Diversity Oriented Synthesis of Pyrano[2,3-c]pyrazoles and their Characterization

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Abstract:
A series of novel 1,4-dihydropyrano[2,3-c]pyrazole derivatives has been synthesized by one-pot three-component cyclocondensation reaction of aromatic aldehydes, malononitrile and substituted pyrazolin-5-ones in the presence of piperidine as catalyst. The products were characterized by various spectroscopic tools like FT-IR, mass, ^{1}H NMR spectroscopy and elemental analyses.

Keywords: *1,4-dihydropyrano[2,3-c]pyrazole, Cyclocondensation, Piperidine, Spectroscopic tools*

1. Introduction

Pyran and fused pyran derivatives have attached a great deal of interest due to their association with various kinds of biological properties. They have been reported for their antimicrobial [1-4], antiviral [5, 6], anticonvulsant [7], cytotoxic [8] and antigenotoxic [9] activities. The incorporation of another heterocyclic moiety in pyrans either in the form of a substituent or as a fused component may changes its properties and converts it into an altogether new and important heterocyclic derivative.
Pyrazole have attracted particular interest over the last few decades due to use of such ring system as the core nucleus in various drugs. They are well-known for their activities such as antidiabitic [10], antipyretic [11], anti-inflammatory [12], anti-hypertansive [13], antitumour [14], peptide deformylase inhibitor [15], and antidepressant agents [16]. Considering the importance of pyran and pyrazole derivatives, it was thought worthwhile to synthesize new compounds incorporating both these moieties.

It is pertinent to mention that a large number of pyrazole fused and pyrazole substituted pyran derivatives are reported as biologically important compounds and their chemistry have received considerable attention of chemists in recent days [17-21]. Thus, pyranopyrazoles exhibit useful biological properties such as antimicrobial [22], and anti-inflammatory [23]. Furthermore Dihydropyrano [2,3-*c*]pyrazoles showed molluscicidal activity [24, 25] and was identified as a screening hit for Chk1 kinase inhibitor [26].

Over the last years, the chemistry of dihydropyrano[2,3-*c*]pyrazoles has received great interest. The first approach to synthesize these substances was undertaken by Otto [27], in which he initiated the reaction sequence by the base-catalyzed cyclization of 4-aryliden-5-pyrazolone. In a further report, this same group showed that weak bases can also be used for a Michael-type cyclization [28]. Extending the work of Otto, Klokol and colleagues performed the direct conversion of 3-methyl-3-pyrazolin-5-one with malononitrile in the presence of a weak base [29]. Recent methods for the synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazoles include synthesis in aqueous media, under microwave irradiation, and under solvent-free conditions [30].

Thus, in view of the diverse therapeutic activity of pyrano[2,3-*c*]pyrazoles, we report one-pot synthesis of pyrano[2,3-*c*]pyrazole derivatives (**4a-j**) by three-component reaction, a scaffold from which a diverse range of other biologically important New Chemical Entities (NCE's) could be generated. A

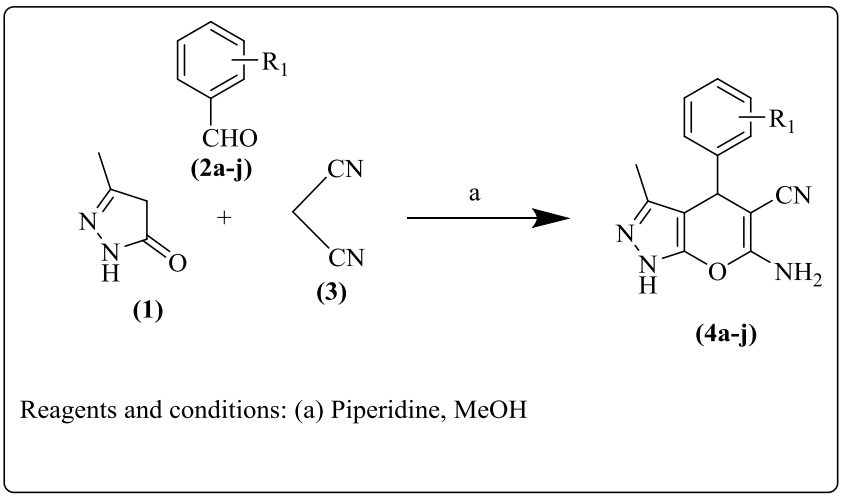
series of novel 1,4-dihydropyrano[2,3-*c*]pyrazole derivatives (**4a-j**) has been synthesized by one-pot three-component cyclocondensation reaction of aromatic aldehydes, malononitrile and substituted pyrazolin-5-ones in the presence of piperidine as catalyst.

2. Experimental Section

Melting points were determined in open glass capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine. IR spectra were recorded Shimadzu FT-IR-8400 instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. ^{1}H NMR was determined in DMSO-d_6 solution on a Bruker Ac 400 MHz spectrometer. Elemental analysis of the all the synthesized compounds was carried out on Elemental Vario EL III Carlo Erba 1108 model and the results are in agreements with the structures assigned.

3. General procedure for the 3,6-diamino-4-(aryl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4a-j)

A mixture of the malononitrile (0.01 mol), 3-methyl-1H-pyrazol-5(4*H*)-one (0.01 mol) and an appropriate aromatic aldehyde (0.01 mol) in 8-10 mL of MeOH with catalytic amount of piperidine were refluxed for 10-12 h. After completion of the reaction, the reaction mixture was filtered to give the solid products **(4a-j)**, which were recrystallized from ethanol.



Reagents and conditions: (a) Piperidine, MeOH

Table 1: Physical data for pyrano[2,3-*c*]pyrazoles (4a-o)

Code	R_1	M.F.	M.W.	M.P. ºC	Yield %
4a	H	$C_{14}H_{12}N_4O$	252	201-203	70
4b	4-F	$C_{14}H_{11}FN_4O$	270	169-171	78
4c	4-Cl	$C_{14}H_{11}ClN_4O$	286	188-190	81
4d	4-Br	$C_{14}H_{11}BrN_4O$	331	147-149	72
4e	4-NO_2	$C_{14}H_{11}N_5O_3$	297	221-223	69
4f	4-CH_3	$C_{15}H_{14}N_4O$	266	173-175	86
4g	4-OH	$C_{14}H_{12}N_4O_2$	268	207-209	76
4h	4-OCH_3	$C_{15}H_{14}N_4O_2$	282	179-181	70
4i	3,4-OCH_3	$C_{16}H_{16}N_4O_3$	312	142-144	68
4j	3-Cl	$C_{14}H_{11}ClN_4O$	286	183-185	77

6-amino-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4a)

IR (cm^{-1}): 3485 (N-H stretching of free primary amine), 3230 (N-H stretching of pyrazolo ring), 3111 (C-H stretching of aromatic ring), 2195 (C≡N stretching of the nitrile group), 1631 (C=N stretching of pyrazolo ring), 1599 (N-H deformation pyrazolo ring), 1184 (N-N deformation of pyrazolo ring), 1051 (C-H in plane bending of aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 2.11 (s, 3H), 4.68 (s, 1H,

H), 5.48 (s, 2H, H), 7.16-7.22 (m, 3H, H), 7.26-7.30 (m, 2H, H), 11.88 (s, 1H, H); MS: *m/z* 252; Anal. Calcd. for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N, 22.21; O, 6.34. Found: C, 64.53; H, 4.23; N, 25.55; O, 6.00%.

6-amino-4-(4-fluorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4b)
IR (cm^{-1}): 3487 (N-H stretching of free primary amine), 3234 (N-H stretching of pyrazolo ring), 3091 (C-H stretching of aromatic ring), 2196 (C≡N stretching of the nitrile group), 1631 (C=N stretching of pyrazolo ring), 1593 (N-H deformation pyrazolo ring), 1182 (N-N deformation of pyrazolo ring), 1049 (C-H in plane bending of aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 2.16 (s, $3H_a$), 4.31 (s, 1H), 5.22 (s, 2H), 6.98-7.03 (t, 2H), 7.16-7.19 (m, 2H), 11.92 (s, 1H); MS: *m/z* 270; Anal. Calcd. for $C_{14}H_{11}FN_4O$: C, 62.22; H, 4.10; F, 7.03; N, 20.73; O, 5.92. Found: C, 59.42; H, 3.80; F, 6.97; N, 19.73; O, 5.02.%.

6-amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4c)
IR (cm^{-1}): 3485 (N-H stretching of free primary amine), 3290 (N-H stretching of pyrazolo ring), 3109 (C-H stretching of aromatic ring), 2198 (C≡N stretching of the nitrile group), 1641 (C=N stretching of pyrazolo ring), 1595 (N-H deformation pyrazolo ring), 1182 (N-N deformation of pyrazolo ring), 1028 (C-H in plane bending of aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 2.06 (s, 3H), 4.62 (s, 1H), 5.40 (s, 2H), 7.11-7.17 (m, 3H), 7.22-7.26 (m, 2H), 11.85 (s, 1H); MS: *m/z* 287; Anal. Calcd. for $C_{14}H_{11}ClN_4O$: C, 58.65; H, 3.87; Cl, 12.36; N, 19.54; O, 5.58. Found: C, 58.60; H, 3.01; Cl, 11.32; N, 18.91; O, 5.01%.

6-amino-4-(4-bromophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4d)
IR (cm^{-1}): 3487 (N-H stretching of free primary amine), 3292 (N-H stretching of pyrazolo ring), 3098 (C-H stretching of aromatic ring), 2195 (C≡N stretching of the nitrile group), 1645 (C=N stretching of pyrazolo ring), 1590 (N-H deformation pyrazolo ring), 1181 (N-N deformation of pyrazolo ring), 1022 (C-H in plane bending of aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 2.12 (s, 3H), 4.69 (s, 1H, H), 5.49 (s, 2H, H), 7.18-7.24 (m, 3H, H), 7.28-7.32 (m, 2H, H), 11.90 (s, 1H, H); MS: *m/z* 331; Anal. Calcd. for $C_{14}H_{11}BrN_4O$: C, 50.78; H, 3.35; Br, 24.13; N, 16.92; O, 4.83. Found: C, 49.08; H, 3.01; Br, 23.03; N, 15.02; O, 4.13%.

6-amino-3-methyl-4-(4-nitrophenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4e)
IR (cm^{-1}): 3481 (N-H stretching of free primary amine), 3296 (N-H stretching of pyrazolo ring), 3091 (C-H stretching of aromatic ring), 2191 (C≡N stretching of the nitrile group), 1644 (C=N stretching of pyrazolo ring), 1591 (N-H deformation pyrazolo ring), 1184 (N-N deformation of pyrazolo ring), 1026 (C-H in plane bending of aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 2.12 (s, 3H), 4.61 (s, 1H, H), 5.44 (s, 2H, H), 7.15-7.21 (m, 3H, H), 7.24-7.28 (m, 2H, H), 11.85 (s, 1H, H); MS: *m/z* 298; Anal. Calcd. for $C_{14}H_{11}N_5O_3$: C, 56.57; H, 3.73; N, 23.56; O, 16.15. Found: C, 55.97; H, 3.13; N, 22.06; O, 15.15%.

6-amino-3-methyl-4-(p-tolyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4f) IR (cm^{-1}): 3479 (N-H stretching of free primary amine), 3271 (N-H stretching of pyrazolo ring), 3111 (C-H stretching of aromatic ring), 3047 (C-H symmetrical stretching of CH_3 group), 2966 (C-H asymmetrical stretching of CH_3 group), 2193 (C≡N stretching of the nitrile group), 1639 (C=N stretching of pyrazolo ring), 1602 (N-H deformation pyrazolo ring), 1367 (C-N stretching of pyrazolo ring), 1188 (N-N deformation of pyrazolo ring), 1026 (C-H in plane bending of aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 2.31 (S, 3H), 4.65 (s, 1H), 5.45 (s, 2H), 7.20-7.26 (m, 3H), 7.30-7.34 (m, 2H, H), 11.80 (s, 1H, H); MS: *m/z* 266; Anal. Calcd. for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04; O, 6.01. Found: C, 67.01; H, 5.00; N, 20.01; O, 5.01 %.

6-amino-4-(4-hydroxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4g)
IR (cm^{-1}): 3469 (N-H stretching of free primary amine), 3276 (N-H stretching of pyrazolo ring), 3116 (C-H stretching of aromatic ring), 3043 (C-H symmetrical stretching of CH_3 group), 2960 (C-H asymmetrical stretching of CH_3 group), 2190 (C≡N stretching of the nitrile group), 1633 (C=N stretching of pyrazolo ring), 1606 (N-H deformation pyrazolo ring), 1364 (C-N stretching of pyrazolo ring), 1181 (N-N deformation of pyrazolo ring), 1022 (C-H in plane bending of aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 2.12 (S, 3H), 3.67 (S, 1H), 4.60 (s, 1H), 5.41 (s, 2H), 7.15-7.21 (m, 3H), 7.22-7.26 (m, 2H), 11.85 (s, 1H, H); MS: *m/z* 268 Anal. Calcd. for $C_{14}H_{12}N_4O_2$: C, 62.68; H, 4.51; N, 20.88; O, 11.93. Found: C, 62.08; H, 4.01; N, 20.08; O, 11.03%.

6-amino-4-(4-methoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4h)
IR (cm^{-1}): 3398 (N-H stretching of free primary amine), 3321 (N-H stretching of pyrazolo ring), 3101 (C-H stretching of aromatic ring), 3020 (C-H symmetrical stretching of CH_3 group), 2966 (C-H asymmetrical stretching of CH_3 group), 2193 (C≡N stretching of the nitrile group), 1654 (C=N stretching of pyrazolo ring), 1606 (N-H deformation pyrazolo ring), 1253 (C-O-C asymmetrical stretching of ether linkage), 1172 (N-N deformation of pyrazolo ring), 1107 (C-O-C symmetrical stretching of ether linkage), 1026 (C-H in plane bending of aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 2.12 (S, 3H), 3.97 (S, 3H), 4.78 (s, 1H), 5.46 (s, 2H), 7.20-7.26 (m, 3H), 7.31-7.35 (m, 2H), 11.86 (s, 1H); MS: *m/z* 282; Anal. Calcd. for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 19.85; O, 11.33. Found: C, 63.02; H, 4.80; N, 19.05; O, 10.13%.

6-amino-4-(3,4-dimethoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4i)
IR (cm^{-1}): 3391 (N-H stretching of free primary amine), 3317 (N-H stretching of pyrazolo ring), 3108 (C-H stretching of aromatic ring), 3010 (C-H symmetrical stretching of CH_3 group), 2960 (C-H asymmetrical stretching of CH_3 group), 2195 (C≡N stretching of the nitrile group), 1655 (C=N stretching of pyrazolo ring), 1608 (N-H deformation pyrazolo ring), 1254 (C-O-C asymmetrical stretching of ether linkage), 1176 (N-N deformation of pyrazolo ring), 1101 (C-O-C symmetrical stretching of ether linkage), 1024 (C-H in plane bending of aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 2.42 (S, 3H), 3.87 (S, 3H), 3.97 (S, 3H), 4.86 (s, 1H), 5.40 (s, 2H), 6.20 (s, 2H), 7.12-7.18 (m, 3H), 7.22-7.26 (m, 2H), 11.82 (s, 1H); MS: *m/z* 312; Anal. Calcd. for $C_{16}H_{16}N_4O_3$: C, 61.53; H, 5.16; N, 17.94; O, 15.37. Found: C, 61.03; H, 4.76; N, 17.14; O, 14.97%.

6-amino-4-(3-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4i)
IR (cm^{-1}): 3485 (N-H stretching of free primary amine), 3290 (N-H stretching of pyrazolo ring), 3109 (C-H stretching of aromatic ring), 2198 (C≡N stretching of the nitrile group), 1641 (C=N stretching of pyrazolo ring), 1595 (N-H deformation pyrazolo ring), 1182 (N-N deformation of pyrazolo ring), 1028 (C-H in plane bending of aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 2.06 (s, 3H), 4.62 (s, 1H), 5.40 (s, 2H), 7.11-7.17 (m, 3H), 7.22-7.26 (m, 2H), 11.85 (s, 1H); MS: *m/z* 287; Anal. Calcd. for $C_{14}H_{11}ClN_4O$: C, 58.65; H, 3.87; Cl, 12.36; N, 19.54; O, 5.58. Found: C, 58.60; H, 3.01; Cl, 11.32; N, 18.91; O, 5.01%.

4. Results and Discussion

The reaction mechanism reaction occurs *via* an *in situ* initial formation of the arylidene malonoitrile, containing the electron-poor C=C double bond, from the Knoevenagel condensation between aromatic aldehydes and malononitrile by loss of water molecules. Finally, Michael addition of pyrazolone to the initially formed unsaturated nitrile, i.e. nucleophilic attack of hydroxyl moiety to the cyano moiety affords cyclized pyran derivatives. The confirmation of synthesized pyrano[2,3-c]pyrazoles was done on the basis of various spectroscopic techniques. For pyrano[2,3-*c*]pyrazoles **(4a-j)**, confirmatory bands for primary amine (-NH_2) and nitrile (C≡N) stretching band was observed at 3400-3500 cm^{-1} and 2190-2220 cm^{-1} respectively. Another characteristic band for N-H deformation was observed at 1580-1620 cm^{-1}, which suggested the formation of pyranopyrazoles ring system. Systematic

fragmentation pattern was observed in mass spectral analysis. Molecular ion peak was observed in agreement with molecular weight of respective compound. ^{1}H NMR spectra confirmed the structures of pyrano[2,3-*c*]pyrazoles **(4a-j)** on the basis of following signals: singlet for primary amino groups proton was observed at 5.91-6.62 δ ppm and a singlet for the methine proton of pyran ring at 4.52-4.64 δ ppm. The aromatic ring protons and *J* value were found to be in accordance with substitution pattern on phenyl ring.

In conclusion, we report herein the diversity oriented, simple and efficient approach towards the synthesis of pyrano[2,3-c]pyrazoles. The approach may be utilized for synthesis of other derivatives of pyrano[2,3-c]pyrazoles having potential biological activities.

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