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DBU Catalyzed One Pot Four-Component Synthesis of Pyrano Pyrazole Derivatives with their Antioxidant Activity

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ABSTRACT

A green, efficient and simple procedure has been developed for the synthesis of Pyrano [2,3-*c*] Pyrazoles from a one pot four component condensation of Ethylacetoacetate, Malononitrile, Hydrazine hydrate and different substituted aromatic Aldehydes using 1,8-diazabicyclo [*5.4.0*] undec-7-ene (DBU) as catalyst in ethanol-water. The synthesized Pyrano [2,3-*c*] Pyrazoles were screened for their Antioxidant activity. These newly synthesized compounds were evaluated by their using various spectroscopic techniques and also elemental analysis.

Keywords : Pyrano pyrazoles, MCRs, DBU

I. INTRODUCTION

Multicomponent Reactions (MCRs) are very proficient in the synthesis of organic molecule[1-3]. In this protocol single step reaction gives magnificent yield without any isolation of intermediate and intimately associated with the principals of green chemistry.[4]

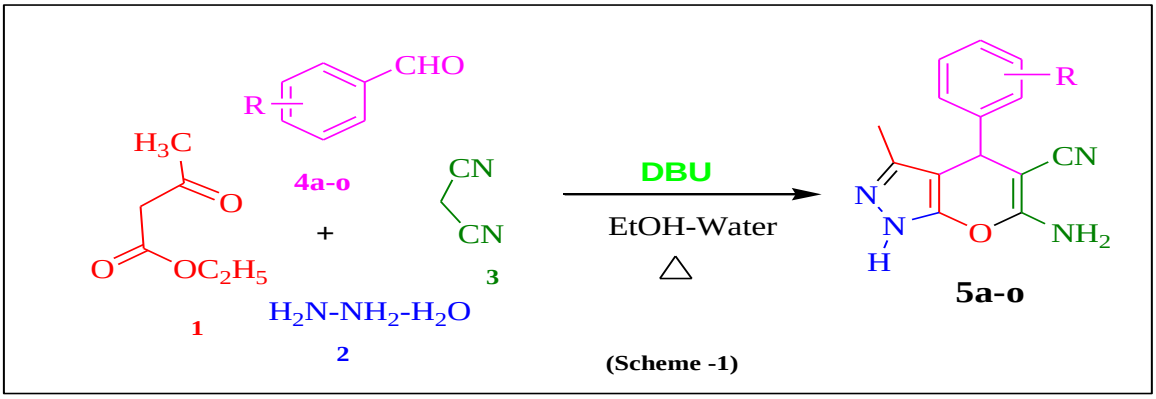
Pyrano pyrazole derivatives has vital role in the class of organic compounds because of their broad spectrum of biological as well as pharmacological importance. The Pyrano pyrazole moieties of the drug with wide medicinal application such as antimicrobial[5-6], antitumor[7], antipyretic[8], anti-inflammatory[9], antidepressant[10], antihypertensive[11], and peptide deformylase inhibitor[12]. Moreover, Dihydro pyrano [2,3-*c*] pyrazole showed hypotensive and hypoglycemic agents[13], mollusicidal activity[14] and as well as a screening hit for Chkl kinase inhibitor[15].

Chemists have reported various methods for the synthesis of Pyrano pyrazole derivatives. Various method of four component synthesis by using Thiamine hydrochloride (VB_1)[16], CsF[17], ZnO nanoparticle[18], CAPB[19], $NaHSO_3$ using ultrasound mediated,[20] TBAHS,[21] and molecular iodine non recoverable[22] also have

been reported. Overall, all these reported methods are effective but requires long time, expensive catalyst. So in order to overcome these problems, keeping green approach in mind, in this present investigation we have reported synthesis of the Pyrano pyrazole derivatives by simple, efficient and eco-friendly method. We have synthesized Pyrano pyrazoles derivatives by using as a catalyst.

We decisive to investigate DBU as an homogeneous catalyst for the synthesis of dihydropyrano [3,2-*c*]chromene derivatives in aquous ethanol. Catalyst used (DBU) 1,8-diazabicyclo[*5.4.0*]undec-7-ene acts as homogeneous catalyst and it execute much organic transformation under placid condition. As a part of our constant efforts toward the development of well-organized, cost-effective and novel methods using green catalysts and solvents, we investigated the activity of the readily available and environmentally benign DBU as catalyst for the synthesis of pyrano pyrazole derivatives.

RESULT AND DISCUSSION:



(Scheme -1)

As a Initial steps, we have focused on model reaction (**Scheme 1**) by refluxing equimolar amount of Ethylacetoacetate **(1)** (3.0 mmol), Hydrazine hydrate (80%) **(2)** (3.0 mmol),Malononitrile **(3)** (3.0 mmol), and different substituted aromatic aldehydes **(4)** (3.0 mmol) in ethanol-water (1:1) buy using DBU (1,8-diazabicyclo[*5.4.0*]undec-7-ene) (10 mol%) for three hour at 60^{0}C which results in the formation of compound **5b** with 80% yield (Table 1, entry 7). The investigating the effectiveness of different polar and non polar solvent using catalytic amount of DBU (10 mol%). Solvent optimization clearly suggested that ethanol-water is the best solvent for the desired transformation due to fast reaction rate and high yield (Table1, entry 7). The other polar protic solvents gives moderate yield (Table1, entry 6).while other a protic solvent like DCM, THF, Acetonitrile, and Toluene displayed slow reaction rates leading lower yield (Table1, entry 1-4). Also,carried out the model reaction using different stoichiometric amount of DBU catalyst. The catalyst screening result are summarized in Table 2. It was observed that the excellent yield was achieved by using 10 mol% of DBU (1,8-diazabicyclo[*5.4.0*]undec-7-ene) (Table 2, entry 6).

After optimization the reaction condition, the scope of the method was investigated with a series of substituted aromatic aldehydes and the result are summarized in Table 3.

These synthesized products (5a-o) were completely characterized from IR, 1H-NMR, Mass and 13C-NMR spectroscopic technique and also elemental analysis. We proposed tentative plausible mechanism for

the formation of Pyrano [2,3-c] pyrazoles (5a-o) in the presence of DBU as a catalyst. The overall, mechanism takes place according to Knoevenagels-Micheal reaction (Scheme-II).

Table 1. Optimization of the reaction conditions using different solvents.[a]

Entry	Solvent	Reaction Time (h)	Yield (%)[b]
1	DCM	7.0	30
2	THF	6.5	35
3	Acetonitrile	6.0	40
4	Toluene	5.5	45
5	Ethanol	3.0	65
6	Water	3.0	70
7	Ethanol-Water	3.0	80

[a] ***Reaction conditions:*** Ethylacetoacetate **(1)** (3.0 mmol), hydrazine hydrate (80%) **(2)** (3.0 mmol), malononitrile **(3)** (3.0 mmol), and different substituted aromatic aldehydes **(4)** (3.0 mmol) in Ethanol-Water and DBU (1,8-diazabicyclo[*5.4.0*]undec-7-ene) were refluxed at 60°.

[b] Isolated yields.

Table 2: Optimization Study for the amount of DBU (1,8-diazabicyclo[*5.4.0*]undec-7-ene) (.[a]

Entry	Catalyst (mole %)	Temperature (°C)	Reaction Time (h)	Yield %[b]
1	01	60	3.0	30
2	02	60	3.0	50
3	05	60	3.0	60
4	06	60	3.0	60
5	08	60	3.0	70
6	10	60	3.0	80
7	15	60	3.0	80

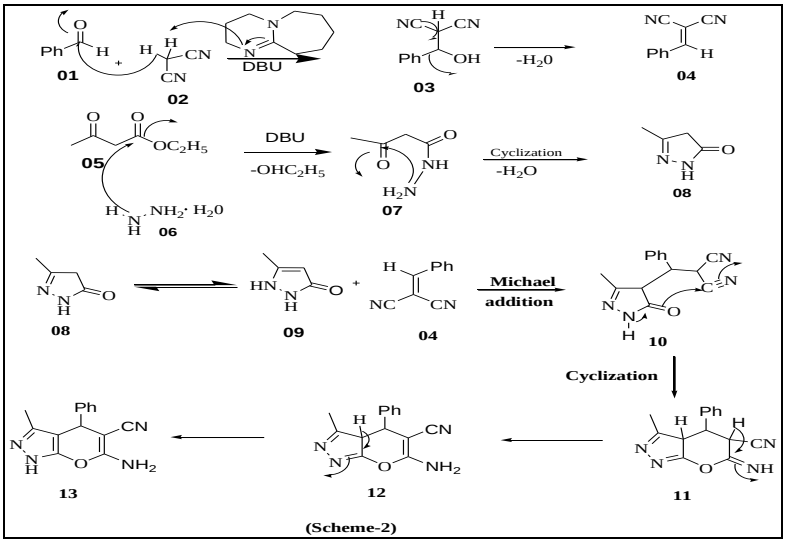
[a] ***Reaction conditions:*** Ethylacetoacetate **(1)** (3.0 mmol), Hydrazine hydrate (80%) **(2)** (3.0 mmol), Malononitrile **(3)** (3.0 mmol), and different substituted Aromatic aldehydes **(4)** (3.0 mmol) in Ethanol-Water and DBU (1,8-diazabicyclo[*5.4.0*]undec-7-ene) as a catalyst were refluxed for three hours at 60°C. [b] Isolated yields.

Table 3. Synthesis of pyrano [2,3-*c*] pyrazoles derivatives .[a]

Entry	Ar	Time (Hrs)	Yield%[a]	M.P. (⁰C)	
				Found	Lit.[Ref]
5a	C_6H_5	3.5	68	245-246	244-245[22]
5b	4'-OCH_3 -C_6H_4	3.0	80	209-210	209-211[22]
5c	4'-CH_3 -C_6H_4	3.0	78	205-207	205-207[23]
5d	4'-Br -C_6H_4	3.0	70	179-181	177-179[24]
5e	4'-Cl -C_6H_4	3.5	70	233-235	234-235[23]
5f	4'-NO_2 -C_6H_4	4.0	60	248-250	251-252[23]
5g	4'-OH -C_6H_4	3.0	75	221-223	223-225[25]
5h	4'-F -C_6H_4	3.5	65	172-174	170-171[23]
5i	4'-OCH_3, 3'-OCH_3-C_6H_3	3.0	80	310-312	311-313[23]
5j	4'- OCH_3 ,3'-OH-C_6H_3	3.0	80	242-244	244-246[22]
5k	3'- Br -C_6H_4	3.5	66	223-224	223-225[23]
5l	3'- NO_2 -C_6H_4	3.5	56	193-195	190-192[26]
5m	3'- OH -C_6H_4	3.0	72	223-225	221-223[27]
5n	2'- OH -C_6H_4	3.0	65	207-208	207-209[28]
5o	2'- Cl -C_6H_4	3.5	68	143-144	143-145[28]

[a] ***Reaction conditions:*** Ethylacetoacetate **(1) (3.0 mmol),** Hydrazine hydrate(80%) **(2) (3.0 mmol),** Malononitrile **(3) (3.0 mmol),** and different substituted Aromatic aldehydes **(4) (3.0 mmol)** in Ethanol-Water and DBU (1,8-diazabicyclo[*5.4.0*]undec-7-ene) as a catalyst were refluxed for three hours at 60⁰C.[b] Isolated yields.

Probable Mechanism:



Experimental:

Melting points were determined on electro-thermal melting point apparatus and are uncorrected. IR (KBr) spectra were recorded using Perkin-Elmer FTIR spectrophotometer. Mass spectral data were recorded on liquid chromatography mass spectrometer (Shimadzu 2010Ev) using ESI probe. The ^{1}H and ^{13}C NMR spectra were recorded on spectrometer at 300MHz using TMS as an internal standard. All the reactions were monitored by thin layer chromatography, carried out on 0.25 mm thick silica gel-G plate using iodine vapour for detection.

General procedure for the synthesis of 4-substituted derivatives of 4- phenyl Pyrano [2,3-c] pyrazoles (5a-5o):

A mixture of Ethylacetoacetate **(1)** (3.0 mmol), Hydrazine hydrate (80%) **(2)** (3.0 mmol), Malononitrile **(3)** (3.0 mmol), was refluxed independently with different substituted Aromatic aldehydes **(4)** (3.0 mmol) in presence of DBU (1,8-diazabicyclo[*5.4.0*]undec-7-ene) (10 mol%) as catalyst in ethanol-water as solvent for three hours at 60^{0}C.The progress of reaction were monitored by TLC, the product obtained was filtered, and recrystallized from ethanol (5ml) to give the pure products of **5(a-o),** (Table **3**).

Spectral Characterization of Representative Compounds.

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

Yellow solid, IR (KBr / cm^{-1}) 3410,3340 (-NH_2), 3120(-NH) , 2220 (–C≡N) , 1665 (C=N), 1270(-C-O-C-) ; ^{1}H NMR (300MHz, DMSO-d_6 / ppm) δ 1.72(s,3H); 4.5 (s,1H,-CH); 6.70(s, 2H); 7.10-7.40 (m,5H, Ar-H); 12.06(s,1H,-NH); EI-MS (m/z: RA %): 253 ($M^{+\cdot}$ +1, 100%). Elemental analysis calculated data for $C_{14}H_{12}N_4O$; C, 66.65; N, 22.11. Found: C, 66.63; N, 22.09.

6-amino-1,4-dihydro-4-(4-methoxyphenyl)-3-methylpyrano[2,3-c]pyrazole-5-carbonitrile (5b):

Yellow solid, IR (KBr/ cm^{-1}) 3400 , 3250 (-NH_2), 3110 (-NH) , 2192 (–C≡N), 1655 (C=N), 1250 (-C-O-C-) ; ^{1}H NMR (300MHz, DMSO-d_6 / ppm) δ 1.70 (s,3H); 3.7 (s,3H, Ar–OCH_3); 4.5(s,1H,-CH); 7.0 (s,2H); 7.2 -6.7 (m,4H, Ar-H); 12.0(s,1H,-NH); EI-MS (m/z: RA %): 283 ($M^{+\cdot}$ +1, 100%). ^{13}C NMR (300 MHz, DMSO–d6 / ppm) δ: 36.8, 55.5, 99.2, 114.0, 120.1,127.2, 129.6, 144.2, 159.0. Elemental analysis calculated data for $C_{15}H_{14}N_4O_2$; C, 63.82 ; N, 19.82. Found: C, 63.79; N, 19.80.

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

Yellow solid, IR (KBr/ cm^{-1}) 3317 , 3409 (-NH_2), 3190 (-NH) , 2190 (–C≡N) 1647 (C=N), 1157 (-C-O-C-) ; ^{1}H NMR (300MHz, DMSO-d_6 / ppm) δ 1.77 (s,3H); 2.26 (s,3H, Ar–OCH_3); 4.54(s,1H,-CH); 6.8 (s,2H); 7.02 -7.12 (m,4H, Ar-H); 12.07 (s,1H,-NH); EI-MS (m/z: RA %): 267 ($M^{+\cdot}$ +1, 100%). Elemental analysis calculated data for $C_{15}H_{14}N_4O$; C, 67.65 ; N, 21.40. Found: C, 67.63; N, 21.38.

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

White solid, IR (KBr/ cm^{-1}) 3474 , 3325 (-NH_2), 3190 (-NH) , 2192 (–C≡N) 1658 (C=N), 1157 (-C-O-C-) ; ^{1}H NMR (300MHz, DMSO-d_6 / ppm) δ 1.7 (s,3H); 4.6 (s,1H,-CH); 6.93 (s,2H); 7.12 -7.52 (m,4H, Ar-H); 12.14 (s,1H,-NH); EI-MS (m/z: RA %): 330($M^{+\cdot}$) 332 ($M^{+\cdot}$ +1, 100%). ^{13}C NMR (300 MHz, DMSO–d6 / ppm) δ: 35.0, 56.0, 97.2, 119.0, 120.1, 131.0, 143.0, 154.0, 160.0. Elemental analysis calculated data for $C_{15}H_{14}BrN_4O$; C, 50.77 ; N, 16.92. Found: C, 50.75; N, 16.90.

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

White solid, IR (KBr / cm^{-1}) 3425 , 3325 (-NH_2), 3174 (-NH) , 2200 (–C≡N) 1647 (C=N), 1184 (-C-O-C-) ; ^{1}H NMR (300MHz, DMSO-d_6 / ppm) δ 1.79 (s,3H); 4.63 (s,1H,-CH); 6.93 (s,2H); 7.18 -7.20 (m,4H, Ar-H); 12.00 (s,1H,-NH); EI-MS (m/z: RA %): 287($M^{+\cdot}$) 288 ($M^{+\cdot}$ +1, 100%). Elemental analysis calculated data for $C_{15}H_{14}ClN_4O$; C, 58.65 ; N, 19.54. Found: C, 58.63; N, 19.54.

Biological Evaluation:

Antioxidant Activity:

a) **DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging assay** :

DPPH (1, 1-diphenyl-2-picrylhydrazyl) radical scavenging assay was proceed by reported method. Take 1 ml (1 mM) of the test sample is added to equimolar quantity of 0.1 mM solution of DPPH in ethanol. After incubation at room temperature for 25 min, then the DPPH reduction was takes places and measured by Reading the absorbance at 517 nm. Ascorbic acid (1mM) used as reference compound.

The compound **5(d, f, k, l & o),** (Table 4) showed remarkable antioxidant activity against DDPH radical scavenging activity with reference of ascorbic acid**.**

b) **OH radical scavenging assay:**

Hydroxy radicals scavenging activity was measured with Fenton's reaction (Rollet –Labelle et al., 1998). The reaction mixture contained 60 µl of $FeCl_2$ (1mM), 90 µl of 1,10-phenanthroline(1mM), 2.4 ml of phosphate buffer (pH 7.8),150 µl of 0.17M H_2O_2 and 1.5 ml of individual newly synthesized organic compounds (1mM). The reaction mixture was kept at room temperature for 5 minutes incubation and the absorbance was recorded at 560 nm using UV-Visible spectrophotometer. Ascorbic acid (1mM) was used as the reference compound. The OH radical scavenging activity, the OH radical in which oxygen species are most reactive. The effective OH radical stabilizing potential observed strong absorption maximum at 560 nm using standard Ascorbic acid (89.5 ± 0.021) drug.

The compound **5(d, f, k & l),** (Table 4) showed remarkable antioxidant activity against OH radical scavenging activity with reference of ascorbic acid.

Table 4 : Antioxidant activity of tested compounds (5a-5o.)

Entry	Compound Code	% Radical scavenging activity	
		DPPH radical scavenging	OH radical scavenging
01	**5a**	55.7 ± 1.03	53.2 ± 1.39
02	**5b**	68.5 ± 0.79	60.3 ± 2.20
03	**5c**	60.2 ± 0.54	65.2 ± 1.30
04	**5d**	81.1 ± 1.50	80.2 ± 1.28
05	**5e**	79.1 ± 0.72	73.6 ± 0.69
06	**5f**	**88.5 ± 1.68**	**84.2 ± 1.40**

07	**5g**	50.2 ± 0.32	55.2 ± 1.66
08	**5h**	60.4 ± 0.66	65.2 ± 2.00
09	**5i**	58.2 ± 1.44	49.2 ± 0.80
10	**5j**	61.2 ± 0.08	45.2 ± 2.10
11	**5k**	**89.5 ± 2.68**	**86.2 ± 0.28**
12	**5l**	**82.8 ± 1.04**	**86.2 ± 0.10**
13	**5m**	44.0 ± 0.30	55.8 ± 2.11
14	**5n**	58.1 ± 1.60	59.2 ± 1.80
15	**5o**	82.7 ± 1.70	78.2 ± 2.60
16	**Ascorbic Acid (Standard)**	**91.4 ± 0.021**	**89.5 ± 0.021**

Conclusion:

The method we used for the synthesis of 4-substituted derivatives of Pyrano [2,3-c] pyrazoles derivatives by using DBU (1,8-diazabicyclo[*5.4.0*]undec-7-ene) is efficient catalyst. The product can be easily isolated by simple workup technique, requires ambient reaction condition, short time, less expensive and give excellent yield. Among these synthesized compounds few compounds shows potent antioxidant activity.

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