© 2017 IJSRST | Volume 3 | Issue 8 | Print ISSN: 2395-6011 | Online ISSN: 2395-602X
Themed Section: Science and Technology

Multicomponent One-Pot Synthesis and Biological Evaluation of Pyrano[2,3-C] Pyrazoles

Nirul V. Gothi
Arts, Science & R. A. Patel commerce college, Bhadran, Gujarat, India

ABSTRACT

Despite recent advances in molecular biology and the progress in combinatorial synthetic methodology, the rate of introduction of new medicines has decreased markedly over the past two decades [1]. Structural diversity in a focused collection of potential therapeutics is believed to increase the positive hit rate. Most medicines in use are still small synthetic organic molecules that often contain a heterocyclic ring.

Keywords : Pyrazoles, Biological Evaluation, One-Pot Synthesis, MCRs, TLC, MeOH

I. INTRODUCTION

However, the range of easily accessible and suitably functionalized heterocyclic building blocks for the synthesis of structurally diverse libraries is rather limited. Therefore, the development of new, rapid and clean synthetic routes towards focused libraries of such compounds is of great importance to both medicinal and synthetic chemists [2]. Undoubtedly, the most efficient strategies involve multicomponent reactions (MCRs), which have emerged as a powerful tool for the rapid introduction of molecular diversity. Consequently, the design and development of (new) MCRs for the generation of heterocycles receives growing interest [3-6].

Laufer et al. [7] have synthesized 1,4-dihydropyrano[2,3-c]pyrazoles with various substituents at the 1-, 3-, and 4-position. Given the large number of commercially available aldehydes and the easy access to hydrazines and β-keto esters, this method should be applicable to synthesis of libraries with high diversity.

The corresponding β-keto esters were synthesized either according to Yuasa and Tsuruta [8] or by deprotonation of esters and subsequent reaction with ethyl acetate. This second procedure (deprotonation of esters), described in a patent application for the synthesis of ethyl 3-oxo-3-(pyridin-4-yl)propanoate [9], is more advantageous because the reaction can be performed using ethyl acetate as both the solvent and reagent without further purification. The reaction was performed at room temperature overnight, and nearly all products precipitated as discrete crystals.

Shestopalov et al. [10] demonstrated that a four-component reaction of aromatic aldehydes, malononitrile, β-ketoesters, and hydrazine hydrate successfully yields 6-aminopyrano[2,3-c]pyrazol-5-carbonitriles without the need of prior pyrazolin-5-ones isolation [48]. The multicomponent synthesis of pyranopyrazoles was carried out by simultaneously refluxing all four starting materials in ethanol for 15 min. in the presence of Et_3N. They showed that aromatic aldehydes with electronwithdrawing, electron-donating, withdrawing and donating groups, as well as napthaldehydes and hetero-aromatic aldehydes can be successfully reacted with β-ketoesters, malonodinitrile, and hydrazine hydrate to yield final pyrano[2,3-c]pyrazoles with high regio-selectivity.

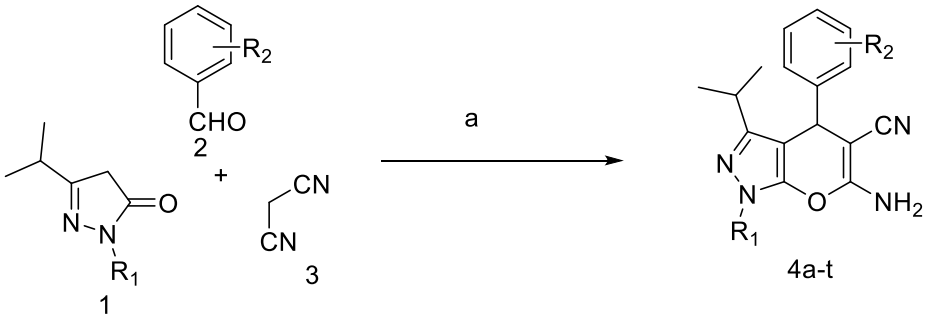
II. EXPERIMENTAL

Materials and Methods

Melting points were determined in open 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.

Reaction Scheme



Reagent and conditions; (a) Piperidine, MeOH

Table 1. Physical data of synthesized compounds

Code	R_1	R_2	M.F.	M.W.	M.P. ºC	Yield %	R_{f1}	R_{f2}
4a	H	H	$C_{16}H_{16}N_4O$	280	201-203	70	0.55	0.70
4b	H	4-F	$C_{16}H_{15}FN_4O$	298	169-171	78	0.51	0.65
4c	H	4-Cl	$C_{16}H_{15}ClN_4O$	314	188-190	81	0.61	0.78
4d	H	4-Br	$C_{16}H_{15}BrN_4O$	358	147-149	72	0.57	0.72
4e	H	4-NO_2	$C_{16}H_{15}N_5O_3$	325	221-223	69	0.48	0.67
4f	H	4-CH_3	$C_{17}H_{18}N_4O$	294	173-175	86	0.60	0.74
4g	H	4-OH	$C_{16}H_{16}N_4O_2$	296	207-209	76	0.52	0.68
4h	H	4-OCH_3	$C_{17}H_{18}N_4O_2$	310	179-181	70	0.62	0.79
4i	H	3,4-OCH_3	$C_{18}H_{20}N_4O_3$	340	142-144	68	0.50	0.68
4j	H	3-Cl	$C_{16}H_{15}ClN_4O$	314	183-185	77	0.56	0.76
4k	H	3-Br	$C_{16}H_{15}BrN_4O$	358	206-208	73	0.49	0.69
4l	H	3-NO_2	$C_{16}H_{15}N_5O_3$	325	227-229	82	0.47	0.68
4m	H	3-OH	$C_{16}H_{16}N_4O_2$	296	234-236	62	0.52	0.73
4n	H	2-Cl	$C_{16}H_{15}ClN_4O$	314	168-170	70	0.50	0.70
4o	H	2-NO_2	$C_{16}H_{15}N_5O_3$	325	213-215	66	0.58	0.74
4p	C_6H_5	H	$C_{22}H_{20}N_4O$	356	157-159	75	0.61	0.81
4q	C_6H_5	4-F	$C_{22}H_{19}FN_4O$	374	162-164	79	0.56	0.67
4r	C_6H_5	4-Cl	$C_{22}H_{19}ClN_4O$	390	142-144	83	0.49	0.65
4s	C_6H_5	4-Br	$C_{22}H_{19}BrN_4O$	434	200-202	67	0.53	0.72
4t	C_6H_5	4-NO_2	$C_{22}H_{19}N_5O_3$	401	187-189	79	0.59	0.78

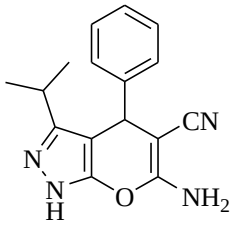
Synthesis of 2-cyano-N-(substituted)acetamides

Synthesis of 3-isopropyl-1H-pyrazol-5(4H)-one/3-isopropyl-1-phenyl-1H-pyrazol-5 (4H)-one was prepared by known literature method [11].

General procedure for the synthesis of 6-amino-1,2-dihydro-4-(aryl)-2-oxo-1-(pyridin-2-yl)pyridine-3,5-dicarbonitriles (4a-t)

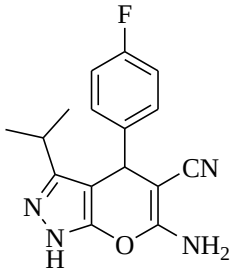
A mixture of the malononitrile (0.01 mol), 3-isopropyl-1H(or phenyl)-pyrazol-5(4H)-one (0.01 mol) and an appropriate aromatic aldehyde (0.01 mol) in 8-10 mL of MeOH with catalytic amount of piperidine were refluxed for 10-12 h. After completion of the reaction, the reaction mixture was filtered to give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

6-amino-1,4-dihydro-3-isopropyl-4-phenylpyrano[2,3-c]pyrazole-5-carbonitrile (4a)



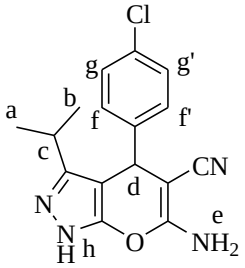
Yield: 70%; mp 201-203 ºC; MS: m/z 280; Anal. Calcd. for $C_{16}H_{16}N_4O$: C, 68.55; H, 5.75; N, 19.99. Found: C, 68.55; H, 5.75; N, 19.99%.

6-amino-4-(4-fluorophenyl)-1,4-dihydro-3-isopropylpyrano[2,3-c]pyrazole-5-carbonitrile (4b)



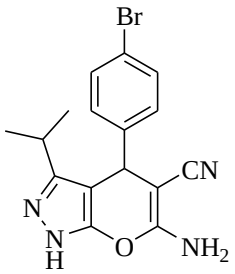
Yield: 78%; mp 169-171 ºC; MS: m/z 298; Anal. Calcd. for $C_{16}H_{15}FN_4O$: C, 64.42; H, 5.07; N, 18.78. Found: C, 64.42; H, 5.07; N, 18.78%.

6-amino-4-(4-chlorophenyl)-1,4-dihydro-3-isopropylpyrano[2,3-c]pyrazole-5-carbonitrile (4c)



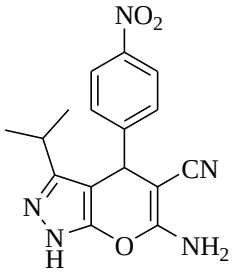
Yield: 81%; mp 188-190 ºC; IR (cm^{-1}): 3485 (N-H stretching of free primary amine), 3290 (N-H stretching of pyrazolo ring), 3109 (C-H stretching of aromatic ring), 2198 (C≡N stretching of the nitrile group), 1641 (C=N stretching of pyrazolo ring), 1595 (N-H deformation pyrazolo ring), 1182 (N-N deformation of pyrazolo ring), 1028 (C-H in plane bending of aromatic ring), 813 (C-H out of plane bending for 1,4-disubstituted aromatic ring), 748 (C-Cl stretching); ^{1}H NMR (DMSO-d_6) δ ppm: 0.85-0.87 (d, 3H, H_a, J = 6.8 Hz), 1.01-1.03 (d, 3H, H_b, J = 6.9 Hz), 2.50-2.56 (m, 1H, H_c), 4.58 (s, 1H, H_d), 6.47 (s, 2H, H_e), 7.14-7.16 (d, 2H, $H_{ff'}$), 7.27-7.30 (d, 2H, $H_{gg'}$), 12.00 (s, 1H, H_h); MS: m/z 314; Anal. Calcd. for $C_{16}H_{15}ClN_4O$: C, 61.05; H, 4.80; N, 17.80. Found: C, 61.05; H, 4.80; N, 17.80%.

6-amino-4-(4-bromophenyl)-1,4-dihydro-3-isopropylpyrano[2,3-c]pyrazole-5-carbonitrile (4d)



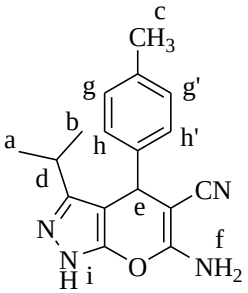
Yield: 72%; mp 147-149 ºC; MS: m/z 358; Anal. Calcd. for $C_{16}H_{15}BrN_4O$: C, 53.50; H, 4.21; N, 15.60. Found: C, 53.50; H, 4.21; N, 15.60%.

6-amino-1,4-dihydro-3-isopropyl-4-(4-nitrophenyl)pyrano[2,3-c]pyrazole-5-carbonitrile (4e)



Yield: 69%; mp 221-223 ºC; MS: m/z 325; Anal. Calcd. for $C_{16}H_{15}N_5O_3$: C, 59.07; H, 4.65; N, 21.53. Found: C, 59.07; H, 4.65; N, 21.53%.

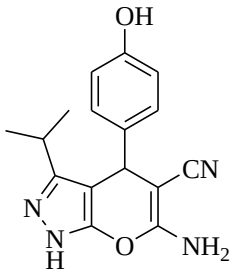
6-amino-1,4-dihydro-3-isopropyl-4-p-tolylpyrano[2,3-c]pyrazole-5-carbonitrile (4f)



Yield: 86%; mp 173-175 ºC; 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

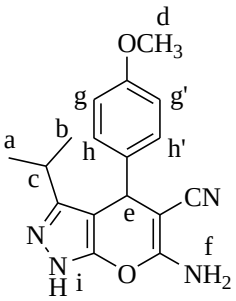
plane bending of aromatic ring), 813 (C-H out of plane bending for 1,4-disubstituted aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 0.86-0.88 (d, 3H, H_a, J = 6.8 Hz), 1.01-1.03 (d, 3H, H_b, J = 6.9 Hz), 2.30 (s, 3H, H_c), 2.51-2.58 (m, 1H, H_d), 4.54 (m, 1H, H_e), 5.91 (s, 2H, H_f), 7.00-7.10 (m, 4H, $H_{g\text{-}h'}$), 11.80 (s, 1H, H_i); MS: m/z 294; Anal. Calcd. for $C_{17}H_{18}N_4O$: C, 69.37; H, 6.16; N, 19.03. Found: C, 69.37; H, 6.16; N, 19.03%.

6-amino-1,4-dihydro-4-(4-hydroxyphenyl)-3-isopropylpyrano[2,3-c]pyrazole-5-carbonitrile (4g)



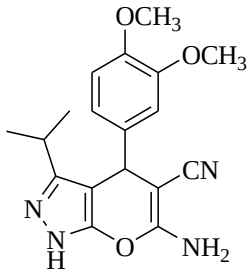
Yield: 76%; mp 207-209 ºC; MS: m/z 296; Anal. Calcd. for $C_{16}H_{16}N_4O_2$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.85; H, 5.44; N, 18.91%.

6-amino-1,4-dihydro-3-isopropyl-4-(4-methoxyphenyl)pyrano[2,3-c]pyrazole-5-carbonitrile (4h)



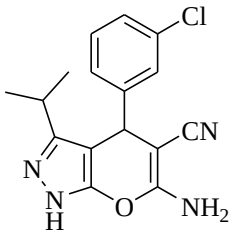
Yield: 70%; mp 179-181 ºC; IR (cm^{-1}): 3398 (N-H stretching of free primary amine), 3321 (N-H stretching of pyrazolo ring), 3101 (C-H stretching of aromatic ring), 3020 (C-H symmetrical stretching of CH_3 group), 2966 (C-H asymmetrical stretching of CH_3 group), 2193 (C≡N stretching of the nitrile 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), 819 (C-H out of plane bending for 1,4-disubstituted aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 0.84-0.86 (d, 3H, H_a, J = 6.8 Hz), 1.00-1.02 (d, 3H, H_b, J = 6.9 Hz), 2.51-2.58 (m, 1H, H_c), 3.75 (s, 3H, H_d), 4.52 (s, 1H, H_e), 6.36 (s, 2H, H_f), 6.80-6.83 (d, 2H, $H_{gg'}$), 7.06-7.08 (d, 2H, $H_{hh'}$), 11.96 (s, 1H, H_i); MS: m/z 310; Anal. Calcd. for $C_{17}H_{18}N_4O_2$: C, 65.79; H, 5.85; N, 18.05. Found: C, 65.79; H, 5.85; N, 18.05%.

6-amino-1,4-dihydro-3-isopropyl-4-(3,4-dimethoxyphenyl)pyrano[2,3-c]pyrazole-5-carbonitrile (4i)



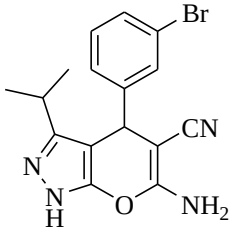
Yield: 68%; mp 142-144 ºC; MS: m/z 340; Anal. Calcd. for $C_{18}H_{20}N_4O_3$: C, 63.52; H, 5.92; N, 16.46. Found: C, 63.52; H, 5.92; N, 16.46%.

6-amino-4-(3-chlorophenyl)-1,4-dihydro-3-isopropylpyrano[2,3-c]pyrazole-5-carbonitrile (4j)



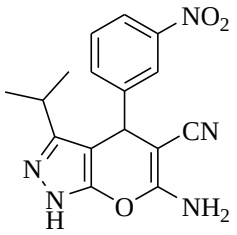
Yield: 77%; mp 183-185 ºC; MS: m/z 314; Anal. Calcd. for $C_{16}H_{15}ClN_4O$: C, 61.05; H, 4.80; N, 17.80. Found: C, 61.05; H, 4.80; N, 17.80%.

6-amino-4-(3-bromophenyl)-1,4-dihydro-3-isopropylpyrano[2,3-c]pyrazole-5-carbonitrile (4k)



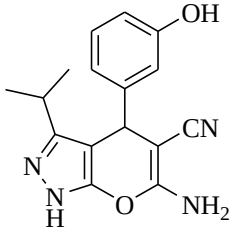
Yield: 73%; mp 206-208 ºC; MS: m/z 358; Anal. Calcd. for $C_{16}H_{15}BrN_4O$: C, 53.50; H, 4.21; N, 15.60. Found: C, 53.50; H, 4.21; N, 15.60%.

6-amino-1,4-dihydro-3-isopropyl-4-(3-nitrophenyl)pyrano[2,3-c]pyrazole-5-carbonitrile (4l)



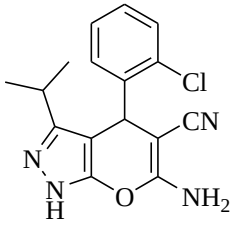
Yield: 82%; mp 227-229 ºC; MS: m/z 325; Anal. Calcd. for $C_{16}H_{15}N_5O_3$: C, 59.07; H, 4.65; N, 21.53. Found: C, 59.07; H, 4.65; N, 21.53%.

6-amino-1,4-dihydro-4-(3-hydroxyphenyl)-3-isopropylpyrano[2,3-c]pyrazole-5-carbonitrile (4m)



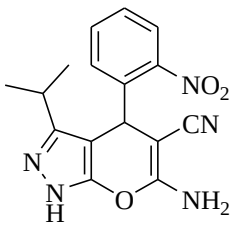
Yield: 62%; mp 234-236 ºC; MS: m/z 296; Anal. Calcd. for $C_{16}H_{16}N_4O_2$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.85; H, 5.44; N, 18.91%.

6-amino-4-(2-chlorophenyl)-1,4-dihydro-3-isopropylpyrano[2,3-c]pyrazole-5-carbonitrile (4n)



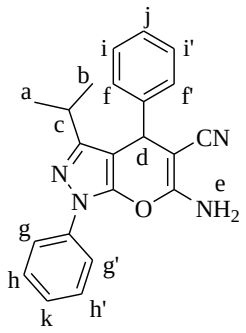
Yield: 70%; mp 168-170 ºC; MS: m/z 314; Anal. Calcd. for $C_{16}H_{15}ClN_4O$: C, 61.05; H, 4.80; N, 17.80. Found: C, 61.05; H, 4.80; N, 17.80%.

6-amino-1,4-dihydro-3-isopropyl-4-(2-nitrophenyl)pyrano[2,3-c]pyrazole-5-dicarbonitrile (4o)



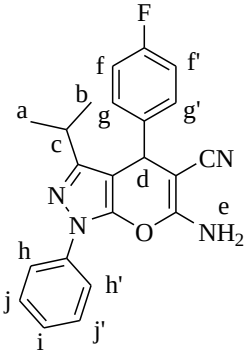
Yield: 66%; mp 213-215 ºC; MS: m/z 325; Anal. Calcd. for $C_{16}H_{15}N_5O_3$: C, 59.07; H, 4.65; N, 21.53. Found: C, 59.07; H, 4.65; N, 21.53%.

6-amino-1,4-dihydro-3-isopropyl-1,4-diphenylpyrano[2,3-c]pyrazole-5-carbonitrile (4p)



Yield: 75%; mp 157-159 ºC; IR (cm^{-1}): 3471 (N-H stretching of free primary amine), 3321 (N-H stretching of pyrazolo ring), 3063 (C-H stretching of aromatic ring), 2196 (C≡N stretching of the nitrile group), 1658 (C=N stretching of pyrazolo ring), 1581 (N-H deformation pyrazolo ring), 1338 (C-N stretching of pyrazolo ring), 1180 (N-N deformation of pyrazolo ring), 1026 (C-H in plane bending of aromatic ring), 846 (C-H out of plane bending for 1,4-disubstituted aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 0.81-0.83 (d, 3H, H_a, J = 6.8 Hz), 1.00-1.02 (d, 3H, H_b, J = 6.9 Hz), 2.51-2.57 (m, 1H, H_c), 4.56 (s, 1H, H_d), 6.29 (s, 2H, H_e), 7.14-7.31 (m, 10H, $H_{ff\text{-}k}$); MS: m/z 356; Anal. Calcd. for $C_{22}H_{20}N_4O$: C, 74.14; H, 5.66; N, 15.72. Found: C, 74.14; H, 5.66; N, 15.72%.

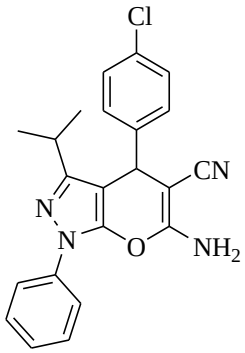
6-amino-4-(4-fluorophenyl)-1,4-dihydro-3-isopropyl-1-phenylpyrano[2,3-c]pyrazole-5-carbonitrile (4q)



Yield: 79%; mp 162-164 ºC; IR (cm^{-1}): 3458 (N-H stretching of free primary amine), 3325 (N-H stretching of pyrazolo ring), 3063 (C-H stretching of aromatic ring), 2200 (C≡N stretching of the nitrile group), 1664 (C=N stretching of pyrazolo ring), 1600 (N-H deformation pyrazolo ring), 1342 (C-N stretching of pyrazolo ring), 1155 (N-N deformation of pyrazolo ring), 1024 (C-H in plane bending of aromatic ring), 813 (C-H out of plane bending for 1,4-disubstituted aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 0.89-0.91 (d, 3H, H_a, J = 6.8 Hz), 1.04-1.06 (d, 3H, H_b, J = 6.9 Hz), 2.43-2.48 (m, 1H, H_c), 4.64 (s, 1H, H_d), 6.62 (s, 2H, H_e), 6.90-7.76 (m, 10H, $H_{ff'\text{-}jj'}$); MS: m/z 374; Anal. Calcd. for $C_{22}H_{19}FN_4O$: C,

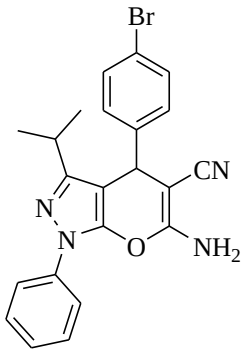
70.57; H, 5.11; N, 14.96. Found: C, 70.57; H, 5.11; N, 14.96%.

6-amino-4-(4-chlorophenyl)-1,4-dihydro-3-isopropyl-1-phenylpyrano[2,3-c]pyrazole-5-carbonitrile (4r)



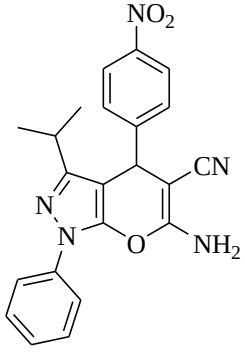
Yield: 83%; mp 142-144 ºC; MS: m/z 390; Anal. Calcd. for $C_{22}H_{19}ClN_4O$: C, 67.60; H, 4.90; N, 14.33. Found: C, 67.60; H, 4.90; N, 14.33%.

6-amino-4-(4-bromophenyl)-1,4-dihydro-3-isopropyl-1-phenylpyrano[2,3-c]pyrazole-5-carbonitrile (4s)



Yield: 67%; mp 200-202 ºC; MS: m/z 434; Anal. Calcd. for $C_{22}H_{19}BrN_4O$: C, 70.57; H, 5.11; N, 14.96. Found: C, 70.57; H, 5.11; N, 14.96%.

6-amino-1,4-dihydro-3-isopropyl-4-(4-nitrophenyl)-1-phenylpyrano[2,3-c]pyrazole-5-carbonitrile (4t)



Yield: 79%; mp 187-189 ºC; MS: m/z 401; Anal. Calcd. for $C_{22}H_{19}N_5O_3$: C, 65.83; H, 4.77; N, 17.45. Found: C, 65.83; H, 4.77; N, 17.45%.

III. RESULTS AND DISCUSSION

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 [12-15], antiviral [16, 17], anticonvulsant [18], cytotoxic [19] and antigenotoxic [20] activities. The incorporation of another heterocyclic moiety in pyrans either in the form of a substituent or as a fused component 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 [21], antipyretic [22], anti-inflammatory [23], anti-hypertansive [24], antitumour [25], peptide deformylase inhibitor [26], and antidepressant agents [27]. 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 [28-31]. Thus, pyranopyrazoles exhibit useful biological properties such as antimicrobial [32], insecticidal [33], and anti-inflammatory [34]. Furthermore Dihydropyrano [2,3-c]pyrazoles showed molluscicidal activity [35, 36] and was identified as a screening hit for Chk1 kinase inhibitor [37].

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 [38], 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 [39]. 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 [40]. 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 [41].

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-t) 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-t) 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 mixture refluxing under methanol gives 1,4-dihydropyrano[2,3-c]pyrazole derivatives. The products were characterized by FT-IR, mass, ^{1}H NMR spectroscopy and elemental analyses.

IV. CONCLUSION

This paper describes the applications of multicomponent one-pot synthesis and brief review of the reported synthetic strategies for the synthesis of pyranopyrazole derivatives. Pyranopyrazoles have been the subject of intense research due to the interesting pharmacological activities found for several of their derivatives. It 3 includes synthesis of thirty novel pyrano[2,3-c]pyrazoles, which 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.

V. REFERENCES

[1]. Newton, R. sp2 2002, 16; (see: http://www.sp2.uk.com)

[2]. (a) Teague, S. J.; Davis, A. M.; Leeson, P. D.; Oprea, T. I. Angew. Chem., Int. Ed. Engl. 1999, 38, 3743; (b) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. Acc. Chem. Res. 1996, 29, 123.

[3]. Domling, A.; Ugi, I. Angew. Chem., Int. Ed. Engl. 2000, 39, 3168.

[4]. Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. Chem. Eur. J. 2000, 6, 3321.

[5]. Orru, R. V. A.; de Greef, M. Synthesis 2003, 1471.

[6]. Tempest, P. A. Curr. Opin. Drug Discovery Dev. 2005, 8, 776.

[7]. Lehmann, F.; Holm, M.; Laufer, S. J. Comb. Chem. 2008, 10, 364.

[8]. Yuasa, Y.; Tsuruta, H.; Yuasa, Y. Org. Process Res. Dev. 1998, 2, 412.

[9]. Mendes, E.; Vernieres, J. C.; Keane, P. E.; Bachy, A. Eur. Patent EP A1 346208, 19891213, 1989.

[10]. Litvinov, Y. M.; Shestopalov, A. A.; Rodinovskaya, L. A.; Shestopalov, A. M. J. Comb. Chem. 2009, 11, 914.

[11]. Vogel's Textbook of Practical Organic Chemistry, Fifth Edition, ELBS, Longman Scientific and Technical: England. 1989, Reprinted 1994, 1150.

[12]. El-Agrody, A. M.; Abd El-Latif, M. S.; El-Hady, N. A.; Fakery, A. H.; Bedair, A. H. Molecule 2001, 6, 519.

[13]. Bedair, A. H.; El-Hady, N.A.; Abd El-Latif, M. S.; Fakery, A. H.; El-Agrody, A. M.; Il Farmaco 2000, 55, 708.

[14]. El-Agrody, A. M.; El-Hakim, M. H.; Abd El-Latif, M. S.; Fakery, A. H.; El-Sayed, E. M.; El-Ghareab, K. A, Acta. Pharm. 2000, 50, 111.

[15]. Eid, F. A.; Abd El-Wahab, A. H. F.; El-Hag Ali, G. A. M.; Khafagy, M. M. Acta. Pharm. 2004, 54, 13.

[16]. Perez-Perez, M.; Balzarini, J.; Rozenski, J.; De Clercq, E.; Herdewijn, P. Bioorg. Med. Chem. Lett. 1995, 5, 1115.

[17]. Shamroukh, A. H.; Zaki, M. E. A.; Morsy. E. M. H.; Abdel-Motti, F. M.; Abdel-Megeid, F. M. E. Arch. Pharm. 2007, 340, 236.

[18]. Aytemir, M. D.; Calis, U.; Ozalp, M. Arch. Pharm. 2004, 337, 281.

[19]. Melliou, E.; Magiatis, P.; Mitaku, S.; Skaltsounis, A. L.; Pierre, A.; Atassi, G.; Renard, P.; Bioorg. Med. Chem. 2001, 9, 607.

[20]. Chabchoub, F.; Messaad, M.; Mansour, H. B.; Chekir-Ghedira, L.; Salem, M. Eur. J. Med. Chem. 2007, 42, 715.

[21]. Regaila, H. A.; El-Bayonk, A. K. Hammad, M. Egypt J. Chem. 1979, 20,197.

[22]. Shafiee, A.; Bagheri, M.; Shekarchi, M.; Abdollahi, M.; J. Pharm. Sci. 2003, 6, 360.

[23]. Ren, X. L.; Li, H. B.; Wu, C.; Yang, H. Z. ARKIVOC 2005, 15, 59.

[24]. Almansa, C.; Gomez, L. A.; Cavalcanti, F. L.; de Arriba, A. F.; Garcia-Rafanell, J.; Forn, J. J. Med. Chem. 1997, 40, 547.
[25]. Park, H. J.; Lee, K.; Park, S. J.; Ahn. B.; Lee, J. C.; Cho, H.; Lee, K. Bioorg. Med. Chem. Lett. 2005, 15, 3307.
[26]. Cali, P.; Naerum, L.; Mukhija, S.; Hjelmencrantz, A. Biorg. Med. Chem. Lett. 2004, 14, 5997.
[27]. Prasad. Y. R.; Rao, A. L.; Prasoona, L.; Murali, K.; Kumar, P. R. Bioorg. Med. Chem. Lett. 2005, 15, 5030.
[28]. Mojtahedi, M. M.; Jalali, M. R.; Bolourtchian, M. Synth. Commun. 2006, 36, 51.
[29]. Pavlik, J. W.; Ervithayasuporn, V.; MacDonald, J. C.; Tantayanon, S. ARKIVOC 2009, 8, 57.
[30]. Guard, J. A. M.; Steel, P. J. ARKIVOC 2001, 7, 32.
[31]. Kanwal, P.; Gupta, V. K.; Brahmbhatt, D. I.; Patel, M. A. Analytical Sci. 2007, 23, 237.
[32]. Jin, T.; Zhao, R.; Li, T. ARKIVOC 2006, 11, 176.
[33]. El-Tamany, E. S.; El-Shahed, F. A.; Mohamed, B. H. J. Serb. Chem. Soc. 1999, 64, 9.
[34]. Ismail, Z. H.; Aly, G. M.; El-Degwi, M. S.; Heiba, H. I.; Ghorab, M. M. Egyp. J. Biot. 2003, 13, 73.
[35]. Zaki, M. E. A.; Soliman, H. A.; Hiekal, O. A.; Rashad, A. E. Z. Naturforsch C. 2006, 61, 1.
[36]. Abdelrazek, F. M.; Metz, P.; Metwally, N. H.; El-Mahrouky, S. F. Arch. Pharm. 2006, 339, 456.
[37]. Abdelrazek, F. M.; Metz, P.; Kataeva, O.; Jaeger, A.; El-Mahrouky, S. F. Arch. Pharm. 2007, 340, 543.
[38]. Foloppe, N.; Fisher, L. M.; Howes, R.; Potter, A.; Robertson Alan, G. S.; Surgenor, A. E. Bioorg. Med. Chem. 2006, 14, 4792.
[39]. Otto, H. H. Arch. Pharm. 1974, 307, 444.
[40]. Otto, H. H.; Schmelz, H. Arch. Pharm. 1979, 312, 478.
[41]. Klokol, G. V.; Krivokolysko, S. G.; Dyachenko, V. D.; Litvinov, V. P. Chem. Heterocycl. Compd. 1999, 35, 1183.