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Chem-grafted Zn-SSA as an Efficient Heterogeneous Catalyst to Synthesize 2-Pyridinones

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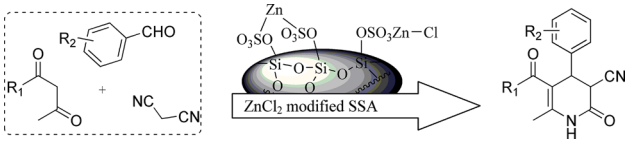
Abstract Chemo-selectivity is always a hard problem in preparing 2-pyridinones. Silica sulfuric acid (SSA) modified with zinc chloride (Zn–SSA) was found to be a high efficient heterogeneous catalyst to solve this problem. Under Zn–SSA and solvent-free conditions, the one-pot cyclocondensation of 1,3-dicarbonyl compounds, malononitrile and arylaldehydes to afford 2-pyridinones was conveniently implemented. The heterogeneous reaction was much efficient and promising in pharmaceutical study and industrial production.

Graphical Abstract Improving chemo-selectivity is always a hard problem in preparing 2-pyridinones. Silica sulfuric acid (SSA) modified with zinc chloride (Zn–SSA) was found to be efficient heterogeneous catalyst to solve this problem. Under Zn-SSA and solvent-free conditions, the one-pot cyclocondensation of 1,3-dicarbonyl compounds, malononitrile and arylaldehydes to afford 2-pyridinones was conveniently implemented. The heterogeneous reaction was much efficient and promising in pharmaceutical study and industrial production.



Keywords 2-pyridinones · Silica sulfuric acid · Lewis acid · Heterogeneous catalyst

1 Introduction

Nowadays, cancer has become a major health problem to human beings. According to the world cancer report 2014, new cases diagnosed will sharply increase 57 % than that of 2012 in the next two decades [1]. Finding a safe and reliable chemical drug is still a hard task. Pyridinone derivatives have been demonstrated exhibiting important role in regulating cell cycle, apoptosis, DNA repair, senescence and angiogenesis [2]. Thus more and more synthetic methods for these compounds are presented [3–8].

Multi-substituted pyridinones, especially with cyano, carbonyl and alkyl groups (Scheme 1, compound **5**), are important intermediates or building blocks for functional chemicals. The common method to synthesize these pyridinones is through the cyclocondensation reaction of carbonyls and nitrogen-containing compounds. Krauze et al. [9] reported a condensation reaction of 2-benzylidene-3-oxobutanoate with cyanoacetamide in EtOH and Et_3N to afford 3,4-dihydropyridin-2-one in 37 % yield. Another important synthetic routes to compound **5** is through the cleavage-recyclization reaction of pyrans (Scheme 1, from **4** to **5**), which sometimes gives

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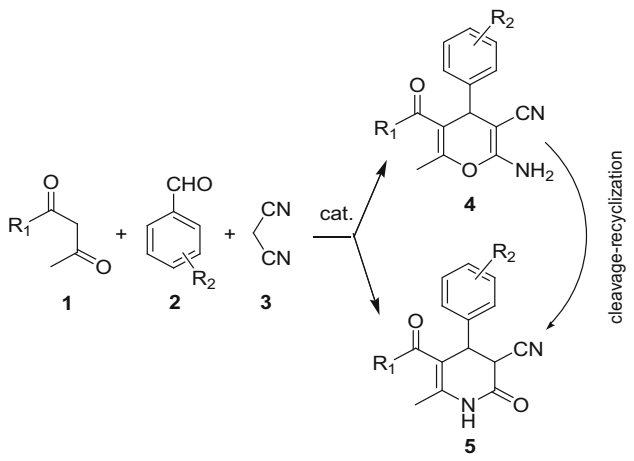


Scheme 1 Reaction route of 3,4-dihydropyridin-2-ones

pyridinone with high yield [10]. In 2012, Pradhan et al. [11] reported two highly efficient and green protocols to synthesize 3,4-dihydropyridin-2-one derivatives. Combining with aldehyde and ethyl acetoacetate, malononitrile or cyanoacetamide were utilized as different starting materials and vitamin B1 and PEG-SO_3H as catalysts. Dehghan et al. [12] demonstrated a four-component reaction of cyanoacetamide, aryl aldehydes, acetoacetate, and ammonium carbonate as an efficient way to synthesize 3,4-dihydro-1H-pyridin-2-ones and 2-pyridones.

Nevertheless, the major problem still exists. These catalysts such as PEG–SO_3H is difficult to prepare and not stable in reaction, and their solubility makes them hard be isolated from reaction mixture. In addition, the cyclocondensation reaction of carbonyls and methylene compounds always gives the mixture of two skeletons of products for its bad chemo-selectivity, as illustrated in Scheme 1. The tedious workup process increases the cost of production and leads to many defects in economical and technical aspects, hence more efforts to improve the reaction efficiency are still demanded.

Nowadays, the development of sustainable chemical processes has posed a great demand for heterogeneous catalysts to promote organic reactions. To obtain better selectivity, cost-effectiveness and operational simplicity, many Bronsted acids or Lewis acids have been loaded on solid materials, and lots of achievements have been presented [13]. Silica sulfuric acid (SSA), an easily prepared catalyst, has been widely investigated as a versatile promoter that makes a lot of reaction processes more convenient, economical, and environmentally benign [14–26]. The further modification of SSA with metal salts (M-SSA) was also reported recently and the further research is under way [27, 28].

In the heterogeneous synthetic method of 2-pyridinones, ZnO and PEG-SO_3H has been successfully used by Pradhan [11] and Bhattacharyya [29]. However, in addition to the shortcomings of PEG–SO_3H and ZnO, which is difficult to be recovered, this step by step reaction is humble in total yield and economy. To make the cyclocondensation of 1,3-dicarbonyl compound, malononitrile and benzaldehyde more simple and effective, we attempted to use SSA and M-SSA as heterogeneous catalysts, and thus a one-pot and solvent-free method was obtained.

2 Experimental

Typical procedure for the preparation of catalysts: Silica sulfuric acid (SSA, 2.5 mmol H^+/g) was prepared according to ref. [31]. In a 250 ml suction flask equipped with a gas inlet tube for conducting of HCl gas over an adsorbing solution (i.e. water), 0.05 mol metal chloride was dissolved in 50 mL anhydrous methanol. SSA (40 g, 0.1 mol sulfur content) was slowly added with constantly stirring. The mixture was refluxed for 2 h, and then filtered. The obtained solid was washed repeatedly with methanol until chlorine could not be detected from its eluate, and calcined for 2 h at 300 °C to give the desired catalyst M-SSA.

Typical procedure for the preparation of 2-pyridinone **5**: Ethyl acetoacetate or acetylacetone (40 mmol), malononitrile (42 mmol), and benzaldehyde (40 mmol), and catalyst (0.1 eq) were added in flask, the mixture was heated to reflux with stirring for about 5 h. After completion of the reaction (indicated by TLC), the catalyst was filtered and recovered, and the mixture was kept overnight in ice-box. Then the obtained residue was filtered and recrystallized with ethanol to give the pure products **5**.

2.1 5-Cyano-4-(4-methoxyphenyl)-2-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylic ethyl ester (5a)

White solid, IR(KBr, cm^{-1}): 3230.14, 2977.83, 2863.52, 2840.91, 2260.79, 1703.88, 1633.85. ^{1}H NMR (400 MHz, d_6-$CDCl_3$) δ(ppm): 1.19–1.23(t, 3H, –CH_3), 2.44(s, 3H, –CH_3), 3.79(s, 3H, –OCH_3), 4.10–4.16(q, 2H, –OCH_2–), 4.12–4.14(d, 1H, pyridine-H), 4.38–4.40(d, 1H, pyridine-H), 6.77–6.80(d, 2H, Ar–H), 7.09–7.11(d, 2H, Ar–H), 7.48(brs, 1H, –NH). ^{13}C NMR (100 MHz, d_6-DMSO) δ(ppm): 14.47, 18.48, 41.35, 41.97, 55.47, 60.24, 106.42, 114.48(2C), 116.29, 129.25(2C), 130.13, 147.67, 159.25, 163.53, 165.92.

2.2 5-Cyano-4-(4-methoxyphenyl)-2-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylic methyl ester (5b)

White solid, IR(KBr, cm^{-1}): 3236.87, 2954.84, 2851.15, 2258.06, 1704.07, 1639.66. H NMR (400 MHz, d_6-$CDCl_3$)

δ(ppm): 2.47(s, 3H, pyridine-H), 3.70(s, 3H, Ar–OCH_3), 3.81(s, 3H, acyl–OCH_3), 4.13–4.14(d, 1H, $J = 6.8$ Hz, pyridine-H), 4.47–4.49(d, 1H, $J = 6.4$ Hz, pyridine-H), 6.97–6.90(d, 2H, $J = 8.8$ Hz, Ar–H), 7.18-7.21(d, 2H, $J = 8.4$ Hz, Ar–H), 7.98(brs, 1H, –NH). HRMS of [$C_{16}H_{16}N_2O_4 + H^+$]: calcd: 300.1144, found: 300.1157.

2.3 5-Cyano-2-methyl-6-oxo-4-phenyl-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid methyl ester (5d)

IR(KBr, cm^{-1}): 3237.79, 2983.87, 2884.33, 2258.06, 1696.79, 1641.04. ^{1}H NMR (400 MHz, d_6-$CDCl_3$) δ(ppm): 2.43(s, 3H, –CH_3), 3.67(s, 3H, –OCH_3), 4.15–4.16(d, 1H, $J = 6.8$ Hz, pyridine-H), 4.48–4.50(d, 1H, $J = 7.2$ Hz, pyridine-H), 7.24–7.26(d, 2H, $J = 7.2$ Hz, Ar–H), 7.32–7.33(d, 2H, $J = 6.8$ Hz, Ar–H), 7.35–7.37(t, 1H, Ar–H), 8.48(brs, 1H, –NH). HRMS of [$C_{15}H_{14}N_2O_3 + H^+$]: calcd: 270.1038, found: 270.1049.

2.4 5-Acetyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro-pyridine-3-carbonitrile (5 h)

IR(KBr, cm^{-1}): 3235.61, 2989.46, 2862.57, 2259.11, 1723.26, 1648.72. ^{1}H NMR (400 MHz, d_6-DMSO) δ(ppm): 2.04(s, 3H, pyridine–CH_3), 2.28(s, 3H, –CH_3), 4.14–4.16(d, 1H, $J = 6.8$ Hz, pyridine-H), 4.25–4.27(d, 1H, $J = 7.2$ Hz, pyridine-H), 7.18–7.36(m, 5H, $J = 7.2$ Hz, Ar–H), 9.44 (brs, 1H, –NH). HRMS of [$C_{15}H_{14}N_2O_2 + H^+$]: calcd: 255.1089, found: 255.1066.

3 Results and Discussion

Homogeneous catalysts, piperidine (HHPy) and H_2SO_4, were firstly used to the one-pot reaction of ethyl acetoacetate, malononitrile, and benzaldehyde (Scheme.1), no additional solvent was added. After the completion of the reaction which was monitored with TLC, the products were isolated, and their yields were illustrated in Fig. 1. In order to compare the catalyzation of different solid acids, SSA and M-SSA were successively employed to promote this one-pot reaction (Scheme 1), and the result was also presented in Fig. 1.

It is shown in Fig. 1 that the structure of product is mainly controlled by the acidity and alkalinity of catalysts. It gave 2-aminopyran **4** as main product when alkali catalyst such as piperidine was used, while 2-pyridinone **5** was obtained in high yield when employing the catalyst with suitable acidity. Using strong acid, such as sulfuric acid, the mixture of product **4** and **5** was obtained. Solid acid SSA showed better performance in selectivity than sulfuric acid, although a certain amount of 2-aminopyran was also

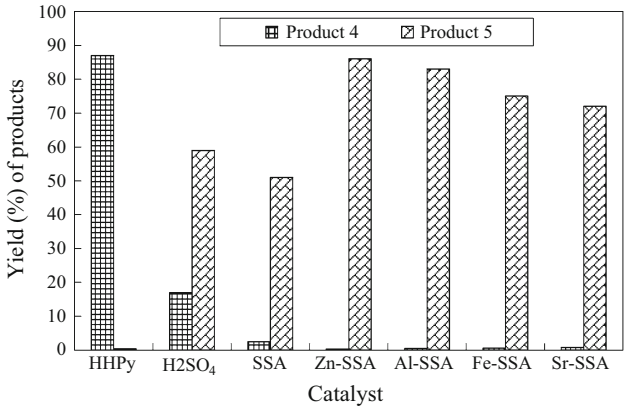


Fig. 1 Result of one-pot reaction of ethyl acetoacetate, malononitrile, and benzaldehyde under different catalysts

presented, and its performance was evidently improved when modified with Lewis acids, among which zinc dichloride modified SSA (Zn–SSA) displayed the best activity and selectivity.

The good performance of Zn-SSA may be due to proper proportion of L/B acid sites. The FTIR spectrum of pyridine absorption (Fig. 2) shows the change of Lewis acidity of Zn-SSA along with the loading amount of $ZnCl_2$. With the increase of impregnated $ZnCl_2$, the peak area around 1540 cm^{-1}, which indicates the characteristic of pyridinium ion revealing the Brønsted acidic character of the surface, decreases gradually, while the peak area around 1450 cm^{-1}, which represents Lewis acid sites, increases evidently. The acidity changes no more after $ZnCl_2$ loading reaches 1.6 mmol on 1 g SSA. The figure shows that the nature of solid catalyst SSA is clearly modified by Lewis acid.

Figure 3 shows typical isotherms and the corresponding pore size distribution (PSD). The sharp peaks in the PSD plots confirm the narrow size distributions of Zn–SSA, and

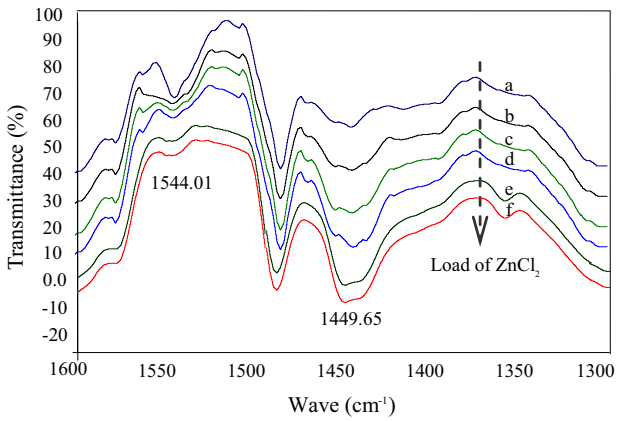


Fig. 2 FTIR spectrum of pyridine absorption indicating the change of caid sites with the loading of $ZnCl_2$. Amount of $ZnCl_2$ adding to 1 g SSA: (*a*). 0.0 mmol, (*b*). 0.4 mmol, (*c*): 0.8 mmol, (d). 1.2 mmol, (*e*). 1.6 mmol, (*f*). 2.0 mmol

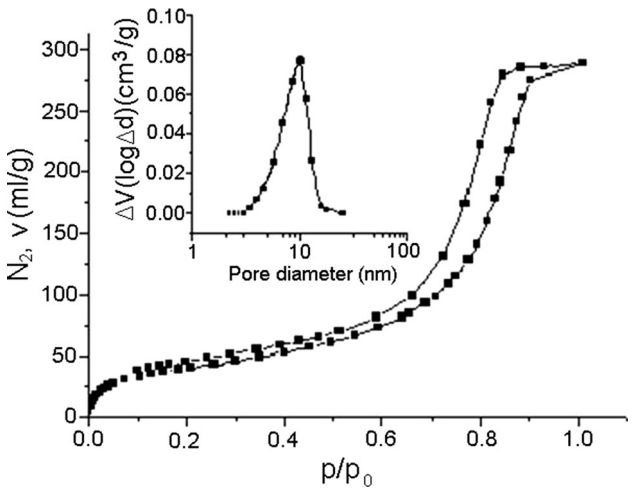


Fig. 3 Nitrogen sorption isotherms for Zn–SSA. Inset diagram shows the pore size distribution (PSD) of the corresponding sample

all pores being in the mesoporous range. The BET specific surface is around 151 m^2/g which coincide with SSA, it indicates that chemical modification did not influence the catalyst surface area.

Using ethyl acetoacetate, malononitrile, and benzaldehyde as materials, we investigated the relationship of selectivity for 2-pyridinone and Lewis acidity. Table 1 shows the changes of 2-pyridinone selectivity with Lewis acidity of Zn-SSA, in which a, b, c, d and e represent different catalysts as like as Fig. 2. It indicates that 2-pyridinone selectivity increase with the rising of Lewis acidity, it reaches the peak at about 1.6 mmol $ZnCl_2$ loading upon 1 g SSA.

Table 1 The relationship of 2-pyridinone selectivity with Lewis acidity of Zn–SSA. As like Fig. 2a–e represent SSA modified with different amount of $ZnCl_2$

Zn–SSA	A	B	C	D	E
Selectivity for 2-pyridinone (%)	96.2	97.6	98.4	99.0	99.8

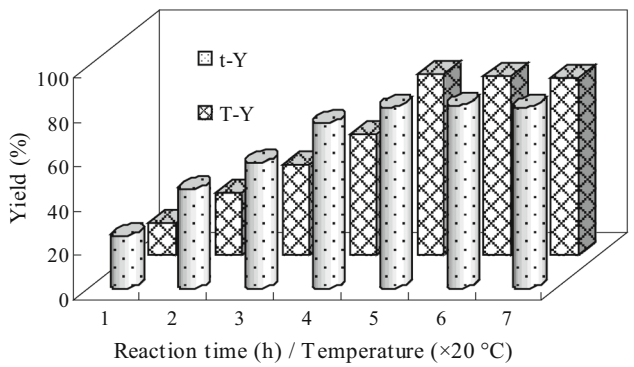


Fig. 4 Result of one-pot reaction of ethyl acetoacetate, malononitrile, and benzaldehyde under different catalysts

Using the same reaction, we optimized temperature and time, and the result is illustrated in Fig. 4. The figure shows that the yield of 2-pyridinone increases with the elevation of temperature and time till reaching their peaks. The optimal temperature and time is 140 °C and 5 h, respectively.

The recovery and reusability of Zn–SSA was also investigated. The catalyst was separated by simple filtration after reaction, washed three times with methanol, and then evaporated and dried in a vacuum at 100 °C, and at last reused for consecutive catalytic runs under similar experimental conditions. Figure 5 shows the results of reused five runs, and it reveals the high stability of the catalyst under the experimental conditions.

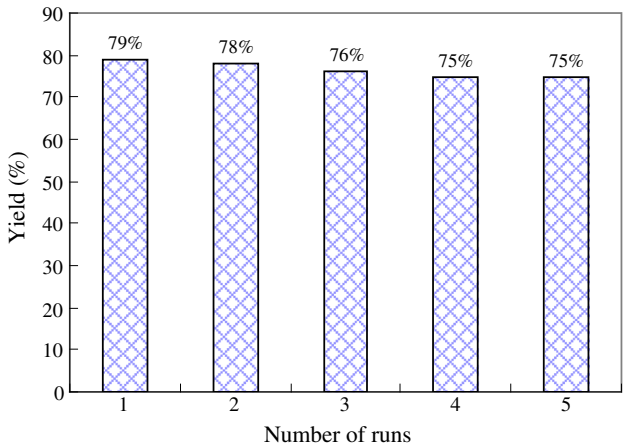


Fig. 5 The reusability of Zn–SSA (five runs with the same experimental conditions)

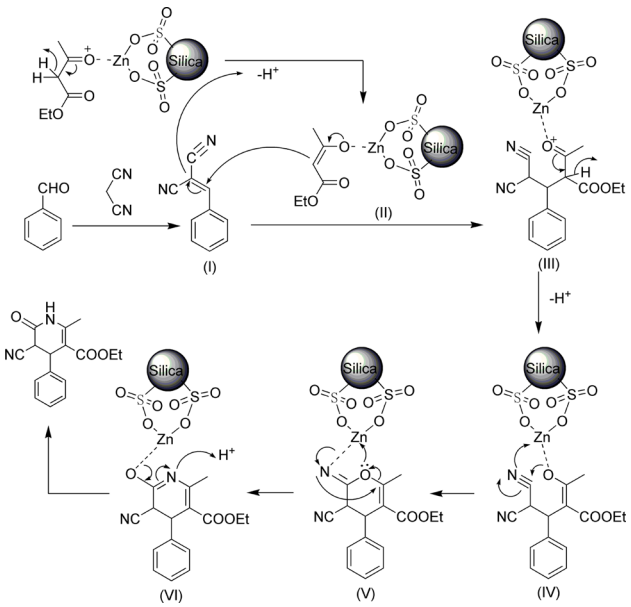
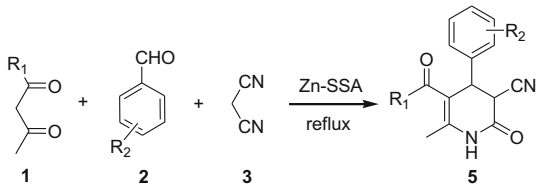


Fig. 6 Proposed mechanism

Table 2 One-pot cyclocondensation of 1,3-dicarbonyl compounds, arylaldehydes and malononitrile



Entry	1	2	Yield of **5** (%)[a]	Mp (°C) (Data of ref.)
a	R_1 = OEt	R_2 = 4-OMe	79	185–187 (182) [11]
b	R_1 = OMe	R_2 = 4-OMe	78	174–176
c	R_1 = OEt	R_2 = H	86	141–143 (143–145) [32]
d	R_1 = OMe	R_2 = H	85	177–179
e	R_1 = OMe	R_2 = 3-NO_2	86	212–214 (211–213) [33]
f	R_1 = OEt	R_2 = 3-NO_2	91	174–176 (175–176) [34]
g	R_1 = OEt	R_2 = 4-NO_2	89	103–104 (103) [11]
h	R_1 = Me	R_2 = H	75	122–124 (156) [29]
i	R_1 = Me	R_2 = 2-NO_2	90	106–108 (106–107) [35]
j	R_1 = Me	R_2 = 4-NO_2	92	106–107 (105–106) [35]
k	R_1 = Me	R_2 = 4-Cl	86	175–177 (173–174) [35]

Using 0.1eq. Zn-SSA (based on molar content of zinc on silica gel) as catalyst, all reactants refluxed 5h under solvent-free conditions

[a] Isolated yields

The mechanism of Zn–SSA promoted elimination is proposed as Fig. 6. Zinc atom becomes a high active particle with electrophilic power for the effect of silica vitriolic groups, and results in its combination with the acyl oxygen of ethyl acetoacetate to produce the conformation of enol species (II). Then the attack of enol to ethylenic bond of compound (I) leads to the intermediate (III), which becomes an enol type again to occur the intramolecular nucleophilic attack of oxygen to cyano to give dihydropyran (V). Under the effect of Zn–SSA, the pyran becomes dihydropyridine (VI) via Dimroth rearrangement [30, 31], and at last affords pyridin-2-one product through the protonation of unsaturated nitrogen and tautomerism of enol (VI).

With catalyst Zn–SSA, we carried out a series of one-pot and solvent-free reactions among reactants **1**, **2** and **3**, and the result was presented in Table 2. It clearly shows that all employed 1,3-dicarbonyl compounds (including acetyl acetone) react readily with aryl aldehydes and malononitrile to give 2-pyridinones. Electron withdrawing substituent, such as nitro group, seems beneficial to the reaction (entry **e**, **f**, **g**, **i**, **j**), and give the targeted product in higher yield.

4 Conclusions

A series of 5-cyano-2-pyridinones have been successfully synthesized by heterogeneous method with novel catalyst Zn–SSA. Such catalyst showed high activity and selectivity toward the cyclocondensation of ethyl acetoacetate, malononitrile, and benzaldehyde, thus provides a simple, efficient and eco-friendly synthetic method for multi-substituted 2-pyridinones. The reaction which can be easily realized in one-pot and solvent-free conditions, is much promising in pharmaceutical study and industrial production.

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