Solvent Free Synthesis Of Pyrano[2,3-c]pyrazoles Derivatives By Green Protocol Using NMPyTs.

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Abstract : An efficient, green and facile multi-component one pot synthesis of Pyrano [2, 3-c] pyrazoles has been described on reaction with various aryl aldehyde, malononitrile, ethyl acetoacetate, hydrazine hydrate under solvent free condition using ionic liquid (NMPyTs) as a catalyst. This protocol offers the significant advantages in terms of simplicity, very good yields, simple workup procedure, short reaction time no need of purification and this method is eco-friendly benign. This work focused on the recent developments in multicomponent synthesis of Pyrano [2,3-c]pyrazole and its derivatives. The structures of prepared derivatives were confirmed using their IR, 1HNMR, 13CNMR and ESI-MS spectroscopic method.

Key words: Benzaldehyde, malononitrile, ethylacetoacetate, hydrazine hydrate, Ionic liquid, Grinding, Pyrano [2, 3-c] pyrazoles derivatives.

I. INTRODUCTION

The recent years is the modern year of the green chemistry, more and more chemists are devoted to the research of the 'green synthesis' which means the reagent, solvent and catalyst are environmental friendly. Multi-component reactions have great contribution in organic synthesis of compounds and important organic molecules from simple and easily available starting materials, and have powerful resources for drug discovery **[1].**

Pyrano [2, 3-c] pyrazole moieties are the biologically important platform because of their wide application in medicinal chemistry. These moieties have anti-cancer**[2] ,** anti-inflammatory**[3]** anti-microbial**[4]**, fungicidal**[5],** insecticidal**[6],** molluscicidal[7], analgesic**[8]**, antiviral**[9]** , antidepressant**[10]**. A large number of catalysts reported for this transformation at various reaction conditions those catalyst are $(KF.H_2O)$**[11]**, (DBSA)**[12]**, (TEBA)**[13]**, (NaOH)**[14]**, [binim]OH**[15]**, $(SAB\text{-}Pr\text{-}NH_2)$**[16]**, (β-cyclodextrine-SO_3H**[17]**, [Hmim][H_2SO_4]**[18]** and many more paper was published on this moiety by using different solvent, catalyst, and methods.

Our work to developed biologically important Pyrano[2, 3-c] pyrazole by a new synthetic method, a detailed literature survey revealed that only few numbers of grinding methods published for synthesis of Pyrano[2, 3-c] pyrazole**[19]**.The above mentioned results indicate that NMPyTs (ionic liquid) as a catalyst proved to be an efficient catalyst for this conversion. The catalyst NMPyTs was prepared from the reported method **[20].** The present work describe synthesis of Pyrano[2, 3-c] pyrazole derivatives of substituted aryl aldehyde, malononitrile, ethyl acetoacetate and hydrazine hydrate in the presence of catalytic amount of N-methyl pyridinium toluene sulfonate (NMPyTs) as a green and reusable ionic liquid under solvent free condition (scheme-I).

II. Experimental:-

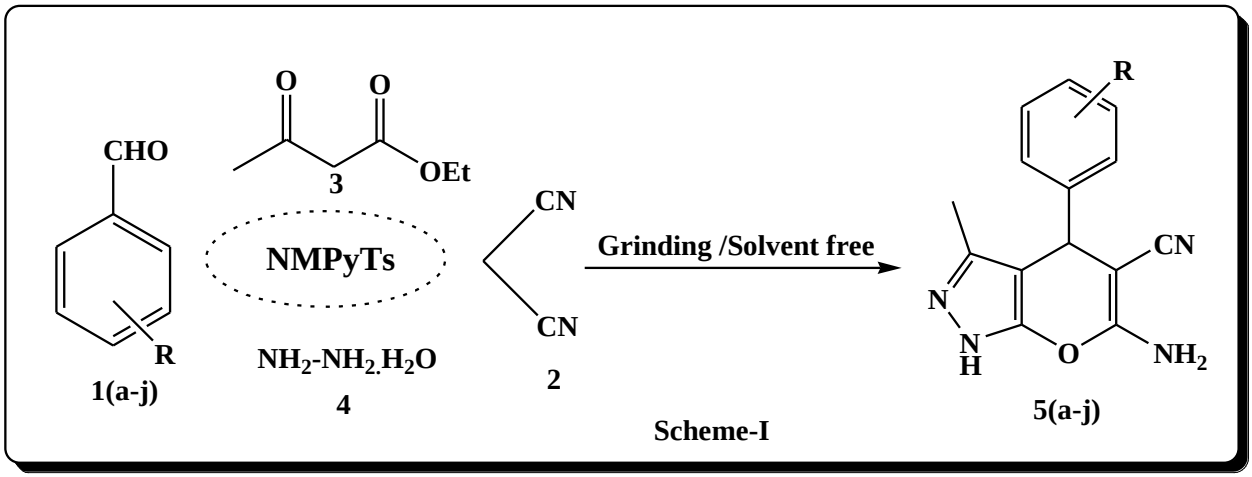
Generals

All chemicals were purchased and used without any further purification. Reactions were monitored by thin layer chromatography on silica gel plates visualizing with Iodine Chamber. Melting points were recorded in open capillary tubes. ^1H NMR were recorded on a Bruker Advance 400 MHz and ^{13}C NMR were recorded on a Bruker DRX 100 MHz spectrometer. Chemical shift values δ/ppm are expressed in (parts per million) ppm relative to TMS. Mass spectra were recorded on a macro mass spectrometer by ESI method.

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

A mixture of substituted aryl aldehyde 1(1mmol), malononitrile 2(1mmol), ethyl acetoacetate 3(1mmol), and hydrazine hydrate 4(1mmol) in boiled (120 ºC) Ionic Liquid (NMPyTs) 3% mol was added in mortar and ground. The reaction mixture was grinding until completion of the reaction monitored by TLC (ethyl acetate-hexane, 2:8). When the reaction were completed then the reaction mixture takes place ice cold water and stirred for 15-20 min. The crude product was collected by simple filtration, washed with water and dried. The entire product were characterised by physical constant and crystallization.

Scheme I



III. Result and Discussion:-

To demonstrate the superiority of the present work in comparison with previous reported results in the synthesis of Pyrano [2,3-c] pyrazole derivatives (Table-I). It is evident that NMPyTs can act as an effective catalyst with respect to reaction times and yields of the product (5a-j, scheme I). There are many methods in decade to prepared Pyrano [2, 3-c] pyrazole derivatives by using different solvent, catalyst, and condition (Table 1). From all the observation and methods we reports simple and facile synthesis of Pyrano [2, 3-c] pyrazole derivatives by treatment of equimolar mixture of aryl aldehyde, malononitrile, ethyl acetoacetate, and hydrazine hydrate catalyzed by NMPyTs (ionic liquid) under solvent free condition by grinding method (Scheme I, Table1).

Table 1:- Comparison of the results of NMPyTs with those of other catalysts reported in the literature in the synthesis of Pyrano [2, 3-c] pyrazole derivatives.

Entry	Catalyst	Solvent	Condition	Time (min)	Yield(%)[b]	Year
1	No Catalyst	H_2O	Grinding	40	40-45	-
2	$KF.2H_2O$	-	Grinding	90	71-93	2005
3	DBSA	H_2O	Reflux	180	82-94	2006
4	TEBA	-	R.T.	50	87-97	2010
5	NaOH	H_2O	Reflux	60	90-92	2011
6	[binim]OH	-	Reflux	60	87-91	2012
7	SAB-Pr-NH_2	EtOH	R.T.	120	85-90	2015
8	β-cyclodextrin-SO_3H	H_2O	Reflux	30	90-93	2015
9	[Hmim][H_2SO_4]	EtOH	Stirring	30	90-92	2016
10	NMPyTs	EtOH:H_2O	Stirring	15	91	2017
11	NMPyTs	Solvent free	Grinding	10	80-95	[a]Present work

[a]*Reaction condition*: Substituted aromatic aldehyde (1mmol), malononitrile (1mmol), ethyl acetoacetate (1mmol), hydrazine (1mmol), in catalytic amount of Ionic liquid.

Our initial work started with screening of solvent because of one important aspect of good synthesis is the elimination of solvent in chemical processes or the replacement of hazardous solvent. Here we investigated different solvent (Table 2) in the above reaction and performed the model reaction. First we tried the solvent CH_3CN it got the 70 % yield in 45 min, when solvent THF, it got the 78% yield in 40 min, when solvent DMF, it got the 80% yield in 55 min, when solvent CH_2Cl_2, it got the 85% yield in 35 min, when solvent EtOH, it got the 90% yield in 25 min, but when we performed the solvent free reaction in catalytic amount of NMPyTs then we got the 95% of yield in only 7-15 min(Table 2, Entry 6).

Table 2: Optimization of solvent

Entry	Solvent	Time (min)	% of yield
1	CH_3CN	45	70
2	THF	40	78
3	DMF	55	80
4	CH_2Cl_2	35	85
5	ETOH	25	90
6	No Solvent	7-15	95

[a]*Reaction condition*: Substituted aromatic aldehyde (1mmol), malononitrile (1mmol), ethyl acetoacetate (1mmol), hydrazine (1mmol), in catalytic amount of Ionic liquid.

We also investigated and performed the model reaction (scheme I) by treating equimolar mixture of (Substituted aryl aldehyde) for eg. 4-chloro benzaldehyde, malononitrile, ethylacetoacetate and hydrazine hydrate without any solvent and catalyst and it was found that, the reaction was not possible because no product was formed in large time i.e. 90 min (Table 3, Entry 1). As the reaction required a catalyst, we perform the reaction using 1 mol% NMPyTs without any solvent and the result declared that the reaction was possible with moderate yield (Table3, Entry 2). To improve the % of yield of the product in the absence of solvent, we continued our efforts by changing the mol% i.e. 1% to 5 % mol and performed the model reaction. We observed that 3% mol of catalyst was satisfactorily done the reaction, because of it got the 90% yield in 10 min (Table3 Entry 4). We observed also that increases the mol % of catalyst i.e. 4%, 5% and above, then % of yield of product decreases and time was increases (Table 3 Entry 4, 5). From this investigation we observed that 3% mol of NMPyTs catalyst is very remunerative for the model reaction.

Table 3: Optimization of the catalytic amount of NMPyTs for model reaction

Entry	Catalyst	Time (min)	% of yield
1	No catalyst	90	00
2	1 % mol	55	65
3	2% mol	30	85
4	**3**% mol	**10**	**90**
5	4% mol	20	82
6	5% mol	35	75

[a]*Reaction condition*: Substituted aromatic aldehyde (1mmol), malononitrile (1mmol), ethyl acetoacetate (1mmol), hydrazine (1mmol), in catalytic amount of Ionic liquid.

Varying the reactivity in the % of catalyst showed that 3% mol of NMPyTs is the favorable and fetching catalyst for the model reaction (Table-3). By this modification in the model reaction, we were synthesized 5a-5j derivatives. (Table 4)

Table 4: Synthesized of 6-amino-4-aryl-3-1,4-dihydropyrano [2,3-c] pyrazole-5-carbonitrile derivatives (5a-j)

Entry	R	Time (min)	% of yield	Melting Pt. (°C)	
				Found	Lit.[ref]
5a	H	15	80	243	245-246[21]
5b	4-Cl-	10	90	233	234-235[22]
5c	2-Cl-	14	88	212	--
5d	4-OH-	11	90	225	223-224[23]
5e	4-OMe-	13	86	215	212-213[23]
5f	4-Br-	10	92	190	188-190[23]
5g	3-NO_2-	12	82	230	232-233[22]
5h	**4-NO_2-**	**7**	**95**	**250**	**251-252[22]**
5i	4-CH_3-	14	85	200	197-198[22]
5j	4-F-	12	87	192	190-192[23]

[a]*Reaction condition*: Substituted aromatic aldehyde (1mmol), malononitrile (1mmol), ethyl acetoacetate (1mmol), hydrazine (1mmol), in catalytic amount of Ionic liquid.

Spectral data of synthesized compounds (5a-5j)

1)6-amino-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5a)
White solid powder, M. Pt. 243 (°C)
IR(KBr cm^{-1}): 3455, 3367, 3113, 2188, 1650, 1612, 1609, 1487, 1390, 1245, 1034, 855.^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm): 1.78(s, 3H, CH_3), 4.65(s, 1H, CH), 6.90 (s, 2H, NH_2), 7.13-7.42 (m, 5H, Ar-H), 12.18(s, 1H, NH), ^{13}C NMR (100 MHz,$CDCl_3$ δ/ppm): 12.0, 25.5, 70.0, 112.8, 126.5, 127.6, 129.7, 140.0, 140.5, 155.3, 161.1. ESI-MS data: m/z =253[M^+]
2) 6-amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5b)
White solid powder, M.Pt.233(°C)
IR(KBr cm^{-1}): 3482, 3260, 2941, 2255, 1645, 1612, 1512, 1393, 1267, 1205, 1056,755.^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm):1.80(s, 3H, CH_3), 4.55(s, 1H, CH), 6.95 (s, 2H, NH_2), 7.15-7.40 (m, 4H, Ar-H), 12.3(s, 1H, NH), ^{13}C NMR (100 MHz,$CDCl_3$ δ/ppm): 11.6, 24.5, 70.6, 112.2, 126.6, 127.9, 130.3, 141.2, 143.0, 158.3, 160.1. ESI-MS data: m/z =364[M^+]
3)6-amino-4-(2-chlorophenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile(5c)
White solid powder, M.Pt.212(°C)
IR(KBr cm^{-1}): 3478, 3257, 2944, 2258, 1649, 1617, 1513, 1390, 1266, 1212, 1055,745.^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm):1.82(s, 3H, CH_3), 4.59(s, 1H, CH), 6.98 (s, 2H, NH_2), 7.10-7.35 (m, 4H, Ar-H), 12.1(s, 1H, NH), ^{13}C NMR (100 MHz,$CDCl_3$ δ/ppm): 11.9, 24.8, 70.1, 114.2, 128.6, 125.9, 133.3, 143.2, 141.0, 156.3, 159.1. ESI-MS data: m/z =364[M^+]
4)6-amino-4-(4-hydroxyphenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5d)
White solid powder, M. Pt. 225(°C)
IR(KBr cm^{-1}): 3470,3450, 3250, 2940, 2268, 1657, 1615, 1510, 1394, 1260, 1215, 1060,.^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm):1.72(s, 3H, CH_3), 4.49(s, 1H, CH), 6.80 (s, 2H, NH_2), 6.60-6.98 (m, 4H, Ar-H), 11.9(s, 1H, NH), 12.5 (s, 1H, OH)^{13}C NMR (100 MHz,$CDCl_3$ δ/ppm): 12.1, 25.8, 71.1, 113.2, 120.6, 126.9, 131.3, 142.5, 143.0, 154.3, 156.1. ESI-MS data: m/z =270[M^+]
5)6-amino-4-(4-methoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile(5e)
Light yellow solid powder, M. Pt. 215(°C)

IR(KBr cm^{-1}): 3478, 3252, 2930, 2198, 1650, 1609, 1500, 1396, 1255, 1180, 1030,877,800,560.^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm):1.77(s, 3H, CH_3)3.67(s, 3H OCH_3), 4.48(s, 1H, CH), 6.70 (s, 2H, NH_2), 6.80-7.40 (m, 4H, Ar-H), 12.3(s, 1H, NH). ^{13}C NMR (100 MHz,$CDCl_3$ δ/ppm): 11.4, 24.8, 55.6, 70.3, 114.2, 115.6, 127.2, 139.3, 143.5, 143.9, 155.3, 160.1. ESI-MS data: m/z =283[M^+]

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

Light yellowish solid powder, M.Pt.190 (°C)

IR(KBr cm^{-1}): 3480, 3252, 2940, 2253, 1647, 1611, 1514, 1394, 1269, 1216, 1057,745.^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm):1.80(s, 3H, CH_3), 4.51(s, 1H, CH), 6.93 (s, 2H, NH_2), 6.900-7.30 (m, 4H, Ar-H), 12.3(s, 1H, NH), ^{13}C NMR (100 MHz,$CDCl_3$ δ/ppm): 11.3, 24.2, 70.4, 114.0, 129.0, 126.0, 133.7, 143.5, 142.0, 158.3, 160.1. ESI-MS data: m/z =330[M^+]

7)6-amino-3-methyl-4-(3-nitrophenyl)-1,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile(5g)

Brown solid powder, M.Pt.230 (°C)

IR(KBr cm^{-1}): 3380, 3272, 2940, 2283, 1632, 1451, 1410,.^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm):1.85(s, 3H, CH_3), 4.90(s, 1H, CH), 7.14 (s, 2H, NH_2),7.90(s, 1H Ar-H) 8.15-8.10 (m, 4H, Ar-H), 12.18(s, 1H, NH), ^{13}C NMR (100 MHz,$CDCl_3$ δ/ppm): 11.5, 23.2, 70.6, 112.9, 127.7, 126.4, 130.7, 133.5, 135.3, 150.3,154.6, 160.3. ESI-MS data: m/z =298[M^+]

8)6-amino-3-methyl-4-(4-nitrophenyl)-1,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile(5h)

Brown solid powder, M.Pt.250 (°C)

IR(KBr cm^{-1}): 3383, 3275, 2190, 1625, 1466, 1412.^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm):1.75(s, 3H, CH_3), 4.40(s, 1H, CH), 7.64 (s, 2H, NH_2), 7.80-8.10 (m, 4H, Ar-H), 12.6(s, 1H, NH), ^{13}C NMR (100 MHz,$CDCl_3$ δ/ppm): 11.8, 23.4, 70.2, 112.7, 127.9, 126.1, 130.3, 135.4, 141.7, 150.6,154.1, 160.5. ESI-MS data: m/z =298[M^+]

9)6-amino-3-methyl-4-p-tolyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile(5i)

White solid powder, M.Pt.200 (°C)

IR(KBr cm^{-1}): 3489, 3265, 3160, 2939,2010,1625, 1599, 1510, 1412, 1272,1187,1055,840.^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm):1.78(s, 3H, CH_3),2.30(s, 3H CH_3) 4.46(s, 1H, CH), 6.64 (s, 2H, NH_2), 6.60-6.99 (m, 4H, Ar-H), 12.9(s, 1H, NH), ^{13}C NMR (100 MHz,$CDCl_3$ δ/ppm): 11.3, 22.2, 71.4, 112.4, 117.2, 128.1, 129.5, 135.7, 141.3, 144.6,154.3, 160.0. ESI-MS data: m/z =267[M^+]

10) 6-amino-4-(4-fluorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile(5j)

White solid powder, M.Pt.192 (°C)

IR(KBr cm^{-1}): 3484, 3265, 2939, 2259, 1643, 1616, 1519, 1390, 1269, 1215, 1102, 1075.^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm):1.83(s, 3H, CH_3), 4.56(s, 1H, CH), 6.90 (s, 2H, NH_2), 7.10-7.50 (m, 4H, Ar-H), 12.4(s, 1H, NH), ^{13}C NMR (100 MHz,$CDCl_3$ δ/ppm): 11.7, 24.9, 71.6, 112.8, 126.2, 127.3, 130.9, 141.5, 143.3, 159.3, 161.4. ESI-MS data: m/z =270[M^+]

IV. Conclusion

In conclusion, Environmentally begin one pot strategy has been discover with the catalyst ionic liquid (NMPyTs), successfully which generate green platform for the synthesis of Pyrano[2-3 C] pyrazole derivatives with good yield under solvent free condition using substituted aryl aldehyde, malononitrile, ethylacetoacetate and hydrazine hydrate. Operational simplicity, solvent free approach, simple workup, high % of yield, neat and clean synthesis is notable advantages of this protocol.

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