Ag/TiO$_2$ Nano Thin Films Catalyzed Efficient Synthesis of 6-Amino-4-Aryl-3-Methyl-1,4-Dihydropyran[2,3-C] Pyrazole-5-Carbonitriles At Green Conditions

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ABSTRACT

Ag/TiO$_2$ nano thin films was found to be efficient and green heterogeneous catalyst for the synthesis of dihydropyran[2,3-c]pyrazole derivatives via a one-pot three-component reaction between 3-methyl-1$\text{H}$-pyrazol-5(4$\text{H}$)-one or 3-methyl-1(phenyl)-pyrazol-5(4$\text{H}$)-one, aldehydes and malononitrile at room temperature. Ag/TiO$_2$ and TiO$_2$ films were prepared by spray pyrolysis technique and the effect of substrate temperature and silver incorporation on optical, morphological and structural properties were investigated by XRD, AFM, spectrophotometry and photoluminescent spectroscopy. The results of this study shows adding of Ag to TiO$_2$ films increased the optical absorption due to plasmonic behavior of Ag free electrons. XRD analysis was revealed the Hexagonal structure with Anatase phase and 101 prefer crystal orientation which is prefer phase for photocatalyst applications.

Keywords: Ag/TiO$_2$, nano thin films, dihydropyran[2,3-c]pyrazole, 3-methyl-1$\text{H}$-pyrazol-5(4$\text{H}$)-one, 3-methyl-1(phenyl)-pyrazol-5(4$\text{H}$)-one, aldehydes, malononitrile

INTRODUCTION

Titanium dioxide is the most popular and efficient semiconductor photo catalyzer due to its strong oxidative ability of photo generated electron-hole pairs on its surface¹². This efficient photo catalysis has been studied extensively due to many industrial applications. Unfortunately, this semiconductor has limited catalytic efficiency due to its wide energy band gap; it is just sensitive to UV radiation. The energy band gap of bulk TiO$_2$ is 3 eV and 3.2 eV for rutile and anatase phases,
respectively. TiO₂ as a photo catalysis have been widely studied in anatase and rutile phases. Its photo catalytic activity in anatase phase is more than other phases.

In recent years nano-composite thin films, due to their industrial application, have been studied by many researchers. Ag/TiO₂ nano particles have been widely used in photo electrochemical and photo catalyst applications. One of the most important problems which decrease the photocatalyst efficiency is electron-hole recombination. It is well experienced that noble metal doping reduces the electron-hole recombination rate and hence increases the photocatalytic efficiency. In this work, Ag/TiO₂ nanocomposite films was deposited on microscope glass slides and also inside of beakers by spray pyrolysis technique and the effect of silver incorporation on optical, crystal structure, surface morphology and recombination rate were characterized and reported.

Combinatorial methods employing multicomponent reactions have recently become the focus of considerable interest because of their swift and convenience of synthesis of various classes of compounds. Multicomponent reactions (MCRs), defined as one-pot reactions in which at least three functional groups are joined via covalent bonds, gradually gain importance in synthetic organic chemistry.

Nitrogen-containing heterocycles, key element and widespread structural motif in many drugs, are important design feature of medicinal agents in medicinal chemistry. Moreover, they can act as biomimetic and active pharmacophores. Pyrazoles are among the most commonly investigated organic nitrogen-containing heterocycles compounds with 5-membered ring. Pyrazoles have many applications in the field of pharmaceutical industry, and medical chemistry due to their biological activities such as antifungal, antiviral, anticancer, and anti-inflammatory properties. Due to these properties, they are widely utilized in the pharmaceutical industry, medicinal chemistry and they are also important core in natural products. In addition pyrazoles have been used for treatment of type 2 diabetes, obesity, thrombopiotininmimetics and antiangiogenesis because of their kinase inhibitory effects. Furthermore, some pyrazoles are employed in polymer and supramolecular chemistry, in the food industry, and as UV stabilizers and cosmetic colorings and in some cases it was observed that these compounds also have liquid crystal properties. Dihydropyrano[2,3-c]pyrazoles, are one of the most important pyrazole compounds and they have received considerable attention owing to their biological activity and they have been utilize as a template for medicinal chemistry. They exhibited many biological activities like antimicrobial, insecticidal, and anti-inflammatory. Moreover, dihydropyrano[2,3-c]pyrazoles exhibit molluscidial activity, and has been identified as a screening kit for Chk1 kinase inhibitor. Because of the importance of these compounds, a number of methods have been reported for their synthesis in the presence of various catalysts such as ionic liquids, organic bases, amylbery, glycine, per-6-amino-b-cyclodextrin, and iodine.

In recent years, we investigated the synthesis of these compounds in the presence of diverse green catalysts such as trichloroacetic acid, cellulose, L-proline and in green media. In continuation of our research on multi-component reactions, herein we would like to describe the synthesis of dihydropyrano[2,3-c]pyrazole derivatives, our attention was drawn to the of Ag/TiO₂ nano thin films as an effective and highly reusable catalyst and the synthesis of dihydropyrano[2,3-c]pyrazole was investigated in the presence of this catalyst.

RESULTS AND DISCUSSIONS

In the opinion of experiment of this new process at first we examined the reaction of aldehydes 1, malononitrile 2 and 3-methyl-1H-pyrazol-5(4H)-one or 3-methyl-1(phenyl)-pyrazol-5(4H)-one 3 in EtOH at room temperature in the proximity of Ag/TiO₂ nano thin films to get the forecasted dihydropyrano[2,3-c]pyrazole derivatives. differences temperature and solvent were tested to optimize the reaction position. The results exhibited that the reaction proceeds with good yields when EtOH was used at room temperature. Try again, when we examined the reaction in absence of catalyst, no significant change in the reaction mixture after 48 hours has been seen which showed the catalyst
has good effect on reaction yields. With the optimal conditions in hand, we found the scope of the reaction for the construction of various dihydropyrano[2,3-c]pyrazoles.

Finally, we increased the reaction with various aldehydes including both electron withdrawing and electron-donating substituents. The reactions are generally clean, and desired products 4a-r was obtained in good yields. The results are summarized in Table 1.

According to our results, we can propose the reaction mechanism shown in Scheme 2. Initially, Knoevenagel condensation reaction between aldehyde and malononitrile in the presence of catalyst lead to the formation of alkene A. Thereafter, Micheal addition reaction between intermediate A and B lead to intermediate C. Intramolecular cyclization of intermediate C by attack of hydroxyl group to nitrile group in the presence of titanium oxide lead to intermediate E. Finally, imine-enamine tautomerization of E gives desirable product 4.

We also investigated the recycling of the Ag/TiO$_2$ nano thin films as the catalyst using the model reaction of 3-methyl-1(phenyl)-pyrazol-5(4H)-one, malononitrile and 4-methoxybenzaldehyde. When the reaction is done, the crude product was purified by filtration and washed with EtOH (3 × 2 mL) to give the desired products. Then, the vial Ag/TiO$_2$ nano thin films washed with EtOH and checking the reusability under similar reaction conditions. The results showed that Ag/TiO$_2$ nano thin films is

![Scheme 1: Synthesis of dihydropyrano[2,3-c]pyrazole derivatives 4a-r](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>R</th>
<th>Product</th>
<th>Time (min)</th>
<th>yield (%)$^a$</th>
<th>O.b. m.p (°C)</th>
<th>Lit. m.p (°C)</th>
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<tbody>
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<td>168-170 [43]</td>
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<tr>
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<td>4-Br-C$_6$H$_5$</td>
<td>Ph</td>
<td>4b</td>
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<td>85</td>
<td>213-215</td>
<td>213-215[43]</td>
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<tr>
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<td>4-NO$_2$-C$_6$H$_4$</td>
<td>Ph</td>
<td>4c</td>
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<td>170-171</td>
<td>169-171[43]</td>
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<tr>
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<td>Ph</td>
<td>4d</td>
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<td>Ph</td>
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<td>4-OH-C$_6$H$_5$</td>
<td>H</td>
<td>4q</td>
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<td>H</td>
<td>4r</td>
<td>20</td>
<td>80</td>
<td>174-176</td>
<td>175-177[45]</td>
</tr>
</tbody>
</table>

$^a$Yields refer to the isolated pure products.
a stable catalyst in reaction media and reused four times without significant loss of its catalytic activity (Fig. 1). Catalyst could be recovered because all eighteen derivatives of dihydropyrano[2,3-c]pyrazole were synthesis from only one Ag/TiO$_2$ nano thin films.

To show the value of the present procedure in comparison with reported results in the other documents, we compared result of Ag/TiO$_2$ nano thin films with reported catalysts in the synthesis of derivatives of dihydropyrano[2,3-c]pyrazole, such as γ-alumina $^{50}$, TEAA (triethylammonium acetate) $^{51}$, trichloroacetic acid $^{52}$, imidazole $^{53}$, ceric sulfate $^{52}$, ultrasound irradiation $^{54}$, nanosized magnesium oxide $^{55}$, L-proline $^{56}$, $\text{H}_3\text{PO}_4/\text{Al}_2\text{O}_3$ $^{57}$, cellulose $^{58}$ (Table 2). As it is shown in Table 2, Ag/TiO$_2$ nano thin films remarkably improved the synthesis of 1,4-dihydropyrano[2,3-c]pyrazole in different terms, for example in terms of reaction conditions.

**Experimental**

All reagents were purchased from Merck and Sigma-Aldrich and used without further purification. All yields refer to isolated products after purification. Products were characterized by comparison physical data with authentic samples and spectroscopic data (IR and NMR). The NMR spectra were recorded on a Bruker Avance DRX 300 MHz instrument. IR spectra were recorded on a JASCO FT-IR 460 plus spectrophotometer and Avance, respectively.

**Scheme 2: Proposed mechanism for the synthesis of dihydropyrano[2,3-c]pyrazole**

General procedure for the synthesis of 3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile derivatives

To a magnetic stirred solution of aromatic aldehydes 1 (1.0 mmol), malononitrile 2 (1.0 mmol) and 3-methylpyrazol-5(4$\text{H}$)-one 3 (1.0 mmol) in EtOH (2 mL) Ag/TiO$_2$ nano thin films was added at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the crude solid product was filtered for separation of product and washed with EtOH (3x2 mL) to give the pure product. All of the products are known.
Selected spectroscopic data of some products are given below:

6-amino-1,4-dihydro-3-methyl-4-(2,4-dichlorophenyl)-1-phenylpyrano[2,3-c]pyrazole-5-carbonitrile (4f): IR (KBr, cm\(^{-1}\)): 3458, 3325, 2198, 1660; \(^1\)H NMR (400 MHz, (DMSO-d\(_6\)): \(\delta = 1.77\) (s, 3H, CH\(_3\)), 5.15 (s, 1H, CH), 7.32-7.43 (m, 5H, NH\(_2\) and ArH ), 7.47-7.51 (m, 2H, ArH), 7.61 (s, 1H, ArH), 7.77 (d, 2H, \(J = 8.0\) Hz, ArH).

6-amino-1,4-dihydro-3-methyl-4-(4-methoxyphenyl)-1-phenylpyrano[2,3-c]pyrazole-5-carbonitrile (4g): IR (KBr, cm\(^{-1}\)): 3392, 2933, 2197, 1663; \(^1\)H NMR (400 MHz, (DMSO-d\(_6\)): \(\delta = 1.80\) (s, 3H, CH\(_3\)), 3.64 (s, 3H, OCH\(_3\)), 4.64 (s, 1H, CH), 6.92 (d, \(J = 8.0\) Hz, 2H, Ar), 7.19 (br, 2H, NH\(_2\)), 7.20 (d, \(J = 8.0\) Hz, 2H, Ar), 7.33 (t, \(J = 8.0\) Hz, 1H, Ar), 7.50 (t, \(J = 8.0\) Hz, 2H, Ar), 7.68 (d, \(J = 8.0\) Hz, 2H, Ar).

6-amino-1,4-dihydro-3-methyl-4-(3-ethoxy-4-hydroxyphenyl)-1-phenylpyrano[2,3-c]pyrazole-5-carbonitrile (4h): IR (KBr, cm\(^{-1}\)): 3420, 3329, 2195, 1663; \(^1\)H NMR (400 MHz, (DMSO-d\(_6\)): \(\delta = 1.29-1.32\) (t, 3H, J =7.2 HzCH\(_2\)), 1.84 (s, 3H, CH\(_3\)), 3.95-4.01 (q, 2H, J =7.2 Hz CH\(_2\)), 4.59 (s, 1H, CH), 6.62-7.80 (m, NH\(_2\) and ArH ), 8.86 (s, 1H, OH).

6-amino-1,4-dihydro-3-methyl-4-(biphenyl-4-yl)-1-phenylpyrano[2,3-c]pyrazole-5-carbonitrile (4i): IR (KBr, cm\(^{-1}\)): 3471, 3328, 2185, 1645; \(^1\)H NMR (400 MHz, (DMSO-d\(_6\)): \(\delta = 1.76\) (s, 3H, CH\(_3\)), 4.87 (s, 1H, CH), 7.30-7.94 (m, NH\(_2\) and Ar).

6-amino-1,4-dihydro-3-methyl-4-(naphthalen-2-yl)-1-phenylpyrano[2,3-c]pyrazole-5-carbonitrile (4m): IR (KBr, cm\(^{-1}\)): 3390, 3200, 2180, 1655; \(^1\)H NMR (400 MHz, (DMSO-d\(_6\)): \(\delta = 1.76\) (s, 3H, CH\(_3\)), 4.88 (s, 1H, CH), 7.29 (br, 2H, NH\(_2\)), 7.33-7.96 (m, 12H, Ar).

6-amino-1,4-dihydro-3-methyl-4-(4-methoxyphenyl)pyrano[2,3-c]pyrazole-5-carbonitrile (4o): IR (KBr, cm\(^{-1}\)): 3455, 3320, 2190, 1654; \(^1\)H NMR (300 MHz, (DMSO-d\(_6\)): \(\delta = 1.76\) (s, 3H, CH\(_3\)), 4.55 (s, 1H, CH), 6.85 (br, 2H, NH\(_2\)), 6.88 (s, 1H, CH), 7.07 (d, \(J = 9.0\) Hz, 2H, Ar), 12.03 (s, 1H, NH).

6-amino-1,4-dihydro-3-methyl-4-(2-chlorophenyl)pyrano[2,3-c]pyrazole-5-carbonitrile (4p): IR (KBr, cm\(^{-1}\)): 3470, 3240, 2180, 1638; \(^1\)H NMR (300 MHz, (DMSO-d6): \(\delta = 1.77\) (s, 3H, CH\(_3\)), 5.08 (s, 1H, CH), 6.99 (br, 2H, NH\(_2\)), 7.18-7.43 (m, 4H, Ar), 12.16 (s, 1H, NH).

**CONCLUSION**

In this research, we used Ag/TiO\(_2\) nano thin films for first time as a catalyst for the Synthesis of dihydropyrano[2,3-c]pyrazole derivatives. The efficient features of this protocol are simple
performing reaction, cleaner reaction, use of green and reusable nano catalyst. Satisfactory yields of products, as well as a simple isolation and reduced reaction times of the products make it a useful protocol for the green synthesis.

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REFERENCES


