An Efficient Multi-component Synthesis of 6-Amino-3-methyl-4-Aryl-2,4-dihydropyrano[2,3-c]Pyrazole-5-carbonitriles

G. Santhosh Kumar, C. Kurumurthy, B. Veeraswamy, P. Sambasiva Rao, P. Shanthan Rao & B. Narsaiah

Fluoroorganic Division, Indian Institute of Chemical Technology, Tarnaka, Hyderabad, 500607, India

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An Efficient Multi-component Synthesis of 6-Amino-3-methyl-4-Aryl-2,4-dihydropyrano[2,3-c]Pyrazole-5-carbonitriles

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Multi-component reactions are effective in building complex molecules in a single step in a minimum amount of time and with facile isolation procedures; they have high economy and thus have become a powerful synthetic strategy in recent years. The multi-component protocols are even more attractive when carried out in aqueous medium. Water offers several benefits, including control over exothermicity, and the isolation of products can be carried out by single phase separation technique. Pyranopyrazoles are a biologically important class of heterocyclic compounds and in particular dihydropyrano[2,3-c]pyrazoles play an essential role in promoting biological activity and represent an interesting template in medicinal chemistry. Heterocyclic compounds bearing the 4-H pyran unit have received much attention in recent years as they constitute important precursors for promising drugs. Pyrano[2,3-c]pyrazoles exhibit analgesic, anti-cancer, anti-microbial and anti-inflammatory activity. Furthermore dihydropyrano[2,3-c]pyrazoles show molluscidal activity and are used in a screening kit for Chk 1 kinase inhibitor activity. They also find applications as pharmaceutical ingredients and bio-degradable agrochemicals. Junek and Aigner first reported the synthesis of pyrano[2,3-c]pyrazole derivatives from 3-methyl-1-phenylpyrazolin-5-one and tetracyanoethylene in the presence of triethylamine. Subsequently, a number of synthetic approaches such as the use of triethylamine, piperazine, piperidine, N-methylmorpholine in ethanol, microwave irradiation, solvent-free conditions, cyclodextrins (CDs), different bases in water, γ-alumina, and L-proline have been reported for the synthesis of 6-amino-4-alkyl/aryl-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles. Recently, tetraethylammonium bromide (TEABr) has emerged as mild, water-tolerant, eco-friendly and inexpensive catalyst. To the best of our knowledge, quaternary ammonium salts, more specifically TEABr, have not

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Address correspondence to B. Narsaiah, Fluoroorganic Division, Indian Institute of Chemical Technology, Tarnaka, Hyderabad -500607, India. E-mail: narsaiahbanda84@gmail.com
been used as catalysts for the synthesis of pyrano[2,3-c]pyrazoles, and we decided to investigate the application of TEABr as a catalyst for the synthesis of a series of pyrazole-fused pyran derivatives via multi-component reactions.

Initial reactions of ethyl acetoacetate (1, 2.0 mmol), 98% hydrazine hydrate (2, 2.5 mmol), benzaldehyde (3a, 2.0 mmol), and malononitrile (4, 2.0 mmol) (Scheme 1) conducted in water without catalyst, led to no reaction.

The same reaction was performed in water using TEABr. The product 2,4-dihydropyrano[2,3-c]pyrazole (5a) was formed in 90% yield in water using TEABr as catalyst presumably via initial formation of the pyrazolinone ring followed by condensation with benzylidene malononitrile (generated in situ from benzaldehyde and malononitrile).

The use of other catalysts such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), tetrabutylammonium bromide (TBABr) and neat grinding of the components gave marginally low yields.

### Table 1

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<thead>
<tr>
<th>Cmpd</th>
<th>R</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>lit. mp (°C)</th>
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<tr>
<td>5a</td>
<td>C₆H₅</td>
<td>15</td>
<td>90</td>
<td>244–245</td>
<td>244–245⁴²</td>
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<tr>
<td>5b</td>
<td>4-CH₃C₆H₄</td>
<td>10</td>
<td>88</td>
<td>208–209</td>
<td>206–207⁴²</td>
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<tr>
<td>5c</td>
<td>4-CH₃OC₆H₄</td>
<td>20</td>
<td>82</td>
<td>211–213</td>
<td>210–212⁴²</td>
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<tr>
<td>5d</td>
<td>4-BrC₆H₄</td>
<td>10</td>
<td>88</td>
<td>178–180</td>
<td>179–180⁴²</td>
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<tr>
<td>5e</td>
<td>4-ClC₆H₃</td>
<td>10</td>
<td>90</td>
<td>234–236</td>
<td>234–235⁴²</td>
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<tr>
<td>5f</td>
<td>3-FC₆H₄</td>
<td>10</td>
<td>89</td>
<td>181–184</td>
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<tr>
<td>5g</td>
<td>4-CNC₆H₄</td>
<td>15</td>
<td>91</td>
<td>196–198</td>
<td>196–198³⁹</td>
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<td>5h</td>
<td>4-NO₂C₆H₄</td>
<td>25</td>
<td>80</td>
<td>192–194</td>
<td>193–195⁴²</td>
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<tr>
<td>5i</td>
<td>3-NO₂C₆H₄</td>
<td>30</td>
<td>76</td>
<td>250–252</td>
<td>251–253⁴²</td>
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<tr>
<td>5j</td>
<td>2,4-F₂C₆H₃</td>
<td>15</td>
<td>85</td>
<td>178–179</td>
<td>176–178⁴⁴</td>
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<tr>
<td>5k</td>
<td>3-CF₃C₆H₄</td>
<td>20</td>
<td>84</td>
<td>188–190</td>
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<tr>
<td>5l</td>
<td>2,5-(CH₃)₂C₆H₃</td>
<td>25</td>
<td>88</td>
<td>202–204</td>
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<td>5m</td>
<td>2-Furyl</td>
<td>30</td>
<td>78</td>
<td>175–177</td>
<td>175–177⁴⁰</td>
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<td>5n</td>
<td>2-Thienyl</td>
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<td>75</td>
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<td>190–191⁴⁰</td>
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<tr>
<td>5o</td>
<td>Styryl</td>
<td>30</td>
<td>70</td>
<td>180–182</td>
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<tr>
<td>5p</td>
<td>n-Propyl</td>
<td>15</td>
<td>68</td>
<td>162–164</td>
<td>—</td>
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</table>
yields. The scope of present protocol was extended to variously substituted aldehydes and 2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile derivatives were obtained in high yields.

In summary, we have devised a simple, rapid, green method via a four-component reaction for the synthesis of 6-amino-4-alkyl/aryl-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles by using TEABr (10 mol%) as a catalyst and water as the solvent.

Experimental Section

IR spectra were recorded as KBr pellets on a Perkin-Elmer FT-IR 240-C spectrophotometer using KBr optics. 

**Typical Procedure:** A mixture of the aromatic aldehyde (2 mmol), malononitrile (0.13 g, 2 mmol), ethyl acetoacetate (0.26 g, 2 mmol) 98% hydrazine hydrate (0.12 g, 2.5 mmol) and TEABr (10 mol%) was placed in 5 ml of water as a solvent in a round bottom flask. The mixture was stirred and heated at reflux for 10–30 min. After completion of the reaction, the content was allowed to cool to room temperature, and the precipitated solid product was collected through filtration, washed with water followed by chloroform (2 × 10 ml) and dried to afford products as colorless solids. Compounds 5c, 5d, 5h, 5i, 5n were purified by column chromatography using n-hexane and ethyl acetate in 1:3 ratio and other products were isolated in pure form without purification.

6-Amino-3-methyl-4-phenyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5a).

IR (cm⁻¹): 3420 (−NH₂), 3400 (−NH₂), 2198 (−CN); 

H NMR (CD₃)₂CO, 300 MHz: δ 1.89 (s, 3H, CH₃), 4.55 (s, 1H, CH = ), 6.25 (br, s, 2H, NH₂), 7.17–7.44 (m, 5H, Ar-H); 

MS (ESI): m/z [(M+H)+]: 253 [(M+Na)+]: 275. 

**Anal.** Calcd for C₁₄H₁₂N₄O: C, 66.65; H, 4.79; N, 22.21. Found: C, 66.32; H, 4.82; N, 22.11.

6-Amino-4-(4-methoxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5b).

IR (cm⁻¹): 3426 (−NH₂), 3409 (−NH₂), 2199 (−CN); 

H NMR (DMSO-d₆, 300 MHz): δ 1.85 (s, 3H, CH₃), 3.79 (s, 3H, CH₃), 4.50 (s, 1H, CH = ), 6.15 (br, s, 2H, NH₂), 6.82 (d, J = 8.68 Hz, 2H, Ar-H), 7.09 (d, J = 8.68 Hz, 2H, Ar-H). 

MS (ESI): m/z [(M+H)+]: 283 [(M+Na)+]: 305. 

**Anal.** Calcd for C₁₅H₁₄N₄O₂: C, 63.82; H, 5.00; N, 19.85. Found: C, 63.62; H, 5.10; N, 19.82.
6-Amino-4-(4-bromophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5c).
IR (cm$^{-1}$): 3425 (−NH$_2$), 3400 (−NH$_2$), 2200 (−CN); $^1$H NMR ((CD$_3$)$_2$CO, 300 MHz): δ 1.84 (s, 3H, CH$_3$), 4.56 (s, 1H, −CH=), 6.02 (br, s, 2H, NH$_2$), 7.11 (d, $J$ = 7.96 Hz, 2H, Ar-H), 7.43 (d, $J$ = 7.96 Hz, 2H, Ar-H).
MS (ESI): m/z [(M+H)$^+$]: 331.
Anal. Calcd for C$_{15}$H$_{14}$N$_4$O$_2$: C, 50.77; H, 3.35; N, 16.92. Found: C, 50.48; H, 3.48; N, 16.79.

6-Amino-4-(4-chlorophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5d).
IR (cm$^{-1}$): 3418 (−NH$_2$), 3398 (−NH$_2$), 2198 (−CN); $^1$H NMR ((CD$_3$)$_2$CO, 300 MHz): δ 1.83 (s, 3H, CH$_3$), 4.55 (s, 1H, −CH=), 6.07 (br, s, 2H, NH$_2$), 7.13 (d, $J$ = 7.38 Hz, 2H, Ar-H), 7.83 (d, $J$ = 7.38 Hz, 2H, Ar-H).
MS (ESI): m/z [(M+H)$^+$]: 287.

6-Amino-3-methyl-4-(4-nitrophenyl)-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5e).
IR (cm$^{-1}$): 3424 (−NH$_2$), 3405 (−NH$_2$), 2199 (−CN); $^1$H NMR (DMSO-d$_6$, 300 MHz): δ 1.84 (s, 3H, CH$_3$), 4.54 (s, 1H, −CH=), 6.05 (br, s, 2H, NH$_2$), 7.49 (d, $J$ = 8.18 Hz, 2H, Ar-H), 7.95 (d, $J$ = 7.18 Hz, 2H, Ar-H).
MS (ESI): m/z [(M+H)$^+$]: 298.
Anal. Calcd for C$_{14}$H$_{11}$N$_5$O$_3$: C, 56.56; H, 3.73; N, 23.56. Found: C, 56.35; H, 3.63; N, 23.62.

6-Amino-4-(3-fluorophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5f).
IR (cm$^{-1}$): 3424 (−NH$_2$), 3398 (−NH$_2$), 2201 (−CN); $^1$H NMR (DMSO-d$_6$, 300 MHz): δ 1.83 (s, 3H, CH$_3$), 4.55 (s, 1H, −CH=), 6.07 (br, s, 2H, NH$_2$), 7.32 (d, $J$ = 8.12 Hz, 2H, Ar-H), 7.54 (d, $J$ = 8.12 Hz, 2H, Ar-H).
MS (ESI): m/z [(M+H)$^+$]: 271.

6-Amino-4-(4-cyanophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5g).
IR (cm$^{-1}$): 3424 (−NH$_2$), 3399 (−NH$_2$), 2201 (−CN); $^1$H NMR (DMSO-d$_6$, 300 MHz): δ 1.83 (s, 3H, CH$_3$), 4.54 (s, 1H, −CH=), 6.07 (br, s, 2H, NH$_2$), 7.32 (d, $J$ = 8.12 Hz, 2H, Ar-H), 7.54 (d, $J$ = 8.12 Hz, 2H, Ar-H).
MS (ESI): m/z [(M+H)$^+$]: 278.
Anal. Calcd for C$_{15}$H$_{11}$N$_5$O: C, 64.97; H, 4.00; N, 25.26. Found: C, 64.65; H, 3.86; N, 25.13.
6-Amino-3-methyl-4-(p-tolyl)-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5h).
IR (cm$^{-1}$): 3422 (–NH$_2$), 3398 (–NH$_2$), 2199 (–CN); $^1$H NMR (DMSO-d$_6$, 300 MHz): $\delta$
1.84 (s, 3H, CH$_3$), 2.32 (s, 3H, CH$_3$), 4.53 (s, 1H, –CH=), 5.66 (br, s, 2H, NH$_2$), 6.85 (d, $J = 8.68$ Hz, 2H, Ar-H), 7.10 (d, $J = 8.68$ Hz, 2H, Ar-H).
MS (ESI): m/z [(M+H)$^+$]: 267 [(M+Na)$^+$]: 299.

6-Amino-3-methyl-4-(3-nitrophenyl)-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5i).
IR (cm$^{-1}$): 3419 (–NH$_2$), 3399 (–NH$_2$), 2200 (–CN); $^1$H NMR (DMSO-d$_6$, 300 MHz): $\delta$
1.84 (s, 3H, CH$_3$), 4.56(s, 1H, –CH=), 6.07 (br, s, 2H, NH$_2$), 7.05–7.12 (m, 3H, Ar-H), 8.52 (s, 1H, Ar-H).
MS (ESI): m/z [(M+H)$^+$]: 298.
Anal. Calcd for C$_{14}$H$_{11}$N$_5$O$_3$: C, 56.56; H, 3.73; N, 23.56. Found: C, 56.38; H, 3.65; N, 23.78.

6-Amino-4-(2,4-difluorophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5j).
IR (cm$^{-1}$): 3422 (–NH$_2$), 3401 (–NH$_2$), 2198 (–CN); $^1$H NMR (DMSO-d$_6$, 300 MHz): $\delta$
1.89 (s, 3H, CH$_3$), 4.94 (s, 1H, –CH=), 5.78 (br, s, 2H, NH$_2$), 6.77–6.89 (m, 2H, Ar-H), 7.10–7.18 (m, 1H, Ar-H).
MS (ESI): m/z [(M+H)$^+$]: 271.
Anal. Calcd for C$_{14}$H$_{10}$F$_2$N$_4$O: C, 58.33; H, 3.50; N, 19.44. Found: C, 58.10; H, 3.42; N, 19.68.

6-Amino-3-methyl-4-(3-(trifluoromethyl)phenyl)-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5k).
IR (cm$^{-1}$): 3420 (–NH$_2$), 3402 (–NH$_2$), 2199 (–CN); $^1$H NMR (DMSO-d$_6$, 300 MHz): $\delta$
1.87 (s, 3H, CH$_3$), 4.58(s, 1H, –CH=), 6.07 (br, s, 2H, NH$_2$), 7.05–7.12 (m, 3H, Ar-H), 8.52 (s, 1H, Ar-H).
MS (ESI): m/z [(M+H)$^+$]: 321.
Anal. Calcd for C$_{15}$H$_{11}$F$_3$N$_4$O: C, 56.25; H, 3.46; N, 17.49. Found: C, 56.01; H, 3.39; N, 17.40.

6-Amino-4-(2,5-dimethylphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5l).
IR (cm$^{-1}$): 3421 (–NH$_2$), 3400 (–NH$_2$), 2200 (–CN); $^1$H NMR (DMSO-d$_6$, 300 MHz): $\delta$
1.76 (s, 3H, CH$_3$), 2.23 (s, 3H, CH$_3$), 2.30 (s, 3H, CH$_3$), 4.81 (s, 1H, –CH=), 5.93 (br, s, 2H, NH$_2$), 6.82 (s, 1H, Ar-H), 6.90 (d, $J = 7.55$ Hz, 1H, Ar-H), 6.98 (d, $J = 7.84$ Hz, 1H, Ar-H). MS (ESI): m/z [(M+H)$^+$]: 281.

6-Amino-4-(2-furyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5m).

IR (cm⁻¹): 3422 (−NH₂), 3405 (−NH₂), 2199 (−CN); ¹H NMR ((CD₃)₂CO, 300 MHz): δ
1.87 (s, 3H, CH₃), 4.57 (s, 1H, −CH= ), 6.65 (br, s, 2H, NH₂), 6.11–6.27 (m, 1H, Ar-H),
7.20 (d, 2H, Ar-H).
MS (ESI): m/z [(M+H)⁺]: 243.
Anal. Calcd for C_{14}H_{12}N_{4}O: C, 59.50; H, 4.16; N, 23.13. Found: C, 59.21; H, 4.08; N,
23.02.

6-Amino-3-methyl-4-(2-thienyl)-2,4-dihydropyrano [2,3-c]pyrazole-5-carbonitrile (5n).

IR (cm⁻¹): 3422 (−NH₂), 3405 (−NH₂), 2199 (−CN); ¹H NMR ((CD₃)₂CO, 300 MHz): δ
1.87 (s, 3H, CH₃), 4.57 (s, 1H, −CH= ), 6.65 (br, s, 2H, NH₂), 6.11–6.27 (m, 1H, Ar-H),
7.20 (d, 2H, Ar-H).
MS (ESI): m/z [(M+H)⁺]: 259.
Anal. Calcd for C_{12}H_{10}N_{4}OS: C, 55.80; H, 3.90; N, 21.69. Found: C, 55.53; H, 3.82;
N, 21.81.

6-Amino-2,4-dihydro-3-methyl-4-styryl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5o).

IR (cm⁻¹): 3415 (−NH₂), 3400 (−NH₂), 2199 (−CN); ¹H NMR (DMSO-d₆, 300 MHz): δ
2.01 (s, 3H, CH₃), 4.68 (s, 1H, −CH= ), 6.58 (br, s, 2H, NH₂), 6.27–7.20 (m, 7H, Ar-H).
MS (ESI): m/z [(M+H)⁺]: 279.
Anal. Calcd for C_{16}H_{14}N_{4}O: C, 69.05; H, 5.07; N, 20.13. Found: C, 69.31; H, 5.12;

6-Amino-3-methyl-4-(n-propyl)-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5p).

IR (cm⁻¹): 3420 (−NH₂), 3390 (−NH₂), 2200 (−CN); ¹H NMR (DMSO-d₆, 300 MHz): δ
0.99(t, 3H, CH₃), 1.31–1.36 (m, 4H, −CH₂−CH₂−), 1.80 (s, 3H, CH₃), 3.56 (s, 1H, −CH=),
6.55 (br, s, 2H, NH₂).
MS (ESI): m/z [(M+H)⁺]: 219.
Anal. Calcd for C_{11}H_{14}N_{4}O: C, 60.53; H, 6.47; N, 25.67. Found: C, 60.31; H, 6.82;
N, 25.53.

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