J. Chem. Sci. (2018) 130:151
https://doi.org/10.1007/s12039-018-1543-z

REGULAR ARTICLE

Iron(III)-catalyzed selective direct olefination of dihydropyrimidinone with aromatic aldehyde

MOHABUL A MONDAL[a,b,*], ABDUL ASHIK KHAN[b] and KANCHAN MITRA[b]
[a]Department of Chemistry, Jadavpur University, Kolkata, West Bengal 700 032, India
[b]Department of Chemistry, University of Gour Banga, Malda, West Bengal 732 103, India
E-mail: mohabula.mondal@jadavpuruniversity.in

MS received 28 May 2018; revised 3 August 2018; accepted 20 August 2018; published online 30 October 2018

Abstract. Herein, we describe a practical approach for direct vinylogous aldol condensation of Biginelli product for carbon–carbon double bond formation at methyl group of 6-methyl dihydropirimidinone by using hydrated ferric chloride. With aromatic aldehydes, the method yields stereoselectively *trans* products. The olefination reaction is applicable with aldehyde without chelating (with Fe III) functional group. DHPMs with carboxylate ester and arylidene at C-6 methyl are not known. The method opens up a new avenue for the synthesis of a wide variety of DHPMs. The olefin products were subjected to dihydroxylation reaction.

Keywords. C6-olefination of DHPMs; vinylogous aldol condensation; ferric chloride; dihydropyrimidinones.

1. Introduction

Dihydropyrimidin-2(1*H*)-ones (DHPMs) are one of the most attended heterocyclic compounds in medicinal chemistry owing to its wide pharmacological properties. Modified DHPMs are evaluated as inhibitor of Hsp90 C-terminal domain for tuning cellular signaling[1]; exploited against pathogens (bacteria,[2] virus,[3] fungus,[4] parasite[5]), as anti-inflammatory agent,[6] and as calcium channel antagonism/inhibition.[7] Apart from that DHPMs are used as antimuscarinic,[8] acetylcholinesterase,[9] antithyroid,[10] antidiabetic,[11] $GABA_A$ agonism,[12] tyrosinase inhibition,[13] and carbonic anhydrase.[14] Wide application of the DHPMs in the medicinal chemistry promoted extensive research on the modification[15] of the DHPM since the discovery of the product by Biginelli[16] in 1893. Most of the reports describe modification[17] at either N1 or C2 oxygen or N3 or the aromatic ring present at C4 of the DHPM (Figure 1). The modification at C5 also known through conjugation of carboxylate group to the other bioactive scaffolds. Modification at C-6 methyl is most challenging as it is comparatively less reactive.

Reported functionalization at C-6 methyl involves bromination followed by desired modification from the bromo derivatives (**2**).[18] Most common modifications of dibromide (**2b**) involve treatment of hydrazine to pyridazone fused bicyclic compound,[19] NaN_3/HMPA to C-6 nitrile group, NaN_3 to construct tetrazole at C-6,[20] AgOAc to carboxyaldehyde at C-6.[19] Direct functionalization at C-6 is extremely rare. Reported direct functionalizations at C-6 methyl group are regioselective chlorination,[21] monobromination,[18] nitrolic acid synthesis on the treatment of nitric acid.[22] Regioselective deprotonation at C-6 on the treatment of excess strong base such as LDA followed by attachment of electrophile might be another general and alternative path for C-6 functionalization.[23] Direct oxidation with SeO_2 resulted in poor (10%) yield of C-6 carbaldehyde.[24] On the other hand, DHPMs are unreactive under direct aqueous base catalyzed condensation reaction onto **1a**.[25] In some cases, overheating and lengthy reaction time led to usual product formation.[26] In 2014, Zhang and co-workers reported that direct vinylogous aldol condensation is not suitable for DHPM **1** having ester functional group.[27] To the best of our knowledge, there was no report for direct vinyl analogue aldol on compound **1**. As the esters in **1** are easy to modify and **1** is readily available, it is desirable to get C-6 modification directly by olefination. To our knowledge,

*For correspondence

Electronic supplementary material: The online version of this article (https://doi.org/10.1007/s12039-018-1543-z) contains supplementary material, which is available to authorized users.

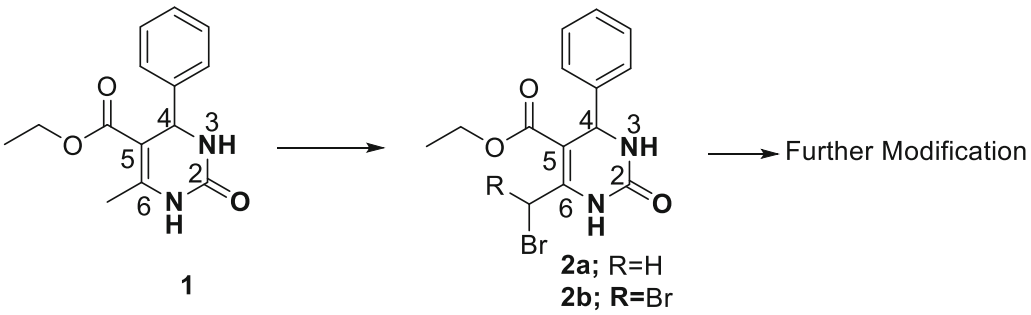
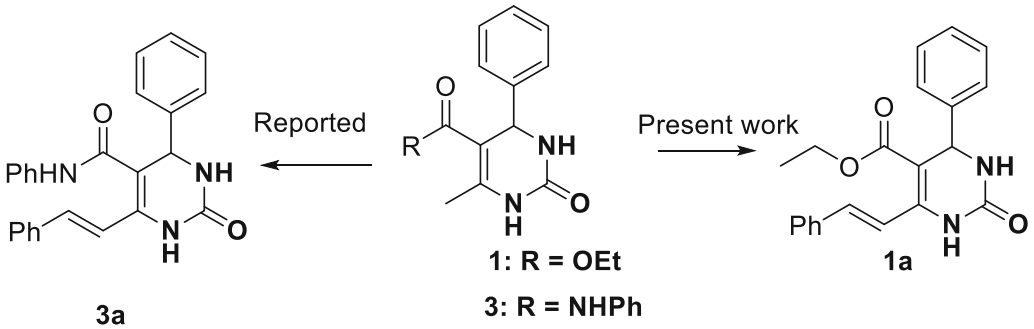


Figure 1. Chemical modification of the Biginelli product.



Scheme 1. Olefination of C-6 methyl group of DHPMs.

only **1a** is known and the reported procedure involves Biginelli type condensation of cinnamoylacetoacetic ester with urea and benzaldehyde.[25] The compound **1a** was also observed as a side product during synthesis of **1** in the presence of *p*-toluene sulphonate as a catalyst in xylene from benzaldehyde, ethyl acetoacetate and urea. However, attempt to synthesize compound **1a** from **1** was unsuccessful.[28] Moreover, the behavior of DHPM towards aqueous base is not generalized.[26] Herein, we report the study on the direct formation of compound **1a** from easy accessible Biginelli product **1** in presence of $FeCl_3{\cdot}6H_2O$ and excess aldehyde as a useful method (Scheme 1). Except for **1a** all other compounds mentioned here are not reported before. Furthermore, the aldol condensation product was subjected to dihydroxylation to make diol at the double bond. All the compounds are characterized by LCMS and ^{1}H NMR successfully.

2. Experimental

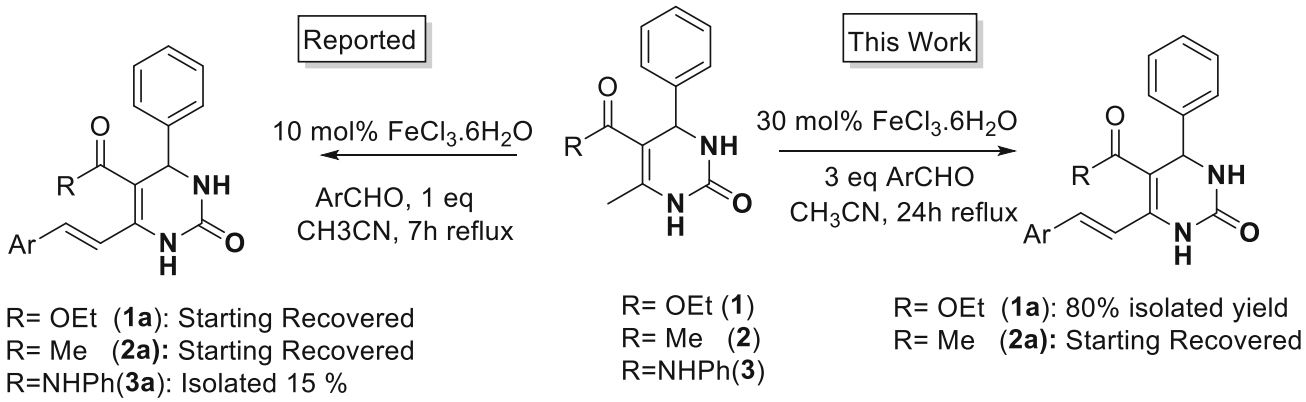
2.1 *Materials and physical measurements*

Commercially available reagents were used without further purification. All the reactions were monitored by TLC (TLC Silica Gel 60 F254) and it was observed under UV light (254 nm). Yields refer to the isolated product, as mentioned in the experimental section, after column chromatographic purification. ^{1}H-NMR data were obtained using a Bruker 400 MHz spectrometer in DMSO-D_6 solution. Melting points were measured on Instrument India melting point apparatus using an open capillary tube and are corrected with standard benzoic acid. Mass Spectrometry was done on LCMS using ZORBAX EXT (4.6 × 50 mm, 5μ) column, NH_4OAc (10 mM): CAN::90:10 for liquid chromatogram.

2.2 *Experimental procedure for the synthesis of ethyl (E)-2-oxo-4-phenyl-6-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1a**)*

Ferric chloride hexahydrate (78 mg, 0.28 mmol) was added to a mixture of ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (250 mg, 0.96 mmol) and benzaldehyde (306 mg, 2.88 mmol) in 10 mL acetonitrile, and refluxed for 24 h. After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with water (50 mL) when crude product separated out from the mixture as brown solid. The crude product, isolated by filtration was purified by column chromatography to get desired product **1a** as light yellow solid (268 mg, 0.77 mmol, 80%).

M.p.: 210–212 °C; ^{1}H-NMR (400 MHz, DMSO-d_6,): 9.22 (s, 1H); 7.93 (d, J = 16 Hz, 1H); 7.85 (m, 1H); 7.50–7.28 (m, 11H); 5.26 (bs, 1H); 4.06 (q, J = 8 Hz, 2H); 1.15 (t, J = 8 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6,): 156.6, 152.9, 145.1, 144.7, 136.4, 135.2, 129.5, 129.4, 128.9, 127.9, 127.5, 126.7, 120.0, 101.4, 60.3, 54.4, 14.5; **LCMS:** Calculated MS 349.15 for $C_{21}H_{21}N_2O_3[MH]^+$, Found m/z = 349.2 $[MH]^+$



Scheme 2. Olefination at C-6 methyl position of DHPMs.

Table 1. Optimization of the method under different reaction conditions.

Entry	Catalyst (30 mol%)	Solvent	Time	Heating	Isolated yield
1	Anh. $FeCl_3$	Anh. acetonitrile	24	Reflux	Trace
2	$Y(NO_3)_3{\cdot}6H_2O$	Acetonitrile	24	Reflux	No reaction
3	NaOH	Acetonitrile	5	Reflux	Complex
4	$FeCl_3{\cdot}6H_2O$	Acetonitrile	24	Reflux	80% pdt isolated
5	Conc. HCl	Neat	4	Reflux	Complex
6	L-proline	Methanol	12	Reflux	No reaction
7	$FeCl_3{\cdot}6H_2O$	THF	24	Reflux	Trace
8	$FeCl_3{\cdot}6H_2O$	DMF	24	120 °C	No reaction
9	$FeCl_3{\cdot}6H_2O$	DMSO	24	120 °C	No reaction
10	$FeCl_3{\cdot}6H_2O$	Methanol	24	Reflux	No reaction
11	$FeCl_3{\cdot}6H_2O$	Ethanol	24	Reflux	No reaction
12	$FeCl_3{\cdot}6H_2O$	Water	24	Reflux	No reaction
13	$FeCl_3{\cdot}6H_2O$	Neat heat at 120 °C	24	120 °C	No reaction

a. Reactions are monitored by TLC.
b. All the reactions are carried out with 1 equivalent DHPMs, 3 equivalent benzaldehyde, 30 mol% $FeCl_3.6H_2O$.

^{1}H NMR of **1a** is known and exactly matched with the reported data.

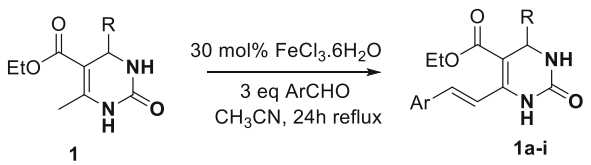
Other compounds (**1b**–**k**) are synthesized according to **1a** and the spectroscopic data are available with this article in the supporting information section.

3. Results and Discussion

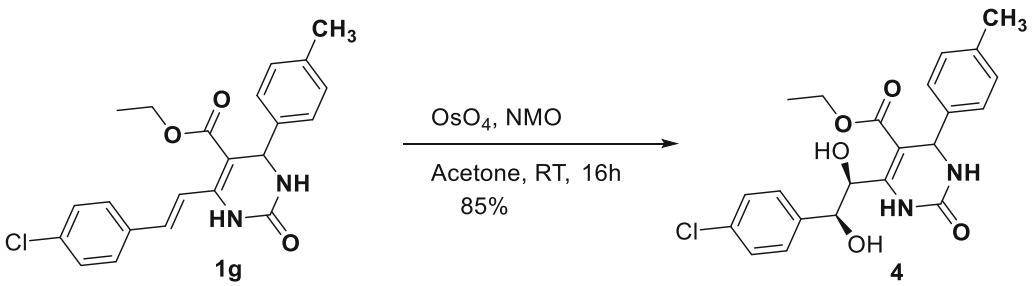
In continuation of our present study towards the synthesis of modified DHPMs *via* C-6 methyl functionalization, we have selected the reported procedure[27] vinyl analogue aldol reaction of **1** with an aromatic aldehyde in presence of $FeCl_3{\cdot}6H_2O$ for initial study (Scheme 2). According to the report, isolation of desired compound **1a** from the compound **1** was unsuccessful in presence 10 mol% catalyst and one equivalent aldehyde under reflux for 7 h. We observed similar results as mentioned in the report for the substrate **2** and **3**. However, we found that the presence of excess aldehyde (3 equivalent) and 30 mol% $FeCl_3$ loading under refluxing condition for 24 h, compound **1** gave desired product **1a** in good yield (Scheme 2).

Once having encouraging result, we have carried out screening of different reaction conditions with the substrate **1** and benzaldehyde. Results are summarized in Table 1. Surprisingly, anhydrous $FeCl_3$ fails to give desired product in dry acetonitrile. This indicates that water molecule have certain role in the catalytic process. While the water stable mild Lewis acid $Y(NO_3)_3 \cdot 6H_2O$ was unable to give product **1a** as mentioned in Table 1. Aqueous NaOH or HCl resulted in complex reaction mixture from which desired product **1a** could not be isolated. DHPM ring opening is the major reaction pathway. Common organic solvents like THF, DMF, DMSO, methanol, ethanol and water were not suitable for the reaction (Table 1, entry 7–12). The method is not suitable at room temperature as the substrate **1** is

Table 2. $FeCl_3.6H_2O$ catalyzed vinyl analogues aldol reaction of DHPMs.



Entry	Aldehyde	R	Product	Yield
1	Benzaldehyde	Ph	**1a**[25]	80
2	4-Bromobenzaldehyde	Ph	**1b**	70
3	4-Chlorobenzaldehyde	Ph	**1c**	66
4	2-Chlorobenzaldehyde	Ph	**1d**	72
5	4-Methylbenzaldehyde	Ph	**1e**	58
6	4-Bromobenzaldehyde	4-Bromophenyl	**1f**	61
7	4-Chlorobenzaldehyde	4-Methlphenyl	**1g**	63
8	4-Methylbenzaldehyde	4-Methlphenyl	**1h**	63
9	4-Methylbenzaldehyde	4-Chlorophenyl	**1i**	67
10	4-Methoxybenaldehyde	4-Methlphenyl	**1j**	63
11	Benzaldehyde	4-Chlorophenyl	**1k**	58
12	3-Nitrobenzaldehyde	Ph	**No reaction**	
13	4-hydroxybenzaldehyde	Ph	**No reaction**	
14	3-Pyridinecarboxaldehyde	Ph	**No reaction**	



Scheme 3. Dihydroxylation of the **1g**.

not soluble in acetonitrile. Best result could be obtained from hydrated ferric chloride in CH_3CN under refluxing condition, as mentioned in Scheme 2.

With this optimized condition, we have studied the substrate scope of the method. Best result obtained from **1a** and benzaldehyde. Product **1a** was isolated by column chromatography in 80% yield. Reaction with substituted benzaldehyde (entry 2–5, Table 2) gave moderate yield. However, 3-nitrobenzaldehyde, 4-hydroxybenzaldehyde and 3-Pyridinecarboxaldehyde do not react under this condition. All cases (entry 12–14, Table 3), starting **1** was recovered after 24 h reflux in acetonitrile. This was attributed to complexation of a Fe^{3+} ion with the functional group of the aldehyde instead off activation of DHPM. Careful analysis of the products (**1a–k**) by ^{1}H-NMR ($J = \sim 16$ Hz) indicate that newly formed double bond is in *trans* form.

The product **1a** is known and the synthetic procedures are different from the one described here. New compounds (**1b–k**, Table 2) are characterized by ^{1}H-NMR and LCMS and found to be supportive and sufficient for identification.

Products **1a–i** could be used for synthesizing a large number of structurally different DHPMs for pharmaceutical use. For instance, we have carried out dihydroxylation of the product **1g** using OsO_4 in presence of NMO in acetone and observed the product **4** as shown in Scheme 3.

4. Conclusions

In conclusion, direct vinylogous aldol condensation reaction with hydrated ferric chlorides was successful under 30 mol% catalyst and excess use of aldehyde (typically 3 equivalents). Higher catalyst concentration reduces reaction time. Here, we have reported 10 (**1b–k**) new compounds with sufficient spectral information. The method is applicable for aldehyde without

a chelating functional group at aldehyde component. Further study in this regard is required to generalise. The reported compounds may be used for synthesizing a large number of highly demanding DHPMs. We studied dihydroxylation reaction on C-6 olefin containing DHPM with OsO_4 and observed dihydroxylation product. Further progress in this regards is underway in our laboratory.

Supplementary Information (SI)

The supplementary information contains an experimental procedure for other compounds, spectroscopic data and spectra (NMR and LCMS). They are available at www.ias.ac.in/chemsci.

Acknowledgements

We thank the SERB New Delhi, for financial support under EMR scheme (EMR/2014/000542).

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