Tetrahedron Letters 50 (2009) 662–666

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A direct oxidative route for the synthesis of pyrimidines using heteropolyacids

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ARTICLE INFO

Article history:
Received 16 August 2008
Revised 17 November 2008
Accepted 25 November 2008
Available online 30 November 2008

Keywords:
Pyrimidines
Heteropolyacids
Recyclable catalyst
Keggin

ABSTRACT

Pyrimidines are synthesized via a direct oxidative one-pot, three-component, reaction between a 1,3-diketone, benzaldehydes and ammonium acetate in the presence of catalytic amounts of Keggin-type heteropolyacids under refluxing conditions in good yields.

Pyrimidines are of chemical and pharmacological interest[1,2] and compounds containing the pyrimidine ring system have been shown to possess antitumor, antibacterial, antifungal, antimalarial and anticonvulsant activities.[1–5] Some are valuable drugs for the treatment of hyperthyroidism, acute leukemia in children and adult granulocytic leukemia.[5] Furthermore, several pyrimidines are used in polymer and supramolecular chemistry.[6,7] Conjugated molecules which have a pyrimidine core as the key unit have received much attention and they are prospective candidates for light emitting devices[8] and molecular wires.[9]

2,4,6-Trisubstituted pyrimidines have been synthesized using various procedures including the reaction of amidines with α,β-unsaturated ketones,[10] dimerization–oxidative fragmentation of aryl-β-arylvinylimines,[11] condensation of phenacyldimethylsulfonium salts, aldehydes, and ammonia,[12] reaction of alkynes and nitriles in the presence of TfOH,[13] rearrangement of 2,4,5-trisubstituted-imidazolines,[14] the one-pot, three-component reaction of aryl halides, terminal propargyl alcohols and amidinium salts based upon a coupling-isomerization–cyclocondensation sequence,[15] arylation of halogenated pyrimidines via a Suzuki coupling reaction,[16] reaction of α,α-dibromo oxime ethers with Grignard reagents,[17] microwave-assisted reaction of amidines and alkynones,[18] and sequential assembly of aryl groups onto a pyrimidine core (2-methylthiopyrimidine).[19] However, in some of these methods the reactants including amidines, unsaturated ketones, aryl-β-arylvinylimines, sulfonium salts, imidazoline derivatives, and dihalo oxime ethers have to be synthesized separately, making them time consuming.

Due to the interesting properties of pyrimidines, the development of synthetic methods which enable a facile access to this heterocycle are desirable.

The development of methods using heteropolyacids (HPAs) as catalysts for synthetic processes related to fine chemicals, such as flavors and pharmaceuticals[20] has been under attention in the last decade. Catalysts based on heteropolyacids have many advantages over liquid acid catalysts. They are not corrosive and are environmentally benign and present fewer disposal problems. Solid heteropolyacids have attracted much attention in organic synthesis owing to easy work-up procedures and reduction of cost and waste due to recycling of the catalysts.[21]

Herein we report the synthesis of pyrimidines via the one-pot reaction of a 1,3-diketone, benzaldehydes and ammonium acetate in the presence of catalytic amounts of Keggin-type heteropolyacids (HPA) (Scheme 1).

In connection with our previous work using heteropolyacids,[22] we decided to employ the oxidative potential of Keggin-type heteropolyacids as well as their acidic properties as catalysts for a simple and efficient synthesis of pyrimidines.

We investigated the reaction of 1,3-diketones, benzaldehydes and ammonium acetate in the presence of catalytic amounts of Keggin-type heteropolyacids including $H_6[PMo_9V_3O_{40}]$, $H_5[PMo_{10}V_2O_{40}]$, $H_4[PMo_{11}VO_{40}]$ and $H_3[PMo_{12}O_{40}]$. Various parameters were investigated to obtain the optimum reaction conditions. The results on the synthesis of pyrimidines in the presence of catalytic amounts of $H_6[PMo_9V_3O_{40}]$ are summarized in Table 1.

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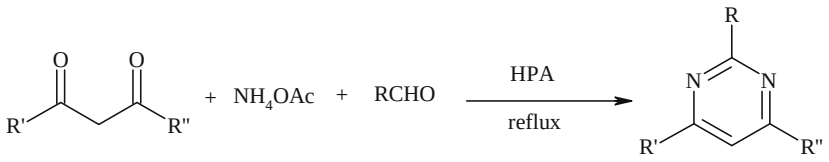
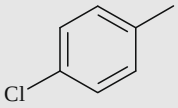
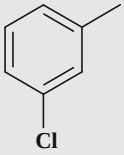
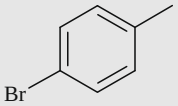
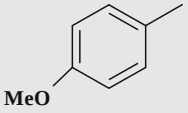
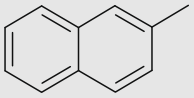
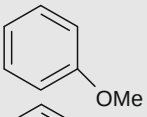
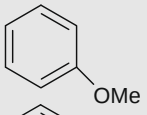
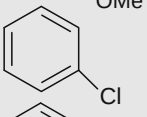
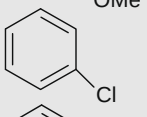
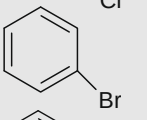
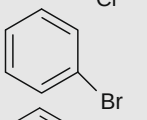
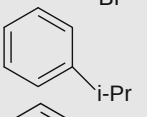
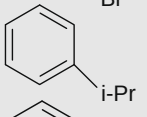
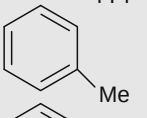
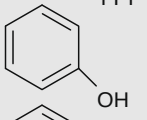
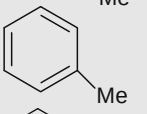
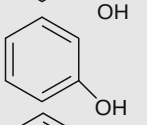
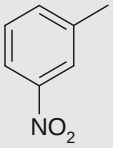
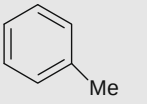
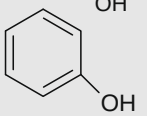
0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.11.105



Scheme 1.

Table 1
Synthesis of pyrimidines using $H_6[PMo_9V_3O_{40}]$ as catalyst under reflux (Scheme 1)

Entry	R	R′	R″	Time (h)	Yield[a] (%)
1	Ph	Ph	Ph	5	67
2		Ph	Ph	4.5	70
3		Ph	Ph	4.5	70
4		Ph	Ph	5	65
5		Ph	Ph	5	67
6		Ph	Ph	6.5	60
7	H	Ph	Ph	4	73
8	*n*-Bu	Ph	Ph	4.5	70
9	*n*-Pr	Ph	Ph	4.5	70
10	*n*-Bu			5.5	62
11	*n*-Bu			5	65
12	*n*-Bu			5	65
13	*n*-Bu			6	62
14	Me			6	63
15	Ph			6	64
16				6	65

[a] Yield refers to isolated products.

Considering a previous report on the potential of heteropolyacids for the oxidation of aldehydes to the corresponding benzoic acids,[23] a plausible mechanism for this reaction involves the initial oxidation of aldehydes to benzoic acids, then imination of the 1,3-diketone and nucleophilic attack of the imine on the benzoic acid (Scheme 2).

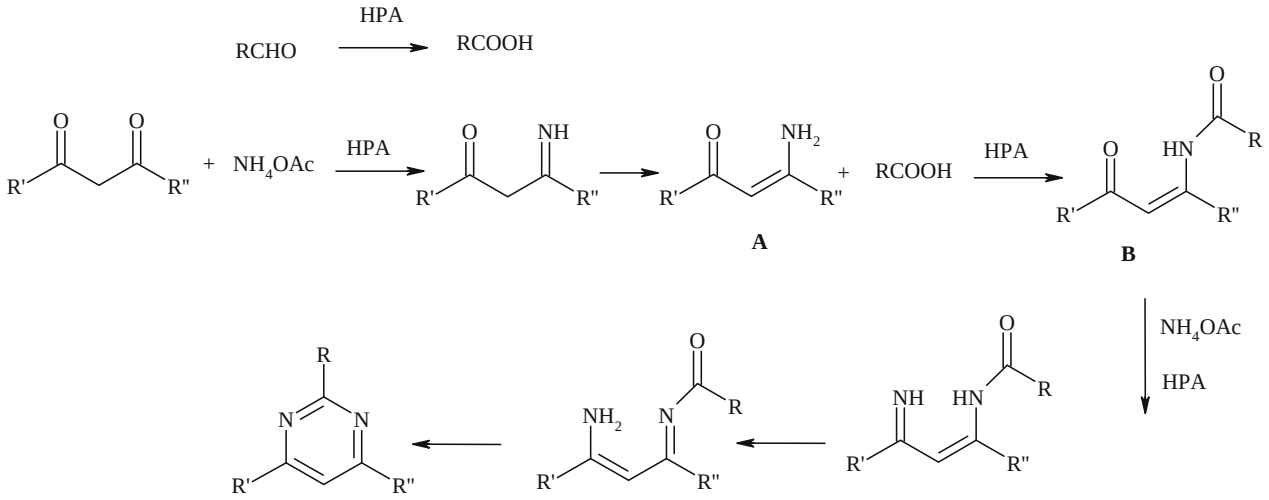
Another possible mechanism is double imination of the 1, 3-diketone, nucleophilic attack on the aldehyde and cyclization followed by the oxidation to the pyrimidine (Scheme 3).

To elucidate possible mechanistic routes, the reaction was monitored over a short time scale. The products were isolated and detected using GCMS and IR spectroscopy. The presence of a benzoic acid was clearly evident at an early stage of the reaction.

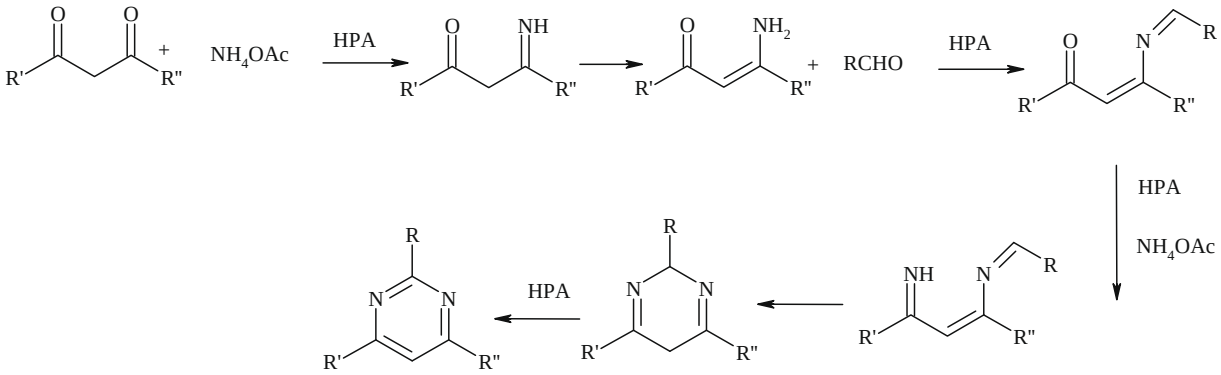
Further investigation on the reaction mechanism involved reaction of 1,3-diphenylpropane-1,3-dione, benzoic acid and ammonium acetate in the presence of a catalytic amount of $H_6[PMo_9V_3O_{40}]$ (Scheme 4) which led to the synthesis of 2,4,6-triphenylpyrimidine. This result supports the proposed mechanism shown in Scheme 2.

Heteropolyacids have both acidic and oxidative properties.[22–24] During the synthesis of pyrimidines from 1,3-diketones, benzoic acids and ammonium acetate, the heteropolyacid acts as an acidic catalyst, but in the reaction of 1,3-diketones, benzaldehydes and ammonium acetate, both acidic and oxidative properties of the heteropolyacid are in action.

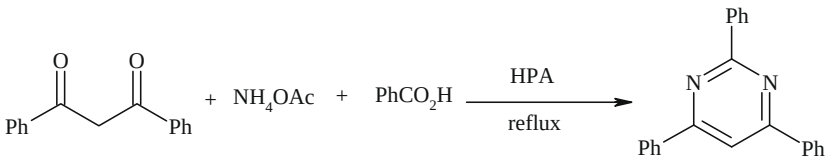
Although these observations help to establish the dominance of the mechanism in Scheme 2, for further clarification on the reaction mechanism, the synthesis of 2,4,6-triphenylpyrimidine was selected as a model reaction. Thus we synthesised the proposed intermediates of this reaction, that is, 3-amino-1, 3-diphenylpropenone**, A**, and *N*-(3-oxo-1,3-diphenylpropenyl)-benzamide**, B**.



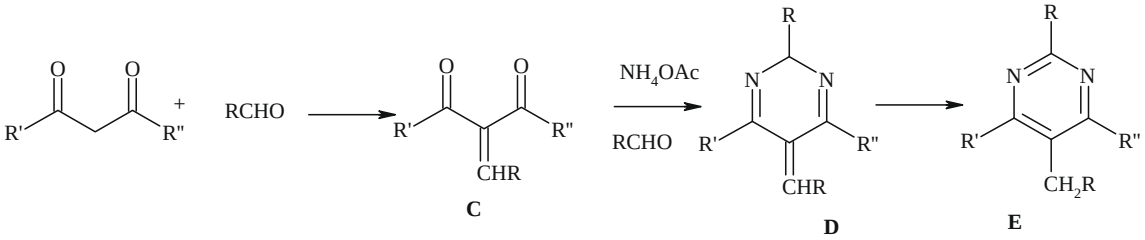
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

3-Amino-1,3-diphenylpropenone **A**, reacted with benzoic acid and ammonium acetate in the presence of $H_6[PMo_9V_3O_{40}]$ to afford 2,4,6-triphenylpyrimidine. Reaction of **B** with ammonium acetate in the presence of $H_6[PMo_9V_3O_{40}]$ also produced 2,4,6-triphenylpyrimidine. These results support the mechanism shown in Scheme 2.

In a previous report on the synthesis of pyrimidines via the one-pot condensation of β-dicarbonyl compounds, NH_4OAc and aldehydes,[25] several by-products were formed and harsh oxidation conditions, low yields and long reaction times were reported (Scheme 5).

Using the Keggin HPAs we detected alkene **C** only as a by-product in small amounts. As by-product **C** can only be formed from condensation of aldehydes and not benzoic acids with the 1,3-dicarbonyl compound, the small amount of this by-product supports the mechanism shown in Scheme 2.

To confirm that **C** was not an intermediate, we resubmitted it to the reaction. It was observed that neither the amount of this by-product nor the yield of pyrimidine changed.

This observation shows that **C** is only a by product and does not lead to pyrimidines by liberation of benzaldehyde.

To study the effect of the catalyst on this reaction, the synthesis of two pyrimidine derivatives were selected as model reactions and the yields of the products obtained using the Keggin heteropolyacids $H_5[PMo_{10}V_2O_{40}]$, $H_4[PMo_{11}VO_{40}]$, $H_6[PMo_9V_3O_{40}]$ and $H_3[PMo_{12}O_{40}]$ were compared and the results are reported in Table 2. The order of efficiency of these catalysts is as follows: $H_6[PMo_9V_3O_{40}] > H_5[PMo_{10}V_2O_{40}] > H_4[PMo_{11}VO_{40}] > H_3[PMo_{12}O_{40}]$. Thus, $H_6[PMo_9V_3O_{40}]$ was selected as the catalyst of choice for the synthesis of pyrimidines.

To determine the optimum amount of catalyst, the reaction was investigated using 0.1%, 0.3% and 0.5 mol % of $H_6[PMo_9V_3O_{40}]$. The results are shown in Table 3. It is clear that the yields depend on the amount of catalyst, the optimum amount of which was 0.3 mol % for all derivatives.

Synthesis of pyrimidines: To a mixture of 1,3-diketone, (10 mmol), benzaldehyde (10 mmol) and ammonium acetate (20 mmol), a catalytic amount of $H_6[PMo_9V_3O_{40}]$ (0.03 mmol) was added and the mixture was refluxed in CH_3CN (10 mL). The progress of the reaction was monitored by TLC. Upon completion, the catalyst was filtered off and the products were recrystallized from ethanol.

Table 2
Effect of various Keggin-type heteropolyacids on the yields of 2,4,6-triphenyl pyrimidines and 2-(4-chlorophenyl)-4,6-diphenylpyrimidine

Entry	R	Catalyst	Yield[a] (%)
1	Ph	$H_6[PMo_9V_3O_{40}]$	67
2	Ph	$H_5[PMo_{10}V_2O_{40}]$	64
3	Ph	$H_4[PMo_{11}VO_{40}]$	62
4	Ph	$H_3[PMo_{12}O_{40}]$	60
5	4-ClC_6H_4	$H_6[PMo_9V_3O_{40}]$	70
6	4-ClC_6H_4	$H_5[PMo_{10}V_2O_{40}]$	67
7	4-ClC_6H_4	$H_4[PMo_{11}VO_{40}]$	65
8	4-ClC_6H_4	$H_3[PMo_{12}O_{40}]$	61

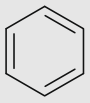
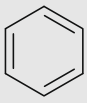
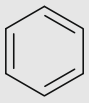
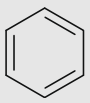
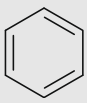
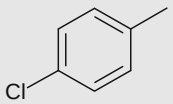
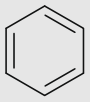
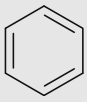
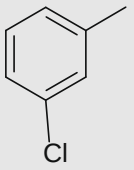
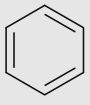
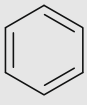
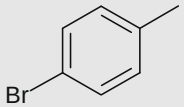
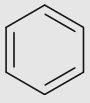
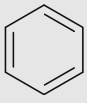
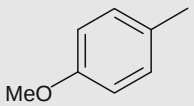
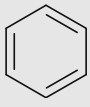
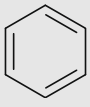
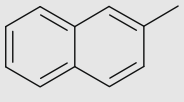
[a] Yield refers to isolated products.

Table 3
The results of using different amounts of $H_6[PMo_9V_3O_{40}]$ in the synthesis of 2,4,6-triphenylpyrimidines and 2-(4-chlorophenyl)-4,6-diphenyl-pyrimidine under reflux

Entry	R	Catalyst amount (mol %)	Yield[a] (%)
1	Ph	0.1	64
2	Ph	0.3	67
3	Ph	0.5	67
4	4-ClC_6H_4	0.1	65
5	4-ClC_6H_4	0.3	70
6	4-ClC_6H_4	0.5	71

[a] Yield refers to isolated products.

Table 4
A comparison of the recyclability of $H_6[PMo_9V_3O_{40}]$ for the synthesis of some pyrimidine derivatives over five runs

Entry	R′	R″	R	Yield[a] (%)				
				1st	2nd	3rd	4th	5th
1				67	65	63	60	59
2				70	68	66	64	63
3				70	88	86	86	64
4				65	63	62	60	68
5				67	65	63	62	61
6				60	58	56	54	54

[a] Yield refers to isolated products.

All the products were identified by comparison of their physical and spectroscopic data with those of authentic samples.[19,26,27]

Reusability of the catalyst: At the end of the reaction, the catalyst could be recovered by filtration. The recycled catalyst was washed with dichloromethane and subjected to a second reaction process. To confirm that the catalyst had not dissolved in the solvent the filtered catalyst was weighed before reuse and the results showed that the catalyst was not soluble in CH_3CN. Table 4 compares the efficiency of $H_6[PMo_9V_3O_{40}]$ in the synthesis of pyrimidines over five runs. The results show that the yield of product after five runs was only slightly reduced.

Acknowledgement

M.M.H. gratefully acknowledges partial financial support from the presidential office project no 87066/26.

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