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REGULAR ARTICLE

Catalyst-free green synthesis of dihydropyrano[2,3-*c*]pyrazole scaffolds assisted by ethylene glycol (E-G) as a reusable and biodegradable solvent medium

FARZANEH MOHAMADPOUR
School of Engineering, Apadana Institute of Higher Education, Shiraz, Iran
E-mail: mohamadpour.f.7@gmail.com

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Abstract. We revealed a catalyst-free, green and rapid one-pot four-component tandem strategy for the preparation of dihydropyrano[2,3-*c*]pyrazoles – a biologically significant scaffold – *via* Knoevenagel-Michael cyclocondensation based on green chemistry principles. Highlights of the current practice are the application of non-hazardous reaction circumstances, catalyst-free, operational simplicity, use of inexpensive initiating substances, isolation of pure product *via* easy filtration thus preventing the requirement for column chromatography, metal-free, excellent yields, time-saving aspects of the reaction. However, the green ethylene glycol (E-G) can be recycled at least six times with no considerable reduction in activity making it greatly advantageous in addressing the industrial requirements and environmental worries.

Keywords. Catalyst-free; ethylene glycol (E-G); green protocol; reusable solvent medium; dihydropyrano[2,3-*c*]pyrazoles.

1. Introduction

Over the previous years by increased demand for sustainable, environmentally friendly, and effective synthesis approaches in green chemistry, catalyst-free, solvent-mediated protocols for preparing the organic mixtures has emerged as a key approach considering their low cost, simple workup, decreased pollution, and preventing the influence of the catalyst on sensitive substrates. In the organic synthesizing procedure, the reaction medium has a key role in encouraging the contact within the reactants and even altering the reaction progress. Hence, the search for green reaction solvents with exclusive functions and features is still significant in the present green organic synthesis investigation. Recently, extensive attention has been driven by ethylene glycol (E-G) as a kind of a green and financially viable alternative to the conventional solvents. It includes favorable features like non-corrosiveness, stability, and decent solubility in organic compounds. Also, ethylene glycol (E-G) was also used as a green reaction environment in some convenient organic reactions[1] to prepare some important compounds.

Biochemists and synthetic organic chemists have been fascinated by the structures comprising the pyranopyrazole derivatives as a result of their biological and pharmaceutical activities[2] (Figure 1). There are reports in the literature regarding pyranopyrazole derivatives, biodegradable agrochemicals,[3] an inhibitor of the human Chk1 kinase,[4] anticancer,[5a] analgesic,[5b] molluscicidal[6] and antimicrobial.[7]

There are numerous approaches for synthesizing these compounds using various catalysts such as ZrO_2 NPs,[8] choline chloride/Urea deep,[9] isonicotinic,[10] molecular sieves,[11] meglumine,[12] CAPB,[13] L-proline/KF-alumina,[14] CTACl,[15] lipase,[16] bovine serum albumin,[17] β-cyclodextrin,[18] morpholine triflate,[19] TPSPPTNM,[20] [Dabco-H][AcO],[21] Fe_3O_4@SiO_2 nanoparticle-supported IL,[22] sodium ascorbate,[23] nano-SiO_2/DABCO,[24] NaF,[25] nano-SiO_2,[26] theophylline[27] and $[HMIM]C(NO_2)_3$.[28] It was shown that these reported procedures lead to numerous cases. Though, some of the synthetic policies contain also

*For correspondence

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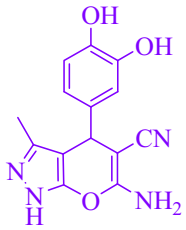
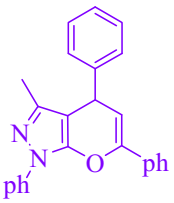
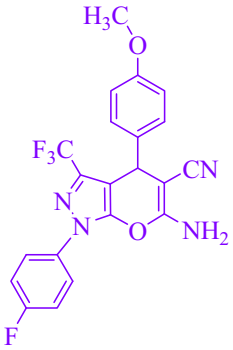


Inhibitor of human chk1 kinase

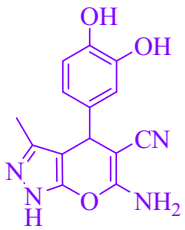


Antimicrobial

Molluscicide

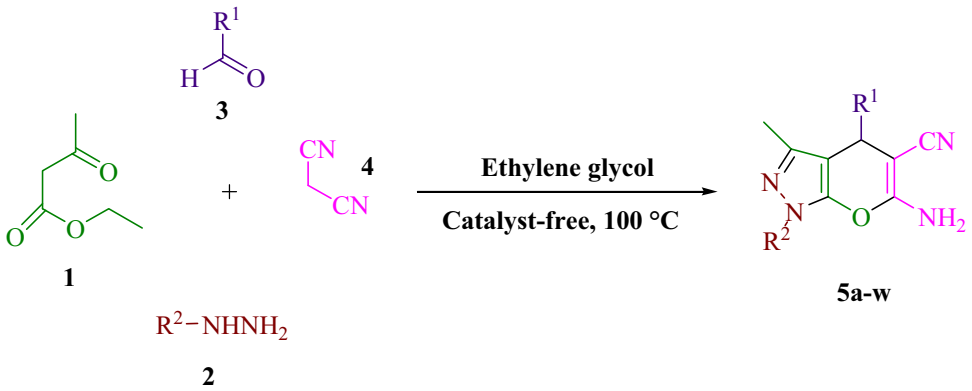


Anticancer agent



Inhibitor of human chk1 kinase

Figure 1. Biologically active molecules with dihydropyrano[2,3-c]pyrazole scaffold.



Scheme 1. Synthesis of dihydropyrano[2,3-*c*]pyrazole scaffolds.

restrictions regarding the expensive reagents, metal catalyst, environmental hazard, long reaction time, harsh reaction circumstances, monotonous workup process, unacceptable yield, and using the homogeneous catalyst that is separated problematically from the reaction mixture and reused. Nevertheless, developing green, mild and modest measures is the leading objective of green chemistry to remove the usage and creation of hazardous materials. Owing to the above-mentioned difficulties and due to our current severe attention on environmentally benign protocols[29–32] the search for eco-safe, simple and effective strategies capable of promoting organic reactions under green circumstances has attracted a huge deal of interest in producing dihydropyrano[2,3-*c*]pyrazole scaffolds. Hence, here the catalyst-free and environmentally friendly synthesis of dihydropyrano[2,3-*c*]pyrazole scaffolds are reported *via*

ethylene glycol (E-G) as a green, reusable and biodegradable promoting media *via* tandem Knoevenagel-Michael cyclocondensation reaction of ethyl acetoacetate, hydrazine hydrate/phenylhydrazine, aromatic/aliphatic aldehydes and malononitrile provided the anticipated products in outstanding yields and short reaction times which might solve some cost problems in the industry. Subsequently, we studied the recyclability of the green ethylene glycol for the above reaction. However, the E-G can be recycled at least six times with no considerable reduction in activity making it greatly advantageous in addressing the industrial requirements and environmental worries.

2. Experimental

2.1 *General information*

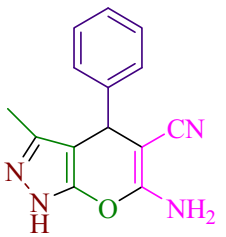
Utilizing an Electrothermal 9100 device, all compounds' melting points were found. Moreover, recording nuclear magnetic resonance, ^{1}H NMR spectra were carried out on a Bruker DRX-400 and Bruker DRX-300 Avance tool with DMSO-d_6 as a solvent. All solvents and reagents were bought from Acros, Merck, and Fluka chemical companies and were utilized with no additional purification.

2.2 *Overall process of preparing (5a-w)*

A mixture of ethyl acetoacetate (**1**, 1 mmol), hydrazine hydrate/phenylhydrazine (**2**, 1 mmol), aromatic/aliphatic aldehydes (**3**, 1 mmol) and malononitrile (**4**, 1 mmol) was added E-G (3 mL), and the obtained mixture was heated in an oil-bath (100 °C) (Scheme 1). After completing the reaction (monitored by TLC via n-hexane-EtOAc (4:1) as an eluent), the mixture was chilled to room temperature and poured on the warm water. Ethylene glycol is soluble in warm water but the product is insoluble. The created precipitate was filtered, rinsed with water and the crude product was purified by recrystallizing from ethanol to obtain the pure product (**5a-w**). To eliminate water, the aqueous filtrate was distilled at 100 °C and thus reusing the separated E-G. The recovered E-G was effectively utilized in consecutive runs (six runs) including the use of the fresh medium with no further efficiency loss and with insignificant E-G loss (Figure 2).

2.3 *Comparing the spectroscopic information, the products were categorized (^{1}HNMR)*

2.3a *6-amino-3-methyl-4-phenyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5g)*:



5g

Yield: 94%; M.p. 243–245 °C; ^{1}H NMR (300 MHz, DMSO-d_6): 1.79 (3H, s, CH_3), 4.61 (1H, s, CHAr), 6.89 (2H, s, NH_2), 7.18 (2H, d, J = 9.2 Hz, ArH), 7.21-7.26 (1H, m, ArH), 7.31-7.36 (2H, m, ArH), 12.11 (1H, s, NH).

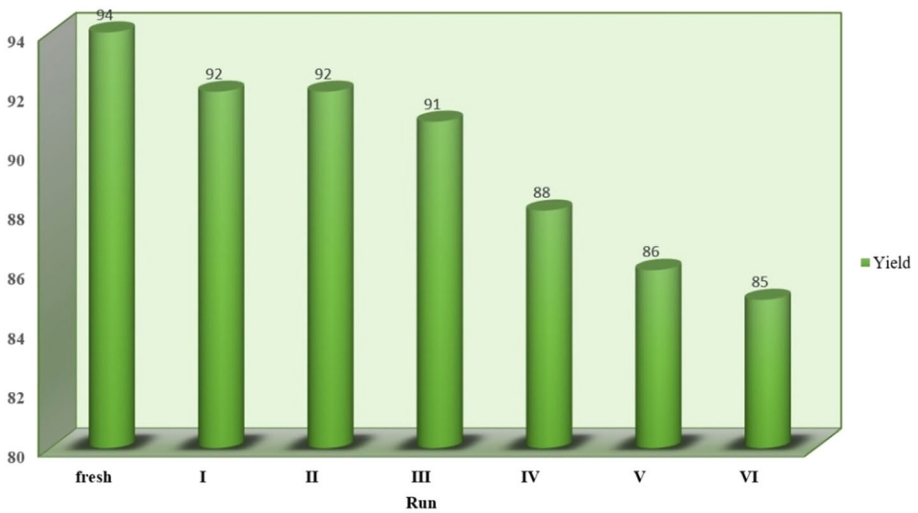
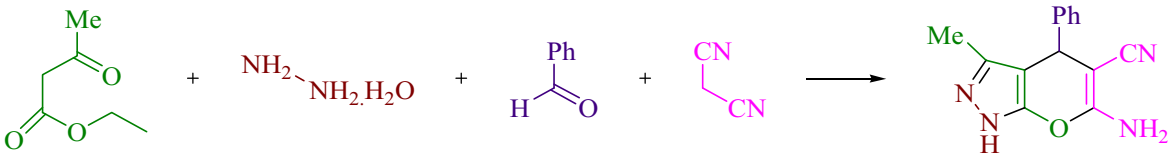


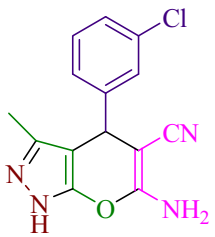
Figure 2. The recyclability of the ethylene glycol in the preparation of **5g**.

Table 1. Optimizing the reaction circumstance in the existence of various solvents and temperatures on the yield of **5g**.



Entry	Solvent (3 mL)	Temperature (°C)	Time (min)	Isolated Yields (%)
1	E-G	rt	420	31
2	E-G	40 °C	360	47
3	E-G	60 °C	180	58
4	E-G	80 °C	100	73
5	E-G	90 °C	80	85
6	E-G	**100 °C**	**80**	**94**
7	E-G	110 °C	80	95
8	H_2O	Reflux	360	67
9	H_2O/EtOH (1:1)	Reflux	360	62
10	EtOH	Reflux	420	58
11	MeOH	Reflux	420	43
12	Solvent-free	100 °C	480	Trace
13	DMSO	100 °C	480	Trace
14	THF	Reflux	480	Trace
15	DMF	100 °C	480	Trace
16	CH_3CN	Reflux	480	Trace
17	$CHCl_3$	Reflux	480	Trace
18	DCM	Reflux	480	Trace

2.3b *6-amino-4-(3-chlorophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5q)*:



5q

Yield: 87%; M.p. 229–231 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 1.77 (3H, s, CH_3), 5.08 (1H, s, CHAr), 7.19–7.45 (6H, m, ArH and NH_2), 12.15 (1H, s, NH).

3. Results and Discussion

In the beginning, we took into account synthesizing the 6-amino-3-methyl-4-phenyl-2,4-dihydropyrano[2,3-*c*] pyrazole-5-carbonitrile (**5g**) in the was studied in various solvents under catalyst-free circumstances at different temperatures in a model system in the four-element reaction between a combination of ethyl acetoacetate (1 mmol), hydrazine hydrate (1 mmol), benzaldehyde (1 mmol) and malononitrile (1 mmol). Some solvents like DMSO, THF, DMF, CH_3CN, $CHCl_3$ and DCM were also examined and only a small quantity of products was found in these solvents and solvent-free conditions (Table 1, entries 12–18). Whereas, the reaction continued slowly in H_2O, H_2O/EtOH (1:1), EtOH and MeOH, the yield and reaction rate increased (Table 1, entries 8–11). According to the detected determining influence of alcoholic solvents on the reaction, we then studied the effectiveness of ethylene glycol as a solvent for this reaction. An outstanding yield of 94% was created by using green E-G (3 mL) as a solvent with no further catalyst at 100 °C for 80 min (Table 1, entry 6). As observed in Table 2 and Scheme 1, it was indicated that this technique can work with various substrates. It should be noted that for purifying the products (**5a-w**), a modest filtration and recrystallized with ethanol is needed. Also, the recommended mechanism for synthesizing 6-amino-3-methyl-4-phenyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**5g**) is demonstrated in Scheme 2.

Table 2. Synthesis of dihydropyrano[2,3-*c*]pyrazole scaffolds.

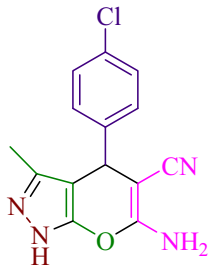
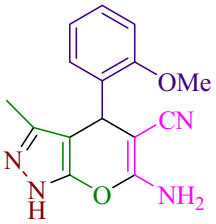
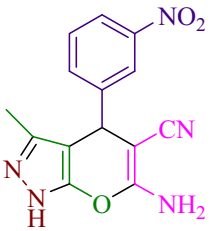
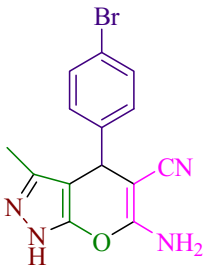
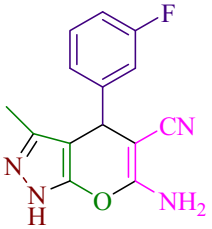
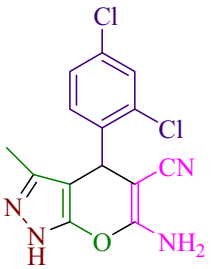
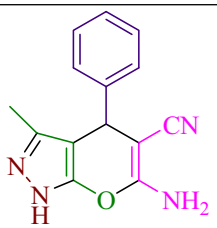
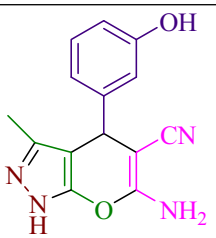
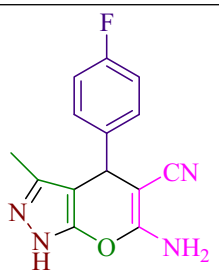
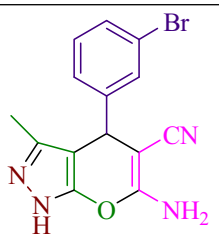
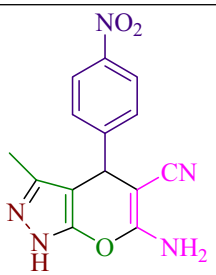
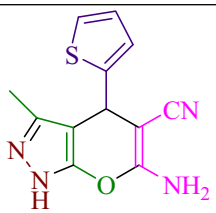
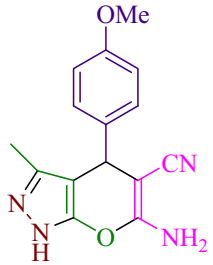
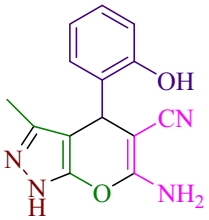
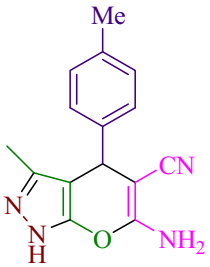
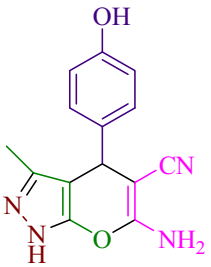
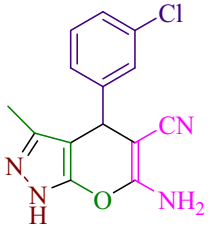
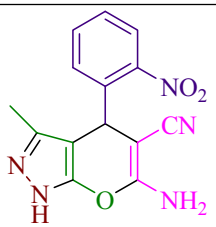
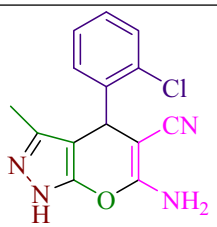
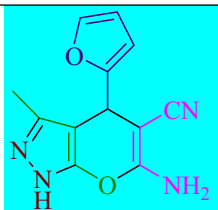
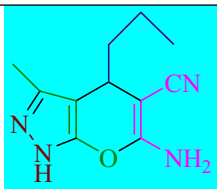
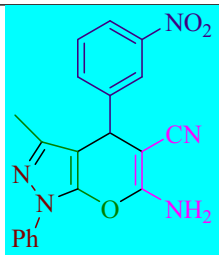
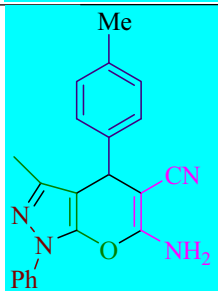
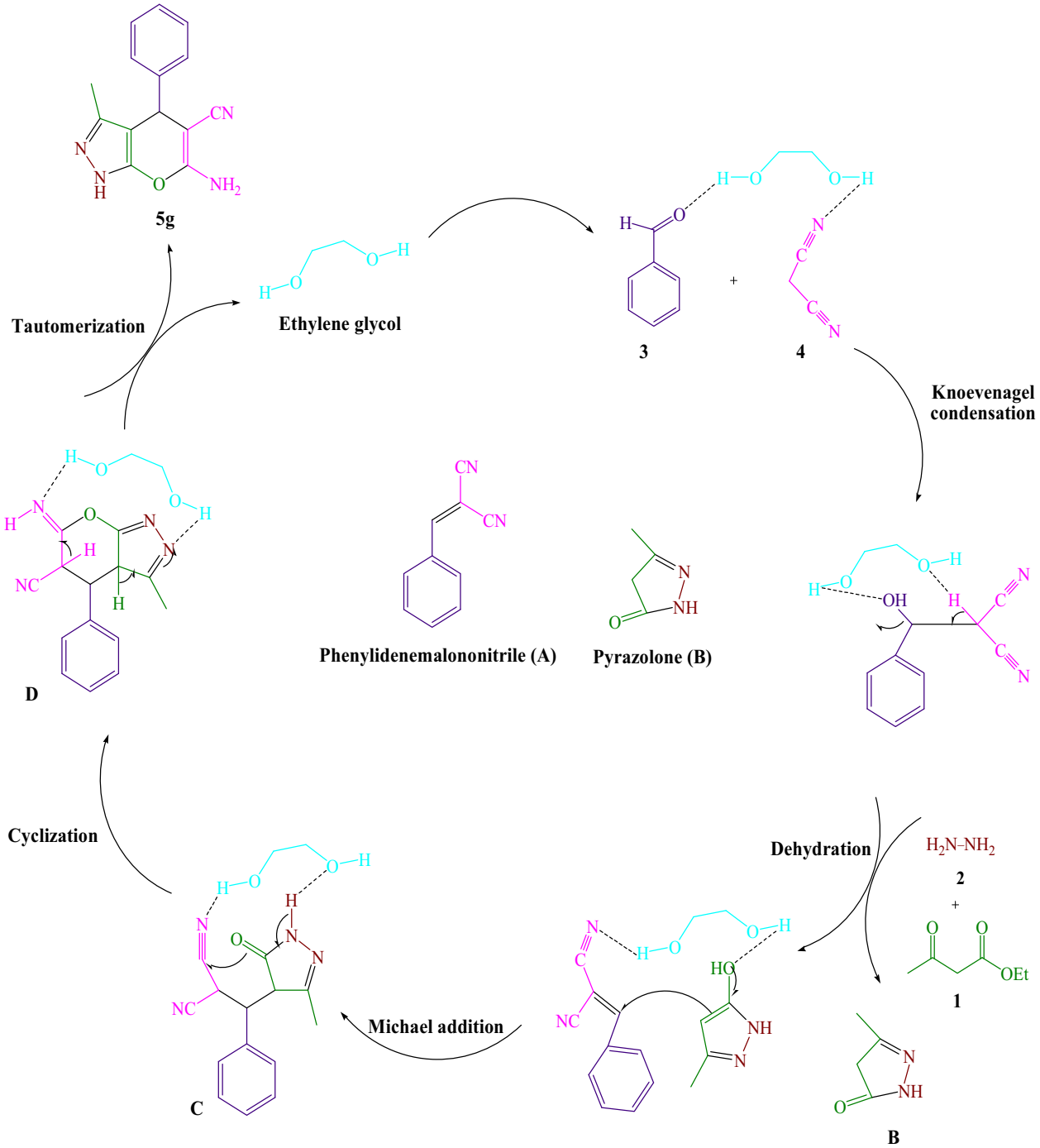
 **5a** (90 min, 83%) Mp. 234-236 °C Lit. 234-235 °C [12]	 **5b** (80 min, 91%) Mp. 250-252 °C Lit. 249-250 °C [12]	 **5c** (75 min, 90%) Mp. 191-193 °C Lit. 190-193 °C [13]
 **5d** (90 min, 85%) Mp. 180-182 °C Lit. 180-181 °C [8]	 **5e** (70 min, 96%) Mp. 240-242 °C Lit. 242-243 °C [12]	 **5f** (90 min, 81%) Mp. 228-230 °C Lit. 229-230 °C [12]
 **5g** (80 min, 94%) Mp. 243-245 °C Lit. 244-246 °C [13]	 **5h** (85 min, 83%) Mp. 227-229 °C Lit. 225-228 °C [13]	 **5i** (70 min, 94%) Mp. 245-247 °C Lit. 244-245 °C [12]
 **5j** (85 min, 82%) Mp. 222-224 °C Lit. 223-224 °C [13]	 **5k** (75 min, 93%) Mp. 249-251 °C Lit. 248-249 °C [12]	 **5l** (95 min, 81%) Mp. 226-228 °C Lit. 224-226 °C [18]

Table 2. continued

 **5m** (90 min, 84%) Mp. 209-211 °C Lit. 210-212 °C **[12]**	 **5n** (80 min, 86%) Mp. 206-208 °C Lit. 208-210 °C **[18]**	 **5o** (75 min, 95%) Mp. 207-209 °C Lit. 205-208 °C **[13]**
 **5p** (85 min, 79%) Mp. 222-224 °C Lit. 220-223 °C **[11]**	 **5q** (80 min, 87%) Mp. 229-231 °C Lit. 230-231 °C **[12]**	 **5r** (70 min, 94%) Mp. 245-247 °C Lit. 243-244 °C **[12]**
 **5s** (80 min, 85%) Mp. 242-244 °C Lit. 245-246 °C **[12]**	 **5t** (90 min, 83%) Mp. 228-230 °C Lit. 230-231 °C **[12]**	 **5u** (105 min, 76%) Mp. 143-145 °C Lit. 144-145 °C **[23]**
 **5v** (80 min, 94%) Mp. 208-210 °C Lit. 207-209 °C **[28]**	 **5w** (75 min, 91%) Mp. 177-179 °C Lit. 179-181 °C **[28]**	



Scheme 2. Recommended mechanistic path for synthesizing 6-amino-3-methyl-4-phenyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**5g**).

4. Conclusions

In conclusion, in the present work, it was demonstrated that a reusable and biodegradable solvent medium, green E-G, can be used as a greatly efficient and availability media for catalyst-free one-pot mild 4-component synthesizing dihydropyrano[2,3-*c*]pyrazole scaffolds *via* tandem Knoevenagel-Michael cyclocondensation reaction. Completing the reactions takes thoroughly less time while obtaining the products in outstanding yields. This green method includes noticeable properties such as catalyst-free, reusable and biodegradable promoting media, direct work-up without column chromatographic separation, cost-effective, mild and simple synthesis, one-pot procedure, and high atom-economy.

Supplementary Information (SI)

Supplementary information associated with this article is available at www.ias.ac.in/chemsci.

Acknowledgements

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