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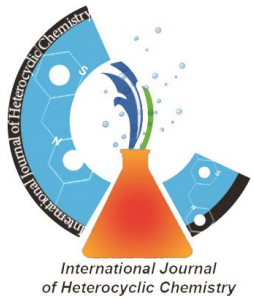


PREPARATION OF TRISUBSTITUTEDPYRIMIDINES USING FERRIC PHOSPHATE

Farahnaz K. Behbahani,* Banafsheh Yazdanparast

**Farahnaz K. Behbahani, Department of Chemistry, Karaj Branch, Islamic Azad University, Karaj, Iran. Tel: +98 0261 4418145. Fax: +98 0261 4418156. Email: Farahnazkargar@yahoo.com*

Abstract: Ferric phosphate accelerated condensation reaction of aldehydes, 1,3-dicarbonyl compounds and amuniom acetate refluxing ethanol that remains a common theme in current literature.

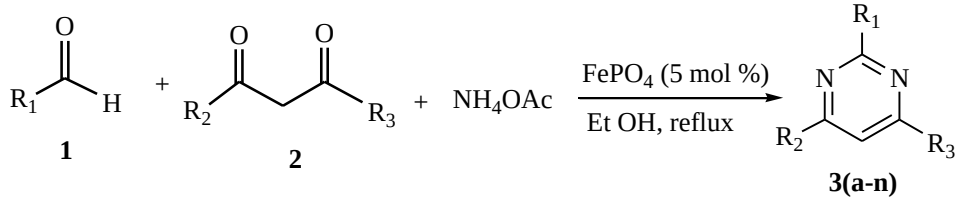
Keywords: Condensation, Cyclization, Heterocycles, Pyrimidines, Ferric phosphate

INTRODUCTION

Pyrimidines include a large number of natural products, pharmaceuticals, and functional materials,[1] such as trimethoprim,[2] sulfadiazine,[3] Gleevec [4] and Xeloda.[5] natural and unnatural polymers also contain pyrimidines.[6] The first report was developed by nitric acid oxidative degradation of uric acid. [7] Since this early report many important contributions describing a variety of methodes for preparation of pyrimidines have been reported.[8]

2,4,6-Trisubstituted pyrimidines have been prepared using various procedures including the reaction of amidines with a,b-unsaturated ketones,[9] dimerization–oxidative fragmentation of aryl-b-arylvinylimines,[10] one-pot condensation of b-dicarbonyl compounds, NH_4OAc and aldehydes,[11,12] condensation of phenacyldimethylsulfonium salts, aldehydes, and ammonia,[13]reaction of alkynes and nitriles in the presence of TfOH,[14] rearrangement of 2,4,5-trisubstituted imidazolines,[15] one-pot, three-component reaction of aryl halides, terminal propargyl alcohols and amidinium salts based upon a coupling-isomerization–cyclocondensation sequence,[16] arylation of halogenated pyrimidines via a Suzuki coupling reaction,[17] reaction of a,a-dibromo oxime ethers with Grignard reagents,[18] microwave-assisted reaction of amidines and

alkynones,[19] sequential assembly of aryl groups onto a pyrimidine core (2-methylthiopyrimidine),[20] the synthesis of pyrimidines using heteropolyacids [21] and Microwave-assisted synthesis of 2,4,6-triarylpyrimidines under solvent-free conditions.[22]
However, in some these methods the reactants such as amidines, unsaturated ketones, aryl-b-arylvinylimines, sulfonium salts, imidazoline derivatives, and dihalo oxime ethers have to be synthesized initially, hence these methods are relatively expensive and time consuming.
Owing to the important properties of pyrimidines, the development of synthetic methods which enable a facile access to this heterocycle are demand. In present research we report fairly greener route to the synthesis of 2,4,6-triarylpyrimidines using1,3-dicarbonyl compounds, aldehydes and NH_4OAc in the presence of iron(III) phosphate as a reusable catalyst from green chemistry point of view (Scheme 1)



R_1= Ph,4-Cl-C_6H_4, 4-Br-C_6H_4, 4-Nitro-C_6H_4, 4-MeO-C_6H_4 , 2-Me-C_6H_4 , 4-HO-C_6H_4,

3-MeO-C_6H_4, n-Pr , n-Bu , 4-$N(Me)_2$-C_6H_4, Ph-CH=CH, Cyclohexyl

R_2= Ph , Me , 4-But -C_6H_4

R_3=Ph , Me, 4-MeO-C_6H_4

Scheme 1 Synthesis of 2,4,6-triarylpyrimidines

EXPERIMENTAL

Mps were measured by using the capillary tube method with an electro thermal 9200 apparatus. IR spectra were recorded on Perkin Elmer FT-IR spectrometer did scanning between 4000–400 cm^{-1}. ^1H NMR and ^{13}C-NMR spectra were obtained on Bruker DRX-400MHZ NMR instrument in $CDCl_3$. All the products(entries 1-13, Table 2) were identified by comparison of their physical and spectroscopic data with those of authentic samples. [18]

Synthesis of 2,4,6-triaryl pyrimidines. A mixture of 1,3-diketone, (10 mmol), benzaldehyde (10 mmol), ammonium acetate (20 mmol) and catalytic amount of $FePO_4$ (5.0 mol%) was refluxed in ethanol (10 ml). The progress of the reaction was monitored by TLC and the spot were detected either UV light or by placing in iodine chamber. Upon completion of the reaction, the catalyst was filtered off and the crude product recrystallized from ethanol/water.

RESULTS AND DISCUSSION

In continuing our own study using iron(III) phosphate[23, 24] we interest to employ the oxidative potential of $FePO_4$[25] as well as their acidic properties as catalyst for a simple and efficient synthesis of 2,4,6-trisubstitutedpyrimidines. We investigated the reaction of 1,3-diketones, aldehydes and ammonium acetate in the presence of catalytic amounts of $FePO_4$. Various parameters were investigated to obtain the optimum reaction conditions.
To study the effect of the catalyst amount on this reaction, the synthesis of 2,4,6-triphenyl pyrimidine was selected as model reaction using $FePO_4$.The results are reported in Table1.

Table1 Synthesis of 2,4,6-triphenyl pyrimidine using different amount of $FePO_4$

Entry	Catalyst (mol %)	Time(h)	Yield (%)

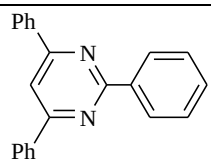
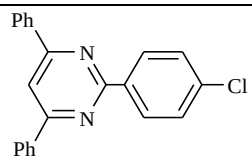
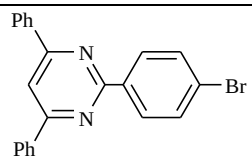
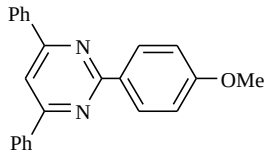
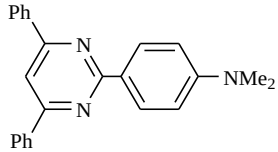
1	0	24	10
2	2	4.0	45
3	5	4.0	80
4	10	4.0	80

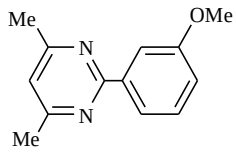
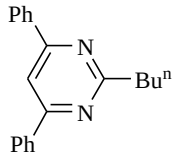
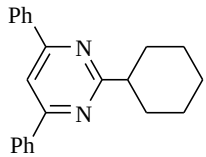
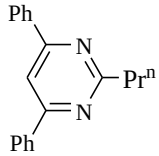
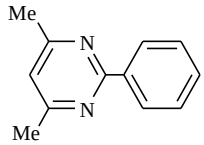
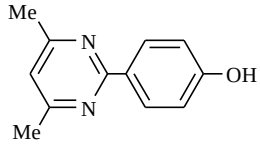
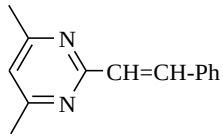
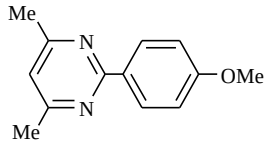
It is clear that the yield depend on the amount of catalyst, the optimum amount of which was 5.0 mol% for all derivatives.

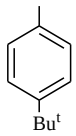
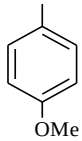
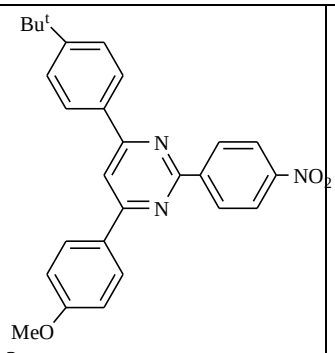
On the basis of the above results, a facile three component one synthesis of trisubstituted primidines was envisaged using various aldehydes, 1,3-diketones and ammonium acetate in the presence of 5 mol% of iron(III) phosphate and ethanol under reflux condition in a green organic reaction.

The results on the synthesis of pyrimidines in the presence of catalytic amounts of $FePO_4$ are summarized in Table 2.One can see Table 2 demonstrates that good to high yields of trisubstituted pyrimidines are obtained across the selected aldehydes including those that bear an electron-withdrawing group. The use of electron-rich aromatic aldehydes also leads to good yields of products.

Table 2 $FePO_4$-catalyzed synthesis of 2,4,6-trisubstituted pyrimidines

Entry	**R_1**	**R_2**	**R_3**	**Product**	**Time (h)**	**Yield[a] (%)**	**MP(°C) Found**	**Reported**
1	Ph	Ph	Ph	 3a	5.0	80	177-186	184-185[1]
2	4-Cl-C_6H_4	Ph	Ph	 3b	6	78	200-205	219-220[1]
3	4-Br-C_6H_4	Ph	Ph	 3c	5	77	228-234	237[2]
4	4-OMe-C_6H_4	Ph	Ph	 3d	4	79	95-110	128[2]
5	4-NMe_2-C_6H_4	Ph	Ph	 3e	5	89	34-38	[3]

6	3-OMe-C_6H_4	Ph	Ph	 3f	6	75	106-111 [3]
7	Bu^n	Ph	Ph	 3g	10	69	60-65 73[2]
8	Cyclohexyl	Ph	Ph	 3h	9	72	107-112 120[2]
9	Pr^n	Ph	Ph	 3i	11	70	49-53 56[2]
10	Ph	CH_3	CH_3	 3j	7	70	80-87 79-80[4]
11	2-HO-C_6H_4	CH_3	CH_3	 3k	8	77	68-73 81[5]
12	Ph-CH=CH	CH_3	CH_3	 3l	6	75	39-46 47-50[6]
13	4-OMe-C_6H_4	CH_3	CH_3	 3m	4	79	84-92 91-92[7]

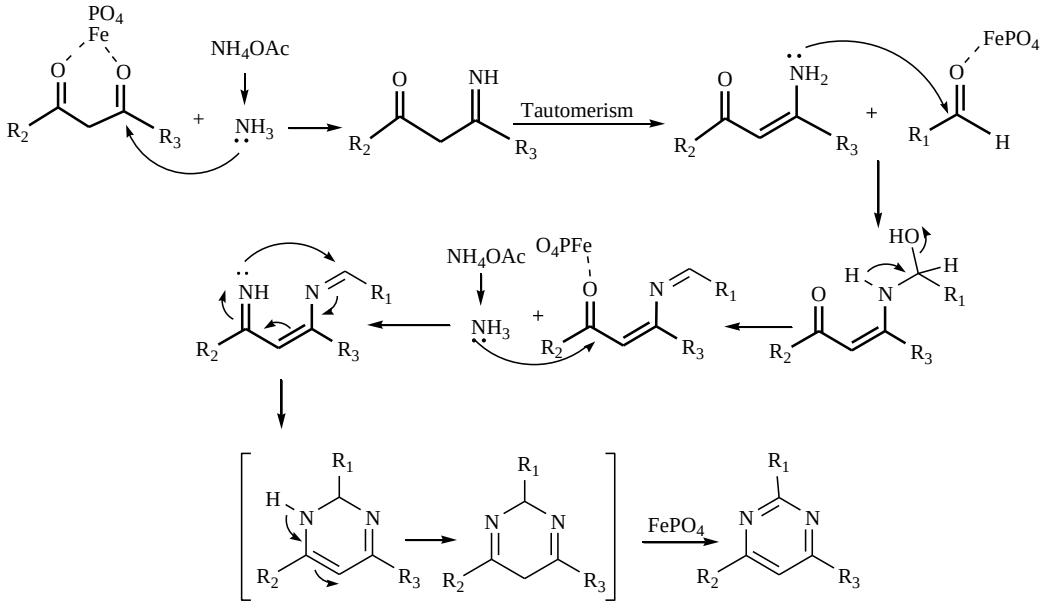
14	4-NO_2-C_6H_4			 3n	4	88	65-70	NEW

a) Yields refer to isolated yield.

The overall greenness of this reaction was high as minimum amount of environmentally benign ethanol and $FePO_4$ were used during the course of reaction. Moreover, it is important to note that in all cases, after completion of the reaction $FePO_4$ filtrated off and reused for another run.

Trisubstituted primidines were also precipitated on dilution of the reaction mixture with water and were isolated by a simple filtration. The dried product that obtained showed a single spot on TLC and was pure enough for all practical purposes. Another advantage of this research is synthesis of 4-(4-tert-butylphenyl)-6-(4-methoxyphenyl)-2-(4-nitrophenyl) pyrimidine for first time as a new primidine (entries 14, Table 2). We are willing to survey their biological properties in future.

A plausible mechanism [21] for the formation of trisubstituted primidines is proposed as shown in Scheme 2.



Scheme 2 A plausible mechanism for the formation of trisubstituted pyrimidines

$FePO_4$ is Lewis acid because of the hard character of its metal cation, so that it can activate the carbonyl group (C=O) to decrease the energy of transition state. This reaction involves the initial imination/enamination tautomerization of the 1,3-diketone followed by nucleophilic attack of the ketenamine on the aldehyde. Dehydration/imination and cyclization/aromatzation afforded trisubstituted primidines.

4-(4-tert-butylphenyl)-6-(4-methoxyphenyl)-2-(4-nitrophenyl)pyrimidine (entry 14)

IR(KBr,) 3393.05, 3071.42, 2959.60, 2901.09, 1925.92, 1604.24, 1509.01, 1509.01, 1456.81 1434.86, 1306.55, 1259.82, 1232.12, 1172.28, 1109.99, 1028.40, 842.91, 752.83, 698.26, 633.42 cm^{-1}; ^{1}HNMR($CDCl_3$, 400MHz) 1.37 (s, 9H), 3.89 (s,3H) , 6.78(s,1H) , 6.98 (d , *J*=8.67 Hz, 2H) , 7.50 (d, *J* = 8.28 Hz , 2H) , 7.69 (d , *J* = 8.43Hz , 2H) ,7.91 (d, *J* =8.28 Hz , 2H), 7.97(d , *J* = 8.67 Hz , 2H),8.15(d, *J* =8.43Hz , 2H) ppm; ^{13}CNMR ($CDCl_3$, 400MHz) 164.7, 162.5, 161.5, 160.7, 150.0, 136.8, 130.0, 128.5, 127.1, 125.6, 121.6, 114.8, 102.5, 55.9, 40.7, 31.4 ppm; GC/Mass: 439; Elemn. Anal. Calcd. for $C_{27}H_{25}N_3O_3$: C, 73.78; H, 5.73; N, 9.56; Found: C, 73.58; H, 5.59; N, 9.45.

RECYCLING OF THE CATALYST

At the end of the reaction, the catalyst could be recovered by filtration. The recycled catalyst was washed with ethyl acetate and subjected to a several reaction process. Table 3 compares the efficiency of $FePO_4$ in the synthesis of triphenyl pyrimidine over 4 runs.

Entry	Aldehyde	Run/ Yield (%)
1	Benzaldehyde	1st/80
2	"	2nd/78
3	"	3th/78
4	"	4th/77

Table 3 Recycling and reusing of the catalyst for the synthesis of 2,4,6-triphenyl primidinehas been shown.

CONCLUSION

In conclusion, we have developed a simple, one-pot, four-component procedure for the preparation of 2,4,6-trisubstitutedpyrimidines of potential synthetic and pharmacological interest. The use of commercial materials, the green one-pot reaction, easy work up and simple purification of the products are the main advantages of this method. This method appears to have a broad scope with respect to variation in substitution at the 2-, 4-, and 6- position of pyrimidine. Thus it could be a novel methodology besides previous procedures.

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