Pergamon

Tetrahedron Letters 40 (1999) 1019–1020

TETRAHEDRON
LETTERS

Synthetic Applications of Samarium(II) Iodide Mediated Regioselective Cleavage of Phenylsulfonyl Activated Cyclopropyl Ketones

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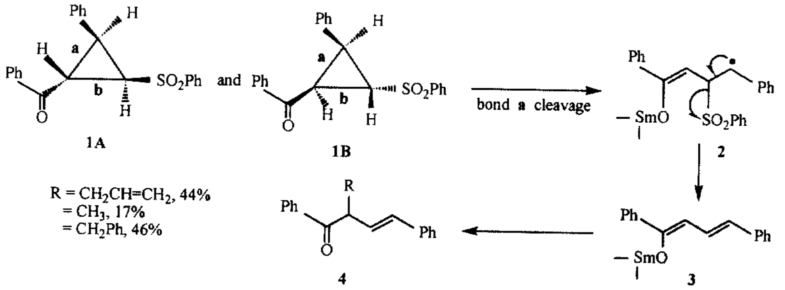
Received 28 September 1998; revised 17 November 1998; accepted 23 November 1998

Abstract: Reductive cleavage of phenylsulfonyl activated cyclopropyl ketones with samarium(II) iodide led regioselectively to samarium enolates or dienolates. These were trapped with some alkylating agents.

One electron reductive cleavage of cyclopropyl ketones to the corresponding acyclic radical species has become an increasingly important synthetic methodology. The fragmentation of the cyclopropyl ketone rings through the intermediacy of cyclopropyl carbinyl radicals has been induced by lithium in liquid ammonia,[1] by stannyl radicals,[2] by photoinduced electron transfer[3] and more recently by samarium(II) iodide (SmI_2).[4,5] In view of the recent results disclosed by Molander[5b] on the reactions of bicyclic cyclopropyl ketones with SmI_2, we wish to report our studies on the regioselective cleavage of phenylsulfonyl activated cyclopropyl ketones by this powerful one electron reducing agent. These results provide mechanistic insight and illustrate potential synthetic applications of these reactions. The tandem regioselective cleavage of these activated cyclopropanes followed by the β-elimination of the β-phenylsulfonyl radical[6] leading to β,γ-unsaturated ketones (Scheme I) and the intermolecular electrophilic trapping of the samarium enolates have been demonstrated.

Scheme I

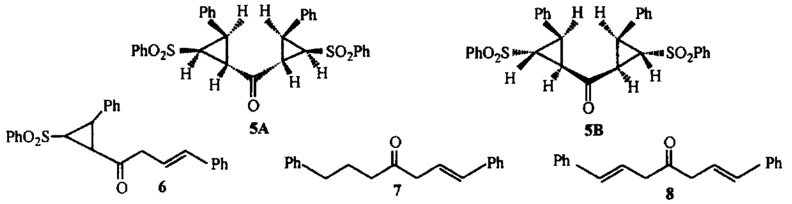


The exploratory studies were carried out using an approximately 4:1 diastereomeric mixture of **1A** and **1B**[7,8] with SmI_2 in THF. Different molar ratios of SmI_2 (1.2 and 2 equivalents) and proton sources (*t*-BuOH and MeOH) were utilized. It was found that the conditions giving the highest yield of **4** (R=H, 87%) were 1.2 equivalents of SmI_2 in THF at -20 °C for 15 minutes and then at RT (30 °C) for additional 15 minutes. The presence of HMPA (8 or 5 equivalents)[9] did not affect the product yield. The reaction was fast at -20 °C judging from the instantaneous disappearance of a purple colour of the SmI_2 solution. The reaction of isomers **1A** and **1B** with SmI_2 under the same conditions gave the product **4** (R=H) in comparable yields to that of the diastereomeric mixture. The formation of the product **4** (R=H) could be rationalized as depicted in Scheme I. The regioselective cleavage of bond **a** gave the β-phenylsulfonyl radical **2** which underwent β-elimination to the (*E*)-β,γ-unsaturated ketone **4** (R=H, *J* of olefinic protons = 15.8 Hz). The main driving force for the regioselectivity is attributed to the formation of the phenyl-stabilized radical **2**, and the formation of a conjugated olefinic bond.

The reaction of the bis-cyclopropyl ketone **5** (as an approximately 1:1 diastereomeric mixture of **5A** and **5B**) with 2.4 equivalents of SmI_2 required both HMPA (8 equivalents) and *t*-BuOH to give the monocyclopropyl ketone **6** in 67% yield together with the acyclic ketones **7** and **8** in 9% and 3% yields, respectively. When 5 equivalents of SmI_2 were employed under the same conditions, the acyclic ketone **7** was isolated in 21% yield along with 7% and 3% yields of the compounds **6** and **8**, respectively. Presumably,

PII: S0040-4039(98)02514-3

compound **7** was derived from the further reduction of a styryl double bond with the excess SmI_2.[10] In spite of the moderate yield of the product **7**, this procedure provides a novel entry to the C_6-C_7-C_6 carbon framework of the naturally occurring diarylheptanoids.[11]

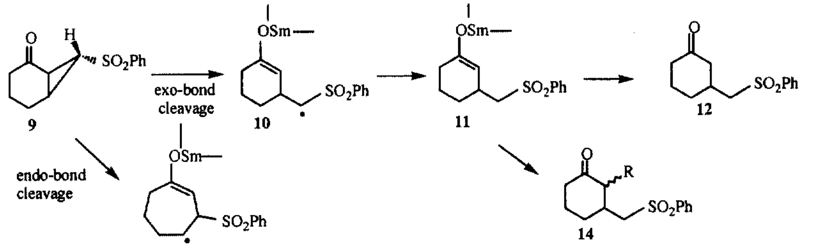


5A **5B** **6** **7** **8**

In order to probe further the regioselective cleavage of *β*-phenylsulfonyl activated cyclopropanes, the bicyclic cyclopropyl ketone **9** was chosen as a substrate. The possible modes of bond cleavage are shown in Scheme II. The reaction of **9** with 1.2 equivalents of SmI_2 and HMPA (8 equivalents) gave the cyclohexanone **12** in 58% yield as the sole product. In this reaction, stereoelectronic control[12] is the overriding factor and leads to the exclusive cleavage of the exocyclic cyclopropyl bond yielding the intermediate **10**. No product derived from the *β*-phenylsulfonyl radical **13** was detected.

The *in situ* intermolecular trapping of the samarium enolates **2** and **11** was briefly investigated. The addition of electrophiles (allyl bromide, methyl iodide and benzyl bromide) gave the alkylated products **4** and **14** in moderate yields. It should be noted that the trapping of enolate **2** gave only the *α*-alkylated products **4**. The results provide the second example of reactions of samarium dienolates with electrophiles.[13]

Scheme II



R = $CH_2CH{=}CH_2$, 29%; CH_3, 37%; CH_2Ph, 40%

In summary, our studies have provided preliminary mechanistic insight and illustrate the synthetic potential of the regioreductive cleavage of activated cyclopropyl ketones. Further work is in progress.

Acknowledgement: We wish to thank the Thailand Research Fund for the award of the Senior Research Scholar to VR and the International Program in the Chemical Sciences for partial financial support.

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7. All compounds were characterized by spectral data and elemental analysis. The structure and the relative stereochemistry of **1B** were determined X-ray crystallographically. The relative stereochemistry of **5A** and **5B** was established by NMR correlation with **1A** and **1B**. The details will be published elsewhere.
8. Compounds **1**, **5** and **9** were synthesized from the reactions of chloromethyl phenyl sulfone with the corresponding *α,β*-unsaturated carbonyl compounds, using LDA/THF-HMPA (10:1)/-78 °C to RT, overnight, in 57%, 24% and 39% yields, respectively.s
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