Indian Journal of Fundamental and Applied Life Sciences ISSN: 2231– 6345 (Online)
An Open Access, Online International Journal Available at www.cibtech.org/sp.ed/jls/2014/04/jls.htm
2014 Vol. 4 (S4), pp. 779-784/Zhiani et al.
Research Article

A RAPID AND GREEN METHOD FOR SYNTHESIS OF β-AMINO KETONES (MANNICH REACTION) USING AN ACID CATALYST NANO- SIO_2

***Rahele Zhiani[1], Afsaneh Tavakoli-Nishaburi[1], Fatemeh Abedi[1] and Marjan Moradi[2]**
[1]*Department of Chemistry, Neyshabur Branch, Islamic Azad University, Neyshabur, Iran*
[2]*Young Researchers and Elite Club, Quchan Branch, Islamic Azad University, Quchan, Iran*
** Author for Corresponce*

ABSTRACT
In this work we have reported a simple new catalytic method for the synthesis of β-amino carbonyl compounds by one-pot three-component Mannich reaction of cetophenone, aromatic aldehydes and aromatic amines using an nano-SiO_2 acidic catalyst as an efficient and reusable, catalyst.High yields, relatively short reaction times and easy work up are just a few of the advantages of this procedure.

Keywords: *β-amino Ketones; Catalyst; Mannich Reaction; Nano-SiO_2; Synthesis*

INTRODUCTION
One of the important goals in organic chemistry is the development of new methodologies for the synthesis of functionalized biologically active compounds with structural diversity from simple and readily available precursor molecules.

β-Amino carbonyl compounds are important intermediates for various pharmaceutical and natural product syntheses including β-amino alcohols, β-amino acids, and lactams (Simplício *et al.*, 2007), (Mandloi *et al.*, 2005).

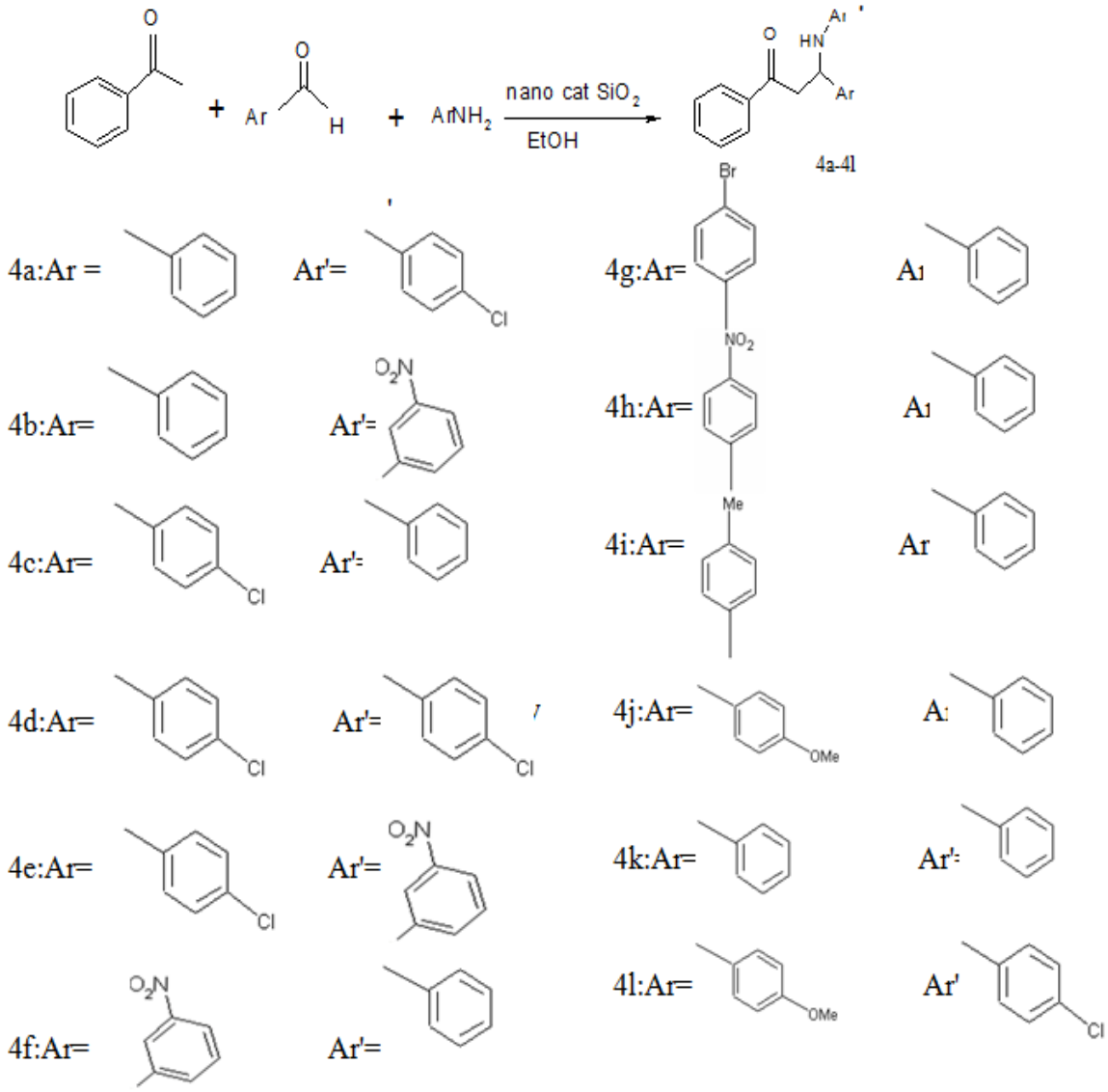
Therefore, the development of new synthetic methods leading to β-amino carbonyl compounds or their derivatives has attracted much attention. However, the classic Mannich reaction has limited applications. But the preferred route is to use a one-pot three-component strategy that gives a wide range of structural variations.

Recently, some one-pot Mannich reactions on the user of ketones, aldehydes and amines have been catalyzed by organic or mineral acids likes- proline (List *et al.*, 2002), $CeCl_3$-$7H_2O$ (Dai *et al.*, 2010), p-dodecyl benzene sulfonic acid (DBSA) (Manabe and Kobayashi, 1999),

L-proline (List, 2000), urea derivatives (Wenzel and Jacobsen 2002), $Zn(BF_4)_2$ (Brindaban *et al.*, 2002), $Yb(OTf)_3$ (Komoto and Kobayashi, 2004), $Cu(OTf)_2$ (Wolfgang *et al.*, 2001), $TiCl_4$ (Periasamy *et al.*, 2005), $ZrOCl_2$-$8H_2O$ (Knüppel, 2005), $Bi(OTf)_3$-$4H_2O$ (Ollevier *et al.*, 2006), $Zn(OTf)_2$ (Salter *et al.*, 2006), $H_3PW_{12}O_{40}$ (Azizi *et al.*, 2006), $NbCl_5$ (Wang *et al.*, 2007), guanidine hydrochloride (GuHCl) (Heravi *et al.*, 2011), rare earth per fluoro octanoate (Wang *et al.*, 2005), silica supported aluminum chloride (Li *et al.*, 2007), and a few others.

However, these methods have some drawbacks such as long reaction time, use of costly and non-recoverable catalysts, use of toxic reagents, and requirement of special effort for catalyst preparation. Nano SiO_2 sulfuric acid is an excellent acidic catalyst, which is frequently used to promote some important reactions (Salehi *et al.*, 2005), (Khodaei *et al.*, 2005), (Wu *et al.*, 2006).

We report herein full details of a novel, convenient, and simple procedure to realize a one-pot three-component reaction of aldehydes, amines, and ketones, catalyzed by using an nano-SiO_2 acid catalyst, for the preparation of β-amino carbonyl compounds in EtOH (Scheme 1).



Scheme 1: Mannich reaction catalyzed by Experimental

Chemicals were either prepared in our laboratories or purchased from Merck, Fluka and Aldrich Chemical Companies. All yields refer to isolated products. The products were characterized by comparing of their physical data with those of known samples or by their spectral data.

The catalyst was synthesized according to the known literature. Melting points were recorded on an electro thermal type 9100 melting point apparatus. The IR spectra were obtained using a 4300 Shimadzu spectrophotometer as KBr disks. The ^{1}H NMR (500 MHz) spectra were recorded with a Bruker DRX500 spectrometer.

General Procedure for the Synthesis of β-amino Carbonyl Compounds by nano SiO_2 Catalyzed Mannich Reaction. To a mixture of acetophenone (2 mmol), aromatic aldehyde (2 mmol) and aromatic amine (2 mmol) in ethanol (7 ml), nano-SiO_2 acid catalyst (0.10 g) was added. The mixture was stirred at room temperature and the reaction was monitored by TLC. Upon completion, the mixture was heated up to boiling. The catalyst was dissolved in hot ethanol and centrifugation at 2000–3000 rpm.

The product was collected from the centrifugation after cooling to room temperature and recrystallized from ethanol to give compounds 4a-l in high yields**.**

RESULTS AND DISCUSSION

Nano-SiO_2 acid catalyst is a dry, non volatile, odourless and white crystalline solid with outstanding physical property and stability. The crystals can be kept in the laboratory for many years without change. It is commercially available and is very cheap, highly reactive and eco-friendly.

Initially, the synthesis of compound 4a was selected as a model reaction to optimize the reaction conditions. The reaction was carried out by stirring a mixture of acetophenone (2 mmol), benzaldehyde (2 mmol) and 4-chloroaniline (2 mmol) in ethanol in the presence of various amount of nano-SiO_2 acidic as a catalyst. The efficiency of the reaction is affected mainly by the amount of nano-SiO_2 acid catalyst (Table 1).

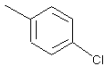
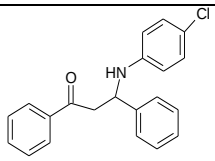
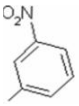
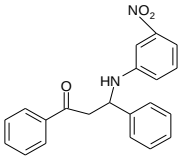
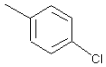
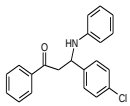
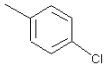
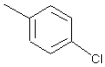
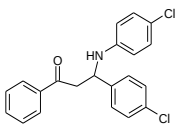
Table 1: Effect of the amounts of nano-SiO_2 acid catalyst on the model reaction

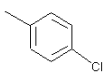
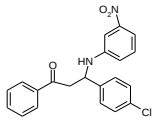
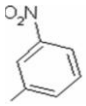
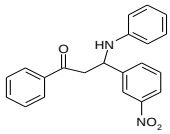
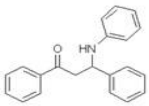
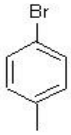
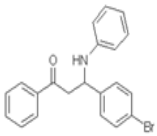
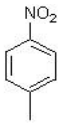
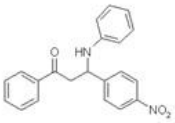
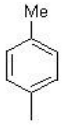
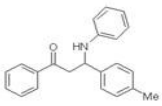
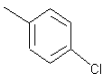
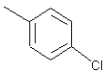
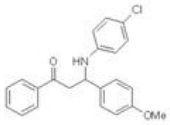
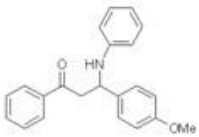
Entry	Catalyst (g)	Time (h)	Yield (%)
1	None	10	None
2	0.04	8	70
3	0.06	7	75
4	0.08	5.30	78
5	0.10	4.30	90
6	0.12	4.30	90
7	0.15	5	94

No products were produced in the absence of the catalyst (entry 1). To give the product, the catalyst is necessary for the reaction. Increasing the amount of the catalyst increased the yield of the product 4a. The optimal amount of nano-SiO_2 acid catalyst was 0.10 g (entry 5); increasing the amount of the catalyst beyond this value did not increase the yield noticeably (entries 6-7).

In order to evaluate the generality of this model reaction, other aldehydes and amines were tested for the Mannich reactions with acetophenone in ethanol at room temperature. The type of aldehydes and amines had no significant effect on the reaction. The results are summarised in (Table 2).

Table 2: Nano-SiO_2 acid catalyzed Mannich reaction[a]

Entry	Ar	Aŕ	Products[b]	Time (h)	Yield (%)[c]	mp (°C) Found	Reported
1			 4a	4:30	90	174-176	170-171
2			 4b	4:00	81	146-148	138-139
3			 4c	6:30	87	117-118	114-115
4				4:20	85	124-126	118-119

5			4d 	5:15	88	142-144	132-133
6			4e 	7:00	78	140-142	131-132
7			4f 	3:25	87	168-170	170-171
8			4g 	6:20	89	137-139	123-127
9			4h 	6:15	86	115-117	105-106
10			4i 	5:35	88	138-140	134-135
11			4j 	4	87	162-164	158-160
12			4k 	6:10	86	153-156	142-143
			4l				

[a]Acetophenone (2 mmol), aromatic aldehyde (2 mmol), aromatic amine (2 mmol) in ethanol at rt.

[b]All the products were characterized by IR spectral data and comparision of their melting points with those of authentic samples. Also, the structures of some products were confirmed by ^{1}H NMR spectral data.
[c]Isolated yields.

Conclusion

In conclusion, we have described herein an efficient methodology for the Mannich reaction among acetophenone, aromatic aldehydes and aromatic amines at room temperature. The catalyst can be recovered and reused, thus making this procedure more environmentally acceptable. In addition, our method does not use expensive reagents or high temperatures. Further investigations on the synthetic applications of SiO_2-nanoparticles are in progress and will be reported in due course.

REFRENCES

Akiyama T, Matsuda K and Fuchibe K (2005). HCl-catalyzed Stereoselective Mannich Reaction in H2O-SDS. System**.** *Synlett* **1**(2) 322-324.

Azizi N, Torkiyan Lalleh and Saidi MR (2006). Highly Efficient One-Pot Three-Component Mannich Reaction in Water Catalyzed by Heteropoly Acids. *Organic Letters* **8**(10) 2079-2082.

Brindaban C, Sampak S and Sankar K (2002). Zinc tetrafluoroborate catalyzed mannich reaction of aldimines and silylenol ethers in aqueous medium. *Tetrahedron Letters* **58**(5) 983-988.

Dai Y, Li B, Quan H and Lu C (2010). $CeCl_3$ as an efficient catalyst for one-pot synthesis of B-amino ketones by three-component mannich reaction. *Chinese Chemical Letters* **21**(1) 31.
efficient catalyst for acetylation of aldehydes and sugars. *Tetrahedron Letters* **62**(34) 7995-7998.

Heravi M, Zakeri M and Mohammadi N (2011). guanidin hydrochloride: an active and simple catalyst for mannich type reaction in solvent-free condition. *Chinese Chemical Letters* **22**(7) 797-800.

Khodaei M, Khosropour AR and Fattahpour P (2005). A modification procedure for Dakin-West reaction: An efficient and convenient method for one-pot synthesis of β-acetamido ketones using silica sulfuric acid as catalyst. *Tetrahedron Letters* **46**(12) 2105.

Knuppel S, Wang C, Kehr G, Frohlich R and Erker G (2005). Bis(enamino-Cp) Group 4 metal complex chemistry: developing a Mannich-type carbon-carbon coupling reaction at the bent metallocene famework. *Journal of Organometallic Chemistry* **690**(1) 14–32.

Komoto I and Kobayashi S (2004). Lewis acid catalysis in supercriticalcarbon dioxid. Use of poly(ethylene glycol) derivations and perfluoroalkylbenzene as surfactant molecules which enable efficient catalysis in SCCO2. *Journal of Organic Chemistry* **69**(3) 680-688.

Li H, Zeng H and Shao H (2009). Bismuth(III) chloride-catalyzed one-pot Mannich reaction: three-component synthesis of beta-amino carbonyl compounds. *Tetrahedron Letters* **50**(49) 6858-6860.

Li Z, Ma X, Liu J, Feng X, Tian G and Zhu A (2007). Silica-supported aluminum chloride: a recyclable and reusable catalyst for one-pot three-component Mannich-type reactions. *Journal of Molecular Catalysis A* **272**(1-2) 132–135.

List B (2000). The direct catalytic asymmetric three-component mannich reaction. *Journal of the American Chemical Society* **122** 9336-9339.

List B, Pojarliev P, Biller W and Martin H (2002). The proline-catalyzed direct asymmetric three-component mannich reaction: scope, optimization, and application to the highly enantioselective synthesis of 1,2-amino alcohols. *Journal of the American Chemical Society* **124**(5) 827-833.

Manabe K and Kobayashi S (1999). Mannich-type reactions of aldehydes, amines, and ketones in a colloidal. *Organic Letters* **1**(12) 1965-1967.

Mandloi D, Joshi S, Khadikarc P and Khosla N (2005). QSAR study on the antibacterial activity
of some sulfa drugs: building blockers of Mannich bases. *Bioorganic and Medicinal Chemistry Letters* **15** 405-411.

Ollevier T, Nadeau E and Guay-Begin A (2006). Direct-type catalytic three-component mannich reaction in aqueous media. *Tetrahedron Letters* **47**(47) 8351-8354.

Periasamy M, Suresh S and Ganesan S (2005). Stereoselective synthesis of syn-β-amino esters using the TiCl4/R3N reagent system**.** *Tetrahedron Letters* **46**(33) 5521-5524.

Salehi P, Dabiri M, Zolfigol MA and Bodaghi Fard MA (2005). Sulfuric acid: an efficient reusable catalyst for the one-pot synthesis of 3,4-dihydropyrimidin-2(1<i>H<i>)-ones. *Tetrahedron Letters* **44**(14) 2889-2891.

Salter M, Kobayashi J, Shimizu Y and Kobayashi S (2006). Direct-type catalytic three-component mannich reactions leading to an effecting synthesis of A, B-diamino acid derivations. *Organic Letters* **8**(16) 3533-3536.

Simplício A, Clancy J and Gilmer J (2007). β-Aminoketones as prodrugs with pH-controlled activation. *International Journal of Pharmacy* **336**(2) 208-214.

Wang L, Han J, Sheng J, Tian H and Fan Z (2005). Rare earth perfluorooctanoate [$RE(PFO)_3$] catalyzed one-pot Mannich reaction: three component synthesis of β-amino carbonyl compounds. *Catalysis Communications* **6**(3) 201-204.

Wang R, Li BG, Huang TK, Shi L and Lu X (2007). $NbCl_5$-catalyzed one-pot Mannich-type reaction: Three component synthesis ofbeta-amino carbonylcompounds. *Tetrahedron Letters* **48** 2071-2073.

Wenzel A and Jacobsen E (2002). Asymmetric catalytic mannich reaction catalyzed by urea derivationes: enantioselective synthesis of beta-aryl-beta-amino acids. *Journal of the American Chemical Society* **124** 2959- 2964.

Wolfgang N, Kandasamy S and Tommy B (2001). Amine-catalyzed direct asymmetric Mannich-type reactions. *Tetrahedron Letters* **42**(2) 199-201.

Wu H, Shen Y, Fan L, Wan Y and Shi D (2006). Solid silica sulfuric acid (SSA) as a novel and sugars. Tetrahedron Letters 62(34) 7995-7998.