Indian Journal of Chemistry
Vol. 45B, October 2006, pp. 2325-2329

An environmentally benign protocol for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones using solid acid catalysts under solvent-free conditions

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Received 12 June 2006

Phosphotungstic acid/sulfated zirconia catalyzed one-pot condensation of aryl aldehydes, urea derivatives and β-diketones under microwave irradiation rapidly affords substituted 3,4-dihydropyrimidin-2(1*H*)-ones in excellent yields and high purity. The low cost catalysts have exhibited remarkable reactivity and reusability for the aforementioned synthesis.

Keywords: Phosphotungstic acid, sulfated zirconia, solvent-free synthesis, 3,4-dihydropyrimidin-2(1*H*)-ones, multicomponent condensation, green chemistry

IPC Code: Int.Cl.[8] C07D

In recent years, organic synthesis involving environment friendly protocol under solvent free conditions is being explored world wide due to stringent environment and economic regulations[1-3]. Majority of the existing processes in organic synthesis involves homogeneous, corrosive liquid acid catalysts, such as H_2SO_4, HCl and complexes of boron trifluoride, triflic acid. However, processes involving conventional liquid acids are inherently associated with problems such as high toxicity, corrosion, catalyst waste, difficulty of separation and recovery. Replacement of these conventional liquid acids by solid acid catalyst is highly desirable to achieve effective catalyst handling and product purification and to decrease waste production. Several solid acid catalysts such as zeolites, clays, composite oxides, MCM family of materials with tailor made acid functionality and pore structures have been reported in literature[1,2]. However, the sulfated metal oxides and heteropoly acids surpass the above mentioned catalysts in terms of their strong acidic properties[4,5]. These two classes of materials display strong Lewis and Brönsted acidic sites and the ratio of which can be controlled by suitable choice of the preparation conditions. Moreover, the acid strength of these materials, often equivalent to or greater than 100% H_2SO_4, is conducive to do reactions under mild conditions[4,5]. The mild reaction conditions also ensure greater selectivity to a preferred product compared to high temperature reactions. The HPAs, by virtue of their strong acid sites and redox characteristics have been used as catalysts under homogeneous as well as heterogeneous conditions[5,6]. The advantage of using HPAs under homogeneous condition lies in their high solubility in polar solvents such as water, alcohols and nitriles etc. After completion of the catalytic cycles, they can be easily isolated from the organic reaction media. These used catalysts can subsequently recrystallized and reused for successive cycles. As far as catalysis is concerned, Keggin type heteropoly acids have been widely investigated, because of their high structural and thermal stability with well defined acidic and redox properties. In recent years, the potential application of HPAs in synthetic organic chemistry have been illustrated for reactions such as deprotection of *t*-butyldimethylsilane[7], regioselective aerobic oxygenation of nitrobenzene to 2-nitrophenol[8] and oxidation of aliphatic, benzylic and allylic alcohols using dimethyl sulfoxides as oxygen transfer agents[9]. Similarly, the application of sulfated metal oxide catalysts such as sulfated zirconia has been demonstrated for several industrially important reactions such as isomerization of light *n*-alkanes, hydroisomerization, hydrocracking, alkylation and oligomerizations under mild conditions[10-13]. The strength of the surface acidic sites in sulfated zirconia has been found to be greater than many of the conventional solid acid catalysts such as silica-alumina, clays and zeolites[2-4]. Generation of acidic sites on sulfated oxides thought to proceed by a two

stage reaction mechanism involving grafting of the sulfate species during impregnation step followed by dehydration of the grafted species at higher temperatures [2]. Different reaction schemes have been proposed in literature to account for the observed Brönsted and Lewis acidity in sulfated zirconia[14]. The surface exposed low coordinated positively charged Zr species act as Lewis acid sites whereas the water molecules coordinated to the Zr ions act as source of Brönsted acidic centers. Although there are few investigations on the application of HPAs and sulfated zirconia in organic synthesis, still there is vast scope to explore these materials in synthesis, particularly involving multi-component condensation under solvent free conditions.

3,4-Dihydropyrimidin-2(1*H*)-ones (DHPMs) and their synthetic analogues are importance class of compounds with promising biological activities such as antibacterial, antiviral, anti-inflammatory and antitumor[15]. For example, the aryl derivatives of dihydropyrimidones SQ32926 and SQ32547 show similar pharmacological properties as that of dihydropyridines[16]. Other biological activities of DHPMs include α_{1a} adrenergic receptor antagonists as drug candidates for the treatment of benign prostatic hyperplasia[17]. Recently, monastrol has been identified as a lead compound of a new class of anticancer agents acting as cell division (mitosis) blockers (**Figure 1**, ref.18).

The synthesis of DHPMs is thus of significant importance in organic synthesis due to their wide range of biological activities. In continuation of our interest to develop greener protocols for organic transformations, we herein report the application of HPAs and sulfated zirconia as catalysts for synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones using a multi-component condensation approach.

Experimental Section

Phosphotungstic acid, zirconium oxychloride, conc. sulfuric acid and liquid ammonia solution were obtained from S. D. Fine Chemicals Ltd. India. Melting points were determined using a Micro Scientific Works apparatus and are uncorrected. IR spectra were recorded on a JASCO IR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer. Reactions were monitored by TLC on 0.2 mm silica gel F-254 plates. A conventional household microwave oven operating at 900 W was used as an energy source for the reaction. All the products are characterized by comparing their IR, ^{1}H NMR and melting points with those reported in literature.

Preparation of sulfated zirconia

The sulfated zirconia catalysts were prepared by equilibrium adsorption of sulfate species on the surface of hydrous zirconium oxide samples. The hydrous zirconia materials were prepared by precipitation method using $ZrOCl_2.8H_2O$ and liquid ammonia solutions. Required amount of zirconyl chloride solution were added dropwise to 200 mL of deionised water whose *p*H was previously adjusted to 11 by addition of liquid ammonia solution. During the addition of zirconyl chloride solution, the *p*H of the mixture was found to decrease due to the hydrolysis of the zirconium salt. The *p*H was maintained at 11.0 by controlled addition of ammonia solution to the reaction mixture. The precipitated solution was stirred for 6 hr at room temperature followed by filtration and washing with double distilled water until free from chlorine ($AgNO_3$ test). The hydroxide precipitate were subsequently dried at 120°C overnight and calcined at 400°C for 2 hr to generate hydrous zirconium oxide. The sulfation experiment was carried out by suspending the ZrO_2 powder in 0.5 *M* H_2SO_4 solution. After 24 hr of stirring, the precipitate was filtered, washed with 0.05 *M* H_2SO_4, dried at 120°C, and calcined for 1 hr at 500°C to yield the sulfated zirconia catalyst.

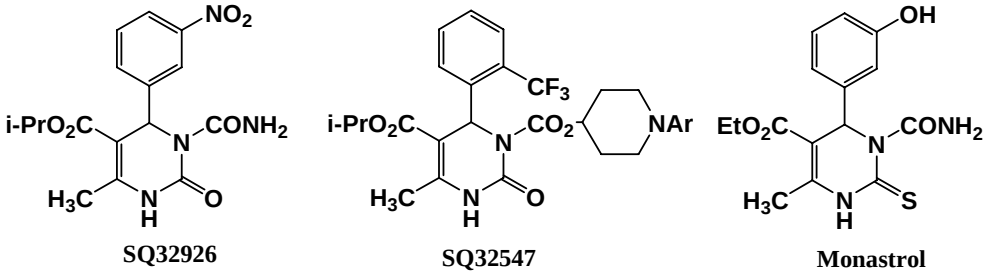


Figure 1

Synthesis of ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate

A neat mixture of benzaldehyde (1 mmole), urea (1.5 mmole), ethyl acetoacetate (1 mmole) and PWA (0.05 mole %) in a beaker was exposed to microwave for three successive irradiation of 30 s each with cooling and mixing interval of 30 s (total exposure time 90 s). The reaction mixture was allowed to cool and the ensuing solid contents were stirred with water (20 mL) at room temperature for 1 hr. The solid product was filtered, washed with water, dried and upon recrystallization from ethanol afforded the pure ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate in 92% yield (entry 1); m.p. 204-205°C; IR (KBr): 3240, 3100, 1740, 1700, 1650 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.13 (t, 3H, J = 7.50 Hz, CH_3), 2.26 (s, 3H, CH_3), 4.01 (q, 2H, J = 7.52 Hz, OCH_2), 5.15 (d, 1H, J = 3.00 Hz, H-4), 7.21-7.40 (m, 5H, Ar-H), 7.76 (s, 1H, NH), 9.24 (s, 1H, NH). In case of sulfated zirconia catalyst, the reaction product was recovered from a 10 mL hot methanol solution after filtering out the heterogeneous catalyst.

Results and Discussion

The synthesis of DHPMs has been accomplished by classical Biginelli reaction, involving condensation of aldehydes, urea derivatives and β-dicarbonyl compounds under strong acidic conditions[19]. In the past, many reagents have been utilized to improve the reaction conditions and yields of the products[20-24]. Some of the existing procedures involve strong acids namely sulphuric acid, hydrochloric acid, borontrifluoride etherate, copper triflate etc., under harsh reaction conditions and yields are moderate to good. Further, some of the procedure requires use of more stoichiometric amounts of Lewis acids, longer reaction time and separation of product from catalysts. Additionally, a few of the reagents found to react rapidly with water and get deactivated. Recently, microwave irradiation has improved the time and yield of Biginelli reaction under solvent-free conditions[25,26].

In the present investigation, a reaction mixture consisting of aryl aldehyde, urea and ethyl acetoacetate in presence of PWA was exposed to microwave intermittently for 30 seconds (**Table I**). The homogeneous mixture quickly turned solid at room temperature and led to the isolation of pure 3,4-dihydropyrimidin-2(1*H*)-one in good yield (**Scheme I**). The amount of PWA was varied and found that 0.05 mole % is ideally suited for the efficient condensation of all the three-components.

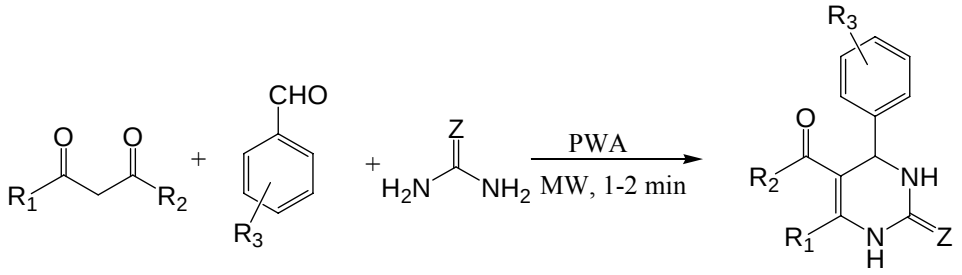
Under similar condition, aromatic aldehydes bearing electron-withdrawing and -donating groups afforded the corresponding DHPMs in high yields and purity (**Table I**). In order to study the generality of this protocol, acetylacetone and benzoylacetone were used in place of ethyl acetoacetate. Reaction was found to proceed relatively faster in case of benzoylacetone and the corresponding products were obtained in high yields. Furthermore, replacing urea with thiourea does not influence the outcome of the reaction significantly. During the work-up of reaction mixture, PWA was separated as aqueous solution, evaporated to dryness, regenerated at 250°C and reused. The catalyst has been successfully reused, second and third time and obtained DHPM in almost similar yield (entry 1, **Table I**, 89% and 86%, respectively). In absence of heteropoly acids, the

Table I — PWA-catalyzed one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones

Entry[a]	R_1	R_2	R_3	Z	Time (s)	Yield[b] (%)	m.p.
1	CH_3	OC_2H_5	H	O	90	92	198-200
2	CH_3	OC_2H_5	*p*-NO_2	O	60	89	206-207
3	CH_3	OC_2H_5	*m*-NO_2	O	90	92	228-229
4	CH_3	OC_2H_5	*p*-Cl	O	90	95	213-215
5	CH_3	OC_2H_5	*p*-OCH_3	O	120	89	199-201
6	CH_3	OC_2H_5	H	S	120	91	194-196
7	CH_3	CH_3	H	O	90	95	233-234
8	CH_3	CH_3	OCH_3	O	120	91	169-170
9	CH_3	CH_3	*p*-NO_2	O	90	96	230-232
10	CH_3	C_6H_5	H	O	90	95	203-204
11	CH_3	C_6H_5	OCH_3	O	90	89	218-220

[a]All products were identified using comparison of their physical and spectral data (IR and NMR) with those reported in the literature[20-25]

[b]Isolated yields



(Scheme I)

Table II — Sulfated zirconia-catalyzed synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones

Entry [a]	R_1	R_2	R_3	Z	Time (s)	Yield [b] (%)	m.p.
1	CH_3	OC_2H_5	H	O	90	86	198-200
2	CH_3	OC_2H_5	*p*-NO_2	O	60	94	206-207
3	CH_3	OC_2H_5	*m*-NO_2	O	90	91	228-229
4	CH_3	OC_2H_5	*p*-Cl	O	90	91	213-215
5	CH_3	OC_2H_5	*p*-OCH_3	O	120	79	199-201
6	CH_3	OC_2H_5	H	S	120	90	194-196
7	CH_3	CH_3	H	O	90	91	233-234
8	CH_3	CH_3	OCH_3	O	120	84	169-170
9	CH_3	CH_3	*p*-NO_2	O	90	94	230-232
10	CH_3	C_6H_5	H	O	90	88	203-204
11	CH_3	C_6H_5	OCH_3	O	90	81	218-220

[a] All products were identified using comparison of their physical and spectral data (IR and NMR) with those reported in the literature [20-25]
[b] Isolated yields

reaction remains incomplete and impurities were increased upon further exposure to microwave for an extended period.

In case of the sulfated zirconia catalyst, the reaction was found to complete in a time span of 90-120 seconds with good yields of all the products. The variety of substrates containing different functional groups/substituents were explored and found that this protocol is very useful in preparing wide variety of 3,4-dihydropyrimidin-2(1*H*)-ones in high yield. After completion of the reaction, the solid mixture was taken into 10 mL of hot methanol to dissolve the product.

The heterogeneous sulfated zirconia catalyst was easily separated from the solution mixture by simple filtration. The used sulfated zirconia catalysts were reactivated by heat treatment at 400°C for 1 hr in air. The regenerated catalyst was reused for three consecutive circles without loosing its activity (entry-2, **Table II**, 94%, 1st; 91%, 2nd; 89%, 3rd). Overall, it is observed that both the catalysts are highly active for multiple-component condensation and rapidly afforded all the products in fairly good yields. The protocol described herein is advantageous in terms of preclusion of toxic solvents, catalytic amount of reagent, shorter reaction time, high yield and purity of the products.

Conclusion

In conclusion, a simple, efficient and cost effective method is described for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones. This environmentally benign and safe procedure is advantageous in terms of experimentation, catalyst reusability, yields of the products, short reaction times and preclusion of toxic solvents. Additionally, this protocol is adaptable to parallel synthesis and generation of combinatorial library of potentially biological active DHPMs.

Acknowledgement

Financial support from the institute is gratefully acknowledged.

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