**ORIGINAL RESEARCH ARTICLE**

# AN ENVIRONMENT FRIENDLY GREEN PROTOCOL FOR THE SYNTHESIS OF NOVEL COMPOUNDS IN AQUEOUS MEDIA WITH THEIR BIOLOGICAL EVALUATION

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**ABSTRACT**:

A clean, simple, green, environmental friendly and waste minimizing synthesis of 6-amino-4-aryl-3-methyl-1-phenyl-1,4-dihydropyrano [2,3-*c*] pyrazole-5-carbonitriles was accomplished in good to excellent yields *via* the one-pot three component condensation of 3-methyl-1-phenyl- 2-pyrazolin-5-one, aromatic aldehyde, and malononitrile in aqueous medium. The reaction has the advantages of good yield, less pollution; ease of separation, and of being environment friendly.

**KEYWORDS:** Green synthesis; Aqueous medium; Aromatic aldehyde; Malononitrile.

## INTRODUCTION:

Increasing urbanization and industrialization have resulted in a dramatic increase in the volume of wastes generated worldwide, particularly of sewage sludge or biosolids generated as a byproduct from waste water treatment. Waste management has become a major environmental challenge, and land application of biosolids is generally considered the best option of disposal because it offers the possibility of recycling

plant nutrients, provides organic material, improves a soil's chemical and physical properties, and enhances crop yields. However, the benefits from biosolids application have to be weighed against potential deleterious effects such as risks of excessive leaching of nitrate, contamination of soils and crops with human pathogens and heavy metals, nutritional disorders in crops, increase of soil salinity, contamination of groundwater with pesticides, hormones, and pharmaceuticals, and decreased stability of native soil organic matter. For these reasons, this special issue focuses on the agronomic and environmental implications of soil application of biosolids and presents the most recent scientific information on the subject.

Papers in special issue cover various aspects of the release of nutrients from biosolids and their effect on the growth of cereal and fruit crops, pasture, and trees on a range of soils in diverse locations. Papers also report on the residual nutrient effects of biosolids, their release of potentially damaging heavy metals, and effects on soil organisms, thus providing a broad view of the soil-agronomic advantages and environmental implications of recycling organic matter and nutrients from sewage treatment systems into soils. Green chemistry is about the design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances. Environmental chemistry is the chemistry of the natural environment, and of pollutant chemicals in nature. Green synthesis seeks to reduce and prevent pollution.

Water is perhaps one of the greener solvents, one can imagine in terms of costs, availability, safety and environmental impact. But because of the low solubility of most organic compounds in it and its great reactivity towards some organic compounds (e.g.organometallics), the use of water as solvent was limited to hydrolysis reactions until the pioneering works of (Breslow and Grieco )in the early 1980s. Since then, many striking examples have appeared in the literature showing that water has unique properties as a solvent that can sometimes lead to surprising results

Pyrano pyrazole is a fused heterocycle comprised of pyrazole and pyran rings which are known as the sub-structural units of several biologically active compounds.[1,2] Polyfunctionalised benzopyrans have been widely used as medicinal intermediates due to their biological and pharmacological properties such as antibacterial, molluscicidal, anthelminitic,hypnotic and insecticidal activity.[3-9] Some 2-amino-4*H*-pyrans can be used as photoactive materials.[10] The 4*H*-pyran ring is also a structural unit of a number of natural products.[11-13] 1,4-Dihydropyrano[2,3-*c*]pyrazoles are generally prepared by one-pot three component condensations of

malononitrile,aldehyde and 3-methyl-1-phenyl-2-pyrazolin-5-one using $KF/Al_2O_3$ in DMF at room temperature.[14] The utilisation of water as reaction medium for the synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazoles is demonstrated by using various phase transfer catalysts such as triethylbenzylammonium chloride (TEBA)[15] and hexadecyltrimethylammonium bromide (HTMAB).[16]Similarly, the use of the neutral organo-catalyst DL-proline using the grinding technique[17] and a surfactant such as *p*dodecylbenzenesulfonic acid[18] (DBSA) has recently been demonstrated.

Solvent-free reaction conditions along with microwave irradiation technique using piperidine as the base have also been introduced for the synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazoles.[19] In recent years, the catalytic activity of sulfamic acid has emerged as a useful acid imparting high regio- and chemoselectivity in various chemical transformations.[20--23] The versatility of sulfamic acid because of its low cost, eco-friendly nature and ready availability as a common organic chemical encouraged us to explore it in various multi-component reactions under benign reaction conditions. Here we report another remarkable catalytic activity of cesium chloride in water for the one-pot three-component condensation of malononitrile, an aromatic aldehyde and 3-methyl-1-phenyl-2-pyrazolin-5-one, to form a variety of 6-amino-4-aryl-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles**.**

**MATERIALS AND METHODS**:

Melting points are uncorrected. IR spectra were recorded on a Shimadzu FTIR-1710 spectrophotometer. $^1H$ NMR spectra were recorded at 400 MHz in $CDCl_3$ using TMS as internal standard.

**Experimental:**

*Typical experimental procedure:*

A mixture of aromatic aldehyde (3 mmol), malononitrile (3 mmol),3- ethyl-1-phenyl-2-pyrazolin-5-one and Cesium chloride in water (20 ml) was refluxed for the time period as mentioned in Table 1. After the completion of reaction, it was cooled at room temperature and poured into crushed ice to get solid product which was filtered off. The crude products were recrystallised from ethanol to give pure 1,4-dihydropyrano[2,3-*c*] pyrazole in good to excellent yields.

The physical details and spectral analysis for the new product are given below:

*6-Amino-4-(3,4-dimethoxyphenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile* (**4d**): Yellow crystalline solid, m.p. 191–193°C. IR (KBr): τmax 3490, 3330, 3017, 2937, 2896, 2198,1666, 1589, 13811242 1122, 882 cm‑1. NMR ($CDCl_3$): δ 1.92 (s, 3H,$CH_3$), δ 3.81 (s, 3H, $OCH_3$), δ 3.83 (s, 3H, $OCH_3$), δ 4.67 (s, 1H, ArCH),δ 6.33 (s, 2H, br., $NH_2$), 6.88 (s, 1H, ArH), 6.72 (d, *J* = 8.28 Hz, 1H,

ArH), 6.79 (d, *J* = 8.28 Hz, 1H, ArH), 7.29–7.37 (m, 5H, ArH). Anal.Calcd for $C_{21}H_{18}N_4O_3$: C, 67.37; H, 4.85; N, 14.96; found: C, 67.29;H, 4.83; N, 14.99%.

**RESULTS AND DISCUSSION:**

Initially, we examined the reaction of benzaldehyde (3 mmol), malononitrile (3 mmol) and 3-methyl-1-phenyl-2- pyrazolin-5-one (3 mmol) in water (20 ml) using cesium chloride as the catalyst. The room-temperature stirring of the reaction mixture for 3–5 h did not result in the formation of the expected product. Therefore we carried out the reaction by heating under reflux for 7–13 h, using TLC to monitor progress. When the reaction was complete, the mixture was cooled to room temperature and a solid product was precipitated. The entire reaction mixture was poured onto crushed ice and the solid was filtered off. The crude product was recrystallised from ethanol to afford analytically pure product in 82% yield. The scope of this three-component condensation was then extended using a range of aromatic aldehydes, and the results are summarised in Table 1.

**Table 1: Details of Ar, reaction time and percent yield of compounds:**

| Entry | Ar | Reaction time/h | Product | Yield /% | Melting-point/°C Found |
|---|---|---|---|---|---|
| **1** | $C_6H_5$ | 6 | White | 70% | 167-168 |
| **2** | $4CH_3C_6H_5$ | 8 | White | 80% | 168-170 |
| **3** | $4ClOC_6H_5$ | 5 | Yellow | 80% | 175-177 |
| **4** | $4OHC_6H_5$ | 5 | White | 80% | 208-209 |
| **5** | $4NO_2OC_6H_5$ | 5 | Cream | 60% | 185-187 |
| **6** | $2ClOC_6H_5$ | 4 | Green | 70% | 178-180 |
| **7** | $3,4(CH_3O)_2C_6H_5$ | 3 | White | 70% | 191-193 |
| **8** | $4CH_3OC_6H_5$ | 4 | White | 80% | 167-170 |
| **9** | $2OHOC_6H_5$ | 9 | White | 60% | 168-171 |
| **10** | $OSC_5H_4$ | 9 | White | 64% | 220-223 |

Thus the methoxy substituted aromatic aldehydes (Table 1, entries) underwent a clean three component condensation to form the corresponding 1,4-dihydropyrano[2,3-*c*]pyrazoles in excellent yields. Other aromatic aldehydes produced 1,4-dihydropyrano[2,3-*c*] pyrazole in good yields. However, *p*-dimethylamino benzaldehyde (Table 1, entry 10) failed to produce any 1,4-dihydropyrano[2,3-*c*] pyrazole. A similar failure was reported earlier.[18] The isolated

pyrano[3,2-*c*] pyrazole derivatives were completely characterised by IR and $^{s}$H NMR, and the melting points of known compounds were consistent with those of the references reported. For example, the IR spectra for **4a** exhibited sharp bands at 3471, 3257 cm–1 due to $NH_2$ and 2198 cm–1 due to CN. The $^{1}$H NMR spectrum of **4a** exhibited a characteristic peak at δ = 4.62 ppm for H-4 and a broad singlet peak at δ = 6.71 ppm due to the $NH_2$ group.

The synthesis of 1,4-dihydropyrano[2,3‑*c*]pyrazole-5-carbonitriles by one-pot three component condensation of aromatic aldehydes, malononitrile and 3- methyl-1-phenyl-2-pyrazolin-5-one in the presence of catalytic quantity of cesium chloride in water is reported. This one-pot synthesis is characterised by mild reaction conditions, broad scope, high yields, and preparative simplicity.

**Table 2: Antimicobial activity of compound (4a-4j):**

| **Entry** | **Compounds** | **Zone of Inhibition in mm** | | | |
|---|---|---|---|---|---|
| | | ***S.aureus*** | ***B.subtilis*** | ***E.coli*** | ***S.typhi*** |
| 1 | 4a | 06 | 12 | 10 | 10 |
| 2 | 4b | **18** | **20** | **16** | **12** |
| 3 | 4c | 10 | 10 | 12 | 14 |
| 4 | 4d | 14 | 12 | **18** | 12 |
| 5 | 4e | **16** | **18** | **20** | **14** |
| 6 | 4f | 07 | 12 | 10 | 10 |
| 7 | 4g | **08** | **10** | **14** | **12** |
| 8 | 4h | 10 | 10 | 12 | 14 |
| 9 | 4i | 14 | 12 | **17** | 12 |
| 10 | 4j | **10** | **18** | **18** | **14** |
| 11 | **Norfloxacin** | **14** | **24** | **20** | **16** |
| 12 | **Streptomycin** | **16** | **18** | **20** | **18** |

**BIOLOGICAL ACTIVITY:**

**Antimicrobial activity:**

The synthesized compounds were evaluated for their antibacterial activity against gram positive species ***S. aureus*** and ***B.subtilis*** and gram negative species *E.coli* and S.*typhi* by paper diffusion method. All the synthesized compounds were dissolved in dimethyl sulphoxide (DMSO).

The synthesized compounds exhibited zone of inhibition at **06-20mm** in diameter where as standard **Norfloxacin** exhibited zone of inhibition at 14 and 24 in diameter against ***S. aureus*** and ***B.subtilis*** and 20 and 16mm in diameter against ***E.coli*** and ***B.subtilis*** and 20 and 18mm in diameter against ***S. aureus*** and ***B.subtilis*** respectively. Amongst the synthesized compounds **(4b, 4e,4g.4j)** shows higher zone of inhibition against ***S. aureus***. Compounds **(4b, 4d, 4e,4g,4i,4j)** shows higher zone of inhibition against *E.coli*, compounds **(4b, 4e,4j)** shows higher zone of inhibition against ***B.subtilis*** and ***S. aureus*** shows higher zone of inhibition against ***S.typhi*** as compaired to other compounds.

**CONCLUSION:**

In conclusion, we have synthesized an environmental friendly efficient and facile method for the synthesis of novel compounds. The product formed can be easily isolated by simple workup technique, requires ambient reaction condition, short time, less expensive and give good yield. These synthesized compounds show biological activity.

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