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# Monosodium Glutamate: An Efficient and Green Catalyst for the Synthesis of Bis(pyrazol-5-ol)s Under Solvent Free Condition.

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**ABSTRACT**
An environmentally benign, facile and an efficient direct simple approach to construct the library of bis(pyrazol-5-ol)s derivatives has been developed by using Monosodium Glutamate (MSG) as a green catalyst under solvent free condition. This method proceeds through the tandem Knoevenagel-Michael reaction. The present synthetic route is a green protocol offering several advantages, such as high yield of products, shorter reaction time, mild reaction conditions, minimizing chemical waste and exclusion of environmentally hazardous solvent make this protocol widely acceptable.

**KEYWORDS**
Aromatic aldehyde, Ethyl acetoacetate, Phenyl hydrazine, Monosodium Glutamate.

## 1. INTRODUCTION

Heterocyclic compounds are the important sorts of organic compounds, which are widely used in medicinal chemistry. The drugs which contain the core of heterocycles in its skeletons shows various biological activities such as antifungal activity, anti-inflammation, anti-bacterial, antioxidants, anticonvulsant, ant allergic, herbicidal activity and anticancer etc.[1] Medicinal chemistry occupies an important position to establish a relationship between chemical structure and pharmacological activity.

The N-Heterocyclic compounds acquired undisputed significant position in organic synthesis reflection of their wide range of biological activities. Nitrogen containing heterocycles such as pyrazoles and pyrazolone are most privileged scaffolds they constitute an important class of natural and synthetic products. Pyrazolone is 5-membered heterocycle containing two adjacent nitrogen atoms. It can be viewed as a derivative of pyrazole possessing an additional keto (C=O) group. Pyrazolone are amongst the oldest synthetic pharmaceuticals, starting with the introduction of antipyrine (phenazone) in 1880's.[2][3] The synthesis of pyrazolone was first reported in 1883 by Ludwig knorr, via a condensation reaction ethyl acetoacetate and phenyl hydrazine.[4] The pyrazolone compounds generally act as analgesics which include dipyrone (metamizole), aminopyrine ampyrone, famprofazone, morazone, nifenazone, piperylone and propyphenazone are widely used. Pyrazolone have been studied as ligands[5] and also used as extractant for some metal ions.[6] Pyrazolone ring containing compounds are known to display massive range of pharmacological activities such as antimicrobial,[7] antifungal,[8] anti-inflammatory, analgesic, antipyretic,[9] herbicidal[10] and also unique electrical and optical properties.[11] Pyrazolone derivatives were attracted much attention due to their various biological activities such as antitumor,[12] selective COX-2 inhibitory,[13] cytokine inhibiters,[14] agrochemicals, dyes and pigments.4,4'-(arylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ols) are being used as gastric secretion stimulatory,[15] antidepressant,[16] antibacterial[17] and ant filarial agents.[18] 4,4'-(arylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ols) are applied as fungicides, pesticides,[19] insecticides[20] and dyestuffs.[21-23] Credit to their wide pharmacological applicability synthetic chemist from all over the world are engaged in development of direct approach to this important motif.

Multicomponent reactions [MCR] have revolutionized the world of organic synthesis an alternative tool to conventional linear synthesis to construct complex molecular structure in one-pot single-step approach. A multicomponent reaction includes special incentives such as high atom economy, lower costs, shorter reaction time and environmental friendliness. [24] A quite significant number of modifications have been developed by the huge efforts of researcher's over the past decade for the synthesis of this biologically important motif. The most common, efficient and acceptable approach for realization of bis(pyrazol-5-ol)s is cyclocondensation of aromatic aldehyde (5 mmol), β-ketoester (10 mmol) and phenyl hydrazine (10 mmol)**.** The different catalytic strategies have been proposed for the construction of bis(pyrazol-5-ol)s such as Ce(SO4)2,[25] [MIm]ClO4,[26] Cellulose Sulfuric acid,[27] Silica Vanadic acid,[28] Pyridine trifluoroacetate or acetic acid,[29] [(TMEDSA)(HSO4)],[30] [(Et3NH)(HSO4)].[31]

Unfortunately, above mentioned methods suffer from some limitations such as use of heavy metals, harsh solvent, poor yield, complex workup procedure, catalyst preparation and isolation. Due to these limitations of well-established protocols there is continuous need of development of new, efficient and green methodology for this fortunate compound. The development of simple access route to complex molecular scaffold in environmental benign manner is key challenge for the organic chemist to fulfill Green chemistry principles. All organic synthetic routes apply different kinds of volatile solvents which contributes on large scale to the pollution and depletion of our resources. Hence from last few years researchers are targeting development of greener solvent as a reaction medium. The aim is to replace routine hazardous solvents and reduce their harsh effects. It will be quite acceptable and well come approach if reaction is carried out in solvent free condition.

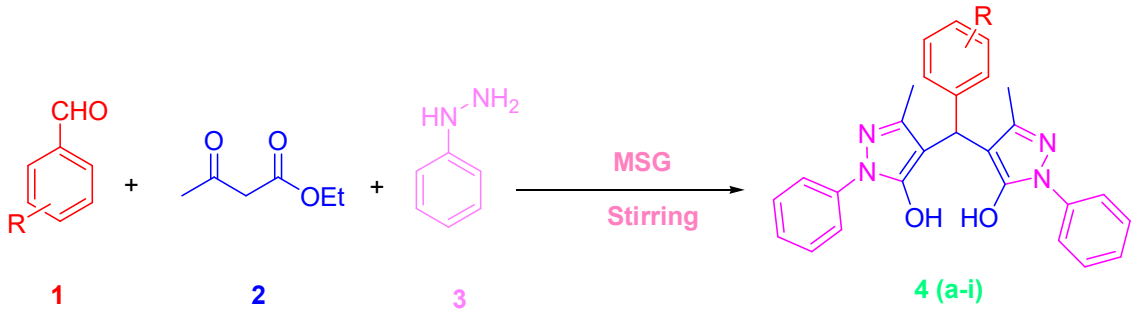
In present work attempt has been made to synthesis 4, 4'-(arylmethylene) bis(3-methyl-1-phenyl-1H-pyrazol-5-ols) and its derivatives by using Monosodium Glutamate as a green catalyst under solvent free condition to follow and satisfy Green chemistry principles. We use monosodium glutamate as a catalyst for synthesis because of MSG offering green protocol for reaction such as mild reaction condition, high yield of product, shorter reaction time, minimizing chemical waste, easy work up procedure and not using heavy metal based catalyst. Monosodium glutamate is most abundant naturally occurring non-essential amino acid,] safe for human consumption, as a flavour enhancer and food additive also important neurotransmitters in human brain, playing a key role in learning and memory. Here we tried to cash double benefit of using green protocol with solvent free economic strategy. Here in we wish to report first time Monosodium Glutamate catalysed green tactic for the synthesis of 4,4'-(arylmethylene) bis(1H-pyrozol-5-ol) by cyclocondensation of aromatic aldehyde (5 mmol), β-ketoester (10 mmol) and phenyl hydrazine (10 mmol) under solvent free condition. (Scheme 1)

## 2. MATERIALS AND METHODS

All the chemicals and synthetic grade reagents were procured from Sigma Aldrich India and Merck chemicals and were used without further purification. Melting points were recorded in open capillaries using Buchi melting-point B-540 apparatus. $^{1}$H NMR spectra were recorded on Bruker instrument (400 MHz) and chemical shifts are reported in δ ppm. IR spectra were run on Shimazdu FTIR 8300. The reaction mixture stirred on Digital display magnetic Stirrer (U51909DL2003PTC121305).

### *2.1. Preparation of 4,4'-(arylmethylene) bis(1H-pyrozol-5-ol)*

In a typical procedure, a mixture of aromatic aldehyde 1 (5 mmol), ethyl acetoacetate 2 (10 mmol) and phenyl hydrazine 3 (10 mmol) was stirred in presence of monosodium glutamate at $60^{0}$C under solvent free condition for an appropriate period of time. After the completion of reaction (monitored by TLC), the reaction mixture was cooled to room temperature and then water was added to the solution with stirring. The precipitate was collected by filtration and evaporation of the mother liquor under reduced pressure led to the recovery of catalyst which could be reused for next run. The products (4a-i) were purified by recrystallization.




**Scheme 1.** 4,4'-(arylmethylene) bis(1H-pyrozol-5-ol).

## 3. RESULTS AND DISCUSSION

The focus of our research is to develop an eco-efficient methodology that decreases both the amount of waste generated and use of hazardous chemicals**.** The investigation was carried out for the catalytic evaluation of monosodium glutamate for the optimum reaction conditions. The formation of 4,4'-(aryl methylene)bis(1H-pyrazol-5ol)s was explored by designing model reaction between benzaldehyde (5 mmol), ethyl acetoacetate (10 mmol) and phenyl hydrazine (10 mmol) for the formation of 4,4'-[(arylmethylene)]bis(3-methyl-1-phenyl-1H-pyrazol-5-ol) at various temperature and catalytic loading. In order to optimize reaction conditions, the reaction was investigated at various catalytic amount of catalyst. In our initial attempt this model reaction was carried out in absence of catalyst much low yield of product was obtained (Table 1, entry-1). This result revealed that role of catalyst is crucial in this reaction. To access the catalytic potential of MSG we loaded 5, 10, 15 & 20 mol % and found with loading of 10 mol % of MSG we achieved highest yield of 88 % (Table 1, entry-3). Increasing the amount of catalyst than 10 mol % resulted in decrease in yield (Table 1, entries-4, 5). In next step to find out optimized temperature condition we found 60°c as optimum temperature to carry this transformation with highest amount of product yield. To examine the effect of solvent, we employed different solvents such as acetonitrile, dichloromethane, chloroform, ethanol and water (Table 1, entries-6-10). The results revealed that solvent free condition is most fruitful for his transformation. Hence solvent free condition is selected to carry subsequent reactions.

**Table 1.** Optimization of reaction conditions.

| **Entry** | **Catalyst Quantity** | **Solvent** | **Time (Min)** | **Yield (%)** |
|---|---|---|---|---|
| **1** | No Catalyst | Solvent free | 130 | 19 |
| **2** | 5 | Solvent free | 75 | 62 |
| **3** | 10 | Solvent free | 27 | 88 |
| **4** | 15 | Solvent free | 52 | 85 |

| | | | | |
|---|---|---|---|---|
| **5** | 20 | Solvent free | 65 | 80 |
| **6** | 10 | Acetonitrile | 78 | 49 |
| **7** | 10 | Dichloromethane | 75 | 45 |
| **8** | 10 | Chloroform | 68 | 54 |
| **9** | 10 | Ethanol | 65 | 70 |
| **10** | 10 | Water | 79 | 55 |

*3.1. Reaction conditions*

Benzaldehyde (1 mol), EAA (2 mol), Hydrazine Hydrate (2 mol), MSG. [a]Isolated yields.

Inspired by the efficiency of optimized protocol its scope and applicability further tested. In order to evaluate general applicability of this proposed protocol was carried out with various aromatic and heterocyclic aldehydes substrate along with ethyl acetoacetate and phenyl hydrazine. To our delight both electron donating and electron withdrawing groups were well tolerated (Table 2, (1-9)). Aldehydes with electron withdrawing group participated readily in the condensation reaction, providing corresponding 4,4'-(aryl methylene) bis(1H-pyrazol-5ol) derivatives in good to excellent yields (Table 2, 2 & 6). We were pleased as acid sensitive substrate like furfural converted into corresponding product smoothly with yield of 81% (table 2, entry-9). The progress of the reaction was monitored by thin-layer chromatography (TLC). The crude products obtained were recrystallized by ethanol.

Monosodium Glutamate is salt of nonessential amino acid Glutamic acid. It has both acidic as well as basic catalytic sites. It exists as zwitter ionic salts showing the characteristic of both ionic liquids as well as zwitterions. It might be participated in the reaction by increasing the electrophilicity of aryl aldehydes which in turn enhances its reactivity. The successful application of MSG as an ecofriendly catalyst in combination of solvent free condition is fascinating and is likely to open the gateway to the other principal organic transformations.

**Table 2.** Monosodium glutamate catalysed synthesis of 4,4'-(aryl methylene) bis(1H-pyrazol-5ol) derivatives under solvent free condition at 60°c.[a]

| **Entry** | **R** | **Product** | **Time (min.)** | **[b]Yield (%)** | **M.P. (°c)** | |
|---|---|---|---|---|---|---|
| | | | | | **Found** | **Recorded** |
| **1** | $C_6H_5$-CHO | a | 32 | 88 | 175-177 | 171-172 |
| **2** | 4-Cl$C_6H_4$-CHO | b | 27 | 91 | 215-217 | 207-209 |
| **3** | 4-OMe$C_6H_4$-CHO | c | 39 | 82 | 178-180 | 173-175 |
| **4** | 4-OH$C_6H_4$-CHO | d | 38 | 80 | 150-152 | 154-157 |
| **5** | 3-OH$C_6H_4$CHO | e | 36 | 84 | 164-168 | 165-168 |
| **6** | 4-$NO_2C_6H_4$-CHO | f | 26 | 92 | 236-238 | 230-232 |
| **7** | 4-$CH_3C_6H_4$CHO | g | 39 | 85 | 205-207 | 203-204 |
| **8** | 2-HO$C_6H_4$CHO | h | 38 | 82 | 229-230 | 230-231 |
| **9** | Furfural | i | 37 | 81 | 175-177 | 181-183 |

[a]Reaction Condition: aromatic aldehydes (5 mmol), ethylacetoacetate (10 mmol), phenyl hydrazine (10 mmol), MSG (10 mol %), 60°c, solvent free condition. [b]Isolated yield.

*3.2. Physical and spectroscopic data of some representative compounds.*

The peaks at 3313 $cm^{-1}$ & 1073 $cm^{-1}$ were assigned to the stretching for OH & C-N vibrations respectively of pyrazolone ring in FT-IR spectrum of bis(pyrazol-5-ol) respectively. The peak at 1501$cm^{-1}$ confirmed presence of pyrazolone skeleton. Vibrational peaks at 2834 $cm^{-1}$, 1593 $cm^{-1}$ & 1442 $cm^{-1}$ shown presence of C-C stretching vibrations in aromatic ring. $^{1}H$ NMR spectrum of bis(pyrazol-5-ol) shows protons at 4.8 ppm presence of CH Of methine. The protons of methyl group attached to ring were shown at 2.5 ppm (singlet). The presence of $CH_3$ group attached to ring & CH moiety also conform by $^{13}C$-NMR signal at 11.53 & 33.66 ppm respectively.

***a) 4,4'-[(arylmethylene)]bis(3-methyl-1-phenyl-1H-pyrazol-5-ol).***

Melting Point:- 175-177 °c, IR (KBr) ($\nu_{max,}$ $cm^{-1}$): 3313(OH), 2834,1593,1442(C=C), 1073(C-N); $^{1}H$ NMR (500.13 MHz, $CDCl_3$): δ 3.80(OH), 4.80(1H,CH), 2.20(6H,$CH_3$), 7.10-7.65(m,15H,Aromatic H); $^{13}C$ NMR (125.75 MHz,$CDCl_3$): δ 11.53, 33.66, 121.34, 126.20, 126.40, 127.16, 128.33, 128.85, 140.86, 146.43.

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

Melting Point:- 218-220 °c, IR (KBr) ($\nu_{max,}$ $cm^{-1}$): 3743(OH), 2918,1676,1587(C=C), 1123(C-N), 778(Ar-Cl); $^{1}H$ NMR (500.13 MHz, $CDCl_3$): δ 3.75(OH), 4.78(1H,CH), 2.49(6H,$CH_3$), 7.11-7.65(m,14H,Aromatic H); $^{13}C$ NMR (125.75 MHz,$CDCl_3$): δ 12.92, 29.70, 76.70, 121.14, 122.62 124.95, 126.58, 128.22, 128.95, 136.19, 150.76, 151.63.

***c) 4,4'-[(4-methoxyphenyl)methylene)]bis(3-methyl-1-phenyl-1H-pyrazol-5-ol)***

Melting Point:- 178-180 °c, IR (KBr) ($\nu_{max,}$ $cm^{-1}$): 3244(OH), 2916,1649,1602(C=C), 1105(C-N), 1023(Ar-OMe); $^{1}H$ NMR (500.13 MHz, $CDCl_3$): δ 3.80(OH), 3.9(1H,CH), 2.5(6H,$CH_3$), 7.22-8.04(m,14H,Aromatic H); $^{13}C$ NMR (125.75 MHz,$CDCl_3$): δ 11.88, 33.31, 56.04, 120.21, 121.79, 126.74, 128, 129.33, 129.70, 145.45, 145.66,158.32.

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## 5. CONCLUSION

An eco-friendly strategy for synthesis of 4,4'-(arylmethylene)bis(1H-pyrazol-5ol)s by solvent free green catalysed multicomponent reaction has been demonstrated. The current protocol has several advantages of simple experimental procedures, high yield of products, inexpensive subtract, minimizing chemical waste, inexpensive and clean catalyst. This method using Monosodium Glutamate (MSG) is value addition to the reported methods. We believe that this MSG protocol can be used as a stepping stone to carry out other organic synthesis.

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