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ARTICLE TYPE

Cascade imination, Buchwald-Hartwig cross coupling and cycloaddition reaction: synthesis of pyrido[2,3-*d*]pyrimidines

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A novel and efficient palladium catalyzed method was developed for the synthesis of wide range of pyrido[2,3-*d*]pyrimidines, using readily available *β*-bromovinyl/aryl aldehydes and 6-amino-1,3-dialkyluracils as the starting materials with good yields. This reaction proceeds via cascade imination/Buchwald-Hartwig cross coupling/cycloaddition reactions under microwave irradiation and solvent free conditions.

The pyrido[2,3-*d*]pyrimidine heterocycles are of tremendous biological importance due to their wide range of biological properties such as anti-inflammatory, analgesic, antihypertensive, antiviral, antimicrobial, antiasthmatic and anticancer activities.[1] Some of the biologically active pyrido[2,3-*d*]pyrimidine derivatives are shown in Figure 1. In view of their very high biological and pharmaceutical importances, synthesis of these pyrido[2,3-*d*]pyrimidine derivatives have received considerable attentions in the literature. Typically, these heterocycles were synthesized by the reaction of 6-aminouracils with *α*,*β*-unsaturated carbonyl compounds,[2] Meldrum's acid derivatives[3] 3-chloro-2-propeniminium salts[4] and electron-rich enamines[5]. Moreover, multi-component reactions were used to obtain these heterocycles.[6] Recently, Kolos and coworkers reported an elegant synthetic method for pyrido[2,3-*d*]pyrimidines by the reaction of 3-(hetero)aroylacrylic acids or their methyl esters with 6-amino-1,3-dimethyluracil.[7] In spite of various reports for the synthesis of pyrido[2,3-*d*]pyrimidines, there is still lack of a facile and environmentally benign general strategy for the synthesis of these important fused heterocycles.

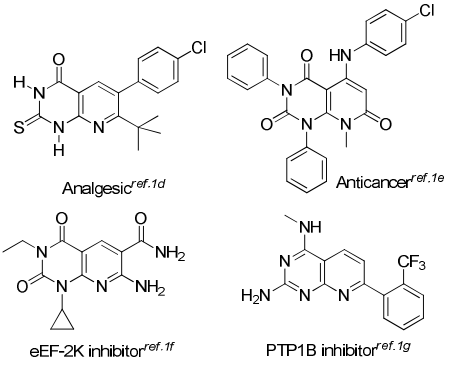


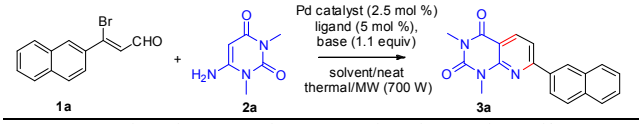
Figure 1. Examples of bioactive pyrido[2,3-*d*]pyrimidines

Chemical reactions performed under Microwave heating have couple of advantages such as decreased reaction time, high yield of products and enhancement of the chemo-, regio- and stereoselectivity of the reactions. Several novel transition-metal catalyzed reactions are known in the literature which have been performed under microwave heating.[8] As a part of our ongoing research interests in the synthesis of biologically important *N*-containing heterocycles, utilizing *β*-bromovinyl/aryl aldehydes as the versatile synthons,[9] herein, we wish to report an efficient Pd catalyzed synthesis of pyrido[2,3-*d*]pyrimidines using *β*-halovinyl/aryl aldehydes and 6-amino-1,3-dialkyluracils as the starting materials in solvent-free conditions under microwave irradiation.

We started our studies by examining the reaction of *β*-bromovinyl aldehyde **1a** (1.0 mmol), with equimolar amount of 6-amino-1,3-dimethyluracil (**2a**, 1.0 mmol). To our delight, heating the reaction mixture at 120 ^{o}C for 12 hours in presence of $PdCl_2$ (2.5 mol %), K_2CO_3 (1.1 mmol) and PPh_3 (5.0 mol %), afforded pyrido[2,3-*d*]pyrimidine derivative **3a** in 54% yield (Table 1, entry 1), which was fully characterized by ^{1}H NMR, ^{13}C NMR and mass spectroscopy. Screening of other palladium catalysts, such as $PdCl_2(PPh_3)_2$, $Pd(dppf)Cl_2$, $Pd(OAc)_2$ and $Pd(TFA)_2$, revealed $Pd(OAc)_2$ as the most effective catalyst to synthesize **3a** (Table 1, entries 2-5). Then we studied the effect of ligand on this cascade reaction. The ligand xantphos turned out to be the best ligand amongst the screened ligands (dppf, 1,10-phen) to carry out this reaction under thermal conditions (Table 1, entries 6-8). This reaction provided inferior results when the base K_2CO_3 was replaced with base Na_2CO_3 or Cs_2CO_3 or NaO^{t}Bu (Table 1, entries 9-11). Moreover, screening of solvents such as DMSO and CH_3CN provided lower yield of **3a** (Table 1, entries 12-13). In order to curtail the reaction time when we studied the influence of microwave (MW) irradiation (700 W, 120 ^{o}C, 14 bar), we observed a significant reduction in reaction time from 12 hours to 5 minutes to perform this reaction in DMF (Table 1, entry 14). Subsequently, because of the various advantages of solvent-free reactions,[10] we performed the reaction under solvent free condition. Gratifyingly, under this condition we obtained slight increase of **3a** to 91% in 5 minutes of reaction time under microwave irradiation (Table 1, entry 15). Our attempt to perform the reaction without catalyst could not provide **3a** under the solvent free condition (Table 1, entry 16).

With the optimized reaction conditions in hand (Table 1, entry 11), we then explored the feasibility of the reaction by selecting some representative *β*-halovinyl/aryl aldehydes **1a-m** and 6-

Table 1. Optimization of the reaction conditions for the synthesis of **3a**[a]



Entry	Pd catalyst	Solvent	Ligand	Thermal/ MW	**3a** (%)[b]
1	$PdCl_2$	DMF	PPh_3	120 °C	54
2	$PdCl_2(PPh_3)_2$	DMF	PPh_3	120 °C	47
3	$Pd(dppf)Cl_2$	DMF	PPh_3	120 °C	50
4	$Pd(OAc)_2$	DMF	PPh_3	120 °C	72
5	$Pd(TFA)_2$	DMF	PPh_3	120 °C	61
6	$Pd(OAc)_2$	DMF	dppf	120 °C	64
7	$Pd(OAc)_2$	DMF	xantphos	120 °C	84
8	$Pd(OAc)_2$	DMF	1,10-phen	120 °C	69
9[c]	$Pd(OAc)_2$	DMF	xantphos	120 °C	77
10[d]	$Pd(OAc)_2$	DMF	xantphos	120 °C	72
11[e]	$Pd(OAc)_2$	DMF	xantphos	120 °C	63
12	$Pd(OAc)_2$	DMSO	xantphos	120 °C	71
13	$Pd(OAc)_2$	CH_3CN	xantphos	120 °C	49
14	$Pd(OAc)_2$	DMF	xantphos	MW	87
15	$Pd(OAc)_2$	Neat	xantphos	MW	91
16	-	Neat	-	MW	0

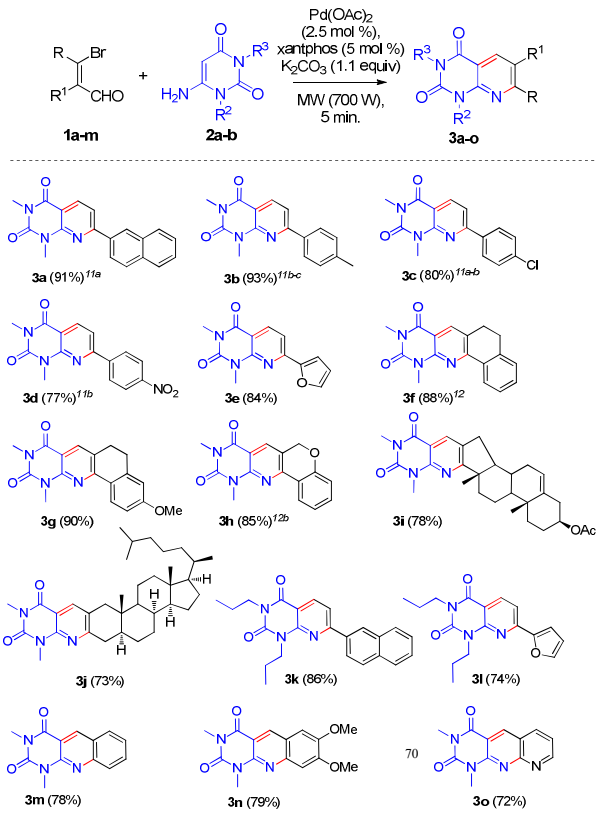
[a]All reactions were performed in presence of K_2CO_3 (1.1 equiv) for 12 hours (thermal) or for 5 minutes (microwave) unless otherwise mentioned; [b]Isolated yield. [c]Na_2CO_3 (1.1 equiv) was used. [d]Cs_2CO_3 (1.1 equiv) was used. [e]NaO^{t}Bu (1.1 equiv) was used.

amino-1,3-dialkyluracils **2a-b** (Table 2). The *β*-aryl substituted *β*-bromovinyl aldehydes (**1b-d**) with electron donating and electron-withdrawing groups such as methyl, chloro and nitro present in the aromatic ring reacted smoothly with 6-amino-1,3-dimethyluracil **2a** to afford pyrido[2,3-*d*]pyrimidines **3b-d**[11] in 77-93% yields. Thus, this reaction indicated diversity in functional group tolerance. Similarly, the heterocycle substituted *β*-bromovinyl aldehyde **1e** reacted with **2a** under the optimized reaction conditions to afford 7-furyl substituted pyrido[2,3-*d*]pyrimidine **3e** in 84% yield. The cyclic *β*-bromovinyl aldehydes **1f-h** were also converted to pyrido[2,3-*d*]pyrimidines **3f-h**[12] in good yields (85-90%). Because of the importance of steroids fused with heterocycles,[13] we attempted to extend the scope of this reaction with steroidal *β*-bromovinyl aldehydes. As shown in Table 2, the cascade reactions of steroidal *β*-bromovinyl aldehydes **1i-j** with **2a** were tested under the above reaction conditions to afford corresponding steroidal pyrido[2,3-*d*]pyrimidines **3i-j** in 73-78% yields. In addition, the reactions of *β*-bromovinyl aldehydes **1a** and **1e** with 6-amino-1,3-dipropyluracil **2b** proceeded smoothly to provide pyrido[2,3-*d*]pyrimidines **3k-l** in 74-86% yields. Next, we carried out the reaction of *ortho*-bromobenzaldehydes **1k-m** with **2a** under the optimized reaction condition to provide the aryl fused pyrido[2,3-*d*]pyrimidines **3m-o** in 72-79% yields. The formation of isomer **3** was proved by comparison of new spectral and physical data with those reported in the literature for compound **3b**.[11b]

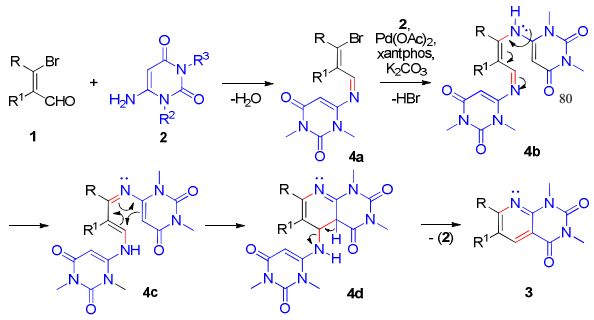
The formation of pyrido[2,3-*d*]pyrimidine **3** is envisaged to occur via a mechanism which is shown in Scheme 1. First, the aldehyde **1** reacts with 6-amino-1,3-dialkyluracil **2** to produce imine **4a**, which on subsequent Buchwald-Hartwig cross coupling reaction with another molecule of **2** affords intermediate **4b**. Then, rearrangement of electron generates probably azadiene intermediate **4c**, which on six-electron cyclization and subsequent elimination of one molecule of **2** affords the final compound **3**.

To the best of our knowledge, this is the first example of C-5 alkylation of 6-amino-1,3-dialkyluracils via cascade imination/coupling/cycloaddition reaction which finally leads to the formation of pyrido[2,3-*d*]pyrimidines.

Table 2. Synthesis of pyrido[2,3-*d*]pyrimidine derivatives[a]



[a]*Reaction conditions:* A grinded mixture of *β*-bromovinyl/aryl aldehydes (1.0 mmol), 6-amino-1,3-dialkyluracils (1.0 mmol), $Pd(OAc)_2$ (2.5 mol%), xantphos (5.0 mol%) and K_2CO_3 (1.1 mmol) was irradiated in a closed vessel in a Synthos 3000 microwave reactor at 700 Watt (120 °C and 14 bar) for 5 minutes; Isolated yields.



Scheme 1. Proposed mechanism for the formation of **3**

Conclusions

In conclusion, we have developed a novel environmentally benign procedure for the efficient synthesis of biologically important pyrido[2,3-*d*]pyrimidines. A variety of *β*-halovinyl/aryl aldehydes undergo this reaction with 6-amino-1,3-dialkyluracils in presence of palladium catalyst under microwave irradiation via cascade imination/coupling/cycloaddition. Several features such

as solvent-free synthesis, energy efficiency, less catalyst loading and operation simplicity make this procedure greener.

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† Electronic Supplementary Information (ESI) available: [Copies of ^{1}H NMR, ^{13}C NMR spectra of compounds **3a-o**].See DOI: 10.1039/b000000x/

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