Phosphotungstic acid catalysed one-pot synthesis of 5-alkoxycarbonyl-4-aryl-3,4-dihydropyrimidin-2-ones

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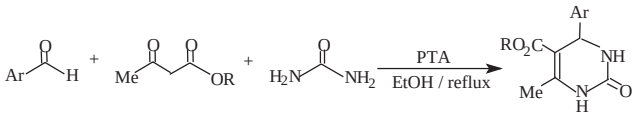
5-Alkoxycarbonyl-4-aryl-3,4-dihydropyrimidin-2-ones are synthesised by the one-pot reactions of aldehydes, β-ketoesters and urea using a catalytic amount of phosphotungstic acid (PTA) in ethanol. The modified Biginelli cyclocondensation not only shortens the reaction period and simplifies the operation, but also improves the yields.

Keywords: Biginelli reaction, dihydropyrimidinones, phosphotungstic acid, synthesis

Many dihydropyrimidinones exhibit a wide range of biological activities such as antiviral, antimicrobial, antitumor, and anti-inflammatory effects.[1] They have emerged as the integral backbones of several calcium channel blockers, antihypertensive agents and α_{1a}-antagonists.[2] Furthermore, several alkaloids containing the dihydropyrimidine core unit have been isolated from marine sources, which also exhibit interesting biological properties.[3] Most notable among these are the batzelladine alkaloids which have been found to be potent HIVgp-120-CD4 inhibitors.[4] Strategies for the synthesis of the dihydropyrimidinone nucleus have varied from one-pot to multistep approaches. The simple and direct method, originally reported by Biginelli for the synthesis of dihydropyrimidinones often suffers from low yields of products in the cases of substituted aromatic and aliphatic aldehydes.[5] Subsequent multi-step synthesis produced somewhat higher yields but these lack the simplicity of the original one-pot Biginelli procedure.[6] Therefore, the Biginelli reaction continues to attract the attention of researchers in the hope of discovering a milder and efficient procedure for the synthesis of dihydropyrimidiones. Within the past few years, several modified and improved procedures for the one-step synthesis of dihydropyrimidiones have been published. Hu and Kappe[7] reported the use of BF_3•Et_2O/CuCl and PPE (polyphosphate ester)-mediated reagents which gave moderate to high yields of dihydropyrimidinones, but these reactions required long reaction times (15–18h). More recently, montmorillonite KSF[8] has also been employed for the transformation but again needs a long reaction time (10–48h) to obtain good yields. There are many other methods for the synthesis.[9-16] However, in spite of their potential utility, these techniques all suffer from drawbacks such as long reaction time, low yields and cumbersome product-isolation procedures.

In recent years, heteropoly acids (HPA) have proved to be practical and useful catalysts in a variety of organic reactions.[17] HPA are superior to common inorganic acids for their high reactivity, ease of handling, low cost, lack of odour, non-volatility and excellent stability. This prompted us to investigate their use in the synthesis of dihydropyrimidinones from aldehydes with γ-ketoesters and urea. In this manuscript, we wish to report a general and practical route for the Biginelli cyclocondensation reaction in the presence of phosphotungstic acid (PTA) [Scheme 1].

In order to be able to carry out such Biginelli condensations in a faster and more efficient way, we investigated the influence of several catalysts including hydrogen chloride and various heteropoly acids to promote the model condensation reaction between benzaldehyde (**1a**), ethyl acetoacetate (**2**, R=Et) and urea (**3**) in boiling ethanol. The results are shown in the Table 1 from which it can be seen that PTA proved to be the most effective catalyst and was far superior to HCl. In further experiments, we examined the effects of the solvent



1 **2** **3** **4**

Scheme 1

Table 1 Studies on the model Biginelli reaction[a]

Catalyst[b]	Solvent	Yield (%)
HCl	EtOH	54
STA	EtOH	91
PMA	EtOH	92
PTA	EtOH	94
PTA	MeCN	80
PTA	C_6H_5Me	67
PTA	H_2O	62

[a]Reaction between **1a, 2** (R=Et) and **3**.
[b]STA– silicotungstic acid; PMA– phosphomolybdic acid; PTA– phosphotungstic acid.

medium; these results are also shown in Table 1 from which we conclude that ethanol is the most suitable solvent.

Subsequently, the treatment of a series of substituted aryl aldehydes, β-ketoesters and urea gave the corresponding dihydropyrimidinones under our preferred conditions and the experimental results are summarised in Table 2. These cyclocondensations proceeded smoothly in refluxing ethanol and can be accomplished within 2–4.5 hours. Many pharmacologically relevant substitution patterns on the aromatic ring could be introduced with good yields. Some aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents also reacted well and gave the corresponding products in moderate to excellent yields. Compared with the classical Biginelli method, the procedure not only preserves the simplicity of the process but also gives the products in good to excellent yields and the reaction time is shortened.

In conclusion, the use of phosphotungstic acid (PTA) in ethanol is proposed for the synthesis of Biginelli dihydropyrimidinones and their derivatives.

Experimental

^{1}H NMR spectra of the products were measured on a Bruker 400 (400 MHz) spectrometer using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal reference. Infrared spectra were reported on a Perkin-Elmer 983G spectrometer (KBr). Melting points were determined using a XT4 melting point apparatus and were uncorrected.

General procedure for the synthesis of dihydropyrimidinones: A mixture of ethyl acetoacetate or methyl acetoacetate (5.5 mmol), aldehyde (5 mmol) and urea (10 mmol) in ethyl alcohol (10 ml) was heated under reflux in the presence of phosphotungstic acid (4 mol%) for the appropriate time (Table 2). The progress of the reaction was monitored by thin layer chromatography (TLC). After the reaction was completed, the mixture was cooled to room temperature and poured onto crushed ice. The solid was filtered off, washed with ice-cold water,

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Table 2 Synthesis of 3,4-dihydropyrimidin-2-ones catalysed by PTA

Product	Ar	R	Time /h	Yield[a] /%	M.p./°C Found	Lit.
4a	C_6H_5	Et	3.0	94	203–205	202.4[18]
4b	4-$Me_2NC_6H_4$	Et	3.0	87	255–258	256–258[18]
4c	4-$CH_3OC_6H_4$	Et	3.0	78	201–203	201–202[18]
4d	4-HOC_6H_4	Et	4.5	83	228–230	227–229[18]
4e	2-HOC_6H_4	Et	4.0	53	201–202	201–202[18]
4f	3,4-$(OCH_2O)C_6H_3$	Et	5.0	69	186–188	187–188[18]
4g	4-ClC_6H_4	Et	4.0	89	212–214	213–215[6]
4h	3-ClC_6H_4	Et	4.0	70	190–192	192–193[9]
4i	2-ClC_6H_4	Et	4.0	61	217–219	215–218[7]
4j	4-$O_2NC_6H_4$	Et	4.0	64	207–209	207–208.5[18]
4k	3-$O_2NC_6H_4$	Et	3.0	84	226–228	226–227.5[18]
4l	2,4-$Cl_2C_6H_3$	Et	2.0	88	248–250	248–250[14]
4m	4-HO-3-$MeOC_6H_3$	Et	4.5	69	232–234	232–233[18]
4n	C_6H_5	Me	3.0	75	209–212	209–212[6]
4o	4-$CH_3OC_6H_4$	Me	3.0	72	191–193	192–194[6]
4p	4-ClC_6H_4	Me	4.5	85	205–208	204–207[6]
4q	2,4-$Cl_2C_6H_3$	Me	2.5	74	242–244	242–244[19]
4r	4-$O_2NC_6H_4$	Me	3.0	86	235–238	235–237[6]

[a]Yields refer to isolated products.

and then recrystallised from ethanol (95%). All the products were known compounds and were characterised by IR, ^{1}H NMR spectral data and melting points. Spectroseohie data for 4b are given below:

4b: IR ν_{max}: 3420, 3242, 3120, 2976, 1710, 1650, 1530 cm^{-1}; ^{1}H NMR: δ_H 7.67(1H, s, NH-1), 7.20(2H, d, *J**=8.4Hz, Ar-2/6), 6.67(2H, d, *J**=8.4Hz, Ar-3/5), 5.45(1H, s, NH-3), 5.33(1H, s, H-4), 4.09(2H, q, *J*=6.8Hz, $CH_3\mathbf{CH_2}$), 2.95(6H, s, $(CH_3)_2N$), 2.35(3H, s, CH_3), 1.21(3H, t, *J*=6.8Hz, $\mathbf{CH_3}CH_2$). (For the AA 'xx' system J* = J_{23} + J_{25})

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