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Highly efficient solvent-free synthesis of novel pyranyl pyridine derivatives via β-enaminones using ZnO nanoparticles

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ABSTRACT

Highly efficient ZnO nanoparticle catalyzed one-pot solvent-free synthesis of novel pyridine derivatives by three-component reaction of β-enaminones, different active methylene compounds, and ammonium acetate via Michael addition, cyclodehydration, and elimination sequence is reported. The catalyst was recyclable up to six catalytic cycles without a significant loss in the catalytic activity. This new protocol has the advantages of environmental friendliness, higher yields, solvent-free, low loading of catalyst, shorter reaction times, and convenient operation procedure. ZnO nanoparticles were characterized by XRD, SEM, and TEM analyses.

The greenest solvent, in terms of reducing waste, is no solvent. Due to the toxic, flammable, and expensive nature of organic solvents,[1] special emphasis has been placed toward solvent-free reactions. Overall the advantages of solvent-free organic synthesis are shorter reaction times, cleaner reaction products, and environmentally more benign conditions compared with the classical reactions.[2] The use of nano-sized inorganic solid oxides as heterogeneous catalysts has received much attention because of their high level of chemoselectivity, environmental compatibility, simplicity of operation, and their availability at low cost.[3] Catalytic efficiency depends on the surface area of the catalyst. As nanoparticles provide a very large surface area because of their high surface to volume ratio and low-coordinated sites, their use as catalysts is quite encouraging.[4]

Among the nitrogen-containing heterocycles, pyridine derivatives constitute one of the most important classes of compounds as they widely occur as key structural subunits in numerous natural products that exhibit many interesting biological activities.[5–7] These derivatives possess a large spectrum of biological activities like anti-prion,[8] anti-hepatitis B virus,[9] anti-bacterial,[10] and anti-cancer.[11] Recently, some of these compounds have been recognized as potential targets for the development of new drugs for the treatment of Parkinson's disease, hypoxia, asthma, kidney disease, epilepsy, cancer, and Creutzfeldt–Jakob disease.[12–14]

β-Enaminones turned out to be simple synthetic intermediates for the subject of the present synthesis due to the presence of ambident nucleophilic character of enamine moiety and the ambident electrophilic character of enone moiety. Taking advantage of their electronic properties we used heteroaryl β-enaminones for the synthesis of these substituted pyridines. Synthesis of these substituted pyridines is reported by the reaction of β-enaminones with β-dicarbonyls in the presence of ammonium acetate in refluxing acetic acid,[15] using Montmorillonite K10 in 2-propanol,[16] $K_5CoW_{12}O_{40}{\cdot}3H_2O$,[17] and $CeCl_3$/NaI.[18] However, these methods exhibit limited substrate tolerance and reactivity, suffer from low yields, and use of toxic solvents. Owing to numerous advantages due to its eco-friendly nature, ZnO NPs have been explored as a powerful catalyst for several organic transformations.[19–21] On the basis of our progressive endeavors in exploring novel one-pot reactions[22,23] we, herein, report an efficient ZnO nanoparticle catalyzed, solvent-free, regioselective synthesis of novel substituted pyridines through Michael addition, cyclodehydration, and elimination sequence.[24]

To recognize the optimization of the reaction conditions, the reaction was studied by employing a series of catalysts in solvents and solvent-free conditions with the expectation to maximize the product yield in short reaction time (Table 1). Initially, β-enaminone **1a**, ethyl acetoacetate **3b**, and ammonium acetate were refluxed in AcOH as the solvent without any catalyst. The reaction took a longer time period of 24 h to complete and afforded product in less yield (Table 1, entry 1), demonstrating the need of a catalyst. The reaction was then studied in the presence of catalysts such as sulfamic acid, P_2O_5, P_2O_5–silica, $NaHSO_4$–SiO_2, ZnO, MgO, and ZnO NPs under solvents EtOH and AcOH, and solvent-free reaction conditions (Table 1). Among all the catalysts and solvents, ZnO NPs under solvent-free condition proved to be most efficient in terms of reaction time and product yield.

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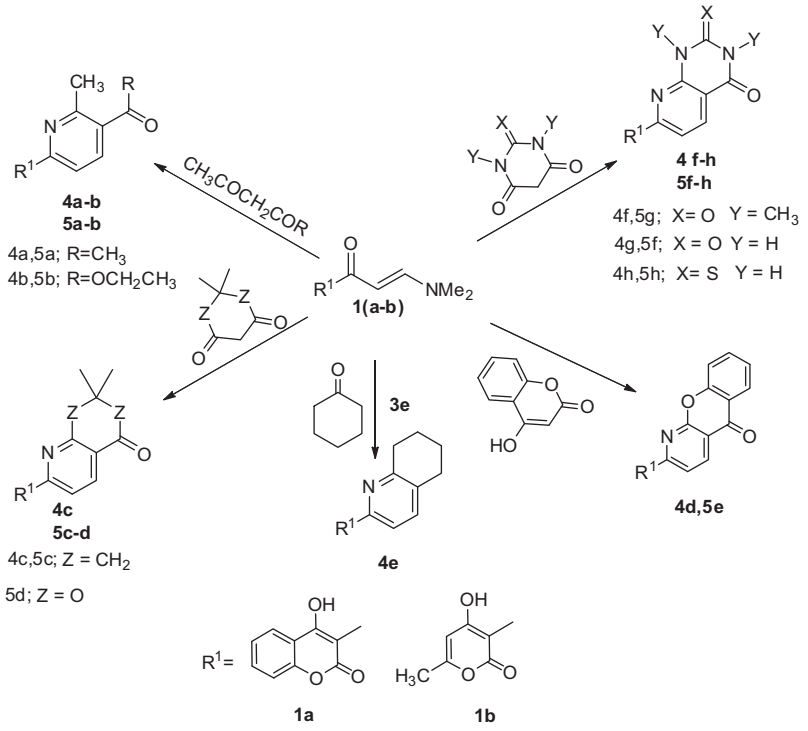
Table 1
Effect of different catalysts and solvents on model reaction[a]

Entry	Catalyst	Solvent	Temp (°C)	Time[b]	Yield[c] (%)
1	Nil	AcOH (5 ml)	Reflux	24 h	65
2	Sulfamic acid (10 mol %)	AcOH (5 ml)	Reflux	—	—
3	P_2O_5 (10 mol %)	Solvent-free	100	6 h	73
4	P_2O_5–silica (200 mg)	Solvent-free	100	2 h	84
5	$NaHSO_4$–silica (200 mg)	Solvent-free	70	2.5 h	75
6	ZnO (bulk) (10 mol %)	Solvent-free	90	2.5 h	85
7	MgO (bulk) (10 mol %)	Solvent-free	90	3.2 h	83
8	ZnO Nps (10 mol %)	EtOH (5 ml)	Reflux	4 h	88
9	ZnO Nps (10 mol %)	AcOH (5 ml)	Reflux	6 h	76
10	ZnO Nps (10 mol %)	Solvent-free	70	40 min	96

[a] Reaction of enaminone **1a** (1 mmol), ethyl acetoacetate **3b** (1 mmol), and ammonium acetate (6 mmol).
[b] Reaction progress monitored by TLC.
[c] Isolated yield.

Taking ZnO nanoparticles as the right catalyst for the experiment, we then concentrated our attention on designing and also generalizing the favorable conditions for the reaction. The presence of 10 mol % ZnO NPs showed best results of 96% product yield (Table 2, Supplementary data). The study of the effect of temperature on the rate of reaction showed that at 70 °C the product yield was maximum (Table 3, Supplementary data). Therefore, at a constant temperature of 70 °C under solvent-free condition, 10 mol % ZnO NPs were used as catalyst for this reaction as the maximum yield (96%) was obtained under these conditions. Hence, these optimized reaction conditions were applied for all experiments taking equimolar amounts of β-enaminone **1a**, active methylene compounds **3a–i** and ammonium acetate under solvent-free conditions in the presence of 10 mol % ZnO NPs (Scheme 1). All the reactions proceeded smoothly and afforded a library of pyridine derivatives in excellent yields (89–96%) (Table 2).

The structures of the final products (**4a–h**, **5a–h**) were well characterized by using spectral (IR, ^1H, ^{13}C NMR, and ESI-MS) and elemental analysis data. The IR Spectrum of **4b** showed a peak at 3200 cm^{-1} for the OH group of benzopyran moiety. Strong absorption bands at 1691 and 1714 cm^{-1} were assigned to coumarin carbonyl and carbonyl group of ethyl ester. The ^1H NMR spectrum showed a singlet at δ 19.32 which was assigned to proton of the OH group. The spectrum gave distinctive peaks for protons of CH_3 and CH_2 of ester functionality as a triplet at δ 1.43 (J = 7.1 Hz) and quartet at δ 4.4 (J = 7.1 Hz), respectively. The presence of the pyridine ring was confirmed by distinctive doublets of H_a and H_b protons at δ 9.02 and δ 8.44, respectively. The methyl protons of pyridine moiety showed a singlet at δ 2.99. The ^{13}C NMR also showed distinctive peaks for CH_3 and CH_2 carbons of ester functionality at δ 14.27 ppm and δ 61.87 ppm, respectively. The carbonyl carbons of ethyl ester and coumarin moiety showed peaks at δ 163.79 ppm and δ 156.26 ppm, respectively. Further structural confirmation was provided by ESI-Mass spectrum which showed the molecular ion peak as the base peak at m/z 326.1 (M^++1). Encouraged by these results we then studied the generality



Scheme 1. Synthesis of pyridine derivatives by the reaction of **1a** and **1b** with active methylene compounds (**3a–i**), ammonium acetate catalyzed by ZnO NPs under solvent-free conditions at 70 °C.