Communications

An Efficient and Clean One-Pot Synthesis of 3,4-Dihydropyrimidine-2-(1H)-ones Catalyzed by $SrCl_2 \cdot 6H_2O$-HCl in Solvent or Solvent-Free Conditions

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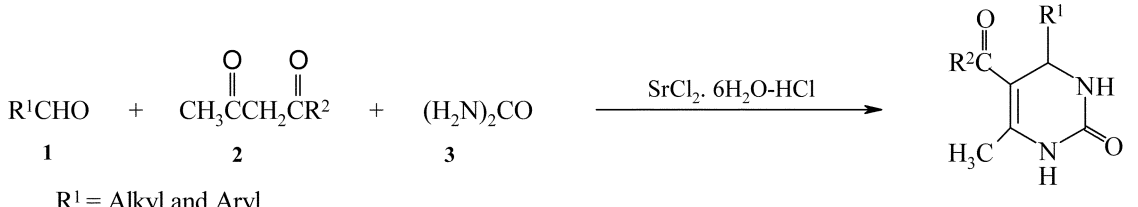
In recent years, 3,4-dihydropyrimidin-2(1H)-one derivatives have gained much interest for their biological and pharmaceutical properties,[1-4] such as HIV gp-120-CD4 inhibitors, calcium channel blockers, α-adrenergic and neuropeptide Y antagonists, as well as antihypertensive, antitumor, antibacterial and anti-inflammatory agents. The scope of this pharmacophore has been further increased by the identification of monastrol as a novel cell-permeable lead compound for the development of new anticancer drugs bearing the dihydropyrimidinone core. Thus the development of facile and environmentally friendly synthetic methods towards dihydropyrimidinones constitutes an active area of investigation in organic synthesis. The first synthetic method for the preparation of 3,4-dihydropyrimidine-2(1H)-ones (DHPMs) was reported by Biginelli[5] that involves the one-pot three component condensation of aldehydes, β-dicarbonyl compounds and urea or thiourea in ethanol under strongly acidic conditions producing DHPMs, albeit in low yields. In the view of the pharmaceutical importance of these compounds, many improved catalytic methods have been developed.[6-10] Although these methods have their own merits, long reaction times, harsh reaction conditions, unsatisfactory yields and use of large quantity of catalyst or organic solvent limit their practical applications. Therefore improvements with respect to the above have been continuously sought. In this paper, we wish to report an efficient and convenient procedure for the synthesis of DHPMs from the alkyl or aryl aldehydes using $SrCl_2 \cdot 6H_2O$-HCl catalyst system (Scheme 1).

$SrCl_2 \cdot 6H_2O$ was chosen for its nontoxicity and further it is inexpensive. First we investigated the catalytic effect of the $SrCl_2 \cdot 6H_2O$ and found that it greatly catalyzes the reaction when used with small amount of HCl(aq). Here, we presume the added HCl (aq) would act as a co-catalyst, activating the strontium salts. As shown in Table 1, the product yields were low (28-78%) after 18 h, when the reactions were carried out with HCl(aq) alone (as classical Biginelli reaction). The reactions were much slow when HCl(aq) was replaced with $SrCl_2 \cdot 6H_2O$, as we obtained DHPMs after long reaction time (> 20 h). But when we used 50 mol% of the Lewis acid with 1-2 drop of HCl, the yields increased (85-93%) as well as the reaction rates (6 h). We extended this reaction condition to a series of alkyl or aryl aldehydes under reflux condition in ethanol (2 mL per mmol of aldehyde) as solvent. Although the reaction afforded the products in high yields in other solvents like acetonitrile, we chose ethanol for economical and environmental acceptability. The results are summarized in Table 1(Method A).[11] Both aromatic aldehydes bearing either activating or deactivating groups reacted well with β-ketoesters to yield the corresponding DHPMs in high to excellent yields (Entries 1-23). Acid-sensitive substrates such as cinnamaldehyde also well proceeded to give the DHPMs without any side products (Entry 23). However, aliphatic aldehydes such as butanal as observed previously are quite resistant to our reaction conditions.[6d]

We next examined the same reaction conditions without a solvent. The results showed that the solvent-free condensation reactions are much faster (20 min), providing the corresponding products in much higher yields than condition A (Table 1, method B).

In conclusion, we have found an efficient, inexpensive and straightforward procedure for one-pot synthesis of dihydropyrimidinones using $SrCl_2 \cdot 6H_2O$-HCl catalyst system. Also



1 2 3 4

R^1 = Alkyl and Aryl
R^2 = Ethoxy and Methoxy

Scheme 1

Table 1. Synthesis of DHPMs catalyzed with $SrCl_2.6H_2O$-HCl in EtOH or under solvent-free condition

Entry	Product	R^1	R^2	Yield (%)[a]		Mp (°C)	
				A[b]	B[c]	Found	Reported
1	**4a**	C_6H_5	Me	92 (42)[d]	96	210-211	209-211[7]
2	**4b**	4-Cl	Me	91 (56)[d]	92	205-207	206-208[7]
3	**4c**	4-CH_3	Me	90	91	201-202	203[7]
4	**4d**	3,4-$(CH_3O)_2$	Me	88	88	150-153	150-152[7]
5	**4e**	4-OH-3-CH_3O	Me	85	89	221-222	220-222[7]
6	**4f**	4-CH_3O	Me	89 (28)[d]	94	193-194	192-194[7]
7	**4g**	4-NO_2	Me	88 (41)[d]	92	235-237	236-237[7]
8	**4h**	4-F	Me	86	90	193-194	192-194[12]
9	**4i**	2,4-$(Cl)_2$	Me	90	94	252-254	254-255[12]
10	**4j**	C_6H_5	Et	93 (78)[d]	97	201-203	202-203[7]
11	**4k**	4-Cl	Et	89 (56)[d]	94	214-216	215-216[7]
12	**4l**	4-CH_3	Et	90	95	170-171	170[7]
13	**4m**	3,4-$(CH_3O)_2$	Et	90	93	176-178	176-177[7]
14	**4n**	4-OH-3-CH_3O	Et	86 (43)[d]	90	232-233	231-232[7]
15	**4o**	4-CH_3O	Et	90 (61)[d]	95	202-203	201-202[7]
16	**4p**	4-NO_2	Et	87 (58)[d]	91	207-208	208-209[7]
17	**4r**	3-NO_2	Et	90	92	226-227	227-228[7]
18	**4s**	2,4-$(Cl)_2$	Et	92 (69)[d]	95	247-249	248-250[7]
19	**4t**	4-F	Et	88	93	184-186	185-186[13]
20	**4u**	3-OH	Et	90	94	165-167	164-166[14]
21	**4v**	4-Br	Et	89	92	195-198	197[7]
22	**4w**	4-$N(CH_3)_2$	Et	90	96	255-257	256-258[7]
23	**4x**	C_6H_5-CH=CH	Et	86	88	231-234	232-235[12]
24	**4q**	$CH_3(CH_2)_2$	Et	20	25	153-155	152-154[7]

[a]Isolated yields. [b]Method A: cat. $SrCl_2{\cdot}6H_2O$/HCl in EtOH, reflux 6 h. [c]Method B: cat. $SrCl_2{\cdot}6H_2O$/HCl, 100 °C 20 min). [d]Classical Biginelli conditions (cat. HCl in EtOH, reflux 18 h).

found was the performance of the catalyst system is greatly facilitated when used without solvents, important from the view point of industry or green chemistry. Moreover, non-hygroscopic, inexpensive and non-toxic nature of the catalyst for this transformation is other noteworthy merit of this procedure.

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11. General procedure for the preparation of dihydropyrimidinones **4**. *With a solvent*: A mixture of aldehyde (**1**, 10 mmol), β-dicarbonyl compound (**2**, 10 mmol), urea (**3,** 15 mmol), $SrCl_2{\cdot}6H_2O$ (5 mmol) and conc. HCl (1-2 drops) in ethanol (20 mL) was heated under reflux for 6 h. After cooling, the reaction mixture was poured into crushed ice and stirred for several minutes. The solid products were filtered, washed with cold water and a mixture of ethanol-water and then dried. The solid product was recrystalized from ethanol or ethylacetate/n-hexane.
Solvent-free (the same scale as the above): A mixture of aldehyde, β-dicarbonyl compound, urea and catalyst was treated with one drop of conc. HCl and heated at 100 °C for 20 min. The reaction mixture was diluted with 5 mL of ethanol, stirred and poured into crushed ice. The isolation procedure was the same as above method. The products were characterized by IR, ^{1}H NMR and via comparison of their melting points with the reported ones.
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