Synthesis And Spectral Characterization of 4-Pyrazole Substituted Pyrano Pyrazole Derivatives

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Abstract- *A series of substituted pyrano [2, 3-C] Pyrazole derivatives were synthesized by the one pot reaction of pyrazole aldehydes, malononitrile, hydrazine hydro chloride and ethyl aceto acetate under microwave irradiaton in good yields. MCRs are powerful tools in the modern drug discovery process and allow the fast, automated, and high through put generation of organic compounds.The main objectives of the present study are to synthesis a series of pharmaceutically interesting pyrano pyrazole derivatives via a sample, straight forward and multi component reaction and to characterize the synthesized compounds by* ^{1}*H-NMR,* ^{13}*C-NMR, MASS spectroscopy, and Elemental Analysis.*

Keywords- Pyrazolealdehydes, malononitrile, hydrazinehydro chloride and ethyl aceto acetate synthesis.

I. INTRODUCTION

Multi component reaction [MCR] are powerful tools in the modern drug discovery process and allow the fast, automated, and high throughput generation of organic compounds in the fast years the pharmaceutical industry has focused more and more on diversity – oriented and biased combinatorial libraries –furthermore, the discovery of novel MCRs can be considered and an interesting topic for academic research that also satisfies a practical interest of applied science.

The major advantages of MCR include lower costs, shorter reaction times, high-atom, economy, energy savings and the avoidance of time consuming and expensive purification process. It is established that MCRs are generally much more environmentally Friendly. And offer rapid access to large compound libraries with diverse functionalities.

As part of our efforts to develop new synthetic methods in heterocyclic chemistry, herein we report for the first time, a catalyst-free , four component reaction of pyrazolealdehyde, hydrazine di hydro chloride, ethyl aceto acetate, and malononitrile for the synthesis of novel substituted pyrano [2,3-c] pyrazoles.

Pyranopyrazoles are fused heterocyclic compounds that exhibit a wide range of biological activities such as anti-inflammatory activities, and anti-cancer agents.

Encouraged by these results, we further investigate MCRs in order to construct heterocyclic by using different reaction conditions.

II. EXPERIMENTAL

Scheme1

Synthesis of 6 amino 4-(1, 3-di phenyl -1Hpyrazol-4-yl) -3-methyl -2, 4-dihydro pyrano [2, 3-c] pyrazole-5-carbonitrile.

The mixture of hydrazine hydrochloride (0.169g) ,malononitrile(0.106g),ethyl aceto acetate(0.209g), pyrazole aldehyde(1) (0.4g) in presence of ethyl acetate (10ml) was stirred for 3 hrs., completion of the reaction was confirmed by TLC .The solid formed was separated by filtration and purified by recrystallization from ethanol: petroleum ether (20%) mixture to afford a pure yield.

Scheme 2

Synthesis of 6amino-4-(3-(4-chlorophenyl)-phenyl-1H-pyrazol-4-yl) 3 methyl 2,4dihydropyrano [2,3-c] pyrazole-5-Carbonitrile.

The mixture of phenylhydrazine (0.19g) ,malononitrile(0.16g),ethyl aceto acetate(0.29g), pyrazole aldehyde(2) (0.4g) in presence of ethyl acetate (10ml) was stirred for 3 hrs., completion of the reaction was confirmed by TLC .The solid formed was separated by filtration and purified by recrystallization from ethanol: petroleum ether (20%) mixture to afford a pure yield.

Scheme 3

Synthesis of 6amino4-(3-(4-bromophenyl-1-phenyl-1H-pyrazol-4-yl)-methyl 2, 4dihydropyrano [2, 3-c] pyrazole-5-carbonitrile.

The mixture of phenylhydrazine (0.19g) ,malononitrile(0.115g),ethyl aceto acetate(0.30g), pyrazole aldehyde(3)(0.4g) in presence of ethyl acetate (10ml) was stirred for 3 hrs., completion of the reaction was confirmed by TLC .The solid formed was separated by filtration and purified by recrystallization from ethanol: petroleum ether (20%) mixture to afford a pure yield.

III. MATERIALS AND METHODS

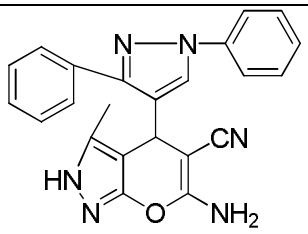
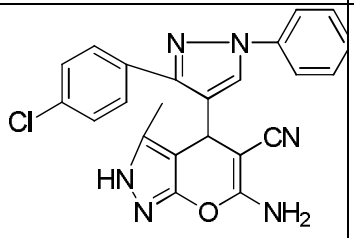
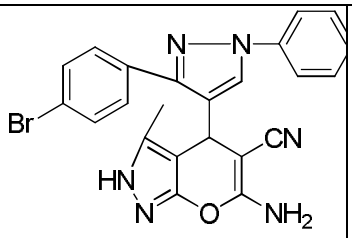
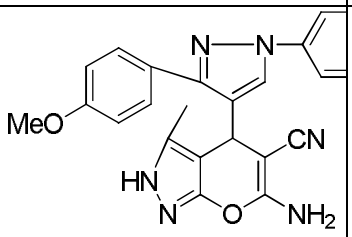
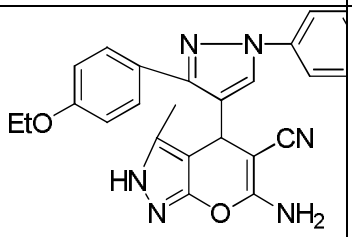
ANALYTICAL TECHNIQES USED

Infrared spectra were recorded on Perkin- Elmer FT-IR spectra photometer using KBr pellet and the wave number with constant cell (2mm) was recorded in (cm^{-1}).

^{1}H and ^{13}C spectra were recorded on a JEOL NMR 400MHz spectra photometer in DMSO solutions. Chemical shifts are reported in parts per million (ppm) relative to tetra methyl silane (TMS) as an internal standard and coupling constant (J) are given in hertz (HZ), with respect to 500MHz, 300MHz ,125MHz.

Analytical TLC one pre- coated aluminum sheets of silica gel of 0.25 nm thickness and spots are visualized using HEBER- UV viewer.

Table 1. Condensation of pyrazole aldehydes, malononitrile, phenyl hydrazineand ethyl aceto acetate in EtOH with no catalyst under ultrasound irradiatio

S.NO	PRODUCT	YIELD %	TIME
1.		98	2 hrs.
2.		95	2 hrs.
3.		97	3 hrs.
4.		96	3hrs.
5.		98	2 hrs.

6 amino 4-(1, 3-di phenyl -1H-pyrazol-4-yl)-3-methyl-2, 4-dihydro pyrano [2, 3-c] pyrazole-5-carbonitrile.

Rfvalue:0.35(10%EA:PE)**IR(ν_{max}cm^{1})**:3234,3115,3100,3056, 2950,213234,31160,1800,1675,1623,1450,1360,1230,1060.**^{1}H NMR(400MH$_Z$,DMSO)**1.96(s,3H),4.72(s,1H),7.3(s,1H)7.527 .71(m,5H),7.547.62(m,5H),8.55(s,2H),12.0(s,1H).**^{13}CNMR(4 00MH$_Z$,DMSO)δ:**14.0,21.5,59.6,112.3,113.0,117.4,118.3,119 ,119.4,120,121.3,123,125,126,127,128,129,129.5,133,134.3,1 39,163.**Mass:M/e:**380.14**ElementalAnalysis**:C,70.04,H;4.60; N, 21.29; O, 4.06.**Found**: C,70.02; H,4.58; N,21.29; O,4.02.

Rfvalue0.40(10%EA:PE)**IR(ν_{max}cm^{1})**:3233,3116,3102,3058,2 952,2161,1160,1802,1676,1625,1452,1361,1233,1064.**^{1}HNM R(400MHzDMSO)δ:**1.93(s,3H),4.71(s,1H),7.4(s,1H)7.517.7 3(m,5H),7.53-7.64(m, 5H), 7.56(d,2H)7.97(d,2H)8.53(s,2H),12.2(s,1H)**^{13}CNMR(400MH zDMSOδ:**14.2,21.3,59.5,112.4,113.1,117.5,118.2,117.3,118,1 19.3,121,122,122.5,123,125,126,127,129.3,131,134,137,160. **Mass:m/e:**458.0**ElementalAnalysis**:C,57.53;H,3.29;Br,17.40; N,18.30;O.3.48.
Found:C, 57.52; H, 3.27; Br, 17.39; N, 18.28; O.3.46

Rfvalue:0.40(10%EA:PE)**IR(ν_{max}cm^{1})**:3233,3116,3102,3058, 2952,2161,1160,1802,1676,1625,1452,1361,1233,1064.**^{1}HN MR(400MHzDMSO)δ:**1.93(s,3H),4.71(s,1H),7.4(s,1H)7.517. 73(m,5H),7.537.64(m,5H),7.56(d,2H)7.97(d,2H)8.53(s,2H),12 .2(s,1H)**^{13}CNMR(400MHzDMSOδ:**14.2,21.3,59.5,112.4,113.

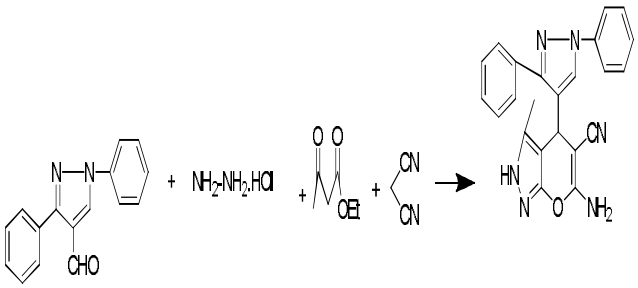
1,117.5,118.2,117.3,118,119.3,121,122,122.5,123,125,126,127,129.3,131,134,137,160.**Mass:m/e:**458.05**ElementalAnalysis**:C,57.53;H,3.29;Br,17.40;N,18.30;O.3.48.**Found:**C, 57.52; H, 3.27; Br, 17.39; N, 18.28; O.3.46.

Rfvalue:0.42(10%EA:PE)**IR(ν_{max}cm^{1})**:3236,3117,3105,3059,2955,2164,1165,1804,1677,1626,1454,1360,1235,1067.**^{1}HNMR(400MHzDMSO)δ:**1.94(s,3H),3.82(s,3H)4.74(s,1H),7.5(s,1H)7.55-7.70(m, 5H), 7.54-7.66(m,5H),7.57(d,2H)7.99(d,2H)8.54(s,2H),12.5(s,1H)**^{13}CNMR(400MHzDMSOδ:**14.5,21.6,59.8,112.0,113.3,117.7,118.4,117.5,120,120.3,123124,124.5,125,126,127,128,130.3,132,135,139,161.**Mass:m/e:**410.15**Elemental Analysis**: C, 67.31; H, 4.42; N, 20.48; O, 7.80.**Found:**C, 67.30; H, 4.41; N, 20.46; O, 7.79

Rfvalue:0.45(10%EA:PE)**IR(ν_{max}cm^{1})**:3237,3119,3107,3060,2958,2169,1168,1809,1680,1630,1459,1363,1237,1068.**^{1}HNM(400MHDMSO)δ:**1.33(d,3H)1.97(s,3H),3.86,3H),4.08(q,2H),4.75(s,1H),7.6(s,1H)7.547.65(m,5H),7.557.67(m,5H),7.59(d,2H)7.98(d,2H)8.56(s,2H),12.6(s,1H)**^{13}CNMR(400MHzDMSOδ:**14.8,21.7,59.9,112.2,113.4,117.5,118.6,117.7,121,121.3,122125,125.5,126,127,128,129,130.5,133,136,140,163.**Mass:m/e:**438.18**ElementalAnalysis**:C,67.91;H,4.75;N,19.80;O,7.54.**Found:**C, 67.90; H, 4.74; N, 19.78; O, 7.52

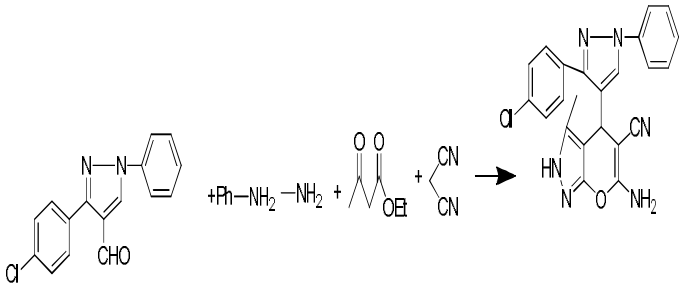
IV. RESULTS AND DISCUSSION

Although polyheterocycles can be obtained from well-chosen starting materials, a Knoevenagel based reaction was recently reported for the simultaneous construction of two different fused heterocycles from acyclic precursors. In fact, a four component Knoevenagel–Michael additioncyclization sequence has been studied for the synthesis of dihydro pyrano [2,3C]pyrazole5carbonitrilederivatives.fromhydrazinehydrate, malononitrile, ethyl aceto acetate and pyrazolealdehyde.



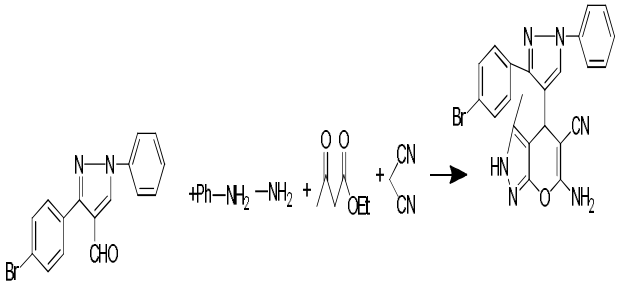
1

Synthesis of 6 amino 4-(1, 3-di phenyl -1Hpyrazol-4-yl) -3-methyl -2, 4-dihydro pyrano [2, 3-c] pyrazole-5-carbonitrile.



2

Synthesis of6amino-4-(3-(4-chlorophenyl)-phenyl-1H-pyrazol-4-yl)3methyl 2,4dihydropyrano [2,3-c] pyrazole-5-Carbonitrile.



3

Synthesis of6amino4-(3-(4-bromophenyl-1-phenyl-1H-pyrazol-4-yl)-methyl 2, 4dihydropyrano [2, 3-c] pyrazole-5-carbonitrile.

V. CONCLUSION

A simple straightforward, and highly efficient multicomponent one-pot synthesis of series of pharmaceutically interesting pyrano pyrazole derivatives have been developed based on a low cost and environmentally begin via tandem reaction of hydrazine dihydro chloride, malononitrile, pyrazole aldehyde, and ethyl aceto acetate in ethyl acetate at room temperature.

High atom –economy good yields, eco-friendliness, and mild reaction conditions are some of the important features of this protocol .the synthesized compounds were characterized by ^{1}H-NMR, ^{13}C-NMR, MASS spectroscopy, and Elemental Analysis.

VI. ACKNOWLEDGEMENT

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