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The use of selenium containing intermediates to mediate or catalyze new organic reactions

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Abstract

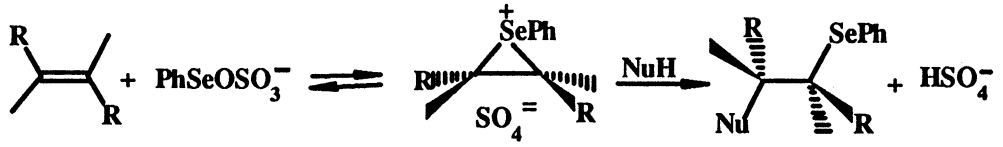
Ammonium peroxydisulfate reacts with diphenyl diselenide to produce phenylselenenyl sulfate which acts as a strong selenenylating agent of unsaturated compounds. The same oxidizing agent also reacts with alkyl phenyl selenides giving rise to substitution or elimination products and regenerating the selenenylating species. A multi step one pot procedure, which requires only catalytic amounts of diphenyl diselenide, is presented and illustrated by several new or traditional conversions of functional groups. Iodobenzene diacetate can also be employed to oxidize PhSeSePh and to effect the selenenylation of unsaturated compounds. When sodium azide is employed the fastest process becomes the oxidation of the azido anions to azido radicals. The azido phenylselenenylation products are thus formed as the result of a radical addition. These versatile compounds have been employed to effect the syntheses of pyridine derivatives and of lactams.

The phenylseleno group is a very useful and versatile functionality which can be easily introduced into organic molecules, through either nucleophilic or electrophilic processes, and which can then be easily removed with simple oxidative or reductive methods. The great synthetic utility of the phenylseleno group is demonstrated from its extensive utilization in numerous natural products syntheses, as well as many other synthetic studies (Ref. 1-9). In every case the introduction and the removal of the PhSe group are effected stepwise and require the use of stoichiometric amounts of the selenium containing precursor. The scope of the present research is to demonstrate that in certain cases it is possible to effect the two processes in one pot and, most interesting, with catalytic amounts of the simplest organic selenium derivative, i.e. diphenyl diselenide.

The most common reagents employed to effect the electrophilic phenylselenenylation of unsaturated compounds are PhSeCl and PhSeBr. These however give rise to some undesirable processes such as incorporation of the halide anions and considerable decrease in selectivity. Furthermore, very often the addition products react with the selenenylating agents, with rates similar to those of the starting products, giving rise to deselenenylated compounds (Ref. 10,11). Several phenylselenenylating agents which do not contain nucleophilic counter anions have been therefore introduced. Some of them were prepared from PhSeCl, like the phenylseleno phthalimido (Ref. 12), or generated *in situ*, with silver salts, like the antimonate, phosphate (Ref. 13), sulfonate (Ref. 14) or triflate (Ref. 15). In other cases the phenylselenenylating agent was produced *in situ* from the oxidation of PhSeSePh. This can be realized electrochemically, photochemically or chemically. Some years ago we have introduced the use of ammonium peroxydisulfate (Ref. 16-18), and more recently that of iodobenzene diacetate (Ref. 19). Arylsulfonyl peroxides have also been employed (Ref. 20). This paper describes several conversions of functional groups which are made possible by the oxidation of PhSeSePh with ammonium peroxydisulfate or with iodobenzene diacetate.

According to the equation reported below, it is suggested that the reaction of PhSeSePh with ammonium peroxydisulfate is an electron transfer process which produces the radical cation of the PhSeSePh. Fragmentation of this new reactive species eventually gives phenylselenenyl sulfate. Since the sulfate is a resonance stabilized non nucleophilic counter anion, the Phenylselenenyl sulfate behaves as a strong electrophilic reagent.

$$PhSeSePh + S_2O_8^{=} \longrightarrow [PhSeSePh^{+\cdot}\ SO_4^{-\cdot}\ SO_4^{=}] \longrightarrow 2\ PhSeOSO_3^{-}$$

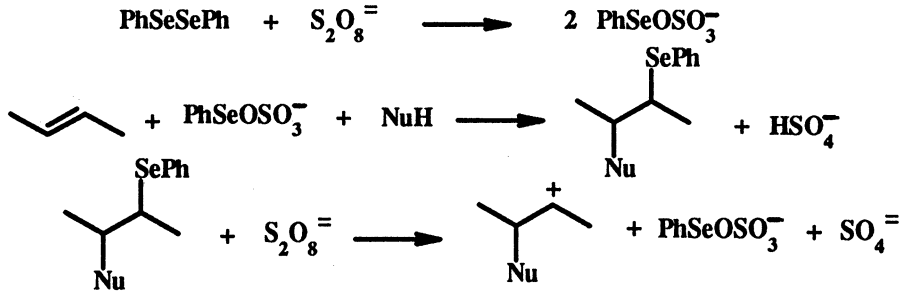


The reactions with alkenes in the presence of several nucleophiles proceeded smoothly to give the corresponding addition products. Stereospecific seleno alkoxylation, hydroxylation, amidation and sulfamidation processes were described. In some cases these reactions were not completely regiospecific (Ref. 16-18). In a similar way, phenylselenenyl sulfate reacted with alkenes containing internal nucleofiles to give ring closure reactions. Products of seleno etherification and seleno lactonization were obtained starting from different kind of substrates (Ref. 21-24).

These examples demonstrate the great versatility of this reagent and its utility in synthesis with considerable advantages over the previously reported ones. However, the use of PhSeSePh and ammonium peroxydisulfate is not limited to this aspect, but it opens the way to much more interesting processes in which PhSeSePh can be used as catalyst. All the reactions reported above were carried out with a small excess of PhSeSePh, since it was observed that the formed alkyl phenyl selenides could react with ammonium peroxydisulfate. It was soon clear that these selenides suffered deselenenylation regenerating the electrophilic species according to the reaction reported below. Radical cations of PhSeR are probably involved as rective intermediates in this fragmentation process also.

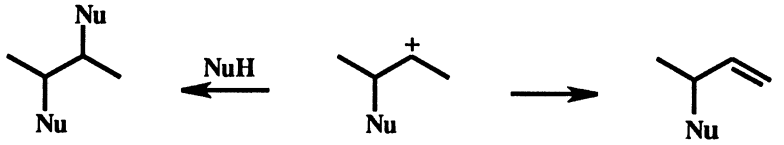
$$PhSeR + S_2O_8^{=} \longrightarrow PhSeOSO_3^{-} + SO_4^{=} + R^{+}$$

These observations allowed us to develop a multi step one pot procedure to effect several conversions of functional groups.

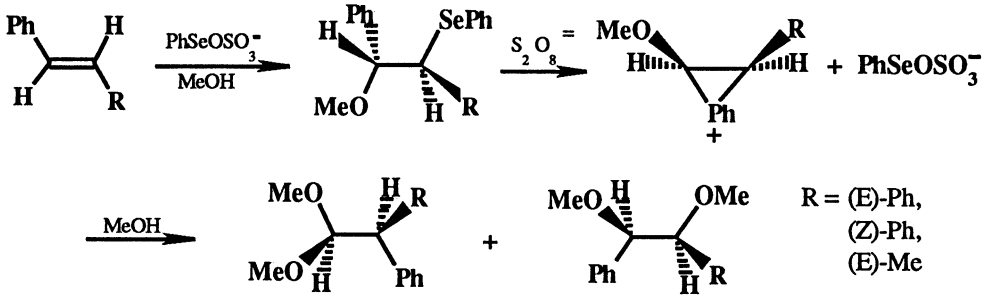


In fact, by using an excess of ammonium peroxydisulfate and only catalytic amounts of PhSeSePh, it is possible to effect in one pot all the following steps: the production of the selenenylating agent and its addition to an unsaturated compound, the oxidation of the resulting alkyl phenyl selenide and its fragmentation to a carbocation and phenylselenenyl sulfate. Depending on the structure of the starting unsaturated compound and on the

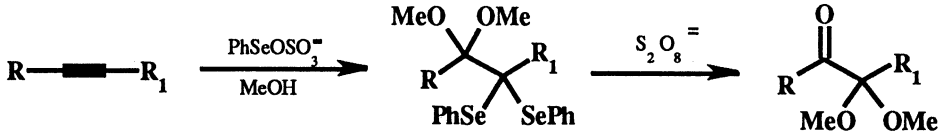
experimental conditions empoyed, the carbocation can evolve towards the substitution or the elimination products.



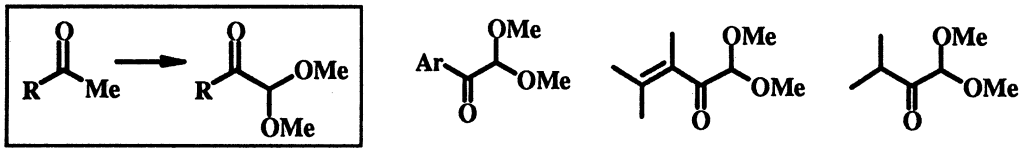
The first example of the utilization of this procedure is represented by the conversion of styrene derivatives into the corresponding 1,1- and 1,2-dimethoxy alkanes. The addition occurs stereospecifically in methanol to afford the products of seleno methoxylation. These are then oxidized by the peroxydisulfate and the elimination of the PhSe group is assisted by the phenyl group. The formation of an intermediate phenonium ion explains the phenyl migration to give the 1,1-dimethoxy compounds as well as the retention of configuration observed in the 1,2-dimethoxy derivatives (Ref. 16,17).

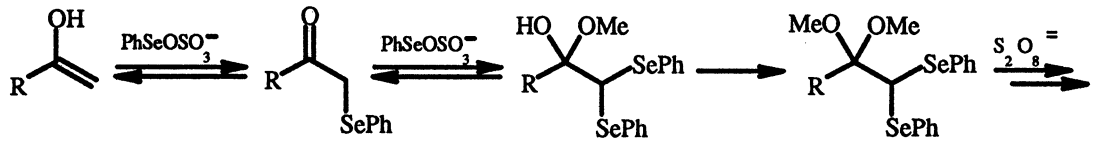


In the case of alkynes, the reaction proceeds to afford the products of double addition which are then deselenenylated by the excess of peroxydisulfate to give a tetramethoxy alkane. Under the conditions employed, deprotection occurs to afford α-keto acetals or α-keto ketals from terminal or internal alkynes respectively (Ref. 25).



An interesting case was observed with methyl ketones which, under the same conditions, gave α-keto acetals in good yield. This reaction seems to be of general application since it can be applied to aryl, vinyl as well as alkyl methyl ketone with excellent results in every case (Ref. 26).

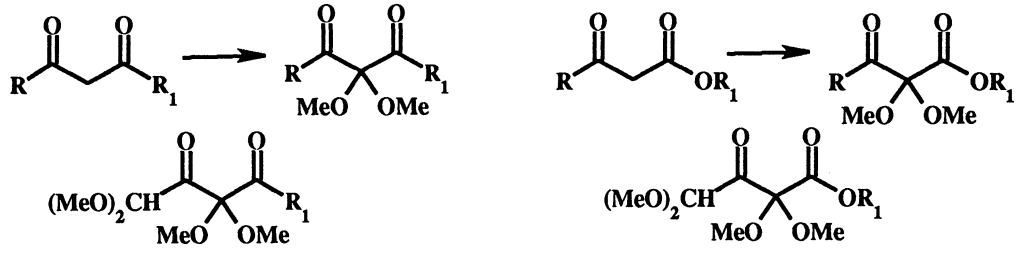




As indicated in the scheme, it is suggested that the addition occurs on the enolic form of the ketones to give the α-phenylseleno derivatives. These then give further addition to afford the same products which are formed from double addition to terminal alkynes. Reaction with peroxydisulfate then produces the observed products. The proposed course of the reaction was supported by isolation and identification of the products suggested to be involved as

intermediates. For this purpose experiments were carried out under controlled reaction conditions.

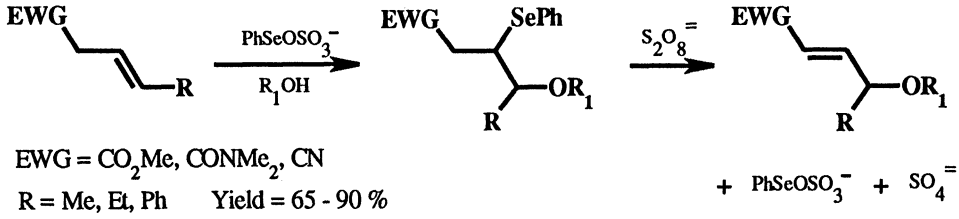
A further interesting transformation was observed with β-diketones and β-keto esters. When treated with ammonium peroxydisulfate and catalytic amounts of PhSeSePh in methanol, these compounds were converted into the corresponding monoprotected vicinal tricarbonyl compounds. Whenever the group linked to ketonic carbonyl was a methyl, a further product was formed. This was identified as the diprotected vicinal tetracarbonyl compound. the formation of these products represents a further example of the easiness with which the MeCO group is converted into the α-keto acetal under these experimental conditions (Ref. 27).



All the reactions descibed above were carried out in methanol. Similar good results were obtained using other alcohols also. Some experiments were also effected in water and in ethylene glycol. The structures of products obtained were those expected on the basis of the general course of these reactions.

In all the examples described so far the phenyl alkyl selenides were deselenenylated by the peroxydisulfate to afford the products in which the PhSe group is substituted by an alkoxy group. In these cases therefore the proposed carbocation intermediate evolves by association with the nucleophilic solvents. In order to observe its evolution towards the elimination products other conditions must be satisfied. First of all it could be suggested that the reactions must be carried out in non nucleophilic solvents. This however is not strictly necessary. We have observed that the structure of the starting unsaturated compound is the most important factor. Elimination reaction can become the preferred reaction pathway whenever an electron withdrawing group is present in the β position in respect to the carbon carbon double bond. Thus the driving force of these reactions is represented by the conjugation between this group and the double bond which is going to be formed. All the examples reported below refer to deselenenylation reactions with elimination in compounds which possess these prerequisites.

The first example of this type refers to β,γ-unsaturated esters, amides and nitriles which, on treatment with excess peroxydisulfate and catalytic amounts of PhSeSePh, in methanol or in water, gave, respectively, the γ-methoxy or the γ-hydroxy α,β-unsaturated derivatives (Ref. 28).

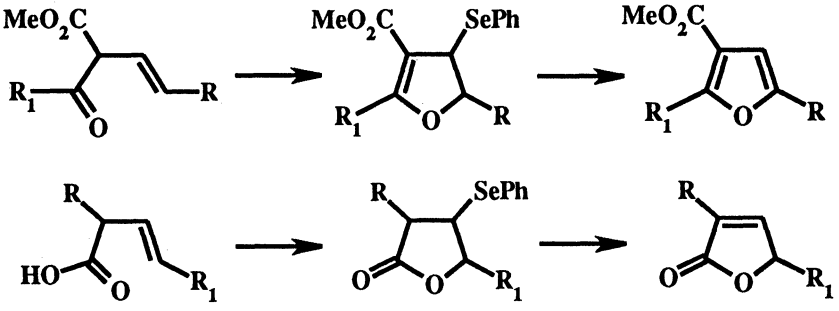


Very likely this conversion can also be effected stepwise by selenoxides elimination. Our procedure however is much more convenient since the entire process occurs in one pot and with catalytic amounts of the simplest selenium containing reagent.

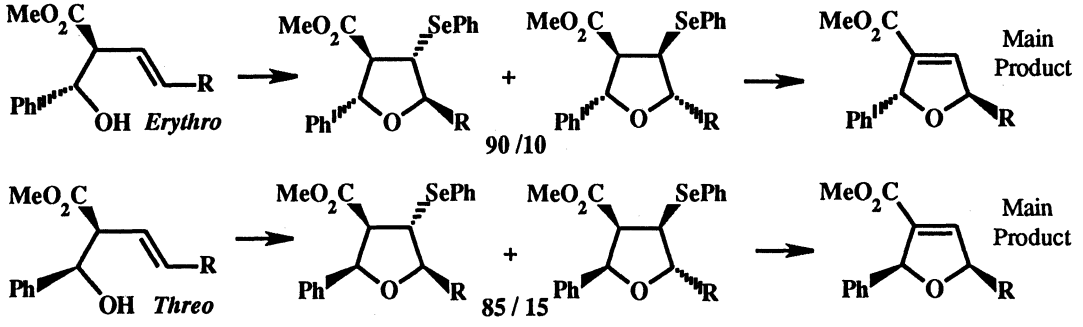
When effected in ethylene glycol this rection gives rise to interesting products which, under basic conditions, can be easily converted into dioxane derivatives.

When applied to alkenes containing internal nucleophiles, this procedure gives rise to ring closure reactions. Two interesting examples are described in the following scheme. The first

case refers to the direct conversion of α-vinyl β-dicarbonyl compounds into furans (Ref. 28) and the second to that of 3-butenoic acids into butenolides. In this latter reaction the carboxy group acts both as the internal nucleophile and as the electron withdrawing group which facilitates the elimination process (Ref. 28).



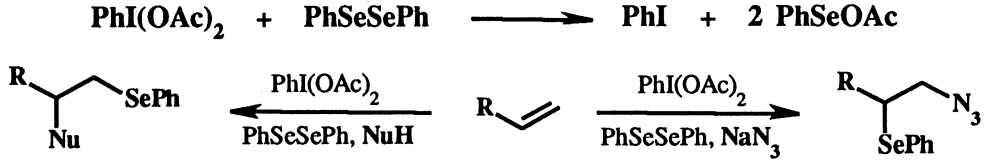
The one pot conversion of 3-alkenols into 2,5-dihydrofurans, which is illustrated in the following scheme, represents a further example of the versatility of our procedure. The reaction is very easy and proceeds with excellent yield. As observed in all the previously studied cases, the ring closure reaction is a *trans* stereospecific process. However, a detailed proton nmr investigation was required in order to establish the stereochemistry of the starting alkenols and of the final reaction products, as well as of the intermediate phenylseleno tetrahydrofurans. Therefore, experiments were carried out, under controlled reaction conditions, in order to isolate these intermediates. The *erythro* and *threo* configurations were assigned on the basis of the observation that in one case the protons of the carbomethoxy group of the two tetrahydrofurans have the normal value of 3.7-3.8 δ, whereas in the other case these protons were considerably shielded to 3.1-3.3 δ. This effect can be attributed to the phenyl group in the 5 position when it has a *cis* relationship with the carbomethoxy group. This can only occur in the two tetrahydrofurans deriving from the *threo* stereoisomer. In both cases the formation of one the two tetrahydrofurans was largely preferred. It is reasonable to assume that this stereoisomer is the one in which the PhSe and the carbomethoxy group are in *trans*. As a consequence, the *erythro* alkenol give mainly the *trans* dihydrofuran and the *threo* give mainly the *cis* derivative. The stereochemical assignments were confirmed by extensive differential NOE experiments of the four intermediate phenylseleno tetrahydrofurans and of the two final dihydrofurans (Ref. 28).



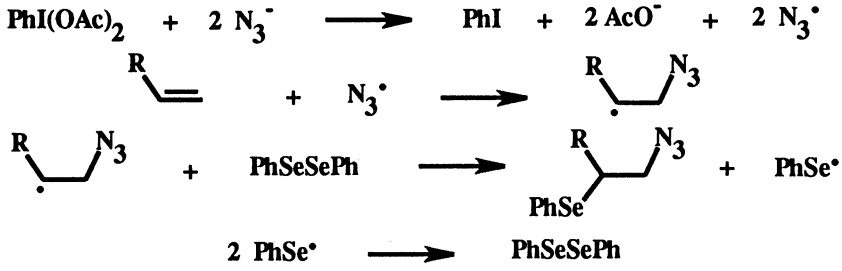
The examples described in this paper clearly demonstrate that ammonium peroxydisulfate and diphenyl diselenide represents a very useful system to produce a strongly phenylselenenylating agent which finds general application with considerable advantage over the other commonly employed reagents. However, the most important and unique property of this system is that it allows to effect several important conversions in a very easy way and with only catalytic amounts of PhSeSePh.

Another strong phenylselenenylating agent which we have recently introduced is the phenylselenenyl acetate which is produced *in situ*, in methylene chloride, from the reaction of

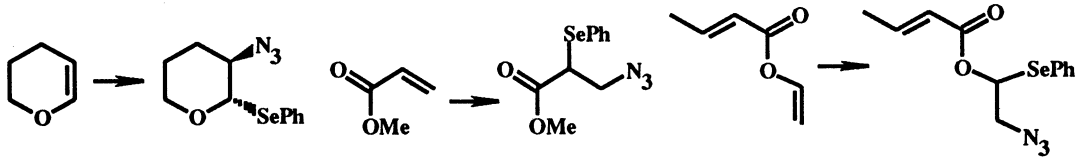
PhSeSePh with iodobenzene diacetate. The reactions with external or internal oxygen nucleophiles gave excellent results. Thus, under the appropriate conditions, reactions of seleno acetoxylation, alkoxylation, hydroxylation, etherification and lactonization were all carried out successfully (Ref. 28). With this new procedure it was also possible, using sodium azide as the nucleophile, to effect the azido phenylselenenylation of alkenes. In this case however the addition reaction occurred with an anti Markovnikov regiochemistry and it was not stereospecific. From the results of several parallel experiments we demonstrated that, under the conditions employed, the azido selenenylation of alkenes is a radical process (Ref. 19).



Thus the fastest reaction occurring in this case is the oxidation of the azido anion to the azido radical. This adds to the alkene to give a carbon radical which is trapped by the PhSeSePh. The proposed reaction mechanism is indicated in the following scheme.The addition of the PhSe radical to alkenes is a reversible process (Ref. 29) and therefore the favoured fate of this intermediate is the dimerization.



Owing to its radical nature this addition reaction can take place with several different kind of alkenes. This is examplified in the following scheme which shows the regioselectivity and the chemoselectivty of the addition when it is applied to enol ethers, α,β-unsaturated esters and α,β-unsaturated vinyl esters (Ref. 19).



The product of seleno azidation of alkenes have considerable synthetic importance sine they contain two very versatile functional groups. Both the PhSe and the azido group can in fact be easily converted.

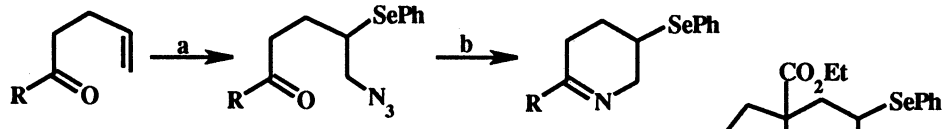
We now report several examples of the utilization of these compounds to develop new simple methods for the syntheses of important compounds which can be obtained with traditional methods only through a tedious series of steps.

The following examples are based on the use of the aza-Wittig reaction (Ref. 30). The reaction of an azide with triphenylphosphine generates imino phosphoranes which easily react with carbonyl compounds forming a carbon nitrogen double bond. With appropriate substrates, the intramolecular version of this reaction gives rise to nitrogen containing heterocyclic compounds.

The first example concerns the synthesis of tetrahydropyridines from γ,δ-unsaturated ketones.

As illustrated in the following scheme the seleno azides obtained from these compounds, when treated with triphenylphosphine in benzene, are transformed into the corresponding imino

phosphoranes which directly afford the cyclic compounds. Good yields are obtained in all the cases investigated (Ref. 28). The tetrahydropyridines obtained in this way can be used for further conversions since they still contain the PhSe group.

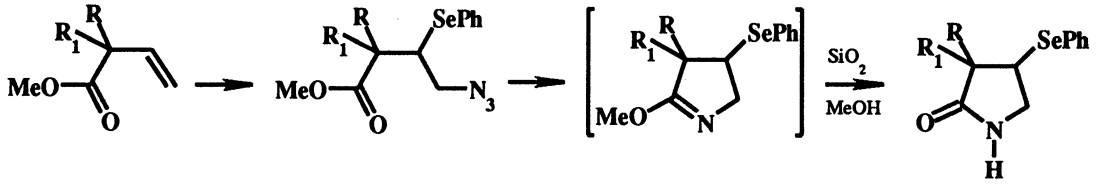


R = Me	71 %	74%
R = Ph	68 %	83 %
R = 2-Thienyl	68 %	67 %

78 %

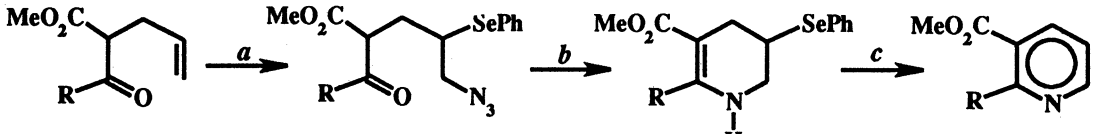
a) $PhI(OAc)_2$, PhSeSePh, NaN_3 b) PPh_3 in Benzene

The aza-Wittig reaction also occurs with the carbonyl of an ester group. This can be used to develop a new synthesis of lactams. Thus from the seleno azides of β,γ-unsaturated esters the cyclization reaction affords the imidates represented in parentheses in the scheme. These compounds can be identified by spectroscopic methods, but they are not easy to isolate. We found that the simple treatment with silica gel in methanol produces their transformation into γ-lactams. δ-Lactams can be equally obtained starting from γ,δ-unsaturated esters (Ref. 28).



$R = R_1 = H$	65 %	60 %
$R = H, R_1 = Me$	60 %	71 %
$R = R_1 = Me$	72 %	54 %
$R = Me, R_1 = PhCH_2$	63 %	87 %

Finally, in the molecules containing both the carbonyl group of a ketone and of an ester, like the α-allyl β-keto esters reported in the following scheme, the reaction involves selectively the ketone and affords phenylseleno carbomethoxy tetrahydropyridines. The double bond in this case becomes conjugated with the carbomethoxy group. When these compounds are treated with hydrogen-peroxide in methanol, the resulting selenoxides suffer spontaneous elimination. Dehydrogenation also occurs easily in this case since the final products are the aromatic pyridine derivatives. This reaction sequence can be advantageously employed to build up a 2 substituted pyridine nucleus. As indicated in the scheme we have used this procedure to obtain the three isomeric 2,2'-, 2,3'-, and 2,4'-bipyridyls containing the carbomethoxy group in the 3 position (Ref. 28).



R = Ethyl	52 %	82 %	55 %
R = Phenyl	50 %	75 %	90 %
R = 2-Pyridyl	65 %	80 %	76 %
R = 3-Pyridyl	60 %	85 %	87 %
R = 4-Pyridyl	62 %	90 %	82 %

a) $PhI(OAc)_2$, PhSeSePh, NaN_3 *b*) PPh_3, Benzene, 40°C, 4h *c*) H_2O_2 / CH_3OH, 0°C → r.t.

Acknowledgement

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