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RESEARCH ARTICLE

One Pot, Four-Component for the Synthesis of Pyrano Pyrazole Derivatives using TBAHS as Green Catalyst and their Biological Evaluation

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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 Tetrabutyl ammonium hydrogen sulphate (TBAHS) as green 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, TBAHS, Antioxidant activity.

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]

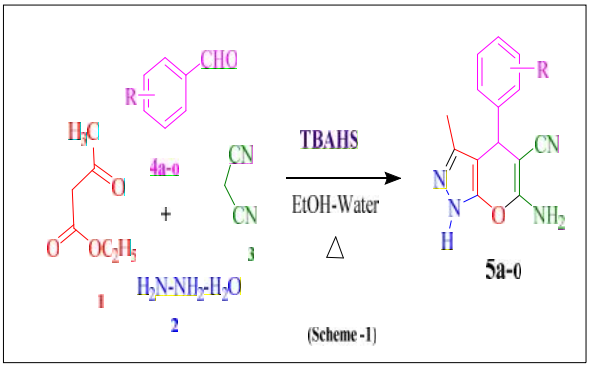
Pyranopyrazole derivatives has vital role in the class of organic compounds because of their broad spectrum of biological as well as pharmacological importance. The pyranopyrazole moieties of the drug with wide medicinal application such as antimicrobial[5-6], antitumor[7], antipyretic[8], anti-inflammatory[9], antidepressant[10], anti hypertensive[11], and peptide deformylase inhibitor[12]. Moreover, Dihydropyrano [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] and molecular iodine non recoverable[21] also have been reported. Overall, all these reported methods are effective but requires long time, expensive catalyst. So in order to overcome problem, keeping green approach in mind, in this present investigation we have reported synthesis of the pyranopyrazole derivatives by simple, efficient and ecofriendly method. We have synthesized pyranopyrazoles derivatives by using tetrabutyl ammonium hydrogen sulphate (TBAHS) as a green catalyst.

Acidic TBAHS act as a phase transfer catalyst (PTC) and it perform much organic transformation under mild condition. Thus new route utilizing a MCR protocol, for the synthesis of Pyrano [2,3-*c*] Pyrazoles can attacks considerable attention in the search of method for rapid entry of these heterocycles. Consequently, we thought that there is scope for further innovation towards milder reaction condition, short reaction time and better yield in

choosing TBAHS for this multicomponent reaction (MCRs).

RESULT AND DISCUSSION:



As a Initial steps, we have focused on model reaction (**Scheme 1**) by refluxing equimolecular 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 Tetrabutyl ammonium hydrogen sulphate (TBAHS) (20 mol%) for one and half hour at 50^0C which results in the formation of compound **5b** with 85% yield (Table 1, entry 7). The investigating the effectiveness of different polar and non polar solvent using catalytic amount of TBAHS (20 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 aprotic solvent like DCM,THF, Acotonitrile, and toluene displayed slow reaction rates leading lower yield (Table1, entry 1-4). Also, carried out the model reaction using different stoichiometric amount of TBAHS catalyst. The catalyst screening result are summarized in Table 2. It was observed that the excellent yield was achieved by using 20 mol% of TBAHS (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. With the presence of both electron-poor and electron-rich substituents in the ortho-, meta-, or para-positions, the reaction proceeded fairly well and afforded with desired product give Pyrano [2,3-c] pyrazoles with high of yields (Table 3, entries **5b-c, 5g ,5i** and **5m-n**), but the electron rich benzaldehydes like (Table 3, entries **5d-f, 5k ,** and **5o**) it gives Pyrano [2,3-c] pyrazoles with good yield.

These synthesized products **(5a-o)** were completely characterized from IR, ^{1}H-NMR, Mass and ^{13}C-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 TBAHS. 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	2.0	85

[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 TBAHS were refluxed at 50.
[b] Isolated yields.

Table 2: Optimization Study for the amount of TBAHS.[a]

Entry	Catalyst (mole %)	Temperature (^{0}C)	Reaction Time (h)	Yield %[b]
1	01	50	2.0	30
2	02	50	2.0	50
3	05	50	2.0	60
4	10	50	2.0	60
5	15	50	2.0	70
6	20	50	2.0	85
7	25	50	2.0	85

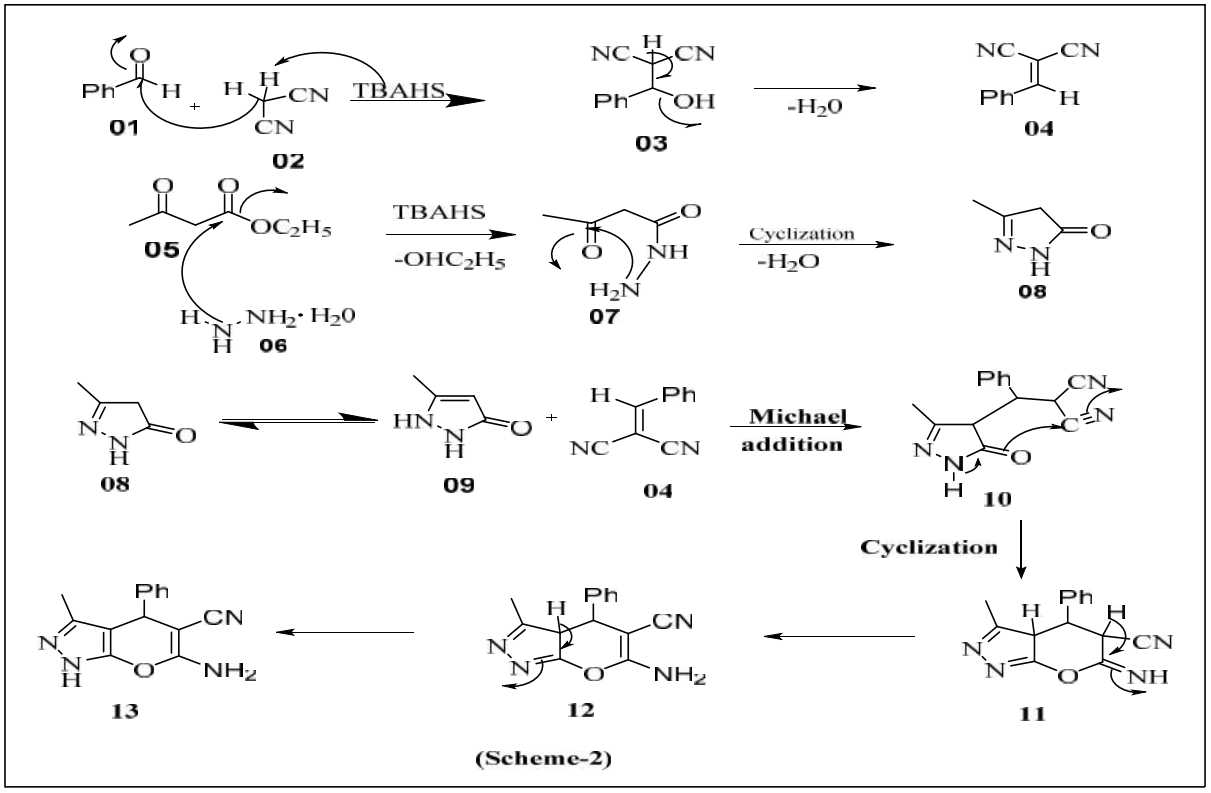
[a] ***Reaction conditions:*** Ethylacetoacetate **(1)** (3.0 mmol), hydrazine hydrate (80%) **(2)** (3.0 mmol), malononitrile **(3)** (3.0 mmol), and different substituted aromatic aldehydes **(4)** (3.0 mmol) in Ethanol-Water and TBAHS were refluxed at 50.
[b] Isolated yields.

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

Entry	Ar	Time (Hrs)	Yield%[a]	M.P. (^{0}C)	
				Found	Lit.[Ref]
5a	C_6H_5	2.5	68	243-245	244-245[22]
5b	4'-OCH_3 -C_6H_4	2.0	85	208-210	209-211[22]
5c	4'-CH_3 -C_6H_4	2.0	80	206-208	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	2.0	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	2.0	82	310-312	311-313[23]
5j	4'- OCH_3 ,3'-OH-C_6H_3	2.0	82	242-244	244-246[22]
5k	3'- Br -C_6H_4	3.5	66	221-223	223-225[23]
5l	3'- NO_2 -C_6H_4	4.5	56	193-195	190-192[26]
5m	3'- OH -C_6H_4	2.0	72	223-225	221-223[27]
5n	2'- OH -C_6H_4	2.0	65	205-206	207-209[28]
5o	2'- Cl -C_6H_4	3.5	68	142-144	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 TBAHS were refluxed at 50℃.
[b] Isolated yields.



(Scheme-2)

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 ^1H 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 Tetrabutyl ammonium hydrogen sulphate (TBAHS) (20 mol%)as a green catalyst in ethanol-water as solvent for two hours at 50^0C. After completion of the reaction (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) , 2190 (–C≡N) , 1665 (C=N), 1270(-C-O-C-) ; ^1H NMR (300MHz, DMSO-d_6 / ppm) δ 1.72(s,3H); 4.7 (s,1H,-CH); 6.80(s,br, 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}) 3460 , 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,br,2H); 7.0 -6.8 (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,br,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,br,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}) 3409 , 3305 (-NH_2), 3174 (-NH) , 2187 (–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,br,2H); 7.18 -7.20 (m,4H, Ar-H); 12.14 (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	80.1 ± 1.50	80.2 ± 1.28
05	5e	79.1 ± 0.72	73.6 ± 0.69
06	5f	86.5 ± 1.68	89.2 ± 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	85.2 ± 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	80.7 ± 1.70	76.2 ± 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 with by using PTC catalyst Tetrabutyl ammonium hydrogen sulphate (TBAHS) is efficient method. 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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