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A facile synthesis of steroidal and nonsteroidal pyrimidines under microwave irradiation

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ABSTRACT

The synthesis of steroid/nonsteroid fused pyrimidines is described by the base mediated reaction of steroidal/nonsteroidal α,β-unsaturated ketones with amidine derivatives in good yields under microwave irradiation.

The pyrimidine derivatives are of great pharmaceutical importance due to their wide range of biological activities such as analgesic, anti-HIV, anti-viral, anti-inflammatory, anti-microbial, anti-tubercular etc.[1] Moreover, the pyrimidine scaffold is also found in various biologically active natural products.[2] The development of new methods for the synthesis of steroids bearing heterocycles has become an important goal for the chemists due to the remarkable biological activities of these heterocycle annelated steroids.[3] Some of the biologically active pyrimidines and steroidal pyrimidine derivatives are shown in Figure 1. As the annelation leads to beneficial alternations to the biological activity of steroidal molecules, in last few decades, various methodologies have been developed for the synthesis of steroids annelated with heterocycles such as pyrrole, pyrazole, pyridine, isoxazole and pyran moieties.[3,4] Nevertheless, the efforts made towards the development of novel synthetic strategy for steroidal pyrimidines synthesis is still limited in the literature. The steroidal D-ring fused pyrimidine was synthesized by Wang et al. using multi-component reaction of steroid-17-ones, urea and aromatic aldehydes.[5] Peseke and co-workers developed two steps synthesis of steroidal D-ring fused pyrimidine by using androstenolone acetate as the starting material.[6] Recently, we also developed new methods for facile synthesis of pyrimidine annelated steroids by the multi-component reactions.[7]

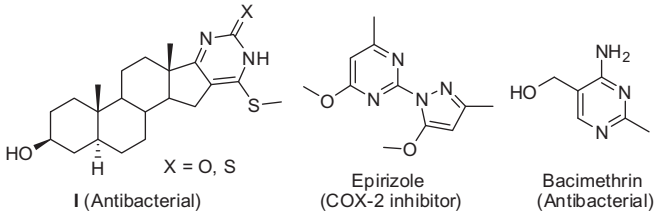

Figure 1. Examples of pharmaceutically important steroidal/nonsteroidal pyrimidines.

In the last decade, microwave irradiation has proved to be an efficient tool to perform the organic reactions at shorter reaction time with high yields and higher selectivities.[8] Owing to the importance of heterocycle fused steroids and in continuation of our interests in development of newer methodology for the synthesis of D-ring annelated heterosteroids,[9] herein, we wish to report a base induced reaction of commercially available steroidal α,β-unsaturated ketone 16-dehydropregnenolone acetate (16-DPA)/nonsteroidal α,β-unsaturated ketones with amidine hydrochlorides under microwave irradiation for the synthesis of steroidal and nonsteroidal pyrimidines.

Initially, we selected 16-DPA (**1a**) and benzamidine hydrochloride (**2a**) as the model substrates for the synthesis of compound **3a** (Table 1). Refluxing a mixture of **1a** and **2a** in isopropanol in the presence of base NaOMe (two equivalents) for twelve hours furnished pyrimidine **3a** in 26% yield (entry 1, Table 1). After having the product **3a** in hand it was identified from ^{1}H NMR, ^{13}C NMR

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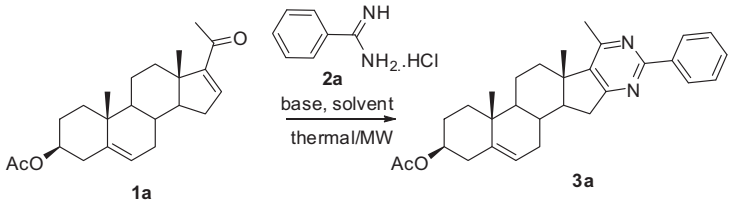
0040-4039/

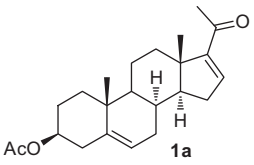
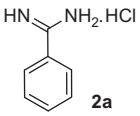
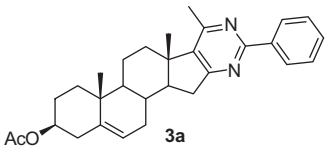
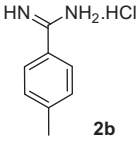
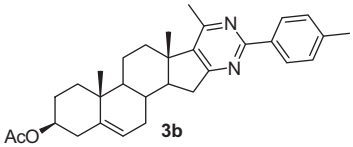
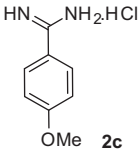
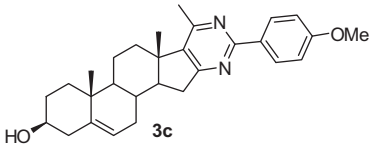
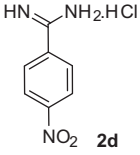
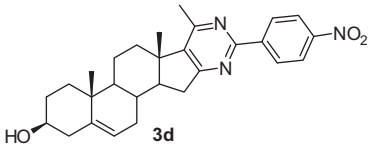
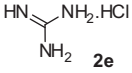
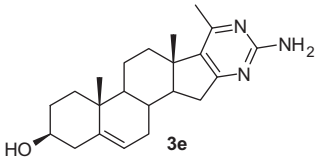
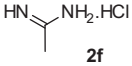
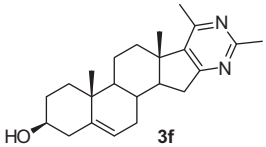
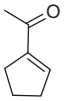
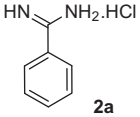
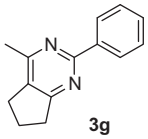
Table 1
Optimization of the reaction conditions[a]



Entry	Base	Solvent	Thermal/MW	Time	Yield[b] (%)
1	NaOMe	^{i}PrOH	110 °C	12 h	23
2	NaO^{t}Bu	^{i}PrOH	110 °C	12 h	61
3	KO^{t}Bu	^{i}PrOH	110 °C	12 h	69
4	KOH	^{i}PrOH	110 °C	12 h	15
5	NaH	Toluene	110 °C	12 h	20
6	KO^{t}Bu	^{i}PrOH	MW	10 min	83

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), base (2.0 mmol), solvent (5.0 mL), 110 °C/700 W, 12 h/10 min.
[b] Isolated yields.

Table 2
Synthesis of steroidal and non steroidal pyrimidines

Entry	Ketone	Amidine	Product	Yield[a] (%)
1	 **1a**	 **2a**	 **3a**	83
2	**1a**	 **2b**	 **3b**	85
3	**1a**	 **2c**	 **3c**	86
4	**1a**	 **2d**	 **3d**	78
5	**1a**	 **2e**	 **3e**	73
6	**1a**	 **2f**	 **3f**	77
7	 **1b**	 **2a**	 **3g**	76