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Aqua mediated indium(III) chloride catalyzed synthesis of fused pyrimidines and pyrazoles

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ABSTRACT

The utilization of water as solvent and indium trichloride as promoter for the three-component combinatorial synthesis of a variety of bioactive pyrimidine and pyrazole derivatives (**2–10**) from aldehydes, 1,3-dicarbonyl compounds, and electron-rich amino heterocycles like 6-amino-1,3-dimethyl uracil and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine catalyzed by indium trichloride under reflux has been studied. A new class of pyrimidine derivatives (**2**) has also been synthesized and the structure was confirmed by single crystal X-ray analysis. The reactions are environmentally benign, reaction product could be isolated easily and the catalyst could be recycled, which makes it an appealing synthetic protocol.

Indium trichloride[1] has invoked enormous interest as a green and mild Lewis acid of high potential to construct carbon–carbon or carbon–heteroatom bonds in various organic transformations due to its low toxicity, air and water compatibility, ease of handling, and high solubility in water and organic solvents. Performing organic reactions in water has become highly enviable in recent years to meet environmental considerations.[2,3] Multi-component reactions (MCRs) leading to interesting heterocyclic scaffolds, which blends the economic aspects with environmental ones are particularly useful for the combinatorial chemistry[4] as they provide the opportunity to introduce several diversity elements in a single step.[5] Many heterocyclic compounds containing the pyrazole ring display a broad spectrum of pharmacological and biological activities, such as anti-bacterial, anti-depressant, anti-hyperglycemic, anti-inflammatory, and anti-tumor.[6] Pyrazolopyridines possess biological activities such as potent cyclin dependent kinase 1 (CDK1) inhibitor,[7] HIV reverse transcriptase inhibitors,[8] CCR1 antagonists,[9] protein kinase inhibitors,[10] and cGMP degradation inhibitors, besides several herbicidal and fungicidal activities.[11] Pyridopyrimidines also exhibit promising biological and pharmacological activities such as anti-folate,[12] anti-bacterial,[13] tyrosine kinase inhibitors,[14] antimicrobial,[15] calcium channel antagonist,[16] anti-inflammatory,[17] analgesic,[17] anti-leishmania,[18] tuberculostatic,[19] anti-convulsant,[20] diuretic and potassium-sparing,[21] and anti-aggressive activities.[22]

Literature search reveals that the synthesis of pyrimido pyrimidines can be achieved using [bmim]Br,[23] pyrazolo quinolines using ethylene glycol under MW irradiation,[24a] or diammonium hydrogen phosphate,[24b] and indeno fused pyrazolopyridines using L-proline[24c] as a catalyst. Though, indium trichloride[25] has been reported for the synthesis of N-heterocycles there is no such report on the generalized and combinatorial synthesis of all these derivatives via MCR methodology using indium trichloride as a catalyst. In view of our work aimed at developing environmentally benign strategies for the synthesis of heterocyclic compounds with high diversity,[26] we decided to investigate the synthesis of target compounds.

We report herein a new, convenient, diversity-oriented, and highly efficient protocol for the synthesis of novel pyrimidine-2,4-diones (**2**), pyrimido[4,5-*b*]quinolines (**3–5**), pyrimido[2,3-*d*]pyrimidines (**6**), pyrazolo[3,4-*b*]quinolin-5-ones (**7**), pyrazolo[4,3-*e*]pyridin-5-ones (**8**), pyrazolo[4,3-*e*]pyridine-5(1*H*)-ones (**9**), and pyrazolo[3,4-*b*]quinoline-5,10-diones (**10**) via three component condensation of aldehydes, 1,3-dicarbonyl compounds and electron-rich amino heterocycles like 6-amino-1,3-dimethyl uracil and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine catalyzed by indium trichloride in water under reflux (Fig. 1).

In our initial endeavor to synthesize pyrimido[4,5-*b*]quinoline derivatives, a reaction of 4-chlorobenzaldehyde (1.0 mmol), 6-amino-1,3-dimethyl uracil (1.0 mmol) and dimedone (1.0 mmol) was carried out in water in the absence of any catalyst under reflux conditions. The reaction did not proceed to completion even after 14 h and a number of spots were observed on TLC (Table 1, entry 1).

To explore the suitable reaction conditions, the above model reaction was performed in the presence of various catalysts (20 mol %) such as NaBr, LiBr, $AlCl_3$, $InCl_3$, $CeCl_3$, and TMSCl in water under reflux. The results are summarized in Table 1. The

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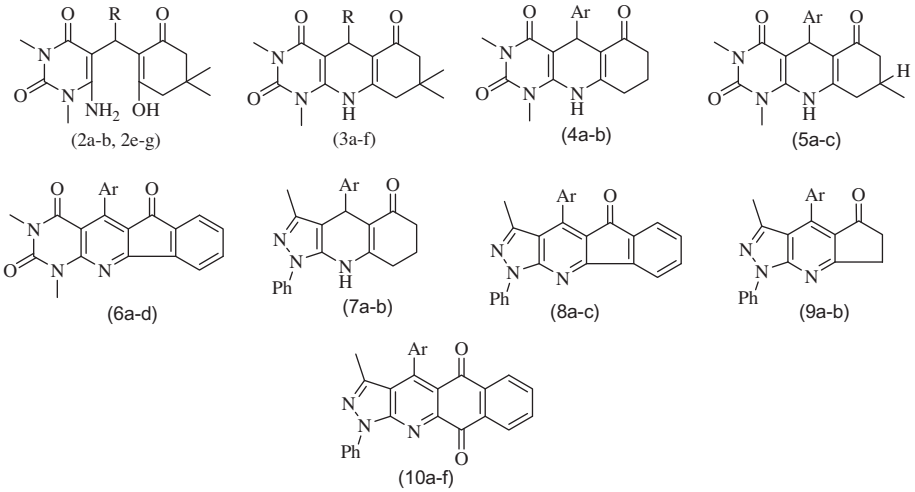


Figure 1. General structure of pyrimidine-2,4-diones (**2**), pyrimido[4,5-*b*]quinolines (**3**–**5**), pyrimido[2,3-*d*]pyrimidines (**6**), pyrazolo[3,4-*b*]quinolin-5-ones (**7**), pyrazolo[4,3-*e*]pyridin-5-ones (**8**), pyrazolo[4,3-*e*]pyridine-5(1*H*)-ones (**9**), and pyrazolo[3,4-*b*]quinoline-5,10-diones (**10**).

Table 1
Optimization of reaction conditions[a]

Entry	Catalyst (mol %)	Solvent	Temp	Time	Yield (%) (product)
1	None	H_2O	Reflux	14 h	–[b]
2	LiBr (20)	H_2O	Reflux	6 h	–[b]
3	$AlCl_3$ (20)	H_2O	Reflux	6 h	–[b]
4	NaBr (20)	H_2O	Reflux	6 h	–[b]
5	$InCl_3$ (20)	H_2O	Reflux	15 min	92 (**2a**)
6	$InCl_3$ (20)	H_2O	Reflux	1 h	91 (**3a**)
7	$CeCl_3$ (20)	H_2O	Reflux	3 h	70[d] (**2a**)[c]
8	TMSCl (20)	H_2O	Reflux	3 h	63[d] (**2a**)[c]
9	$InCl_3$ (15)	H_2O	Reflux	30 min	79 (**2a**)
10	$InCl_3$ (25)	H_2O	Reflux	15 min	92 (**2a**)
11	$InCl_3$ (20)	EtOH/H_2O (1:1, v/v)	rt	1 h	86 (**2a**)
12	$InCl_3$ (20)	EtOH/H_2O (1:1, v/v)	Reflux	1 h	87 (**3a**)

[a] Reactions were carried out using equimolar amounts of 6-amino-1,3-dimethyl uracil, 4-chlorobenzaldehyde, and dimedone.
[b] Incomplete reaction with number of spots on TLC.
[c] Mixture of **2a** and **3a**.
[d] Yields after column chromatography.

reactions performed using 20 mol % of NaBr, LiBr, and $AlCl_3$ as catalysts, were found to be incomplete and gave a complex reaction mixture (Table 1, entries 2–4). Then we conducted the above reaction in the presence of $InCl_3$ (20 mol %) in water under reflux. The reaction was observed to be complete after 15 min as analyzed by TLC using petroleum ether/ethyl acetate (60:40) as eluent. The solid product was filtered, washed with ethanol, and characterized by IR, NMR, and mass spectral analyses and found to be 6-amino-5-[(4-chlorophenyl)-(2-hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl)methyl]-1,3-dimethyl-1*H*-pyrimidine-2,4-dio ne (**2a,** 92%) (Table 1, entry 5) which was not the targeted pyrimido[4,5-*b*]quinoline. The product **2** has been proposed as an intermediate in the synthesis of pyrimido[4,5-*b*]quinolines (**3**). The structure of **2a** was also confirmed by single crystal X-ray analysis (Fig. 2).[27]

In order to confirm if **2a** could be cyclized to give reported pyrimidoquinolines, the above reaction was repeated and monitored by TLC. It was observed that the product **2a** was formed after 15 min However if the reaction was continued further, complete disappearance of **2a** was observed after another 45 min and a new product was formed which was identified to be 5-(4-chlorophenyl)-1,3,8,8-tetramethyl-5,8,9,10-tetrahydro-1*H*,7*H*-pyrimido[4,5-*b*]quinoline-2,4,6-trione (**3a**, 91%) (Table 1, entry 6) by spectral analysis after work-up. Reactions conducted using $CeCl_3$ and TMSCl, as

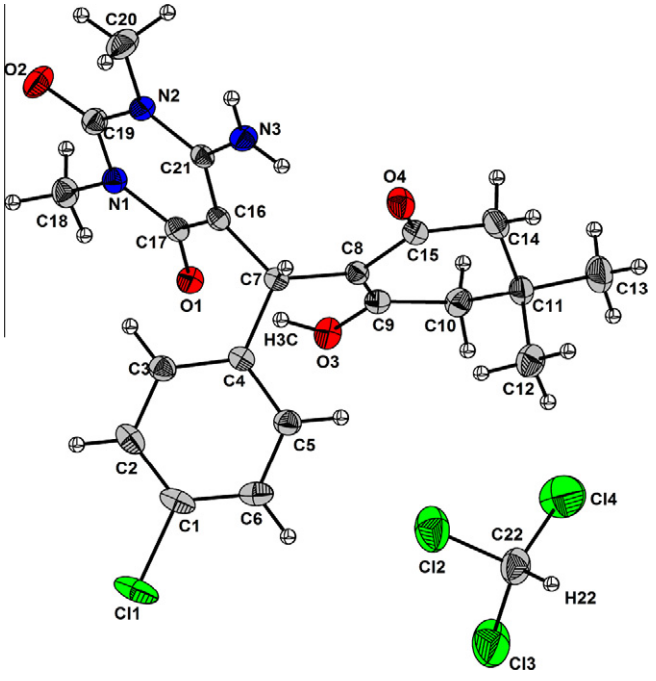
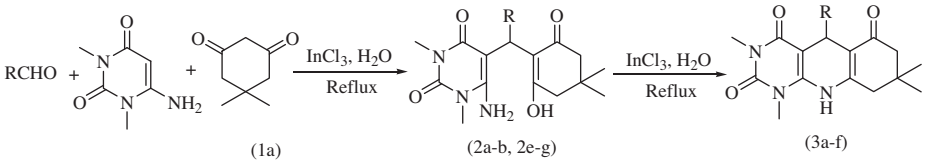


Figure 2. X-ray crystallographic structure of **2a.**

Table 2
Synthesis of 6-amino-5-[aryl-(2-hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl)methyl]-1,3-dimethyl-1*H*-pyrimidine-2,4-diones (**2**) and 5-aryl-1,3,8,8-tetramethyl-5,8,9,10-tetrahydro-1*H*,7*H*-pyrimido[4,5-*b*]quinoline-2,4,6-triones (**3**) (Scheme 1)[a]

R	Product (**2**)				Product (**3**)				
	Entry	Time (min)	Yield (%)	Mp (° C) (Obsd)	Entry	Time (min)	Yield (%)	Mp (° C) (Obsd)	Mp (° C) (Lit.)[23]
4-ClC_6H_4	**2a**	15	92	190–192	**3a**	60	91	290–292	292–294
4-BrC_6H_4	**2b**	15	92	185–187	**3b**	60	90	280–282	281–283
4-HOC_6H_4	**2c**	Not isolated			**3c**	60	90	>300	–
4-$CH_3OC_6H_4$	**2d**	Not isolated			**3d**	60	89	>300	>300
4-$O_2NC_6H_4$	**2e**	15	93	168–170	**3e**	60	91	222–224	–
2-Thiophenyl	**2f**	15	91	218–220	**3f**	90	89	296–298	295–296
$(CH_3)_2CH$	**2g**	15	92	230–232					

[a] Reactions were carried out using equimolar amounts of 6-amino-1,3-dimethyl uracil, aldehyde, and dimedone in water under reflux using 20 mol % of $InCl_3$.

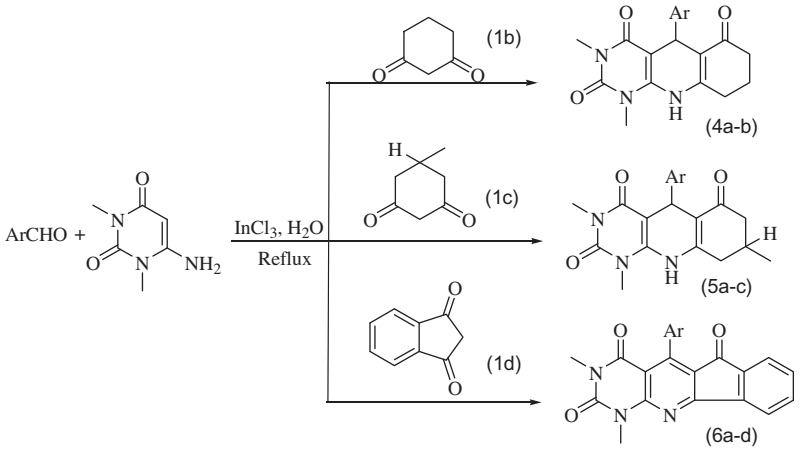


Scheme 1. Synthesis of 6-amino-5-[aryl-(2-hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl) methyl]-1,3-dimethyl-1*H*-pyrimidine-2,4-diones and 5-aryl-1,3,8,8-tetramethyl-5,8,9,10-tetrahydro-1*H*,7*H*-pyrimido[4,5-*b*]quinoline-2,4,6-triones.

Table 3
$InCl_3$ catalyzed three component synthesis of pyrimidoquinoline/pyridopyrimidine derivatives (Scheme 2)[a]

Entry	Ar	1,3-Dicarbonyl compound	Time (min)	Yield (%)	Mp (° C)	
					Obsd	Lit.[23]
4a	4-ClC_6H_4	**1b**	45	92	222–224	310–313
4b	4-$O_2NC_6H_4$	**1b**	60	93	>300	301–303
5a	4-ClC_6H_4	**1c**	50	91	268–270	–
5b	4-$O_2NC_6H_4$	**1c**	60	92	268–270	–
5c	4-BrC_6H_4	**1c**	60	91	>300	–
6a	4-ClC_6H_4	**1d**	60	88	>300	>300
6b	4-$CH_3C_6H_4$	**1d**	60	87	>300	>300
6c	4-$O_2NC_6H_4$	**1d**	60	90	252–254	254–256
6d	3-$O_2NC_6H_4$	**1d**	60	89	>300	>300

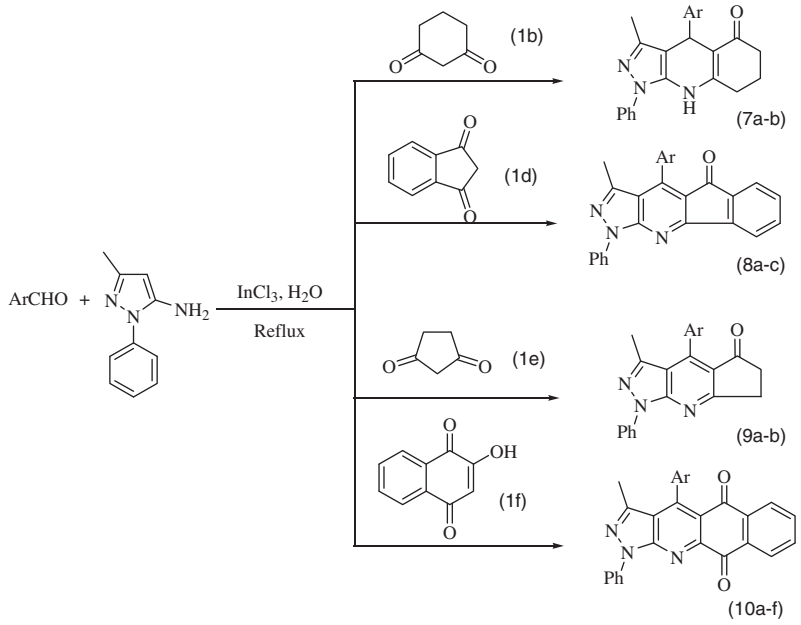
[a] Reactions were carried out using equimolar amount of 6-amino-1,3-dimethyl uracil, aldehyde, and 1,3-dicarbonyls in water under reflux using 20 mol % of $InCl_3$.



Scheme 2. Synthesis of pyrimidoquinolines/pyridopyrimidines.

catalysts in water under reflux showed the formation of a new product on TLC corresponding to **2a** after 45 min, besides the starting materials. The reactions were complete after 3 h, using $CeCl_3$ and TMSCl but yielded a mixture of **2a** and **3a** (Table 1, entries 7 and 8).

Subsequently, to assess the effect of amount of the catalyst on the reaction time and yield of the product **2a**, we attempted the above condensation reaction using 15 mol % and 25 mol % of $InCl_3$. The reaction when conducted using 15 mol % of the catalyst required longer time for completion (30 min) while on increasing the amount of the catalyst to 25 mol %, no significant improvement



Scheme 3. Synthesis of pyrazole derivatives.

Table 4
$InCl_3$ catalyzed synthesis of pyrazole derivatives (Scheme 3)[a]

Entry	Ar	1,3-Dicarbonyl compound	Time (min)	Yield (%)	Mp (° C)	
					Obsd	Lit.
7a	4-$O_2NC_6H_4$	**1b**	45	91	175–178	–[24ab]
7b	4-ClC_6H_4	**1b**	45	89	180–182	–[24ab]
8a	4-$CH_3OC_6H_4$	**1d**	60	87	220–222	222–224[24c]
8b	4-ClC_6H_4	**1d**	60	89	270–272	271–272[24c]
8c	4-$O_2NC_6H_4$	**1d**	45	93	>300	318-319[24c]
9a	4-ClC_6H_4	**1e**	45	88	181–183	–
9b	4- $F_3CC_6H_4$	**1e**	60	92	240-242	–
10a	C_6H_5	**1f**	60	86	264-266	266–267[24b]
10b	4-$CH_3OC_6H_4$	**1f**	50	89	272–274	274–275[24b]
10c	4-$O_2NC_6H_4$	**1f**	45	90	>300	326–328[24b]
10d	3-$O_2NC_6H_4$	**1f**	45	91	288–290	288–289[24b]
10e	4-FC_6H_4	**1f**	60	89	280–282	281–283[24b]
10f	4-ClC_6H_4	**1f**	60	87	242–244	243–245[24b]

[a] Reactions were carried out using equimolar amount of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine, aldehyde, and 1,3-dicarbonyls in water under reflux using 20 mol % of $InCl_3$.
[b] Compounds are known but their melting points are reported for the first time.

in the time or yield of the product, **2a** was observed (Table 1, entries 9 and 10).

The condensation of 4-chlorobenzaldehyde (1.0 mmol), 6-amino-1,3-dimethyl uracil (1.0 mmol), and dimedone (1.0 mmol) could also be achieved in water/ethanol (1:1, v/v) at room temperature using 20 mol % of $InCl_3$ and gave 86% of uncyclized intermediate product **2a** (Table 1, entry 11). However it could not be cyclized to give the product **3a** even after 24 h at room temperature. This could be due to the fact that cyclization by the loss of water molecule from NH_2 and OH groups of **2a** to form the cyclized product **3a,** probably requires high temperature. This emerges from the fact that the above reaction in water/ethanol (1:1, v/v) does undergo cyclization at higher temperature under reflux though in slightly inferior yields (87%) (Table 1, entry 12).

Thus refluxing all the components in the presence of 20 mol % of $InCl_3$ in water proved to be the optimum conditions for this reaction (Table 1). Therefore, reactions of substituted aromatic, heteroaromatic, and aliphatic aldehydes were carried our under the optimized reaction conditions. The condensations proceeded satisfactorily to give the products **2** which on subsequent reactions could be cyclized to give pyrimidoquinolines **3** and no undesirable side reactions were observed. It is noteworthy that in case of electron-deficient aldehydes the uncyclized products were obtained (Table 2, entries 2a, 2b, 2e), whereas electron-rich aldehydes like 4-hydroxybenzaldehyde, 4-methoxybenzaldehyde were more likely to provide the pyrido[2,3-*d*]pyrimidines directly, without isolation of the corresponding uncyclized intermediates. These results are listed in Table 2 (Scheme 1). [28]

The optimized reaction conditions for three component condensation were also evaluated by using other cyclic 1,3-dicarbonyl compounds, such as cyclohexane-1,3-dione (**1b**), 5-methyl-cyclohexane-1,3-dione (**1c**), and indane-1,3-dione (**1d**).

Condensations with cyclohexane-1,3-dione (**1b**) led to the formation of stable dihydropyrimido[4,5-*b*]quinolines (Table 3, entries 4a–b) while condensations with 5-methyl-cyclohexane-1,3-dione (**1c**) led to the formation of novel dihydropyrimido[4,5-*b*]quinolines (Table 3, entries 5a–c). Condensations with indane-1,3-dione (**1d**) yielded the aromatized pyrido[2,3-*d*]pyrimidines (Table 3, entries

6a–d) in good yields. The formation of pyrido[2,3-d]pyrimidines is compatible with the literature[18] report which has stated that the dihydro[2,3-*d*]pyrimidine-2,4-diones are unstable to air and oxidized to corresponding aromatized product (Scheme 2). Furthermore to explore the generality and diversity of the protocol, we extended the present methodology for the condensation of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine, aromatic aldehydes, and cyclic diketones like cyclohexane-1,3-dione (**1b**), indane-1,3-dione (**1d**), cyclopentane-1,3-dione (**1e**), and 2-hydroxy-1,4-naphthoquinone (**1f**) using $InCl_3$ as catalyst in water under reflux (Scheme 3).

All the reactions proceeded smoothly and gave 4-aryl-3-methyl-1-phenyl-1,4,6,7,8,9-hexahydropyrazolo[3,4-*b*]quinolin-5-ones (Table 4, entries 7a–b) as the sole product with cyclohexane-1,3-dione (**1b**) and the fully aromatized product that is 4-aryl-3-methyl-1-phenyl-1*H*-indeno[1,2-*b*]pyrazolo[4,3-*e*]pyridin-5-ones (Table 4, entries 8a–c), novel 4-aryl-3-methyl-1-phenyl-6,7-dihydro cyclopenta[*b*]pyrazolo[4,3-*e*]pyridine-5(1*H*)-ones (Table 4, entries 9a-b), and 4-aryl-3-methyl-1-phenyl-1*H*-benzo[*h*] pyrazolo[3,4-*b*]quinoline-5,10-di-ones (Table 4, entries 10a–f) with indane-1,3-dione (**1d**), cyclopentane-1,3-dione (**1e**), and 2-hydroxy-1,4-naphthoquinone (**1f**) respectively in good yields.

Apart from the greener reaction conditions, the products could be isolated by simple filtration in excellent yields. The possibility to recover and recycle $InCl_3$ also offers another significant advantage. Because $InCl_3$ is soluble in reaction medium (water) and the products are insoluble in water, the recovered filtrate containing the catalyst could be recycled. Studies using 6-amino-1,3-dimethyluracil, 4-chlorobenzaldehyde, and dimedone (**1a**) as model substrates showed that the recovered filtrate could be successively recycled in subsequent reactions without any significant decrease of yield of **3a**. A marginal loss of the yield was observed in first two runs (91% and 89%), while in third and fourth run the yield dropped to 75% and 65%, respectively.

In conclusion, we have described a facile, environmentally benign one-pot and three-component method for the synthesis of pyrimidine/pyrazole annulated heterocyclic systems using 20 mol % $InCl_3$ as catalyst in water. The advantages of this method include operational simplicity, high yields, and the reusability of the reaction media

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.04.001.

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27. Crystallographic data for compound **2a** in this paper have been deposited with the Cambridge Crystallographic Data centre as supplemental publication No. CCDC-855405. Copies of the data can be obtained, free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or email: deposit@ccdc.cam.ac.uk).
28. *General procedure for the synthesis of 6-amino-5-[aryl-(2-hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl)methyl]-1,3-dimethyl-1H-pyrimidine-2,4-dione (**2**):* In a typical experiment, a mixture of 4-chlorobenzaldehyde (0.14 g, 1.0 mmol), 6-amino-1,3-dimethyluracil (0.15 g, 1.0 mmol), dimedone (0.14 g, 1.0 mmol), $InCl_3$ (20 mol % or 0.2 mmol), and 10 mL of water was placed in a 50 mL round-bottomed flask and the mixture was stirred under reflux. The reaction was complete within 15 min as analyzed by TLC using petroleum ether/ethyl acetate (60:40) as eluent. The reaction mixture was allowed to cool to room temperature. The precipitate formed was collected by filtration at pump, washed with water and ethanol to yield 0.49 g (92%) of pure 6-amino-5-[(4-chlorophenyl)-(2-hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl)methyl]-1,3-dimethyl-1*H*-pyrimidine-2,4-dione (**2a**) as identified by spectral data.
*General procedure for the synthesis of pyrimidine/pyrazole derivatives (**3**–**10**):* A mixture of aldehyde (1.0 mmol), 6-amino-1,3-dimethyl uracil/3-methyl-1-phenyl-1*H*-pyrazol-5-amine (1.0 mmol), dimedone/cyclohexane-1,3-dione/indane-1,3-dione/cyclopentane-1,3-dione/5-methyl-cyclohexane-1,3-dione/2-hydroxy-1,4-naphthoquinone (1.0 mmol), $InCl_3$ (20 mol % or 0.2 mmol), and 10 mL of water was placed in a 50 mL round-bottomed flask and stirred under reflux for an appropriate time as mentioned in Tables 2 or 3 or 4. The progress of the reaction was monitored by TLC (eluent/methanol/chloroform). After completion of the reaction, the reaction mixture was allowed to cool at room temperature. The precipitate formed was collected by filtration at pump, washed with water and ethanol to obtain pure pyrimidine/pyrazole derivatives (**3–10**). The products were identified by spectral data. The aqueous filtrate containing $InCl_3$ was used as such for investigating the recyclability of the catalyst.