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An efficient and regioselective one-pot multi-component synthesis of pyrimido[4,5-*d*]pyrimidine derivatives in water

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ABSTRACT

Pyrimido[4,5-*d*]pyrimidine derivatives **4** have been prepared in an efficient and regioselective manner in water via multi-component reaction of isothiocyanate **1**, aromatic aldehyde **2**, *N,N*-dimethyl-6-amino uracil **3** in the presence of *p*-toluenesulfonic acid (*p*-TSA) as a Lewis acid catalyst.

The use of hazardous solvents, expensive and toxic reagents, multistep synthesis and production of unwanted side-products are some of the drawbacks in synthetic organic chemistry.[1] Now a days, water is becoming a solvent of choice in organic synthesis because it is non-toxic, non-corrosive, non-flammable, cheap and environment friendly.[2] Furthermore, reaction in water has unique reactivity and selectivity, and can be easily separated from organic products by simple methods.[3] Accordingly, the development of synthetically useful reactions in water is gaining considerable attention of the scientific community.[4]

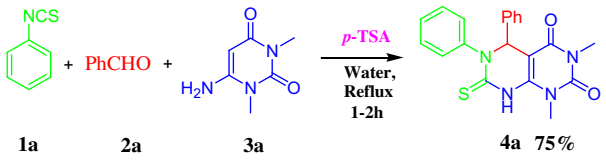
In multi-component reaction (MCR), three or more components combine in one pot process to afford a single product.[5] These reactions, by virtue of their convergence, low energy consumption, minimum waste production, facile execution, high selectivity and productivity, represent an important platform for the design and discovery of various drugs and drug related molecules.[6,7]

Pyrimido[4,5-*d*]pyrimidine derivatives are well known as bronchodilators,[8] vasodilators,[9] antiallergic,[10] antihypertensive,[11] and anticancer[12] agents. Therefore, lot of efforts have been made towards the synthetic manipulation of uracil for the preparation of pyrimido[4,5-*d*]pyrimidine derivatives, which usually requires forcing conditions, long reaction times and complex synthetic pathways.[13] Therefore, there is a need to develop more efficient and sustainable chemical process for the synthesis of pyrimido[4,5-*d*]pyrimidines.

In continuation of our interest in the design and discovery of new reactions for the synthesis of heterocycles[14] herein we report *p*-TSA-catalysed efficient and regioselective multi-component synthesis of pyrimido[4,5-*d*]pyrimidine derivatives using water as solvent (Scheme 1).

Initially, a mixture containing isothiocyanate **1a** (1 mmol), benzaldehyde **2a** (1 mmol) and *N,N*-dimethyl 6-amino uracil **3a** (1 mmol) was reacted in the absence of any catalyst (Table 1, entry-1) under reflux condition in water, but the reaction did not occur. When the reaction was conducted in the presence of catalytic amount of *p*-TSA, a satisfactory result was obtained.[15] Use of 20 mol % of *p*-TSA (Table 1, entry-4), was found to be sufficient for obtaining optimum yields of the desired pyrimido[4,5-*d*]pyrimidine **4a.** Further decrease or increase in the amount of catalyst (Table 1, entries-2–3 and 5) did not improve the yield of the product.

Encouraged by the yield of product, we extended the reaction by using different Brønsted bases and Lewis acids (Table 1, entries 6–10) but no satisfactory results were obtained. Generalization of



Scheme 1. Synthesis of pyrimido[4,5-*d*]pyrimidine derivatives **4a** reflux condition in water.

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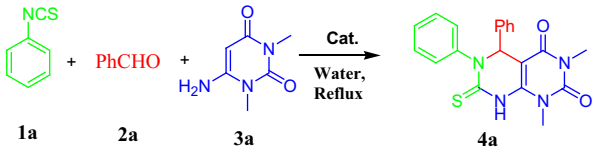
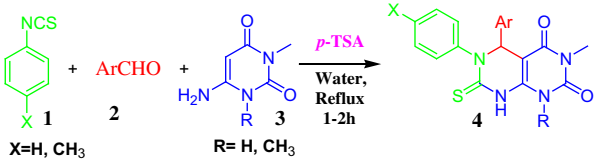
Table 1
Catalyst screening for compound **4a**[a]



Entry	Catalyst (mol %)	Time (h)	Yield[b] (%)
1	—	4	NR[c]
2	*p*-TSA (5)	2	60
3	*p*-TSA (10)	2	70
4	*p*-TSA (20)	1	75
5	*p*-TSA (30)	2	55
6	Et_3N	3	50
7	DBU	4	20
8	$InCl_3$	2	40
9	$Yb(OTf)_3$	2	30
10	CH_3COOH	1.5	45

[a] Benzaldehyde (1 mmol), phenylisothiocyanate (1 mmol) and *N,N*-dimethyl-6-aminouracil (1 mmol), *p*-TSA catalyst.
[b] Isolated yield.
[c] No reaction.

Table 2
Synthesis of compound **4**



Entry	Isothiocyanate	R	Aldehyde	Product	Yield[a] (%)
1	C_6H_5NCS	CH_3	*p*-ClPh	**4b**	70
2	C_6H_5NCS	CH_3	*p*-CH_3Ph	**4c**	80
3	C_6H_5NCS	CH_3	*p*-OCH_3Ph	**4d**	82
4	C_6H_5NCS	CH_3	*p*-BrPh	**4e**	71
5	C_6H_5NCS	CH_3	*p*-NO_2Ph	**4f**	67
6	C_6H_5NCS	CH_3	*o*-BrPh	**4g**	63
7	C_6H_5NCS	H	Ph	**4h**	73
8	C_6H_5NCS	H	*p*-ClPh	**4i**	68
9	C_6H_5NCS	H	*p*-CH_3Ph	**4j**	79
10	C_6H_5NCS	H	*p*-OCH_3Ph	**4k**	80
11	C_6H_5NCS	H	*p*-NO_2Ph	**4l**	65
12	C_6H_5NCS	H	*p*-BrPh	**4m**	66
13	C_6H_5NCS	H	*o*-BrPh	**4n**	60
14	C_7H_8NCS	CH_3	Ph	**4o**	77
15	C_7H_8NCS	CH_3	ClPh	**4p**	72
16	C_7H_8NCS	CH_3	*p*-CH_3Ph	**4q**	78
17	C_7H_8NCS	CH_3	*p*-OCH_3Ph	**4r**	84

[a] Isolated yield.

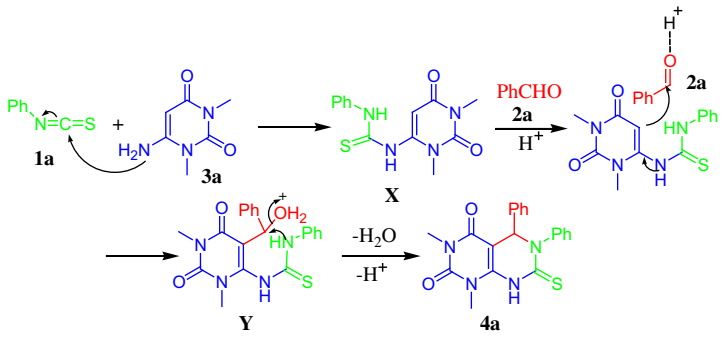
the reaction was done by employing substituted isothiocyanate **1**, different aromatic aldehydes **2** and 6-amino uracil **3** in the presence of *p*-TSA (20 mol %) in refluxing water. The results are summarized in Table 2.

Next, the substrate scope of the reaction was investigated by using various aromatic aldehydes in the reaction process. All the reactions, consisting of those involving *ortho*- and *para*-substituted benzaldehydes, proceed smoothly and afforded the novel pyrimido[4,5-*d*]pyrimidine derivatives in moderate to good yields (Table 2). Electronic effects could be observed in the reaction process. The electron-donating group (EDG) at the *para* position of the benzaldehydes required less reaction time to give comparatively high yields of the product (Table 2, entries 2–3, 9–10 and 16–17) while stronger EWG-substituted ones gave evidently poor yields (Table 2, entries-1, 4–5, 8, 11–12 and 15). *ortho*-Substituted benzaldehydes, irrespective of EDG or EWG, afforded the corresponding pyrimido[4,5-*d*]-pyrimidine derivatives in relatively lower yields, indicating an obvious steric effect (Table 2, entries 6 and 13). We also tried the reaction using lower aliphatic aldehydes viz. acetaldehyde and propanal, but no satisfactory results were obtained and we could not get the desired product.

The structures of the compound pyrimido[4,5-*d*]pyrimidine derivative **4a** were fully characterized by ^1H and ^{13}C NMR, MS, IR spectra and elemental analysis. In IR spectrum, stretching frequencies at 1707 and 3214 cm^{-1} confirmed the presence of C=O functional groups and characteristic NH proton of compound **4a** respectively. The ^1H NMR spectrum showed a sharp singlet at δ 5.59 for single proton and broad distinct singlet in the region of δ 7.46 corresponds to NH proton along with the two methyl protons resonate at 3.15 and 3.65 ppm. The mass spectrum compound **4a** shows a sharp distinguishable peak *m*/*z* at 379.6 $[M+H]^+$. Further, the structure was confirmed from the analysis of 2D NMR spectra (HMQC). Similarly, compounds **4b–r** were synthesized and characterized.

A plausible mechanism for the regioselective formation of products **4a** is shown in Scheme 2. Initially, the intermediate **X** is formed in situ from the reaction of phenylisothiocyanate **1a** with *N,N*-dimethyl-6-amino uracil **3a**. Then, nucleophilic attack of intermediate **X** to aldehyde **2a** in the presence of the catalyst gave intermediate **Y** which upon cyclization and dehydration afforded the desired product **4a**.

In conclusion, we have developed an efficient method for the regioselective synthesis of pyrimido[4,5-*d*]-pyrimidine derivatives via one pot three-components reaction under reflux condition in water. Environmentally benign, inexpensive, and economically feasible catalyst (*p*-TSA) was used as catalyst in the reaction process. The water can be reused for the next cycle, so the waste can be reduced effectively.



Scheme 2. Plausible mechanism of compound **4a**.

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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.2013.12.095.

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15. *General procedure for synthesis of pyrimido[4,5-d]pyrimidines:* A mixture of phenylisothio-cyanate **1a** (1 mmol, 0.135 g), benzaldehyde **2a** (1 mmol, 0.106 g) and *N,N*-dimethyl-6-amino uracil **3a** (1 mmol, 0.155 g) in water (5 mL) was refluxed for 1 h in the presence of catalytic amount of *p*-TSA (20 mol %). After completion of the reaction (monitored by TLC), the mixture was cooled to room temperature, filtered and washed with water (25 mL). The crude product was purified by recrystallization from EtOH to give **4a**. Yield: Yield: 75% (284 mg); mp. 269–270 °C; IR (KBr) ν_{max}: 3214, 2822, 1707.4, 1676.7 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.15 (s, 3H), 3.65 (s, 3H), 5.59 (s, 1H), 7.02–7.34 (m, 10H), 7.46 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.36, 30.38, 35.61, 105.80, 125.22, 125.82 (2C), 126.50 (2C), 126.88, 128.04, 128.29 (2C), 128.45 (2C), 129.60, 138.09, 139.92, 145.86, 150.81; MS (EI): 379.68 $(M+H)^+$; Anal. Calcd for $C_{20}H_{18}N_4O_2S$: C, 63.47; H, 4.79; N, 14.80. Found: C, 63.29; H, 4.61; N, 14.29.