Pentafluorophenylammonium triflate (PFPAT): an efficient, practical, and cost-effective organocatalyst for bigginelli reaction

Samad Khaksar, Roshanak Najafi Moghaddamnejad

Chemistry Department, Ayatollah Amoli Branch, Islamic Azad University, Amol, Iran

Abstract A simple, inexpensive, environmentally friendly and efficient route for the synthesis of 3,4-dihydropyrimidin-2(1H)-one derivatives via the one-pot three-component Biginelli reaction using pentafluorophenylammonium triflate (PFPAT) as a catalyst is described. PFPAT organocatalyst is air-stable, cost-effective, easy to handle, and easily removed from the reaction mixtures.

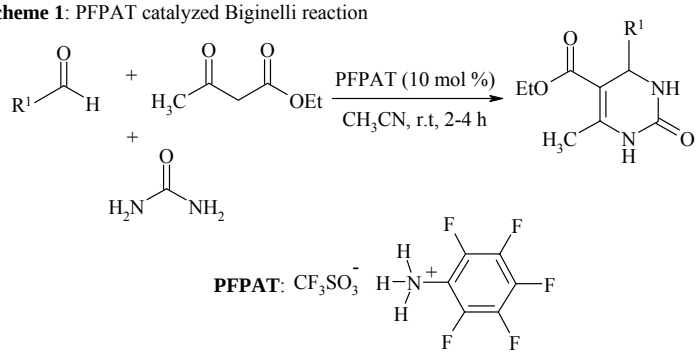
Keywords: Pentafluorophenylammonium triflate**,** Organocatalyst, Acidity**,** 3,4-dihydropyrimidin-2(1H)-one**,** Biginelli

Introduction

3,4-Dihydropyrimidine-2-(1*H*)-ones (DHPMs) have received considerable attention in recent times because of their applications as antiviral, antibacterial, antitumor, and antihypertensive agents, α-1a- adrenergic antagonists and neuropeptied Y (NPY) antagonists, and furthermore, these compounds have emerged as the integral backbones of several calcium channel blockers [1–6]. Some marine alkaloids containing the dihydropyrimidine core unit show interesting biological properties; batzelladine alkaloids have been found to be potent HIV gp-120-CD4 inhibitors [7–9]. Moreover, the 3,4-DHPMs motif is present in many products isolated from natural material such as several species of sponges. The representatives such as batzelladines, ptilomycalines and crambescidines [10] exhibit many biological activities such as anticancer, antifungal, anti HIV etc. In order to improve the yield of dihydropyrimidinones, a few other multistep approaches using aldehyde [11] or acetoacetate [12] equivalents in modified Biginelli reactions have been developed. Nevertheless, the original Biginelli reaction offers the most simple, cost-effective and reasonable access to these important compounds. Despite the usefulness of the Biginelli reaction, the efficiency of this method is considerably limited due to the strongly acidic and harsh reaction conditions. Recently, many synthetic methods for preparing these compounds have been developed to improve and modify this reaction by microwave [12–16] and ultrasound irradiation [17–19] and by using Lewis acids as well as Brønsted acids promoters. $FeCl_3$/tetracthyl orthosilicate [20], triflates [21,22], metal bromide [23,24], polyoxometalate [25], strontium(II) nitrate [26], cerium(III) chloride [27], Li(OTf) [28], $Ln(OTf)_3$ [29], heteropoly acids [30–34], ion exchange resins, polymer based solid acid [35,36], l-proline [37,38], chiral phosphoric acid [39], TMSCl [40], hexaaquaaluminium(III) tetrafluoroborate [41] and and use of ionic liquids [42-43] were used to replace the strong protic acid used in the classic Biginelli reaction. Although these methods are quite satisfactory, many of them employed considerable amounts of hazardous organic solvents either for carrying out the reactions or for extraction and purifications (column chromatography) or for both, which are not environmentally friendly. Moreover, several of these reactions were carried out at higher temperatures and using costly reagents. Furthermore, these methods are not suitable in terms of the recent trends in process chemistry, due to the use of metallic catalysts. Therefore, a method using a nonmetallic catalyst is

desirable. Pentafluorophenylammonium triflate (**PFPAT**) has emerged as a highly efficient and effective potential Brønsted acid catalyst imparting high regio- and chemo-selectivity in various chemical transformations [44], due to its low toxicity, air and water compatibility, operational simplicity, and remarkable ability to suppress side reactions in acid sensitive substrates. In this regard and in connection with our previous work [45], herein, in this paper, we describe a one-pot method for the Biginelli reaction using using **PFPAT** as an efficient novel organocatalyst (Scheme 1).

Scheme 1: PFPAT catalyzed Biginelli reaction

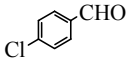
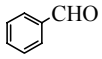
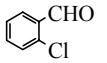
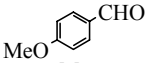
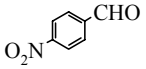
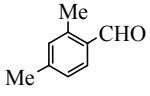
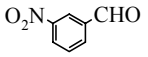
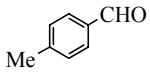
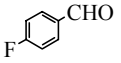
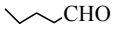
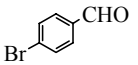
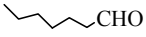
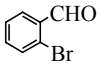
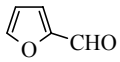
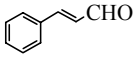


Results and Discussion:

In an initial endeavor, the reaction was carried out by simply mixing 4-chlorobenzaldehyde, ethyl acetoacetate, and urea (Table 1, entry 1) in acetonitrile at r.t. The corresponding 3,4-dihydropyrimidin-2(1H)-one derivative **4a** was obtained in high yield (97%) after 2h. After some efforts a catalytic amount of PFPAT(10 mol%) was found superior for this functional transformation. Using these optimized reaction conditions, the scope and efficiency of this approach was explored for the synthesis of a wide variety of substituted 3,4- dihydropyrimidin-2(1H)-ones and results are summarized in Table 1. A wide range of structurally varied aldehyde reacted smoothly and quickly to give the corresponding 3,4-dihydropyrimidin-2(1H)-one in high yield and purity as listed in Table 1. In all cases, aromatic aldehydes substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and gave the products in good yields. It could also be concluded that the aldehydes bearing electron-withdrawing groups required shorter time and gave higher yields (Table 1, entry 1-7). This method is even effective with aliphatic aldehydes, which normally produce low yields due to their intrinsic lower reactivity (Table 1, entry 12, 13). The remarkable feature of this improved protocol is the wide stability of

a variety of functional groups, such as ethers, alkyl, nitro, and halides under the present reaction conditions.

Table 1:
PFPAT -catalyzed synthesis of dihydropyrimidinones

Entry	Aldehyde	Product	Time	3 Yield %	Entry	Aldehyde	Product	Time	3 Yield %
1		**4a**	2 h	97	**8**		**4h**	3 h	90
2		**4b**	2.5	95	**9**		**4i**	3.5 h	85
3		**4c**	2 h	96	**10**		**4j**	4 h	90
4		**4d**	3 h	90	**11**		**4k**	3 h	90
5		**4e**	2h	92	**12**		**4l**	4 h	90
6		**4f**	2 h	90	**13**		**4m**	4 h	90
7		**4g**	3 h	90	**14**		**4n**	4 h	90
					15		**4o**	4 h	85

Furthermore, the reaction conditions are mild enough to perform these reactions with acid sensitive aldehydes such as furfuraldehyde and cinnamaldehyde, without any decomposition or polymerization, and with enolizable aldehydes such as butyraldehyde. In all cases, the pure product was isolated by simple filtration, without any chromatography or cumbersome workup procedure.

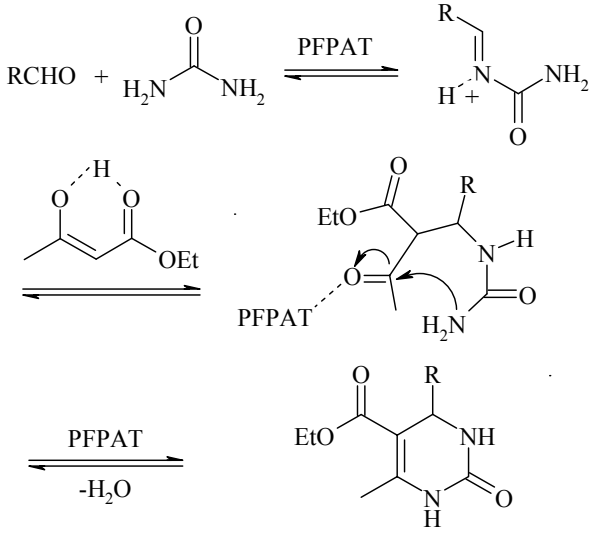
This reaction has been performed in different organic solvents such as diethyl ether, CH_2Cl_2, $CHCl_3$, MeCN, THF, dioxane, and methanol in the presence of PFPAT at r.t and a low yield (<50%) of the dihydropyridine was obtained. Although the amount of catalyst has been optimized to 10 mol%, lesser amounts (5 mol%) also worked with longer reaction times. In order to show the merit of the present work in comparison with some reported protocols, we compared the results of the synthesis of 5-ethoxycarbonyl-4-chlorophenyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (Table 1, entry 1) in the presence of CuI [46], $SbCl_3$ [47], $Cu(NTf_2)_2$ [48], $H_3PMo_{12}O_{40}$ [49], Propane phosphonic acid anhydride [50], $ZrOCl_2$ [51], Pyrazolidine dihydrochloride [52] and **PFPAT** with respect to the reaction times and temperature (Table 2). The yield of product in the presence of **PFPAT** is comparable with these catalysts.

However, other catalyst in the table 2 required longer reaction times than **PFPAT** and also needed higher temperature.

Table 2
Comparison the results of the synthesis of 5-ethoxycarbonyl-4-chlorophenyl-6-methyl-3,4-dihydro-pyrimidin-2(1H)-one using different catalysts

Entry	Catalyst	Time (h)	Yield (%)	Temperature(°C)	Reference
1	CuI	1.5	84	90	46
2	$SbCl_3$	22	89	Reflux	47
3	$Cu(NTf)_2$	24	74	r.t	48
4	$H_3PMo_{12}O_{40}$	6	80	Reflux	49
5	Propan phosphonic acid	6	69	Reflux	50
6	$ZrOCl_2.8H_2O$	2	42.5	100	51
7	Pyrazolidine dihydrochloride	4	92	Reflux	52
8	PFPAT	2	97	r.t	This work

A plausible mechanism for the formation of 3,4-dihydropyrimidin-2(1H)-one derivatives **(4a–o)** in the presence of **PFPAT** is proposed in Scheme 2.



Scheme 2:Proposed mechanism of the reaction

The highly hydrophobic wall of pentafluorophenyl moiety effectively repels H_2O produced by the dehydration steps [44].

In summary, an efficient protocol for one-pot three component condensation of Biginelli reaction catalyzed by **PFPAT** was developed. In contrast to the existing methods using potentially hazardous catalysts/additives, the present method offers the following competitive advantages: (i) **PFPAT** is easy-to prepare from commercially available pentafluoroaniline and triflic acid, (ii) short reaction time, (iii) ease of product isolation/purification by non-aqueous work-up, (iv) no side reaction, (v) low

costs and simplicity in process and handling and (vi) 3,4-dihydropyrimidin-2(1H)-one are produced by an environmentally benign process.

Experimental

Typical experimental procedure: A mixture of aldehyde (2 mmol), β-dicarbonyl compound (2 mmol), urea (3 mmol), and **PFPAT** (0.04 g), was stirred at r.t. in a vial. After completion of the reaction as indicated by TLC, the organic phase was washed with 1 M NaOH aqueous solution (1 ml). The separated organic phase was evaporated under reduced pressure to give a crude product, which was purified by recrystallization from hot ethanol to afford pure products. Products were characterized by comparison of their physical and spectral data with those of authentic samples.[52] Spectroscopic data for selected examples follow:

5-Ethoxycarbonyl-4-(4-fluorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (4e): Mp: 180–182 °C; IR (KBr) υ: 1092, 1223, 1649, 1702, 1726, 3122, 3245 cm−1. ^{1}H NMR (400 MHz, DMSO-d_6): δ: 1.10 (t, J = 7.0 Hz, 3H), 2.28 (s, 3H), 3.99 (q, J = 7.0 Hz, 2H), 5.16 (d, J = 3.7 Hz, 1H), 7.18–7.27 (m, 4H), 7.82 (s, 1H, NH), 9.36 (s, 1H, NH).

5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one.(4i) Mp: 202–203 °C; IR (KBr): υ: 3246, 3111, 2985, 2956, 2931, 1730, 1703. ^{1}H NMR (400 MHz, DMSO-d_6): δ= 9.14(s, 1H, NH); 7.67 (s, 1H, NH); 7.15 (d, J = 8.6 Hz, 2H); 6.88 (d, J = 8.7 Hz, 2H); 5.10 (d, J = 3.2 Hz, 1H); 3.98 (q, J = 7.1 Hz, 2H); 3.74 (s, 3H); 1.10 (t, J = 7.1 Hz, 3H).

Acknowledgements

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