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# A Rapid and Convenient Synthesis of Pyranopyrazole Derivatives

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## *ABSTRACT*

*To demonstrate fast and highly efficient synthesis of series of pyranopyrazole derivatives via four component reaction of aldehydes, malononitrile, ethyl acetoactate and hydrazine hydrate. The most important feature of this new methodology use sodium phosphate as a catalyst, the pyranopyrazole is obtained at room temperature, very short time reaction, easy workup process and high yield.*

***Keywords:*** *Multi-component reactions, Aromatic aldehydes, Sodium phosphate, Malononitrile, Pyrazoles.*

## INTRODUCTION

Multicomponent reaction is a process in which three or more accessible components are combined together in one-pot to produce a final product which shows the features of all the input reactants and therefore, offers the greatest possibilities for molecular diversity in one step with minimum synthetic time and effort. The structural diversity in the outcomes of MCRs can be increased expeditiously by systematic variation of each input [1], which opens up opportunities for researchers interested in small molecular weight compounds with biological activities [2].

Pyrano [2, 3-*c*] pyrazole is a fused heterocycle comprised of pyrazole and pyran rings which are known as the sub structural units of several biologically active compounds [3, 4]. Benzopyrans have been widely used as medicinal intermediates due to their biological and pharmacological properties such as antibacterial, molluscicidal, anthelminitic, hypnotic and insecticidal activity [5]. Some 2-amino-4*H*-pyrans can be used as photoactive materials [6].

1,4-Dihydropyrano[2,3-*c*]pyrazoles are generally prepared by one-pot three component condensations of malononitrile, aldehydes and 3-methyl-1-phenyl-2-pyrazolin-5-one using KF/Al2O3 in DMF at room temperature [7]. The utilization 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) [8] and hexadecyltrimethylammonium bromide (HTMAB) [9]. Similarly, the use of the neutral organo catalyst DL-proline using the grinding technique [10] and a surfactant such as *p*-dodecylbenzenesulfonic acid [11] (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 [12]. A clean and simple 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, an aromatic aldehydes, and malononitrile catalysed by sulfamic acid in ethanol [13]. activity of Cesium fluoride has emerged as a useful acid imparting high regio- and chemo selectivity in various chemical transformations [14-17].

The pyranopyrazole moiety represents a fascinating template in the pharmaceutical field and is responsible for the wide spectrum of biological activities of molecules containing this significant unit [18]. Such compounds can act as antidepressant [19], hypertensive [20], hypoglycemic [21], and anticancer [22] agents. On the other hand, the pyrano pyrimidine scaffold, as a key member of the pyrimidine family, has received considerable attention due to the broad range of antitumor [23], antibronchitic [24], hepatoprotective [25], and pronounced antitubercular and antimicrobial activities [26]. The significant biological activity of pyrano pyrimidine derivatives is a result of their occurrence in the structures of various natural products [27]. In the course of our ongoing investigations toward the synthesis of novel heterocycle via MCRs [28].

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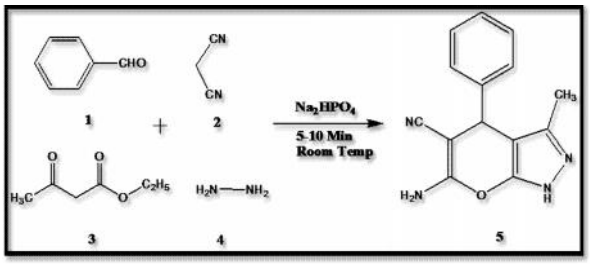
## EXPERIMENTAL SECTION

Melting points are uncorrected. IR spectra were recorded on a Shimadzu FTIR-1710 spectrophotometer. 1H NMR spectra were recorded at 400 MHz in CDCl3 using TMS as internal standard.

**Experimental Procedure:**

A mixture of aromatic aldehyde (0.02 mol), malononitrile (0.02 mol), ethyl acetoacetate (0.02 mol), hydrazine hydrate (0.02 mol) and Sodium phosphate (5 mol %) was stirred for the 5-10 min, the solid was obtained. Filter the crude product. The crude products were recrystallized from EtOH to give pure 1,4-dihydropyrano[2,3-*c*]pyrazole in good to excellent yields.




**Spectral Data:**

**6-amino-3-methyl-4-phenyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5):**

**FT-IR (KBr) *ν*max (cm-1):** 1040, 2200, 3172, 3310، 3364.**$^1$H-NMR (400 MHz, DMSO-*d*6) *δ*:** 1.72(s, 3H), 4.55 (s, 1H), 6.88 (s, 2H), 7.15 (m, 3H), 7.29-7.33 (m, 2H), 12.10 (s, 1H), **$^{13}$C-NMR (100 MHz, DMSO-*d*6) *δ*:** 9.70, 36.15, 57.18, 97.62, 120.74, 124.69, 128.42, 126.39, 135.53, 144.40, 154.73, 160.83.

**6-amino-3-methyl-4-Chlorophenyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5b):**

**FT-IR (KBr) *ν*max (cm-1):** 1056, 2194, 3210, 3322, 3418; **$^1$H-NMR (400 MHz, DMSO-*d*6) *δ*:** 1.84(s, 3H), 4.75 (s, 1H), 7.24 (s, 2H), 7.32 (d, *J* = 6.0 Hz, 2H), 7.41 (d, *J* = 6.0 Hz, 2H), **$^{13}$C-NMR (150 MHz, DMSO-*d*6) *δ*:** 13.06, 36.58, 58.71,100.01, 119.86, 120.01, 125.42,

129.03, 130.18, 132.30, 142.69, 142.89, 145.03, 145.33, 147.95, 159.75.

**6-amino-3-methyl-2-Methoxyphenyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5f)**:
**FT-IR (KBr) *ν*max(cm-1):** 1059, 2186, 2837, 3206, 3327, 3384.**$^1$H-NMR (400 MHz, DMSO-*d*6) *δ*:**1.80 (s, 3H), 3.79 (s, 3H), 5.02 (s, 1H), 6.92-6.94 (m, 1H), 7.02-7.04 (m, 1H), 7.10-7.12 (m, 1H),7.22-7.24 (m, 3H), 8.09 (d, *J* = 9.1 Hz, 2H), 8.00 (d, *J* = 8.0 Hz, 2H). **13C-NMR (100 MHz, DMSO-*d*6) *δ*:** 12.33, 29.86, 55.66, 57.28, 99.95, 111.47, 119.17, 119.80, 120.84, 125.03, 128.43, 129.12, 130.66, 142.42, 144.20, 144.99, 147.27, 156.64, 159.76

## RESULT AND DISCUSSION

To develop new methods for the synthesis of biologically active nitrogen containing heterocyclic compounds using Sodium phosphate. We wish to report method for the rapid synthesis of pyranopyrazole derivatives, utilizes a one-pot four-component reaction of, aromatic aldehydes (1) malononitrile (2) ethyl acetoacetate (3), and hydrazine hydrate (4) in the presence of Sodium phosphate within 5-10 min. The product yields, reaction time, melting point are summarized in **Table No.1**.

**Table No. 1: Synthesis of pyranopyrazole derivatives**

| Entry | Ar | Reaction Time (Min) | Yield % | Melting point (°C) | |
|---|---|---|---|---|---|
| | | | | Found | Reported [29] |
| **5a** | Benzaldehyde | 5 | 89 | 240 | 244-245 |
| **5b** | 4-Cl Benzaldehyde | 5 | 82 | 236 | 233-234 |
| **5c** | 4-Br Benzaldehyde | 10 | 87 | 197 | 198-200 |
| **5d** | 4-Methoxy Benzaldehyde | 15 | 78 | 212 | 211-213 |
| **5e** | 4-OH Benzaldehyde | 10 | 85 | 223 | 224-226 |
| **5f** | 4-Nitro Benzaldehyde | 5 | 94 | 255 | 251-252 |
| **5g** | 4- fluro Benzaldehyde | 5 | 92 | 246 | 245-246 |
| **5f** | 2-Methoxy Benzaldehyde | 5 | 89 | 125 | 251-252 |

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