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# A Clean and Highly Efficient Synthesis of 4,4'-(Arylmethylene)bis(3-methyl-1H-pyrazol-5-ol) derivatives using $Mg(SO_4).7H_2O$ as Homogeneous catalyst.

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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(4*H*)-one in the presence of a catalytic amount of $Mg(SO_4).7H_2O$ 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, $H^1$NMR and $^{13}$C 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, $Mg(SO_4).7H_2O$, 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].

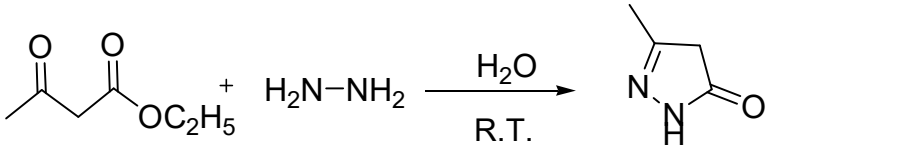
The most common method for the synthesis of 4, 4′-(arylmethylene)bis(1*H*-pyrazol-5-ol)s is the one-pot pseudo-three-component condensation of aldehydes with 3-methyl-1-phenyl-5-pyrazolone. Some catalysts have been used for this transformation including acetic acid or piperidine [13], sodium dodecyl sulfate [14], THSB [15], silica-bonded S-sulfonic acid [16] $PEGSO_3H$ [17], PEG-400 at 110$^oC$ [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 $Mg(SO_4).7H_2O$ 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 regent 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 $^{13}C$ 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.

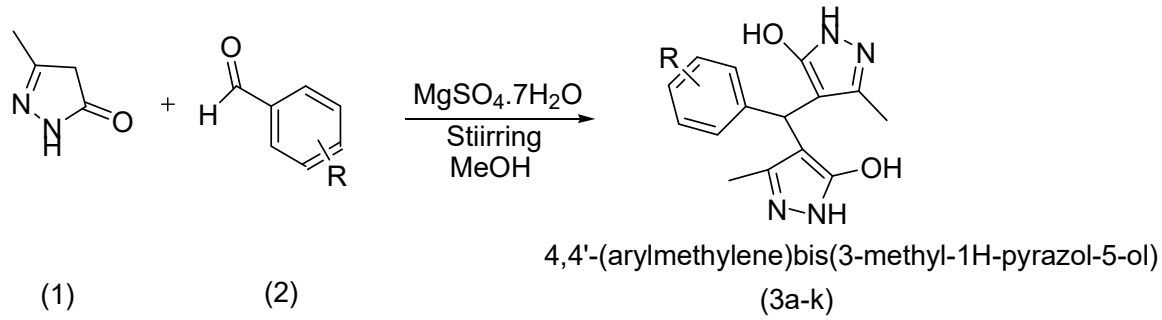



3-methyl-1*H*-pyrazol-5(4*H*)-one

**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), $Mg(SO_4).7H_2O$ (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 $MgSO_4.7H_2O$ 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 | $Mg(SO_4).7H_2O$ (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'-[(phenyhnethylene)bis(3-methyl-l-plienyl-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; $^1$H NMR (500 MHz, DMSO-$d_6$ δ): 2.49 (s, 6H, $CH_3$), 4.94 (s, 1H, CH), 7.15-7.70 (m, 14H, Ar-H), 12.44 (s, 1H, OH), 13.98 (s, 1H, OH); $^{13}$CNMR(125.17 MHz, DMSO-$d_6$ 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. 'H NMR (400 MHz, DMSO-$d_6$)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-l-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. $^1$H NMR (400 MHz, DMSO-$d_6$)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- lH-pyrazol-5-ol)(3d)***

White powder IR ($cm^{-1}$): 3463 (OH), 2927, 1625, 1574 (C=C); $^1$H NMR (500 MHz; DMSO; $Me_4Si$); δ 2.30 (s, 6H, $CH_3$), 4.95 (s, 1H, CH), 7.22-7.70 (m, 14H, $H_{aromatic}$), 12.50 (s, 1H, OH), 13.87 (s,1H, OH); $^{13}$C NMR (125.13 MHz; DMSO; $Me_4Si$); 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; $^1$H NMR (500 MHz; DMSO; $Me_4Si$) δ; 2.12 (s, 6 H, 2 $CH_3$), 3.72 (s, 3 H, $OCH_3$), 4.73 (s, 1 H, CH), 6.77-7.28 (m, 14H, $H_{aromatic}$); $^{13}$C NMR (125.13 MHz; DMSO; $Me_4Si$); 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- lH-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. $^1$H NMR (400 MHz, DMSO-$7_6$) 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 $MgSO_4.7H_2O$ 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.

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## 6. REFERENCES

1. Wei, F., Zhao, B. X., Huang, B., Zhang, L., Sun, C. H., Dong, W. L., Shin, D.S.& Miao, J. Y. (2006). Design, synthesis, and preliminary biological evaluation of novel ethyl 1-(2′-hydroxy-3′-aroxypropyl)-3-aryl-1H-pyrazole-5-carboxylate. *Bioorganic & Medicinal Chemistry Letters*, *16*(24), 6342-6347.
2. Tanitame, A., Oyamada, Y., Ofuji, K., Fujimoto, M., Iwai, N., Hiyama, Y Suzuki, K., Ito, H., Terauchi, H., Kawasaki, M., Nagai, K., Wachi, M., Yamagishi, J. (2004). Synthesis and antibacterial activity of a novel series of potent DNA gyrase inhibitors. Pyrazole derivatives. *Journal of Medicinal Chemistry*, *47*(14), 3693-3696.
3. Sugiura, S., Ohno, S., Ohtani, O., Izumi, K., Kitamikado, T., Asai, H., & Fujimura, H. (1977). Syntheses and anti-inflammatory and hypnotic activity of 5-alkoxy-3-(N-substituted carbamoyl)-1-phenylpyrazoles. *Journal of Medicinal Chemistry*, *20*(1), 80-85.
4. Wiley, R. H., & Behr, L. C. (1967). Pyrazoles, pyrazolines, pyrazolidines, indazoles and condensed rings.
5. Rosiere, C. E., & Grossman, M. I. (1951). An analog of histamine that stimulates gastric acid secretion without other actions of histamine. *Science*, *113*(2945), 651-651.
6. Tanitame, A., Oyamada, Y., Ofuji, K., Terauchi, H., Kawasaki, M., Wachi, M., & Yamagishi, J. I. (2005). Synthesis and antibacterial activity of a novel series of DNA gyrase inhibitors: 5-[(E)-2-arylvinyl] pyrazoles. *Bioorganic & Medicinal Chemistry Letters*, *15*(19), 4299-4303.
7. Mahajan, R. N., Havaldar, F. H., & Fernandes, P. S. (1991). Syntheses and biological activity of heterocycles derived from 3-methoxy-i-phenyl-ih-pyrazole-5 carboxylate. *Journal of the Indian Chemical Society*, *68*(4), 245-246.
8. Chauhan, P. M. S., SINGH, S., & Chatterjee, R. K. (1993). Antifilarial Profile of Substituted Pyrazoles: A New Class of Antifilarial Agents. *Chem Inform*, *24*(47).

**9.** Singh, D., & SINGH, D. (1991). Synthesis and antifungal activity of some 4-arylmethylene derivatives of substituted pyrazolones. *Journal of the Indian Chemical Society*, *68*(3), 165-167.

**10.** Londershausen, M. (1996). Approaches to new parasiticides. *Pesticide Science*, *48*(4), 269-292.

**11.** Lecher, H. Z. (1955). The chemistry of synthetic dyes and pigments. *Journal of the American Chemical Society*, *77*(22), 6089-6089.

**12.** Addison, A. W., & Burke, P. J. (1981). Synthesis of some imidazole-and pyrazole derived chelating agents. *Journal of Heterocyclic Chemistry*, *18*(4), 803-805.

**13.** Singh, D., & Singh, D. (1984). 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). *Journal of Chemical and Engineering Data*, *29*(3), 355-356.

**14.** Wang, W., Wang, S. X., Qin, X. Y., & Li, J. T. (2005). Reaction of aldehydes and pyrazolones in the presence of sodium dodecyl sulfate in aqueous media. *Synthetic Communications*, *35*(9), 1263-1269.

**15.** Karimi-Jaberi, Z., Pooladian, B., Moradi, M., & Ghasemi, E. (2012). 1, 3, 5-Tris (hydrogensulfato)benzene: A new and efficient catalyst for synthesis of 4, 4′-(arylmethylene) bis (1h-pyrazol-5-ol) derivatives. *Chinese Journal of Catalysis*, *33*(11-12), 1945-1949.

**16.** Niknam, K., Saberi, D., Sadegheyan, M., & Deris, A. (2010). 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 Letters*, *51*(4), 692-694.

**17.** Hasaninejad, A., Shekouhy, M., Zare, A., Ghattali, S. H., & Golzar, N. (2011). PEG-$SO_3$ H as a new, highly efficient and homogeneous polymeric catalyst for the synthesis of bis (indolyl) methanes and 4, 4′-(Arylmethylene)-bis (3-methyl-1-phenyl-1hpyrazol-5-ol)s in water. *Journal of the Iranian Chemical Society*, *8*(2), 411-423.

**18.** Hasaninejad, A., Zare, A., Shekouhy, M., &Golzar, N. (2011). Efficient synthesis of 4, 4′-(arylmethylene)-bis (3-methyl-1-phenylpyrazol-5-ol) derivatives in PEG-400 under catalyst-free conditions. *Organic Preparations and Procedures International*, *43*(1), 131-137.

**19.** Sujatha, K., Shanthi, G., Selvam, N. P., Manoharan, S., Perumal, P. T., & Rajendran, M. (2009). Synthesis and antiviral activity of 4, 4′-(arylmethylene) bis (1H-pyrazol-5-ols) against peste des petits ruminant virus (PPRV). *Bioorganic &Medicinal Chemistry Letters*, *19*(15), 4501-4503.

**20.** Elinson, M. N., Dorofeev, A. S., Nasybullin, R. F., & Nikishin, G. I. (2008). Facile and convenient synthesis of 4, 4′-(arylmethylene) bis (1H-pyrazol-5-ols) by electrocatalytic tandem Knoevenagel-Michael reaction. *Synthesis*, *12*, 1933-1937.