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An efficient synthesis of 3,4-dihydropyrimidin-2-ones catalyzed by NH_2SO_3H under ultrasound irradiation

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Abstract

The condensation of aldehydes, β-keto esters and urea catalyzed by NH_2SO_3H in ethanol results dihydropyrimidinones in high yields under ultrasound irradiation.

Keywords: Biginelli reaction; Dihydropyrimidinones; Synthesis; Ultrasound irradiation

1. Introduction

Dihydropyrimidinones have attracted increasing interest due to their diverse therapeutic and pharmacological properties, such as antiviral, antibacterial, antihypertensive and antitumor effects [1]. Some of them have been successfully used as calcium channel blockers, antihypertensive agents and α_{1a}-antagonists [2]. Several alkaloids isolated from marine sources also exhibit interesting biological activities, whose molecular structures contain the dihydropyrimidinone unit [3]. Biginelli reaction for the synthesis of dihydropyrimidinones has received renewed attention and many improved procedures have been reported consequently. Reviews have also been published [1,4].

The one-pot condensation of an aldehyde, a β-keto ester and urea, originally reported by Biginelli in 1893, often affords unsatisfactory yields (20–50%) [5]. Even though multi-step strategies have been developed to increase the total yield, these methods lack the simplicity of the one-pot, one-step procedure [6]. In 1998, Hu discovered a one-pot combination of $BF_3 \cdot OEt_2$, a transition metal salt and a proton source that improved the yield of this reaction [7], and Kappe reported polyphosphate ester as an efficient catalyst for this condensation [8]. Recently, the acidic clay, montmorillonite KSF was also utilized [9]. Furthermore, Lewis acids $FeCl_3 \cdot 6H_2O$ [10] and $LaCl_3 \cdot 7H_2O$ [11] which required relatively shorter reaction times and gave higher yields have been found to be efficient for synthesis of dihydropyrimidinones. Qian [12] and Ranu [3] have performed the condensation of an aldehyde, a β-keto ester and urea catalyzed by $Yb(OTf)_3$ and $InCl_3$ respectively. In addition, there are some other methods such as microwave-assisted [13], solid-phase [6d,14], and fluorous-phase [15] syntheses. However, in spite of their potential utility, some of the reported methods suffer from drawbacks such as longer reaction times, higher temperatures, expensive catalysts, lower yields and cumbersome product isolation procedures.

Ultrasound has increasingly been used in organic synthesis in the last three decades. Compared with traditional methods, this technique is more convenient and easily controlled. A large number of organic reactions can be carried out in higher yields, shorter reaction time and milder conditions under ultrasound irradiation [16].

Amidosulfonic acid (NH_2SO_3H) has been extensively used as a catalyst for many organic reactions, such as the esterification of carboxylic acids, the oxidation of aromatic aldehydes to carboxylic acids, the preparation of amines by decarbonylation of carboxamides with sodium hypochlorite and the synthesis of anthroquinonecarboxamides from anthroquinonecarboxylic acids

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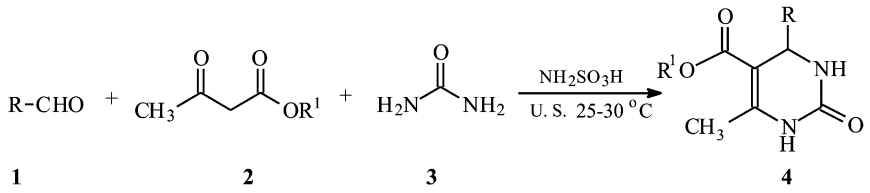

1 2 3 4

Scheme 1.

[17a]. Recently, Jin et al. have reported the synthesis of dihydropyrimidinones catalyzed by amidosulfonic acid with moderate yields, which required longer reaction times when performed under silent conditions under reflux [17b]. All of the results stated above prompted us to study the possibility of using the Biginelli reaction under ultrasound irradiation. In this paper, we wish to describe an efficient and mild procedure for the synthesis of dihydropyrimidinones (**4**) via condensation of aldehydes (**1**), β-keto esters (**2**) and urea (**3**) catalyzed by NH_2SO_3H under ultrasound irradiation (Scheme 1).

2. Method

2.1. Apparatus and analysis

Liquid aldehydes were purified by distillation prior to use. Melting points are uncorrected. IR spectra were recorded on a Bio-Rad FTS-40 spectrometer (KBr). ^1H NMR spectra were measured on a Bruker AVANCE (400 MHz) spectrometer using TMS as internal standard and $CDCl_3$ or DMSO as solvent. MS were determined on a VG-7070E spectrometer (EI, 70 eV). Sonication was performed in Shanghai Branson-CQX ultrasonic cleaner (with a frequency of 25 KHz and a nominal power 250 W) and SK 250 LH ultrasonic cleaner (with a frequency of 40, 59 KHz and a nominal power 250 W; Shanghai Kudos ultrasonic instrument Co., Ltd.). The reaction flasks were located in the maximum energy area in the cleaner, where the surface of reactants is slightly lower than the level of the water. The reaction temperature was controlled by addition or removal of water from ultrasonic bath.

2.2. General procedure

Aldehyde (**1**, 2 mmol), β-keto ester (**2**, 2.2 mmol), urea (**3**, 3.0 mmol), ethanol (10 ml) and NH_2SO_3H (1.5 mmol) were mixed in a 50 ml conical Pyrex flask. The mixture was irradiated in the water bath of the ultrasonic cleaner at 25–30 °C for a period as indicated in the table (sonication was continued until the aldehyde disappeared, as indicated by TLC). After completion of the reaction, the resulting suspension was filtered. The collected solid was washed with water and ethanol, and then dried. The pure product for ^1H NMR analysis was obtained by recrystallization from hot 95% ethanol. All the products were confirmed by comparing their melting points, IR, MS and ^1H NMR data with literature data.

3. Results and discussion

The results are summarized in Tables 1 and 2. It can easily be seen that the condensation of a series of aldehydes with β-keto esters and urea leading to dihydropyrimidinones gives good yields under ultrasound irradiation.

In order to improve the yield, we did the experiment with different ratios of aldehyde, β-keto ester and urea. When the molar ratio is 1:1.1:1.5, the reaction gave the best results. Further, we studied the influence of the amount of the catalyst on the reaction time and yield. As shown in Table 1, increasing the quantity of the catalyst can improve the reaction yields and shorten reaction time. For example, when the amount of the catalyst is 0.5 mmol, the yield is 73% within 80 min, whereas using 1.5 mmol NH_2SO_3H, the reaction needed 40 min to give

Table 1
Condensation of benzaldehyde, ethyl acetoacetate and urea under different conditions[a]

Entry	Amount of catalyst, mmol	Frequency of ultrasound, kHz	*t*, min	Yield, %
1	0.5	25	80	73
2	1.0	25	60	95
3	1.5	25	40	97
4	2.0	25	30	98
5	1.5	40	60	86
6	1.5	59	80	75

[a] Benzaldehyde (2 mmol), ethyl acetoacetate (2.2 mmol), urea (3.0 mmol); reaction temperature 25–30 °C.

Table 2
Synthesis of dihydropyrimidinones catalyzed by NH_2SO_3H under ultrasound irradiation

Entry	R	R_1	*t*, min	Yield, % (lit.) [a]	M.p., °C (lit.)
a	C_6H_5	C_2H_5	40	97 (90) [17b]	202–204 (202.4) [18]
	C_6H_5	C_2H_5	40	62[b]	202–204
	C_6H_5	C_2H_5	40	69[c]	202–204
b	4-$CH_3OC_6H_4$	C_2H_5	30	98 (91) [17b]	200–202 (201–202) [18]
c	2-HOC_6H_4	C_2H_5	40	91 (19) [18]	199–201 (201–202) [18]
d	4-HOC_6H_4	C_2H_5	40	92 (79) [17b]	226–228 (227–229) [18]
e	3-ClC_6H_4	C_2H_5	40	94 (87) [17b]	193–194 (192–193) [19]
f	4-ClC_6H_4	C_2H_5	40	94 (80) [17b]	212–214 (213–215) [7]
g	3-$O_2NC_6H_4$	C_2H_5	40	94 (86) [17b]	225–227 (226–227.5) [18]
h	4-$O_2NC_6H_4$	C_2H_5	30	91 (86) [17b]	208–210 (207–208.5) [18]
i	2,4-$Cl_2C_6H_3$	C_2H_5	40	86 (69) [20]	251–252 (249–250) [20]
j	4-HO-3-$CH_3OC_6H_3$	C_2H_5	30	96 (84) [17b]	232–233 (232–233) [18]
k	$C_6H_5CH{=}CH$	C_2H_5	25	90 (71) [18]	237–239 (238–239.5) [18]
l	Furyl	C_2H_5	40	87 (36) [18]	202–204 (204.5–205) [18]
m	$CH_3(CH_2)_4CH_2$	C_2H_5	60	89 (89) [17b]	152–154 (151–152) [18]
n	$CH_3CH_2CH_2$	C_2H_5	60	70 (87) [17b]	153–155 (153–155) [21]
o	3,4-$(OCH_2O)C_6H_3$	C_2H_5	50	89 (72) [17b]	187–189 (187–188) [18]
p	4-$CH_3C_6H_4$	C_2H_5	40	87 (73) [13c]	168–170 (170–171) [13c]
q	C_6H_5	CH_3	40	96 (86) [17b]	211–213 (209–212) [7]
r	4-$CH_3OC_6H_4$	CH_3	40	97 (96) [17b]	193–195 (192–194) [7]
s	4-$O_2NC_6H_4$	CH_3	50	92 (72) [17b]	235–237 (235–237) [7]
t	4-ClC_6H_4	CH_3	40	92 (78) [17b]	204–205 (204–207) [7]
u	2,4-$Cl_2C_6H_3$	CH_3	40	85 (83) [12]	255–257 (254–255) [12]

[a] Conditions reported in literature: NH_2SO_3H as catalyst in EtOH refluxing for 0.5–4 h [17b]; HCl as catalyst in EtOH refluxing for 18 h [18].
[b] Stirred without ultrasound.
[c] Presonicated NH_2SO_3H, stirred at 25–30 °C without ultrasound.

4-phenyl-5-(ethoxycarbonyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one in 97% yield under ultrasound irradiation. We also observed the effect of different frequency of ultrasound irradiation on this reaction. It shows that lower frequency of ultrasound irradiation improved the result. For example, when the frequency was 25 kHz, the reaction required 40 min and resulted the desired product in 97% yield, while under 59 kHz ultrasound irradiation, the condensation reaction was completed in 80 min with 75% yield. Therefore, the one-pot condensation was carried out at the molar radio of aldehyde, β-keto ester, urea and catalyst 1:1.1:1.5:0.75 in aqueous ethanol at 25–30 °C under 25 kHz ultrasound irradiation (Table 2).

As shown in Table 2, the condensation of β-keto esters and urea with a variety of aldehydes affords product **4** in good yield. The ultrasound technique represented a better procedure in terms of the higher yield, milder reaction conditions and easier workup. For example, compounds **4a** and **4q** were obtained in 97% and 96% yields respectively at 25–30 °C under ultrasound for 40 min. However, in the classical method [17b], they were prepared in 90% and 86% yields catalyzed by NH_2SO_3H at refluxing temperature for 3 and 2.5 h respectively. Most importantly, aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents all reacted very well, giving excellent yields. Also, the reactivity of aliphatic aldehydes, β-keto ester and urea in the presence of amidosulfonic acid was investigated under ultrasound. Biginelli reaction of *n*-hexyl aldehyde, ethyl acetoacetate and urea in aqueous ethanol at 25–30 °C for 60 min afforded 4-hexyl-5-(ethoxycarbonyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**4m**) in 89% yield, whereas classical conditions gave the same yield at refluxing temperature for 3 h [17b]. Similarly, cinnamic aldehyde (**1k**) also gave the product (**4k**) in 90% yield, whereas classical conditions gave only 71% yield [18]. However, the condensation of *n*-butyl aldehyde, ethyl acetoacetate and urea gave lower yield (70%) than that of refluxing conditions catalyzed by the same catalyst, and we found that a prolonged period of ultrasonication did not increase the yield.

We also performed the condensation of benzaldehyde, ethyl acetoacetate and urea catalyzed by amidosulfonic acid with stirring without sonication. The condensation reaction was carried out at 25–30 °C for 40 min to produce **4a** in 62% yield. We also did another experiment: presonicated amidosulfonic acid, then added all reactant and stirred the reaction mixture for 40 min at 25–30 °C. This reaction gave **4a** in 69% yield, whereas **4a** was obtained in 97% yield at 25–30 °C for 40 min under ultrasound. It is apparent that the ultrasound can accelerate Biginelli reaction.

4. Conclusion

In conclusion, we have described a rapid and convenient procedure for the synthesis of dihydropyrimidinones catalyzed by NH_2SO_3H under ultrasound irradiation.

Acknowledgements

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