



ONE POT SYNTHESIS OF PYRANOPYRAZOLES USING SODIUM LACTATE AS AN EFFICIENT CATALYST

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An efficient one pot synthesis of pyranopyrazoles has been achieved by the four-component condensation of hydrazine hydrate, ethyl acetoacetate, aldehydes and malononitrile using sodium lactate as a catalyst in aqueous ethanolic medium under reflux condition. The method is simple and green to afford pyranopyrazoles in a short time. It provides a new base catalyst that readily gives product from moderate to excellent yields.

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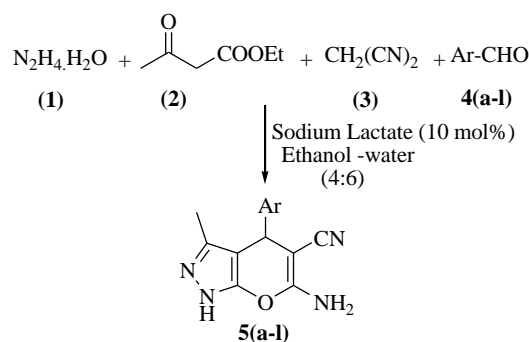
Introduction

Addition of three or more starting materials in one pot and their transformation to final product without isolation of intermediate provides a significant tool for organic synthesis. After the Strecker's amino acid synthesis, many successful attempts were made for organic transformations such as the synthesis of pyranopyrazoles which is one of the most important heterocycles of great biological significance. Pyranopyrazoles scaffolds are reported for various biological activities such as analgesic, anti-inflammatory,¹ anti-bacterial,² anti-microbial,³ and antitumor activity.⁴

Many methods are reported for the synthesis of pyranopyrazoles involving the use of three or four component condensation using CeCl₃,⁵ InCl₃,⁶ La(NO₃)₃,⁷ ionic liquids such as [(CH₂)₄SO₃HMIM][HSO₄],⁸ [H-NMP][MeSO₃],⁹ cetyltrimethylammonium chloride,¹⁰ amino acids such as glycine,¹¹ L-tyrosine,¹² nano-particles such as CuI,¹³ Fe₃O₄,¹⁴ Fe₃O₄@SiO₂,¹⁵ 1,3,5-triazine-2,4,6-triamine modified nano rice husk silica,¹⁶ MgO,¹⁷ ZnO,^{18,19} and vitamin B₁ on silica coated ferrite (Fe₂O₃@SiO₂) nanoparticles.²⁰ Some heterogeneous catalysts like cerium (IV) carboxymethylcellulose,²¹ acidic montmorillonite K-10 clay²² are also documented for the one pot synthesis of pyranopyrazoles. Organic acids catalysing the synthesis of these heterocycles include citric acid,²³ and L-Proline.²⁴ Pyranopyrazoles can also be synthesized by using organic base catalysts like triethyl amine,²⁵⁻²⁷ triethanol amine,²⁸ piperazine, piperidine, pyrrolidine and morpholine,²⁹ salts like ammonium chloride,³⁰ and sodium benzoate.³¹

However many of these methods have several drawbacks such as costly catalysts, harsh reaction condition and poor yields. In addition, the problem of waste remains an environmental question. In the present work, we report

sodium lactate as a new environmentally benign base catalyst for the four-component synthesis of pyranopyrazoles from hydrazine hydrate, ethyl acetoacetate, malononitrile and various aldehydes (Scheme 1).



Scheme 1. Four component pyranopyrazole synthesis.

Experimental

Melting points were recorded in open capillaries and are uncorrected. Structures of the synthesized products were assigned on the basis of spectral analysis. IR spectra were recorded on Shimadzu IR Affinity 1 spectrophotometer using KBr pellets. ¹H NMR spectra were recorded in DMSO-d₆ on a BRUKER AVANCE II 400 MHz spectrometer and the chemical shifts were expressed in ppm relative to TMS. Mass spectra were recorded on a Macro mass spectrometer by Electron Spray technique. Sodium lactate (60 %) solution was purchased from Loba Chemicals Pvt. Ltd. Progress of the reaction was monitored on silica pre-coated TLC plates in 40 % ethyl acetate: n-hexane.

General procedure

A mixture of ethyl acetoacetate (1 mmol), hydrazine hydrate (1 mmol) and sodium lactate solution (10 mol %) was mixed thoroughly. To it 40 % aqueous ethanol (5 mL) was added followed by aldehyde (1 mmol) and malononitrile (1 mmol) and the resulting mixture was stirred for a while and then refluxed for appropriate time (Table 1). After completion of reaction, as monitored by TLC, the reaction mixture was allowed to cool and poured onto 50 g

of crushed ice. The solid obtained was then filtered, dried and recrystallized from ethanol.

Table 1. Synthesis of pyranopyrazoles.

Product	Ar	Time (min.)	Yield (%) [*]	M. P. (°C)
5a	4-OMe-C ₆ H ₄	10	94	210-211
5b	C ₆ H ₅	15	90	244-245
5c	4-Cl-C ₆ H ₄	10	91	233-234
5d	2-Cl-C ₆ H ₄	10	90	245-246
5e	4-OH-C ₆ H ₄	15	84	222-223
5f	4-Br-C ₆ H ₄	10	85	178-180
5g	4-NO ₂ -C ₆ H ₄	10	86	253-254
5h	3-NO ₂ -C ₆ H ₄	15	82	190-192
5i	4-Me-C ₆ H ₄	15	83	207-208
5j	3-OMe-4-OH-C ₆ H ₃	20	79	234-235
5k	2-Furyl	20	85	216-218
5l	4-(Piperidin-1-yl)-C ₆ H ₄	15	74	167-169

^{*}Anisaldehyde (1 mmol), ethyl acetoacetate (1 mmol), malononitrile (1 mmol), hydrazine hydrate (1 mmol), 5 mL of 40 % ethanol solution.

Results and Discussion

Commonly, sodium lactate is used for medical applications and is obtained by the treatment of sodium hydroxide with lactic acid. Lactic acid is considered as a green chemical in organic synthesis. Hence we selected its sodium salt for the one pot four component syntheses of pyranopyrazoles. From literature survey, most of the condensation reactions are reported under basic conditions. An aqueous solution of sodium lactate being basic in nature, we used it for the one pot four component condensation purposes.

Table 2. Optimization of reaction conditions for the model reaction.

No.	Ethanol %	Sodium lactate	Temp., °C	Time, min.	Yield, %
1	--	--	RT	60	--
2	--	5	RT	60	31
3	50	5	60	50	65
4	50	5	Reflux	45	73
5	50	10	Reflux	10	92
6	40	10	Reflux	10	94
7	30	10	Reflux	10	81

In order to optimize the reaction conditions, we selected anisaldehyde as a prototype aldehyde. The first attempt was carried out under solvent free condition using anisaldehyde (1 mmol), hydrazine hydrate (1 mmol), malononitrile (1 mmol), ethyl acetoacetate (1 mmol) and sodium lactate (5 mol %) at room temperature, which resulted in poor yield of the corresponding product. Then we switched to the use of aqueous ethanol as an environmentally benign and easily available solvent. Ethanol-water system provides an ease for the dissolution for the reactants. To find the effective solvent and optimum catalyst amount, the model reaction was tried with varied solvent proportions and different amounts of sodium lactate. Initially 50 % aqueous-ethanol

medium was used under catalyst free condition and a trace product formation was observed at room temperature. Later addition of 5 mol % of sodium lactate improved the yield at but only to a small extent (Table 2, Entry 2).

To improve yield of the model reaction, the reaction mass was heated at 60°C and then to reflux condition. Reflux condition afforded better yield than at 60° C (Table 2, Entry 3 and 4) and thus good yield was obtained under reflux condition. To improve the yield, we increased the amount of sodium lactate to 10 mol % which resulted in an excellent yield of the desired product up to 92 %. To achieve the principles of green chemistry, we tried to reduce percentage of ethanol in the solvent system and found nearly the same efficiency in 40 % ethanol (Table 2, Entry 6). Further decrease in ethanol percentage resulted in decrease in yield of the desired product (Table 2, Entry 7). Hence, 40 % ethanol in water was found to be appropriate and used for further reactions in the presence of 10 mol % sodium lactate.

6-Amino-1,4-dihydro-4-(4-methoxyphenyl)-3-methylpyrano[2,3-c]pyrazole-5-carbonitrile (5a)

IR (KBr, cm⁻¹): 1516, 1600, 2191 (CN), 3117, 3266 (NH₂), 3484 (NH). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 1.80 (s, 3H, Ar-CH₃), 3.74 (s, 3H, OCH₃), 4.55 (s, 1H, CH), 6.82-6.88 (m, 4H, Ar-H), 7.09 (s, 2H, NH₂), 12.08 (s, 1H, NH); ¹³C NMR (100 MHz, DMSO-*d*₆) δ = 9.71, 35.43, 54.95, 57.61, 97.85, 113.72, 120.80, 128.46, 135.54, 136.45, 154.73, 157.93, 160.66. MS (ESI) *m/z* 283.5 (M+1).

6-Amino-1,4-dihydro-3-methyl-4-phenylpyrano[2,3-c]pyrazole-5-carbonitrile (5b)

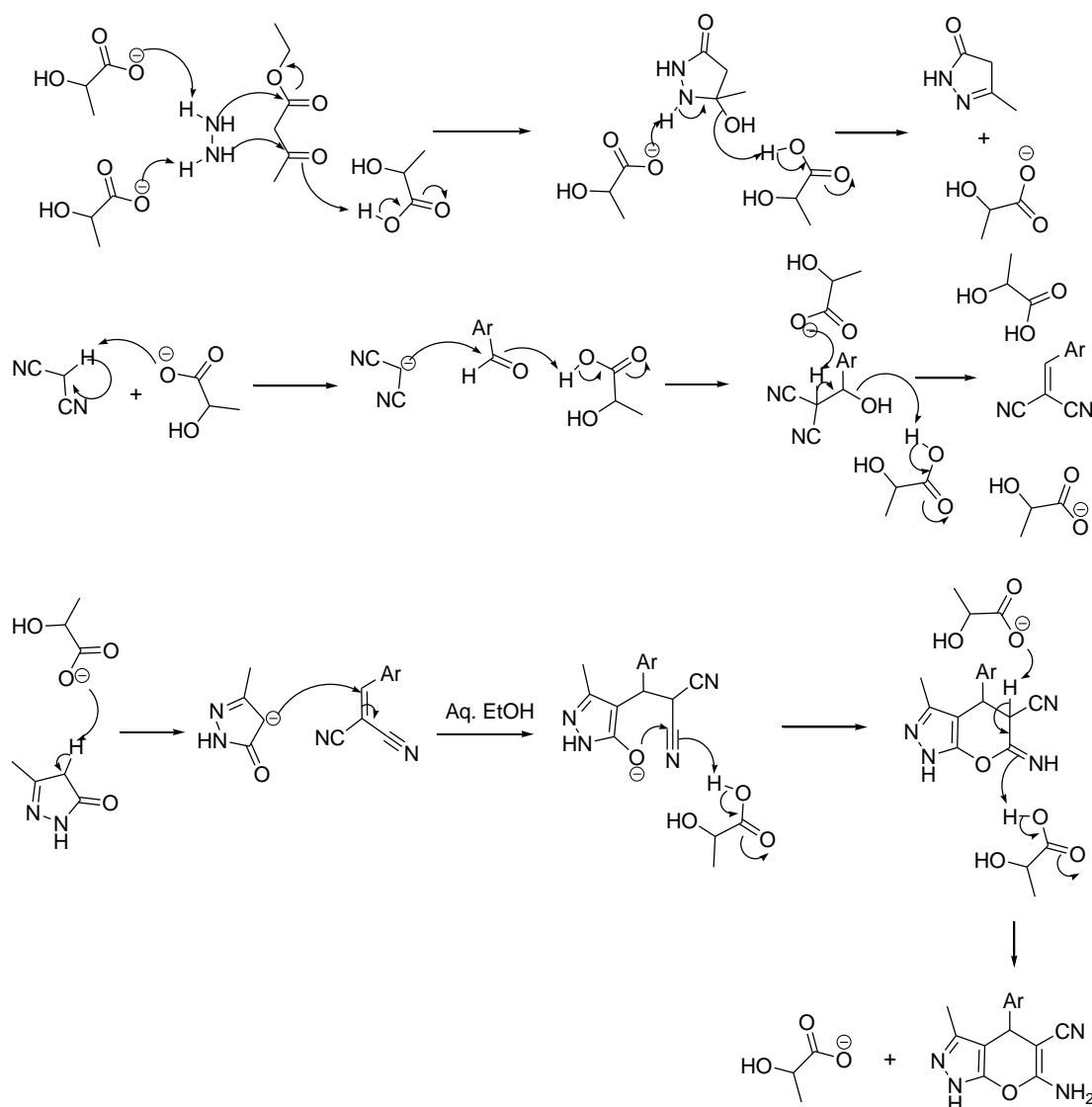
IR (KBr, cm⁻¹): 1512, 1593, 2194 (CN), 3167, 3356 (NH₂), 3410 (NH). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 1.78 (s, 3H, Ar-CH₃), 4.60 (s, 1H, CH), 6.85 (s, 2H, NH₂), 7.10-7.40 (m, 5H, Ar-H), 12.10 (s, 1H, NH); ¹³C NMR (100 MHz, DMSO-*d*₆) δ = 9.5, 26.8, 42.4, 48.6, 97.86, 113.1, 126.1, 127.46, 128.5, 138.40, 159.50, 174.1. MS (ESI) *m/z* 253 (M+1).

6-Amino-4-(4-chlorophenyl)-1,4-dihydro-3-methyl pyrano[2,3-c]pyrazole-5-carbonitrile (5c)

IR (KBr, cm⁻¹): 1510, 1595, 2191 (CN), 3117, 3255 (NH₂), 3483 (NH). ¹H NMR (400 MHz, DMSO-*d*₆) δ = 1.80 (s, 3H, Ar-CH₃), 4.64 (s, 1H, CH), 6.94 (s, 2H, NH₂), 7.20 (d, *J*=8Hz, 2Ar-H), 7.37 (d, *J*=8Hz, 2Ar-H), 12.15 (s, 1H, NH); ¹³C NMR (100 MHz, DMSO-*d*₆) δ = 9.70, 35.56, 56.79, 97.17, 120.61, 128.42, 129.33, 131.22, 135.67, 143.44, 154.69, 160.89. MS (ESI) *m/z* 287.4 (M+1).

6-Amino-4-(2-chlorophenyl)-1,4-dihydro-3-methylpyrano[2,3-c]pyrazole-5-carbonitrile (5d)

IR (KBr, cm⁻¹): 1523, 1611, 2195 (CN), 3120, 3265 (NH₂), 3480 (NH); ¹H NMR (400 MHz, DMSO-*d*₆) δ = 1.81 (s, 3H, Ar-CH₃), 4.65 (s, 1H, CH), 6.98 (s, 2H, NH₂), 7.24-7.37 (m, 4H, Ar-H), 13.72 (s, 1H, NH); ¹³C NMR (100 MHz, DMSO-*d*₆) δ = 13.42, 56.18, 60.59, 102.20, 119.41, 127.23, 129.10, 129.48, 130.29, 131.35, 132.05, 141.34, 157.90, 160.23. MS (ESI) *m/z* 287.23 (M+1).



Scheme 2. Possible mechanism for the synthesis of pyranopyrazoles using sodium lactate.

6-Amino-1,4-dihydro-4-(4-hydroxyphenyl)-3-methylpyrano[2,3-c]pyrazole-5-carbonitrile (5e)

IR (KBr, cm^{-1}): 1582, 1642, 2220 (CN), 3059, 3340 (NH_2), 3415 (NH). ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ = 1.99 (s, 3H, Ar- CH_3), 4.50 (s, 1H, CH), 6.10 (d, J = 8 Hz, 2H, Ar-H), 6.42 (s, 2H, NH_2), 7.00 (d, J = 8 Hz, 2H, Ar-H), 11.12 (s, 1H, OH); 12.07 (s, 1H, NH); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ = 12.1, 25.43, 71.90, 113.22, 119.5, 127.72, 130.80, 141.40, 144.0, 153.04, 154.44, 159.84. MS (ESI) m/z 269.10 (M+1).

6-Amino-4-(4-bromophenyl)-1,4-dihydro-3-methylpyrano[2,3-c]pyrazole-5-carbonitrile (5f)

IR (KBr, cm^{-1}): 1512, 1640, 2220 (CN), 3075, 3280 (NH_2), 3411 (NH). ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ = 1.92 (s, 3H, Ar- CH_3), 4.45 (s, 1H, CH), 6.45 (s, 2H, NH_2), 7.04 (d, J = 8 Hz, 2H, Ar-H), 7.43 (d, J = 8 Hz, 2H, Ar-H), 12.08 (s, 1H, NH); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ = 11.12, 24.14, 70.76, 112.14, 119.11, 128.39, 120.80, 130.18, 135.01, 143.90, 153.73, 159.10. MS (ESI) m/z 331.2 (M+1).

6-Amino-1,4-dihydro-3-methyl-4-(4-nitrophenyl)pyrano[2,3-c]pyrazole-5-carbonitrile (5g)

IR (KBr, cm^{-1}): 1512, 1610, 2198 (CN), 3277, 3380 (NH_2), 3474 (NH). ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ = 2.02 (s, 3H, Ar- CH_3), 4.71 (s, 1H, CH), 6.24 (s, 2H, NH_2), 7.49 (d, J = 8 Hz, 2Ar-H), 8.16 (d, J = 8 Hz, 2Ar-H), 12.18 (s, 1H, NH); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ = 11.33, 25.50, 56.79, 97.17, 120.61, 128.42, 129.33, 131.22, 135.67, 143.44, 154.69, 160.89. MS (ESI) m/z 298.3 (M+1).

6-Amino-1,4-dihydro-3-methyl-4-(3-nitrophenyl)pyrano[2,3-c]pyrazole-5-carbonitrile (5h)

IR (KBr, cm^{-1}): 1509, 1624, 2192 (CN), 3271, 3385 (NH_2), 3470 (NH). ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ = 2.02 (s, 3H, Ar- CH_3), 4.74 (s, 1H, CH), 6.37 (s, 2H, NH_2), 7.53-7.63 (m, 2H, 2Ar-H), 8.02-8.07 (m, 1H, Ar-H), 8.11 (s, 1H, Ar-H), 12.19 (s, 1H, NH); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): 11.10, 26.3, 72.1, 112.4, 121.2, 127.6, 129.48, 133.11, 135.21,

142.7, 147.1, 151.3, 154.3, 160.67. MS (ESI) m/z 298.11 (M+1).

6-Amino-1,4-dihydro-3-methyl-4-p-tolylpyrano[2,3-c]pyrazole-5-carbonitrile (5i)

IR (KBr, cm^{-1}): 1507, 1621, 2184 (CN), 3109, 3260 (NH_2), 3453 (NH); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 2.02 (s, 3H, Ar- CH_3), 2.49 (s, 3H, CH_3), 4.72 (s, 1H, CH), 5.72 (s, 2H, NH_2), 7.24 (d, 2H, $J=8$ Hz, 2Ar-H), 7.61 (d, 2H, $J=8$ Hz, 2Ar-H), 11.92 (s, 1H, NH); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ = 9.7, 20.4, 35.7, 55.1, 97.7, 117.7, 120.7, 127.6, 128.9, 135.3, 141.6, 154.7, 160.7; MS (ESI) m/z 267.1 (M+1).

6-Amino-1,4-dihydro-4-(4-hydroxy-3-methoxyphenyl)-3-methylpyrano[2,3-c]pyrazole-5-carbonitrile (5j)

IR (KBr, cm^{-1}): 1472, 1581, 2154 (CN), 3162, 3370 (NH_2), 3481 (NH). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 1.63 (s, 3H, Ar- CH_3), 3.42 (s, 3H, OCH_3), 4.58 (s, 1H, CH), 6.72 (s, 2H, NH_2), 6.93 (d, 1H, Ar-H), 7.38-7.43 (m, 2H, Ar-H), 10.42 (s, 1H, OH), 12.78 (s, 1H, NH); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ = 9.7, 34.25, 53.64, 56.64, 97.72, 104.57, 113.61, 115.16, 119.70, 128.12, 134.39, 135.86, 153.62, 157.59, 160.58. MS (ESI) m/z 299.12 (M+1).

6-Amino-4-(furan-2-yl)-1,4-dihydro-3-methylpyrano[2,3-c]pyrazole-5-carbonitrile (5k)

IR (KBr, cm^{-1}): 1502, 1613, 2214 (CN), 3221, 3385 (NH_2), 3427 (NH); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 1.88 (s, 3H, Ar- CH_3), 4.56 (s, 1H, CH), 6.52 (s, 2H, NH_2), 6.84 (m, 1H, Ar-H), 7.04 (m, 1H, Ar-H), 7.33 (m, 1H, Ar-H), 12.17 (s, 1H, NH); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ = 9.76, 34.19, 58.92, 57.61, 104.84, 110.63, 117.94, 138.44, 145.52, 155.12, 158.18, 163.70. MS (ESI) m/z 243.2 (M+1).

6-Amino-1,4-dihydro-3-methyl-4-(4-(piperidin-1-yl)phenyl)pyrano[2,3-c]pyrazole-5-carbonitrile (5l)

IR (KBr, cm^{-1}): 1540, 1620, 2230 (CN), 3140, 3252 (NH_2), 3470 (NH). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 1.51-1.61 (m, 6H, 3 CH_2), 1.80 (s, 3H, Ar- CH_3), 3.09 (t, 4H, 2 CH_2), 4.47 (s, 1H, CH), 6.76 (s, 2H, NH_2), 6.85 (d, $J=8$ Hz, 2H, Ar-H), 6.98 (d, $J=8$ Hz, 2H, Ar-H), 12.04 (s, 1H, NH); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ = 9.75, 23.83, 25.33, 35.38, 49.55, 57.73, 98.02, 115.67, 120.91, 127.87, 134.31, 135.45, 150.37, 154.75, 160.63. MS (ESI) m/z 336.5 (M+1).

Possible mechanism

The lactate anion helps to accumulate a negative charge on nitrogen to get condensed with ethyl acetoacetate affording pyrazolone (I). Simultaneously, aldehyde and malononitrile undergo Knoevenagel condensation to give arylidene intermediate (II). The reaction of deprotonated pyrazolone with the arylidene intermediate (II), followed by cyclization and tautomerization gives the desired pyranopyrazole product and with regeneration of the lactate anion (Scheme 2).

Conclusion

The present investigation underlines the efficiency of sodium lactate as a base catalyst and the ease of its handling in the experiments. The work up of reaction is quite simple and easy. Sodium lactate acts as a catalyst for the one pot four component syntheses of pyranopyrazoles in aqueous ethanol as an environmentally benign solvent. Thus, this protocol is simple, fast, efficient and serves as a green route for the one pot four component syntheses of pyranopyrazoles.

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