Heterocyclic Letters
Vol. 8| No.3|553-560|May-July|2018
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

SYNTHESIS OF PYRANO[2,3-*D*]PYRIMIDINE DIONESDERIVATIVES USING IRON(III) PHOSPHATE

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Abstract: Uracil and its fused derivatives, such as pyrano[2,3-d]pyrimidines, pyrido[2,3-d]pyrimidines or pyrimido[4,5-d]pyrimidines are recognized by synthesis as well as biological chemists.The general procedures have been reported for the preparation of pyrano [2,3-d] pyrimidine-2,4(1H,3H)-diones including the reaction of arylidenemalononitriles with barbituric acid under different conditions. In this paper pyrano[2,3-d]pyrimidine derivatives were synthesized by a condensation reaction between barbituric acid, malononitrile and various aromatic aldehydes using iron(III) phosphate as a green catalyst under solvent free conditions at 150 °C. Benchmark reaction was opitimized under solvent free conditions and varying of the catalyst amounts. Some known and new derivatives of pyrano[2,3-d]pyrimidine were also prepared by this method. All known compounds were charactrized by FTIR, ^{1} HNMR,^{13} CNMR and melting point analysis and structure of new compounds were identified by FTIR, ^{1} HNMR,^{13} CNMR,mass spectrometery and elemental analysis. The proposed mechanism has been presented to show role of $FePO_4$in the synthesis of pyrano[2,3-*d*]pyrimidine diones derivatives. Comparison of this method with those of previously reported has been revealed to merit this new protocol. The others advantages of this method are simple as no special apparatus,reagents or chemicals,easy work up, reusable and recycable of the catalyst, and the formed compoundsare filtered and purified just by simple crystallization.

Keywords:multicomponent; pyrano pyrimidine; $FePO_4$; catalyst; synthesis; aldehyde; malononitril; barbituric acid; condensation reaction

Introduction

Pyranes are subunits in a variety of important natural products, including carbohydrates, alkaloids, polyether antibiotics, pheromones, and iridoids. [i] Uracil and its fused derivatives, such as pyrano[2,3-d]pyrimidines, pyrido[2,3-d]pyrimidines or pyrimido[4,5-d]pyrimidines are recognized by synthesis as well as biological chemists. These ring systems have diverse pharmacological activity such as antitumor, cardiotonic, hepatoprotactive, antihypertensive,

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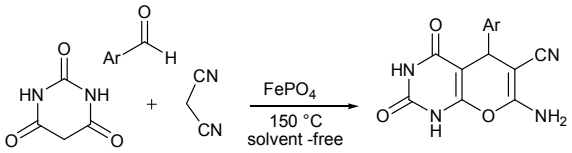
antibronchitic, and antifungal activity. [ii-v]The general procedures have been reported for the preparation of pyrano [2,3-d] pyrimidine-2,4(1H,3H)-diones including the reaction of arylidenemalononitriles with barbituric acid under traditional hot reaction conditions[vi,vii]or microwave irradiation.[viii] In these methods the arylidenemalononitriles are previously derived from malononitrile and aldehydes. Recently, direct condensation of aldehydes, malononitrile and barbituric acid in aqueous media has been reported under ultrasound irradiation, [ix] or catalyzed by diammonium hydrogen phosphate.[x]Different catalysts such as L-proline, [xi]N-methylmorpholine[xii][BMIm]BF_4,[xiii] 1,4-dioxane[vi,xiv] $H_{14}[NaP_5W_{30}O_{110}]$,[xv] $[KAl(SO_4)_2]$[xvi] under heating also dibutyl amine (DBA)[xxiii]and Et_3N under microwave irradiation.[xviii] The catalyst free procedures for the preparation of the pyrano pyrimidine diones were also investigated using microwave irradiation,[viii]ultrasonic,[ix] heating with water[xix] and ball-milling technique.[xx] In this communications, a straightforward and efficient method for the synthesis of pyrano[2,3-*d*]pyrimidine diones derivatives from the reaction of barbituric acid, malononitrile and various aromatic aldehydes using iron(III) phosphate as a green catalyst is reported (Scheme 1).



Scheme 1 Synthesis ofPyrano[2,3-d]pyrimidine derivatives

Results and discussion

To evaluate the catalytic activity of iron (III) phosphate in the synthesis of pyrano[2,3-d]pyrimidines, initially, to optimize the reaction conditions, the reaction of benzaldehyde (2.0 mmol), malononitril (2.5 mmol) and barbituric acid (2.0 mmol) was subjected as a simple model reaction in the presence of different catalytic amounts of the catalyst under solvent-free conditions. It was found that 20 mol% of the catalyst efficiently catalyzed the model reaction in high yields and short reaction times (Table 1). The reaction was not successful in the absence of the catalyst (entry 1).

Table 1 Optimizing of catalytic amount of the catalyst in the synthesis of7-amino-2,3,4,5-tetrahydro-1,3-dimethyl-2,4-dioxo-5-phenyl-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile

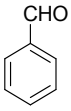
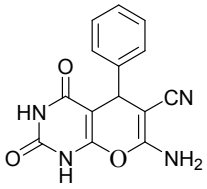
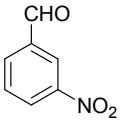
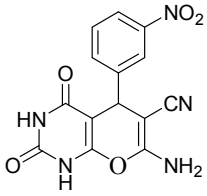
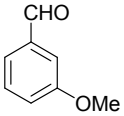
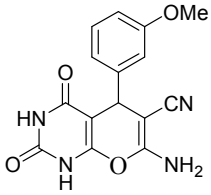
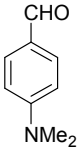
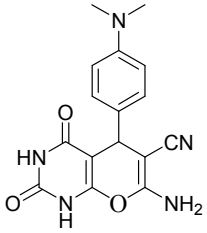
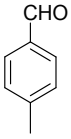
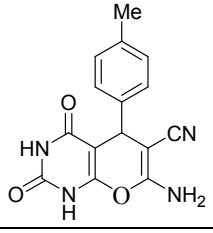
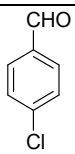
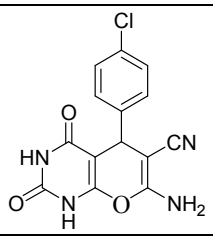
Entry	$FePO_4$ (mol%)	Time (h)	Yield%[a]
1	-	24	20
2	10	12	58
3	15	9	72
4	20	8.0	82

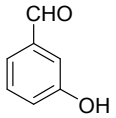
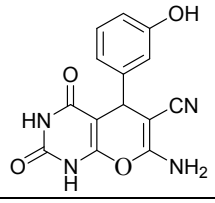
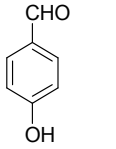
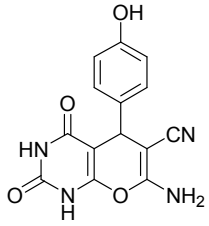
[a]**Reaction condition:** benzaldehyde (2.0 mmol), barbituric acid (2.0 mmol), malononitril (2.5 ml) under solvent free condition and at 150 °C

After optimization of the reaction condition, a variety of aldehydes were also examined and it was found that in all cases the 150 °C temperature was enough to complete the reaction. Because no excess of reagents was used, the products were generally obtained with no waste and no further tremendous purification processes were needed. In most cases the products were obtained in enough pure form, or a simple crystallization was enough, if it was necessary. The results are summarized in Table 2. The products were characterized by comparison of their spectral data and melting points with those reported in literature. It is noteworthy that all the products show a characteristic single peak in the ^1H NMR spectra at

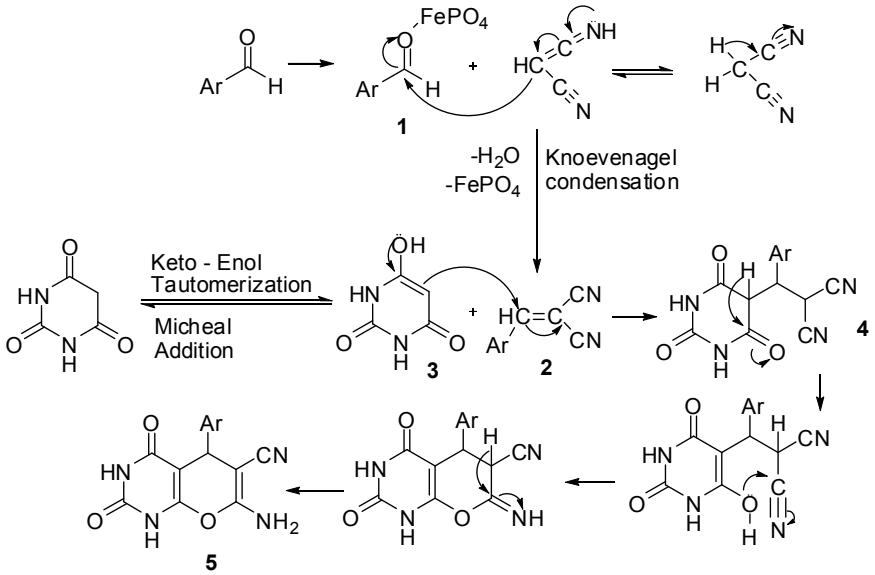
about 4.2-4.8 ppm, which corresponds to the benzylic proton of the ArCH group. These results have been previously reported for the same and for similar structures.
Therefore, we reported one-pot synthesis of pyrano[2,3-d]pyrimidine-2,4(1*H*,3*H*)-diones in high to excellent yields by three component reaction of an aldehyde, malononitrile, and barbituric acid using iron (III) phosphate without any solvent.

Table 2: Synthesis of pyrano[2,3-*d*]pyrimidine diones using iron(III) phosphate.

Entry	**Aldehyde**	**Product**	**Time (min)**	**Yield%**	**M.P. ° C**	
					Found	**Reported[ref.]**
1			25	82	226-230	224-225[xiii]
2			5	90	258-263	255-258[xxi]
3			30	76	200-205	new
4			120	45	176-180	new
5			80	81	219-225	225[xxi]
6			110	88	235-242	234-237[xxi]

7			30	79	232-237	new
8			150	81	238-239	240-241[xxii]

The proposed mechanism for the synthesis of pyrano[2,3-*d*]pyrimidine diones derivatives using iron(III) phosphate has been shown in Scheme 2. $FePO_4$-activated carbonyl group of aromatic aldehydes **1** was attacked by malononate in a knoevenagel condensation reaction to form arylidenemalononitrile**2**. Tautomerization of barbituric acid **3** and its Micheal addition to arylidenemalononitrile**2** obtainedintermediate **4.** Cyclization reaction, and then imine-enamine tautomerization resulted the desired product **5.**



Scheme 2 Suggested mechanism for the preparation of pyrano[2,3-*d*]pyrimidine diones derivatives using iron(III) phosphate

Literature surveys revealed that various acidic conditions have been employed in this reaction as demonstrated in Table 3.

Table 3 Comparition of $FePO_4$ and various catalysts in the synthesis of 7-amino-2,3,4,5-tetrahydro-1,3-dimethyl-2,4-dioxo-5-(3- nitro phenyl)-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile

Entry	**Catalyst (mol%)**	**Solvent**	**Condition**	**Time(min)**	**Yield%**[a]	**Ref.**
1	$H_{14}[NaP_5W_{30}O_{110}]$(01)	EtOH	Reflux	30	90	xv
2	[a][BMIm]BF_4 (10)	[BMIm]BF_4	90˚C	180	84-92	xiii

3	Zn[(L)proline]$_2$(17)	EtOH	Reflux	30	90	xi
4	Microwave irradiation	H_2O	r.t	3	90-92	xxii
5	Free	Free	Ball-milling	15	≥99	xx
6	SBA-Pr-SO_3H (5)	Free	140˚C	15	80	xxi
7	Kal$(SO_4)_2$(10)	H_2O	80 ℃	40	81	xvi
8	Free	dioxane	Reflux	2	60-70	xiv
9	dibutylamine (DBA)(20)	EtOH, H_2O	Reflux,rt.	110	86	xxiii
10	*N*_methylmorpholine(6.25)	DMF	90-95°C	15	87-90	xii

[a][BMIm]BF_4: 1-Butyl-3-methylimidazolium Tetrafluoroborate

Experimental

Synthesis of pyrano[2,3-*d*]pyrimidine diones using iron(III) phosphate. General procedure:

In on neck flask, malononitril (2.0 mmol), aryl aldehyde(2.5 mmol), and barbituric acid(2.0 mmol), and iron (III) phosphate (20 mol%) were stirred under solvent-free condition and at 150 °C. Analytical TLC of all reactions was performed on Merck precoated plates (silica gel 60 F-254 on aluminum). After completion of the reaction, ethanol (20 ml) was added and stirred for 10 minutes and the catalyst was removed by filtration. After evaporating of the solvent the resulting solid product was purified from ethanol/water and identified by measuring of melting point by 9200 Electro Thermal instrument, Perkin Elmer FT-IR spectrometer and ^{1}HNMR spectra on Bruker DRX- 300 MHZ NMR instrument.

The reusability of the catalyst was also investigated on the model reaction. The heterogeneous nature of the catalyst allowed its facile recovery by simple filtration, washing with ethanol and drying at 50 ºC to provide an opportunity for recycling experiments. The separated catalyst was reused in the mentioned reaction for the synthesis of three times without considerable loss of its catalytic activity (Table 4).

Table 4: Reusability of the catalyst

Runs	1	2	3
Yield%	82	80	80

[a]**Reaction condition:** benzaldehyde (2.0 mmol), barbituric acid (2.0 mmol), malononitril (2.5 ml) under solvent free condition and at 150 °C

Physical and spectra data

7-Amino-2,3,4,5-tetrahydro-1,3-dimethyl-2,4-dioxo-5-phenyl-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile.This compound was obtained in 82 % yield as a light yellowcolor solidcrystals; ^{1}HNMR ($CDCl_3$, 250MHz): δ 11.77(s, 1H, NH), 11.03(s, 1H, NH), 8.48(s, 2H, NH_2), 6.96-7.78(m, 5H, ArH), 4.16(s, 1H, CH) ppm.IR(KBr cm^{-1}): 3420 (NH), 3226 (NH), 2222 (CN), 1740 (C=O), 16560 (NC=O), 1350 (C=O), 110 (C=O), 800 (C=C);m.p = 226-230^{o}C (dec) [13];time = 25 min.

7-Amino-2,3,4,5-tetrahydro-1,3-dimethyl-5-(3-nitrophenyl)-2,4-dioxo-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile. This compound was obtained in 90 % yield as a white color solidcrystals;^{1}HNMR ($CDCl_3$, 250MHz): δ 12.10(s, 1H, NH), 11.01(s, 1H, NH), 8.2(m, 1H,

ArH), 8.00(m, 1H, ArH), 7.65(m, 1H, ArH), 7.50(m, 1H, ArH), 7.26(s, 2H, NH_2), 4.43(s, 1H, CH) ppm.; IR (KBr cm^{-1}): 4318.14 (NH), 2194.31 (CN), 1710.31 (C=O), 1662.29 (NC=O), 1347.88 (C=O), 1107.94 (CO), 1536 (C=C), 793.19(NO_2);m.p: 258-263 °C (dec).

7-Amino-2,3,4,5-tetrahydro-5-(3-methoxyphenyl)-1,3-dimethyl-2,4-dioxo-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile. This compound was obtained in 76 % yield as a white color solidcrystals; ^{1}HNMR ($CDCl_3$, 250 MHz): δ = 120.1(s, 1H, NH), 11.00(s, 1H, NH), 6.67-7.03(s, 2H, NH_2), 4.615(s, 1H, CH), 4.47(m, 1H, ArH), 4.1(m, 1H, ArH), 3.73(s, 3H, -OCH_3), 3.6(m, 1H, ArH), 3.4(m, 1H, ArH) ppm.; IR(KBr cm^{-1}): 3394.31 (NH), 2193.66 (CN), 1718.21 (CO), 1679.89 (NC=O), 1395.34 (C=O), 1155.14 (C=O), 1034.17 (C=O), 697.41 (C=C);m.p: 200-205 °C (dec).

7-Amino-2,3,4,5-tetrahydro-2,4-dioxo-5-p-tolyl-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile.

This compound was obtained in 81 % yield as a light yellow colorsolidcrystals; ^{1}HNMR (CDCl3, 250 MHz,): δ 12.00(s, 1H, NH), 11.09(s, 1H, NH), 6.95-7.17(m, 6H, ArH, NH_2), 4.13(s, 1H, CH), 2.47(s, 3H, CH_3) ppm. Mass (m/z): 296 (M+), 285, 149 (100).[1]; IR(KBr cm^{-1}): 3432.00 (NH), 2222.32 (CN), 1769.0 (CO), 1675.16 (NC=O), 1376.52 (CO), 1221.46, 814.71 (C=C), m.p : 219-225 °C (dec).

7-Amino-5-(4-chlorophenyl)-2,3,4,5-tetrahydro-1,3-dimethyl-2,4-dioxo-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile. This compound was obtained in 88% yield as a creamy colorsolidcrystals; ^{1}HNMR ($CDCl_3$, 250 MHz,): δ = 12.20(s,1H, NH), 11.50(s, 1H, NH), 7.94(s, 2H, NH_2), 7.24-7.36(m, 4H, ArH), 5.28(s, 1H, CH) ppm. [1].;IR(KBr cm^{-1}): 3421.91 (NH), 2226.59 (CN), 1769.53 (C=O), 1673.56 (NC=O), 1324.20 (CO), 1094.95 (CO), 827.55 (C-Cl). m.p: 235-242°C (dec).

7-Amino-2,3,4,5-tetrahydro-5-(3-hydroxyphenyl)-1,3-dimethyl-2,4-dioxo-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile. This compound was obtained in 79% yield as a yellow colorsolid crystals; ^{1}HNMR ($CDCl_3$, 250 MHz): δ = 12.1(s, 1H, NH), 11.05(s, 1H, NH), 8.40(m, 1H, ArH), 8.27(m, 1H, ArH), 8.0(m, 1H, ArH), 7.57(s, 1H, ArH), 7.22(brd s, 2H, NH_2), 4.43(s, 1H, CH), 4.33(s, 1H, OH) ppm; IR (KBr cm^{-1}): 3368.14 (NH), 3213 (OH), 2242.03 (CN), 1716.45 (CO), 679.01 (NCO), 1324.48, 1181.43 (CO), 785.73 (C=C).;m.p: 232-237 °C (dec).

Conclusion

In conclusion we have developed a multicomponent synthesis of pyrano pyrimidine diones in good yields. In comparison with previous investigations, we presented $FePO_4$ as an efficient and active catalyst. Our method are simple as no special apparatus,reagents or chemicals,easy work up, reusable and recycable of the catalyst, and the formed compoundsare filtered and purified just by simple crystallization.

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Received on April 22, 2018.