Sulfated zirconia and phosphotungstic acid catalyzed synthesis of some biologically potent heterocyclic compounds

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Abstract
Sulfated zirconia and phosphotungstic acid (PWA) have been used as catalysts for the synthesis of some biologically potent 3,4-dihydropyrimidin-2(*1H*)-ones and aryl-14H-dibenzo[*a.j*]xanthenes under solvent free conditions. Both the solid acid catalysts are found to be active for the synthesized compounds under mild reaction conditions. The 3,4-dihydropyrimidin-2(*1H*)-ones were synthesized in a single step using multi-component condensation of aryl aldehyde, urea derivatives and β-dicarbonyl compounds using PWA or sulfated zirconia as catalysts. The generality of this protocol has been demonstrated by synthesizing a variety of functional dihydropyrimidin-2(*1H*)-ones in excellent yield and short reaction time. Phosphotungstic acid has also been demonstrated as an efficient catalyst for the condensation of aryl aldehydes and β-napthol to produce aryl-14H-dibenzo[*a.j*]xanthenes under solvent-free conditions. The reaction is found to proceed quickly in presence of catalytic amount of phosphotungstic acid and brief exposure to microwave to afford the products in good yield.

Keywords: Sulfated zirconia; 3,4-dihydropyrimidin-2(*1H*)-ones; Phosphotungstic acid; aryl-14H-dibenzo[*a.j*]xanthenes; Microwave irradiation; solvent-free conditions

1. Introduction

In recent years, organic synthesis involving greener process and under solvent free conditions is being explored world wide due to stringent environment and economic regulations [1]. Homogeneous, corrosive liquid acid catalysts, such as H_2SO_4, HCl and complexes of BF_3 are frequently used in organic synthesis. However, processes involving conventional acids are inherently associated with problems such as high toxicity, corrosion, catalyst waste, difficulty in separation and recovery. Replacement of these conventional acids by solid catalyst is desirable to achieve effective catalyst handling, product purification and to decrease waste production. Considering the facts that most of the organic reagents involved in fine chemical synthesis are sensitive to high temperatures, it is desirable to choose catalysts which can catalyze organic transformations under mild conditions. In this context, the sulfated metal oxides and heteropoly acids deserve special mention. Both the classes of catalysts possess strong surface acidic sites, easily recoverable and reusable properties, environment friendly and are stable in many reaction media. Sulfated zirconia has been demonstrated to be efficient catalyst for several industrially important reactions such as isomerization,

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hydroisomerization, hydrocracking, alkylation and oligomerization reactions under mild reaction conditions [2-4]. Similarly, new applications of hetropoly acids in synthetic organic chemistry has been disclosed in recent years which include deprotection of t-butyldimethylsilane [5], regioselective aerobic oxygenation of nitrobenzene to 2-nitrophenol [6] and oxidation of aliphatic, benzylic and allylic alcohols using dimethyl sulfoxides as oxygen transfer agents [7]. Thus it is highly desirable to explore and exploit the potential of these catalysts for organic reactions involving synthesis of fine chemicals.

Synthesis of 3,4-dihydropyrimidin-2(1H)-ones has received significant attention in natural and synthetic organic chemistry because of their promising therapeutic and pharmacological properties [8-10]. Some of 3,4-dihydropyrimidin-2(1H)-ones has been evaluated as antihypertensive agents, calcium channel blockers, and α_1-1a- antagonists. Recently, monastron, has been identified as a lead compound of a new class of anticancer agents [11]. First synthesis of these dihydropyrimidones was reported by Biginelli involving one-pot condensation of 1,3-dicarbonyl compound, aldehyde, and urea under strongly acidic conditions [12]. The major drawback of this method was the low to moderate yields that are frequently encountered when using substituted aromatic aldehydes. Since then various reagents have been employed for this conversion. These include among others: BF_3.OEt, $FeCl_3$, $InCl_3$, $BiCl_3$, $LaCl_3$, $LiClO_4$, Iodine, clays, etc [8]. However, most of these methods suffer from drawbacks such as stoichiometric amounts of catalysts, purification of products, extended reaction time and moderate yields. Recently, use of microwave irradiation as an unconventional energy source has greatly improved the time and yield of Biginelli reaction under solvent-free conditions [13]. A rapid protocol that proceeds under catalytic condition and in quantitative yield is highly desirable. Particularly, reaction under solvent-free conditions offers many advantages such as high yield, selectivity, short reaction time and reduces environmental pollution [14].

Xanthenes are an important class of biologically active heterocycles with potential applications as antibacterial, anti-inflammatory and antiviral agents [15]. These compounds are also used as dyes, fluorescent probes for detection of biomolecules and in laser technologies [16, 17]. In past years, many synthetic methods have been reported for preparation of xanthenes which include reaction of β-Naphthol with aldehydes or acetals under acidic conditions, cyclocondensation between 2-hydroxyaromatic aldehydes and 2-tetralone, cyclodehydrations, alkylations γ to the heteroatoms, and intramolecular phenyl carbonyl coupling reactions of benzaldehydes and acetophenones [18-21]. However, most of these synthetic procedures involve conventional methods and suffer from drawbacks such as longer reaction times, low yields, harsh reaction conditions and utilization of excess of reagents and catalysts. Recently, sulfamic acid and molecular iodine have also been reported to be highly active for synthesis of benzoxanthenes from β-naphthol and aromatic aldehydes [16, 17]. In continuation of our interest to develop environment friendly protocols using solid acid catalysts under solvent free conditions, we report the synthesis of

3,4-dihydropyrimidin-2(1H)-ones and aryl-14H-dibenzo[a.j]xanthene using sulfated zirconia and PWA catalysts under solvent free conditions and microwave irradiation [22, 23].

2. Experimental

2.1 Reagent and analysis

Zirconium oxychloride and liquid ammonia solution were obtained from S. D. Fine Chemicals Ltd. India. Phosphotungstic acid was procured from C. D. H. Ltd., India. Melting points were measured on a Micro Scientific Works apparatus and are uncorrected. IR spectra were recorded on a JASCO IR spectrophotometer. ^{1}H NMR spectra were recorded on Bruker 400 MHz NMR spectrometer. Reactions were monitored by thin layer chromatography on 0.2 mm silica gel F-254 plates. A conventional household microwave oven operating at 900 W was used for irradiation. All the products are known compounds and are characterized by comparing their IR, ^{1}H NMR and melting points with those reported in literature.

2.2 Preparation of sulfated zirconia

The sulfated zirconia catalyst was prepared by equilibrium adsorption of sulfate species on the surface of hydrous zirconium oxide samples. The hydrous zirconia catalysts were prepared by precipitation method using $ZrOCl_2.8H_2O$ and liquid ammonia solutions. Required amount of zirconyl chloride solution was added dropwise to 200 mL of deionised water whose pH was previously adjusted to 11.0 by addition of liquid ammonia solution. During the addition of zirconyl chloride solution, the pH of the mixture was found to decrease due to the hydrolysis of the zirconium salt. The pH was maintained at 11.0 by controlled addition of ammonia solution to the reaction mixture. The precipitated solution was stirred for 12 h 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 overnight at 120 ^oC and calcined at 400 ^oC for 2 h to generate hydrous zirconium oxide. The sulfation experiment was carried out by suspending the hydrous ZrO_2 powder in 0.5 M H_2SO_4 solution. After 24 hr of stirring, the oxide residue was filtered, washed with 0.05 M H_2SO_4, dried at 120^oC, and calcined for 1 hr at 500^oC to yield the sulfated zirconia catalyst.

2.3 Preparation of ethyl 6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate

A neat mixture of *m*-nitrobenzaldehyde (1 mmol), urea (1.5 mmol), ethyl acetoacetate (1 mmol) and the solid acid catalyst (100 mg) in a 20 ml beaker was exposed to microwave for three successive irradiation of 30 s each with cooling and mixing interval of 30 s (90 seconds). After each successive irradiation the progress of the reaction was monitored using TLC. After the completion of the reaction, in case of heteroply acid, the reaction mixture was transferred into 20 ml of distilled water and stirred for 1 h. The solid product so obtained was filtered and recrystallized from ethyl acetate to afford pure ethyl 6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate. In case of sulfated zirconia catalyzed reaction, the solid reaction mixture was taken into hot methanol and the catalyst was removed by simple filtration under hot condition. The final product was recovered from the methanolic solution and recrystallized from ethyl acetate. Using similar procedure other

compounds indicated in Table 1 were prepared.

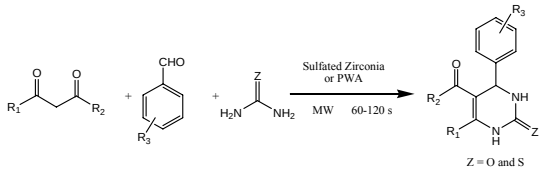
2.4 Preparation of 14-(4-Nitrophenyl)-14H-dibenzo[a.j]xanthene

The xanthenes were also prepared using a similar protocol described in section 2.3. Briefly, a neat mixture of *p*-nitrobenzaldehyde (1 mmol), β-napthol (2 mmol) and phosphotungstic acid (100 mg) in a 20 ml beaker was exposed to microwave irradiation for 60 s in two successive irradiations. After the completion of the reaction, the reaction mixture was transferred to 20 ml of double distilled water, stirred for 1 h, filtered and the ensuing solid product was recrystallized.

3. Results and Discussion

3.1 Synthesis of 3,4-dihydropyrimidin-2(1H)-ones

The synthesis of 3,4-dihydropyrimidin-2(*1H*)-ones was carried out by one pot condensation of aryl aldehydes, urea derivatives and β-diketones using sulfated zirconia or phosphotungstic acid as catalysts (Scheme 1). Initially, the reaction conditions were varied by using different amount of substrates and catalysts, in different polar and nonpolar solvent and using the conventional oil bath as a heating source. The preferred ratio of aryl aldehyde, β-diketones and urea was found to be 1:1:1.2 and 100 mg of the catalyst ideally suited for the efficient condensation of three-components. Further increase in the catalyst amount did not show any marked increase in the yield of the products. Moreover, it was observed that the reaction proceeds rapidly under solvent free conditions and microwave radiation significantly accelerates the reaction rate for this multi-component condensation reaction.



(Scheme 1)

The optimized reaction condition for 1 mmol scale of the reactants requires 100 mg of sulfated zirconia or PWA under solvent-free conditions using microwave irradiation. Table 1 shows the yields of the different 3,4-dihydropyrimidin-2(*1H*)-ones prepared using the optimized protocol. Both the catalysts are found to be highly active for the condensation of aryl aldehydes, urea derivatives and β-diketones, and all the reactions completed within 90-120 seconds. Under similar reaction condition, aromatic aldehydes containing electron-withdrawing and donating groups afforded the corresponding 3,4-dihydropyrimidin-2(*1H*)-ones in high yields and purity. The acetylacetone and benzoylacetone were also used in place of ethyl acetate as the β-diketones which are found to be equally effective and corresponding products were achieved in high yields. Furthermore, replacing urea with thiourea also yields the corresponding 3,4-dihydro pyrimidin-2(*1H*)-ones.

Variation of different substituents and functional groups in the substrates effectively demonstrates the generality of this procedure for synthesis of structurally diverse 3,4-dihydropyrimidin-2(*1H*)-ones. After the completion of the reaction, the sulfated zirconia catalyst was recovered by simple filtration from a hot methanolic solution of the product. The used sulfated zirconia catalyst was reactivated by heat treatment at 400^{o}C for 1 hr in air. The regenerated catalyst

Table 1. PWA or sulfated zirconia catalyzed synthesis of 3,4-dihydropyrimidin-2(*1H*)-ones

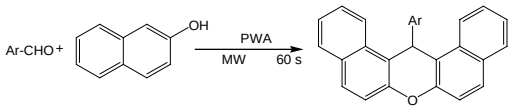
Entry[a]	R_1	R_2	R_3	Z	Time (s)	Yield[b] (%)	
						PWA	sulfated zirconia
1	CH_3	OC_2H_5	H	O	90	92	86
2	CH_3	OC_2H_5	*p*-NO_2	O	60	89	94
3	CH_3	OC_2H_5	*m*-NO_2	O	90	92	91
4	CH_3	OC_2H_5	*p*-Cl	O	90	95	91
5	CH_3	OC_2H_5	*p*-OCH_3	O	120	89	79
6	CH_3	OC_2H_5	H	S	120	91	90
7	CH_3	CH_3	H	O	90	95	91
8	CH_3	C_6H_5	H	O	90	95	88

[a]All the products are characterized by mp, ^{1}H NMR and IR. [b] Yields refers to pure and isolated products

was used for the second consecutive cycle without significantly loosing its activity (Entry 2, yields, 94%, 1st; 91%, 2nd). In case of the PWA catalyst, the reaction residue was dispersed in 20 ml of double distilled water and stirred for 1 h at room temperature. The solid 3,4-dihydropyrimidin-2(*1H*)-ones were filtered and recystallized. The PWA being a water soluble acid was recovered from the aqueous solution and reactivated with known procedures. Overally, the method described for the synthesis of 3,4-dihydropyrimidin-2(*1H*)-ones involving sulfated zirconia or PWA as catalysts is advantageous in terms of solvent free condition, shorter reaction time, high yields and purity of the products.

3.2 Phosphotungstic acid catalyzed synthesis of aryl-14H-dibenzo[a.j]xanthenes

Phosphotungstic acid was also used as an environmentally benign solid acid catalyst for synthesis of aryl-14H-dibenzo[*a.j*]xanthenes by the condensation of β-napthol and aryl aldehydes (Scheme 2). As mentioned in the previous section, the reaction conditions are varied to optimize the protocol. It was observed that 100 mg of phosphotungstic acid is quite efficient for the condensation of β-napthol and aryl aldehydes to produce the corresponding xanthenes under solvent free condition and microwave irradiation.



(Scheme 2)

The generality of the protocols was also ascertained by taking different aryl aldehydes bearing electron withdrawing and releasing groups. Table 2 shows the yields of the different aryl-14H-dibenzo[*a.j*]xanthenes prepared using the optimized protocol. The reaction was found to proceed rapidly for all the aryl aldehydes. The catalyst was found to be highly active to afford all the products in good yields upon brief exposure of reaction mixture to microwave irradiation. After completion of the reaction, the residue was dispersed in 20 ml of double distilled water and stirred for 1 h at room temperature. The solid products were removed from the aqueous mixture by simple filtration and purified by

Table 2. PWA catalyzed one-pot synthesis of aryl-14H-dibenzo[*a.j*]xanthene

Entry	Ar-CHO	Time (s)	Yield (%)	MP (^oC)
1	C_6H_5CHO	90	91	184
2	*p*-NO_2 C_6H_4CHO	60	94	314
3	*m*-NO_2 C_6H_4CHO	60	88	214
4	*p*-CH_3O-C_6H_4CHO	90	85	204
5	*p*-Cl-C_6H_4CHO	60	92	285

recystallization from an appropriate solvent. The PWA catalyst was recovered from the aqueous solution and reused for a second consecutive cycle without any marked decrease in the activity. Overally, this protocol is quite simple and convenient to obtain aryl-14H-dibenzo[*a.j*]xanthenes in high yield and purity, that precludes the use of toxic solvents and hazardous conventional mineral and organic acids as catalysts. Furthermore, this method is advantageous in term of short reaction time, quantitative yield of the products and catalyst recyclability.

4. Conclusion

In this report, we have developed two novel protocols for synthesis of 3,4-dihydropyrimidin-2(*1H*)-ones and aryl-14H-dibenzo[*a.j*]xanthene using environmentally benign sulfated zirconia or phosphotungstic acid as solid acid catalysts. The catalysts due to their inherent surface strong acidic sites are highly active for the described organic transformations. The protocol is advantageous in term of simple experimentation, solvent free conditions, catalyst reusability, high yield and purity of the product and short reaction time. Furthermore, the protocols described in this work are amenable for the parallel synthesis of the biologically important 3,4-dihydropyrimidin-2(*1H*)-ones and aryl-14H-dibenzo[*a.j*]xanthenes.

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