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ARTICLE TYPE

Exploration of uracils: Pot and step economic production of pyridine core containing templates by multicomponent aza-Diels-Alder reaction

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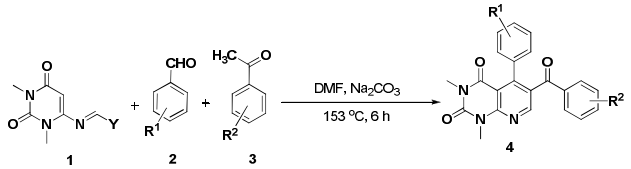
An efficient pot and step economic protocol for synthesis of pyrido[2,3-*d*]pyrimidine derivatives from a multicomponent aza-Diels-Alder reaction of uracil analogues, aromatic aldehydes and acetophenones in presence of Na_2CO_3 in DMF was developed. The key step of the reaction is *in situ* generation of the reactive dienophile from aldehyde and acetophenone and their subsequent reaction with diene to give the desired product.

Introduction

Multicomponent reactions (MCRs) are one pot synthetic operations where concurrent combination of more than two common and convenient reactants furnishes a single product containing significant portions of all reacting counterparts. Spectacular results have been obtained by synthetic organic chemists for construction of complex and structurally diverse molecules by using MCRs with advantages such as high degree of synthetic efficiency, molecular diversity and step-economy.[1] The concept of aza-Diels-Alder reaction strategy is successfully applied in numerous multicomponent reactions for construction of electrifying molecules.[2]

Over the years, pyridine containing molecules has attracted much attention due to its extensive availability throughout nature. The field of pyridine and its derivatives is a promising area of research as this structural motif appears in a large number of pharmaceutical agents and natural products.[3] Very recently, Saikia *et al.* developed a convenient method to synthesize pyrido[2,3-*d*]pyrimidines which were found to possess remarkable activities against microorganisms such as *B. subtilis*, *S. aureus*, *K. pneumonia* and *E. coli*.[4a] PD180970 (a novel pyrido[2,3-*d*]pyrimidine derivative), was successfully applied to inhibit Bcr-Abl and induce apoptosis in Bcr-Abl expressing leukemic cells.[4b] Pyrido[2,3-*d*]pyrimidine is also known to act as potent inhibitor of dihydrofolate reductase (DHFR);[4c,4d] a target site in most of the parasitic diseases. In 2012, Škedelj's group showed that 6-arylpyrido[2,3-*d*]pyrimidines had notable action as ATP-competitive inhibitor of bacterial D-alanine: D-alanine Ligase (Ddl).[4e] These discoveries have stimulated considerable interest in the synthesis of pyridine containing carbocycles through new and efficient routes.

Uracil or pyrimidine-2,4-dione is one of the four essential components in the nucleic acid of RNA. A wide range of works on uracil are reported by synthetic chemists[5] as well as biologists.[6] General methods for the synthesis of uracil derivatives involve the annulation reactions starting from suitably substituted uracils and related systems.[7] We have recently synthesized a series of iminoquinazolinedione derivative from vinyl uracils without using any solvent or catalyst.[7f] We also developed efficient methodologies for syntheses of some complex tetrahydroquinazolinedione and dihydropyrido[2,3-*d*]pyrimidine derivatives[7g] and, method for the formation of a library of dihydropyrido[4,3-*d*]pyrimidines was also well-documented by applying vinyl uracils in a microwave-assisted multicomponent reaction.[7h,7i] 6-(Morpholinomethyleneamino)-1,3-dimethyluracil **1a** is a reactive diene for [4+2]- cycloaddition reactions and a diverse array of potential products can be obtained by its synthetic manipulation. The molecule can simply be synthesized within two hours from N,N-dimethyl-6-aminouracil, morpholine and triethyl orthoformate under reflux conditions and subsequent recrystallization of the crude solid from ethanol.[8] In continuation to our studies on uracil molecules,[7f-7n] we describe in this paper an efficient three-component aza-Diels-Alder procedure for the synthesis of various pyrido[2,3-*d*]pyrimidine derivatives from the equimolar reaction mixture of 6-(morpholinomethyleneamino)-1,3-dimethyluracil, aromatic aldehydes and acetophenones in DMF (Scheme 1). To the best of our knowledge, only one report was available in the literature for the synthesis of uracil derivatives using 6-(morpholinomethyleneamino)-1,3-dimethyluracil as one of the starting reactants[7i] and thus we believe, our work will be able to draw considerable attention of organic chemists to explore the diene properties of 6-(morpholinomethyleneamino)-1,3-dimethyluracil.



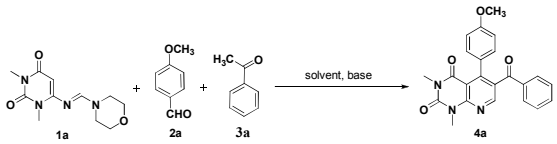
Scheme 1 Synthesis of pyrido[2,3-*d*]pyrimidines.

Results and discussion

Our initial effort was to develop an appropriate solvent system and reaction condition to perform the proposed reaction. The model reaction of 6-(morpholinomethyleneamino)-1,3-dimethyluracil (**1a**, 1 mmol), *p*-anisaldehyde (**2a**, 1 mmol) and acetophenone (**3a**, 1 mmol) was investigated under different solvent systems, and the results obtained are indicated in Table 1.The reaction did not occur in dry condition and the starting

materials were recovered quantitatively. It was observed that all solvent systems showed 'no progress with no base' in either reflux or stirring conditions (entries 2-11, Table 1). We were excited to notice that presence of catalytic amount of an organic base (e. g., morpholine, piperidine and pyrrolidine) could initiate the reaction but only in solvents with high boiling points, particularly in DMF. However, the percentage of conversion into product was very less (entries 12-16, Table 1). We then changed our methodology and planned to carry out a series of reactions at the boiling point of all solvents with moderately stronger bases. It was observed that good to better results were obtained when the reaction was carried out in presence of catalytic amount of inorganic bases (entries 19-24, Table 1). Because of easy handling and availability we preferred Na_2CO_3[9] over other bases and the model reaction was screened in presence of Na_2CO_3 at various concentrations. We found that more than 80% of the product, 6-benzoyl-5-(4-methoxyphenyl)-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4-dione **4a** could be obtained within 6 hours, when the reaction mixture with Na_2CO_3 (10 mol%) was vigorously stirred in DMF at its boiling point. The yield of the product was unaffected by a further increase in the loading of the catalyst but a lower yield of the product was obtained from the reaction with 20 mol% of Na_2CO_3. By considering the side effects associated with the use of dimethyl sulfoxide (DMSO) for example, sedation, headache, nausea, dizziness, burning eyes, constipation etc. DMF was considered as better solvent for the cycloaddition. We have also taken aim to reduce the time of the reaction for formation of the product by application of microwaves but very poor conversion into product was observed under microwave conditions. Using the optimized reaction conditions, the feasibility of the reaction scheme was studied in detail by varying the uracils, aldehydes and acetophenones and the results obtained are summarized in Figure 1.

Table 1 Optimization studies for synthesis of pyrido[2,3-*d*]pyrimidine **4a**[a]

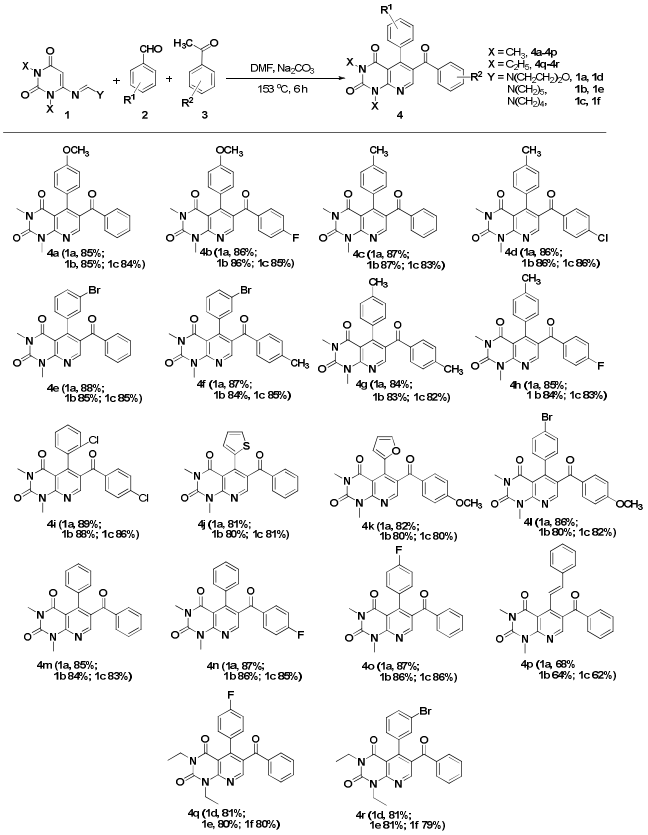


Entry	Solvent	Base	Yield (%)[d]
1	Neat	-	NR[b]
2	Water	-	NR[b]
3	Chloroform	-	NR[b]
4	DCM	-	NR[b]
5	DCE	-	NR[b]
6	MeOH	-	NR[b]
7	EtOH	-	NR[b]
8	Acetonitrile	-	NR[b]
9	Toluene	-	NR[b]
10	DMF	-	NR[b]
11	DMSO	-	NR[b]
12	EtOH	Morpholine	NR
13	Acetonitrile	Piperidine	NR
14	Water	Piperidine	NR
15	DMF	Morpholine	trace
16	DMSO	Pyrrolidine	trace
17	*o*-xylene	Na_2CO_3, 10 mol%	trace
18	DMF	Na_2CO_3, 5 mol%	40[c]
19	DMF	Na_2CO_3, 10 mol%	85[c]
20	DMF	Na_2CO_3, 15 mol%	85[c]
21	DMF	Na_2CO_3, 20 mol%	70[c]
22	DMSO	Na_2CO_3, 10 mol%	72[c]
23	DMF	K_2CO_3, 10 mol%	70[c]
24	DMF	Cs_2CO_3, 10 mol%	70[c]
25	DMF	Et_3N	12[c]

[a]Reaction conditions: A mixture of 6-(morpholinomethyleneamino)-1,3-dimethyluracil (**1a**, 1 mmol), *p*-anisaldehyde (**2a**, 1 mmol), acetophenone (**3a**, 1 mmol) was [b]refluxed/stirred for 10 h without base; [c]vigorously stirred in presence of a base at the boiling point points of solvents till the completion of reaction. [d]Isolated yield.

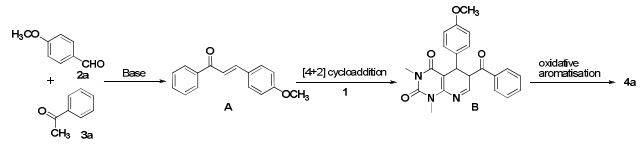
During our generalization studies we were satisfied to find that the reaction was effective with aldehydes and acetophenones bearing electron-withdrawing and, -donating substituents on the aromatic ring. In all cases, regiospecific formation of the aromatic pyrido[2,3-*d*]pyrimidine templates were observed in excellent yields together with trace amounts of corresponding α, β-unsaturated ketones arising from aromatic aldehydes and acetophenones as byproduct which were removed during column chromatography. It can be mentioned here that yields of the products were better with aldehydes and acetophenones bearing electron withdrawing groups on both and/or on either sides of the aromatic rings. A lower yield of product was observed when heteroaromatic and conjugated aromatic aldehydes were employed (relative to the reaction with 6-(morpholinomethyleneamino)-1,3-dimethyluracil, benzaldehyde and acetophenone). It was observed that 6-(morpholinomethyleneamino)-1,3-dimethyluracil **1a** was more reactive than 6-(piperidinylmethyleneamino)-1,3-dimethyluracil **1b**, 6-(pyrrolidinylmethyleneamino)-1,3-dimethyluracil **1c**, and vinyl uracils prepared from N,N-diethyl-6-aminouracil (**1d-1f**); leading to better yields of pyrido[2,3-*d*]pyrimidines. However, the reaction failed when aliphatic aldehydes and ketones were employed and only the condensation product between the aldehyde and ketone was formed. An attempt to perform the reaction with aliphatic aldehydes and ketones at high temperatures led to the decomposition of the starting materials. All of the products obtained were characterized by different methods such as, IR and NMR spectroscopy, mass spectrometry and elemental analysis.

Figure 1 Synthesis of pyrido[2,3-*d*]pyrimidine derivatives[a]



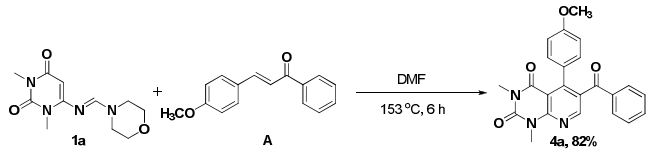
[a]Reaction conditions: A mixture of vinyl uracil (**1**, 1 mmol), substituted aldehyde (**2**, 1 mmol), substituted acetophenone (**3**, 1 mmol), and Na_2CO_3 (10 mol%) was vigorously stirred in DMF (5 ml) at 153 °C till the completion of reaction (as indicated by TLC).

A plausible mechanism for the formation of the pyrido[2,3-*d*]pyrimidine is shown in Scheme 2. It is believed that the base promotes the formation of α, β-unsaturated ketone **A** between *p*-anisaldehyde **2a** and acetophenone **3a** which then undergoes a cycloaddition reaction with the diene system of uracil **1**, followed by elimination of the amine moiety to generate dihydropyrido[2,3-*d*]pyrimidine derivative **B**. Oxidative aromatisation of **B** under the reaction conditions then leads to the formation of pyrido[2,3-*d*]pyrimidines **4a**.



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

To verify our proposed mechanism, a two component reaction was carried out between a pre-formed unsaturated ketone **A** and 6-(morpholinomethyleneamino)-1,3-dimethyluracil **1a** under the same reaction conditions (Scheme 3). As expected, the derivative **4a** was obtained in comparable yield (82%). We further confirmed our mechanistic postulate by monitoring the model reaction at different time intervals (by thin layer chromatography) and observed that an intense spot appeared with R_f value 0.75 (ethyl acetate: hexane 1:2) within less than two hours. After two hours we stopped the reaction and isolated the compound responsible for the spot whose NMR spectra corresponded to **A**. These consequences showed that the experimental results were highly consistent with the proposed mechanism. Earlier we reported a two-component reaction of uracil amidine **1g** with α, β-unsaturated compound **B** in ethanol to generate very limited numbers of pyrido[2,3-*d*]pyrimidines **4′** in 6 hr.[10] But it is noteworthy that the multicomponent reaction with 10 mol% Na_2CO_3 in alcoholic medium was reluctant to undergo transformation despite long reaction time (Figure 2). The step and pot economy principle (pre-functionalization of α, β-unsaturated ketone was not required) together with good yields associated with our new methodology make the approach more economical and useful over previous scheme to synthesize pyrido[2,3-*d*]pyrimidines.



Scheme 3 Synthesis of pyrido[2,3-*d*]pyrimidine **4a** by two-component reaction.

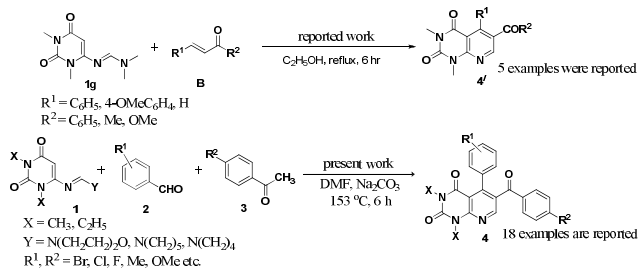


Figure 2 Comparison between reported and present work.

Conclusions

In summary, we have demonstrated an aza-Diels-Alder reaction which efficiently leads to the synthesis of a diverse range of pyrido[2,3-*d*]pyrimidine derivatives. A wide variety of substituted aromatic aldehydes, cinnamaldehyde, heteroaromatic aldehydes, and substituted acetophenones were shown to undergo the reaction with different uracil molecules to give exclusive amount of desired products. Overall, our developed methodology requires simple and easily available starting materials and we consider that this reaction will create interest among chemists to investigate the diene behavior of some uracil derivatives.

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Notes and references

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Exploration of uracils: Pot and step economic production of pyridine core containing templates by multicomponent aza-Diels-Alder reaction

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Substituted pyrido[2,3-*d*]pyrimidines can be obtained with good yields *via* a multicomponent aza-Diels-Alder reaction from easily available starting materials. The diene behaviour of different uracil derivatives was also elaborately investigated to synthesize desired products.