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$NaIO_4$-Catalyzed One-Pot Synthesis of Dihydropyrimidinones at Room Temperature under Solvent-Free Conditions

X. Jing*, Z. Li, X. Pan, Y. Shi and C. Yan
College of Chemistry and Chemical Engineering, Yangzhou University, Yangzhou 225002, P. R. China

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Sodium periodate efficiently catalyzed the three-component Biginelli reaction of an aldehyde, α β-keto ester or β-keto ketone, and urea or thiourea at room temperature under solvent-free conditions and afforded the corresponding 3,4-dihydropyrimidine-2-(1H)-ones in excellent yields.

Keywords: Pyrimidinones, Sodium periodate, Biginelli reaction, Solvent-free conditions

INTRODUCTION

With the advent of the present century, green chemistry established itself as a major driving force for organic chemistry to develop environmentally benign routes to a myriad of materials [1]. The feasibility of performing multi-component reactions under solvent-free conditions with solid catalysts could enhance their efficiency from an economic as well as ecological point of view. Thus, solvent free chemical reactions offer several advantages in preparative, simplifying work-up, formation of cleaner products, enhanced selectivity, reduction of byproducts, reduction in the waste produced, and much improved reaction rates [2].

Dihydropyrimidinones are an important class of compounds which are becoming increasingly significant due to their therapteutic and pharmacological activities [3]. Several functionalized dihydropyrimidines have been found to exhibit a wide spectrum of biological effects [4] including antiviral, antitumor,antibacterial and anti-inflammatory activities. In addition, 4-aryldihydropyrimidines have emerged [5] as potent calcium channel blockers, antihypertensive, α_{1a}-adrenergic and neuropeptide antagonists. Further, dihydropyrimidinones-5-carboxylate core units are found to be potent-HIV gp-120-CD_4 inhibitors [6]. The simple and direct method originally reported by Biginelli [7] for the synthesis of dihydropyrimidinones which involves three component condensation reactions (*i.e.*, aldehyde, β-keto ester and urea) often suffers from low yields particularly in case of substituted aromatic and aliphatic aldehydes [8]. Even though high yields could be achieved by following complex multi-step procedures [9], these methods lack the simplicity of original one-pot Biginelli protocol.

Therefore, Biginelli reaction continues to attract the attention of researchers for the discovery of a milder and efficient procedure for the synthesis of dihydropyrimidinones. Since the beginning of the present century, many catalysts, such as BF_3·OEt, PPE, KSF clay, $InCl_3$, $FeCl_3$, $RuCl_3$ and Lanthanide triflates, have been found to be effective [10] for this transformation. However, many of these one-pot procedures generally require strong protic or Lewis acids, prolonged reaction times, and high temperatures. Yadav [11a] reported that neutral $LiClO_4$ works well in the Biginelli reaction, but toxic solvent of acetonitrile is needed [11b, 12-18]. Thus, the use of a neutral alternative, and less

*Corresponding author. E-mail: jingxiaobi@yahoo.com.cn

hazardous solvents, or even those that do not need solvents at all, would extend the scope of useful one-pot Biginelli reaction for the synthesis of dihydropyrimidinones.

In this work, we report a simple and efficient method for the synthesis of dihydropyrimidinones using a catalytic amount of $NaIO_4$ at room temperature under solvent-free conditions.

EXPERIMENTAL

Melting points were obtained on a hot-plate microscope apparatus and were uncorrected. ^1H and ^{13}C NMR spectra were recorded with a Bruker AV-600 spectrophotometer. IR spectra were obtained on a Nicolet FT-IR 740 spectrometer (KBr disc).

General Procedure

A mixture of aldehyde (5 mmol), β-keto ester (5 mmol), urea (10 mmol) and $NaIO_4$ (20% w/w of aldehyde) was stirred at room temperature for an appropriate time. After completion of the reaction, the mixture turned into solid, which was filtered and crystallized from methanol to afford the pure product.

The spectral (^1H NMR, ^{13}C NMR and IR) of some representative compounds are given below:

(4g): ^1H NMR ($CDCl_3$, 600 MHz) δ: 2.22 (s, 3H), 2.37 (s, 3H), 5.54 (d, 1H), 5.85 (s, 1H), 7.26 (s, 1H), 7.64-7.65 (d, 1H), 7.9 (s, 1H), 8.53-8.54 (d, 1H), 8.60 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 17.3, 19.7, 52.6, 110.4, 123.1, 133.8, 137.7, 145.5, 147.2, 149.4, 161.5, 193.5; IR (KBr): 1002, 1031, 1110, 1254, 1332, 1380, 1437, 1454, 1614, 1688, 2969, 3092, 3220 cm^{-1}.

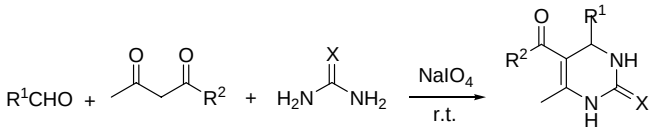
(4y): ^1H NMR ($CDCl_3$, 600 MHz) δ: 1.13 (t, J = 7.1 Hz , 3H), 2.32 (s, 3H), 4.04 (q, J = 7.0 Hz, 2H), 5.36 (s, 1H), 5.82 (d, 1H), 6.86-7.33 (m, 9H), 8.06 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 12.9, 17.5, 54.3, 58.9, 99.9, 115.9, 116.8, 117.8, 120.0, 122.2, 128.6, 128.9, 144.4, 145.2, 151.8, 155.7, 156.4, 164.3; IR (KBr): 1096, 1162, 1245, 1289, 1326, 1385, 1485, 1588, 1653, 1709, 2980, 3113, 3243 cm^{-1}.

(4i): ^1H NMR (DMSO-d_6, 600 MHz) δ: 2.15-2.25 (t, J = 7.1 Hz, 6H), 3.30 (s, 3H), 3.31 (s, 3H), 3.96-3.99 (q, J = 7.1 Hz, 4H), 5.10 (d, 2H), 7.16-7.17 (d, 2H), 7.65 (s, 2H), 8.29-8.30 (d, 2H), 9.13 (s, 2H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 14.0, 17.7, 53.8, 56.0, 59.2, 100.1, 126.2, 143.7, 148.4, 152.1, 165.4; IR (KBr): 1023, 1091, 1236, 1278, 1328, 1374, 1445, 1718, 1901, 2983, 3119, 3307 cm^{-1}.

RESULTS AND DISCUSSION

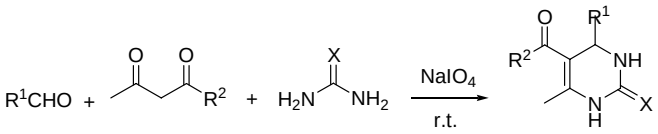
Our first finding was that the reaction of benzaldehyde and urea with ethyl acetoacetate in the presence of a catalytic amount of $NaIO_4$ in refluxing ethanol afforded the desired dihydropyrimidinone in 85% yield. We then examined this reaction in different solvents and under different reaction temperatures, whereby the reaction gave better yields under neat conditions, and the products were obtained in good yields when the temperature was reduced to ambient with the prolonged reaction time (Tables 1 and 2).

Table 1. Formation of DHMP in Different Solvents and Solvent-Free Conditions



Entry	Solvent	Time (h)	Temperature (°C)	Yield (%)
1	Ethanol	3	refluxing	85
2	MeCN	3	refluxing	72
3	CH_2Cl_2	12	refluxing	33
4	THF	12	refluxing	68
5	H_2O	20	refluxing	<10
6	Solvent-free	6	r.t.	90

Table 2. $NaIO_4$-Catalyzed Synthesis of DHMP and Derivatives



1 2 3 4

Entry	R^1	R^2	X	Product	Yield	Mp (°C)	
						Found	Reported
1	C_6H_5	OEt	O	4a	96	201-202	201-203 [10a]
2	C_6H_5	Me	O	4b	94	235-236	232-234 [11]
3	4-(CH_3)-C_6H_4	OEt	O	4c	95	170-171	170-172 [11]
4	4-(CH_3)-C_6H_4	Me	O	4d	92	228-229	-
5	4-(CH_3)-C_6H_4	OEt	S	4e	87	193-194	192-194 [17]
6	3-Pyridyl	OEt	O	4f	90	212-213	-
7	3-Pyridyl	Me	O	4g	89	182-183	-
8	Salicyl	OEt	O	4h	89	198-200	201-203 [11]
9	Salicyl	Me	O	4i	88	192-193	-
10	2-Furyl	OEt	O	4j	92	206-207	206-208 [10a]
11	2-Furyl	Me	O	4k	90	208-209	-
12	4-(OH)-3-(OCH_3)-C_6H_3	OEt	O	4l	94	232-233	231-233 [12]
13	4-(OH)-3-(OCH_3)-C_6H_3	Me	O	4m	91	233-234	-
14	3-(NO_2)-C_6H_4	OEt	O	4n	90	226-227	226-228 [12]
15	3-(NO_2)-C_6H_4	Me	O	4o	87	248-250	-
16	4-(OH)-C_6H_4	OEt	O	4p	93	225-226	226-228 [12]
17	4-(OH)-C_6H_4	Me	O	4q	87	256-258	-
18	4-(OH)-C_6H_4	OEt	S	4r	86	192-193	193-194 [16]
19	4-(Cl)-C_6H_4	OEt	O	4s	94	209-210	210-212 [11]
20	4-(NMe_2)-C_6H_4	OEt	S	4t	88	210-211	-
21	4-(NMe_2)-C_6H_4	OEt	O	4u	95	254-255	256-258 [13]
22	4-(OCH_3)-C_6H_4	OEt	O	4v	94	199-200	199-201 [11]
23	4-(NO_2)-C_6H_4	OEt	O	4w	92	205-206	206-207 [10a]
24	4-(Br)-C_6H_4	OEt	O	4x	93	208-209	205-208 [12]
25	3-(OPh)-C_6H_4	OEt	O	4y	94	192-193	193-194 [10a]
26	3-(Br)-C_6H_4	OEt	O	4z	92	178-179	-
27	Terephthaloyl	OEt	O	4Ⅰ	95	>300	-
28	Ethyl	OEt	O	4Ⅱ	90	183-184	186-188 [14]
29	Propyl	OEt	O	4Ⅲ	91	160-161	156-157 [11]
30	Hexyl	OEt	O	4Ⅳ	93	163-165	161-162 [10a]
31	Heptyl	OEt	O	4Ⅴ	90	148-150	152 [15]
32	Octyl	OEt	O	4Ⅵ	89	108-110	-

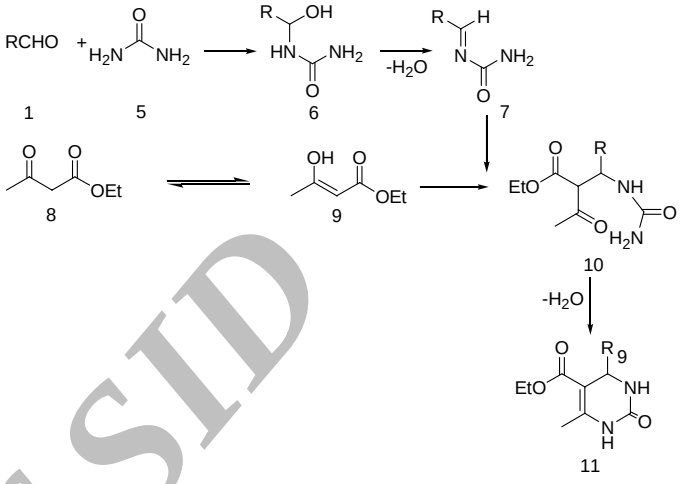
All the melting points (except the products of entry 4, 6, 7, 9, 11, 13, 15, 17, 20, 26, 27 and 32 are hitherto unknown) are in good agreement with those of literature report.

Several activated and deactivated aromatic aldehydes and aliphatic aldehydes underwent the reaction to give the corresponding dihydropyrimidinones in good yields. The experimental procedure was very simple, convenient, and had the ability to tolerate a variety of other functional groups such as methoxy, nitro, hydroxy, halides, and olefins under the reaction conditions. Thiourea was used as one of the ingredients with similar success to provide the corresponding 3,4-dihydropyrimidin-2(1H)-thiones, which were also of interest with respect to their biological activities. The results are summarized in Table 2, which clearly indicates the generality and scope of the reaction with respect to various aromatic, heterocyclic, unsaturated, and aliphatic aldehydes.

We propose a mechanism of the $NaIO_4$ catalyzed reaction as shown in Scheme 1. The aldehyde reacts with urea to form an acyl imine intermediate 6, which immediately eliminates one molecule of H_2O to produce a conjugated imino-ketone as a Michael system 7. In addition, in the presence of $NaIO_4$, the formation of highly stable enol of the ß-ketoester 8 is somehow facilitated in the reaction mixture. Addition of the enol 9 to the imino-ketone 7 *via* a Michael addition reaction results in the formation of 10, and subsequently with the elimination of a molecule of H_2O results in 11.

In Table 3, we have compared our results of the synthesis of DHMP catalyzed by $NaIO_4$ with those catalyzed by $LiClO_4$ reported in literature [11a]. It shows that the DHMP can be easily obtained without any solvent in room temperature and catalyzed by $NaIO_4$. On the contrary, when the reaction was catalyzed by $LiClO_4$, the refluxing temperature and the toxic solvent was needed.

In summary, we have developed a simple and efficient method for the synthesis of dihydropyrimidinones using a catalytic amount of $NaIO_4$ under solvent-free conditions and atambient temperature. Mild reaction conditions, high yields of the products, ease of work-up, compatibility with various functional groups, the ecologically clean procedure, and the simplicity and neutral reaction conditions, are all characteristics that make the present method significant addition to the already existing methodologies for heterocyclics synthesis.



Scheme 1

ACKNOWLEDGEMENTS

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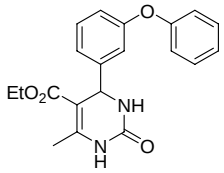
Table 3. Comparison of Synthesis of DHMP Catalyzed by $NaIO_4$ and that Reported with $LiClO_4$ [10a]

DHMP (4y)	Catalyst	Reaction conditions		Reaction time (h)	Yield (%)
		Temperature	Solvent		
	$LiClO_4$	Refluxing	CH_3CN	6	90
	$NaIO_4$	Room temperature	None	6	94

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