Tetrahedron Letters 53 (2012) 4687–4691

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

# Nano crystalline ZnO catalyzed one pot multicomponent reaction for an easy access of fully decorated 4*H*-pyran scaffolds and its rearrangement to 2-pyridone nucleus in aqueous media

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ARTICLE INFO

*Article history:*
Received 29 May 2012
Revised 14 June 2012
Accepted 16 June 2012
Available online 29 June 2012

*Keywords:*
Nano structured ZnO
4*H*-Pyrans
3,4-Dihydropyridin-2-one
Organic acid catalyzed rearrangement

ABSTRACT

A green and highly efficient protocol has been developed for the synthesis of 4*H*-pyran scaffolds installing a one-pot three-component coupling reaction of an aldehyde, malononitrile, and a 1,3-diketo compound using nano structured ZnO as the catalyst in aqueous alcoholic medium. A greener method to synthesize 3,4-dihydropyridin-2-one has also been developed by rearranging 4*H*-pyran derivatives in aqueous medium applying *p*-TSOH as the right catalyst source. A wide spectrum of functional groups was tolerated in both the developed synthetic protocols with good to excellent yield of the targeted molecules.



Polyfunctionalized 4*H*-pyran derivatives are important to the synthetic chemists due to their pronounced biological and pharmacological activities.[1] These compounds are used as anti-coagulants, anticancer agents, spasmolytics, anti-anaphylactics, etc.[2,3] In addition,4*H*-pyrans containing heterocyclic rings (compound **I**, Fig. 1) are increasingly used for their pharmacological activities.[4] Furthermore, a number of 2-amino-4*H*-pyran derivatives are useful as photoactive materials.[5] Generally, 3-substituted-6-amino-4-aryl-5-cyano-2-methyl-4*H*-pyrans are prepared from arylidenemalononitriles and activated methylene compounds in the presence of organic bases.[6] It is also necessary to mention that the synthesis of 2-pyridone nucleus is a challenge to the synthetic and medicinal chemists as its derivatives have important biological and pharmacological activities.[7–9] It has been shown that 3,4-dihydropyridin-2-one derivative possesses HIV-1 specific reverse transcriptase inhibition capability.[10] Compounds **II** and **III** (Fig. 1) have been found to show hypolipidemic and **5a**-reductase inhibitory activities, respectively. In view of the immense importance of 4*H*-pyran and 2-pyridone derivatives there is renewed interest in developing new methodologies for the synthesis of these compounds.

Quite a good number of methods have been already reported in the literature for the synthesis of 6-amino pyran derivatives. Reagents, such as TMG-[bmim][X],[11] tetrabutylammonium bromide,[12] rare earth perfluorooctanoates,[13] hexadecyltrimethylammonium bromide,[14] silica nanoparticles,[15] and nano metal oxide/ionic liquid combocatalyst[16] have been already employed to achieve the synthesis of 6-amino pyran derivatives. But, so far only a few methods are available for the synthesis of 2-pyridone derivatives.[17] Although these methods have their own merits, still these classical reactions have significant limitations like harsh reaction conditions, use of mineral acids,[17] low yields, tedious work-up procedure. Thus, it is desirable to design an efficient and convenient method to construct such heterocyclic molecules.

In continuation of our interest in developing methodologies for carbon–carbon bond formation using nano metal oxide as catalyst[18,19] herein we disclose an efficient and high yielding protocol for the synthesis of 4*H*-pyran derivatives starting from aldehyde,

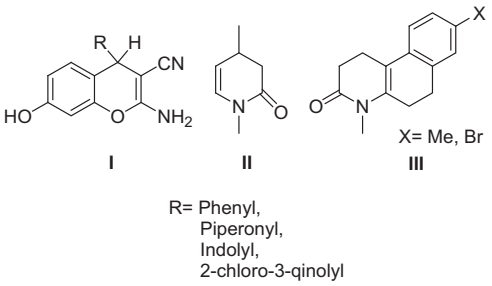


**Figure 1.** Biologically active 2-amino pyran and 3,4-dihydropyridin-2-one derivatives.

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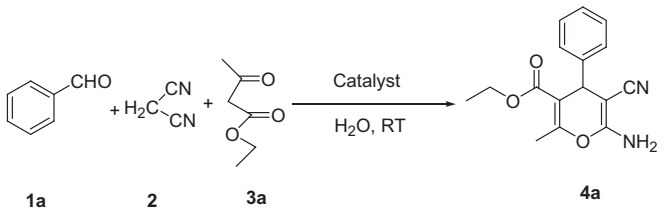
http://dx.doi.org/10.1016/j.tetlet.2012.06.086




**Scheme 1.** Synthesis of 6-amino pyran derivative via a three component coupling of benzaldehyde (**1a**), malononitrile (**2**), and ethylacetoacetate (**3a**).

**Table 1**
Optimization of reaction condition using different catalysts[a]

| Entry | Catalyst | Time (h) | Yield[b] (%) |
|---|---|---|---|
| 1 | — | 24 | Trace |
| 2 | MgO (10 mol %) | 6 | 32 |
| 3 | CaO (10 mol %) | 6 | 36 |
| 4 | Nano $Al_2O_3$ (10 mol %) | 6 | 42 |
| 5 | Nano $SiO_2$ (10 mol %) | 6 | 46 |
| 6 | L-Proline (10 mol %) | 6 | 58 |
| 7 | $Bu_4NBr$ (10 mol %) | 6 | 52 |
| 8 | Bulk ZnO (10 mol %) | 3 | 68 |
| 9 | Nano ZnO (10 mol %) | 3 | 84 |

[a] Benzaldehyde (**1a**) (1 mmol), malononitrile (**2**) (1 mmol), and ethylacetoacetate (**3a**) (1 mmol) were stirred in 5 mL water at room temperature in the presence of 10 mol % of the catalyst.
[b] Isolated yield of the pure product.

malononitrile, and 1,3-diketone in aqueous alcoholic medium using nano crystalline ZnO as the catalyst. As 4*H*-pyran nucleus is very much sensitive to aqueous acid due to its cyclic enol-ether ligation, we also demonstrate here the acid-catalyzed rearrangement of 4*H*-pyran leading to the very easy access of 2-pyridone derivative.

Initially, we focused on systematic evaluation of different catalysts for the model reaction of benzaldehyde (**1a**), malononitrile (**2**), and ethylacetoacetate (**3a**) in water at room temperature (Scheme 1). We have applied a wide range of catalysts including MgO, CaO, Nano $Al_2O_3$, Nano $SiO_2$, L-proline, $Bu_4NBr$, Bulk ZnO, and Nano ZnO to improve the yield for the specific synthesis of 2-amino pyran derivatives. As shown in Table 1, the reaction did not take place without any catalyst (Table 1, entry 1). As mentioned in Table 1, most interesting result was obtained with ZnO as the catalyst and the yield of the desired product was maximized when nano crystalline ZnO was used replacing bulk ZnO (Table 1, entries 8 and 9).

We then tried to screen the reaction in various organic solvents in order to optimize the reaction conditions using nano ZnO as catalyst (Table 2). The results revealed that solvents show great effect on the catalytic activity of ZnO. The highest yield was obtained with solvent system water/ethanol (1:1) (Table 2, entry 9).

As nano ZnO had emerged as the most suitable catalyst for the reaction in 1:1 ethanol/water media, we then tried to optimize the catalyst load for the cyclocondensation reaction leading to the rapid formation of 4*H*-pyran nucleus. Our optimization studies revealed that the yield increased smoothly with catalyst load up to 10 mol % and then remained unaltered up to 25 mol % after that there was a sharp drop in the yield (Fig 2). This drop may be attributed to the coagulation of ZnO nano particles which decreased the effective surface area of the catalyst.

We next concentrated on the scope of this reaction with a variety of aldehydes and a series of 1,3-diketo compounds (Scheme 2)

**Table 2**
Solvent screening for the model reaction[a]

| Entry | Solvent | Yield[b] (%) |
|---|---|---|
| 1 | $Et_2O$ | 38 |
| 2 | $CHCl_3$ | 47 |
| 3 | $CH_2Cl_2$ | 43 |
| 4 | Toluene | 56 |
| 5 | Acetone | 64 |
| 6 | DMSO | 68 |
| 7 | DMF | 72 |
| 8 | $H_2O$ | 84 |
| 9 | $H_2O$ + ethanol (1:1) | 96 |
| 10 | Ethanol | 92 |

[a] Benzaldehyde (**1a**) (1 mmol), malononitrile (**2**) (1 mmol), and ethylacetoacetate (**3a**) (1 mmol) were stirred in 5 mL solvent in the presence of 10 mol % nano ZnO at room temperature for 3 h.
[b] Isolated yield of the pure product.

to check the viability of this protocol in obtaining a library of substituted 4*H*-pyrans (Table 3).

The optimized methodology[21] tolerated a wide spectrum of aldehydes and dicarbonyl compounds with good to excellent yield of the targeted molecules. The aromatic aldehydes with electron withdrawing groups reacted faster with slightly improved yields than their electron donating counter parts. The method is also applicable to aliphatic aldehydes (Table 3, entry 9) and heterocyclic aldehydes (Table 3, entries 8, 18, 26, and 27). The catalyst can be recycled five times without significant loss of the activity. The reusability of the catalyst was checked for the synthesis of 6-amino-5-cyano-2-methyl-4-phenyl-4*H*-pyran-3-carboxylic acid ethyl ester (Table 3, entry 1). The study revealed that even after five cycles, the catalyst was able to carry out the reaction offering almost same catalytic activity.

As we observed the excellent catalytic activity of nano ZnO (rod like morphology)(characterized by SEM, X-ray diffraction study) (particle sizes are found to lie between 10 and 11 nm, Supplementary data) in this synthesis, we could propose a plausible mechanistic insight of the reaction which involves, consequent Knoevenagel condensation, Michael addition and finally intra molecular ring closure leading to the formation of 4*H*-pyran derivative catalyzed by nano ZnO as presented in Scheme 3. In the first step, the Knoevenagel condensation between aldehyde and malononitrile was catalyzed by amphoteric nano ZnO which during the removal of acidic proton from active methylene group of malononitrile unit acted like a base and during dehydration, it showed its acidic behavior. During ring closure, the catalyst played the key role where ZnO acted as a mild acid and not only minimized the 1,2 dipolar repulsion between the geminal nitrile groups but also activated one of the nitrile groups by polarization (through coordi-

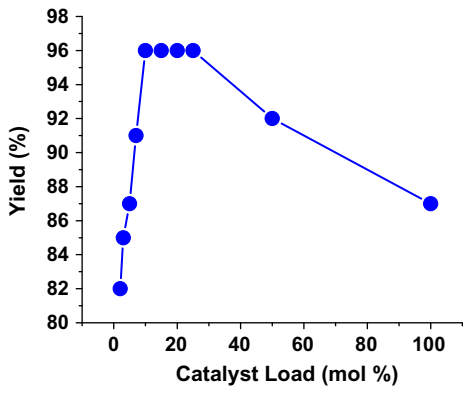



**Figure 2.** Catalyst load optimization study.