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Rapid communication

Tin (II) chloride catalyzed one pot efficient and novel preparation of dihydropyrimidin-2(1*H*)-ones

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A new method for the preparation of dihydropyrimidin-2(1*H*)-ones is reported using tin chloride dihydrate as mild Lewis acid catalyst in one pot three component coupling reaction of 1,3-diketones, aldehydes and urea.

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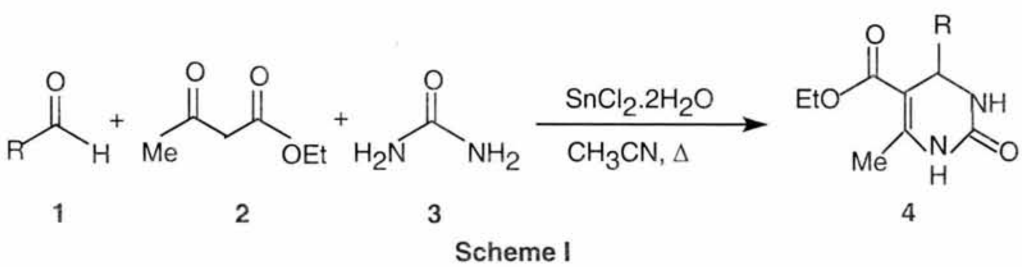
There has been considerable interest in the development of preparative methods for the production of dihydropyrimidin-2(1*H*)-ones (DHPMs). This seems to be because of their biological significance as well as to understand the mechanism of reaction involved which is commonly called Biginelli Condensation[1]. These compounds (DHPMs) have shown promising activities as calcium channel blockers (e.g. their structural resemblance to dihydropyridine group of clinically used drugs like nifedipine, efonidipine, elinidipine etc), anti-hypertensive agents and α-1a antagonists[2]. This skeleton is also found in alkaloids isolated from marine source, which are found to be potent H1V gp-120-CD4 inhibitors[3].

Because of these diverse type of biological activities this heterocyclic system is of great interest to medicinal chemistry for molecular manipulation and to biologists for further pharmacological evaluations. The original Biginelli 7synthesis reported more than a century ago[1] involves the refluxing of aldehyde, urea and diketone in ethanolic HCl which requires longer times and even then give lower yeilds. To improve this position several attempts have been made involving strong Lewis acids coupled with metal salts like $BF_3.Et_2O$[4], KSF[5], Indium halides[6] , lanthanide triflates[7] and many more[8].

However, the practical application of these methods still have some limitations like expensive chemicals, tedious work, corrosive Lewis acids which require sufficient care in handling, consequently there is still need to develop safer and efficient method for production of dihydropyrimidine derivatives.

In continuation of our work for the development of Biginelli Reaction[9a,b] and emphasizing on the use of safer, mild, economical and readily available catalyst, herein, we report an attaractive advancement in this reaction using tin chloride dihydrate as catalyst in the one pot three component coupling of 1,3-dicarbonyl compounds, urea and aldehyde to yield DHPMs in excellent yields (**Scheme I**).

The reaction is complete within 5-7 hr, work-up is simple, Lewis acid used is readily available and yields are excellent. This method is fairly general and applicable to heterocyclic as well as large range of aromatic aldehydes. In a typical example, a solution of ethyl acetoacetate (1.30g, 10 mmoles), urea (0.6g, 10 mmoles) and benzaldehyde (1.06g, 10 mmoles) in dry acetonitrile (25 mL) was stirred for a few minutes at room temp. To this solution tin chloride dihydrate (225 mg, 10 mol%) was added and resulting solution was refluxed with stirring for 6 hr under nitrogen atmosphere. After completion of reaction (monitored by TLC), the reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The solid thus obtained was washed with ice-cold water and recrystallised from ethanol to afford pure **4a**, m.p. 201-02 (lit.[10] m.p. 202-03°C) in 90% yield. Similarly, the products **4b-h** were obtained and are listed in **Table I**.



Scheme I

Table I — $SnCl_2.2H_2O$ mediated synthesis of dihydropyrimidin-2(1*H*)-ones **4a-h**

Entry	Product	R	Reaction time (hr)	m.p. (°C) Observed	m.p. (°C) Reported	Yield[a] (%)
1	**4a**	Ph	6	201-02	202-03[10]	90
2	**4b**	4-(OCH_3) C_6H_4	7	200-01	199-01[7]	80
3	**4c**	4-(OH) C_6H_4	5.5	227-28	227-29[10]	80
4	**4d**	3-(NO_2) C_6H_4	5	224-27	226-27[7]	81
5	**4e**	4-(NO_2) C_6H_4	5	209-11	207-10[7]	85
6	**4f**	4-(Cl) C_6H_4	5.5	211-13	210-12[7]	88
7	**4g**	Ph CH = CH	7	231-32	232-35[7]	80
8	**4h**	2-Furyl	6	205-06	204-05[10]	80

[a]Yields refer to pure isolated products, characterized by mp and spectral (IR, ^{1}H NMR, and MS) data.

Further increase in reaction time gave no significant improvement, rather decomposition of starting materials occurred. Use of 10 mol% of $SnCl_2.2H_2O$ is sufficient for these reactions and higher amount of $SnCl_2.2H_2O$ did not provide fruitful results i.e. it did not increase the yields. When other salts like nickel halides or iron chloride used under these conditions gave the products in quite high yield (from 80-90%). It is pertinent to mention here that the use of nickel chloride hexahydrate and ferric chloride hexahydrate is already reported. These authors used these salts[11] in addition to Beginelli conditions i.e. alocohlic HCl and nickel chloride hexahydrate or ferric chlorice hexahydrate. In contrast we do not use additional proton source or any other additive and also sensitive nucleus like furan could servive which is an added advantage of this new method using dry acetonitrile. Another important aspect of this procedure is the survival of several functionalities including nitro, chloro, hydroxy, methoxy and conjugated carbon-carbon double bond during the course of reaction. Our present method does not involve any strong Lewis acids like BF_3 or $AlCl_3$ or expensive salts of rare earth. In the present method there is increase in the yields from 20-50% to 78-90% while reaction time is reduced from 18-48 hr to 5-7 hr only.

In conclusion this method is simple, efficient, mild, economical, environment friendly and has the ability to tolerate a variety of aldehydes and provides an attractive alternate for the synthesis of DHPMs.

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References

1 (a) Biginelli P, *Gazz Chim Ital*, 23, **1893**, 360.
(b) Cappe C O, *Tetrahedron*, 49, **1993**, 6937.
(c) Wipf P & Cunninghum A, *Tetrahedron Lett*, 36, **1995**, 7819.
(d) Studer A, Jager P, Wipf P & Curran D P, *J Org Chem*, 62, **1997**, 2917.
2 (a) Atwal K S, Rovnyk G C, O'Relly B C & Schwartz J, *J Org Chem*, 54, **1989**, 5898.
(b) Atwal K S, Swanson B N, Unger S E, Floyd D M, Moreland S, Hedberg A & O'Relly B C, *J Med Chem*, 34, **1991**, 806.
(c) Boy G C, Atwal K S, Hebderg A, Kiball S D, Moreland S, Goygoutoy J Z, O'Relly B C, Schuartz J & Malley M F, *J Med Chem* 35, **1992**, 3254.
(d) Kappe C O & Fabian W M F, *Tetrahedron*, 53, **1997**, 2803.
3 (a) Patil A D, Kumar N V, Kokke W C, Ben M F, Freyer A J, DeBrosse C, Mai S, Truneh A, Faulkner D J, Carte B, Bree A L, Hertzberg R P, Johnson R K, Westley J W & Potts B C M, *J Org Chem*, 60, **1995**, 1182.
(b) Snider B, Chin J, Patial A D & Freyer A, *Tetrahedron Lett*, 37, **1996**, 6977.
(c) Rao A V R, Gurjar M K & Vasudevan J, *J Chem Soc, Chem Common*, **1995**, 1369.
4 Hu E H, Sidler D R & Dolling U H, *J Org Chem*, 63, **1998**, 3454.
5 Bigi F, Corloni S, Frullanti B, Maggi R & Sartori G, *Tetrahedron Lett*, 40, **1999**, 3465.
6 Fu N, Yuan Y, Cao Z, Wang S, Wang J & Pappe C, *Tetrahedron*, 58, **2002**, 4801.
7 Mai Y, Qian C Wough & Yang M, *J Org Chem*, 65, **2000**, 3864.
8 For some recent reports see : (a) Bose D S, Fatima L & Mereyala H B, *J Org Chem*, 68, **2003**, 587.
(b) Sabitha G, Reddy G S K K, Reddy J S & Yadav J S, *Synlett*, **2003**, 858.
(c) Shaabni A, Bazgir A & Teimouri F, *Tetrahedron Lett*, 44, **2003**, 857.
(d) Xia M & Wang Y, *Tetrahedron*, 43, **2002**, 7703.
(e) Kidwai M, Sexena S, Mohan R & Venkataramanan R, *J Chem Soc, Perkin Trans I*, **2002**, 1845.
9 (a) Baruah P P, Gadhal S, Prajapati D & Sandhu J S, *Chem Lett*, 10, **2002**, 1038.
(b) Gohain M, Prajapati D & Sandhu J S, *Synlett*, **2004**, 235.
10 Folkers K, Harwood H J & Johnson T B, *J Am Chem Soc*, 54, **1932**, 3751.
11 Lu J & Bai Y, *Synthesis*, **2002**, 466.