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Glycerol mediated, one pot, multicomponent synthesis of dihydropyrano[2,3-*c*]pyrazoles

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ABSTRACT

Multi component, one pot synthesis of various dihydropyrano[2,3-*c*]pyrazole derivatives from the condensation of ethyl acetoacetate, hydrazine, aromatic aldehyde and malononitrile has been described using glycerol, as environmentally benign, economical, and easily available solvent. The targeted molecules are obtained in excellent yield without use of any additional catalyst.

1. Introduction

The development of green methodologies with the choice of green solvents and solvents from renewable resources has gained much interest in recent years [1-5]. With this concern, use of water has attracted much attention [6-11], however water based processes are still subject to limitations due to solubility problems of highly hydrophobic substrates. On the other hand, excellent solvent properties like low toxicity (LD_{50} (oral rat) 12600 mg/kg), biodegradability, low-flammability, long liquid range (Boiling point 290 °C), low vapor pressure and solubility of polar organic compounds made the glycerol an excellent option to use as solvent for organic synthesis [12]. Further with the present emphasis and increasing demand of biodiesel, which is responsible for the excess production of glycerol as by-product, triggered the discovery of processes that use glycerol for the synthesis of value added chemicals, as reaction medium and for other applications [13-19]. Recently glycerol has been used for Heck and Suzuki coupling [20-22], Michael addition [23], Fridel-Crafts type addition, epoxide ring opening [24], synthesis of xanthenes [25] and very recently for the production of benzodiazepines and octahydroacridines [26,27].

In addition, pyranopyrazoles are important class of heterocyclic chemistry. Compounds containing pyranopyrazole scaffold are biological active and have applications as pharmaceutical ingredients and biodegradable agrochemicals [28-31]. Pyrano[2,3-c]pyrazole derivatives show many bioactivities such as antimicrobial [32], insecticidal [33], anti-inflammatory activities [34] and molluscicidal activity [35,36]. Pyrano[2,3-c]pyrazoles are known have application in screening kit for Chk1 kinase inhibitor [37,38] and also used as photoactive material [39].

These molecules can be synthesized by the reaction of pyrazol-5-one with tetracyanoethylene [28], arylidene malononitrile using catalysts like TEA [29-31]. In addition multi-component procedures have been developed using catalysts like DBSA [40], MgO [41], imidazole [42], β-cyclodextrin [43], $Ba(OH)_2$ [44]. The already reported procedures have many advantages over one another, but few methods have one or another drawback like solubility of reactants, tedious work-up procedures and hazardous regents or solvents. Therefore, development of clean and efficient procedure for the synthesis of dihydropyrano[2,3-c]pyrazoles is still timely. In the present paper, we have described a catalyst free, one pot, multicomponent protocol for the synthesis of dihydropyrano[2,3-c]pyrazoles using glycerol as an economical, easily available and environment friendly solvent (Scheme 1).

2. Experimental

2.1. Instrumentation

Materials were obtained from commercial suppliers and were used without further purifications. Melting points were recorded in open end capillaries and are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ solution on a Bruker Avance II 400 MHz spectrometer; chemical shifts (δ) are reported in ppm relative to TMS as internal standard. The IR spectra were recorded at Perkin-Elmer Spectrum II infra-red spectrophotometer.

2.2. Synthesis

2.2.1. General procedure for synthesis of 6-amino-4-(aryl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile

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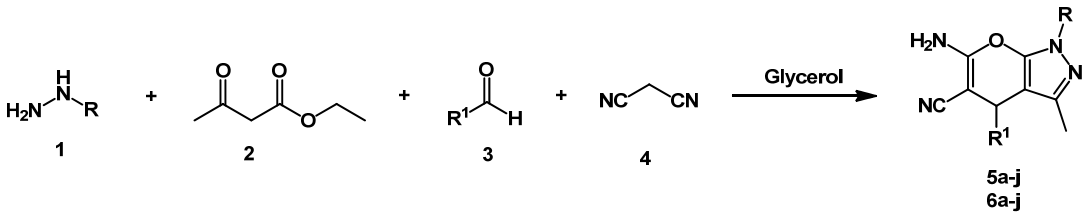


Scheme 1

In a conical flask, hydrazine hydrate (1 mmol), ethylacetoacetate (1 mmol), aldehyde (1 mmol) and malononitrile were added successively in glycerol (2 mL). Reaction mixture was stirred at 80 °C. After the completion of reaction (monitored by TLC), diluted the reaction mixture with ice cold water. Filtered the solid thus obtained and recrystallized with ethanol (Scheme 1).

6-Amino-5-cyano-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-c]pyrazole (**5a**): Color: White crystals. M.p.: 243-245 °C. FT-IR (KBr, ν, cm^{-1}): 3450, 3370, 3116, 2195, 1645, 1610, 1605, 1483, 1390, 1240, 1022, 860. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.80 (s, 3H, CH_3), 4.62 (s, 1H, CH), 6.95 (s, 2H, NH_2), 7.16-7.45 (m, 5H, Ar-H), 12.16 (br s, 1H, NH). Anal. calcd. for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N, 22.21. Found: C, 66.51; H, 4.70; N, 22.07%.

6-Amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**5b**): Color: White crystals. M.p.: 233-235 °C. FT-IR (KBr, ν, cm^{-1}): 3490, 3253, 2930, 2260, 1650, 1610, 1508, 1399, 1270, 1200, 1050, 750. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.78 (s, 3H, CH_3), 4.54 (s, 1H, CH), 6.59 (s, 2H, NH_2), 7.1-7.2 (m, 4H, Ar-H), 11.94 (br s, 1H, NH). Anal. calcd. for $C_{14}H_{11}N_4ClO$: C, 58.65; H, 3.87; N, 19.54. Found: C, 58.61; H, 3.80; N, 19.51%.

6-Amino-3-methyl-4-(3-nitrophenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**5f**): Color: White crystals. M.p.: 218-220 °C. FT-IR (KBr, ν, cm^{-1}): 3510, 3260, 2945, 2332, 1670, 1620, 1525, 1410, 1283, 1225, 1100, 950, 850. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.83 (s, 3H, CH_3), 4.80 (s, 1H, CH), 6.84 (s, 2H, NH_2), 7.5-8.1 (m, 4H, Ar-H), 12.09 (br s, 1H, NH). Anal. calcd. for $C_{14}H_{11}N_5O_3$: C, 56.56; H, 3.73; N, 23.56. Found: C, 56.60; H, 3.76; N, 23.51%.

6-Amino-5-cyano-4-(4-methoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole (**5h**): Color: White crystals. M.p.: 208-210 °C. FT-IR (KBr, ν, cm^{-1}): 3481, 3253, 2925, 2191, 1642, 1600, 1492, 1392, 1258, 1172, 1031, 870, 804, 565. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.75 (s, 3H, CH_3), 3.69 (s, 3H, OCH_3), 4.50 (s, 1H, CH), 6.83 (s, 2H, NH_2), 7.04-7.5 (m, 4H, Ar-H), 12.05 (br s, 1H, NH). Anal. calcd. for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 19.85. Found: C, 63.71; H, 5.15; N, 19.94%.

6-Amino-3-methyl-4-(4-methylphenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**5j**): Color: White crystals. M.p.: 240–242 °C. FT-IR (KBr, ν, cm^{-1}): 3492, 3250, 3150, 2930, 2200, 1620, 1595, 1508, 1410, 1260, 1180, 1050, 835. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.80 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 4.50 (s, 1H, CH), 6.57 (s, 2H, NH_2), 6.81-7.10 (m, 4H, Ar-H), 11.93 (br s, 1H, NH). Anal. calcd. for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found: C, 68.10; H, 5.20; N, 20.01%.

2.2.2. General procedure for synthesis of 6-amino-4-(aryl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile

In a conical flask, pheynyl hydrazine (1 mmol), ethylacetoacetate (1 mmol), were added in glycerol (2 mL) and stirred for 10 min at 80 °C. Then, aldehyde (1 mmol) and malononitrile were added successively and stirred the reaction mixture at the same temperature. After the completion of reaction (monitored by TLC), diluted the reaction mixture with ice cold water. Filtered the solid thus obtained and recrystallized with ethanol (Scheme 1).

6-Amino-5-cyano-3-methyl-1,4-diphenyl-1,4-dihydropyrano[2,3-c] pyrazole (**6a**): Color: White crystals. M.p.: 169-170 °C. FT-IR (KBr, ν, cm^{-1}): 3472, 3320, 2195, 1660, 1590, 1264, 1125, 1027, 753. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.93 (s, 3H, CH_3), 4.62 (s, 1H, CH), 6.99 (s, 2H, NH_2), 7.16-7.32 (m, 10H, Ar-H). Anal. calcd. for $C_{20}H_{16}N_4O$: C 73.15, H 4.91, N 17.06; Found C 73.19, H 5.01, N 17.10%.

6-Amino-4-(4-chlorophenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole (**6b**): Color: White crystals. M.p.: 175-176 °C. FT-IR (KBr, ν, cm^{-1}): 3468, 3325, 2200, 1662, 1596, 1390, 1262, 1122, 1016, 752. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.83 (s, 3H, CH_3), 4.51 (s, 1H, CH), 6.73 (s, 2H, NH_2), 6.75-7.90 (m, 9H, Ar-H). Anal. calcd. for $C_{20}H_{15}ClN_4O$: C 66.21, H 4.17, N 15.44; found C 66.26, H 4.19, N 15.52%.

6-Amino-4-(2-chlorophenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole (**6c**): Color: White crystals. M.p.: 143-145 °C. FT-IR (KBr, ν, cm^{-1}): 3472, 3324, 2194, 1656, 1592, 1389, 1264, 1125, 1028, 752. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.90 (s, 3H, CH_3), 4.52 (s, 1H, CH), 6.62 (s, 2H, NH_2), 6.9-7.6 (m, 9H, Ar-H). Anal. calcd. for $C_{20}H_{15}ClN_4O$: C 66.21, H 4.17, N 15.44; found C 66.26, H 4.22, N 15.48%.

6-Amino-4-(4-nitrophenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole (**6d**): Color: White crystals. M.p.: 195-197 °C. FT-IR (KBr, ν, cm^{-1}): 3430, 3340, 2192, 1665, 1596, 1354, 1124, 832, 754. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.80 (s, 3H, CH_3), 4.96 (s, 1H, CH), 6.98 (s, 2H, NH_2), 7.32-8.20 (m, 9H, Ar-H). Anal. calcd. for $C_{20}H_{15}N_5O_3$: C 64.34, H 4.05, N 18.76; found C 64.40 H 4.08, N 18.80%.

6-Amino-4-(3-nitrophenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole (**6f**): Color: White crystals. M.p.: 191-193 °C. FT-IR (KBr, ν, cm^{-1}): 3420, 3330, 2194, 1675, 1598, 1390, 1264, 1126, 1030, 752. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.82 (s, 3H, CH_3), 4.91 (s, 1H, CH), 7.40 (s, 2H, NH_2), 7.20-8.12 (m, 9H, Ar-H). Anal. calcd. for $C_{20}H_{15}N_5O_3$: C 64.34, H 4.05, N 18.76; found C 64.38 H 4.10, N 18.81%.

6-Amino-4-(4-hydroxyphenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole (**6g**): Color: White crystals. M.p.: 209-211 °C. FT-IR (KBr, ν, cm^{-1}): 3414, 3314, 2178, 1658, 1594, 1398, 1258, 1128, 1026, 754. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.78 (s, 3H, CH_3), 4.56 (s, 1H, CH), 7.12 (s, 2H, NH_2), 6.72-7.78 (m, 9H, Ar-H), 9.38 (s, 1H, OH). Anal. calcd. for $C_{20}H_{16}N_4O_2$: C 69.76, H 4.68, N 16.27; found C 69.82, H 4.72, N 16.31%.

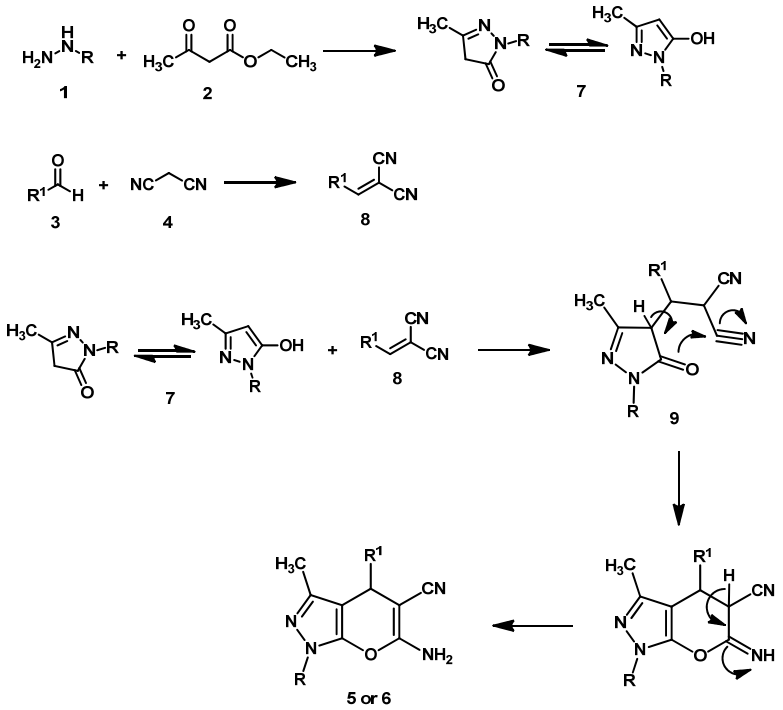
6-Amino-4-(4-methoxyphenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c] pyrazole (**6h**): Color: White crystals. M.p.: 175-177 °C. FT-IR (KBr, ν, cm^{-1}): 3395, 3322, 2192, 1660, 1595, 1394, 1250, 1128, 813. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.81 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 4.57 (s, 1H, CH), 7.2 (s, 2H, NH_2), 6.8-8.1 (s, 9H, Ar-H). Anal. calcd. for $C_{21}H_{18}N_4O_2$: C 70.38, H 5.06, N 15.63; found C 70.42, H 5.11, N 15.68%.

6-Amino-4-(4-methylphenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole (**6j**): Color: White crystals. M.p.: 140-142 °C. FT-IR (KBr, ν, cm^{-1}): 3414, 3314, 2178, 1658, 1594, 1398, 1258, 1128, 1026, 754. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.81 (s, 3H, CH_3), 2.1 (s, 3H, CH_3), 4.5 (s, 1H, CH), 6.85 (s, 2H, NH_2), 7.1-8.01 (m, 9H, Ar-H). Anal. calcd. for $C_{21}H_{18}N_4O$: C 73.67, H 5.30, N 16.36; found C 73.71, H 5.34, N 16.42%.

Table 1. Effect of solvent on the synthesis of compounds **5a** and **6a**.

Product	Yield, %[a]			
	EtOH	MeOH	Glycerol	CH_3CN
5a	87	88	93	80
6a	86	87	92	82

[a] Yield refers to pure isolated product.



Scheme 2

3. Results and discussion

At first, reaction between hydrazine **1**, ethyl acetoacetate **2**, benzaldehyde **3**, and malononitrile **4**, was carried out as a test reaction in different solvents like methanol, ethanol, acetonitrile and glycerol. Glycerol as solvent provides the good results as compared to other organic solvents (Table 1).

In a typical experimental procedure, a mixture of hydrazine hydrate (10 mmol, 0.5 g) **1**, ethyl acetoacetate (10 mmol, 1.30 g) **2**, benzaldehyde (10 mmol, 1.06 g) **3** and malononitrile (10 mmol, 0.66 g) **4** were added in glycerol (10 mL) and stirred in a pre-heated bath at 80 °C. After the completion of reaction (*vide* TLC), reaction mixture was cooled to room temperature and water (50 mL) was added. Solid thus separated was filtered and dried, recrystallized from ethanol to afford **5a**, 6-amino-5-cyano-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-c]pyrazole, in 93% yield, colorless crystals, melting point 243-245 °C. Structure of compound **5a** is confirmed by advanced spectroscopic techniques. In ^{1}H NMR spectrum, singlet is observed at δ 12.16 ppm for N-H proton and multiplet for five aromatic proton of phenyl ring is observed between δ 7.16-7.45 ppm and for NH_2 group, a signal is observed at δ 6.95 ppm and a singlet observed at δ 1.80 ppm represented -CH_3 group. In IR spectrum, N-H stretching is observed at 3370 cm^{-1} and CN stretching is observed at 2195 cm^{-1}.

To check the versatility of this process, we have reacted hydrazine hydrate/phenyl hydrazine, ethylacetoacetate, and malononitrile with different aldehydes and results are summarized in Table 2. Reactions proceed smoothly with aldehydes bearing electron withdrawing as well as electron donating substituents (Table 2). This method tolerates various functionalities like nitro, ether, halogen etc. on the aldehydes. Efficacy of this method is fairly general and afforded the resultant products in excellent yield and products are obtained by simple work up.

Taking into account the reports of the literature [32], we have proposed a route (Scheme 2) for the formation of compound **5** and **6**. In the first step, condensation of hydrazine and ethylacetoacetate take place to form **7** and Knoevenagal condensation take place between malononitrile and aldehyde to form arylidenepropanedinitrile **8**, then the Michael addition of compound **7** to **8** occur to form **9**. Then attack of nucleophilic oxygen of **9** on CN take place to form desired product **5** or **6**.

4. Conclusion

In conclusion, the present work provides an excellent route for the production of 6-amino-4-(aryl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile and 6-amino-4-(aryl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile without use of any hazardous reagent. In addition, use of environmentally benign, economical and easily available glycerol as solvent proves the merit of this protocol. The targeted molecules are obtained in excellent yield (86-93%) without any side product.

Acknowledgements

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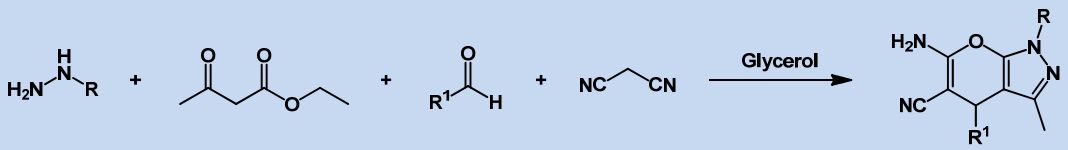
Table 2. Synthesis of 1,4-dihydropyrano[2,3-c]pyrazole derivative.



Sample no	Product [a]	R^1	R	Yield (%) [b]	Melting point (°C)
1	**5a**	C_6H_5	H	93	243-245
2	**5b**	4-Cl C_6H_5	H	92	233-235
3	**5c**	2-Cl C_6H_5	H	90	246-248
4	**5d**	4-$NO_2C_6H_5$	H	92	249-252
5	**5e**	2-$NO_2C_6H_5$	H	86	210-212
6	**5f**	3-$NO_2C_6H_5$	H	90	218-220
7	**5g**	4-OHC_6H_5	H	90	202-204
8	**5h**	4-$OMeC_6H_5$	H	92	208-210
9	**5i**	C_6H_5CH=CH	H	88	200-202
10	**5j**	4-MeC_6H_5	H	89	240-242
11	**6a**	C_6H_5	Ph	92	169-170
12	**6b**	4-Cl C_6H_5	Ph	91	175-176
13	**6c**	2-Cl C_6H_5	Ph	88	143-145
14	**6d**	4-$NO_2C_6H_5$	Ph	87	195-197
15	**6e**	2-$NO_2C_6H_5$	Ph	89	199-200
16	**6f**	3-$NO_2C_6H_5$	Ph	91	191-193
17	**6g**	4-OHC_6H_5	Ph	90	209-211
18	**6h**	4-$OMeC_6H_5$	Ph	92	175-177
19	**6i**	C_6H_5CH=CH	Ph	87	140-142
20	**6j**	4-$CH_3C_6H_4$	Ph	89	176-177

[a] Products were characterized with spectral techniques and compared with authentic samples.
[b] Yield refers to pure isolated product.

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