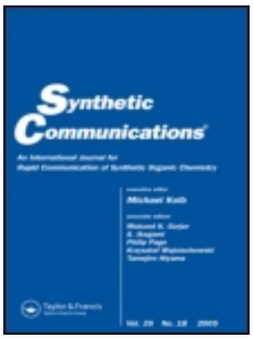

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Xanthan Sulfuric Acid: An Efficient, Biosupported, and Recyclable Solid Acid Catalyst for the Synthesis of 4,4'-(Arylmethylene)bis(1H-pyrazol-5-ols)

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

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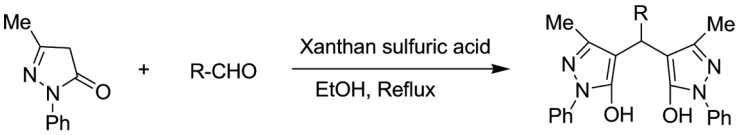
GRAPHICAL ABSTRACT



1 **2** **3(a-m)**

Abstract *A simple and efficient method has been developed for the synthesis of 4,4′-(arylmethylene)bis(1H-pyrazol-5-ols) by the condensation reaction between substituted aldehydes, and 1-phenyl-3-methylpyrazol-5-one in the presence of xanthan sulfuric acid (XSA) as a solid acid catalyst. This method is simple and cost-effective with short reaction times. Yields are excellent with high purity, and the catalyst could be easily recycled.*

Keywords Aldehydes; 4,4′-(arylmethylene)bis(1H-pyrazol-5-ols); biosupported; 1-phenyl-3-methylpyrazol-5-one; xanthan sulfuric acid

INTRODUCTION

Synthesis of nitrogen-containing heterocyclic systems occupies an important role in the realm of natural and synthetic organic chemistry because of their therapeutic and pharmacological properties.[1] In particular, pyrazoles and their derivatives have attracted considerable attention because of their wide variety of biological activities, including anti-inflammatory,[2] antipyretic,[3] gastric secretion stimulatory,[4] antidepressant,[5] antibacterial,[6] antifilarial,[7] bactericidal, fungicidal,[8] and promising inhibitory activities against monoamine oxidase for the treatment of diseases such as Parkinson's and Alzheimer's.[9] The conventional chemical approach to 4,4′-(arylmethylene)bis(3-methyl-1-phenyl-pyrazol-5-ols) involves the successive Knoevenagel synthesis of the corresponding arylidenepyrazolones, its base-promoted Michael reaction, and one-pot tandem Knoevenagel–Michael

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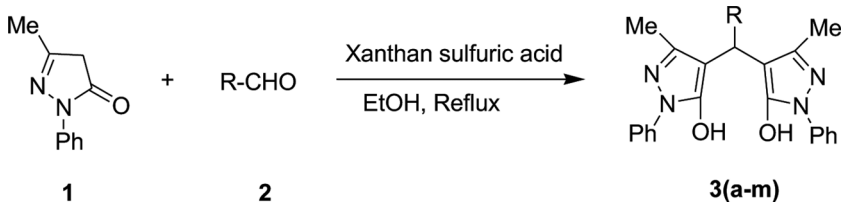
reaction of arylaldehydes with 2 equiv. of 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one performed under a variety of reaction conditions.[10,11] The first set of procedures utilizes the catalysis of the components with piperidine in ethanolic solution.[12] The second set of methods involves the uncatalyzed tandem Knoevenagel–Michael reaction under neutral conditions in either ethanol[13] or benzene[14] solutions. Although it affords the corresponding 4,4′-(arylmethylene)bis(1H-pyrazol-5-ols) in reliable 70–90% yields, the reaction requires 3–12 h of initial reflux with a further 24 h under ambient temperature to go to completion. Wang et al.[15] reported its synthesis in water using sodium dodecyl sulfate as the surfactant catalyst over a 1-h period, but the process needs a temperature of 100 °C. Finally, Elinson et al. utilized electrocatalytic procedure for its synthesis.[16] Further, Perumal and coworkers reported the synthesis and antiviral activity of 4,4′-(arylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ols) using ceric ammonium nitrate (CAN) as a catalyst.[17] However, most of the methods suffer from at least one limitation that may include moderate yields, long reaction times, harsh reaction conditions, or tedious workup procedures. Therefore, the search continues for a better catalyst for the synthesis of 4,4′-(arylmethylene)bis(3-methyl-1-phenyl-pyrazol-5-ols) in terms of operational simplicity, reusability of catalyst, low cost, and greater selectivity.

Xanthan and its derivatives[18–20] have some unique properties that make them attractive alternatives for conventional organic or inorganic supports for catalytic applications. Xanthan is the most abundant bacterial exopolysaccharide in the world, which is produced through fermentation, and it has been widely studied during recent decades, as it is a biodegradable material and a renewable resource. Unlike other gums, it is very stable under a wide range of temperatures and pH values. Xanthan sulfuric acid [21] can be easily prepared by the reaction of xanthan with chlorosulfonic acid; the number of acidic (H^+) sites in the xanthan sulfuric acid determined by acid–base titration was 0.6 meq/g.

RESULTS AND DISCUSSION

Our research group has developed various new synthetic methodologies for the synthesis of both building blocks and heterocyclic compounds using new reagents.[22] Thus, in continuation of our interest in the development of new methodologies, we describe herein the synthesis of a 4,4′-(arylmethylene)bis(3-methyl-1-phenyl-pyrazol-5-ols) in ethanol catalyzed by xanthan sulfuric acid (Scheme 1).

We investigated the efficiency of xanthan sulfuric acid compared to various sulfur analog acidic catalysts. The results are summarized in Table 1. Xanthan sulfuric



Scheme 1. Synthesis of 4,4′-(arylmethylene)bis(1H-pyrazol-5-ols) with xanthan sulfuric acid.

Table 1. Effect of catalysts on yield

Entry	Catalyst	Yield (%)[a]
1	Xanthan sulfuric acid	95
2	Silica sulfuric acid	88
3	Sulfuric acid in acetic acid	52
4	No catalyst	15

[a]Isolated yield.

Table 2. Influence of the catalytic amounts of xanthan sulfuric acid

Entry	Catalyst (g)	Time (min)	Yield (%)[a]
1	None	60	Trace
2	0.01	15	25
3	0.03	15	55
4	0.05	15	79
5	0.08	30	95
6	0.08	15	95

[a]Isolated yield.

acid was found to be the most effective catalyst based on the product yield. The reaction did not proceed in the absence of catalyst (yield less than 15%).

We examined the amount of catalyst required in this reaction. The best results were obtained using 0.08 g of catalyst (95%). Using lesser amounts of catalyst resulted in lesser yields, and in the absence of catalyst the yield of the product was found to be very poor Table 2.

EXPERIMENTAL

All the melting points are uncorrected. The progress of the reaction was monitored by thin-layer chromatography (TLC). Infrared (IR) spectra (KBr) were recorded on a Shimadzu FTIR model 8010 spectrometer, and the ^{1}H NMR spectra was determined on a Varian Gemini 200-MHz spectrometer using tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on a Jeol JMS D-300 spectrometer. CHN analysis was done on a Carlo Erba EA 1108 automatic elemental analyzer. All solvents and reagents were purchased from Aldrich and Fluka.

Typical Procedure

A mixture of aldehyde (1 mmol), 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (2 mmol), and xanthane sulfuric acid (0.08 g) in ethanol (5 mL) was heated under refluxing conditions for an appropriate time according to Table 3. After the completion of the reaction (as monitored by TLC), the reaction mixture was filtered and washed with ethanol (2×20 mL) to separate the catalyst. Then the filtrate was evaporated under reduced pressure to afford a pure product. Further purification

Table 3. Synthesis of 4,4′-(arylmethylene)bis(1H-pyrazol-5-ols) with xanthan sulfuric acid

Entry	Aldehydes	Product	Time (min)	Yield (%)[a]	Mp (°C)
1	Benzaldehyde	3a	15	95	166–167[16]
2	3-Methylbenzaldehyde	3b	25	91	242–243 [17]
3	4-Methylbenzaldehyde	3c	25	90	203–204[17]
4	3-Hydroxybenzaldehyde	3d	25	92	165–168[23]
5	4-Hydroxybenzaldehyde	3e	30	91	152–153[15]
6	4-Nitrobenzaldehyde	3f	15	90	230–232[15]
7	2-Chlorobenzaldehyde	3g	25	90	236–237[15]
8	4-Chlorobenzaldehyde	3h	20	94	207–209[15]
9	4-Methoxybenzaldehyde	3i	25	92	148[11]
10	2-Furfuraldehyde	3j	15	95	189–190[17]
11	2-Naphthaldehyde	3k	25	85	185–186
12	4-Oxo-*4H*-chromene-3-carbaldehyde	3l	30	78	202
13	6-Nitro-4-oxo-*4H*-chromene-3-carbaldehyde	3m	30	76	190

[a]Yields refer to pure solid products; all products were characterized by spectral data.

Table 4. Effect of reusability of catalyst on yield[a]

Run	Cycle	Yield (%)[b]
1	0	95
2	1	92
3	2	88
4	3	76

[a]Reaction conditions: mixture of benzaldehyde (1 mmol), 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (2 mmol), and xanthane sulfuric acid (0.08 g) in ethanol (5 mL) was heated under reflux.
[b]Yields refer to the pure, isolated, recovered catalyst.

was followed by crystallization from ethanol. The recovered catalyst was reused for subsequent runs (Table 4).

Analytical Data

Table 3, Entry 11. IR (KBr): 3421, 2949, 1610 cm^{-1}; ^1H NMR (DMSO-d_6): $\delta = 2.33$ (s, 6 H, 2 CH_3), 5.23 (s, 1H, CH), 6.95–7.78 (m, 17 H, Ar); MS (*m/z*): 487 (M^+). Anal. Calcd. for $C_{31}H_{26}N_4O_2$: C, 76.52; H, 5.39; N, 11.51; Found: C, 76.25; H, 5.24; N, 12.10.

Table 3, Entry 12. IR (KBr): 3439, 2945, 1604 cm^{-1}; ^1H NMR (DMSO-d_6): $\delta = 2.46$ (s, 6 H, 2 CH_3), 5.21 (s, 1H, CH), 6.19 (s, 1H, CH) 7.21–7.86 (m, 14 H, Ar); MS (*m/z*): 504 (M^+). Anal. calcd. for $C_{30}H_{24}N_4O_4$: C, 71.42; H, 4.79; N, 11.10; found C, 71.21; H, 4.70; N, 11.18.

Table 3, Entry 13. IR (KBr): 3411, 2951, 1609 cm^{-1}; ^1H NMR (DMSO-d_6): $\delta = 2.34$ (s, 6 H, 2 CH_3), 5.24 (s, 1H, CH), 6.21 (s, 1H, CH) 7.18–7.88 (m, 13 H,

Ar); MS (m/z): 549 (M^+). Anal. calcd. for $C_{30}H_{23}N_5O_6$: C, 65.57; H, 4.22; N, 12.74. found: C, 65.46; H, 4.34; N, 12.61.

CONCLUSION

We have developed a simple and efficient method for the synthesis of 4,4′-(arylmethylene)bis(1H-pyrazol-5-ols) using xanthan sulfuric acid. The short reaction times, simple workup, good yields, mild reaction conditions, and recyclability of the catalyst are features of this new procedure.

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