

1,3,5-Tris(hydrogensulfato) Benzene: A New and Efficient Catalyst for Synthesis of 4,4'-(arylmethylene)bis(1*H*-pyrazol-5-ol) Derivatives

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Abstract: 1,3,5-Tris(hydrogensulfato) benzene (THSB) was easily prepared by the reaction between phloroglucinol and chlorosulfonic acid in dichloromethane at room temperature. This compound was then used as an efficient catalyst for the synthesis of 4,4'-(arylmethylene)bis(1*H*-pyrazol-5-ols) through the condensation reactions of 1-phenyl-3-methylpyrazol-5-one with several different aromatic aldehydes in ethanol at 75 °C. The present methodology offers several advantages over existing methodologies, such as excellent yields, simple procedure, easy work-up and ecofriendly reaction conditions.

Key words: 1,3,5-tris(hydrogensulfato) benzene; aromatic aldehydes; 1-phenyl-3-methylpyrazol-5-one; 4,4'-(arylmethylene)bis(1*H*-pyrazol-5-ols); ethanol; multicomponent reaction

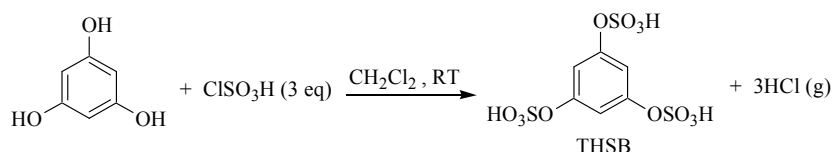
Heterocycles represent the largest of the classical divisions in organic chemistry by far and are of immense importance both biologically and industrially. Pyrazoles are an important class of heterocyclic compound. Examination of the chemical literature reveals that a great many synthetic pyrazole derivatives have been reported, with applications across a wide range of fields, where they have been used as pharmaceuticals, agrochemicals, and photographic agents. 2,4-Dihydro-3*H*-pyrazol-3-one derivatives, including the 4,4'-(arylmethylene)bis(1*H*-pyrazol-5-ols) have a broad spectrum of approved biological activity, and have been used as anti-inflammatory [1], antipyretic [2], gastric secretion stimulatory [3], antidepressant [4], antibacterial [5], antiviral [6], and antifilarial agents [7]. They have also used as fungicides [8], insecticides [9], and dyestuffs [10–13].

Over the years, multicomponent reactions [14–16] (MCRs) have become increasingly popular as tools for enabling the introduction of sufficient molecular diversity and complexity. These reactions have gained significant popularity in recent years because of their atom-economy and straightforward reaction design, which also allows for substantial minimization in the levels of waste generated from the process with considerable saving in labor, time, and costs [17–19]. MCRs leading

to the generation of interesting heterocyclic scaffolds are particularly useful for the construction of diverse chemical libraries of ‘drug like’ molecules.

Recently, several different three component one-pot condensation reactions have been reported between 1-phenyl-3-methylpyrazol-5-one and a variety of different aldehydes for the construction of 4,4'-(arylmethylene)bis(1*H*-pyrazol-5-ol) derivatives [6, 20–32]. Several different catalysts have been reported to promote this reaction, including ceric ammonium nitrate (CAN) [6], sodium dodecyl sulfate (SDS) as a surfactant catalyst [20], ETBA [21], NaBr [22], [Cu(3,4-tmtppa)](MeSO₄)₄ [23], silica-bonded S-sulfonic acid (SBSSA) [24], silica sulfuric acid (SSA) [25], H₂O [26], sulfuric acid ([3-(3-silicapropyl)sulfanyl] propyl)ester (SASPSPE) [27], xanthan sulfuric acid [28], PEG-SO₃H [29], ionic liquid [HMIM]HSO₄ [30], 3-minopropylated silica gel (AP-SiO₂) [31], and phosphomolybdic acid [32].

Although some of these methods afford moderate to high yields of the corresponding products, the majority suffer from one or more of the following disadvantages, including (1) the use of a costly catalyst; (2) the requirement for a tedious work-up procedure; (3) the need for high temperatures; and (4) long reaction times. Herein, we report the development of a



Scheme 1. Preparation of THSB.

mild, efficient, and environmentally benign procedure for the synthesis of 4,4'-(arylmethylene)bis(1*H*-pyrazol-5-ol) derivatives from the condensation reaction of aldehydes and 1-phenyl-3-methylpyrazol-5-one in the presence of 1,3,5-tris(hydrogensulfato) benzene (THSB) as an efficient and new catalyst.

1 Experimental

1.1 General

All of the chemicals were purchased from Merck and Aldrich. Melting points were determined in open capillary tubes and are uncorrected. IR measurements were carried out using KBr pellets on a Fourier transform infrared (FT-IR) spectrometer (Manufacturer, City, State/Country). ^1H (250 MHz) and ^{13}C (62.5 MHz) NMR spectra were recorded on a Bruker Avance 250 spectrometer (Bruker, City, State/Country) in $\text{DMSO}-d_6$ using tetramethylsilane (TMS) as an internal reference. All of the products have been reported previously in the literature and were characterized according to their spectral and physical data. Reaction monitoring for the progress of all of the reactions was carried out by thin-layer chromatography (TLC) using silica gel 60 GF₂₄₅ precoated sheets and were visualized using a UV-lamp at a wave length of 254 nm. All chemicals and solvents were of reagent grade and the latter were distilled and dried before use. The elemental analyses were performed with an Elementar Analysensysteme GmbH VarioEL in CHNS mode.

1.2 Preparation of THSB

A solution of chlorosulfonic acid (8.74 g, ca. 5 ml, 75 mmol) in CH_2Cl_2 (20 ml) was added to phloroglucinol (3.15 g, 25 mmol) in a drop-wise manner over a period of 1 h at room temperature (Scheme 1). HCl evolved immediately. Upon

completion of the addition, the mixture was shaken for 3 h, and the residual HCl was removed by suction. The solid residue was washed with *n*-hexane (10 ml) and filtered to give the desired product as a yellow solid material in 95% yield.

1.3 General procedure for the one-pot synthesis of 4,4'-(arylmethylene)bis(1*H*-pyrazol-5-ol) derivatives

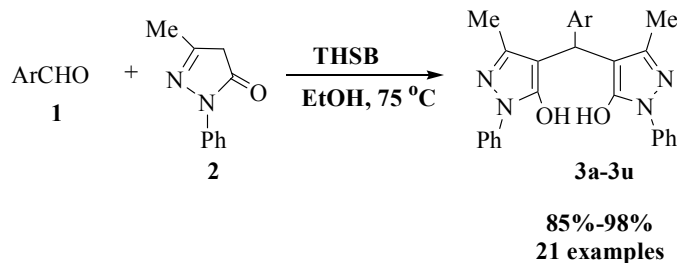
THSB (0.04 mmol, 0.014 g) and silica gel (0.006 g) were added to a solution of aromatic aldehyde **1** (1 mmol, Scheme 2) and 1-phenyl-3-methylpyrazol-5-one **2** (2 mmol, scheme 2) in ethanol (2 ml), and the resulting mixture was stirred at 75 °C for the specified period of time, as indicated in Table 1. Upon completion of the reaction, as confirmed by TLC, the reaction mixture was cooled to room temperature. The resulting precipitated product was then filtered and washed with *n*-hexane (10 ml) to afford the pure product **3** (**3a–3u**) as a white powder.

1.4 Characterization of some representative compounds

THSB. Pale yellow solid. IR (KBr, cm^{-1}): 3403, 1284, 1174, 578. ^1H NMR (250 MHz, $\text{DMSO}-d_6$): 5.82 (s, 3H, ArH). Anal. Calcd For $\text{C}_6\text{H}_6\text{O}_{12}\text{S}_3$: C, 19.67; H, 1.65; S, 26.26; Found: C, 19.57; H, 1.59; S, 26.19.

4,4'-[(4-Chloro-3-nitrophenyl)methylene]bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (Table 1, Entry 10, **3j**). Pale yellow solid. IR (KBr, cm^{-1}): 3425, 3054, 2923, 1598, 1570, 1530, 1501, 1368, 750. ^1H NMR (250 MHz, $\text{DMSO}-d_6$): 2.32 (s, 6H, 2CH₃), 5.80 (s, 1H, CH), 7.23 (d, 2H, $J=2.5$ Hz, ArH), 7.25 (d, 4H, $J=2.5$ Hz, ArH), 7.54–7.57 (m, 1H, ArH), 7.65–7.66 (m, 5H, ArH), 7.84 (s, 1H, ArH); ^{13}C NMR (62.5 MHz, $\text{DMSO}-d_6$): 11.9, 104.1, 121.1, 122.9, 124.6, 126.2, 129.1, 129.4, 131.7, 133.3, 137.4, 144.0, 146.7, 147.8. Anal. Calcd For $\text{C}_{27}\text{H}_{22}\text{ClN}_5\text{O}_4$: C, 62.85; H, 4.30; N, 13.57; Found: C, 62.74; H, 4.25; N, 13.50.

4,4'-[(2-Methoxyphenyl)methylene]bis(3-methyl-1-phenyl-

Scheme 2. Synthesis of the 4,4'-(arylmethylene)bis(1*H*-pyrazol-5-ol) derivatives catalyzed by THSB.

1H-pyrazol-5-ol) (Table 1, Entry 14, **3n**). Yellow solid. IR (KBr, cm^{-1}): 3427, 3062, 2922, 1598, 1575, 1497, 1241, 756. ^1H NMR (250 MHz, $\text{DMSO}-d_6$): 2.26 (s, 6H, 2CH_3), 3.79 (s, 3H, OCH_3), 5.18 (s, 1H, CH), 6.82–6.93 (m, 2H, ArH), 7.11–7.24 (m, 3H, ArH), 7.41 (t, 4H, $J = 7$ Hz, ArH), 7.60 (d, 1H, $J = 7.5$ Hz, ArH), 7.67–7.70 (m, 4H, ArH); ^{13}C NMR (62.5 MHz, $\text{DMSO}-d_6$): 12.0, 27.8, 55.9, 111.2, 120.4, 121.0, 125.9, 127.7, 128.9, 129.3, 130.5, 130.7, 130.9, 131.1, 146.6, 156.2. Anal. Calcd For $\text{C}_{28}\text{H}_{26}\text{N}_4\text{O}_3$: C, 72.09; H, 5.62; N, 12.01; Found: C, 71.98; H, 5.57; N, 11.93.

1,4-Diphenylene-4,4'-(methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (Table 2, **3u**). White cream solid. IR (KBr, cm^{-1}): 3415, 3026, 1590, 1495, 1410, 1350, 1290, 1120, 1020, 860, 745, 690. ^1H NMR (250 MHz, $\text{DMSO}-d_6$): 2.28 (s, 12H, CH_3), 5.07 (s, 2H, CH), 7.17 (s, 4H, CH), 7.23 (t, 4H, $J = 7.1$ Hz, Ar), 7.41 (t, 8H, $J = 7.8$ Hz, Ar), 7.69 (d, 8H, $J = 7.9$ Hz, Ar), 12.43 (br, 2H, OH) 14.10 (2H, s, OH); ^{13}C NMR (62.5 MHz, $\text{DMSO}-d_6$): 12.6, 33.6, 121.5, 128.0, 129.7, 140.9, 147.0, 155.0. Anal. Calcd for $\text{C}_{48}\text{H}_{42}\text{N}_8\text{O}_4$: C, 72.52; H, 5.32; N, 14.09; Found: C, 72.35; H, 5.29; N, 13.85.

2 Results and discussion

1,3,5-Tris(hydrogensulfato) benzene (THSB) was easily prepared by the addition of chlorosulfonic acid to phloroglucinol (1,3,5-benzenetriol) at room temperature. This reaction proceeded smoothly and cleanly, with HCl gas being immedi-

ately evolved from the reaction mixture. Furthermore, the catalyst itself was safe and easy to handle (Scheme 1).

In connection with our ongoing work towards the development of new synthetic routes for the construction of complex heterocyclic compounds, such as the newly discovered 2-amino-4H-pyran-3-carbonitriles [33], 2,3-dihydro quinoxalin-4(1H)-ones [34], tetrahydrobenzo[*a*]xanthen-11-ones [35], and dihydropyrano[2,3-*c*]pyrazoles [36], herein we report the three-component condensation reaction of aromatic aldehydes **1** with 1-phenyl-3-methylpyrazol-5-one **2** in ethanol in the presence of THSB as a novel catalyst with a reaction time of 2–5 min, allowing for the one-pot formation of 4,4'-(arylmethylene)bis(1H-pyrazol-5-ols) **3** in excellent yields (Scheme 2).

For the initial optimization of the reaction conditions, the condensation reaction of 4-chlorobenzaldehyde with 1-phenyl-3-methylpyrazol-5-one was investigated in ethanol as a model reaction. The best result was achieved when 4-chlorobenzaldehyde was reacted with 1-phenyl-3-methylpyrazol-5-one (in a 1:2 molar ratio) in the presence of THSB (X wt%) at 75 °C for 2 min (Table 1, entry 2).

These conditions were therefore selected as the optimized conditions and employed for the condensation reaction of a variety of different aryl aldehydes with 3-methyl-1-phenyl-5-pyrazolone to give the corresponding 4,4'-(arylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) derivatives. The results are summarized in Table 1.

Table 1 Synthesis of 4,4'-(arylmethylene)bis(1H-pyrazol-5-ols)

Entry	Ar	Product	Time (min)	Isolated yield (%)	Melting point (°C)	
					This work	Reported
1	C_6H_5	3a	5	93	169–171	170–172 [25]
2	4-ClC ₆ H ₄	3b	2	95	215–216	215–217 [25]
3	2-ClC ₆ H ₄	3c	2	95	235–237	235–237 [25]
4	4-BrC ₆ H ₄	3d	3	98	183–185	183–185 [26]
5	4-FC ₆ H ₄	3e	3	90	182–184	182–184 [32]
6	4-CNC ₆ H ₄	3f	3	98	212–214	210–212 [25]
7	4-NO ₂ C ₆ H ₄	3g	3	96	225	224–226 [32]
8	3-NO ₂ C ₆ H ₄	3h	4	95	151–154	152–154 [32]
9	2,4-Cl ₂ C ₆ H ₃	3i	3	98	227–229	227–229 [24]
10	4-Cl-3-NO ₂ C ₆ H ₃	3j	2	95	237–238	—
11	4-CH ₃ C ₆ H ₄	3k	3	92	201–203	202–204 [25]
12	3-CH ₃ C ₆ H ₄	3l	4	90	238–241	242–243 [28]
13	4-OCH ₃ C ₆ H ₄	3m	3	90	176–179	176–178 [32]
14	2-OCH ₃ C ₆ H ₄	3n	5	90	211–214	210–213 [30]
15	4-OHC ₆ H ₄	3o	5	90	154–157	155–157 [24]
16	2-pyridyl–	3p	3	98	229–231	232–233 [6]
17	3-pyridyl–	3q	3	95	239–240	238–240 [25]
18	2-naphthyl–	3r	3	95	204–206	206–208 [25]
19	2-furyl–	3s	3	95	188–191	188–190 [32]
20	(CH ₃) ₂ CH	3t	3	90	211–212	213–214 [32]
21	CHOC ₆ H ₄	3u	5	85	209–212	214–216 [27]

Reaction conditions: aromatic aldehyde (1 mmol), 1-phenyl-3-methylpyrazol-5-one (2 mmol), THSB (0.014 g), 75 °C, EtOH (2 ml).

^aReaction conditions: terephthaldehyde (1 mmol), 1-phenyl-3-methylpyrazol-5-one (4 mmol), THSB (0.014 g), 75 °C, EtOH (2 ml).

Table 2 Comparison of the results obtained using THSB with other catalyst for the synthesis of the 4,4'-(arylmethylene)bis(1*H*-pyrazol-5-ols)

Entry	Reagent and conditions	Time (min)	Yield (%)	Ref
1	CAN (5 mol%), H ₂ O, RT	10–25	88–94	[6]
2	SBSSA (0.1 g), EtOH (10 ml), reflux	40–240	80–90	[24]
3	SSA (0.08 g), EtOH:H ₂ O (10 ml), 70 °C	20–150	78–93	[25]
4	—, H ₂ O (20 ml), Reflux	360–480	72–84	[26]
5	SASPSPE (0.1 g), EtOH (10 ml), reflux	120–240	75–90	[27]
6	xanthan sulfuric acid (0.08 g), EtOH (5 ml), reflux	15–30	76–95	[28]
7	PEG-SO ₃ H (1.5 mol%), H ₂ O, Reflux	15–120	76–94	[29]
8	[HMIM]HSO ₄ (10 mol%), EtOH, RT	20–75	40–92	[30]
9	AP-SiO ₂ (3.22 g), CH ₃ CN (10 ml), RT	5–45	90–98	[31]
10	phosphomolybdic acid (10 mol%), EtOH (5 ml), RT	210–330	91–96	[32]
11	THSB (0.014 g), EtOH (2 ml), 75 °C	2–5	90–98	present method

As shown in Table 1, all of the aromatic aldehydes **1** reacted successfully with 1-phenyl-3-methylpyrazol-5-one **2** in the presence of THSB in ethanol at 75 °C, to afford the corresponding products **3** in excellent yields. Aromatic aldehydes containing electron-withdrawing (e.g., nitro and halide groups) and electron-donating groups (e.g., hydroxyl and alkoxy groups) were employed and reacted well to give the corresponding products **3** in excellent yields under these reaction conditions, leading to the conclusion that the electronic nature of the substituents on the aromatic ring had no discernible impact on the course of the reaction.

The practicality and synthetic efficiency of this reaction was highlighted by the reaction of terephthalaldehyde with 1-phenyl-3-methylpyrazol-5-one to give structurally complex di(bis-pyrazol-5-ol) Table 1 [25,27].

To highlight the advantages of the THSB catalyst over the other catalysts reported in the literature, the results obtained using this catalyst were compared with those obtained from other catalysts for the synthesis of 4,4'-(arylmethylene) bis(1*H*-pyrazol-5-ols). From Table 2, it is clear that THSB appeared to promote the reaction more effectively than a number of other catalysts, particularly in terms of the time required to complete the reaction and the reaction yield. This method offers some advantages in terms of very fast reaction times, simplicity of performance, low cost, and it follows along the line of green chemistry.

3 Conclusions

In conclusion, we have described the development of an efficient one-pot three-component condensation reaction of aromatic aldehydes with 1-phenyl-3-methylpyrazol-5-one in ethanol for the synthesis of 4,4'-(arylmethylene)bis(1*H*-pyrazol-5-ol) derivatives, with the process being catalyzed by 1,3,5-tris(hydrogensulfato) benzene (THSB) as a novel catalyst. This new method has the advantages of higher yields, mild reaction conditions, shorter reaction times, and is a convenient and environmental friendly

procedure. We are currently exploring further applications of the THSB catalyst to other organic reactions in our laboratory.

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