

# Sulfamic acid catalysed one-pot three-component condensation for the synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazoles

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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 aldehyde, and malononitrile catalysed by sulfamic acid in ethanol.

**Keywords:** multi-component reactions, sulfamic acid, malononitrile, pyrazolinones, fused pyrans, pyrazoles

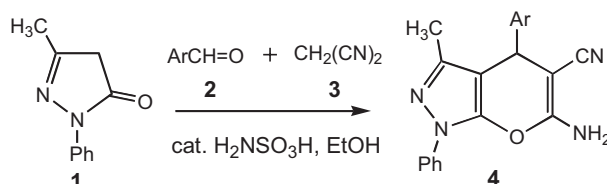
Pyrano[2,3-*c*]pyrazole is a fused heterocycle comprised of pyrazole and pyran rings which are known as the sub-structural units of several biologically active compounds.<sup>1,2</sup> Poly-functionalised benzopyrans have been widely used as medicinal intermediates due to their biological and pharmacological properties such as antibacterial, molluscicidal, anthelmintic, hypnotic and insecticidal activity.<sup>3–9</sup> Some 2-amino-4*H*-pyrans can be used as photoactive materials.<sup>10</sup> The 4*H*-pyran ring is also a structural unit of a number of natural products.<sup>11–13</sup>

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<sub>2</sub>O<sub>3</sub> in DMF at room temperature.<sup>14</sup> 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)<sup>15</sup> and hexadecyltrimethylammonium bromide (HTMAB),<sup>16</sup> Similarly, the use of the neutral organo-catalyst DL-proline using the grinding technique<sup>17</sup> and a surfactant such as *p*-dodecylbenzenesulfonic acid<sup>18</sup> (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.<sup>19</sup>

In recent years, the catalytic activity of sulfamic acid has emerged as a useful acid imparting high regio- and chemo-selectivity in various chemical transformations.<sup>20–23</sup> 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 sulfamic acid 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.

## Results and discussion

Initially, we examined the model reaction of benzaldehyde (3 mmol), malononitrile (3 mmol) and 3-methyl-1-phenyl-2-pyrazolin-5-one (3 mmol) in ethanol (20 ml) using sulfamic acid as the catalyst. When sulfamic acid (5 mmol%) was added to the above stirred reaction mixture at room temperature, a red brown colour is observed. 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



**Scheme 1** 1,4-Dihydropyrano[2,3-*c*]pyrazoles.

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 reaction did not proceed in the absence of sulfamic acid. The optimum yield of the product was obtained when 5 mol% of sulfamic acid was employed.

The scope of this three-component condensation was then extended using a range of aromatic aldehydes, and the results are summarised in Table 1. Thus the methoxy substituted aromatic aldehydes (Table 1, entries b–d) underwent a clean three component condensation to form the corresponding 1,4-dihydropyrano[2,3-*c*]pyrazoles in excellent yields. Other aromatic aldehydes (Table 1, entries e–i) with electron-releasing and withdrawing substituents produced 1,4-dihydropyrano[2,3-*c*]pyrazole in good yields. However, *p*-dimethylaminobenzaldehyde (Table 1, entry 10) failed to produce any 1,4-dihydropyrano[2,3-*c*]pyrazole. A similar failure was reported earlier.<sup>18</sup>

The isolated pyrano[3,2-*c*]pyrazole derivatives **4a–j** were completely characterised by IR and <sup>1</sup>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<sup>–1</sup> due to NH<sub>2</sub> and 2198 cm<sup>–1</sup> due to CN. The <sup>1</sup>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<sub>2</sub> group.

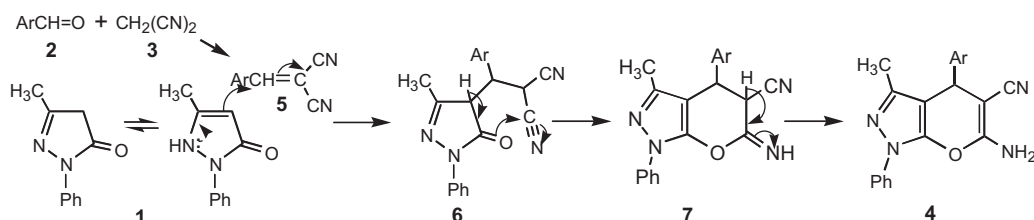
A tentative reaction mechanism for the three-component synthesis of 6-amino-4-aryl-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles is shown in Scheme 2. The aromatic aldehyde **2** can react with malononitrile **3** to form the dicyano-olefin **5** through Knoevenagel condensation. 3-Methyl-1-phenyl-2-pyrazolin-5-one **1** can then react with **5** via a Michael-type addition to form **6** which may undergo cyclisation via **7** to form the final product **4**.

In summary, a highly efficient methodology for 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 sulfamic acid is reported. This one-pot synthesis is characterised by mild reaction conditions, broad scope, high yields, and preparative simplicity.

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**Table 1** Synthesis of 6-amino-4-aryl-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles using sulfamic acid as the catalyst (5 mol%) in ethanol as solvent

| Entry | Ar                                                                 | Reaction time/h | Product   | Yield <sup>a</sup> /% | Melting-point/°C |                           |
|-------|--------------------------------------------------------------------|-----------------|-----------|-----------------------|------------------|---------------------------|
|       |                                                                    |                 |           |                       | Found            | Reported <sup>16,18</sup> |
| 1     | C <sub>6</sub> H <sub>5</sub>                                      | 10              | <b>4a</b> | 82                    | 169–171          | 168–170                   |
| 2     | 4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>                   | 11              | <b>4b</b> | 81                    | 170–172          | 170–172                   |
| 3     | 3,4-(OCH <sub>2</sub> O)C <sub>6</sub> H <sub>3</sub>              | 13              | <b>4c</b> | 77                    | 172–174          | 174–176                   |
| 4     | 3,4-(CH <sub>3</sub> O) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> | 13              | <b>4d</b> | 78                    | 191–193          | –                         |
| 5     | 4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>                    | 12              | <b>4e</b> | 81                    | 175–177          | 176–178                   |
| 6     | 4-HOC <sub>6</sub> H <sub>4</sub>                                  | 10              | <b>4f</b> | 74                    | 210–212          | 211–212                   |
| 7     | 4-ClC <sub>6</sub> H <sub>4</sub>                                  | 9               | <b>4g</b> | 83                    | 176–178          | 174–175                   |
| 8     | 3-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>                    | 10              | <b>4h</b> | 79                    | 187–189          | 188–190                   |
| 9     | 4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>                    | 11              | <b>4i</b> | 81                    | 194–196          | 194–196                   |
| 10    | 4-(CH <sub>3</sub> ) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>   | 14              | <b>4j</b> | 0                     | –                | –                         |

<sup>a</sup>Isolated yield after recrystallisation.**Scheme 2** Proposed mechanism for the formation of dihydro-pyranopyrazoles **4**.

## Experimental

Melting points are uncorrected. IR spectra were recorded on a Shimadzu FTIR-1710 spectrophotometer. <sup>1</sup>H NMR spectra were recorded at 400 MHz in CDCl<sub>3</sub> using TMS as internal standard.

### Typical experimental procedure:

A mixture of aromatic aldehyde (3 mmol), malononitrile (3 mmol), 3-methyl-1-phenyl-2-pyrazolin-5-one and sulfamic acid (5 mol%) in EtOH (20 ml) was refluxed for the time period as mentioned in Table 1. TLC monitored the progress of reaction. 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 EtOH 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):  $\nu_{\text{max}}$  3490, 3330, 3017, 2937, 2896, 2198, 1666, 1589, 1381, 1242, 1122, 882 cm<sup>-1</sup>. NMR (CDCl<sub>3</sub>):  $\delta$  1.92 (s, 3H, CH<sub>3</sub>), 3.81 (s, 3H, OCH<sub>3</sub>), 3.83 (s, 3H, OCH<sub>3</sub>), 4.67 (s, 1H, ArCH), 6.33 (s, 2H, br., NH<sub>2</sub>), 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<sub>21</sub>H<sub>18</sub>N<sub>4</sub>O<sub>3</sub>: C, 67.37; H, 4.85; N, 14.96; found: C, 67.29; H, 4.83; N, 14.99%.

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