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# A FACILE SINGLE-POT SYNTHESIS OF PYRANOPYRAZOLES SCAFFOLD AS A GREEN APPROACH

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**ABSTRACT**

A straightforward and environmentally friendly one-step method has been developed to synthesize pyranopyrazole with the aid of ultrasound in a water-based setting. This approach provides ease of operation and aligns with the tenets of green chemistry.

**Keywords:** Pyranopyrazole, Four Component Reaction, Green Reaction, Aqueous Medium.

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## INTRODUCTION

The initial multicomponent reaction, dating back to 1850 and attributed to Strecker, marked the inception of a series of reported reactions in literature.[1] Multicomponent reactions (MCRs) represent a distinct category of synthetically valuable organic processes, involving three or more diverse starting materials converging into a final product through a one-pot procedure.[2] Recognized for their efficiency in organic and medical chemistry, MCRs have garnered substantial interest from both industrial and academic sectors.[3] Particularly when conducted in aqueous media, MCRs have emerged as valuable tools for synthesizing chemically and biologically significant compounds, owing to their ecological awareness and environmentally friendly characteristics. Water, being a plentiful and safe substance in nature, is often referred to as a benign 'Universal Solvent'.[4] The pursuit of alternative reaction media, aiming to replace volatile, flammable, and frequently toxic solvents commonly employed in organic synthesis, stands as a crucial objective in advancing green chemical processes.[5] Pyrano pyrazole, a fused heterocyclic compound, introduces functional diversity to molecules and offers a promising area for exploring biological activity. The synthesis of pyranopyrazole dates back to 1973, initiated by the reaction between 3-methyl-1-phenylpyrazolin-5-one and tetracyanoethylene.[6] Pyranopyrazole scaffolds have found widespread application as intermediates in medicine due to their valuable biological and pharmacological properties, including anticoagulant, spasmolytic, hypnotic, diuretic,[7] insecticidal,[8] anti-inflammatory,[9] anticancer,[10] antibacterial, antifungal,[11] and antimicrobial[12] effects. A comprehensive literature review underscores the crucial role of fluorine in novel drug discovery, influencing the physical and biological properties of molecules. Leveraging its high electronegativity, the inclusion of fluorine in a molecule can enhance biopotency, bioavailability, metabolic stability, and lipophilicity.[13] Recently, ultrasound irradiation has found application in organic synthesis, offering a time-efficient, convenient, and easily controlled alternative to traditional methods.[14] Various synthetic strategies have been explored for pyranopyrazole synthesis, employing catalysts such as piperidine,[15] Dodecylbenzene Sulfonic Acid (DBSA),[16] PTSA,[17] [SIPIM] $HSO_4$,[18] citric acid,[19] β-cyclodextrin,[20] ammonium chloride ($NH_4Cl$),[21] $ZrO_2$-NPs,[22] PS-PTSA,[23] and Thiamine hydrochloride.[24] In continuation of our research work and presently addition to environmentally friendly synthetic approaches, we present a one-pot multicomponent synthesis of pyranopyrazole. This involves the reaction of substituted aromatic aldehyde, malononitrile, ethyl acetoacetate, and hydrazine hydrate in an aqueous medium under ultrasound irradiation conditions.

## EXPERIMENTAL

### Material and Methods

All reagents and chemicals were of analytical grade and used without further purification. Sonification was performed in an ultrasonic cleaner with a frequency of 25 KHz and a nominal power of 250 W. The reaction temperature was controlled by the addition or removal of water from the ultrasonic bath.


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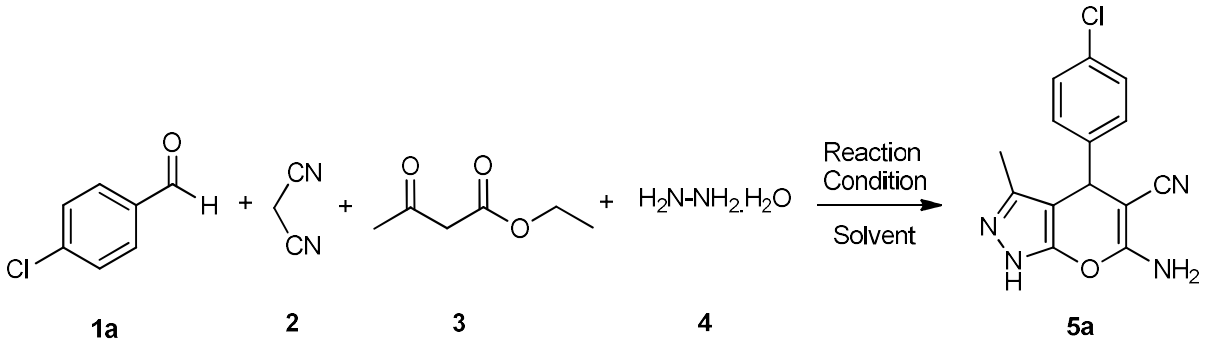



Scheme -1: Screening of Solvent and Reaction Condition

The progress of the reaction was monitored on TLC. The solid product obtained was filtered, washed with water, and recrystallized from ethanol to afford pure products. All the products were confirmed by comparing their melting points, IR, and 1H NMR data with literature data.

**Effect of Solvents and Reaction Condition**

Various solvents were evaluated at room temperature, reflux, and under ultrasound irradiation to ascertain the optimal choice, as detailed in Table-1. The results demonstrated that employing water as a solvent yielded a maximum 92% yield (Table-1, Entry 3), while other solvents, such as ethanol, and reactions without solvents, showed marginal improvement (Table-1, Entries 1, 2, 4, 5, 7, and 8). Consequently, water under ultrasonic irradiation was selected for subsequent investigations. In our study, we synthesized and screened a model reaction for the compound substituted Pyranopyrazole 5a using the ultrasound irradiation method (Scheme-1, Table-1, Table-2). The reaction involving compound 1a (1 mmol), compound 2 (1 mmol), compound 3 (1.2 mmol), and compound 4 (1.2 mmol) was chosen as a model reaction to optimize conditions. Water emerged as the superior solvent, and ultrasound irradiation proved to be the most effective reaction condition (Table-1, Entry 3), surpassing other less efficient solvents (Table-1, Entries 1-2, 4–5, and 7–8). Initial yields were relatively low, but further optimization increased water's efficacy, resulting in 80–92% yields (Table-1, entries 3, 6, and 9). To enhance the condensation reaction efficiency, various solvents were explored (Table-1, entries 1-9). Among them, 1 mL of water consistently yielded the best results, with yields of 62%, 90%, and 80% (Table-1, entries 1, 6, and 9). Notably, water as a solvent with ultrasound irradiation method was selected due to its 92% yield and shorter reaction time (Table-1, entry 3). Consequently, subsequent reactions were conducted in water under ultrasound irradiation, resulting in shortened reaction times, minimized thermal decomposition, and higher isolated yields. Comparing ultrasonic irradiation with the conventional method, the former proved superior, as it facilitated faster reactions and higher product yields. For this reason, we further prepared derivatives from the above standard reaction condition (Scheme-2, Table-2).

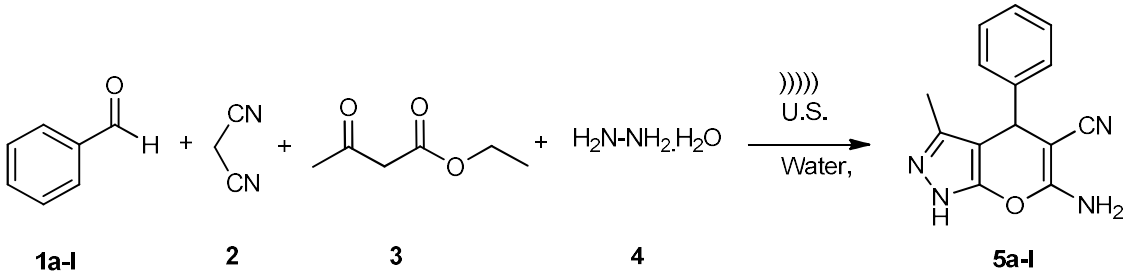
Table-1: Optimization of the Reaction Conditions

| Entry | Solvent | Temperature (°C) | Time (min) | Yield(%) |
|---|---|---|---|---|
| 1 | $H_2O$ | Room temperature | 360 | 10 |
| 2 | $H_2O$ | Reflux | 240 | 15 |
| 3 | $H_2O$ | Ultrasound | 30 | 92 |
| 4 | Ethanol | Room temperature | 378 | 20 |
| 5 | Ethanol | Reflux | 300 | 30 |
| 6 | Ethanol | Ultrasound | 50 | 90 |
| 7 | Without Solvent | Room temperature | 420 | 20 |
| 8 | Without Solvent | Reflux | 300 | 25 |
| 9 | Without Solvent | Ultrasound | 100 | 80 |

**General Procedure for the Synthesis of Substituted Pyranopyrazole (5a-l)**

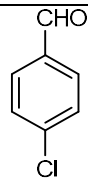
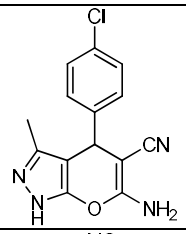
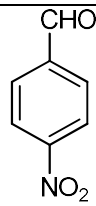
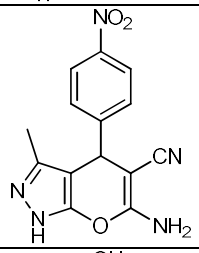
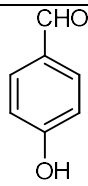
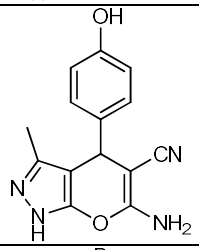
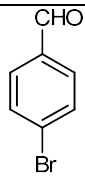
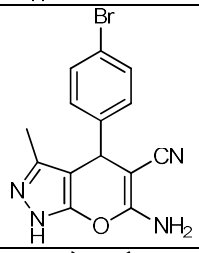
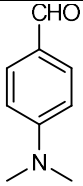
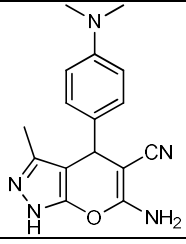
To a round bottom flask substituted aromatic aldehyde (1mmol), malononitrile (1mmol), ethyl acetoacetate (1mmol), and hydrazine hydrate (1mmol) in water were added. The reaction involved substituted benzaldehyde (**1a-l**) (1 mmol), compound 2 (1 mmol), ethyl 3-oxobutanoate 3 (1.2 mmol), and compound 4 (1.2 mmol) and water. The combination was exposed in the water bath of an ultrasonic cleaner at rt for a

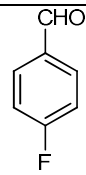
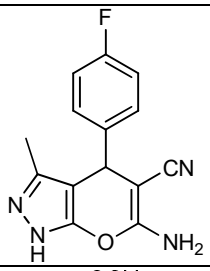
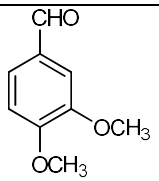
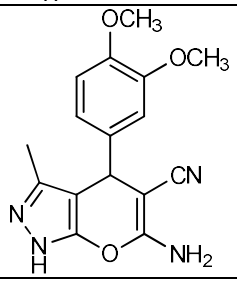
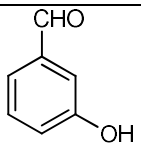
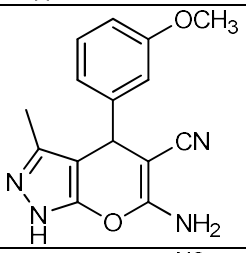
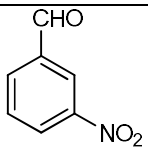
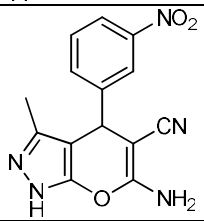
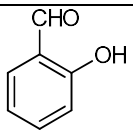
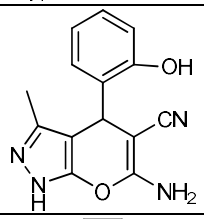
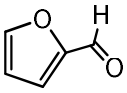
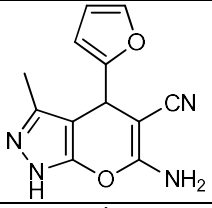
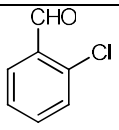
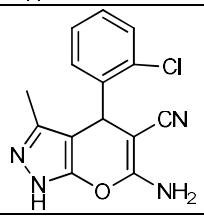
period as shown in Scheme-2, Table-2. The advancement of the reaction was tracked through TLC (10% ethyl acetate: n-hexane). The resulting product was combined with water and ethyl acetate (2:8) in three separate 10 mL portions. The combined solvent extracts underwent vacuum concentration. Subsequently, the compounds underwent recrystallization in ethanol to yield the purified product (**5a-l**).




Scheme-2: Synthesis of Pyrano-Pyrazole Derivative

Table-2: Physical Data of Pyrano-Pyrazole Derivative

| Entry | Aldehydes | Products | Time (min) | Yield (%) | M.P.($^0$C) Found | Lit.[Ref] |
|---|---|---|---|---|---|---|
| **5a** |  |  | 30 | 90 | 174-176 | 175[9] |
| **5b** |  |  | 30 | 92 | 193-195 | 195[9] |
| **5c** |  |  | 35 | 94 | 220-222 | 222-224[10] |
| **5d** |  |  | 30 | 92 | 178-180 | 177[9] |
| **5e** |  |  | 45 | 90 | 224-225 | 225-227[10] |

| | | | | | | |
|---|---|---|---|---|---|---|
| **5f** |  |  | 30 | 92 | 169-170 | 169-171[10] |
| **5g** |  |  | 40 | 93 | 188-190 | 188-190[10] |
| **5h** |  |  | 30 | 94 | 175-177 | - |
| **5i** |  |  | 45 | 90 | 190-192 | 190-192[10] |
| **5j** |  |  | 30 | 92 | 208-210 | 208-210[10] |
| **5k** |  |  | 45 | 93 | 174-176 | 176-178[10] |
| **5l** |  |  | 40 | 92 | 144-146 | 144-146[10] |

**Spectral Characterization of Representative Compounds**

**Compound (5a)**

White solid, IR (KBr) $cm^{-1}$: 879, 1255, 1372, 1581, 1627, 2929, 3025, 3425. $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ppm: 1.91 (s, 3H), 5.18 (s, 1H), 6.91 (s, br, 2H), 7.11-7.80 (m, 4H), 12.44 (s, 1H).

**Compound (5b)**
IR (KBr) $cm^{-1}$: 3471, 3231, 3122, 2191, 1649, 1622 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$) ppm.: 1.77 (s ,3H), 4.62 (s ,1H), 7.05 (s, 2H), 7.44 (d, 2H), 8.19 (d, 2H) ,12.20 (s, 1H) ppm.

**Compound (5c)**
Off-white solid, IR (KBr) $cm^{-1}$: 877, 1270, 1366, 1582, 1644, 2921, 3055, 3351, 3411 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm: 1.91 (s, 3H), 4.97 (s, 1H), 5.67 (s, 1H), 6.82 (s, br, 2H), 7.18-7.69 (m, 4H), 12.15 (s, 1H).

**Compound (5d**
IR (KBr) $cm^{-1}$: 3386, 2922, 2852, 2188, 1643, 1598, 1514, 1491, 1402, 1018, 873; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ppm: 1.81 (s, 3H, $CH_3$), 4.57 (s, 1H, CH), 7.32 (d, 2H, $J$ =8.4 Hz, ArH), 7.45 (d, 2H, $J$ = 8.6 Hz, ArH), 12.06 s, 1H, NH).

**Compound (5e):**
Yellow solid, IR (KBr) $cm^{-1}$: 3383, 3171, 2956, 2187, 1642, 1602, 1396, 1277, 867. $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ppm: 12.10 (s, 1H), 6.70-7.15 (m, 4H), 6.55 (bs, 2H), 4.40 (s, 1H), 2.85 (s, 6H), 1.77 (s, 3H).
**Analytical Discussion (If Any)**

## RESULTS AND DISCUSSION

To enhance the reaction efficiency, we conducted the synthesis involving 4-hydroxybenzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), and hydrazine hydrate (1 mmol) using ultrasound irradiation methods at room temperature (Table-2). The results revealed that aldehydes with electron-withdrawing groups yielded higher yields compared to those with electron-donating groups.

## CONCLUSION

In summary, we successfully implemented a one-pot multicomponent synthesis of pyranopyrazole using an environmentally friendly synthetic approach with ultrasound irradiation. This method utilizes water as a solvent and offers benefits such as a brief reaction duration, straightforward workup, solvent efficiency, and atom economy.

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## CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

## AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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