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A facile approach to the synthesis of structurally diverse 6,8a-dihydropyrido[2,3-*d*]pyrimidine derivatives *via* a three-component domino reaction

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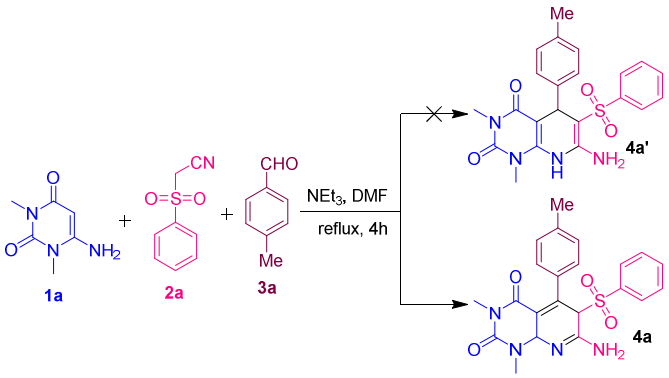
A concise and efficient approach to the synthesis of structurally diverse 6,8a-dihydropyrido[2,3-*d*]pyrimidine derivatives has been accomplished by a three-component reaction involving sulfonyl acetonitrile, an aromatic aldehyde, and 6-aminouracil. The method involves domino Knoevenagel condensation/Michael addition/ cyclization cascade in the presence of triethylamine in refluxing ethanol.

Introduction

The development of reliable and highly selective Multicomponent reactions (MCRs), continues to be an important challenge in organic synthesis, especially, in the synthesis of diversely substituted molecular scaffolds in the field of biologically active compounds and natural product chemistry.[1] Compared with step-by-step transformations, MCRs provide complex molecular architecture from simple and readily available starting materials with a high degree of selectivity and diversity.[2] Generally, the selectivity in MCRs can be affected by various factors, such as catalysts, ligands, reaction conditions, additives, or the structural features of the reactants. In this regard, MCRs have been used extensively in the construction of innumerable chemical libraries. For example, Yan and co-workers developed several MCRs, which showed the role of catalyst, solvent, substrates to generate molecular diversity.[3] In particular, the generation of molecular diversity by varying the structural features of the reactants are emerging as an efficient tool towards the synthesis of novel heterocyclic compounds.[4]

Pyrimidines have been recognized as an important class of heterocyclic compounds and widely studied by the chemists as well as biologists, due to its presence in numerous natural products and structurally diverse synthetic derivatives.[5] Among pyrimidine-containing compounds, fused pyrimidines, particularly pyrido[2,3-*d*]pyrimidine derivatives are found in a large variety of substances that exhibit important biological activities.[6] For example, this heterocyclic structural motif is present in several protein kinase inhibitors such as AZD8055, a selective ATP-competitive mammalian target of rapamycin kinase inhibitor, used for the treatment of antitumor,[7] piritrexim, a lipophilic inhibitor of the human dihydrofolate reductase (DHFR) that displays high potency for the treatment of metastatic urothelial cancer.[8] Recently, M. H. Flight in Nature Reviews Drug Discovery,[9] highlighted the work of Stover et al.[10] where 1.6 million compounds from Pfizer compound library were screened for antibacterial activity. This study resulted in the finding of three pyrido[2,3-*d*]pyrimidine derivatives as potent synthetic antibacterials, that selectively targeted the biotin carboxylase of bacteria. Also, substances that contains the pyrido[2,3-*d*]pyrimidine framework have other stimulating biological properties such as anticardiovascular,[11] antihypersensitive,[12] anti-inflammatory,[13] antifolate,[14] insecticidal,[15] and antiviral[16] activities. Due to the biological activities of compounds bearing pyrimidine moieties[7] deserve the synthesis of resourceful analogues. A plethora of methods[17] have been reported for the synthesis of pyrido[2,3-*d*]pyrimidines and related compounds. As part of our continued research interest towards the development of highly expedient multicomponent reactions for the synthesis of diverse pyrimidine containing heterocyclic compounds of biological importance,[18] we report herein the synthesis of a novel class of structurally diverse 6,8a-dihydropyrido[2,3-*d*]pyrimidine derivatives using a three-component one-pot protocol under mild reaction conditions.

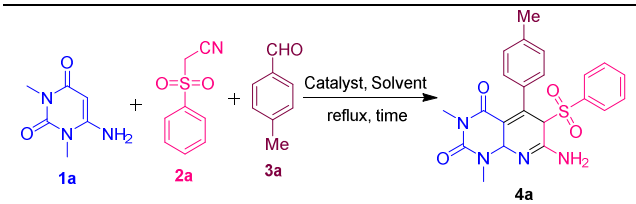


Scheme 1. Three-component reaction of 1,3-dimethyl-6-aminouracil **1a**, phenylsulfonyl acetonitrile **2a**, and 4-methylbenzaldehyde **3a**.

Results and discussion

We Initiated our study by choosing 1,3-dimethyl-6-aminouracil **1a**, phenylsulfonyl acetonitrile **2a,** and 4-methylbenzaldehyde **3a** as model substrates. In a typical experiment, **1a** (1 mmol), **2a** (1 mmol) and **3a** (1 mmol) were refluxed in 8 mL of dimethylformamide (DMF) by using triethylamine (30 mmol%) as a catalyst (Scheme 1). In contrast to earlier reports,[19] we obtained the unexpected 7-amino-1,3-dimethyl-6-(phenylsulfonyl)-5-(*p*-tolyl)-6,8a-dihydropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **4a** in 61% yield (Table 1, entry 1) within 4 hours. To the best of our knowledge, no method for the synthesis of 6,8a-dihydropyrido[2,3-*d*]pyrimidine core have been reported in the literature yet.

Table 1. Optimization conditions for the synthesis of 6,8a-dihydropyrido[2,3-*d*]pyrimidine derivative **4a**.[a]



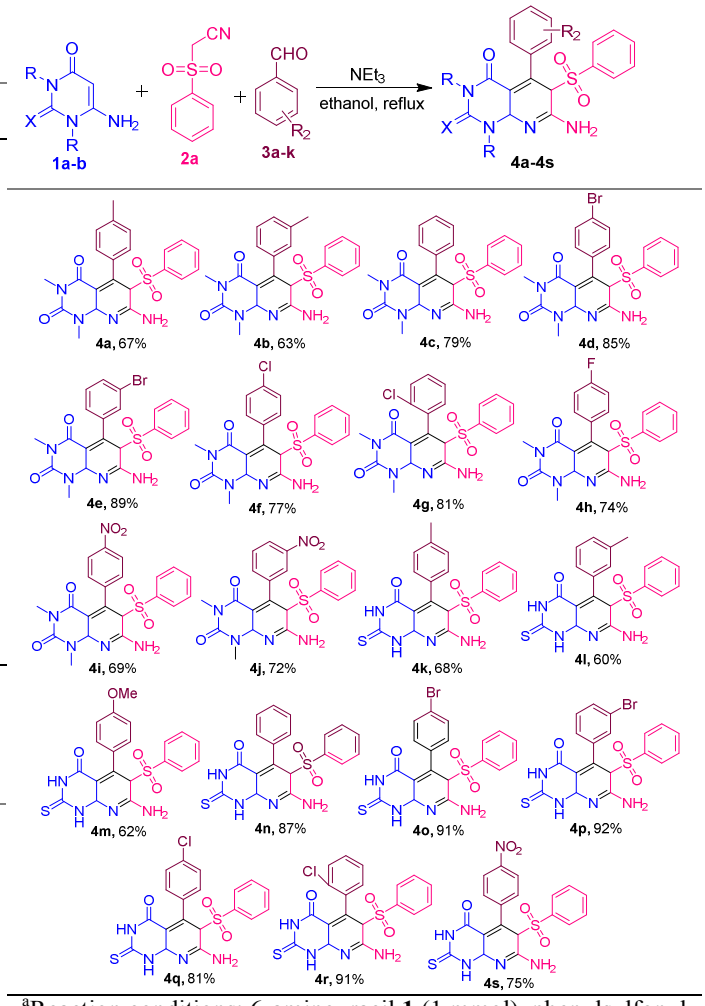
Entry	Solvent (8 mL)	Catalyst (30 mol%)	Time (hours)	Yield (%)[b]
1	DMF	NEt_3	4	61
2	acetonitrile	NEt_3	4	65
3	ethanol	NEt_3	4	67
4	methanol	NEt_3	4	66
5	water	NEt_3	6	10
6	ethanol	-	7	-[c]
7	ethanol	$InCl_3$	7	-[c]
8	ethanol	PTSA	7	-[c]
9	ethanol	L-proline	7	trace
10	ethanol	piperidine	4	62
11	ethanol	pyrrolidine	5	58
12	ethanol	DABCO	5	55
13	ethanol	DBU	5	57
14	ethanol	morpholine	6	61
15	ethanol	DMAP	6	52
16	ethanol	Pyridine	7	-[c]
17	ethanol	NaOH	6	51
18	ethanol	K_2CO_3	6	48
19	ethanol	NEt_3	4	68[d]

[a]Reaction conditions: 1,3-dimethyl-6-aminouracil **1a** (1 mmol), phenylsulfonyl acetonitrile **2a** (1 mmol)**,** and 4-methylbenzaldehyde **3a** (1 mmol) were used. [b]Isolated yield. [c]Product not observed. [d]Reaction was carried out in 10 mmol scale (50 mL of ethanol was used as solvent).

In order to optimize the reaction conditions, we investigated various solvents, base, and acid catalysts. Among the all solvents (Table 1, entries 1–5), ethanol provided the best yield (Table 1, entries 3), and the work-up of the reaction was more convenient with ethanol. The reaction proceeded smoothly to afford product **4a** when 30 mol% of organic bases such as piperidine, pyrrolidine, DABCO, DBU, morpholine, DMAP were used as catalysts (Table 1, entries 10–15). Even inorganic bases like NaOH and K_2CO_3 were also provided the product **4a**, but with less yield in comparison with organic bases (Table 1, entries 17, 18). When pyridine was used as a base catalyst, we afforded the Knoevenagel condensed product of **2a** and **3a**, but not **4a** (Table 1, entries 16). The reaction failed to give the product **4a** when we applied the acid catalysts such as $InCl_3$, PTSA instead base catalysts (Table 1, entries 7, 8). The reaction afforded only trace product in the presence of L-proline, even after 7 hours of reflux (Table 1, entries 9). We also performed the model reaction in the absence of the catalyst, but this attempt failed to afford the product **4a** (Table 1, entry 6). Thus, we chose triethylamine and ethanol as the best catalyst and solvent for the reaction of 6-aminouracil **1**, alkylsulfonyl acetonitrile **2,** and aromatic aldehyde **3**.

With the optimised reaction conditions, we then explored the generality of the method for the synthesis of 6,8a-dihydropyrido[2,3-*d*]pyrimidines **4** by employing differently substituted aromatic aldehydes **3** (Table 2). As shown in Table 2, the aromatic aldehydes bearing electron-withdrawing groups such as bromo, chloro, fluoro, and nitro gave better yields than with electron-releasing groups. However, this transformation with heteroaromatic and aliphatic aldehydes such as indole-3-carbaldehyde, thiophene-2-carbaldehyde, furan-2-carbaldehyde and acetaldehyde failed to give compound **4** even after 10 hours of reflux.

Table 2. The generality of the method for the synthesis of 6,8a-dihydropyrido[2,3-*d*]pyrimidine derivative **4a – 4s**.[a]

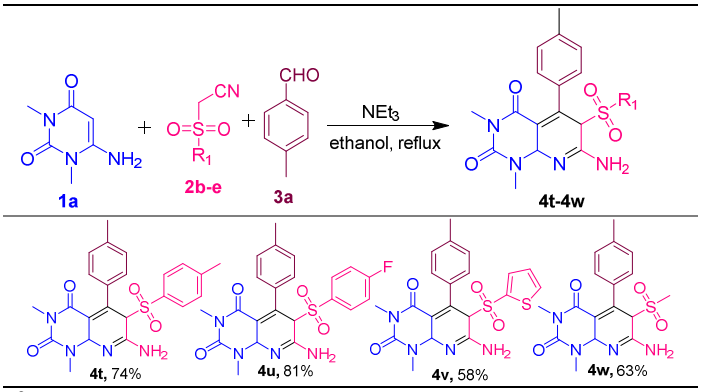


[a]Reaction conditions: 6-aminouracil **1** (1 mmol), phenylsulfonyl acetonitrile **2a** (1 mmol)**,** and aromatic aldehyde **3** (1 mmol) were used. [b]Isolated yield.

We further extended our study with different alkylsulfonyl acetonitriles **2b-e**, to explore the feasibility of the reaction. This protocol accepts a variety of alkylsulfonyl acetonitriles, where alkyl group can be an aromatic, heteroaromatic, and aliphatic group, obtained results are summarized in Table 3. Surprisingly the reaction

proceeded smoothly with the heteroaromatic 2-(thiophen-2-ylsulfonyl)acetonitrile **2d** and aliphatic 2-(methylsulfonyl)acetonitrile **2e** to give the product **4v** and **4w**. It indicates that the alkyl substituents attached to sulfonyl functional group don't have the negative effect towards the formation of the product **4** as like heteroaromatic aldehydes. But the alkyl groups attached to sulfonyl functional group has shown significant change in the yield of the product. The structure of 6,8a-dihydropyrido[2,3-*d*]pyrimidine derivatives **4** were assigned by IR, mass, ^{1}H NMR, and ^{13}C NMR spectra.

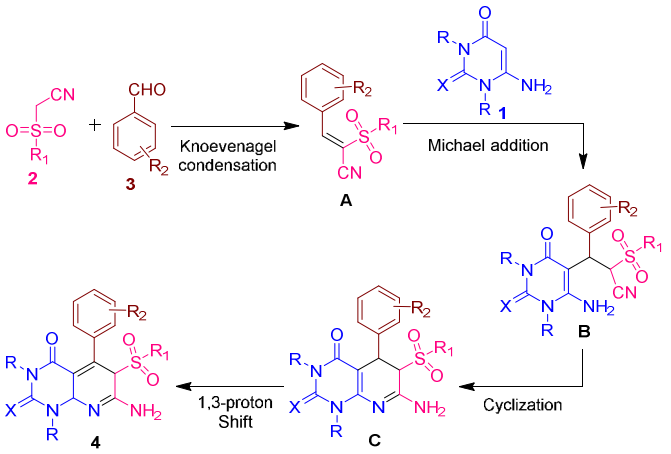
Table 3. The feasibility of the method with alkylsulfonyl acetonitriles for the synthesis of 6,8a-dihydropyrido[2,3-*d*]pyrimidine derivatives **4t – 4w**.[a]



[a]Reaction conditions: 1,3-dimethyl-6-aminouracil **1a** (1 mmol), alkylsulfonyl acetonitrile **2** (1 mmol), and 4-methyl benzaldehyde **3a** (1 mmol) were used. [b]Isolated yield.

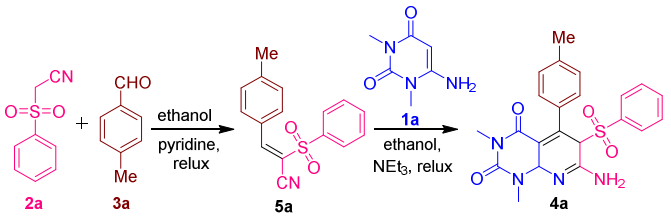
For example, the mass spectrum of **4g** showed a molecular ion peak at m/z = 460.1, which is corresponding with the proposed structure. In the IR spectrum of **4g**, two absorptions at 3399 and 3356 cm^{-1} attributed to NH_2, and other absorption bands at 1632, 1595, 1499, 1450, 1384, 1352, 1302, 1213, 789 cm^{-1}, related to C=O, C=C, SO_2, and C–Cl stretching vibrations, indicating the most significant functional groups in the product. The ^{1}H NMR spectrum of **4g** exhibited two singlets at δ = 8.71 and 8.33 ppm (exchangeable with deuterium), which can be assigned to the NH_2 group. Nine aromatic hydrogen signals resonate as two multiplets at δ = 7.72 – 7.65, 7.56 –7.49 ppm, two triplets at δ = 7.29, 7.19 ppm, and one doublet at δ = 6.79 ppm. The resonance for the two CH protons appeared as singlets at δ = 4.97, 4.36 ppm. Remaining six N-methyl hydrogens appeared at δ = 3.04 ppm as a singlet. The ^{1}H-decoupled ^{13}C-NMR spectrum of **4g** showed 19 distinct resonances, N-methyl groups in the pyrimidine ring appear at δ = 29.61, 27.64 ppm and two significant SP^3 carbons in the pyridine ring showed signals at δ = 34.05, 66.00 ppm. The most important resonance for amidine carbon appeared at δ = 159.02 ppm, and the peaks at δ = 160.932, 154.65 ppm indicates two amide carbonyl carbons. The described analytical data of **4g** confirmed the proposed structure.

A plausible mechanism for the synthesis of 6,8a-dihydropyrido[2,3-*d*]pyrimidine derivatives **4** has been proposed in Scheme 2. It is assumed that Knoevenagel condensation product **A** is formed between alkylsulfonyl acetonitrile **2** and aromatic aldehyde **3** which then participates in Michael addition with 6-aminouracil **1** to form the Michael adduct **B**. Then the formed Michael adduct **B** undergoes intramolecular cyclization to produce intermediate **C**. A subsequent 1,3-proton shift of the intermediate **C** forms the final product **4**.



Scheme 2. Plausible mechanism for the formation of **4**.

To support our mechanistic postulate, a two component reaction was carried out between the Knoevenagel condensation product **5a** (synthesized from phenylsulfonyl acetonitrile **2a** and 4-methyl benzaldehyde **3a**) and 6-aminouracil **1a** under the similar reaction conditions (Scheme 3). As expected, the derivative **4a** was obtained in comparable yield (65%). We further confirmed our mechanistic postulate by monitoring the model three-component reaction (by thin layer chromatography) at different time intervals and observed a spot corresponds to Knoevenagel condensation product **5a** appeared with R_f value 0.75 (ethyl acetate:hexane 2:8) within 30 minutes. These experiments supports our assumption that the experimental results were highly consistent with the proposed mechanism.



Scheme 3. Stepwise experiments for the synthesis of **4a**.

Conclusions

In conclusion, we have demonstrated a facile and efficient one-pot, three-component reaction strategy for the synthesis of structurally diverse 6,8a-dihydropyrido[2,3-*d*]pyrimidine derivatives. A novel class of pyrido[2,3-*d*]pyrimidine derivatives were obtained in good to excellent yields from this atom-economical procedure without the requirement of the traditional column chromatography. The present method provides large substrate scope, tolerated a variety of aromatic aldehydes, 6-aminouracils, and alkylsulfonyl acetonitriles. Further, we believe that our developed methodology can be regarded as a valuable protocol for production of novel pyrido[2,3-*d*]pyrimidine derivatives and will create interest among chemists towards the synthesis of combinatorial libraries.

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Notes and references

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