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Facile synthesis of enol ethers by cleavage of α-bromoacetals and α-bromoketals mediated by SmI_2

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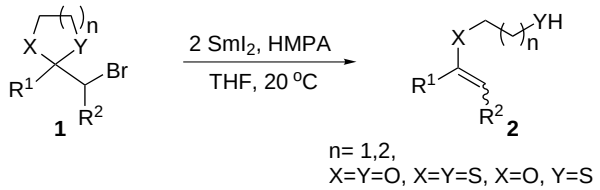
Abstract—α-Bromocyclicacetals, α-bromocyclicketals and α-bromocyclicthioketals, derived from cyclic and acyclic ketones and aldehydes, reacted with samarium diiodide at −78°C in THF to furnish the corresponding enol ethers or thioenol ethers containing hydroxy or thiol moieties in high yields. © 2001 Published by Elsevier Science Ltd.

Enol ethers are useful intermediates in organic synthesis and have been studied intensively.[1] The most useful preparative techniques involve the pyrolytic cracking of acetals and ketals, usually in the presence of acid catalysts.[2] Such vigorous conditions often limit the generality of the synthetic procedures, particularly when the substrates contain other sensitive functional groups. A cleavage of acetals or ketals with trimethylsilyliodide (TMSI)[3] or triisobutylaluminum (TIBA)[4] has been reported. Recently, Gasman et al. carried out a cleavage of acetals or ketals using trimethyltrifluoromethanesulfonate in the presence of tertiary amine (DIEA) via a cationic process.[5] The reaction required a long reaction time and high reaction temperature. However, the base sometimes causes difficulties when separating the product from the starting materials.

SmI_2 has a strong oxophilicity and is a powerful electron donor. Various reductions, reductive coupling and cyclizations have been reported.[6] Unusual eliminations and cleavage reactions using the oxophilicity and Lewis acidity of samarium have been discovered. Cleavage reactions of epoxides,[7] cyclopropanes,[8] or tetrahydropyrane derivatives[9] gave very useful intermediates or compounds in organic synthesis. Molander and coworkers reported a cleavage reaction of acetals with SmI_2 via rearrangement of a radical.[10] It is well known that alkylhalides rearrange to alkyl radicals using SmI_2.[11] Such radicals can be expected to convert into anion intermediates by a further one-electron transfer from SmI_2. On the supposition that α-haloacetal may form an anion-type intermediate in the reaction with SmI_2, cleavage of α-haloacetals, α-haloketals and α-halothioketals has been examined using SmI_2. We have found that α-halocyclicacetals, α-halocyclicketals and α-halocyclicthioketals reacted readily with SmI_2 to furnish the corresponding enol ethers or thioethers, containing alcohol or thiol moieties, in high yields (Scheme 1).

In a typical reaction procedure, an SmI_2 solution (0.1 M, 10 ml) was added dropwise at −78°C to a solution of α-bromocyclopentane 1,3-dioxane acetal (run 2; 110 mg, 0.5 mmol) and HMPA (521 μl, 3.0 mmol) in THF (5 ml) under an argon atmosphere. The mixture was stirred for 10 min and then quenched with saturated ammonium chloride (5 ml). The mixture was extracted with Et_2O (2×20 ml), and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated. The crude product was then purified by silica gel column chromatography (ethyl acetate:*n*-hexane = 1:2). All the products obtained were identified by ^1H and ^{13}C NMR spectral data and mass spectroscopy.

Compared with the previous methods for the preparation of enol ethers, the present cleavage reactions,



Scheme 1.

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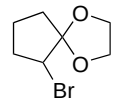
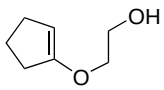
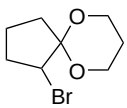
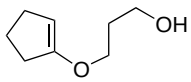
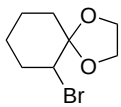
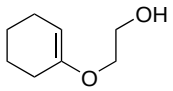
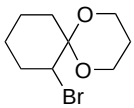
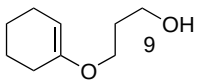
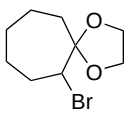
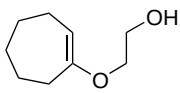
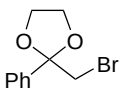
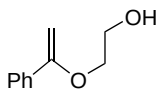
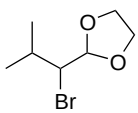
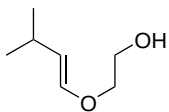
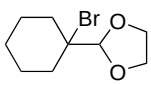
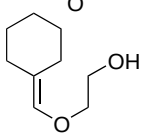
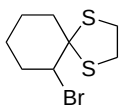
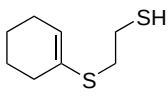
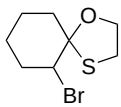
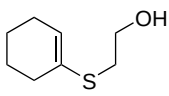
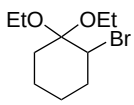
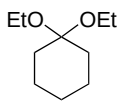
mediated by SmI_2, required short reaction times under mild reaction conditions. Our new method also has the advantage of not only obtaining enol ethers but also enol thioethers containing alcohol or thiol moieties at the β- or γ-position. Treatment of SmI_2 (2 equiv.) in the presence of HMPA at −78°C in THF afforded enol ethers or enol thioethers in excellent yields within 30 min. The results obtained are summarized in Table 1. HMPA strengthens the electron-donor effect of samarium coordination between samarium and oxygen atoms.[11a] The cleavage reaction gives lower yields in the absence of HMPA under the same reaction conditions.

Bromocyclicacetals were prepared via two-step α-brominations[12] of ketones with NBS–AIBN, TMPTB or Br_2 and the usual acetal formations.[13] α-Bromocyclopentane, α-bromocyclohexane and α-bromocycloheptane ketals gave enol ethers. The primary (run 6), secondary, and tertiary bromoacetals (run 8) were converted into enol ethers. The cleavage of dioxolanebromide (runs 1 and 3) was three times faster than that of dioxanebromide (runs 2 and 4), most probably due to ring strain. Dithiolane also gave thio enol ether in high yields. In the case of thiooxolane, a cleavage reaction occurred at the oxygen atom to give the thioenol ether.

Table 1. Reductice cleavage reaction of α-bromo acetals

Run	Substrate	Temp. (°C)	Time (min)	Products	Yields (%)[a]
1		-78	3		91
2		-78	10		90
3		-78	3		92
4		-78	10		1
5		-78	3		89
6		-78 to rt	30		87
7		-78 to rt	30		82
8		-78	10		81
9		-78 to rt	15		87
10		-78 to rt	15		81
11		-78	110		75[b]

a: Isolated yields. *b*: The debrominated product was isolated instead of the enol ether.

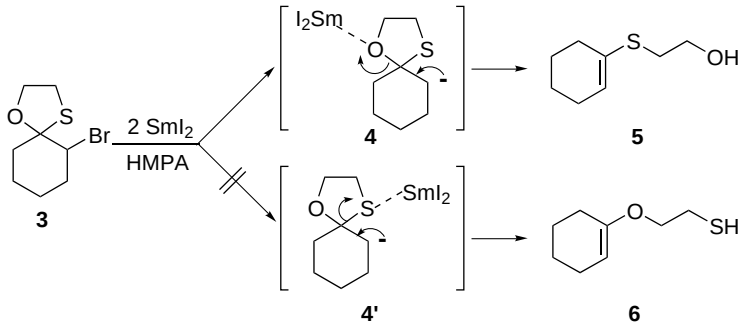


Figure 1. Chemoselective cleavage of 1,3-thiooaline acetal.

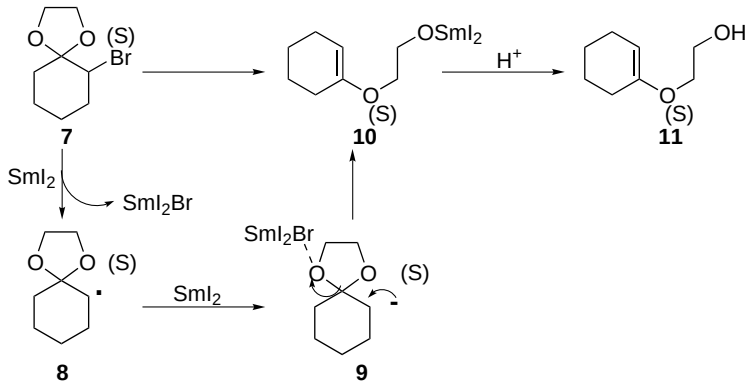


Figure 2. Possible mechanism.

A chemically selective cleavage of α-bromocyclohexane 1,3-thiooxolane acetal **3** afforded 1-[(2-hydroxy)-ethoxy]cyclohexane **5** in 81% yield. No product **6**, formed by S–C bond cleavage, could be detected (Fig. 1). The oxophilicity between oxygen and samarium must be stronger than the thiophilicity between sulfur and samarium.

Cleavage of diethyl cyclohexyl ketal did not occur; the only reduction product obtained was the main product (run 11). Thus, ring strain seems to play an important role in this cleavage reaction.

Although the reaction mechanism is not clear, it appears to be initiated by the formation of radical samarium coordinated complex (**8**) by abstraction of bromine. Samarium metal is a strong electron donor and lengthens the lifetime of the generated radical species **8**. Compound **8** converts to anion **9** via a one-electron transfer from SmI_2.[14,15] The anion attacks the adjacent carbon to cleave the C–O bond to form **10** (Fig. 2). The cleavage reaction, via movement of anions, should occur more rapidly than the reduction reaction.

In summary, a new type of cleavage of α-bromoacetals, α-bromoketals and α-bromothioketals has been achieved using SmI_2. The reactions provide alternative methods for the synthesis of functionalized enol ethers or enol thioethers under mild reaction conditions over a short reaction time.

Acknowledgements

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