

# Preparation of silica-bonded *N*-propyltriethylenetetramine as a recyclable solid base catalyst for the synthesis of 4,4'-(arylmethylene)bis(1*H*-pyrazol-5-ols)

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Received: 5 October 2011 / Accepted: 25 December 2012 / Published online: 28 February 2013  
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**Abstract** Silica-bonded *N*-propyltriethylenetetramine was prepared via the reaction between 3-silicapropyl chloride and triethylenetetramine. This heterogeneous solid base was used as a catalyst for the synthesis of 4,4'-(arylmethylene)bis(1*H*-pyrazol-5-ols) by a one-pot condensation of aromatic aldehydes with 3-methyl-1-phenyl-5-pyrazolone in 72–93 % yields. The catalyst could be recycled several times without any additional treatment.

**Keywords** Heterogeneous catalyst · Solid base · Silica-bonded *N*-propyltriethylenetetramine · Catalyst · Aldehydes · Heterocycles

## Introduction

Based-catalyzed condensation and addition reactions are important in the industrial production of drugs, fragrances, and chemical intermediates [1–6]. In addition, solid base catalysts are used not only for condensation reactions but also in particular for asymmetric organic syntheses [7, 8], other organic syntheses [9–12], and characterization of active centers [13]. The potential use of microporous and mesoporous base catalysts in fine chemical production is enormous [14]. These heterogeneous catalysts are known to suppress side reactions, which include self-condensation and oligomerization, resulting in better selectivity and

product yield. It also avoids the complex neutralization and separation steps needed to recover the homogeneous base catalysts from the reaction mixture. The recovered solid catalysts can be readily regenerated for further use.

Pyrazoles are an important class of bioactive drug target in the pharmaceutical industry, as they are the core structure of numerous biologically active compounds [15, 16]. For example, they exhibit antianxiety, antipyretic, analgesic, and anti-inflammatory properties. 2,4-Dihydro-3*H*-pyrazol-3-one derivatives including 4,4'-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) have a broad spectrum of biological activity, being used as anti-inflammatory [17], antipyretic [18], gastric secretion stimulatory [19], antidepressant [20], antibacterial [21], and antifilarial agents [22]. Moreover, the corresponding 4,4'-(arylmethylene)bis(1*H*-pyrazol-5-ols) are applied as fungicides [23], pesticides [24], insecticides [25], dyestuffs [26], and as chelating and extracting reagents for different metal ions [27].

In spite of the extensive application of 4,4'-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) [16], few methods have been reported for the preparation of these interesting compounds. These methods include application of piperidine in ethanolic solution [28], tandem Knoevenagel–Michael reaction in benzene solutions [29–31], application of sodium dodecyl sulfate in aqueous media [32], and electrocatalytic synthesis [33]. Nevertheless, most of these methods suffer from limitations such as moderate yields, long reaction times, harsh reaction conditions, application of hazardous solvents, and/or tedious workup procedures. Therefore, finding an efficient and a practicable protocol for the preparation of 4,4'-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) is of obvious importance.

Recently, ceric ammonium nitrate (CAN) [34], ionic liquid under ultrasonic irradiation [35], silica-bonded

**Electronic supplementary material** The online version of this article (doi:10.1007/s00706-012-0910-6) contains supplementary material, which is available to authorized users.

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Scheme 1

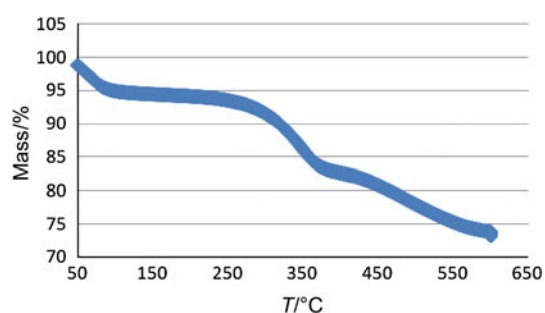
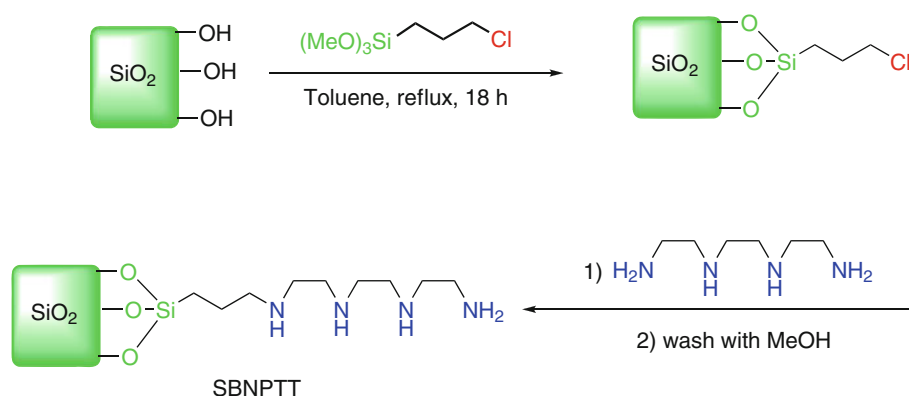


Fig. 1 TGA of SBNPTT

*S*-sulfonic acid [36], silica sulfuric acid [37], and sulfuric acid [[3-(3-silicapropyl)sulfanyl]propyl]ester [38] were reported for the synthesis of 4,4'-(arylmethylene)bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ols). Continuing our studies on the application of heterogeneous catalysts in chemical transformations [36–43], we herein describe the preparation of silica-bonded *N*-propyltriethylenetetramine (SBNPTT) as illustrated in Scheme 1 and its use as a catalyst for the synthesis of 4,4'-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ols).

## Results and discussion

The thermogravimetric analysis (TGA) curves of SBNPTT show the mass loss of organic materials as they decompose upon heating (Fig. 1). The initial weight loss from SBNPTT up to 100 °C is due to removal of physically adsorbed solvent and surface hydroxyl groups. The weight loss of about 11.43 % between 250 and 340 °C and 8.93 % between 370 and 450 °C is contributed to the thermal decomposition of organic groups. The covalent chemical bonds between the linker and surface imparted high thermal stability to the catalyst.

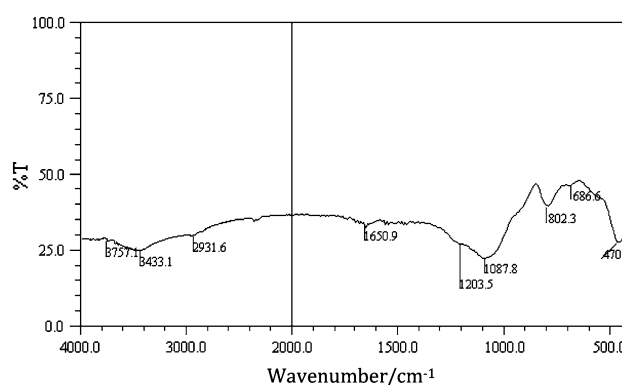
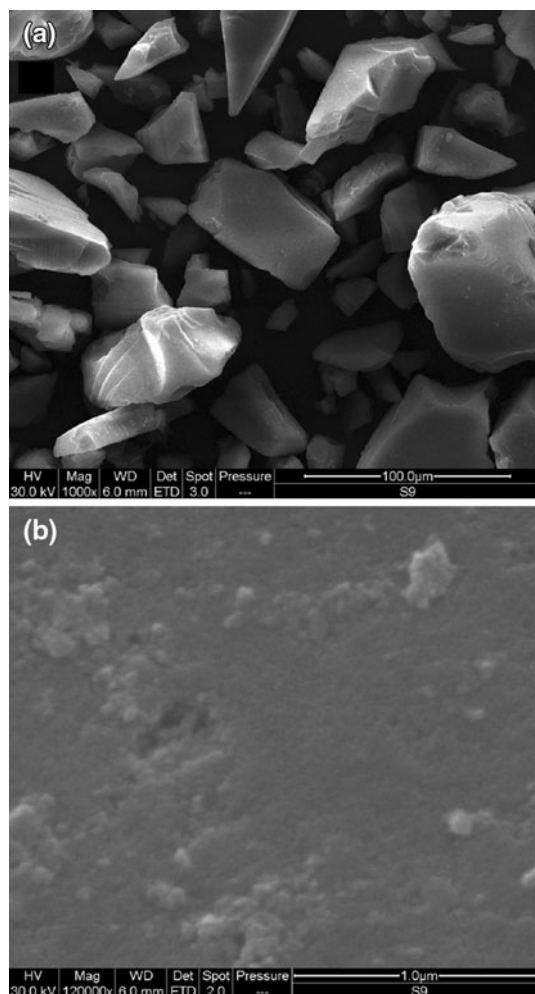


Fig. 2 FT-IR of SBNPTT

Figure 2 shows Fourier transform infrared (FT-IR) spectra for SBNPTT. The major peaks for silica ( $\text{SiO}_2$ ) are broad anti-symmetric Si–O–Si stretching from 1,240 to 1,000  $\text{cm}^{-1}$  and symmetric Si–O–Si stretching near 800–785  $\text{cm}^{-1}$ . The band assigned to silanol groups is located at 3,757  $\text{cm}^{-1}$ ; its intensity is small, indicating that most of the silanols had reacted. For the amine functional group, the FT-IR absorption range of the H–N–H asymmetric and symmetric stretching modes lie at 3,500 to 3,300  $\text{cm}^{-1}$ , overlapped with broad OH stretching bands. The N–H bending mode lies around 1,643  $\text{cm}^{-1}$ .

The confirmation of the presence of a mesoporous structure was performed by SEM and  $\text{N}_2$  adsorption–desorption measurements. The microscopic features of the catalyst were observed with SEM (Fig. 3). In this figure we can see the morphology of the silica substrate.

Additionally, the  $\text{N}_2$  adsorption–desorption isotherm showed a characteristic type IV isotherm, indicating the presence of mesopores. The average pore diameter was determined to be 8 nm by the Barret–Joyner–Halenda (BJH) method based on the isotherm. These observations revealed that the mesoporous structure was successfully



**Fig. 3** SEM of SBNPTT: scale bar **a** 100  $\mu\text{m}$ , **b** 1  $\mu\text{m}$

formed. The Brunauer–Emmett–Teller (BET) surface area using nitrogen adsorption isotherms at the temperature of liquid nitrogen gave the results of  $a_{s,\text{BET}} = 83.75 \text{ m}^2 \text{ g}^{-1}$  and a total pore volume of  $19.23 \text{ cm}^3 \text{ g}^{-1}$  (see Supplementary Material).

To study the effect of catalyst loading on the condensation reaction of aromatic aldehydes with 3-methyl-1-phenyl-5-pyrazolone the reaction of 4-chlorobenzaldehyde and 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one was chosen as a model reaction (Table 1). The results show clearly that SBNPTT is an effective catalyst for this condensation and in the absence of SBNPTT the condensation reaction gave very low yield after 24 h. The optimal amount of SBNPTT was 0.03 g (2.77 mol %) per 1 mmol of aldehyde in refluxing ethanol. In addition, the result of this condensation in the presence of commercial amines such as triethylamine, morpholine, piperazine, and triethylenetetramine and sodium acetate is shown in Table 1.

Therefore, we employed the optimized conditions (0.03 g  $\text{mmol}^{-1}$  of SBNPTT in ethanol under reflux

**Table 1** Condensation reaction of 4-chlorobenzaldehyde with 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one in the presence of different amounts of catalysts

Entry	Catalyst	Catalyst loading	Time/min	Yield/% <sup>a</sup>
1	No catalyst	–	24 h	<10
2	SBNPTT	0.02 g	20	83
3	SBNPTT	0.03 g	15	93
4	SBNPTT	0.07 g	13	93
5	$\text{Et}_3\text{N}$	0.25 mmol	20	55 <sup>b</sup>
6	Morpholine	0.25 mmol	20	70
7	Piperazine	0.25 mmol	20	72
8	Triethylenetetramine	0.25 mmol	30	58
9	NaOAc	0.25 mmol	30	55

Reaction conditions: 4-chlorobenzaldehyde (1 mmol), 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (2 mmol),  $10 \text{ cm}^3$  EtOH, reflux

<sup>a</sup> Isolated yield

<sup>b</sup> Also, a by-product was observed

conditions) for the condensation reaction of various aryl aldehydes with 3-methyl-1-phenyl-5-pyrazolone into the corresponding 4,4'-(arylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ols) (Scheme 2).

As shown in Table 2, both aromatic and heteroaromatic aldehydes reacted with 3-methyl-1-phenyl-5-pyrazolone to afford 4,4'-(arylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ols) in excellent yields. On the other hand, benzaldehydes with electron-donating or electron-withdrawing groups, i.e., methyl-, methylthio-, and 3,4,5-trimethoxybenzaldehyde (Table 2, entries 2–4) or 4-nitro-, 3-nitro-, and 4-cyanobenzaldehyde (Table 2, entries 10–12), were condensed into the corresponding 4,4'-(arylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ols) **3b–3d** and **3j–3l** in high yields. 3-Pyridinecarbaldehyde, 2-thiophenecarbaldehyde, and furfural (Table 2, entries 14–16) were converted into the corresponding products **3n**, **3o**, and **3p** in 83, 72, and 76 % yield, respectively. 2-Naphthalinecarbaldehyde was converted into corresponding product **3m** in 85 % yield (Table 2, entry 13). It should be mentioned that in the case of lower isolated yields, the conversion was not 100 % and small amounts of starting materials remained. There were not any by-products.

The practical synthetic efficiency of this reaction was highlighted by the reaction of terephthalaldehyde and isophthalaldehyde with 3-methyl-1-phenyl-5-pyrazolone to give structurally complex pyrazol-5-ol derivatives **4a**, **4b** (Scheme 3).

The possibility of recycling the catalyst SBNPTT was examined using the reaction of 4-chlorobenzaldehyde and 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one under the optimized conditions. Upon completion, the reaction mixture was washed with warm ethanol ( $3 \times 30 \text{ cm}^3$ ). The

recovered catalyst was washed with diethyl ether, dried, and reused for subsequent runs. The recycled catalyst was reused six times without any additional treatment. No appreciable loss in the catalytic activity of SBNPTT was observed (Fig. 4).

In conclusion, we have prepared some 4,4'-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) by a tandem condensation reaction of aromatic aldehydes with two equivalents of 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one in the presence of SBNPTT as a solid base catalyst in refluxing ethanol.

## Experimental

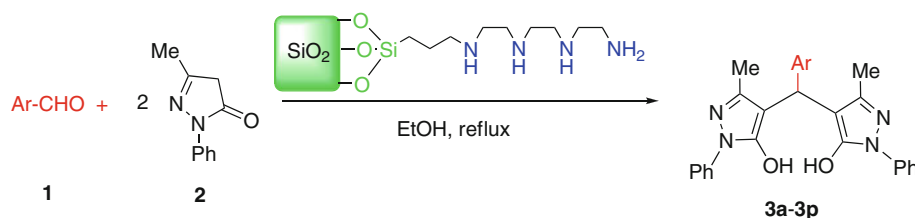
Chemicals were purchased from Fluka, Merck, and Aldrich. All the products are known compounds and were

characterized by comparison of their IR, <sup>1</sup>H NMR, and <sup>13</sup>C NMR spectroscopic data and their melting points with reported values [29–38].

### Preparation of silica-bonded *N*-propyltriethylenetetramine (SBNPTT)

Chloropropyl silica was prepared by a known procedure as previously reported [46]. To a mixture of 25 g chloropropyl silica in 250 cm<sup>3</sup> anhydrous xylene, 25 cm<sup>3</sup> of triethylenetetramine was added and the mixture was refluxed with stirring for 24 h. The reaction was then stopped and the modified silica was cooled to room temperature, transferred to a vacuum glass filter, and washed with xylene and a large excess of ethanol in turn. The resulting SBNPTT was dried under vacuum overnight at 80 °C and 26.4 g was obtained. The pH of 0.1 g of this solid base at 25 °C was determined by a pH-ISE conductivity titration controller (Denver Instrument Model 270) to be 9.7.

Scheme 2



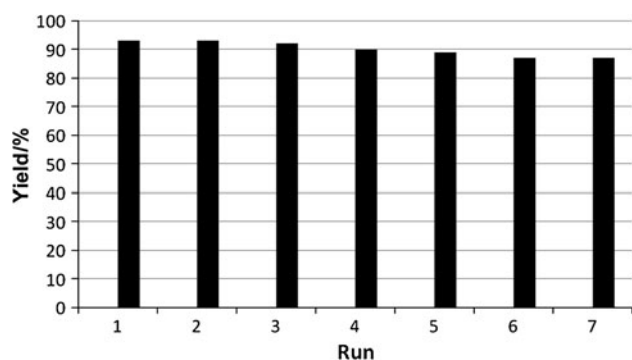
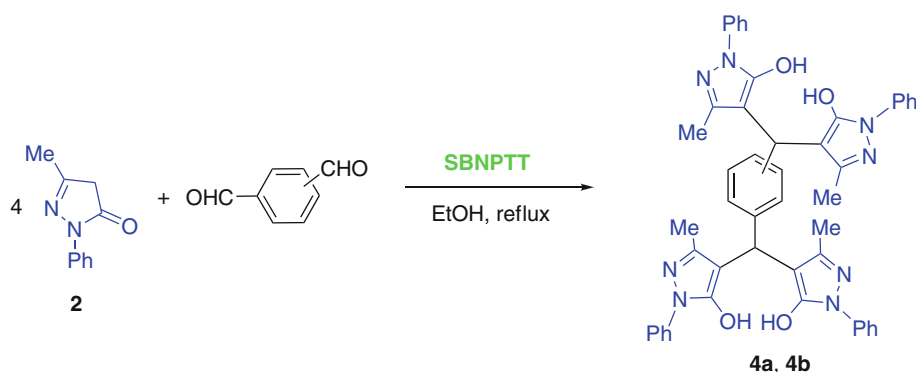
**Table 2** Preparation of 4,4'-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) derivatives catalyzed by SBNPTT in ethanol under refluxing conditions

Entry	Ar (1)	Product	Time/min	Yield/% <sup>a</sup>	M.p./°C	Lit. m.p./°C
1	C <sub>6</sub> H <sub>5</sub> -	<b>3a</b>	30	90	170–172	171–172 [32]
2	4-Me-C <sub>6</sub> H <sub>4</sub> -	<b>3b</b>	35	89	202–204	203 [29]
3	4-MeS-C <sub>6</sub> H <sub>4</sub> -	<b>3c</b>	35	91	201–203	201–203 [36]
4	3,4,5-(MeO) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub> -	<b>3d</b>	45	90	195–197	195–197 [38]
5	2-HO-C <sub>6</sub> H <sub>4</sub> -	<b>3e</b>	35	86	227–229	230–231 [33]
6	2-Br-C <sub>6</sub> H <sub>4</sub> -	<b>3f</b>	20	88	198–200	198–200 [38]
7	4-Cl-C <sub>6</sub> H <sub>4</sub> -	<b>3g</b>	15	93	215–217	210 [29]
8	2,4-(Cl) <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> -	<b>3h</b>	20	90	227–229	228–230 [32]
9	4-F-C <sub>6</sub> H <sub>4</sub> -	<b>3i</b>	35	87	181–183	182 [29]
10	4-O <sub>2</sub> N-C <sub>6</sub> H <sub>4</sub> -	<b>3j</b>	60	89	225–227	224–226 [32]
11	3-O <sub>2</sub> N-C <sub>6</sub> H <sub>4</sub> -	<b>3k</b>	70	90	151–153	149–150 [32]
12	4-(CN)-C <sub>6</sub> H <sub>4</sub> -	<b>3l</b>	35	88	210–212	210–212 [36]
13	2-Naphthalenyl-	<b>3m</b>	100	85	206–208	206–208 [37]
14	3-Pyridyl-	<b>3n</b>	120	83	238–240	238–240 [37]
15	2-Thienyl-	<b>3o</b>	120	72	181–183	181–183 [36]
16	2-Furanyl-	<b>3p</b>	120	76	189–191	189–190 [44]
17	3-OHC-C <sub>6</sub> H <sub>4</sub> -	<b>4a</b>	120	82	191–192	190–194 [45]
18	4-OHC-C <sub>6</sub> H <sub>4</sub> -	<b>4b</b>	120	84	214–216	218–220 [45]

Reaction conditions: aromatic aldehyde (1 mmol), 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (2 mmol), 0.03 g catalyst SBNPTT, 10 cm<sup>3</sup> EtOH, reflux

<sup>a</sup> Isolated yield

Scheme 3



**Fig. 4** Recyclability of SBNPTT as catalyst in the condensation reaction of 4-chlorobenzaldehyde (1 mmol) and 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (2 mmol) in the presence of 0.03 g of SBNPTT in refluxing ethanol. Reaction time 15 min

*General procedure for the synthesis of 4,4'-(arylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ols)*

Aromatic aldehyde (1 mmol) was added to a flask containing a mixture of 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (2 mmol) and 0.03 g SBNPTT (2.77 mol %) in 10 cm<sup>3</sup> warm ethanol and heated under reflux for an appropriate time. After completion of the reaction, as indicated by TLC, the reaction mixture was washed with warm ethanol (3 × 30 cm<sup>3</sup>). After cooling the crude products were precipitated and purified by recrystallization from ethanol (95 %). The recovered catalyst was washed with diethyl ether, dried, and reused for subsequent runs.

**Acknowledgments** We are thankful to the Persian Gulf University Research Council for the partial support of this work. Also, we are thankful to the School of Chemistry, Manchester University for running NMR, BET, CHN, TGA, and SEM.

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