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Microwave-assisted synthesis of dihydropyrimidin-2(1*H*)-ones using graphite supported lanthanum chloride as a mild and efficient catalyst

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Abstract—Graphite supported lanthanum chloride efficiently catalyzes the three-component coupling of β-ketoesters, aldehydes and urea/thiourea to afford corresponding dihydropyrimidinones in good yields under microwave irradiation.

Dihydropyrimidinones (DHPMs) named Biginelli compounds are known to exhibit a wide range of biological activities such as antiviral, antitumour, antibacterial and anti-inflammatory actions.[1–3] Appropriately functionalized DHPMs have emerged as potent calcium channel blockers,[4] antihypertensive agents[5] α_{1a} adrenergic antagonists.[6] Several marine alkaloids containing the DHPM core unit have shown interesting biological properties. In particular, batzelladine alkaloids have been found to be potent HIV gp-120-CD4 inhibitors.[7]

The original one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones was first reported by Pietro Biginelli in 1893 performing the three-component cyclocondensation reaction of ethyl acetoacetate, benzaldehyde and urea under Brönsted acid catalysis. However, this reaction suffers from the harsh conditions, high reaction times and frequently low yields.[8]

This has led to multi-step synthetic strategies that produce somewhat better yields but lack the simplicity of one-pot synthesis.[9]

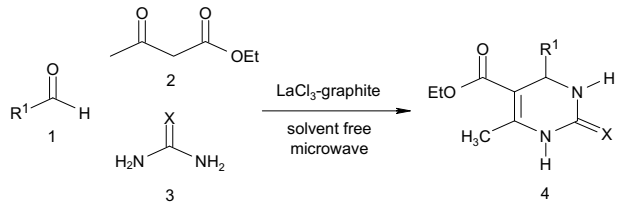
In recent years, new methods for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones have been developed by different groups.

In order to improve the efficiency of the Biginelli reaction different Lewis catalysts such as $ZrCl_4$,[10] $BiCl_3$,[11] LiBr,[12] $Mn(OAc)_3{\cdot}2H_2O$,[13] $InCl_3$,[14] $Cu(OTf)_2$,[15] $Zn(OTf)_2$,[16] $FeCl_3{\cdot}6H_2O$,[17] $LiClO_4$,[18] $CuCl_2$[19] and chloroacetic acid[20] have been reported.

Microwave heating has emerged as a powerful technique to promote a variety of chemical reactions.[21] Microwave reactions under solvent-free conditions and/or in the presence of a solid support, such as clays, alumina, silica and graphite, resulting in shorter reaction times and higher product yields than those obtained by using conventional heating offer low cost together with simplicity in processing and handling.[22]

In continuation of our interest in microwave-assisted synthesis,[23] we wish to report the $LaCl_3$-graphite catalyst system catalyzed synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones **4** under microwave conditions (Scheme 1).

The selection of $LaCl_3$ as a catalyst is done on the basis of report of Lu et al., in which they obtained dihydro-



Scheme 1.

Keywords: Dihydropyrimidine; Lanthanum chloride; Biginelli reaction; Microwave.
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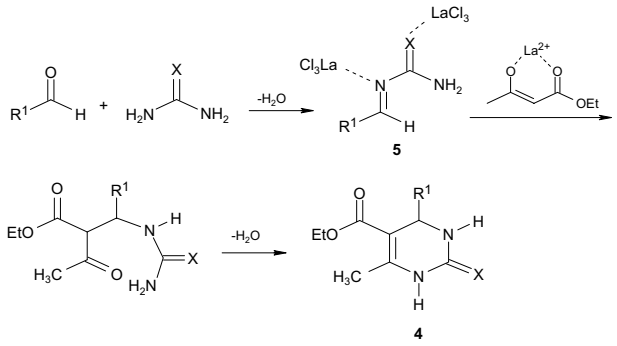
Table 1. Graphite supported lanthanum chloride synthesis of dihydropyrimidin-2(1*H*)-ones and thiones under microwave irradiation

Entry	Product	R^1	X	Yield (%)	Mp (°C)	
					Observed	Reported
1	**4a**	Ph	O	85	196–198	198–200[20]
2	**4b**	4-ClC_6H_4	O	80	208–210	211–213[20]
3	**4c**	2-ClC_6H_4	O	65	211–214	216–218[28]
4	**4d**	4-$O_2NC_6H_4$	O	75	202–204	205–207[28]
5	**4e**	4-$CH_3C_6H_4$	O	80	209–212	213–216[20]
6	**4f**	3-$O_2NC_6H_4$	O	75	225–228	229–230[27]
7	**4g**	2-$CH_3OC_6H_4$	O	60	255–258	260–262[27]
8	**4h**	$CH_3CH_2CH_2$	O	58	177–179	180–182[20]
9	**4i**	$(CH_3)_2CH$	O	50	194–196	196–197[20]
10	**4j**	Ph	S	86	198–200	202–204[20]
11	**4k**	4-O2NC$_6$H$_4$	S	80	106–108	109–111[30]
12	**4l**	3-O2NC$_6$H$_4$	S	74	202–204	206–207[28]
13	**4m**	4-ClC_6H_4	S	80	180–183	184–185[20]
14	**4n**	4-$CH_3C_6H_4$	S	84	185–188	189–192[29]



Scheme 2.

pyrimidinones in long reaction time (5 h).[24] Therefore, we developed the catalyst by impregnation of $LaCl_3$ on graphite support[25] which is a strong microwave absorbent and enhances the reaction temperature rapidly and subsequently increases the yield of products.

To optimize the reaction conditions, the reaction of benzaldehyde, ethyl acetoacetate and urea was selected as model to investigate the effects of the catalyst at different amounts of catalyst on the yield. The best result was obtained by carrying out the reaction with 1:1.2:1.5 mol ratios of aldehyde, 1,3-dicarbonyl urea/thiourea at 180 W power of microwave and the 35 mol% of catalyst for 8 min under microwave irradiation.[26]

To study the generality of this process, several examples were studied and are summarized in Table 1. In all cases studied, the three-component reaction proceeded fastly to give the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones in good yields.

This reaction may proceed via acyl imine intermediate **5**,[31] formed by the reaction of the aldehyde and urea which was catalyzed by HCl and stabilized by $LaCl_3$. Subsequent addition of β-ketoester enolate to the acylimine, followed by cyclization and dehydration, afforded the corresponding dihydropyrimidinones (Scheme 2).[32]

This method not only preserved the simplicity of Biginelli's one-pot condensation but also improved the yields of dihydropyrimidinones in shorter reaction time as against the longer reaction times required for other catalysts.

The procedure gives the products in good yields and avoids problems associated with solvent use such as cost, handling, specifically safety, because of fire hazard due to occurrence of sparks in microwave ovens.

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25. *General procedure for the preparation of catalyst.* $LaCl_3{\cdot}7H_2O$ (10 mmol, 3.70 g) was dissolved in 10 ml H_2O and then graphite (1.85 g) in 5 ml EtOH was added. The catalyst was collected after evaporating the solvent and dried at 100 °C for 1 h.
26. *General procedure for the preparation of 3,4-dihydropyrimidin-2(1H)-ones/thiones*. A mixture of appropriate aldehyde (10 mmol), ethylacetoacetate (12 mmol), urea/thiourea (15 mmol), catalyst (1.5 g, ~35 mol%) and one drop conc HCl was placed in an erlenmeyer flask. The mixture was placed in a microwave oven (Butane) and irradiated for a period of 1 min at a time. After each irradiation the reaction mixture was removed from the microwave oven for shaking. The total period of microwave irradiation was 8 min. Then ethanol was added to the reaction mixture and catalyst was removed by filtration. The filtrate was poured into the crushed ice water and the resulting precipitate was recrystallized from ethanol.
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32. Spectral data for selected compounds:*5-(Ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one* (**4a**). IR (KBr): 3230, 3131, 2982, 1699, 1650 cm^{-1}, ^1H NMR (DMSO-d_6, 500 MHz): δ = 1.10 (t, J = 7.1 Hz, 3H, CH_3), 2.25 (s, 3H, CH_3), 3.99 (q, J = 7.1 Hz, 2H, CH_2), 5.15 (d, J = 3.2 Hz, 1H, CH), 7.23–7.34 (m, 5H, arom CH), 7.73 (s, 1H, NH), 9.18 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz) δ = 14.94, 18.64, 54.83, 60.04, 100.13, 127.11, 128.12, 129.25, 145.73, 149.22, 152.99, 166.20. *5-(Ethoxycarbonyl)-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1H)-thione* (**4n**). IR (KBr): 3329, 3180, 3156, 2982, 1691, 1592 cm^{-1}, ^1H NMR (DMSO-d_6, 500 MHz): δ = 1.11 (t, J = 7.1 Hz, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 4.01 (q, J = 7.1 Hz, 2H, CH_2), 5.14 (d, J = 3.0 Hz, 1H, CH), 7.11 (d, J = 8.0 Hz, 2H, arom CH), 7.15 (d, J = 8.0 Hz, 2H, arom CH), 9.61 (s, 1H, NH), 10.30 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz) δ = 14.89, 18.01, 21.53, 54.61, 60.42, 101.70, 127.16, 129.92, 137.76, 141.47, 145.73, 166.01, 175.03.