

An Eco-Friendly Protocol for Synthesis of β -aminoketones via Mannich Reaction Using Citric Acid: A Biodegradable Catalyst

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Abstract: A simple, highly efficient and eco-friendly protocol for synthesis of β -aminoketones via Mannich reaction from aromatic aldehydes, anilines, and aromatic ketones at ambient temperature in the presence citric acid is described. Using this method, β -aminoketones are produced in high to excellent yields under mild and green condition.

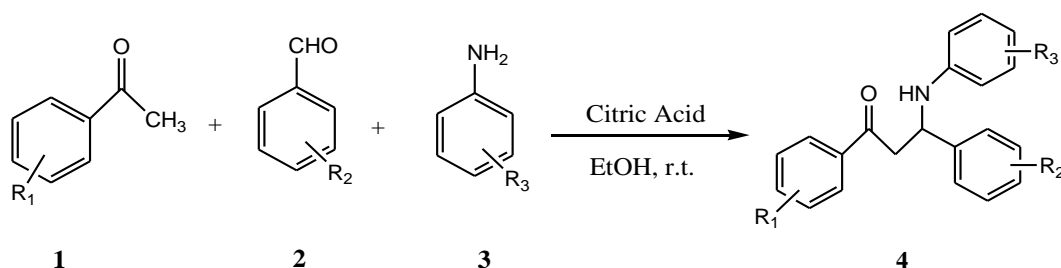
Keywords: Citric acid, Mannich reaction, β -amino carbonyl compounds, One-pot reaction.

I. Introduction:

Mannich reactions are among the most significant carbon-carbon bond forming reactions in synthetic organic chemistry [1, 2]. They provide β -amino carbonyl compounds, which are important synthetic intermediates for various pharmaceuticals and natural products [3, 4]. β -amino carbonyl derivatives are found in a number of biologically active natural products [5]. The reported Mannich reactions have been catalyzed by various Lewis or Brønsted acid catalysts such as silica-supported AlCl_3 [6], $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ [7], NbCl_5 [8], BiCl_3 [9], CAN [10], $\text{HClO}_4 \cdot \text{SiO}_2$ [11], $\text{Bi}(\text{OTf})_3$ [12], $\text{Zn}(\text{OTf})_2$ [13], ionic liquid [14-17], sulphamic acid [18-20], $\text{Fe}(\text{Cp})_2\text{PF}_6$ [21], Cu-nanoparticles [22], $[\text{RE}(\text{PFO})_3]$ [23], silica based tin(II) catalyst [24], PEG- SO_3H [25] ZSM-5- SO_3H [26], carbon based solid acid [27], polyaniline/ SiO_2 [28], lipase [29], saccharose [30], heteropolyacid salts [31]. However, most of the reported methods for the Mannich reaction suffer from drawbacks such as long reaction times and harsh reaction conditions, toxicity, and difficulty in product separation, which limit its use in the synthesis of complex molecules. Furthermore, some of them are corrosive and volatile, and often cause the environment problems. Therefore, the development of simple, efficient, high yielding, and environmentally friendly methods using new catalysts for the Mannich reaction is still necessary.

Utilization of naturally as well as easily available and biodegradable catalyst for organic synthesis is achieving enormous significance in the last few years as a result of both the novelty of concept and, more importantly, the fact that the efficiency and selectivity of these reactions meet the standards of established organic reactions. In this regard, Citric acid keeps the potential of performing the role of ideal catalyst. It is a relatively strong acid. Citric acid and its salts are widely used because they are nontoxic, relatively non-corrosive, safe to handle and easily biodegraded. Citric acid has been explored as powerful catalyst for various organic transformations [32-35].

In the continuation of our work, to explore the green chemistry goals [36], we offer the synthesis of β -amino carbonyl compounds by reacting various types of aldehydes, aromatic ketones, and aromatic amines catalyzed by citric acid.



Scheme 1. Citric acid-catalyzed one-pot Mannich reaction.

II. Results And Discussion:

To explore the use of citric acid as a catalyst, Mannich-type reaction of acetophenone (1), benzaldehyde (2) and aniline (3) for the preparation of β -amino carbonyl compounds compound 4 was considered as a standard model reaction (Scheme 1). Model reaction in the absence of catalyst did not led to

desired product formation. It means intervention of catalyst was must for initiation of the reaction. To obtain best reaction conditions, different acid catalysts were screened for the model reaction viz. oxalic acid, Malonic acid, succinic acid and citric acid. The reaction in the presence of oxalic acid, Malonic acid and succinic acid was performed, and the product was obtained in moderate yields (**Table 1**). In comparison with these, citric acid proved to be most efficient catalyst which delivered the desired product in higher yield. To determine exact requirement of catalyst for the reaction, we investigated the model reaction using different concentrations of citric acid. During this study, we observed that, 20 mol% citric acid proved to be an efficient catalyst to carry out the reaction smoothly.

The model reaction was further investigated using different solvent systems, whether, the reaction rate could be accelerated and, the product yield could be enhanced. During this study solvent system like ethanol, methanol, water and aqueous ethanol were tested but, use of ethanol proved to be suitable. To evaluate the temperature effect on reaction rate, model reaction was performed at different temperatures. It was found that, room temperature was found to carry out the reaction efficiently in excellent yield. Encouraged by this result, in further set of experiments, in order to build the generality of the reaction, a series of aldehydes, aromatic ketones, and aromatic amines were investigated under the optimized reaction conditions. All of these substrates were found to be compatible under the optimized reaction conditions delivering the products in good yields. A variety of aromatic aldehydes with either electron-donating or electron-withdrawing groups were converted to β -amino carbonyl compounds in good to excellent yields. All the results are summarized in Table 2.

Table 1. Mannich reaction of acetophenone, benzaldehyde and aniline catalyzed by different catalysts^a

Entry	Catalyst	Conc. (mol %)	Time (h)	Yield ^b (%)
1	---	---	24	NR
2	Oxalic acid	10	14	63
3	Malonic acid	10	16	66
4	Succinic acid	10	16	68
5	Citric acid	10	12	74
6	Citric acid	15	10	82
7	Citric acid	20	10	90
8	Citric acid	25	12	87

^a All reactions of acetophenone (2 mmol), benzaldehyde (2 mmol) and aniline (2 mmol) were carried out in ethanol (5 mL) at room temperature. ^b Yields refer to the isolated products.

Table 2. Citric acid catalyzed Mannich reactions of ketones, aldehydes and amines

Entry	R ₁	R ₂	R ₃	Yield(%) ^a /Time (h)	m.p. ^o C		Ref. No.
					Found	Reported	
4a	H	H	H	90 (10)	168-170	169-170	6
4b	H	4-NO ₂	H	92 (13)	180-82	179-180	6
4c	H	4-CH ₃	H	88 (14)	137-139	134-135	6
4d	H	4-Cl	H	91 (12)	116-118	114-115	6
4e	H	4-OCH ₃	H	88 (13)	166-168	165-168	7
4f	H	4-Br	H	90 (12)	122-125	123-127	10
4g	H	H	3-NO ₂	86 (13)	137-139	138-139	23
4h	H	H	4-NO ₂	78 (14)	181-183	179-180	6
4i	H	H	2-NO ₂	74 (16)	162-164	158-162	10
4j	H	H	4-CH ₃	92 (12)	167-169	166-168	30
4k	H	H	4-Cl	88 (08)	168-170	170-71	6
4l	H	H	3-Cl	84 (08)	133-35	130-32	25
4m	H	H	4-OCH ₃	90 (12)	161-163	163-165	25
4n	4-CH ₃	H	H	90 (16)	140-142	139-140	9
4o	4-NO ₂	H	H	88 (15)	116-118	114-116	9

^aIsolated yields.

III. Experimental:

1.1. Chemicals and Apparatus:

All purchased chemicals were of analytical grade and used without further purification. Silica gel coated aluminium sheets (Merck made) were used for thin layer chromatography to monitor progress of reactions. Melting points were determined in an open capillary tube and are uncorrected. IR spectra were recorded on Shimadzu FT-IR 157 spectrophotometer (KBr). ¹H NMR spectra were recorded using CDCl₃ as solvent and TMS as internal standard at 300 MHz on Bruker DRX-300 NMR spectrophotometer. All the products were characterized by IR spectral data and comparison of their melting points with those reported in

literature and found to be identical. Also, the structures of some products were confirmed by ^1H NMR spectral data.

1.2. General procedure for the synthesis β -amino carbonyl compounds 4:

To mixture of aromatic ketone **1** (260 mg, 2 mmol), aromatic aldehydes **2** (212 mg, 2 mmol) and anilines **3** (186 mg, 2 mmol) in (5 mL) ethanol, citric acid (84 mg, 20 mol %) was added. The mixture was stirred at room temperature for the appropriate time indicated in **Table 2**. After completion of reaction (TLC check), the reaction mixture was placed at ambient temperature to evaporate EtOH and H_2O to give the crude product. The crude product was washed with water to remove excess of acid and product purified by recrystallization from ethanol or acetone/ethanol (2:3) to afford the pure products.

Selected spectral data:

Entry (4e): IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$: 3376 (NH), 1670 (CO). **^1H NMR** (300 MHz, TMS, CDCl_3): 3.47-3.40 (m, 2H), 3.62 (s, 3H, -OCH₃), 4.96 (t, 1H), 6.47 (d, J 8.1 Hz, 2H, Ar-H), 6.52 (t, 1H, Ar-H), 6.90-6.86 (m, 2H, Ar-H), 7.23 (d, J 8.2 Hz, 2H, Ar-H), 7.33-7.28 (m, 2H, Ar-H), 7.44-7.41 (m, 2H, Ar-H), 7.54-7.51 (m, 1H, Ar-H), 7.89 (d, J 7.5 Hz, 2H, Ar-H).

Entry (4j): IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$: 3387 (NH), 1667 (CO). **^1H NMR** (300 MHz, TMS, CDCl_3): 2.47 (s, 3H, -CH₃), 3.62-3.45 (m, 2H), 4.47 (t, 1H), 6.91 (d, J 8.5 Hz, 2H, Ar-H), 6.97 (d, J 7.9, 2H, Ar-H), 7.07-7.03 (m, 2H, Ar-H), 7.15 (d, J 6.3 Hz, 2H, Ar-H), 7.32-7.28 (m, 1H, Ar-H), 7.49-7.46 (m, 2H, Ar-H), 7.69-7.66 (m, 1H, Ar-H), 7.83 (d, J 7.9 Hz, 2H, Ar-H).

Entry (4o): IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$: 3382 (NH), 1676 (CO). **^1H NMR** (300 MHz, TMS, CDCl_3): 3.44-3.57 (m, 2H), 5.10 (t, 1H), 6.48 (d, J 6.2 Hz, 2H, Ar-H), 6.69-6.63 (m, 2H, Ar-H), 6.80-6.83 (m, 1H, Ar-H), 7.14 (d, J 7.6 Hz, 2H, Ar-H), 7.23-7.26 (m, 1H, Ar-H), 7.31-7.35 (m, 2H, Ar-H), 7.62 (d, J 6.3 Hz, 2H, Ar-H); 7.92 (d, J 7.2 Hz, 2H, Ar-H).

IV. Conclusion:

In summary, we have developed an efficient, mild and clean synthetic protocol for three components, one-pot method for the synthesis of β -amino carbonyl derivatives in the presence of citric acid as a highly efficient catalyst at ambient temperature. In this method, attempt has been made for exploitation of the catalytic activity of citric acid in organic transformation. This new strategy has several advantages, such as excellent yield, mild reaction conditions, low cost, simple experimental as well as isolation procedures, and finally, it is in agreement with the green chemistry protocols. These advantages will make this method become an attractive greener technique for the synthesis of β -amino carbonyl derivatives, compared to the existing methods.

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References:

- [1]. M. Arend, B. Westermann, N. Risch, Modern variants of the Mannich reaction, *Angew. Chem. Int. Ed.* Vol. 37, No. 8, 1998, pp. 1044–1070.
- [2]. S. Kobayashi, H. Ishitani, Catalytic enantioselective addition to imines, *Chem. Rev.* Vol. 99, No. 5, 1999, pp. 1069–1094.
- [3]. R. Muller, H. Goesmann, H. Waldmann, N,N-Phthaloylamino acids as chiral auxiliaries in asymmetric Mannich-type reactions, *Angew. Chem. Int. Ed.* Vol. 38, No. 1-2, 1999 pp. 184–187.
- [4]. H. Bohme, M. Haake, in: E.C. Taylor (Ed.), *Advances in Organic Chemistry*, vol. 7, John Wiley and Sons, New York, 1976, p. 107.
- [5]. F.A. Davis, J.M. Szewczyk, Synthesis and applications of nonracemic β -amino aldehydes to the asymmetric synthesis of piperdines:(+)-dihydropinidine, *Tetrahedron Lett.* Vol. 39 No. 33, 1998, pp. 5951–5954.
- [6]. Z. Li, X.L. Ma, J. Liu, et al., Silica-supported aluminum chloride: a recyclable and reusable catalyst for one-pot three-component Mannich-type reactions, *J. Mol. Catal. A: Chem.*, Vol. 272, No. 1-2, 2007, pp. 132–135.
- [7]. Y. Dai, B.D. Li, H.D. Quan, C.X. Lu, $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ as an efficient catalyst for one-pot synthesis of β -amino ketones by three-component Mannich reaction, *Chin. Chem. Lett.*, Vol., 21, No. 1, 2010, pp. 31–34.
- [8]. R. Wang, B-G Li, T-K Huang, L. Shi, X-X Lu, NbCl_5 -Catalyzed one-pot Mannich-type reaction: three component synthesis of β -amino carbonyl compounds, *Tetrahedron Lett.* Vol. 48, No. 12, 2007, pp. 2071-2073.
- [9]. H. Li, H. Zeng, H. Shao, Bismuth(III) chloride-catalyzed one-pot Mannich reaction: three-component synthesis of β -amino carbonyl compounds, *Tetrahedron Lett.*, Vol. 50, No. 49, 2009, pp. 6858–6860.
- [10]. M. Kidwai, D. Bhatnagar, N.K. Mishra, et al., CAN catalyzed synthesis of β -amino carbonyl compounds via Mannich reaction in PEG, *Catal. Commun.*, Vol. 9, No. 15, 2008, pp. 2547–2549.
- [11]. M.A. Bigdeli, F. Nemati, G.H. Mahdavinia, HClO_4 - SiO_2 catalyzed stereoselective synthesis of β -amino ketones via a direct Mannich-type reaction, *Tetrahedron Lett.* Vol. 48, No. 38, 2007, pp. 6801–6804.
- [12]. O. Thierry, N. Etienne, Synthesis of β -Amino Esters by Bismuth Triflate Catalyzed Three-Component Mannich-Type Reaction, *Synlett*, Vol. 2, 2006, pp. 219-222.
- [13]. Y.Y. Yang, W.G. Shou, Y.G. Wang, Synthesis of β -amino carbonyl compounds via a $\text{Zn}(\text{OTf})_2$ -catalyzed cascade reaction of anilines with aromatic aldehydes and carbonyl compounds, *Tetrahedron*, Vol. 62, No. 43, 2006, pp. 10079–10086.

- [14]. H. Xing, T. Wang, Z. Zhou, Y. Dai, The sulfonic acid-functionalized ionic liquids with pyridinium cations: Acidities and their acidity-catalytic activity relationships, *J. Mol. Catal. A: Chem.*, Vol. 264, No. 1-2, 2007, pp. 53-59.
- [15]. S. Sahoo, T. Joseph, S.B. Halligudi, Mannich reaction in Brønsted acidic ionic liquid: A facile synthesis of β -amino carbonyl compounds, *J. Mol. Catal. A: Chem.*, Vol. 244, No. 1-2, 2006, pp. 179-182.
- [16]. F. Dong, F. Zhenghao, L. Zuliang, Functionalized ionic liquid as the recyclable catalyst for Mannich-type reaction in aqueous media, *Catal. Commun.* Vol. 10, No. 8, 2009, pp. 1267-1270.
- [17]. C. Yue, Aromatic Compounds Mannich Reaction Using Economical Acidic Ionic Liquids Based on Morpholinium Salts as Dual Solvent-Catalysts, *Syn. Comm.* Vol. 40, No. 24, 2010, pp. 3640-3647.
- [18]. M. Xia, Y-D Lu, A novel direct and one-pot Mannich synthesis of fluorinated β -aminobutanones with sulfamic acid as a green catalyst, *J. Fluorine Chem.*, Vol. 127, No. 8, 2006, pp. 1119-1124.
- [19]. H. Zeng, H. Li, H. Shao, One-pot three-component Mannich-type reactions using Sulfamic acid catalyst under ultrasound irradiation, *Ultrason. Sonochem.* Vol. 16, No. 6, 2009, pp. 758-762.
- [20]. H-T Luo, Y-R Kang, H-Y Nie, L-M Yang, Sulfamic Acid as a Cost-Effective and Recyclable Catalyst for β -Amino Carbonyl Compounds Synthesis, *J. Chin. Chem. Soc.*, Vol. 56, No. 1, 2009, pp. 186-195.
- [21]. R.I. Kureshy, S. Agrawal, S. Saravanan, et al., Direct Mannich reaction mediated by $\text{Fe}(\text{Cp})_2\text{PF}_6$ under solvent-free conditions, *Tetrahedron Lett.* Vol. 51, No. 3, 2010, pp. 489-494.
- [22]. M. Kidwai, N.K. Mishra, V. Bansal, et al., Novel one-pot Cu-nanoparticles-catalyzed Mannich reaction, *Tetrahedron Lett.* Vol. 50, No. 12, 2009, pp. 1355-1358.
- [23]. L. Wang, J. Han, J. Sheng, H. Tian, Z. Fan, Rare earth perfluorooctanoate $[\text{RE}(\text{PFO})_3]$ catalyzed one-pot Mannich reaction: three component synthesis of β -amino carbonyl compounds, *Catal. Commun.*, Vol. 6 No. 3, 2005, pp. 201-204.
- [24]. R.K. Sharma, D. Rawat, G. Gaba, Inorganic-organic hybrid silica based tin (II) catalyst: synthesis, characterization and application in one-pot three-component Mannich reaction, *Catal. Commun.* Vol. 19, No. 1, 2012 pp. 31-36.
- [25]. X.C. Wang, L.J. Zhang, Z. Zhang, Z.J. Quan, PEG-OSO₃H as an efficient and recyclable catalyst for the synthesis of β -amino carbonyl compounds via the Mannich reaction in PEG-H₂O, *Chin. Chem. Lett.* Vol. 23, No. 4, 2012, pp. 423-426.
- [26]. A. R. Massah, R. J. Kalbasi, N. Samah, Highly Selective Synthesis of β -Amino Carbonyl Compounds over ZSM-5-SO₃H under Solvent-free Conditions, *Bull. Korean Chem. Soc.*, Vol. 32, No. 5, 2011 pp. 1703-1708.
- [27]. A. Davoodnia, A. Tavakoli-Nishaburi, N. Tavakoli-Hoseini, Carbon-based Solid Acid Catalyzed One-pot Mannich Reaction: A Facile Synthesis of β -Amino Carbonyl Compounds, *Bull. Korean Chem. Soc.*, Vol. 32, No. 2, 2011 pp. 635-638.
- [28]. A. A. Yelwande, B. R. Arbad, M. K. Lande, Polyaniline/SiO₂ catalyzed one-pot Mannich reaction: β -amino carbonyl synthesis, *J. Korean Chem. Soc.* Vol. 55, No. 4, 2011, pp. 644-649.
- [29]. Li K, He T, Li C, Feng X-W, Wang N, Yu X-Q, Lipase-catalysed direct Mannich reaction in water: utilization of biocatalytic promiscuity for C-C bond formation in a "one-pot" synthesis, *Green Chem.* Vol. 11, 2009, pp. 777-779.
- [30]. M. R. Mousavi, N. Hazeri, M. T. Maghsoodlou, S. Salahi, S. M. Habibi-Khorassani, Entirely green protocol for the synthesis of β -amino ketones using saccharose as a homogenous catalyst, *Chin. Chem. Lett.* Vol. 24, No. 5, 2013, pp. 411-414.
- [31]. W-Y Li, Y-X Zong, J-K Wang, Y-Y Niu, Sulfonated poly(4-vinylpyridine) heteropolyacid salts: A reusable green solid catalyst for Mannich reaction, *Chin. Chem. Lett.* Vol. 25, No. 4, 2014, pp. 575-578.
- [32]. Jung M. E., Yoo D., Synthesis of the C₁-C₁₂ Fragment of the Tedanolides. Aldol-Non-Aldol Approach, *Org Lett.* Vol. 9, No. 18, 2007, pp. 3543-3546.
- [33]. Enugala R., Nuvvula S., Kotra V., Green Approach for the Efficient Synthesis of Quinolines Promoted by Citric Acid, *Heterocycles*, Vol. 75, No. 4, 2008 pp. 2523-2533.
- [34]. E. Ramu, V. Kotra, N. Bansal R. Varala, S. R. Adapa, Green Approach For The Efficient Synthesis of Biginelli Compounds Promoted By Citric Acid Under Solvent-Free Conditions, *Rasayan J. Chem.* Vol.1 No. 1, 2008 pp. 188-194.
- [35]. Q-S. Ding, J-L. Zhang, J.-Xi Chen, et al., Tandem Synthesis of 2,3-Dihydroquinazolin-4(1H)-ones on Grinding under Solvent-Free Conditions, *J. Heterocyclic Chem.* Vol. 49, No.2, 2012, pp. 375-380.
- [36]. M. Z. Ahmed, N. T. Patel, K. A. Shaikh, M. A. Baseer, S. Shahid, V. A. Patil, Atom efficient grinding technique for the synthesis of hydrazones catalyzed by citric acid, *Elixir Org. Chem.* Vol. 43, 2012 pp. 6583-6585.