

RING CONTRACTIONS THROUGH RADICAL INTERMEDIATES

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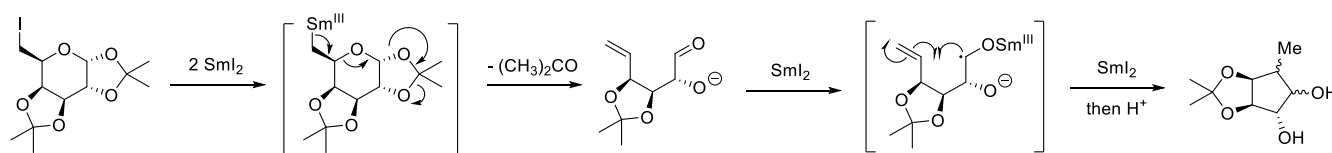
INTRODUCTION

Ring contractions allow structural diversification of complex molecules, by providing compounds with smaller rings and sometimes yielding highly strained cyclopropanes and cyclobutanes. Many ring contraction reactions involve cation, anion, or even carbene intermediates, but some of them occurs through radical intermediates. They emerge from various reaction conditions, and even enzymes exhibit ring contractions via generation of radical intermediates.

RING CONTRACTIONS INDUCED BY FREE RADICAL REAGENTS

Free radicals can undergo ring fragmentation or cyclization, and they can be applied to perform ring contraction. Chiara and coworkers reported that four equivalents of SmI_2 , a SET (single electron transfer) reagent, reacts with protected 6-deoxy-6-iodohexopyranosides to form cyclopentanetetraols.¹ The first two equivalents reduce the C-I bond, which triggers fragmentation into the aldehyde intermediate. The aldehyde reacts again with SmI_2 to generate the ketyl radical and the 5-*exo-trig* cyclization gives the five-membered ring.

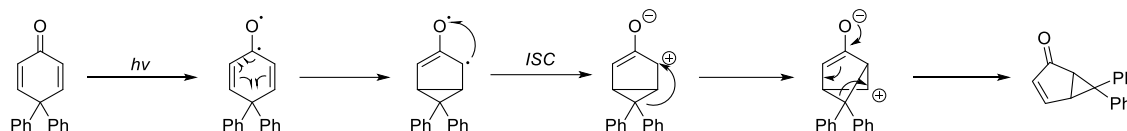
Figure 1. SmI_2 -induced ring contraction of sugar derivative



PHOTOCHEMICALLY GENERATED RADICALS

Light can also form radical species by exciting chromophores. A well-studied example is the ring contraction of 4,4-diphenylcyclohexadienone, which Zimmerman and coworkers used to explain photochemical rearrangement of α -santonin.² When the compound is irradiated with UV light, the carbonyl group is excited into biradical triplet state. The intermediate rearranges into a bicyclic 1,3-biradical and then undergoes ISC (intersystem crossing) to relax into the zwitterion. Two consecutive 1,2-shifts of the zwitterion yields the ring contraction product. Direct 1,3-shift is forbidden since it involves four electrons and follows Hückel aromatic transition state.

Figure 2. Photochemical ring contraction mechanism of 4,4-diphenylcyclohexadienone



Photon can also cleave weak bonds, exemplified with the rearrangement of *N*-chlorolactams, reported by Lessard and coworkers.³ N-Cl bond is first broken to provide the lactamyl radical, then it undergoes radical 1,2-shift itself or performs cationic 1,2-migration as the *N*-acylnitrenium ion.

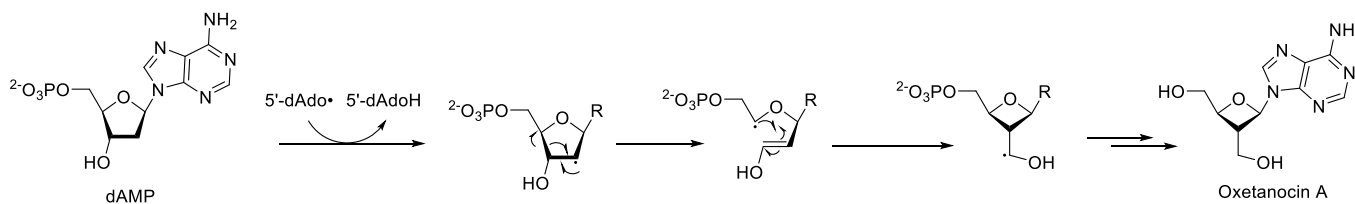
RING CONTRACTIONS BY GAS EXTRUSION

Biradical species can also be formed by releasing a gas and rapidly recombine into ring contraction products. Levin and coworkers discovered a method for nitrogen deletion of secondary amines, including azacycles into corresponding carbocycles.⁴ Amines react with anomeric amide and yield hydrazides that readily transform into isodiazenes. They release nitrogen gas and produce biradical species that recombine into ring contraction products. The authors suggested the existence of radical intermediates using cyclopropylmethyl groups, also known as “radical clocks” that open into homoallyl radicals.

RADICAL RING CONTRACTIONS IN BIOLOGICAL SYSTEMS

Enzymes also show ring contractions by introducing radicals to substrates. Radical SAM enzymes generate 5'-deoxyadenosyl (5'-dAdo) radicals through electron transfer from the [4Fe-4S] cluster to SAM (*S*-adenosylmethionine). OxsB, a radical SAM enzyme, can catalyze the ring contraction of dAMP by forming radical at 2' position.⁵ Ring opening of the intermediate then closing results in the four-membered ring, which eventually leads to oxetanocin A, a natural product having antiviral activity.

Figure 3 Mechanism of action of radical SAM enzyme OxsB in biosynthesis of oxetanocin A



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