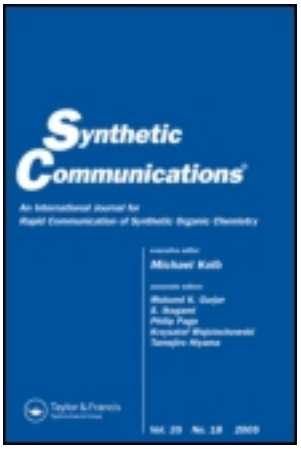

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Silica Sulfuric Acid, an Efficient and Recyclable Solid Acid Catalyst for the Synthesis of 4,4′-(Arylmethylene)bis (1H-pyrazol-5-ols)

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SILICA SULFURIC ACID, AN EFFICIENT AND RECYCLABLE SOLID ACID CATALYST FOR THE SYNTHESIS OF 4,4′-(ARYLMETHYLENE)BIS (1*H*-PYRAZOL-5-OLS)

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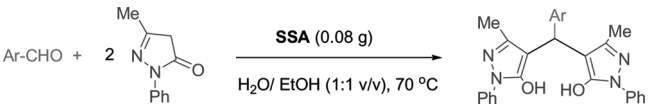
GRAPHICAL ABSTRACT



Abstract *Silica sulfuric acid (SSA) is employed as a recyclable catalyst for the condensation reaction of aromatic aldehydes with 3-methyl-l-phenyl-5-pyrazolone. This condensation reaction is performed in a mixture (1:1 v/v) of water–ethanol at 70 °C, giving 4,4′-alkylmethylene-bis(3-methyl-5-pyrazolones) in 75–93% yields.*

Keywords Aldehydes; 4,4′-(arylmethylene)bis(1*H*-5-pyrazol-5-ols); 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one; silica sulfuric acid; solid acid

INTRODUCTION

Pyrazoles are an important class of bio-active drug targets in the pharmaceutical industry, as they are the core structure of numerous biologically active compounds.[1–3] For example, they exhibit anti-anxiety, 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 approved biological activity, being used as anti-inflammatory,[4] antipyretic,[5] gastric secretion stimulatory,[6] antidepressant,[7] antibacterial[8] and antifilarial agents.[9] Moreover, the corresponding 4,4′(arylmethylene)-bis-(1*H*-pyrazol-5-ols) are applied as fungicides,[10] pesticides,[11]insecticides,[12] and dyestuffs[13–15] and as the chelating and extracting reagents for different metal ions.[16,17]

The conventional chemical approach to 4,4′(arylmethylene)bis(3-methyl-1-phenyl-pyrazol-5-ols) synthesis involves the successive Knoevenagel synthesis of the corresponding arylidenepyrazolones and base-promoted Michael reaction, and also one-pot tandem Knoevenagel–Michael reaction of arylaldehydes with 2 equivalents

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of 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one performed under a variety of reaction conditions.[18,19] The first set of procedures utilizes the catalysis of the components with piperidine in ethanolic solution.[20,21] The second set of methods involves the noncatalyzed tandem Knoevenagel–Michael reaction under neutral conditions in either ethanol[22] or benzene[23] solutions. Although it affords the corresponding 4,4′(arylmethylene)bis(1*H*-pyrazol-5-ols) reliable in 70–90% yields, the reaction requires 3–12 h of initial reflux with a further 24-h period under ambient temperature to go to completion. Wang et al. reported its synthesis in water using sodium dodecyl sulfate as surfactant catalyst over a 1-h period, but the process requires a temperature of 100 °C.[24] Elinson et al. utilized an electrocatalytic procedure for its synthesis.[25] Further, Perumal and co-workers reported the synthesis and antiviral activity of 4,4′(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) using ceric ammonium nitrate (CAN) as a catalyst.[26] However, most of the methods suffer from at least one limitation, including moderate yields, long reaction times, harsh reaction conditions, or tedious workup procedures.

Silica sulfuric acid (SSA) has been widely used as a reusable, heterogeneous, inexpensive, solid Brønsted acid catalyst and has received much attention.[27–29] There has been increasingly awareness of the use of solid acids such as SSA for synthesizing organic intermediates and fine chemicals.[30–35] SSA is a strong Brønsted and Lewis acid, presumably arising from the formation of SiO_2-SO_3H sites on the surface. This heterogeneous catalyst can be easily separated from the reaction media, has greater selectivity, and is recyclable, easier to handle, more stable, nontoxic, and insoluble in organic solvents. In the current study, it was hoped that SSA would be a superior proton source to the standard acidic solid supports for the preparation of 4,4′(arylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) under heterogeneous conditions.

RESULTS AND DISCUSSION

In a set of initial experiments, benzaldehyde was allowed to react with two equivalents of 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one in the presence of varying quantities of SSA in a mixture of water–ethanol (1:1 v/v) at 70 °C. The results clearly show that SSA is an effective catalyst for this condensation, and in the absence of SSA the condensation reaction gave very poor yield after 24 h. Although lower catalyst loading of 0.05 g of SSA accomplished this condensation, 0.08 g of SSA per 1 mmol of aldehyde was optimum in terms of reaction time and isolated yield. Also, the model reaction was examined under optimum amounts and room temperature. The gas chromatographic (GC) yield of the corresponding product was 70% (Table 1, entry 19). In addition, the results of this condensation in the presence of commercially available solid acids such as amberlyst, montmorillonite K10, zeolite-HY, and H_2SO_4 are shown in Table 1.

The effects of different solvents on the model reaction were investigated. The yield of the reaction in a mixture of EtOH–H_2O (1:1 v/v) was great and the reaction time was shorter (Table 2). Therefore, we employed the optimized conditions [0.08 g $mmol^{-1}$ of SSA in a mixture of water–ethanol (1:1 v/v) at 70 °C] for the condensation reaction of various aryl aldehydes with 3-methyl-l-phenyl-5-pyrazolone into the corresponding 4,4′-(arylmethylene) bis (3-methyl-1-phenyl-1H-pyrazol-5-ols) (Scheme 1).

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

Entry	Catalyst	Catalyst loading (g)	Time (min)	Yield (%)[b]
1	No catalyst	–	24 h	<10
2	SSA	0.05	90	80
3	SSA	0.08	60	93
4	SSA	0.15	240	88
5	SSA	0.20	240	80
6	Zeolite-HY	0.1	120	45
7	Zeolite-HY	0.2	120	71
8	Zeolite-HY	0.3	120	87
9	Amberlyst	0.1	120	35
10	Amberlyst	0.2	120	55
11	Amberlyst	0.3	120	73
12	Montmorillonit K10	0.1	120	60
13	Montmorillonit K10	0.2	120	65
14	Montmorillonit K10	0.3	120	85
15	H_2SO_4	0.2 mmol	240	44[c]
16	H_2SO_4	1.0 mmol	180	44[c]
17	H_2SO_4	4.0 mmol	70	45[c]
18	H_2SO_4	10.0 mmol	40	47[c]
19	SSA	0.08	480	70[d]

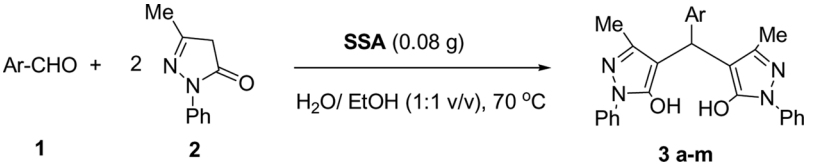
[a]Reaction conditions: benzaldehyde (1 mmol), 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (2 mmol), H_2O/EtOH (10 mL) at 70 °C.
[b]Isolated yield.
[c]The same yield was obtained for a by-product.
[d]GC yield of conversion at room temperature.

As shown in Table 3, both aromatic and heteroaromatic aldehydes reacted with 3-methyl-l-phenyl-5-pyrazolone to afford 4,4′(arylmethylene)-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) in excellent yields. Benzaldehydes with electron-donating or electron-withdrawing groups, that is, 4-methylbenzaldehyde and 3,4-dimethoxybenzaldehyde (Table 3, entries 2 and 11) or 4-nitro, 3-nitro, and 4-cyanobenzaldehyde (Table 3, entries 5–7), were condensed into the corresponding 4,4′(arylmethylene)-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) **3b**, **3k**, and **3e–g** respectively in good yields.

Table 2. Condensation reaction of benzaldehyde with 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one in different solvents (10 mL)[a]

Entry	Solvent	Time (min)	Yield (%)[b]
1	CH_2Cl_2	240	55
2	CH_3CN	240	60
3	CH_3CH_2OH	150	85
4	H_2O	180	<25
5	CH_3CH_2OH: H_2O (1:1)	60	93
6	CH_3CH_2OH: H_2O (1:2)	120	90

[a]Reaction conditions: benzaldehyde (1 mmol), 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (2 mmol), and catalyst SSA (0.08 g), at 70 °C.
[b]Isolated yield.



Scheme 1. Synthesis of 4,4′(arylmethylene)-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) derivatives catalyzed by SSA.

The acid-sensitive substrates 3-pyridine carbaldehyde and thiophene-2-carbaldehyde (Table 3, entries 13 and 14) were converted into the corresponding products **3 m** and **3n** in 86% and 75% yields, respectively.

The practical synthetic efficiency of this reaction was highlighted by the reaction of terephthaldehyde with 3-methyl-1-phenyl-5-pyrazolone to give structurally complex pyrazol-5-ol derivatives (**4**) (Scheme 2).

The possibility of recycling the catalyst was examined using the reaction of benzaldehyde and 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one under the optimized conditions. Upon completion, the reaction mixture was washed with warm ethanol (3×30 mL). The recovered catalyst was washed with diethyl ether, dried, and reused for subsequent runs. The recycled catalyst could be reused eight times without any additional treatment. No observation of any appreciable loss in the catalytic activity of SSA was made (Figure 1).

In conclusion, we have prepared some new 4,4′(arylmethylene)-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) by a tandem condensation reaction of aromatic

Table 3. Preparation of 4,4′(arylmethylene)-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) derivatives catalyzed by SSA (0.08 g) in a mixture of water–ethanol at 70 °C[a]

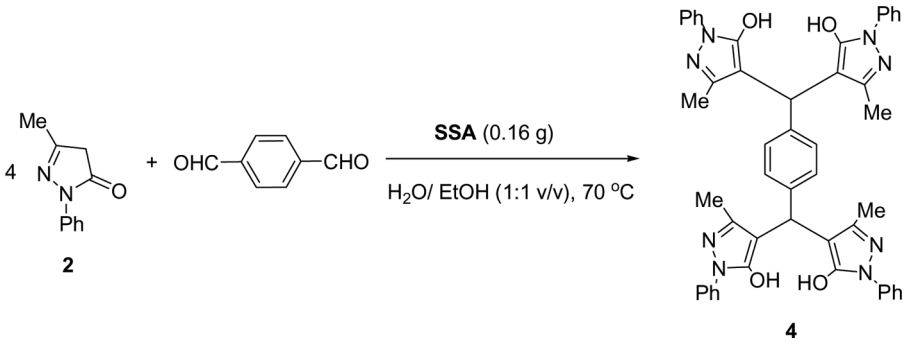
Entry	Ar (3)	Product	Time (min)	Yield (%)[b]	Mp (°C)	Lit. mp (°C)
1	C_6H_5-	**3a**	60	93	170–172	171–172[24]
2	4-Me-C_6H_4-	**3b**	50	82	202–204	203[19]
3	4-Cl-C_6H_4-	**3c**	70	90	215–217	210[19]
4	2-Cl-C_6H_4-	**3d**	75	78	235–237	236–237[24]
5	4-O_2N-C_6H_4-	**3e**	20	90	225–227	224–226[24]
6	3-O_2N-C_6H_4-	**3f**	40	83	151–153	149–150[24]
7	4-(CN)-C_6H_4-	**3g**	50	91	210–212	210–212[32]
8	4-HO-C_6H_4-	**3h**	80	82	155–157	152–153[24]
9	3-HO-C_6H_4-	**3i**	130	84	165–168	165–168[32]
10	4-MeS-C_6H_4-	**3j**	75	90	201–203	201–203[32]
11	3,4-$(MeO)_2$-C_6H_3-	**3k**	70	87	195–197	195–197[32]
12	2-naphthyl-	**3l**	65	90	206–208	—
13	3-pyridyl-	**3m**	40	86	238–240	—
14	2-thienyl-	**3n**	150	75(80)[c]	181–183	181–183[32]
15	-C_6H_4-	**4**	45	90[d]	213–216	—

[a]Reaction conditions: aromatic aldehyde (1 mmol) and 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (2 mmol) in a mixture of (1:1 v/v) of H_2O-EtOH (10 ml) and SSA (0.08 g) at 70 °C.

[b]Isolated yield.

[c]Conversion.

[d]Terephthaldehyde (1 mmol), and 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (4 mmol), in a mixture of (1:1 v/v) of H_2O–EtOH (10 ml) and SSA (0.16 g).



Scheme 2. Synthesis of di(bis-pyrazol-5-ols).

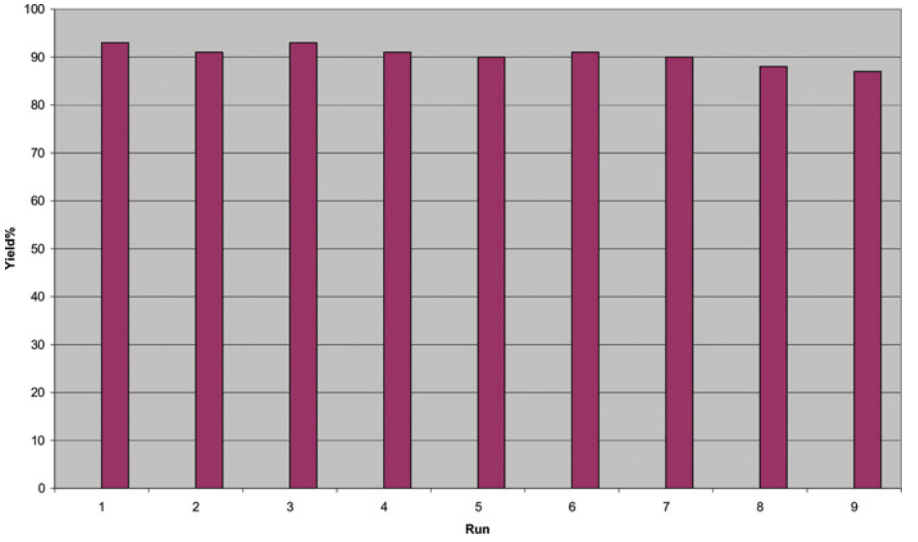


Figure 1. Recyclability of SSA (0.08 g) in the reaction of benzaldehyde (1 mmol) and 5-methyl-2-phenyl-2,4-dihydro-3*H*pyrazol-3-one (2 mmol) in H_2O/EtOH (1:1 v/v) at 70 °C. Reaction time 60 min.

aldehydes with 2 equiv of 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one in the presence of SSA in a mixture of water–ethanol (1:1 v/v) at 70 °C.

EXPERIMENTAL

Chemicals were purchased from Fluka, Merck, and Aldrich Chemical Companies. All the products were characterized by comparison of their infrared (IR), ^{1}H NMR, and ^{13}C NMR spectroscopic data and their melting points with the reported values.[19–24] Amberlyst (Alderich, Dowex Maraton C [mesh 30–40]), montmorillonite K10 (Sigma-Aldrich, powder, pH 3–4), and Zeolite (Sigma-Aldrich,

powder, catalyst support, ammonium Y zeolite) were purchased from Sigma-Aldrich Chemical Companies. **SSA** was prepared according to the previously reported procedure[27] (0.05 g of equal to 0.13 mmol).[27c]

General Procedure for the Synthesis of 4,4′(Arylmethylene)-bis-(3-methyl-1-phenyl-1H-pyrazol-5-ols) Derivatives

A mixture of aromatic aldehyde (1 mmol), 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (2 mmol), and SSA (0.08 g) in a mixture of water–ethanol (1:1 v/v) (10 mL) was added to a flask and heated with stirring at 70 °C for an appropriate time. After completion of the reaction, as indicated by thin-layer chromatography (TLC), the reaction mixture was washed with warm ethanol (3 × 30 mL). After cooling, the crude products were precipitated. The crude products were purified by recrystallization from ethanol (95%). The recovered catalyst was washed with diethyl ether, dried, and reused for subsequent runs.

Spectral Data

4,4′-(Phenylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (3a). Mp 170–172 °C (lit.[24] 171–172 °C); IR (KBr): 3400, 3080, 2900, 1593, 1494, 1410, 1275, 1020, 730, 690 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 2.32 (s, 6H), 4.96 (s, 1H), 7.17–7.27 (m, 7H), 7.44 (t, 4H, $J = 7.72$ Hz), 7.71 (d, 4H, $J = 7.91$ Hz), 13.96 (brs, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 33.13, 120.52, 125.55, 125.88, 127.17, 128.12, 128.90, 142.22, 146.29.

4,4′-[(4-Methylphenyl)methylene]bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (3b). Mp 202–204 °C (lit.[19] 203 °C); IR (KBr): 3440, 3075, 3830, 1590, 1495, 1408, 1294, 1020, 800, 744, 688 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz), δ: 2.24 (s, 3H), 2.30 (s, 6H), 4.90 (s, 1H), 7.07 (d, 2H, $J = 8.29$ Hz), 7.13 (d, 2H, $J = 8.10$ Hz), 7.24 (t, 2H, $J = 7.35$ Hz), 7.44 (t, 4H, $J = 7.72$ Hz), 7.70 (d, 4H, $J = 7.91$ Hz), 13.93 (brs, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 18.55, 32.39, 114.85, 120.47, 125.49, 128.08, 128.89, 132.27, 137.39, 146.18, 155.49.

4,4′-[(4-Chlorophenyl)methylene]bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (3c). Mp 215–217 °C (lit.[19] 210 °C); IR (KBr): 3430, 3085, 2920, 1595, 1490, 1410, 1290, 804, 742, 690 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 2.30 (s, 6H), 4.98 (s, 1H) 7.22–7.28 (m, 4H), 7.35 (d, 2H, J = 8.48 Hz), 7.44 (t, 4H, J = 7.91 Hz), 7.71 (d, 4H, J = 7.91 Hz), 13.90 (brs, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 32.56, 120.54, 125.62, 128.00, 128.90, 129.13, 130.56, 137.18, 141.14, 146.23.

4,4′-[(2-Chlorophenyl)methylene]bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (3d). Mp 235–237 °C, (Lit.[24] 236–237 °C); IR (KBr): 3450, 3070, 2910, 1610, 1555, 1495, 1395, 1360, 1300, 835, 740, 690 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 2.29 (s, 6H), 5.14 (s, 1H), 7.22–7.33 (m, 4H), 7.40 (d, 1H, $J = 7.82$ Hz), 7.44 (t, 4H, $J = 7.57$ Hz), 7.70 (d, 4H, $J = 7.57$ Hz), 7.80 (d, 1H, $J = 7.06$ Hz), 13.92 (brs, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 32.41, 120.67, 123.62, 126.92, 128.05, 128.93, 129.45, 130.32, 135.94, 137.36, 140.60, 141.18.

4,4′-[(4-Nitrophenyl)methylene]bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (3e). Mp 225–227 °C, (lit.[24] 224–226 °C); IR (KBr): 3440, 3090, 2920, 1595, 1495, 1410, 1340, 744, 689 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 2.28 (s, 6H), 5.06 (s, 1H), 7.18 (t, 2H, $J = 7.06$ Hz), 7.38 (t, 4H, $J = 7.31$ Hz), 7.45 (d, 2H, $J = 8.32$ Hz), 7.64 (d, 4H, $J = 7.82$ Hz), 8.10 (d, 2H, $J = 8.58$ Hz), 13.81 (brs, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 34.45, 121.91, 124.65, 127.03, 129.92, 130.25, 147.20, 147.58, 151.63.

4,4′-[(3-Nitrophenyl)methylene]bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (3f). Mp 151–153 °C, (lit.[24] 149–150 °C); IR (KBr): 3420, 3085, 2910, 1595, 1495, 1340, 758, 735, 692, 598 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 2.35 (s, 6H), 5.14 (s, 1H), 7.26 (t, 2H, $J = 7.31$ Hz), 7.45 (t, 4H, $J = 7.57$ Hz), 7.60 (t, 1H, $J = 8.32$ Hz), 7.68–7.74 (m, 5H), 8.06–8.10 (m, 2H), 13.91 (brs, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 32.80, 120.63, 121.21, 121.70, 125.78, 125.81, 128.98, 129.71, 134.34, 137.39, 144.56, 146.30, 147.72.

4,4′-[(4-Cyanophenyl)methylene]bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (3g). Mp 210–212 °C, (lit.[32] 210–212 °C); IR (KBr): 3420, 3090, 2921, 2230, 1595, 1495, 1410, 1290, 810, 750, 690 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.33 (s, 6H), 5.07 (s, 1H), 7.25 (t, 2H, J = 7.31 Hz), 7.42–7.46 (m, 6H), 7.40 (d, 4H, $J = 7.82$ Hz), 7.76 (d, 2H, $J = 8.32$ Hz), 13.89 (brs, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 33.23, 119.00, 120.61, 125.57, 128.38, 128.94, 133.36, 142.59, 148.15. Elemental analysis: for $C_{28}H_{23}N_5O_2$: C, 72.87; H, 5.02; N, 15.17. Found: C, 72.96; H, 4.97; N, 15.33.

4,4′-[(4-Hydroxyphenyl)methylene]bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (3h). Mp 155–157 °C, (lit.[24] 152–153 °C); IR (KBr): 3420, 3150, 3090, 2920, 1593, 1492, 1410, 1270, 744, 690 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 2.30 (s, 6H), 4.85 (s, 1H), 6.67 (d, 2H, $J = 7.72$ Hz), 7.05 (d, 2H, $J = 7.16$ Hz), 7.24 (t, 2H, $J = 5.0$ Hz), 7.42–7.45 (m, 4H), 7.66–7.77 (m, 4H), 9.19 (s, 1H), 13.96 (brs, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 18.55, 32.39, 114.85, 120.47, 125.49, 128.08, 128.89, 132.27, 137.39, 146.18, 155.49.

4,4′-[(3-Hydroxyphenyl)methylene]bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (3i). Mp 165–168 °C, (lit.[32] 165–168 °C); IR (KBr): 3410, 3150, 3080, 2920, 1592, 1495, 1270, 1168, 1042, 750, 690 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.42 (s, 6H), 4.98 (s, 1H), 6.67 (dd, 1H, $J_1 = 8.14$ Hz, $J_2 = 1.5$ Hz), 6.76–6.80 (m, 2H,), 7.17 (t, 1H, $J = 7.82$ Hz), 7.36 (t, 2H, $J = 7.31$ Hz), 7.56 (t, 4H, $J = 7.82$ Hz), 7.83 (d, 4H, $J = 7.82$ Hz), 9.34 (s, 1H), 14.08 (brs, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 32.52, 114.20, 119.54, 120.48, 128.92, 128.97, 132.72, 137.47, 143.67, 147.04, 157.17. Elemental analysis: for $C_{27}H_{24}N_4O_3$: C, 71.67; H, 5.35; N, 12.38. Found: C, 71.22; H, 5.22; N, 12.32.

4,4′-[(4-Methylthiophenyl)methylene]bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (3j). Mp 201–203 °C, (Lit.[32] 201–203 °C); IR (KBr): 3425, 3085, 2918, 1592, 1495, 1186, 779, 748 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.3 (s, 6H), 2.43 (s, 3H), 4.92 (s, 1H), 7.18 (s, 4H), 7.25 (t, 2H, $J = 7.31$ Hz), 7.44 (t, 4H, $J = 7.82$ Hz), 7.70 (d, 4H, $J = 7.82$ Hz), 13.92 (brs, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 14.96, 31.86, 120.45, 120.55, 126.88, 127.82, 128.92, 129.71,

131.41, 136.44, 143.57, 146.97, 147.57. Elemental analysis for $C_{28}H_{26}N_4O_2S$: C, 69.69; H, 5.43; N, 11.61. Found: C, 69.22; H, 5.64; N, 11.67.

4,4′-[(3,4-Dimethoxyphenyl)methylene]bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (3k). Mp 195–197 °C (lit.[32] 195–197 °C); IR (KBr): 3428, 3085, 2920, 1580, 1508, 1410, 1133, 1025, 804, 685 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.33 (s, 6H), 3.67 (s, 3H), 3.71 (s, 3H), 4.90 (s, 1H), 6.82–6.88 (m, 2H), 6.91 (d, 1H, $J = 1.77$ Hz), 7.25 (t, 2H, $J = 7.31$ Hz), 7.45 (t, 4H, $J = 7.94$ Hz), 7.72 (d, 4H, $J = 7.57$ Hz), 14.06 (brs, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 32.91, 55.45, 111.54, 111.66, 119.28, 120.58, 125.56, 134.90, 146.17, 147.21, 148.37. Elemental analysis for $C_{29}H_{28}N_4O_4$: C, 70.15; H, 5.68; N, 11.28. Found: C, 69.78; H, 5.78; N, 11.22.

4,4′-[(2-Naphthyl)methylene]bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (3l). Mp 206–208 °C; IR (KBr): 3410, 3030, 1590, 1490, 1392, 1360, 1280, 1020, 810, 780, 740, 690 (cm^{-1}); ^1H NMR (DMSO-d_6, 500 MHz), δ: 2.36 (s, 6H), 5.14 (s, 1H), 7.24 (t, 2H, $J = 6.9$ Hz), 7.41–7.45 (m, 7H), 7.71–7.73 (m, 5H), 7.81–7.85 (m, 3H), 12.41 (brs, 1H), 13.93 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz), δ: 12.50, 34.22, 121.46, 125.80, 126.30, 126.83, 127.36, 128.16, 128.52, 128.59, 129.79, 132.54, 133.73, 140.55, 147.19. Elemental analysis for $C_{31}H_{26}N_4O_2$: C, 76.52; H, 5.39; N, 11.51. Found: C, 76.35; H, 5.30; N, 11.46.

4,4′-[(3-Pyridyl)methylene]bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (3m). Mp 238–240 °C; IR (KBr): 3410, 3050, 2900, 1595, 1490, 1410, 1345, 1280, 1020, 850, 790, 745, 695 (cm^{-1}); ^1H NMR (DMSO-d_6, 500 MHz), δ: 2.34 (s, 6H), 5.05 (s, 1H), 7.23 (t, 2H, $J = 7.1$ Hz), 7.34 (t, 1H, $J = 6.0$ Hz), 7.43 (t, 4H, $J = 7.5$ Hz), 7.71–7.73 (m, 5H), 8.41 (d, 1H, $J = 3.6$ Hz), 8.51 (s, 1H), 12.10 (brs, 1H), 14.12 (brs, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz), δ: 12.54, 31.96, 104.68, 121.45, 124.22, 126.44, 129.76, 136.16, 138.25, 138.91, 147.04, 147.61, 149.32. Elemental analysis: for $C_{26}H_{23}N_5O_2$: C, 71.38; H, 5.30; N, 16.01. Found C, 71.20; H, 5.25; N, 15.87.

4,4′-[(2-Thienyl)methylene]bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (3n). Mp 181–183 °C, (lit.[32] 181–183 °C); IR (KBr): 3420, 3080, 2920, 1595, 1490, 1410, 1284, 779, 690 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 2.32 (s, 6H), 5.13 (s, 1H), 6.75–6.77 (m, 1H), 6.90–6.92 (m, 1H), 7.24–7.30 (m, 3H), 7.45 (t, 4H, $J = 7.82$ Hz), 7.71 (d, 4H, $J = 7.82$ Hz) 14.01 (brs, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 29.43, 120.58, 124.05, 124.15, 126.75, 128.94, 132.99, 134.13, 147.73. Elemental analysis for $C_{25}H_{22}N_4O_2S$: C, 67.85; H, 5.01; N, 12.66. Found: C, 67.38; H, 4.99; N, 12.25.

1,4-Diphenylene-4,4′-(methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (4). Mp 213–216 °C; IR (KBr): 3410, 3020, 1590, 1490, 1410, 1350, 1290, 1120, 1020, 850, 745, 690 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 2.29 (s, 12H), 5.05 (s, 2H), 7.17 (s, 4H), 7.22 (t, 4H, $J = 7.1$ Hz), 7.41 (t, 8H, $J = 7.8$ Hz), 7.69 (d, 8H, $J = 7.9$ Hz), 12.41 (brs, 2H) 14.11 (s, 2H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 12.51, 33.69, 121.50, 127.84, 129.72, 140.93, 147.07, 155.01. Elemental analysis for $C_{48}H_{42}N_8O_4$: C, 72.52; H, 5.32; N, 14.09. Found: C, 72.35; H, 5.29; N, 13.85.

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REFERENCES

1. McDonald, E.; Jones, K.; Brough, P. A.; Drysdale, M. J.; Workman, P. Discovery and development of pyrazole-scaffold Hsp90 inhibitors. *Curr. Top. Med. Chem.* **2006**, *6*, 1193–1203.
2. Elguero, J. In *Comprehensive Heterocyclic Chemistry*; A. R. Katritzky, C. W. Rees, and E. F. V. Scriven (Eds.); Pergamon: Oxford, 1996; vol. 5.
3. Elguero, J.; Goya, P.; Jagerovic, N.; Silva, A. M. S. Pyrazoles as drugs: Facts and fantasies. *Targets Heterocycl. Syst.* **2002**, *6*, 52–98.
4. Sugiura, S.; Ohno, S.; Ohtani, O.; Izumi, K.; Kitamikado, T.; Asai, H.; Kato, K. Syntheses and anti-inflammatory and hypnotic activity of 5-alkoxy-3-(N-substituted carbamoyl)-1-phenylpyrazoles, 4. *J. Med. Chem.* **1977**, *20*, 80–85.
5. Behr, L. C.; Fusco, R.; Jarboe, C. H. In *The Chemistry of Heterocyclic Compounds, Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles, and Condensed Rings*; A. Weissberger, (Ed.); Interscience: New York, 1967.
6. Rosiere, C. E.; Grossman, M. I. An analog of histamine that stimulates gastric acid secretion without other actions of histamine. *Science* **1951**, *113*, 651–651.
7. Bailey, D. M.; Hansen, P. E.; Hlavac, A. G.; Baizman, E. R.; Pearl, J.; Defelice, A. F.; Feigenson, M. E. 3,4-Diphenyl-1H-pyrazole-1-propanamine antidepressants. *J. Med. Chem.* **1985**, *28*, 256–260.
8. Mahajan, R. N.; Havaldar, F. H.; Fernandes, P. S. *J. Indian Chem. Soc.* **1991**, *68*, 245–246.
9. Chauhan, P. M. S.; Singh, S.; Chatterjee, R. K. *Indian J. Chem., Sect. B* **1993**, *32*, 858–861.
10. Singh, D.; Singh, D. *J. Indian Chem. Soc.* **1991**, *68*, 165–167.
11. Londershausen, M. Review: Approaches to new parasiticides. *Pestic. Sci.* **1996**, *48*, 269–292.
12. Lubs, H. A. (Ed.). *The Chemistry of Synthetic Dyes and Pigments*; American Chemical Society: Washington, DC, 1970.
13. Uzoukwu, A. B. The synthesis and crystal structures of 1-phenyl-3-methyl-4-butanolypyrazol-5-one and of two pyrazolonato complexes of iron. *Polyhedron* **1993**, *12*, 2719–2724.
14. Maurya, R. C.; Verma, R. *Indian J. Chem., Sec. A* **1997**, *36*, 596–598.
15. Garnovskii, A. D.; Uraev, A. I.; Minkin, V. I. Metal complexes from aryl and hetarylazocompounds. *Arkivoc* **2004**, *3*, 29–41.
16. Sridhar, R.; Perumal, P. T.; Etti, S.; Shanmugam, G.; Ponnusamy, M. N.; Prabavathy, V. R.; Mathivanan, N. Design, synthesis, and antimicrobial activity of 1*H*-pyrazole carboxylates. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 6035–6040.
17. Sivaprasad, G.; Perumal, P. T.; Prabavathy, V. R.; Mathivanan, N. Synthesis and anti-microbial activity of pyrazolylbisindoles—Promising antifungal compounds. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6302–6305.
18. Hamama, W. S. Pyrazolones as versatile precursors for the synthesis of fused and binary heterocycles. *Synth. Commun.* **2001**, *31*, 1335–1345.
19. Li, X.-L.; Wang, Y.-M.; Tian, B.; Matsuura, T.; Meng, J.-B. The solid-state Michael addition of 3-methyl-1-phenyl-5-pyrazolone. *J. Heterocycl. Chem.* **1998**, *35*, 129–134.
20. Singh, D.; Singh, D. Syntheses of 1,3-disubstituted 4-arylidenepyrazolin-5-ones and the keto and enol forms of 4,4′-arylidenebis(1,3-disubstituted pyrazolin-5-ones). *J. Chem. Eng. Data* **1984**, *29*, 355–356.

21. Mitra, A. S.; Rout, M. K. *J. Indian Chem. Soc.* **1961**, *38*, 893.
22. Pavlov, P. T.; Goleneva, A. F.; Lesnov, A. E.; Prokhorova, T. S. Biological activity of some pyrazolone derivatives. *Pharm. Chem. J.* **1998**, *32*, 370–372.
23. Buzykin, B. I.; Lonshchakova, T. I. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1971**, 2224–2226.
24. Wang, W.; Wang, S.-X.; Qin, X.-Y.; Li, J.-T. Reaction of aldehydes and pyrazolones in the presence of sodium dodecyl sulfate in aqueous media. *Synth. Commun.* **2005**, *35*, 1263–1269.
25. Elinson, M. N.; Dorofeev, A. S.; Nasybullin, R. F.; Nikishin, G. I. Facile and convenient synthesis of 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ols) by electrocatalytic tandem Knoevenagel–Michael Reaction. *Synthesis* **2008**, *12*, 1933–1937.
26. Sujatha, K.; Shanthi, G.; Selvam, N. P.; Manoharan, S.; Perumal, P. T.; Rajendran, M. Synthesis and antiviral activity of 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ols) against peste des petits ruminant virus (PPRV). *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4501–4503.
27. (a) Zolfigol, M. A. Silica sulfuric acid/$NaNO_2$ as a novel heterogeneous system for production of thionitrites and disulfides under mild conditions. *Tetrahedron* **2001**, *57*, 9509–9511; (b) Salehi, P.; Zolfigol, M. A.; Shirini, F.; Baghbanzadeh, M. Silica sulfuric acid and silica chloride as efficient reagents for organic reactions. *Curr. Org. Chem.* **2006**, *10*, 2171–2189; (c) Shaterian, H. A.; Ghashang, M.; Feyzi, M. Silica sulfuric acid as an efficient catalyst for the preparation of 2H-indazolo[2,1-b]phthalazine-triones. *Appl. Catal. A: Gen.* **2008**, *345*, 128–133.
28. (a) Niknam, K.; Zolfigol, M. A.; Khorramabadi-Zad, A.; Zare, R.; Shayegh, M. Silica sulfuric acid as an efficient and recyclable catalyst for the methoxymethylation of alcohols under solvent-free conditions. *Catal. Commun.* **2006**, *7*, 494–498; (b) Niknam, K.; Karami, B.; Zolfigol, M. A. Silica sulfuric acid–promoted aromatization of 1,2-dihydroquinolines by using $NaNO_2$ as oxidizing agent under mild and heterogeneous conditions. *Catal. Commun.* **2007**, *8*, 1427–1430.
29. (a) Pore, D. M.; Soudagar, M. S.; Desai, U. V. Potassium phosphate or silica sulfuric acid–catalyzed conjugate addition of thiols to α,β-unsaturated ketones at room temperature under solvent-free conditions. *Tetrahedron Lett.* **2006**, *47*, 9325–9328; (b) Wang, Y.; Yuan, Y.-Q.; Guo, S.-R. Silica sulfuric acid promotes aza-Michael addition reactions under solvent-free condition as a heterogeneous and reusable catalyst. *Molecules* **2009**, *14*, 4779–4789; (c) Veisi, H. Silica sulfuric acid (SSA) as a solid acid heterogeneous catalyst for one-pot synthesis of substituted pyrroles under solvent-free conditions at room temperature. *Tetrahedron Lett.* **2010**, *51*, 2109–2114.
30. (a) Wu, H.; Shen, Y.; Fan, L. Y.; Wan, Y.; Zhang, P.; Chen, C. F.; Wang, W. X. Stereoselective synthesis of β-amino ketones via direct Mannich-type reaction catalyzed with silica sulfuric acid. *Tetrahedron* **2007**, *63*, 2404–2408; (b) Modaresi, A. R.; Nasrollahzadeh, M.; Khamooshi, F. Solvent-free preparation of primary carbamates using silica sulfuric acid as an efficient reagent. *Arkivoc* **2007**, *16*, 238–245.
31. (a) Niknam, K.; Saberi, D.; Nouri Sefat, M. Silica-bonded S-sulfonic acid as a recyclable catalyst for chemoselective synthesis of 1,1-diacetates. *Tetrahedron Lett.* **2009**, *50*, 4058–4062; (b) Niknam, K.; Saberi, D.; Mohagheghnejad, M. Silica bonded *S*-sulfonic acid: A recyclable catalyst for the synthesis of quinoxalines at room temperature. *Molecules* **2009**, *14*, 1915–1926; (c) Niknam, K.; Saberi, D.; Baghernejad, M. Silica-bonded S-sulfonic acid, a recyclable catalyst for the synthesis of coumarins. *Chin. Chem. Lett.* **2009**, *20*, 1444–1448; (d) Niknam, K.; Saberi, D. Silica-bonded *N*-propyl sulfamic acid as an efficient catalyst for the formylation and acetylation of alcohols and amines under heterogeneous conditions. *Tetrahedron Lett.* **2009**, *50*, 5210–5214; (e) Niknam, K.; Saberi, D. Preparation of sulfuric acid ([3-(3-silicapropyl)sulfanyl]propyl)ester: A new and recyclable catalyst for the formylation and acetylation of alcohols under heterogeneous conditions. *Appl. Catal.*

A: Gen. **2009**, *366*, 220–225; (f) Niknam, K.; Saberi, D.; Baghernejad, M. Preparation of silica-bonded S-sulfonic acid: A recyclable catalyst for the synthesis of bis-indolylmethanes. *Phosphorus, Sulfur Silicon Relat. Elem.* **2010**, *185*, 875–882; (g) Niknam, K.; Panahi, F.; Saberi, D.; Mohagheghnejad, M. Silica-bonded S-sulfonic acid as recyclable catalyst for the synthesis of 1,8-dioxo-decahydroacridines and 1,8-dioxo-octahydroxanthenes. *J. Heterocycl. Chem.* **2010**, *47*, 292–300; (h) Niknam, K.; Saberi, D.; Nouri Sefat, M. Silica-bonded S-sulfonic acid: An efficient and recyclable solid acid catalyst for the three-component synthesis of a-amino nitriles. *Tetrahedron Lett.* **2010**, *51*, 2959–2962.

32. Niknam, K.; Saberi, D.; Sadegheyan, M.; Deris, A. Silica-bonded S-sulfonic acid: An efficient and recyclable solid acid catalyst for the synthesis of 4,4′-(arylmethylene)bis(1H-pyrazol-5-ols). *Tetrahedron Lett.* **2010**, *51*, 692–694.