# One-pot Preparation of $\beta$ -amino Carbonyl Compounds by Mannich Reaction Using MgO/ZrO<sub>2</sub> as Effective and Reusable Catalyst

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# Abstract

A new one-pot and efficient three-component condensation of aldehydes, ketones, and amines in the presence of MgO/ZrO<sub>2</sub> as an inexpensive and effective catalyst for the synthesis of  $\beta$ -amino carbonyl compounds by Mannich reaction is described. The present methodology offers several advantages, such as good yields, short reaction times and a recyclable catalyst with a very easy work up.

Keywords: Multi-component reaction, MgO/ZrO<sub>2</sub>, heterogeneous catalyst,  $\beta$ -amino Carbonyl compounds

# 1. Introduction

The synthesis of natural molecules, pharmaceuticals and other nitrogenous biologically active compounds has long been a significant branch of organic synthesis. (B. List, 2002; 2000; R. O. Duthaler, 2003) The Mannich reaction provides one of the most basic and useful methods for the synthesis of such compounds. Multi-component reactions (MCRs) are important for the achievement of high levels of brevity and diversity. They allow more than two simple and flexible building blocks to be combined in practical, time-saving one-pot operations, giving rise to complex structures by simultaneous formation of two or more bonds, according to the domino principle. (Zhu, J., 2005) MCRs contribute to the requirements of an environmentally friendly process by reducing the number of synthetic steps, energy consumption and waste production. Researchers have transformed this powerful technology into one of the most efficient and economic tools for combinatorial and parallel synthesis. (Zhu, J., 2005; Beck, B., 2000) Due to their inherent simple experimental procedures and their one-pot character, they are perfectly suited for automated synthesis.

An amine, two carbonyl compounds and catalysts are used to produce  $\beta$ -amino carbonyl compounds (Scheme1)

 $\beta$  -amino carbonyl compounds are very useful in pharmaceutical and other biologically related areas of chemistry. One of the many synthetic routes to these compounds is the Mannich reaction which brings together three compounds under appropriate catalytic conditions. These simplified reaction systems fulfill several of the principles of green chemistry including the use of recyclable catalysts and reduced auxiliaries. Mannich reaction is one of the most important C-C bond forming reactions in organic synthesis for the preparation of secondary and tertiary amine derivatives (M. Arend, 1998). These amines are further used for the synthesis of many intermediates, biologically active and natural products such as alkaloids and polyketides. The products of Mannich reaction are mainly  $\beta$  -amino carbonyl compounds and its derivatives that are used for the synthesis of amino alcohols, peptides, and lactams and as precursors to optically active amino acids. The conventional catalysts for classical Mannich reaction of aldehydes, ketones and amines involve mainly organic and mineral acids like proline (B. List, 2002; 2000; R.O. Duthaler, 2003), acetic acid (K. Mogilaiah, 2002),

*p*-dodecylbenzenesulfonic acid (K. Manabe, 2001) and some Lewis acids (S. Kobayashi, 2002; P. Desai, 2000). They often suffer from the drawbacks of long reaction times and harsh reaction conditions, toxicity and difficulty in product separation, which limit its use in the synthesis of complex molecules. Yarahmadi et.al (Hamid Reza Shaterian, 298-313) have synthesized  $\beta$ -amido ketones and esters in four-component condensation reaction using ferric hydrogensulfate as effective and reusable catalyst. Trissa Joseph et.al (Suman Sahoo, 2006) have synthesized  $\beta$ -amino carbonyl compounds by using Bronsted ionic liquids as a solvent and catalyst. Guoying Zhao, Tao Jiang et.al (2004) has carried out Mannich reaction by using ionic liquids as a solvent and catalyst. Recently, we have investigated heterogeneous basic catalyst MgO/ZrO<sub>2</sub> for the Knovenagel condensation reaction (Gawande M. 2006). In continuation of our study for the development of heterogeneous catalysis (Gawande M. 2005, 2007, 2006) and applications in organic synthesis. Herewith, we are present application of MgO/ZrO<sub>2</sub> for synthesis of  $\beta$ -amino carbonyl compounds. To best of our knowledge, this is first report for the synthesis of  $\beta$ -amino carbonyl compounds over MgO/ZrO<sub>2</sub>.

# 2. Experimental

# 2.1 Chemicals

All the aldehydes, ketones, amines, were obtained from S.D. Fine Chemicals, Mumbai, and used without further purification. For Mannich reactions, the aldehydes used were Piperonal (1a), *p*-methoxy benzaldehyde (2a), 3-chloro-benzaldehyde (3a), 3-chloro-benzaldehyde (4a) and benzaldehyde (5a). The amines included aniline (1b), 2-nitroaniline (2b) and 4-bromoaniline (3b) and the ketones were acetophenone (1c) and *p*-hydroxy acetophenone (2c).

# 2.2 General procedure for the synthesis of catalyst

In typical experiment for the preparation of  $MgO/ZrO_2$ with mole а varving compositions(0.44:0.56,0.35:0.65,0.25:0.75,0.14:0.86) an appropriate amount of magnesium nitrate[MgO(NO<sub>3</sub>)<sub>2-</sub> .6H<sub>2</sub>O] and zirconium oxy chloride[ZrOCl<sub>2</sub>.8H<sub>2</sub>O] were dissolved separately in deionised water and mixed together. Dilute ammonia solution was added dropwise with vigorous stirring until the precipitation was complete (PH=10). The resultant solution was filtered and washed with distilled water till free from chloride ions. The residue was dried for 24 hours at 383K in an oven and further calcined at 873 K for 6 hours, in a muffle furnace in air. The % and mole composition of MgO/ZrO<sub>2</sub> are given in following **Table 1.** 

#### 2.3 Procedures for Mannich reaction

In a typical experiment, 10 mmol amine, 10 mmol aldehyde, 10 mmol ketone, and 0.35/0.65 Wt. % of catalyst in acetonitrile were loaded into a magnetically stirred glass reactor under reflux condition at 80 °C. The reaction mixture turned turbid after a certain reaction time and at last became very viscous and close to solid. After reaction, the mixture was washed with distilled water (15 mL) and filtered. The solid product was re-crystallized using ethanol or a mixture of ethanol and benzene and then dried at 50 °C under vacuum until constant weight. The reusability of the catalyst was checked by the reaction of benzaldehyde, aniline and acetophenone in the presence of acetonitrile using MgO/ZrO<sub>2</sub> ( $_{0.35:065}$ ) under reflux condition at 80 °C. The results indicate that the catalyst can be used five times without any loss of its activity. (**Table 2**)

#### 3. Results and discussion

In this article, we wish to report a mild, convenient and efficient protocol for the synthesis of  $\beta$ -amino carbonyl compounds by Mannich reaction using MgO/ZrO<sub>2</sub> as a novel catalyst. First, we optimized the mole ratio of MgO/ZrO<sub>2</sub> for the reaction benzaldehyde, acetophenone, and aniline. The mole ratio of MgO/ZrO<sub>2</sub> was chosen to be 0.35/0.65 wt. %

(Table 3). The most efficient reaction went to completion in 8 hours at 80°C

The Mannich reactions of aldehydes, ketones and amines in presence of MgO/ZrO<sub>2 (0.35:065)</sub> catalyst were carried under reflux condition at 80 °C and are summarized in **Table 4**.

# 4. Conclusions

MgO/ZrO<sub>2 (0.35:065)</sub> has been successfully used as catalyst for Mannich reactions using aldehydes, amines, and ketones. Utilization of this catalyst has several advantages: (1) high yield and high reaction rate can be achieved; (2) the preparation of catalyst is simple; (3) the catalyst can be easily recycled and reused; (4) this protocol provides further examples of the capacity of MgO/ZrO<sub>2 (0.35:065)</sub> to be fashioned for specific chemical applications. The main contribution of this work is synthesizing MgO/ZrO<sub>2(0.35:065)</sub> successfully, which shows a balance between recyclisation and activity for the Mannich reaction.

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Table 1. Mixed oxides of MgO/ZrO<sub>2</sub>

Entry	Mixed oxides of MgO/ZrO <sub>2</sub>				
	MgO Wt%	ZrO <sub>2</sub> Wt.%	MgO/ZrO <sub>2</sub>		
1	5	95	0.14/0.86		
2	10	90	0.25/0.75		
3	15	85	0.35/0.65		
4	20	80	0.44/0.56		



Scheme 1.

Table 2. Recyclability of the catalyst in the reaction of benzaldehyde, aniline and acetophenone in the presence of acetonitrile using MgO/ZrO<sub>2 (0.35:065)</sub> under reflux condition at 80  $^{\circ}$ C.

Run no.	Yield (%)		
1	91		
2	90 89		
3			
4	87		
5	87		

Table 3. Reaction of benzaldehyde, acetophenone and aniline using various ratio of MgO/ZrO<sub>2</sub> under reflux condition at 80 °C

Entry	MgO/ZrO <sub>2</sub> (Wt.%)	Time/h	Yield%
1	0.14/0.86	12	77
2	0.14/0.86	16	85
3	0.35/0.65	8	91
4	0.44/0.56	12	81
5	0.14/0.86	13	79

Table 4. Three-component Mannich reactions of aldehydes, amines, and ketones in the presence of MgO/ZrO<sub>2</sub>  $_{(0.35:065)}$  catalyst at 80  $^{\rm o}C$ 

Entry	Aldehyde	Ketone	Amine	Time/h	Yield (%)
1	1a	1c	1b	08	91
2	2a	1c	1b	08	66
3	3a	1c	1b	05	62
4	4a	1c	1b	04	31
5	5a	1c	1b	12	89
6	1a	1c	2b	12	67
7	2a	1c	2b	12	54
8	3a	1c	2b	12	87
9	4a	1c	2b	12	81
10	5a	1c	2b	12	83
11	1a	1c	3b	12	0