

NUCLEOPHILIC VINYLIC SUBSTITUTIONS ON UNACTIVATED SUBSTRATES.

THE BEHAVIOUR OF STYRYL ALKYL SULPHIDES AND SELENIDES TOWARDS SULPHUR AND SELENIUM NUCLEOPHILES.

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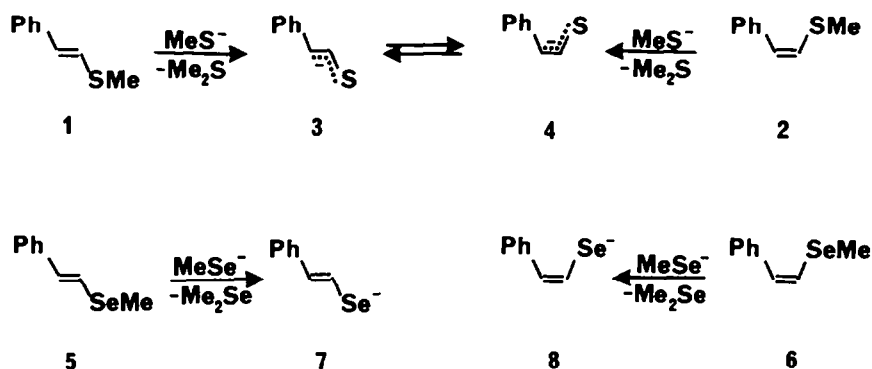
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**Abstract.** Sodium alkanethiolates or lithium methyl selenide react with styryl alkyl sulphides and selenides, in DMF at 100°C, to give the products of vinylic or aliphatic substitution. The two nucleophilic reagents are extremely selective. In the case of RSNa the attack at the vinylic carbon atom is much faster than that at the aliphatic carbon atom and the (Z)- or (E)- styryl alkyl sulphides are obtained as the result of a stereospecific vinylic substitution which occurs with retention of configuration. On the contrary, in the case of MeSeLi, under the same experimental conditions, the only reaction occurring is the aliphatic substitution which affords the vinyl thiolate anions, as an equilibrium mixture of the (E)- and (Z)- isomers, or the vinyl selenide anions which retain the configuration of the starting styryl alkyl selenides.

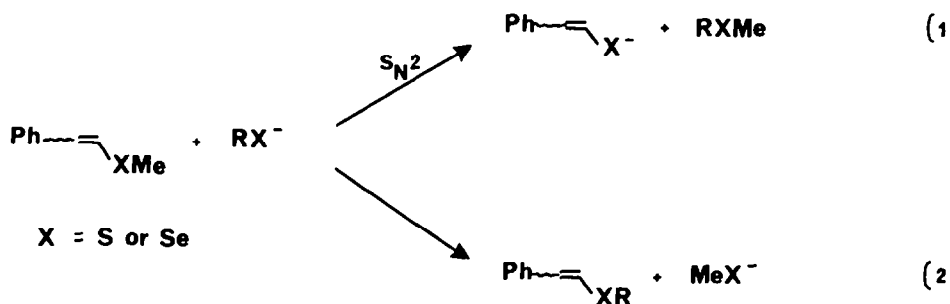
In a recent series of papers we have shown that sulphur, oxygen and selenium nucleophiles, when used in dipolar aprotic solvents, can easily effect aromatic substitution reactions on unactivated aryl halides. In this way several very simple and useful syntheses have been developed.<sup>1,2</sup> Sulphur<sup>3</sup> and selenium<sup>4</sup> nucleophiles also reacted with unactivated vinyl halides to give the vinyl alkyl or aryl sulphides and selenides; in every case these reactions were stereospecific and occurred with retention of configuration. The use of sodium methanethiolate and of lithium methyl selenide afforded the corresponding methylthio and methylselenyl derivatives. For instance, starting from the (E)- or (Z)- $\beta$ -bromostyrenes, compounds (1), (2), (5) and (6) (Scheme 1) were obtained in almost quantitative yields. If however the reactions were carried out under more severe experimental conditions (excess of nucleophilic reagent, higher temperature, longer reaction time), the initially formed  $\beta$ -(methylthio)styrenes and  $\beta$ -(methylselenyl)styrenes gave rise to a demethylation reaction which very likely occurred with an S<sub>N</sub>2 mechanism.<sup>5</sup> Interesting enough, whereas the (E)- (1) and (Z)- $\beta$ -(methylthio)styrene (2) gave rise to the same equilibrium mixture of the two isomeric anions (3) and (4), the demethylation of the (E)- (5) and (Z)- $\beta$ -(methylselenyl)styrene (6) gave instead the styryl selenide anions (7) and (8), respectively (Scheme 1). In the latter case therefore the selenide anions retain the configuration of the starting products and do not interconvert.<sup>6</sup> This property has been used to develop a very convenient stereospecific synthesis of vinyl alkyl selenides<sup>6</sup> and divinyl selenides.<sup>7</sup>

## SCHEME 1



All these results indicate that the attack of sulphur and selenium nucleophiles on styryl methyl sulphides and selenides occurs at the carbon atom of the methyl group to give an  $S_N2$  reaction (equation 1, Scheme 2). In principle another process is also possible in these substrates, namely the attack at the vinylic carbon atom to give a nucleophilic vinylic substitution (equation 2, Scheme 2). However in the examples investigated so far and collected in Scheme 1, even if this second process took place, it could not be evidenced since the nucleophiles and the leaving groups are the same and this type of reaction usually occurs with retention of configuration; the products of the nucleophilic vinylic substitution would therefore be identical to the starting products. Some preliminary evidences that the vinylic substitution process can actually take place were obtained during the work concerning the dealkylation of vinyl alkyl selenides.<sup>6</sup>

## SCHEME 2

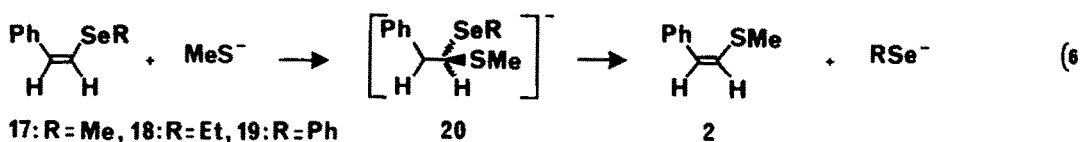
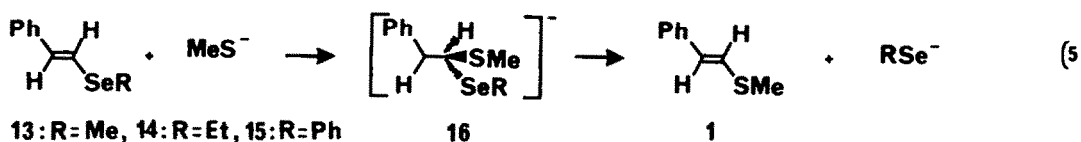
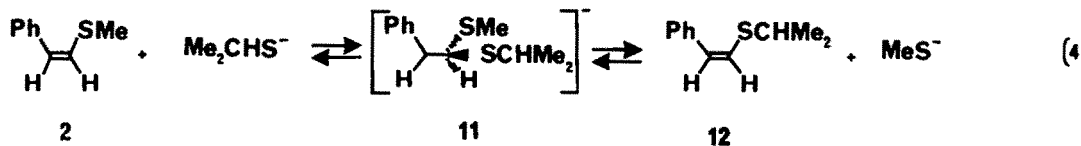
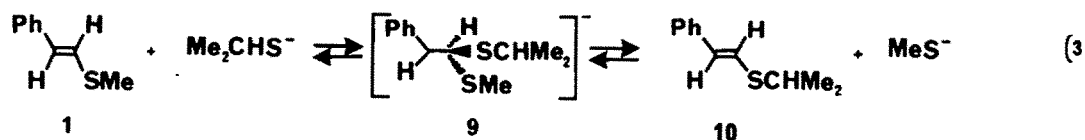


We now report the results of an investigation carried out with the aim of finding in which cases and under which conditions the vinyl alkyl sulphides and selenides can react with sulphur and selenium nucleophiles to give the products of vinylic substitution and what is its importance in respect to the  $S_N2$  process. For this purpose several  $\beta$ -(alkylthio)styrenes and  $\beta$ -(alkylselenyl)-styrenes were allowed to react with sodium alkanethiolates and lithium methyl selenide.

## RESULTS AND DISCUSSION

All the reactions described in this paper were carried out in DMF at 100°C. The reactions of (E)-**(1)** and (Z)-β-(methylthio)styrene **(2)** with sodium isopropanethiolate (equations 3 and 4, Scheme 3) afforded the (E)- **(10)** and (Z)-β-(isopropylthio)styrene **(12)** in 87 and 95% yields, respectively; the reaction time was 18 h. Compounds **(10)** and **(12)** reacted with sodium methanethiolate (equations 3 and 4, Scheme 3) to give **(1)** and **(2)** in 72 and 75% yields, respectively. Since the reactions can proceed in both directions, in order to obtain a complete transformation, the sodium alkanethiolates were used in large excess (10 mol) in respect to the β-(alkylthio)styrenes. In order to detect the

SCHEME 3



presence of the dealkylation products, i.e. the **(3)** and **(4)** anions, the reaction mixtures were treated with excess EtI prior to work up; glc analysis demonstrated that β-(ethylthio)styrenes were not present. These results indicate that, under the experimental conditions employed, the only reaction which takes place is the vinylic substitution, indicating that in every case the attack of the sulphur nucleophile at the vinylic carbon atom is much faster than the attack at the aliphatic carbon atom. This result is not unexpected in the case of compounds **(10)** and **(12)** since the S<sub>N</sub>2 process would require the attack at a secondary carbon atom; however, once **(10)** and **(12)** have been transformed into **(1)** and **(2)**, respectively, an excess of the MeS anion is still present in

the reaction mixture and the attack at the methyl carbon atom could now easily occur. This, however, under the conditions employed, was not observed. Similarly the reactions of (1) and (2) with an excess of  $\text{Me}_2\text{CHSNa}$  gave exclusively compounds (10) and (12). Clearly the attack of the sulphur nucleophile at the aliphatic carbon atom of these styryl alkyl sulphides is a process which can occur only under more severe experimental conditions. The reactions of (1) and (2) with  $\text{MeSNa}$ , described in the introduction, were run in hexamethylphosphoramide.<sup>3</sup> In this solvent all these reactions were much faster than in  $\text{DMF}$ <sup>1</sup> and the products were demethylated after 8 h at 80°C. On the light of the results described above it can be suggested that also in HMPA the vinylic substitution is the faster process, but it could not be revealed since the reaction products are identical to the starting products.<sup>8</sup>

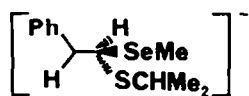
A similar reactivity was also observed in the case of the (E)- (13), (14), (15) and (Z)- styryl alkyl and phenyl selenides (17), (18), (19). From the reactions of these compounds with  $\text{MeSNa}$  the only products obtained were (1) and (2), respectively (reactions 5 and 6, Scheme 3). With the selenides the reactions occurred more easily than with the sulphides; a complete transformation was in fact obtained after 4 - 5 h and with the use of only 3 mol of  $\text{MeSNa}$ . From (13), (14) and (15) the (E)- $\beta$ -(methylthio)styrene was obtained in 75, 86 and 82% yields, and from (17), (18) and (19) the (Z)- $\beta$ -(methylthio)styrene was obtained in 87, 86 and 73% yields, respectively. The absence of the dealkylation products, i.e. of the anions (7) or (8), was demonstrated by glc analysis of the reaction mixtures after treatment with an appropriate alkyl iodide. In the cases of the phenyl derivatives (15) and (19) another reaction could in principle compete with the vinylic substitution, namely an aromatic nucleophilic substitution which would afford thioanisole as the reaction product (together with the (3) and (4) anions). This process does not occur since no traces of  $\text{PhSMe}$  were found when the reaction mixtures were analyzed by glc.

The reactions described above represent new and interesting examples of nucleophilic vinylic substitutions occurring on unactivated substrates. In previous works we have shown that these reactions occur with vinyl halides.<sup>3,4</sup> The present investigation demonstrates that sulphur nucleophiles can effect the vinylic substitution also in the case of vinyl sulphides and selenides. All these reactions occur with complete retention of configuration and, by analogy with previous works,<sup>9,10</sup> they can be seen as bimolecular substitutions which involve nucleophilic attack at the vinylic carbon atom holding the leaving  $\text{RS}$  or  $\text{RSe}$  groups. Whether these substitutions can be considered as single- or multistep processes, i.e. whether (9), (11), (16) and (20) are only transition states or whether they are reaction intermediates, it remains an open question which requires further and more detailed investigations. Whereas the reaction of the alkanethiolate anions with a vinyl alkyl sulphide (equations 3 and 4) is a reversible process, the reaction of the same anions with a vinyl alkyl selenide (equations 5 and 6) is irreversible, since, as we shall see below, the selenide anion does not effect the vinylic substitution on vinyl alkyl sulphides.

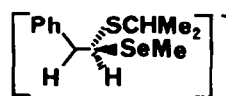
A completely different reactivity pattern was observed when the  $\beta$ -(methylthio)styrenes and the  $\beta$ -(methylselenyl)styrenes were treated with lithium methyl selenide. The reaction of (1) with an excess of  $\text{MeSeLi}$  (10 mol) was complete in 24 h; after this time the starting product was completely consumed and no other neutral product was formed. The reaction mixture was cooled at 25°C and treated with an excess of methyl iodide. A 3.5 : 1 mixture (glc and nmr) of (1) and (2) was obtained indicating that the only process which takes place in this case is the  $\text{S}_\text{N}2$  demethylation reaction

to give an equilibrium mixture of the two anions (3) and (4) (Scheme 1). The same 3.5 : 1 mixture was obtained from the reaction of (2) with MeSeLi under conditions identical to those described above. Reaction yields, based on isolated product after column chromatography, were 85 and 90%, respectively.

Under the same experimental conditions (100°C in DMF, with 10 mol of MeSeLi) the (E)- (10) and the (Z)-β-(isopropylthio)styrene (12) were recovered unchanged after 48 h. In this case the S<sub>N</sub>2 reaction is difficult since it requires the addition at a secondary carbon atom. The fact that (10) and (12) do not give any reaction product could indicate that the selenium anion does not effect the attack at the vinylic carbon atom. The same result, however, could be obtained also if this attack does occur since the resulting anions (21) and (22) are expected to evolve towards the starting products because the selenium anion is a better leaving group than the sulphur anion.<sup>2</sup>



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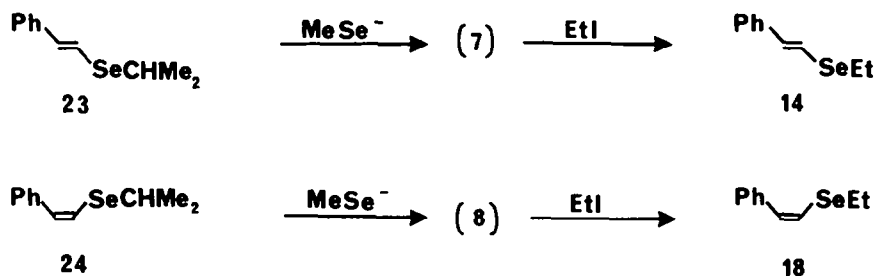
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The reactions of the styryl alkyl or styryl phenyl selenides with MeSeLi occurred much more easily than those of the styryl alkyl sulphides; a complete transformation was in fact obtained after 1 - 4 h and with only 4 mol of lithium methyl selenide.

The (E)- (14) and (Z)-β-(ethylselenyl)styrene (18), after 1 h, were stereospecifically converted into the vinyl selenide anions (7) and (8), respectively; the addition of isopropyl iodide to the reaction mixtures gave the (E)- (23) and the (Z)-β-(isopropylselenyl)styrene (24) in 90 and 88% yields, respectively. Thus (14) and (18) react in the same way as the corresponding methyl derivatives (5) and (6)<sup>6</sup> (see Scheme 1).

Also in the case of (23) and (24) the reactions took place easily (4 h) and afforded (7) and (8), respectively; the addition of ethyl iodide gave (14) and (18) in 92 and 86% yields. (Scheme 4).

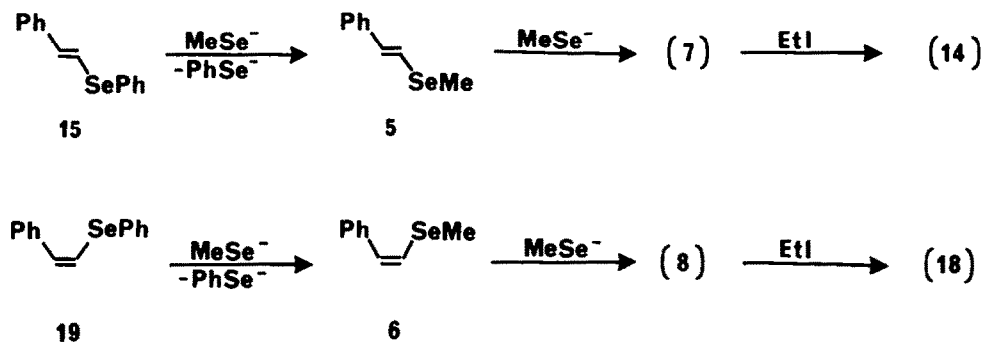
## SCHEME 4



The formation of (7) and (8) could be explained assuming that the selenium anion effects the  $S_N2$  process or assuming that it effects the vinylic substitution to give the methyl derivatives (5) and (6) which are then very rapidly dealkylated. This second hypothesis seems less likely since the progress of the reaction was followed by glc and the presence of (5) and (6) could not be detected, not even at the early reaction stages. This result could be explained assuming that the process of dealkylation of (5) and (6) is much faster than the process of their formation from (23) and (24). Such reactivity difference however does not seem justified since (as we shall see below) from the reaction of the phenyl derivatives (15) and (19) the (methylselenenyl)styrenes (5) and (6) could be easily found as reaction intermediates. Thus the results obtained from (23) and (24) seem to be better explained assuming that the anions (7) and (8) are directly formed through an  $S_N2$  process. As we have seen this reaction does not occur in the case of the  $\beta$ -(isopropylthio)styrenes neither with MeSNa nor with MeSeLi. The success of this reaction is probably due to the combination of a strong nucleophile, as the MeSe anion, with substrates which possess good leaving groups as the selenium anions (7) and (8).

Finally, the reactions of the phenyl derivatives (15) and (19) with MeSeLi afforded the anions (7) and (8) (3 and 1 h, respectively). These however do not form through a nucleophilic aromatic substitution. At the early reaction stages, in fact, the glc analysis of the reaction mixtures showed the presence of the  $\beta$ -(methylselenenyl)styrenes (5) and (6), together with unreacted (15) and (19), and the PhSe anion (This was identified as the PhSeEt after treatment of small aliquots of the reaction mixture with ethyl iodide). In this case therefore two consecutive reactions are taking place with comparable rates: first the vinylic substitution on (15) and (19) to give (5) and (6) which then suffer dealkylation to (7) and (8) (Scheme 5).

## SCHEME 5

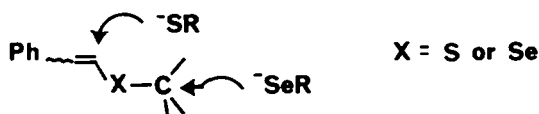


The treatment of the reaction mixture from (15) with ethyl iodide afforded PhSeEt (70%) and (14) (85%); similarly, PhSeEt (72%) and (18) (90%) were obtained from (19).

The conversions of (15) and (19) into (5) and (6) represent new examples of nucleophilic vinylic substitutions which are effected by the methyl selenide anions. From the results discussed above it is clear that with this nucleophile this reaction can occur only with the vinyl selenides and

more precisely with those selenides in which the aliphatic substitution is impossible or extremely difficult.

The whole of the results described in this paper thus demonstrate that the reactions of the styryl alkyl sulphides and selenides with sodium alkanethiolates or with lithium methyl selenide take two different courses with great selectivity. In the case of MeSNa or Me<sub>2</sub>CHSNa the attack at the vinylic carbon atom is much faster than that at the aliphatic carbon atom and the (E)- or (Z)-β-(alkylthio)styrenes are obtained in good yields as the result of a new stereospecific nucleophilic vinylic substitution which occurs with retention of configuration. On the contrary, in the case of MeSeLi the only reaction which occurs is the aliphatic substitution; thus, from the



styryl alkyl sulphides the vinyl thiolate anions are obtained as an equilibrium mixture of the (E)- and (Z)-isomers, whereas, from the styryl alkyl selenides, the configurationally stable vinyl selenide anions are produced with retention of configuration. The only case in which the MeSeLi effects the nucleophilic vinylic substitution is that of the styryl phenyl selenides where the aliphatic substitution is obviously impossible.

In every case the reactions with the styryl alkyl selenides occur more easily than those with the corresponding styryl alkyl sulphides. The preference of the selenium nucleophile for the attack at the aliphatic carbon atoms is not unprecedented; thus, lithium methyl selenide seems to be the best reagent to effect the S<sub>N</sub>2 cleavage of esters<sup>11</sup> as well as the selective dealkylation of aryl alkyl ethers, thioethers and selenoethers containing other functional groups which can also react with nucleophilic reagents.<sup>2</sup>

#### EXPERIMENTAL

NMR spectra were recorded (CDCl<sub>3</sub> solutions, Me<sub>4</sub>Si as reference) at 90 MHz on a Varian EM390 instrument. Glc analyses were performed on a Hewlett-Packard 5830A chromatograph with a 20 in., 10% UCW 982 column. Elemental analyses were carried out on a Carlo Erba Model 1106 Elemental Analyzer. Commercial (FLUKA) sodium methanethiolate was used without further purification. Sodium isopropanethiolate<sup>12</sup> and lithium methyl selenide<sup>3</sup> were prepared as described in previous works. The sulphides (1), (2), (10) and (12) were prepared as described in the literature.<sup>3</sup> The syntheses of the selenides (13), (17), (15) and (19)<sup>4</sup> and those of (14), (18), (23) and (24)<sup>6</sup> were effected, starting from the β-bromostyrenes, according to the procedures described in previous works. Their physical, nmr and analytical data are reported below.

(E)-β-(Methylselenenyl)styrene, (13), oil. δ 7.4 - 7.2 (m, 5H), 7.0 (d, 1H, J = 16 Hz), 6.5 (d, 1H, J = 16 Hz), 2.15 (s, 3H). Anal. Calcd for C<sub>9</sub>H<sub>10</sub>Se: C, 54.83; H, 5.12. Found: C, 54.05; H, 5.25.

(Z)-β-(Methylselenenyl)styrene, (17), oil. δ 7.45 - 7.2 (m, 5H), 6.85 (d, 1H, J = 10.2 Hz), 6.5 (d, 1H, J = 10.2 Hz), 2.15 (s, 3H). Anal. Calcd for C<sub>9</sub>H<sub>10</sub>Se: C, 54.83; H, 5.12. Found: C, 54.75; H, 5.05.

(E)-β-(Phenylselenenyl)styrene, (15), oil. δ 7.4 - 7.2 (m, 8H), 7.15 (d, 1H, J = 16 Hz), 6.8 (d, 1H, J = 16 Hz). Anal. Calcd for C<sub>14</sub>H<sub>12</sub>Se: C, 64.86; H, 4.68. Found: C, 64.80; H, 4.55.

(Z)- $\beta$ -(Phenylselenenyl)styrene, (19), m.p. 44 - 5°C (Lit.<sup>13</sup> m.p. 45 - 7°C).  $\delta$  7.65 - 7.5 (m, 2H), 7.45 - 7.2 (m, 8H), 6.9 (d, 1H, J = 10.2 Hz), 6.75 (d, 1H, J = 10.2 Hz). Anal. Calcd for C<sub>14</sub>H<sub>12</sub>Se: C, 64.86; H, 4.68. Found: C, 65.05; H, 4.75.

(E)- $\beta$ -(Ethylselenenyl)styrene, (14), oil.  $\delta$  7.4 - 7.2 (m, 5H), 7.0 (d, 1H, J = 16 Hz), 6.7 (d, 1H, J = 16 Hz), 2.8 (q, 2H, J = 7 Hz), 1.5 (t, 3H, J = 7 Hz). Anal. Calcd for C<sub>10</sub>H<sub>12</sub>Se: C, 56.87; H, 5.74. Found: C, 57.00; H, 5.85.

(Z)- $\beta$ -(Ethylselenenyl)styrene, (18), oil.  $\delta$  7.45 - 7.15 (m, 5H), 6.8 (d, 1H, J = 10.2 Hz), 6.4 (d, 1H, J = 10.2 Hz), 2.75 (q, 2H, J = 7 Hz), 1.45 (t, 3H, J = 7 Hz). Anal. Calcd for C<sub>10</sub>H<sub>12</sub>Se: C, 56.87; H, 5.74. Found: C, 57.05; H, 5.65.

(E)- $\beta$ -(Isopropylselenenyl)styrene, (23), oil.  $\delta$  7.25 - 7.05 (m, 5H), 6.85 (d, 1H, J = 16 Hz), 6.7 (d, 1H, J = 16 Hz), 3.3 (spt, 1H, J = 7 Hz), 1.4 (d, 6H, J = 7 Hz). Anal. Calcd for C<sub>11</sub>H<sub>14</sub>Se: C, 58.66; H, 6.28. Found: C, 58.50; H, 6.30.

(Z)- $\beta$ -(Isopropylselenenyl)styrene, (24), oil.  $\delta$  7.4 - 7.1 (m, 5H), 6.85 (d, 1H, J = 10.2 Hz), 6.65 (d, 1H, J = 10.2 Hz), 3.3 (spt, 1H, J = 7 Hz), 1.4 (d, 6H, J = 7 Hz). Anal. Calcd for C<sub>11</sub>H<sub>14</sub>Se: C, 58.66; H, 6.28. Found: C, 58.00; H, 6.25.

Reactions of styryl alkyl or aryl sulphides and selenides with MeSNa, Me<sub>2</sub>CHSNa and MeSeLi. All these reactions were carried out according to the following general procedure.<sup>2</sup>

To a solution of MeSNa or Me<sub>2</sub>CHSNa or MeSeLi in DMF (25 ml) the vinyl sulphide or selenide (0.01 mol) was added and the mixture was stirred under nitrogen at 100°C. The progress of the reaction was monitored by glc and tlc. When the starting product was consumed, the reaction mixture was cooled to 25°C and, when necessary, treated with an alkyl iodide (0.04 mol; 0.1 mol in the case of the reactions of (1) and (2) with MeSeLi). The mixture was poured on water and extracted with ether. The organic layer was washed with water, dried and evaporated. The residue was analyzed by tlc, glc and nmr and then chromatographed through a silica gel column, using light petroleum or mixtures of light petroleum and ethyl ether (up to 10%) as eluant. The amounts of MeSNa, Me<sub>2</sub>CHSNa and MeSeLi, the reaction times, the alkyl iodide employed and the reaction yields (based on isolated products after column chromatography and calculated from the amount of the vinyl sulphide or selenide employed) are reported under the Result and Discussion section. The reaction products were identified by comparison of their physical and spectral properties with those of authentic compounds.

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