# Knoevenagel condensation at room temperature using $SeO_2/ZrO_2$ catalyst in water-medium and solvent-free conditions

## Vijaya Banothu[a], Manohar Basude*[b] and Satyanarayana Battu[a]

*[a]Department of Chemistry, University College of engineering, Osmania University, Hyderabad, India*
*[b]Department of Chemistry, Nizam College, Osmania University, Hyderabad, India*
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**ABSTRACT**

*A simple protocol is described for the synthesis of alkenes derivatives in excellent yields by Knoevenagel condensation of aromatic aldehyde with active methylene compounds in water, acetonitrile and solvent free condition using selenium promoted $ZrO_2$ solid catalyst at room temperature. The performance of the catalyst was effective in presence of water. Zirconia and selenium promoted $ZrO_2$ solid catalyst exhibited the same crystallite size of 28 nm and tetragonal phase but different activity. The catalyst can be easily recovered by filtration, higher yield of product and can be recycled efficiently.*

**Key words:** Knoevenagel condensation; Aromatic aldehyde; Tetragonal Zirconia; Solvent free
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## INTRODUCTION

Knoevenagel condensation of aromatic aldehyde with active methylene compounds has been extensively investigated in view of its significance in carbon-carbon bond formation in organic synthesis [1]. The Knoevenagel condensation is a key step in the commercial production of antimalarial drug lumifantrine a component of coartem [2].This reaction has been widely used in synthesis of coumarin and their derivatives an important group of organic compounds used as additives to food and cosmetics [3]. It has numerous applications in synthesis of fine chemicals and in synthesis of carbocyclic as well as heterocyclic compounds of biological significance [4, 5]. There is considerable interest in the Knoevenagel products because of their biological activity, for example, tryphostins, such as α-cyanothiocinnamide, are known to inhibit autophosphorylation of the EGF receptor, in addition to possessing antiproliferative effects on keratinocytes [6].

Different catalysts have been employed to accomplish this reaction. Bases such as amines, alkali alkoxides, alkali hydroxide, pyridine, piperidine and ammonium salts catalyze the reaction in presence of organic solvents [7-9]. Knoevenagel condensation is also catalyzed by lemon juice in the absence of solvent [10]. These catalysts are in homogeneous phase with the reagents, effective in catalyzing the reaction but difficult to separate and are not recycled. Lewis acids like $CuCl_2$ [11], $LaCl_3$ [12] and $ZnCl_2$[13] catalyze this reaction in solvent free condition. The use of conventional Lewis acids like $CuCl_2$, $LaCl_3$ and $ZnCl_2$ pose significant problems in handling, disposal and regeneration due to their toxic and corrosive nature.

The green chemistry perspective is to reduce or eliminate the use and generation of hazardous substances. Economic considerations and environmental evaluations have pushed the chemical industry to adopt new eco friendly catalysts and cleaner technologies with minimum disposal. Generally liquid phase reactions are carried out in presence of

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organic solvents. Many of the organic solvents are toxic and their use must be minimized or avoided. Water as solvent and solvent free organic reactions represents environmentally benign procedures [14]. However, the past decade has witnessed the emergence of heterogeneous catalysts comprising of inorganic materials such as clays[15,16], zeolites [17-19], hydrotalcites [20], solid bases[21] and modified silica [22] owing to their environmentally benign properties, which aptly applied in this reaction. Ionic liquids are also eco-friendly alternatives to organic solvent and recyclable. Lewis acid ionic liquids are also exploited for Knoevenagel condensation [23, 24].

From the environmental and economic perspective present work is focused on development of new zirconia based heterogeneous catalyst and using aqueous media or solvent free condition to perform Knoevenagel condensation. Zirconia has high thermal stability and acid-base properties. Zirconia based solid acid catalysts are thoroughly investigated for several organic transformations and synthesis of fine chemicals [25, 26]. Among the solid acid catalysts reported, sulfated zirconia received much attention due to its high activity to catalyze many reactions even at low temperatures but at higher temperature gets deactivated and forms sulphuric acid in presence of water [27]. However, above problems can be overcome by synthesizing solid super acids by incorporating $MoO_3$, MgO and other metal oxides into zirconia[28-31].Herein, we report the preparation of $SeO_2/ZrO_2$ catalyst and Knoevenagel condensation of aromatic aldehyde with active methylene compounds over $SeO_2/ZrO_2$ catalyst at room temperature in presence of water, acetonitrile and in solvent free condition.

## EXPERIMENTAL SECTION

$SeO_2/ZrO_2$ catalyst was prepared using $ZrOCl_2.8H_2O$, $Na_2SeO_3.5H_2O$ as precursors and the sample obtained was calcined at 923 K for 6 h in air atmosphere [28].

The powder X-ray diffraction patterns of catalyst were recorded on XRD 7000 Schimadzu instrument by using nickel filtered $CuK_\alpha$ radiation and scintillation counter detector. $^1H$ spectra were recorded in $CDCl_3$ using BRUKER AV-III 400 MHz. FTIR spectra recorded using BRUKER OPTICS, Germany TENSOR 27.
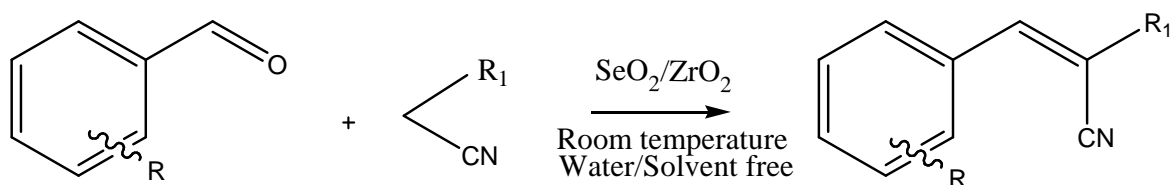
**Knoevenagel condensation of aromatic aldehyde with active methylene compounds**
In this study used commercially available chemicals are used without any further purification. In a typical experimental procedure a mixture of aromatic aldehyde (2mmol) and malononitrile/ethyl cyanoacetate compound (2.1mmol) is taken in a 25 ml round bottomed flask and 0.1 g of the catalyst was added. The reaction mixture was stirred in water or acetonitrile and solvent free condition. The progress of the reaction is followed by TLC and complete disappearance of aldehyde is treated as completion of the reaction. The catalyst was separated from the reaction mixture after completion of the reaction by filtration and reused. The mixture was extracted with ether. The organic layer was dried over sodium sulphate and solvent was removed under vacuum using rotator-evaporator. The product was subjected silica gel column chromatography using ethyl acetate in petroleum ether as eluent to get pure product. Isolated yields are determined quantitatively, qualitatively by NMR, IR and compared with authentic samples.

## RESULTS AND DISCUSSION

Knoevenagel condensation of aromatic aldehyde with active methylene compounds is basically a base catalyzed reaction. In Knoevenagel condensation the activation of methylene via abstraction of proton to generate an anion is a prerequisite for the initiation of the reaction. In Mg-Al-O-t-Bu-hydrotalcite higher activity of the catalyst is ascribed to the presence of anion –OtBu paired with Mg and Al main frame hydrotalcite which more effectively abstracts a proton from activated methylene group to promote the higher rate of reaction [32]. Zirconia's acidic and basic properties can be altered by incorporating suitable promoter atom. Incorporation of promoter atoms like molybdenum, tungsten, iron, alumina and bismuth enhance the surface acidity. For Comparison of activity of various zirconia based catalysts, Knoevenagel condensation of 4-nitro benzaldehyde with malononitrile under solvent free condition at room temperature is used as model reaction. Table 1 shows the results of the Knoevenagel condensation. In this study the samples $ZrO_2$ and selenium promoted $ZrO_2$ exhibit only the tetragonal phase but the average crystallize size of the samples is28 nm. Pure $ZrO_2$ and selenium promoted $ZrO_2$ do not have the same activity in Knoevenagel condensation of aromatic aldehyde with active methylene compounds in liquid phase at room temperature. Alkenes derivatives are obtained in 0.5-4 hrs time over selenium promoted $ZrO_2$ where as pure zirconia is totally inactive. In addition to this sodium selenate which was used to impregnate on zirconia is also

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almost inactive in catalyzing the Knoevenagel condensation of aromatic aldehyde with active methylene compounds under similar condition. Molybdenum and tungsten promoted catalysts also exhibit tetragonal phase but the activity is not comparable with that of selenium promoted $ZrO_2$ catalyst. Incorporation of promoter into the zirconia lattice alters the bulk and surface properties of zirconia. This higher activity of selenium promoted $ZrO_2$ may be due to lattice defects created by promoter selenium and notable redox properties. Knoevenagel condensation of various aliphatic, aromatic and heterocyclic aldehydes with malononitrile on sulfate-ion promoted solid acid catalyst requires heating of the reaction mixture and more time for the completion of the reaction [33]. In selenium promoted zirconia catalyst incorporation of promoter atom selenium may probably be creating basic sites altering textural properties of the catalyst thereby increasing its basicity. Higher activity of selenium promoted zirconia catalyst for Knoevenagel condensation of 4-nitro benzaldehyde with malononitrile under solvent free condition at room temperature may be due to basic properties of the catalyst.



**Scheme I: Knoevenagel condensation of aromatic aldehyde with active methylene compounds at room temperature in water-medium and solvent-free condition on novel SeO₂/ZrO₂ catalyst**

**Table 1 Comparison of activity of promoted zirconia catalysts for Knoevenagel condensation of 4-nitro benzaldehyde with malononitrile under solvent free condition**

| Entry | Catalyst | Time (h) | Yield[a] (%) |
|-------|----------|----------|-----------|
| 1 | $ZrO_2$ | 24 | No reaction |
| 2 | $Na_2SeO_3.5H_2O$ | 6 | 18 |
| 3 | $SeO_2 / ZrO_2$ | 0.75 | 96 |
| 4 | $MoO_3 / ZrO_2$ | 2 | 84 |
| 5 | $WO_3 / ZrO_2$ | 5 | 75 |

[a] *Isolated yields.*

**Table 2 Influence of solvent on activity of selenium promoted zirconia catalyst for Knoevenagel condensation of 4-nitro benzaldehyde with malononitrile**
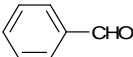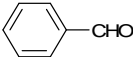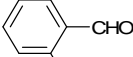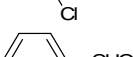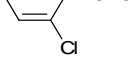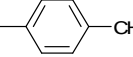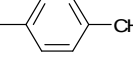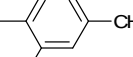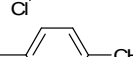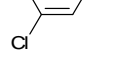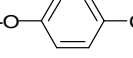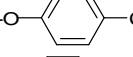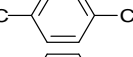
| Entry | Solvent | Time (h) | Yield[a] (%) |
|-------|---------|----------|-----------|
| 1 | Acetonitrile | 1.5 | 92 |
| 2 | DMF | 2 | 90 |
| 3 | Ethanol | 2.5 | 90 |
| 4 | Chloroform | 3.5 | 88 |
| 5 | Water | 0.5 | 96 |
| 6 | Solvent free | 0.75 | 96 |

[a] *Isolated yields.*

The influence of the solvent on Knoevenagel condensation catalyzed by $SeO_2/ZrO_2$ was investigated using the same model reaction between 4-nitro benzaldehyde with malononitrile at room temperature and the results are given in table 2. In presence of water and solvent free condition the reaction was completed in 0.5 h and 0.75 h. The reaction was slowest in presence of non polar solvent chloroform.

Knoevenagel condensation of various aromatic aldehyde with active methylene compounds did not take place in the absence of the catalyst. The catalytic activity of selenium promoted zirconia was investigated for the Knoevenagel condensation of various aromatic aldehydes with active methylene compounds in presence of water, acetonitrile and solvent free condition for comparison. The results are presented in the tables 3. All the reactions investigated were completed in 0.5 - 5 h duration producing alkenes derivatives with 80-96% yield. Aromatic aldehyde with electron withdrawing group (4-Nitro benzaldehyde) offer yield of 96% under solvent free condition and the reaction was completed in 0.75 h with malononitrile. Knoevenagel condensation of 4-Nitro benzaldehyde with ethyl cyanoacetate was completed in 2.5 h with yield of 92%. In the case of the electron releasing groups reasonably good yields

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**Table 3 Selenium promoted ZrO₂ catalyst for Knoevenagel condensation of aromatic aldehydes with active methylene compounds in water, acetonitrile and under solvent free condition**

| Entry | R | $R_1$ | Solvent free condition | | Water | | Acetonitrile | | ref[b] |
|-------|---|-------|------------|-----------|-----------|-----------|-----------|-----------|------|
| | | | Time (h) | Yield[a] (%) | Time (h) | Yield[a] (%) | Time (h) | Yield[a] (%) | |
| 1 | (benzaldehyde) CHO | -CN | 3 | 94 | 2.5 | 94 | 3.5 | 90 | 12 |
| 2 | (benzaldehyde) CHO | -COOC₂H₅ | 3.0 | 92 | 2.75 | 92 | 3.5 | 88 | 12 |
| 3 | 2-Cl-CHO | -CN | 2.5 | 90 | 2 | 92 | 2.5 | 88 | 9 |
| 4 | 2-Cl-CHO | -COOC₂H₅ | 4 | 88 | 3.5 | 88 | 3 | 85 | 9 |
| 5 | Cl-CHO | -CN | 1.5 | 93 | 1 | 93 | 3 | 89 | 30 |
| 6 | Cl-CHO | -COOC₂H₅ | 3 | 91 | 2.5 | 91 | 3.5 | 86 | 30 |
| 7 | Cl,Cl-CHO | -CN | 2 | 94 | 1.5 | 94 | 3.5 | 89 | 9 |
| 8 | Cl,Cl-CHO | -COOC₂H₅ | 3.5 | 90 | 3 | 90 | 3.5 | 86 | 9 |
| 9 | H₃C-O-CHO | -CN | 4.5 | 84 | 3.75 | 84 | 4 | 84 | 12,30 |
| 10 | H₃C-O-CHO | -COOC₂H₅ | 5 | 80 | 4.5 | 80 | 4.5 | 80 | 12,30 |
| 11 | H₃C-CHO | -CN | 3.5 | 94 | 3 | 94 | 4.5 | 88 | 12 |
| 12 | H₃C-CHO | -COOC₂H₅ | 4.5 | 89 | 4 | 89 | 5 | 84 | 12 |
| 13 | O₂N-CHO | -CN | 0.75 | 96 | 0.5 | 96 | 1.5 | 92 | 30 |
| 14 | O₂N-CHO | -COOC₂H₅ | 2.5 | 92 | 2 | 92 | 3 | 90 | 30 |

[a] *Isolated yields.*
[b] *All the products were characterized by IR and ¹H NMR spectra comparing with those of authentic samples.* [9, 12, 30]

are obtained and more reaction time is required to complete the reaction. Malononitrile is more reactive compared to ethyl cyanoacetate and the reaction with malononitrile required short time for completion of the reaction. This may be attributed to the fact that abstraction of a proton from the active methylene group of ethyl cyanoacetate is difficult due to lower acidity. Higher yields of alkenes derivatives are obtained in water medium and solvent free conditions. Considering environmental impact, water is the best solvent for Knoevenagel condensation catalyzed by SeO₂/ZrO₂ and this catalyst facilitates solvent free reaction also.

The reaction is completed in shorter time with the increase in amount of the catalyst. The reusability of the catalyst is investigated using 0.1 g of the catalyst to catalyze condensation of 4-Nitro benzaldehyde with malononitrile under solvent free condition. After completion of the reaction the catalyst was filtered out and the same wet catalyst was directly used for the next cycle without any additional treatment. There is no appreciable change in activity for 5-6 runs.

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## CONCLUSION

In conclusion we have demonstrated that all the catalysts used to study Knoevenagel condensation have tetragonal phase but different activities. This can be attributed to difference in redox potential of the promoter atom and acid-base properties. All the catalysts exhibited higher activity in presence of water. Among tested catalysts selenium promoted zirconia gave high yield of 96% in shorter duration. Catalyst can be easily separated from the reaction mixture and recycled. A green heterogeneous process and catalyst is developed for C-C bond formation.

## REFERENCES

[1] Jones, G. Organic Reactions; Wiley: New York, **1967**; vol. 15, 204-599.
[2] Ulrich, B.;, Peter, C. F.;  Andreas, S. *Org. Process Res. Dev*. **2007**, 11(3),      341 – 345.
[3] O'Kennedy, R.;Thornes, R. D. Coumarins*:* Biology, Applications and Mode of Action,  Wiley &    Sons, Chichester, **1997**.
[4] Freeman, F. *Chem. Rev.***1980**, 80, 329-350.
[5] Tiettze, L. F. *Chem. Rev*. **1996**, 96, 115-136.
[6] Lyall, R. M.; Zilberstein, A.;Gazit, A.; Gilon, C.; Levitzky, A.;Schlessinger,J. J. *J. Biol. Chem*. **1989**,264, 14503-14509.
[7] Saeed, B.;,Morteza, B.;Shohreh,H.;Peyman, S. *Synth.    Commun*. **2006**, 36, 3703-3711.
[8] Junjie, H.;Yanfen,  J.;Yingpeng,S.;Xuegog, S.;Xinfu,P. *Catal. Commun*. **2008**, 9,   2077-2079.
[9] Zhou, Z;Sun, Y. *Synth. Commun*. **2011**, 41, 3162-3168.
[10] Deshmukh, M. B.;  Suresh S Patil.; Jadhav, S. D.; Pawar,P. B. *Synth. Commun*. **2012**, 42(8), 1177-1183.
[11] Orazio, A.;Paolino, F.;,Amedeo, M. *Synth. Commun*. **1983**, 13, 1203-1208.
[12] Narsaiah,A. V.; Nagaiah, K. *Synth. Commun.***2003**, 33, 3825-3832.
[13] ShanthanRao, P.; Venkataratnam, R. V. *Tetrahedron Lett.***1991**, 32, 5821-5822.
[14] Chemistry of waste minimization, ed. J.H.Clark,Chapman and Hall, London, **1995**.
[15] Bigi, F.;Chesini, L.;Maggi, R.; Sartory,G. *J. Org. Chem*. **1999**, 64, 1033-1035.
[16] Fatemeh, T,; Mohammad, T.;Elaheh, H.;Elham, Z. *J. Mol. Catal.A: Chem*. **2013**,  366, 36-42.
[17] Shunmugavel, S.;Muthaiahpillai,P.;Martin, H.;Velayutham, M. *Appl. Catal*. **2006**, 298(10), 8-15.
[18] Leandro Martins,   Karla Moreira Vieira,   Luiz Marcelo Rios, Dilson Cardoso. *Catal.Today*. **2008**, 133-135, 706-710.
[19] Fengxia Zhu, Didi Yang, Fang Zhang Hexing Li. *J. Mol. Catal.A: Chem.***2012**, 363-364, 387-397.
[20] Lakshmi Kantam, M.; Choudary, B. M.; Venkat Reddy, Ch.; Koteshwar Rao, K.; Figueras,  F. *Chem.  Commun*. **1998**, 1033-1034.
[21] Yoshio, O. *J. Catal*. **2003**,216, 406-415.
[22] Inaki,Y.;Kajita,Y.; Yoshida, H.; Ito,K.; Hattori, T. *Chem. Commun*. **2001**, 2358-2359.
[23] Zhang,Y.;  Zia, C. *Appl. Catal. A: Gen*. **2009**, 366, 141-147.
[24] Yue, C.; Mao, A.; Wie, Y.; LU, M. *Catal. Commun.***2008**, 9, 1571-1574.
[25] Arata,K.;  Hino, M.    *Chem.  Phys*. **1990**, 26,  213-237.
[26] Yamaguchi, T. *Catal.Today.***1994**, 20, 199- 218.
[27] Reddy, B.M.;  Meghashyam, P. *Chem. Rev*. **2009**, 109, 2185-2208.
[28] Reddy, B M.; R Reddy, V. R.; Manohar, B. *Synth. Commun*. **1999**, 29(7), 1235-1239.
[29] Manoj B. G.;Radha V. J. *Catal. Commun*.  **2006**, 12(7), 931-935.
[30]  Manohar, B; S Prasad; S Rajkumar; P Lingaiah. *J. Chem. Pharm. Res.,* **2012**, 4(2), 1136-1146.
[31] B Manohar, *J. Chem. Pharm. Res*. **2012**, 4(6), 3031-3035.
[32]  Choudary,B. M.;  LakshmiKantam, M.; Kavita, B, Venkat Reddy,Ch.; Figueras, F. *Tetrahedron*. **2000**, 56, 9357-9364.
[33] Benjaram M. Reddy, Meghshyam K.  Patil, Komateedi N. Rao, Gunugunuri K. Reddy. *J. Mol. Catal*. A: **2006**, 258, 302-307.