Journal of Sciences, Islamic Republic of Iran 34(2): 129 - 136 (2023) http://jsciences.ut.ac.ir
University of Tehran, ISSN 1016-1104

One-pot, Multi-component Synthesis of Dihydropyrano(2,3-c)pyrazoles Catalysed by Preheated Fly-Ash in Aqueous Medium

A.K. Pandey[1], K. Mishra[2], S.C. Shrivastava[1*], P. Shukla[1], A. Tripathi[3]

[1] *Department of Chemistry, University of Allahabad, Prayagraj, UP-211002, India*
[2] *Department of Chemistry, CMP Degree College, Prayagraj (A constituent PG college of Unversity of Allahabad, Prayagraj) UP-211002, India*
[3] *K.S. Saket P.G. College, A Government-Aided PG college of DR RML Avadh University, Ayodhya, UP-224123, India*

Received: 29 July 2022 / Revised: 17 January 2023 / Accepted: 31 May 2023

Abstract

A facile one-pot multicomponent protocol for the synthesis of bio-active dihydropyrano(2,3-c)pyrazole derivatives from ethyl acetoacetate, hydrazine hydrate, malononitrile and aryl aldehydes using preheated-fly-ash as catalyst for the first time.These environmentally begin multicomponent cyclocondensations offer some interesting advantages, advantages of this methodology are the use of nontoxic solvent, cost-effective and easy availability of catalyst, ease of the work-up, high yields (up to 95%), and green protocol.

Keywords: Pyrazole; Green Protocol; Multi Component; Preheated Fly-Ash; Antimicrobial; Model Reaction.

Introduction

One of the most challenging tasks for synthetic organic chemists in the area of medicinal and heterocyclic chemistry is the approaches for the synthetic methodologies to achieve functionalized and fused heterocyclic moieties. There are numerous approaches for the synthesis of functionalized and fused heterocyclic moieties using multicomponent (MCRs) reactions and during the last few years synthesis of these moieties has received great attention (1). Multicomponent reactions (MCRs) are those reactions in which three or more starting materials react all together to form a expected product (2). These approaches have various significant over classical, stepwise procedures, important to formation of several bonds in single step multi-component reactions (MCRs) are highly valuable reactions and widely used in the construction of bioactive heterocyclic in which three or more starting materials react all together to form a expected product (3). Furthermore, MCRs also comply with the ideologies of green chemistry, without the need for intermediate separations or purifications with substantial time and cost savings (4). Hence, Multi-component reactions (MCRs) have been attracted much attention for the production of structural scaffolds or combinatorial libraries for heterocyclic chemistry and drug discovery.Between the different group of nitrogen-containing heterocyclic compoundsPyrano(2,3-c)pyrazoles are an important class of heterocyclic compounds thatplay an significant role as biologically active compounds and represent an interestingtemplate in medicinal chemistry (5).

* Corresponding author: Tel: +91 8005190141; Email: subhash.chem.au@gmail.com

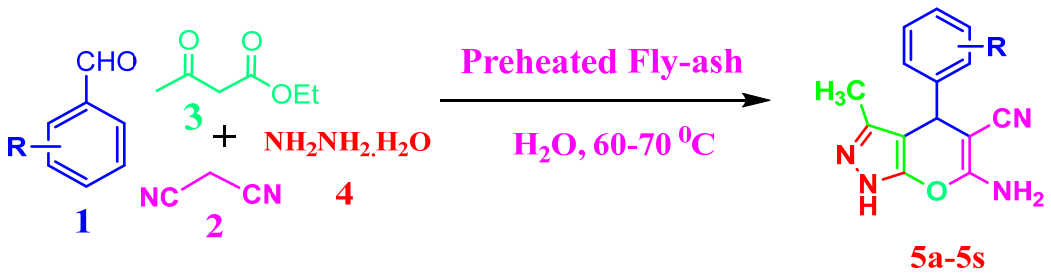
Structures containing the Pyrano(2,3-c) pyrazoles derivatives have attracted synthetic organic chemists and biochemists because of their significant pharmaceutical and biological activities. Many recent reports have confirmed that pyranopyrazole derivatives are important class of heterocyclic compounds with natural and synthetic molecules that exhibited numerous biological and pharmaceutical activities (6) such as anti-inflammatory (7) and insecticidal (8), antimicrobial (9), anticancer (10), analgesic (11), antibacterial (12), antitumor (13), fungicidal (14) activity. Due to their wide range of biological significance as well astheir industrial and synthetic applications, there are several methods reported for the preparation of various classes of dihydropyrano (2,3-c) pyrazole derivatives, most of which have been carried out by using a variety of catalysts. Although, the reported methods are effective, they have limited applicability by the use of toxic catalysts, long reaction times, low yields of products and the use of toxic organic solvents. Recently, some environment-compatible catalysts such as ZrO_2 nanoparticles (15) ionic liquid(16), melamine (17) CeO_2/ZrO_2 (18), Pd(0) (19) proline (20) (Dabco-H)(AcO) (21) Ag/TiO_2 (22) nano -$CuFe_2O_4$ (23) taurine (24) Although each of these methods have their own advantages, some of them often suffer from one or more disadvantages such as use of long reaction time, expensive reagents and catalysts, hard reaction conditions, high temperature, tedious work-up procedures, and generation of large amounts of toxic wastes, which leads to negative impact on environment low product yield, nonrecyclable, hazardous organic solvents, limiting their opportunity for use in practical applications. Therefore, there is still a great desire for more green protocols, general, efficient, feasible, high-yielding, and cost-effective methods using new and efficient catalysts for the synthesis of this class of heterocyclic compounds. Fly an industrial waste (pollutant) is seen as applicable for catalysing reaction, which have pharmacological, industrial and therapeutic significance, such as Beckmann adjustment, Knoevenagel condensation, and numerous comparative reactions (25-26). Hence, herein we report an eco-safe, highly efficient and inexpensive preheated fly-ash catalysed procedure for synthesis of dihydropyrano(2,3-c)pyrazole, scaffolds via multicomponent Knoevenagel cyclocondensation between aromatic aldehydes, malononitrile, hydrazine hydrate, and ethyl acetoacetate in water as green solvent at 70-80 ^{0}C temperature (Scheme 1) which might solve some cost problems in industry.

Materials and Methods

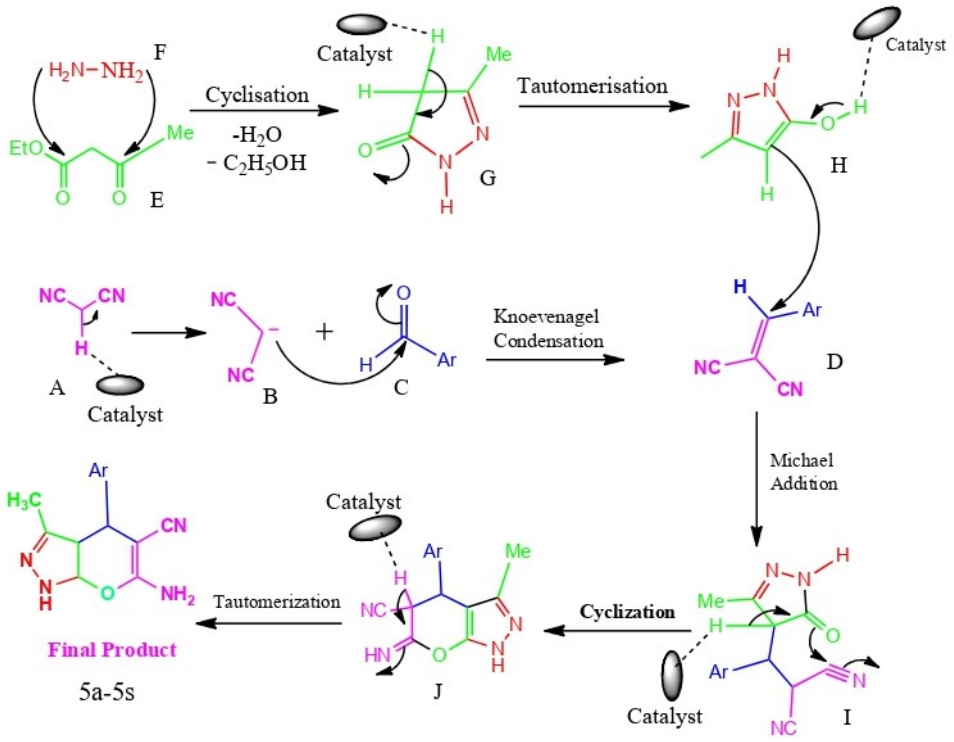
Fly-ash was collected from a local sugar factory Sugar factory Lakhimpur-Kheri, Uttar Pradesh, India. All chemicals were purchased from *Alfa Aesar* and Sigma Aldrich were used without purification. NMR spectra were recorded on 500 MHz for ^{1}H NMR and 125.75 MHz for ^{13}C NMR using TMS as an internal reference for both of the cases. Here chemical shifts were reported in parts per million (ppm) and melting points were monitored by open glass capillary method and were uncorrected. Physical and spectral data of the obtained products (5a-5s) were compared with reported literature data.

General process for synthesis of 6-amino-1,4-dihydropyrano(2,3-c)pyrazole-5-carbonitrile derivatives

The catalyst has been prepared by the procedure reported in the literature (27). Anequi-molar quantities of aromatic aldehydes 1 (2 mmol), malononitrile2 (2 mmol), ethyl acetoacetate 3 (2 mmol) hydrazine hydrate 4 (2 mmol), catalyst preheated fly-ash (0.50 g) and water solvent were heated at 70-80 ^{0}C for 60-90 minutes. After completion of (monitored by TLC), reaction the reaction mixture was cooled. The precipitate was collected by suction filtration and washed using cold ethanol. The crude product was recrystallized using ethanol. The insoluble catalyst has been recycled by washing with ethyl acetate followed by drying in an oven at 100 °C for one hour and reused for further reactions. Specific details of synthesised product are mentioned (5a-5s) in Table 3.



Scheme 1. The synthesis of dihydropyrano[2,3-c]pyrazole derivatives catalysed by preheated Fly-ash catalyst in water.



Scheme 2. Possible mechanism for the formation of dihydropyrano[2,3□c]pyrazole derivatives

We have also proposed a possible mechanism for the synthesis of final products (5a-5s) (Scheme 2). The nitrile anion (B) was formed by the removal of acidic hydrogen from cyanoacetonitrile (A) catalyzed by Preheated Fly-ash catalyst. Finally, the intermediates (D) are formed through the Knoevenagel condensation reaction pathway of the intermediate nitrile anion (B) with aldehydes derivatives (C). On other hand, compound (G), was obtained by the reaction of ethyl acetoacetate (E) and hydrazine hydrate (F) which was enolised in the presence of Preheated Fly-ash catalyst to formed compound (H). Consequently, the compound (H) formed undergoes condensation with the Knoevenagel adducts (D) via Michael addition type addition, which results formation of an adduct (I) (Michael adducts). Then there is subsequent intramolecular nucleophilic cyclization with the help of Preheated Fly-ash catalyst followed by tautomerization to afford the desired compounds (5a-5s).

Results and Discussion

A new, facile, efficient and cost-effective method has been designed for the synthesis of dihydropyrano(2,3‑c) pyrazole derivatives. In this method, we applied a cheap and eco-friendly catalyst Preheated-Fly ash, (derived from an industrial waste pollutant). The dihydropyrano(2,3‑c) pyrazole compounds (5a–5s) were synthesised through the one pot reaction of substituted aldehydes, malononitrile, ethyl acetoacetate and hydrazine hydrate using preheated preheated-fly-ash as catalyst in a high-yield (90-95%) with simple workup procedure (Scheme 1).

With these investigative results in hand, our next objective was to increase the product yield obtained in the earlier study. The only way in mind was the addition of a varying suitable catalyst (Table 1) and solvents (Table 2) amount that could increase efficiency of the present method in terms of product yield as well as reaction time. In consideration of this basis and having the knowledge of recently investigated preheated fly ash reaction medium, it was decided to utilize this system for our reaction. When actually this reaction medium was applied for the model reaction, we were delighted to know that the reaction was completing within only 90 min (1.5hr) and that too at 60-70 ^{0}C temperature affording the product in good yield (Table 1, entry 6). Additionally, some more trials were taken with varying quantities of preheated fly ash and water to know their proper amount to be utilized for the reaction in an order to attain the best experimental conditions. Our investigation emphasized that the presence of 0.50 g of preheated fly ash in combination with water for the reaction affords the highest yield of the product (Table 3 entry 5a-5s). This may be due to the achievement of best

Table 1. Comparison of various amount catalysts (Preheated-Fly ash) in water employed in model reaction synthesis (5a-5s).

Entry	Catalyst (gm)	Tem (^{0}C)	Time (min)	Yield (%)
1.	No Catalyst	rt	90	Negligible
2.	No Catalyst	reflux	90	10
3.	0.20	rt	90	70
4.	0.20	Reflux	90	80
5.	0.50	rt	60	86
6.	0.50	60-70	60	90-95

Table 2. Screening of solvents in model synthesis of dihydropyrano[2,3-c] pyrazole derivatives (5a-5s) using catalysts Preheated-Fly ash.

Entry	Solvent	Yields (%)
1.	Dichloromethane (DCM)	15-25
2.	Tetrahydrofuran (THF)	20-30
3.	Acetonitrile	35-40
4.	Ethanol	70-75
5.	Water	90-95

Table 3. Synthesis of dihydropyrano[2,3-c] pyrazole derivatives (5a-5s) using catalysts Preheated-Fly ash.

Entry	Aldehyde	Compound[d]	Yield[b](%)	M.P.(°C)[c]
1.	4-cyano)-	5a	95	219–220
2.	4-fluoro)-	5b	92	172–173
3.	4-methylthio)-	5c	90	218-220
4.	4-H)-	5d	95	245-247
5.	4-chloro)-	5e	93	233-335
6.	4-hydroxy)-	5f	90	224-225
7.	2-hydroxy)-	5g	90	210-111
8.	2-chloro)-	5h	93	146-148
9.	4-methoxy)-	5i	90	210-112
10.	4-dimethylamino)-	5j	92	166-168
11.	4-nitrophenyl)-	5k	94	250-252
12.	4-(furan-2-yl)-	5l	96	216-217
13	3-hydroxyphenyl)-	5m	93	258-260
14.	4-bromophenyl)-	5n	94	178-180
15.	4-(3,4-dimethoxyphenyl)-	5o	92	188-189
16.	4-(3-bromophenyl)-	5p	90	219-221
17.	4-(3-nitrophenyl)	5q	94	194-196
18.	4-(2-nitrophenyl)-	5r	93	176–178
19.	4-(m--tolyl)-	5s	94	152–154

[a]Reaction of of aromatic aldehydes (2 mmol), ethyl acetoacetate (2 mmol), malononitrile (2 mmol), hydrazine hydrate (2 mmol), and catalyst preheated fly-ash 0.50 g in water solvent.
[b]Isolated yield.
[c]All the melting point are uncorrected compared with reference[28-35].
[d]All the synthesised compounds were characterised by ^{1}H NMR, IR, and^{13}CNMR were compared with the reference compound

concentration of reaction mixture, since lowering or increasing the amount of preheated fly ash leads to decreased rate of reaction. We investigated the effects of the amount of catalyst Preheated Fly ash in the model reaction using water solvent, for formation of dihydropyrano(2,3‑c) pyrazole derivatives studied (Table 1, entry 1-6). Next, in the catalyst free conditions, the reaction take place in negligible (10%) amount, even in the presence of solvent at prolonged reaction time at room temperature. Further, 25% yields were obtained when excess water solvents at refluxed condition without adding catalyst in reaction mixture. The efficiency of catalyst with increasing amount of catalyst from 0.5gm was also investigated. On increasing the amount of catalyst and temperature in our model reaction we found that using 0.2gm of catalyst yield was increased 70% to 80% on room temperature and refluxed condition respectively. Furthermore, model reaction gives 90-95% yield on applying 0.5gm of catalyst at 60-70 ^{0}C in 90 minutes. To our surprise, reaction in aqueous media at 60-70 ^{0}C temperature it was observed that reaction proceed towards the desired product in satisfactory yield (90-95 %) and it was the best reaction condition of our model synthesis.

We have also investigated that the different aromatic aldehydes having electron-withdrawing groups and electron donating groups employed and reacted well to give corresponding dihydropyrano(2,3-c) pyrazole-5-carbonitrile derivatives. It has been observed that the time required to complete the reactions is slightly lower in the case of aldehydes containing electron donating group as substituent (o & p position). The present protocol was found well applicable for dihydropyrano(2,3-c) pyrazole-5-carbonitrile moieties (Table 3 entry 5a-5s) with respect of yield and reaction time but failed to give corresponding dihydropyrano(2,3-c) pyrazole-5-carbonitrile derivatives when aliphatic aldehydes such as formaldehyde and acetaldehyde were used under optimized reaction conditions. To select the best solvent, various solvents (Table 2, entry 1-5) such as Water, Ethanol, Dichloromethane, Acetonitrile, and Tetrahydrofuran (THF) were studied for the probe reaction with 0.50 gm of preheated-fly-ash as catalyst at 70-80 ^{0}C. It has been observed that the poor yield was obtained with other organic solvents namely Dichloromethane, Acetonitrile, and Tetrahydrofuran (THF) while the best yield was obtained in water (Table 2, entry 1-5). The result of this study other aromatic aldehydes has been reacted in water and the results are listed in (Table 3 entry 5a-5s). The present methodology provides the products in appropriate time leading with good to excellent yields of products due to the catalytic effect of Preheated-Fly-ash without any additional chromatographic purification and is non-hazardous to environment.

Spectral data of some representative compound

6-Amino-4-(4-cyanophenyl)-3-methyl-1,4-dihydropyrano(2,3-c)pyrazole-5-carbonitrile(5a)

M.P. 219–220 ^{0}C. Yellow solid; IR (KBr, cm^{-1}): 3482, 3238, 3116, 2229, 2187, 1646, 1592, 1485, 1409, 1058. **^{1}H NMR (DMSO-d$_6$)**: 2.11-2.15 (s, 3H, -CH_3), 4.86-4.87 (s, 1H, CH), 6.64-6.71 (s, 2H, NH_2), 7.11-7.14 (d, J = 8.1 Hz, 2H), 7.34-7.41 (d, J = 8.1 Hz, 2H), 12.08 (s, 1H acidic). **^{13}C NMR (DMSO-d$_6$):** 13.73, 15.94, 57.12, 110.57, 111.34, 116.61, 118.47, 121.87, 137.85, 143.55, 159.34, 162.91, 169.12.

6-Amino-4-(4-fluorophenyl)-3-methyl-1,4-dihydropyrano(2,3-c) pyrazole-5-carbonitrile **(5b).M.P.**172–173 ^{0}C.Yellow solid; **IR** (KBr, cm^{-1}): 3485, 3234, 21944, 1638, 1594, 1510, 1395, 1228. **1 H NMR (DMSO-d$_6$)**: d 2.16 (s, 3H, CH_3), 4.84 (s, 1H, CH), 6.73 (s, 2H, NH2), 7.15 (d, J = 8.2 Hz, 2H), 7.30-7.37 (d, J = 8.2 Hz, 2H), 12.04-12.11 (s, 1H, NH). **^{13}C NMR (DMSO-d$_6$):** 13.84, 16.24, 57.27, 109.25, 111.54, 116.91, 119.43, 134.87, 141.31, 157.14, 159.83, 166.64.

6-Amino-3-methyl-4-(4-(methylthio)phenyl)-1,4-dihydropyrano(2,3-c)pyrazole-5-carbonitrile **(5c).M.P.** 218-220 ^{0}C.Yellow solid; **IR** (KBr, cm^{-1}): 3475, 2190, 1646, 1495, 1409, and 1051. **^{1}H NMR (DMSO-d$_6$)**: 2.04-2.11 (s, 3H, CH_3), 2.24-2.37 (s, 3H, SCH_3), 4.74-4.51 (s, 1H, CH), 6.61-6.67(s, 2H, -NH2), 6.91-7.04 (d, J = 8.1 Hz, 2H), 7.31-7.34 (d, J = 8.1 Hz, 2H), 11.87-11.94 (s, 1H, NH). **^{13}C NMR (DMSO-d$_6$):** 14.14, 16.23, 23.41, 56.34, 108.14, 111.58, 116.98, 119.17, 133.64, 142.17, 155.41, 157.67, 161.41;

6-Amino-3-methyl-4-phenyl-1,4-dihydropyrano-(2,3-c) pyrazole-5-carbonitrile, (5d)

M.P. 245-47°C.White solid.**IR** (KBr, cm^{-1}): 3412, 3345, 3318, 3065, 3038 (Aromatic), 2930 (-Me), 2208, and 1487 cm^{-1}.**^{1}H NMR (500 MHz, DMSO-d$_6$)**: δH (ppm) 1.85 (s, 3H, Me), 4.63 (s, 1H, 4H), 6.47 (s, 2H), 7.18-7.27 (m, 5H), 12.13 (s, 1H). **^{13}C NMR (100 MHz, DMSO-d$_6$)**: δ (ppm) 9.95, 35.43, 55.74, 113.36, 117.31, 125.17, 129.46, 135.73, 139.79, 156.54, 161.78.

6-Amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano(2,3-c)pyrazole-5-carbonitrile, (5e)

M.P. 233-335°C.White solid.**IR** (KBr, cm^{-1}): 3408, 3391, 3317 (-NH-), 3060, 3017 (Ph), 2931 (-Me), 2211 (-CN), 1480 (-NH-), 1058 and 815 cm^{-1}. **^{1}H NMR (500 MHz, DMSO-d6):**δH (ppm) 1.77 (s, 3H, CH3), 4.67 (s, 1H, 4H), 6.91 (s, 2H), 7.11-7.17 (d, 2H, J = 8.40 Hz,), 7.35-7.39 (d, 2H, J = 8.40 Hz), 12.11 (s, 1H, NH). **^{13}C NMR (100 MHz, DMSO-d$_6$)**: δC (ppm) 135.52, 56.68, 97.17, 120.61, 128.45, 129.21, 129.31, 129.57, 130.21, 131.27, 135.68, 143.46, 154.56, 160.87.

6-Amino-4-(4-hydroxyphenyl)-3-methyl-1,4-dihydropyrano(2,3-c)pyrazole-5carbonitrile (5f)

M.P. 224-225°C.Light yellow solid.**IR** (KBr, cm^{-1}): 3452 (HO-), 3410, 3395 (NH_2), 3322 (-NH), 3053, 3021, 2921 (-Me), 2200, 1477 (-NH) and 793 cm^{-1}. **^{1}H NMR (500 MHz, DMSO-d$_6$)**: δH (ppm) 1.87 (s, 3H, CH3), 4.88 (s, 1H, 4H), 6.76 (s, 2H, NH2), 6.95 (s, 1H), 7.21-7.27 (d, 2H, J = 8.40 Hz, Ar), 7.33-7.37 (d, 2H, J = 8.40 Hz, Ar-), 12.08 (s, 1H, -NH). **^{13}C NMR (100 MHz, DMSO-d$_6$):**δC (ppm) 9.91, 35.47, 55.72, 98.47, 121.21, 128.34, 129.27, 129.47, 130.72, 135.68, 144.55, 156.65, 161.84.

6-Amino-4-(2-hydroxyphenyl)-3-methyl-1,4-dihydropyrano(2,3-c)pyrazole-5 carbonitrile, (5g)

M.P. 210-111°C.Yellow solid.**IR** (KBr, cm^{-1}): 3452 (-OH), 3408, 3392 (-NH), 3330 (-NH-), 3067, 3034 (aromatic), 2932 (-Me), 2225 (-CN), 1489 (-NH), 740 cm^{-1} (-OH). **^{1}H NMR (500 MHz, DMSO-d$_6$):**δH (ppm) 1.91 (s, 3H, Me), 4.64 (s, 1H, 4H), 6.72 (s, 2H, NH2),

7.06 (s, 1H, acidic), 7.21-7.33 (m, 4H, Ar-), 10.73 (s, 1H, -NH). **^{13}C NMR (100 MHz, DMSO-d$_6$):**δC (ppm) 9.77, 28.65, 54.96, 89.49, 104.84, 115.38, 119.54, 120.84, 123.63, 127.48, 128.89, 136.57, 148.36, 158.68, 160.09, 162.81.

6-Amino-4-(2-chlorophenyl)-3-methyl-1,4-dihydropyrano(2,3-c) pyrazole-5-carbonitrile, (5h)

M.P.146-148°C.white solid.**IR** (KBr, cm^{-1}): 3410, 3394 (-NH), 3310 (-NH), 3068, 3036 (Aromatic), 2935 (-Me), 2209 (-CN), 1486 (-NH), 1068, 752. **^{1}H NMR (500 MHz, DMSO-d6)**: δH (ppm) 1.85 (s, 3H, Me), 4.97 (s, 1H, 4H), 6.75 (s, 2H, -NH), 7.11-7.41 (m, 3H, Ar), 7.74-7.84 (m, 1H, Ar), 11.27 (s, 1H, -NH). **^{13}C NMR (100 MHz, DMSO-d$_6$)**: δC (ppm) 9.73, 29.37, 55.85, 88.87, 104.49, 115.17, 120.39, 121.37, 123.79, 126.28, 128.45, 137.99, 147.28, 158.67, 163.87.

6-*Amino-4-(4-methoxyphenyl)-3-methyl-1,4-dihydropyrano(2,3-c)pyrazole-5-carbonitrile (5i)*

M.P. 210-112°C. Light yellow solid. **IR** (KBr, cm^{-1}): 3415, 3395 (NH-), 3320 (-NH), 3078, 3022 (Aromatic), 2933 (-Me-), 2216 (-CN), 1482(-NH), 1368, 1560 and, 778. **^{1}H NMR (500 MHz, DMSO-d$_6$)**: δH (ppm) 1.78 (s, 3H, Me), 3.67 (s, 3H, -OMe), 4.57 (s, 1H, 4H), 6.86 (s, 2H, NH-), 7.36-7.39 (d, 2H, J = 7.96 Hz, Arromatic), 7.73-7.77 (d, 2H, J = 8.04 Hz, Ar), 12.17 (s, 1H, NH-). **^{13}C NMR (100 MHz, DMSO-d$_6$)**: δC (ppm) 9.84, 27.93, 55.17, 99.35, 111.79, 112.75, 121.45, 128.46, 127.59, 134.47, 135.26, 163.42.

6-Amino-4-(4-(dimethylamino) phenyl)-3-methyl-1,4-dihydropyrano(2,3-c)pyrazole-5-carbonitrile(5j)

M.P. 166-168°C.Light brown solid IR (KBr, cm^{-1}): 3405, 3378 (-NH), 3353 (-NH-), 3064, 3033 (Aromatic), 2932 (-Me), 2223 (NC-), 1498 and 810. **^{1}H NMR (500 MHz, DMSO-d$_6$)**: δH (ppm) 1.83 (s, 3H, -Me), 2.79 (s, 6H, - Me), 4.58 (s, 1H, 4H), 6.65 (s, 2H, NH-), 6.59 (d, 2H, J = 8.4 Hz, Ar), 6.97 (d, 2H, J = 7.6 Hz, Ar), 11.72 (s, 1H, -NH). **^{13}C NMR (100 MHz, DMSO-d$_6$)**: δC (ppm) 10.28, 29.49, 57.52, 86.52, 104.24, 119.83, 125.40, 133.37, 133.24, 133.73, 140.93, 160.114, 163.10.

6-Amino-4-(4-nitrophenyl)-3-methyl-1,4-dihydropyrano(2,3-c)pyrazole-5-carbonitrile(5k)

M.P.250-252°C.Yellow solid. IR (KBr, cm^{-1}): 3414, 3389 (NH_2), 3323 (-NH-), 3073, 3025 (Aromatic), 2936 (-CH_3), 2209 (-CN), 1485 (-NH-), 1358, 1563 (-NO_2), 818 (para-NO_2). **^{1}H NMR (500 MHz, DMSO-d$_6$)**: δH (ppm) 1.84 (s, 3H, -CH_3), 4.86 (s, 1H, 4H), 7.05 (s, 2H, -NH_2), 7.42-7.45 (d, 2H, J = 8.48 Hz, Ar-H), 8.22-8.28 (d, 2H, J = 8.48 Hz, Ar-H), 12.24 (s, 1H, NH). **^{13}C NMR (100 MHz, DMSO-d$_6$):**δC (ppm) 9.74, 35.82, 55.87, 96.54, 120.49, 123.84, 128.83, 135.86, 146.36, 152.27, 154.62, 161.35.

6-Amino-4-(furan-2-yl)-3-methyl-1,4-dihydropyrano(2,3-c) pyrazole-5-carbonitrile, (5l)

M. P. 216-217°C.Brown solid.**IR** (KBr, cm^{-1}): 3413, 3384 (NH-), 3325 (-NH-), 3089, 3025, 2935 (-Me), 2215, 1496 (-NH-) and 1208. **^{1}H NMR (500 MHz, DMSO-d$_6$)**: δH (ppm) 1.86 (s, 3H, CH_3), 4.69 (s, 1H, 4H), 6.54 (s, 2H, NH-), 6.89 (d, 1H, Furan), 7.17 (t, 1H, Furan-H), 7.39 (d, 1H, Furan-H), 12.18 (s, 1H, NH). **^{13}C NMR (100 MHz, DMSO-d$_6$)**: δC (ppm) 9.79, 34.24, 58.95, 104.86, 110.57, 113.48, 118.49, 138.74, 145.86, 154.67, 158.23, 163.11.

6-Amino-4-(3-hydroxyphenyl)-3-methyl-1,4-dihydropyrano(2,3-c)pyrazole-5-carbonitrile, (5m)

M. P. 258-260°C.White solid. IR (KBr, cm^{-1}): 3458 (-OH), 3410, 3377 (NH-), 3314 (-NH-), 3062, 3037 (Aromatic H), 2935 (-Me), 2210 (-CN), 1492 (-NH-), and 778. **^{1}H NMR (500 MHz, DMSO-d$_6$)**: δH (ppm) 1.95 (s, 3H, Me), 4.86 (s, 1H, 4H), 6.79 (s, 2H, NH_2), 6.99 (s, 1H, -OH), 7.58 (t, 1H, J = 8.0 Hz, Ar-H), 7.66 (d, 1H, J = 7.6 Hz, Ar-H), 8.15-8.10 (m, 2H, Ar-H), 11.25 (s, 1H, -NH). **^{13}C NMR (100 MHz, DMSO-d$_6$)**: δC (ppm) 9.59, 28.88, 58.25, 113.79, 122.37, 124.22, 129.48, 130.60, 136.78, 141.39, 147.38, 152.37, 155.66, 162.35.

6-Amino-4-(4-bromophenyl)-3-methyl-1,4-dihydropyrano(2,3-c)pyrazole-5-carbonitrile, (5n)

M.P. 178-180°C.White solid.**IR** (KBr, cm^{-1}): 3409, 3393 (NH-), 33175 (-NH), 3068, 3028 (Aromatic), 2930 (-Me), 2202 (-CN), 1622, 1487 (-NH), 1064, and 810 cm^{-1}.**^{1}H NMR (500 MHz, DMSO-d$_6$)**: δH (ppm) 2.19 (s, 3H, CH_3), 4.78 (s, 1H, 4H), 6.57 (s, 2H, NH_2), 7.46-7.45 (d, 2H, J = 8.48 Hz, Aromatic -H), 7.54-7.53 (d, 2H, J = 8.42-8.41 Hz, Ar-H), 10.95-10.96 (s, 1H, -NH). **^{13}C NMR (100 MHz, DMSO-d$_6$):**δC (ppm) 9.67, 27.228, 40.51, 98.08, 113.80, 113.99, 120.88, 129.80, 131.59, 138.17, 139.23, 158.99.

6-Amino-4-(3,4-dimethoxyphenyl)-3-methyl-1,4-dihydropyrano(2,3-c)pyrazole-5-carbonitrile, (5o)

M.P. 188-189°C.White solid.**IR** (KBr, cm^{-1}): 3385, 3384 (NH_2), 3312 (-NH-), 3068, 3014 (Aromatic), 2927 (-Me), 2205 (-CN), 1485 (-NH), 2592 (-OMe), 707 and 809 (para-OMe).**^{1}H NMR (500 MHz, DMSO-d$_6$):**δH (ppm) 1.95-1.99 (s, 3H, Me), 3.85-3.89 (s, 6H,), 4.73 (s, 1H, 4H), 6.79 (s, 2H,), 7.51-7.69 (m, 2H, Ar-H), 7.92-7.99 (s, 1H, Ar-H), 11.41-11.50 (s, 1H,). **^{13}C NMR (100 MHz, DMSO-d$_6$)**: δC (ppm) 9.71, 31.69, 56.82, 60.22, 99.13, 102.39, 104.40, 121.84, 124.59, 126.49, 134.51, 145.69, 153.20, 156.15, 163.19.

6-Amino-4-(3-bromophenyl)-3-methyl-1,4-dihydropyrano(2,3-c) pyrazole-5-carbonitrile (5p)

M.P. 219-221°C.Yellow solid: **IR** (KBr, cm^{-1}): 3408, 3391, 3317 (-NH-), 3060, 3017 (Ph), 2931 (-Me), 2211 (-CN), 1480 (-NH-), 1061 and 815 cm^{-1}. **^{1}H NMR (500 MHz, DMSO-d6):**δH (ppm) 1.79 (s, 3H, CH3), 4.88 (s, 1H, 4H), 6.17 (s, 2H), 7.20-7.32 (d, 2H, J = 8.40 Hz,), 7.43-7.47 (d, 2H, J = 8.40 Hz), 12.20 (s, 1H, NH). **^{13}C NMR (100 MHz, DMSO-d_6)**: δC (ppm) 135.61, 56.69, 97.20, 120.70, 128.66, 129.50, 129.50, 129.70, 130.40, 131.48, 135.89, 143.78, 154.65, 160.99.

6-Amino-1,4-dihydro-3-methyl-4-(3-nitrophenyl)pyrano(2,3-c)pyrazole-5-carbonitrile (5q)

M.P. 194-196°C**Yellow solid** IR ((KBr, cm^{-1}): 1041, 2195, 3117, 3234, 3474. **^{1}H NMR (500 MHz, DMSO-d6):***δ*: 1.87(s, 3H), 4.81 (s, 1H), 7.19 (s, 2H), 7.69-7.50 (m, 2H), 8.11 (s, 1H), 8.19-8.13 (m, 1H), 12.20 (s, 1H). **^{13}C NMR (100 MHz, DMSO-d_6)**: *δ*: 9.70, 35.69, 56.11, 96.69, 120.41, 121.89, 121.90, 130.20, 134.35, 135.80, 146.71, 147.79, 154.67, and 161.18.

6-Amino-3-methyl-4-(2-nitrophenyl)-2,4-dihydropyrano(2,3-c)pyrazole-5-carbonitrile (5r)

M.P. 176–178 ^{0}CWhite solid; (KBr, cm^{-1}): 3445(NH), 3300 (NH2), 3202(NH), 2210 (CN), 2980 (C=C–H), 1371 (CN), 1604 (C= C aromatic), 1070(C-O-C); **^{1}H NMR (500 MHz, DMSO-d6):**δH: 2.39 (s, 3H, CH3), 5.18 (s, 1H, CH=), 6.90 (br, s, 2H, H2N-),7.44 (m, 2H, Ar–H), 7.89(m, 2H, Ar–H), 12.15 (s, 1H); **^{13}C NMR (100 MHz, DMSO-d_6)**: = 165, 159, 158, 147,138, 132, 131, 129, 128, 122, 119, 107, 61, 57, 31, 12 ppm

6-Amino-3-methyl-4-(m--tolyl)-2,4-dihydropyrano(2,3-c) pyrazole-5-carbonitrile (5s)

m.p.: 152–154 ^{0}C,White solid; IR (KBr, cm^{-1}): 3383(H2N-), 3338 (NH2), 3223(NH), 2191 (CN), 2960(=C–H), 1398 (C=N), 1604 (C= C aromatic), 1060(C-O-C) ; **^{1}H NMR (500 MHz, DMSO-d6):** δH:2.31 (s, 3H, CH3), 3.79 (s, 3H, Me), 4.28 (s, 1H, C-H=), 6.61 (br, s, 2H, NH2),6.79– 6.79 (m, 4H, Ar–H), 12.15 (s, 1H); **^{13}C NMR (100 MHz, DMSO-d_6)**: δ = 165.1, 158, 157, 146.7, 128, 118, 114, 112, 108, 58, 56, 55, 12 ppm.

Conclusion

In Conclusion, we have developed a new, easy, efficient method for eco-compatible preparation of dihydropyrano(2,3‑c)pyrazole in an aqueous medium with preheated fly ash, (an industrial waste pollutant) as an efficient catalyst. The mildness of the conversion, the experimental simplicity, compatibility with various functional groups, excellent yield of product (up to 95%) and the ease of separation, nontoxic, and recyclability of the catalyst, make this approach attractive for synthesizing a variety of such derivatives.

References

1. Gu Y. Multicomponent reactions in unconventional solvents: state of the art. Green Chem. 2012;14:2091-2118.
2. Kanchithalaivan S, Sivakumar S, Ranjith Kumar R, Elumalai P, Ahmed QN and Padala AK. Four Component Domino Strategy for the Combinatorial Synthesis of Novel 1,4-Dihydropyrano[2,3 c]pyrazol-6-amines. ACS Combinat Sci. 2013;15(12):631-638.
3. Sunderhaus JD and Martin SF. Applications of Multicomponent Reactions to the Synthesis of Diverse Heterocyclic Scaffolds. Chemistry (Weinheiman der Bergstrasse, Germany). 2009;15(6):1300-1308.
4. Brauch S, van Berkel SS and Westermann B. Higher-order multicomponent reactions: beyond four reactants. Chem Soc Rev. 2013;42(12):4948-4962.
5. Naim MJ, Alam O, Farah Nawaz M, Alam J and Alam P. Current status of pyrazole and its biological activities. J Pharm BioAllied Sci. 2016;8(1):2-17.
6. Ganta RK, Kerru N, Maddila S and Jonnalagadda SB. Molecules. 2021;26:3270-3301.
7. Al-Amiery AA, Al-Bayati RI, Saed FM, Ali WB, Kadhum AAH and Mohamad AB. Novel Pyranopyrazoles: Synthesis and Theoretical Studies. Molecules. 2012;17:10377-10389.
8. Zolfigol MA, Tavasoli M, Moosavi-Zare AR, Moosavi P, Kruger HG, Shiri M and Khakyzadeh V. Synthesis of pyranopyrazoles using isonicotinic acid as a dual and biological organocatalyst. RSC Adv. 2013;3:25681-25685.
9. Smith RH, Jorgensen WL, Tirado-Rives J, Lamb ML, Janssen PA, Michejda CJ and Kroeger Smith MB. Prediction of Binding Affinities for TIBO Inhibitors of HIV-1 Reverse Transcriptase Using Monte Carlo Simulations in a Linear Response Method. J Med Chem. 1998;41(26):5272-5286.
10. Wang JL, Liu D, Zhang Z, Shan S, Han X, Srinivasula SM, Croce CM, Alnemri ES and Huang Z, Structure-based discovery of an organic compound that binds Bcl-2 protein and induces apoptosis of tumor cells. Proceed Natl Acad Sci. 2000;97(13):7124-7129.
11. Kuo SC, Huang LJ, and Nakamura H. Studies on Heterocyclic Compounds 6. Synthesis and Analgesic and Antiinflammatory Activities of 3,4-Dimethylpyrano[2,3-c]pyrazol-6-one Derivatives. J Med Chem. 1984;27(4):539-544.
12. Chougala BM, Samundeeswari S, Holiyachi M, Shastri LA, Dodamani S, Jalalpure S and Sunagar VA. Synthesis, characterization and molecular docking studies of substituted 4- coumarinylpyrano[2,3-c]pyrazole derivatives as potent antibacterial and antiinflammatory agents. Eur j med chem. 2017;125:101-116.
13. Colotta V, Catarzi D, Varano F, Melani F, Filacchioni G, Cecchi L, Trincavelli L, Martini C and Lucacchini A. Synthesis and A1 and A2A adenosine binding activity of

some pyrano [2,3-c] pyrazol-4-ones. IL Farmaco. 1998;53:189-196.
14. Zhang CY, Liu XH, Wang BL, Wang SH and Li ZM. Synthesis and Antifungal Activities of New Pyrazole Derivatives via 1,3-dipolar Cycloaddition Reaction. Chem Biol Drug Design. 2010;75(5):489-493.
15. Saha A, Payra S and Banerjee S. One-pot multicomponent synthesis of highly functionalized bio-active pyrano[2,3-c]pyrazole and benzylpyrazolyl coumarin derivatives using ZrO_2 nanoparticles as a reusable catalyst. Green Chem. 2015;17(5):2859-2866.
16. Ebrahimi J, Mohammadi A, Pakjoo V, Bahramzade E and Habibi A. Highly efficient solvent-free synthesis of pyranopyrazoles by a Brønsted-acidic ionic liquid as a green and reusable catalyst. J Chem Sci. 2012;124(5):1013-1017.
17. Valiey E, Dekamin MG and Alirezvani Z. Melamine-modified chitosan materials: An efficient and recyclable bifunctional organocatalyst for green synthesis of densely functionalized bioactive dihydropyrano[2,3-c]pyrazole and benzylpyrazolyl coumarin derivatives. Int J Biol Macromol. 2019;129:407-421.
18. Maddila SN, Maddila S, Werner, E. van Zyl and Sreekantha BJ. CeO2/ZrO2 as green catalyst for one-pot synthesis of new pyrano[2,3-c]-pyrazoles. Res Chem Intermed. 2017;43:4313-4325.
19. Saha M and Pal AK. Palladium (0) Nanoparticles: A Novel and Reusable Catalyst for the Synthesis of Various Pyran Derivatives. Adv Nanoparticles. 2012;1(3):61-70.
20. Guo SB, Wang SX and Li JT. D,L-Proline-Catalyzed One-Pot Synthesis of Pyrans and Pyrano[2,3-c]pyrazole Derivatives by a Grinding Method under Solvent-Free Conditions. Synthet Commun. 2007;3713:2111-2120.
21. Liu T, Lai YH, Yu YQ and Xu DZ. A facile and efficient procedure for one-pot four-component synthesis of polysubstituted spiro pyrano[2,3-c]pyrazole and spiro 1,4-dihydropyridine catalyzed by Dabco-based ionic liquid under mild condition. New J Chem. 2018;42(2):1046-1051.
22. Fatahpour M, Sadeh FN, Hazeri, Maghsoodlou MT, Hadavi MS and Mahnaei S. Ag/TiO2 nano-thin films as robust heterogeneous catalyst for one-pot, multi-component synthesis of bis (pyrazol-5-ol) and dihydropyrano [2,3-c] pyrazole analogs. J Saudi Chem Soc. 2017;21(8):998-1006.
23. Pradhan K, Paul S and Das AR. Magnetically retrievable nano crystalline CuFe2O4 catalyzed multi-component reaction: a facile and efficient synthesis of functionalized dihydropyrano [2,3-c] pyrazole, pyrano [3, 2-c] coumarin and 4 H-chromene derivatives in aqueous media. Catalys Sci Technol. 2014;4(3):822-831.
24. Mali G, Shaikh BA, Garg S, Kumar A, Bhattacharyya S, Erande R and Chate AV. Design, Synthesis, and Biological Evaluation of Densely Substituted Dihydropyrano [2,3-c] pyrazoles via a Taurine-Catalyzed Green Multicomponent Approach. ACS Omega. 2021;6(45):30734-30742.
25. Thirunarayanan G and Sekar KG. Preheated fly-ash catalyzed cyclization ofchalcones: Synthesis of some substituted pyrazole-1-carbothioamides and spectral correlations in 3-(3, 4-dichlorophenyl)-5-(substituted phenyl)-4, 5-dihydro-1H-pyrazole-1 carbothioamides. Int Lett Chem Physics Astronomy. 2013;10:18-34.
26. A.K .Pandey, A. Kumar, P. Singh and S. K. Srivastava. Activated fly-ash promoted cost effective and green synthesis of hexahydroacridine-1,8(2H,5H)-diones in aqueous medium. Heterocycl Lett. 2021;11(4):675-682.
27. Arulkumaran R, Vijayakumar S, Sakthinathan SP, Kamalakkannan D, Ranganathan K, Suresh R, Sundararajan R, Vanangamudi G and Thirunarayanan G. Preheated FLY-ASH catalyzed aldol condensation: efficient synthesis of chalcones and antimicrobial activities of some 3-thienyl chalcones. J Chil Chem Soc. 2013;58(2):1684-1690.
28. Tafti A, Mirjalili BF, Bamoniri A and Salehi N. Rapid four-component synthesis of dihydropyrano[2,3-c]pyrazoles using nano-eggshell/Ti(IV) as a highly compatible natural based catalyst. BMC Chem. 2021;15(1):1-8.
29. Pandey AK, Kumar and Shrivastava SC. Sugarcane Bagasse Ash-Based Silica-Supported Boric Acid (SBA-SiO2-H3BO3): A Versatile and Reusable Catalyst for the Synthesis of 1, 4Dihydropyrano [2,3-c] pyrazole Derivatives. Russian J Organ Chem. 2021;57(4):653-660.
30. Mishra M, Nizam A, Jomon KJ and Tadaparthi K. A New Facile Ultrasound-Assisted Magnetic Nano-[CoFe2O4]-Catalyzed One-Pot Synthesis of Pyrano [2, 3-c] pyrazoles. Russian J Organ Chem. 2019;55(12):1925-1928.
31. Kiyani H, Samimi H, Ghorbani F and Esmaieli S. One-pot, four-component synthesis of pyrano [2,3-c] pyrazoles catalyzed by sodium benzoate in aqueous medium. Curr Chem Lett. 2013;2(4):197-206.
32. Shahbazi S, Ghasemzadeh MA, Shakib P, Zolfaghari MR and Bahmani M. Synthesis and antimicrobial study of 1, 4-dihydropyrano [2, 3-c] pyrazole derivatives in the presence of amino-functionalized silica-coated cobalt oxide nanostructures as catalyst. Polyhedron. 2019;170:172-179.
33. Mohamadpour F. Catalyst-free green synthesis of dihydropyrano[2,3-c]pyrazole scaffolds assisted by ethylene glycol (E-G) as a reusable and biodegradable solvent medium. J Chem Sci. 2020;132(1):72-80.
34. Shrivas P, Pandey R, Zodape S, Wankhade A and Pratap U. Green synthesis of pyranopyrazoles via biocatalytic one-pot Knoevenagel condensation–Michael-type addition–heterocyclization cascade in non-aqueous media. Res Chem Intermed. 2020;46(5):2805-2816.
35. Reddy GM, Kumari AK, Reddy VH and Garcia JR. Novel pyranopyrazole derivatives comprising a benzoxazole core as antimicrobial inhibitors: Design, synthesis, microbial resistance and machine aided results. Bioorgan Chem. 2020;100:103908.