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$P_2O_5.SiO_2$: An efficient catalyst for the one-pot synthesis of 1,2,4,5-tetrasubstituted imidazoles

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Silica supported phosphorus pentoxide (P_2O_5/SiO_2) is an efficient, readily available and reusable catalyst for the synthesis of 1,2,4,5-tetrasubstituted imidazoles using benzil, an aromatic aldehyde and an amine in the presence of ammonium acetate.

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1. Introduction

Neat P_2O_5 is an inexpensive, heterogeneous, commercially available and selective acidic reagent which react with water to produce phosphoric acid. It is difficult to handle due to moisture sensitivity. Silica supported phosphorus pentoxide (P_2O_5/SiO_2) is less hygroscopic, more stable and reactive than neat P_2O_5. Recently, P_2O_5/SiO_2 was applied for acetals [1] and acylals [2] formation, the synthesis of Z-aldoximes [3], sulfonylation [4], nitration [5] of aromatic compounds, Ritter [6] and Schmidt [7] reactions and condensation of indoles with carbonyl compounds [8]. The presence of an imidazole ring in many biological systems such as Losartan, Olmesartan, Trifenagrel, Eprosartane [9], natural and pharmacologically active [10] compounds has instituted a diverse array of synthetic approaches to these heterocycles [11].However, despite intensive efforts, only a handful of general methods exist for the construction of tetrasubstituted imidazoles. Recently, the synthesis of 1,2,4,5-tetrasubstituted imidazoles has been catalyzed by silica gel or Zeolite HY [12], silica gel/$NaHSO_4$ [13], molecular iodine [14], $K_5CoW_{12}O_{40}.3H_2O$ [15], heteropolyacids [16], $HClO_4$-SiO_2 [17], $InCl_3.3H_2O$ [18], ZrCl4 [19], and $BF_3.SiO_2$ [20].

2. Experimental

2.1. General

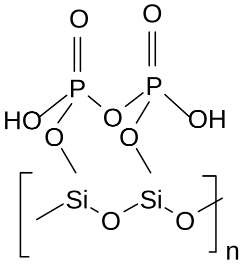
Melting points were measured with an Büchi melting point B-540 B.V.CHI apparatus and are uncorrected. IR spectra were recorded with a Bruker, Eqinox 55 spectrometer. ^1H NMR spectra were recorded with a BRUKER 400 MHz AVANCE spectrometer. NMR spectra were obtained on solutions in $CDCl_3$. All the products are known compounds, which were characterized by IR and ^1H NMR spectral data and their mp's compared with literature reports.

2.2. General procedure for the synthesis of 1,2,4,5- tetrasubstituted imidazoles

Benzil (5 mmol), amine (10 mmol), aldehyde (10 mmol), ammonium acetate (10 mmol) and $P_2O_5.SiO_2$ (50% w/w) (0.5 g) were placed in a round bottom flask. The reactants were mixed and heated at 140 ºC for 2.5 hours (Table 2). The progress of the reaction was followed by TLC. After completion of the reaction, the mixture was cooled to room temperature. Chloroform was added to the mixture which was filtered to remove the catalyst. After evaporation of the solvent, an oily residue or an impure solid was obtained. By adding ethanol and water to the residue, a milky to yellow solid was obtained. The solid was then crystallized from ethanol. All the products are known and were identified by comparison of their physical and spectral data with those of authentic samples.

3. Results and discussion

For identification of the structure of P_2O_5/SiO_2,we studied five IR spectra of P_2O_5, H_3PO_4, P_2O_5/SiO_2, H_3PO_4/SiO_2 and SiO_2 (Fig. 1). In all of the spectrums, OH stretching band is observed and strong intermolecular hydrogen bonding occurs in the hydroxyl groups. Therefore, the resulting O-H absorption is broad. Infrared spectra of P_2O_5/SiO_2 and H_3PO_4/SiO_2 are similar. In both of them, the absorbtion Si-OH and Si-O-Si bands are appeared in 797 or 800 cm^{-1} and ~1100 cm^{-1}, respectively. In H_3PO_4 spectrum, the absorbtion of Si-O-Si and Si-OH bands are not observed. Because of variety of O-H bands in P_2O_5/SiO_2 spectrum, the O-H band is broader than O-H band in SiO_2 spectrum. In P_2O_5/SiO_2 spectra, stretching band of SiO-H appear in 3406 cm^{-1}, stretching and bending bands of P(O)OH appear 2933, 2363 cm^{-1} and 1638 and 1000 cm^{-1}, respectively. The strong peak at 1250 cm^{-1} is stretching band of P=O and the strong peak at 1092 cm^{-1} is stretching band Si-O-Si.[26] Also the strong peak at 900 cm^{-1} is stretching band of P–O–P and the weak peak at 797 cm^{-1} is related to stretching band of remaining Si–OH. As shown in Fig. 1, in structure of P_2O_5/SiO_2, the majority of hydroxyl groups in SiO_2 (SiO-H) react with P_2O_5. Therefore, hydroxyl band in SiO_2 (797 cm^{-1}) is very weak. Based on these results, we suggest the following structure for P_2O_5/SiO_2 (Scheme 1).



Scheme 1. The proposed structure for P_2O_5/SiO_2.

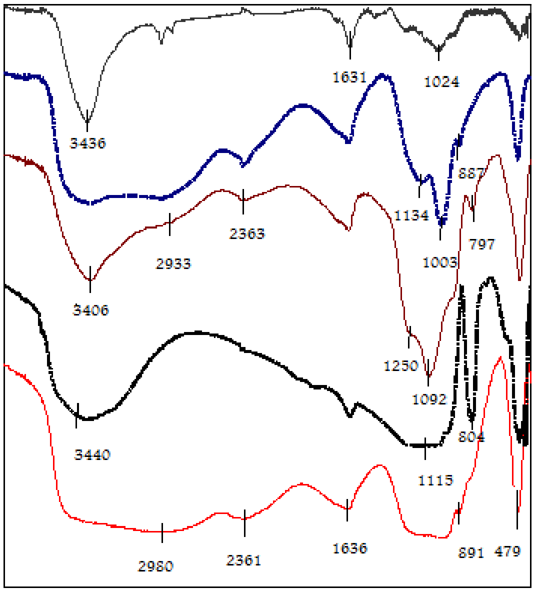
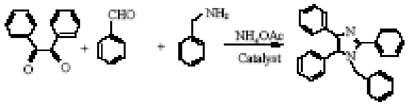


Fig 1. FT-IR spectrum of: (a) P_2O_5, (b) H_3PO_4, (c) 50%P_2O_5/SiO_2, (d) SiO_2, (e) H_3PO_4/SiO_2.

In continuation of our investigations on solid acids in organic synthesis, we investigated the synthesis of 1,2,4,5-tetrasubstituted imidazoles in the presence of various solid acids under thermal and solvent-free conditions. Herein, we report that P_2O_5/SiO_2 is an efficient and reusable catalyst for the synthesis of 1,2,4,5-tetrasubstituted imidazoles and is comparable with some other catalysts such as $K_5CoW_{12}O_{40}.3H_2O$, $HClO_4$-SiO_2, $BF_3.SiO_2$ and $SiO_2/NaHSO_4$. To optimize the reaction conditions, the reaction of benzaldehyde, benzyl amine, benzil and ammonium acetate was used as a model reaction (Table 1). This reaction under different conditions such as ultrasonic and microwave irradiation and normal heating was demonstrated. An unmodified domestic MW oven at 475 W and ultrasonic apparatus, BANDELIN, HD 3200 was used. Reactions at different conditions and various molar ratio of substrates in the presence of $P_2O_5.SiO_2$ revealed that the best conditions were normal heating under solvent-free at 140 ºC and a molar ratio of aldehyde:amine:benzil:ammonium acetate: 50 % $P_2O_5.SiO_2$ equal to 2:2:1:2:0.35. The reusability of the $P_2O_5.SiO_2$ catalyst was also examined. After each run, the product was filtered, the solvent evaporated and the residue (reagent) was washed with $CHCl_3$ and reused. Apparently, treatment with $CHCl_3$ removes tars more efficiently from the catalyst surface (Table 1, entry 21). This catalyst was reusable, although a gradual decline in activity was observed. The applicability of our protocol to a large scale process was examined with 50 mmol of benzil, 100 mmol of 4-methyl benzaldehyde and 100 mmol of benzylamine which gave 1-benzyl-2-(4-methyl phenyl)-,4,5-di-phenyl imidazole in 85% yield. Next, benzil, various aldehydes and amines were used as substrates for the synthesis of 1,2,4,5-tetrasubstituted imidazoles (Scheme 2 and Table 2).

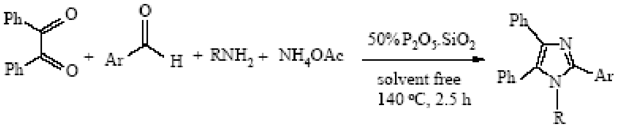
Table 1. Acid catalyzed synthesis of 1-benzyl-2,4,5-triphenyl- imidazole[a].



Entry	Catalyst	Temp. (℃)/ Time (min)/ Yield(%)[b]	Ref.
1	$H_4[PMo_{11}VO_{40}]$ (1 mol %)	78/8/88	16
2	$K_5CoW_{12}O_{40}.3H_2O$ (0.1 mol %)	140/120/95 MW/2/95	15
3	$SiO_2/HClO_4$ (1 mol %)	140/6/96	17
4	Zeolite HY (1 g)	MW/6/83	12
5	$InCl_3.3H_2O$(10 mol %)	r.t./450/85	18
6	$ZrCl_4$ (20 mol %)	r.t./60/79	19
7	37% BF_3/SiO_2 (21 mol %)	140/120/86	20
8	$ZnCl_2$ (70 mol %)	140/120/80	-
9	$AlCl_3$ (70 mol %)	140/180/82	-
10	$Al(HSO_4)_3$(30 mol %)	140/240/69	-
11	$H_3PW_{12}O_{40}$ (3.5 mol %)	140/150/78	-
12	$Mg(HSO_4)_2$(31 mol %)	140/240/77	-
13	Silica sulfuric acid (0.1 g)	140/150/60	-
14	P_2O_5 (70 mol %)	140/150/80	-
15	Silica gel (0.1 g)	140/150/72	-
16	Silica gel (1 g)	MW/6/87	12
17	10% P_2O_5/SiO_2 (7 mol %)	140/150/77	-
18	30% P_2O_5/SiO_2 (21 mol %)	140/120/85	-
19	50% P_2O_5/SiO_2 (35 mol %)	140/120/92	-
20	70% P_2O_5/SiO_2 (49 mol %)	140/120/93	-
21	50% P_2O_5/SiO_2 (35 mol %) 2nd run	140/120/85	-

[a]The used amount of benzaldehyde, benzyl amine, benzil and ammonium acetate is 2:2:1:2 mmol.

[b]Isolated yield.



Scheme 2

Table 2. P_2O_5/SiO_2 catalyzed synthesis of 1,2,4,5-tetrasubstituted Imidazoles ^{a}**.**

Ent.	Ar	R	Yield (%)^{b}	M.P. °C$^{ref.}$
1	C_6H_5	C_6H_5	79	216 – 218[17]
2	C_6H_5	$C_6H_5CH_2$	87	163 – 165[15]
3	C_6H_5	Cyclohexyl	56	167 – 169[12]
4	C_6H_5	CH_3CH_2	60	115 – 117[12]
5	4-ClC_6H_4	C_6H_5	78	149 – 151[14]
6	4-ClC_6H_4	$C_6H_5CH_2$	79	162 – 165[17]
7	2-ClC_6H_4	$C_6H_5CH_2$	80	140 – 142[17]
8	4-OHC_6H_4	$C_6H_5CH_2$	62	134 – 135[17]
9	4-$CH_3C_6H_4$	C_6H_5	75	185 – 188[16]
10	4-$CH_3C_6H_4$	$C_6H_5CH_2$	90	165 – 166[12]
11	4-$CH_3C_6H_4$	Cyclohexyl	70	162 – 164[12]
12	3-$OMeC_6H_4$	$C_6H_5CH_2$	90	128 – 130[17]
13	2-$NO_2C_6H_4$	$C_6H_5CH_2$	89	152 – 155[17]
14	$(CH_3)_2CH$	$C_6H_5CH_2$	55	129-130[17]

^{a}Molar ratio of benzil:aldehyde: amine :ammonium acetate: 50% $P_2O_5.SiO_2$ is 1:2: 2:2:0.35.

^{b}Isolated yield

4. Conclusion

In conclusion, we have demonstrated an simple method for the synthesis of 1,2,4,5-tetrasubstituted imidazoles using $P_2O_5.SiO_2$ as an reusable, eco-friendly, inexpensive and efficient reagent. Short reaction times, High yield, Scale- up, simplicity of operation and easy work-up are some advantages of this method.

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