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Poly Phosphoric Acid Impregnated on Silica Gel (PPA-SiO_2): A Versatile and Reusable Catalyst for the Synthesis of 1,2,4,5-Tetrasubstituted Imidazoles under Solvent-free and Microwave Irradiation Conditions

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ABSTRACT

A remarkable acceleration in the synthesis of 1,2,4,5-tetrasubstituted imidazoles catalyzed by silica gel supported poly phosphoric acid in high yields under solvent-free and microwave irradiation conditions, with very short reaction time is described. This methodology offers momentous improvements over various options for the synthesis of 1,2,4,5-tetrasubstituted imidazoles with regard to yield of produces, simplicity in operation and green aspects by avoiding toxic catalysts and solvents.

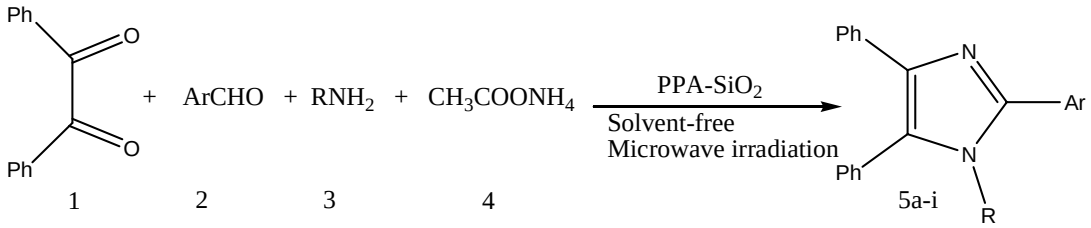
Key words: Tetrasubstituted imidazole, PPA-SiO_2, solvent-free conditions, Multi-component reaction, Microwave irradiation.

INTRODUCTION

The multi-or three-component, one pot reactions are highly important because of their wide range of applications in pharmaceutical libraries for drug discovery[1-5]. MCRs are extremely convergent, producing a remarkably high increase of molecular complexity in gust one step. Microwave irradiation promoted organic condensation has attracted intense interest as a synthetically useful technique for the preparation of a variety of heterocyclic compounds[6-9]. As an important member of the five-membered ring heterocycles, imidazoles moiety is present in a wide range of naturally occurring molecule[10,11]. Compounds with imidazol moiety have many pharmaceutical activities[12,13]. The biological important of the imidazol ring system has made it a common structure in numerous synthetic compounds, such as fungicides[14], herbicides[15], plant growth regulators[16] and therapeutic agents[17]. Various methods have been reported for the synthesis of tetrasubstituted imidazole, including four components condensation of 1,2-diketones, aromatic aldehydes, primary amines and

ammonium acetate in the presence of several catalysts such as HY zeolite[18], carbon-based solid acid[19] and molecular iodine[20], $InCl_3.3H_2O$ [21], 3-methyl-1-(4-sulfonicacid)-butylimiduzolium hydrogen sulfate[22] and $HClO_4$-SiO_2 [23], BF_3. SiO_2 [24], bronsted acidic liquid[25], ZnO [26] heterocope rearrangement[27] and condensation of a 1, 2-diketone with aryl nitril and primary amine under microwave irradiation[28]. However, most of the methods to prepare tetrasubstituted imidazole derivatives suffer, from certain drawbacks including long reaction times, unsatisfactory yields and often, harsh reaction conditions. To avoid these limitations, the discovery of mild and efficient catalyst with high catalytic activity, and very short reaction time, under solvent-free and microwave irradiation conditions is still being actively pursued for the synthesis of tetrasubstituted imidazoles. There is an increasing interest in the use of environmentally feasible reagents, particularly in solvent-free conditions avoiding organic solvents during reactions in organic synthesis leads to a clean, efficient and economical technology, not only with the increased safety simplicity of workup and reduction of cost, but also increased amount of reactants can be achieved in the same equipment without huge modifications. Reactivity and sometimes selectivity may be enhanced without dilution[29]. Although, the catalytic applications of silica supported reagents for organic synthesis have been established, to the best of our knowledge, there is no report in the literature on the use of PPA-SiO_2 in synthesis of tetrasubstituted imidazole, under microwave irradiation conditions.

It has been realized in recent years that solid-supported reagents, such as silica gel-supported acids, could be used as a multipurpose acid catalyst[30-34]. In continuation of our work on the development of useful synthetic methodologies by employing solid acid catalyst and use of microwave irradiation[35-38], in this article, we report that PPA-SiO_2 is a highly efficient and economical viable catalyst for the one-pot synthesis of 1,2,4,5-tetrasubstituted imidazoles (5a-i) from benzil 1, aromatic aldehydes 2, primary amines 3 and ammonium acetate 4 under solvent-free and microwave irradiation conditions (Scheme 1).



Scheme 1: Synthesis of 1,2,4,5-tetrasubstituted imidazoles

EXPERIMENTAL

All chemical were available commercially and used without additional purification. The catalyst was synthesized according to the literature[39]. Melting points were recorded on an electro thermal type 9100 melting point apparatus. The IR spectra were obtained using a 4300 shimadzu spectrophotometer as KBr disks. The ^1H NMR (500MHz) spectra were recorded with a Bruker DRX 500 spectrometers.

Preparation of the catalyst (PPA-SiO_2)

PPA (2.1g) was charged in the round-bottom flask and $CHCl_3$ (100ml) was added. After the mixture was stirred at 50°C for 1h SiO_2 (200-400 mesh, 4.9g) was added to the solution and mixture was stored for another 1h. The $CHCl_3$ was removed with rotary evaporator and the resulting solid was dried in vacuum at r.t for 3h.

General procedure for the synthesis of 1,2,4,5-tetrasubstituted imidazole

A mixture of benzil (1mmol), aromatic aldehyde (1), primary amine (1mmol), ammonium acetate (1) and PPA-SiO_2(10) was subjected to microwave irradiation at 600w for indicated time. The

progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, boiling ethanol was added and the mixture stirred for 3 min. The catalyst was filtered under hot condition. After cooling the filtrate, the precipitated solid was filtered and recrystallized from ethanol to give compounds 5a-i in high yields(see Table 1). The structures of the products were confirmed by ^{1}H NMR, IR spectra and comparison with authentic samples prepared by reported methods[18-28].

Recycling and reusing of the catalyst

At the reaction mixture was cooled to room temperature and hot ethanol was added. The catalyst was recovered by filtration, dried at 100°C under vacuum for 2h and reused in another reaction. The catalyst could be reused at least four times with only slight reduction in the catalytic activity of the catalyst.

RESULTS AND DISCUSSION

The application of microwave irradiation to organic synthesis for conducting reaction at accelerated rates is an emerging technique. In fact, in recent years, the use of microwave has become popular among chemists both as a means to improve classical organic rections (shortening rection times and/or improving yields) and promote new reactions[40-42]. Availability of suitable commercial microwave equipments, domestic ovens and

Table 1: Effect of PPA-SiO_2 amount on the model reaction[a]

Entery	Catalyst (mg)	Time (min)	Yield (%)[b]
1	Non	120	……
2	5	30	75
3	10	15	88
4	15	20	87
5	20	20	85

[a]1mmol benzil, 1mmol benzaldehyde, 1mmol aniline, and 1mmol ammonium acetate, under solvent-free and microwave irradiation conditions at 600w.
[b]isolated yield.

Table 2: Synthesis of 1,2,4,5-tetrasubstituted imidazoles 5a-i[a]

Entry	Ar	R	Product[b]	Time (min)	Yield (%)[c]	m.p.(°C)	
						Found	Reported
1	C_6H_5	C_6H_5	5a	15	88	214-216	213-215[25]
2	4-ClC_6H_4	C_6H_5	5b	20	95	145-147	146-148[25]
3	4-ClC_6H_4	4-ClC_6H_4	5c	20	96	188-190	188-190[25]
4	4-MeC_6H_4	4-ClC_6H_4	5d	15	95	169-171	168-170[25]
5	4-MeC_6H_4	4-MeC_6H_4	5e	15	94	188-190	190-192[25]
6	4-MeC_6H_4	C_6H_5	5f	15	92	179-181	183-184[25]
7	4-MeC_6H_4	$CH_2C_6H_4$	5g	12	93	160-161	163-165[25]
8	C_6H_5	$CH_2C_6H_4$	5h	12	97	162-164	161-163[25]
9	4-$MeOC_6H_4$	$CH_2C_6H_4$	5i	15	87	157-158	155-157[25]

[a]1mmol benzil, 1mmol aromatic aldehyde, 1mmol primary amine, 1mmol ammonium acetate, and 10mg PPA-SiO_2 under solvent-free and microwave irradiation conditions at 600w.[b]All the products were characterized by comparision of their spectroscopic and physical data with authentic samples synthesized by reported procedures.[c]isolated yields.

monomode reactors has also contributed to the development of this technique significantly. Therefore, in this paper, we decided to investigate the efficiency of PPA-SiO_2 as solid acid catalyst in the synthesis of 1,2,4,5-tetrasubstituted imidazoles under microwave irradiation conditions. To initiate our study, in order to optimize the reaction conditions, the one-pot synthesis of 1,2,4,5-tetraphenyl imidazole (5a) was used as a model reaction. The reaction was carried out by microwave irradiation a mixture of benzil(1), benzaldehyde(1), aniline (1) and ammonium acetate (1) under various amount of PPA-SiO_2 as catalyst under solvent-free and microwave irradiation conditions at 600w (Table 1). The efficiency of the reaction is affected mainly by the amount of PPA-SiO_2 (Table1). No products were produced in the absence of catalysts (Entry 1). To give the product, the catalyst is necessary for the reaction. Increasing the amount of the catalyst, increased the yield of the product 5a. The optimal amount of PPA-SiO_2 was 10 mg (Entry 3), increasing the amount of the catalyst beyond this value did not increase the yield noticeably(Entries 4,5).

Table 3: Reusability of catalyst for model reaction

Entry Cycle	1 Fresh	2 First	3 Second	4 Third
Yield(%)[a]	88	86	86	84

[a]Isolated yield

Based on the above result, this process was then extended to variety of aromatic aldehydes and primary amines at the optimized system. The type of aldehydes and amines had no significant effect on the reaction. In all cases, aromatic, aldehydes and primary amines with substituents carrying either electron donating or electron- withdrawing groups reacted successfully and gave the expected products in high yields in very short reaction time. The results are summarized in table 2.

The reusability of the catalyst was checked by the same model reaction under optimized conditions. After completion of the reaction, the catalyst was filtered under hot condition, washed with ethanol, dried and reused for the same reaction process. As shown in table 3, the catalyst could be reused at least four times with only slight reduction in the catalytic activity of the catalyst.

CONCLUSION

In summary, we have successfully developed a very simple, mild and efficient methodology for the preparation of a wide variety of tetrasubstituted imidazoles through one-pot multicomponent reaction of benzil, aromatic aldehyde, primary amines and ammonium acetate employing PPA-SiO_2 as the recyclable solid acid catalyst under solvent-free and microwave irradiation conditions for the first time. Other advantages of this protocol are high yields, short reaction time, easy work-up and omitting any volatile and hazardous organic solvents.

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