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APPLICATIONS OF FREE RADICAL REACTIONS IN HETEROCYCLIC CHEMISTRY

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Dedicated to Professor T.R. Govindachari on the occasion of his 60th birthday

Organic oxygen and nitrogen free radicals are easily generated and can be used for the preparation of heterocyclic systems. In the present review, the application of such intramolecular as well as intermolecular radical reactions to the synthesis of various polycyclic compounds is discussed.

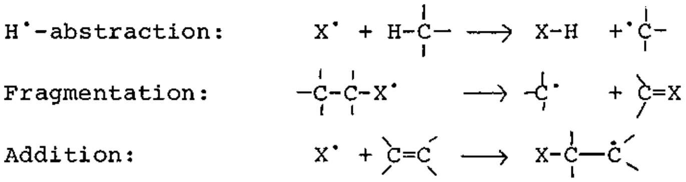
1. Introduction

Free radical chemistry has long been and still is generally associated with polymer chemistry. The fact that free radicals are highly reactive species led to the erroneous conclusion that their reactions cannot easily be controlled and are therefore unsuitable for preparative purposes in organic chemistry. This generalization is untenable, and it is the purpose of this review to demonstrate that, under carefully controlled conditions, free radical reactions can have interesting and useful applications in preparative chemistry[1]. Obviously, in view of the high reactivity of free radicals, the condition which distinguishes a useful from a useless reaction is that the rate of the desired reaction must be much faster than that of any competing reaction. This condition is particularly easily satisfied in an <u>intramolecular</u> reaction, the rate of which will, in the majority of cases, always be very much faster than that of a corresponding bimolecular reaction. It is more difficult, but by no means impossible, to define a <u>bimolecular</u> reaction which fulfils the above condition for usefulness. In this case, the structures of both partners must be carefully chosen in order to favour one particular reaction over competing side reactions. There is another point which deserves consideration in this context: the reaction of a free radical species with another organic molecule (saturated or unsaturated) always produces another free radical, which will undergo further reactions. In order to make a reaction preparatively useful, this sequence of events has to be interrupted by stabilizing a newly produced free radical centre in an appropriate way. The necessity for the presence of radical-trapping agents dictates the choice of the reactions used in the formation of the starting radical species.

Heteroatoms play an important role in free radical chemistry: free radicals on heteroatoms such as oxygen or nitrogen are easily generated, and secondly heteroatoms can serve to stabilize free radicals on adjacent carbon atoms. A large proportion of the reactions to be discussed below are concerned with the formation of tetrahydrofurane or pyrrolidine compounds. However, in cases in which radical stabilization becomes important, other heterocycles will also be involved.

2. General Reaction Types

The most prominent reactions of oxygen and nitrogen radicals in organic compounds are the following:



(X = O or N)

These reactions will be treated in the subsequent sections. In these reactions, the oxygen or nitrogen radical respectively is generated in one of the following three ways:

Homolysis: $\rangle N\text{-}X \longrightarrow N^{\cdot} + X^{\cdot}$; $-O\text{-}X \longrightarrow -O^{\cdot} + X^{\cdot}$ (X = e.g. halogen)

One-electron oxidation: $-O^{-} \longrightarrow -O^{\cdot}$ (e.g. with Pb^{+4})

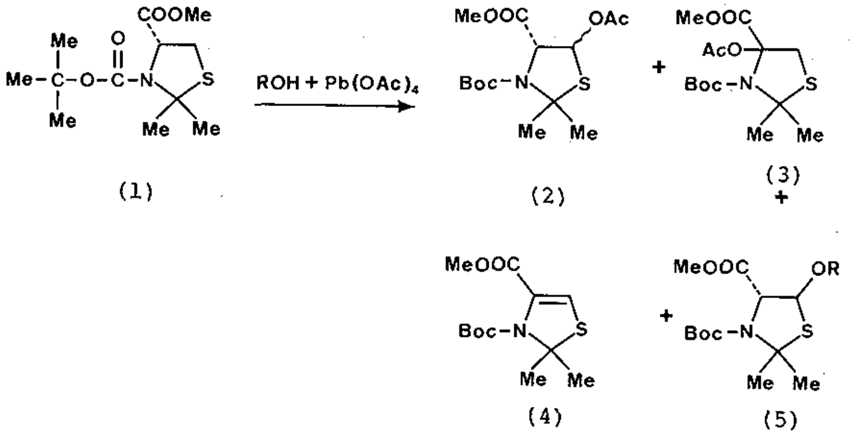
$\pi \rightarrow \pi^{*}$-excitation: $C{=}\underline{\bar{O}} \longrightarrow \overset{\circ}{C}\ -\underline{\bar{O}}^{\cdot}$

3. Hydrogen Abstraction

3.1. By oxygen radicals

Owing to the very high bond energy of the O-H bond (~115 kcal/mol) oxygen free radicals are capable of abstracting carbon-bound hydrogen atoms from almost any organic compound. Extensive investigations[2] have revealed that in bimolecular reactions oxygen radicals show some degree of selectivity in their attack on primary, secondary and tertiary C-H-bonds.

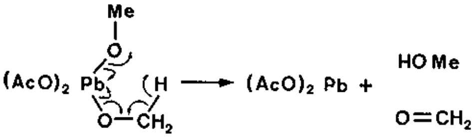
In particularly favourable cases (cf. Scheme 1) this selectivity can be utilized in preparative bimolecular reactions.



Scheme 1

Of the 21 bonds in the protected cysteine molecule (1), 18 are incorporated in methyl groups. Attack on the tertiary α-hydrogen atom of cysteine is sterically very much hindered.

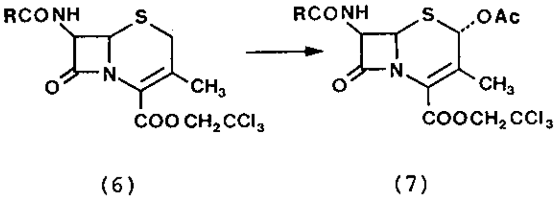
In view of the preference of hydrogen abstraction on secondary hydrogens over attack on primary ones, selectivity could be expected. Treatment of (1) with t-butoxy radicals produced by irradiation of a solution of t-butanol and lead tetraacetate in benzene resulted in the substitution product (2) as the major product (65 %) in the form of a mixture of two isomers, the one with a trans orientation of the carbomethoxy and acetoxy groups largely predominating. Lead tetraacetate also served as a radical-trapping agent by oxidizing the carbon radical produced in the hydrogen-abstracting step to a carbonium ion, the precursor of (2), (4) and (5) (R = $OC(CH_3)_3$). Only to a very minor extent was the product (3) derived from the abstraction of the tertiary hydrogen atom observed. Owing to the relatively rapid fragmentation of t-butoxy radicals to methyl radicals and acetone, t-butanol and lead tetraacetate had to be applied in a considerable excess. However, in avoiding the fragmentation of the attacking oxy radical species by substituting methanol or isopropanol for t-butanol, it is not possible to augment the yield of the desired abstraction reaction, because in this case disproportionation of the alkoxy radicals to methanol and formaldehyde or isopropanol and acetone is the only reaction observed. The extremely high rate of the latter reaction suggests an intramolecular mechanism e.g. as depected in Scheme 2.



Scheme 2

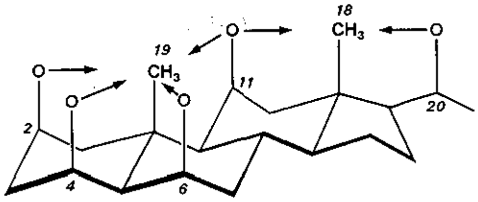
The dialkoxy lead species required for a light-induced disproportionation of this nature is formed in an equilibrium reaction between (excess) alcohol and lead tetraacetate.

Appreciable concentration of the dialkoxy lead species can however be avoided by keeping the alcohol concentration low throughout the reaction (slow addition of methanol or isopropanol to an irradiated solution of (1) and lead tetraacetate). Under such conditions, the results are closely comparable to those obtained with t-butanol (Scheme 1). The same photochemical reaction (t-butanol and lead tetraacetate) can also be applied to the cephalosporin derivative (6)[3], in which the secondary hydrogen atom substituted in the reaction is in an allylic position and therefore additionally "activated" (Scheme 3).

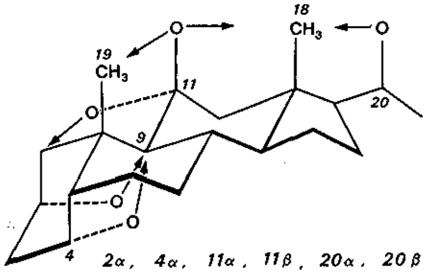


Scheme 3

The success of intramolecular hydrogen abstraction by oxy radicals depends on the relative orientation of the oxy radical and hydrogen to be abstracted (an optimal distance of 2.5 - 3.0 Å between oxygen and hydrogen-bearing carbon atoms has been deduced[4]) and on the rigidity of the system. Steroids offer a particularly suitable framework for intramolecular hydrogen abstraction and have been extensively studied[5]. Steroidal oxy radicals have been produced by thermal or photolytic lead tetraacetate treatment[6], by decomposition of hypohalites (especially hypoiodites produced from alcohols by lead tetraacetate-iodine treatment[4,7]) or by photo decomposition of nitrite esters[8,9,10]. The yields and the direction of substitution (tetrahydrofuranes in the case of 'lead tetraacetate reaction'[6]; tetrahydrofurane, hemiacetals or lactones in the case of the 'hypoiodite reaction'[7] and hydroxy-oxime- from nitrite photolysis) are indicated in Table 1.



2β, 4β, 6β, 11β, 20α, 20β



2α, 4α, 11α, 11β, 20α, 20β

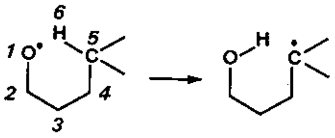
YIELDS OF INTRAMOLECULAR SUBSTITUTION (SEC. ALCOHOLS)

	2β	4β	6β	11β		20α	20β	2α	4α	11α
				(18)	(19)					
$Pb(OAc)_4$ therm.	60-71	60-74	12-90	4	8	47-80	20-50	52	~85	50-90
$Pb(OAc)_4$ $h\nu$		75	94	16.5	30	~ 70	~ 60			
Hypoiodite	54	72-85	60-95	5-13	8-35	~ 60	48-74		~45	30-50
Nitrite	28-40		36-74	5-60	10-33	60-65	15-36			

Table 1

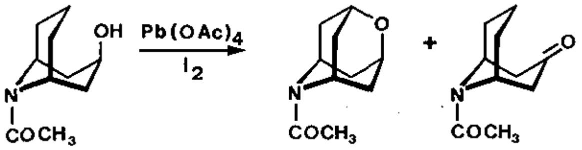
The ranges indicated are to a large extent due to various substituents on the steroid skeleton (not indicated in the formulae) which change the conformation and therefore the distance between the oxygen and C-H bond attacked. It is noteworthy that the highest yields (90 - 95%) have been reached in the hypoiodite and lead tetraacetate reactions with 6β-hydroxysteroids. These processes are important in the commercial preparation of 19-nor-steroid, which find extensive application in fertility control.

From the steroid examples as well as from many other cases reported in the literature it has repeatedly been concluded that a six-atom cyclic arrangement



is a prerequisite for successful intramolecular hydrogen transfer. This is, of course, not true, since atoms 2,3 and 4 are in no way involved in the hydrogen transfer.

A 1,5 hydrogen transfer, however, seems to occur particularly easily, as under these conditions the optimal spatial relations are most easily achieved. But if this spatial orientation of the centres involved can be obtained otherwise, the internal hydrogen transfer occurs quite readily. An example of 1,6 hydrogen transfer, in which a pyrane ring is formed[11] [(8)⟶ (9)] is shown in Scheme 4.



(8) (9) 35% (10) 25%

Scheme 4

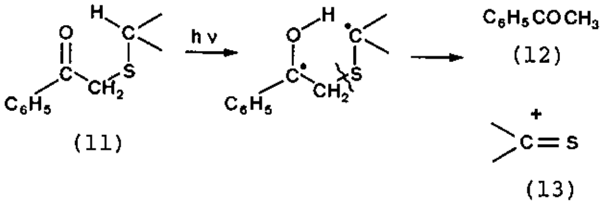
Whether the formation of the ketone (10) is due to heterolytic decomposition of the hypoiodite or to an intermolecular transfer of the hydrogen atom next to oxygen to the carbon free radical formed after the initial hydrogen abstraction by the oxygen radical has not been determined (in the latter case both products could be formed from a common intermediate[12]).

In general the highest yields of ethers from alcohols are obtained in rigid systems in which the ether formation is not accompanied with any significant distortion of the geometry.

For reasons of entropy, lower yields are obtained in flexible systems.

3.2. Hydrogen abstraction via excited carbonyl systems

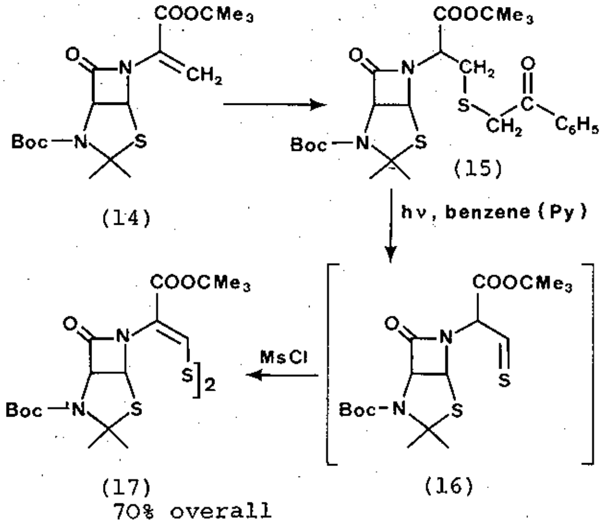
One of the most extensively studied hydrogen abstraction reactions is the Norrish Type II cleavage of ketones. An interesting variant of this cleavage is the photochemical decomposition of phenacyl ethers or thioethers described by Caserio[13] and Padwa[14]. In Scheme 5 the photochemical cleavage of the thioether (11) to acetophenone (12) and the corresponding thioketone (13) is depicted.



Scheme 5

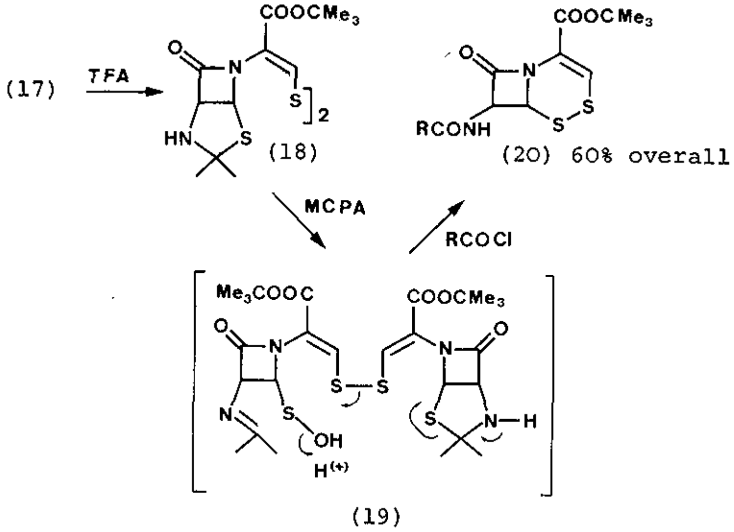
The thioether reaction, in particular, is a very efficient process and has been applied to a complicated heterocyclic system (Scheme 6) by Woodward, Burri and Paioni[15].

It is, however, important that the thiocarbonyl compound formed in the primary reaction can be transformed into a stable derivative [in the case presented, by treatment of the intermediate (16) with excess methane sulphonyl chloride to the dien-disulphide (17)].



Scheme 6

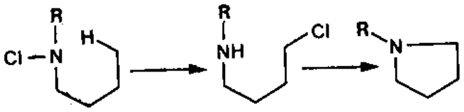
The product (17) could be converted (Scheme 7) by treatment with trifluoracetic acid, followed by metachloroperbenzoic acid and thienylacetyl chloride into a thio-analogue (20) of a cephalosporin derivative which showed interesting antibacterial activity.



Scheme 7

3.3. Hydrogen abstraction by nitrogen radicals

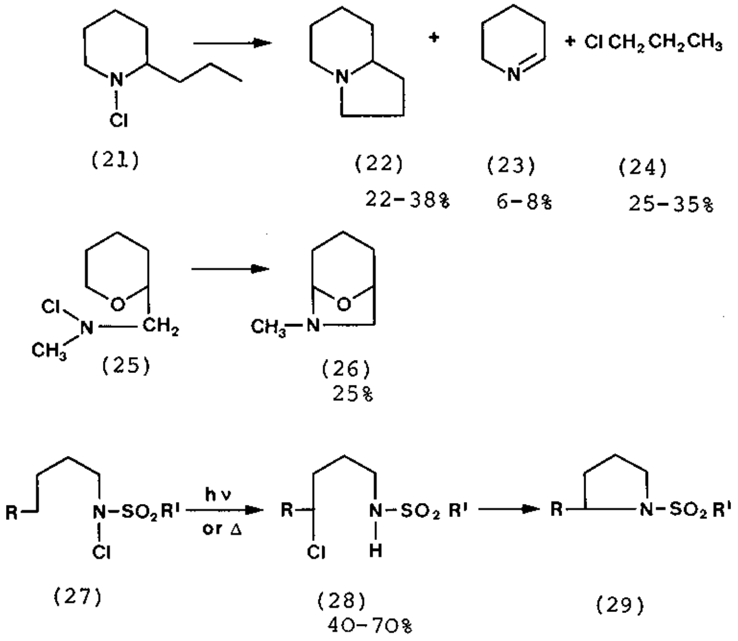
Most of the factors discussed in the previous sections in connection with oxy radicals also apply to hydrogen abstraction by nitrogen radicals. In fact, the Hofmann-Löffler reaction[16] (Scheme 8)



Scheme 8

was discovered long before the oxygen analogues, but the radical nature of the transformation was only fairly recently[17] established.

Scheme 9 shows some typical examples:



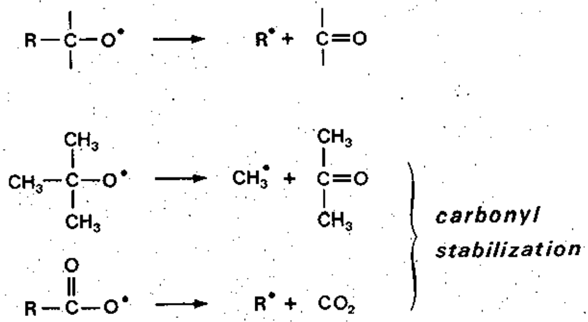
Scheme 9

As in the case of oxygen radicals, fragmentation [(21) ⟶ (23) + (24)] can compete with hydrogen abstraction [(21) ⟶ (22)][18]. Cyclic as well as aliphatic chloroamines undergo the reaction[19], and it is not necessary that the amine should have a basic character[20]. Very often, however, it is an advantage to perform the reaction in a strongly acidic medium. In this case the chloroamine is first protonated and the N-Cl-bond in the so formed chloroammonium salt is homolytically cleaved.

In the majority of the cases five-membered heterocycles of the pyrrolidine type are formed, after treatment of the intermediate amino (ammonium) chlorides with base.

4. Fragmentation

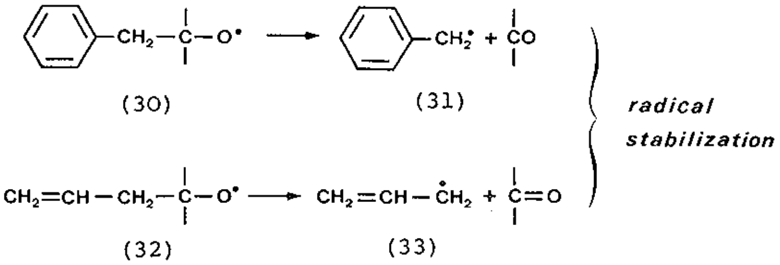
The fragmentation of an oxy radical into a carbonyl fragment and a carbon radical is always a competing reaction for hydrogen abstraction.



Scheme 10

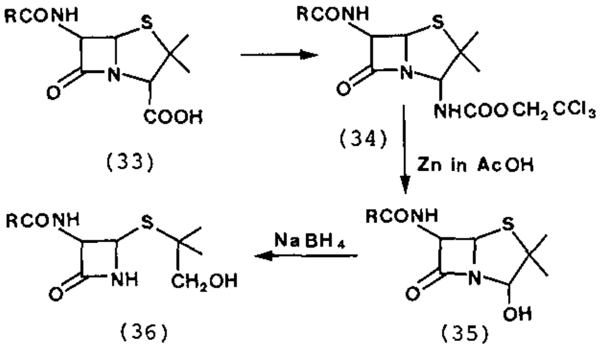
The extent to which fragmentation predominates over hydrogen abstraction is largely determined by the stability of the fragments produced. It is quite clear that primary and secondary oxy radicals, which yield aldehydes, are less prone to fragmentation than tertiary oxy radicals, which decompose into a ketonic fragment. In the case of carboxy radicals the production of CO_2 is energetically so much favoured that essentially no hydrogen abstraction by carboxy radicals can be observed.

But not only the stability of the carbonyl fragment is important; the production of stabilized carbon radicals on fragmentation can also facilitate fragmentation reactions. Homobenzylic (30) and homoallylic (32) oxy radicals decompose extremely rapidly (Scheme 11):



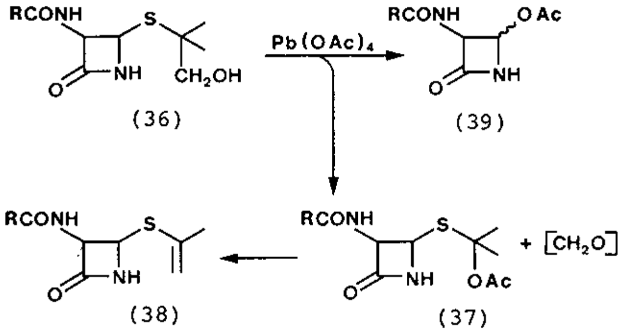
Scheme 11

In special cases, such fragmentations can be used in the synthesis of heterocyclic compounds. For example, penicillin (33) can be converted through a series of conventional steps to the degradation product (36) as indicated in Scheme 12.



Scheme 12

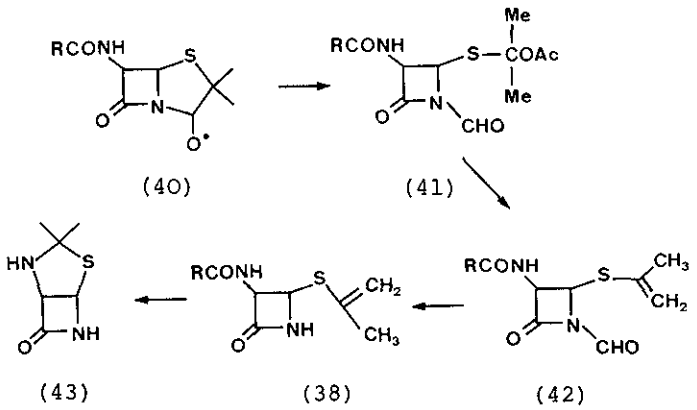
When (36) is treated with lead tetraacetate under irradiation (Scheme 13) some fragmentation does occur despite the fact that the carbonyl fragment (formaldehyde) is certainly not stabilized to any appreciable degree, though the carbon radical formed gains some stability through interaction with the adjacent sulphur atom.



Scheme 13

The carbon radical picks up an acetoxy group (probably after oxidation to a carbonium ion), and since the hemithioacetalacetate (37) formed in a yield of about 30 % is thermally unstable, the thioethanol ether (38) is the product finally isolated. To a small extent (5-10 %), fragmentation proceeds even further, producing the acetoxy-acetidinone (39) indicated[21].

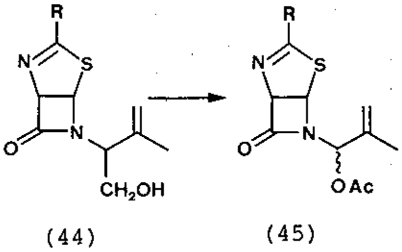
The yield in the fragmentation process can be dramatically improved by stabilizing the carbonyl fragment also. The intermediate carbinol amide (35), which on reduction with sodium borohydride gives the primary alcohol (36) (Scheme 12), provides an excellent opportunity for doing so: instead of formaldehyde an amide carbonyl is formed (Scheme 14).



Scheme 14

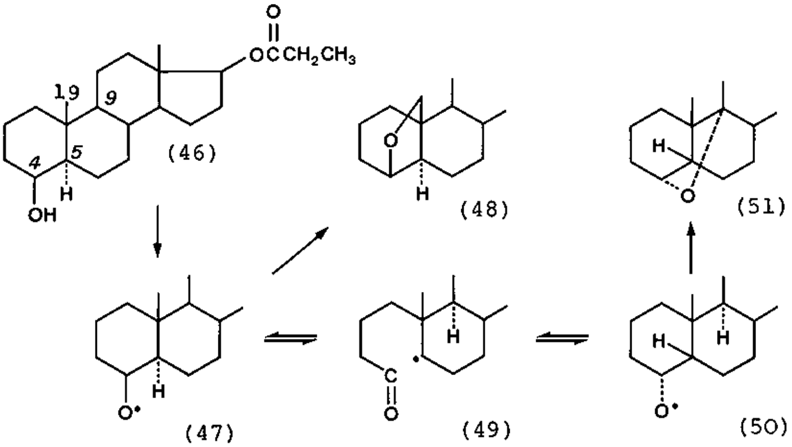
If the carbinolamide (35) is treated with lead tetraacetate under irradiation, fragmentation occurs almost quantitatively and after thermal treatment in solution (to remove acetic acid) to form the thioenolether (42) and hydrolysis of the formyl group (with aqueous ammonia) compound (38) is formed in a yield of about 75 %. It can easily be transformed into the bicyclic final product (43)[21].

In another case (also taken from penicillin chemistry), the carbon radical produced by fragmentation of a primary alcohol (44) with lead tetraacetate is stabilized by nitrogen as well as by an allylic double bond[22]. Again the reaction is of preparative value (Scheme 15).



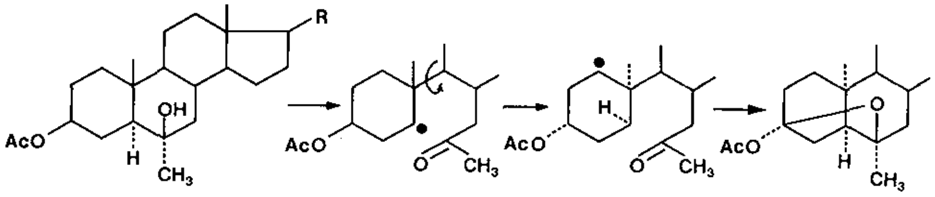
Scheme 15

The fact that the fragmentation reaction of an oxy radical to a carbonyl and a carbon radical can be a reversible reaction gives rise, under special circumstances, to interesting stereochemical changes. Two examples from the steroid field exemplify this statement.



Scheme 16

In the reaction of a 4β-hydroxy steroid (of the 5α H series) (46) with lead tetraacetate (Scheme 16) 65 % of the expected 4β,19 ether (48) is produced by direct hydrogen abstraction [by the 4β-oxy radical (47)] from the angular methyl group. As a minor product the 4α, 9α-ether (51) (of the 5β H series) is formed in a yield of approx. 10 % via (49) and (50). The stereochemical changes at C_4 and C_5 are a consequence of the reversible fragmentation reaction indicated[23].



(52) (53) (54) (55)

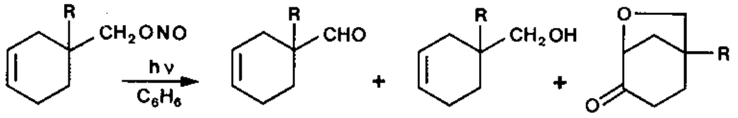
Scheme 17

An even more complicated rearrangement is involved in the lead tetraacetate oxidation of a 6β-hydroxy-6α-methyl-steroid (52) (Scheme 17). Here, between the fragmentation to (53) and recyclization to form (55), a "trans-annular" hydrogen transfer occurs and the rotation of the A-ring simulates an inversion of the angular methyl as well as of the 3-acetoxy group[24].

5. Addition Reactions

Much more common than the addition of radicals to carbonyl compounds (as observed in reversible fragmentation reactions) are addition reactions to carbon-carbon double bonds.

Especially in cases when additions occur intramolecularly, they can be of preparative value. Two examples, the addition of an oxygen and a nitrogen radical to a double bond (Scheme 18 and 19), illustrate this.

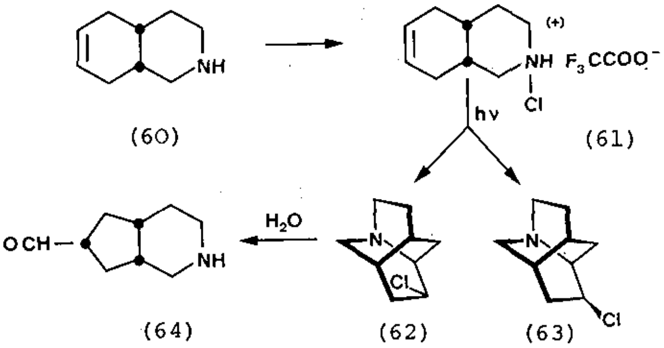


(56) (57) (58) (59)

R = H, CH_3 11% 60% 29%

Scheme 18

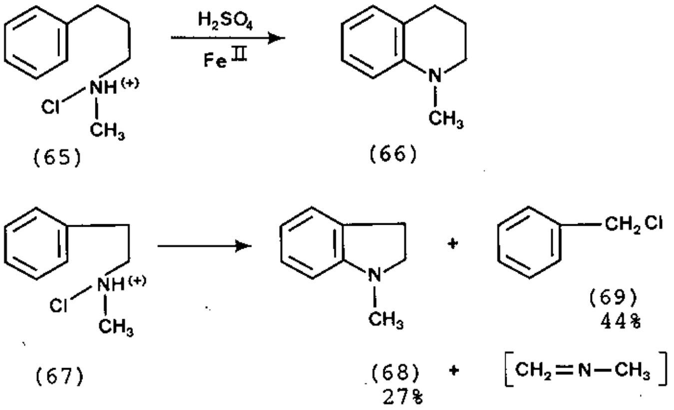
In the flexible system of the nitrite ester (56), photolysis gives - besides the disproportionation products [aldehyde (57) and alcohol (58)[25]] - 29 % of the addition product of the oxy radical and NO, which is isolated not as an oxime but rather in the keto form[26].



Scheme 19

Since the nitrogen radical formed from the N-chloro-derivatives (61) of the cis-octahydroisoquinoline (60) is less flexible (and intermolecular reaction is suppressed by protonation), the addition yield is very high: the two chloro-azatwistanes (62) and (63) are formed in a total yield of over 90 %. The assignment of the structure was based on NMR-spectral evidence as well as on the easy hydrolytic rearrangement of one of the isomers to the aminoaldehyde (64)[27,28].

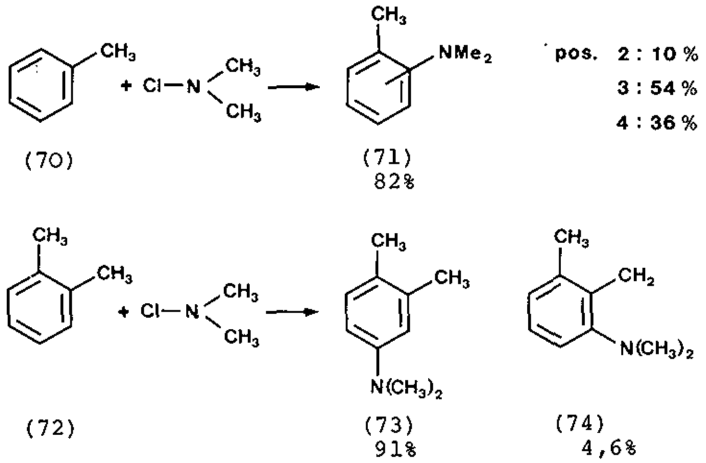
The reactions are not limited to addition to olefinic bonds, but addition to aromatic rings can also occur (Scheme 20).



Scheme 20

In the case of the N-chloro-phenylpropylammonium salt (65) the ring closure to the tetrahydroquinoline (66) occurs in high yield[29]. However[30], in accord with the rules described above in the phenyl ethyl amine case (67), fragmentation competes with ring closure, since the fragmentation produces a benzyl type radical [(67) ⟶ (69)].

The bimolecular analoguous amine addition can also be of preparative importance, as the examples illustrated in Scheme 21 indicate.



Scheme 21

Especially in the case of substituted phenyl rings, uniform products can be obtained in high yields[30].

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