



## The Synthesis of 2,3-dihydroquinazolin-4(1H)-ones Using Zinc Oxide Nanotubes Modified by SiO<sub>2</sub> as a Catalyst with Recyclable effect

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### ABSTRACT

Zinc oxid nano tubes have attracted much attention in recent years. Hardly, direct uses of zinc oxid nano tubes which modified by SiO<sub>2</sub> as a catalyst with recyclability has been applied for several organic reactions. The average particle size of ZnO catalysts is 57 nm, it has been characterized by XRD. Nano tubes surfaces have high density defects. The condensation of isatoic anhydride and an aromatic aldehyde exposed to ammonium acetate in the presence of few amounts of zinc oxide nano tubes modified by SiO<sub>2</sub> as a catalyst can be a simple, suitable and efficient method for the quinazolin derivatives synthesis, the positive aspect is recyclable ability of the catalyst. It is clear that some characterization of catalyst such as combination of the small particle size and high-density surface defects of zinc oxid nano tubes which modified by SiO<sub>2</sub> is the basic reason for unique catalytic activity of the catalyst. The practical and simple method led to unbeatable yields of the 2,3-Di hydro quinazolin-4(1H)-one derivatives at short times under mild conditions.

**Keywords:** Reusable catalyst, 2,3-Dihydroquinazolin-4(1H)-one derivatives, zinc oxide nanotubes, SiO<sub>2</sub>.

### INTRODUCTION

Heterogenization of homogeneous catalysts has been a fantastic area of research from the industrial point of view. This approach, relieves the ability to use simultaneously the benefits of

homogeneous catalysts (high activity and selectivity, etc.) and engineering promotes of heterogeneous catalysts (easy catalyst separation, easily regeneration, long catalytic life, thermal stability and recyclable ability)<sup>1</sup>. Since solid acids have many promotes such as decreased reactor



and depletion of plant corrosion problems, simplicity in handling and more environmentally safe disposal<sup>2-7</sup>, the application of solid acids have important role in organic transformation. 2,3-di hydro quinazolinones are a class of hetero cycles which possess a wide range of high activities, pharmaceutically including anti fertility, antibacterial, antitumor, anti-fungi and *Monoamine-oxidase inhibitor* (MAOI)<sup>8-11</sup>, so they have attracted much attention recently. Several synthetic methods for the preparation of 2,3- dihydro quinazolinones have been reported, the most direct procedure includes accumulation of alkyl, aryl and heteroaryl aldehydes with anthranilamide in the presence of p-toluene sulfonic acid as a catalyst<sup>12-14</sup>. Also, the synthesis of 2,3-dihydroquinazolinones was accomplished by reductive cyclisation of o-nitro benzaldehyde or oazido benzamide<sup>15,16</sup>. Some of the stylish reported methods include materials as isatoic anhydride, and aldehydes exposed to ammonium acetate or primary amine in the presence of different types of reagents or catalysts, namely p-toluenesulfonic acid<sup>17</sup>, amberlyst-15 microwave-assisted<sup>18</sup>, montmorillonite K-10<sup>19</sup>, silica sulfuric acid<sup>20</sup>, ionic liquid<sup>21</sup>, Zn(PFO)<sup>2 22</sup>, and ceric ammonium nitrate<sup>23</sup>, silica-bonded N-propylsulfamic acid (SBNPSA)<sup>24</sup>. Recently, zinc oxid nanotubes are faced with increasing attentions because of fascinating chemical and physical characteristics and having potential technological applications<sup>25</sup>, these are distinct both from those of the bulk phase and those from isolated atoms or molecules. The preparation<sup>26</sup> and applications<sup>27,28</sup> of nano-sized zinc oxid nanotubes modified by SiO<sub>2</sub>

have been already published in some papers and the reactions such as formylation and acetylation of hydroxyl groups have been reported<sup>3</sup>.

## MATERIALS AND METHODS

### Instrumentation

The commercial necessary materials were purchased from Fluka (Buchs, Switzerland), Merck (Darmstadt, Germany), and Aldrich(Germany). TLC (silica-gel 60 F254, n-hexane: ethyl acetate) was used for monitoring of the reaction. A FTIR Shimadzu- 470 Spectrometer was used for IR spectra. the <sup>1</sup>HNMR Spectra were achieved with a Bruker-Instrument DPX- 400 MHz Avance 2 model. The similarity of their spectra and physical data were applied for identification of products and their characterizatons. The Powder X-ray diffraction (XRD) patterns were obtained on a Bruker Advance D8 Diffractometer with Cu K $\alpha$  radiation ( $\lambda=0.154$  nm). A Philips CM 200 FEG/HRTEM instrument (high resolution transmission electron microscope) operated at 200 Kv was usedd for TEM measurements.

### Recyclability

One of the excellences of zinc oxide nanotubes modified by SiO<sub>2</sub> is separating them from the reaction mixture, on the other hand, they have recycling power. They participated as the same reaction again as a catalyst and their catalytic activity such as their efficacy was checked in subsequent reactions. Fig. 1 shows the relation between the number of cycles of the reaction and the catalytic activity according to the yield.

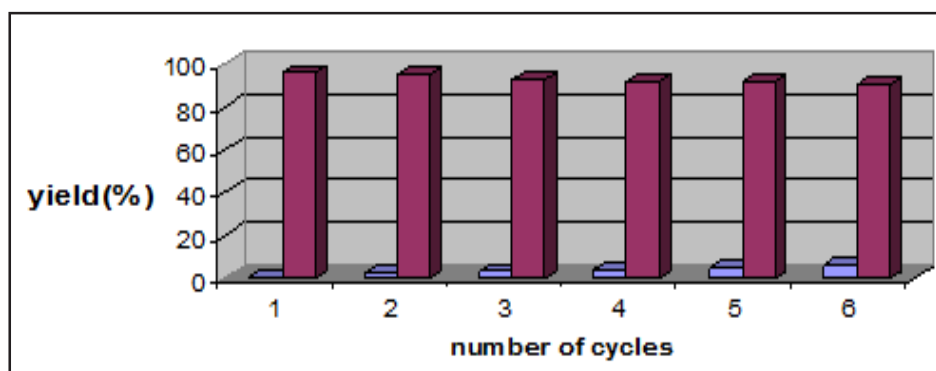


Fig 1. Recyclability of zinc oxid nanotubes modified by SiO<sub>2</sub> for the formation of 2,3-di hydro quinazolinones derivatives

### General procedure for the synthesis of 2,3-dihydroquinazolinones

A mixture of isatoic anhydride (1 mmol), ammonium acetate (3 mmol) besides substituted aromatic aldehydes (1 mmol), zinc oxide nanotubes modified by SiO<sub>2</sub> (1.0 mmol%) under solvent free conditions were applied at 120 °C for the appropriate time. In order to find when the reaction is completed, it should be monitored by TLC (thin layer chromatography). Finally, after completion, the reaction mixture should be cooled to the room temperature, filtered and washed with water (2 × 5 mL). Purification of the solid products were done by recrystallization of the catalyst from ethyl acetate, hence the catalyst was taken apart the pure product. Afterwards melting point of the product(s) were measured and the yield of the reaction was determined.

### RESULT AND DISCUSSION

The characterization of the catalyst was done by XRD; it shows high-density defects on nano tubes surfaces (Fig. 2). Zinc oxide nano tubes modified by SiO<sub>2</sub> as catalyst were used to establish the reaction of synthesis of derivatives of 2,3-Dihydro quinazolinones. The condensation reaction of isatoic anhydride and an aromatic aldehyde exposed to ammonium acetate ammonium acetate (1b) redounds to the product. To estimate the optimization conditions of the reaction, various amounts of zinc oxide nano tubes modified by SiO<sub>2</sub> were taken in the range of 0.5-2.0 mmol% at 120 °C (Table). The reaction surveys at different concentrations of the catalyst showed that the condensation reaction could be efficiently proceeded using 1 mmol% of the catalyst under solvent free conditions and thermal conditions.

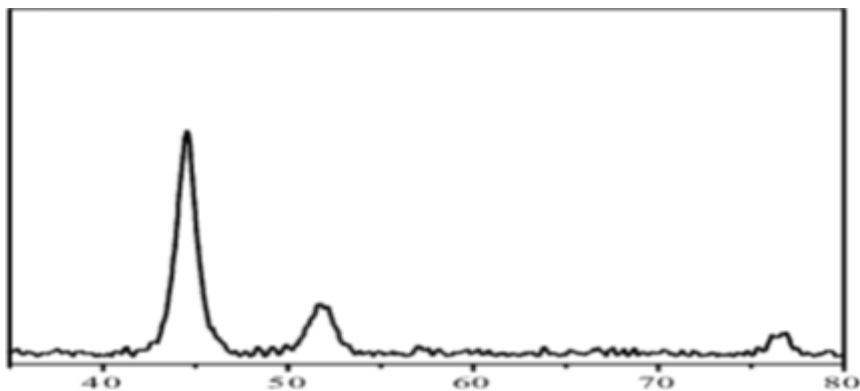


Fig. 2. XRD pattern zinc oxide nanotubes modified by SiO<sub>2</sub> catalyst

Before, some studies have been showed new routes by using solid acid catalysts to synthesize heterocycles with favorable substitutes<sup>29-32</sup>. In this research has been reported a valid and an efficient procedure in order to synthesize 2,3-dihydroquinazolinones. This reaction is a kind of one-pot condensation which the reactants are isatoic anhydride, aldehydes and NH<sub>4</sub>OAc or primary amine. It has been performed in the presence of few amounts of zinc oxide nanotubes modified by SiO<sub>2</sub> as an inexpensive catalyst (Fig. 3). The effect of catalyst on the condensation of mentioned reactants was studied which was the corresponding of 2,3-dihydroquinazolinones production. The condensation reaction of isatoic anhydride, NH<sub>4</sub>OAc and 4-chloro-benzaldehyde was chosen as a model reaction in solvent free

conditions (Table.1). The results show clearly that zinc oxide nano tubes modified by SiO<sub>2</sub> is an effective catalyst for this transformation whereas in the absence of zinc oxide nano tubes modified by SiO<sub>2</sub> the reaction could not take place, even after 120 minutes. (Table.1, entry 1). The best result has been obtained with an amount of (1.0 mmol%) zinc oxide nano tubes modified by SiO<sub>2</sub> in terms of reaction time and isolated yield. To demonstrate the generality of this process, many of aldehydes with divers substitution and different structurally were employed to synthesize the corresponding products which engendered very good yields (Table. 2). Also, a wide range of aniline derivatives and 2-phenylethyl amine were used and finally 2,3-dihydroquinazolinones were obtained in efficiency yield. The possibility of the catalyst

recycling was examined, therefore the reaction of isatoic anhydride and 4-chloro benzaldehyde with  $\text{NH}_4\text{OAc}$  in the presence of zinc oxide nano tubes modified by  $\text{SiO}_2$  was studied in solvent free conditions.

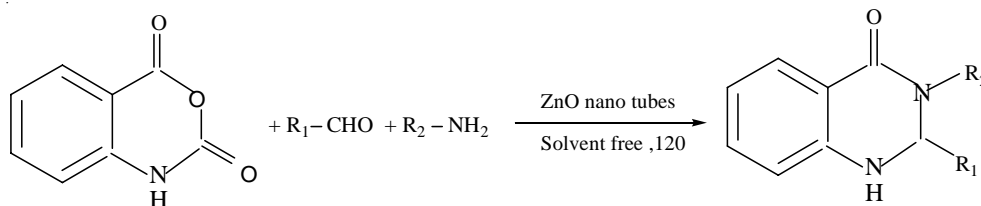
The studies were extended with various aromatic aldehydes in order to prepare a series of 2,3-Di hydro quinazolinones derivatives, the generality of the reaction was demonstrated in optimized conditions (Scheme 1).

**Table 1: The reaction of isatoic anhydride, ammonium acetate and 4-chlorobenzaldehyde exposed to different amounts of zinc oxide nano tubes modified by  $\text{SiO}_2$  catalyst in solvent free<sup>a</sup> conditions**

Entry	The amounts of catalyst (mmol)	Time (min.)	Yield (%) <sup>b</sup>
1	-	120	-
2	0.5	30	84
3	1.0	20	92
4	2.0	20	92

<sup>a</sup> The molar ratios of isatoic anhydride,  $\text{NH}_4\text{OAc}$  and 4-chlorobenzaldehyde at 120 °C have been found before.

<sup>b</sup> Isolated Yield.



**Scheme 1. synthesis of 2,3-dihydroquinazolinones catalyzed with zinc oxide nano tubes modified by  $\text{SiO}_2$  in solvent free conditions.**

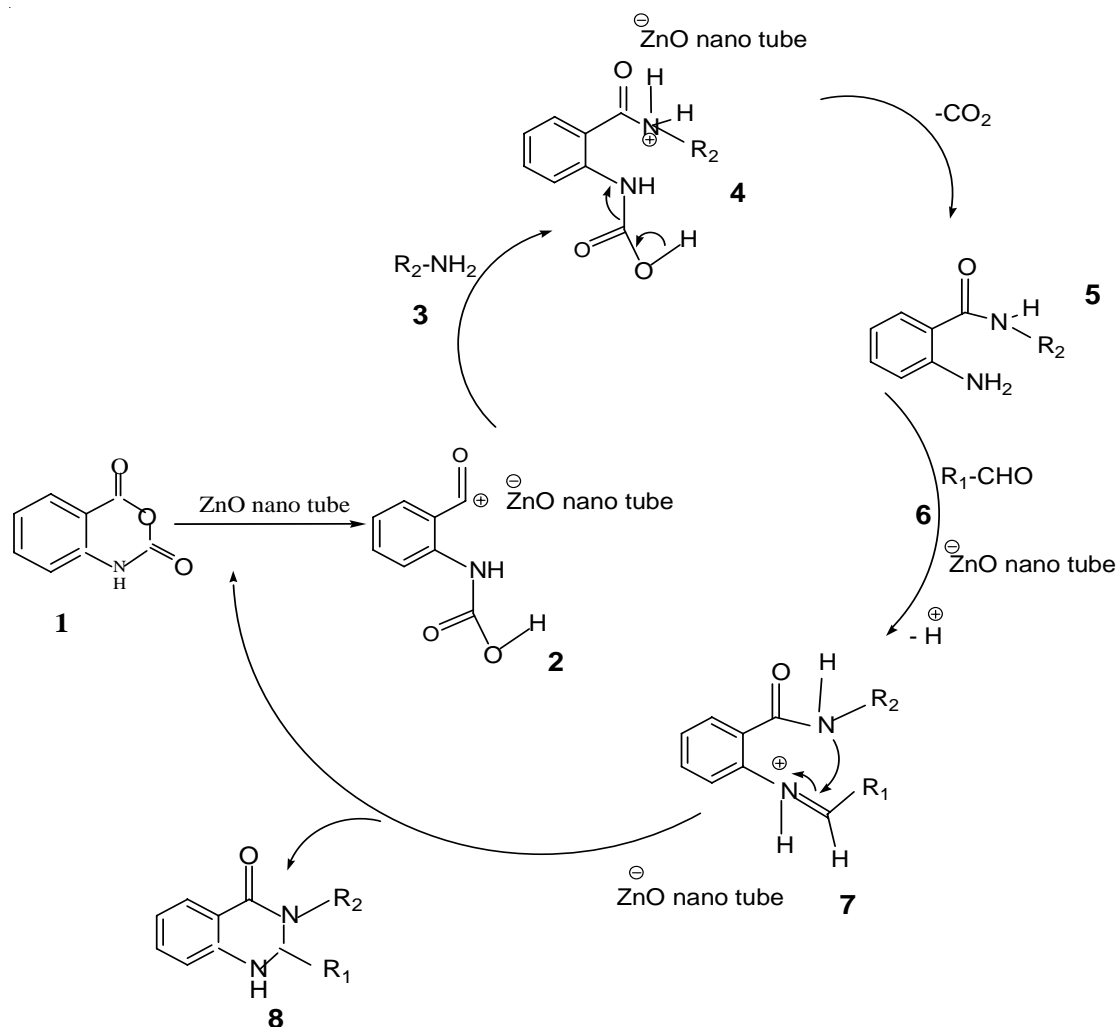
**Table 2: Synthesis of 2,3-dihydroquinazolinone derivatives catalyzed with zinc oxide nano tubes modified by  $\text{SiO}_2$  in solvent free conditions**

Entry	$\text{R}_1$	$\text{R}_2$	Product	Time (min.)	Yield (%) <sup>b</sup>
1	4- $\text{CH}_3\text{C}_6\text{H}_4$	H	3a	120	86
2	4- $\text{CH}_3\text{OC}_6\text{H}_4$	H	3b	2.5	88
3	4- $\text{ClC}_6\text{H}_4$	H	3c	80,120 <sup>c</sup>	84, 81 <sup>c</sup>
4	4- $\text{BrC}_6\text{H}_4$	H	3d	3.0	87
5	2-Thionyl	H	3e	3.0	81
6	4- $\text{CH}_3\text{C}_6\text{H}_4$	$\text{C}_6\text{H}_5$	3f	3.0	84
7	4- $\text{ClC}_6\text{H}_4$	$\text{C}_6\text{H}_5$	3g	2.5	86
8	4- $\text{FC}_6\text{H}_4$	$\text{C}_6\text{H}_5$	3h	3.0	83
9	2-Thionyl	$\text{C}_6\text{H}_5$	3i	3.0	83
10	4- $\text{CH}_3\text{C}_6\text{H}_4$	$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2$	3j	3.0	83
11	4- $\text{CH}_3\text{C}_6\text{H}_4$	4- $\text{HO-C}_6\text{H}_4$	3k	3.0	82

<sup>a</sup> The molar ratios of isatoic anhydride: aldehyde: ammonium acetate has been found before. (1 mmol%) zinc oxide nano tubes modified by  $\text{SiO}_2$  at solvent free condition.

<sup>b</sup> Isolated Yield.

<sup>c</sup> The reaction was accomplished exposed to reused catalyst.



**Scheme 2.** Proposed mechanism for the synthesis of 2,3-dihydroquinazolinones exposed to zinc oxide nano tubes modified by SiO<sub>2</sub>

As it was pointed, the reaction mixture was solvent free. The product was recrystallized and separated from catalyst using hot ethanol. The catalyst after recycling could be employed four times without any treatment. Catalyst turnover is perfect and there is no decreased efficiency (Table. 2). For the mentioned one-pot reaction, some possible mechanisms had been reported before by Baghbanzadeh, co-workers<sup>17</sup> and Wang *et al.*,<sup>22</sup>. According to the experimental results, a credible mechanism has been proposed in Scheme 2. In the presence of zinc oxide nano tubes which is modified by SiO<sub>2</sub> as catalyst, first the isatoic anhydride (1) is rearranged and formed an intermediate (2) with positive charge on carbonyl

group, then the N-nucleophilic amine (3) attack occurs on the carbonyl group of the intermediate (2) to produce another species as intermediate (4), which after decarboxylation reaction followed by proton transfer, in turn affords the intermediate named (5). Subsequently, the aldehyde activated by zinc oxid nanotubes modified by SiO<sub>2</sub>, participate in a condensation reaction with (5) to proceeds the imine intermediate (7), which the general cyclic process forms finally yields proposed product (8). In conclusion, heterogeneous conditions get easy and clean work-up approach, with high yields which this method could be practical for multi-component reactions because of the catalyst recovery. So the present methodology could be a significant manner which added to other methods.

Compound 3i: mp 198–200 8C. IR (neat): 3285.62, 3024.37, 1631.68, 1609.55, 1503.79, 1483.88, 1387.95, 1366.74, 1317.89, 1258.12, 1191.04, 1158.03, 1069.94, 836.88, 793.58, 754.82, 713.91, 694.77  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz, DMSO-d<sub>6</sub>): d 6.53 (d, 1H, J = 2.5 Hz), 6.77 (dt, 1H, J<sub>1</sub> = 7.55 Hz, J<sub>2</sub> = 1.01 Hz), 6.82 (d, 1H, J = 7.81 Hz), 6.86 (dd, 1H, J<sub>1</sub> = 5.03 Hz, J<sub>2</sub> = 3.51 Hz), 6.97 (d, 1H, J = 3.52 Hz), 7.21-7.26 (m, 1H), 7.32-7.41 (m, 6H), 7.72 (d, 1H, J = 2.75 Hz), 7.73 (dd, 1H, J<sub>1</sub> = 7.81 Hz, J<sub>2</sub> = 1.5 Hz).  $^{13}\text{C}$  NMR (100 MHz, DMSO-d<sub>6</sub>): d 69.56, 115.28, 115.66, 118.15, 125.93, 126.34, 126.36, 126.40, 126.52, 127.97, 128.71, 133.84, 140.49, 144.63, 146.38, 161.59. Anal. Calcd for C<sub>18</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>: C, 70.62; H, 4.63; N, 9.16; S, 10.51; Found: C, 70.41; H, 4.52; N, 9.07; S, 10.36.

Compound 3j: mp 152-154 8C. IR (neat): 3282.12, 3027.52, 1628.2, 1609.22, 1583.63, 1506.14, 1485.19, 1408.12, 1311.41, 1173.38, 822.38, 750.44, 693.89  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz, DMSO-d<sub>6</sub>): d 6.31 (d, 1H, J = 2.5 Hz), 6.73 (dt, 1H, J<sub>1</sub> = 7.55 Hz, J<sub>2</sub> = 1.01 Hz), 6.77 (d, 1H, J = 7.79 Hz), 7.11-7.23 (m, 3H), 7.28-7.33 (m, 3H), 7.32-7.37 (m, 2H), 7.41-7.46 (m, 2H), 7.65 (d, 1H, J = 2.5 Hz), 7.76 (dd, 1H, J<sub>1</sub> = 7.83 Hz, J<sub>2</sub> = 1.5 Hz).  $^{13}\text{C}$  NMR (100 MHz, DMSO-d<sub>6</sub>): d 72.09, 114.88, 115.18, 115.29, 115.34, 117.66, 126.14, 126.48, 127.99, 128.67, 128.79, 128.89, 133.85, 136.88, 140.64, 146.59, 160.69, 162.28, 163.11. Anal. Calcd for C<sub>23</sub>H<sub>22</sub>N<sub>2</sub>O: C, 80.69; H, 6.51; N, 8.22; Found: C, 80.53; H, 6.37; N, 8.03.

Compound 3k: mp 249-253 8C. IR (neat): 3311.08, 3119.81, 3015.72, 2891.34, 2359.39, 1633.77, 1612.59, 1595.97, 1580.45, 1514.48, 1444.67, 1421.48, 1266.71, 1225.65, 1150.56, 1117.88, 1018.55, 870.02, 839.52, 806.59, 770.74, 752.55, 695.39  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz, DMSO-d<sub>6</sub>): d 2.11 (s, 3H), 5.94 (d, 1H, J = 2.5 Hz), 6.54-6.62 (m, 4H), 6.92 (dt, 2H, J<sub>1</sub> = 8.83 Hz, J<sub>2</sub> = 2.02 Hz), 6.99

(d, 2H, J = 8.07 Hz), 7.12-7.15 (m, 3H), 7.39 (d, 1H, J = 2.28 Hz), 7.61 (dd, 1H, J<sub>1</sub> = 7.64 Hz, J<sub>2</sub> = 1.5 Hz), 9.35 (s, 1H).  $^{13}\text{C}$  NMR (100 MHz, DMSO-d<sub>6</sub>): d 20.73, 73.15, 114.62, 115.12, 115.42, 117.32, 126.56, 127.91, 127.95, 128.89, 132.24, 133.53, 137.60, 138.02, 146.64, 155.55, 162.34. Anal. Calcd for C<sub>21</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>: C, 76.44; H, 5.51; N, 8.49; Found: C, 76.25; H, 5.33; N, 8.29.

## CONCLUSION

In summary, we have established a new application of zinc oxide nanotubes modified by SiO<sub>2</sub> as an effective, suitable and reusable catalyst. A practical and simple method which redounds to excellent yields of the 2,3-Di hydro quinazolin-4(1H)-one derivatives under mild conditions and within short times. The reason proposed for higher catalytic activity of zinc oxide nano tubes modified by SiO<sub>2</sub> is a combination effect of the small particle size and high-density surface defects. In these reactions, ammonium acetate and different types of aromatic aldehydes as initial materials have potential green chemistry advantages. This method is reasonable from economic point of view and environmentally, due to little waste production. Some advantages like as simple preparation, stability of catalyst, easy handling, short reaction times, having a procedure with simple work-up and the high yields of products, put this reaction at the best existing methodologies. No necessary of using toxic organic solvents as media, is another positive sight.

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