Tetrahedron Vol. 35, pp. 2607 to 2610
Pergamon Press Ltd., 1979. Printed in Great Britain

RING OPENING REACTIONS—XV

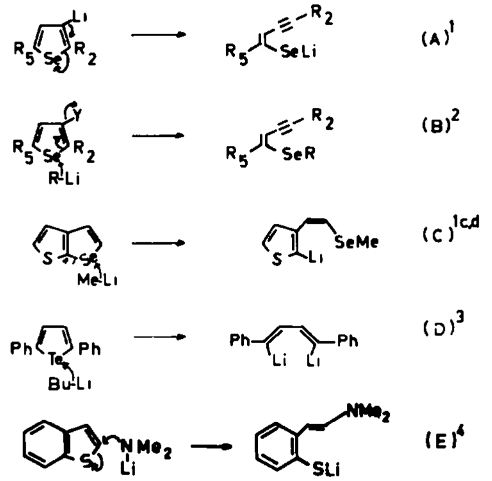
THE REACTION OF SOME 2,5-DISUBSTITUTED SELENOPHENES WITH BUTYL- AND PHENYLLITHIUM

S. Gronowitz*, A. Hallberg and T. Frejd
Division of Organic Chemistry 1, Chemical Center, University of Lund, P.O. Box 740, S-220 07 Lund, Sweden

(*Received in UK* 8 *June* 1979)

Abstract—The reactions of 2,5-dimethoxyselenophene with butyl- and phenyllithium have been examined. In view of the formation of dibutyl- and diphenylselenide, respectively, together with some dienes, a reaction sequence could be formulated in which the first step is an attack on the selenium atom by the lithium reagent.

Several ring-opening reactions of selenophenes have been discovered during the past few years,[1] and some characteristic reaction types are shown in Scheme 1.



Scheme 1.

These and other base-induced ring-opening reactions have been systematized and reviewed recently,[2] and it is apparent that ring-opening reactions of heterocyclic compounds in general are very common. However, most of these reactions are of the eliminative ring fission type (reactions A and B, Scheme 1), and much less is known about substitutional ring-openings (reactions C–E, Scheme 1). Some fused selenophenes,[1c,d] 2,5-diphenyltellurophene[3] and benso[b]thiophene[4] have been shown to undergo this latter reaction type and we have now found evidence that some non-fused selenophenes are also cleaved in a substitution-type reaction.

RESULTS

In connection with our studies of the syntheses and reactions of methoxythiophenes and methoxyselenophenes, we studied the reaction of 2,5-dimethoxyselenophene (1) with BuLi and PhLi in THF and diethyl ether. The reactions were quenched with dimethyl sulfate and the organic extracts analyzed by glc-mass spectrometry. Reaction conditions and results are summarized in Table 1. No trace of 2,5 - dimethoxy - 3 - methylselenophene could be found, which is to be expected based on a similar reaction of 2,5-dimethoxythiophene.[5] Instead, a 55% yield of dibutylselenide (2) was obtained when 1 was treated with 3 eq of BuLi. In addition, approximately 30% of butyl methyl selenide (3) was formed. When only one eq of BuLi was used, the yield of dibutylselenide was reduced to 30%, that of butyl methyl selenide to 10%, and 10% of 1 was recovered. The four-carbon backbone of the selenophene ring was transformed into the dienes 4 and 5, which were isolated by preparative glc. The stereoselectivity of the reaction could not be accurately determined, since at least 5 seemed to isomerize under the glc conditions. The structural proof of 4 was based on a correct mass number (*m*/*e* 142, 100%) and the presence of three singlets in NMR. Compound 5, which was the main component, also had a correct mass number (*m*/*e* 264 ^{80}Se) and the fragmentation of a butyl selenol (M-HSeBu), indicating a butyl selenide.[6] Its NMR spectrum was somewhat complicated due to the presence of an isomer (20%). The butyl resonances appeared as broad and partly resolved multiplets, but the resonances of the methoxy and vinyl groups were clearly resolved (in acetone-d_6) as two singlets and an AB quartet, respectively.

Unfortunately, no UV-data for substances similar to 5 seem to be available in the literature, but using Woodward's method for calculating λ_{max} for dienes, one arrives at a calculated value of 271 nm,[13] which is in good agreement with one of the experimentally found maxima (280 nm) for 5.

When 1 was treated with PhLi instead of BuLi at room temperature, the reaction was slower. After 20 hr, followed by quenching with dimethylsulfate, only 18% of diphenyl selenide was obtained, together with 27% of 1 and approximately 30% of methyl phenyl selenide. Several unidentified compounds were also formed, but 3 - methyl - 2,5 - dimethoxyselenophene could not be detected. In the reaction between 1 and lithium diisopropylamide, a large number of compounds was formed, which were not identified.

Recently, Luppold *et al.*[3] reported that 2,5 - diphenyltellurophene underwent ring cleavage with the BuLi/TMEDA reagent to give dienes upon hydrolysis or trapping of the intermediate divinyl lithium derivative with various electrophiles (Scheme 1, react D). Our attempts with 2,5-diphenylselenophene under the same

Table 1. Results and conditions of the reactions of some selenophenes with organolithium reagents[a]

Entry		RLi	Eq.	Time h	Solvent	RSeR %
1[b)]	**1** (R'=OMe)	C_4H_9Li	3	2	ether	55
2[c)]	**1**	C_4H_9Li	1	2	ether	30
3	**1**	C_6H_5Li	2	20	ether	18
4	**13** (R'=Ph)	C_4H_9Li	3	20	THF	4
5	**14** (R'=Me)	C_4H_9Li	3	20	ether	0

[a)] Dimethyl sulfate as trapping agent

[b)] The same amount of $C_4H_9SeC_4H_9$ was obtained when the reaction mixture was quenched with water.

[c)] Methyl iodide as trapping agent gave the same result as dimethyl sulfate.

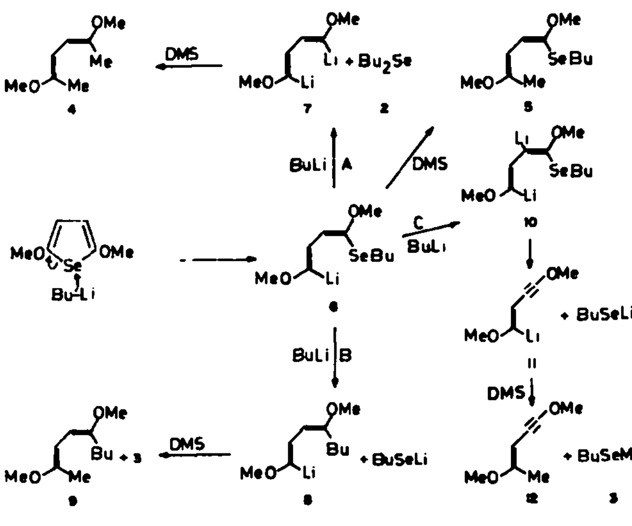
conditions showed that ring-cleavage had occurred. However, we could find no trace of a di-vinyl di-lithium derivative to give 1,4 - diphenyl - 1,3 - butadiene upon hydrolysis. Instead, 5,8 - diphenyl - 5,7 - dodecadiene (13) was formed as the main product (Scheme 3).

In the absence of TMEDA and in THF as solvent, 2,5-diphenylselenophene gave a low yield of dibutyl selenide (4%). A similar experiment with 2,5-dimethylselenophene gave no reaction at all.

DISCUSSION

The products obtained in the reactions with 2,5-dimethoxyselenophene can be rationalized according to the following scheme (Scheme 2). Attack of BuLi on the selenium atom leads to the ring-opened intermediate **6**, which upon reaction with dimethyl sulfate gives **5**.[13] Intermediate **6** has two reactive centers towards nucleophiles, namely the Se atom and its neighbouring vinyl carbon, which is a masked carbonyl carbon (ketene mono seleno-acetal). Further reaction with BuLi can give dibutyl selenide and the dilithium derivative **7** (through Se-attack) or butyl selenolate and the mono lithium derivative **8** (through carbon attack, perhaps by an addition-elimination process). All the nucleophiles thus formed should subsequently be trapped by the added dimethyl sulfate to give **3** and the dienes **4** and **9**.[7]

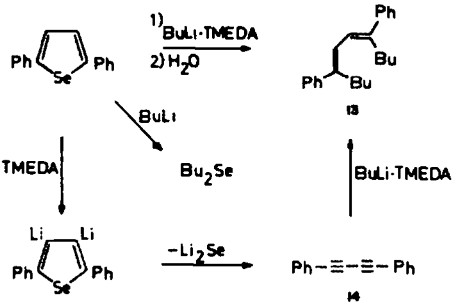
Conceivably, **6** could also be deprotonated by BuLi to give the dilithium derivative **10**, which easily eliminates butyl selenolate. The fate of the resulting "carbon"-fragment **11** is obscure (compound **12** could not be identified), but having masked carbonyl functions it may well react further with BuLi or other nucleophiles present in the reaction mixture, and also take part in addition reactions (over the triple bond)[12] to give intractable products. Thus, both routes B and C explain the formation of butyl methyl selenide. However, since we could not detect compound **9**, route C seems more likely: we can see no reason why **9** should not be stable under the same conditions as **4**. The formation of diphenyl



Scheme 2.

selenide and phenyl methyl selenide in the reactions with PhLi could be explained by similar reaction sequences.

The formation of 13 from 2,5-diphenylselenophene and BuLi/TMEDA apparently takes place through β-lithiation of the heterocycle followed by ring-opening (elimination type, Scheme 3), since 3,4 - dimethyl - 2,5 - diphenylselenophene, which has blocked β-positions, does not react under the same conditions. The ring-opening of 2,5 - diphenylselenophene probably leads to 1,4-diphenylbutadiyne (14), which reacts further with BuLi/TMEDA to give 13 after hydrolysis.[14] Whether 14 is formed from a lithiated 2,5-diphenylselenophene or the monolithium derivative through consecutive eliminations is not clear. In any case, it seems that 2,5-diphenylselenophene behaves quite differently from its Te-analogue.

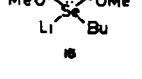


Scheme 3.

It is interesting that dibutyl selenide is formed with 2,5-diphenylselenophene and BuLi in THF (without TMEDA) but not with the BuLi/TMEDA reagent. This may reflect a change of the nucleophilicity/basicity ratio of BuLi upon TMEDA complexation, with the complex being more basic. However, with the more polarizable Te atom, the nucleophilic attack on the heteroatom is still the favoured reaction, and the ring-opening of 2,5-diphenyltellurophene may be formulated as depicted in Scheme 1, Formula D.

If the first step is a direct substitution on selenium it is also somewhat surprising that 2,5-dimethoxy- and to some extent 2,5-diphenylselenophene are attacked on the Se atom by BuLi, while 2,5-dimethylselenophene is not. One would expect that the strongly electron-releasing OMe groups would increase the electron density at the Se atom, thus making the approach unfavourable for the nucleophile ("butyl anion"). ^{77}Se NMR measurements seem to confirm that the electron density of the Se atom is higher for 2-methoxyselenophene than for 2-methylselenophene, since the ^{77}Se shift of the former substance appears at 91.3 ppm higher field than that of selenophene, while that of the latter appears at 3.8 ppm lower field.[8]

To overcome these problems one may argue that it is the Li atom of BuLi that is initially coordinated to the O atoms of the OMe groups.[10] This coordination would decrease the electron density at the Se atom, since one pair of the non-bonded electrons of the OMe groups would be tied up, making the inductive withdrawal effect of the OMe groups more important.[9] The Bu anion would then easily attack the Se atom. Thus it is possible that the tetracoordinated species 15 lies on the reaction coordinate leading to 6.[11]



15

EXPERIMENTAL

All experiments were performed in dry solvents under N$_2$. NMR spectra were recorded on a Jeol MH 100 and a Jeol FX 60 equipped with a ^{1}H probe.

The UV spectra were recorded on a Cary 16 spectrophotometer. Mass spectra were recorded with an LKB 900 mass spectrometer at 70 eV and gas chromatograms were recorded with a Varian 1400 gas chromatograph. Peak areas were calculated by triangulation.

The reaction of the 2,5-disubstituted selenophenes with organolithium reagents. The organolithium reagent (1.5 M BuLi in hexane and 0.8 M PhLi in ether) was added to 10 mmol of the selenophene derivative in 100 ml of anhyd ether or THF with ice cooling. The mixtures were quenched with Me$_2$SO$_4$, followed by addition of ammonia and extraction with ether. The ethereal phases were washed with water, dried (MgSO$_4$) and analysed with glc/ms (3% SE30, 1.9 m, Varaport 30, 100/120 mesh, 100–200°, 10°/min). The yields of dibutyl selenide and diphenyl selenide were determined through comparison of the increase of the glc peak integrals upon addition of known amounts of the authentic materials. From this type of calibration, the yields of butyl methyl selenide (in the reactions with BuLi) and methyl phenyl selenide (in the reactions with PhLi) were both estimated to be 30%. In the reactions between BuLi and 2,5 - dimethoxy - selenophene, the dienes 4 and 5 were formed in various amounts (for their isolation *vide infra*). The conditions and yields are given in Table 1.

2,5 - *Dimethoxy* - 2,4 - *hexadiene* (5) *and* 1,4 - *dimethoxy* - 1 - *butylseleno* - 1,3 - *pentadiene* (5). To a soln of 191 mg (1.00 mmol) 2,5 - dimethoxyselenophene to 10 ml anhyd ether, 0.72 ml (1.1 mmol) 1.53 M BuLi in hexane was added in one portion. After 2 hr at room temp., 0.31 ml (5.0 mmol) MeI was added to the dark mixture and after another hr the mixture was hydrolysed with water followed by aq ammonia and worked up as above. Careful removal of the solvent gave a crude product from which 4 (minor) and 5 (major) could be isolated in the pure state in small amounts by preparative glc (15% SE30, 6 m, Chromosorb W 40–60 mesh, 205°). 2,5 - *Dimethoxy* - 2,4 - *hexadiene* (4). NMR (CDCl$_3$): 5.16 (s, 2H, =CH); 3.57 (s, 6H, OCH$_3$); 1.89(s, 6H, CH$_3$). MS(*m*/*e*, %): 142(100), 127(97), 99(48), 95(22), 69(25), 67(48), 43(88). C$_8$H$_{14}$O$_2$ requires: M.wt. 142. 1,4 - *Dimethoxy* - 1 - *butylseleno* - 1,3 - *pentadiene* (5). The compound decomposed on attempted purification with preparative tlc (silica gel, hexane/EtOAc 90/10) and appeared to isomerise (probably by rotation around one of the ethylene bonds) under glc conditions, since the isomer ratio varied with column temp. NMR (CDCl$_3$): 5.79(d, 1H, =CH); 5.46(d, 1H, =CH); 3.65(s, 3H, OCH$_3$); 3.57(s, 3H, OCH$_3$); 2.90–2.60(m, 2H, Se–CH$_2$); 1.86(m, 3H, =C–CH$_3$); 1.80–1.20(m, 4H, CH$_2$); 0.88(t, 3H, CH$_3$). $J_{\text{H-C-C-H}}$ 10.5 Hz, $J_{\text{CH}_3\text{-CH}_2}$ = 7.0 Hz.

The integrals include 20% of an isomer with the following NMR data: 5.90(d, =CH); 5.48(d, =CH); 3.62(s, OCH$_3$); 3.58(s, OCH$_3$). $J_{\text{H-C-C-H}}$ 10.5 Hz. The other signals coincide with those of the main component. MS *m*/*e*(%): 264(44) ^{80}Se, 249(3) ^{80}Se, 221(10) ^{80}Se, 207(39) ^{80}Se, 142(12), 127(13), 126(100), 112(34), 111(41), 83(20), 57(20), 43(23), 41(20). UV (ethanol, c 3.02 × 10^{-2}) $\lambda_{max}(\epsilon)$: 253(15000), 280(14000).

The reaction between 2,5 - *diphenylselenophene and* BuLi/TMEDA. To a suspension of 284 mg (1.00 mmol) 2,5-diphenylselenophene in 50 ml anhyd ether, the pre-prepared BuLi/TMEDA reagent (from 3.1 ml (4.7 mmol) of 1.52 M BuLi in hexane and 500 mg TMEDA in 15 ml of anhyd ether) was added. The mixture turned red and the selenophene derivative dissolved. After stirring for 30 min, the dark soln was hydrolysed with 0.5 M aq HCl. The ethereal phase was washed with water, dried (MgSO$_4$) and evaporated to give 280 mg of a crystalline mass. The NMR (acetone-d$_6$) spectrum of the crude product showed only aromatic and Bu signals in the proportions 1 : 1. Tlc (silica gel, hexane/EtOAc 95 : 5) showed a faint spot of starting material and a dominant polar one. Glc showed mainly one peak which, however, appeared to consist of two components; the starting material (*m*/*e* 284, ^{80}Se) and 5,8 - diphenyl - 5,7 - dodecadiene (13) *m*/*e* (%): 318(3), 316(8), 260(93), 202(100), 173(38). The diene 13 was also formed when 1,4 - diphenyl-butadiyne was treated with 2 eq of BuLi/TMEDA at room temp. for 1 hr.

Under the same conditions, 3,4 - dimethyl - 2,5 - diphenylselenophene gave only the starting material, even though some reaction seemed to have occurred since the selenophene derivative dissolved upon the addition of BuLi/TMEDA and the mixture turned deep red.

Acknowledgements—Grants from the Swedish Natural Science Research Council to S.G. and T.F. and from the Royal Physiographic Society in Lund to A.H. are gratefully acknowledged. We thank Miss Ingrid Pettersson for a sample of 2,5-dimethoxyselenophene and Mr. Andreas Konar for samples of 2,5 - diphenyl- and 3,4-dimethyl-2,5-diphenylselenophene.

REFERENCES

[1a] S. Gronowitz and T. Frejd, *Acta Chem. Scand.* **23**, 2540 (1969); *Ibid.* **24**, 2656 (1970); *Ibid.* **B30**, 313, 439 (1976); *Int. J. Sulfur Chem.* **A2**, 165 (1972): [b] T. Frejd, *Chem. Scripta* **10**, 133 (1976); [c] V. P. Litvinov, I. P. Konjajeva and Ya. L. Goldfarb, *Izv. Akad. Nauk, Ser. Khim.* **25**, 477 (1976); [d] F. B. Iteke, L. Christiaens and M. Renson, *Tetrahedron* **32**, 689 (1976).

[2] S. Gronowitz and T. Frejd, *Chem. Heterocyclic Compounds* **14**, 353 (1978); C. J. M. Stirling, *Chem. Revs.* **78**, 517 (1978).

[3] E. Luppold, E. Müller and W. Winter, *Z. Naturforsch.* **31B**, 1654 (1976).

[4] A. E. M. Beyer and H. Kloosterziel, *Recueil, J. Roy. Netherl. Chem. Soc.* **96**, 178 (1977).

[5] "Direct lithiation of 2,5-dimethoxythiophen with BuLi at room temperature gave a strongly exothermic reaction leading to polymeric products" (J. M. Barker, P. R. Huddleston and S. W. Shutler, *J. Chem. Soc. Perkin I* 2483 (1975).

[6] Vinyl alkyl selenides with *trans*-β-hydrogens have a strong tendency to lose the fragments of the alkylselenol in the mass spectrometer. (T. Frejd, unpublished results).

[7] A quarternisation (by Me_2SO_4)-dequarternisation pathway of **6** and **2** to give **3** is less likely, since the amount of **2** is the same whether the reaction is quenched with Me_2SO_4 or water (Table 1, Entry 1).

[8] S. Gronowitz, I. Johnson and A.-B. Hörnfeldt. *Chem. Scripta* **8**, 8 (1975).

[9] Similar arguments have been used to explain the directed metallation of anisole: R. A. Finnegan and J. W. Altshuld, *J. Organometal. Chem.* **9**, 193 (1967); see also Ref. 10.

[10] The directive effect of an OMe group on lithium reagents is well established; D. W. Slocum and B. P. Koonsvitsky, *J. Org. Chem.* **38**, 1675 (1973).

[11] Tetracoordinated selenium species have been proposed as intermediates in the reactions between selenides and BuLi: W. Dummont, P. Bayet and A. Krief; *Angew. Chem.* Internat. Ed. **13**, 804 (1974).

[12] Additions of lithium derivatives to methoxy acetylenes: J. G. A. Kooyman, H. P. G. Hendriks, P. P. Montijn, L. Brandsma and J. F. Arens, *Rec. Trav. Chim.* **87**, 69 (1968).

[13] The increment of an alkylseleno group was estimated to be 40 nm. This value was arrived at by evaluating the UV spectra of 2-methyl-seleno- and 2-methylthio-2-hexen-4-yne with λ_{max} 282 (log 3.93) and 272 (log 4.10), respectively. The alkylthio increment has a standard value of 30 nm.

[14] The structure of **13** has not been accurately determined and should be regarded as a preliminary one. It may well be that BuLi adds in another way to give an isomeric compound.

[15] At present, it cannot be decided whether the reaction is a direct nucleophilic substitution on selenium or occurs through electron-transfer to give a radical anion.

Note added in proof. A coordination of Li^+ by a 5-ethoxy group has just been suggested to play a role in the ring opening of some 5-ethoxy-2-oxazolyllithium derivatives: P. A. Jacobi, S. Ueng and D. Carr, *J. Org. Chem.* **44**, 2042 (1979).