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REDUCTIVE CLAISEN REARRANGEMENTS OF ALLYLOXYANTHRAQUINONES. A REVIEW

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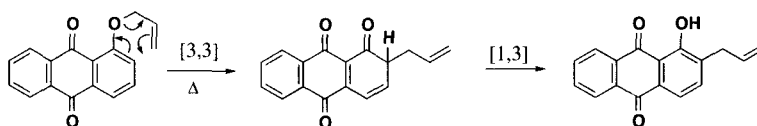
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INTRODUCTION

The Claisen rearrangement¹⁻⁴ (*Scheme 1*) is an excellent method for functionalizing anthraquinones because its rate is largely independent of electronic effects.^{5a} This independence can be attributed to the lack of charge separation in the transition state.⁶ Many allyloxyanthraquinones which are readily available from hydroxyanthraquinones by the Williamson ether synthesis or by the Mitsunobu reaction, undergo thermal Claisen rearrangement in high yield (70-90%) at 160-250° (*Table 1*). However, some substrates are resistant to Claisen rearrangement, 2-allyloxyanthraquinones rearranging only when there is a free phenol *peri* to the quinone while only one allyloxy group of 1,4-bis(allyloxy)anthraquinones undergo rearrangement. These failures have been attributed to hydrogen bonding^{7,8} or electronic effects.⁹

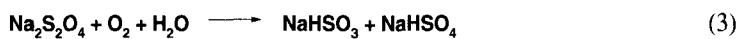
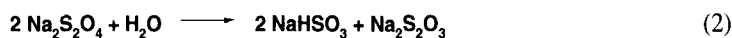
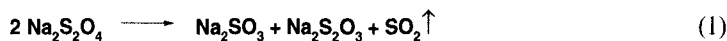


Scheme 1

1,4-Bisallyl ethers can be induced to undergo a double rearrangement by masking the free phenol after the first rearrangement,^{8,10} but the overall yields are unsatisfactory. During an attempt to remove hydrogen bonding by reductive acetylation of the quinone before rearrangement,⁸ rearranged products were isolated at the unprecedented and comparatively low temperature of 140°. Further investigation showed that sodium dithionite reduction of allyloxyanthraquinones in dimethylformamide-water gave excellent yields (90-100%) of rearranged products, at an even lower temperature of 105°.^{8,11} Subsequently, these reductive Claisen conditions have completely replaced the thermal Claisen rearrangement as a method of anthraquinone functionalization (*Table 2*).

I. SCOPE OF REARRANGEMENT

Nevertheless, inconsistent results from reductive Claisen rearrangements with sodium dithionite have been observed. Conditions that have been changed, and noted to affect the course of reductive rearrangement, include the solvent or solvent mixture,¹² temperature of reaction,¹³ duration of reaction,^{8,14} concentration of substrate, amount of substrate, reductant used,^{8,15} ratio of reductant to substrate,¹⁶⁻¹⁸ temperature at which the reagents are mixed,¹⁴ order in which the reagents are mixed,¹⁹ pH,^{13,20} presence of oxygen,²⁰ and the method of workup. Recently, it has been shown that the single most important factor affecting yields and reproducibility of the reductive Claisen rearrangement is the quality of the sodium dithionite.²¹ While sodium dithionite is a strong reductant which is often used to reduce anthraquinones,²²⁻²⁷ it is not a stable compound, decomposing rapidly on heating at temperatures greater than 190° (*Eq. 1*).²⁸ If moisture is present, it undergoes slow disproportionation (*Eq. 2*)^{28,29} and if the solid is exposed to both oxygen and moisture, it is rapidly oxidized to a mixture of sodium bisulfite and sodium bisulfate (*Eq. 3*).²⁹ When produced, sodium dithionite has one water of crystallization and this is sufficient to allow both disproportionation and autoxidation to occur.^{28,29} The reagent can be standardized by gravimetric or titrimetric methods.^{30,31}

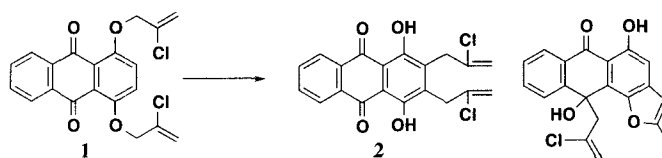


Since some recorded reductive Claisen rearrangements had clearly been carried out with sodium dithionite of less than optimum quality, the possible catalytic effect of the reagent has been investigated by the current authors. When 4 mol% of sodium dithionite was gradually added to an acidic solution of a *bis*(chloroallyloxy)anthraquinone at reflux, the doubly rearranged product was obtained in 25% yield in only 20 minutes. However, the remaining material was a complex mixture of products which contained no starting material. Thus, even with a catalytic amount of reductant, the reaction was still much faster than hitherto reported rearrangements,^{8,14} indicating that a reductant which only reduces anthraquinones slowly would be advantageous. Hocking *et al.* have reported that reducing sugars reduce anthraquinone slowly. The most rapid of those reductions which they investigated was that with glucose which reduces anthraquinone completely in 48 hours at room temperature.^{32,33} By comparison, sodium dithionite reduces anthraquinone completely in less than 20 minutes at room temperature.^{32,33} However, the reduction of anthraquinone by glucose requires basic conditions, which are incompatible with a chloroallyl side-chain. Nevertheless, glucose promotes reductive Claisen rearrangement under basic conditions affording doubly rearranged products in an optimized yield of 80% if slightly more than one equivalent of sodium hydrogen carbonate is employed as base, and the reaction is stopped when starting material has completely disappeared (8-10 minutes). The amount of base is critical since increasing its proportion promotes the formation of furans, while diminishing its concentration causes the formation of both singly and doubly rearranged products and

decreases the rate of reaction. Sodium acetate is not sufficiently basic to afford good yields. Glucose can be used catalytically but its use results in decreased yields.

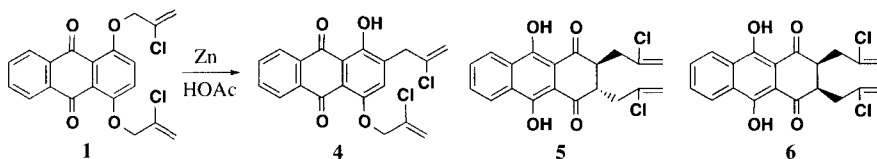
Mal has reported the glucose-promoted Claisen rearrangement of monoallyl-oxyanthraquinones,¹⁵ and noted that heating with glucose (2.5-3.0 equivalents) in dimethylformamide for 5-24 hours gives moderate yields of rearranged products. However, the yields reported for rearrangement of a chloroallyl side-chain were low, and furanic products predominated. Mal also observed that rearrangement could be accelerated by adding aqueous sodium hydrogen carbonate, rearrangement then requiring only 30 minutes. The more rapid reaction was attributed to carbanionic acceleration of the rearrangement. From our own work, it is clear that rearrangement under basic conditions is even faster than Mal indicates. Additionally, although carbanionic acceleration may account for some of the acceleration of rearrangements under basic conditions, our studies on the catalytic effect of glucose indicate that the main accelerating effect of the base is upon the rate of reduction.

Use of sodium dithionite with sodium hydrogen carbonate also affords good yields of doubly rearranged products if the amount of base and duration of the reaction are carefully controlled. For example, heating 1,4-bis(chloroallyloxy)anthraquinone (**1**) with sodium dithionite and sodium hydrogen carbonate (1 equiv.) for 2 minutes affords the doubly rearranged product **2** in 83% yield and the rearranged furan (**3**) (6%) (Scheme 2). The dithionite-promoted rearrangement is significantly faster than the glucose-promoted rearrangement.



Scheme 2

Use of zinc (1 equiv.) with a refluxing solution of bis(chloroallyloxy)anthraquinone in refluxing acetic acid for 1 min affords the singly rearranged material **4** (79%) along with a mixture of the reduced doubly rearranged compounds **5** and **6** (18%) (Scheme 3). Although zinc can operate catalytically, the reaction proceeds for only a short time and then stops so that multiple additions of zinc are required. Production of reduced doubly rearranged products **5** and **6** gives compounds which effectively act as reductant-traps, halting propagation of the desired quinone reduction.



Scheme 3

Since two of the decomposition products of dithionite (bisulfite and thiosulfate) are themselves reductants, their use for reductive Claisen rearrangements of allyloxyanthraquinones was

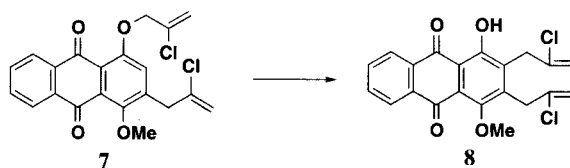
investigated. Sodium bisulfite itself is a poorly defined mixture of bisulfite, metabisulfite, and water which is prone to autoxidation (Eq. 4).³⁴ Thus, sodium metabisulfite which is shelf-stable, well-defined and generates two equivalents of sodium bisulfite on contact with water (Eq. 5),³⁵ was used as an equivalent for sodium bisulfite.



Thus, *bis*(chloroallyloxy)anthraquinone (**1**) was heated in dimethylformamide-water with the mixture of sodium bisulfite (generated from sodium metabisulfite) and sodium bisulfate (generated from an equimolar mixture of sulfuric acid and sodium hydroxide) which would be obtained by complete autoxidation of the quantity of dithionite that had been used in a previously reported double rearrangement of the compound **1**.¹⁴ To avoid a possible photo-reduction of the anthraquinone, light was excluded from the reaction. Upon cooling, the doubly rearranged product precipitated in a yield (78%) close to the originally reported yield.¹⁴

The very presence of rearranged materials in this reaction was surprising, since bisulfite is not a strong reductant. However, bisulfite was confirmed as the promoter of the rearrangement since no rearrangement occurred when the bisether was heated in dimethylformamide-water by itself, or with sodium bisulfate, or when the heated mixture was exposed to light. Optimized metabisulfite-promoted rearrangements require 3 to 5 hours, depending upon the scale, and afford doubly-rearranged products in 86-90% yield. Sulfuric acid can be substituted for the bisulfate, but at least one equivalent of acid is required to prevent a lowered yield and the formation of furanic products. Tlc analysis shows that the reaction proceeds through the intermediacy of the singly rearranged product. Indeed, when a reaction with the chloroallyloxyanthraquinone was stopped after 25 minutes the singly rearranged material was obtained in 95% yield, a yield again comparable with that reported in the literature.⁸

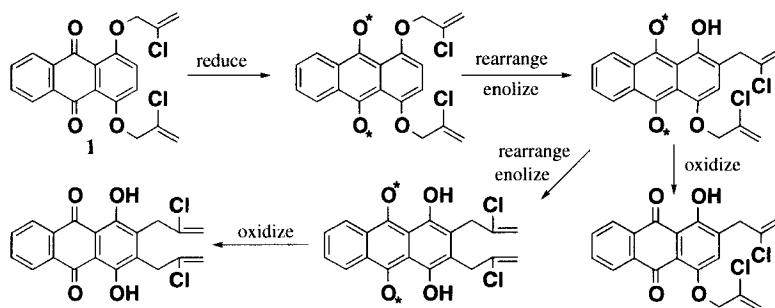
Rearrangements promoted by bisulfite proceed more rapidly and less cleanly when the reductant is added to a preheated solution of the ether. They also proceed with catalytic proportions of the reductant. The parallels between metabisulfite-promoted rearrangement and early rearrangements suggested that metabisulfite may be able to effect rearrangement without demethoxylation, a side-reaction which was a feature of early rearrangement studies. In the event, metabisulfite effected clean rearrangement of the 4-methoxychloroallyloxyanthraquinone (**7**) in 98% yield (Scheme 4) without demethoxylation, in contrast to the extensive demethoxylation caused by sodium dithionite.



Scheme 4

II. MECHANISTIC CONSIDERATIONS

To date, a simple scheme has been used to account for products identified from reductive Claisen rearrangements of substrates such as 1,4-bis(2-chloro-2-propenyl)-9,10-anthraquinone (**1**) (*Scheme 5; in this Scheme and subsequent ones, asterisks indicate unknown state of reduction*). It was proposed that the quinone was reduced to a semiquinone or hydroquinone, which rearranged and enolized to give the singly rearranged compound in a reduced state. This initial product was either oxidized, to give the singly rearranged product, or rearranged a second time before being oxidized, to give the doubly rearranged product. Deallylated and furanized products were accounted for by standard chemistry.



Scheme 5

Activation of 1,4-bis(2-chloro-2-propenyl)-9,10-anthraquinone (**1**) is required for rearrangement. Rearrangement is not spontaneous in neutral or acidic dimethylformamide-water mixtures, and even when activated, allyl ethers still require heating to effect rearrangement. For example, in two literature syntheses, anthraquinone allyl ethers were reduced to their hydroquinone states without rearrangement. Hauser was able to hydroxymethylate an anthraquinone allyl ether by a Marschalk reaction¹² and Baldwin was successful in reductively methylating an anthraquinone allyl ether.³⁶ Nevertheless, it has been indicated that rearrangement of reduced allyloxyanthraquinones can occur at temperatures as low as 50°.³⁷

However, it is difficult to account for some results by the reaction scheme proposed above. One of the most difficult of these results is the widely varying rates of reaction that are observed. Some reactions clearly indicate that Claisen rearrangement of activated allyloxyanthraquinone is very rapid, while other reactions proceed much more slowly. Several factors could account for these differing rates, *viz.* reduction of the quinone to different oxidation states, the effects of pH, or catalysis, each of which is considered below.

III. REDUCTION OF THE QUINONE

Anthraquinones have three important oxidation states, *viz.* the quinone, semiquinone, and hydroquinone, and it could be that they have different propensities for rearrangement. The predominant state formed on reduction depends upon the reductant, the pH, and the solvent system.

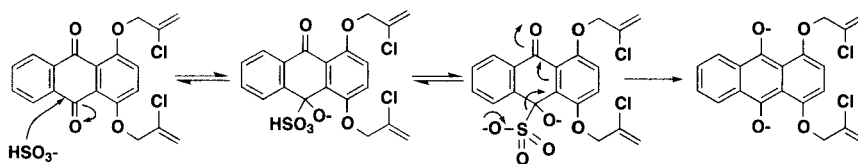
Although dithionite can act as a one- or two-electron reductant,³⁸⁻⁴⁰ it is in equilibrium with the sulfur dioxide radical anion (sulfoxylate radical anion) (Eq. 6), which is usually the reductant



when dithionite is present.⁴⁰ For example, the rate of autoxidation of dithionite is half-order with respect to the concentration of dithionite.^{28,40} Even when a substrate can be reduced by dithionite, the rate of this reduction is often several orders of magnitude lower than the rate of reduction by sulfur dioxide radical anion^{38,39} despite the fact that, at room temperature in water, the equilibrium is strongly in favor of dithionite ($K = 1.4 \times 10^{-9} \text{ molL}^{-1}$, $k_{\text{forward}} = 1.7 \text{ s}^{-1}$).⁴⁰ Sulfur dioxide radical anion is a one electron reductant. The sulfur dioxide formed upon the loss of an electron reacts with water to give bisulfite and a free proton (Eqs. 7 and 8.)

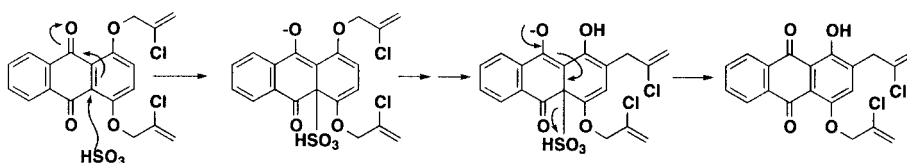


Bisulfite does not appear to have been used as a reductant for anthraquinones. However, it can form addition complexes with ketones (and quinones),^{35b} so that a possible transfer of electrons is from such a complex (Scheme 6).



Scheme 6

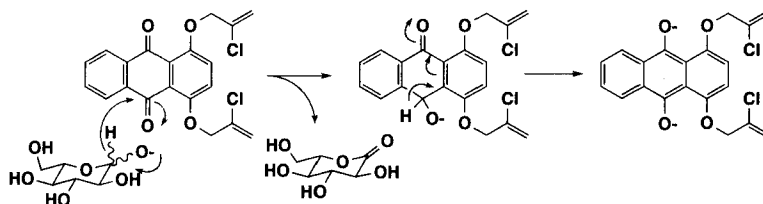
Bisulfite does not necessarily have to reduce the quinone to effect an activation that could allow the chloroallyl groups to rearrange. Bisulfite can add to aromatic systems (Bücherer reaction) and to the double bonds of benzo- and naphtho-quinones.^{35b} If bisulfite could add to the aromatic ring of an allyloxyanthraquinone, it could activate the system to Claisen rearrangement without actually reducing the quinone (Scheme 7).



Scheme 7

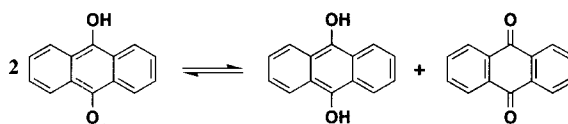
The reduction of anthraquinones by glucose probably occurs by a crossed Cannizzaro reaction. The Cannizzaro reaction can proceed through transfer of hydride from the mono- or dianion of an aldehyde hydrate to a carbonyl acceptor^{5b} or through a single electron transfer mechanism.⁴¹ In the case of glucose, it is probably the pyranose form rather than an aldehyde hydrate which is the acti-

vated intermediate; deprotonation of the anomeric hydroxyl group would give an intermediate which could transfer hydride ion (Scheme 8). The Cannizzaro reaction requires basic conditions and indeed Hocking found that base was required to reduce anthraquinone with glucose.^{32,33}



Scheme 8

The pH obviously affects the protonation state of the quinone or reduced quinone, but also has more subtle effects. The semiquinone form of an anthraquinone is in equilibrium with the quinone and hydroquinone (Scheme 9). Under acidic conditions, the semiquinone is unstable with respect to the hydroquinone and quinone and therefore disproportionates. Under basic conditions, the semiquinone is stable, and it can form from conproportionation of the quinone and hydroquinone. This is a consequence of the effect of the pH upon the protonation state altering the relative energies of the first and second reduction potentials of the quinone.⁴²



Scheme 9

The solvent can also affect the equilibrium between semiquinone, hydroquinone, and quinone. For example, while the semiquinones of anthracyclinones disproportionate rapidly in water, they become quite stable in aqueous dimethyl sulfoxide or dimethylformamide.

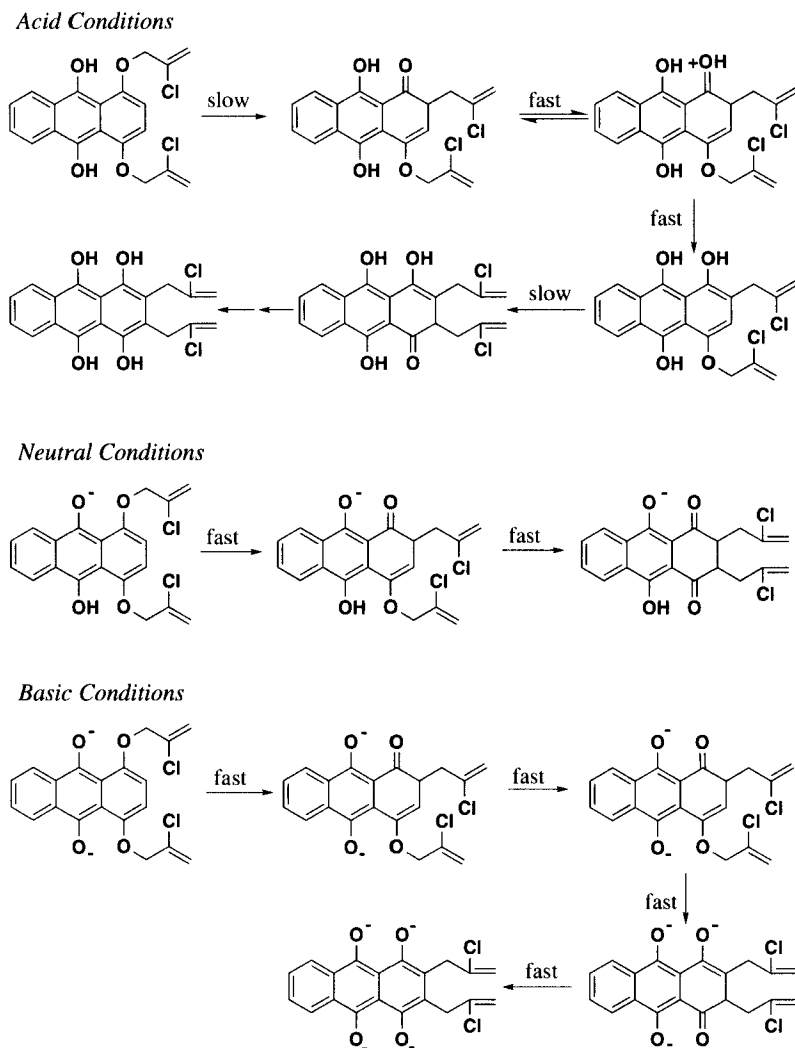
Even when the conditions are well controlled, it is difficult to predict the active or even predominant state of the anthraquinone without additional experiments. Indeed, it may be that more than one oxidation state is occupied. Thus, it would be difficult to determine effects of the oxidation state upon the rate of rearrangement.

IV. EFFECTS OF pH

Notwithstanding the effects that it has upon reduction potentials, the pH appears to affect the rate of rearrangement: acidic conditions inhibit rearrangement and basic conditions accelerate it. Reactions of *bis*(chloroallyloxy)anthraquinone in the presence of base proceed rapidly to give the doubly rearranged product. Similarly, reactions in which neither acid nor base is added also produce doubly rearranged products, albeit in reduced form. However, reactions to which acid is added proceed more slowly.

A reasonable explanation for these differences in rates is that rearrangement is faster when the phenolic groups of the reduced anthraquinone are deprotonated. Indeed, there is a growing body of knowledge indicating that Claisen rearrangements are accelerated by π -electron-donating groups and especially by anions.^{4,43-51} Although the most recent studies utilizing this anion-accelerating effect are for aliphatic Claisen rearrangements, the earliest examples were for aromatic Claisen rearrangements.^{43,48}

With this explanation, mechanisms can be proposed for the sequences of rearrangement and enolization or enolate formation processes that occur under the various conditions used (*Scheme 10*).



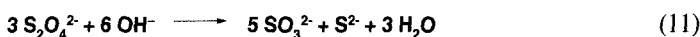
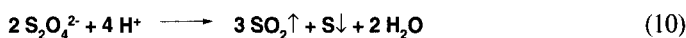
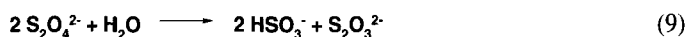
Scheme 10

However, the variations in rate observed in changing from basic to acidic conditions do not span the range of rates observed, so that a further explanation of the rate differences is required.

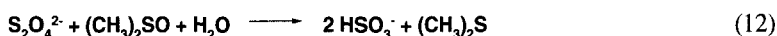
V. CATALYSIS

Rearrangement can be induced by a catalytic amount of reductant. The existence of a catalytic pathway is especially important in the light of the decomposition of dithionite, a process which means that less than a stoichiometric proportion of reductant can often be present. Moreover, sodium dithionite is not the only reductant which is rendered ineffective by some of the conditions that are used.

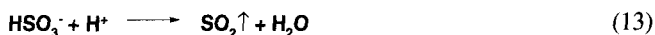
The disproportionation of dithionite (*Eq. 9*) is more rapid in solution than for the hydrate, and is further accelerated by heat or acid. Additionally, in acidic solution, the products of dithionite disproportionation, namely bisulfite and thiosulfate, are also unstable so that the overall decomposition of dithionite in acidic media produces sulfur dioxide and sulfur (*Eq. 10*). Dithionite is also unstable under strongly basic conditions, undergoing a different disproportionation to give sulfite and sulfide (*Eq. 11*) (dithionite has $pK_{a1} = 0.4$ and $pK_{a2} = 2.5$).²⁸



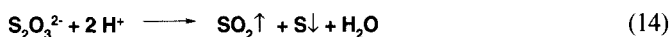
It has also been noted that dithionite decomposes when in contact with dimethyl sulfoxide.²⁷ Although the reaction was not specified, it could well involve the reduction of dimethyl sulfoxide by dithionite (*Eq. 12*). This reaction is important in view of Hauser's solution to the problem of demethoxylation during reductive Claisen rearrangements by use of dimethyl sulfoxide as solvent.⁵² In this case, the dithionite is probably converted into bisulfite, which then becomes the actual promoter of rearrangement.



Bisulfite is removed from solution by acidification. An acidified solution of bisulfite gives off sulfur dioxide (*Eq. 13*) in a similar fashion to the expulsion of carbon dioxide from acidified bicarbonate solutions (sulfite has $pK_{a1} = 1.9$ and $pK_{a2} = 7.2$).

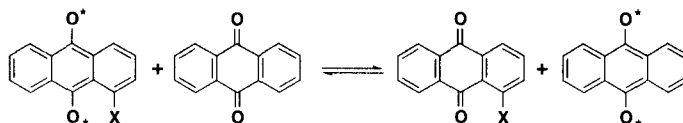


One of the disproportionation products of dithionite is thiosulfate which is a weaker reductant than bisulfite. Its action as a reductant in the reductive Claisen rearrangement has not been investigated, but it is important to note that in acidic solution thiosulfate decomposes to sulfur dioxide and sulfur (*Eq. 14*), so that bisulfite could become the major reductant.



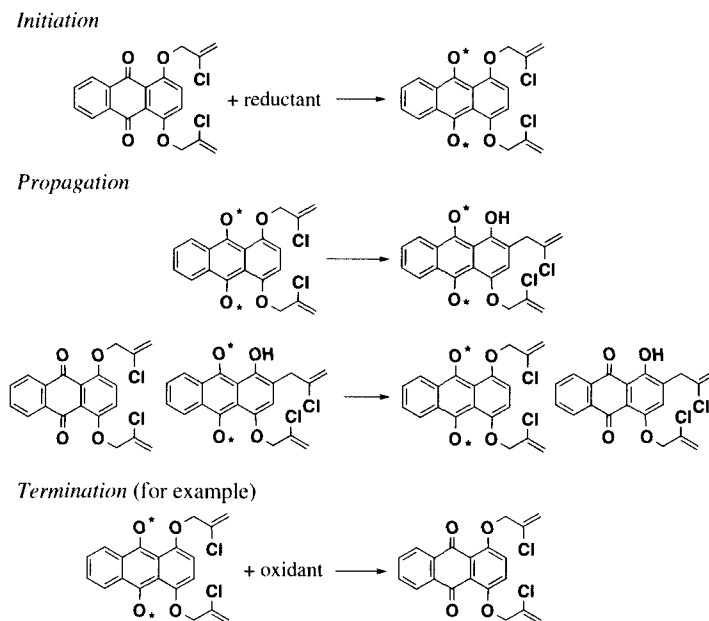
Once a quinone has been reduced, oxygen can consume reductant. Autoxidation probably proceeds in single electron steps, since semiquinones are produced when solutions of anthrahydroquinone are exposed to oxygen.

It eventuates that it is possible for a reductant to catalyze Claisen rearrangements since, in solution, there is often a rapid transfer of electrons between reduced and non-reduced quinones (*Scheme 11*). This transfer of electrons suggests a mechanism for catalytic rearrangement of an allyloxanthraquinone: initiation could proceed by reduction of the quinone, and propagation by



Scheme 11

rearrangement and then transfer of the electrons to an unrearranged anthraquinone. Termination could occur by oxidation of a reduced anthraquinone (*Scheme 12*). This proposed catalytic cycle readily accounts for the return of oxidized products from reductive rearrangements, the widely varying rates of reaction, and the highly selective rearrangement of *bis*(allyloxy)anthraquinones.

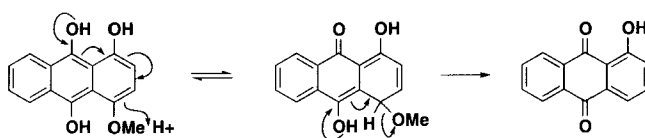


Scheme 12

Selective rearrangement is a consequence of the non-random transfer of electrons amongst anthraquinones. Electrons will be transferred to the most easily reduced substrate. The ease with which an anthraquinone can be reduced depends upon the substituents. Electron-donating substituents

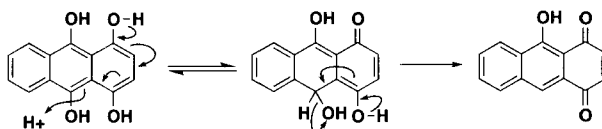
make the quinone more difficult to reduce while electron-withdrawing substituents facilitate reduction.^{53,54} Thus, transfer of electrons from the rearranged anthraquinone to the starting material, which has fewer electron-donating groups, is favored. It appears that electron transfer is faster than rearrangement, so that none of the singly rearranged material is activated for a second rearrangement until all of the starting material has been consumed.

Because rearrangement can progress without consuming reductant, it becomes important to classify reactions as reductant consuming, reductant conserving, or independent of reductant to determine whether or not they will proceed with the quantity of reductant present. Loss of a leaving group from an anthraquinone is a reductant-consuming process. For example, when a methoxy group is lost from an anthraquinone in the hydroquinone state, the final product is a quinone even though there is no external oxidant. This accounts for the observation that rearrangement of an anthraquinone can occur with (stoichiometric reductant) or without (catalytic reductant) demethoxylation (*Scheme 13*).



Scheme 13

A deoxygenation observed recently⁵⁵ is similarly a reductant-consuming process (*Scheme 14*).



Scheme 14

The formation of products in which an allyl group appears at a position which originally was a quinone carbonyl⁵⁵ is also reductant-consuming, regardless of whether the allyl group is transferred inter- or intramolecularly. Similarly, the formation of *leuco* products⁵⁵ is reductant-consuming, although in this case tautomerization can return compounds that are able to transfer electrons.

Formation of furans and deallylation can occur independently of whether the quinone is reduced. However, deallylation may also occur by reductant-consuming pathways.

CONCLUSION

The original scheme for reductive Claisen rearrangement has to be replaced by one involving a complex set of competitive processes where the final product distribution is determined by the balance between these processes which is established by the conditions.

It is now known that the quinone has to be activated for rearrangement to occur. However, in competition with the activation of the quinone are processes that destroy reductant or deactivate the quinone. Whether deactivation or activation is favored is determined by the conditions. For example,

the temperature at which a reductant is added to a reaction can determine whether the quinone is reduced or the reductant is destroyed. A significant variable is the pH of the reaction medium, to which several important effects can be attributed: basic conditions accelerate rearrangements, allow rapid autoxidation, improve stability and effectiveness of reductants, and accelerate the formation of furans from chloroallyl side-chains; acidic conditions diminish the effectiveness of reductants and inhibit rearrangements, autoxidation, and furan formation.

Recent work has indicated that reductively promoted rearrangements proceed much more rapidly and at much lower temperatures than has previously been suggested. However, perhaps the most important feature of the reductive Claisen rearrangement is that reductants are required only catalytically to effect rearrangement. Indeed, it is likely that it is the catalytic nature of the reaction which allows highly selective single rearrangement. Moreover, because rearrangement is induced by a catalytic amount of reductant, it can occur without processes that require a stoichiometric measure of reductant. Demethoxylation is one of the more important process requiring a stoichiometric amount of the reductant, and cases have been observed where rearrangement occurs with or without demethoxylation. It should also be noted that, in addition to requiring a stoichiometric measure of reductant, demethoxylation is slower than oxidation by oxygen, dimethyl sulfoxide, or another quinone and only becomes the favored process when these other processes cannot occur.

Although sodium metabisulfite is now the reagent of choice for effecting Claisen rearrangement because it is stable and gives reproducible results, many questions about its method of action and synthetic scope remain unanswered. For example, it is not known whether or not the addition of acid merely provides a convenient method of generating a catalytic amount of reductant. Also, it is not clear how anthraquinones are activated by bisulfite or whether bisulfite addition complexes can be found. Other unanswered questions are: can reduced anthraquinones be found? Is heating required? Can bisulfite remove a methoxy group? What effects upon rate and product distribution do basic conditions cause?

The scope for removal of a methoxy group by metabisulfite is a particularly pertinent question. A comparison of the rapid dithionite-promoted demethoxylation with slow demethoxylation observed previously suggests that the latter could have been promoted by bisulfite. Demethoxylation by metabisulfite will probably require the use of neutral or basic conditions to prevent the loss of sulfur dioxide before reduction occurs.

VII. TABULAR SURVEY

The existing work has been divided into three tables, which cover thermally induced rearrangements, dithionite induced rearrangements, and rearrangements induced by other reagents. Within each table, substrates are arranged in order of: the number of rearranged allyloxy groups (all mono-allyloxy before all *bis*-allyloxy; there are no compounds with three or more); position of rearranged allyloxy groups (all 1-allyloxy before all 2-allyloxy); rearranging allyl substituents in order of location and then alphabetically (for example, 1-methyl, 2-chloro, 2-methyl...); and

substituents on the anthraquinone in order of location and then alphabetically.

If a reference gives more than one set of reaction conditions, a range of conditions or those conditions for which the expected product predominates are given. The highest yield of each product is given, but if the highest yield was not obtained for the given conditions, it is indicated by an asterisk (*). Note that even if starting material was recovered, it is not included in the products. The following abbreviations are used: n.r. = no reaction, n.a. = not available; yield or conditions not reported, — = none of the expected product was observed.

For thermal rearrangements, boiling points are: decalin 189-191°, *o*-dichlorobenzene (DCB) 179-180°, *N,N*-diethylaniline 217°, benzylamine 184-185°. Unless noted, reductive rearrangements were performed at reflux in dimethylformamide-water (bp. 105°).

TABLE 1. Thermal Claisen Rearrangements

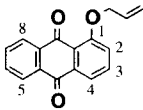
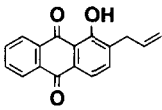
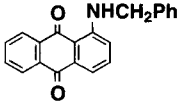
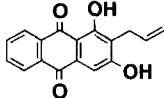
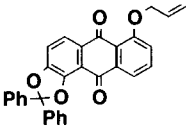
Starting Material	Conditions	Expected Products (%)	Other Products (%)	Ref
				
unsubstituted	sealed tube, 180°, 12 h	70		(9)
unsubstituted	diethylaniline, 185°, 6 h	62		(56)
unsubstituted	<i>o</i> -xylene, 5% PhCH ₂ NH ₂ , 150°, 4 h	88*	 trace*	(9)
3-carbomethoxy-methyl-8-methoxy	<i>o</i> -DCB, reflux	85-90		(57)
3-hydroxy-methyl-8-methoxy	n.a.	96		(58)
3-methoxy	<i>o</i> -DCB, reflux, 16 h	76		(59)
3-(tetrahydropyran-2-yloxy)	<i>o</i> -DCB, reflux, 15 h	—	 81	(59)
4,5-dimethoxy	n.a.	"good"		(60)
5-hydroxy-6-(2-propenyl)	<i>o</i> -DCB, reflux, 20 h	51	deallylated; trace	(10)
	<i>o</i> -DCB, dimethylaniline, reflux, 4.5 h	66*	deallylated; 19*	(61)
8-methoxy	diethylbenzylamine, 200°, 4 h	57	deallylated; 20	(62)

TABLE I continued... Thermal Claisen Rearrangements

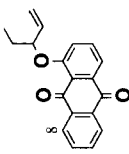
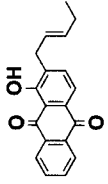
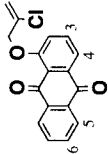
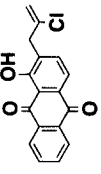
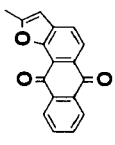
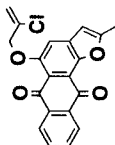
Starting Material	Conditions	Expected Products (%)	Other Products (%)	Ref
 8-methoxy	dimethylamine, 170°, 1 h	 85		(37)
 unsubstituted	<i>o</i> -DCB, reflux, 48 h	 55	deallylated; 13 deallylated; 7	(7)
unsubstituted	diethylamine, acetic anhydride, 200°, 6 h	42	 7	(7)
3-(2-chloro-2-propenyl)-4-hydroxy	<i>o</i> -DCB, reflux, 40 h	9	de- <i>O</i> -allylated; 45 doubly deallylated; 2	(63)
5-hydroxy-6-(2-chloro-2-propenyl)	<i>o</i> -DCB, reflux, 20 h	44		(10)
 <i>o</i> -DCB, reflux, 6.5 h		85		(7)

TABLE 1 continued... Thermal Claisen Rearrangements

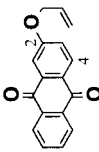
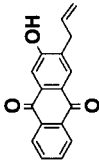
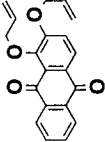
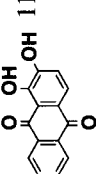
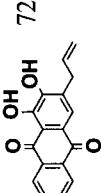
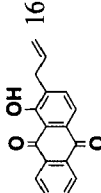
Starting Material	Conditions	Expected Products (%)	Other Products (%)	Ref
	unsubstituted sealed tube, 240°, 96 h			(9)
4-hydroxy	46 h	n.r. "good"		(59)
				
unsubstituted	decalin, reflux	—	  	(64) 72 16

TABLE 1 continued... Thermal Claisen Rearrangements

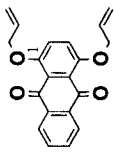
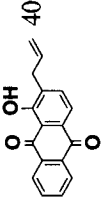
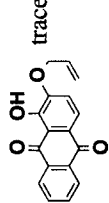
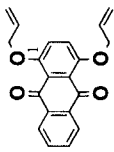
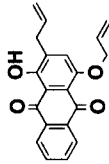
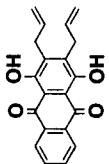
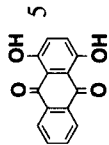
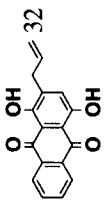
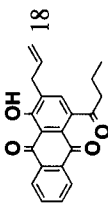
Starting Material	Conditions	Expected Products (%)	Other Products (%)	Ref
 unsubstituted	<i>o</i> -xylene, reflux, 96 h (with or without 5% PhCH ₂ NH ₂)	—	 40 (9)  trace (65)	
 unsubstituted	<i>o</i> -DCB, reflux, 25 h	 —  14	 5 (7)  32 (66)  18	

TABLE 1 continued... Thermal Claisen Rearrangements

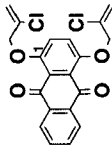
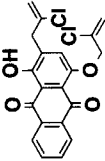
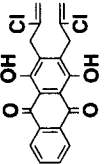
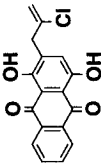
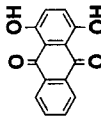
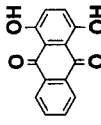
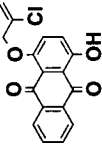
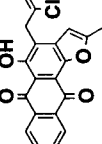
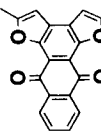
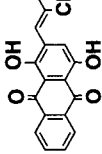
Starting Material	Conditions	Expected Products (%)	Other Products (%)	Ref
				(7)
unsubstituted	<i>o</i> -DCB, reflux, 20-60 h	56		21* (7)
		16*		3*
				6*
unsubstituted	<i>o</i> -xylene, 10% PhCH ₂ NH ₂ , reflux, 60 h	—		40 (9)
		—		15
		—		5

TABLE I continued... Thermal Claisen Rearrangements

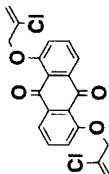
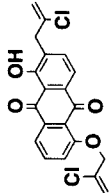
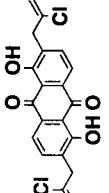
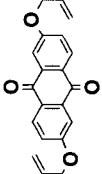
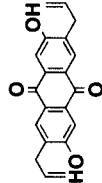
Starting Material	Conditions	Expected Products (%)	Other Products (%)	Ref
 unsubstituted	<i>o</i> -DCB, reflux 20 h	 56  20		(10)
 unsubstituted	sealed tube, 240°, 96 h	 n.r.		(9)

TABLE 2. Claisen Rearrangements Promoted by Dithionite

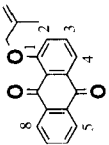
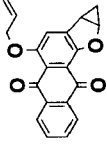
Starting Material	Conditions	Expected Products (%)	Other Products (%)	Ref
				
unsubstituted	reflux, 0.6 h	100		(8)
3-(2-chloro-2-propenyl)-4-methoxy	85-90°, 100 min	83		(67)
(4 <i>R</i> ,6 <i>R</i>)-3-(4',6'-dimethyl-1,3-dioxan-2-yl)-4-methoxy	NaHCO ₃ , reflux, 1 h	87		(68)
(4 <i>R</i> ,5 <i>R</i>)-3-(4',5'-dimethyl-1,3-dioxolan-2-yl)-4-methoxy	NaHCO ₃ , reflux, 2.5 h	87		(68)
3-(1-propenyl)-4-methoxy	reflux, 1.5 h	36*	4-demethoxy; 16*	(69)
3-(1-propenyl)-4-methoxy	(i) 90-95° 1 h (ii) reflux, 50 min	95		(70)
3-(2-propenyl)-4-methoxy(6 <i>R</i>)-3-(4',4',6'-trimethyl-1,3-dioxan-2-yl)-4-methoxy	NaHCO ₃ , reflux, 1.5 h reflux, 25 min	97		(69)
	reflux, 25 min	53*	4-demethoxy; 5*	(71)
	(i) NaHCO ₃ , 80° 3 h (ii) air, 30 min	6		(72)
4-benzyl-6-(2-propenyl)anthraquinone	80-90°, 50 min	88		(68)
5-hydroxy-4-benzyl-6-(2-propenyl)anthraquinone	reflux, 4 h	96		(73)
5-methoxy-6-(2-propenyl)anthraquinone	reflux, 25 min	100		(72)

TABLE 2 continued... Claisen Rearrangements Promoted by Dithionite

Starting Material	Conditions	Expected Products (%)	Other Products (%)	Ref
	reflux, 4 h	17	deallylated: 20	(61)
8-methoxy	(i) NaOH, 70°, 2 h (ii) O ₂ , 30 min	64		(74)
8-methoxy	90°	64	48* 	(75)
			21*	
4-hydroxy	70°	—	63 	(76)

TABLE 2. continued... Claisen Rearrangements Promoted by Dithionite

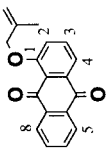
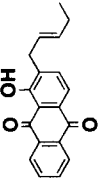
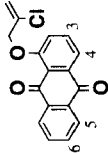
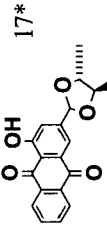
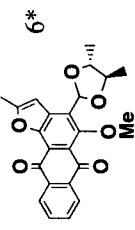
Starting Material	Conditions	Expected Products (%)	Other Products (%)	Ref
 8-methoxy	(i) 50-70°, 1-2 h, (ii) air, r.t. 1 h	 87-90		(37) (77)
 unsubstituted	reflux, 2 h	78		(8)
3-(2-chloro-2-propenyl)-4-methoxy	reflux, 3 h	80		(78)
3-(2-chloro-2-propenyl)-4-methoxy	reflux, 15 min	14		(55)
(4 <i>R</i> ,5 <i>R</i>)-3-(4',5'-dimethyl-1,3-dioxolan-2-yl)-4-methoxy	75°-reflux 1.5-4.5 h NaHCO ₃ some in DMSO-H ₂ O	52*	 17*	(16)
			 6*	

TABLE 2. continued... Claisen Rearrangements Promoted by Dithionite

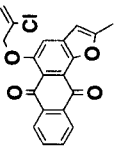
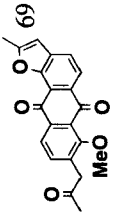
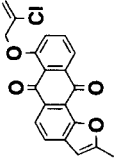
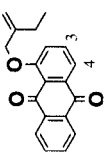
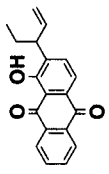
Starting Material	Conditions	Expected Products (%)	Other Products (%)	Ref
3-(1-propenyl)-4-methoxy	90-100°, 3 h	87		(67)
3-(4',6'-trimethyl-1,3-dioxan-2-yl)-4-methoxy	reflux, 4 h, NaHCO ₃	47*		(18)
	reflux, 2 h	94		(8)
4-methoxy	reflux, 2 h	95		(79)
5-methoxy-6-(2-chloro-2-propenyl)	(i) reflux, 2 h, (ii) KOH reflux 1.5 h (iii) HCl r.t. overnight	—		(80)
	reflux, 2.5 h	98		(10)
	(i) DMSO-H ₂ O 100° 1 h (ii) O ₂ , 15-20 min		86	(12)
3-hydroxymethyl-4-methoxy	(i) 100°, 1.5 h (ii) O ₂ , 15 min	—	4-demethoxy; 86	(12)
3-hydroxymethyl-5-methoxy	(i) 100°, 1.5 h (ii) O ₂ , 0.5 h	96		(81)

TABLE 2. continued... Claisen Rearrangements Promoted by Dithionite

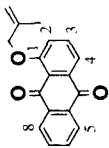
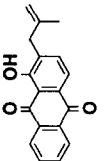
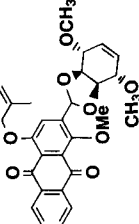
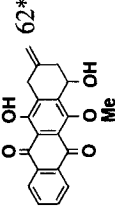
Starting Material	Conditions	Expected Products (%)	Other Products (%)	Ref
				
unsubstituted	reflux, 2 h	92		(8)
3-dimethoxymethyl-4-methoxy		46*		(19)
	NaOH or NaHCO ₃ 90°-reflux, 3-4.5 h some in DMSO-H ₂ O	54*	4-demethoxy; 73*	(17)
(4' <i>R</i> ,6' <i>R</i>)-3-(4',6'-dimethyl-1,3-dioxan-2-yl)-4-methoxy		91	4-demethoxy; <1	(82)
(4' <i>R</i> ,6' <i>R</i>)-3-(4',6'-dimethyl-1,3-dioxan-2-yl)-4-methoxy		35*	4-demethoxy; 66*	(19)
(4' <i>R</i> ,5' <i>R</i>)-3-(4',5'-dimethyl-1,3-dioxolan-2-yl)-4-methoxy	reflux, 1 h	95		(69)
(4' <i>R</i> ,5' <i>R</i>)-3-(4',5'-dimethyl-1,3-dioxolan-2-yl)-4-methoxy	NaHCO ₃ , 80°-reflux, 0.3-4 h some in DMSO-H ₂ O	95*	4-demethoxy; 49*	(16)
(1,3-dioxolan-2-yl)-4-methoxy	NaHCO ₃ , reflux, 3 h	91*	4-demethoxy; 20*	(20)
3-formyl-4-methoxy		46*		62* (13) (19) (20)

TABLE 2. continued... Claisen Rearrangements Promoted by Dithionite

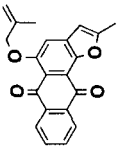
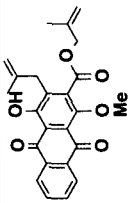
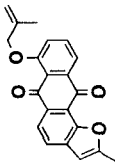
Starting Material	Conditions	Expected Products (%)	Other Products (%)	Ref
	reflux, 0.3 h	92	 4*	(8)
3-hydroxymethyl-5-methoxy-6-(2-methyl-1-propenyl)-5-methoxy	reflux	94		(83)
5-methoxy-6-(2-methyl-1-propenyl)	reflux, 2 h	94		(84)
5-methoxy-6-(2-methyl-1-propenyl)	reflux, 1.75 h	83		(85)
5-methoxy-6-(2-methyl-2-propenyl)	reflux, 1 h	86		(85)
	reflux, 5.7 h	87		(85)

TABLE 2. continued... Claisen Rearrangements Promoted by Dithionite

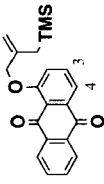
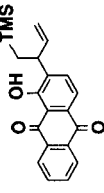
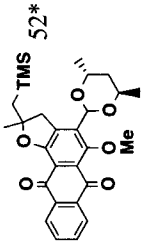
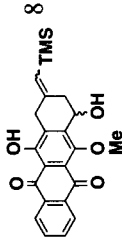
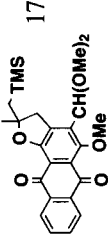
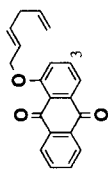
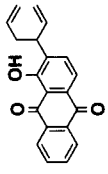
Starting Material	Conditions	Expected Products (%)	Other Products (%)	Ref
 (4 <i>R</i> ,6' <i>R</i>)-3-(4',6'-dimethyl-1,3-dioxan-2-yl)-4-methoxy		 83	4-demethoxy; 29  52*	(19)
3-formyl-4-methoxy		—	 8	(19)
3-dimethoxymethyl-4-methoxy	65-70° 60 min	—	4-demethoxy; 42  17	(19)
 3-(methoxymethoxy)	(i) 70°, 1 h (ii) air, 1 h	 86		(86)

TABLE 2. continued... Claisen Rearrangements Promoted by Dithionite

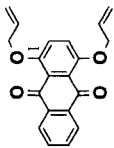
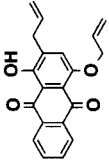
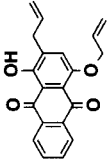
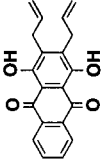
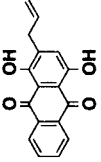
Starting Material	Conditions	Expected Products (%)	Other Products (%)	Ref
				
unsubstituted	0-4 eq. NaOH, reflux, 1-7 h	32* 	72* 	(8) 38*
unsubstituted	60-70°, 1.5 h	88	7	(69) <1
unsubstituted 3-(1,3-dioxolan-2-yl)	H ₂ SO ₄ , reflux, 30 min NaOH, reflux, 1 h	98	—	(87) mixture of both expected and product (65) below, 41% 

TABLE 2. continued... Claisen Rearrangements Promoted by Dithionite

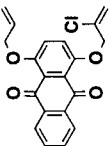
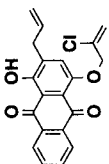
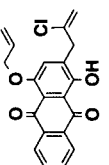
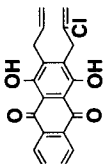
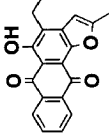
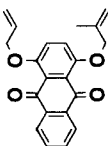
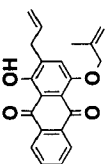
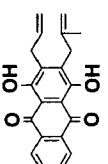
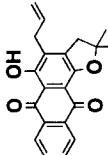
Starting Material	Conditions	Expected Products (%)	Other Products (%)	Ref
	unsubstituted NaHCO_3 60°-reflux 2.5 to 9 h	 49*  31*  30*	 15* (67)	
	unsubstituted 0-4 eq. NaOH, reflux 1-1.5 h	 < 4*  25*	 14* (67)	

TABLE 2. continued... Claisen Rearrangements Promoted by Dithionite

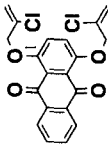
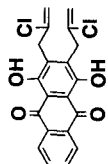
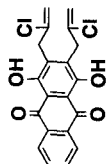
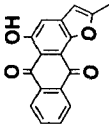
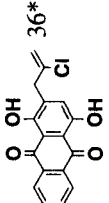
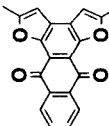
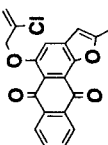
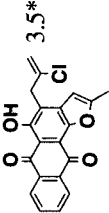
Starting Material	Conditions	Expected Products (%)	Other Products (%)	Ref
 unsubstituted	reflux 2.5 h	 96	 —	(8)
unsubstituted	0-10 eq. NaOH reflux 1-5 h	—	 33*	(8)
			 36*	
			 46	
			 3*	
			 3.5*	
unsubstituted	reflux 2 or 3 h	—	79	(14)

TABLE 2. continued... Claisen Rearrangements Promoted by Dithionite

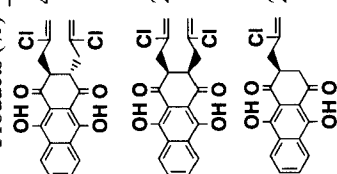
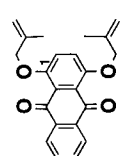
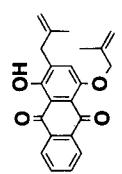
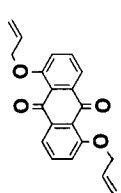
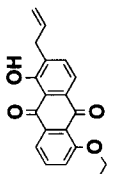
Starting Material	Conditions	Expected Products (%)	Other Products (%)	Ref
unsubstituted	65°, 5 min	—		42 (55) 20 20
	unsubstituted	92		(20)
	unsubstituted	90		(88)
unsubstituted	reflux, 1.75 h	—	—	(88)
unsubstituted	reflux, 6.5 h	—	89	(88)
unsubstituted	reflux, 2.5 h	56	26	(10)

TABLE 2. continued... Claisen Rearrangements Promoted by Dithionite

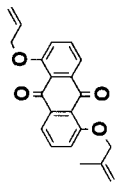
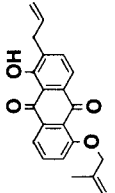
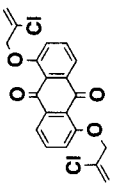
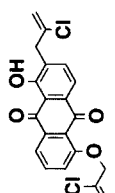
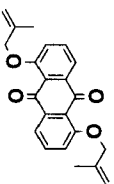
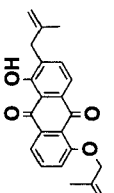
Starting Material	Conditions	Expected Products (%)	Other Products (%)	Ref
	unsubstituted	 89	—	(67)
	(i) reflux, 3 h (ii) NaOH, reflux 0.75 h	—	—	
	unsubstituted	 97	—	(10)
unsubstituted	reflux, 2.5 h	—	—	(10)
	reflux, 8 h	94	—	
	unsubstituted	 87	—	(85)
unsubstituted	reflux, 1.33 h	—	—	(85)
	reflux, 3 h	90	—	

TABLE 3. Claisen Rearrangements Promoted by Reductants Other than Dithionite

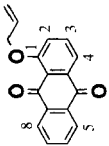
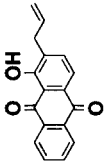
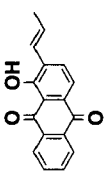
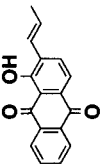
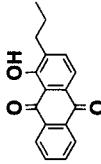
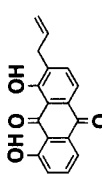
Starting Material	Conditions	Expected Products (%)	Other Products (%)	Ref
				
unsubstituted	2.5-3.0 eq. glucose, DMF, 125°, 8 h	65		7 (15)
unsubstituted	2.5 eq. glucose, DMF, 100°, 30 min, 2.5 eq. aq. NaHCO ₃			mixture of expected plus two products below, 50%
				
				
8-acetoxy	2.5-3.0 eq. glucose, DMF, 100°, 6 h	—		

TABLE 3. continued... Claisen Rearrangements Promoted by Reductants Other than Dithionite

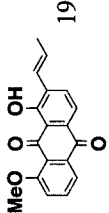
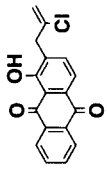
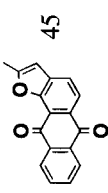
Starting Material	Conditions	Expected Products (%)	Other Products (%)	Ref
8-methoxy	2.5-3.0 eq. glucose, DMF, 125°, 20 h	46	 19	(15)
8-methoxy	2.5 eq. glucose, DMF, 100°, 30 min, 2.5 eq. aq. NaHCO ₃	60	 5	(15)
unsubstituted	2.5-3.0 eq. glucose, DMF, 130°, 15 h	5	 45	(15)
3-(2-chloro-2-propenyl)-4-methoxy	Na ₂ S ₂ O ₅ ; 30 min	98		(55)

TABLE 3. continued... Claisen Rearrangements Promoted by Reductants Other than Dithionite

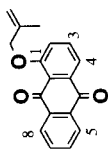
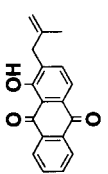
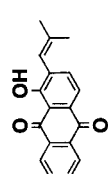
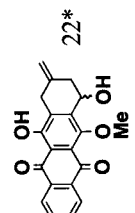
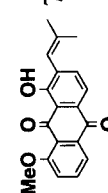
Starting Material	Conditions	Expected Products (%)	Other Products (%)	Ref
				
unsubstituted	2.5-3.0 eq. glucose, DMF, 125°, 12 h	46		(15) 19
unsubstituted	2.5 eq. glucose, DMF, 100°, 30 min, 2.5 eq. aq. NaHCO ₃	55		(15)
3-(1,2-dihydroxy-propyl)-4-methoxy	2 eq. Na ₂ S ₂ O ₅ , reflux, 30 min	86		(89)
(4 <i>R</i> ,6 <i>R</i>)-3-(4,6'-dimethyl-1,3-dioxan-2-yl)-4-methoxy	2 eq. Na ₂ S ₂ O ₅ , reflux, 1.7 h	93		(19)
3-formyl-4-methoxy	2 eq. Na ₂ S ₂ O ₅ , reflux, 1.7 h	39*		(19) 22*
5-methoxy	Zn, HOAc-toluene 10:1, reflux	80		(36)
8-methoxy	2.5-3.0 eq. glucose, DMF, 125°, 24 h	63		7 (15)

TABLE 3. continued... Claisen Rearrangements Promoted by Reductants Other than Dithionite

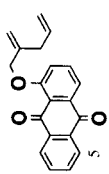
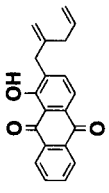
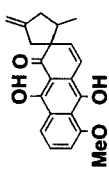
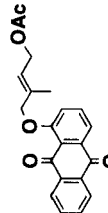
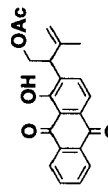
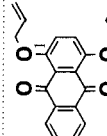
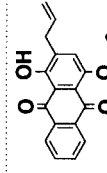
Starting Material	Conditions	Expected Products (%)	Other Products (%)	Ref
 5-methoxy	Zn, HOAc-toluene 10:1 reflux, 0.25-3 h	 97*	 34*	(36)
 unsubstituted	2.5-3.0 eq. glucose, DMF, 120°, 5 h	 83		(15)
 unsubstituted	2 eq. Na ₂ S ₂ O ₅ , reflux, 20 min	 96	—	(19)

TABLE 3. continued... Claisen Rearrangements Promoted by Reductants Other than Dithionite

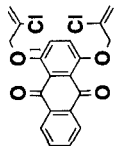
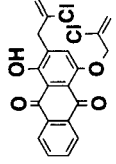
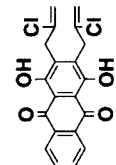
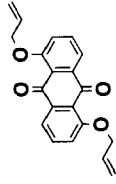
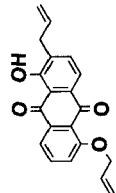
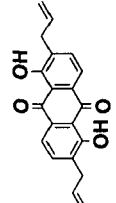
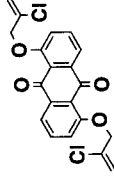
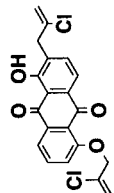
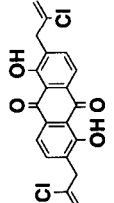
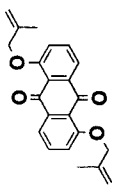
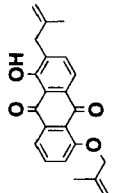
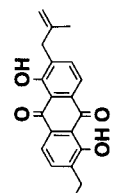
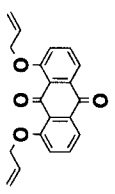
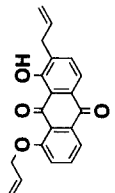
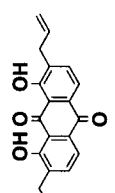
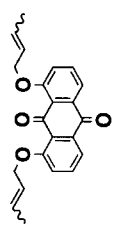
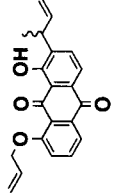
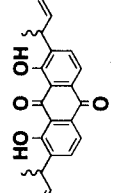
Starting Material	Conditions	Expected Products (%)	Other Products (%)	Ref
 unsubstituted	1.4 eq. Na ₂ S ₂ O ₅ 1.4 eq. H ₂ SO ₄ , reflux, 25 min	 95	 —	(55)
unsubstituted	1.4 eq. Na ₂ S ₂ O ₅ 1.4 eq. H ₂ SO ₄ , reflux, 4 h	—	90	(55)
 unsubstituted	2 eq. Na ₂ S ₂ O ₅ , reflux, 50 min	 91	 —	(90)
 unsubstituted	2 eq. Na ₂ S ₂ O ₅ reflux, 50 min	 96	 —	(90)

TABLE 3. continued... Claisen Rearrangements Promoted by Reductants Other than Dithionite

Starting Material	Conditions	Expected Products (%)	Other Products (%)	Ref
 unsubstituted	2 eq. Na ₂ S ₂ O ₃ , 70°	 86	 —	(90)
 unsubstituted	2 eq. Na ₂ S ₂ O ₃ , reflux	 53	 —	(91)
 unsubstituted	2 eq. Na ₂ S ₂ O ₃ , reflux	 67	 5	(92)

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