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Organocatalytic domino Knöevenagel-Michael reaction in water for the regioselective synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidines and pyrido[2,3-*d*]pyrimidin-2-amines

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An organocatalyzed simple and general route towards the regioselective synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidines and pyrido[2,3-*d*]pyrimidin-2-amines is developed *via* L-proline catalyzed domino reaction of 2-aminobenzimidazole or 2,6-diaminopyrimidin-4-one with aldehydes and β-ketoesters in water. High yields within shorter reaction time, simple purification, and environmentally benign mild reaction conditions are the key features that make the protocol significantly applicable.

Introduction

Development of simple, cost effective and environment friendly procedure, especially in aqueous medium, is a central theme of green synthetic technology programs. Taking into account that water is the solvent of choice for nature's biological chemistry, the application of water in organic synthesis is of high priority nowadays. The use of water as the reaction solvent is highly advantageous because of its abundance, non-toxicity and non-flammability.[1] In addition, water facilitates novel solvation and molecular assembly processes leading to remarkable modes of reactivity and selectivity.[1,2]

The significance of aqueous media reaction has been further enhanced by the advent of organocatalysis, in 2000 marked by the pioneering works of List[3] and McMillan,[4] where small organic molecules are used in substochiometric amount to catalyze organic transformations which, in overall, has brought a new synthetic outlook, especially in asymmetric synthesis.[5] Not only their requirement in substochiometric amount, but organocatalysts offer many advantages in synthesis because they are air and water stable, easily handled experimentally, relatively nontoxic, cost-effective and readily separated from the crude reaction mixture.[6] More significantly, the ability of organocatalysts to promote a wide range of reactions by different activation modes makes it ideal for application in domino reactions, which proceed in a one-pot procedure to build complex frameworks from simple starting compounds in a single operation.[6b,7] These organocatalyzed domino reactions are relatively very new synthetic concepts and are often highly efficient and follow, in some way, different biomimetic pathways, with the same principles that are found in biosynthesis in nature.[7f] It is, therefore, noteworthy to mention that such design of synthetic routes to privileged heterocyclic scaffolds of medicinal relevance (Fig 1) by combining the synthetic efficiency of domino reactions with organocatalysis is a very important challenge that has received relatively little attention.[7,8]

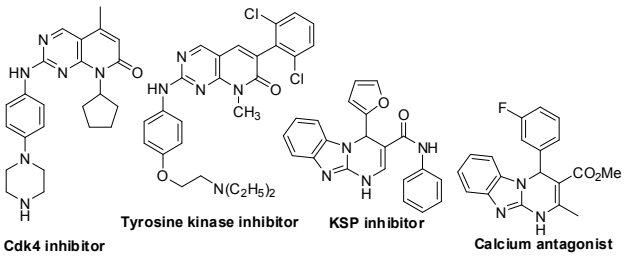

Fig. 1 Some examples of bioactive fused pyrimidines.

Benzo[4,5]imidazo[1,2-*a*]pyrimidines and pyrido[2,3-*d*]pyrimidines are biologically relevant fused pyrimidine derivatives of the classical Biginelli products[9] which have been well known for their significant therapeutic and biological properties. The former is known for potential antineoplastic,[10] calcium antagonist,[11] T-cell activities[12], and also as inhibitors of Kinesin spindle protein (KSP)[13] and DNA-topoisomerase I.[14] The latter also has been proven to act as CC chemokine receptor 4 (CCR4) antagonist,[15] and also as potential inhibitors of tyrosine kinase (TK),[16] cyclin-dependent kinase-4 (Cdk4),[17] and dihydrofolate reductase.[18] Due to their importance, benzo[4,5]imidazo[1,2-*a*]pyrimidines have been synthesized by condensation of 2-aminobenzimidazole, aldehydes and β-ketoesters using a number of catalysts such as AcONa,[11,19] sulfamic acid,[20] silica sulfuric acid,[21] [bmim]BF_4,[22] *N*,*N*′-

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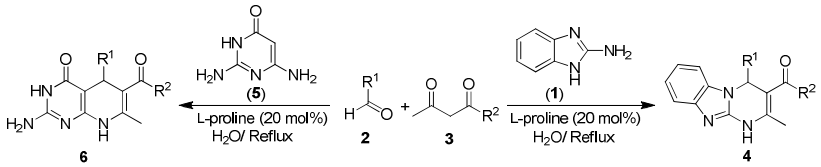


Scheme 1 One-pot regioselective synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidines and pyrido[2,3-*d*]pyrimidin-2-amines.

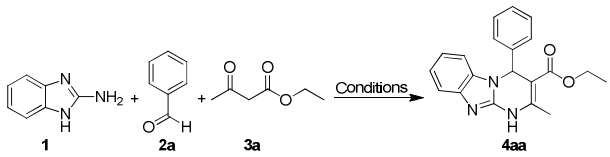
dichlorobis(2,4,6-trichlorophenyl)urea,[23] α-zirconium sulfophenylphosphonate,[24] melaminetrisulfonic acid,[25] thiamine hydrochloride (VB_1),[26] MgO,[27] H_3PO_4-Al_2O_3[28], 1,1,3,3-*N*,*N*,*N*′,*N*′-tetramethylguanidium trifluoroacetate (TMGT)[29], $Zn(ClO_4)_2.6H_2O$[30] and also by microwave irradiation.[31] On the other hand, to the best of our knowledge, there are only four known synthetic methods for methyl 2-amino-7-methyl/ethyl-4-oxo-5-alkyl/aryl-3,4,5,8-tetrahydropyrido[2,3-*d*]pyrimidine-6-carboxylates from the reaction of 2,6-diaminopyrimidin-4-one, aldehydes and β-ketoester: two by NaOAc[32] and $ZnBr_2$[33] catalyzed thermal heating and the other two by microwave irradiation.[34] While the efficiency of the modified synthetic procedures are not understated, such as the VB_1 catalyzed method which is generally unstable to heat, however, a number of them suffer from one or more drawbacks, such as unsatisfactory yields, high temperature, long reaction times, multistep sequences, and limited substrate scope. Moreover, the use of toxic organic solvents, ionic liquids, metals, acids and salts as catalyst increases the waste generation and cost of the synthesis. In addition, while the classical Biginelli reaction has received intensive inputs for procedural improvements, on the other hand, efforts for competent synthetic procedures for the biologically potential fused Biginelli pyrimidines: benzo[4,5]imidazo[1,2-*a*]pyrimidines and pyrido[2,3-*d*]pyrimidin-2-amines, are relatively underexplored which, therefore, requires significant attention.

With these backgrounds and our continued efforts on developing synthetic procedures relevant to green chemistry,[35] we wish to present herein a simple, general and straightforward organocatalytic procedure by for the regioselective synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidines and pyrido[2,3-*d*]pyrimidin-2-amines through L-proline catalyzed domino Knöevenagel-Michael reaction of 2-aminobenzimidazol or 2,6-diaminopyrimidin-4-one with aldehydes and β-ketoesters in water under mild reaction conditions (Scheme 1). It may noted that, L-proline is a well known cost effective and environmentally benign catalyst with remarkable efficacy in promoting diversity of synthetic transformations involving Aldol, Mannich, Michael and analogous reactions, which overcomes major drawbacks of heterogeneous catalysts like long reaction time, metal-leaching and structural stability.[36] The present synthesis has been proved to be operationally simple and cost effective with mild reaction conditions in water, affording high to excelling yields within short reaction time with simple purification process.

Results and Discussion

Initially, a mixture of 2-aminobenzimidazole (**1,** 1mmol), benzaldehyde (**2a**, 1mmol) and ethylacetoacetate (**3a**, 1 mmol) in 5 mL of water was refluxed in the presence of 10 mol% L-proline for 6 h. Much to our delight the reaction yielded ethyl-2-methyl-4-phenyl-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carboxylate (**4aa**) in 65% yield (Table 1, entry 1). Inspired by this result, when the reaction was then set for optimization it was found that 20 mol% of L-proline gave the best result with 91% yield in 3 h (Table 1, entry 3). Next, some potential non-toxic Lewis catalysts and other organocatalysts were also tested to find the best effect of the reaction but none of the reactions showed any satisfactory result (Table 1, entries 5-9) than compared to L-proline catalysis. Further, when the effect of solvents such as EtOH, MeOH and toluene in the reaction, with L-proline as the catalyst, was studied the desired

Table 1 Optimization of the reaction[a]



Entry	Catalyst (mol%)	Solvent[b]	Temp. (°C)	Time (h)	Yield[c] (%)
1	L-Proline (10)	H_2O	Reflux	6	65
2	L-Proline (15)	H_2O	Reflux	3	80
3	L-Proline (20)	H_2O	Reflux	3	91
4	L-Proline (25)	H_2O	Reflux	3	91
5	$FeCl_3.6H_2O$ (20)	H_2O	Reflux	3	20
6	$InCl_3$ (20)	H_2O	Reflux	3	30
7	$NiSO_4.6H_2O$ (20)	H_2O	Reflux	3	17
8	Glycine (20)	H_2O	Reflux	3	15
9	Thioureadioxide (20)	H_2O	Reflux	3	15
10	L-proline (20)	EtOH	Reflux	3	75
11	L-proline (20)	MeOH	Reflux	3	73
12	L-proline (20)	Toluene	Reflux	3	65
13	----------	H_2O	Reflux	12	20
14	L-Proline (20)	H_2O	RT[d]	24	10

[a]Reaction scale: **1** (1 mmol), **2a** (1 mmol) and **3a** (1 mmol). [b]5 mL. [c]Isolated yield. [d]RT ≈ 25 °C.

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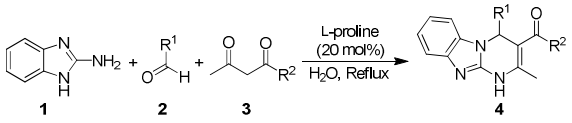
product could be isolated but relatively in low yields (Table 1, entries 10-12). On the other hand, an attempt to obtain the desired product under catalyst-free condition and at room temperature failed (Table 1, entries 13-14). Thus, based on these results, 20 mol% L-proline in water under reflux condition is regarded as the optimum reaction conditions for this method.

Table 2 Synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidines[a]



1 2 3 4

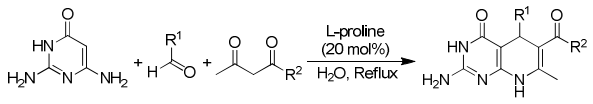
Entry	R^1	R^2	Product	Time (h)	Yield[b] (%)
1	C_6H_5	OEt	**4aa**	3	91
2	2-ClC_6H_4	OEt	**4ab**	3	92
3	3-FC_6H_4	OEt	**4ac**	3	90
4	4-$OMeC_6H_4$	OEt	**4ad**	2.5	88
5	3,5-$(OMe)_2C_6H_3$	OEt	**4ae**	3	85
6	2-Furyl	OEt	**4af**	3.5	80
7	2-Pyridyl	OEt	**4ag**	3.5	93
8	2-Napthyl	OEt	**4ah**	4	80
9	$C_6H_5CH_2$	OEt	**4ai**	4	80
10	Butyl	OEt	**4aj**	4	75
11	2-FC_6H_4	OMe	**4bk**	3	87
12	3-BrC_6H_4	OMe	**4bl**	3.5	80
13	4-ClC_6H_4	OMe	**4bm**	3.5	81
14	4-$NO_2C_6H_4$	OMe	**4bn**	3.5	85

[a]Reaction Scale: **1** (1mmol), **2** (1mmol), **3** (1 mmol) and H_2O (5 mL). [b]Isolated yield.

Subsequently, with this optimized reaction condition the scope of the reaction was studied by reacting 2-aminobenzimidazole (**1**) with various aldehydes (**2**) and β-ketoesters (**3**) for the synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidines. As shown in Table 2, various aromatic aldehydes participated well in the reaction to generate the desired product in good to excellent yields. The presence of electron withdrawing or donating group in *ortho*-, *meta*- and *para*- position of benzene ring of benzaldehyde has no significant impact on the reaction and their corresponding products were obtained successfully (Table 2, **4aa**-**4ae** and **4bk**-**bn**). Heteroaromatic aldehydes like furan-2-carbaldehyde and 2-pyridinecarboxyldehyde also participated well in the reaction to give their corresponding products **4af** and **4ag** in 80% and 93% yields respectively (Table 2, entries 6 and 7). Gratifyingly, aliphatic aldehydes like valeraldehyde and phenylacetaldehyde also reacted efficiently to generate their resultant products **4aj** and **4ai** with respective yields of 75% and 80%. The synthesis was also extended towards polyaromatic aldehyde like 2-naphthaldehyde and its corresponding product **4ah** was obtained in 81% yield. Further generality of the scope was also observed when the reactions of methyl acetoacetate (**3b**), used instead of ethyl acetoacetate (**3a**), with 2-aminobenzimidazole (**1**) and various aldehydes (**2**) efficiently produced the methyl analogs of benzo[4,5]imidazo[1,2-*a*]pyrimidines (Table 2, **4bk-4bn**).

Furthermore, the scope of the method was also extended by exploring towards regioselective synthesis of pyrido[2,3-*d*]pyrimidin-2-amines, under the same optimized reaction conditions. The synthesis was carried out by reacting 2,6-diaminopyrimidin-4-one (**5**) with various aldehydes (**2**) and β-ketoesters (**3**) (Table 3). Various benzaldehydes reacted smoothly with **5** and ethyl acetoacetate (**3a**) to furnish the desired product in good to high yields, without any substantial electronic and steric hindrances from the substitutents of the benzene ring. With similar effect, the reaction involving heteroaromatic aldehyde such as furan-3-carbaldehyde also gave its resultant product **6bh** in good yield of 80%. In addition, aliphatic aldehydes like phenylacetaldehyde also reacted efficiently and gave its resultant pyrido[2,3-*d*]pyrimidin-2amine **6ae** in 80% yield. Moreover, the use of methyl acetoacetate (**3b**), by replacing ethyl acetoacetate (**3a**), also showed equal competency and produced their corresponding methyl derivatives of pyrido[2,3-*d*]pyrimidin-2-amines (Table 3, **6bf-bh**).

Table 3 Synthesis of pyrido[2,3-*d*]pyrimidin-2-amines[a]



5 2 3 6

Entry	R^1	R^2	Product	Time (h)	Yield[b] (%)
1	C_6H_5	OEt	**6aa**	3	82
2	3-$NO_2C_6H_5$	OEt	**6ab**	2.5	88
3	4-$CH_3C_6H_4$	OEt	**6ac**	3	81
4	2,5-$(OMe)_2C_6H_3$	OEt	**6ad**	3	80
5	$C_6H_5CH_2$	OEt	**6ae**	3.5	82
6	2-BrC_6H_5	OMe	**6bf**	3	83
7	3-ClC_6H_4	OMe	**6bg**	3.5	76
8	3-Furyl	OMe	**6bh**	3.5	80

[a]Reaction Scale: **5** (1 mmol), **2** (1 mmol), **3** (1 mmol) and H_2O (5 mL). [b]Isolated yield.

All the synthesized compounds were characterized by ^1H, ^{13}C NMR, IR, mass spectral and elemental analysis. The known compounds were further authenticated from literature reports. The products (Table 2, **4aa**-**4bn**) were purified by simple filtration process and (Table 3, **6aa**-**6bh**) were purified by column chromatography.

In order to establish the probable reaction mechanism, initially we refluxed benzaldehyde (**2a**) and ethyl acetoacetate (**3a**) in the presence of 20 mol% of L-proline for 1 h which resulted in the formation of ethyl 2-benzylidene-3-oxobutanoate (**7a**) in 45% yield. However in the absence of any catalyst, **7a** was formed only in trace amount. Next we investigated the L-

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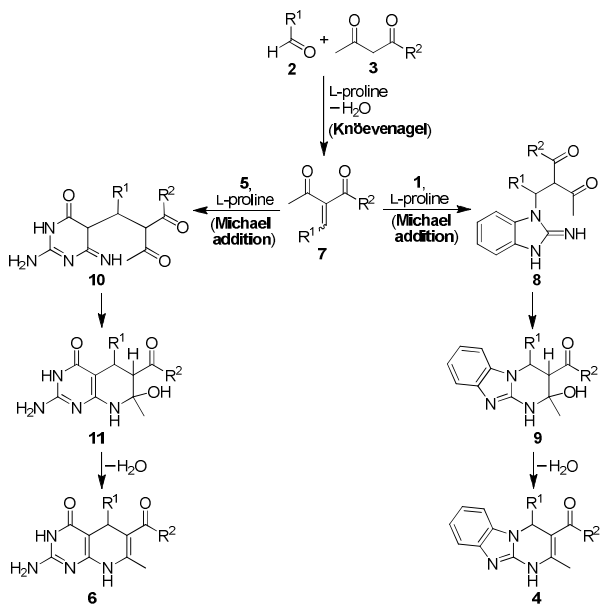

Scheme 2 The possible mechanism for the L-proline catalyzed reaction.

proline catalyzed step-wise condensation reaction between **7a**, prepared *in situ*, and 2-aminobenzimidzole (**1**) by refluxing it for 2 h which resulted the target compound **4aa** in 75% yield; while without catalyst only 20% product formation could be observed and the reaction was slightly sluggish. This proves that L-proline has a catalytic role in both the steps. Thus based upon these observations and literature reports[26,36f] a mechanism is proposed as shown in Scheme 2. It is believed that the reaction proceeds by initial Knöevenagel condensation between benzaldehyde (**2**) and *β*-ketoester (**3**) to generate the Knöevenagel adduct **7** followed by Michael addition of 2-aminobenzimidazole (**1**) or 2,6-diaminopyrimidin-4-one (**5**) followed by cyclization and dehydration *via* the intermediate **8** and **9** or **10** and **11** to yield the final product **4** or **6** respectively (Scheme 2).

Conclusions

In conclusion we have developed a simple, general and environment-friendly protocol for regioselective synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidines and pyrido[2,3-*d*]pyrimidin-2-amines through L-proline catalysed domino Knöevenagel-Michael reaction of 2-aminobenzimidazole or 2,6-diaminopyrimidin-4-one with aldehydes and β-ketoesters under mild reaction conditions. This application of water as reaction medium along with L-proline as an organocatalyst expand the scope of less explored aqueous media domino reaction. The efficiency of organocatalysis, wide substrate scope, easy work up procedure and simple purification process under mild reaction conditions significantly widens the procedural scopes for the synthesis of a huge library of important benzo[4,5]imidazo[1,2-*a*]pyrimidines and pyrido[2,3-*d*]pyrimidin-2-amines.

Experimental

All reagents were purchased from commercial suppliers and were used without further purification. IR spectra were recorded on a SHIMADZU infrared spectrometer as KBr pellets with absorption in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded in DMSO-d_6 on 300 MHz or 400 MHz or 600 MHz Bruker NMR spectrometer at 25 ^oC and resonances (δ) are given in ppm relative to tetramethylsilane. Data are reported as follows: chemical shift (δ), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constants in Hz with integration. LCMS were obtained on Waters ZQ 4000 and equipped with ESI source. Melting points were determined using Veego VMP-D and not corrected. Elemental analysis was done on Perkin Elmer Series II Analyzer 2400. Column chromatography was performed on silica gel (200-300 mesh) using ethyl acetate: hexane (1:1) as the eluent. Thin Layer Chromatography (TLC) was performed using Merck pre-coated silica gel or silica gel G and the components were visualized under a UV or an iodine chamber.

General procedure for the synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidines (4aa-4bn)

A mixture of 2-aminobenzimidazole (**1**, 1 mmol), aldehyde (**2**, 1mmol) and β-ketoester (**3**, 1 mmol) in 5 mL of water was refluxed for appropriate time in the presence of 20 mol% of L-proline as catalyst (Table 2). On completion of the reaction as indicated by TLC, the crude reaction mass was allowed to cool and the precipitate was filtered and washed with water (10 mL x 3) to get the pure product.

General procedure for the synthesis of pyrido[2,3-*d*]pyrimidin-2-amines (6aa-6bh)

A mixture of 2,6-diaminopyrimidin-4-one (**5**, 1mmol), aldehyde (**2**, 1 mmol) and β-ketoester (**3**, 1 mmol) was refluxed in 5 mL of water for appropriate time in the presence of 20 mol% of L-proline as catalyst (Table 3). On completion of the reaction as indicated by TLC the reaction mass was allowed to cool and the precipitate was filtered and purified by column chromatography to afford pure products.

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