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An Efficient, Three-Component Synthesis of 3,4-Di Hydropyrimidin-2(1H)-Ones Using LaCl3/ClCH2COOH as Environmentally Benign and Green Catalytic System

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Abstract

An improved, simple, and facile synthesis of 3,4-dihydropyrimidin-2(1H)-ones by employing three-component, one-pot condensation reaction of β-keto ester, aromatic aldehydes, and urea or N-methylurea using LaCl3/ClCH2COOH as an inexpensive and green chemistry catalyst system under solvent-free conditions described. Compared with the classicalBiginelli reaction conditions, this method has the advantages of good to excellent yields (80-99%) and short reaction time.

Keywords: Dihydropyrimidinones; Lanthanum(III)chloride; Solvent –free; One-pot condensation.

Introduction

Multi-component reactions (MCRs) are powerful and useful synthetic tools to produce complex organic molecules, and this is due to formation of carbon-carbon and carbon-heteroatom bonds in a one-pot path way [1-2].

One of the famous MCRs is synthesize of Dihydropyrimidinones (DHPMs) which was first reported by the Italian chemist Pietro Biginelli more than 100 years ago; it involves a three-component one-pot condensation of benzaldehyde, ethyl acetoacetate and urea under strongly acidic conditions [3]. Since the 3,4-dihydropyrimidin-2 (1H)-ones indicate biochemical and pharmacological activities, they can serve as the integral backbones of several calcium channel blockers [4] and antihypertensive agents [5] and α-1a-antagonists [6].

In addition, several marine alkaloids containing the dihydropyrimidinone-5-carboxylate motifs also show interesting biological activities [7].

In recent years several methods for the synthesis of DHPMs have been developed to improve and modify this reaction by means of microwave irradiation [8], ultrasound irradiation[9], promoted by PPh_3 [10] Lewis acids such as Boric acid [11], $KA1(S0_4)2.12H_2O$ supported on silica gel [12], Sr $(OTf)_2$ [13], Indium (III) halides [14], Bi $(N0_3)_3$ [15] 12-tungstophosphoric acid [16] Cu $(OTf)_2$ [17], sulfonated β-cyclodextrine [18], sulfated tungstate [19], Lanthanum chloride [20] and Chloroacetic acid [21].

However, the combination of solvents, toxic reagents, low yields and long reaction times makes some of these previously reported protocols environmentally hazardous. Because of the importance of these compounds, there has been considerable interest to explore green, rapid and higher yielding protocol.

Although the last two reported method for synthesis of 3,4-dihydropyrimidin-2(1H)-ones consume 5 and 3-5

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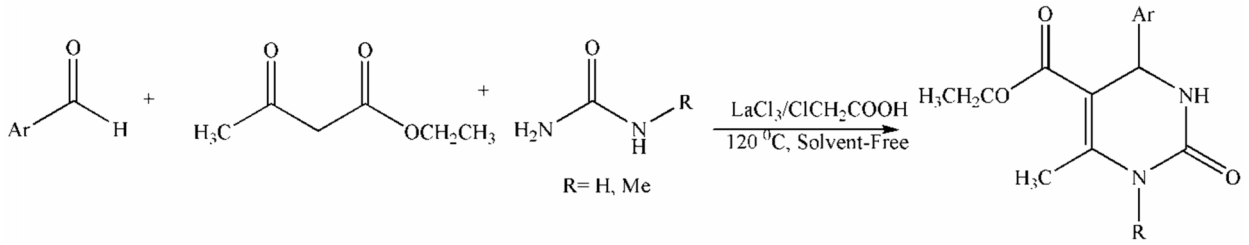

Figure 1. The synthesis of 3,4-dihydropyrimidin-2(1H)-one derivatives using $LaCl_3/ClCH_2COOH$.

hours respectively, we discovered that combination of the two mentioned reagent led to comparable decrease in reaction times.

Materials and Methods

General: Starting materials, solvents, and reagents were either prepared in our laboratories or purchased from Merck, Fluka chemical companies, and were used without purification. The products were characterized by their spectral data. IR spectra were recorded by using a BRUKER FT- IR spectrophotometer with KBr plates, ^1H and ^{13}C NMR spectra were recorded on a Bruker 400-MHz spectrometer with chloroform as a solvent and tetramethylsilan(TMS) as an internal standard. Melting points were recorded on an electrothermal apparatus and were uncorrected.

In all cases, the final products were precipitated out from the reaction mixture and were purified by recrystallization.

The catalyst is reusable, due to its insolubility in organic solvents, and it displayed high activity which afforded the corresponding products in excellent yield.

General procedure for preparation of the amides:

A solution of ethyl acetoacetate (1 mmol), aldehyde (1 mmol) and urea or N- methylurea (1.5 mmol), lanthanum (III) chloride (0.24 mmol), in chloroacetic acid (2 mmol) was heated at 120 ^0C for appropriate duration of time (Table 2). The progress of the reaction was checked by TLC (chloroform/ petroleum 2/1) and after completion of the reaction, the mixture was diluted with EtOH/ H_2O (2/1) and then the crude product was recrystallized from EtOH (96%) to afford the pure product.

Various kinds of aromatic aldehydes (2a-2o) were used in the one-pot reaction under $LaCl_3/ ClCH_2COOH$ catalyst for 1.5h and the results are illustrated in table 1.

Spectral Data for Selected Compounds

Ethyl -1, 2, 3, 4 -tetrahydro- 6-methyl- 2-oxo- 4-phenylpyrimidine- 5-carboxylate (Entry 1):

IR (KBr, ν (cm^{-1})): 3244 (NH), 3113 (CH arom), 2978 (CH aliph), 1700 (C=O), 1646 (C=O), 1219 (C-O), 1089cm^{-1}. ^1H NMR ($CDCl_3$): δ (ppm): 1.18 (t, 3H, CH_3), 2.37 (s, 3H, CH_3), 4.10 (q, 2H, CH_2), 5.42 (d, 1H, CH), 5.67 (s, 1H, NH), 7.27- 7.34 (m, 5H, arom), 7.94 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ (ppm): 14.1, 18.7, 55.8, 60.0, 101.4, 126.6, 127.9, 128.7, 143.6, 146.1, 153.1, 165.6.

Ethyl-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate (Entry 2):

IR (KBr, ν (cm^{-1})): 3243(NH), 3117, 2976(C-H aliph), 1714(C=O), 1647(C=O), 1227(C-O), 1093cm^{-1}. ^1H NMR ($CDCl_3$): δ (ppm): 1.19(t, 3H, CH_3), 2.36(s, 3H, CH_3), 4.10(q, 2H, CH_2), 5.40(d, 1H, CH), 5.72(s, 1H, NH), 7.26- 7.32(m, 4H, arom), 7.84(s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ (ppm): 14.1, 18.8, 55.2, 60.1, 101.1, 128.0, 128.9, 133.7, 142.1, 146.3, 152.9, 165.4.

Ethyl-1,2,3,4-tetrahydro-1,6-dimethyl-2-oxo-4-phenylpyrimidine-5-carboxylate (Entry 12):

IR (KBr,ν (cm^{-1})): 3244(NH), 3113(CH arom), 2978(CH aliph), 1700(C=O), 1646(C=O), 1219(C-O),1089cm^{-1}. ^1H NMR ($CDCl_3$): δ (ppm): 1.11(t, 3H, CH_3), 2.45(s, 3H, CH_3), 3.16(s, 3H, CH_3), 4.03(q, 2H, CH_2), 5.32(d, 1H, CH), 5.57(s, 1H, NH), 7.17-7.25(m, 5H, arom). ^{13}C NMR ($CDCl_3$): δ (ppm): 14.1, 16.5, 30.3, 53.9, 60.2, 104.2, 126.2, 127.8, 128.7, 143.3, 149.2, 153.9, 166.0.

Ethyl -1,2,3,4-tetrahydro-4-(2-methoxyphenyl)-1,6-dimethyl-2-oxopyrimidine-5-carboxylate (Entry 14):

IR (KBr, ν(cm^{-1})): 3243(NH), 3117(CH arom), 2976(CH aliph), 1714(C=O), 1647(C=O), 1227(C-O), 1093cm^{-1}. ^1H NMR ($CDCl_3$): δ (ppm): 1.03(t, 3H, CH_3), 2.54(s, 3H, CH_3), 3.10(s, 3H, CH_3), 3.80(s, 3H, OCH_3), 3.95- 4.04(q, 2H, CH_2), 5.59(d, 1H, CH), 5.75(s, 1H, NH), 6.77- 7.17(m, 4H, arom). ^{13}C NMR

Table 1. Synthesis of 3,4-dihydropyrimidin-2(1H)-ones

Entry	Ar	R	Times(min)	Yield[a] (%)	M.p. (^{0}C)	
					Found	Reported
2a	C_6H_4	H	20	99	200-202	198-200 [21]
2b	4-ClC_6H_4	H	10	81	213-215	211-213 [21]
2c	3-$O_2NC_6H_4$	H	15	88	229-231	229-231 [25]
2d	2,4-$(Cl)_2C_6H_3$	H	10	82	246-248	246-248 [21]
2e	2-ClC_6H_4	H	10	97	217-219	217-219 [26]
2f	4-OHC_6H_4	H	5	80	233-234	233-234 [26]
2g	4-$O_2NC_6H_4$	H	15	87	212-214	213-214 [27]
2h	2-$OMeC_6H_4$	H	10	89	253-255	254-255[27]
2i	2-OHC_6H_4	H	5	84	200-202	200 [27]
2j	4-MeC_6H_4	H	10	98	212-214	213-216 [21]
2k	4-BrC_6H_4	H	10	85	232-234	233-234[28]
2l	C_6H_4	Me	5	65	171-174	170-174 [29]
2m	4-$O_2NC_6H_4$	Me	10	99	143-145	144-145 [29]
2n	2-$OMeC_6H_4$	Me	5	80	148-149	147-149 [29]
2o	4-BrC_6H_4	Me	5	85	148-150	149-150 [29]

Table 2. Optimization of temperature using $LaCl_3$/ $ClCH_2COOH$ as catalyst

Entry	Temperature (^{0}C)	Time (min)	Yield[a] (%)
1	60	180	75
2	80	125	82
3	100	90	90
4	120	55	94
5	130	50	94

Table 3. Comparison the results of the synthesis of ethyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate using different catalysts.

Entry	Catalyst	Reaction time	Yield%[ref]
1	$Bi(N0_3)_3$	6h	80[15]
2	PPh_3(10%)	10h	70[10]
3	$InBr_3$(10%)	10h	79[14]
4	H_3PMoO_{40} (2%)	5h	75[16]
5	Montmorilonite KSF	48h	82[22]
6	Zeolite	12h	80[23]
7	Yb(III)-resin	48h	80[24]
8	$LaCl_3$	5h	95[20]
9	$ClCH_2COOH$	3h	92[21]
10	$LaCl_3$/ $ClCH_2COOH$	20 min	99(This work)

($CDCl_3$): δ (ppm): 14.1, 16.5, 30.2, 48.6, 55.3, 60.0, 110.5, 120.4, 126.2, 129.0, 151.0, 154.2, 156.9, 166.2.

Ethyl -4-(4-bromophenyl)-1,2,3,4-tetrahydro-1,6-dimethyl-2-oxopyrimidine-5-carboxylate (Entry 15):

IR (KBr,ν (cm^{-1})): 3244(NH), 3113(CH arom), 2978(CH aliph), 1700(C=O), 1646(C=O), 1219(C-O),1089cm^{-1}. ^{1}H NMR ($CDCl_3$): δ (ppm): 1.28(t, 3H, CH_3), 2.44(s, 3H, CH_3), 3.15(s, 3H, CH_3), 4.04(q, 2H, CH_2), 5.28(d, 1H, CH), 5.61(s, 1H, NH), 7.05- 7.36 (m, 4H, arom). ^{13}C NMR ($CDCl_3$): δ (ppm): 14.1, 16.6, 30.3, 53.4, 60.3, 103.8, 121.7, 128.0, 131.8, 142.3, 149.6, 153.6, 165.8.

Results and Discussion

The amount of $LaCl_3$ was optimized on the reaction of 2-chlorobenzaldehyde, ethyl acetoacetate and urea. The results are shown and the proper amount was 0.06gr (0.24mmol) $LaCl_3$ (Figure 2).

To optimize the temperature in the mentioned reaction, we have carried out a model study with benzaldehyde, ethyl acetoacetate and urea using $LaCl_3$/$ClCH_2COOH$ at various temperatures under solvent-free conditions. Table 2 clearly demonstrates that 120^{0}C is an effective temperature in terms of reaction time and yields.

After optimizing the conditions, the generality of this method was examined by the reaction of ethyl acetoacetate with different kinds of aromatic aldehydes (2a-2o) and urea/ methyl urea using $LaCl_3$/$ClCH_2COOH$ as catalyst under solvent-free condition.

In order to show the merit of the present work, we compared the results of the synthesis of ethyl 1,2,3,4-

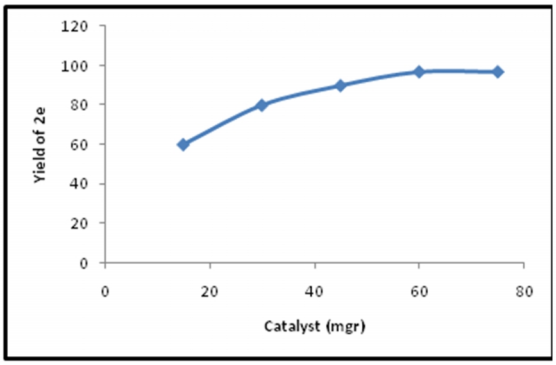

Figure 2. Optimization of the catalyst.

Table 4. Recyclability of LaCl3/ClCHCOOH

Run no	Yield (%)
1	94
2	89
3	85

tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate (Entry 1 in Table l) with some previously reported catalysts. The yield of product in the presence of $LaCl_3$/ $ClCH_2COOH$ is comparable to the reported catalysts. However, reaction in the presence of these catalysts required longer reaction times than this work (Table 3).

The reusability of the catalyst was checked by the reaction of benzaldehyde, ethyl acetoacetate and urea in the presence of $LaCl_3$/$ClCH_2COOH$ under solvent free condition at 120 ^{0}C. The results indicate that the catalyst can be used three times without any loss of its activity (Table 4).

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