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Synthesis of 1,3,5-tri-substituted pyrazoles promoted by $P_2O_5.SiO_2$

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ABSTRACT

Silica supported phosphorus pentoxide ($P_2O_5 \cdot SiO_2$) is an efficient catalyst for synthesis of 1,3,5-substituted pyrazoles via the condensation of 1,3-diketones and hydrazines. Simplicity of procedure, mild condition, being solvent-free, high yields, and easy workup are some advantages of this protocol.

Keywords: *$P_2O_5.SiO_2$, 1,3,5-tri-substituted pyrazoles, 1,3-diketones, Hydrazines, Solvent-free*

1. Introduction

Pyrazole derivatives have a wide range of biological activities. They can be used as anti-inflammatory [1], antipyretic [2], gastric secretion stimulatory [3], antidepressant [4], anti rheumatoid arthritis [5], antibacterial [6], anticonvulsant [7] antitumor [8], antipsychotic [9], antimicrobial [10], antiviral [11], antifungal and antifilarial agents [12]. They also serve as herbicides [13], fungicides [14], pesticides [15] dyestuffs [16], and insecticides [17].

pyrazoles can be synthesized *via* 1,3-dipolar cycloaddition of diazo compounds [18], reaction of chalcones [19] and hydrazines, a four-component coupling of terminal alkynes, hydrazine, carbon monoxide, and aryl iodides [20], and the direct condensation of 1,3-diketones and hydrazines in the presence of an acidic catalyst [21]. The last one is the simplest and most straightforward procedure for the synthesis of pyrazoles. A variety of catalysts such as H_2SO_4 [22], polystyrene supported sulfonic acid [23], layered zirconium sulfophenyl phosphonate [a-$Zr(CH_3PO_3)_{1.2}(O_3PC_6H_4SO_3H)_{0.8}$] [24], $Sc(OTf)_3$ [25], Y-zeolite [26] and $Mg(ClO_4)_2$ [27] have been employed to affect this transformation.

Neat P_2O_5 is an inexpensive, heterogeneous, commercially available and selective acidic reagent which reacts with water to produce phosphoric acid. It is difficult to handle due to its moisture sensitivity. Silica supported phosphorus pentoxide ($P_2O_5 \cdot SiO_2$) is less hygroscopic, more stable and reactive than neat P_2O_5. Recently, $P_2O_5 \cdot SiO_2$ was applied for acetals [28] and acylals [29] formation, the synthesis of Z-aldoximes [30], sulfonylation [31], nitration [32] of aromatic compounds, ritter [33] and schmidt [34] reactions, and condensation of indoles with carbonyl compounds [35].

2. Experimental

2.1. General

The products were characterized by elemental analysis, ATR of FT-IR, ^{1}H-NMR, and ^{13}C-NMR spectra. IR spectra were run on a Bruker, Eqinox 55 spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were obtained by a Bruker Avans 400 and 500 MHz spectrometers (DRX). Elemental analyses were done by Costech ECS 4010 CHNS-O analyser. Melting points were determined by a Buchi melting point B-540 B.V.CHI apparatus and are uncorrected.

2.2. Synthesis of 37% $P_2O_5 \cdot SiO_2$

3.7 g of P_2O_5 was added to a suspension of 6.3 g of silica gel in chloroform in a beaker. The suspension was mixed for 20 minutes, filtered, washed with chloroform and dried in room temperature. The obtained white solid can be stored in a suitable vessel at least for 6 months.

2.3. General procedure for the synthesis of pyrazole derivatives

A mixture of 1, 3-diketone (2 mmol), hydrazine derivatives (2 mmol) and 37% $P_2O_5 \cdot SiO_2$ (0.16 g) or nano-48% $P_2O_5 \cdot SiO_2$ (0.04 g) was heated at 120 ˚C. The progress of the reaction was monitored by TLC. After the completion of the reaction, the mixture was washed with chloroform and filtered to recover the catalyst. The filtrate was evaporated and the crude product was re-crystallized from ethanol and
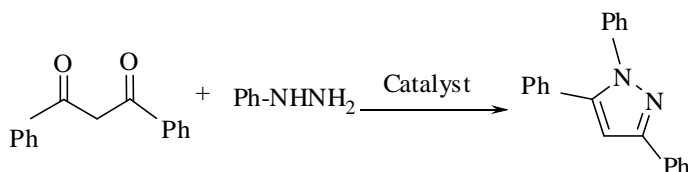
water to afford the pure pyrazole derivatives in 70-94% yields.

The selected spectral data

1-(2-Chlorophenyl)-3,5-diphenyl-pyrazole (Table 2, entry 10). IR (ATR, neat, cm^{-1}): 1598, 1543, 1488, 1458, 1360, 1212, 1074, 971, 806, 757, 691.^{1}H NMR (400 MHz, CDCl$_3$ ppm) δ: 6.90 (s, 1 H), 7.28 (m, 4 H), 7.38 (m, 3 H), 7.43 (4 H), 7.52 (m, 1 H), 7.94 (d, *J*= 8.4 Hz, 2 H). ^{13}C-NMR (100 MHz, CDCl$_3$ ppm) δ: 103, 126, 127.6, 127.9, 128.1, 128.4, 128.5, 128.7, 130.1, 130.3, 130.5, 132.4, 133.05, 138.2, 146.3, 152.4.

3. Results and Discussion

In continuation of our investigations on the applications of solid acids in organic synthesis [36, 37], we have studied the synthesis of pyrazoles derivatives in the presence of P$_2$O$_5$·SiO$_2$ *via* condensation of 1,3-diketones and hydrazines. The reaction of phenylhydrazine (2 mmol) with 1,3-pentanedione (2 mmol) was investigated for the optimization of the reaction conditions (Table 1). At different temperatures and various molar ratios of substrates in the presence of P$_2$O$_5$·SiO$_2$, the reaction revealed that the best conditions were solvent-free at 120 ℃ and a ratio of

Table 1. Synthesis of 1,3,5-triphenyl-pyrazole in various conditions.

Entry	Catalyst (g)	Solvent	Conditions	Time (h)	Yield (%)	Ref.
1[a]	-	Solvent-free	120 ℃	2	12	-
2[a]	25% P$_2$O$_5$·SiO$_2$ (0.1)	Solvent-free	120 ℃	2	50	-
3[a]	30% P$_2$O$_5$·SiO$_2$ (0.1)	Solvent-free	120 ℃	2	55	-
4[a]	37% P$_2$O$_5$·SiO$_2$ (0.1)	Solvent-free	120 ℃	2	76	-
5[a]	45% P$_2$O$_5$·SiO$_2$ (0.1)	Solvent-free	120 ℃	2	60	-
6[a]	50% P$_2$O$_5$·SiO$_2$ (0.1)	Solvent-free	120 ℃	2	65	-
7[a]	37% P$_2$O$_5$·SiO$_2$ (0.03)	Solvent-free	120 ℃	2	42	-
8[a]	37% P$_2$O$_5$·SiO$_2$ (0.05)	Solvent-free	120 ℃	2	65	-
9[a]	37% P$_2$O$_5$·SiO$_2$ (0.08)	Solvent-free	120 ℃	2	81	-
10[a]	37% P$_2$O$_5$·SiO$_2$ (0.08), 2nd run	Solvent-free	120 ℃	2	79	-
11[a]	37% P$_2$O$_5$·SiO$_2$ (0.08), 3rd run	Solvent-free	120 ℃	2	79	-
12[a]	37% P$_2$O$_5$·SiO$_2$ (0.08), 4th run	Solvent-free	120 ℃	2	78	-
13[a]	37% P$_2$O$_5$·SiO$_2$ (0.08)	Water	120 ℃	2	14	-
14[a]	37% P$_2$O$_5$·SiO$_2$ (0.08)	EtOH	120 ℃	2	72	-
15[a]	37% P$_2$O$_5$·SiO$_2$ (0.08)	CHCl$_3$	120 ℃	2	-	-
16[a]	37% P$_2$O$_5$·SiO$_2$ (0.08)	CH$_2$Cl$_2$	120 ℃	2	-	-
17[a]	37% P$_2$O$_5$·SiO$_2$ (0.08)	Solvent-free	25 ℃	2	20	-
18[a]	37% P$_2$O$_5$·SiO$_2$ (0.08)	Solvent-free	100 ℃	2	74	-
19[a]	37% P$_2$O$_5$·SiO$_2$ (0.08)	Solvent-free	140 ℃	2	72	-
20[a]	48% nano-P$_2$O$_5$·SiO$_2$ (0.02)	Solvent-free	120 ℃	2	84	-
21[b]	H$_2$SO$_4$ (0.1 drop)	Solvent-free	r. t.	1	86	[22]
22[b]	polystyrene supported sulfonic acid (0.1 ml of 20% PSSA solution)	Solvent-free	r. t.	0.04	92	[23]
23[b]	[a-Zr(CH$_3$PO$_3$)$_{1.2}$(O$_3$PC$_6$H$_4$SO$_3$H)$_{0.8}$] (0.025)	Solvent-free	40 ℃	2	95	[24]
24[b]	Sc(OTf)$_3$ (2 mol%)	Solvent-free	r. t.	0.35	94	[25]
25[b]	Y-Zeolite (1)	CH$_2$Cl$_2$	r. t.	2	84	[26]

[a]phenyl hydrazine (1mmol) and 1, 3-diphenyl-1, 3-propanedione (1 mmol) were applied.

[b]phenyl hydrazine (1mmol) and 2, 4-pentanedione (1 mmol) were applied.
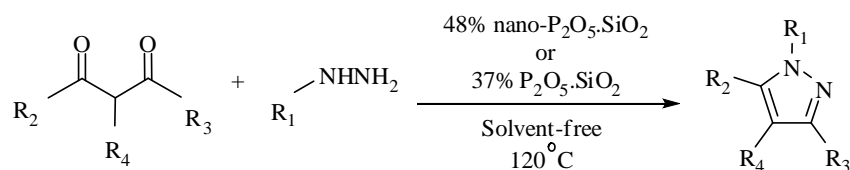
Scheme 1.

1,3-diketone (mmol): hydrazine derivatives (mmol): 37% $P_2O_5 \cdot SiO_2$ or 48% nano-$P_2O_5 \cdot SiO_2$ of 1: 1: 0.08 (0.02) g. Herein, we report that $P_2O_5 \cdot SiO_2$ or nano- $P_2O_5 \cdot SiO_2$ are efficient catalysts for the synthesis of pyrazoles derivatives and are comparable with some other applied catalysts (Table 1). The applicability of the present method to a large scale process was examined with 20 mmol of phenylhydrazine and 20 mmol of 1,3-diphenyl-1,3-propanedione under thermal conditions which gave 1,3,5-triphenyl-pyrazole in a 72% yield. The current method is simple, efficient and less time-consuming for the synthesis of pyrazoles. 1,3-diketones and various hydrazines were used as substrates for the synthesis of pyrazoles under normal heating (Scheme 1 and Table 2).

4. Conclusion

In conclusion, we have demonstrated a simple method for the synthesis of pyrazoles using $P_2O_5 \cdot SiO_2$ as a readily available, eco-friendly, inexpensive and efficient catalyst. Short reaction times, high yields, scale-up, clean process, simple methodology, easy work-up, and green conditions are the advantages of this protocol.

Acknowledgements

Table 2. Condensation of 1,3-diketones and hydrazine in the presence of 37% $P_2O_5 \cdot SiO_2$ or 48% nano-$P_2O_5 \cdot SiO_2$.

Entry	R_1	R_3	R_4	R_2	Yield^a/Yield^b (%)	m.p. (^{o}C)	Ref.
1	2,4- $O_2N-C_6H_4$	C_6H_5	H	C_6H_5	92/94	149-150	[27]
2	2,4- $O_2N-C_6H_4$	C_6H_5	H	CH_3	73/76	128-130	[24]
3	2,4- $O_2N-C_6H_4$	CH_3	H	CH_3	80/85	121-122	[25]
4	2,4- $O_2N-C_6H_4$	CH_3	Cl	CH_3	72/78	167-168	[27]
5	C_6H_4	C_6H_5	H	C_6H_5	86/88	137-138	[26]
6	C_6H_4	C_6H_5	H	CH_3	74/76	55-57	[25]
7	C_6H_4	CH_3	H	CH_3	72/74	oil	[25]
8	C_6H_4	CH_3	Cl	CH_3	70/75	oil	[23]
9	H	C_6H_5	H	CH_3	72/74	203-205	[22]
10	2- $Cl-C_6H_4$	C_6H_5	H	C_6H_5	75/78	126-127	-
11	4- $Br-C_6H_4$	CH_3	Cl	CH_3	82/88	87-88	-
12	4- $Me-C_6H_4$	C_6H_5	H	C_6H_5	70/75	104-105	-

^{a}The ratio of 1,3-diketone (mmol): hydrazine (mmol):37% $P_2O_5 \cdot SiO_2$ (g) is 1:1: 0.08 g.

^{b}The ratio of 1,3-diketone (mmol): hydrazine (mmol) : 48% $P_2O_5.SiO_2$ (g) is 1:1: 0.02 g.

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