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Reactivity of Steroidal 1-Azadienes toward Carbonyl Compounds under Enamine Catalysis: Chiral Penta- and Hexacyclic Steroids

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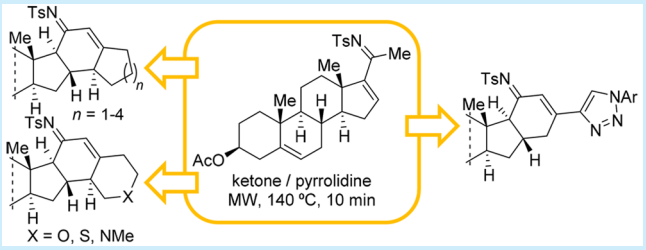
Supporting Information

ABSTRACT: The synthesis and reactivity of a steroidal *N*-sulfonyl-1-azadiene, derived from 16-dehydropregnenolone acetate, toward carbonyl compounds under enamine catalysis is disclosed. An unexpected annulation reaction was observed involving an initial stereoselective conjugate addition of the *in situ* generated enamine to the steroidal 1-azadiene. The developed diastereoselective synthetic methodology is a novel approach to a new class of chiral pentacyclic and hexacyclic steroids.

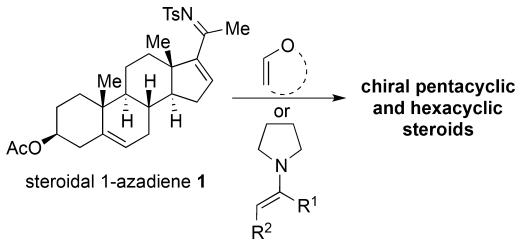


1-Azadienes, also called α,β-unsaturated imines, are useful and versatile building blocks for the synthesis of cyclic and acyclic nitrogen-containing compounds.[1] The introduction of an electron-withdrawing group on the nitrogen, such as the sulfonyl group, enhances the electrophilic character of these conjugated imines. Therefore, *N*-sulfonyl-1-azadienes participate in inverse electron-demand hetero-Diels−Alder reactions with electron-rich dienophiles,[2] and diastereoselective[2e] and enantioselective versions[2f] of this approach to six-membered heterocycles have been reported. Nevertheless, *N*-sulfonyl-1-azadienes react with electron-deficient vinyl ketones via phosphine-catalyzed asymmetric [4 + 2] annulation.[3] *N*-Sulfonyl-1-azadienes, having two electrophilic carbons, can undergo enantioselective conjugate additions[4] but can also participate in 1,2-additions.[5] Nickel(II)-catalyzed cascade conjugate addition of *N*-sulfonyl-1-azadienes with 2-silyloxyfuran leads to 3a,4,7,7a-tetrahydrofuro[3,2-*b*]pyridin-2(3H)-ones.[6] *N*-Sulfonyl-1-azadienes undergo other transformations, namely, phosphine-catalyzed annulations with allenoates[7] and allene ketones[8] to afford cyclopentenes and eight-membered heterocycles, respectively, and enantioselective [6 + 4] annulation with vinyl oxetanes to give ten-membered heterocycles.[9] Interesting reactivity was also observed for 3-styryl-1,2-benzoisothiazole-1,1-dioxides, which incorporate a *N*-sulfonyl-1-azadiene moiety. These conjugated imines have been used to prepare spirocyclic,[10a] six-membered carboxylic, and heterocyclic compounds.[10b−d]

Steroids are an important class of both naturally occurring and synthetic compounds with a variety of biological activities.[11] Synthetic modification of steroidal scaffolds is a strategy used to modulate their biological properties. Successful transformations include the introduction of side chains/heterocycles or heterocycles fused at positions 16 and/or 17 of the D-ring. Galeterone, is an example of a C-17 substituted *N*-heterocycle steroid that has successfully completed phase III of clinical studies for prostate cancer treatment.[12] Recently, we have described the synthesis and anticancer activity of new chiral heterocycle-fused steroids, derived from 16-dehydropregnenolone acetate (16-DPA) and other steroidal scaffolds, via unprecedented [8π + 2π] cycloaddition reactions with diazafulvenium methides.[13]

The rich reactivity pattern of *N*-sulfonyl-1-azadienes combined with our interest in the modulation of steroidal scaffolds[13] led us to explore the reactivity of steroidal 1-azadiene **1**, derived from 16-DPA, toward electron-rich dienophiles as an approach to a new class of pentacyclic and hexacyclic steroids (Scheme 1).

Scheme 1. Synthetic Strategy: Reactivity of Steroidal 1-Azadiene 1 toward Electron-Rich Dienophiles



The direct condensation of 16-DPA with *p*-toluenosulfonamide, using different reaction conditions and dehydrating agents such as molecular sieves, $MgSO_4$, DCC/DMAP,[14] $Ti(Oi\text{-}Pr)_4$,[15] or $TiCl_4$,[2f] or even carrying out the reaction in refluxing toluene with a Dean−Stark apparatus did not afford the desired 1-azadiene. However, the synthesis of steroidal 1-azadiene **1** was achieved following the general strategy used by Boger et al. for

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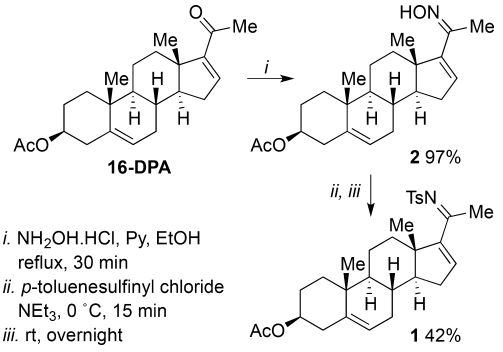
the synthesis of *N*-sulfonyl-1-azadienes.[2c] First, 16-DPA was converted into the corresponding oxime **2**,[16] by reaction with hydroxylamine hydrochloride. Then, oxime **2** underwent a radical rearrangement[17] upon treatment with *p*-toluenesulfinyl chloride[18] in the presence of triethylamine to give steroidal 1-azadiene **1** in 42% yield (Scheme 2).

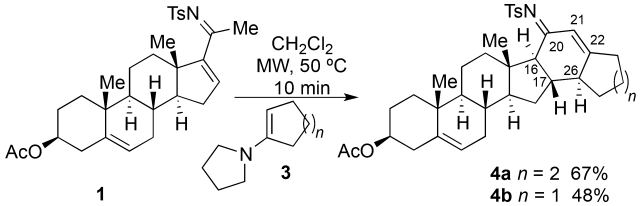
Scheme 2. Synthesis of Steroidal 1-Azadiene 1



Initially, we explored the reactivity of conjugated imine **1** toward electron-rich dienophiles expecting to obtain the corresponding Diels–Alder cycloadducts, the pentacyclic, or hexacyclic steroids. However, attempts to carry out the reaction with enol ethers (e.g., ethyl vinyl ether, 2,3-dihydrofuran) only led to the recovery of the starting steroidal 1-azadiene.

A very interesting and unexpected result was obtained when we studied the reaction of steroidal 1-azadiene **1** with enamines (Scheme 3). *N*-Tosyl-1-azadiene reacted with 1-pyrrolidino-1-

Scheme 3. Synthesis of Hexacyclic Steroids 4a–b



cyclohexene (**3a**), in dichloromethane under microwave irradiation at 50 °C for 10 min, giving chiral hexacyclic steroid **4a** in 67% yield as the only product (Scheme 3). The reaction of 1-pyrrolidino-1-cyclopentene (**3b**) also gave hexacyclic steroid **4b** selectively, in moderate yield. These new chiral compounds, with three new chiral centers, also incorporate a *N*-tosyl-1-azadiene moiety.

The molecular structure of compound **4a** was unambiguously established by X-ray crystallography (Figure 1). This derivative was crystallized as colorless needles in the orthorhombic system within a $P2_12_12_1$ space group, showing one molecule per asymmetric unit. Its molecular structure consists of a hexacyclic steroid bearing two methyls, an acetate, and a tosylimino substituent at positions C18, C19, C3, and C20, respectively. The newly formed chiral centers at positions C16, C17, and C27 display *S* configuration. All distances and angles are within the expected values for similar compounds.[19]

The reaction of 1-azadiene **1** with carbonyl compounds under enamine catalysis would make this synthetic methodology much more versatile. In this context, the reaction of steroidal 1-azadiene **1** with enamines generated *in situ* from the corresponding ketones, using catalytic amounts of pyrrolidine,

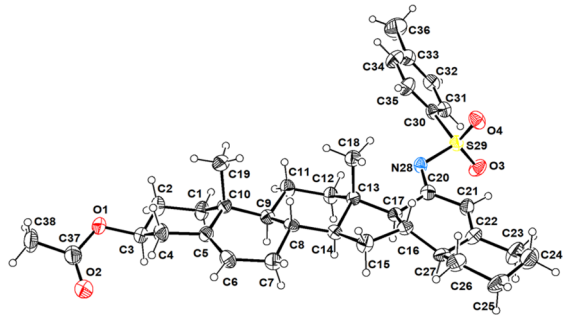
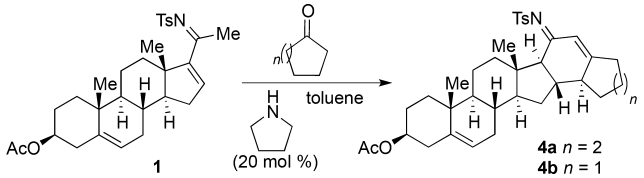


Figure 1. ORTEP-3 diagram of compound **4a**, using 30% probability level ellipsoids.

was explored (Table 1). The reaction with cyclohexanone or cyclopentanone, in the presence of pyrrolidine (20 mol %), in

Table 1. Reaction of Steroidal 1-Azadiene 1 with *in situ* Generated Enamines



entry	reaction conditions	isolated yield (%)
1	reflux, Dean–Stark, 66 h	**4a** 70[a]
2	MW, 140 °C, 10 min	**4a** 65
3	reflux, Dean–Stark, 65 h	**4b** 71[a]
4	MW, 140 °C, 10 min	**4b** 62

[a]5 equiv of ketone was used.

toluene under reflux gave steroids **4a** or **4b** in 70% and 71% yields, respectively (entries 1 and 3). Compounds **4a** and **4b** were obtained in slightly lower yields (65% and 62%, respectively) in a reaction that was carried out under microwave irradiation at 140 °C for 10 min (entries 2 and 4). Despite the decrease in the efficiency, this method allows a significant decrease in reaction time (from 65–66 h to 10 min) and in the required amount of cyclohexanone (from 5 to 1.5 equiv).

The optimized reaction conditions were applied to the synthesis of new chiral hexacyclic steroids **4c–4g**, by reacting 1-azadiene **1** with a selection of cyclic ketones (Scheme 4). Cycloheptane-fused steroid **4c** (50%) and cyclooctane-fused steroid **4d** (28%) could be obtained from the reaction of conjugated imine **1** with cycloheptanone or cyclooctanone, respectively, and in the presence of pyrrolidine.

The synthesis of hexacyclic steroids was also successful using dihydro-2*H*-pyran-4(3*H*)-one, dihydro-2*H*-thiopyran-4(3*H*)-one, and 1-methylpiperidin-4-one as the cyclic ketone, giving the target compounds **4e–4g** in 44%, 67%, and 60% yields, respectively.

The reported results show that conjugated imine **1** does not react with enamines via an aza-Diels–Alder cycloaddition. Nevertheless, steroids **4** could result from a Diels–Alder reaction of the enamines with diene **5** formed via imine–enamine tautomerism (Scheme 5). However, this is very unlikely since the cycloaddition of diene **5** with electron-rich dienophiles would be very unfavorable. Furthermore, the microwave irradiation of a solution of 1-azadiene **1** in toluene, at 140 °C for 10 min, only led to the recovery of the reactant.

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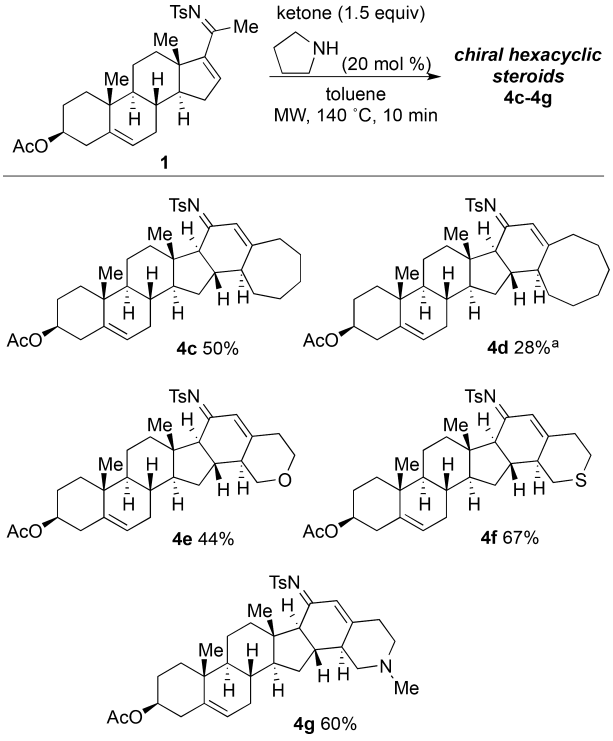
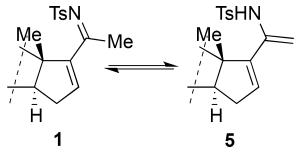
Scheme 4. Synthesis of Chiral Hexacyclic Steroids



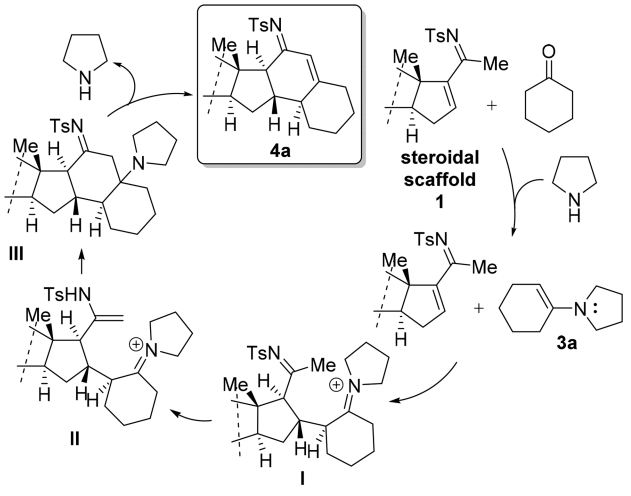
[a]Reaction time: 15 min.

Scheme 5. Imine−Enamine Tautomerism



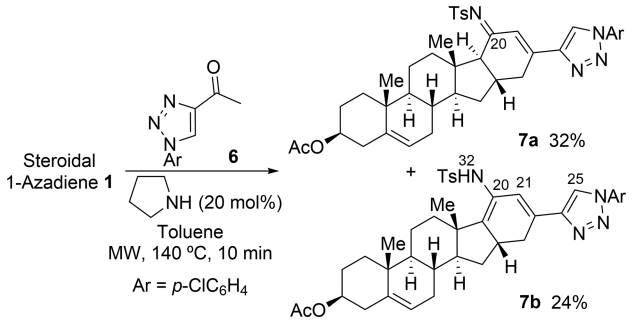
Thus, the synthesis of hexacyclic steroids **4** can be rationalized considering an initial stereoselective conjugate addition of the *in situ* generated enamines to 1-azadiene **1** (Scheme 6). The intermediate, generated in this way, undergoes an imine−enamine isomerization, followed by cyclization and subsequent elimination of pyrrolidine, leading to the target compound. This transformation can be considered a Robinson-type annulation reaction.[20]

Scheme 6. Mechanistic Proposal for the Synthesis of Hexacyclic Steroids, Illustrated for the Reaction of Steroid 1 with Cyclohexanone



This proposal is also consistent with the result observed in the reaction of 1-azadiene **1** with acyclic ketone acetyl-1,2,3- triazole **6**, which was prepared following a previously reported procedure.[21] The pyrrolidine catalyzed reaction gave steroids **7a** and their isomeric derivative **7b** in 56% overall yield (Scheme 7).

Scheme 7. Synthesis of Pentacyclic Steroids 7



The structure of **7b** was established based on bidimensional NMR spectroscopy (see Supporting Information (SI)). The ^{13}C NMR spectrum of compound **7a** shows the presence of an imine carbon (C-20) at 178.8 ppm, while in the ^{13}C NMR of compound **7b**, carbon C-20 is observed at 145.3 ppm. On the other hand, the NOESY spectrum of compound **7b** cross-peaks were observed between proton H-21 (6.56 ppm) and proton H-25 (7.97 ppm) as well as with N*H* proton (H-32, 5.88 ppm). Furthermore, the HMBC spectrum shows a correlation between carbon C-20 with protons H-21 and H-32.

Interestingly, the microwave irradiation at 140 °C for 10 min of a solution of 1-azadiene **1** in toluene in the presence of pyrrolidine (20 mol %) afforded steroid **8** in 52% yield. The ^{1}H and ^{13}C NMR spectra allowed us to conclude that compound **8** incorporates two steroidal moieties (see SI). The ^{1}H NMR spectrum shows signals corresponding to four methyl groups (H-18, H-19, H-18′, and H-19′), two acetyl groups, and two vinylic protons H-6 and H-6′. The molecule has only one *N*-tosyl-1-azadiene group since signals corresponding to two vinylic protons H-21 (7.35 ppm) and H-16′ (6.27 ppm) are observed, but only one tosyl group is present. Additionally, the ^{13}C NMR spectrum shows only one imine carbon (C-20), but carbons corresponding to two acetyl groups are observed.

The formation of compound **8** can be explained by the general mechanism presented in Scheme 8. In this case, enamine **5** generated *in situ* from steroidal 1-azadiene **1** via imine−enamine tautomerism (see Scheme 5) acts as the nucleophile in the initial conjugate addition with another molecule of steroidal 1-azadiene **1**. The imine−enamine tautomerism requires the presence of pyrrolidine since heating a solution of 1-azadiene **1** in toluene in the absence of pyrrolidine only led to the recovery of the starting compound.

In summary, we have developed a pyrrolidine catalyzed diastereoselective reaction of a steroidal *N*-sulfonyl-1-azadiene with carbonyl compounds leading to novel chiral steroids. The use of cyclic ketones allows the synthesis of hexacyclic steroids, whereas with acyclic ketones, pentacyclic steroids are obtained. The reported annulation reaction provides a simple, versatile,

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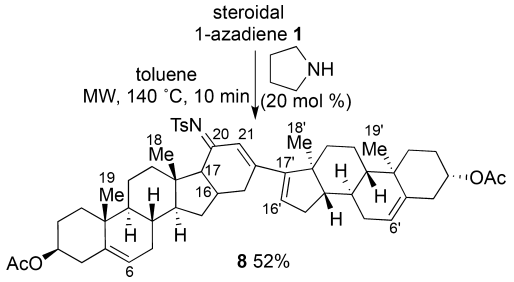
Scheme 8. Synthesis of Compound 8, Which Incorporates Two Steroidal Moieties



and highly selective approach to structurally diverse steroids with potential applications in medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01783.

Experimental details and NMR spectra for all new compounds (PDF)

Accession Codes

CCDC 1847972 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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