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Synthetic application of the Pummerer reaction

A M Moiseenkov, V A Dragan, V V Veselovskii
Zelinskii Institute of Organic Chemistry, USSR Academy of Sciences, Moscow

ABSTRACT. **The latest information on the use of the Pummerer reaction for conversions of primary and secondary sulphoxides in fine organic chemistry is classified and correlated.**

The bibliography includes 171 references.

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I. Introduction

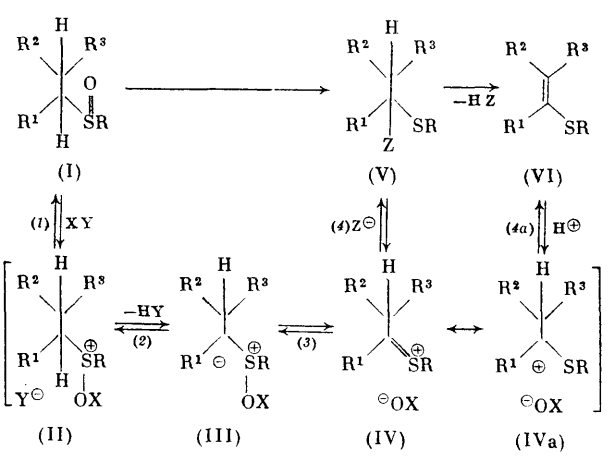
The conversion of sulphoxides by electrophilic reagents to α-substituted sulphides, which was discovered by R Pummerer in 1909,[1] was named after him by Horner[2] half a century later in honour of the original discoverer of this reaction. A number of reviews[3–11] are devoted to a study of its mechanism and certain synthetic aspects. At the same time, the use of the Pummerer reaction (PR) and related conversions in fine organic synthesis, which has undergone a particularly intense development in recent years, has hardly been reviewed at all, if the short selection of material by Welzel[12] and the highly specialised review of Fedorov et al.[13] devoted to the use of the PR in the synthesis of heterocyclic compounds are excluded. This circumstance has prompted us to analyse the available information on this topic, mainly covering the literature of the last ten years.

II. Current theory of the mechanism of the Pummerer reaction

The most comprehensive information about the probable mechanism of the PR is contained in reviews by Oae.[10,11] The overall scheme now reduces to four successive reversible stages *(1)*–*(4/4a)* (Scheme 1), and the rate-determining stage can change depending on the nature of the initial reaction components. Examples are known in which either of these stages becomes rate-determining.[11] The first of them consists of the formation of an oxysulphonium salt (II) (an "activated" sulphoxide)[14] or, in other words, a pre-Pummerer intermediate (PPI), from a primary or secondary sulphoxide (I). The second involves the generation of an oxysulphonium ylid (III) by removal of an α-proton by the counterion. Heterolysis of the S–O bond in the ylid at the third stage leads to the formation of the Pummerer intermediate (PI) proper (IV)/(IVa), which is stabilised finally by an external nucleophile to give an α-substituted sulphide (V) or forms a vinyl sulphide (VI) through elimination of the β-proton. In the case of acyloxysulphonium ions (II), the acyl residue within the corresponding PPI can act as this nucleophile.[11,15]

The reagents XY used to "activate" the initial sulphoxide are usually simple and mixed anhydrides and chorides of carboxylic acids, other halides of (in)organic acids, and the acids themselves, including Lewis acids, catalytic quantities of which added to these "activators" sometimes accelerate the PR, and also certain other reagents.[11,14] Acyloxy and chloride ions are most common among the external nuclephiles $Z^{\ominus}$, although uncharged molecules and functional groups of the substrate that become involved in the PR can fulfil this role. When these compounds are acid-labile, in order to neutralise the acids formed at stages *(2)* and *(4/4a)*, extensive use is made of bases; these are as a rule nitrogenous, including dicyclohexylcarbodiimide, which in particular achieves high enantio-selectivity in a reaction involving chiral sulphoxides.[15,16]

Scheme 1



The existence of the cationoid S-containing species (II)–(IV) as actual intermediates of the PR has so far not been established unequivocally.[10,11] However, the ability of sulphoxides, and in particular DMSO,[6,17] to give thermally labile complexes with different electrophilic reagents, such as adducts with HCl[17] or with trifluoroacetic anhydride (TFAA),[18] the latter decomposing to a PR product even at −30 °C, is well known. Indirect confirmation of the involvement of the PPI (II) in the PR is provided by the large

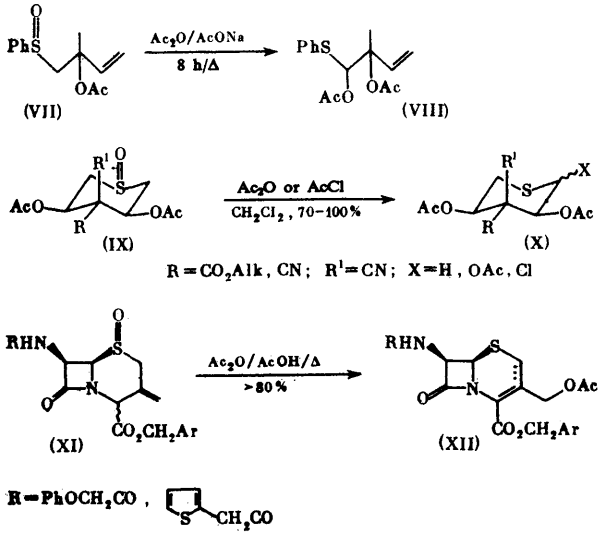
amount of data on the reaction between "activated" sulphoxides and *O*- and *N*-nucleophiles.[11,14]

With regard to the PI (IV/IVa), as representatives of a class of methylenesulphonium salts[11] their instability generally appears to be quite natural. The simplest example of this type of cationoid species, $H_2C{=}\overset{\oplus}{S}Me/SbCl_6$, was obtained from methylthiochloromethane comparatively recently.[19] In relation to the PR, there is only indirect evidence, as in the case of the PPI (II), for the existence of such an intermediate.[10,11] Additional information will be given below (Section VII).

III. Synthesis of α-substituted sulphides, carbonyl compounds, and alcohols

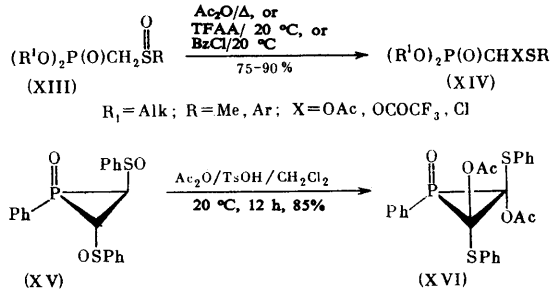
At the present time the Pummerer reaction serves as an extremely valuable synthetic method of achieving a simple conversion from readily available primary and secondary sulphoxides to *gem*-functionalised sulphides. Further hydrolytic, redox, and other conversions of the latter to various carbonyl compounds and their derivatives is simply a question of procedure, the efficiency of which depends in many respects on the nature of the functional groups that are present in the molecule of the initial substrate. Just as important for the overall process as a whole is the nature of the electrophilic and nucleophilic reagents that are used, which has been recorded in most of the reviews mentioned above. The same questions are discussed below with account taken of the latter results concerning the possibility of achieving a selective conversion of the sulphinyl group in the presence of other functional substituents. For example, the isoprene derivative (VII) can be readily converted to the acetoxysulphide (VIII),[20] while sulphoxides (IX) are converted to α-substituted tetrahydrothiopyrans (X)[21] (Scheme 2). In the case of allyl sulphoxides it is possible in this way to introduce an acetoxy group into the γ-position relative to the sulphur atom. In particular, the PR of the cephalosporin derivatives (XI) readily gives γ-acetoxy sulphides (XII),[22] which are apparently formed by allylic isomerisation of the initial *gem*-product.

Scheme 2



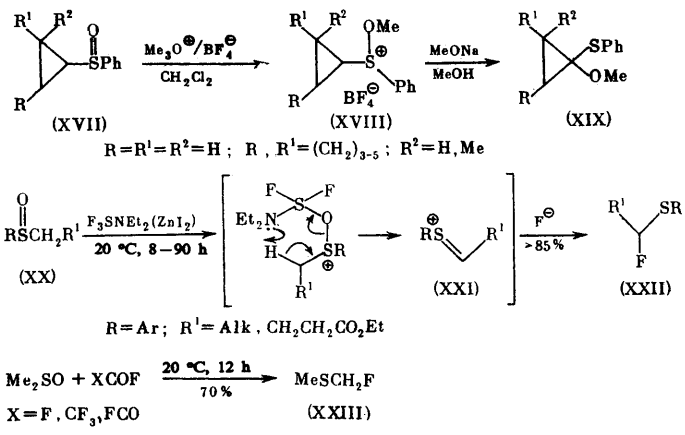
The presence of an electron-withdrawing group at the α-position relative to sulphinyl assists the participation of the latter in the PR, and in addition increases the degree of asymmetric induction for optically active substrates.[11,15] Thus α-phosphoryl sulphoxides (XIII) under different conditions and in high yield are converted to the corresponding acyloxy- or chloro-sulphides (XIV).[23] For example, chiral (XIII) (R^1 = Me, R = *p*-Tol) gives the acetoxy-sulphide (XIV) (X = OAc) with an enantiomeric purity (EP) of about 25%[23] (Scheme 3). Similarly, the phosphirane disulphide (XV) yields *trans*-diacetate (XVI).[24]

Scheme 3



Using the Pummerer reaction it is possible to carry out the synthesis of structures that were only recently considered exotic. For example, cyclopropanone derivatives such as methoxysulphides (XIX) are prepared from (XVII) and a Meerwein salt with a total yield of 40–60% via the stable oxysulphonium salts (XVIII)[25] (Scheme 4). Other such fairly important compounds include the α-fluorides (XXII), which were recently synthesised in almost quantitative yield by "activation" of the sulphur atom in (XX), catalysed in a number of cases by ZnI_2, and apparently occurring via a PI of the type (XXI).[26,27] As a result of the PR of DMSO with certain acyl fluorides, methylthiomethyl fluoride (XXIII) was isolated in high yield.[28]

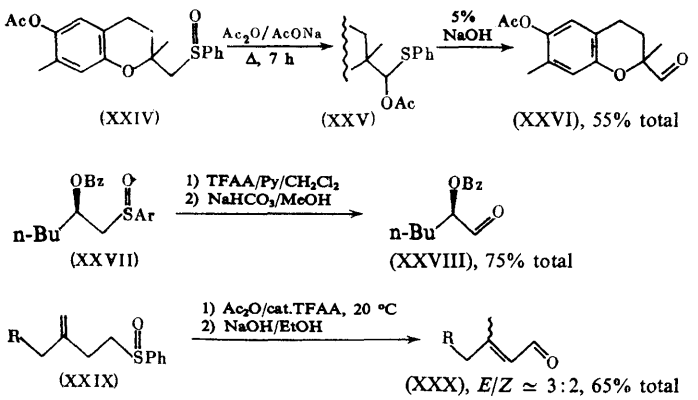
Scheme 4



It stands to reason that α-substituted sulphides (V), in particular their acyloxy derivatives, can be readily converted to the corresponding aldehydes and ketones; and in this sense primary and secondary sulphoxides are latent precursors of such compounds by

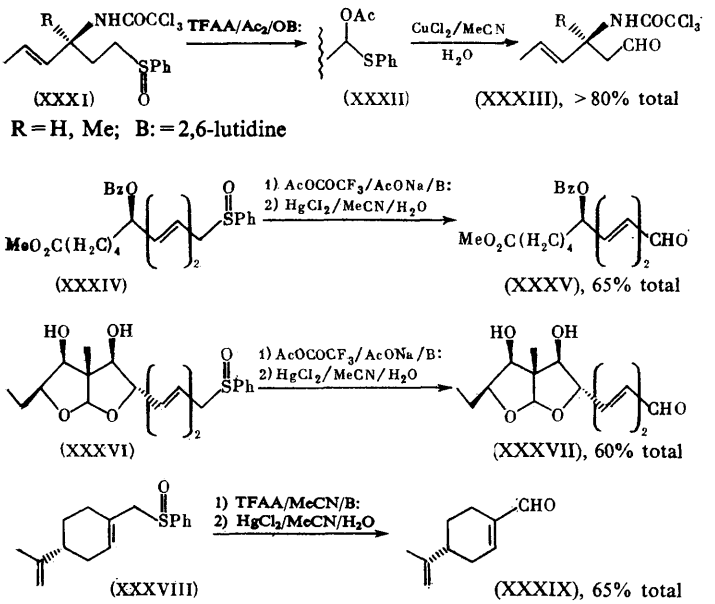
the Pummerer reaction. For example (Scheme 5), in one of the variants for the synthesis of α-tocopherol from the sulphoxide (XXIV) via the acetoxysulphide (XXV), aldehyde (XXVI) is derived.[29] In another case the unstable intermediate *gem*-acetoxysulphide formed by the PR from the chiral sulphoxide (XXVII) is readily converted in high yield in a weakly alkaline medium to the aldehyde (XXVIII) without appreciable racemisation of the α-centre.[30] On the other hand, the β,γ-unsaturated aldehydes initially formed from the isoprenoid homallylic sulphoxides (XXIX) undergo smooth isomerisation to the conjugated aldehydes (XXX).[31]

Scheme 5

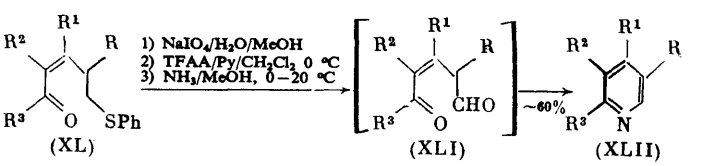


It should be noted that the conditions recorded above for the hydrolytic cleavage of *gem*-acyloxysulphides are not optimal in every case, especially when base- or acid-labile functional groups are present in their molecules. In such cases it is recommended to use Cu(II) and Hg(II) salts, which provide mild conditions for conducting the reaction, as catalysts (c.f. the study of Sugihara et al.).[32] In particular, in the synthesis of certain antitumour antibiotics, the labile β-trichloroacetamidoaldehydes (XXXIII) can be readily obtained from sulphoxides (XXXI) via the hydrolytic cleavage of acetoxysulphides (XXXII) catalysed by $CuCl_2$.[33] The use of $HgCl_2$ for the same purpose is illustrated by the conversion of the functionalised sulphoxides (XXXIV), (XXXVI), and (XXXVIII) without isolation of the intermediate trifluoroacetoxysulphides to the corresponding diene aldehydes (XXXV)[34] and (XXXVII),[35] which have served as building blocks in the total syntheses of 5-desoxy-leukotriene *D* and (±)-asteltoxin (an inhibitor of oxidative phosphorylation) respectively, as well as perillaldehyde (XXXIX)[36] (Scheme 6).

Scheme 6



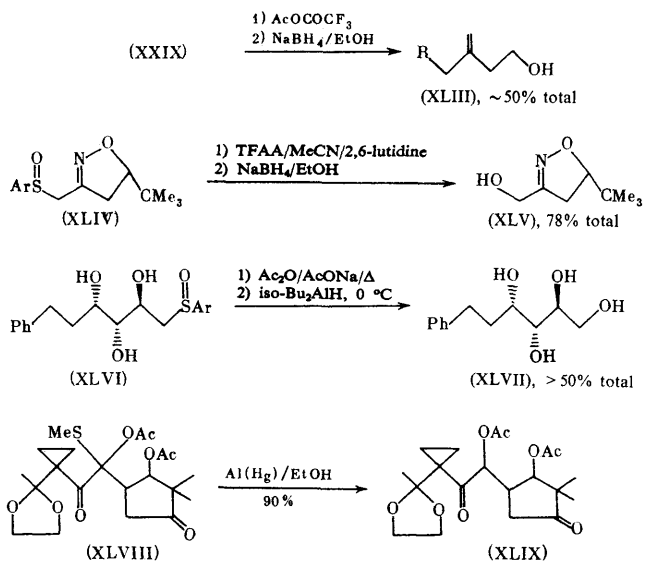
The use of a sulphoxide as a masked carbonyl compound, particularly if the latter is very unstable, is demonstrated by the preparation of pyridines (XLII) from sulphides (XL) once again without isolation of both the intermediate sulphinyls and the glutaconic aldehyde derivatives (XLI).[37] This method is successfully used at a key stage in the synthesis of the neurotoxin molecules—acromelic acids A[38] and B.[39]



R, R^1 = H, Me, $(CH_2)_2OMe$; R^2 = H; R^3 = Me; R^2, R^3 = $(CH_2)_4$

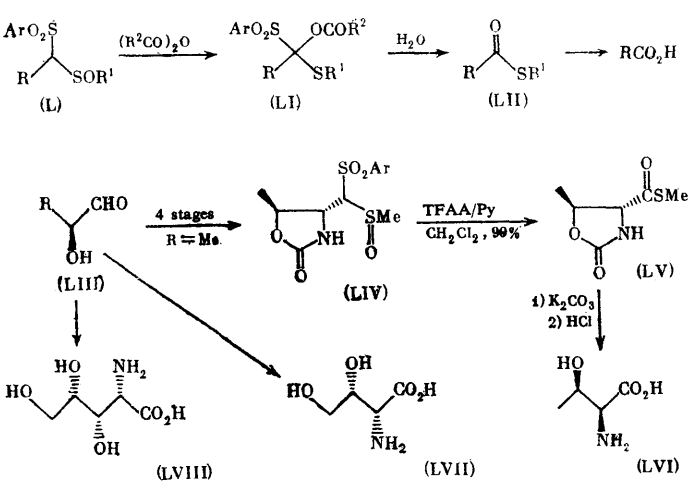
Sufficiently stable products of the PR of a number of acyloxysulphides can provide a direct source of primary and secondary alcohols, and the number of examples of such reactions, which are carried out as a rule in two variants, has steadily increased in recent times. Thus in Scheme 7, hydride reduction of the products of the PR involving (XXIX), and without their isolation, readily yields the corresponding linear γ-terpenols (XLIII),[40,41] which clearly could not be obtained with the inclusion of an intermediate hydrolytic stage (c.f. Scheme 5). Similarly the isoxazolidine sulphoxide (XLIV) is converted to the masked α-ketol (XLV) without saturation of the C=N bond,[42] while (XLVI) is converted to the arabitol derivative (XLVII).[43] Another variant of the reductive conversion from PR products to alcohols and their esters is illustrated by the desulphurisation with an aluminium amalgam of the relatively stable acetoxysulphide (XLVIII) prepared from the corresponding ketosulphoxide to give the α-keto acetate (XLIX)—a key compound in one of the schemes for the total synthesis of illudane sesquiterpenes.[44]

Scheme 7

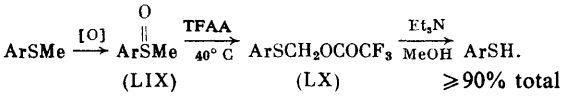


The Pummerer reaction can be readily used for the conversion to carboxylic acids from sulphoxides of the type (L), which contain an effective leaving group such as arylsulphonyl, making it possible to generate the thiol ester (LII) from intermediate (LI) (Scheme 8). In omitting a review of the methods for making the initial structures (L), based primarily on S-containing C_1-synthons,[45] we shall merely note here the recently developed stereocontrolled method of obtaining *syn*-β-hydroxy-α-amino acids from chiral α-hydroxyaldehydes (LIII).[46] Thus, the α-sulphinylsulphone (LIV) in the end gives thioester (LV) in high yield, which is then converted in a conventional manner to *D*-threonine (LVI). *L*-γ-Hydroxythreonine (LVII) and the polyhydroxyamino acid (LVIII) are obtained in a similar manner.

Scheme 8



The possibility of simple demethylation of (hetero)aromatic methylthioesters is an example of the use of the PR in the chemistry of protected groups that is worth considering.[47,48] Thus, the readily available sulphoxides (LIX) are converted in boiling TFAA to the corresponding arylthioesters (LX), which are then cleaved to the required thiophenols in virtually quantitative overall yield.

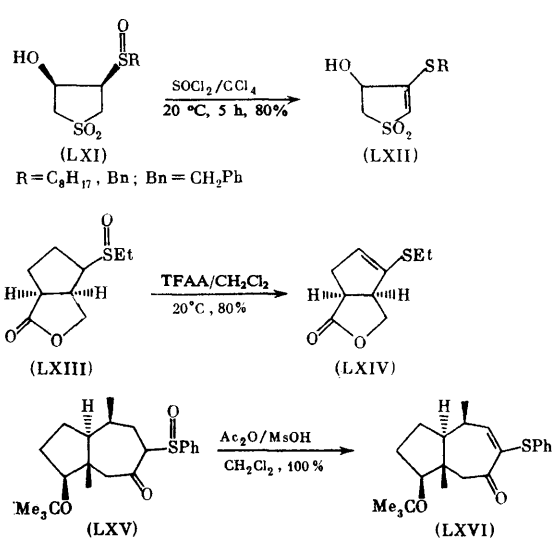


Thus, a primary or secondary sulphinyl group is a fairly versatile source for obtaining α-substitututed sulphides, carbonyl compounds, and their corresponding alcohols via the Pummerer reaction. It should be emphasised that the first of these compounds, primarily *gem*-acyloxysulphides and/or *gem*-chlorosulphides, under certain conditions act as counterparts of cationoid species of the type (IV)/(IVa), which open up new and currently quite extensively used opportunities for forming a C–C bond (see Section VII).

IV. Synthesis and certain properties of vinyl sulphides

Because of the cationoid nature of the PI (IV)/(IVa), one of the methods used to stabilise it involves the elimination of a β-proton to give vinyl sulphides (VI), which can also be formed through α-elimination of the *gem*-derivatives (V), especially if an electron-withdrawing substituent occurs at the β-position relative to the sulphur atom (see several studies).[1–11] Amongst recent examples, the preparation of vinyl sulphides of the type (VI) using $SOCl_2$ and certain other standard reagents such as $Sn(OTf)_2$ (Tf = F_3CSO_2) [54] as "activators" has been reported in a series of studies by Warren et al.[49–53] Similarly, treatment of *cis*-hydroxysulphinyl derivatives of sulpholane (LXI) with $SOCl_2$ gives vinyl sulphides (LXII) in high yield,[55] and the bicyclic sulphoxides (LXIII)[56] and (LXV)[57] on treatment with acid anhydrides readily afford olefins (LXIV) and (LXVI) respectively (Scheme 9).

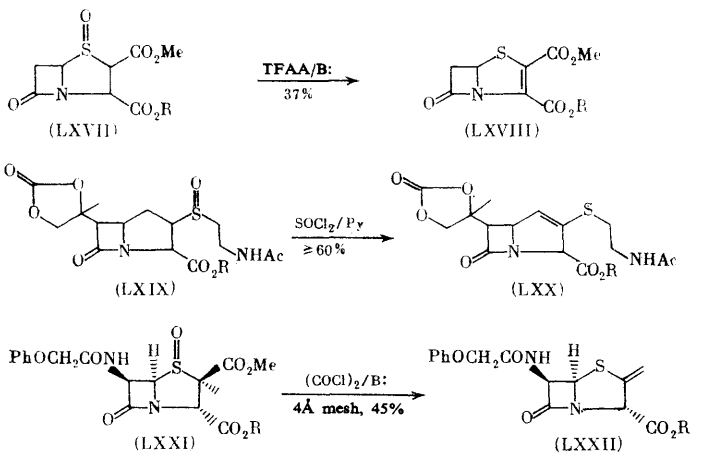
Scheme 9



The Pummerer reaction is very widely used at the present time in the synthesis of penicillin analogues, in particular those containing a vinyl sulphide residue (Scheme 10). Thus, for example, sulphoxides

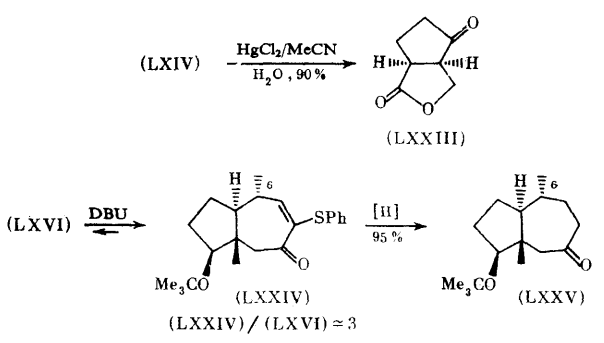
(LXVII) are converted to individual diesters (LXVIII),[58] carbapenams (LXIX) gives sulphides (LXX),[59] and compounds (LXXI), containing a carboxyl group in the vicinity of sulphinyl, are converted to olefins (LXXII).[60]

Scheme 10



B: = 2,6-collidine; R = *p*-$CH_2C_6H_4NO_2$

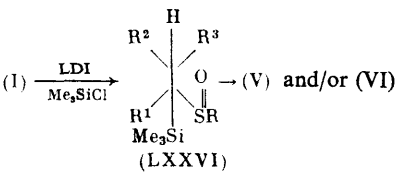
One of the obvious aspects of the synthetic use of vinyl sulphides is their conversion to carbonyl compounds; for example, (LXIV) gives the precursor (LXXIII) of sarkomycin in a recently published scheme of its total synthesis.[56] Exhaustive reduction of the vinyl sulphide function is rarely encountered. In the case of the ketovinyl sulphide (LXXIV) this method has been successfully used for yielding the precursor (LXXV) of the sesquiterpene pseudoguaiane after isomerisation of the C(6) site of the initial epimer (LXVI) using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[57]



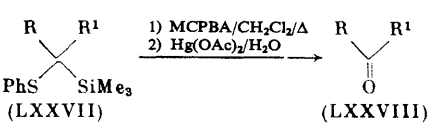
Thus, primary and secondary sulphoxides may be regarded as a direct source of obtaining substituted vinyl thioethers.

V. Silyl variant of the Pummerer reaction

It is well known[61] that thermally labile α-silyl sulphoxides (LXXVI), one of the methods for the synthesis of which is the *C*-silylation of initial compounds (I) deprotonated by lithium diisopropylamide (LDI), readily isomerise to α-silyloxysulphides (V) (Z = $OSiMe_3$). Further study of this silyl variant of the PR (SPR), which accompanies the formation of vinyl sulphides (VI), has identified the considerable possibility of using this reaction by interaction of (I) with silyl halides, in particular trimethylsilyl halides or their equivalents, as "activators" of the process, which evidently involves intermediates (II)–(IV)/(IVa) (X = $SiMe_3$, $SiMe_2Bu$-t, etc.).[62–64] It should be noted that in this case as well as the formation of products purely from the SPR—(V) (Z = $OSiMe_3$) and (VI)—a competing reduction of sulphoxides (I) to the corresponding sulphides occurs at the same time, and this is especially typical for (cyclo)aliphatic compounds.[65]

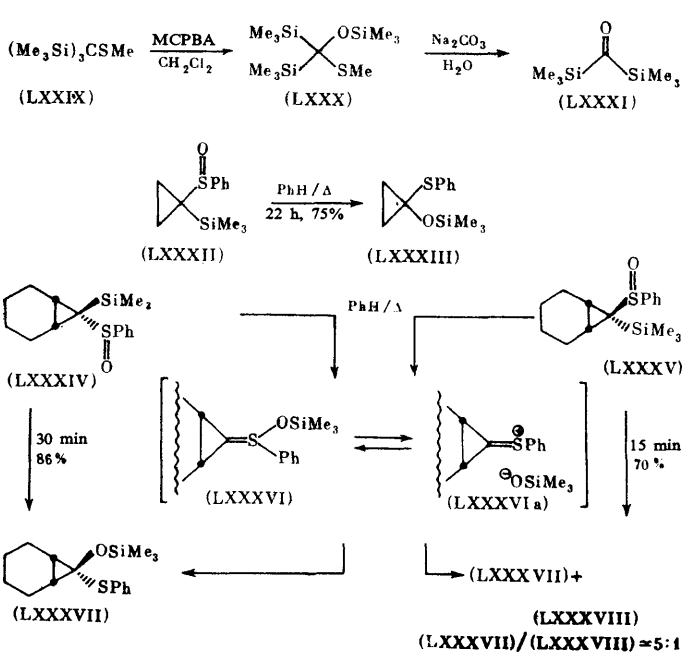


gem-Silyloxysulphides of the type (V) that are accessible using the SPR are, as a rule, very unstable compounds which are readily converted under hydrolytic conditions to the carbonyl products corresponding to the initial (LXXVI). This circumstance has predetermined a method of obtaining them *in situ* from silylsulphide C_1-synthons[45] as an alternative to the *C*-silylation of sulphoxides (I). For example, refluxing in THF or CCl_4 of the products of the oxidation of silylsulphides (LXXVII) by *m*-chloroperbenzoic acid (MCPBA) and subsequent hydrolytic treatment of SPR products catalysed by Hg(II) gives ketones (LXXVIII) in 50–80% yield.[66]



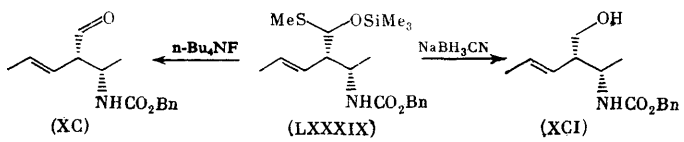
R, R¹ = Alk, All, Bn. Ph; All = $CH_2CH{=}CH_2$.

Scheme 11



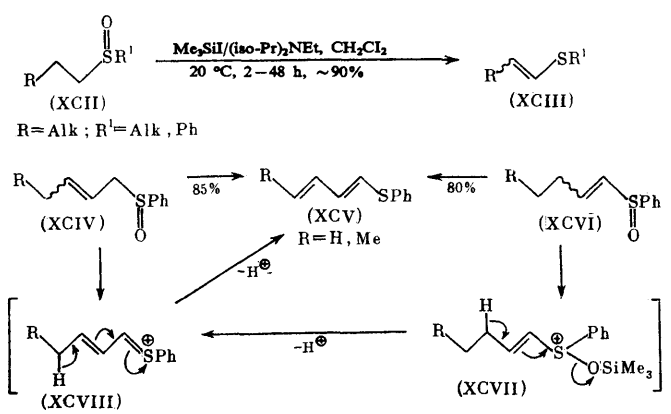
In specific cases the unstable α-silyloxysulphides can be isolated and used as individual compounds. Thus, as in Scheme (11), the tris(trimethylsilyl) sulphide (LXXIX) is smoothly converted to the heteroatomic methane derivative (LXXX), which is then converted to the simplest bis(trimethylsilyl) ketone (LXXXI).[67] Correspondingly, the *gem*-phenylsulphinyltrimethylsilylcyclopropanes (LXXXII), (LXXXIV), and (LXXXV) rearrange in boiling benzene to the cyclopropane derivatives (LXXXIII), (LXXXVII), and (LXXXVIII),[68] which are related to (XIX). The stereochemical result of the reaction in the case of (LXXXIV) and (LXXXV) indicates the preference for *exo*-attack by the counterion on the cation in (LXXXVIa), formed from intermediate (LXXXVI).

Like acyl derivatives (V) (Z = OCOR), the related silyloxy derivatives can be readily converted to the corresponding carbonyl compounds or their hydride reduction products; this is illustrated by the preparation of the aldehyde (XC) and alcohol (XCI) from *gem*-silyloxysulphide (LXXXIX).[69]



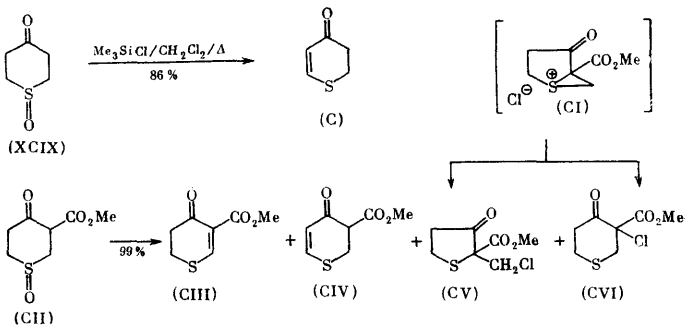
In the same way as the traditional variant, the SPR opens up a simple means of access to a whole range of functionalised vinyl sulphides. Thus, treatment of sulphoxides (XCII) with Me_3SiI in the presence of a Hünig base gives vinyl thioethers (XCIII) in high yield[70] (Scheme 12). In the case of allyl sulphoxides (XCIV) and vinyl sulphoxides (XCVI), whatever their stereochemistry, diene sulphides (XCV) are stereospecifically formed under the same conditions, probably via intermediates (XCVII) and (XCVIII).[70]

Scheme 12



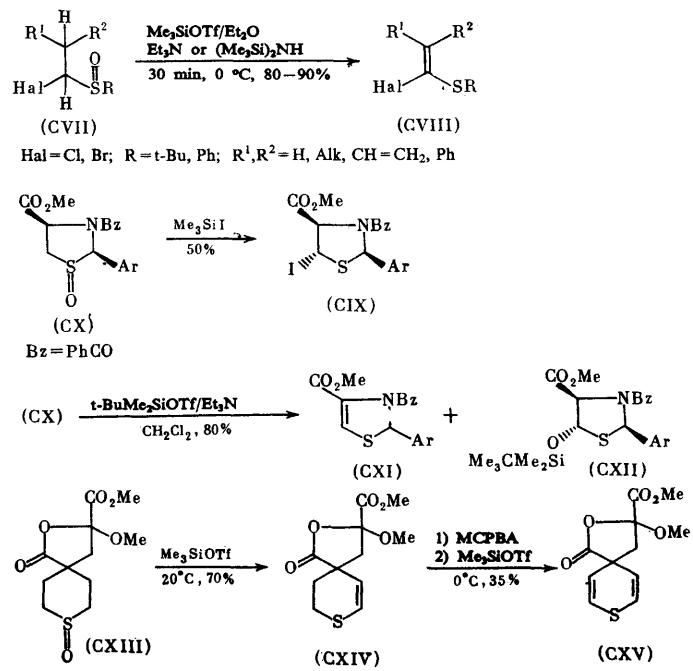
The presence of other functional groups in the vicinity of sulphinyl in molecules involved in the SPR of sulphoxides can cause other processes to take place. For example, in Scheme 13,[71] ketone (XCIX) on treatment with Me_3SiCl is readily converted to ketosulphide (C), whereas ketoester (CII) under the same conditions gives a mixture of sulphides in the ratio (CIII):(CIV):(CV):(CVI) ≃ 75:10:10:5, of which derivatives (CV) and (CVI) are evidently formed from the episulphonium intermediate (CI). It is interesting to note that when Ac_2O or TFAA are used as "activators", the same sulphoxide (CII) mainly (90%) gives a mixture of the (trifluoro)-acetates corresponding to chlorides (CV) and (CVI) in the ratio of ≃ 5:1.[71]

Scheme 13

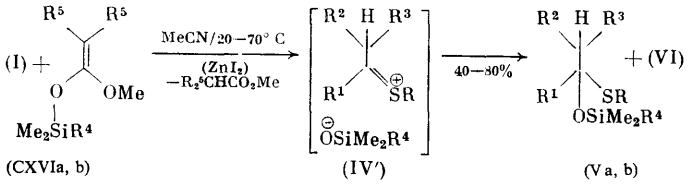


Considerable opportunities for the synthesis of different functionalised vinyl sulphides are opened up by the use of trimethylsilyl trifluorosulphonate (trimethylsilyl triflate, Me_3SiOTf) and other silyl triflates, which on "activation" of the initial sulphoxide liberate a virtually non-nucleophilic counterion. In particular, in Scheme 14, application of this method starting from α-halosulphoxides (CVII) leads to the smooth preparation of a series of acid-labile vinyl sulphides (CVIII), which is difficult to achieve when Me_3SiCl or Me_3SiI are involved.[72,73] Similarly, when the latter is used, the thiazolidine sulphoxide (CX) is mainly converted to the iodide (CIX), whereas with the use of t-$BuMe_2SiOTf$, a mixture of sulphides in the ratio (CXI):(CXII) ≃ 2:1 is obtained from (CX).[74] Finally, by carrying out the SPR with Me_3SiOTf twice, it is possible to synthesise the unstable vinyl sulphide (CXV) in satisfactory overall yield from (CXIII) via the monovinyl sulphide (CXIV).[75]

Scheme 14



Using this silyl variant of the PR, there is a current trend towards research into "activators" that achieve both the mildest conditions for generating the key PPI (II) and the possibility of effective control over the course of subsequent reactions involving the counterion $Y^{\ominus}$. In this respect the use of silyl triflates in combination with different bases appears in many cases to be the best way of suppressing unwanted side reactions. As a development of this approach, the use of the ketenacetals (CXVIa, b) as "activators" of



(CXVIa, b) (IV′) (Va, b)

R^4 = Me (a), t-Bu (b); R^5 = H, Me

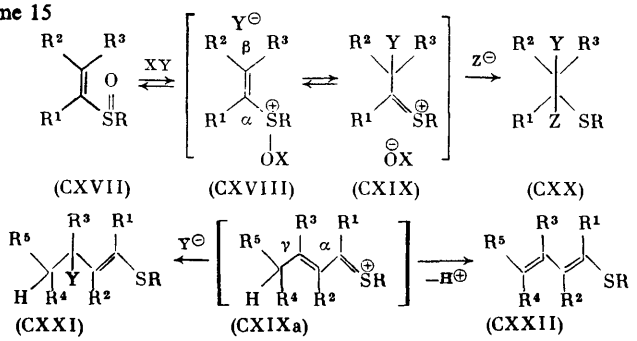
the SPR was recently proposed.[76–78] In this variant when components (I) and (CXVI) are allowed to stand in MeCN in the presence of 1.2–2.4 mole equivalents of ZnI_2, this generally gives a mixture of silyl ethers (Va, b) and vinyl sulphides (VI), whose ratio depends on the nature of the initial substrate (I). The reaction evidently occurs via a stage involving the PI (IV′), which when the trimethylsilyl ketenacetal (CXVIa) is used can react with the carbanion of methyl acetate or methyl isobutyrate formed as a result of decomposition of the latter (see Section VII). This does not occur in the case of acetal (CXVIb), which contains a sterically bulky substituent.

Thus, the SPR provides a simple means of converting sulphoxides to α-silyloxysulphides or related vinyl thioethers that have considerable synthetic potential.

VI. Vinyl sulphoxides in the Pummerer reaction

Up to the present time the Pummerer reaction involving linear and cyclic vinyl sulphoxides (CXVII) (Scheme 15), achieving simple ways for their effective functionalisation, has been studied quite extensively.[79] The main feature of these compounds is that because of the electron-acceptor properties of the PPI (CXVIII), there is the possibility of attack by an external (or internal) nucleophile on its β-centre. A similar stabilisation of the cationoid PI (CXIX) leads in the end to α,β-disubstituted sulphides (CXX). When a hydrogen atom occurs at the γ-position of the initial molecule of (CXVII), the PI, as a result of an allylic shift, can take the form of (CXIXa), which gives the vinylogue derivatives (CXXI) or the diene sulphides (CXXII) (c.f. Scheme 12). Heterolysis of the C–Y bond in the PI (CXIX) will formally give reduction products of the initial vinyl sulphoxides (CXVII).

Scheme 15

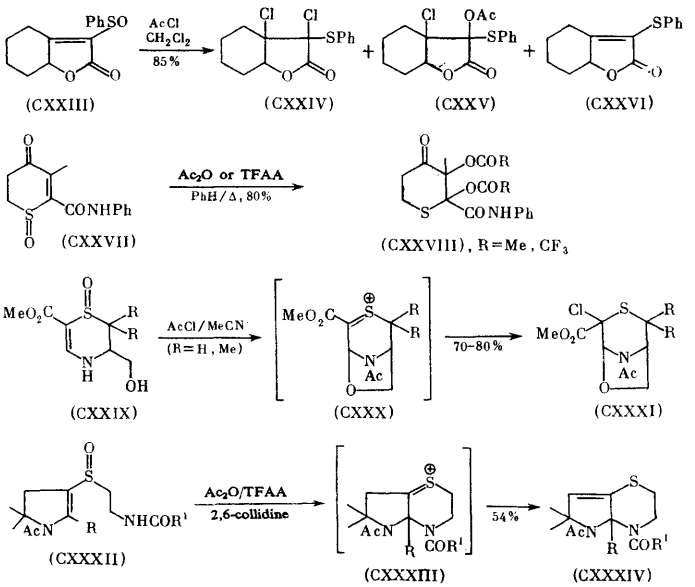


(CXVII) (CXVIII) (CIX) (CXX)

(CXXI) (CXIXa) (CXXII)

All of these PR routes for (CXVII) have been widely introduced at the present time. In particular, in Scheme 16, treatment of the sulphinyllactone (CXXIII) with AcCl gives a mixture of sulphides in the ratio (CXXIV):(CXXV):(CXXVI) ≃ 5:1:1,[79] whereas the diacycloxysulphides (CXXVIII) are obtained from (CXXVII) by treatment with Ac_2O or TFAA.[80,81] Conversion of the sulphoxides (CXXIX)[82] and (CXXXII)[83] to the corresponding bicyclic derivatives (CXXXI) and (CXXXIV) can serve as an example of the intramolecular stabilisation of a PPI of the type (CXVIII) via the intermediate ions (CXXX) and (CXXXIII).

Scheme 16



(CXXIII) (CXXIV) (CXXV) (CXXVI)

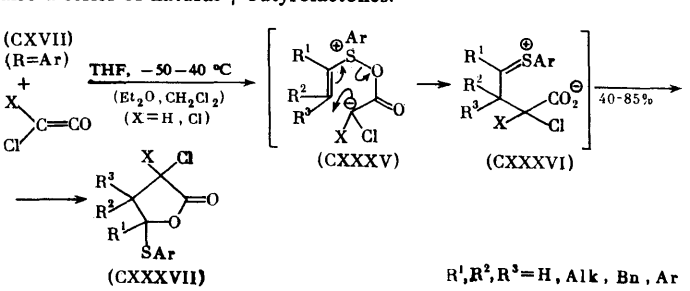
(CXXVII) (CXXVIII), R = Me, CF_3

(CXXIX) (CXXX) (CXXXI)

(CXXXII) (CXXXIII) (CXXXIV)

R = CO_2Me; R^1 = *p*-$CH_2C_6H_4NO_2$

"Activation" of aryl vinyl sulphoxides (CXVII) with chloroketenes which are readily generated from suitable acid chlorides has become the basis of a method that is widely used at the present time to obtain substituted γ-butyrolactones (CXXXVII), including natural products.[84–90] The reaction evidently occurs via the [3,3]rearrangement of the compact zwitterionic PPI (CXXXV) followed by intramolecular cyclisation of the PI (CXXXVI). The relatively high rate of the latter compared to rotation of the C–CS bond accounts for the high enantioselectivity of this process, which makes it possible when using a monosubstituted chloroketene to go from optically active (CXVII) to lactones with three induced chiral centres.[85] The method has been successfully applied to the synthesis of (–)-methyl jasmonate,[86] certain physostigmine alkaloids,[89] and also a series of natural γ-butyrolactones.[87,88,90]



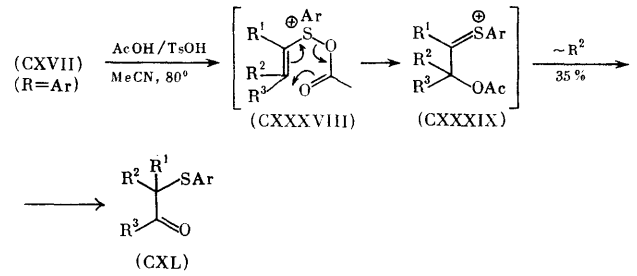
(CXXXV) (CXXXVI)

(CXXXVII)

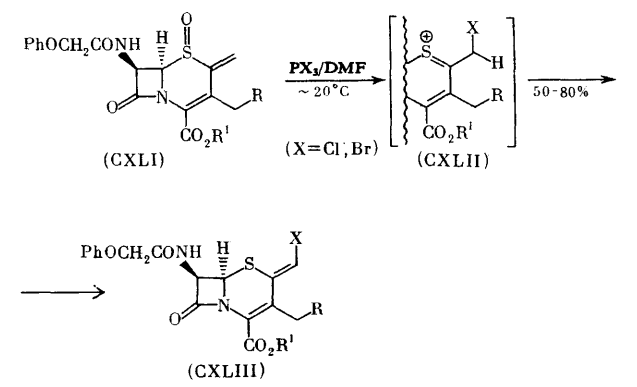
R^1,R^2,R^3 = H, Alk, Bn, Ar

With regard to the possible PR mechanism, one of the ways of stabilising the cationoid PI (CXIX) not included in Scheme 15 may involve a 1,2-shift of the R^2 and R^3 β-substituents. Examples of reactions of this type are for the time being fairly limited, but amongst them special mention should be made of the recently reported skeletal rearrangement of (CXVII) series aryl vinyl sulphoxides to ketosulphides (CXL), induced by TsOH in boiling MeCN and occurring preferentially via the formation of (CXXXVIII) and (CXXXIX)[91] (Scheme 17). The preparation of the halosulphoxides (CXLIII), which are evidently formed via PI (CXLII), under conditions of the Vilsmeier reaction from cephalosporin sulphoxides (CXLI) can be regarded as a specific case.[92] Similarly, the β-indole derivatives of the type (CXLIV), which are formally classed as vinyl sulphoxides, are readily converted by $SOCl_2$, probably via intermediates (CXLV) and (CXLVI), to the α-chloro-β-sulphides (CXLVII).[93,94]

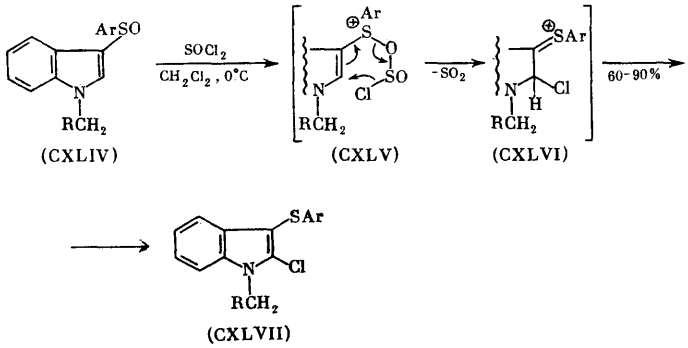
Scheme 17



R^1, R^2, R^3=H, Me: R^1, R^3=-$(CH_2)_4$-



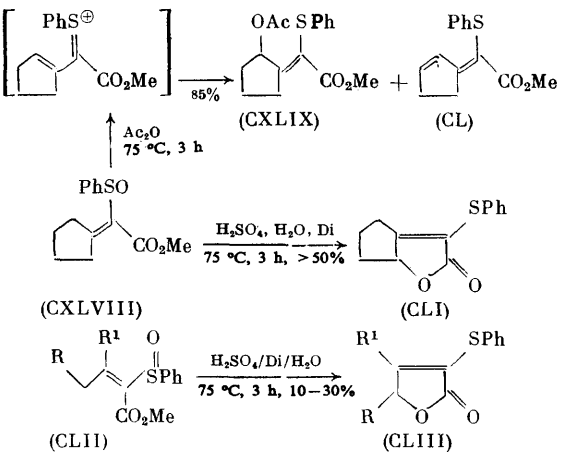
R=H, OAc; R^1=CH_2CCl_3, *p*-$CH_2C_6H_4NO_2$



R=Me, Ph, CO_2Me, CN, Bz

In addition to the routes given above in Scheme 15, the vinyl variant of the PR is illustrated by the conversion of the sulphoxide (CXLVIII) to a mixture of vinyl sulphides in the ratio (CXLIX):(CL) ≃ 3:2 or to the lactone (CLI)[79] (Scheme 18). Similarly, vinyl sulphoxides (CLII) on heating with dilute H_2SO_4 give the dihydrofuranones (CLIII).[79]

Scheme 18



Di = dioxan; R, R^1 = H, Me

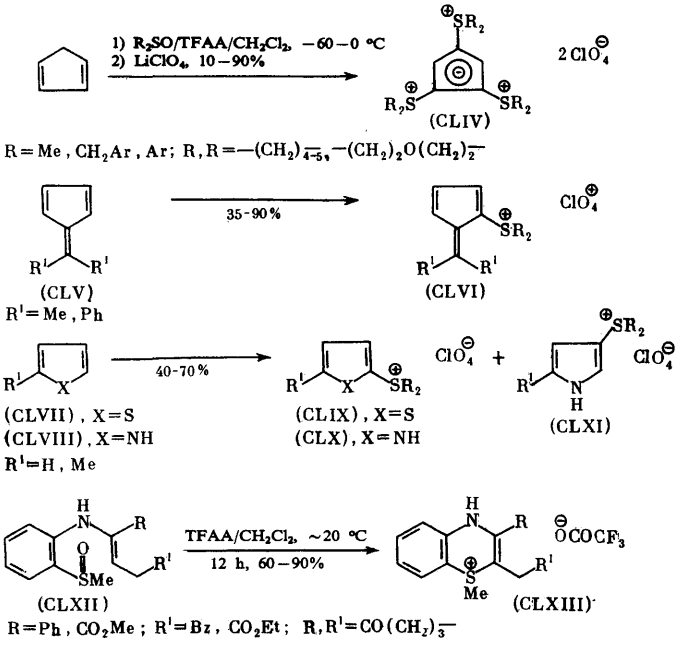
Thus, there is a direct Pummerer route from vinyl sulphoxides to sulphides that are functionalised at the α, β-, and γ-positions.

VII. Electrophilic properties of the intermediates of the Pummerer reaction

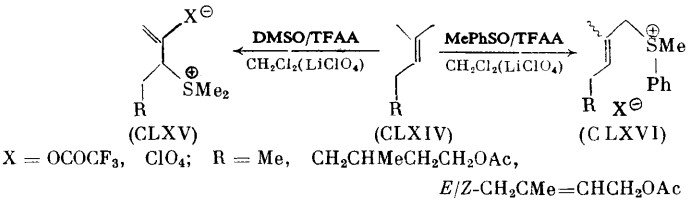
As mentioned above (Section II), the existence of the probable PR intermediates (II) and (IV)/(IVa), which are classified as weakly electrophilic species, has been indirectly supported by the results of the reaction between sulphoxides and different nucleophiles (external and internal). At the same time recent data provide additional information about the nature of the individual stages of this reaction, extending the possibilities for controlling it, and hence new horizons are opened up in the rapidly developing synthetic organic chemistry of sulphur-containing compounds.

In this respect the recently developed method for the synthesis of stable perchlorates of sulphonium salts from cyclopentadiene and (benzo)fulvenes[95-98] (Scheme 19) is of considerable interest. Thus, low-temperature treatment of sulphoxides "activated" by TFAA with cyclopentadiene or fulvenes (CLV) gives the tris-(CLIV) or mono-sulphonium salts (CLVI) in up to 90% yield, which are evidently formed respectively by attack on PPI of the type (II) by these *C*-nucleophiles. Derivatives of thiophene,[99] pyrrole, and indole[100-102] may fulfil a similar role. In particular, thiophenes (CLVII) are readily converted in this way to perchlorates (CLIX), while pyrroles (CLVIII) are converted to a mixture of the regioisomeric salts (CLX) and (CLXI) that is equilibrated on treatment with a proton acid. An example of the intramolecular interaction of a probable PPI with a reactive C=C bond is the smooth conversion of enaminosulphoxides (CLXII) to trifluoroacetates (CLXIII) by treatment with TFAA.[103]

Scheme 19



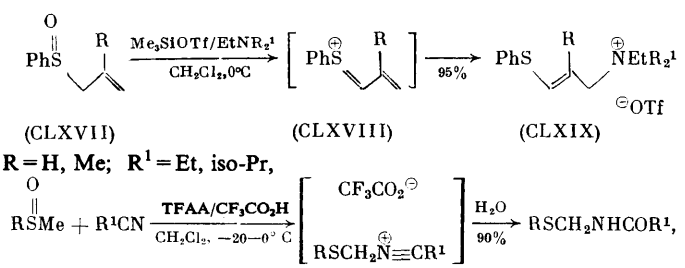
Taking into account the above, the recently established possibility of obtaining the fairly stable dimethyl sulphonium salts (CLXV) in this way from unactivated trisubstituted olefins (CLXIV)[104,105] proved unexpected. It was established in this case that this reaction, formally an ene reaction and accelerated by added quantities of $LiClO_4$, is regiospecific in a series of linear isoprenoid oligoolefins and is accompanied by allylic isomerisation with formation of the terminal sulphonium salt (CLXVI) in the case of thioanisole *S*-oxide.



The results of the synthetic application of the electrophilic properties of PR intermediates at the present time have proved much more fruitful in relation to the PI (IV) than to the evidently much more stable PPI (II). In this case inter- and intra-molecular stabilisation of the probable cationoid species (IV) by nucleophiles is now represented equally well and is illustrated below by the derivation of various α-functionalised sulphides from suitable linear and cyclic sulphoxides.

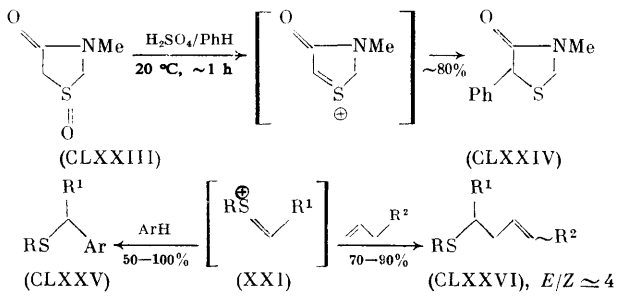
A unique example of this type of intermolecular interaction is the Me_3SiOTf-induced formation of ammonium salts (CLXIX) from allyl sulphoxides (CLXVII) in the presence of tertiary amines, including a Hünig base, which proved to be the only external nucleophiles capable of stabilising the PI (CLXVIII),[106,107] and there is also the Ritter reaction of sulphoxides (CLXX) to amides (CLXXII), which evidently occurs via the formation of nitrile salts (CLXXI)[108] (Scheme 20).

Scheme 20



Recorded cases of the involvement of a PI of the type (IV) in a reaction with external *C*-nucleophiles are much more widespread. Thus, in Scheme 21, the thiazolidine β-ketosulphoxide (CLXXIII) is readily phenylated on treatment with conc. H_2SO_4 in benzene to the ketosulphide (CLXXIV),[109] which is a special case of the (hetero)-arylation of PIs (XXI) that are generated by different methods from linear sulphoxides (XX) and mainly have a β-electron-withdrawing susbtituent, and resulting in products (CLXXV).[110–115] The presence of such a substituent is in no way obligatory for the formation of β-vinyl sulphides (CLXXVI) from PI (XXI) and functionalised terminal alkenes, which occurs quite readily by an ene type of reaction; (CLXXVI) have been successfully used at the key stages of the synthesis of a number of natural products.[116–122]

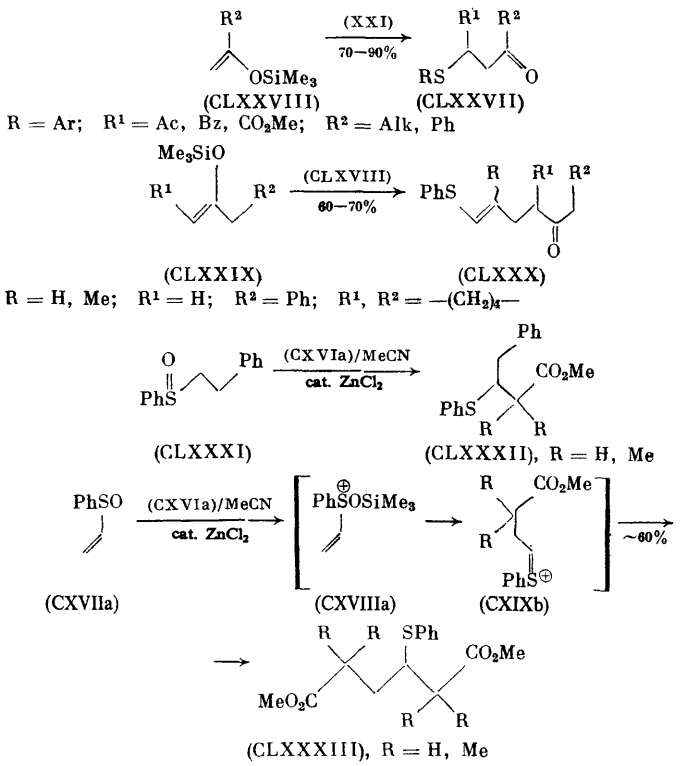
Scheme 21



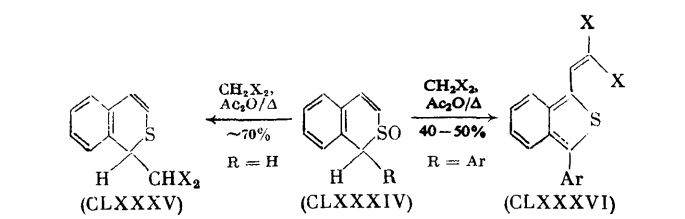
Of the *C*-nucleophiles that are suitable for intermolecular combination with a PI of the type (VI), particular importance is starting to be attached to silyloxyolefins such as (CLXXVIII) and (CLXXIX) (Scheme 22), which are widely used in current synthetic practice to form a C−C bond by a directed aldol condensation.[63,123] In accordance with this approach, the low-temperature generation of PI (XXI) or (CLXVIII), usually carried out with the involvement of "activator" reagents such as $Sn(OTf)_2$ or Me_3SiOTf in the presence of a Hünig base, bis(trimethylsilyl)(trifluoro)acetamide, or Me_3SiI finally gives the corresponding products of α-*S*-ketoalkylation (CLXXVII)[124,125] or γ-*S*-ketoalkylation (CLXXX).[107,126] Similarly, on treatment with an excess of ketenacetal (CXVIa)—an "activator" and *C*-nucleophile at the same time—the sulphoxide (CLXXXI) is readily converted to sulphide (CLXXXII),[77] evidently as a result of attack on a PI of the type (XXI) by the carbanions of methyl acetate or methyl isobutyrate (c.f. Section V). Under such conditions (CXVIa) and vinyl sulphoxide (CXVIIa) give adduct (CLXXXIII),

whose formation can only be logically accounted for by the successive reaction of the above carbanions with PPI (CXVIIIa) and PI (CXIXb).[78]

Scheme 22

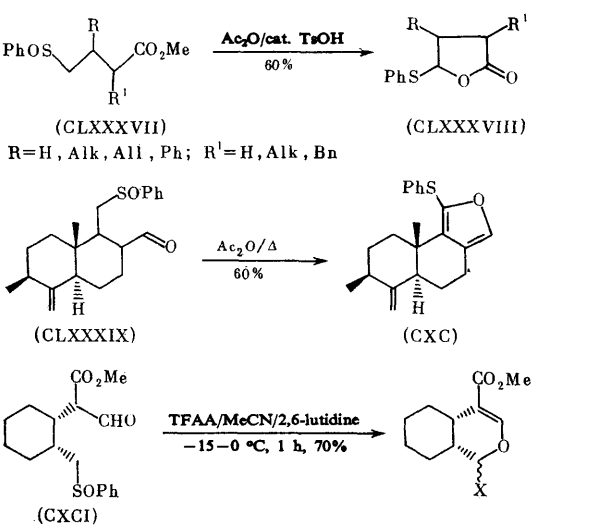


A familiar method for generating *S*-ylids from sulphoxides and C–H acids[11] in the case of derivatives of benzothiapyrans (CLXXXIV) leads to products of their α-*C*-alkylation (CLXXXV) or ring contraction products—benzothiophenes (CLXXXVI).[127]



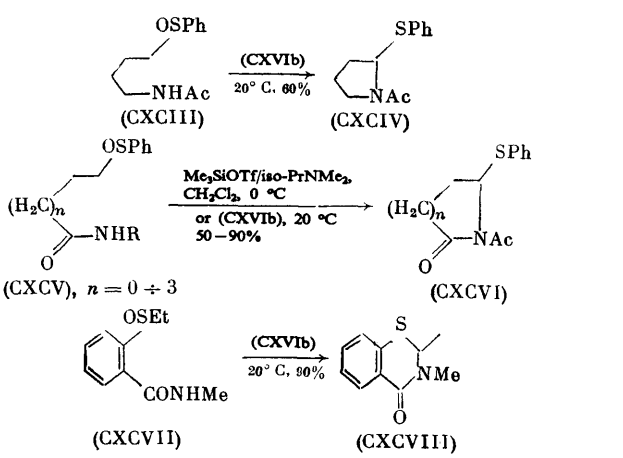
The methods of stabilising PIs of the type (IV) generated *in situ* using internal *O*-, *N*-, or *C*-nucleophiles as predicted from the probable mechanism of the PR open up considerable possibilities for the regiocontrolled synthesis of different heterocyclic and carbocyclic structures from suitable precursors. The conversions of γ-sulphinylcarboxylate esters (CLXXXVII) to lactones (CLXXXVIII),[128] aldehyde (CLXXXIX) to furan (CXC),[129] and sulphoxide (CXCI) to a mixture of (CXCIIa) and (CXCIIb) in the ratio ≃ 1:4, which is subsequently used in the synthesis of the iridoid aglycone of sweroside,[130] can be given as examples (Scheme 23).

Scheme 23



Of *N*-nucleophilic functional groups that are capable of undergoing an intramolecular reaction with a PI, the only known example up to the present time is the amide group.[131–135] For example, in Scheme 24, the amidosulphoxide (CXCIII) in the presence of ketenacetal (CXVIb) readily gives the pyrrolidine derivative (CXCIV),[134] whereas sulphinylamides (CXCV) are readily converted under mild conditions to the heterocyclic sulphides (CXCVI). Treatment of the optically active sulphoxide (CXCV) (n = 0, R = H) with Me_3SiOTf gives the corresponding chiral lactam (CXCVI) with an enantiomeric purity of 70%.[132] By using ketenacetals (CXVIb) in the case of (CXCVII) it is possible to synthesise the benzothiazine (CXCVIII),[134] which is unobtainable when traditional "activators" such as Ac_2O are used.[133]

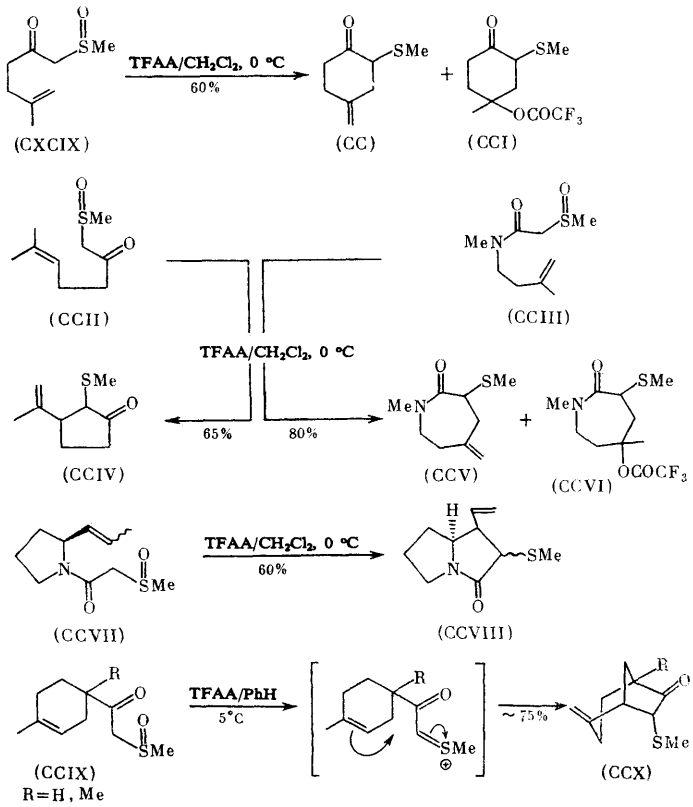
Scheme 24



An unactivated C=C bond within the molecules of unsaturated sulphoxides also can and does serve as a nucleophilic residue that participates in the stabilisation of the corresponding PI, and in all of the known examples this variant of the PR requires β-ketosulphinyl substrates.[136–141] Thus, in Scheme 25, the keto derivative (CXCIX) can be readily converted to the mixture of cyclohexane

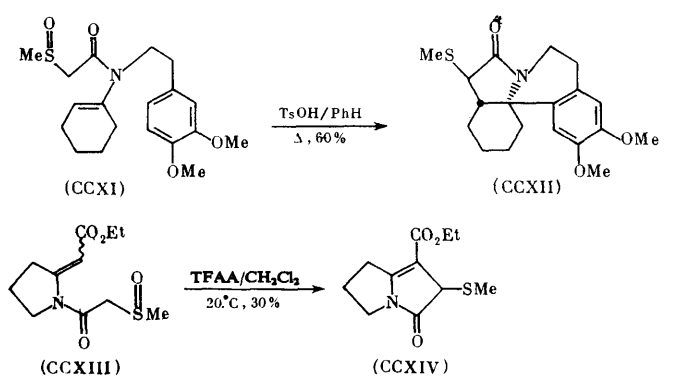
α-ketosulphides (CC) and (CCI).[138] The five-membered product (CCIV) (*cis*:*trans* ≃ 2:1)[138] and seven-membered (CCV) and (CCVI)[139] are obtained from sulphoxides (CCII) and (CCIII) by the same method. The bicyclic compounds (CCVIII)[140] and (CCX)[141] are prepared in high yield by electrophilic cyclisation of the precursors (CCVII) and (CCIX) respectively.

Scheme 25



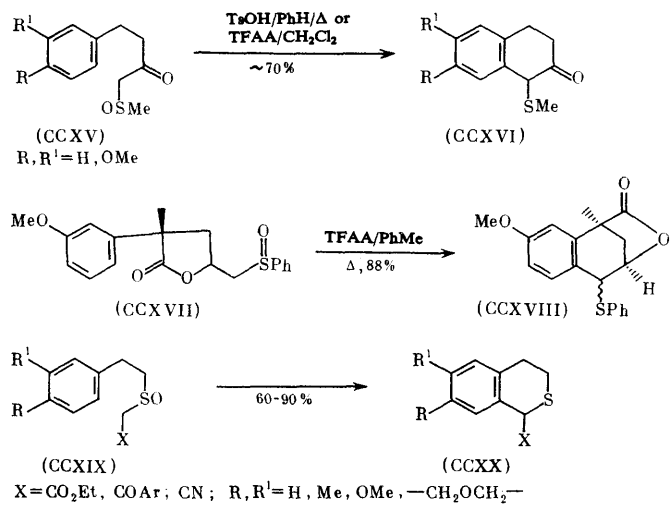
The results of cyclisation of sulphinyl derivatives of enamides by the Pummerer reaction, such as the reactions of (CCXI)[142–145] and (CCXIII)[146] to the erythrinan (CCXII) and pyrrolizidine (CCXIV) respectively, indicate that an increase in nucleophilic capacity of an internal C=C bond is not always accompanied by an increase in the efficiency of the process (Scheme 26).

Scheme 26



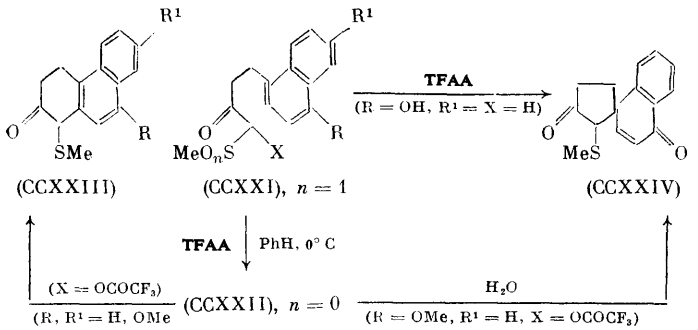
In addition to those reactions considered above, a large number of possible variants of the intramolecular stabilisation of PIs generated by various methods involving a (hetero)aromatic residue of the initial molecule have been reported. Thus, the well-established[147,148] cyclisation of aromatic ketosulphoxides of the type (CCXV) to tetralones (CCXVI) (Scheme 27) has now been considerably extended through examples of the synthesis of related five-, six-, and seven-membered bi- and tri-cyclic structures.[149–153] In particular, the conversion of the phenyl sulphoxide (CCXVII) to the tricyclic lactone (CCXVIII) is used as the basis of the enantio-controlled synthesis of (+)-aphanorphine.[153] The series of benzothiopyrans (CCXX) is prepared in a similar manner from sulphoxides (CCXIX) and a number of their derivatives.[154–158]

Scheme 27



In principle, cyclisation of the above ketosulphoxides induced by carboxylic anhydrides can occur, as a result of equilibrium (*4*) (Scheme 1), with the involvement of *gem*-acyloxysulphides of the type (V) (Z = OCOR) as kinetically independent species. This is quite extensively used (c.f. Section III) for the formation of a C–C bond based on stable *gem*-derivatives of this series,[159,160] and in particular for the two-stage preparation of these cyclisation products.[112–122,136–141] During the direct cyclisation of keto-sulphoxides, *gem*-derivatives of the type (V) can sometimes be isolated[136–141] or detected spectroscopically. Thus, in Scheme 28,[149] analysis of a mixture of (CCXXI) (X = H) and TFAA by NMR spectroscopy indicates that there is a rapid formation of the sulphide (CCXXII) (X = $OCOCF_3$), which is then slowly converted to the tricyclic product (CCXXIII). It is worth noting that treatment of the reaction mixture at this stage with 1 mole equivalent of H_2O gives the spirodiketone (CCXXIV), as does the addition of TFAA in benzene to (CCXXI) (R = OH, R^1 = X = H).

Scheme 28

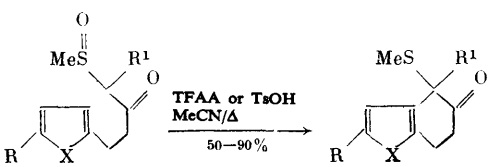


(CCXXIII) (CCXXI), $n = 1$ (CCXXIV)

(CCXXII), $n = 0$

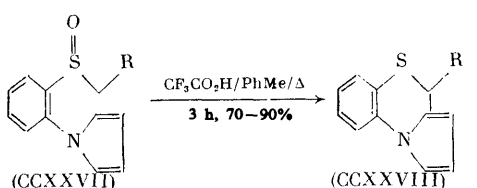
The application of this approach to the synthesis of condensed pyrrole and thiophene derivatives is demonstrated (Scheme 29) by the cyclisation of the precursors (CCXXV) to ketosulphides (CCXXVI) on treatment with different "activating" agents.[161] Similarly, heating of sulphoxides (CCXXVII) with CF_3CO_2H in toluene gives the tricyclic sulphides (CCXXVIII) in high yield.[162]

Scheme 29



(CCXXV) (CCXXVI)

X = NH, S; R = H, Ph; R¹ = H, CONHPh,

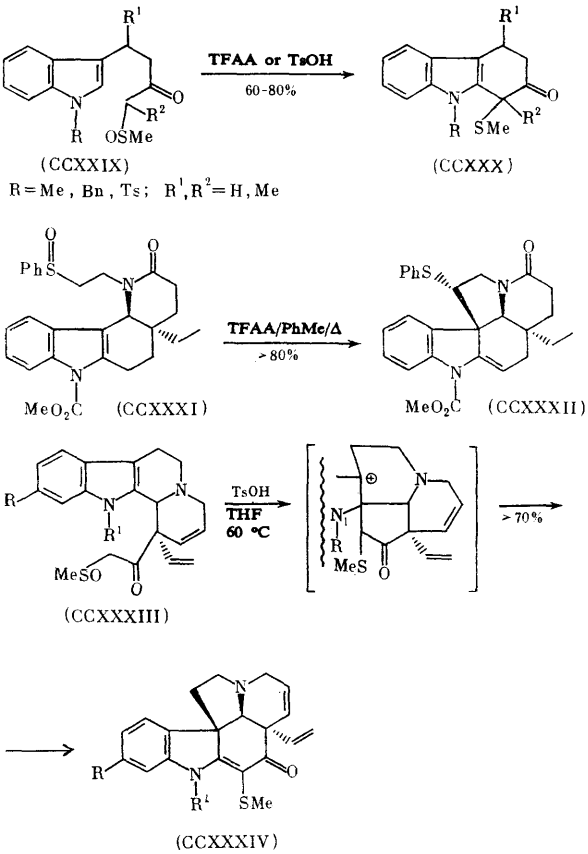


(CCXXVII) (CCXXVIII)

R = CO_2Et, Bz, CN.

The use of the PR for the stereoselective synthesis of polyheterocyclic structures such as indole alkaloids has proved extremely productive. As an illustration, Scheme 30 shows the preparation from the bicyclic precursor (CCXXIX) and tetracyclic precursors (CCXXXI) and (CCXXXIII) of the corresponding tricyclic compound (CCXXX) and pentacyclic compounds (CCXXXII) and (CCXXXIV), which act as key products in the total synthesis of olivacine and ellipticine,[161,163] (±)-8-oxotabersonine,[164] vindorosine, and vindoline.[165,166] These reactions have been used as the basis for the recently developed strategy for the total synthesis of other pentacyclic indole alkaloids.[167–171]

Scheme 30



R = H, OMe; R^1 = Me, CH_2OMe

Thus, sulphoxides can be successfully used in the PR for the intra- and inter-molecular variants of forming a C–C, C–N, C–O, and C–S bond, which is difficult to achieve by other methods.

Thus, the PR at the present time is a powerful tool in fine organic chemistry, making it possible to obtain in different ways from various primary and secondary sulphoxides functionalised linear, carbocyclic and heterocyclic sulphides, sulphonium salts, carbonyl compounds, and other classes of organic compounds.

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