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Heterogeneous PS-DABCO Catalyzed One pot four-Component Synthesis of Pyranopyrazole

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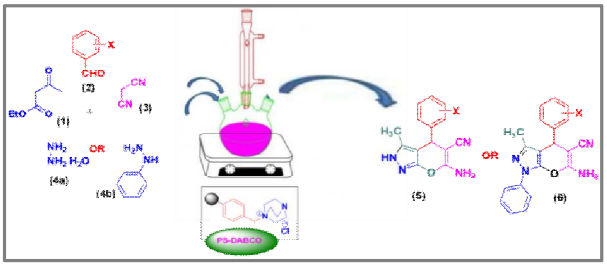
ABSTRACT

An efficient, high-yielding and rapid protocol has been developed for the synthesis of dihydropyrano[2,3-c]pyrazoles derivatives via one-pot, four-component, C-C and C-N bond forming reaction of aryl aldehydes, , ethyl acetoacetate, malononitrile and hydrazine hydrate or phenyl hydrazine by using PS-DABCO as green reusable heterogeneous catalyst. Absence of unwanted products, general applicability, reusability of the catalyst, non-chromatographic purification procedure, green synthesis avoiding toxic reagents and improved and operational simplicity make this protocol a useful, greener, cost effective and practical for both academic as well as industrial purposes.

Graphical Abstract



Keywords: Multicomponent reaction, Pyranopyrazole, Polymer supported DABCO, Heterogeneous catalyst.

INTRODUCTION

In recent years, working green chemistry concepts for the development of safe, sustainable and efficient synthetic procedures have been significantly recognized globally [1]. The development of multi-component reactions (MCRs) designed to produce biologically active compounds have become an important area of research in synthetic organic, combinatorial and medicinal chemistry [2]. One-pot MCRs approaches offer significant advantages over conventional linear-type synthesis by virtue

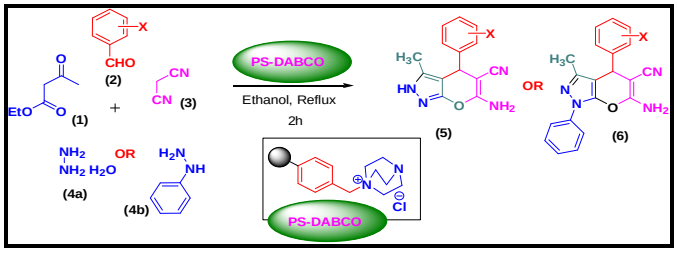
of their building up complex molecules, ease of one pot process, selective convergence, good productivity, facile execution and high yields [3].

Heterocyclic chemistry is of great importance and potential part of the current synthetic organic chemistry, because the steady growing interest in synthesis, a wide variety of heterocyclic compounds are interrelated with their increasing therapeutic activity [4]. Amongst class of heterocycles, one of the very interesting, promising bicyclic oxygen and nitrogen containing heterocycle is the pyrano[2,3-*c*]pyrazole ring system. The pyrano[2,3-*c*]pyrazole like compounds occupies important place and usually found in a wide variety of synthetic pharmaceutical molecules, natural products and potent building blocks for functional materials [5]. Many of these pyrano[2,3-c]pyrazole compounds serve as potential insecticidal [6], antiviral [7], antimicrobial [8], anti-inflammatory [9], anticancer [10], analgesic [11], human CHK1 kinase inhibitor [12], vasodilator [13], molluscicidal [14] activities as well as pharmaceutical ingredients and as biodegradable agrochemicals [15].

Due to above-mentioned importance of dihydropyrano[2,3-*c*]pyrazole derivatives, there is immense scope for the development of new synthetic methods. Conventionally, pyranopyrazole compounds have been synthesized by one-pot four-component condensation through C-C and C-N bond forming annulation reaction of ethyl acetoacetate, aryl-aldehyde, malononitrile and hydrazine hydrate or aryl hydrazine in the presence of different catalysts. Recently a number of methods for the synthesis of pyrano[2,3-*c*]pyrazoles have been reported in literature involving the use of catalysts such as piperidine, piperazine [16], triethyl amine [17], DABCO [18], imidazole [19], cinchona alkaloids [20], glycine [21], meglumine [22], L-proline [23], DBU [24], isonicotinic acid [25], Ferrouscarboxymethylcellulose and Ceriumcarboxymethylcellulose [26], NaF [27], CsF [28], nano-ZrO_2 [29], Vitamin B_1 on silica coated ferrite [30], Amberlist A-21 [31], silica supported tetramethyl guanidine SiO-TMG [32], polystyrene supported *p*-TSA [33], sulphonic acid functionalised IL [DMBSI][HSO_4] [34], [Dabco-H][AcO] [35], morpholine triflate [36], cetyltrimethyl ammonium chloride (CTACl) [37], per-6-amino-β-cyclodextrin [38], biocatalyst bovine serum albumin [39] etc. have been used for the synthesis of pyrano[2,3-*c*]pyrazoles. However these procedures have suffered from the some drawbacks of green chemistry such as high reaction temperature, prolonged reaction time, low yields, requirement of expensive and excess catalysts, recovery and reusability of catalysts etc. Therefore, the demand for green and eco-friendly procedure which uses reusable catalyst necessitated us to develop an alternative method for the synthesis of pyrano[2,3-*c*]pyrazoles.

Polymer supported heterogeneous base catalyst has been of great interest due to several advantages in organic synthesis over liquid bases, such as ease of products separation, isolation and reuse of the catalyst [40]. Literature survey revealed that, the Dabco based ionic liquid or salts are shows good catalytic activities in various C-C and C-N bond forming reactions [41]. Recently Y. Q. Yu and D. Z.Xu [42] have reported the use of PS-DABCO as base catalyst for one pot multicomponent synthesis of β-phosphonomalonates with very good activity.

Considering the advantages of the MCRs technique, in continuation of our earlier work on the synthesis of biologically active heterocyclic compounds by using heterogeneous catalyst [43-49] and an importance of pyranopyrazole molecules;we have used PS-DABCO catalyst for the one-pot four component synthesis of pyranopyrazole derivatives (Scheme 1).



Scheme 1. PS-DABCO catalyzed multicomponent synthesis of pyranopyrazole.

MATERIALS AND METHODS

Chemicals required for the synthesis were obtained from Aldrich, Spectrochem, Loba- Company. Reactions have been monitored by Thin Layer Chromatography on 0.2 mm precoated plates of silica gel G60 F254 (Merck). Visualisation was made with UV light or with an iodine vapour. Melting point ranges were determined in one end open capillaries and are uncorrected. All yields were referred to isolated products after purification. The IR spectra were recorded on Shimadzu-FT-IR-8400 spectrophotometer using the KBr pellet method.^{1}H-NMR spectra were recorded on Bruker Avance II 400MHz and ^{13}C-NMR spectra were recorded on Bruker Avance II 100MHz Spectrophotometer in DMSO-d_6 using TMS as the internal standard. The chemical shift values were recorded on δ-scale and the coupling constants (*J*) were in hertz. Mass spectra (ES-MS, *m/z*) were recorded on Water-Micro Quattro-II mass spectrophotometer. CHN elemental analysis of catalyst was checked on Thermo-Finnigan Italy. Model FLASH EA 1112 series. Thermogravimetric analysis (TGA) was carried out by using a Mettler Toledo TGA/DTA 851e.

General procedure for preparation of dihydropyrano[2,3-*c*]pyrazoles: A 25 mL round bottom flask containing ethyl acetoacetate (**1**) (1.0 mmol), aryl aldehyde (**2a-l**) (1.0 mmol), malononitrile (**3**) (1.0 mmol) and hydrazine hydrate (**4a**) or phenyl hydrazine (**4b**) (1mmol) in 5 mL ethanol in which PS-DABCO (4.0 mol %) was added. The reaction mixture was stirred at reflux temperature for 2h. The reaction progress was monitored by TLC. After completion of reaction, the reaction mixture was diluted with ethanol (5 mL) and separates the catalyst by simple filtration, washed the residue (catalyst) with hot ethanol (2×5 mL), followed by concentrated under reduced pressure. The crude product was then purified by recrystallization in aq. ethanol to give pure product. The selected products were characterized by FTIR, PMR and Mass spectroscopy, whereas the remaining products characterized by their physical constants and were found to be in good agreement with the reported literature.

Spectral data for representative compounds:

6-amino-4-phenyl-3-methyl (2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile(5a): Colour: colour less solid, Yield: 91%, MP = 244-246 °C (Lit.- 244-246°C) [39], IR (cm^{-1}): 3350, 3170, 2180, 1590, 1490, 1395, 1170, 1150, 1070;^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.09 (s, 1H), 7.31(d, *J*= 8, Hz 2H), 7.20 (dd, *J*= 8 & 4 Hz, 3H), 6.87 (s, 2H), 4.59 (s, 1H), 1.78 (s, 3H); Mass (ES-MS, m/z): 251.2 (100%) (M-1).

6-amino-4-)2-chorophenyl)-3-methyl(2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile(5b): Colour: colourless solid, Yield: 76%, MP =246-248 °C (Lit. 245-246°C) [22], IR (cm^{-1}): 3350, 3170, 2160, 1600, 1510, 1390, 1170, 1150, 1070; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.09 (s, 1H), 7.31(d, *J*= 8, Hz 2H), 7.20 (dd, *J*= 8 & 4 Hz, 3H), 6.87 (s, 2H), 4.59 (s, 1H), 1.78 (s, 3H); Mass (ES-MS, m/z): 285.1 (100%) (M-1), 287.1 (35%).

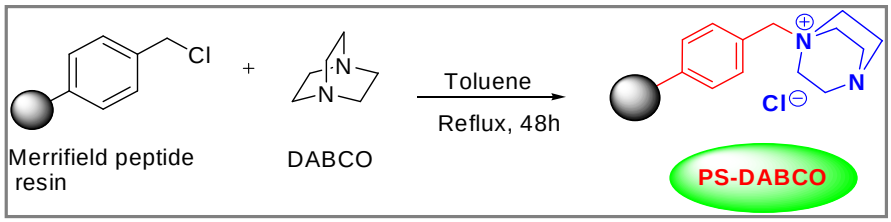
6-amino-4-(4-chlorophenyl)-3-methyl(2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile(5d): Colour: colourless solid, Yield: 91%, MP =236-238°C (Lit. 236-238°C) [39], IR (cm^{-1}): 3370, 3160, 2150, 1590, 1510, 1390, 1170, 1155, 1065;^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.13 (s, 1H), 7.90 (d, 1H), 7.59 (d, *J*= 8 Hz, 1H), 7.38 (d, *J*= 8 Hz, 1H), 7.19 (d, 1H), 6.92 (s, 2H), 4.63 (s, 1H) 1.79 (s, 3H); Mass (ES-MS, m/z): 285.1 (100%), 287.1 (35%) (M-1).

6-amino-1,4-dihydro-3-methyl-1,4-diphenylpyrano[2,3-c]pyrazole-5-carbonitrile(6a): Colour: colourless solid Yield: 84% MP =168-170°C (Lit. 168-170°C) [29], IR (cm^{-1}): 3360, 3010, 2150, 2950, 1610, 1590, 1530, 1490, 1390, 1170, 1155, 1065, 1010; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 7.85 (d, *J*= 7.5 Hz, 2H), 7.49 (t, *J*= 8.0 Hz, 2H), 7.35-7.24 (m, 6H), 7.20 (s, 2H), 4.68 (s, 1H) 1.77 (s, 3H); Mass (ES-MS, m/z): 327.2 (100%) (M-1); 329.3 (100%) (M+1).

6-amino-4-(4-chlorophenyl)-1,4-dihydro-3-methyl-1-phenylpyrano[2,3-c]pyrazole-5-carbonitrile (6b): Colour: colourless solid, Yield: 84%, MP =172-174°C (Lit. 171-172°C) [29], IR (cm^{-1}): 3360, 3015, 2955, 2180, 1610, 1590, 1530, 1490, 1390, 1170, 1155, 1065, 1010; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 7.80 (d, *J*= 8.0 Hz, 2H), 7.49 (t, *J*= 8.5 & 7.5 Hz, 2H), 7.41 (t, *J*= 8.5 Hz, 2H), 7.30 (t, *J*= 8.5 & 7.5 Hz, 3H), 7.26 (s, 2H), 4.72 (s, 1H) 1.79 (s, 3H); Mass (ES-MS, m/z): 361.2(100%) (M-1), 363.2(35%).

RESULTS AND DISCUSSION

Characterization of the PS-DABCO catalyst: Initially we have developed the best polymer supported catalyst, PS-DABCO have been prepared according to the previously reported procedure with small modification (Scheme 2) [42]. The polystyrene resin supported-DABCO (PS-DABCO) catalyst was prepared from Merrifield peptide resin (2 % cross linked, 2.3 mmol Cl g^{-1}, Aldrich) (1 g) reacted with 1,4-diazobicyclo[2,2,2]octane (DABCO) (5 mmol) in toluene gave the DABCO-loaded polystyrene resin supported ionic liquid (PS-DABCO). The obtained (PS-DABCO) IL was characterized by elemental analysis, FT-IR and TG analysis.



Scheme 2: Preparation of PS-DABCO catalyst.

The loading of DABCO on polystyrene resin showed 2.0175 mmol g^{-1} was determined by elemental analysis of PS-DABCO and also characterized by FT-IR to check the attachment of the ionic liquid. A strong band at 1560 cm^{-1} confirms the attachment of the DABCO on Merrifield resin. Furthermore the bands at 1265 and 697 cm^{-1} of $–CH_2$-Cl group absorption disappears in the FT-IR spectra of PS-DABCO, indicating full functionalization of PS-CH_2-Cl.

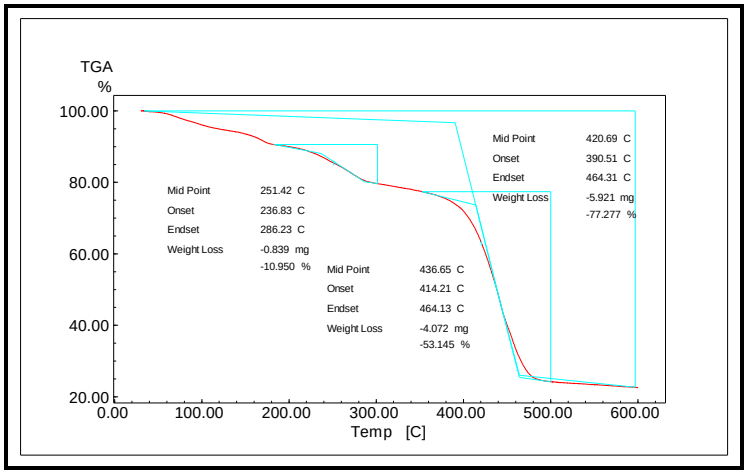


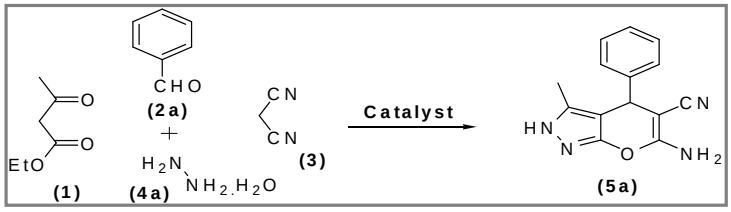
Figure 1. TGA of PS-DABCO catalyst.

Thermo Gravimetric analysis was carried out to investigate the thermal stability of PS-DABCO catalyst shown in (Figure 1). Thermal stability of the PS-DABCO catalyst was investigated using TGA-DTA at a heating rate of 10°C min^{-1} in air over a temperature range of 30-600°C. Weight loss of PS-DABCO catalyst was mainly divided into three temperature regions: 237-286°C, 414–464 °C and 436-464°C. Weight loss from 237°C to 286°C was assigned to the loss (10.95 %) of loosely bound

DABCO molecule or chloride. The large weight loss about 53.14% at temperature between 414°C and 464°C was due to the decomposition of covalently bonded organics. The catalyst was stable up to 237°C and above this temperature they decomposed. Thermogravimetric study suggests that the polymer supported DABCO degrade at considerably higher temperature.

Optimization of reaction conditions: In the initial study, we have focused on to the development of a catalytic system for synthesis of pyrano[2,3-*c*]pyrazoles that would address the limitations of the previously reported reactions. During the optimization of reaction parameters, in the preliminary studies ethyl acetoacetate **(1)** (1.0 mmol), benzaldehyde **(2a)** (1.0 mmol), malononitrile **(3)** (1.0 mmol) and hydrazine hydrate **(4a)** (1.0 mmol) in ethanol were used as the model system. A series of experiments were performed to optimize various reaction parameters, such as the catalyst, catalyst loading, solvent, temperature and time. The proposed transformation was first examined by treating a mixture of model reaction components with various heterogeneous metal and polymer supported catalysts. Among these heterogeneous catalysts examined PS-DABCO was found to be the best, providing excellent yields of the desired product **5a** (Table 1, **entries 1–6**). We have further studied catalyst loadings ranging from 3 to 5 mol% and increasing the catalyst concentration from 3 to 4 mol% which increased the yield of **5a** to 91%, a further increase to 5 mol% did not improve the yields (Table 1, **entries 6-8**).

Table 1. Study of Catalyst and Catalyst loading.[a]



Entry	Catalyst	Catalyst loading (mol %)	Yield[b] (%)
1	--	--	00
2	Fe_3O_4	4	76
3	$CuFe_2O_4$	4	78
4	Nano-CuI	4	86
5	PS-IMZ-Cl	4	69
6	PS-DABCO	4	91
7	PS-DABCO	5	91
8	PS-DABCO	3	79

[a]Reaction condition: (**1**) (1.0 mmol), (**2a**) (1.0 mmol), (**3**) (1.0 mmol) and (**4a**) (1.0 mmol), Ethanol (5 mL), reflux for 2h. [b]Isolated yields.

We have further studied the effects of different solvents in order to enhance the PS-DABCO catalyzed reaction rates. Among the solvents screened for the model reaction we observed that, the reaction performed well in ethanol which gave excellent yields of **5a** (Table 2, **entries 1-6**). We have also studied the effect of the temperature, which showed that the decrease of temperature upto 60°C, decreases the yield of **5a** (Table 2, **entries 2, 7**).

We have further studied the effect of the time on the model reaction, which showed that there is no increase in yield of **5a** with increasing reaction time from 2h to 2.5h, but affect the decrease in time up to 1.5h decreases the yield of **5a.** The reaction time was optimized at 2h (Table 2, **entries 2, 8, 9**). After the study of all reaction parameters, the optimized reaction condition for the dihydropyrano [2,3-*c*] pyrazole synthesis reaction is PS-DABCO catalyst (4.0 mol %) in ethanol was the best solvent at refluxed for 2h.

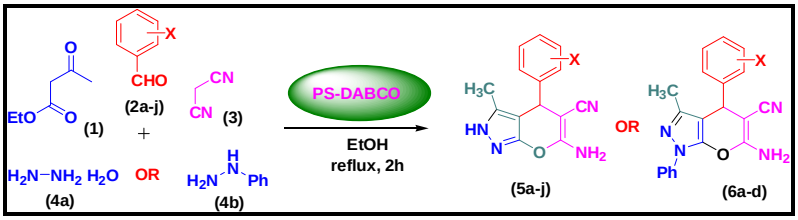
Table 2: Reaction parameter study.[a]

Entry	Solvent	Temp (°C)	Time (h)	Yield[b] 5a (%)
1	Neat	100	2	53
2	**EtOH**	**Reflux**	**2**	**91**
3	MeOH	Reflux	2	76
4	Water	Reflux	2	44
5	ACN	Reflux	2	28
6	Water : EtOH(1:1)	Reflux	2	78
7	EtOH	60	2	68
8	EtOH	Reflux	1.5	72
9	EtOH	Reflux	2.5	91

[a]Reaction condition: (**1**) (1.0 mmol), (**2a**) (1.0 mmol), (**3**) (1.0 mmol), (**4a**) (1.0 mmol), PS-DABCO (4 mol%), solvent (5 mL). [b]Isolated yields.

To further established the scope of optimized PS-DABCO catalyzed C-C and C-N bond forming reaction condition and in order to take a broad view of the synthetic procedure, variety of electronically different aromatic aldehydes (**2**) were reacted with ethyl acetoacetate (**1**), malononitrile (**3**) and hydrazine hydrate (**4a**) or phenyl hydrazine (**5a**). More importantly, aryl aldehydes having electron withdrawing groups as well as electron donating groups reacted efficiently and did not influenced considerably effect on the yields of corresponding desired products. Various electron withdrawing as well as electron releasing substituents are present on the aryl ring such as ether, alkyl, nitro, halo etc. were well tolerated during the reaction and not make more effect on reaction yields. All the obtained results are summarized in table 3. Formation of desired products was confirmed with the help of FT-IR, PMR and mass spectroscopic data.

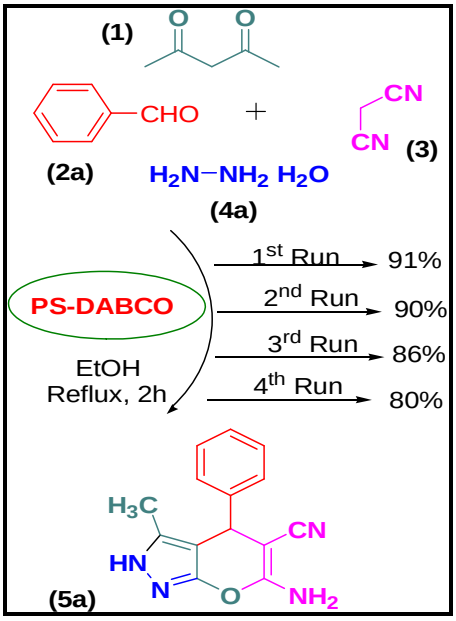
Table 3. PS-DABCOcatalysed synthesis of pyranopyrazoles[a]



Entry	Aldehyde (-X)	Product	Yield[b](%)	MP. (°C) (Obt.) [ref.]
1	-H	**5a**	91	244-246 (244-246) [39]
2	2-Cl	**5b**	76	246-248 (245-246) [22]
3	3-Cl	**5c**	86	160-162 (159-161) [33]
4	4-Cl	**5d**	91	236-238 (236-238) [39]
5	4-OMe	**5e**	90	210-212 (210-212) [39]
6	3,4-di-OMe	**5f**	82	192-194 (195-196) [31]
7	4-F	**5g**	91	170-172 (169-171) [33]
8	2-NO_2	**5h**	79	220-222 (222-224) [31]
9	3-NO_2	**5i**	86	190-192 (190-192) [33]
10	4-NO_2	**5j**	84	248-250 (246-248) [39]
11	-H	**6a**	84	168-170 (168-170) [29]
12	4-Cl	**6b**	86	172-174 (171-172) [29]
13	4-OMe	**6c**	82	172–174 (172-173) [29]
14	4-NO_2	**6d**	80	190-192 (188-190) [29]

[a]Reaction condition: (1) (1.0 mmol), (2) (1.0 mmol), (3) (1.0 mmol), (4a) or (4b) (1.0 mmol), PS-DABCO (4 mol%), ethanol (5 mL), reflux, 2h. [b]Isolated yields.

In order to make our catalytic system more economical, we have focused on the reusability of the PS-DABCO catalyst in this four component one pot C-C and C-N bond forming reaction. As shown in Scheme 3, the catalyst exhibited remarkable activity in the first two consecutive recycles, while a decrease in conversion was observed in the next recycles. After completion of the reaction according to TLC, the reaction mixture was filtered and the catalyst was washed with ethanol (3×5 ml), then dried it at 100°C for 2h and used in the reusability studies.



Scheme 3. Recyclability study of PS-DABCO catalyst.

APPLICATION

The present method was environmentally benign. The procedure offers advantages in terms of better yields, short reaction times, mild reaction conditions, and reusability of the catalyst. The easy separation, high thermal stability of catalyst and an environmentally benign procedure makes this methodology useful contribution to the existing procedures available for the synthesis of pyranopyrazole derivatives as a biologically and pharmaceutically relevant material.

CONCLUSION

We have developed PS-DABCO catalyzed one pot four component reaction for the synthesis of dihydropyrano[2,3-*c*]pyrazoles. The wide variety of dihydropyrano[2,3-*c*]pyrazoles were synthesized in good to excellent yields. Absence of unwanted products, general applicability, reusability of the catalyst, non-chromatographic purification procedure, green synthesis avoiding toxic reagents, improved and operational simplicity made this protocol useful, greener, cost effective and practical for both academic as well as industrial purposes.

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