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ORGANOSELENIUM-MEDIATED REDUCTION OF α,β-EPOXY KETONES TO β-HYDROXY KETONES: A NEW ACCESS TO INTER- AND INTRAMOLECULAR ALDOLS

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Summary: The organoselenium-mediated reduction of α,β-epoxy ketones has been demonstrated to be a promising entry to a variety of cyclic and acyclic aldols.

The synthetic potential of aldols as key intermediates in organic synthesis, inter alia natural products chemistry, has been increased by recent progress in the directed aldol reactions,[1] as well as new developments in the reduction of α,β-epoxy ketones.[2] Particularly, the latter method has gained importance since it allows access into not only acyclic (intermolecular) aldols but also a variety of cyclic (intramolecular) aldols which may be difficult to obtain by the traditional aldol reactions.

Several methods/reagents such as chromium (II) salts,[3] zinc/acetic acid,[4] and electrochemical methods[5] have been previously reported for the reduction of α,β-epoxy ketones to β-hydroxy ketones (aldols). However use of these reagents invariably yield a substantial amount of enone along with other by-products. Although Al/Hg[6] and NaI/NaOAc[7] have been successfully applied for this particular transformation, their examples are rather few. Recently, NaTeH[2a] or SmI_2[2b] have been employed as effective reagents for this particular conversion.

We describe herein the organoselenium-mediated reduction of α,β-epoxy ketones to the corresponding β-hydroxy ketones as a new and promising entry to a wide variety of inter- and intramolecular aldols.

Unaware of a precedent for the epoxy ketone reduction with organoselenium, we investigated a model compound **1**[8] to explore the generality and stoichiometry of the reaction. Thus, treatment of **1** with 3 equiv of ethanolic PhSeNa,[9] generated by $NaBH_4$ reduction of $(PhSe)_2$,[10,11] at 5-10 °C resulted in a rapid reaction (5 min) with the exclusive formation of the desired product **2** (76%) along with $(PhSe)_2$ (ca. 90%) which may be reusable. The yield of **2** could be

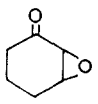
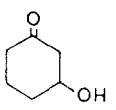
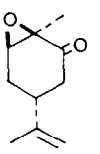
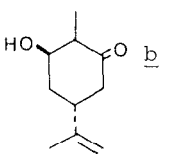
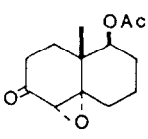
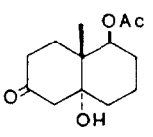
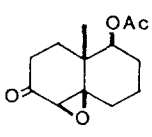
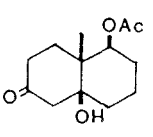
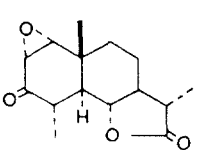
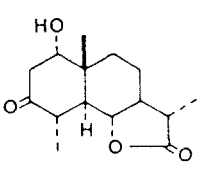
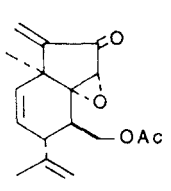
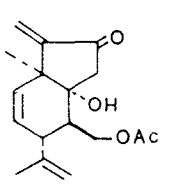
1 **2**

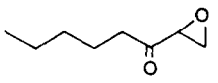
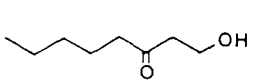
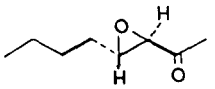
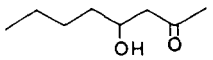
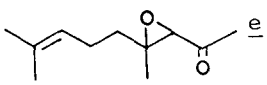
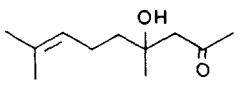
remarkably improved (95%) by the addition of AcOH (0.5 equiv) as buffer to suppress the retro-aldol reaction.

On the other hand, the use of ethanolic PhSeH (3 equiv) generated in situ from PhSeNa by the addition of 3 equiv of AcOH[12] also gave **2** in excellent yield. In this way, both selenium reagents were effective for the conversion of **1** to **2**, however the former reagent is superior to the latter in view of the simple manipulation and isolation of the product.

To illustrate the potential of the present method, a number of reactions of various epoxy ketones were examined and the corresponding β-hydroxy ketones (aldols) were obtained in high yields (Table 1).

Table 1. Reduction of α,β-Epoxy Ketones with PhSeNa (3 equiv) in the Presence of AcOH (0.5 equiv)

entry	substrate	temp (°C)	time (min)	product	yield (%)[a]
1		5	10		84
2		5	10	 [b]	82 (15)[c]
3		r t	10		90 (6)
4		r t	10		91 (5)
5		r t	30		92
6		r t	10		90

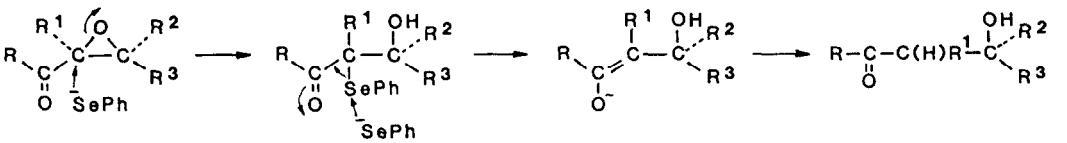
7		r t	10		88[d]
8		5	10		100
9	 [e]	5	10		89

[a] Values in parentheses show yields of α,β-unsaturated ketones.
[b] Isomeric mixture (ca 5:1).
[c] The yield was determined by ^{1}H-NMR.
[d] β-Phenylseleno substitution product was formed in 6% yield.
[e] Mixture of cis- and trans-isomers (11:8).

The major advantage of the new method is that a wide variety of acyclic and cyclic aldols including optically active ones may be derivable since various α,β-epoxy ketones are readily available by the epoxidation of α,β-unsaturated ketones[13] or the epoxidation of allylic alcohols[14] followed by oxidation.

Notable observation of the present method is the non- or negligible formation of enones as well as selenenylated ketones. Important feature also lies in the employment of neutral conditions compatible with polyfunctional groups, e.g. the specific reduction of epoxy ketone moiety coexisting with an enone function (entry 6) should be noted.

The mechanism for the organoselenium-mediated reduction of epoxy ketones may involve an initial phenylseleno substitution at α-carbon followed by the nucleophilic attack of the second molecule of selenolate ion on the selenium atom as shown below.[15,16]



The following experimental is illustrative: Acetic acid (15 μL, 0.25 mmol) was added to an ethanolic solution of PhSeNa, prepared by the reduction of $(PhSe)_2$ (234 mg, 0.75 mmol) with $NaBH_4$ (57 mg, 1.5 mmol) in EtOH (3 mL),[10] and the mixture was stirred for few minutes at room temperature. The resulting

solution was added at once to a solution of **1** (97 mg, 0.5 mmol) in EtOH (2 mL) under argon and stirred for 5 min at room temperature. The reaction mixture was diluted with ethyl acetate and washed with saturated brine. Removal of the solvent left a residue which was purified by Florisil column chromatography to give $(PhSe)_2$ (204 mg) and the pure product **2** (93 mg, 95%).

References and Notes

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9. A lower ratio of the reagent resulted in a mixture of the product **2** and unchanged starting material.
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11. The anion generated in this way has been reported to be a phenyl/borane complex $Na^+[(PhSe)BH_3]^-$ rather than uncomplexed PhSeNa. D. Liotta, W. Markiewicz and H. Santiesteban, Tetrahedron Lett., 4365 (1977).
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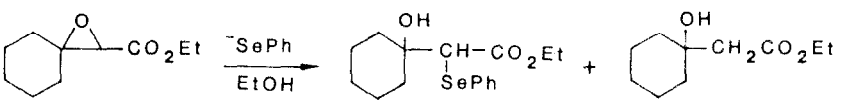
15. Reduction of glycidic ester (i) under the same conditions gave a mixture of the substitution product (ii) and hydroxy ester (iii), and the former was found to be converted to the latter on further treatment with PhSeNa.



(i) (ii) (iii)

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