$NbCl_5$-catalyzed Rapid and Efficient Synthesis of 3,4-Dihydropyrimidinones Under Ambient Conditions

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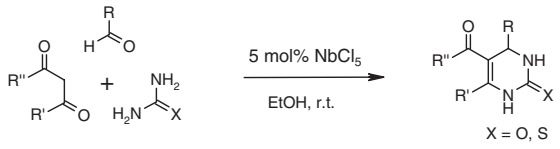
(Received March 18, 2004; CL-040309)

Three-component condensation of an aldehyde, 1,3-dicarbonyl compound and urea or thiourea proceeds smoothly at room temperature in the presence of 5 mol % of $NbCl_5$ under extremely mild conditions to afford the corresponding 3,4-dihydropyrimidines in high to quantitative yields. This method is very useful for the synthesis of a wide range of dipyrimidinones at room temperature from aromatic, heterocyclic, and aliphatic aldehydes.

Many functionalized dihydropyrimidinones have emerged as the integral backbones of several calcium channel blockers, antihypertensives, α_{1a}-adrenergic antagonists, and neuropeptide Y (NPY) antagonists.[1] Particularly, aryl 3,4-dihydropyrimidinones are found to exhibit a wide spectrum of biological activities such as antiviral, antitumor, antibacterial, and antiinflammatory behavior.[2] Furthermore, several alkaloids containing the dihydropyrimidine core structure have been isolated from marine sources, which also exhibit interesting biological properties. Most notably, among these are the batzelladine alkaloids which are found to be potent HIV gp-120-CD_4 inhibitors.[3] Thus, the synthesis of the pyrimidinone nucleus is of much current importance. The simplest and most straightforward procedure for the preparation of pyrimidinones involves three-component one-pot condensation of an aldehyde, (β-ketoester, and urea under strongly acidic conditions.[4] However, this so-called Biginelli reaction often suffers from low yields of products particularly in the case of substituted aromatic and aliphatic aldehydes.[5] This has led to the development of multi-step synthetic strategies, which produce relatively higher yields but lack the simplicity of the original one-pot-Biginelli protocol.[6] The Biginelli one-pot reaction has received renewed interest of researchers for the discovery of milder and efficient procedures for a wide variations of substituents in all three components and better yields. As a result, several improved procedures have recently been reported using Lewis acids as well as protic acids as promoters.[7,8] Besides their potential utility, most of these methods require high temperature and extended reaction times to achieve satisfactory results. Therefore, the development of an efficient and versatile catalyst for Biginelli reaction is an active ongoing research area and thus there is scope for further improvements toward milder reaction conditions, variations of substituents in all three components, and better yields. Recently niobium(V) chloride has emerged as an efficient Lewis acid in promoting various organic transformations such as the Diels–Alder reaction, ring-opening of epoxides, Mukaiyama aldol reaction and allylation of aldehydes, imines and *N*-acyliminium ions under mild conditions.[9,10]

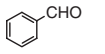
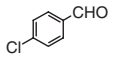
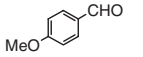
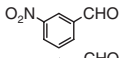
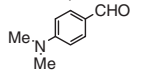
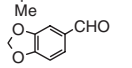
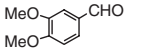
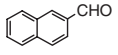
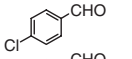
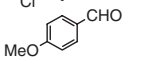
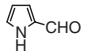
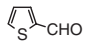
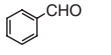
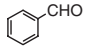
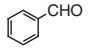
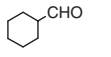
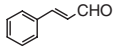
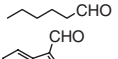
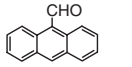
In this report, we describe a simple, convenient, and high yielding protocol for the synthesis of dihydropyrimidinones by a three-component one-pot condensation of an aldehyde, β-keto ester and urea using $NbCl_5$ as a catalyst. Initially, we have carried out a model raction of benzaldehyde, ethyl acetoacetate and urea using 5 mol % of $NbCl_5$ in ethanol (Scheme 1).



Scheme 1.

The reaction proceeded rapidly at room temperature under extremely mild conditions and the product started to precipitate out after 30 min and more than 90% conversion was observed within 2 h. Encouraged by the results obtained with benzaldehyde, we turned our attention towards various substituted aldehydes and 1,3-dicarbonyl compounds. Interestingly, a wide range of substrates including aromatic, aliphatic, heterocyclic, and α,β-unsaturated aldehydes reacted rapidly with ethyl acetoacetate and urea or thiourea to give the corresponding dihydropyrimidinones. Most importantly, aromatic aldehydes carrying either electron-donating or -withdrawing substituents reacted well under the reaction conditions to give the corresponding dihydropyrimidinones in high to quantitative yields with high purity. The crude products obtained are of high purity (>95% by ^{1}H NMR). Many of the pharmacological relevant substitution patterns on the aromatic ring can be introduced with high efficiency using this procedure (Table). Compared to the classical Biginelli method, one additional important feature of the present protocol is the ability to tolerate the variations in all the three components. Another important feature of this procedure is the survival of a variety of functional groups such as olefins, ethers, esters, nitro group, and halides under the reaction conditions. This method is even effective with aliphatic and α,β-unsaturated aldehydes, which normally show extremely low conversions in the Biginelli reaction (Entries p, q, and r, Table). Unlike reported methods, this procedure does not require high temperature[7,8] or anhydrous conditions. Furthermore, this method is not only preserves the simplicity of Biginelli reaction but also produces excellent yields of the products. Thiourea has been used with similar success to produce the corresponding thio-derivatives of dihydropyrimidinones which are also of much interest with respect to their biological activities (Entries i and j, Table).[2a] Besides the β-keto esters, 1,3-diketone was employed to produce a dihydropyrimidinone (Entry o, Table). Decreased reaction times and improved yields are realized due to the increased reactivity of the substrates in the ethanolic solution of niobium(V) chloride. By using this method, the yields of the one-pot Biginelli reaction can be improved from 20–60%[1b] to 70–96% while the reaction time was shortened from 18 h to 2.5–5.0 h. In order to optimize the conditions, we carried out the reactions using different quantities of reactants. The best results were obtained with 0.05:1:1:1.5 ratio of $NbCl_5$, aldehyde, 1,3-dicarbonyl compound and urea or thiourea. In the absence of niobium(V) chloride, the reaction did not proceed at room tem-

Table 1. $NbCl_5$-catalyzed three-component synthesis of 3,4-dihydropyrimidinones[a]

Entry	Aldehyde	X	R'	R''	Time/h	Yield/%[b]
1		O	Me	OEt	2.5	95
2		O	Me	OEt	3.0	93
3		O	Me	OEt	4.0	91
4		O	Me	OEt	2.0	89
5		O	Me	OEt	6.0	85
6		O	Me	OEt	3.0	94
7		O	Me	OEt	3.0	96
8		O	Me	OEt	5.0	90
9		S	Me	OEt	3.5	91
10		S	Me	OEt	4.0	93
11		O	Me	OEt	3.0	70
12		O	Me	OEt	2.5	91
13		O	Me	OMe	3.0	93
14		O	Ph	OEt	5.0	85
15		O	Me	Me	4.0	80
16		O	Me	OEt	4.0	87
17		O	Me	OEt	3.0	90
18		O	Me	OEt	3.5	82
19		O	Me	OEt	3.0	85
20		O	Me	OEt	5.0	91

[a]All the products were characterized by ^{1}H-NMR, IR and mass spectroscopy.

perature even after a long reaction time (8–12 h). The efficacy of other Lewis acids such as $InCl_3$, $CeCl_3$, $GdCl_3$, $TaCl_5$, and YCl_3 was studied for this reaction. Among these catalysts, $NbCl_5$ was found to be superior in terms of conversion and reaction time. This three-component reaction did not proceed at room temperature using the above mentioned catalysts. However, the reaction proceeded with these reagents under reflux conditions. It seems that methanol or ethanol is a much better solvent in terms of conversion than all the other tested solvents which included acetonitrile, dichloromethane and tetrahydrofuran. Furthermore, the use of just 5 mol % of niobium(V) chloride in methanol is sufficient to promote the reaction and no additives such as HCl or CH_3COOH[7e] are required for this conversion. Thus, this procedure provides an easy access to the preparation of substituted pyrimidinones with a wide range of substitution patterns on all three components. To the best of our knowledge, there are only few reports on the one-pot Biginelli reaction at room temperature,[11] as most of the reported methodologies to date are carried out under drastic conditions. The scope and generality of this process is illustrated with respect to various aldehydes, 1,3-dicarbonyl compounds, and urea or thiourea and the results are presented in the Table.

In summary, we found that niobium(V) chloride is an extremely mild and highly efficient Lewis acid for the synthesis of biologically significant aryl-substituted dihydropyrimidinones by means of a three-component condensation of an aldehyde, 1,3-dicarbonyl compound and urea or thiourea in a one-pot operation. This method is applicable for a wide range of substrates including aromatic, aliphatic, α,β-unsaturated and heterocyclic aldehydes and provides a variety of biologically relevant dihydropyrimidinones in high to quantitative yields over a short reaction time.

BVS, JJN thank CSIR, New Delhi, for the award of fellowships.

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12 Experimental procedure: A mixture of β-keto ester (1.0 mmol), aldehyde (1.0 mmol), urea or thiourea (1.5 mmol), and $NbCl_5$ (5 mol %) in methanol (10 mL) was stirred at room temperature for a certain period of time as required to complete the reaction. The progress of the reaction was monitored by TLC. On completion, the solvent was removed under reduced pressure and the resulting product was washed with water, filtered and recrystallized from hot methanol to afford pure dihydropyrimidinone. The spectral data of all the products were identical with those of authentic samples.[6–8] Spectroscopic data for selected products: **3n**: Solid, m.p. 157–158 °C. IR (KBr): ν 3215, 3085, 2978, 1697, 1650 cm^{-1}. ^{1}H NMR (200 MHz, DMSO-d_6): δ 0.90 (t, 3H, J = 6.8 Hz), 3.85 (q, 2H, J = 6.8 Hz), 5.45 (d, 1H, J = 1.9 Hz), 6.55 (brs, NH, 1H), 7.30–7.40 (m, 10 H), 7.80 (brs, NH, 1H). EIMS: m/z: 322 (M^+), 294, 278, 249, 185, 157, 138, 91, 77, 69. **3o**: Solid, m.p. 240–242 °C. IR (KBr): ν 3286, 3251, 2920, 1703, 1675, 1598, 1414, 1327, 1235, 1105, 997, 965, 768 cm^{-1}. ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.10 (s, 3H), 2.25 (s, 3H), 5.30 (d, 1H, J = 2.0 Hz), 7.20–7.30 (m, 5H), 7.60 (brs, NH, 1H), 9.05 (brs, NH, 1H). EIMS: m/z: 230 (M^+), 188, 154, 144, 115, 77, 43.

Published on the web (Advance View) June 26, 2004; DOI 10.1246/cl.2004.926