



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

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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 reactions¹ 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 activities² (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} molluscicidal⁶ and antimicrobial.⁷

There are numerous approaches for synthesizing these compounds using various catalysts such as ZrO₂ 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 TPSPTNM,²⁰ [Dabco-H][AcO],²¹ Fe₃O₄@SiO₂ nanoparticle-supported IL,²² sodium ascorbate,²³ nano-SiO₂/DABCO,²⁴ NaF,²⁵ nano-SiO₂,²⁶ theophylline²⁷ and [HMIM]C(NO₂)₃.²⁸ It was shown that these reported procedures lead to numerous cases. Though, some of the synthetic policies contain also

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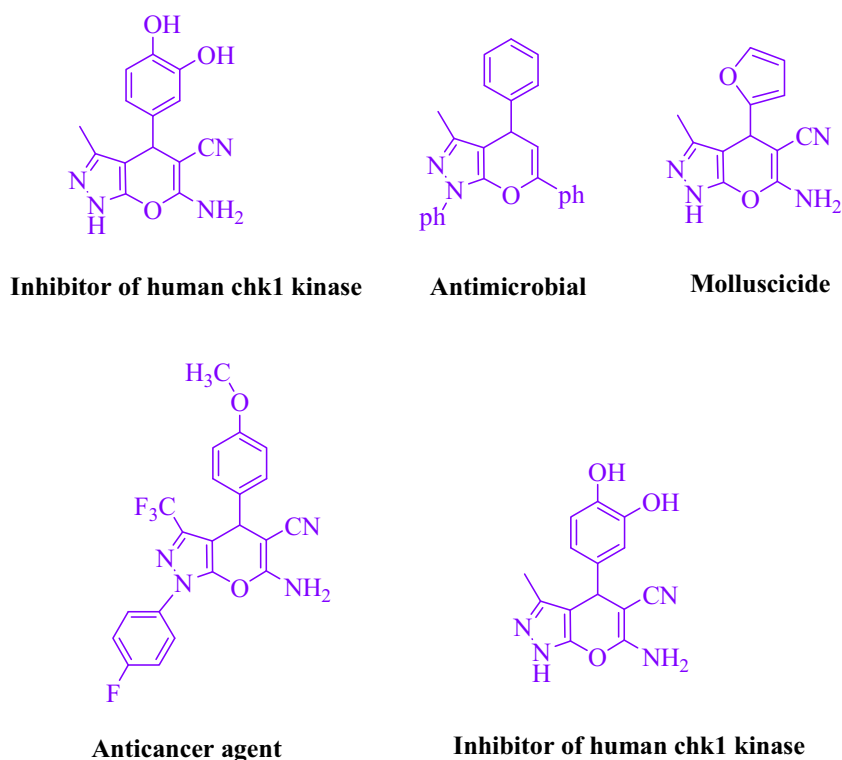
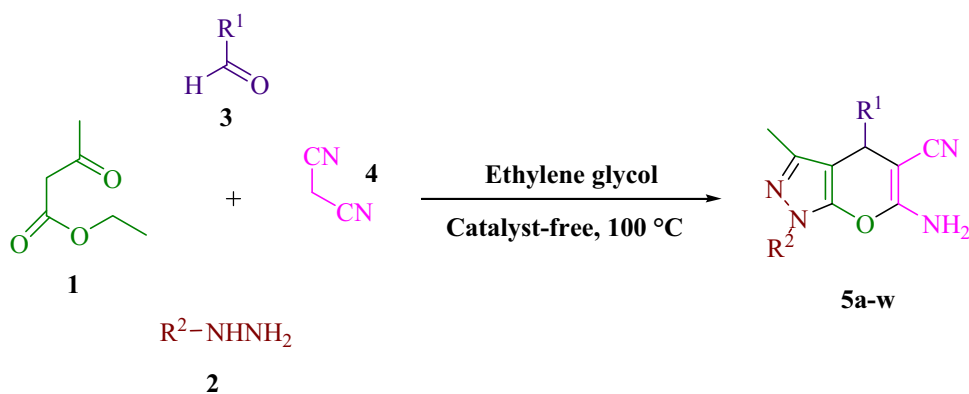


Figure 1. Biologically active molecules with dihydropyrano[2,3-*c*]pyrazole scaffold.



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, ^1H 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.

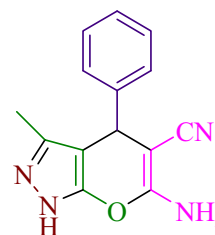
2.2 Overall process of preparing (5a-w)

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 (^1H NMR)

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; ^1H 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).

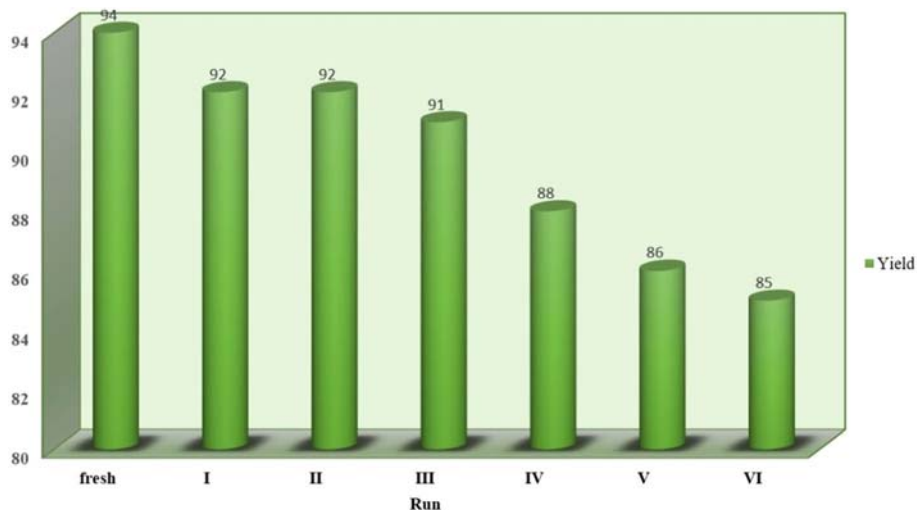
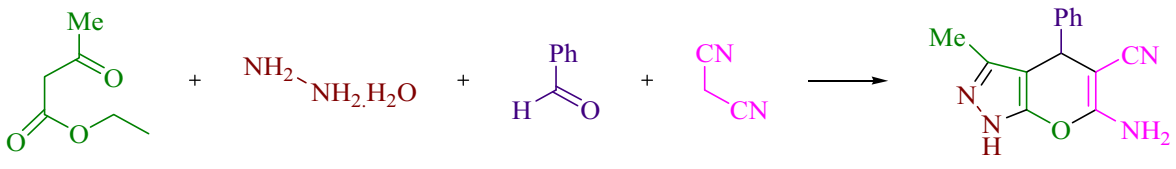
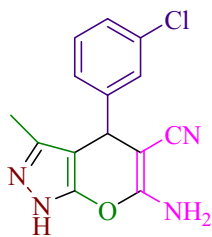


Figure 2. The recyclability of the ethylene glycol in the preparation of **5g**.

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 ₂ O	Reflux	360	67
9	H ₂ O/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 ₃ CN	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-dihydropyranopyrazole-5-carbonitrile (**5q**):

**5q**

Yield: 87%; M.p. 229–231 °C; ¹H NMR (400 MHz, DMSO-d₆): 1.77 (3H, s, CH₃), 5.08 (1H, s, CHAr), 7.19–7.45 (6H, m, ArH and NH₂), 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-dihydropyranopyrazole-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, CH₃CN, CHCl₃ 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 H₂O, H₂O/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-dihydropyranopyrazole-5-carbonitrile (**5g**) is demonstrated in Scheme 2.

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

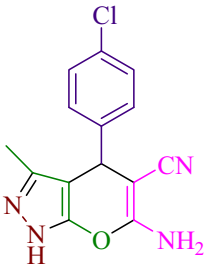
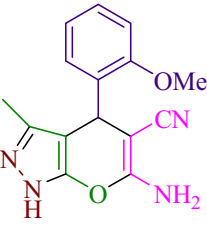
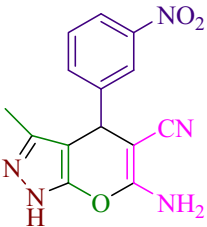
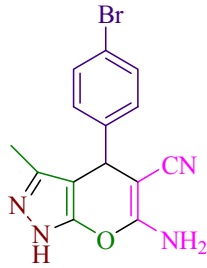
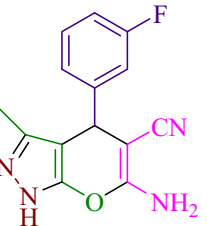
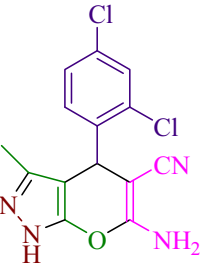
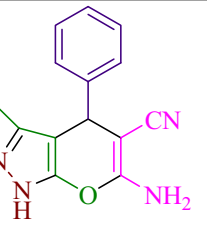
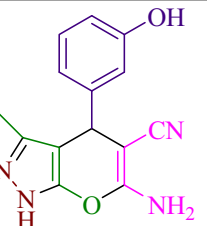
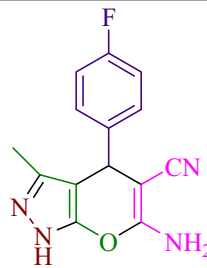
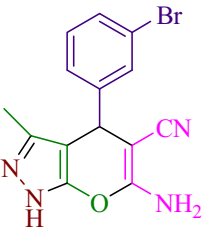
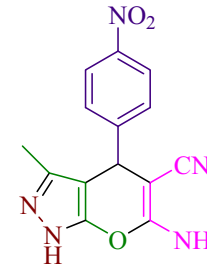
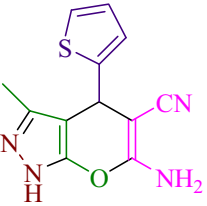
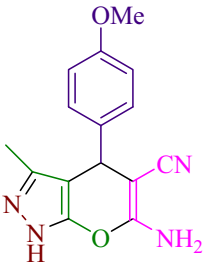
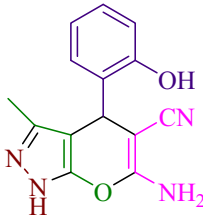
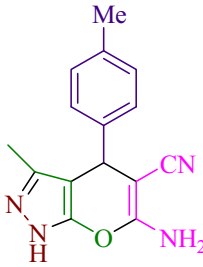
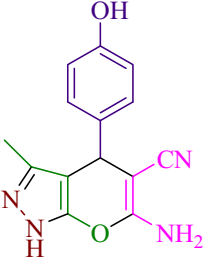
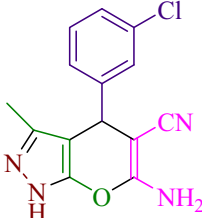
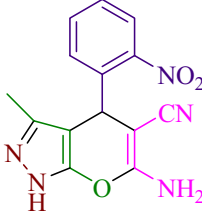
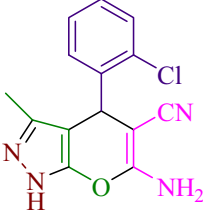
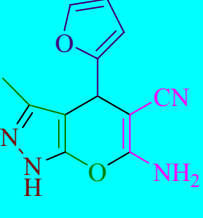
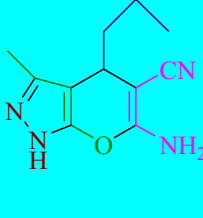
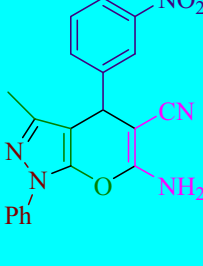
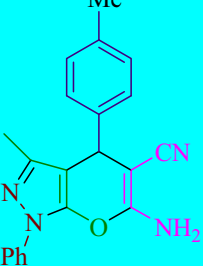
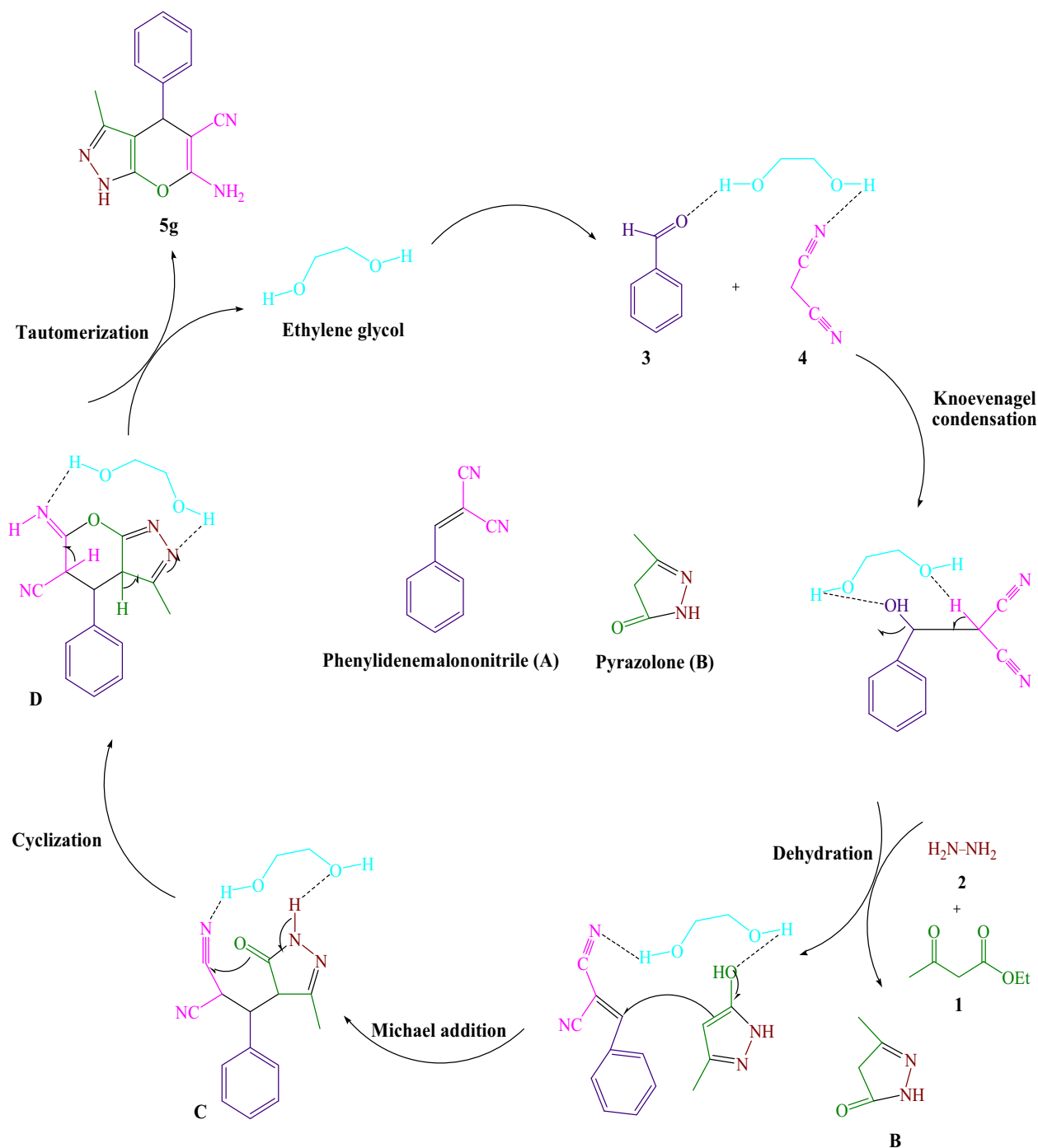
 <p>5a (90 min, 83%) Mp. 234-236 °C Lit. 234-235 °C [12]</p>	 <p>5b (80 min, 91%) Mp. 250-252 °C Lit. 249-250 °C [12]</p>	 <p>5c (75 min, 90%) Mp. 191-193 °C Lit. 190-193 °C [13]</p>
 <p>5d (90 min, 85%) Mp. 180-182 °C Lit. 180-181 °C [8]</p>	 <p>5e (70 min, 96%) Mp. 240-242 °C Lit. 242-243 °C [12]</p>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

Table 2. continued

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



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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References

1. Ibad A, Waseem M A, Ibad F, Ansari K, Lone A M, Watal G and Siddiqui I R 2017 A Green Access to Tetrahydro-1*H*-pyrano [2, 3-*d*] pyrimidines: Visible-Light-Triggered and Ethylene-Glycol-Mediated Multi-component One-Pot Process *Chem. Select.* **2** 4587
2. Chauhan P, Mahajan S and Enders D 2015 Asymmetric synthesis of pyrazoles and pyrazolones employing the reactivity of pyrazolin-5-one derivatives *Chem. Commun.* **51** 12890
3. (a) Junek H and Aigner H 1973 Synthesen mit Nitrilen, XXXV. Reaktionen von tetracyanäthylen mit heterocyclen *Chem. Ber.* **106** 914; (b) Wamhoff H, Kroth E and Strauch K 1993 Dihalogenetriphenylphosphorane in der Heterocyclensynthese; 271: Heterokondensierte 1, 2, 4-Triazololo [1, 5-*c*] pyrimidine aus Enaminonitrilen via O-Ethylformimide *Synthesis* **11** 1129
4. Foloppe N, Fisher L M, Howes R, Potter A, Robertson A G and Surgenor A E 2006 Identification of chemically diverse Chk1 inhibitors by receptor-based virtual screening *Bioorg. Med. Chem.* **14** 4792
5. (a) Wang J L, Liu D, Zheng Z J, Shan S, Han X, Srinivasula S M, Croce C M, Alnemri E S and Huang Z 2000 Structure-based discovery of an organic compound that binds Bcl-2 protein and induces apoptosis of tumor cells *Proc. Natl. Acad. Sci.* **97** 7124; (b) Kuo C, Huang J and Nakamura H 1984 Studies on heterocyclic compounds. 6. Synthesis and analgesic and antiinflammatory activities of 3, 4-dimethylpyrano [2, 3-*c*] pyrazol-6-one derivatives *Med. Chem.* **27** 539
6. Abdelrazek F M, Metz P, Kataeva O, Jaeger A and El-Mahrouky S F 2007 Synthesis and Molluscicidal Activity of New Chromene and Pyrano[2,3-*c*]pyrazole Derivatives *Arch. Pharm.* **340** 543
7. El-Tamany E S, El-Shahed F A and Mohamed B H 1999 Synthesis and biological activity of some pyrazole derivatives *J. Serb. Chem. Soc.* **64** 9
8. Saha A, Payra S and Banerjee S 2015 One-pot multicomponent synthesis of highly functionalized bio-active pyrano[2,3-*c*]pyrazole and benzylpyrazolyl coumarin derivatives using ZrO₂ nanoparticles as a reusable catalyst *Green Chem.* **17** 2859
9. Moshtaghi Zonouz A and Moghani D 2016 Green and highly efficient synthesis of pyranopyrazoles in choline chloride/urea deep eutectic solvent *Synth. Commun.* **46** 220
10. Zolfigol M A, Tavasoli M, Moosavi-Zare A R, Moosavi P, Grehardus Kruger H, Shiri M and Khakyzadeh V 2013 Synthesis of pyranopyrazoles using isonicotinic acid as a dual and biological organocatalyst *RSC Adv.* **3** 25681
11. Gujar J B, Chaudhari M A, Kawade D S and Shingara M S 2014 Molecular sieves: an efficient and reusable catalyst for multi-component synthesis of dihydropyrano [2, 3-*c*] pyrazole derivatives *Tetrahedron Lett.* **55** 6030
12. Guo R Y, An Z M, Mo L P, Yang S T, Liu H X and Wang S X 2013 Meglumine promoted one-pot, four-component synthesis of pyranopyrazole derivatives *Tetrahedron* **69** 9931
13. Tamaddon F and Alizadeh M A 2014 A four-component synthesis of dihydropyrano [2, 3-*c*] pyrazoles in a new water-based worm-like micellar medium *Tetrahedron Lett.* **55** 3588
14. Mecadon H, Rohman M R, Kharbanger I, Laloo B M, Kharkongor I, Rajbangshi M and Myrboh B 2011 l-Proline as an efficient catalyst for the multi-component synthesis of 6-amino-4-alkyl/aryl-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles in water *Tetrahedron Lett.* **52** 3228
15. Wu M, Feng Q, Wan D and Ma J 2013 CTACl as catalyst for four-component, one-pot synthesis of pyranopyrazole derivatives in aqueous medium *Synth. Commun.* **43** 1721
16. Bora P P, Bihani M and Bez G 2013 Multicomponent synthesis of dihydropyrano [2, 3-*c*] pyrazoles catalyzed by lipase from *Aspergillus niger* *J. Mol. Catal. B* **92** 24
17. Dalal K S, Tayade Y A, Wagh Y B, Trivedi D R, Dalal D S and Chaudhari B L 2016 Bovine serum albumin catalyzed one-pot, three-component synthesis of dihydropyrano [2, 3-*c*] pyrazole derivatives in aqueous ethanol *RSC Adv.* **6** 14868
18. Tayade Y A, Padvi S A, Wagh Y B and Dalal D S 2015 β-Cyclodextrin as a supramolecular catalyst for the synthesis of dihydropyrano [2, 3-*c*] pyrazole and spiro [indoline-3, 4'-pyrano [2, 3-*c*] pyrazole] in aqueous medium *Tetrahedron Lett.* **56** 2441
19. Zhou C F, Li J J and Su W K 2016 Morpholine triflate promoted one-pot, four-component synthesis of dihydropyrano [2, 3-*c*] pyrazoles *Chin. Chem. Lett.* **27** 1686
20. Yarie M, Zolfigol M A, Bagheri S, Alonso D A, Khoshnood A, Bayat Y and Asgar A 2018 Triphenyl (3-sulfopropyl) phosphonium trinitromethanide as a novel nanosized molten salt: Catalytic activity at the preparation of dihydropyrano [2, 3-*c*] pyrazoles *J. Mol. Liq.* **271** 872
21. Liu T, Lai Y H, Yu Y Q and Xu D Z 2018 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 a Dabco-based ionic liquid under mild conditions *New. J. Chem.* **42** 1046
22. Ghorbani-Vaghei R, Mahmoodi J, Shahriari A and Maghbooli Y 2017 Synthesis of pyrano[2,3-*c*]pyrazole derivatives using Fe₃O₄@SiO₂@piperidinium benzene-1,3-disulfonate (Fe₃O₄@SiO₂ nanoparticle-supported IL) as a novel, green and heterogeneous catalyst *Appl. Organomet. Chem.* **31** e3816
23. Kiyani H and Bamdad M 2018 Sodium ascorbate as an expedient catalyst for green synthesis of polysubstituted

- 5-aminopyrazole-4-carbonitriles and 6-amino-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles *Res. Chem. Intermed.* **44** 2761
24. Salehi N and Mirjalili F B B 2018 Green Synthesis of Pyrano[2,3-*c*]pyrazoles and Spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazoles] Using Nano-silica Supported 1,4-Diazabicyclo[2.2.2]octane as a Novel Catalyst *Org. Prep. Proced. Int.* **50** 578
25. Konakanchi R, Gondru R, Bharat Nishtala V and Reddy Kotha L NaF-catalyzed efficient one-pot synthesis of dihydropyrano[2,3-*c*]pyrazoles under ultrasonic irradiation via MCR approach 2018 *Synth. Commun.* **48** 1994
26. Patel K G, Misra N M, Vekariya R H and Shettigar R R 2018 One-pot multicomponent synthesis in aqueous medium of 1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile and derivatives using a green and reusable nano-SiO₂ catalyst from agricultural waste *Res. Chem. Intermed.* **44** 289
27. Mohamadpour F 2019 Synthesis of Pyran-Annulated Heterocyclic Systems Catalyzed by Theophylline as a Green and Bio-Based Catalyst *Polycycl. Aromat. Comp.* doi: <https://doi.org/10.1080/10406638.2019.1575246>
28. Zolfigol M A, Afsharnadery F, Baghery S, Salehzadeh S and Maleki F 2015 Catalytic applications of {[HMIM]C(NO₂)₃}: as a nano ionic liquid for the synthesis of pyrazole derivatives under green conditions and a mechanistic investigation with a new approach *RSC Adv.* **5** 75555
29. Mohamadpour F and Lashkari M 2018 Three-component reaction of β-keto esters, aromatic aldehydes and urea/thiourea promoted by caffeine: A green and natural, biodegradable catalyst for eco-safe Biginelli synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones/tiones derivatives under solvent-free conditions *J. Serb. Chem. Soc.* **83** 673
30. Mohamadpour F 2018 Green and Convenient One-Pot Access to Polyfunctionalized Piperidine Scaffolds via Glutamic Acid Catalyzed Knoevenagel- Intramolecular [4+2] aza-Diels-Alder Imin-Based Multi-Component Reaction Under Ambient Temperature *Polycycl. Aromat. Comp.* doi: <https://doi.org/10.1080/10406638.2018.1472111>
31. Mohamadpour F 2019 Glutamic acid as green and bio-based α-amino acid catalyst promoted one-pot access to polyfunctionalized dihydro-2-oxypyrrroles *J. Serb. Chem. Soc.* **84** 1083
32. Mohamadpour F 2019 Theophylline as a Green Catalyst for the Synthesis of 1*H*-Pyrazolo[1,2-*b*]phthalazine-5,10-dione *Org. Prep. Proced. Int.* doi: <https://doi.org/10.1080/00304948.2019.1697611>