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Aziridination of 11-pregnene-3,20-dione using PhI=N-Ses

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Abstract

The copper-catalyzed reaction of [*N*-(Ses)imino]phenyliodinane with 11-pregnene-3,20-dione gave the corresponding aziridine in 53% yield. The Ses protecting group could be conveniently removed using the TASF reagent. Furthermore, nucleophilic ring opening of the protected *N*-Ses-aziridine with thiophenol in the presence of a Lewis acid led to introduction of the thiophenol group at the α-12 position but, unexpectedly, concomitant loss of the Ses group to provide compound **10**.

The synthesis of steroids incorporating an aziridine ring has received continual attention over the past few years. While aziridino steroids are of interest in their own right, for example as inhibitors of some of the various enzymes implicated in steroid biosynthesis[1–4] or as enzyme probes,[5] they can also be considered as reactive intermediates, allowing, in particular, access to amino steroids after nucleophilic ring opening. Amino steroids have been shown to have noteworthy pharmacological activity, for instance on the central nervous system and as anesthetics (e.g. minaxolone,[6,7] ORG20599)[8,9] and, again, as enzyme inhibitors.[1,10]

Aziridine rings can be attached to a steroid nucleus in three different ways. Thus, the steroid can simply be a substituent bound to one of the carbon atoms of the aziridine, as in the 10β-aziridinylestr-4-ene-3,17-dione **1**, prepared by lithium aluminum hydride reduction of a 19-oxime precursor.[1] Alternatively, one of the carbon atoms of the aziridine can be common to one of the carbon atoms of the tetracyclic part of the steroid nucleus, as in 17α,20-aziridine derivative **2**, also prepared by hydride reduction of an oxime precursor.[2] Finally, both aziridine carbons can correspond to two carbon atoms of the steroid ring system, as in compound **3**, derived from triphenylphosphine treatment of a 6-azido-7-hydroxyandrostenedione derivative.[3]

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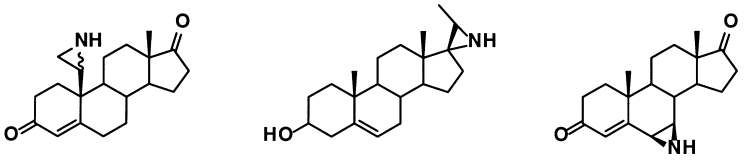
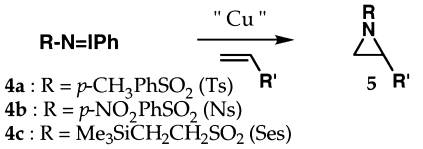


1 2 3

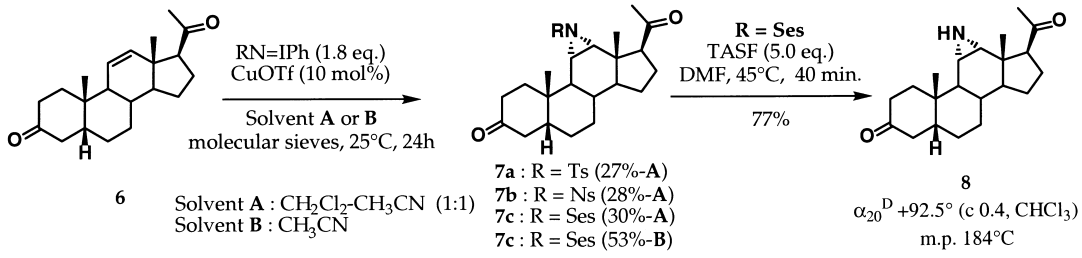
A potentially efficient way of preparing the latter type of aziridinylsteroid would be to react an unsaturated steroid with a nitrene source. Pellacani and co-workers[11] have recently described the aziridination of 3-acetoxy-5,16-pregnadiene-20-one using nitrenes generated from the action of calcium oxide on (arenesulfonyl)oxycarbamates. However, in this case, mixtures of 5,6- and 16,17-mono- and diaziridines of unspecified stereochemistry were formed. Another efficient method of forming aziridines by nitrene addition to double bonds involves the use of [*N*-(arylsulfonyl)imino]phenyliodinanes.[12,13] Thus, the *N*-tosyl and *N*-nosyl derivatives[14] **4a** and **4b**, respectively, provide the corresponding nitrene species in the presence of a copper salt, which can add to both electron-rich or electron-poor C=C double bonds to form aziridines **5** (Scheme 1).[12,15] In addition to an intramolecular version of this reaction,[16] we ourselves have also developed an *N*-alkylsulfonyl analogue of **4a,b**, i.e. the trimethylsilylethanesulfonyl ('Ses') derivative **4c**,[17] which allows facile fluoride ion-promoted cleavage of the *N*-sulfonyl bond after aziridine ring formation.



Scheme 1.

In this communication, we wish to report the first direct aziridination of a representative steroid using these iminoiodinane-type reagents and particularly the 'Ses' reagent **4c**, as well as the unusual reactivity of the resulting aziridinylsteroid in the presence of thiophenol.

Commercial 11-pregnene-3,20-dione **6** (Scheme 2) was chosen as the starting steroid, since it is a convenient precursor of the 3-hydroxypregnan-20-one family of neuroactive steroids.[18] Treatment of **6** at room temperature for 24 h with 1.8 equiv. of the aryliminoiodinanes **4a**, **4b** or **4c** in acetonitrile:dichloromethane (1:1) in the presence of 10 mol% copper(I) triflate gave only modest yields (~30%) of the corresponding aziridines **7a**, **7b** or **7c**, respectively. However, use of

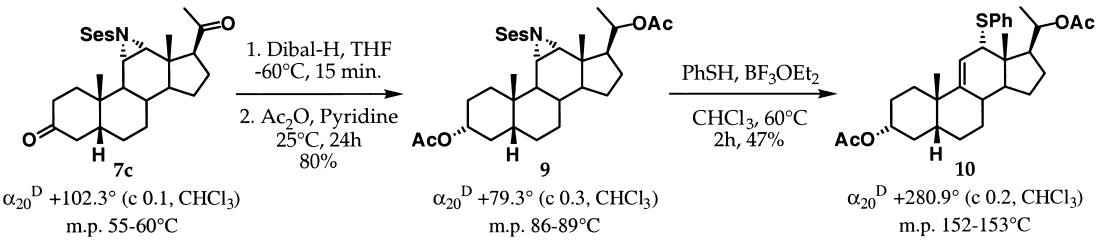


Scheme 2.

acetonitrile as solvent in the case of the Ses-iminoiodinane **4c** afforded the aziridinylsteroid **7c** in a more satisfactory yield (53%). Formation of the aziridine ring was indicated in all three cases by the presence in the ^{1}H NMR spectrum of two doublets appearing in the region of 2.7 and 3.3 ppm. The disappearance of the two vinylic protons of the starting material (at 6.20 and 5.55 ppm) was evidence for the presence of the aziridine ring at the 11,12-position. Both the ^{1}H and ^{13}C spectra showed that only one stereoisomer was formed, i.e. the isomer corresponding to attack of the nitrene from the less-hindered α-face of the steroid. This was evident from the NOESY spectrum of compound **7b**, which showed strong NOE correlations for the β-oriented aziridine hydrogens H-11 (2.87 ppm) and H-12 (3.07 ppm) with the angular methyl protons H-19 and H-18, respectively.

The deprotection of the *N*-Ses-aziridinylsteroid **7c** was then studied. We have shown previously[17] that *N*-Ses-aziridines can be efficiently deprotected using excess tris(dimethylamino)-sulfonium difluorotrimethylsilicate (TASF)[19] in acetonitrile or DMF at room temperature. When compound **7c** was treated with 5 equiv. of TASF under these conditions, only starting material was recovered. However, when the reaction mixture in DMF was heated for 40 min at 45°C, the deprotected aziridinylsteroid **8** was obtained in 77% yield.

We next investigated the possibility of nucleophilic ring opening of the aziridine ring of the *N*-Ses derivative **7c**. To avoid interference from the two electrophilic carbonyl groups, the latter were first reduced with DIBAL-H in THF to give the dialcohol, which was then acetylated using acetic anhydride in pyridine (Scheme 3), affording the 3α,20-diacetate **9** in 80% overall yield. The protected aziridine **9** in chloroform was then treated with an excess of thiophenol, as a model nucleophile, in the presence of 2 equiv. of boron trifluoride etherate. While no reaction was observed after 5 h at room temperature, refluxing of the reaction mixture for 2 h led to formation of a single new product, which was isolated by chromatography on silica gel. The ^{1}H and ^{13}C NMR spectra of this compound showed incorporation of the phenylthio group but loss of the Ses-amino function, with the appearance of a trisubstituted double bond (single vinyl proton at 5.59 ppm).



α_{20}^{D} +102.3° (c 0.1, $CHCl_3$)
m.p. 55-60°C

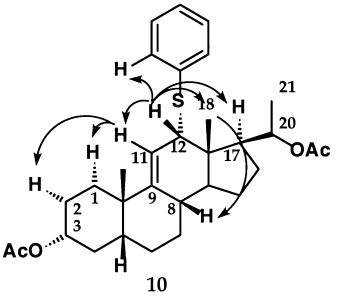
α_{20}^{D} +79.3° (c 0.3, $CHCl_3$)
m.p. 86-89°C

α_{20}^{D} +280.9° (c 0.2, $CHCl_3$)
m.p. 152-153°C

Scheme 3.

This product was assigned structure **10** based on the following spectroscopic evidence: the EIMS showed a molecular ion at *m*/*z* 510 (44%), and as main fragments the loss of the phenylthio group (*m*/*z* 401, 45%) and the subsequent loss of the two acetates (*m*/*z* 341 and 281). The presence of a trisubstituted double bond in ring C is only possible at position 9,11; the olefinic proton H-11 appeared as a double doublet with a 5.9 Hz coupling to the proton at C-12 (bearing the phenylthio group) and a 1.8 Hz allylic coupling to H-8. Concomitantly, H-12 was also observed as a double doublet with a 5.9 Hz coupling to H-11 and a 1.3 Hz homoallylic coupling to H-8. Both long range couplings with H-8 (at 1.95 ppm) were observed as weak

correlations in the 500 MHz COSY 45 spectrum. The NOESY spectrum of **10** provided further evidence for the structural assignments and for the stereochemistry at C-12. Thus, NOE correlations were observed between the phenyl *ortho* hydrogens (at 7.54 ppm) and H-12, and for the pairs H-12/H-11, H-12/H-18 and H-12/H-17, confirming the position of the phenylthio substituent and the double bond in ring C, as well as the equatorial (β) orientation of H-12. NOE correlations for the pairs H-11/H-2α, H-11/H-1α and H-18/H-8 confirmed the above assignments.



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The Lewis acid-catalyzed opening of an *N*-sulfonylaziridine with subsequent loss of the sulfonamide group is, to the best of our knowledge, unprecedented. While aziridines are generally observed to be opened by nucleophiles in an S_N2 fashion, the observation that, in the case of compound **10**,[20] the thiophenol group has, like the precursor aziridine **9**, an α orientation points to probable formation of a carbonium ion at C-12 when aziridine **9** is heated in the presence of $BF_3{\cdot}Et_2O$. Attack of thiophenol would then occur from the less hindered α-face. The involvement of a carbonium ion in the nucleophilic opening of hindered aziridines under acidic conditions has been invoked previously.[21,22] Whether elimination of the sulfonamide group occurs before or after addition of the thiophenol group is currently open to conjecture. It is interesting to note that Breslow and co-workers[23] have recently reported the introduction of a tosylamide group at C-11 of an equilenin steroid substrate using reagent **4a** in the presence of a metalloporphyrin. In this case, however, free-radical processes appear to be involved.

In conclusion, steroid **6** can be efficiently and stereoselectively aziridinated using the *N*-Ses-iminoiodinane reagent **4c**. While the *N*-sulfonyl-aziridinyl steroids **7**, as well as the *N*-deprotected derivative **8**, may themselves have interesting biological properties, they may also offer opportunities for the introduction of substituents at the C-12 position, again in a stereocontrolled fashion. Attempts by others to substitute this position using analogous epoxide steroid derivatives failed.[24] The generality of the unusual but potentially very useful nucleophilic addition–elimination reaction observed with aziridine **7c** is currently under investigation.

Acknowledgements

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