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# Starch solution as a green and biodegradable catalyst for the synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives

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**Abstract:** Starch solution has been used as an eco-friendly catalyst for the synthesis of dihydropyrano[2,3-*c*]pyrazoles via the four-component one-pot reaction between arylaldehydes, hydrazine monohydrate , ethyl acetoacetate and malononitrile at thermal condition. This method provides several advantages such as environmental friendliness, short reaction time, excellent yields and simple workup procedure.

**Keywords:** Dihydropyrano[2,3-*c*]pyrazoles, Four-component reaction, Starch solution, Hydrazine monohydrate.

## Introduction

Multi-component reactions (MCRs) [1-4] are highly relevant in organic and medicinal chemistry, due to significant advantages offered by MCRs over conventional linear-type syntheses. MCRs allow the creation of several bonds in a single operation and have emerged as a powerful synthetic tools in creating molecular diversity and complexity [5-7]. Nitrogen containing heterocyclic compounds are prevalent in natural products and medicinal agents [8] , and their applications in biologically active pharmaceuticals, agrochemicals, and functional materials are becoming more and more important [9,10]. Of these compounds, dihydropyrano[2,3-c]pyrazoles, are very interesting and have received considerable attention as a result of their biological activity and use as a template for medicinal chemistry. Many of these compounds are known to be antimicrobial [11], insecticidal [12] and anti-inflammatory [13]. Furthermore, dihydropyrano[2,3-c]pyrazoles show molluscicidal activity [14] and has been identified as a screening hit for Chk1 kinase inhibitor [15]. Recently, some new catalysts have been reported in facilitating the synthesis of dihydropyrano[2,3-c]pyrazole derivatives including, γ-alumina [16], L-proline [17], ultra sound irradiation [18], trichloroacetic acid [19], ceric sulfate [19] and boiling water [20] . However, the majority of some of these synthetic methods suffer from drawbacks such as requiring strongly basic conditions, expensive and complex catalysts or reagents, many tedious steps, low yields of the products and long reaction times that restrict their usage in practical applications. In continuing our research on multi component reactions in the presence different carbohydrates as biodegradable and green catalyst [21-24], we report herein a four-component one-pot synthesis of dihydropyrano[2,3-*c*]pyrazoles derivatives using starch solution as a biodegradable and green catalyst (Scheme **1**).

## Results and discussion

The reaction of hydrazine monohydrate, ethyl acetoacetate, benzaldehyde and malononitrile was selected as model system for optimizing the reaction

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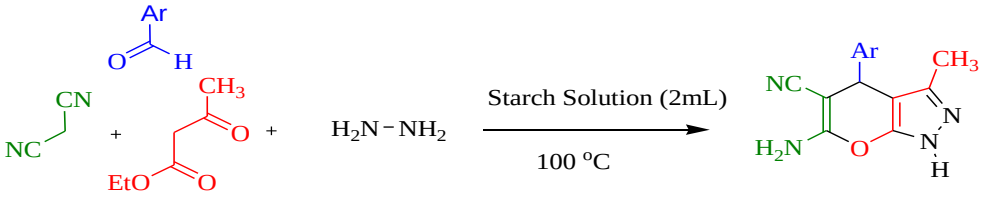
conditions. Catalyst reactivity at different reaction temperatures (ambient temperature, 50, 70, 80, 90, 100, 110 and 120 °C) and the different amount of catalyst (0.5, 1, 2, 3 mL) were investigated. The best result was obtained by carrying out the reaction equimolar ratio of hydrazine monohydrate, ethyl acetoacetate, benzaldehyde and malononitrile, in the presence of (2 mL) starch solution at 100 °C (Tabale **1**).

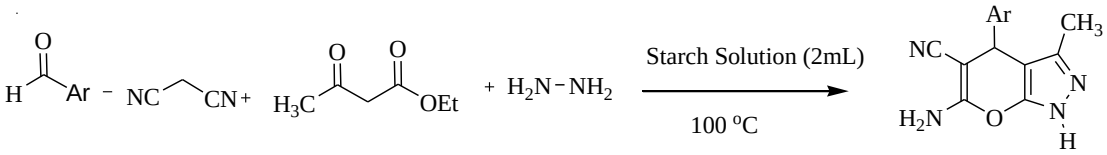



**Scheme 1:** Synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazole derivatives using starch solution (2mL) as catalyst and solvent at 100 °C.

**Table 1**: optimization of amount of catalyst in the synthesis of 1, 4-dihydropyrano[2,3-*c*]pyrazoles under thermal condition.

| Entry | Catalyst (mL) | Time (min) | Isolated Yield (%) |
|---|---|---|---|
| 1 | 0.5 | 25 | 50 |
| 2 | 1 | 20 | 55 |
| 3 | 2 | 10 | 75 |
| 4 | 3 | 10 | 75 |

Using these optimized reaction, the scope and efficiency of the reaction were explored for the synthesis of a wide variety of substituted 1,4-dihydropyrano[2,3-*c*] pyrazoles using hydrazine monohydrate, ethyl acetoacetate, aryl aldehydes and malononitrile (Scheme **2**). The results are summarized in Table **2**.




**Scheme 2:** Synthesis of 1,4-dihydropyrano[2,3-c]pyrazole derivatives using starch solution as catalyst and solvent at 100 °C.

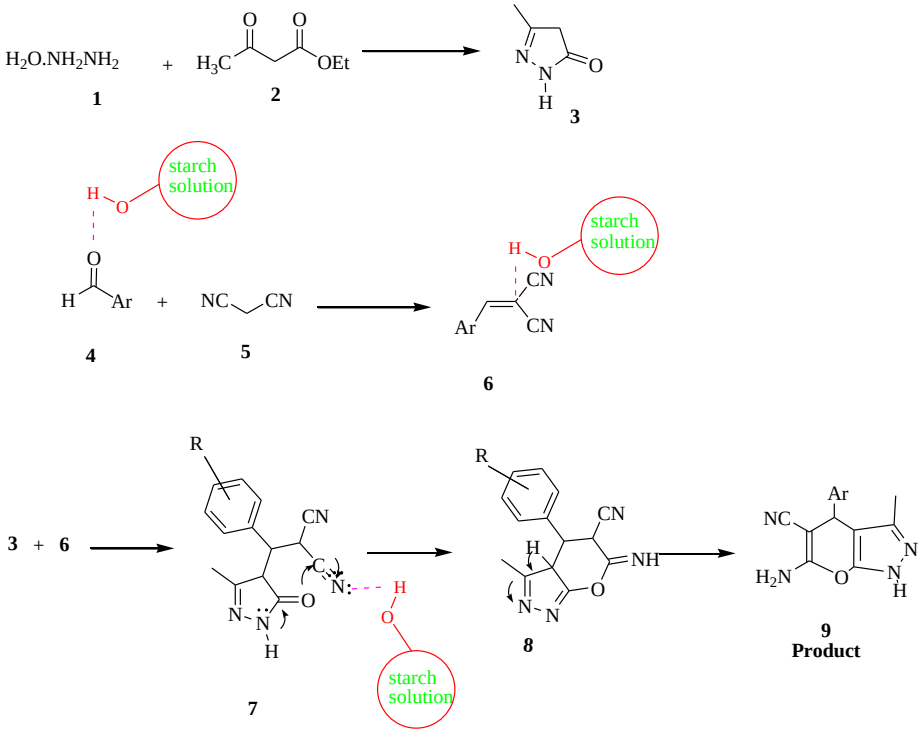
**Table 2:** Preparation of 1,4-dihydropyrano[2,3-*c*]pyrazole derivatives in sturch solution as biodegradable catalyst at 100 °C.

| Entry | **Ar** | **Time (min)** | **Yield%** | **Found M.P.(°C)/[Lit.M.P (°C)]** |
|---|---|---|---|---|
| 1 | $C_6H_5$ | 15 | 75 | 243-245/[244-246][17,18] |
| 2 | 4-$N(CH_3)_2C_6H_4$ | 15 | 75 | 165-168/[167-169] [17,18] |
| 3 | 2-$NO_2C_6H_4$ | 10 | 72 | 218-220/[220-222] [17,18] |
| 4 | 4-$NO_2C_6H_4$ | 10 | 72 | 247-249/[249-252] [17,18] |
| 5 | 3-$NO_2C_6H_4$ | 16 | 72 | 190-192/[193-195] [17,18] |

| | | | | |
|---|---|---|---|---|
| 6 | 2-$ClC_6H_4$ | 17 | 70 | 143-145/[145-147] [17,18] |
| 7 | 4-$ClC_6H_4$ | 18 | 75 | 233-235/[234-236] [17,18] |
| 8 | 2,5-$(CH_3O)_2C_6H_3$ | 25 | 75 | 209-211/[210-212] [17,18] |
| 9 | 2,4-$Cl_2C_6H_3$ | 15 | 80 | 235-237/[235-237] [17,18] |
| 10 | 4-$MeC_6H_4$ | 20 | 84 | 204-206/[206-208] [17,18] |
| 11 | 4-$OHC_6H_4$ | 18 | 85 | 217-218 /[219-221][19] |
| 12 | n-heptanal | 24 hr | Trace | - |

As shown results in table **2**, a variety of aryl aldehydes including electron withdrawing or releasing substituents (*ortho*-, *meta*-, and *para*-substituted) participated well in this reaction and gave the product in good to excellent yield.

A mechanism was proposed for the reaction understudy as shown in scheme **3**. First, pyrazolone **3** was formed by the reaction between **1** and **2**, Knoevenagel condensation between **4** and **5** produced 2-benzylidenemalononitrile **6**, Michael addition of **3** to **6**, and followed cyclization and tautomerization afforded the corresponding product (Scheme **3**).




**Scheme 3:** Proposed mechanism for the synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazole derivatives in starch solution as biodegradable catalyst at 100 °C.

## Conclusion

We have developed a green and straight forward protocol for the four-component synthesis of of 1,4-dihydropyrano[2,3-*c*]pyrazole derivatives using Starch solution as catalyst and solvent under thermal conditions. This procedure provides several advantages such as clean reactions, easy workup, reduced reaction times and eco-friendly promising strategy.

## Experimental

*Apparatus and analysis:*

All reagents were purchased from Merck and Sigma-Aldrich and used without further purification. All yields refer to isolated products after purification, Products were characterized by comparison physical data with authentic samples and spectroscopic data (IR and NMR). The NMR spectra were recorded on a BrukerAvance DRX 90 MHz instrument. The spectra were measured in DMSO-$d_6$ relative to TMS (0.00 ppm). IR spectra were recorded on a JASCO FT-IR 460 plus spectrophotometer. Melting points were determined on an Elecrothermal 9100 apparatus. TLC was performed on Silica–gel Polygram SILG/UV 254 plates.

*General procedure for preparation of starch solution:*

To a magnetically stirred of water (25 mL) at 25 °C, starch (2 g) was added. Since the starch is not completely soluble in water, after 30 minutes the solution was filtered for separation of insoluble starch (amylose) [25]. The filterate (containing 0.95 g starch) was used for synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazole .

*General procedure for the synthesis of 6-amino-4-aryl-3-methyl-1,4-dihydropyrano[2,3- c]pyrazole-5-carbonitrile derivatives:*

A mixture of hydrazine monohydrate (1 mmol) and ethyl acetoacetate (1 mmol) was stirred at 0 °C, until 3-methyl-2-pyrazolin-5-one was precipitated (5 min). Then it was warmed to room temperature. To this reaction mixture, aryl aldehyde (1 mmol) and malononitrile (1mmol) in the presence of starch solution (2 mL) at 100 $^{o}$C was added. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, and diluted with water. The mixture was filtered for separation of the product. The crude product was recrystallized from ethanol to afford the pure pyranopyrazole derivatives in good yields.

Selected spectroscopic data of some products are given below:

*6-Amino-1,4-dihydro-3-methyl-4-(4-hydroxyphenyl) pyrano[2,3-c]pyrazole-5-carbonitrile( Table **2**, Entry 11):*

IR (KBr, $cm^{-1}$) = 3477, 3228, 3120, 2196, 1734, 1651, 1595, 1560, 1401, 1353, 1107, 883, 810, 744, 543; $^{1}$H NMR (90 MHz, (DMSO-$d_6$) $\delta$ (ppm) = 1.77 (3H, S), 4.45 (1H, S), 6.62-6.98 (6H,m), 9.23 (1H, s), 12.00 (1H, s).

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