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# Microwave-assisted Pd-catalyzed synthesis of fused steroidal and non-steroidal pyrimidines from $\beta$ -halo- $\alpha$ , $\beta$ -unsaturated aldehydes

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## ABSTRACT

A Pd-catalyzed protocol has been developed for the synthesis of fused steroidal and non-steroidal pyrimidines from  $\beta$ -halo- $\alpha$ , $\beta$ -unsaturated aldehydes under microwave irradiation. The  $\beta$ -halo- $\alpha$ , $\beta$ -unsaturated aldehydes are synthesized from corresponding ketones using Vilsmeier formylation reaction. This synthetic protocol is utilized to synthesize some more novel steroidal pyrimidine derivatives and are currently being evaluated for their biological activities.

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The pyrimidine heterocyclic core is an important class of compounds which has wide occurrence in nature as substituted and ring fused compounds and derivatives.<sup>1</sup> A number of synthetic pyrimidine base pharmacophores exhibit antibacterial, antimicrobial, anticancer, antihypertensive, cardiac stimulant, antimalarial, anti-HBV, anti-HIV-1, and antirubella virus activities.<sup>2</sup> Pyrimidine derivatives are also used as an emulsion stabilizer in photographic materials<sup>3</sup> and versatile ligands. Their coordination compounds can be considered as model systems for metal-ligand interactions observed in biological systems.<sup>4</sup> Some of the pyrimidine bearing derivatives, such as chemotherapeutics trimethoprim and sulfadiazine, the dihydrofolate reductase inhibitor pyrimethamine, and prazosin are used to treat high blood pressure and anxiety (Fig. 1).<sup>5</sup>

Heterosteroids emerge as an important area of research and enormous efforts have been made for their synthesis because of inherent biological activities.<sup>6</sup> A great deal of attention has been made to annelate steroidal moiety with pyrazole, pyridine, isoxazole, pyrrole, tetrazole, isothiazole rings using various synthetic strategies.<sup>7</sup> Due to emerging interests of pyrimidine derivatives as potential drugs, the synthesis of annelated steroidal pyrimidine ring system has become a subject of great interest.<sup>8</sup> For example, Clinton and his co-workers have described the preparation of biologically active steroidal[3,2-*b*]pyrimidines from condensation of 2-hydroxymethylene-3-ketosteroids with acetamidine-hydrochloride.<sup>9</sup> Laitonjam et al. utilized 2-bis(methylthio)methylene-3ketosteroid and guanidine nitrate for the synthesis of A-ring fused steroidal pyrimidine.<sup>10</sup> Hong-Min et al. reported the preparation of steroidal[17,16-*d*][1,2,4]triazolo[1,5-*a*]pyrimidines and their biological evaluation as potential anticancer agents.<sup>11</sup> However, adequate catalytic methods to steroidal pyrimidines are limited and effort to accomplish a more general and versatile synthetic method for rapid library generation is viewed as an interesting task.

Earlier, we have reported the synthesis of pyrimidines and dihydropyrimidines from steroidal  $\beta$ -formylenamides and 2-hydroxy-

NH<sub>2</sub>

MeO

MeO

ÓМе

Trimethoprim



Sulfadiazine

NH:

Figure 1. Some important molecules having pyrimidine molecular unit.







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#### Table 1

Optimization studies for the synthesis of steroidal pyrimidine **3a**<sup>a,b</sup>



Entry	Catalyst (mol %)	Ligand	Base	Solvent	Reaction time (min)	Yield <sup>b</sup>
1	Cul(2)	L-Proline	Cs <sub>2</sub> CO <sub>3</sub>	DMSO	8	40
2	CuI(2)	L-Proline	Cs <sub>2</sub> CO <sub>3</sub>	DMF	10	45
3	CuI(2)	Ethylenediamine	Cs <sub>2</sub> CO <sub>3</sub>	DMSO	10	41
4	Cul(2)	1,10-Phenanthroline	Cs <sub>2</sub> CO <sub>3</sub>	DMF	8	40
5	$Pd(OAc)_2(2)$	1,10-Phenanthroline	Cs <sub>2</sub> CO <sub>3</sub>	DMF	8	60
6	$Pd(OAc)_2(2)$	Ph₃P	Cs <sub>2</sub> CO <sub>3</sub>	DMF	15	70
7	$Pd(OAc)_2(2)$	<sup>t</sup> Bu <sub>3</sub> P	Cs <sub>2</sub> CO <sub>3</sub>	DMF	8	70
8	$Pd(OAc)_2(2)$	Cy <sub>3</sub> P	Cs <sub>2</sub> CO <sub>3</sub>	DMF	8	75
9	$Pd(OAc)_2(2)$	BINAP	Cs <sub>2</sub> CO <sub>3</sub>	DMSO	8	65
10	$Pd(OAc)_2(2)$	BINAP	Cs <sub>2</sub> CO <sub>3</sub>	DMF	8	81
11	$Pd(OAc)_2(2)$	BINAP	K <sub>2</sub> CO <sub>3</sub>	DMF	8	73
12	$Pd(OAc)_2(2)$	BINAP	K <sub>3</sub> PO <sub>4</sub>	DMF	8	74
13	$Pd(OAc)_2(5)$	BINAP	Cs <sub>2</sub> CO <sub>3</sub>	DMF	8	80
14	$Pd(OAc)_2(1)$	BINAP	Cs <sub>2</sub> CO <sub>3</sub>	DMF	8	77
15	-	BINAP	Cs <sub>2</sub> CO <sub>3</sub>	DMF	10	nd

The bold values signifies the optimized condition for the product 3a.

<sup>a</sup> Reaction conditions: compound **2a** (1.0 mmol), benzamidine hydrochloride(1.2 mmol), base (4 mmol), catalyst (2 mol %), ligand (4 mol %) in respective solvent (2 mL), MW 130 W, 8 bar pressure at 140 °C.

<sup>b</sup> Isolated yield; nd: product **3a** was not detected.

methylene-3-ketosteroids using microwave and ultrasound technique.<sup>12–14</sup> In continuation of our interest in  $\beta$ -halo- $\alpha$ , $\beta$ -unsaturated aldehydes,<sup>7h,15</sup> and to extend the scope of this protocol, we envisage that reacting benzamidine and acetamidine hydrochloride with  $\beta$ -halo- $\alpha$ , $\beta$ -unsaturated aldehydes will lead to 2-substituted pyrimidines under microwave irradiation.

Initially, the reaction of 3<sub>β</sub>-acetoxy-16-formyl-17-bromo-androst-5,16-diene (1a) with benzamidine hydrochloride was performed under the standard conditions of CuI, L-proline, and Cs<sub>2</sub>CO<sub>3</sub> in DMSO/DMF at 90 °C for 12 h.<sup>16</sup> Only trace amounts of the desired product 3a was observed under these conditions. However, when the reaction was conducted in microwave irradiation at 140 °C, for 8 min and 8 bar, the desired product 3a was obtained in 40% yield. As a consequence, to improve the yield, the reaction conditions were screened using various ligands and two solvents (DMF and DMSO) with copper iodide(I) (Table 1, entries 1-4), but no improvement was observed on the yield of 3a. In an attempt to increase the yield of the reaction further, we proposed a number of catalytic systems using Pd(OAc)<sub>2</sub> with a variety of ligands, bases, and solvents (Table 1, entries 5-14). As indicated in Table 1, Pd catalyzed systems were found to be better than Cu catalyzed system. In terms of the ligands which were screened, 1,10-phenanthroline, Ph<sub>3</sub>P, <sup>t</sup>Bu<sub>3</sub>P, Cy<sub>3</sub>P, and BINAP<sup>17</sup> afforded the desired product up to 81% yield. Three bases, namely K<sub>2</sub>CO<sub>3</sub>, K<sub>3</sub>PO<sub>4</sub>, and Cs<sub>2</sub>CO<sub>3</sub> were tested, and  $Cs_2CO_3$  was found to be the most efficient among them. Additionally, we found that DMF was the most suitable reaction media for the reaction, giving rise to product **3a**. However in the absence of catalyst, the product **3a** was not observed (Table 1, entry 15). The detailed optimization studies are summarized in Table 1.

After the optimization process for the catalytic system, various steroidal and non steroidal pyrimidine derivatives were synthesized using our optimized conditions. We have performed the reactions varying the amidines with a wide range of structurally diverse  $\beta$ -halo- $\alpha$ , $\beta$ -unsaturated aldehydes and isolated the desired products in good yields.<sup>18</sup> In a typical procedure for the synthesis of D-ring fused pyrimidine, a mixture of  $3\beta$ -acetoxy-17-bromo-16-formyl-androst-5,16-diene (**2a**, 1 mmol), and acetamidine hydrochloride (1.2 mmol) was treated with 2 mol% Pd(OAc)<sub>2</sub> as catalyst, 4 mol% BINAP as the ligand, 4 equiv of Cs<sub>2</sub>CO<sub>3</sub> as the base, and DMF as the solvent at 140 °C under microwave irradiation to afford the desired pyrimidine **3b** with 72% yield (Scheme 1).

The product **3b** was characterized and compared with reported spectral data.<sup>18</sup> The synthetic protocol is also applied for the synthesis of steroidal A-ring fused pyrimidine 3c from their corresponding  $\beta$ -bromo- $\alpha$ , $\beta$ -unsaturated aldehyde with 75% yield. Under the optimized reaction conditions, the steroidal pyrimidine



#### Table 2

Pd-catalyzed synthesis of steroidal and non-steroidal pyrimidine derivatives (3)<sup>a,b</sup>



<sup>a</sup> Reaction conditions: compound **2** (1 mmol), amidine (1.2 mmol), Pd(OAc)<sub>2</sub> (2 mol %), BINAP (4 mol %), Cs<sub>2</sub>CO<sub>3</sub> (4 equiv), DMF (2 mL), MW, 130 W, 8 bar. <sup>b</sup> Isolated yield.

derivative **3c** was obtained in enantiomeric pure form and not epimerized in any stereo center, as the specific rotation of the product **3c** was compared with the reported value (found  $[\alpha]_D^{23}$  +59 (*c* = 2, CHCl<sub>3</sub>); lit.rep.  $[\alpha]_D^{23}$  +61 (*c* = 2, CHCl<sub>3</sub>).<sup>19</sup>

On the other hand, other A-ring fused pyrimidines **3d**, **3e**, and **3f** were synthesized from their corresponding  $\beta$ -chloro- $\alpha$ , $\beta$ -unsatu-

rated aldehydes. The, chloro-formyl substrate required longer reaction time in comparison to bromo-formyl substrate and the  $\beta$ -bromo- $\alpha$ , $\beta$ -unsaturated aldehyde gave comparatively higher yield than the  $\beta$ -chloro- $\alpha$ , $\beta$ -unsaturated aldehydes (Table 2, 3c, and 3m). The starting materials  $\beta$ -halo- $\alpha$ , $\beta$ -unsaturated aldehydes were efficiently synthesized using Vilsmeier reaction.<sup>18</sup> Steroidal



Scheme 2. Proposed catalytic cycle.

A- and D-ring annelated  $\beta$ -halo- $\alpha$ , $\beta$ -unsaturated aldehydes were accomplished, respectively, from the Vilsmeier reaction of commercially available estrone, cholesterol, stigmasterol, and 16-dehydropregnenolone acetate (16-DPA). This synthetic procedure is also effective for the one-pot synthesis of A- and D-ring fused bis-pyrimidine from the corresponding bis-(β-bromo-α,β-unsaturated aldehyde) 3j with 53% yield (Table 2). The non-steroidal  $\beta$ -bromo- $\alpha$ , $\beta$ -unsaturated aldehyde analogue, for example, 2-bromo-cyclohex-1-ene-carbaldehyde reacted with benzamidine hydrochloride under the catalytic conditions to afford pyrimidine (**3k**) in 85% yield. We also used seven membered  $\beta$ -bromo- $\alpha$ , $\beta$ unsaturated aldehyde to synthesize corresponding pyrimidine derivatives (3n) with 84% yield (Table 2). Additionally, other non-steroidal pyrimidines **31**, **3m**, and **3o** were efficiently synthesized from their corresponding  $\beta$ -bromo- $\alpha$ ,  $\beta$ -unsaturated aldehydes (Table 2).

Regarding the mechanism, it is proposed that the  $\beta$ -halo- $\alpha$ , $\beta$ unsaturated aldehyde forms imine I with acetamidine/benzamidine hydrochloride in the presence of base. The in situ generated 'Pd–L' species undergoes oxidative addition to form intermediate II, which forms intermediate III in the presence of base.<sup>20</sup> The intermediate III reductively eliminates Pd–L to give the pyrimidine (Scheme 2).

In conclusion, we have developed a Pd-catalyzed protocol for the synthesis of fused steroidal and non-steroidal pyrimidines from  $\beta$ -halo- $\alpha$ , $\beta$ -unsaturated aldehydes with amidines under microwave irradiation. This approach has been successfully applied to the synthesis of A/D-ring fused pyrimidines. The  $\beta$ -halo- $\alpha$ , $\beta$ -unsaturated aldehydes are synthesized from corresponding ketones using Vilsmeier formylation reaction. This synthetic protocol is utilized to synthesize some more novel steroidal pyrimidine derivatives and they are currently being evaluated for their biological activities.

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# Supplementary data

Supplementary data (experimental details, spectroscopic data and selected copies of <sup>1</sup>H and <sup>13</sup>C NMR of starting and final products) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.10.094.

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