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Trost B M, Salzmann T N & Hiroi K. New synthetic reactions. Sulfenylations and dehydrosulfenylations of esters and ketones. *J. Amer. Chem. Soc.* 98:4887-902, 1976.
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This paper describes the development of a truly general chemo- and regioselective method for introduction of unsaturation into organic compounds. The sequence developed for carbonyl compounds involves sulfenylation, oxidation to a sulfoxide, and thermolysis. The application of this method in the synthesis of bioactive molecules is illustrated. The method extends beyond carbonyl compounds to other molecular systems—the requirement being that these compounds can be readily sulfenylated. [The *SCI*® indicates that this paper has been cited in more than 410 publications.]

Synthetic Dehydrogenation of Carbonyl and Related Compounds

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The trite but commonly true saying that "necessity is the mother of invention" aptly describes our invention of a mild general method for introduction of unsaturation into organic compounds. Our program in insect hormone chemistry led to a research project whose goal was the total synthesis of the insect molting hormones—the ecdysones. We required the ability to introduce a double bond adjacent to an ester in a molecule containing other sensitive functionality. The classic method involved halogenation (normally bromination) followed by base-catalyzed dehydrohalogenation. Both steps of this protocol suffer serious limitations because of lack of chemoselectivity.

In a totally unrelated project, I was struck by the mildness with which an α-sulfinyl ester eliminated the elements of a sulfenic acid to create an α,β-unsaturated ester. While simple alkylsulfoxides were known to eliminate to olefins, normally, rather high temperatures were required—a fact that limited the development of this reaction as a synthetic method.[1] The ability of a carbonyl group to lower the required temperatures suggested this reaction would be synthetically useful if we had an easy way to introduce the sulfur.

For this purpose, the readily accessible stable disulfides appeared most attractive. Fortunately, they proved to be sufficiently electrophilic that they reacted readily with enolates of both esters and ketones. To the extent that one can generate enolates of ketones regioselectively, the resultant enolate can be trapped before equilibration by proper choice of sulfenylation agent in some cases.[2] Such α-thiocarbonyl compounds are versatile intermediates for a number of synthetically useful transformations. For example, a facile decarboxylative elimination to ketones and aldehydes provides a facile route to a key prostaglandin intermediate,[3] followed by oxidation of the sulfide to a corresponding sulfoxide.

Elimination of the sulfenic acid requires temperatures as low as room temperature. Since the sulfenic acid may be reactive with the product and/or the starting material, a sulfenic acid trap is usually added. The eliminations are normally highly regioselective in which dipole-dipole interactions are frequently dominating effects.

The sulfenylated and sulfinylated intermediates are also useful for carbon-carbon bond formation due to the acidifying influence of the sulfur substituent. Oxidation to the sulfoxide and thermolysis effects the equivalent of a dehydrogenative aldol condensation—a process that constitutes a key sequence in the total syntheses of the iridoids plumericin, allamcin, and allamandin.[4] The sodium or potassium enolate of a sulfinylated ester undergoes alkylation in dipolar aprotic solvents. In the same pot, simply elevating the temperature affects an elimination to give a very effective alkylative olefination protocol.[5]

Contemporaneously with our development of this sulfenylation-dehydrosulfenylation protocol, a selenium-based sequence was developed. The stability of the sulfur intermediates, and their lower propensity to undergo side reactions, frequently makes the sulfur-based sequence the method of choice. A total synthesis of the antileukemic agent, (-)-rocaglamide, highlights this difference, since the selenium-based method totally failed whereas the sulfur protocol proceeded in excellent yields.[6] The versatility offered by sulfur in the various intermediates, and the ability to affect sulfenylation of a wide variety of substrates, has promoted a desire to solve a single problem in a total synthesis to a series of powerful methods for the elaboration of complex molecular architecture.

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