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A facile method for the synthesis of steroidal and nonsteroidal 5-methyl pyrazolo[1,5-*a*]pyrimidines

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ABSTRACT

The steroidal and nonsteroidal 5-methyl pyrazolo[1,5-*a*]pyrimidines were synthesized by the reaction of steroidal/nonsteroidal α,β-unsaturated ketones and 3-amino-1*H*-pyrazoles/5-amino-1*H*-pyrazoles in the presence of KO^{t}Bu in ethanol under reflux condition.

The incorporation of a heteroatom or heterocyclic ring to a steroidal moiety not only affects the chemical properties of the steroidal molecule but also alters its pharmacological activities. These heterosteroids are found to have a wide range of biological activities. For example, heterosteroids such as finasteride is a 5α-reductase inhibitor,[1] formestane an aromatase,[2] abiraterone an anticancer drug,[3] and pipecuronium a neuromuscular junction blocking agent.[4] In view of these beneficial outcomes of heterosteroids, enormous efforts are being made to develop new methodologies to annelate steroidal molecule with different heterocycles such as pyridine, pyrazole, isoxazole, pyrrole, and pyrimidine using various synthetic strategies.[5] On the other hand, substituted pyrazolo[1,5-*a*]pyrimidine derivatives as well as cycloalkane ring fused pyrazolo[1,5-*a*]pyrimidine derivatives are of great biological importance because of their wide range of biological activities. For example, some of these pyrazolo[1,5-*a*]pyrimidine derivatives show antitrypanosomal, antischistosomal, CK-2 kinase inhibitor activities, COX-2 selective inhibitor activity, and HMG-CoA reductase inhibitor activity.[6] Some of the biologically active pyrazolo[1,5-*a*]pyrimidine derivatives are shown in Figure 1.

Literature survey revealed that most of the synthetic methods for pyrazolo[1,5-*a*]pyrimidine compounds used the reaction between 5-aminopyrazoles and 1,3-bis-electrophilic compounds, such as alkoxymethylene-β-dicarbonyl, β-dicarbonyl, and β-enaminone compounds.[7] To the best of our knowledge, only one synthetic method for steroidal pyrazolo[1,5-*a*]pyrimidines has been reported by Bajwa and Sykes by the condensation reaction of 3-aminopyrazole with 2-hydroxymethylene-5α-androstan-3-one derivatives and 16-hydroxymethylene-5α-androstan-17-one.[8] In view of the biological importance of substituted

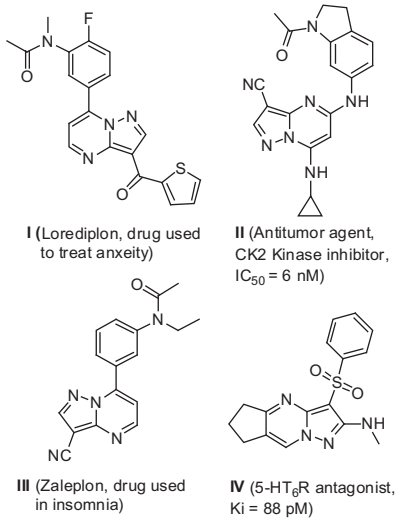

Figure 1. Examples of some bioactive pyrazolo[1,5-*a*]pyrimidine derivatives.

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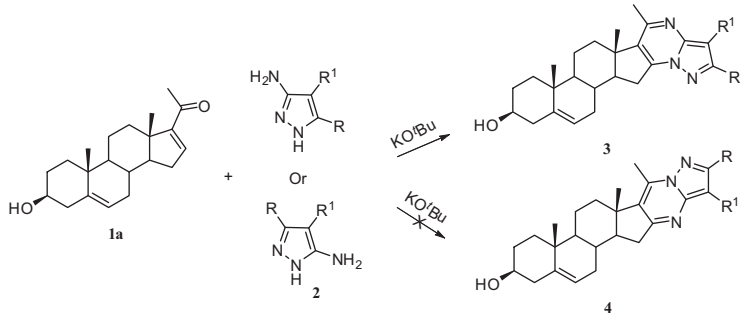


Scheme 1. Base induced synthesis of steroidal pyrazolo[1,5-*a*]pyrimidines.

pyrazolo[1,5-*a*]pyrimidines, heterocycle fused steroids, and in continuation of our research on the development of new methodologies for the synthesis of heterocyclic compounds,[9] herein, we describe a new approach for the synthesis of steroid/nonsteroid fused 5-methyl-pyrazolo[1,5-*a*]pyrimidine derivatives (Scheme 1).

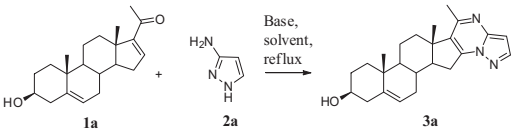
We started the synthesis of steroidal pyrazolo[1,5-*a*]pyrimidine **3a** by the reaction of α,β-unsaturated ketone **1a** (1.0 mmol), 3-amino-1*H*-pyrazole (**2a**, 1.0 mmol), and NaOMe (3.0 mmol) in ethanol. After refluxing for 6 h, the reaction mixture afforded the pyrazolo[1,5-*a*]pyrimidine **3a** in 23% yield (entry 1, Table 1). We observed that increase of duration of the reflux reaction also could not increase the yield of product **3a** (entry 2, Table 1). This compound **3a** was fully characterized by ^{1}H NMR, ^{13}C NMR, and mass spectroscopy. The ^{1}H NMR of compound **3a** exhibited two characteristic aromatic doublet signals at δ 6.57 (J = 1.0 Hz, 1H) and δ 8.06 (J = 1.0 Hz, 1H) for the pyrazolo[1,5-*a*]pyrimidine ring protons. The ^{1}H NMR also showed a singlet signal at δ 2.61 (3H) for the 5-substituted methyl protons of the pyrazolo[1,5-*a*]pyrimidine moiety. Moreover, ^{1}H NMR exhibited a multiplet for the olefin proton at δ 5.37–5.42 (1H), a multiplet for the proton attached to hydroxyl group at δ 3.53–3.57 (1H), a singlet for two angular methyl groups at δ 1.11 (6H), and the characteristic multiplets at δ 0.80–3.40 (18H) for the remaining protons of steroid moiety. The ^{13}C NMR spectrum of **3a** showed signals for eight aromatic carbons at δ 95.3, 120.7, 130.7, 141.3, 144.8, 147.9, 148.9, and 155.1. The EI mass spectra of compound **3a** exhibited molecular ion peak at m/z = 377. After confirming the structure of compound **3a**, in order to determine the ideal base and solvent for the above reaction we investigated some other bases and solvents. When NaH was used as a base, the yield of desired product **3a** decreased to only 19% in toluene (entry 3, Table 1). Further investigation into the base, we noticed that yield of compound **3a** was increased to 76% and 82% when NaO^{t}Bu and KO^{t}Bu were used, respectively, as the base in the above cyclization reaction (entries 4 and 5, Table 1). We also noticed that increase of duration of the KO^{t}Bu induced reflux reaction could not significantly change the yield of **3a** in 24 h (83%, not shown in Table). Moreover, in the absence of base, the reaction of **1a** and **2a** could not provide the desired compound **3a** (entry 6, Table 1).

With the optimized reaction condition in hand (entry 5, Table 1), we studied the reactions of steroidal ketone **1a** with different 3-amino-1*H*-pyrazoles/5-amino-1*H*-pyrazoles **2a–e**, **2g–j** to afford new 5-methyl-pyrazolo[1,5-*a*]pyrimidine fused steroidal derivatives **3b–e**, **3g–j** in 75–82% yields (entries 2–5,7–10, Table 2). It was observed that the substituents present in 3-amino-1*H*-pyrazole and 5-amino-1*H*-pyrazole rings such as methyl, *tert*-butyl, *p*-fluoro-phenyl, *p*-methoxy-phenyl and thiophene moieties have no effect on the yield of pyrazolo[1,5-*a*]pyrimidines in this reaction. Surprisingly, the reaction of steroidal ketone **1a** and 3-amino-1*H*-pyrazole-4-carbonitrile **2f** afforded only 64% yield of pyrazolo[1,5-*a*]pyrimidine derivative **3f** (entry 6, Table 2). To see the scope of this cyclization reaction, we then performed the reaction of nonsteroidal ketone **1b** with 5-amino-1*H*-pyrazoles **2h** and **2g** under the above optimized reaction condition which afforded nonsteroidal 5-methyl-pyrazolo[1,5-*a*]pyrimidine fused compounds **3k–l** in 80–82% yields (entries 11–12, Table 2). In addition, when this base induced reaction of nonsteroidal ketone **1c** was performed with 5-amino-1*H*-pyrazole **2g** and 3-amino-1*H*-pyrazole **2e** we obtained good yield (76–80%) of nonsteroidal 5-methyl-pyrazolo[1,5-*a*]pyrimidine compounds **3m–n**. It is worth noting that all the above reactions afforded only one regioisomer of the product (**3**), although there was a possibility of formation of the other regioisomer (**4**) in the reaction, as shown in Scheme 1. The formation of the regioisomer **3** was confirmed by comparing the spectral data of compound **3n** with the reported spectral data[4].

A probable mechanism for the formation of compound **3a** is shown in Scheme 2. First, **1a** reacts with 3-amino-1*H*-pyrazole (**2a**) to afford imine derivative which on potassium *tert*-butoxide induced deprotonation generates the pyrazolide anion **5a**. Intramolecular aza-Michael addition of **5b**, which is a different resonance form of the anion **5a**, followed by aromatization of the obtained intermediate **5c** furnishes compound **3a**.

In conclusion, a new reaction for the synthesis of biologically important steroidal 5-methyl-pyrazolo[1,5-*a*]pyrimidines and nonsteroidal 5-methyl-pyrazolo[1,5-*a*]pyrimidines was developed using KO^{t}Bu as the base under reflux condition in ethanol. A wide variety of steroidal/nonsteroidal α,β-unsaturated ketones and 3-amino-1*H*-pyrazoles/5-amino-1*H*-pyrazoles undergo this regioselective reaction to afford good yields of steroidal/nonsteroidal 5-methylpyrazolo[1,5-*a*]pyrimidine derivatives.

Table 1
Optimization of reaction conditions for the synthesis of steroidal 5-methyl-pyrazolo[1,5-*a*]pyrimidine **3a**



Entry	Base[a]	Solvent	Time (h)	Yield[b] (%)
1	NaOMe	EtOH	6	23
2	NaOMe	EtOH	24	27
3	NaH	Toluene	12	19
4	NaO^{t}Bu	EtOH	6	76
5	KO^{t}Bu	EtOH	6	82
6	—	EtOH	6	0

[a] Three equivalents of the base were used.
[b] Yield of the isolated product.