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$Mn(OAc)_3 \cdot 2H_2O$-mediated three-component, one-pot, condensation reaction: an efficient synthesis of 4-aryl-substituted 3,4-dihydropyrimidin-2-ones

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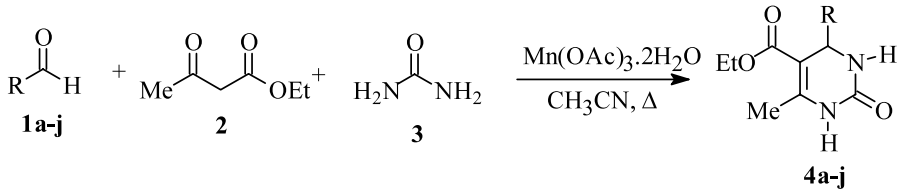
Abstract—4-Aryl-substituted 3,4-dihydropyrimidin-2-ones are synthesized in high yields by one-pot cyclocondensation reactions of aldehydes, β-ketoesters and urea using a catalytic amount of manganese acetate in refluxing acetonitrile.

Over the past decade, dihydropyrimidinones (DHPMs), an important class of compounds,[1–9] have become increasingly significant due to their therapeutic and pharmacological properties.[1] They have emerged as integral backbones of several calcium channel blockers, antihypertensive agents and alpha-la-antagonists.[2] Synthetic strategies for the synthesis of the dihydropyrimidinone nucleus involve both one-pot and multi-step approaches. Furthermore, several marine alkaloids with interesting biological activities containing the dihydropyrimidine-5-carboxylate core unit have recently been isolated.[3] Most notably among these are the batzelladine alkaloids, which were found to be potent HIV gp-120-CD4 inhibitors.[4]

At present, several general methods for the preparation of dihydropyrimidinones are known,[1b,5–8] including various solid-phase modifications suitable for combinatorial chemistry.[9] The most simple and straightforward procedure, first reported by P. Biginelli in 1893, involves the one-pot condensation of a β-ketoester with an aldehyde and urea under strongly acidic conditions, but often suffers from low yields, particularly for substituted aromatic aldehydes.[1,5,6] Several modifications and improvements have been sought. Although high yields can be achieved by the following complex multistep procedures, these methods lack the simplicity of the original, one-pot, Biginelli protocol.[9a,10] The recently reported $BF_3 \cdot OEt_2$ or polyphosphate ester-mediated Biginelli reactions[11] require long reaction times (~18 h) to achieve moderate to high yields of the products. More recently, KSF[12] has also been employed for this transformation but involves a longer reaction time (10–48 h) to obtain good yields. In spite of their potential utility, some of the reported methods suffer from drawbacks such as long reaction times, low yields and cumbersome product-isolation procedures.

In this communication, we describe a simple but effective modification of the Biginelli reaction that produces high yields of the desired dihydropyrimidines while preserving the original one-pot strategy. The reaction of benzaldehyde, ethyl acetoacetate and urea in the presence of a catalytic amount of manganese(III) acetate in refluxing acetonitrile resulted in the formation of dihydropyrimidinone in 96% yield (Scheme 1).



Scheme 1.

Keywords: Biginelli reaction; aldehydes; β-ketoester; pyrimidinones.

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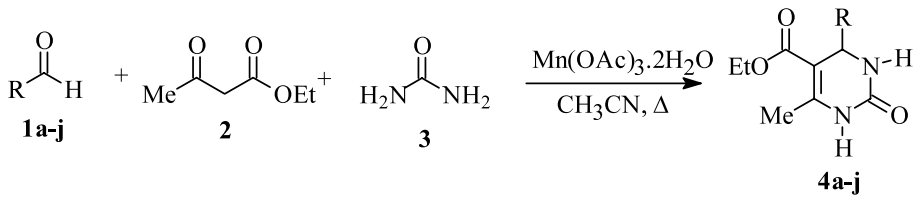
Similarly, various aromatic aldehydes reacted well under the same conditions to give the corresponding dihydropyrimidines in moderate to excellent yields (Table 1). The three-component condensation reactions proceeded smoothly in refluxing acetonitrile and were also completed within 2–4 h. Under these conditions, the yields were significantly increased, to 75–96% for the classical Biginelli method, and the reaction time was shortened from 18 to 2–4 h. Many pharmacologically relevant substitution patterns on the aromatic ring could be introduced with high efficiency. Most importantly, aromatic aldehydes carrying either electron-donating (**4d** 82%, **4e** 94% yield) or electron-withdrawing (**4b**, **4c**, **4h**, **4i** and **4j**) substituents all reacted very well, giving moderate to excellent yields.

Aldehydes containing electron-donating groups afforded highly pure compounds after work-up of the reaction. Several examples illustrating this novel and general method for the synthesis of dihydropyrimidines are summarized in Table 1. The inorganic reagent used in this reaction as a catalyst is inexpensive, easily available and highly efficient for this transformation. The reaction may proceed through the acylimine intermediate (formed in situ by reaction of the aldehyde with urea), which is stabilized by the manganese ion, and the subsequent addition of the β-ketoester enolate to the acylimine, followed by cyclization and dehydration, affords the corresponding dihydropyrimidines (Scheme 2).

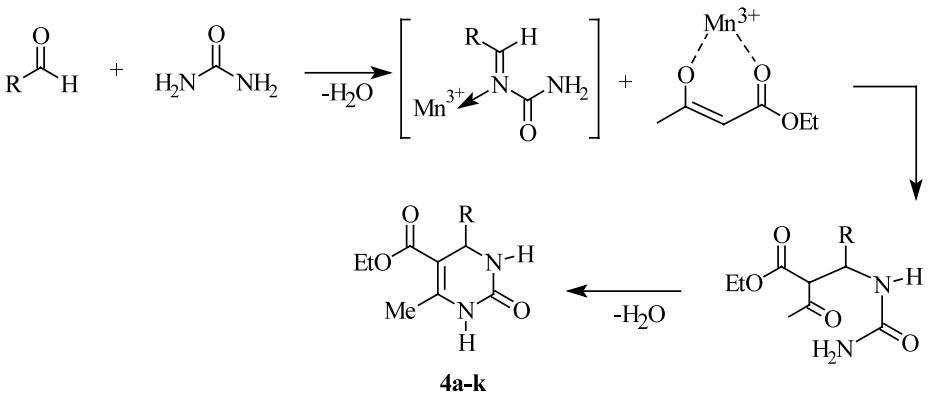
In conclusion, we have described a simple modification of the Biginelli dihydropyrimidine synthesis by using $Mn(OAc)_3$ as the catalyst in refluxing acetonitrile. The yields of the one-pot Biginelli reaction can be increased to 75–96% while the reaction time is shortened from 18–48 to 2–4 h by this procedure. The adopted proce-

Table 1. $Mn(OAc)_3{\cdot}2H_2O$-mediated efficient synthesis of dihydropyrimidin-2-ones[a]



DHPMs	Substrate (R)	Time (h)	Yield (%)	Mp (°C)	
				Found[b]	Reported
4a	C_6H_5	2.0	96	203–205[c]	202
4b	4-(Cl)-C_6H_4	3.5	78	210–212[e]	213
4c	3-(NO_2)-C_6H_4	4.0	75	227–228[d]	226
4d	2,4-($OMe)_2$-C_6H_3	3.0	82	158–160[d]	–
4e	3,4-($OMe)_2$-C_6H_3	3.5	94	174–176[c]	177
4f	4-(OH)-3-(OMe)-C_6H_3	4.0	76	103–105[c]	–
4g	3-(OH)-4-(OMe)-C_6H_3	3.0	85	98–100[d]	–
4h	2-(Cl)-C_6H_4	2.5	76	214–215[d]	214
4i	2-(NO_2)-C_6H_4	4.0	77	206–208[c]	–
4j	4-(OH)-C_6H_4	4.0	79	227–228[c]	227

[a] All products were characterized by IR and ^1H NMR spectroscopy and also by comparison of physical characteristics with authentic samples.
[b] Recrystallized from:
[c] isopropanol;
[d] ethyl alcohol;
[e] ethyl acetate.



Scheme 2.

dure is convenient, involves simple experimental procedure and product isolation; hence, it is a useful addition to the existing methods.

1. Experimental

Melting points were determined using a Mel-Temp. apparatus in open capillary tubes and were uncorrected. The IR spectra were obtained on a Perkin–Elmer Spectrum instrument at 1000 units. ^{1}H NMR spectra were recorded on a Varian Gemini 2000 MHz spectrometer using TMS as an internal standard in DMSO-d_6.

1.1. General procedure for the synthesis of dihydropyrimidin-2-one: for representative compound 4a

A mixture of stoichiometric amounts of benzaldehyde, ethyl acetoacetate, urea and a catalytic amount of manganese(III) acetate dihydrate in acetonitrile (15 ml) was stirred under reflux for the appropriate time (Table 1). After completion of the reaction, as indicated by TLC analysis, the solvent was evaporated, dried and washed with water and the resulting solid compound was filtered under suction and recrystallized from isopropanol to afford the pure product **4a**.

1.2. Spectroscopic data for compound 4a

Solid, mp 203–205°C (isopropanol), yield 96% (lit.,[5] mp 202°C); IR (KBr): ν 3242, 3116, 1725, 1700, 1647 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.12 (t, 3H, J=7.5 Hz, CH_3), 2.28 (s, 3H, CH_3), 4.03 (q, 2H, J=7.5 Hz, OCH_2), 5.17 (d, 1H, J=3.0 Hz, H-4), 7.22–7.41 (m, 5H, H_{arom}), 7.78 (brs, 1H, NH), 9.22 (brs, 1H, NH).

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