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Stereoselective Radical Cascade Approach to Benzo[*a*]quinolizidines

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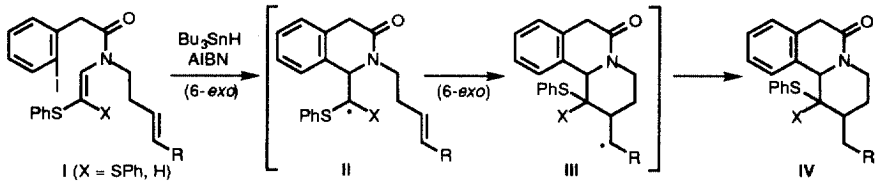
Abstract: The treatment of enamide **15**, having an (*E*)-4-ethoxycarbonyl-3-butenyl group on the nitrogen atom, with Bu_3SnH-AIBN in boiling benzene, afforded a 1.2:1 mixture of two benzo[*a*]quinolizidine stereoisomers **16** and **17** as a result of cascade radical cyclization. A similar treatment of the (*Z*)-4-ethoxycarbonyl-3-butenyl congener **19** gave **16** and **17** in a ratio of 3.4:1. The high stereoselectivity (**16**:**17** = 37:1) from **19** was obtained using Et_3B as the initiator at –78 °C in toluene.

Considerable attention has recently been directed towards the radical cascade approach to polycyclic compounds.[1] As a continuation of our studies on the sulfur-controlled regioselective radical cyclization onto enamides,[2] our interest has now been turned to the synthesis of the benzo[*a*]quinolizidine skeleton **IV** by the radical cascade process which involves a sulfur-controlled 6-*exo* aryl radical cyclization[2c] of *N*-vinylic α-(*o*-iodoaryl)acetamides **I** and successive 6-*exo* cyclization of the resulting intermediate radicals **II** to give **III**. The present paper describes an application of this methodology to the stereoselective synthesis of benzo[*a*]quinolizidines.



We initiated our investigation by examining the cyclization of *N*-[2,2-bis(phenylthio)ethenyl]-α-(*o*-iodoaryl)acetamide **6** having an (*E*)-4-ethoxycarbonyl-3-butenyl group on the nitrogen atom. Compound **6** was synthesized by the condensation of amine **3**, prepared from 3-amino-1-propanol (**1**) in four steps and in 57% total yield, with bis(phenylthio)acetaldehyde[2a] and subsequent *N*-acylation of the resulting enamine **4** with (2-iodo-4,5-dimethoxyphenyl)acetyl chloride (**5**) (Scheme I).

A benzene solution of Bu_3SnH (1.1 equiv.) and azobis(isobutyronitrile) (AIBN) (0.1 equiv.) was slowly added to a solution of **6** in boiling benzene over a period of 3 h to give, in a 59% combined yield, a *ca.* 1:3 mixture of 1-substituted 1,2,3,4-tetrahydroisoquinolin-3-one derivatives **7a** [δ 5.63 (d, J = 15.6 Hz, 1 H, C=C*H*CO), 6.67 (dt, J = 15.6, 7.8 Hz, 1 H, C*H*=CCO)] and **8a** [δ 5.32 (dt, J = 15.6, 6.8 Hz, 1 H, one of CH=CH), 5.43 (dt, J = 15.6, 6.4 Hz, 1 H, one of CH=CH)] having α,β- and β,γ-unsaturated ester moieties on the nitrogen atom, respectively. Unfortunately, no radical cascade product was obtained.

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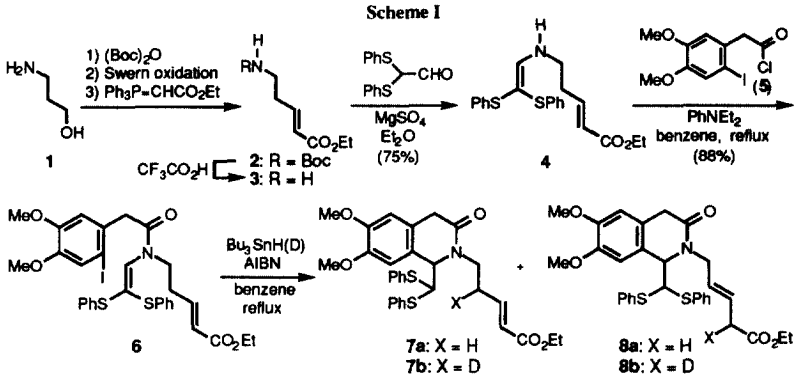
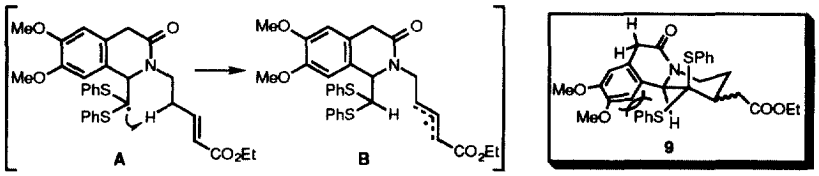
Scheme I



The formation of **7a** and **8a** may be explained as proceeding *via* the translocation reaction of the intermediate of radical **A** formed by a 6-*exo* aryl radical cyclization of **6** and subsequent attack of Bu_3SnH on the resulting radical **B**. This view was supported by the following labelling experiment. Thus, when **6** was treated with Bu_3SnD/AIBN, the deuterium atom was completely incorporated at the γ-position [δ 2.22-2.35 (m, 1H)] of the α,β-unsaturated ester **7b** and at the α-position [δ 2.85 (d, J = 7.3 Hz, 1/2 H), 2.88 (d, J = 6.4 Hz, 1/2 H)] of the β,γ-unsaturated ester **8b**. This result also shows that the translocation reaction of **A** to **B** occurs at a much faster rate than the direct reduction of **A** with Bu_3SnH to **7a**.



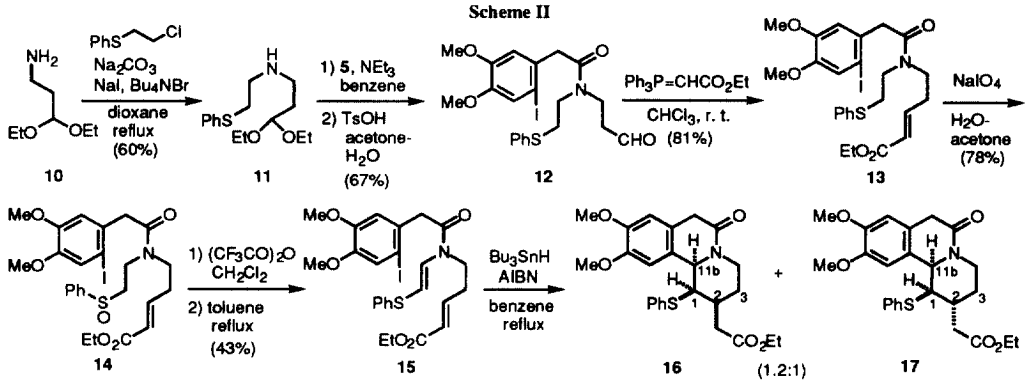
Failure to form the radical cascade product **9** may be ascribed to the severe steric repulsion between the aromatic ring of the isoquinolinone skeleton and one of the phenylthio groups which occupies the equatorial position. We then examined the cyclization of the mono(phenylthio) congener **15**.

The synthesis of **15** was begun by alkylation of the amino acetal **10** with 2-chloroethyl phenyl sulfide[3] to give the amine **11** (Scheme II). *N*-Acylation of **11** with acyl chloride **5** followed by deprotection of the acetal group gave the amide **12**. The Wittig reaction of **12** with $Ph_3P{=}CHCO_2Et$ gave the (*E*)-unsaturated ester **13**,[4] which was oxidized with $NaIO_4$ to give the sulfoxide **14**. Treatment of **14** with $(CF_3CO)_2O$ followed by heating the resulting Pummerer rearrangement product in boiling toluene gave **15**.[5]

The reaction of **15** with Bu_3SnH in the presence of AIBN in boiling benzene gave the expected benzo[*a*]quinolizidine derivative as a mixture of two stereoisomers **16** and **17** in a ratio of 1.2:1 and in 45% combined yield. The ^1H NMR spectrum of the mixture of **16** and **17** showed that the signal due to the proton at the C-11b position of each isomer appeared as singlets at δ 4.73 and 4.90, respectively, thereby indicating both isomers to have the same stereochemical relationship between the two hydrogen atoms at C-11b (axial) and C-1 (equatorial) positions. The signal due to the axial proton on the C-3 position of **16** and **17** appeared at δ 1.52 as a doublet of quartets [J = 4.4, 12.7 Hz ($J_{2\text{-ax},3\text{-ax}}$ = 12.7 Hz)] and at δ 2.22 as a triplet of triplets [J = 13.0, 5.0 Hz ($J_{2\text{-eq},3\text{-ax}}$ = 5.0 Hz)], respectively, indicating the ethoxycarbonylmethyl group at the C-2 position

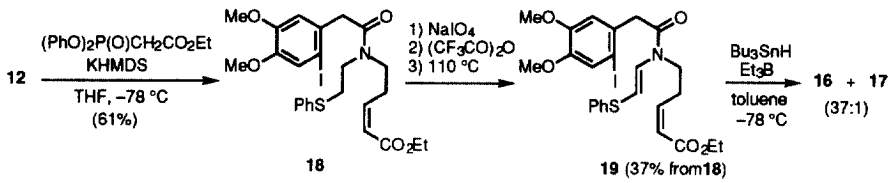
of **16** and **17** to occupy the equatorial and axial positions, respectively. It is relevant to note that the phenylthio groups of both **16** and **17** occupy the axial position so as to probably avoid the steric repulsion between the aromatic ring of the isoquinolinone skeleton.

Scheme II



In an attempt to improve the stereoselectivity in cyclization of **15**, a similar reaction was carried out by using Et_3B as an initiator at room temperature, but this gave also a 1.2:1 mixture of **16** and **17**. We found, however, that compound **19** having a (*Z*)-4-ethoxycarbonyl-3-butenyl group on the nitrogen atom underwent cyclization with high degree of stereoselectivity to give **16** as the major product. Compound **19** was prepared by reaction of aldehyde **12** with $(PhO)_2P(O)CH_2CO_2Et$[6] in the presence of $KN(TMS)_2$ followed by treating the resulting (*Z*)-unsaturated ester **18** as in a manner similar to that described for the preparation of **15** from **13** (Scheme III).[5]

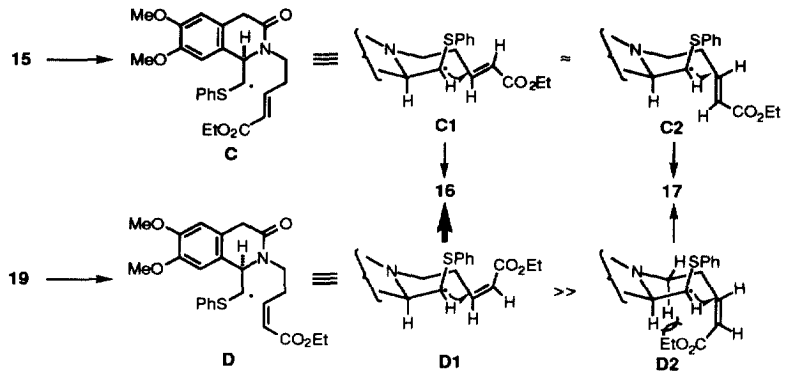
Scheme III



When compound **19** was treated with Bu_3SnH in the presence of AIBN in boiling benzene, the radical cascade products **16** and **17** were obtained in a ratio of 3.4:1 and in 36% combined yield. A similar reaction with Et_3B as an initiator at 0 °C in toluene afforded **16** and **17** in a ratio of 8.1:1. The best stereoselectivity was obtained by treating **19** with Bu_3SnH in the presence of Et_3B at –78 °C in toluene; this reaction gave **16** and **17** in a ratio of 37:1 and in 46% combined yield. Recrystallization (hexane/AcOEt) of the obtained mixture gave the pure isomer **16** (mp 156.5-157 °C).

The stereochemical outcome observed for the cyclization of the (*E*) and (*Z*)-unsaturated esters **15** and **19** may be rationalized in terms of the conformational stability of the intermediate radicals **C** and **D** formed by a 6-*exo* aryl radical cyclization of **15** and **19**, respectively. The two conformers, **C1** and **C2**, and **D1** and **D2**, can be considered for the radicals **C** and **D**, respectively. In the **C1** and **C2** conformers, a remarkable difference in

the stability does not appear to exist, and hence formation of almost equal amounts of **16** and **17** from radical **C** is not unexpected. In contrast, in conformer **D2**, a severe steric repulsion between the ethoxycarbonyl group and two hydrogen atoms on the C-11b and C-4 positions (the numbering system refers to that of the benzo[*a*]quinolizidine) becomes evident, so that the cyclization might proceed *via* the sterically favored conformer **D1** leading to the predominant formation of **16**.[7]



Thus, we revealed that the *N*-[2-(phenylthio)ethenyl]amide **19** having a (*Z*)-4-ethoxycarbonyl-3-butenyl group on the nitrogen atom underwent a cascade radical cyclization with a high level of stereoselectivity to give the (1*R**,2*S**,11b*R**)-benzo[*a*]quinolizidine **16** as the major product.[8] The application of the present methodology to the synthesis of the benzo[*a*]quinolizidine family of alkaloids and related compounds is now in progress.

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5. A small quantity of the corresponding (*Z*)-vinyl sulfide was also obtained.
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