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A facile one-pot synthesis of 7-substituted pyrazolo[1,5-*a*]pyrimidines by base induced three-component reaction

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Abstract: The preparation of steroid/nonsteroid fused 7-substituted pyrazolo[1,5-*a*]pyrimidines is described by a one-pot reaction of steroidal/nonsteroidal ketones, aromatic aldehydes and 3-amino-1*H*-pyrazoles/5-amino-1*H*-pyrazoles in the presence of potassium *tert*-butoxide in good yield under reflux condition in ethanol.

Keywords: Pyrazolo[1,5-*a*]pyrimidine, steroid, potassium *tert*-butoxide, heterocycle, amino-1*H*-pyrazole.

Pyrazolo[1,5-*a*]pyrimidine derivatives are of great pharmaceutical importance because of their wide range of biological activities. For example, they show antitrypanosomal and antischistosomal activities,[1] and many of them are used as COX-2 selective inhibitors, CRF1 antagonists, HMG-CoA reductase inhibitors, histamine-3 receptor ligands and antianxiety agents.[2] Among the pyrazolo[1,5-*a*]pyrimidine derivatives, recently, 7-substituted cycloalkane ring fused pyrazolo[1,5-*a*]pyrimidine derivatives as well as 7-substituted pyrazolo[1,5-*a*]pyrimidines turned out to be very promising molecules due to their interesting biological activities. For example, 7-substituted cyclopentane ring fused pyrazolo[1,5-*a*]pyrimidine derivative **I** (Figure 1) is found to have sub-nanomolar affinity (Ki < 1 nM) as 5-HT_6 receptor antagonist[3]. 7-Substituted pyrazolo[1,5-*a*]pyrimidine derivatives **II** and **III** are known drugs for

the treatment of sleep disorder[4] and cyclopentane ring fused pyrazolo[1,5-*a*]pyrimidine derivative **IV** has the highest affinity (Ki = 88 pM) to the 5-HT_6 receptor[5].

The incorporation of a heterocycle or fusion of a heterocycle in the skeleton of a steroidal molecule changes the activity of the steroidal molecule. Taking advantage of this phenomenon medicinal chemists have been trying to develop new active molecules in the last couple of decades by annulating steroidal moiety with different heterocycles such as pyridine, pyrazole, isoxazole, pyrrole, pyran and pyrimidine using various synthetic strategies.[6] As a part of our continuing research on development of new methodology for the synthesis of novel steroidal and nonsteroidal heterocyclic compounds,[7] herein we report a new one-pot three component approach for the synthesis of steroid and nonsteroid fused 7-aryl substituted pyrazolo[1,5-*a*]pyrimidine derivatives under thermal conditions.

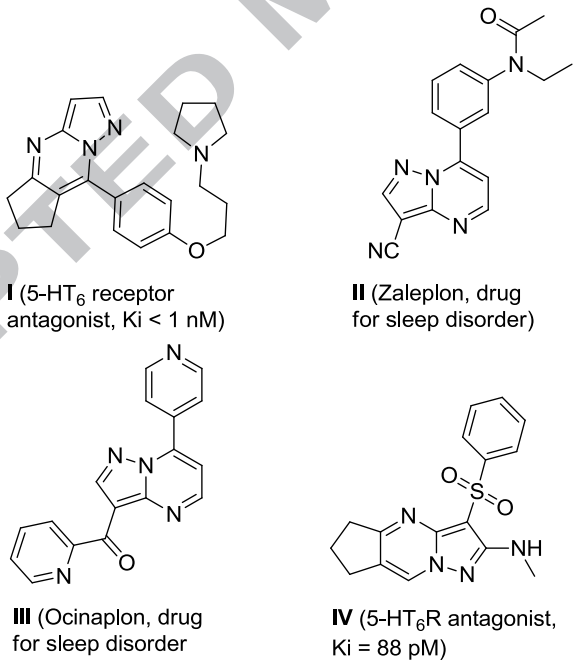


Figure 1: Examples of bioactive pyrazolo[1,5-*a*]pyrimidines

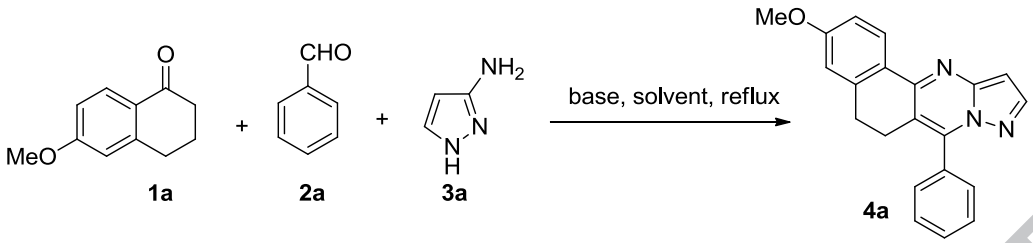
There are few methods reported in the literature for the synthesis of substituted pyrazolo[1,5-*a*]pyrimidines in the last few decades. Most of these synthetic methods used the reaction between

5-aminopyrazoles and 1,3-*bis*-electrophilic compounds, such as *β*-dicarbonyl, alkoxymethylene-*β*-dicarbonyl and *β*-enaminone compounds.[8] Bennani *et al.* reported the synthesis of 7-aryl substituted cycloalkane ring fused pyrazolo[1,5-*a*]pyrimidines by multi-step reactions where they used 2-oxo-cycloalkylcarboxylic acid methyl ester and 2*H*-pyrazol-3-ylamine as the starting meterials.[3] Moreover, acid catalyzed reactions of 2-acetylcycloalkanones with aminopyrazoles have been reported in the literature for the synthesis of 7-methyl substituted cycloalkane ring fused pyrazolo[1,5-*a*]pyrimidines.[5,9]

The diversity-oriented synthesis is the facile preparation of clusters of structurally complex and diverse compounds from simple starting materials.[10] Although 7-aryl substituted cycloalkane fused pyrazolo[1,5-*a*]pyrimidines possess interesting biological activity, to the best of our knowledge a diversity-oriented synthesis using multi-component reaction of very common starting materials has remained unexplored so far for these compounds.

Initially, we selected ketone **1a**, benzaldehyde (**2a**) and 3-amino-1*H*-pyrazole (**3a**) as the model substrates for the multi-component synthesis of compound **4a** (Table 1). Refluxing a mixture of ketone **1a** and benzaldehyde (**2a**) in anhydrous DMF in the presence of base NaOMe (two equivalent) for one hour followed by addition of 3-amino-1*H*-pyrazole (**3a**) and refluxing the reaction mixture for another two hours furnished pyrazolo[1,5-*a*]pyrimidine **4a** in 26% yield (entry 1, Table 1). We observed that increase of duration of the reaction also could not increase the yield of product **4a** (entry 2, Table 1). After having the product **4a** in hand it was identified from ^{1}H NMR, ^{13}C NMR and mass spectral data. The ^{1}H NMR of compound **4a** exhibited two characteristic aromatic doublet signals at δ 6.68 (J = 2.2 Hz, 1H) and at δ 8.01 (J = 2.2 Hz, 1H)

Table 1. Optimization of reaction conditions for the synthesis of pyrazolo[1,5-*a*]pyrimidine **4a**



Entry	Base[a]	Solvent	Time (h)	Yield (%)[b]
1	NaOMe	DMF	3	26
2	NaOMe	DMF	12	27
3	KOMe	DMF	3	29
4	KOH	DMF	3	19
5	NaH	DMF	3	32
6	NaO^{t}Bu	DMF	3	57
7	KO^{t}Bu	DMF	3	59
8	KO^{t}Bu	DMSO	3	50
9	KO^{t}Bu	EtOH	3	79
10	KO^{t}Bu	EtOH	12	76

[a] Two equivalent of the base was used. [b] Yield of the isolated product.

for the pyrazole ring protons. The ^{1}H NMR also showed multiplet signal at δ 7.52-7.63 (5H) for the protons of phenyl ring substituted in pyrazolo[1,5-*a*]pyrimidine moiety. The ^{13}C NMR spectrum of **4a** showed signals for eighteen aromatic carbons. Finally, the structure of the compound **4a** and regioselectivity of the reaction was unambiguously established by X-ray crystallography of compound **4a** (Figure 2).[11] To determine the ideal base and solvent for this multi-component reaction we investigated this model reaction with some other bases and solvents as shown in Table 1. We tried some other bases such as KOMe, KOH and NaH for the above reaction which also could not increase the yield of the compound **4a** to substantial amounts (entry 3-5, Table 1). When we used NaO^{t}Bu and KO^{t}Bu in the above reaction, we noticed that yield of desired product **4a** increased to 57% and 59%, respectively in DMF (entry 6-7, Table 1). Further investigation on the solvent, it was found that ethanol was the most effective among the tested solvents and the yield of **4a** was increased to 79% (entry 9, Table 1), while there was sharp decrease in yield of **4a** to 50% (entry 8, Table 1) when dimethylsulfoxide

was used. Increase of reaction time did not provide increase in yield of product **4a** (entry 10, Table 1). Under the optimized reaction conditions (entry 9, Table 1) the reaction of ketone **1a** with aromatic aldehyde **2b** and 3-amino-1*H*-pyrazole (**3a**) afforded pyrazolo[1,5-*a*]pyrimidine **4b** in 74% yield (entry 2, Table 2). Similarly, the reaction of ketone **1b** and **1c** with aromatic aldehyde **2b** and 3-amino-1*H*-pyrazoles (**3a)** under the above reaction condition afforded nonsteroidal pyrazolo[1,5-*a*]pyrimidines **4c-d** in 65-67% yield.

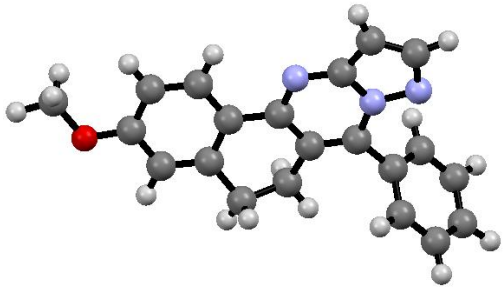
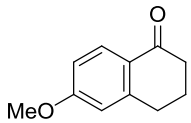
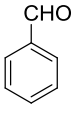
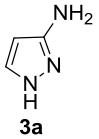
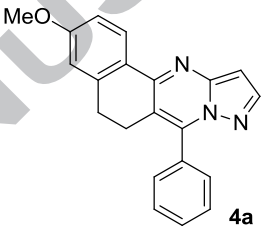
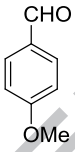
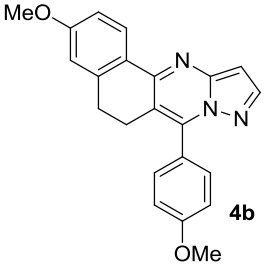
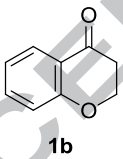
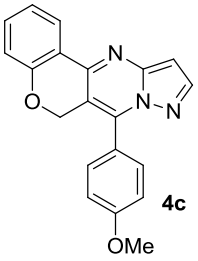
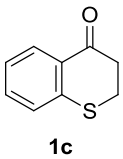
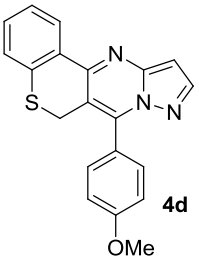


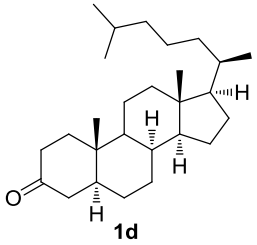
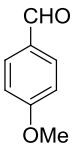
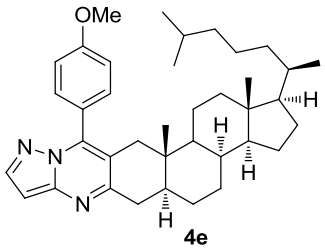
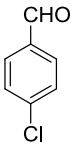
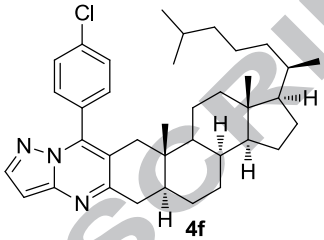
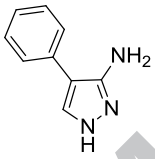
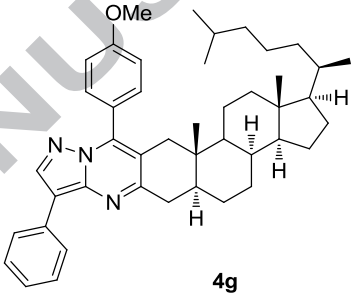
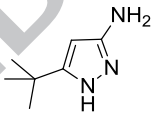
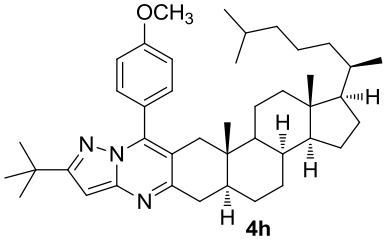
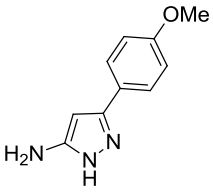
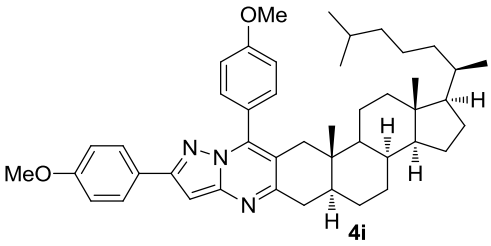
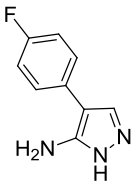
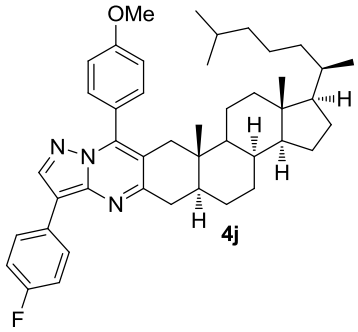
Figure 2. X-ray crystal structure of **4a**.

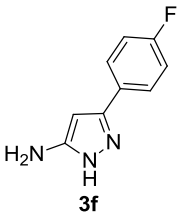
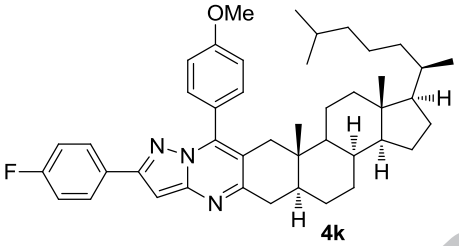
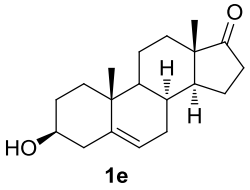
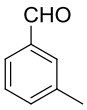
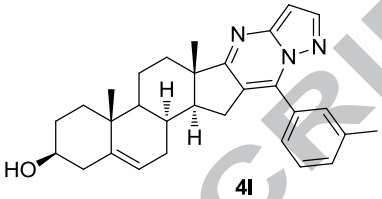
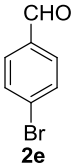
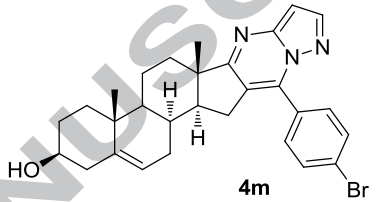
To study the scope of this one pot reaction we then performed the reaction of steroidal ketone **1d** with aromatic aldehydes **2b-c** and different 3-amino-1*H*-pyrazoles/5-amino-1*H*-pyrazoles (**3a-f**) under the above optimized reaction condition which afforded pyrazolo[1,5-*a*]pyrimidine fused heterosteroids **4e-k** in A-ring of steroid in good yields (72-76%). The base catalyzed condensation of aldehyde in the A-ring of steroidal ketone is known to afford 2-alkylidene steroidal 3-ones.[12] Moreover, due to the regioselective nature of the 3-amino-1*H*-pyrazole/5-amino-1*H*-pyrazole addition reaction as determined by the above X-ray crystallographic analysis, the reaction of steroidal ketone **1d**, aldehydes **2b-c** and pyrazoles (**3a-f**) afforded steroidal pyrazolo[1,5-*a*]pyrimidine compounds **4e-k** fused at 2,3-positions of steroids (entries 5-11, Table 2). In addition, when this base induced reaction of steroidal ketone **1e** was performed with aldehydes **2d-e** and 3-amino-1*H*-pyrazole (**3a**) we obtained good yield (70-75%) of D-ring fused steroidal pyrazolo[1,5-*a*]pyrimidines **4l-m**. It was noteworthy that in all the reactions of

steroidal/nonsteroidal ketones with aldehydes and aminopyrazoles under the above reaction conditions afforded only one regioisomer of the pyrazolo[1,5-*a*]pyrimidine derivatives as shown in Table 2. Moreover, it was observed that both electron-releasing groups and electron-withdrawing groups on the aromatic aldehydes as well as substituents in the 3-amino-1*H*-pyrazole and 5-amino-1*H*-pyrazole rings have no effect on the yield of pyrazolo[1,5-*a*]pyrimidines in this one pot reaction.

Table 2. Synthesis of steroidal/nonsteroidal pyrazolo[1,5-*a*]pyrimidines

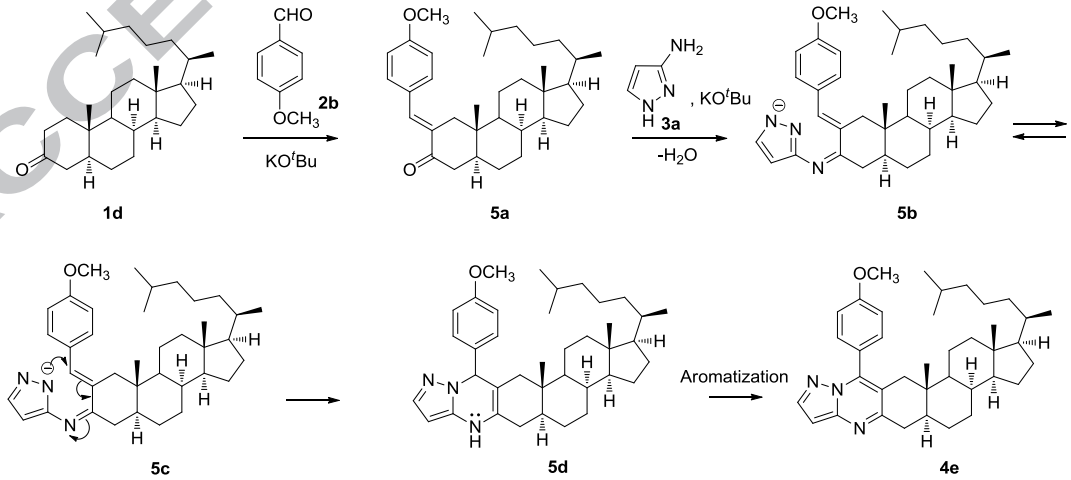
Entry	Ketone	Alde-hyde	Pyrazole	Product	Yield (%)[a]
1	 **1a**	 **2a**	 **3a**	 **4a**	79
2	**1a**	 **2b**	**3a**	 **4b**	74
3	 **1b**	**2b**	**3a**	 **4c**	67
4	 **1c**	**2b**	**3a**	 **4d**	65

5	 **1d**	 **2b**	**3a**	 **4e**	76
6	**1d**	 **2c**	**3a**	 **4f**	75
7	**1d**	**2b**	 **3b**	 **4g**	75
8	**1d**	**2b**	 **3c**	 **4h**	72
9	**1d**	**2b**	 **3d**	 **4i**	74
10	**1d**	**2b**	 **3e**	 **4j**	72

11	**1d**	**2b**	 **3f**	 **4k**	73
12	 **1e**	 **2d**	**3a**	 **4l**	70
13	**1e**	 **2e**	**3a**	 **4m**	75

[a]Yield of the isolated product.

A probable mechanism for the formation of compound **4e** is shown in Scheme 1. First, condensation of ketone **1d** with aldehyde **2b** in presence of base affords 2-benzylidene ketone **5a**. Then **5a** reacts with 3-amino-1*H*-pyrazole (**3a)** to afford its corresponding imine which on deprotonation in presence of potassium *tert*-butoxide generates the pyrazolide anion **5b**. Intramolecular aza-Michael addition of pyrazolide anion **5c** (tautomer of **5b**) followed by aromatization furnishes compound **4e**.



Scheme 1: Proposed mechanism for the formation of steroidal pyrazolo[1,5-*a*]pyrimidine **4e**

In conclusion, a new one-pot reaction for the synthesis of biologically important steroidal A-, D- ring fused pyrazolo[1,5-*a*]pyrimidines and nonsteroidal pyrazolo[1,5-*a*]pyrimidines was developed using KO^{t}Bu as the base under reflux conditions in ethanol. A wide variety of steroidal/nonsteroidal cyclic ketones, aromatic aldehydes and 3-amino-1*H*-pyrazoles/5-amino-1*H*-pyrazoles undergo this highly regioselective reaction to give good yields of pyrazolo[1,5-*a*]pyrimidines derivatives.

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Supplementary Material

Supporting Information (general experimental procedure, characterization data, ^{1}H NMR and ^{13}C NMR spectra) for this article is available online at http://www.....

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Graphical abstract: