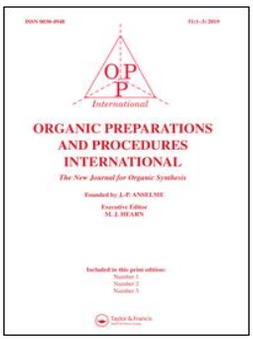

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EXPERIMENTAL PAPER

Catalyst-free Synthesis of Pyrano[2,3-*d*]pyrimidine Scaffolds *via* Knoevenagel-Michael Cyclocondensation Using PEG-400 as a Green Promoting Medium

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Recently, much attention has been given to examining polyethylene glycol 400 (PEG-400) as a green and financially viable alternative to conventional solvents. Its favorable features include non-corrosiveness, stability, and useful solubility for organic compounds. PEG-400 has been used as a convenient green reaction environment for a number of organic reactions.[1–4] Pyrano[2,3-*d*]pyrimidines feature significant pharmacological properties, including antihypertensive,[5] cardiotonic,[6] bronchodilator,[7] antibronchitic[8] and antitumor activities.[9] There are numerous approaches for synthesizing these compounds using such promoters as DABCO-based ionic liquids,[10] L-proline,[11] iron ore pellets,[12] nano-sawdust-OSO_3H,[13] Al-HMS-20,[14] TSA/$B(OH)_3$,[15] Mn/ZrO_2,[16] cellulose-based nanocomposites,[17] DBA,[18] TBAB,[19] Fe_3O_4@SiO_2@$(CH_2)_3$-Urea-SO_3H/HCl,[20] Et_3N-ultrasound,[21] $ZnFe_2O_4$ nanoparticles,[22] microwave irradiation,[23] nickel nanoparticles,[24] $CaHPO_4$,[25] Zn[(L)proline]$_2$[26] and theophylline.[27] It was shown that these reported procedures lead to the desired products, but some of them have undesirable features. Among these we might note expensive reagents, environmental hazards, long reaction times, or the use of homogeneous catalysts that are difficult to separate from the reaction mixture. Given these facts and our own current focus on environmentally benign protocols,[28–32] we investigated the catalyst-free green synthesis of pyrano[2,3-*d*]pyrimidines using PEG-400 as a reusable promoting medium (Scheme 1). The preparation takes place *via* tandem Knoevenagel-Michael cyclocondensation.

As a model, the multicomponent reaction among malononitrile (1 mmol), benzaldehyde (1 mmol), and barbituric acid (1 mmol) was studied in several solvents under catalyst-free circumstances at different temperatures, and the outcomes are provided in Table 1. An outstanding yield of 94% resulted by using PEG-400 as a medium with no catalyst at 100 °C for 80 min (entry 6). With the best conditions in hand, we then applied them to the preparation of a variety of pyrano[2,3-*d*]pyrimidines (Table 2) and found the method broadly applicable, with very good yields (range 76-95%, mean 87%). It is worthy of note that all reactants are soluble in PEG-400, providing a nearly transparent solution at the start of the reaction. By way of contrast, all the products in our study are insoluble in PEG-400. As the reaction takes place, the products are deposited gradually from the reaction mixture.

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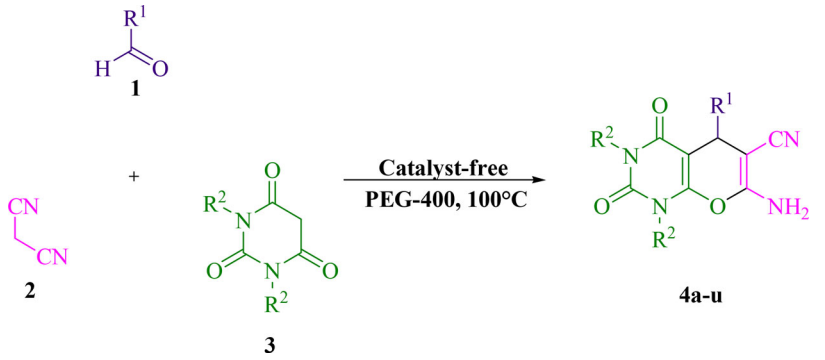


Scheme 1. Synthesis of pyrano[2,3-*d*]pyrimidine scaffolds.

Scheme 2 shows the suggested mechanism for synthesizing pyrano[2,3-*d*]pyrimidines, a key feature of which is the creation of an inclusion complex between PEG-400 and reactants. Thus, the intermediate ylidenemalononitrile (cyano olefin) **A** may be generated *in situ* from the Knoevenagel condensation between PEG-400 solubilized arylaldehyde **1** and active methylene compound **2**. PEG-400 may also catalyze the creation of the enolic form of barbituric acid (or 1,3-dimethylbarbituric acid) **3** by hydrogen bonding. Michael addition to form **C**, followed by cyclizing and tautomerizing, affords the target product **4**.

The recovery and reusability of PEG-400 was investigated in several recurrent runs. After following the optimized protocol for the preparation of **4e** (see Experimental section), the aqueous filtrate containing the PEG-400 was distilled at 100 °C to eliminate water to give PEG-400. The recovered PEG-400 was effectively utilized in five consecutive runs with only minor decreases in yield (92, 91, 88, 86 and 82% respectively) and with insignificant PEG-400 loss.

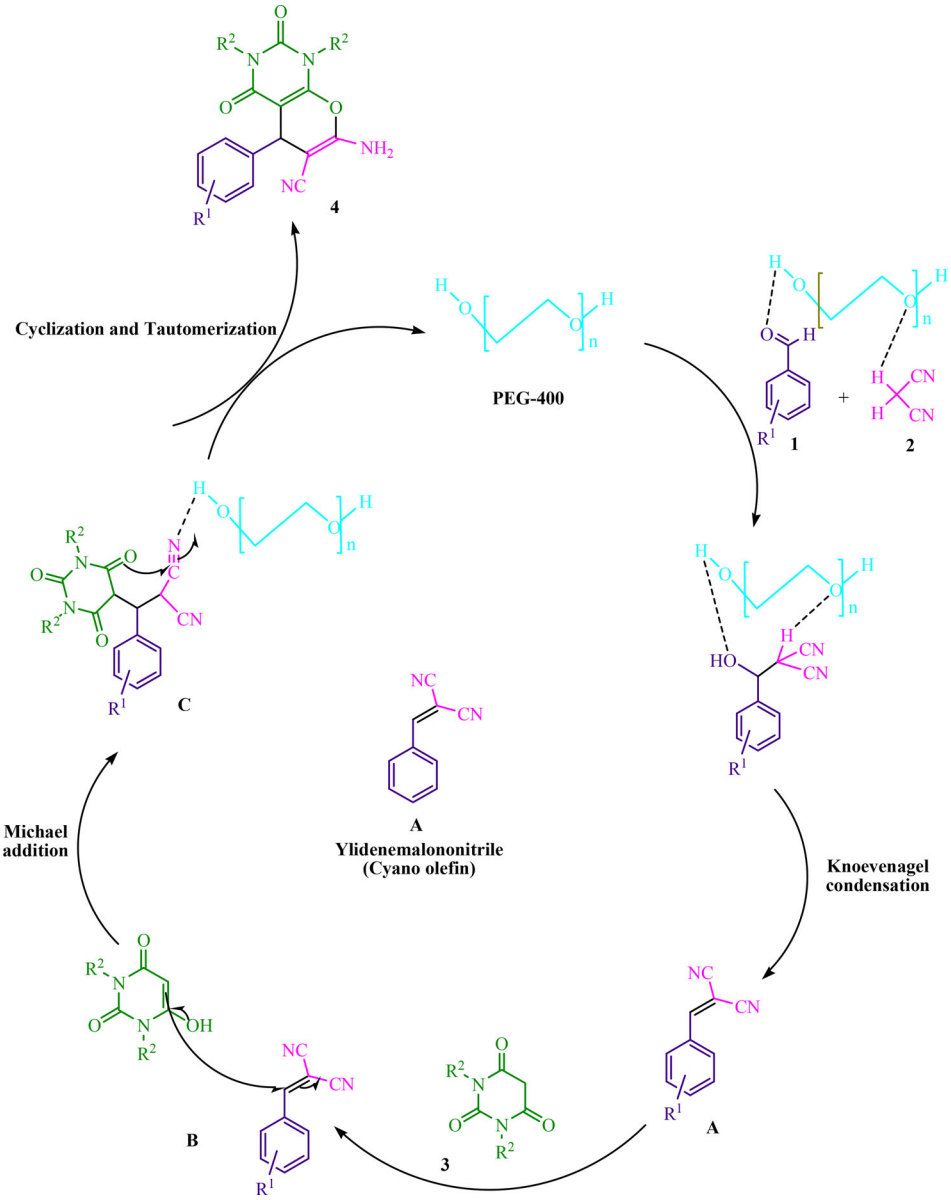
Summing up, we have demonstrated that pyrano[2,3-d]pyrimidines may be conveniently prepared using PEG-400 as an effective green medium. The reactions occur in very good yields (mean 87%) and the yields do not appear to be very dependent on substituents. The reaction occurs without the need for any additional catalyst. It is hoped that the simplicity of the method will encourage further synthesis and study of these highly useful heterocyclic systems.

Experimental section

Utilizing an Electro thermal 9100 device, all compounds' melting points were found and they are uncorrected. ^{1}H NMR spectra were obtained on Bruker DRX-400 and Bruker DRX-300 Avance instruments with DMSO-d_6 as solvent. All solvents and reagents were bought from Acros, Merck, and Fluka chemical companies and were utilized with no additional purification.

Overall process for preparing pyrano[2,3-d]pyrimidines (4a-u)

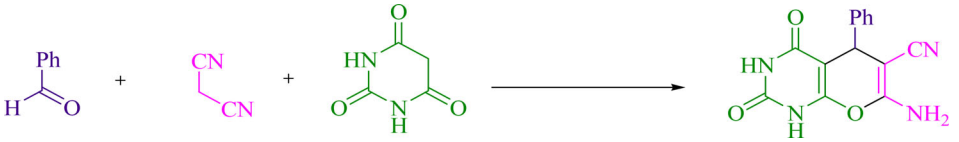
To a mixture of malononitrile (**2**, 1.0 mmol), aryl aldehyde (**1**, 1.0 mmol), barbituric acid (or 1,3-dimethylbarbituric acid) (**3**, 1.0 mmol) was added PEG-400 (3 mL). Then



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

the mixture was heated in an oil-bath (100 °C) (Scheme 1). The reaction progress was monitored by TLC (silica gel) utilizing EtOAc/n-hexane (1:3) as an eluent. The reaction mass was chilled to room temperature after completing the reaction and then poured into cold water. The solid which resulted was filtered, rinsed with water; and the crude solid was recrystallized from ethanol to provide the pure material without requiring more purification. The aqueous filtrate was refined at 100 °C to eliminate water to give PEG-400 which was used for the next run under similar reaction conditions. The polyethylene glycol (PEG-400) was reused through several further runs with little activity loss. All of the pyrano[2,3-d]pyrimidines were known compounds and were identified by matching their melting points with

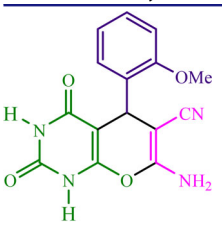
Table 1. Optimizing the preparation of **4e**.



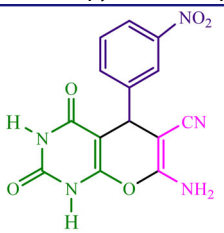
Entry	Solvent (3 mL)	Temp (°C)	Time (min)	Yield (%)[a]
1	PEG-400	rt	420	29
2	PEG-400	40 °C	360	46
3	PEG-400	60 °C	180	58
4	PEG-400	80 °C	120	73
5	PEG-400	90 °C	95	85
6	**PEG-400**	**100 °C**	**80**	**94**
7	PEG-400	110 °C	80	95
8	PEG-200	100 °C	85	76
9	PEG-600	100 °C	80	82
10	H_2O	Reflux	360	68
11	EtOH	Reflux	360	57
12	H_2O/EtOH (1:1)	Reflux	360	61
13	MeOH	Reflux	360	44
14	Solvent-free	100 °C	420	<5
15	DMSO	100 °C	480	<5
16	CH_3CN	Reflux	480	<5
17	$CHCl_3$	Reflux	480	<5
18	THF	Reflux	480	<5
19	DCM	Reflux	480	<5
20	DMF	100 °C	480	<5
21	Toluene	100 °C	480	<5

[a]Isolated yields.

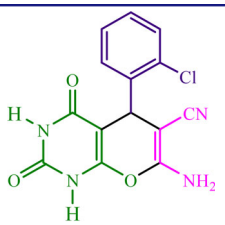
Table 2. Catalyst-free synthesis of pyrano[2,3-*d*]pyrimidines.



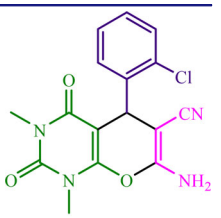
4a (80 min, 91%)
Mp. 229-231 °C
Lit. 230 °C[26]



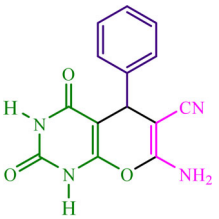
4b (75 min, 92%)
Mp. 261-263 °C
Lit. 259-261 °C[13]



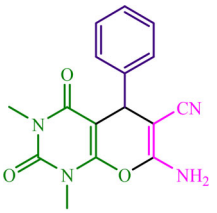
4c (90 min, 89%)
Mp. 212-214 °C
Lit. 211-214 °C[15]



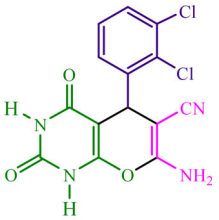
4d (90 min, 86%)
Mp. 241-243 °C
Lit. 243-244 °C[22]



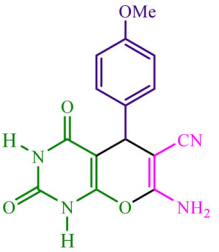
4e (80 min, 94%)
Mp. 222-224 °C
Lit. 224-225 °C[10]



4f (80 min, 93%)
Mp. 238-240 °C
Lit. 237-238 °C[15]

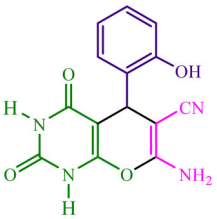


4g (100 min, 83%)
Mp. 244-246 °C
Lit. 243-245 °C[19]

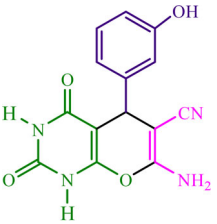


4h (80 min, 89%)
Mp. 270-272 °C
Lit. 272-274 °C[13]

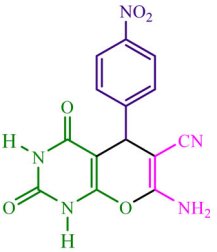
(*continued*)



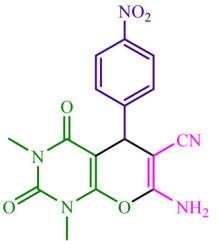
4i (100 min, 87%)
Mp. 168-170 °C
Lit. 169-170 °C[12]



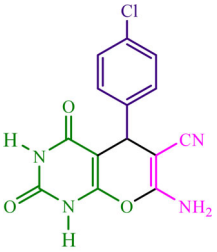
4j (115 min, 84%)
Mp. 160-162 °C
Lit. 158-160 °C[11]



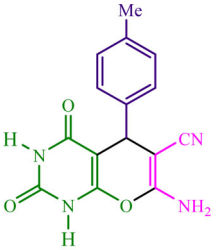
4k (80 min, 92%)
Mp. 234-236 °C
Lit. 236-237 °C[10]



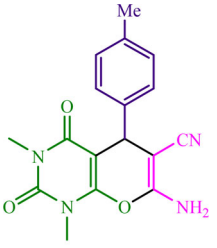
4l (90 min, 87%)
Mp. 216-218 °C
Lit. 214-216 °C[15]



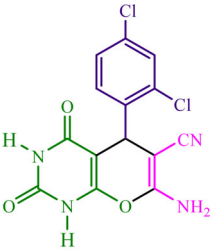
4m (95 min, 81%)
Mp. 234-236 °C
Lit. 235-237 °C[15]



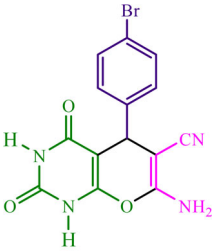
4n (70 min, 92%)
Mp. 225-227 °C
Lit. 226 °C[15]



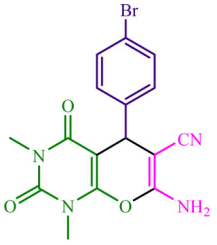
4o (75 min, 94%)
Mp. 203-205 °C
Lit. 205-207 °C[15]



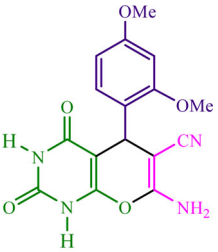
4p (100 min, 78%)
Mp. 241-243 °C
Lit. 241-242 °C[11]



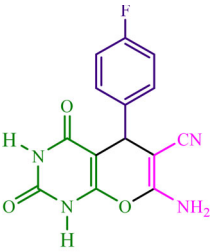
4q (110 min, 76%)
Mp. 242-244 °C
Lit. 240-245 °C[12]



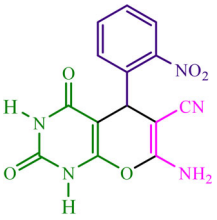
4r (120 min, 79%)
Mp. 211-213 °C
Lit. 210-211 °C[16]



4s (95 min, 86%)
Mp. 225-227 °C
Lit. 227-228 °C[12]



4t (70 min, 95%)
Mp. 258-260 °C
Lit. 256-260 °C[10]



4u (70 min, 93%)
Mp. 255-257 °C
Lit. 254-256 °C[10]

those reported in the literature cited (see Table 2). For the sake of completeness, the ^{1}HNMR data of several examples are presented below.

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

^{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 & NH_2), 10.73 (1H, s, NH), 11.80 (1H, s, NH).

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

^{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-(2,4-di-chlorophenyl)-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]-pyrimidine-6-carbonitrile (4p)

^{1}H NMR (300 MHz, DMSO-d_6): 4.24 (1H, s, CHAr), 7.26-7.51 (5H, m, ArH & NH_2), 10.56 (1H, s, NH), 11.81 (1H, s, NH).

Acknowledgments

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