

At the outset, the Mannich reaction was examined with benzaldehyde, aniline and cyclohexanone in the

presence of PPA/SiO₂ to explore the standard operating conditions. As we know, the solvents played an important role in the Mannich reaction, various solvents were tested for the reaction catalyzed by PPA/SiO₂. As shown in Table 1, Mannich reaction could proceed in H₂O, methanol and EtOH. Among these, EtOH yielded products with the highest selectivity and conversion, while CH₂Cl₂ were found to be less satisfactory in terms of the yield. Therefore, EtOH was selected as the solvent in the continuing study. The effect of the amount of catalyst was also examined in this reaction. It was found that a 5% mol amount of PPA/SiO₂ was sufficient to promote the reaction and larger amounts of the catalyst did not lead to any significant changes in the reaction yield. In addition, there was no reaction in the absence of catalyst, indicating that this was indeed a PPA/SiO₂-catalyzed reaction.

After optimizing the procedure, the studies have focused on the application of PPA/SiO₂ for Mannich reactions with different aldehydes, anilines and cyclohexanone. All the reactions proceeded within the periods ranging from 30 min to 70 min with good to high yields of β -amino carbonyl compounds (Table 2). The *anti/syn* ratio was determined by the integration of the corresponding peak in ¹H MNR spectrum. In most case, the major *anti* diastereoisomers were obtained.

The reusability of the catalyst was checked by separating PPA/SiO₂ from the reaction mixture by simple filtration. The catalyst was then washed with acetone and dried at 60°C for 3 h prior to use in another reaction. From Figure 1, it was found that an above 50% yield could be obtained in the first five minutes, after which the rate of reaction slowed down. The recovered catalyst could be reused at least two additional times in subsequent reactions with a slight decrease in product yield, and the yield

Table 1 Effect of different solvents and catalyst amounts on the Mannich reaction catalyzed by PPA/SiO₂.^a

Entry	Solvent	Amount of catalyst (mol%)	Reaction time (min)	Yield (%) ^b
1	CH ₂ Cl ₂	10	60	Trace
2	H ₂ O	10	60	39
3	CH ₃ OH	10	60	76
4	EtOH	2	30	69
5	EtOH	3	30	86
6	EtOH	5	30	93
7	EtOH	10	30	94
8	EtOH	0	30	0

^aReaction conditions: cyclohexanone (10 mmol), benzaldehyde (10 mmol), aniline (10 mmol), solvent (5ml), 25°C.

^bIsolated yield.

Table 2 Three-component Mannich reactions of aldehydes, amines, and ketone catalyzed by PPA/SiO₂.

Entry	Product	R ₁	R ₂	Time (min)	Yield (%) ^a	<i>Anti/Syn</i> ratio ^b
1	4a	H	H	30	93	88:12
2	4b	H	4-Cl	60	85	65:35
3	4c	H	4-Br	40	89	78:22
4	4d	2-Cl	H	40	84	100:0
5	4e	4-CH ₃ O	4-Cl	60	86	100:0
6	4f	4-CH ₃ O	4-Br	40	91	91:9
7	4g	4-Cl	4-Cl	35	96	95:5
8	4h	H	3-Cl	70	67	50:50

^aIsolated yield.

^bDetermined by ¹H NMR.

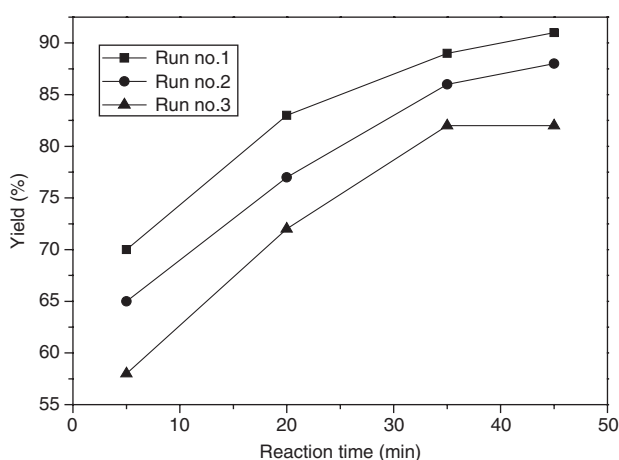
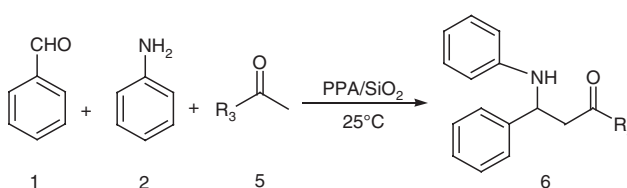


Figure 1 Recyclability of the catalyst in the reaction of benzaldehyde, cyclohexanone and aniline catalyzed by PPA/SiO₂.



Scheme 2 Mannich reactions of ketones, benzaldehyde and aniline.

Table 3 Three-component Mannich reactions of ketones with benzaldehyde and aniline catalyzed by PPA/SiO₂.^a

Entry	Condition	Product	R ₃	Time (h)	Yield (%)
1	EtOH	6a	C ₆ H ₅	5	53
2	Solvent-free	6a	C ₆ H ₅	8	84
3	EtOH	6b	CH ₃	5	0
4	Solvent-free	6b	CH ₃	6	0
5	EtOH	6c	C ₂ H ₅	4	0
6	Solvent-free	6c	C ₂ H ₅	6	0

^aAmount of catalyst: 8 mol%.

Table 4 Comparison of the efficiencies of various catalysts used in the synthesis of 2-[phenyl(phenylamino)methyl]cyclohexanone.

Catalyst	Condition/T (°C)/time (h)	Molar ratio (aldehyde: aniline: ketone)	Yield (%)	Reference
Zn(OTf) ₂	Solvent-free/r.t./4 h	1:1:1.2	93	9
Sulfated MCM-41	EtOH/reflux/6 h	1:1:1	95	11
Cu-nanoparticles	MeOH/r.t., N ₂ /8 h	1:1:1	93	20
SO ₄ ²⁻ /Ce _x Zr _{1-x} O ₂	Solvent-free/r.t., N ₂ /-	1:1:4	82	30
2-Hydroxypyridine	EtOH/r.t./24 h	3:3:1:5	83	31
Silica-supported ZnCl ₂	Solvent-free/r.t./20 min	1:1:1.5	92	32
PPA/SiO ₂	EtOH/r.t./30 min	1:1:1	93	This work

was 82% when the catalyst was recycled three times, which indicated a loss of catalytic activity.

To explore the scope and limitations of this reaction further, the reactions of different ketones with benzaldehyde and aniline were carried out (Scheme 2, Table 3). From Table 3, it could be seen that when acetophenone was used, the desired product could be obtained with 84% yield in 8 h under solvent-free condition which indicated that acetophenone was less reactive than cyclohexanone. And aliphatic ketones did not react with benzaldehyde and aniline under the present reaction conditions.

To show the merit of the present work, we summarized some of the results for the synthesis of 12-[Phenyl(phenylamino)methyl]cyclohexanone obtained by other workers. As shown in Table 4, only catalytic activity of silica-supported ZnCl₂ was close to that of our catalyst, but excess ketone was used in the procedure, which obviously improved the yields of products. Furthermore, the utilization of excess reagent was less environmentally friendly and uneconomical. So our method has the advantages of high yield, short reaction time, low cost and mild reaction conditions in comparison with the results found in the literature.

4 Conclusion

A simple and efficient method for the synthesis of β -amino carbonyl compounds using PPA/SiO₂ as catalyst has been developed, which yields short reaction time, mild reaction conditions, reusable catalyst and is environmentally friendly.

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Bionotes



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