Short communication

An eco-friendly catalytic route for synthesis of 4-amino-pyrazolo[3,4-d]pyrimidine derivatives by Keggin heteropolyacids under classical heating and microwave irradiation

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Abstract

Various solid acid catalysts such as HY-zeolite, silica-supported sulfuric acid, $H_3PW_{12}O_{40}$, $H_3PMo_{12}O_{40}$, and $H_3PW_{12}O_{40}/SiO_2$ have been used for the synthesis of 4-amino–pyrazolo[3,4-d]pyrimidine derivatives from the reaction of 1-substituted-5-amino-4-cyano-pyrazoles and formamid under classical heating and microwave irradiation. The microwave-solid acid combination, leads to a nice and convenient catalytic synthesis of 4-amino-pyrazolo[3,4-d]pyrimidines with much reduced reaction times compared to traditional conditions. Among the above catalysts, heteropolyacid, $H_3PW_{12}O_{40}$ showed the best catalytic activity in term of yields and reaction times.
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1. Introduction

The adenine analogues, 4-amino-pyrazolo[3,4-d]pyrimidines have proved to affect nucleotide synthesis in two different ways. It can either bind to adenine phosphoribosyl transfers, an enzyme responsible for the transfer of phosphoribosyl group from pp-ribose-p to exogenous purine [1,2], or it can inhibit purine synthesis *de novo* (from nonpurine components) [3]. Inhibition of purine synthesis de nove has been considered as the cause of the cytotoxic activity of 4-APP.

Pyrazolopyrimidines have also corticotrophin releasing factor (CRF) antagonist activity [4]. The importance of CRF antagonists is set out in the literature [5,6]. Based on the research described in these two references, CRF antagonist are considered effective in the treatment of a wide range of diseases including stress-related illnesses such as stress-induced depression, anxiety, and headache; abdominal bowel syndrome; inflammatory diseases; immune suppression; alzheimer's disease; anorexia nervosa; hemorrhagic stress. Withdrawal symptoms; drug addiction; and fertility problems, 4-APP, which is not nephrotoxic [7] and protects mice from the renal injury induced by adenine [8], has been largely studied in the past as a possible anti-cancer agent [9–12] and has recently been used as a tool to reduce serum cholesterol and lipoprotein levels [13–14].

The synthesis of aminopyrazolo[3,4-d]pyrimidines has been accomplished by two routes [15]. The treatment of 1-substituted-5-amino-4-cyanopyrazole with boiling formamide in relatively long reaction time or treatment of the latter with sulfuric acid, phosphorus oxychloride and ammonia, respectively [15].

A survey of the literature reveals many and various methods for heterocyclization, using mineral acids such as H_2SO_4 [16] and sulfuric acid supported on to silica gel [17]. Due to the problem of environmental pollution and corroding facilities in conventional industrial processes, it is desirable to replace the conventional catalysts with new type of solid acid catalysts which are well-behaved and environmentally friendly. Solid acid catalysts are not only environmental friendly material but also can be repeatedly used in fixed bed or slurry reactor with easy separation from products, reactants and solvents.

Heteropolyacids (HPAs) as supported or in bulk form, are very interesting solid acid catalysts, can act as green and eco-friendly catalysts [18]. Silica-supported acid $H_3PW_{12}O_{40}$ (PW)

is also a very efficient and environmentally benign solid acid catalyst in the liquid phase. HPAs, especially those of the Keggin series, are widely used as catalyst for the synthesis of fine and specific chemicals [18–23]. Being stronger acids, they generally exhibit higher catalyst activities than conventional catalysts such as mineral acids, ion exchange resins, mixed oxides, zeolites, etc.
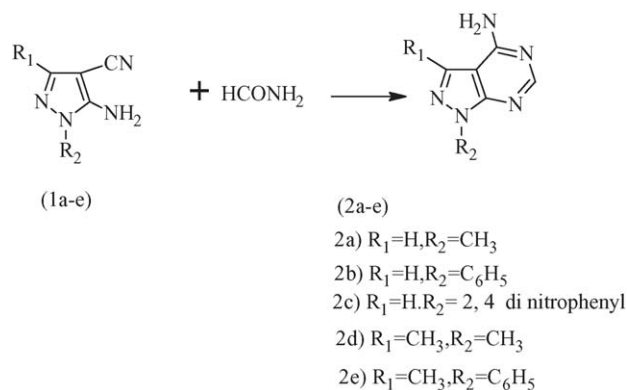
Catalysis by HPAs and related compounds is a field of increasing importance world wide. The reactions, in which they can be used, from dehydration, cyclization, esterification up to amine oxidation or olefin epoxidation, may find wide application in field of industrial chemical production, such as fragrances, pharmaceuticals and foods [21–23].

Recently, in addition to thermal reactions, microwave assisted reaction are well established and have gained popularity as indicated by the large number of papers, reviews and books published on this topic [24]. Using microwave heating offers the possibility of reducing reaction time from hours to minutes and improving product yields. Key advantages of modern scientific microwave apparatus is the ability to control reaction condition precisely monitoring temperatures, pressure and reaction time [25].

In continuation of our interest in organic reactions under microwave irradiation [26] and synthesis of heterocyclic systems [27], and due to our recent interest using heteropolyacids as efficient and reusable catalyst [28], we report herein the conventional and the first microwave assisted synthesis of 4-amino-pyrazolo[3,4-d]pyrimidine derivatives (4-APP), **2(a-e)** from the reaction of pyrazoles **1(a-e)** and formamide, using Keggin HPA catalyst in supported and non-supported form. The results are compared with classical catalysts such as sulfuric acid onto silica gel and HY-zeolite. This work describes the application and superiority of $H_3PW_{12}O_{40}$ (PW), the strongest HPA in the Keggin series for the economical and eco-friendly synthesis of aminopyrazolo[3,4-d]pyrimidines. The microwave results are compared with the outcome of traditional heating in acetic acid as solvent and shows advantages.

2. Results and discussion

Environmental and economical consideration prompts an urgent need to redesign commercially important processes in this context; heterogeneous catalysts play a dramatic role [29]. The use of heterogeneous catalyst in different levels, is useful not only for the possibility to perform environmentally benign

2a) R_1=H, R_2=CH_3
2b) R_1=H, R_2=C_6H_5
2c) R_1=H. R_2= 2, 4 di nitrophenyl
2d) R_1=CH_3, R_2=CH_3
2e) R_1=CH_3, R_2=C_6H_5

Scheme 1.

synthesis but also for the good yields, accompanied by excellent selectivity that can be achieved.

In connection with our program of using heteropolyacid in organic reactions [28], we wish to report the results of our study on the use of solid acids such as silica-supported H_2SO_4, HY-zeolite, Keggin type heteropolyacids, $H_3PW_{12}O_{40}$, $H_3PMo_{12}O_{40}$, and silica-supported $H_3PW_{12}O_{40}/SiO_2$ in the synthesis of 4-amino[3,4-d]pyrimidines under reflux in acetic acid and microwave irradiation conditions in solventless system.

When a mixture of 5-amino-4 cyano-1-substituted-1H-pyrazoles-(**1**) and formamide in acetic acid in the presence of catalytic amount of a selected solid acid was refluxed, 4-amino[3,4-d]pyrimidines were obtained (Scheme 1). The results are summarized in Table 1. Boiling of the reactants in neat acetic acid in the absence of catalyst leads to obtain products in very poor yields.

The same reactions were carried out under solventless conditions under microwave irradiation. The reaction is simply conducted by grinding of an appropriate pyrazole derivative **1** with a selected solid acid and mixing them with formamide thoroughly in a beaker. The mixture was then placed in a micro-oven and irradiated. The progress of reactions were monitored by TLC. The results presented in Table 2 shows the catalytic efficiency of heteropolyacids under microwave irradiation in terms of reaction yields and rate of reactions. 12-Tungestophosphoric acid showed high catalytic activity for the synthesis of 4-amino-[3,4-d]pyrimidines, in both thermal and microwave conditions, whereas, sulfuric acid supported on to silica gel and HY-zeolite were almost inactive in thermal con-

Table 1
Catalytic synthesis of 4-amino[3,4-d]pyrimidines in acetic acid under thermal conditions

Compound	R_1	R_2	Percentage yield of product						mp/ref. (°C)	
			Reaction time (h)	$H_3PW_{12}O_{40}$ (%)	$H_3PMo_{12}O_{40}$ (%)	$H_3PW_{12}O_{40}/SiO_2$ (%)	$H_2SO_4/$ silica gel	HY-zeolite	Found	Reported (lit)
2a	H	CH_3	6	63	35	46	Trace	Trace	266	266–268 [15]
2b	H	CH_3	5	82	58	53	Trace	Trace	208	210 [15]
2c	H	2,4-Dinitrophenyl	8	44	26	29	Trace	Trace	300–302	
2d	CH_3	CH_3	7	59	40	45	Trace	Trace	288	186 [33]
2e	CH_3	Ph	6	75	45	63	Trace	Trace	220–221	

Table 2
Catalytic synthesis of 4-amino[3,4-d]pyrimidines under microwave irradiation (1000 W)

Compound	R_1	R_2	Time (min)	Percentage yield of product					mp/ref. (°C)
				$H_3PW_{12}O_{40}$ (%)	$H_3PMo_{12}O_{40}$ (%)	$H_3PW_{12}O_{40}/$ SiO_2 (%)	H_2SO_4/Silica gel (%)	HY-zeolite (%)	
2a	H	CH_3	12	71	66	59	48	28	266 [33]
2b	H	CH_3	10	88	68	61	38	35	210 [33]
2c	H	2,4-Dinitrophenyl	10	72	61	62	47	38	300
2d	CH_3	CH_3	12	88	72	58	50	43	288 [33]
2e	CH_3	Ph	8	81	77	63	41	32	230

ditions. The lower catalytic activity for 12-molybdophsphoric acid relative to 12-tungstophosphoric acid is probably caused by its high reducibility in organic substances. It is well known that by changing the central atom of heteropolyacid from a high valent to low valent element, its acidity decreases as a result of increasing the negative charge of heteropolyanion [30]. As reported earlier, when tungsten is replaced by molybdenum the negative charge on the oxygen atom increases which lead to decrease in acidity and the yield of reactions [31]. Generally speaking a heteropolyacid with tungsten addenda atom show higher acidity [30,31].

Interestingly, silica-supported sulfuric acid and HY-zeolite were inactive in thermal conditions but the yields of reactions with aforementioned catalysts, under microwave irradiation were quite acceptable.

Microwave assisted synthesis of 4-amino-pyrazolo[3,4-d]pyrimidines has several advantages over classical solution phase. It reduces the reaction time significantly and increases the yield considerably even in the case of pyrazoles containing electron withdrawing group such as cyano which hardly reacts in solution. Finally, it is worth to mention that the heteropolyacids used in this work can catalyze the reaction of pyrazoles **1** with formamid to 4-amino[3,4-d]pyrimidines in acetic acid as inexpensive solvent.

3. Experimental

3.1. Chemicals and apparatus

Phosphotungstic acid and molybdophosphoric acid were purchased from Merck Company. $H_3PW_{12}O_{40}/SiO_2$ was prepared by the known procedure [32]. HY-zeolite and $HCONH_2$ (formamid) were obtained from Merck Company and used as received. All solvents, sulfuric acid, and acetic acid were commercially available. Pyrazoles derivatives were prepared by the known procedures [15,33]. Sulfuric acid was supported onto

silica gel according to previously reported procedure [34]. The melting points were obtained using an electro thermal IA 9100 digital melting point apparatus. The IR spectra were recorded on a Bruker (400–4000 C m^{-1}) spectrometer. ^{1}HNMR spectra were recorded on a 100 MHz spectrometer using TMS as internal standard. Mass spectra were obtained from Varian CH-7 instrument at 70 ev. The microwave oven used, was LG MOD MC-838 WR.

3.2. Synthesis of 4-amino-pyrazolo[3,4-d]pyrimidines 2(a-e)

3.2.1. General procedure

Method 1: A solution of 1(a-e) (0.1 mmol) [15,33], formamide (0.2 mmol) and appropriate solid acid (0.05 mmol) in acetic acid (10 mL) was refluxed for 5–8 h (Table 1). The progress of the reaction was monitored by TLC using chloroform:methanol (9:1). After the reaction was completed, the catalyst was removed by filtration and washed with warmed acetic acid (the catalyst is insoluble in acetic acid). The filtrate was evaporated, and to the residue, water (10 mil) was added. The product was filtered and purified by recrystallization from water/ethanol (Table 1). The catalyst which was filtrated from the reaction, washed with diethyl ether, and dried in oven. It could be reused in the reactions under microwave irradiation and reflux condition without appreciable loss of activity. The catalyst was reused five times. The results of the first and last experiments were almost the same in term of yields and reaction times. All compounds (unknown and known) were characterized by mass, IR and ^{1}HNMR spectra (2a-g) (Table 3).

Method 2: An appropriate pyrazole (0.01 mmol) mixed with excess amounts of formamid (2 mil) and weight equivalent of an appropriate solid acid was added to the mixture in a beaker. The beaker was placed in microwave oven for indicated time (Table 2). The progress of the reaction was monitored by TLC, using chloroform:methanol (9:1) as eluent. Upon completion of

Table 3
H^1-NMR, mass and IR spectral data for (2a-e)

Entry	m/z mass	IR V^{max} Cm^{-1}(KBr)	^{1}HNMR
2a	148 (M$^+$)	3000–3200 (NH$_2$)	(DMSO-d$_6$) 3.92 (3H, CH$_3$, S) 7.68 (2H, br, NH$_2$) 8.10 (1H, S, CH pyrazole ring)
2b	211 (M$^+$)	3320 (NH$_2$), 1592 (Ar-H)	(DMSO-d$_6$) δ 8.4 (m, 3H, Ar-H) 7.51 (br, 2HNH$_2$) 8.2 (2H, m, Ar-H) 8.31 (1H, S, =CH)
2c	301 (M$^+$)	3350–3500 (NH$_2$)	(DMSO-d6) δ 7.2 (br, 2H, NH$_2$) 8.2 (1H, S, =CH) 8.5–9.1 (m, 3H, Ar-H)
2d	163 (M$^+$)	3100 (NH$_2$)	(DMSO-d$_6$) δ 3.36 (3H, S, CH$_3$) 2.42 (S, 3 H, CH$_3$) 7.4 (2H, br, NH$_2$)
2e	225 (M$^+$)	3350 (NH$_2$), 1580 (Ar-H)	(DMSO-d$_6$) δ 2.43 (3H, CH$_3$, S), 7.23 (5H, m, Ar-H) 7.3 (2H, br, NH$_2$) 9.1 (1H, C=H, S)

the reaction the catalyst was removed by filteration and washed with warm diethyl ether (the catalyst is insoluble in formamid and diethyl ether) and dried in oven. It was reused for one more time and the result of the first experiment and second experiment were almost consistent in yields. To the filtrate, water was added and the white crude product was purified by recrystallization from an appropriate mixture of water/ethanol.

4. Conclusion

Solid acid, $H_3PW_{12}O_{40}$ shows genuine catalytic activity in synthesis of 4-amino[3,4-d]pyrimidine. Combination of microwave irradiation and solid state chemistry in the synthesis of pyrazolo[3,4-d]pyrimidines, is very promising in the terms of mildness of reaction conditions, yields and time of reactions. It has also all advantages devoted to solvent-free reactions namely environmentally friendly conditions. $H_3PW_{12}O_{40}$ was the best solid acid as an eco-friendly, inexpensive, and recyclable catalyst for this reaction.

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