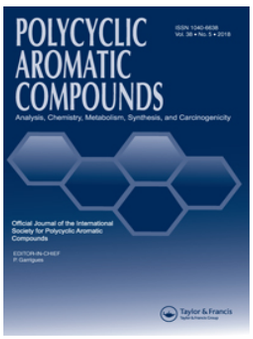

Polycyclic Aromatic Compounds

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Catalyst-Free Three-Component Tandem Green Synthesis of Pyrano[2,3-*d*]Pyrimidine Scaffolds in Ethylene Glycol (E-G) as a Recyclable Reaction Medium

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ABSTRACT

A green, efficient and convenient synthesis of pyrano[2,3-*d*]pyrimidine scaffolds has been developed *via* one-pot three-component reaction of aryl aldehyde derivatives, malononitrile with barbituric acid/1,3-dimethylbarbituric acid using ethylene glycol (E-G) as a solvent as well as catalyst. Eighteen pyrano[2,3-*d*]pyrimidine scaffolds were selected for the library validation. The superiority of this method is environmental safety, catalyst-free, operational simplicity, metal-free, high yields, excellent functional group tolerance, easy workup procedure, less reaction time and the green ethylene glycol can be recovered and reused several times without any loss of efficiency.

ARTICLE HISTORY
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KEYWORDS
Catalyst-free synthesis; ethylene glycol (E-G); recyclable reaction medium; pyrano[2,3-d]pyrimidine scaffolds

Introduction

Multicomponent reactions[1,2] have recently been recognized as a major new expansion in synthetic organic chemistry. They allow the assembly of complex molecules in one pot, thus maximizing synthetic efficiency and reducing costs. In the last few decades there has been a growing emphasis on sustainable chemistry due to the global push to improve green credential. Utilization of multicomponent reactions for sustainable synthesis holds great promise in organic synthesis however this area still remains under-utilized. One major thrust area in green chemistry is the replacement of the toxic organic solvents with sustainable and green solvents.[3] Hence, the search for green reaction solvents with exclusive functions and features is still significant in the present green organic synthesis investigation. Recently, an extensive attention has been driven by ethylene glycol as a kind of a green and financially viable alternative to the conventional solvents. It includes favorable features like noncorrosiveness, stability, and decent solubility in organic compounds. In addition, ethylene glycol (E-G) was also used as a green reaction environment in some convenient organic reactions[4] to prepare some important compounds.

Most of the biologically active potential drugs used currently are synthetic organic molecules that often contain a heterocyclic ring.[5] Despite recent advances in drug-designing molecular biology and combinatorial synthetic methodology, the range of easily accessible and suitable functionalized heterocyclic motifs toward the synthesis of structurally diverse compounds is rather limited.[6] Pyrano[2,3-*d*]pyrimidine derivatives, including attached rings of a uracil and a pyran are analogues of uracil which have different pharmacological properties such as antiallergic,[7] antihypertensive,[8] cardiotonic,[9] bronchiodilator,[10] antibronchitic[11] and antitumor activities.[12] Considering the importance of such compounds, many methods for synthesis of pyrano[2,3-*d*]pyrimidine scaffolds have

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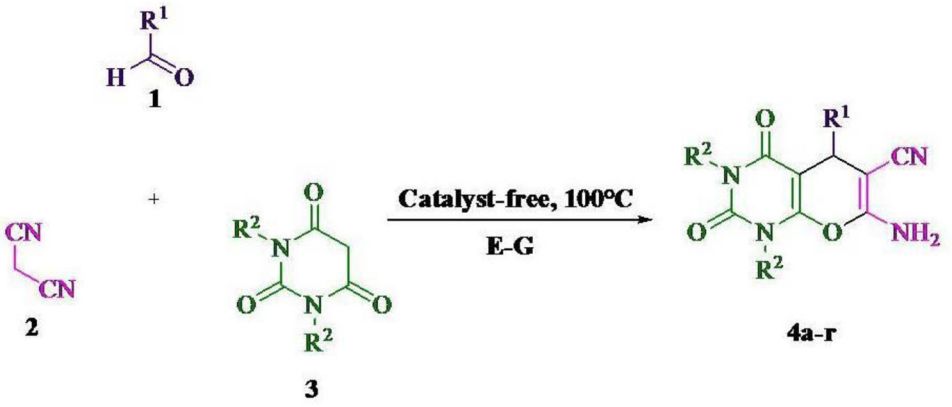


Scheme 1. Catalyst-free synthesis of pyrano[2,3-*d*]pyrimidine scaffolds.

been reported. The conventional synthesis method involves condensation of barbituric acid/1,3-dimethylbarbituric acid with aldehyde derivatives and malononitrile using different catalytic systems such as DABCO-based ionic liquids,[13] L-proline,[14] iron ore pellet,[15] nano-sawdust-OSO_3H,[16] Al-HMS-20,[17] TSA/$B(OH)_3$,[18] Mn/ZrO_2,[19] cellulose-based nanocomposite,[20] DBA,[21] TBAB,[22] Fe_3O_4@SiO_2@$(CH_2)_3$-urea-SO_3H/HCl,[23] Et_3N-ultrasonic,[24] $ZnFe_2O_4$ nanoparticles,[25] microwave,[26] nickel nanoparticles,[27] $CaHPO_4$,[28] Zn[(L)proline]$_2$,[29] theophylline[30] and uric acid.[31] However, most of these methods suffer from such drawbacks as low yields, long reaction times, harsh reaction conditions, tedious work-up procedures, tedious steps for the preparation of catalyst, application of toxic and expensive catalysts, application of hazardous solvents for the work up and lack of generality. Moreover, in most of the reported methods, catalysts are not recyclable. Therefore, development of catalyst-free, efficient, one-pot and green procedure for the synthesis of pyrano[2,3-*d*]pyrimidine scaffolds is of considerable interest. Consequently, in continuation of our ongoing research program on the development of green synthetic routes[32] to important heterocyclic molecules, we herein report a catalyst-free, green and highly efficient one-pot strategy for preparation of pyrano[2,3-*d*]pyrimidine scaffolds *via* three-component Knoevenagel–Michael addition cyclocondensation reaction of aryl aldehyde derivatives, malononitrile with barbituric acid/1,3-dimethylbarbituric acid in ethylene glycol as a green reaction medium. Subsequently, we studied the recyclability of the green E-G for the above reaction. However, the E-G can be recycled at least five runs including the use of fresh medium without significant decrease in catalytic activity, which makes it highly beneficial to address the industrial needs and environmental concerns.

Experimental

General

Melting points all compounds were determined using an Electro thermal 9100 apparatus. Also, nuclear magnetic resonance, ^{1}H NMR spectra were recorded on a Bruker DRX-300 Avance and Bruker DRX-400 Avance instrument with DMSO-d_6 as solvents. In this article, all reagents and solvents were purchased from Merck, Fluka and Acros chemical companies were used without further purification.

General procedure for preparation of pyrano[2,3-d]pyrimidine scaffolds (4a–r)

A mixture of aryl aldehyde derivatives (**1**, 1.0 mmol), malononitrile (**2**, 1.0 mmol), barbituric acid/1,3-dimethylbarbituric acid (**3**, 1.0 mmol) was added E-G (3 mL), and the resulting mixture was heated in an oil-bath (100 °C) (Scheme 1). The progress of the reaction was monitored by TLC using EtOAc–*n*-hexane (2:7) as an eluent. After completion of reaction the reaction mass was

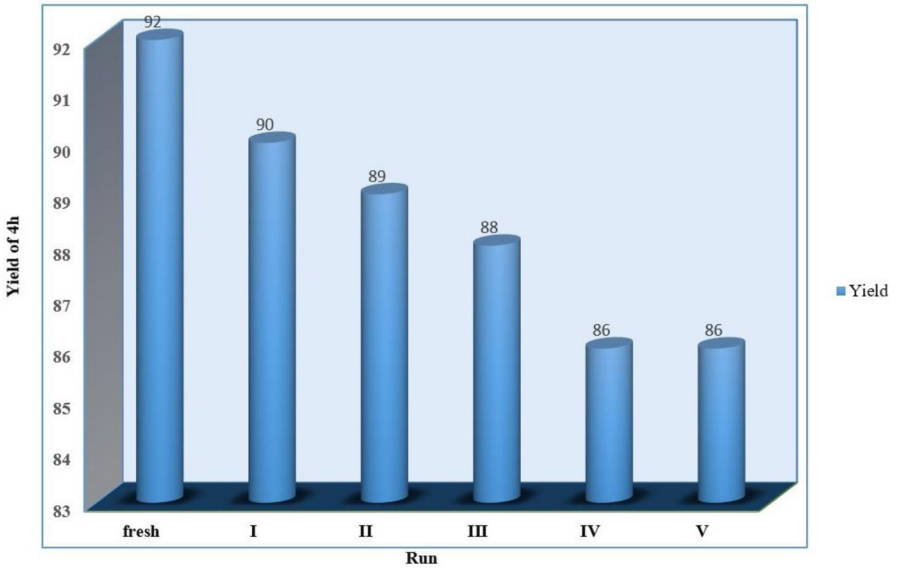
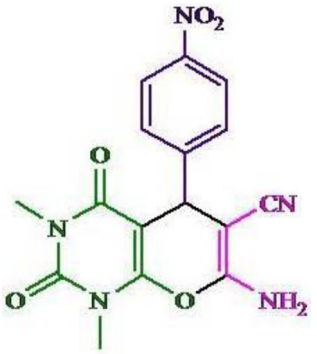


Figure 1. The recyclability of the E-G in the preparation of **4h**.

cooled to room temperature and then poured on hot water. Ethylene glycol (E-G) was dissolved in hot water while the product remained insoluble in water. The obtained solid was filtered, washed with water and crude solid was recrystallized from ethanol to afford pure product without need of any further purification. The aqueous filtrate was distilled at 100 °C to remove water to give E-G which was used for the next run under similar reaction conditions. The E-G was recovered and reused five runs including the use of fresh medium without loss of activity. The findings of this study are shown in Figure 1.

Spectra data some of selected and known products are represented below:

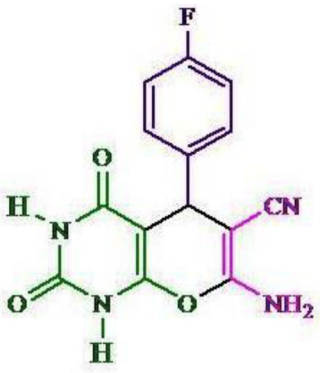
7-Amino-5-(4-nitrophenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]-pyrimidine-6-carbonitrile (4b)



4b

Yield: 89%; M.p. 212-214 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 3.04 (3H, s, CH_3), 3.07 (3H, s, CH_3), 4.53 (1H, s, CHAr), 7.57 (2H, d, $J = 8.8$ Hz, ArH), 7.76 (2H, s, NH_2), 8.16 (2H, d, $J = 8.8$ Hz, ArH).

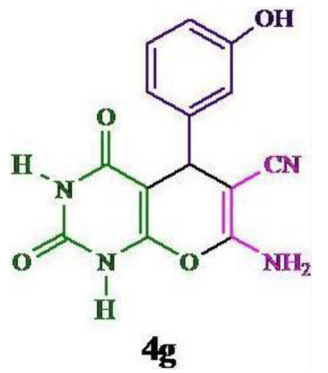
7-Amino-5-(4-fluorophenyl)-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]-pyrimidine-6-carbonitrile (4e)



4e

Yield: 93%; M.p. 256–257 °C; ^{1}H NMR (300 MHz, DMSO-d_6): 4.28 (1H, s, CHAr), 7.18–8.62 (6H, m, ArH and NH_2), 10.73 (1H, s, NH), 11.83 (1H, s, NH).

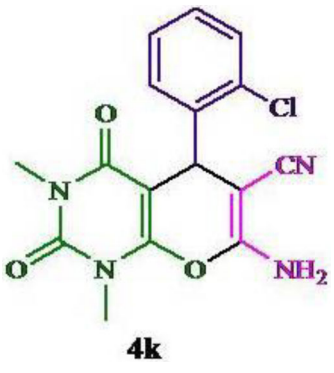
7-Amino-5-(3-hydroxyphenyl)-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]-pyrimidine-6-carbonitrile (4g)



4g

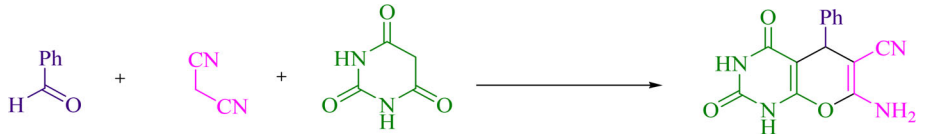
Yield: 79%; M.p. 157–159 °C; ^{1}H NMR (300 MHz, DMSO-d_6): 4.13 (1H, s, CHAr), 7.45–7.72 (6H, m, ArH and NH_2), 9.41 (1H, s, OH), 10.73 (1H, s, NH), 11.86 (1H, s, NH).

7-Amino-5-(2-chlorophenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]-pyrimidine-6-carbonitrile (4k)



4k

Table 1. Effect of solvent and temperature on yield of **4h**[a].

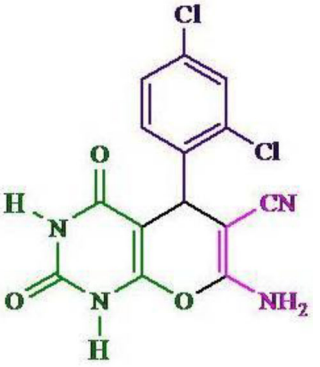


Entry	Solvent (3 mL)	Temperature (°C)	Time (min)	Isolated yields (%)
1	E-G	Rt	480	37
2	E-G	50 °C	360	54
3	E-G	70 °C	180	73
4	E-G	90 °C	100	81
5	**E-G**	**100** °C	**90**	**92**
6	E-G	110 °C	90	93
7	Solvent-free	100 °C	480	trace
8	H_2O	Reflux	360	58
9	H_2O/EtOH (1:1)	Reflux	360	53
10	EtOH	Reflux	360	49
11	MeOH	Reflux	420	36
12	PEG-200	100 °C	85	76
13	PEG-600	100 °C	80	82
14	DCM	Reflux	480	trace
15	DMSO	100 °C	480	trace
16	THF	Reflux	480	trace
17	DMF	100 °C	480	trace
18	$CHCl_3$	Reflux	480	trace

[a]Reaction conditions: benzaldehyde (1.0 mmol), malononitrile (1.0 mmol), barbituric acid (1.0 mmol) in various solvents and temperatures.

Yield: 80%; M.p. 244–246 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 3.31 (3H, s, NCH_3), 3.36 (3H, s, NCH_3), 4.51 (1H, s, CHAr), 7.53–7.59 (4H, m, ArH and NH_2), 8.18 (2H, t, $J = 6.8$ Hz, ArH).

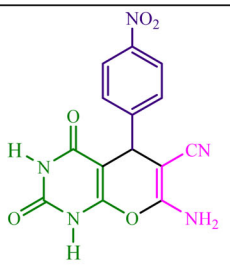
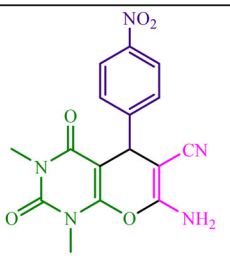
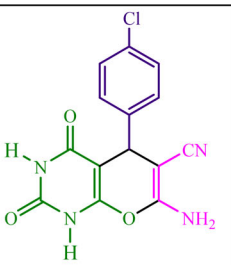
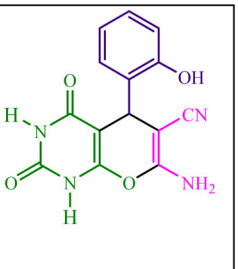
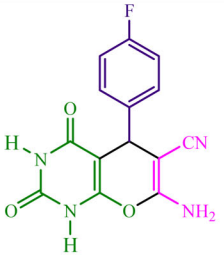
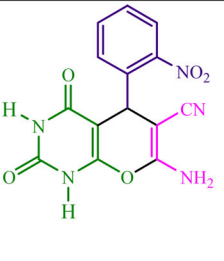
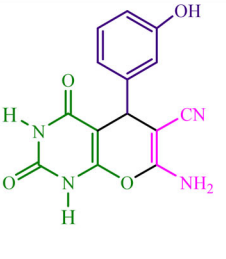
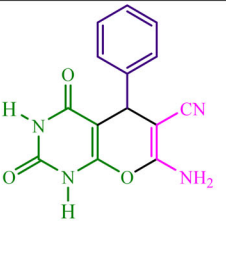
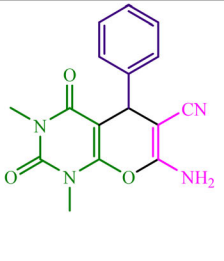
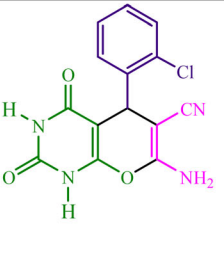
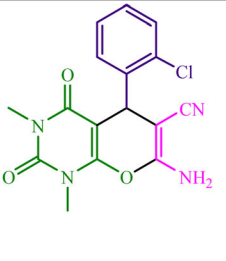
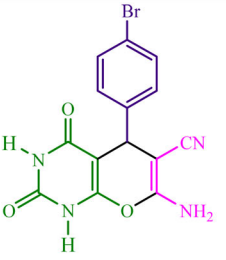
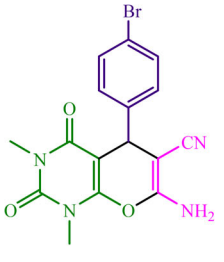
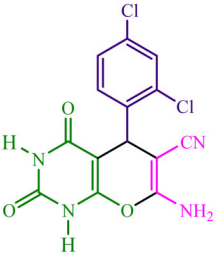
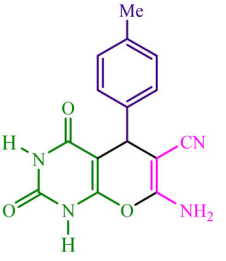
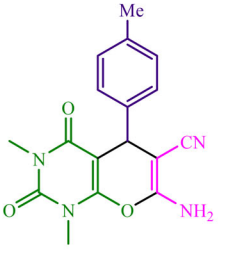
7-Amino-5-(2,4-di-chlorophenyl)-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]-pyrimidine-6-carbonitrile (4n)



4n

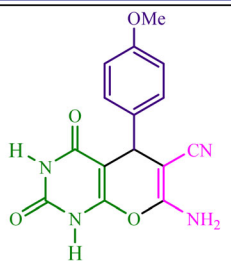
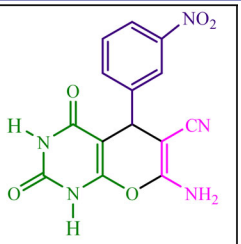
Yield: 82%; M.p. 239–241 °C; ^{1}H NMR (300 MHz, DMSO-d_6): 4.24 (1H, s, CHAr), 7.26–7.51 (5H, m, ArH and NH_2), 10.56 (1H, s, NH), 11.81 (1H, s, NH).

Table 2. Catalyst-free synthesis of pyrano[2,3-*d*]pyrimidine scaffolds.

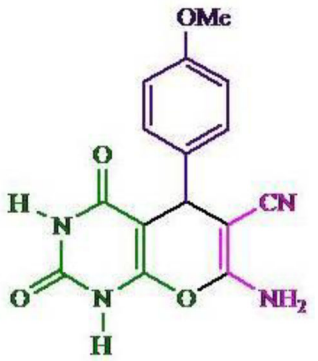
 **4a** (90 min, 93%) Mp. 235-237 °C Lit. 236-237 °C [23]	 **4b** (90 min, 89%) Mp. 212-214 °C Lit. 214-216 °C [18]	 **4c** (110 min, 78%) Mp. 237-239 °C Lit. 235-237 °C [18]	 **4d** (110 min, 81%) Mp. 170-172 °C Lit. 169-170 °C [15]
 **4e** (85 min, 93%) Mp. 256-257 °C Lit. 256-260 °C [13]	 **4f** (80 min, 91%) Mp. 252-254 °C Lit. 254-256 °C [13]	 **4g** (110 min, 79%) Mp. 157-159 °C Lit. 158-160 °C [14]	 **4h** (90 min, 92%) Mp. 225-227 °C Lit. 224-225 °C [13]
 **4i** (90 min, 91%) Mp. 239-241 °C Lit. 237-238 °C [18]	 **4j** (100 min, 83%) Mp. 213-215 °C Lit. 211-214 °C [18]	 **4k** (105 min, 80%) Mp. 244-246 °C Lit. 243-244 °C [25]	 **4l** (115 min, 82%) Mp. 243-245 °C Lit. 240-245 °C [15]
 **4m** (115 min, 85%) Mp. 209-211 °C Lit. 210-211 °C [19]	 **4n** (115 min, 82%) Mp. 239-241 °C Lit. 241-242 °C [14]	 **4o** (85 min, 90%) Mp. 227-229 °C Lit. 226 °C [18]	 **4p** (90 min, 87%) Mp. 206-208 °C Lit. 205-207 °C [18]

(*continued*)

Table 2. Continued.

	
4q (95 min, 92%) Mp. 274-276 °C Lit. 272-274 °C [16]	**4r** (80 min, 94%) Mp. 257-259 °C Lit. 259-261 °C [16]

7-Amino-5-(4-methoxyphenyl)-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]-pyrimidine-6-carbonitrile (4q)

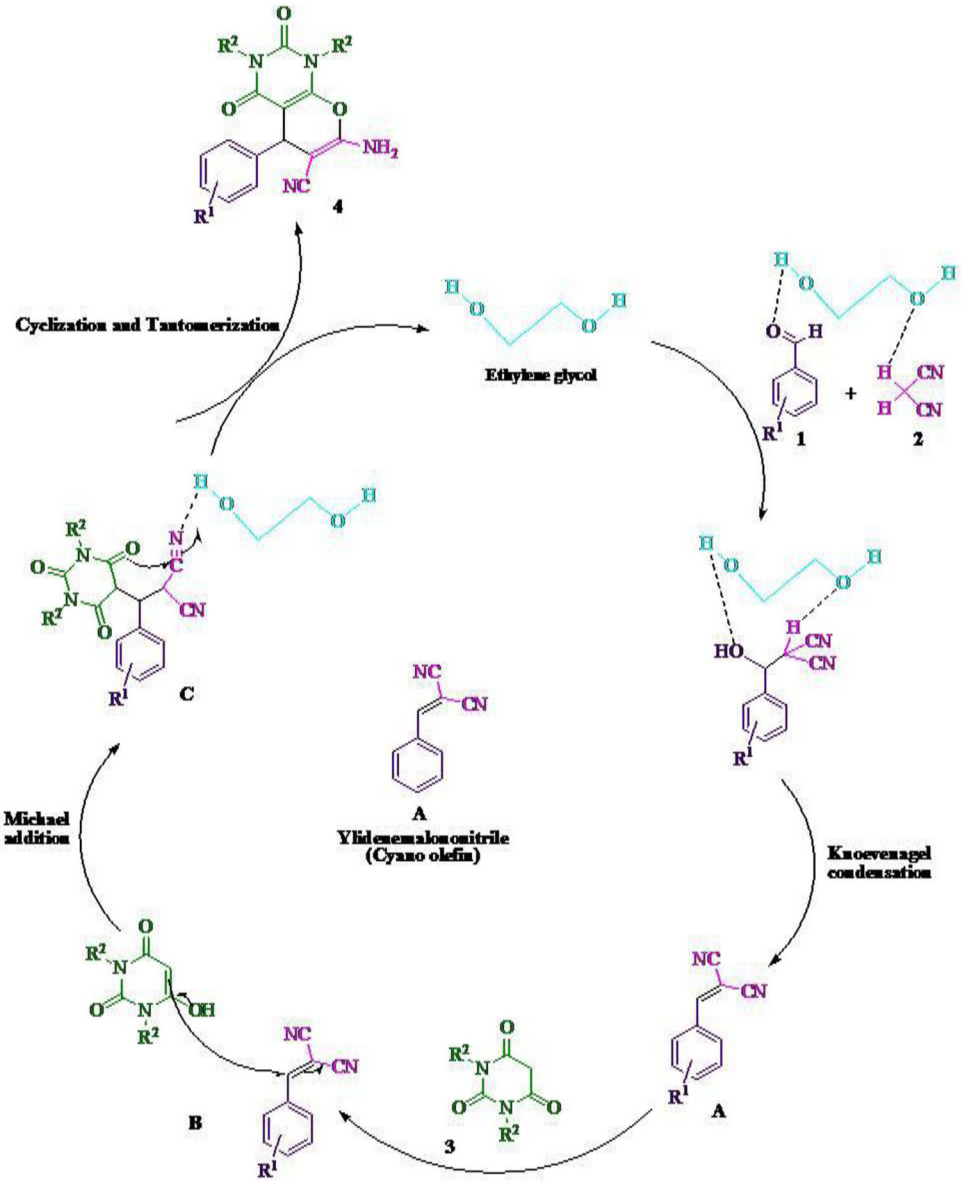


4q

Yield: 92%; M.p. 274–276 °C; ^{1}H NMR (300 MHz, DMSO-d_6): 3.57 (3H, s, OCH_3), 4.46 (1H, s, CHAr), 7.49–8.19 (6H, m, ArH and NH_2), 10.73 (1H, s, NH), 11.80 (1H, s, NH).

Results and discussion

Initially, the reaction between benzaldehyde (1 mmol), malononitrile (1 mmol), and barbituric acid (1 mmol) was investigated in different solvents under catalyst-free conditions at various temperatures, and the results are listed in Table 1. Only a trace amount of products were detected in DCM, DMSO, THF, DMF, $CHCl_3$ and solvent-free conditions (Table 1, entries 7 and 14–18). While the reaction proceeded sluggishly in H_2O, H_2O/EtOH (1:1), EtOH and MeOH, the yield and reaction rate increased (Table 1, entries 8–11). Inspired by the observed determinant effect of alcoholic solvents on the reaction, we then investigated the efficiency of ethylene glycol and polyethylene glycol as a solvent for this reaction. A huge improvement was observed in E-G, PEG-200 and PEG-600 at 100 °C (Table 1, entries 5 and 12, 13). An excellent yield of 92% was produced when green E-G was used as a solvent without any added catalyst at 100 °C for 90 min (Table 1, entry 5). As shown in Table 1, the best results were obtained at 100 °C in the presence



Scheme 2. Proposed mechanistic route for the synthesis of pyrano[2,3-*d*]pyrimidine scaffolds.

of E-G (3 mL). Interestingly, all starting materials are soluble in E-G, so at the start of the reaction, a solution, which seemed to be nearly transparent, was observed. All obtained products were found to be insoluble in E-G, so with progress of the reaction, wrought products sediment slowly from the reaction mixture. Finally, we have reported catalyst-free green synthesis of pyrano[2,3-*d*]pyrimidine scaffolds *via* one-pot, three-condensation domino reaction between aryl aldehyde derivatives (**1**, 1.0 mmol), malononitrile (**2**, 1.0 mmol), barbituric acid/1,3-dimethylbarbituric acid (**3**, 1.0 mmol) in ethylene glycol (E-G) as a recyclable reaction medium (Scheme 1) in high yields and simple work up with no column chromatographic separation and the results are summarized in Table 2.

Proposed mechanism for the synthesis of pyrano[2,3-*d*]pyrimidine scaffolds are shown in Scheme 2. The reaction was promoted by the formation of an inclusion complex between E-G

and arylaldehyde the intermediate ylidenemalononitrile (cyano olefin) **A** was readily formed in situ from Knoevenagel condensation between E-G solubilized aryladelhyde **1** and active methylene compound **2**. This can be evidenced by the steric effects of the arylaldehydes on the reaction efficiency (Table 2). E-G also catalyzed the formation of the enolic form of barbituric acid/1,3-dimethylbarbituric acid **3** through hydrogen bonding stabilization, which could easily react with cyano olefin **A** and give intermediate **B**, followed by cyclization and tautomerization of **C** affords the target products **4**.

Conclusions

In summary, we have established a catalyst-free, green and facile protocol *via* multicomponent reaction leading to pyrano[2,3-*d*]pyrimidine scaffolds. To the best of our knowledge, this is the report where ethylene glycol (E-G) as a recyclable green reaction medium has been used to activate Knoevenagel–Michael cyclocondensation. This protocol offers certain novelties such as catalyst-free, eco-sustainability, metal-free approach, short reaction time, operational simplicity, cleaner reaction profile, high yield and easy isolation/purification of the products. Further ethylene glycol has been recycled five runs without loss of its activity. This base and additive free approach adds atom economy to the protocol.

Disclosure statement

No potential conflict of interest was reported by the authors.

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