
Research Article

Theme- *New horizons in chemical sciences.*

Guest Editor- *R.P. Pawar*

A Clean and Highly Efficient Synthesis of 4,4'-(Arylmethylene)bis(3-methyl-1H-pyrazol-5-ol) derivatives using Mg(SO₄).7H₂O as Homogeneous catalyst.

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Received 13 March 2019; received in revised form 09 August 2019; accepted 16 August 2019

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ABSTRACT

The synthesis of 4,4'-(arylmethylene)bis(3-methyl-1H-pyrazol-5-ol) derivatives was performed effectively by the reaction of aryl aldehydes and 3-methyl-1H-pyrazol-5(4H)-one in the presence of a catalytic amount of Mg(SO₄).7H₂O as an environmentally friendly catalyst in methanol solvent on stirring for half an hour yields 80-94% product. All of the obtained compounds were crystallized from ethanol and characterized by IR, H¹NMR and ¹³C NMR. The method has the advantages of high yields, short reaction time, and simple work-up.

KEYWORDS

4, 4'-(Arylmethylene) bis (3-methyl-1H-pyrazol-5-ol), 3-Methyl-1H-pyrazol-5(4H)-one, Mg(SO₄).7H₂O, Green approach, Multi-component reaction.

1. INTRODUCTION

Pyrazolones and pyrazoles are an important class of bioactive drug targets in the pharmaceutical industry that exhibits a wide range of biological activities [1]. For example, pyrazole derivatives such as 4,40-(arylmethylene)bis(3-methyl-1H-pyrazol-5-ols) have a broad spectrum of approved biological activity, being used as anti-inflammatory [2], antipyretic [3], gastric secretion stimulatory [4], antidepressant [5], antibacterial [6], and anti-filarial agents [7]. Also, these derivatives are applied as fungicides [8], pesticides [9], insecticides [10], and dyestuffs [11], and as the chelating and extracting reagents for different metal ions [12].

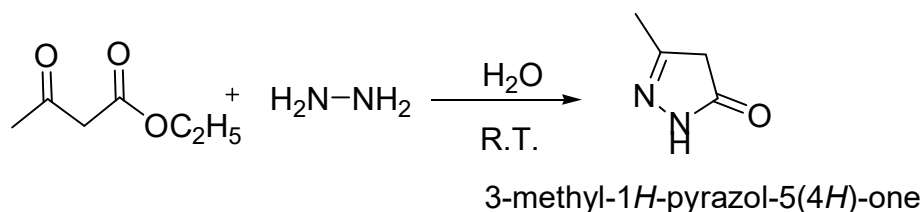
The most common method for the synthesis of 4, 4'-(arylmethylene)bis(1H-pyrazol-5-ol)s is the one-pot pseudo-three-component condensation of aldehydes with 3-methyl-1-phenyl-5-pyrazolone. Some catalysts have been used for this transformation including acetic acid or piperidine [13], sodium dodecyl sulfate [14], THSB [15], silica-bonded S-sulfonic acid [16] PEGSO₃H [17], PEG-400 at 110°C [18], CAN [19] and electro-catalysis procedure [20]. However, most of these synthetic methods suffer from drawbacks such as employing toxic reagent, strongly acidic or basic conditions, expensive and complex catalysts or reagents, harsh reaction conditions, tedious steps, in most of the cases low yields of the products and long reaction for the preparation of 4, 4'-(phenyl methylene) bis (3-methyl-1H-pyrazol-5-ol) by using Mg(SO₄).7H₂O as a catalyst and stirring method at room temperature in MeOH as the solvent.

2. MATERIALS AND METHODS

All the chemicals used were of high purity analytical reagent grade. Hydrazine hydrate (SDFCL), ethyl acetoacetate (Loba Chem), all aldehydes (Alfa Aesar). Organic solvents like ethanol Methanol petroleum ether (RLFCL) were used. Thin layer Chromatography was carried out on silica gel 60/UV254. Melting points of the products were recorded in open capillaries on the digital melting point apparatus (Optics Technology) and were uncorrected. IR and NMR spectra were recorded at SAIF Cochin and ¹³C NMR at IIT Bombay.

2.1. Synthesis of 3-methyl-1H-pyrazol-5(4H)-one

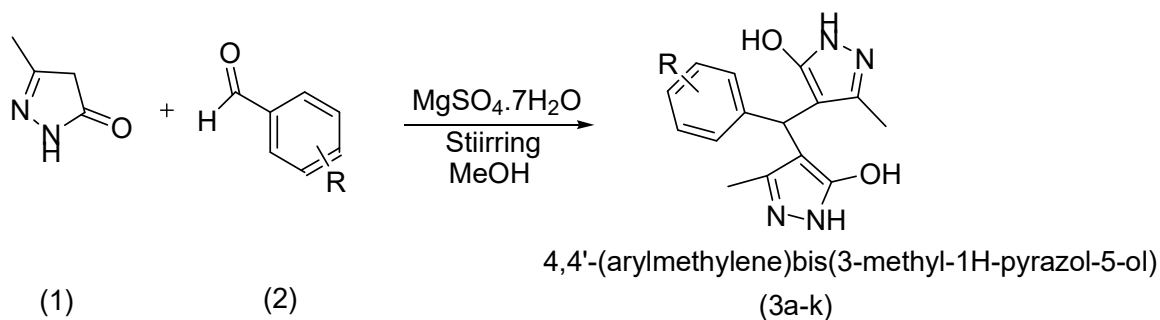
Hydrazine hydrate (0.1mol) was added drop wise to ethyl acetoacetate (0.1mol) and the resulting mixture was stirred at room temperature. After completion of the reaction, the white solid product was collected by filtration.



Scheme 1. Synthesis of 3-methyl-1H-pyrazol-5(4H)-one

2.2. *Synthesis of 4,4'-(arylmethylene)bis(3-methyl-1H-pyrazol-5-ol) derivatives*

To a mixture 3-methyl-1H-pyrazol-5(4H)-one (2 mmol), aldehyde (1mmol) and MeOH (10 mL), Mg(SO₄).7H₂O (2.5 mol %) was added. The mixture was stirred at room temperature 30°C for half-hour. After completion of the reaction, the resulting solid was collected by filtration, recrystallized from ethanol and characterized by spectral analysis.



Scheme 2. Synthesis of 4,4'-(arylmethylene)bis(3-methyl-1H-pyrazol-5-ol) derivatives

3. RESULTS AND DISCUSSION

As a model reaction first investigated the reaction between 3-methyl-1H-pyrazol-5(4H)-one and benzaldehyde catalyzed by MgSO₄.7H₂O at different concentrations. To optimize the catalyst concentration was varied as 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5mol% respectively. The results are summarized in Table1.

Table 1. Amounts of catalyst optimization for the synthesis of 4,4'-(arylmethylene)bis(3-methyl-1H-pyrazol-5-ol) derivatives.

Entry	Mg(SO ₄).7H ₂ O (mol%)	Yield %
1	0.0	No reaction
2	0.5	50
3	1.0	55
4	1.5	57
5	2.0	68
6	2.5	85
7	3.0	85
8	3.5	84
9	4.0	85

To explore the substrate scope, we examined a range of various aromatic aldehydes under the optimized reaction conditions. The results are summarized in Table 2. The structures of the products were established by spectroscopic methods.

Table 2. Synthesis of 4,4'-(arylmethylene)bis(3-methyl-1H-pyrazol-5-ol) derivatives.

Entry	R	Product	Yield %
1	4-H	3a	85
2	3-NO ₂	3b	92
3	4-F	3c	90
4	4-Cl	3d	88
5	4-OCH ₃	3e	87
6	2-OH	3f	91
7	2-Cl	3g	87
8	4-NO ₂	3h	91
9	2,4-Cl ₂	3j	90
10	3-OH	3k	87

4,4'-[(phenylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol)](3a). White powder, Mp. 170-172 °C, IR (cm⁻¹): 3361(OH), 2927, 1625, 1574(C = C), 1400,1101, 787,755; ¹H NMR (500 MHz, DMSO-d₆ δ): 2.49 (s, 6H, CH₃), 4.94 (s, 1H, CH), 7.15-7.70 (m, 14H, Ar-H), 12.44 (s, 1H, OH), 13.98 (s, 1H, OH); ¹³C NMR(125.17 MHz, DMSO-d₆ δ): 11.6, 33.1. 100.5, 105.3, 120.5, 121.5, 125.4, 125.8,127.1, 128.1, 128.3, 142.8, 146.2.

4,4'-((3-Nitrophenyl)methylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) (3b) : Yellow powder m.p.149-150 °C. IR (cm⁻¹): 3068, 2921, 1734, 1600, 1579, 1528, 1500. 1415, 1349, 903, 833, 756, 733, 693. ¹H NMR (400 MHz, DMSO-d₆)δ 5: 8.09-8.07 (m, 2H), 7.75-7.58 (m, 6H), 7.46-7.42 (m, 4H), 7.27-7.23 (m, 2H), 5.14 (s, 1H), 2.35 (s,6H).

4,4'-((4-Fluorophenyl)methylene)bis (3-methyl-1-phenyl-1H-pyrazol-5-ol) (3c) : White powder m.p.190-192 °C. IR (cm⁻¹): 3068, 2921, 1600, 1504, 1415, 1294, 1223, 1158, 805, 753, 692. ¹H NMR (400 MHz, DMSO-d₆)δ 7.70 (d, 4H,7 =8.0 Hz), 7.69-7.42 (m, 4H), 7.29-7.23 (m, 4H), 7.12-7.08 (m,2H), 4.96 (s, 1H), 2.32 (s, 6H).

4,4'-[(4-Chlorophenyl)methylene]bis(3-methyl- 1-phenyl- 1H-pyrazol-5-ol)(3d)

White powder IR (cm⁻¹): 3463 (OH), 2927, 1625, 1574 (C=C); ¹H NMR (500 MHz; DMSO; Me₄Si); δ 2.30 (s, 6H, CH₃), 4.95 (s, 1H, CH), 7.22-7.70 (m, 14H, H_{aromatic}), 12.50 (s, 1H, OH), 13.87 (s,1H, OH); ¹³C NMR (125.13 MHz; DMSO; Me₄Si); δ: 11.50, 32.56, 120.47, 125.51, 127.81, 128.81, 129.04, 130.47, 137.33, 141.11, 146.15.

4,4'-[(4-Methoxyphenyl)methylene]bis(3-methyl- 1-phen- yl- 1H-pyrazol-5-ol) (3e)

White powder IR (cm⁻¹): 3060(OH), 2920, 2836, 1604, 1580, 1404, 1252, 1036, 752, 692; ¹H NMR (500 MHz; DMSO; Me₄Si) δ; 2.12 (s, 6 H, 2 CH₃), 3.72 (s, 3 H, OCH₃), 4.73 (s, 1 H, CH), 6.77-7.28 (m, 14H, H_{aromatic}); ¹³C NMR (125.13 MHz; DMSO; Me₄Si); δ 11.6, 32.4, 54.9, 105.0, 113.5, 120.4, 125.4, 128.1, 128.9, 129.2, 134.6, 137.9, 146.1, 157.5.

4,4'-((2-Chlorophenyl)methylene)bis(3-methyl-1-phenyl- 1H-pyrazol-5-ol) (3g) : White powder m.p. 235-236 °C IR (cm⁻¹): 3066, 2914, 2769, 1615, 1562, 1500, 1458, 1401, 1369, 1301, 1215, 1129, 1086, 1031, 900, 838, 791, 753, 691. ¹H NMR (400 MHz, DMSO-7₆) δ: 7.89- 7.81 (m, 1H), 7.69 (d, 4H, 7 = 7.6 Hz), 7.45-7.38 (m, 5H), 7.32-7.20 (m, 4H), 5.14 (s, 1H), 2.35 (s, 6H).

In all cases, good yields were obtained, regardless of the nature of substituents present on aldehyde. Also, we have noticed an electron-donating group present in aldehyde provides lower yields whereas the electron-withdrawing group provides a higher yield.

4. CONCLUSION

We have demonstrated a rapid and efficient $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ catalyzed synthesis of 4,4'-(arylmethylene)bis (3-methyl-1H-pyrazol-5-ol) derivatives in methanol as solvent. The current methodology has advantages of simplicity, mild reaction condition, and excellent yields of products.

5. ACKNOWLEDGMENT

Authors are thankful to the Principal Balbhim College, Beed, SAIF Cochin for the instrumental facility and IIT Bombay for ^{13}C NMR spectra of the synthesized compounds.

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