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$H_3PMo_{12}O_{40}$ catalyzed three-component one-pot synthesis of 4,6-diarylpyrimidin-2(1*H*)-ones under solvent-free conditions

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Abstract

4,6-Diarylpyrimidin-2(1*H*)-one derivatives have been synthesized from three-component one-pot condensation of acetophenone derivatives, aldehydes and urea in the presence of trimethylsilyl chloride and a catalytic amount of $H_3PMo_{12}O_{40}$ under solvent-free conditions.

Keywords: 4,6-Diarylpyrimidin-2(1*H*)-ones; $H_3PMo_{12}O_{40}$; Solvent-less reactions; Biginelli like reactions; Heteropolyacids

Pyrimidin-2(1*H*)-ones and their derivatives show a wide range of biological, pharmaceutical and therapeutic activities [1–5]. In 1893, Biginelli reported one-step synthesis of 3,4-dihydropyrimidin-2(1*H*)-one in alcohol using strong mineral acid [6]. The scope of the original Biginelli reaction was gradually extended by the variation of all three building blocks, allowing access to a large number of multifunctionalized pyrimidone derivatives. Although, various methods are reported concerning the synthesis of pyrimidine derivatives, few one-pot syntheses [7–9] have been published using aromatic aldehydes, acetophenone derivatives and urea.

The substitution of traditional homogeneous Lewis and Brønsted acid catalysts by solid acid catalysts could constitute a more environmentally friendly alternative to the organic process. Such catalysts offer many advantages including: milder reaction conditions, easier separation of the catalyst from the reaction mixture by filtration, its possible regeneration and reuse, reducing the production of waste and thus harm to the environment.

Heteropolyacids, HPAs are valuable acid catalysts for various reactions which require strong acidity [10].

In continuation of our work on catalytic properties of heteropolyacids and solvent-free reactions [7,8,11], here we wish to report the catalytic activity of $H_3PMo_{12}O_{40}$ as a Keggin type HPA in the one-pot synthesis of 4,6-diarylpyrimidin-2(1*H*)-ones by condensing acetophenone derivatives, aldehydes and urea in the presence of trimethylsilyl chloride, under solvent-free conditions (Scheme 1).

Firstly, we studied the synthesis of 4,6-diphenyl-pyrimidin-2(1*H*)-one under different conditions as a model reaction. A shown in Table 1 the best results were obtained at 70 °C under solvent-free conditions.

This method was further employed to synthesize a variety of pyrimidinones. Electron withdrawing and donating aldehydes react without any significant loss in activity to give the desired products in good yields (Table 2).

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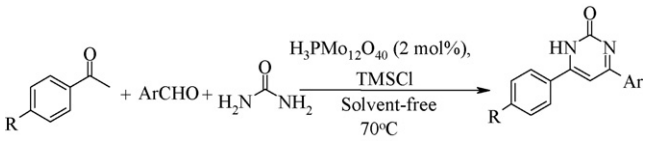


Scheme 1.

Table 1
Condensation of *p*-methoxyacetophenone, *p*-chlorobenzaldehyde and urea under different reaction conditions.

Entry	Solvent	Temperature (°C)	Time (h)	Yield (%)[a]
1	EtOH	78	2	40
2	H_2O	100	2	10
3	$CHCl_3$	62	2	15
4	CH_3CN	80	1 h	80
5	Solvent-free	70	15 min	95
6	Solvent-free	70	15 min	95, 91, 90[b]
7	Solvent-free	45	2	10
8	Solvent-free	25	12	0

[a] Yields are related to isolated pure products.
[b] Catalyst was reused for three times.

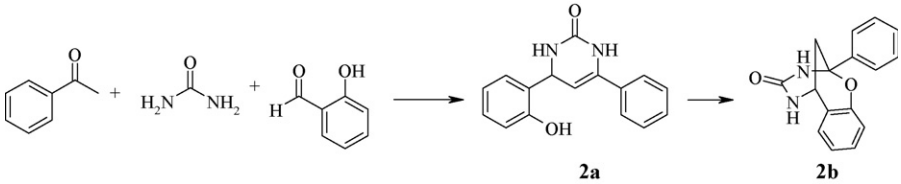
Table 2
Synthesis of 4,6-diarylpyrimidin-2(1*H*)-one derivatives in the presence of a catalytic amount of $H_3PMo_{12}O_{40}$ under solvent-free conditions.

Entry	Ar	R	Product	Time (min)	Yield (%)[a]
1	C_6H_5	H	**1a**	15	95
2	4-ClC_6H_4	H	**1b**	17	90
3	4-BrC_6H_4	H	**1c**	16	91
4	4-$CH_3C_6H_4$	H	**1d**	15	92
5	4-$(CH_3)_2CHC_6H_4$	H	**1e**	15	93
6	4-$CH_3OC_6H_4$	H	**1f**	19	91
7	4-ClC_6H_4	OCH_3	**1g**	18	93
8	C_6H_5	CH_3	**1h**	17	92
9	4-$CH_3C_6H_4$	CH_3	**1i**	17	90
10	4-BrC_6H_4	CH_3	**1j**	17	91
11	4-ClC_6H_4	NO_2	**1k**	25	90
12	2-OHC_6H_4[b]	H	**2b**	15	91

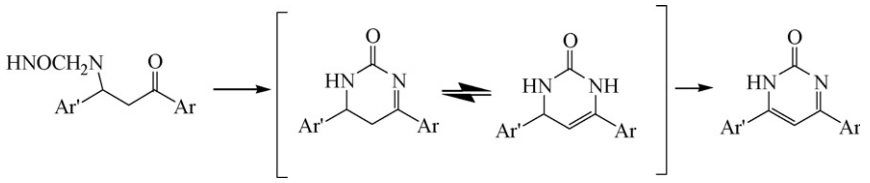
[a] Yields are related to isolated pure products.
[b] **2b** obtained as product.

In the case of 2-hydroxybenzaldehyde we obtained **2b** as major product (80%) (Scheme 2) [7].

To evaluate whether the reaction proceeds via a chalcone intermediate, the chalcone was separately treated with urea in the presence of heteropolyacid and TMSCl but the mixture failed to give any 4,6-diphenyl-1H-pyrimidin-2-one even after 10 h. To study the possibility of generation of HCl in this reaction, we perform the model reaction in the presence of HCl (5 mol%) instead of catalyst and TMSCl and obtained the same results (92%, 40 min). According to these results we propose a probable mechanism for this transformation (Scheme 3).



Scheme 2.



Scheme 3.

It is noteworthy to mention that the catalyst is recyclable and could be reused without significant loss of activity. It was recovered by adding acetonitrile, filtration of product, evaporation of solvent and washing with diethyl ether. The recycled catalyst could be used in other reactions. In the model reaction the results of the first experiment and the subsequent were almost consistent in yield after two runs (95%, 91, 90; Table 1, entry 6). It could be the reason that the heteropolyacid can be used in the catalytic amounts not in stoichiometric amounts.

In summary, we report here a high yielding synthesis of 4,6-diarylpyrimidin-2(1*H*)-ones from readily available ketones, aldehydes and urea in the presence of TMSCl using a catalytic amount of $H_3PMo_{12}O_{40}$ under solvent-free conditions. The conditions are mild and a wide range of functional groups can be tolerated. In solvent-free reactions the purification process is simplified and the reaction is cost efficient and environmentally friendly.

1. Experimental

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Bruker ARX 300 and 500 MHz instrument. IR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27. The reactions were monitored by TLC. All solvents and reagents were purchased from Aldrich and Merck with high-grade quality, and used without any purification. All of the products were known; their physical and spectroscopic data were compared with those of authentic samples and found to be identical [5,7,12].

In a vial equipped with a condenser, a mixture of ketone (1 mmol), aldehyde (1 mmol), urea (1.5 mmol) and TMSCl (1 mmol) was stirred in the presence of $H_3PMO_{12}O_{40}$ (2 mol%) at 70 °C. After completion of the reaction (TLC), acetonitrile was added to the reaction mixture and the obtained solid was washed with water (20 mL) and diethyl ether (20 mL) to eliminate the remained starting materials. All pure products were obtained in excellent yields without any recrystallization (90–95%).

After completion of the model reaction, acetonitrile was added to the reaction mixture and the solid was filtered off. Acetonitrile containing the catalyst was evaporated under reduced pressure. The obtained solid was washed with diethyl ether, dried and reused for the next reaction. In the case of the model reaction the catalyst recovered and reused for three times with only a modest loss in activity (Table 1, entry 6).

1a: M.p. 238–242 °C; IR (KBr) ν_{max} = 3358, 3159, 2960, 1612, 1502 cm^{-1}; ^{1}H NMR (DMSO-*d6*, 300 MHz): δ 7.56–7.67 (m, 7H, H-5 and H_{Ar}), 8.15–8.18 (m, 4H, H_{Ar}). **2b**: M.p. 296–298 °C; IR (KBr) ν_{max} = 3324, 3216, 3075, 2920, 1689, 1498, 1450 cm^{-1}; ^{1}HNMR (DMSO-*d6*, 300 MHz): δ 2.22 (d, 1H, J = 12.92 Hz, CH_2), 2.31 (dd, 1H, J = 12.92, 2.64 Hz, CH_2), 4.01 (d, 1H, J = 3.2 Hz, CH), 6.92–6.97 (m, 2H, H_{Ar}), 7.21–7.26 (m, 2H, H_{Ar} and NH), 7.39–7.47 (m, 4H, H_{Ar}), 7.64–7.67 (m, 2H, H_{Ar}), 7.55 (s, 1H, NH).

Acknowledgments

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