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Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones Catalyzed by Nafion-H Under Ultrasound Irradiation and Solvent-Free Conditions

Q. Wang and W. Pei
College of Chemical Engineering and Materials, Zhejiang University of Technology, Hangzhou 310014, China

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A novel synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones by one-pot cyclocondensation of aldehydes, 1,3-dicarbonyl compounds and urea or thiourea using nafion-H as the catalyst under ultrasound irradiation and solvent-free conditions was developed. Compared with the classical Biginelli reactions, this method consistently enjoys the advantages of mild reaction conditions, excellent yields, easy work up and short reaction time.

Keywords: One-pot, Nafion-H, Biginelli condensation, Ultrasound irradiation, Solvent-free

INTRODUCTION

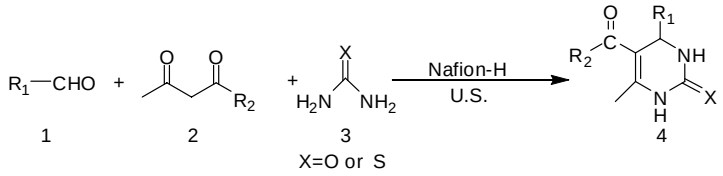
Ultrasound has increasingly been used in organic synthesis in the last three decades [1]. Compared with traditional methods, this technique is more convenient and easily controlled. A large number of organic reactions can be carried out in higher yields, shorter reaction time and milder conditions under ultrasound irradiation. Perfluorinated resin sulfonic acid (nafion-H) [2], an acid catalyst, is extensively used for alkylation [3], acylation [4], nitration [5], acetal synthesis, [6] and in Diels-Alder reaction [7]. The Nafion-H catalyst, an insoluble resin, is inert to corrosive environments, stable up to 201 °C, easy to recover and to reuse.

3,4-Dihydropyrimidin-2(1*H*)-ones (DHPMs) are of considerable interest in industry as well as in academia because of their promising biological activities as calcium channel blockers, antihypertensive agents, and anticancer drugs [8]. Thus, the synthesis of this heterocyclic nucleus is of high importance, and quite a number of synthetic procedures based on the modifications of the century-old Biginelli's reaction [9] involving acid-catalyzed three-component condensation of 1,3-dicarbonyl compound, aldehyde, and urea, have been developed during the past few years. Basically, these methods are all similar, using different Lewis acid catalysts such as BF_3 [10], $FeCl_3$ [11], $InCl_3$ [12], $BiCl_3$ [13], $LaCl_3$ [14], $LiClO_4$ [15], in a solvent such as CH_3CN, CH_2Cl_2, or THF. In addition, several ionic liquids [16], microwave irradiation [17], and combinatorial approaches [18] to 3,4-dihydropyrimidin-2-(1*H*)-ones have also been employed. Obviously, many of these catalysts and solvents are not at all acceptable in the context of green synthesis. Thus, as a part of our program towards green synthesis, we have discovered that Biginelli's reaction proceeds very efficiently by ultrasound irradiation, requiring no solvent, and producing 3,4-dihydropyrimidin-2(1*H*)-ones in high yields (Scheme 1).

EXPERIMENTAL

Liquid aldehydes were purified by distillation prior to use. All compounds were identified by comparison of their spectral data and physical properties with those of the authentic samples. The nafion-H catalyst (beads, 7-9 mesh) was

*Corresponding author. E-mail: qinwang99@hotmail.com



Scheme 1. The synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones catalyzed by nafion-H under ultrasound irradiation

provided by Shanghai Institute of Organic Chemistry. ^{1}H NMR spectra were recorded on a BRUKER AVANCE (400 MHz) spectrometer using TMS as internal standard and $CDCl_3$ or DMSO as solvent. IR spectra were recorded on Mattson 1000 FT-IR spectrometer using KBr pellets. Melting points are uncorrected. Soniation was performed in Shanghai Branson-CQX ultrasonic cleaner (with a frequency of 25 KHz and a nominal power 250 W).

General Procedure for the Synthesis of 3,4-Dihydropyrimidin-2-(1H)-ones

Combinaitons of aldehyde **1** (50 mmol), 1,3-dicarbonyl compound **2** (50 mmol), urea (thiourea) **3** (75 mmol) and nafion-H (100 wt% of the reactants) were mixed together on a desk-top. Then, the mixture was irradiated in the water-bath of the ultrasonic cleaner for some time. After the completion of the reaction (indicated by TLC), the mixture was dissolved in ethanol and poured into ice cold water. The resulting precipitate was filtered and recrystallized from ethanol. All products were confirmed by comparing their melting points, ^{1}H NMR and IR spectral data with literature data. Some of the representative compounds are given below:

Entry 1: m.p.: 202-204 °C, ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.18 (s, 1H, NH), 7.73 (s, 1H, NH), 7.23-7.24 (m, 5H, Ar-H), 5.14 (d, 1H, J = 2.6 Hz, H-4), 3.96 (q, 2H, J = 7.0 Hz, OCH_2CH_3), 2.25 (s, C_6-CH_3), 1.07 (t, J = 7.0 Hz, 3H, OCH_2CH_3); IR (KBr) ν: 3244, 3112, 2979, 1724, 1699, 1651 cm^{-1}.

Entry 2: m.p.: 206-208 °C, ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.20 (s, 1H, NH), 7.74 (s, 1H, NH), 7.22-7.33 (m, 5H, Ar-H), 5.13 (d, J = 3.2 Hz, 1H, H-4), 3.52 (s, 3H, $COOCH_3$), 2.24 (s, 3H, C_6-CH_3). IR (KBr) ν: 3334, 3223, 3106, 2951, 1700, 1666 cm^{-1}.

Entry 13: m.p.: 227-229 °C, ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.26 (s, 1H, NH), 7.59 (s, 1H, NH), 7.25-7.40 (m, 4H, Ar-H), 5.62 (d, J = 2.5 Hz, 1H, H-4), 3.48 (s, 3H, $COOCH_3$), 2.30 (s, 3H, C_6-CH_3); ^{13}C NMR δ: 165.4, 151.3, 149.2, 141.4, 131.6, 129.3, 129.0, 128.6, 127.6, 97.8, 51.3, 50.6, 17.6; IR (KBr) ν: 3367, 3221, 3103, 2948, 1713, 1696 cm^{-1}; MS m/z (%): 280 (M^+, 5.13).

Entry 14: m.p.: 251-253 °C, ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.20 (s, 1H, NH), 7.62 (s, 1H, NH), 7.26-7.43 (m, 4H, Ar-H), 5.67 (s, 1H, H-4), 2.33 (s, 3H, $COCH_3$), 2.04 (s, 3H, C_6-CH_3); ^{13}C NMR δ: 193.8, 151.2, 148.7, 140.6, 131.6, 129.5, 129.2, 128.6, 127.6, 108.4, 51.4, 30.0, 18.7; IR (KBr) ν: 3243, 3093, 2940, 1704, 1621 cm^{-1}; MS m/z (%): 265 (M^+, 2.04).

RESULTS AND DISCUSSION

The results are summarized in Table 1. It can easily be seen that the condensation of a series of aldehydes with 1, 3-dicarbonyl compound and urea/thiourea leading to 3,4-dihydropyrimidin-2(1*H*)-ones gives good yields under ultrasound irradiation and solvent-free conditions.

As shown in Table 1, various aromatic aldehydes carrying either electron-releasing or electron-withdrawing substituents can obtain high yields. It is pleasing to observe the remarkable stability of a variety of functional group such as nitro, hydroxyl, and conjugated carbon-carbon double bound under the reaction conditions. Acid-sensitive aldehyde such as cinnamaldehyde was adopted well without the formation of any side products (entry 11). However, when the aliphatic aldehydes were used as the starting materials, the yield dropped because of the lower activity of carbonyl group in aliphatic aldehydes (entry 10). 3,4-Dihydropyrimidin-2(1*H*)-thiones (entries 17-21), which were also of considerable interest with regard to biological activity, were successfully synthesized under similar conditions. 3, 4-Dihydropyrimidin-2-(1*H*)-ones were achieved in excellent yields without the

Table 1. Synthesis of 3,4-Dihydropyrimidin-2-(1*H*)-ones Catalyzed by Nafion-H under Ultrasound Irradiation and Solvent-Free Conditions

Entry	R_1	R_2	X	Yield (%)[a]	m.p. (°C)	
					Found	Reported
1	C_6H_5	OEt	O	95	202-204	(203-204 [19])
2	C_6H_5	OMe	O	91	206-208	(207-210 [19])
3	C_6H_5	Me	O	90	235-236	(233-236 [19])
4	3-$O_2NC_6H_4$	OEt	O	91	226-228	(227-229 [20])
5	4-HOC_6H_4	OEt	O	90	227-228	(227-228 [20])
6	4-$O_2NC_6H_4$	OEt	O	88	206-208	(207-209 [20])
7	3-ClC_6H_4	OEt	O	89	192-193	(192-193 [20])
8	4-$CH_3OC_6H_4$	OEt	O	92	201-203	(201-203 [20])
9	4-ClC_6H_4	OEt	O	92	212-215	(212-215 [20])
10	CH_3	OEt	O	80	188-189	(189-190 [21])
11	C_6H_5CH=CH	OEt	O	90	232-234	(232-235 [11])
12		OEt	O	85	202-204	(202-204 [22])
13	2-ClC_6H_4	OMe	O	87	227-229	
14	2-ClC_6H_4	Me	O	85	251-253	
15	4-HOC_6H_4	Me	O	89	236-238	(236-238 [23])
16	4-$O_2NC_6H_4$	Me	O	91	239-241	(239-241 [19])
17	C_6H_5	OEt	S	88	205-206	(205-206 [24])
18	C_6H_5	Me	S	85	219-221	(220-222 [12])
19	C_6H_5	OMe	S	84	220-222	(222 [25])
20	4-$CH_3OC_6H_4$	OEt	S	87	135-137	(136-138 [26])
21	4-ClC_6H_4	OEt	S	87	183-185	(180-182 [26])

[a]Yield of isolated product.

formation of any side products, which are normally observed in the presence of other traditional methods. The catalyst could be easily isolated by filtration.

In summary, we have developed a simple and efficient procedure for the synthesis of dihydropyrimidinones or thiones, using nafion-H as catalyst. The crude products obtained are of high purity (>95% by ^{1}H NMR) and do not require any chromatographic separation. Most significantly, the whole operation does not involve any organic solvent at any stage. The mild reaction conditions, rapid conversion, high yields, simple experimental procedure, and catalyst reusability are notable advantages of the present method.

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