

Rapid Communication

AlCl₃ mediated three component cyclocondensation for the synthesis of 5-unsubstituted 3,4-dihydropyrimidin-2(1H)-ones

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5-Unsubstituted-3,4-dihydropyrimidin-2(1H)-ones have been synthesized in excellent yields in aluminium trichloride mediated three component cyclocondensation of aldehyde, urea and enolisable ketones.

Keywords: Aluminium trichloride, potassium iodide, enolisable ketone, aldehyde, urea, 5-unsubstituted-3,4-dihydropyrimidin-2(1H)-ones

IPC: Int.Cl.⁷ C 07 D

The pyrimidine skeleton is of great importance to chemists as well as biologists as it is available in a large variety of naturally occurring compounds and also in clinically useful molecules having diverse biological activities^{1,2}. These include anticancer³ and antiviral⁴ activity. At present nine AIDS knocking agents are in clinical use, *e.g.* AZT, DDC, DDI are pyrimidine derivatives to name a few⁵ and their activity are manifested in the pyrimidine skeleton of **1a**. Another related pyrimidine framework of the **1b** type is very easily accessible *via* multicomponent coupling reactions (MCR) involving urea, active methylene compounds and aldehydes in the presence of a catalyst (**Figure 1**).

In recent years⁶, type **1b** pyrimidine scaffold has been under intensive investigation as it has a very broad pharmacological profile in the form of calcium channel blockers, antihypertensive agents and alpha-1a-antagonists⁷. Certainly this very promising biological profile bodies well for **1b** type of framework. Because of these activities several novel and efficient methods are reported for the production of this Biginelli scaffold. In these new methods, a variety of Lewis acid catalysts are employed *e.g.*

Cu(OTf)₂, La(OTf)₃, CeCl₃.7H₂O, LaCl₃.7H₂O, LiBr, ZrCl₄, InX₃(X=Cl, Br), SnCl₂.2H₂O, Mn(OAc)₃.5H₂O, RuCl₃.xH₂O, *etc.* Clearly, in these intensive studies the major focus has been on the development of new and efficient catalysts and a majority of these developments are reported to be quite fruitful⁸.

The chemistry of C₅-C₆ double bond has been extensively explored in type **1a** skeleton and several careful manipulations of this bond have lead to interesting chemistry⁹ and useful new structures. In contrast, C₅-C₆ double bond in Biginelli scaffold is relatively less explored and only a few useful transformations have been attempted¹⁰ involving very careful multistep manipulations.

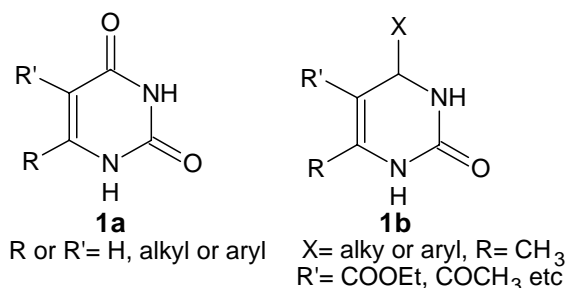
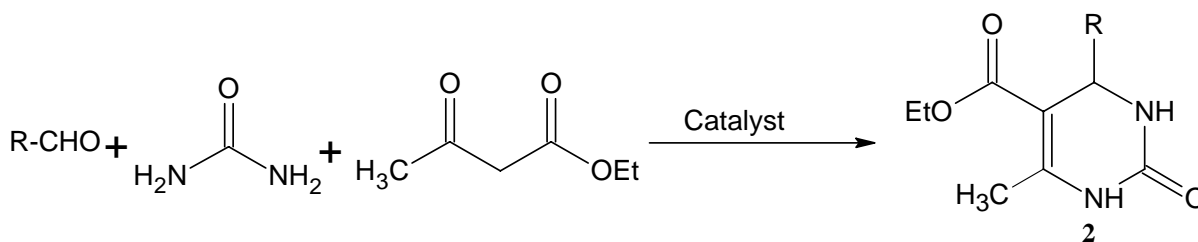


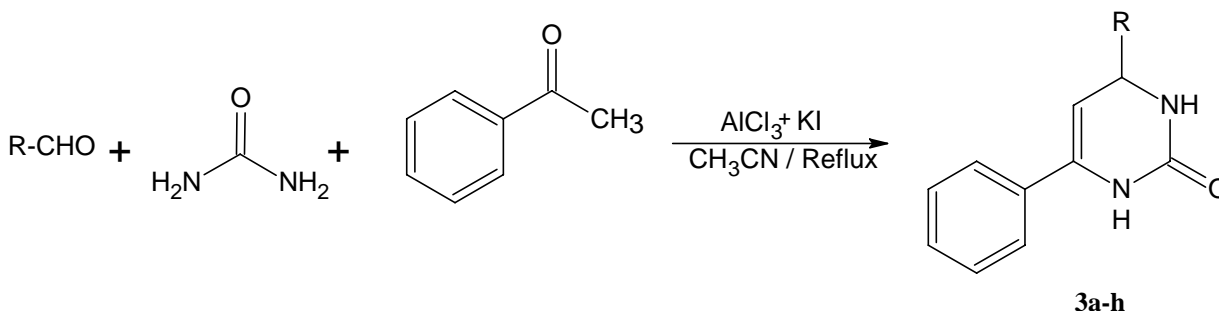
Figure 1

The poorly investigated chemistry of C₅-C₆ bond in Biginelli compounds seems to be because of difficulties faced in manipulating the methyl group at C₆ and ester group at C₅ which are traditionally placed in these positions (see classical Biginelli scaffold **2**, **Scheme I**).

Of course, there are sporadic reports¹¹ of the preparation of C₅ unsubstituted compounds. These involve complex multistep procedures, for example, one reported procedure^{11a} involves careful saponification and thermal decarboxylation which is certainly low yielding drastic step. Another method^{11e} starting from ketocarboxylic acids is equally unattractive. In continuation of the work on both the systems *viz.* **1a,b**^{9,12}, herein are reported the results of the current investigation for the facile one pot synthesis of 5-unsubstituted-3,4-dihydropyrimidin-2(1H)-ones which involves the use of enolisable ketones like acetophenone instead of 1,3-dicarbonyl compounds as used in classical Biginelli reaction and bimetal system AlCl₃ and KI (**Scheme II**).



Scheme I



Scheme II

Initial studies followed the traditional Biginelli reaction (**Scheme I**) which proceeded very smoothly affording high yields¹³ with this catalytic system. After this initial success, these conditions were applied to enolisable ketones, urea and benzaldehyde to obtain 5-unsubstituted-3,4-dihydropyrimidin-2(1*H*)-ones, **3** in 82-90% yields (see **Table I**).

The mechanistic pathway appears to involve the AlCl_3 and KI system which activates the carbonyl function, thereby making the methyl group readily enolisable, which in turn reacts with aldehyde and urea derived imine in the Michael way to produce product **3**. This view is further substantiated when TMSI is found to show some improvement in yields, which is an established carbonyl activating group.

For in-depth study and to evaluate the catalytic efficacy of various Lewis acids in this reaction some other combinations have also been tried (see **Table II**). As is clear from this data in the **Table II**, the most effective combination appears to be the AlCl_3 and KI. Other combinations either give poor yields or are completely ineffective. For example, FeCl_3 and KI produces some significant results but not as good as AlCl_3 and KI system. When $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ is utilized the reaction is complicated¹⁴ and the desired product is not obtained. So is the case with $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$. Even if KI is replaced by trimethylsilyl iodide the yields did not improve significantly. However, it seems to be a good additive.

To conclude, the present investigation describes a simple, facile and efficient single pot bimetal protocol

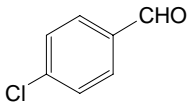
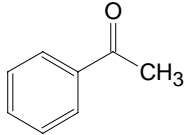
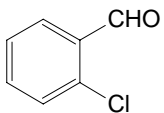
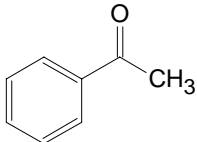
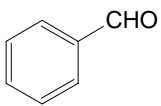
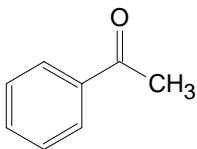
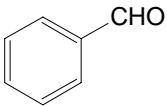
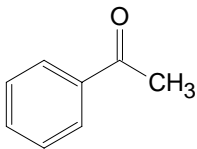
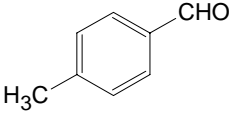
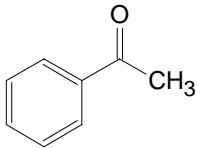
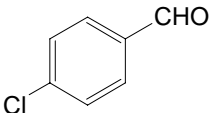
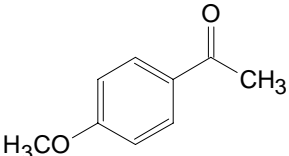
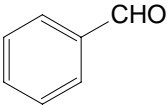
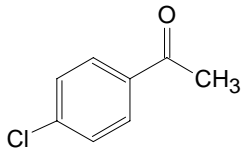
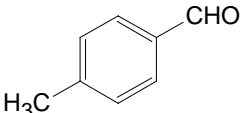
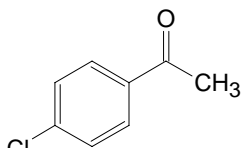
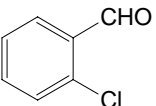
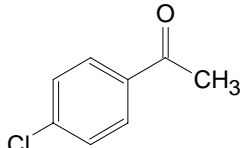
for the synthesis of 5-unsubstituted-3,4-dihydropyrimidin-2(1*H*)-ones utilising readily available and cheap commercial chemicals.

Experimental Section

Melting points were determined by using Buchi melting point apparatus and are uncorrected. IR spectra were recorded in KBr disc on a Perkin-Elmer 240C IR spectrometer. ¹H NMR spectra were recorded on a 90 MHz spectrometer (chemical shift are in δ ppm relative to TMS as internal standard reference).

General procedure for the synthesis of 4,6-diphenyl-3,4-dihydropyrimidin-2(1*H*)-ones: To a mixture of acetophenone (600 mg, 5.0 mmoles) and $\text{AlCl}_3 + \text{KI}$ (0.5 mmole, 10 mol%) in CH_3CN (25 mL) was added benzaldehyde (530 mg, 5.0 mmoles) and urea (450 mg, 7.5 mmoles). Then the reaction mixture was refluxed to complete the reaction as followed by TLC. After completion of reaction, the mixture was brought to RT and poured into ice-cold water. The crude product thus obtained was filtered and purified by recrystallization from EtOH to afford **3c** in 90% yield, m.p. 233-35°C (dec.) Lit. m.p. 235-36°C, as in ref. 14 (**Table I**, entry 3). IR (KBr): 3319, 3185, 1656 cm^{-1} ; ¹H NMR ($\text{DMSO}-d_6$): δ 8.71 (s, 1H), 7.86 (s, 1H), 7.16-7.35 (m, 10H, aromatic), 5.91 (s, 1H), 5.54 (s, 1H). The other 5-unsubstituted-3,4-dihydropyrimidin-2(1*H*)-ones **3b-h** were prepared following similar procedures and compared¹¹.

Table I—AlCl₃ mediated synthesis of 5-unsubstituted-3,4-dihydropyrimidin-2(1*H*)-ones

Entry	Compd	Aldehydes	Ketones	Yield ^a (%)
1	3a			89
2	3b			82
3	3c			90
4				0 ^b
5	3d			85
6	3e			82
7	3f			86
8	3g			84
9	3h			83

^aYields refer to pure isolated product characterized by comparison of spectral and physical data with authentic samples¹⁴^bAt RT

Table II — Synthesis of 5-unsubstituted 3,4-dihydro-pyrimidin-2(1H)-ones in presence of 0.5 mmol of different catalysts^a

Entry	Catalyst	Time (h)	Yield (%)
1	Zn+I ₂	10	n.r.
2	FeCl ₃	26	45
3	FeCl ₃ + KI	19	62
4	FeCl ₃ .6H ₂ O+KI	10-12	n.r.
5	AlCl ₃ .6H ₂ O	16	n.r. ^b
6	AlCl ₃	14	58
7	AlCl ₃ + KI	6-7	90
8	AlCl ₃ + TMSI	6-7	92

n.r. - negligible/no reaction

^aAcetophenone (5 mmole), urea (7.5 mmole), benzaldehyde (5 mmole), CH₃CN, reflux

^bComplex mixture

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