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TETRABUTYLAMMONIUM HEXATUNGSTATE $[TBA]_2[W_6O_{19}]$: AN EFFICIENT CATALYST FOR THE SYNTHESIS OF PYRANO[2,3-*d*]PYRIMIDINE DERIVATIVES UNDER SOLVENT-FREE CONDITIONS

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Abstract: An efficient and one-pot multi-component procedure for the synthesis of pyrano[2,3-*d*]pyrimidine derivatives in the presence of tetrabutylammoniumhexatungstate$[TBA]_2[W_6O_{19}]$ under solvent-free conditions has been developed. Thisheterogeneous catalyst shows environmentally benign character, which can be easily separated from the reaction mixtureand recovered several times without significant loss of catalytic activity. Furthermore, the present method offers several advantages, such as easy experimental and work-up procedures, short reaction times (2-8 min) and excellent yields (96-98 %).

Keywords:pyrano[2,3-*d*]pyrimidine,tetrabutylammoniumhexatungstate, one-pot, multi-component reactions**.**

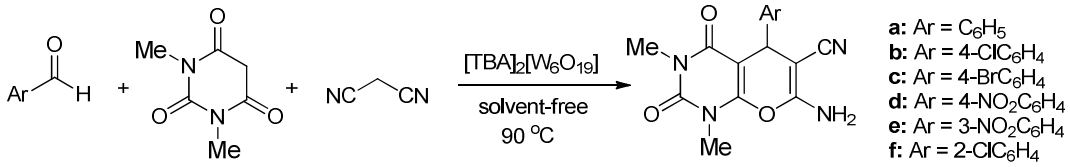
Introduction

Pyrans, a group of heterocyclic compounds, are extremely important in the pharmaceutical and agrochemical industries and in synthetic chemistry. They have a wide range of biological and pharmacological properties, for example anti-allergy, anti-inflammatory, anti-tumor, spasmolytic, diuretic, anti-cancer, anti-coagulant, and anti-anaphylactic activity.[I,II]Uracil and its fused derivatives, such as pyrano[2,3-*d*]pyrimidines, pyrido[2,3-*d*]pyrimidines or pyrimido[4,5-*d*]pyrimidines are well recognized by synthesis as well as biological chemists.These fuseduracils have received considerable attention over the past years due to their wide range of biological activity. Compounds with these ring systems have diverse pharmacological properties such as antiallergic,[III]antihypertensive,[IV]cardiotonic,[V]bronchiodilator,[VI]antibronchitic,[VII] or antitumouractivity.[VIII]

The synthesis of the mentioned compounds containing a pyran and anuracil ring poses significant synthetic challenges. Considering their importance, a considerable number of

methods are found in the literature for the synthesis of these compounds, especially pyrano[2,3-*d*]pyrimidines.[IX-XVI] These methods often suffer from certain drawbacks such as long time procedures, hazardous by-products, unsatisfactory yields, expensive catalysts, toxic organic solvents, and harsh reactionconditions. Therefore, it seemed desirable to develop a more efficient and a general method for the synthesis of pyrano[2,3-*d*]pyrimidines.

Based on our earlier success in the synthesis of biologically interesting products via multi-componentreactions,[XVII-XXVII] in this report, we present the results of an extended investigation on the activity of the tetrabutylammoniumhexatungstate $[TBA]_2[W_6O_{19}]$, as an efficient and powerful catalyst for the synthesis of pyrano[2,3-*d*]pyrimidine derivatives. To the best of our knowledge, there are no examples of the use of this kind of catalyst, for the synthesis of pyrano[2,3-*d*]pyrimidine derivatives from condensation of aromatic aldehydes, 1,3-dimethylbarbituric acid and malononitrile (Scheme 1).



Scheme 1. Synthesis of pyrano[2,3-*d*]pyrimidine derivatives in presence of$[TBA]_2[W_6O_{19}]$ as catalyst.

Experimental

All chemicals were purchased from Merck and Aldrich and used without additional purification. Melting points were recorded on a Stuart SMP3 melting point apparatus. The IR spectra were obtained with KBr disks using a Tensor 27 Bruker spectrophotometer. The ^1H NMR spectra were recorded with a Bruker300 FT spectrometer using TMS as internal standard.

Synthesis of tetrabutylammoniumhexatungestate $[TBA]_2[W_6O_{19}]$

A mixture of sodium tungestatedihydate, $Na_2WO_4.2H_2O$, (99%, 0.1 mol, 33 g), acetic anhydride (40 ml) and N,N-dimethylformamide (30 ml) was heated at 100 °C for 3 h to obtain a white cream. Then a solution of acetic anhydride (20 ml) and HCl (12 N, 18 ml) in N,N-dimethylformamide (DMF) (50 ml) was added with stirring, and the resulting mixture was filtered off to eliminate the undissolved white solid. A solution of tetrabutylammonium bromide (0.047 mol, 15.1 g) in methanol (50 ml) was added with rapid stirring to give a white precipitate. This suspension was stirred for 5 min and the product is filtered. Recrystallization from a minimum amount of hot dimethyl sulfoxide (DMSO) gives colorless diamond-shaped crystals.[XXVIII]

General procedure for the synthesis of pyrano[2,3-d]pyrimidine derivatives4a-f

A mixture of an aromatic aldehyde**1a-f** (1 mmol), 1,3-dimethylbarbituric acid**2** (1 mmol), malononitrile**3**(1 mmol), and $[TBA]_2[W_6O_{19}]$ (0.01 g) was magnetically stirred at 90 ^oCunder solvent-free conditions. The progress of the reaction was monitored by thin-layer chromatography (TLC). Upon completion, the reaction mixture was cooled to room temperature and hot ethanol was added. The catalyst was insoluble in hot ethanol and it could therefore be recycled by a simple filtration. The product was then collected from the filtrate after cooling to room temperature and recrystallized from ethanol to give compounds **4a-f** in high yields.

Analytical data

7-Amino-6-cyano-1,3-dimethyl-5-(4-chlorophenyl)-1,5-dihydro-pyrano[2,3-*d*]pyrimidine-

2,4-dione (**4b**):IR (KBr disc): υ 3374 and 3307 (NH_2), 2196 (CN), 1711 (CO), 1687 (CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ3.09 (s, 3H, N-CH_3), 3.36 (s, 3H, N-CH_3), 4.36 (s, 1H, CH), 7.29 (d, 2H, *J* = 8.4 Hz, arom-H), 7.35 (d, 2H, *J* = 8.4 Hz, arom-H), 7.40 (s br., 2H, NH_2).

7-Amino-6-cyano-1,3-dimethyl-5-(4-bromophenyl)-1,5-dihydro-pyrano[2,3-*d*]pyrimidine-2,4-dione (**4c**):IR (KBr disc): υ3428 and 3300 (NH_2), 2191 (CN), 1704 (CO), 1644 (CO) cm^{-1}; ^1H-NMR (300 MHz, DMSO-d_6): δ 3.08 (s, 3H, N-CH_3), 3.35 (s, 3H, N-CH_3), 4.34 (s, 1H, CH), 7.23 (d, 2H, *J* = 8.4 Hz, arom-H), 7.40 (s br., 2H, NH_2), 7.48 (d, 2H, *J* = 8.4 Hz, arom-H).

7-Amino-6-cyano-1,3-dimethyl-5-(4-nitrophenyl)-1,5-dihydro-pyrano[2,3-*d*]pyrimidine-2,4-dione (**4d**):IR (KBr disc): υ 3389 and 3304 (NH_2), 2205 (CN), 1682 (CO), 1630 (CO) cm^{-1}; ^1H-NMR (300 MHz, DMSO-d_6): δ 3.08 (s, 3H, N-CH_3), 3.37 (s, 3H, N-CH_3), 4.53 (s, 1H, CH), 7.51 (s br., 2H, NH_2), 7.56 (d, 2H, *J* = 8.7 Hz, arom-H), 8.16 (d, 2H, *J* = 8.7 Hz, arom-H).

7-Amino-6-cyano-1,3-dimethyl-5-(3-nitrophenyl)-1,5-dihydro-pyrano[2,3-*d*]pyrimidine-2,4-dione (**4e**):IR (KBr disc): υ 3430 and 3333 (NH_2), 2195 (CN), 1694 (CO), 1636 (CO) cm^{-1}; ^1H-NMR(300 MHz, DMSO-d_6): δ3.07 (s, 3H, N-CH_3), 3.37 (s, 3H, N-CH_3), 4.58 (s, 1H, CH), 7.51 (s br., 2H, NH_2), 7.62 (t, 1H, *J* = 7.8 Hz, arom-H), 7.78 (d, 1H, *J* = 7.8 Hz, arom-H), 8.09-8.13 (m, 2H, arom-H).

7-Amino-6-cyano-1,3-dimethyl-5-(2-chlorophenyl)-1,5-dihydro-pyrano[2,3-*d*]pyrimidine-2,4-dione (**4f**):IR (KBr disc): υ 3393 and 3360 (NH_2), 2195 (CN), 1708 (CO), 1687 (CO) cm^{-1}; ^1H-NMR (300 MHz, DMSO-d_6): δ 3.07 (s, 3H, N-CH_3), 3.37 (s, 3H, N-CH_3), 4.87 (s, 1H, CH), 7.23-7.40 (m, 6H, arom-H and NH_2).

Results and Discussion

Catalytic activity for synthesis of pyrano[2,3-d]pyrimidine derivatives

To achieve the optimization reaction conditions, at first, a mixture 4-chlorobenzaldehyde **1b** (1 mmol), 1,3-dimethylbarbituric acid**2** (1 mmol) and malononitrile **3** (1 mmol) was selected as a model reaction and refluxed in mixture of ethanol and water and absence of catalyst.Only a trace amount of the product was obtained in this conditions after 40 min (Table 1,entry 1). Then the reaction was carried out in different amounts of $[TBA]_2[W_6O_{19}]$ under solvent-free conditions (entries 2-9).The optimum amount of catalyst was 0.01 g and this obtained condition was applyed in the present of different solvents (entries 10-19). We found that yield of the reaction with using the different solvents is lower than solvent-free conditions. Thus, the best result was 0.01 g of catalyst under solvent-free conditions at 90 ^oC for 2 min (entry 4).

Table 1. Screening of the reaction conditions for the synthesis of **4b**[a]

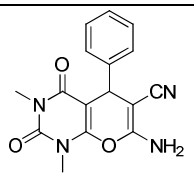
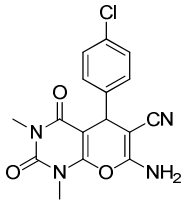
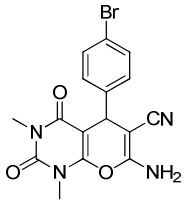
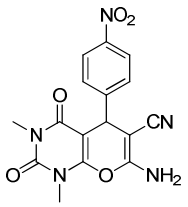
Entry	Catalyst (gr)	Conditions	Time (min)	Temperature (°C)	Yield (%)[b]
1	-----	EtOH+H_2O	40	reflux	trace
2	0.008	Solvent free	10	90	91
3	0.008	Solvent free	7	110	89
4	0.01	Solvent free	2	90	98
5	0.01	Solvent free	1	110	96
6	0.02	Solvent free	5	90	89
7	0.02	Solvent free	4	110	87
8	0.03	Solvent free	9	90	86
9	0.03	Solvent free	8	110	85
10	0.01	DMF	14	70	89

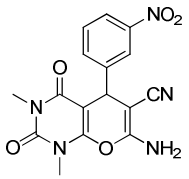
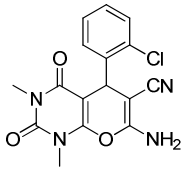
11	0.01	DMF	9	90	88
12	0.01	EtOH+H_2O	14	75	92
13	0.01	EtOH+H_2O	10	reflux	89
14	0.01	CH_3OH	20	50	90
15	0.01	CH_3OH	10	reflux	84
16	0.01	EtOH	19	50	84
17	0.01	EtOH	16	reflux	81
18	0.01	H_2O	22	70	69
19	0.01	H_2O	20	reflux	66

[a] Reaction conditions: 4-chlorobenzaldehyde (1mmol), 1,3-dimethylbarbituric acid (1 mmol) and malononitrile (1 mmol).
[b] Isolated yields

In order to evaluate the generality of this model reaction, we prepared a range of pyrano[2,3-*d*]pyrimidine derivatives under optimized reaction conditions. In all cases, aromatic aldehydes reacted successfully and gave the expected products **4a-f** in excellent yields (96-98 %) and short reaction times (2-8 min). The type of aldehyde had no significant effect on the reaction. The results are shown in Table 2.

Table 2. Preparation of pyrano[2,3-*d*]pyrimidine derivatives using $[TBA]_2[W_6O_{19}]$ as a catalyst[a]

Entry	Ar	Product	Time (min)	Yields (%)[b]
1	C_6H_5	 **4a**	4	96
2	4-ClC_6H_4	 **4b**	2	98
3	4-BrC_6H_4	 **4c**	2	96
4	4-$O_2NC_6H_4$		6	97

		4d		
5	3-$O_2NC_6H_4$		8	98
		4e		
6	2-ClC_6H_4		4	97
		4f		

[a] Reaction conditions: aromatic aldehyde (1 mmol), 1,3-dimethylbarbituric acid (1 mmol), malononitrile (1 mmol) and catalyst (0.01 g) at 90 ºC under solvent-free conditions.
[b] Isolated yields.

The recycling of catalyst ($[TBA]_2[W_6O_{19}]$)was investigated for the synthesis of **4b** and **4e**. For this purpose, after the completion of the reaction, the catalyst was separated from the reaction mixture by simple filtration, dried at 60^{o}C for 1 h, and re-used in the same reaction to give **4b** and **4e** in yields of 98%, 97%, 97%, and 98%, 96%, 95%respectively, for three consecutive runs.

Conclusion

In summary, we have reported a simple catalytic method for the synthesis of pyrano[2,3-*d*]pyrimidine derivatives by one-pot three-component reaction of aromatic aldehyde, 1,3-dimethylbarbituric acid and malononitrile using $[TBA]_2[W_6O_{19}]$ as an efficient, reusable, and green heterogeneous catalyst under solvent-free conditions. High yields, short reaction times, easy work-up and absence of any volatile and hazardous organic solvents are some advantages of this protocol.

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