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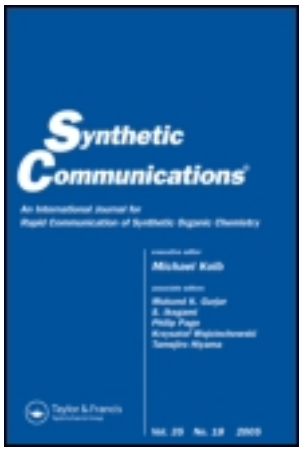

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Simple Protocol for the Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones Using $SnCl_2 \cdot 2H_2O$–LiCl as an Inexpensive Catalyst System[#]

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ABSTRACT

A one-pot synthesis of the 3,4-dihydropyrimidin-2(1H)-ones catalyzed by tin chloride–lithium chloride combination catalyst system involving three component heteroannular cyclization is reported.

Key Words: 3,4-Dihydropyrimidin-2(1H)-one; Organic transformation; Catalyst system.

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INTRODUCTION

Compounds possessing 3,4-dihydropyrimidin-2(1H)-one framework have shown promising biological activity such as calcium channel blocking, anti-hypertensive, α-**1a**-adrenergic antagonistic, etc.[1] The core structure is commonly built up by the reaction between an aldehyde, urea, and β-keto ester under acidic conditions as proposed by Biginelli in 1893.[2] This reaction was reinvestigated by Hinkle and Hey in 1929 by replacing the urea with thiourea, to give the corresponding 3,4-dihydropyrimidin-2(1H)-thione derivative under the same Biginelli conditions.[3] Of late this reaction has attracted the attention of many organic chemists. As a result several reports have appeared for the construction of the core structure by acid catalysts such as $BF_3 \cdot OEt_2$, PPE, KSF, $InCl_3$, $FeCl_3$, $LiClO_4$, $BiCl_3$, $Mn(OAc)_2$, lanthanide triflate, $ZrCl_4$, *p*-toluenesulphonic acid, etc., improving the yields on one side and retaining the simplicity of the Biginelli's approach on the other side in many cases.[4] Encouraged by the surge of catalytic processes and driven by economic factors, we focussed our attention on the development of other alternative reagents that are inexpensive, work under mild and catalytic conditions together resulting in higher yields. Guided by these points and our experience with tin(II) chloride as an excellent Lewis acid[5] for various organic transformations prompted us to explore its suitability for the three component condensation leading to dihydropyrimidin-2-one system.

Tin(II) chloride dihydrate is a well-known reducing agent for nitro and azido groups, a Lewis acid catalyst for C–C bond formation, for deoxygenation of 1,4-endo peroxides, protection of dicarboxylic acids, and as a selective agent for the cleavage of *p*-methoxy benzyl ether.[6] The efficacy of tin chloride for effective heteroannulation in a ruthenium catalyzed alkyl group transfer reaction in amines leading to indoles and quinoline is well known.[7] This property was aptly utilized very recently for the heteroannulation of 2-aminophenols to benzoxazoles.[7]

Intrigued by the role played by tin chloride in so many important organic transformations, its usefulness for the three component heteroannular cyclization was explored. The encouraging results are exhibited in Table 1. Further the co-catalyst lithium chloride could improve the yield. The yield of the condensation increased by two folds when equimolar proportion of LiCl was supplemented with $SnCl_2 \cdot 2H_2O$ in ethyl alcohol medium. The absence of tin chloride proved to be ineffective where as combination catalyst system happened to be the catalyst of choice.

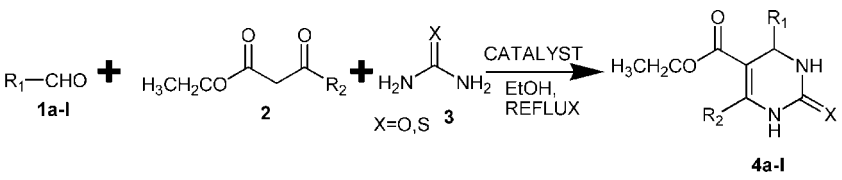

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Table 1. The efficacy of tin chloride for heteroannulation with lithium chloride as co-catalyst.

Entry	R_1	R_2	X	Yield (%)	Melting point (°C) Observed	Melting point (°C) Reported
4a	4-(OCH_3)–C_6H_4	CH_3	O	85[a]	200–202	201–202[4l]
4b	4-(CH_3)–C_6H_4	CH_3	O	80	171–172	170–172[4l]
4c	2,6-$(Cl)_2$–C_6H_3	CH_3	O	60	234–236	—
4d	4-(NO_2)–C_6H_4	CH_3	O	70	206–208	208–209[4b]
4e	4-(F)–C_6H_4	CH_3	O	70	174–176	175[4l]
4f	4-(F)–C_6H_4	CH_3	S	81	192–193	—
4g	4-(OH)–C_6H_3	CH_3	O	82	226–228	227–229[4b]
4h	Ph–CH=CH–	CH_3	O	60	230–232	232[4l]
4i	3-$(OPh)C_6H_3$	CF_3	O	88	163	—
4j	3,4-$(OCH_3)_2C_6H_2$	CH_3	O	86	175–176	177[4k]
4k	4-(OCH_3)–C_6H_4	CH_3	S	80	150–152	150[9]
4l	4-$(CH_3)C_6H_3$	CH_3	S	78	220	—

[a]Without the use of co-catalyst (lithium chloride) the yield was 45%.

An array of aldehydes, urea or thiourea with ethylacetoacetate, and ethyl trifluoroacetoacetate as β-keto esters were employed in order to investigate the scope of the reaction. The three-component reaction proceeds very smoothly in about 6–8 hr time in refluxing ethyl alcohol with 10 mol% each of tin chloride and lithium chloride providing very good yields of the products.

Reducing prowess of tin chloride in alcoholic medium has no effect on the nitro group as is evidenced by the neat product formation and no trace of corresponding amino substituted pyrimidine derivative was observed. The reagent system is found to be equally effective with thiourea, a feature unique to the catalyst system, where as many other reagents failed to give the title compounds under the same conditions. However, the acidity of the reagent system does not provide the dihyrdopyrimidin-2-one when ethyl trifluoromethylacetoacetate was used as the β-keto ester. It rather ended up in hexahydropyrimidine system as pointed out by earlier reports.[8] It is the unique electronic properties of the $-CF_3$ group coupled with the not so acidic nature of the reagent system, prevents the removal of

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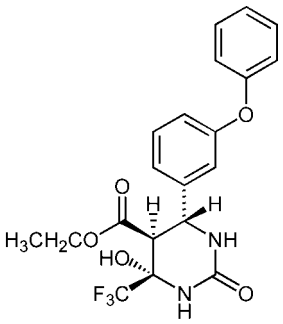
water from the hexahydropyrimidine (**4i**) to yield the dihydropyrimidin-2-one.



4i

In conclusion, we have demonstrated experimentally a simple and straightforward protocol (combination system of $SnCl_2-LiCl$) which provides dihydropyrimidin-2-one system in high yield and high purity while retaining the simplicity of the Biginelli concept. The mildness of the method together with ease of operation should largely extend the scope of this, as an alternate reagent system, which is safe and inexpensive for the three-component Biginelli reaction.

EXPERIMENTAL

General Procedure

A mixture of aldehyde (5 mmol), β-ketoester (5 mmol), urea (5 mmol), and tin(II) chloride–lithium chloride (10 mol% each) were taken in ethanol (15 mL) and refluxed for the requisite time (reaction monitored by tlc). After the completion of the reaction, ethanol was removed under reduced pressure to obtain the product in most of the cases as a solid. This solid was washed with water, filtered and purified further by recrystallisation (hot ethanol/methanol). All the yields mentioned in Table 1 are based on isolated products. Melting points are uncorrected. All the compounds were characterized thoroughly by their spectral (IR, NMR, mass) and physical data. Wherever literature examples were available the data were compared and were found to be identical with authentic samples. Analytical data for a typical example is given below.

4f: Mp192–193°C; ^{1}H NMR (200 MHz, $CDCl_3 + DMSO\text{-}d_6$): δ 1.18 (t, $J = 7$ Hz, 3H, CH_3), 2.38 (s, 3H, CH_3), 4.15 (q, $J = 7$ Hz, 2H, OCH_2),

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5.31 (s, 1H, CH), 7.05 (m, 2H, Ar), 7.45 (m, 2H, Ar), 9.22 and 9.95 (2s, 2H, NH). LRMS: 294 (M^+). Anal. Calcd. For $C_{14}H_{15}FN_2O_2S$: C, 57.14; H, 5.1; N, 9.52; S, 10.88 found. C, 57.10; H, 4.91; N, 9.42; S, 10.71.

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