Synthesis of 3,4,5-substituted furan-2(5H)-ones using ZnO nanostructure as an efficient catalyst

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ABSTRACT

A family of 3,4,5-substituted furan-2(5H)-one derivatives are synthesized from aldehydes, aromatic amines, and acetylenic esters via a one-pot reaction catalyzed by nano-structured ZnO. This procedure presents advantages such as: high yields, simple methodology, and easy work up. Nanostructured ZnO was prepared via simple precipitation of zinc (II) ions in Prunus Cerasus juice media.

Keywords: 3,4,5-substituted furan-2(5H)-one; nanostructured ZnO; Acetylenic esters; Butenolides.

1. INTRODUCTION

Functionalized furan-2(5H)-ones are important heterocyclic compounds, present in diverse natural, biological and medicinal compounds. They are a class of heterocyclic compounds containing furan core named as butenolides which are of synthetic interest since they show a broad area of biological activities. On the other hands, butenolides are versatile building blocks for natural product syntheses [1-7].

In recent years, butenolide derivatives have been received considerable attention, especially for organic and medicinal chemists because these compounds exhibit a broad range of biological activities, such as antimicrobial [8, 9], antifungal [10,11], anti-inflammatory [12], anticancer [13,14] and anti-viral HIV-1 [15, 16]. Therefore, the synthesis butenolide scaffolds have gained great importance in organic synthesis.

The three-component reaction of anilines, aldehydes, and acetylenic esters is one of the newly routes for the preparation of 3,4,5-substituted furan-2(5H)-one derivatives discovered by Murthy et al. using β-cyclodextrin as an efficient catalyst [17]. Since that time various catalytic systems were reported by organic chemists involving the use of SnCl2 [18], ZnO nanoparticles [19], Al(HSO4)3 [20], tetra-n-butylammonium bisulfate [21], PPA/SiO2 [22], SnO nanoparticles [23] and HY zeolite [24].

The widespread interest in the chemistry and therapeutic application of furan-2(5H)-one derivatives is the main reason was given for developments of new strategies for the preparation of substituted furan-2(5H)-ones is still in demands.

As a part of our works on multi-component reactions [25-30], we wish to report a novel nano-structured ZnO synthesis of 3,4,5-substituted furan-2(5H)-ones via a multi-component reaction of aromatic amines, aldehydes and acetylenic esters. This procedure presents a new, efficient and green approach for the preparation of substituted furan-2(5H)-ones in good yields (Scheme 1).

![Scheme 1. Preparation of 3,4,5-substituted furan-2(5H)-one derivatives.](image)

2. EXPERIMENTAL SECTION

2.1. Reagents and Instrumentation. Chemicals were purchased from Merck and Aldrich and used without further purification. The catalyst characterizations were taken on a HITACHI S-4160 field emission scanning electron microscope (FE-SEM) and a D8, Advance, Bruker, axs, X-Ray diffractometer (XRD) (Cu-Kα irradiation). The NMR spectra were recorded on a Bruker Avance DPX 400 MHz instrument. The spectra were measured in DMSO-d6 relative to TMS (0.00 ppm). Elemental analysis was performed on a Heraeus CHN-O-Rapid analyzer. Melting points were determined in open capillaries with a BUCHI 510 melting point apparatus. TLC was performed on silica gel Polygram SIL G/UV 254 plates.

2.2. Preparation of nano-structured ZnO. A water solution of Prunus Cerasus juice (10 mL) was mixed with 10 mL aqueous ammonia (37%) and was drop-wise added into a solution of ZnCl2 (20 mmol in 50 mL of distilled water) drop wise under magnetic stirring. The obtained mixture was stirred at room temperature for 30 min. The resultant dark green precipitate was filtered, washed with distilled water and absolute ethanol and dried at 100 °C for ~2h in an oven to gain homogenous mixture. The precipitate was calcined at 600 °C in an electric furnace using alumina crucibles and maintained at the stable mentioned temperature for 2h.

2.3. General procedure. Aldehyde (1 mmol), acetylenic esters (1 mmol) and aromatic amine (1 mmol), nano-structured ZnO (0.025 g), and ethanol (5 mL) was charged into a round bottom flask. The resulting mixture was allowed to be stirred at reflux condition for the appropriate time (Table 2, monitored by TLC). Upon completion, the solvent was concentrated and the reaction mixture was diluted in CHCl3, the catalyst was isolated by simple filtration, and the crude product was washed with diethyl ether to afford the pure product.

Selected data:

**Methyl 2,5-dihydro-5-oxo-2-phenyl-4-(phenylamino)furan-3-carboxylate (11a)**: 1H-NMR (400 MHz, DMSO-d6): 3.73 (s, 3H, OCH3), 6.08 (s, 1H), 7.09 (t, J = 7.8 Hz, 1H), 7.35-7.44 (m, 5H), 7.49-7.58 (m, 4H), 8.89 (s, 1H, NH) ppm.
3. RESULTS SECTION

The nano-structured ZnO was synthesized via a simple precipitation method with the using of an extract solution of Prunus Cerasus juice.

Mechanism of the formation of nano-structured ZnO.

In green chemistry processes, a medium that using of plant extracts, generally called biosynthesis method which is an environmentally friendly method, as it is reduced the use of expensive and hazardous chemicals and has been utilized widely for the synthesis of nano-structured materials. The understanding of the mechanism of green biosynthesis of nano-structured ZnO by a plant extract is still in its infancy and more investigation is required to be understandable. As it was revealed from the literatures various organic compounds like alkaloids, polyphenols and pigments are present in plant extracts which are able to chelate the metal ions through their hydroxyl and carbonyl groups [31-34].

Prunus Cerasus juice is rich from the polyphenolic compounds such as cyanidin-3-glucoside and cyanidin-3-rutinoside [34] (Scheme 2) which may be the main factor required for the biosynthesis of nano-structured ZnO. These hydroxyl groups of these compounds chelate Zn$^{2+}$ ions. The calcination step is needed for the removing of all organic materials and finally nano-structured ZnO remain as the pure sample.

![Scheme 2: Chemical structure of cyanidin-3-glucoside and cyanidin-3-rutinoside present in Prunus Cerasus juice.](image)

In order to obtain information about the phase characteristics of the synthesized materials, XRD analysis has been made. Figure 1 shows the XRD patterns of ZnO nanocatalyst calcined at 600 °C for 2h. The hexagonal single phase structure (space group P63mc), with lattice parameters $a = 3.2490\AA$, $b = 3.2490\AA$ and $c = 5.2050\AA$, $\beta = 99.5490^\circ$, was observed in the XRD pattern of the powders which are in agreement with the reported standard values (JCPDS 00-005-0664). The characteristic peaks of hexagonal ZnO are 31.75, 34.44, 36.25, 47.54, 56.55, 62.87, 67.91, 69.05, 89.63, 95.31 20°. The crystalline size of the sample was determined using a Scherrer formula from the full width at half maximum (FWHM) of the highest peak of the XRD pattern as 86 nm.

### Table 1: Optimization of the reaction condition.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (g)</th>
<th>T (°C)</th>
<th>Solvent (5 mL)</th>
<th>Time (h)</th>
<th>Yield (%) *</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.05</td>
<td>Reflux</td>
<td>n-Hexane</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>0.05</td>
<td>Reflux</td>
<td>CH$_2$Cl$_2$</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>0.05</td>
<td>Reflux</td>
<td>Et$_2$O</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>0.05</td>
<td>Reflux</td>
<td>EtOAc</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>0.05</td>
<td>Reflux</td>
<td>EtOH</td>
<td>8</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>0.05</td>
<td>Reflux</td>
<td>MeOH</td>
<td>8</td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>0.05</td>
<td>r.t.</td>
<td>70</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>r.t.</td>
<td>EtOH</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>0.025</td>
<td>Reflux</td>
<td>EtOH</td>
<td>8</td>
<td>83</td>
</tr>
<tr>
<td>10</td>
<td>0.075</td>
<td>Reflux</td>
<td>EtOH</td>
<td>5</td>
<td>76</td>
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<td>74</td>
</tr>
<tr>
<td>12</td>
<td>0.25</td>
<td>Reflux</td>
<td>EtOH</td>
<td>10</td>
<td>71*</td>
</tr>
</tbody>
</table>

* Isolated Yields; * ZnO was prepared via a same procedure without using of juice.

FE-SEM analyze was used to determine the morphological structure of the nanstructured ZnO (Figure 2). The particles are regular nearly uniform spherical which some of them have dimensions less than 100 nm.

The catalytic activity of zinc oxide, in the present study, was investigated through the transformation of 1, 2, and 3 into 4 under solvent and solvent-free condition (Scheme 3, Table 1).

The results of performed experiments showed that the solvent has anomalous effect on the productivity of the reaction. Unlike polar solvents which have resulting in moderate to good yields (30-84%), using of non-polar solvents and also solvent-free condition are not effective (0%). Consequently to the obtained results, EtOH is the most suitable solvent for the reaction medium. Next, the effect of catalyst dosage (varying from 0.025-0.25g) on the product yield was investigated. An excellent yield of product was obtained when 0.025 g of catalyst was used. The further increase in the ZnO dosage did not shown any significant increase on the product yield (Table 1).

For comparison a sample of ZnO was prepared via a same procedure without using of juice and was used as a catalyst for the above reaction under optimized condition. The result shows that the prepared sample is less effective catalyst for the preparation of 3,4,5-substituted furan-2(5H)-ones (Table 1).

![Scheme 3: Preparation of methyl 4-(p-tolylamino)-2,5-dihydro-5-oxo-2-phenylfuran-3-carboxylate.](image)

Next, using the optimized conditions, diverse anilines, aldehydes and acetylenic esters reacted together to give the corresponding 3,4,5-substituted furan-2(5H)-ones (Scheme 1.

**Table 1:** Optimization of the reaction condition.
It was found that the yields and product purity for all products including electron-donating and electron-withdrawing groups substituted on the aromatic rings are good (Table 2, products 1a-17a). Aromatic aldehydes and amines bearing electron-withdrawing groups require more time to complete the reaction, whereas this time is less for the donor substitutions.

**Table 2.** Synthesis of 3,4,5-substituted furan-2(5H)-one derivatives (Scheme 1)

<table>
<thead>
<tr>
<th>Product</th>
<th>Aldehyde</th>
<th>Amine</th>
<th>R</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
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<tr>
<td>1a</td>
<td>Benzaldehyde</td>
<td>4-Methylaniline</td>
<td>Me</td>
<td>8</td>
<td>83</td>
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<tr>
<td>2a</td>
<td>Benzaldehyde</td>
<td>4-Methylaniline</td>
<td>Et</td>
<td>8</td>
<td>81</td>
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<tr>
<td>3a</td>
<td>4-Methylbenzaldehyde</td>
<td>4-Methylaniline</td>
<td>Me</td>
<td>7</td>
<td>90</td>
</tr>
<tr>
<td>4a</td>
<td>4-Methylbenzaldehyde</td>
<td>4-Methylaniline</td>
<td>Et</td>
<td>7</td>
<td>84</td>
</tr>
<tr>
<td>5a</td>
<td>4-Chlorobenzaldehyde</td>
<td>4-Methylaniline</td>
<td>Me</td>
<td>8</td>
<td>76</td>
</tr>
<tr>
<td>6a</td>
<td>4-tert-Butylbenzaldehyde</td>
<td>4-Methylaniline</td>
<td>Me</td>
<td>7</td>
<td>89</td>
</tr>
<tr>
<td>7a</td>
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<td>Et</td>
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<td>83</td>
</tr>
<tr>
<td>8a</td>
<td>4-Methylbenzaldehyde</td>
<td>4-Chloroaniline</td>
<td>Me</td>
<td>9</td>
<td>84</td>
</tr>
<tr>
<td>9a</td>
<td>Benzaldehyde</td>
<td>4-Chloroaniline</td>
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<td>10</td>
<td>70</td>
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<td>10a</td>
<td>4-Methylbenzaldehyde</td>
<td>4-Methoxyaniline</td>
<td>Me</td>
<td>6</td>
<td>90</td>
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<td>11a</td>
<td>Benzaldehyde</td>
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<td>Me</td>
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<td>12a</td>
<td>Benzaldehyde</td>
<td>Aniline</td>
<td>Et</td>
<td>10</td>
<td>71</td>
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<td>Aniline</td>
<td>Me</td>
<td>8</td>
<td>84</td>
</tr>
<tr>
<td>14a</td>
<td>4-Methylbenzaldehyde</td>
<td>Aniline</td>
<td>Et</td>
<td>9</td>
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<td>15a</td>
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<td>16a</td>
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<td>Me</td>
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<td>68</td>
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<tr>
<td>17a</td>
<td>2,4-Dichlorobenzaldehyde</td>
<td>Aniline</td>
<td>Me</td>
<td>15</td>
<td>75</td>
</tr>
</tbody>
</table>

*Isolated yields. All known products have been reported previously in the literature and were characterized by comparison of NMR spectra with authentic samples [13-17].

**4. CONCLUSIONS**

In summary, nano-structured ZnO was prepared via a simple precipitation method in a solution of Prunus Cerasus juice as green media and was applied as a mild and efficient green catalyst for the syntheses of 3,4,5-substituted furan-2(5H)-one derivatives. Various substituted amines and aldehydes were used in reaction. All products were obtained in good and excellent yields. From the standpoint of the reaction conditions can be said that the advantages of this method are mild conditions and high yields.
5. REFERENCES

6. ACKNOWLEDGEMENTS
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