## Tetrahedron Letters 52 (2011) 4636-4641

Contents lists available at ScienceDirect

**Tetrahedron Letters** 

journal homepage: www.elsevier.com/locate/tetlet

# One-pot synthesis of dihydropyrano[2,3-*c*]chromenes via a three component coupling of aromatic aldehydes, malononitrile, and 3-hydroxycoumarin catalyzed by nano-structured ZnO in water: a green protocol

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### ARTICLE INFO

Article history: Received 26 May 2011 Revised 20 June 2011 Accepted 27 June 2011 Available online 2 July 2011

Keywords: Dihydropyrano[2,3-c]chromene Green protocol Organic nanofibers Self aggregation

## ABSTRACT

An efficient and green protocol for the synthesis of dihydropyrano[2,3-c]chromene derivatives by onepot, three component coupling reaction of aromatic aldehyde, malononitrile, and 3-hydroxycoumarin has been developed using nano-structured ZnO as the catalyst. The formation of self-assembled organic nanofiber arising from low-molecular-weight molecules has also been performed. The optical properties of the nano-structured organic molecules were studied.

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Multicomponent coupling reaction (MCR) is a powerful synthetic tool for the synthesis of biologically active compounds.<sup>1</sup> Development of such multicomponent coupling reaction strategies in aqueous medium has been of considerable interest, as they provide simple and rapid access to a large number of organic molecules through a sustainable path.<sup>2</sup> One important aspect of green chemistry is the elimination of solvents in chemical processes or the replacement of hazardous solvents with relatively benign solvents. Water being the most environmentally benign, cleanest, cheapest, nonflammable, and naturally occurring solvent having high specific heat capacity is the primary choice. Moreover, in water, significant rate enhancement was observed in many reactions,<sup>3</sup> because of hydrophobic interactions that induce a favorable aggregation of polar components in water.<sup>4</sup>

Pyrano[3,2-*c*]chromene derivatives have received considerable attention of synthetic and medicinal chemists because of their broad spectrum of biological and pharmaceutical activities. These derivatives show antihyperglycemic and antidyslipidemic,<sup>5</sup> cytotoxic,<sup>6</sup> molluscicidal,<sup>7</sup> antiinflammatory,<sup>8</sup> and antifungal activities.<sup>9</sup> These compounds also exhibit a wide spectrum of biological activities,<sup>10</sup> including anticancer,<sup>11</sup> antimalarial<sup>12</sup> and are also widely employed as cosmetics, pigments,<sup>13</sup> and potential biodegradable agrochemicals.<sup>14</sup> Again [3,2-*c*]chromene derivatives are components of numerous natural products like calanolides, calanone, calophyllolides etc.<sup>15</sup>

In view of the great importance of chromene[3,2-c] derivatives, in recent years efforts have been made in developing new methodologies for the synthesis of these compounds. A variety of reagents, such as heteropolyacids,<sup>16</sup> ionic liquid,<sup>17</sup> magnesium oxide,<sup>18</sup> diammonium hydrogen phosphate,<sup>19</sup> tetrabutylammoniumbromide,<sup>20</sup> KF/Al<sub>2</sub>O<sub>3</sub>,<sup>21</sup> and triethylbenzylammonium chloride<sup>22</sup> have been employed to achieve the synthesis of these molecules. The conventional protocol involves a three component condensation of 4-hydroxycoumarin, malononitrile, and aldehyde in presence of solvent or water and under elevated temperature.<sup>16-21</sup> However, there is a maiden report for the synthesis of dihydropyrano[2,3c]chromene derivatives from 3-hydroxycoumarin and condensed product of the malononitrile and aldehyde.<sup>23</sup> But it is a two step process and it takes longer time for completion of the reaction. Herein, we disclose a general, rapid, high yielding, green synthetic protocol<sup>24</sup> for a variety of chromene[2,3-c] derivatives starting from less explored 3-hydroxycoumarin<sup>25</sup> with an objective to find useful applications of dihydropyrano[2,3-c]chromene derivatives.

Since 4-hydroxycoumarin ( $pK_a$  0.735 at 70 °C in water) is enol tautomer of 1,3-dicarbonyl compound, in presence of acid or base it can act as a nucleophile and easily forms chromene[3,2-*c*] derivatives. But, 3-hydroxycoumarin ( $pK_a$  4.23 at 70 °C in water) may be considered as the enol tautomer of 1,2-dicarbonyl compound and hence it is a very poor Michael donor under acidic or basic conditions and the formation of chromene[2,3-*c*] derivatives from it is rather difficult. As nanomaterials are of much potential in organic reaction owing to their high surface to volume ratio and large number of active sites, we considered that catalysis by nanomaterial may take the pivotal role in the synthesis of [2,3-*c*]chromene derivative.





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<sup>0040-4039/\$ -</sup> see front matter  $\circledcirc$  2011 Elsevier Ltd. All rights reserved. doi:10.1016/j.tetlet.2011.06.101

Accordingly, we achieved the synthesis of dihydropyrano[2,3c]chromene derivatives using nano ZnO as catalyst (Scheme 1) and inducing 3-hydroxycoumarin as the potential Michael donor to participate in multicomponent coupling reaction.

In the preliminary stage of investigation we focused on systematic evaluation of different catalysts for the model reaction of 4nitrobenzaldehyde, malononitrile, and 3-hydroxycoumarin at 70 °C in aqueous medium. A wide variety of catalysts including nano aluminum oxide ( $Al_2O_3$ ),  $H_6P_2W_{18}O_{62}$ , 18H<sub>2</sub>O, L-proline, alum, tetrabutylammonium bromide, zeolites, bulk ZnO, and nano ZnO were employed to improve the yield for the specific synthesis of dihydropyrano[2,3-c]chromene derivative. The results are presented in Table 1. Interestingly, when the reaction was carried out in the presence of nano ZnO; it led to the desired product in 91% yield in 2.5 h (Table 1).

During the optimization of the reaction condition, the effect of temperature was monitored (Fig. 1). At 70 °C the yield of the product is maximum. Due to the unavailability of activation energy, the rate of the reaction is very slow at a temperature below 70 °C and



Scheme 1. Synthesis of dihydropyrano[2,3-c]chromene derivatives over nano ZnO.

 Table 1

 Influence of different catalysts for the reaction of 4-nitrobenzaldehyde, malononitrile, and 3-hydroxycoumarin at 70 °C in aqueous medium

Entry	Catalyst	Time (h)	Yield <sup>a</sup> (%)
1	Nano aluminum oxide (Al <sub>2</sub> O <sub>3</sub> )	6	29
2	H <sub>6</sub> P <sub>2</sub> W <sub>18</sub> O <sub>62</sub> , 18H <sub>2</sub> O	7	48
3	L-Proline	6	70
4	Alum	8	53
5	Tetrabutylammonium bromide	6	31
6	Zeolites	8	-
7	Bulk ZnO	6	51
8	Nano ZnO	2.5	91

<sup>a</sup> Isolated yield of the pure compound.



**Figure 1.** Effect of temperature on the reaction of 4-nitrobenzaldehyde, malononitrile and 3-hydroxycoumarin at 70 °C in aqueous medium.

at a higher temperature there might be some sort of polymerization of the Knoevenagel condensation product which lowers the yield of the desired product.

Various solvents were also screened to test their efficiency at 70 °C and the results are summarized in Table 2. It is noteworthy to mention that the polar solvents afforded better yield than the nonpolar ones and the best result was obtained in aqueous medium in which nano ZnO catalyst worked most efficiently by phasing out of the desired product. This also revealed that quantity of the catalyst plays a vital role in realizing the optimized product yield. An increase in the amount of nano ZnO from 3 to 10 mol % increased the yield of the desired product to a great extent (54–91%, Table 2).

On the basis of the above results during the optimization of catalyst and solvent, we then devised a novel three-component one pot synthesis of functionalized pyrano[2,3-*c*]chromene derivatives in aqueous medium in presence of nano ZnO under thermal conditions. To study the scope and limitations of this protocol, we have employed a wide range of aldehydes with 3-hydroxycoumarin and malononitrile. As mentioned in Table 3 (following Scheme 1), the reaction proceeded smoothly with unsubstituted benzaldehyde, electron-withdrawing, and also with electron-releasing *para*substituted benzaldehydes.

With these excellent results in hand, we are now in a position to propose the mechanism of the reaction which involves, Knoevenagel condensation, Michael addition, and then intra molecular cyclization catalyzed by nano ZnO as presented in Scheme 2. In first step, the Knoevenagel condensation is catalyzed by amphoteric nano ZnO which during abstraction of acidic proton from malononitrile unit acts as a base and during dehydration, it shows acidic nature. At the time of cyclization, the particular catalyst plays the key role where ZnO acts as a mild acid and not only minimizes the 1,2 dipolar repulsion but also activates the nitrile group by polarizing the same very efficiently for the intramolecular nucleophilic attack by the OH group leading to the ring closure which ultimately forms the final product and again the catalyst enters into the catalytic cycle.

In addition, when the reaction was scaled up to 2.5 g with 10 mol % nano ZnO at 70 °C in aqueous medium, excellent results were still obtained in 3 h. To take advantage of the elaborated green protocol, solid product was separated from water phase by filtration, and after crystallisation from ethanol, pure chromene derivatives were obtained. This procedure excluded use of expensive silica gel chromatography, and the application of small amount of ethanol instead of chromatographic eluents seems to be promising from green chemistry perspective.

It is noteworthy to mention that in recent years nanofibers have gained a tremendous attention in material science.<sup>26</sup> Nanofiberbased materials are considered to be very promising for broad spectrum of applications, such as, templating of inorganic

Table 2

Solvent effects on the three-component coupling reaction for the synthesis of dihydropyrano[2,3-c]chromene derivatives

Entry	Catalyst <sup>a</sup> (mol %)	Solvent	Temperature (°C)	Yield <sup>b</sup>
1	Nano ZnO (3 mol %)	H <sub>2</sub> O	70	54
2	Nano ZnO (6 mol %)	H <sub>2</sub> O	70	63
3	Nano ZnO (10 mol %)	H <sub>2</sub> O	70	91
4	Nano ZnO (15 mol %)	H <sub>2</sub> O	70	83
5	Nano ZnO (10 mol %)	Toluene	70	49
6	Nano ZnO (10 mol %)	Acetonitrile	70	52
7	Nano ZnO (10 mol %)	DMF	70	67
8	Nano ZnO (10 mol %)	DMSO	70	69
9	Nano ZnO (10 mol %)	Ethanol	70	70

<sup>a</sup> Reaction time: 2.5 h.

<sup>b</sup> Isolated yield of the pure compound.

# Table 3

Nano ZnO catalyzed three component coupling of dihydropyrano[2,3-c]chromene derivative (Scheme 1)

Entry	Aldehyde	Product <sup>b</sup>	Time (h)	Yield (%)	Reference
1	CHO	$ \begin{array}{c}                                     $	3	87	23
2	CHO NO <sub>2</sub>	$O_2N$ $CN$ $NH_2$ $O_2O$ $O_$	2.5	91	23
3	CHO CHO OCH <sub>3</sub>	$H_3CO$ $H_3CO$ $H_1CO$ $H_2$	3	78	23
4	CHO Br	3c $Br$ $CN$ $NH_2$ CH $O3d$	2.5	89	23
5	CHO CH <sub>3</sub>	$H_3C$ $CN$ $NH_2$ $C CN$ $H_2$ $H_$	3	83	-
6	СНО	CN $H_2$ CN $H_2$ CN $H_2$	2.5	89	_
7	CHO F	$3f$ $F_{\downarrow} CN NH_2$ $G = 0$ $2\pi$	2.0	90	-
8	CHO	$V_{C}$ $V_{C}$ $V_{C}$ $V_{C}$ $V_{H_2}$ $V_{C}$ $V_{H_2}$ $V_{C}$ $V_{C}$	2.5	90	-
9	⟨ <sub>S</sub> ↓ <sub>CHO</sub>	$S_{II}$ $S_{II}$ $S_{II}$ $S_{II}$ $NH_2$ $O_{II}$ $O_{III$	3	75	_

Table 3 (continued)



<sup>a</sup> Single crystals were grown from hexane/ethyl acetate solution (Supplementary data).

<sup>b</sup> Products (**3a**-**j**) are characterized from <sup>1</sup>H NMR, <sup>13</sup>C NMR, IR, HR-MS data.



**Scheme 2.** Proposed mechanism for the formation of dihydropyrano[2,3-*c*]chromene derivatives over nano ZnO.

materials,<sup>27</sup> textile application,<sup>28</sup> filtration,<sup>29</sup> and catalysis.<sup>30</sup>Furthermore, nanofibers can be used as potential functional materials for photovoltaics, optoelectronics,<sup>31</sup> optics<sup>32</sup> etc. Thus we focused our attention to generate self aggregated organic-nanofibers involving the synthesised dihydropyrano[2,3-c]chromene derivative.

The application of 'bottom up' method and more specifically 'reprecipitation method' is very much extensively used for the synthesis of organic nanofibers.<sup>33</sup> Therefore; we become fascinated in exploring the possibility of formation of materials of specific morphology with the synthesized compounds. Unfortunately only the compound **3j** had shown the self-aggregating property. Scanning electron microscopic (SEM) images of the dried fibrous materials of the compound **3j** grown slowly from ethylacetate–hexane mixture (1:1) clearly demonstrate that the aggregates in the solid state are bunches of flat linear fiber like structures (Fig. 2) having 300 nm widths.

Conventional nomenclature distinguishes between red-shifted J- and blue-shifted H-aggregate transitions, arising from a parallel and perpendicular alignment of transition dipoles, respectively. The J-aggregates are characterized by very narrow, intense and red shifted absorption relative to the monomer. The UV-absorption spectrum of the self aggregated nanofiber has shown a bathochromic shift and a decrease in the bandwidth relative to the monomer as shown in the Figure 3 and it indicates that the J-aggregation of the compound 3j leads to the formation of the highly ordered stack like architecture. The spectral properties of the self-assembled organic nanofiber are furthermore emphasized in the fluorescence titration study (6  $\times$  10<sup>-3</sup> M to 18  $\times$  10<sup>-3</sup> M) as shown in the Figure 4 and an obvious and remarkable enhancement of the fluorescence intensity was observed when the same experiment was performed for the self-aggregated nano-crystalline compound. This dramatic enhancement of fluorescence as well as the red shift is attributed to the extensive H-bonding interaction between the suitably oriented NH<sub>2</sub> groups of the molecules and a unidirectional aggregation of the monomers leading to I-stacking which is quite presumable due to the asymmetric nature of the molecule.

At the end we must emphasize how intriguing is the formation of fibers from the coumarin derivative. Different type of organic systems have been reported to self organize into fluorescent solid micro- or nano-fibers.<sup>34-36</sup> Concerning the reprecipitation method, the formation of nanowire crystals has already been reported for 1,3-diphenyl-2-pyrazoline<sup>37</sup> and a phenylenediamine derivative,<sup>38</sup> as well as for the polydiacetylene studied by Nakanishi et al.<sup>39</sup> But in all cases the reprecipitation was done either at high temperature or by adding surfactant micelles to the medium<sup>40</sup> to obtain nanostructures but the formation of this type of nanofiber from the organic molecule of low molecular weight is, therefore, rather an uncommon and challenging job which we have achieved very successfully with ease.

The nano ZnO catalyst was also prepared by the bottom up method. It was characterized by SEM, X-ray diffraction study. From the SEM image (Supplementary data) it is evident that the particles have a rod like morphology. The exact crystal plane and particle size were estimated by X-ray diffraction analysis (Supplementary data). In the wide angle study, characteristic peaks due to the crystal planes appeared. The peaks correspond to the  $(1 \ 0 \ 0)$ ,  $(0 \ 0 \ 2)$ ,  $(1 \ 0 \ 1)$ ,  $(1 \ 0 \ 2)$ ,  $(1 \ 0 \ 3)$  and  $(1 \ 1 \ 2)$  planes of ZnO which are



Figure 2. SEM image of the organic nanofiber.



Figure 3. UV absorption spectrum of 3j in self aggregated state (-) and its very dilute methanol solution monomer (-



Figure 4. Fluorescence titration spectra of 3j in methanol and in self aggregated state (-

consistent with standard JCPDS reported values. Applying Sherrer's formula  $D_p = 0.941 \lambda/B \cos\theta$  where  $\lambda = 1.5406$  Å and B is the corresponding FWHM value and accordingly, the particle sizes are found to lie between 10-11 nm.

Most remarkably, we were also able to recycle the catalyst for five times with almost same catalytic activity as illustrated in Figure 5.

In summary, we have developed a convenient and cost effective green synthetic procedure for the preparation of various dihydropyrano[2,3-c]chromene derivatives for the first time involving 3hydroxycoumarin and applying MCR reaction in presence of nano ZnO as the catalyst with comparable percentage yield even on a large scale. This modified protocol offers improved performance over many conventional procedures. It also permits recycling of the catalyst. The versatile protocol provides direct access to the synthesis of self-aggregated organic nanofiber which has sufficient promise. Further detailed photophysical properties and biological assays are under investigation and will be communicated later.



Figure 5. Reusability study of ZnO nano-rod with entry 2, Table 3.

#### Acknowledgments

We gratefully acknowledge the financial support from U.G.C and Calcutta University. S.P. thanks U.G.C, New Delhi, India for the grant of Junior Research fellowship. P.B. thanks CSIR for the Senior Research Fellowship.

# Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.101.

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- General procedure for the synthesis of dihydropyrano [2,3-c]chromene 24. derivatives.

A mixture of an aromatic aldehyde (1.3 mmol), malononitrile (1.3 mmol), 3hydroxycoumarin (1.0 mmol), nano ZnO (10 mol %) in water (5 mL) was stirred at 70 °C for a required period of time (TLC). After completion of the reaction, the reaction mixture was filtered in hot to remove the catalyst and the filtrate was allowed to cool at room temperature. The solid thus appeared was collected by filtration, washed with chilled aqueous ethanol and finally recrystallized from ethanol to get pure product. 3-Amino-5-oxo-1-p-tolyl-1,5dihydro-pyrano[2,3-c]chromene-2-carbonitrile(3e): Yield: (0.275 g, 83%): characteristic: yellow crystalline solid; Mp: 231 °C (from EtOH); IR (KBr):3430 (NH), 3296 (NH), 3173, 2198 (CN), 1727(C=O), 1659, 1597, 1406, 1295, 1165, 1116, 753 cm<sup>-1</sup>;  $\delta_{\rm H}$  (300 MHz, DMSO- $d_6$ ; Me<sub>4</sub>Si):  $\delta$  2.14 (s, 3H, CH<sub>3</sub>), 4.96 (s, 1H, CH), 7.01–7.44 (m, 10H, Ar, NH<sub>2</sub>);  $\delta_{\rm C}$  (75 MHz, DMSO- $d_6$ ; Me<sub>4</sub>Si): δ 20.7, 37.3, 57.3, 116.4, 117.0, 119.6, 124.7, 125.2, 126.7, 127.4, 129.6, 130.3, 134.1, 136.7, 140.2, 150.3, 154.1, 158.9; HR-MS Calcd for C<sub>20</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub> ([M+H]<sup>+</sup>): 331.1083 found: 331.1082.

Rescaled procedure for the preparation of dihydropyrano [2,3-c]chromene derivatives: A mixture of an aromatic aldehyde (8.5 mmol), malononitrile (8.5 mmol), 3-hydroxycoumarin (8.0 mmol), nano ZnO (10 mol %) in water (30 mL) was stirred at 70 °C for a required period of time (TLC). After completion of the reaction, the reaction mixture was filtered in hot to remove the catalyst and the filtrate was allowed to cool at room temperature. The solid thus appeared was collected by filtration, washed with chilled aqueous ethanol and finally recrystallized from ethanol to get pure product.

25. (a) Miky, J. A. A.; Nadia, S. H.; Shmeiss, N. M. M. J. Indian Chem. Soc. 1997, 74, 814; (b) Ghantwal, S. R.; Samant, S. D. J. Indian Chem. Soc. 2000, 77, 100; (c)