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Solvent-free synthesis of novel steroidal 2-aminopyridines

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ABSTRACT

The synthesis of novel steroidal 3-cyano-2-aminopyridines using enaminonitrile and various primary amines was established under solvent-free condition. Structures of the new compounds were characterized by MS, ^{1}H and ^{13}C NMR data and the structure of 2-aminopyridine of the product **5b** was further confirmed by X-ray analysis. The reaction mechanism was proposed on the basis of the key intermediate obtained. The adjacent amine and nitrile groups existed in the final products have the potential for late stage functionalization, which would provide efficient access to steroidal compound collections with structural diversity and complexity.

1. Introduction

Steroids are a family of molecules that play a crucial role in a wide range of biological processes and in human physiology. Their hormonal action *via* binding to a specific receptor is well known and has led to the development of antagonists to treat certain hormone-dependent diseases [1]. Because of the various advantages associated with steroid based chemotherapeutics, recent years have seen an extensive focus of research directed toward the rational modification of steroid molecules. The introduction of heteroatom, heterocycle or replacement of one or more atoms in the structure of the maternal steroids often results in alterations of its biological properties, for example, enhancing the cytotoxicity against some tumor cell lines [2–4]. These compounds could be used for development of new potential therapeutics, as well as tools for probing the spatial orientation of important binding responsive features in target macromolecules. In recent years, a number of steroidal heterocycles with interesting activities have been isolated or synthesized. For example, spironolactone, as the mineralocorticoid antagonist, is a clinically used drug for congestive heart failure [5]. Abiraterone [6,7] and galeterone [8,9] (Fig. 1), which share the similar structure features, namely bearing an *N*-heterocycle at the D-ring, have been used in clinic for the treatment of advanced prostate cancers. It has been suggested that such activity is related to the presence of the heterocyclic moiety in ring D, with the nitrogen lone pair coordinating to the heme iron atom at the active site of the enzyme [10]. Very recently, our group incorporated biologically promising spirooxindole scaffolds into the steroid core, generating a library of steroidal spirooxindoles with good antiproliferative activity (IC_{50} < 10 μM) [11,12] (Fig. 1).

On the other hand, many naturally occurring as well as synthetic compounds containing the pyridine scaffold exhibit interesting pharmacological properties [13]. Pyridine is one of the most popular *N*-heteroaromatics incorporated into the structure of many pharmaceuticals. Among these, cyanopyridines and aminocyanopyridines with different alkyl and aryl groups were found to have antimicrobial [14], antihypertensive [15], cardiovascular, anti-inflammatory [16], anti-cancer [17], analgesic, antipyretic properties [18,19] as well as 1KK-β inhibitory properties [20]. Besides, aminopyridines could be used as intermediate in the manufacture of pharmaceuticals like Piroxicam and moreover, because of their chelating abilities, they can be used as ligands in organic and inorganic chemistry [21–24]. Among them, the 2-amino-3-cyanopyridines, displaying many attractive properties [25], can be prepared from a Michael reaction [26], as well as via a one pot coupling reaction of four components in conventional heating mode or under microwave irradiation and by other methods [27–29], and they could be versatile intermediates in organic synthesis to obtain more complex nitrogen heterocycles [30,31].

One of the key areas of Green Chemistry is the elimination of solvents in chemical processes or the replacement of hazardous solvents by environmentally benign solvents. The promising results obtained by us fully deserve the necessity of developing these types of molecules. In continuation of our previous work in

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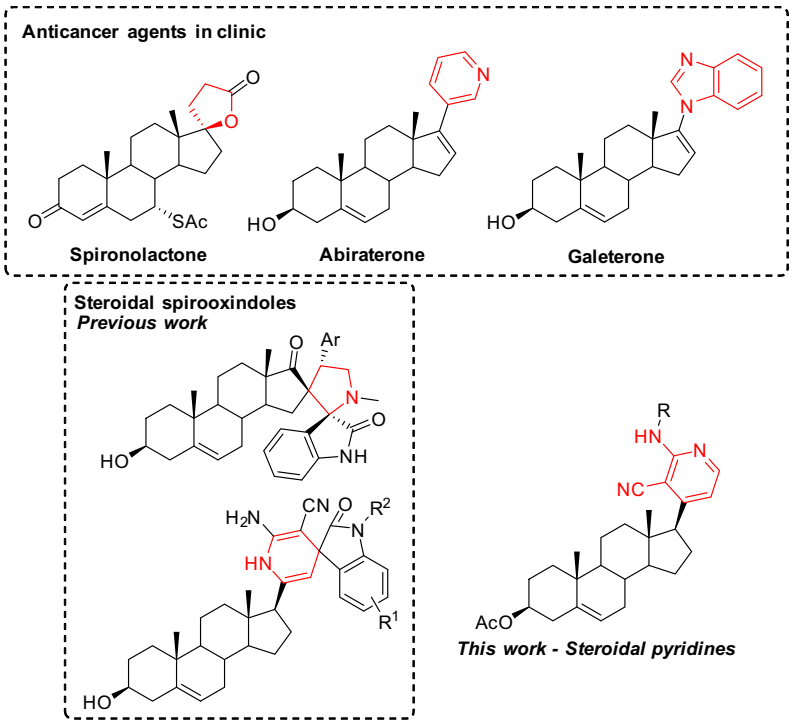


Fig. 1. Steroidal heterocycles with anticancer activity previously reported and the target molecules synthesized in this work.

developing new biologically active modified steroids [32–37], we herein report the preparation of novel steroidal 3-cyano-2-aminopyridines from enaminonitriles and primary amines under solvent-free conditions. To the best of our knowledge, this is the first report about the solventless synthesis of steroidal cyanoaminopyridines.

2. Experimental

2.1. General remarks

Most of reagents and solvents were used directly without special treatment. Thin layer chromatography (TLC) was carried out on glass plates coated with silica gel and visualized by UV light (254 nm). The products were purified by column chromatography over silica gel. Melting points were determined on a Beijing Keyi XT4A apparatus and are uncorrected. All NMR spectra were recorded with a Bruker DPX 400 MHz spectrometer with TMS as an internal standard in $CDCl_3$. Chemical shifts are given as δ ppm values relative to TMS (Most of the peaks due to the steroidal skeleton are merged and could not be differentiated. Thus δ values of only those peaks that distinguish the product and could easily be differentiated are reported). High-resolution mass spectra (HRMS) were recorded on Esquire3000 mass spectrometer by electrospray ionization (ESI).

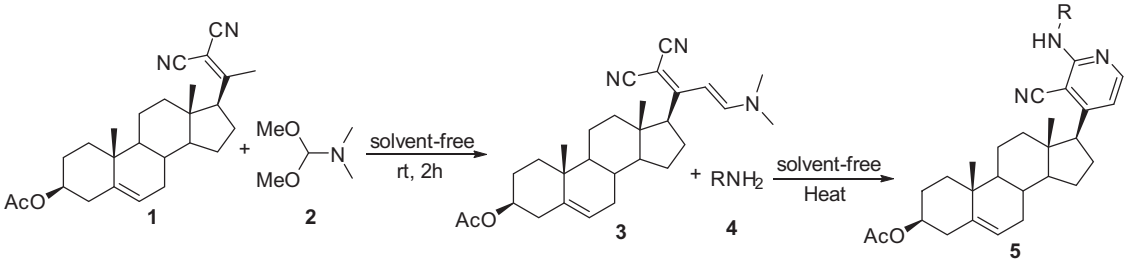
2.2. Synthesis of steroidal enaminonitrile (**3**)

A mixture of the steroidal α, α-dicyanoalkene (**1**) (10 mmol) and *N, N*-dimethylformamide dimethyl acetal (DMFDMA) (10 mmol) was stirred at room temperature without solvent during 2 h. The purple solid obtained was washed several times with diethyl ether (3 × 20 mL) and recrystallized from ethanol to provide product **3** (Scheme 1).

Green solid, yield 86%, m.p. 247.1–248.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 5.38 (d, *J* = 5.8 Hz, 1H), 5.17 (s, 1H), 4.70–4.51 (m, 1H), 3.21 (s, 3H), 2.96 (s, 3H), 2.03 (s, 3H), 1.03 (s, 3H), 0.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 170.5, 151.9, 139.8, 122.2, 118.1, 73.8, 56.6, 49.9, 47.6, 38.1, 36.9, 36.7, 32.0, 31.8, 27.7, 25.0, 21.4, 20.9, 19.3, 14.1. HRMS (ESI): *m/z* calcd for $C_{29}H_{40}N_3O_2$ $(M+H)^+$, 462.3121; found, 462.3111.

2.3. General procedure for the synthesis of steroidal 3-cyano-2-aminopyridines (***5***)

A mixture of compound **3** (10 mmol) and primary amine **4** (10 mmol) was heated for the time indicated in Table 1. After the completion of the reaction (TLC), the residue was purified by column chromatography over silica gel using a mixture of *n*-hexane-EtOAc (8:1) as the eluent to afford desired products **5** (Scheme 1 and Table 1).



Scheme 1. Synthesis of steroidal cyanoaminopyridines (**5a–k**).