

Chapter 5

Sequential Reactions

I.	Introduction.....	82
II.	Advantages and Disadvantages of Sequential Reactions.....	83
III.	Two-Step Sequential Reactions	85
	A. Cyclization-Cyclization	85
	B. Cyclization-Addition.....	85
	C. Cyclization-Rearrangement	86
	D. Fragmentation-Fragmentation.....	87
	E. Addition-Fragmentation.....	87
	F. Cyclization-Fragmentation	87
	G. Fragmentation-Addition.....	89
	H. Hydrogen-Atom-Abstraction--Cyclization	89
	I. Hydrogen-Atom-Abstraction--Addition	90
IV.	Three-Step Sequential Reactions	90
V.	Related Reactions.....	91
	A. Parallel Reactions.....	93
	B. Sequences of Reactions.....	93
	C. Group Migration Reactions.....	94
VI.	Summary	95
VII.	References.....	95

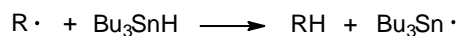
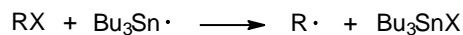
I. Introduction

The propagation phase in a chain reaction is composed of a sequence of elementary reactions. The simple reduction pictured in Scheme 1 consists of two such reactions, and the radical addition shown in Scheme 2 has three elementary reactions in its propagation phase. Even though the overall reaction in each case (Schemes 1 and 2) consists of two or more elementary reactions occurring in sequence, neither overall reaction is described as a sequential one because to merit this designation, radical formation from the substrate and radical conversion to the product are not included.¹ With these beginning and ending steps removed, the reactions shown in Schemes 1 and 2 do not qualify as sequential. [Cascade, domino, and tandem are other names used to describe sequential reactions.]

Elementary radical reactions readily occur in sequence because most produce a new radical poised for further reaction.^{1,2} Since all participants in a sequential reaction, including the intermediate radicals, are present in the reaction mixture at the same time, achieving the selectivity necessary to have each radical react in the desired manner at the correct time is a challenging task,

one that is critical to the success of the overall process. This selectivity is controlled by the rates of the various, possible propagation steps.

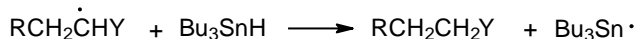
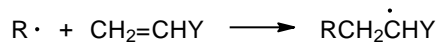
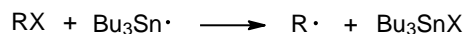
Scheme 1



R· = carbohydrate radical

X = reactive substituent

Scheme 2



R· = carbohydrate radical X = reactive substituent

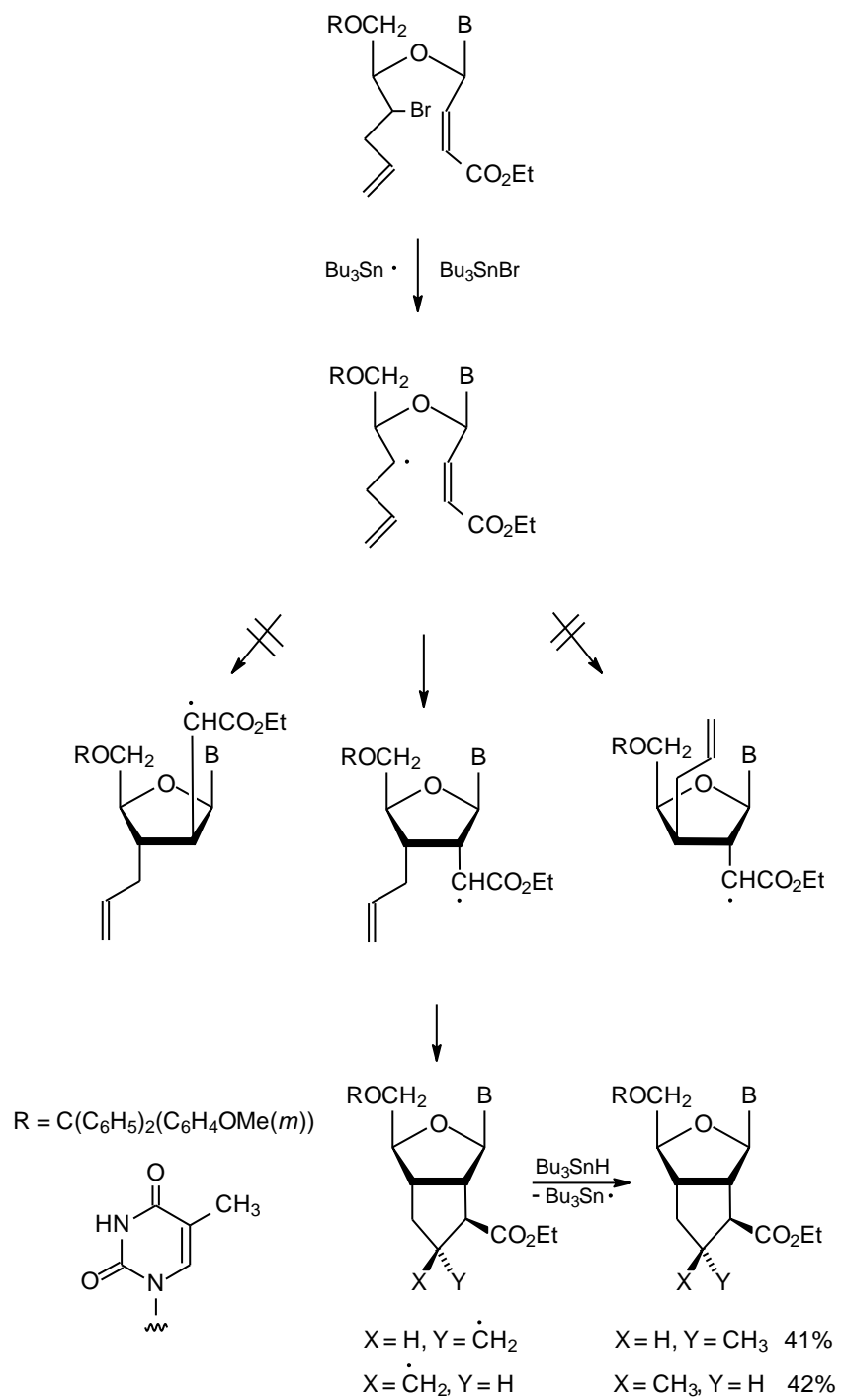
Y = an electron-withdrawing group

Successful, sequential reactions have several common characteristics. Propagation steps are faster than termination steps. Intermediate radicals react rapidly with the correct nonradicals, but avoid reaction with the solvent and initiator. The final radical, but not the intermediate ones, is converted into a stable product.

II. Advantages and Disadvantages of Sequential Reactions

When two or more reactions occur in sequence, there is a savings in time, effort, and chemicals, compared to performing each reaction individually; therefore, sequential reactions can increase synthetic efficiency and provide a positive environmental impact by reducing chemical use.³⁻⁵ An example of this efficiency is seen in the process pictured in Scheme 3, where two new rings form in a single reaction.⁶ There is a price to be paid for this efficiency. It comes in the form of the additional effort that usually is necessary in preparing the starting materials and establishing the reaction conditions so that each step in this more complicated process proceeds in the desired direction.^{4,5} Not only may more synthetic work be required in substrate preparation, but controlling product regio- and stereochemistry also may be more challenging in a process where multiple structural changes occur in a single reaction.

Scheme 3



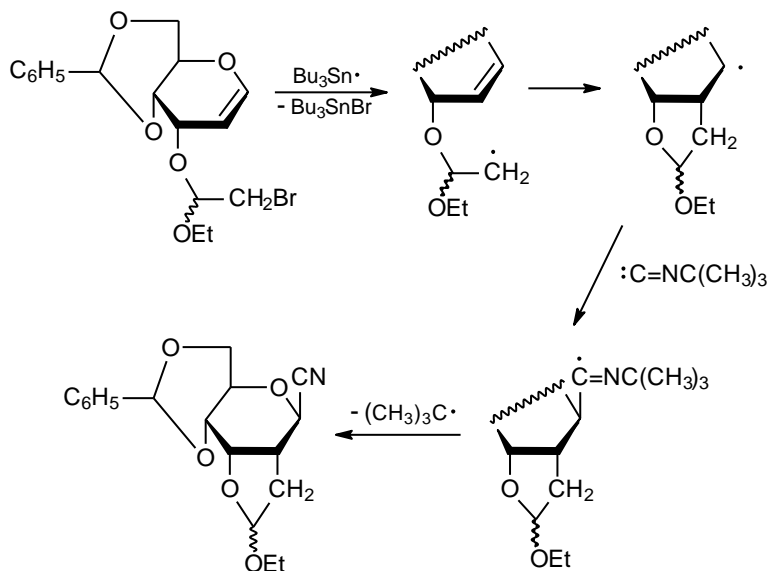
III. Two-Step Sequential Reactions

When planning a sequential reaction, it is natural to gravitate toward elementary reactions that are rapid and occur in a highly predictable fashion; also, because a more complex structure is often the target in a synthetic reaction, forming a carbon–carbon bond is usually one of the goals of a sequential process. Since internal addition of a radical to a multiple bond often is both rapid and predictable and usually involves new carbon–carbon bond formation, many sequential reactions include at least one radical cyclization step; some contain more. Cyclization-cyclization, the first sequential reaction to be discussed, involves forming of two rings.

A. Cyclization-Cyclization

A cyclization-cyclization reaction is one in which two internal addition steps occur in sequence.^{6–14} In a typical reaction at least one of these steps involves radical addition to a carbon–carbon double bond. In the reaction shown in Scheme 3 both steps actually are of this type.⁶ Internal addition also can occur to triple bonds^{7–9} and to carbonyl groups.¹⁰ Products from these reactions are varied and include nucleosides^{6,14} and sugar derivatives with bridged ring systems.^{11–14}

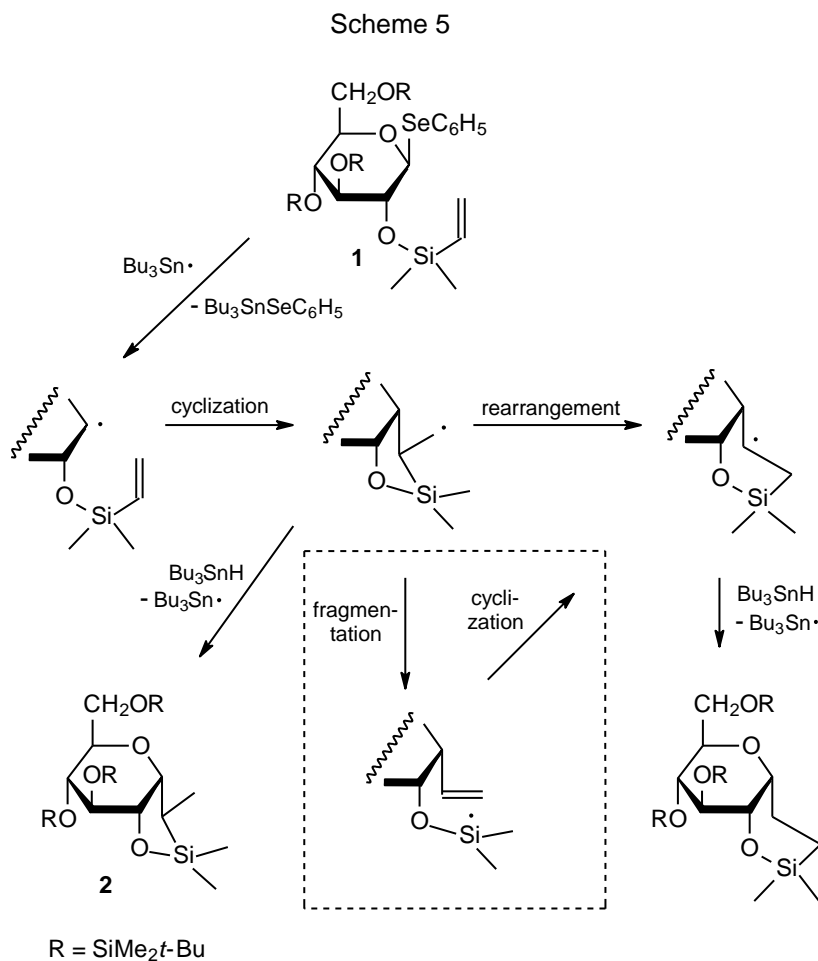
Scheme 4



B. Cyclization-Addition

Combining addition and cyclization steps in a sequential reaction brings together two separate molecules while forming a new ring system.^{15–19} Cyclization typically occurs in the first step, as is seen in the reaction shown in Scheme 4.^{15,16} Ring formation takes place first because intramo-

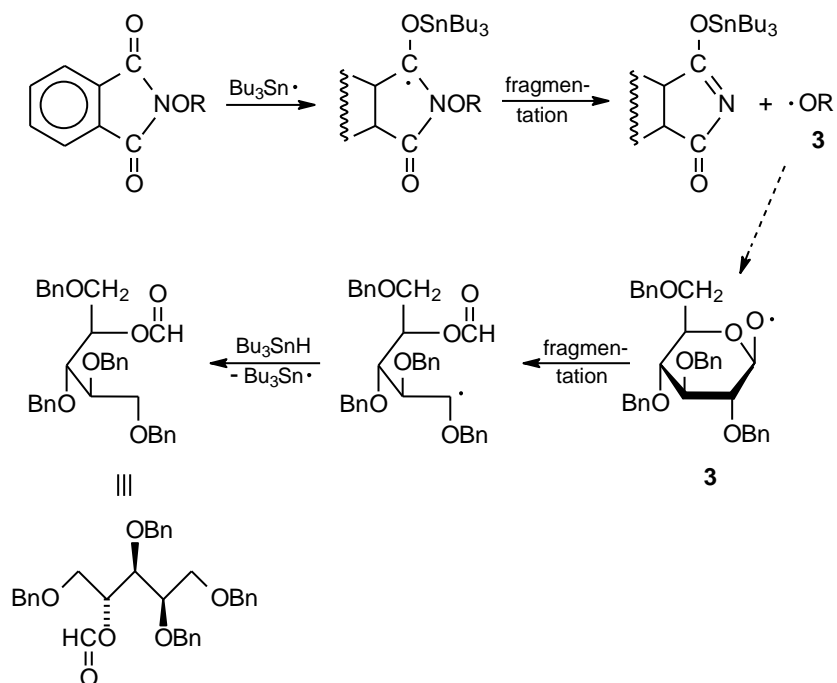
lecular addition of a properly position radical center to a reactive multiple bond typically is faster than intermolecular reaction. The addition step usually is to a compound with a carbon–carbon double bond,^{16–18} but can involve compounds with other types of double bonds^{15,16} or even molecular oxygen.¹⁹



C. Cyclization-Rearrangement

Dimethylvinylsilyl ethers such as **1** undergo sequential, cyclization-rearrangement reactions (Scheme 5²⁰).^{20–26} Reactions of this type require that the hydrogen-atom donor concentration be maintained at a low level to reduce the possibility of forming the silyl ether **2** by hydrogen-atom abstraction prior to rearrangement. As is indicated in the box in Scheme 5, the rearrangement process may take place by a fragmentation-cyclization combination. In such an event the overall process would become a three-step sequential reaction.²⁶

Scheme 6



D. Fragmentation-Fragmentation

Bond fragmentation frequently is one of the steps in a sequential process.²⁷⁻⁵⁴ In the reaction shown in Scheme 6,²⁸ where formation of the alkoxy radical **3** is followed by ring opening, both sequential steps involve β -fragmentation.^{27,28}

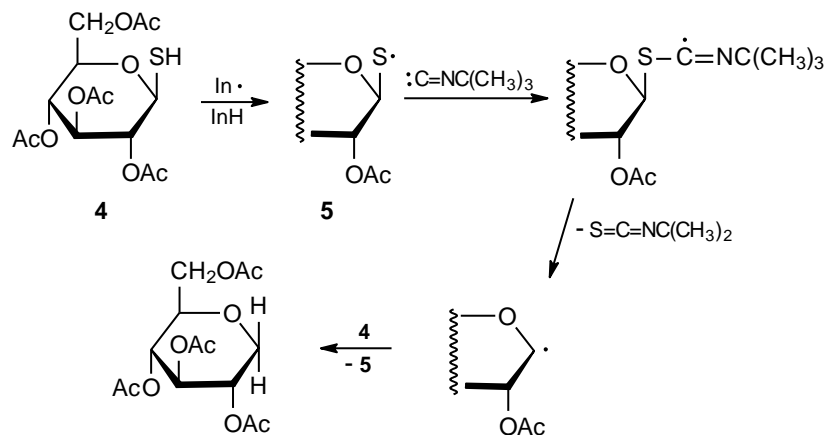
E. Addition-Fragmentation

β -Fragmentation is the second step in the desulfurization process shown in Scheme 7. In this reaction addition of a sulfur-centered radical to an isonitrile is followed by fragmentation of a carbon-sulfur bond to form a pyranos-1-yl radical.²⁹

F. Cyclization-Fragmentation

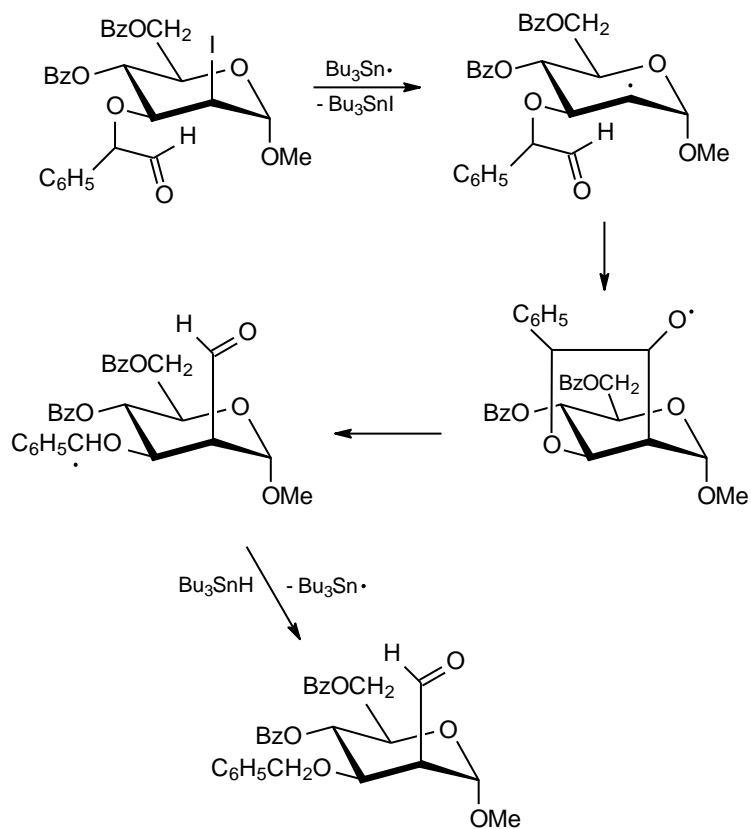
If the first step in a sequential reaction is radical cyclization and the second step is β -fragmentation, the sequential process can cause group repositioning.³⁰⁻³⁵ In the sequence shown in Scheme 8, for example, the aldehyde group moves from the C-3 substituent to C-2.^{30,31} Section V.C contains further discussion of reactions involving group migration.

Scheme 7



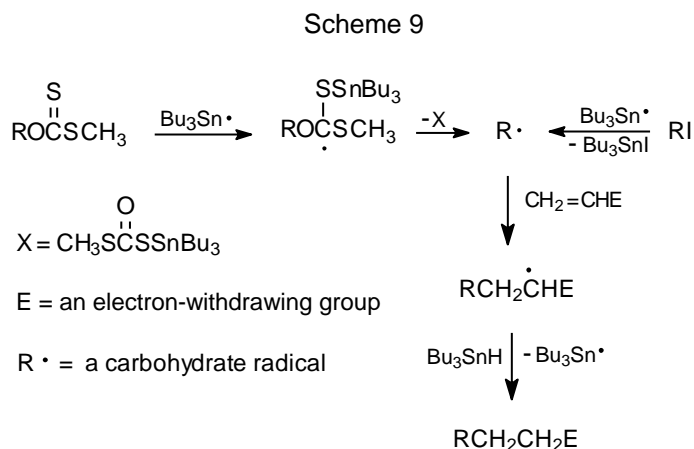
In· = an initiating radical

Scheme 8



G. Fragmentation-Addition

Whenever a carbohydrate radical is generated from an *O*-thiocarbonyl compound, two steps are required; that is, radical formation is followed by β -fragmentation (Scheme 9).³⁷⁻⁵⁴ If radical addition then takes place, the reaction is classified as sequential. This classification is correct but somewhat artificial because its sequential nature is a result of the way in which the carbohydrate radical is generated. When the same radical ($R\cdot$) is produced by halogen-atom abstraction, β -fragmentation is removed from the process, and the reaction is no longer sequential but rather a simple radical addition.



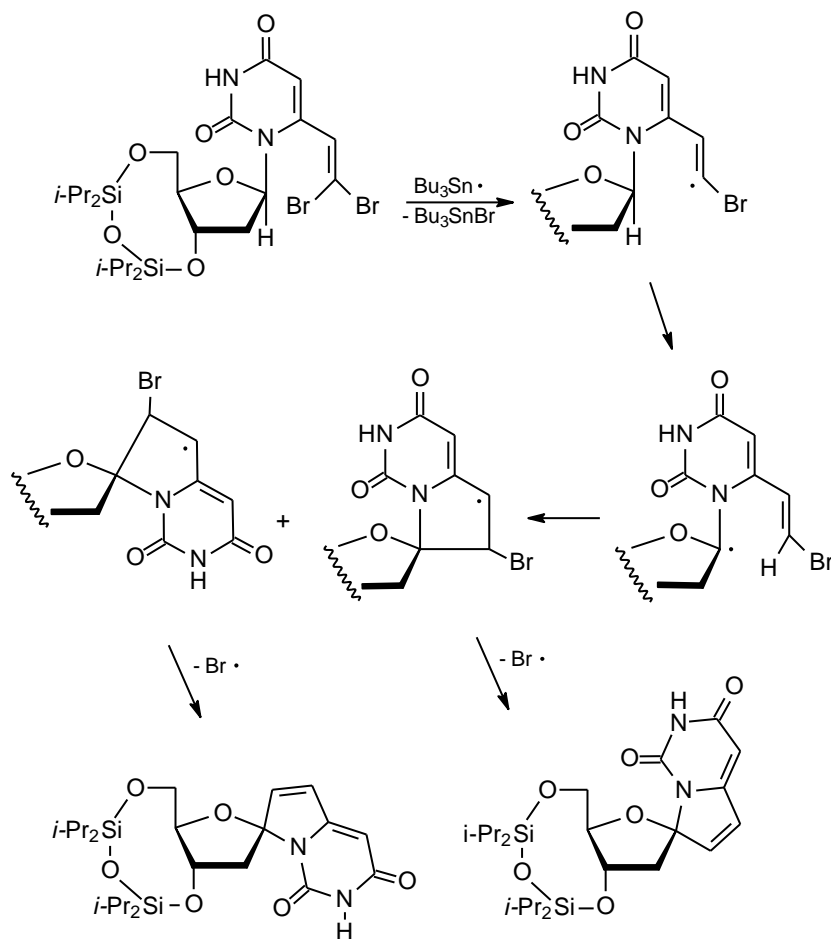
A reaction that generates an alkoxy radical from a phthalimide easily can become sequential because formation of the alkoxy radical takes place by β -fragmentation that follows the initial radical formation.^{27,28,55-57} If a second fragmentation step occurs after alkoxy radical formation,⁵⁵ as it does in the reaction shown in Scheme 6,²⁸ or if internal hydrogen-atom abstraction by the alkoxy radical takes place following the initial β -fragmentation,^{56,57} the overall reaction becomes sequential. Phthalimides, therefore, are like *O*-thiocarbonyl compounds in that they become likely substrates for sequential reaction due to the two-step nature of the formation of carbohydrate radicals. These two reaction types, therefore are formally sequential but do not bring about the greater structural change often associated with a sequential process.

H. Hydrogen-Atom-Abstraction--Cyclization

Only the most reactive carbon-centered radicals (primary, vinyl, or aryl) are able to abstract a hydrogen atom from a carbon-hydrogen bond; consequently, the opportunities for such an abstraction to be part of a sequential process are limited. One way in which this participation can occur is shown in Scheme 10, where hydrogen-atom abstraction places a carbon-centered radical in a position to form a new ring.⁵⁸ Most reported reactions of this type involve a radical formed by

hydrogen abstraction from the carbohydrate portion of a nucleoside. This radical then forms a new ring by adding to a multiple bond attached to the nitrogenous base.^{58–69}

Scheme 10



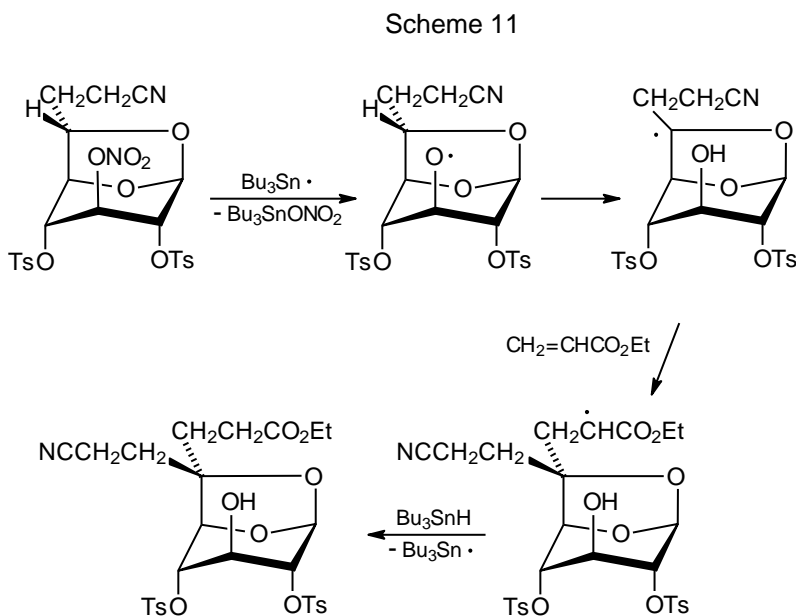
I. Hydrogen-Atom-Abstraction--Addition

An oxygen-centered radical readily abstracts a hydrogen atom from a carbon–hydrogen bond to produce a carbon-centered radical. This new radical then can continue a sequential reaction by adding to a multiple bond.^{70–72} An example of such a sequence is shown in Scheme 11, where the radical produced by hydrogen-atom abstraction adds to the electron-deficient double bond in ethyl acrylate.^{16,70}

IV. Three-Step Sequential Reactions

Three-step sequential reactions often consist primarily of combinations of cyclization and β -fragmentation steps.^{56,73–82} One group of such reactions involves ring opening of cyclic acetals.^{73–77} Since these reactions contain more fragmentation than cyclization, they tend to produce

less complicated structures (e.g., compounds with fewer rings). In the reaction shown in Scheme 12, for example, internal radical addition to a cyano group creates a nitrogen-centered radical. This cyclization then is followed by successive β -fragmentation steps. Together these elementary reactions cause acetal ring opening.⁷³



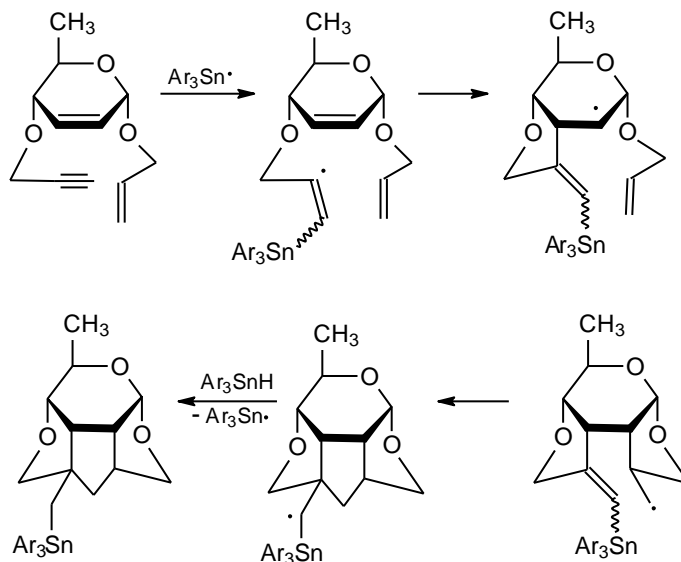
Balancing the advantage gained against additional effort needed to prepare the starting materials and adjust the reaction conditions is always a consideration when conducting a sequential reaction. Such consideration motivated the preparation of the acetal **6** (Scheme 12),^{73–75} when the effort necessary to synthesize **7**, the first acetal used in this type of reaction, significantly offset the advantage derived from the sequential process.^{73,76,77}

The synthetic potential of three-step sequential reactions changes when there is more cyclization than fragmentation. When such a change occurs, reactions can be used to build more complex structures.^{78–81} Specifically, the process shown in Scheme 13, which contains only cyclization steps, generates three new rings in a single reaction.⁸¹

V. Related Reactions

Parallel reactions and sequences of reactions cause multiple structural changes to occur in molecules under a single set of conditions. These reactions are different from sequential reactions, however, in that neither parallel reactions nor sequences of reactions are a series of conversions of one radical into another; rather, they each consist of two or more distinct, complete reactions taking place under a single set of conditions.

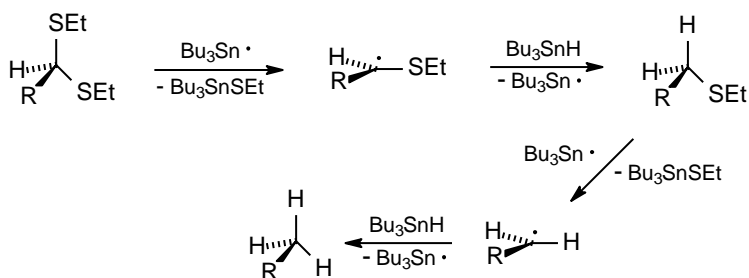
Scheme 13



A. Parallel Reactions

Parallel reactions are ones in which structural change takes place in different parts of the same molecule under a single set of conditions. In the reaction shown in eq 1, for example, the iodine atom in the starting material is replaced by a hydrogen atom, and the azido group in the aglycon is converted to an amino group.^{83,84}

Scheme 14



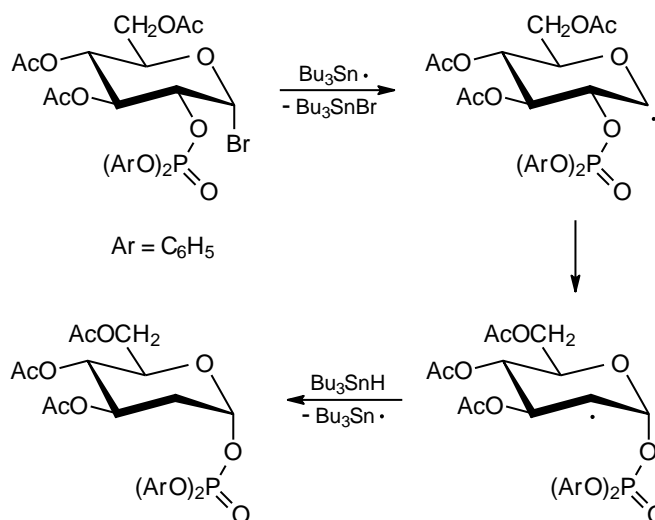
B. Sequences of Reactions

A sequence of reactions occurs when the product from one reaction is a stable compound that becomes the starting material for a second. Both reactions occur in the same reaction mixture under a single set of conditions. Scheme 14, which describes a reaction where two ethylthio groups are successively replaced by hydrogen atoms, is an example of a sequence of reactions.⁸⁵

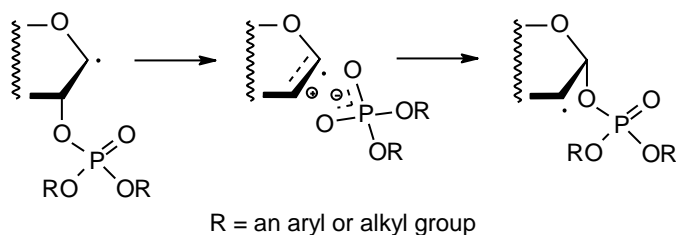
C. Group Migration Reactions

Group migration in radical reactions follows one of two basic pathways. For aldehydo, cyano, and aryl groups, migration takes place by a sequential process consisting of cyclization and β -fragmentation steps. (An aldehydo group migration is pictured in Scheme 8.) If silyl group migration (Scheme 5) is a stepwise process, it too should be included with these sequential, migration reactions.

Scheme 15



Scheme 16



A different mechanism governs group migration in esters. In these reactions radical translocation accompanies group migration (Scheme 15),⁸⁶ but the process cannot be described completely in terms of elementary radical reactions. Considerable evidence supports a mechanism for group migration in esters that involves ion-pair formation (Scheme 16).⁸⁶⁻⁹⁷ This is a sequential process, but only the first step in the sequence (i.e., heterolytic β -fragmentation that produces the ion pair) is an elementary radical reaction. Since the second step, combination of a radical cation and an anion, is not an elementary radical reaction, group migration in esters cannot be classified

as a sequential, radical reaction. (Group migrations reactions in esters are discussed in detail in Chapters 8 and 9 of Volume II.)

VI. Summary

Elementary radical reactions readily occur in sequence because many of these reactions produce new radicals ready for further reaction. Such reactions provide an opportunity for multiple structural change under a single set of reaction conditions; consequently, these reactions, when properly chosen, represent an increase in synthetic efficiency. Two-step sequential reactions often involve radical cyclization in combination with radical addition, β -fragmentation, or hydrogen-atom abstraction. Three-step reactions usually consist of a combination of cyclization and β -fragmentation steps.

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