Transformations of selenadiazoliumyl-*N*-unsubstituted methanides (ylides) to new divinyl selenide derivatives and substituted 1,3,5-selenadiazines. Organoselenium systems from azolium 1,3-dipoles

Richard N. Butler * and Anthony Fox

Chemistry Department, National University of Ireland, Galway, Ireland

Received (in Cambridge, UK) 3rd October 2000, Accepted 3rd January 2001
First published as an Advance Article on the web 1st February 2001

4,5-Diphenyl-1,2,3-selenadiazole and 3,5-diphenyl-1,2,4-selenadiazole were alkylated with trimethylsilylmethyl trifluoromethanesulfonate. Quaternisations occurred at N-3 and N-2 respectively. The salts were desilylated to generate transient selenadiazoliumylmethanide (ylide) intermediates. 4,5-Diphenyl-1,2,3-selenadiazol-3-ium-3-ylmethanide, **3**, was trapped with dimethyl acetylenedicarboxylate and methyl propiolate in a cycloaddition–rearrangement reaction which gave the pyrazolylvinyl vinyl selenides **6** and **7**. 3,5-Diphenyl-1,2,4-selenadiazol-2-ium-2-ylmethanide, **10**, ring-expanded *in situ* to 4,6-diphenyl-2*H*-1,3,5-selenadiazine, **13**.

Interest in organoselenium systems has increased with the recognition of the physiological role of selenium in a second-line anti-oxidant defence against lipid autoxidation,[1] as well as the bioactive nature of some fused bicyclic 1,2,3-selenadiazole systems[2] and organoselenium compounds in general.[3] Transformation of selenium heterocycles has been a major strategy in the synthesis of new organoselenium compounds but the difficulty attached to the instability of selenium azoles has limited the scope of this approach.[4] These difficulties have been overcome in recent years and reliable routes to a range of selenadiazoles have been developed,[4–10] although these substrates are still difficult to work with. Herein we explore the synthetic use of both the 1,2,3- and 1,2,4-selenadiazole systems by generating the first selenadiazolium methanide (ylide) species *in situ*. This work complements our recent reports[11,12] on thiadiazolium ylide systems and earlier work on oxadiazolium systems[13] and extends this chemistry deeper into Group VI. The selenadiazolium systems were the most unstable and difficult members of the group but they provided useful new additions to organoselenium synthetic routes.

Results and discussion

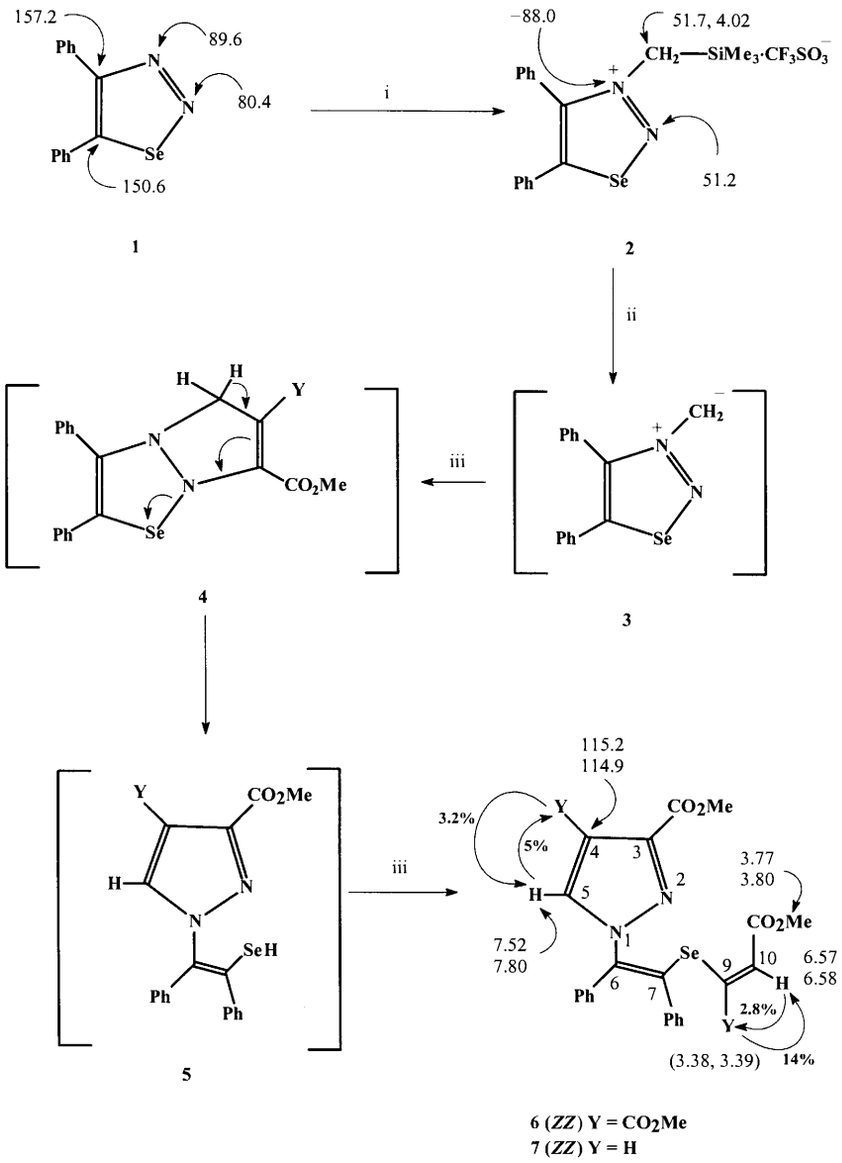
(a) 1,2,3-Selenadiazol-3-ium-3-ylmethanides

When the selenadiazole **1** was heated at 80 °C with trimethylsilylmethyl trifluoromethanesulfonate alkylation occurred at N-3 giving the salt **2** as a dark sticky gum on cooling. ^{1}H and ^{13}C NMR spectra supported the structure and the quaternisation site was confirmed by ^{15}N NMR spectra which showed a large shielding shift of 177.6 ppm at the quaternised 3-N-atom and a smaller shift of 29.2 ppm at the adjacent N-2 site. In general quaternisation of higher azole N-atoms causes a large upfield shift (>100 ppm) in the ^{15}N NMR signal of the quaternised azolium nitrogen and a smaller shift (~25 ppm) on other ring N-atoms.[14,15] Similar shifts have been noted for quaternisation of substituted 1,2,3-thiadiazoles by L'abbé *et al.*[16] and us.[11] The subsequent chemistry also confirmed quaternisation at N-3. Attempted purification of the sticky salt resulted in loss of Se with decomposition. Hence the crude salt was used immediately to generate the unstable 1,3-dipole **3**.

The species **3** was generated at ambient temperatures in dichloromethane by treatment of **2** with CsF (following a literature[17,18] procedure) in the presence of excess dimethyl acetylenedicarboxylate (DMAD) and methyl propiolate. The products isolated on work-up were the new divinyl selenides **6** and **7** (Scheme 1). The formation of these products involves a cycloaddition followed by a 1,4-conjugative elimination which aromatises the newly formed pyrazoline ring (Scheme 1). The vinyl hydrogen selenide intermediate **5** thus generated is trapped by a second molecule of alkyne giving the products. In the solid state the compounds exist in a single form as indicated by a sharp mp, IR spectrum, single spot on TLC and X-ray crystal structure[11] of compound **6** (S for Se). In solution isomerism around the 6–7 double bond produced a mixture of the *ZZ* and *EZ* forms in approximately a 2.5 : 1 ratio for compound **6** and a 3 : 1 *ZZ* : *EZ* ratio for compound **7**. In the *ZZ*-form the 5-H of the pyrazole is shielded by the 6-*C*-phenyl group for both compounds **6** and **7** and appears at δ 7.5–7.7. In the *EZ*-isomer this shielding is not present due to the *E*-configuration of the 6–7 bond which removes the 5-H from the shielding region of the 6-phenyl substituent. These signals, which appear at δ 8.8–8.9 are normal[19,20] for a pyrazole with a vinyl-bond at N-1 and a CO_2R group at C-4. The structure of compound **7** was further supported by NOE difference spectra showing NOE effects between H-4 and H-5 and between H-9 and H-10 and the proton signals for H-4 and H-5 appeared as doublets, confirming the regiochemistry. The linking of the dipole unsubstituted methanide terminus to the alkyne unsubstituted carbon is the regiochemistry expected for a dipole HOMO–dipolarophile LUMO reaction where these sites have the highest orbital coefficients.

Interestingly for compounds **6** and **7** the CO_2Me and the H-atom respectively at C-9 experienced special shielding from the *C*-7-phenyl group. Thus for **6** the 9-CO_2Me methyl signal appeared at δ 3.38 and 3.39 for both isomers, significantly more shielded than the other normal CO_2Me groups, δ 3.6–3.8, and the 9-H atom, although α-vinylic, was more shielded than the 10-H atom which is β-vinylic. Suitable crystals of compounds **6** and **7** could not be grown but we have previously reported[11] an X-ray crystal structure of the more stable sulfur analogue (**6**, *ZZ*, S for Se). The close spectroscopic similarities allow a definite structural assignment of the selenium analogue. This sequence of reactions was also attempted with an H-atom at the selenadiazole 5-position, adjacent to the Se atom, *i.e.* with 4-phenyl-1,2,3-selenadiazole. However,

 DOI: 10.1039/b007974j



Scheme 1 *Reagents*: (i) $Me_3SiCH_2OSO_2CF_3$; (ii) CsF; (iii) $MeO_2C–C\equiv C–CO_2Me$ for product **6**, $H–C\equiv C–CO_2Me$ for product **7**. Shown are some ^1H, ^{13}C and ^{15}N NMR shifts **6**, (*ZZ* and *EZ*), the numbering system applied to the divinyl selenide substituent and NOE for Y = H.

attempted quaternisation with trimethylsilylmethyl triflate resulted in decomposition of the selenadiazole unlike the case with the thiadiazole.

(b) 1,2,4-Selenadiazol-2-ium-2-ylmethanide: ring expansion to a 1,3,5-selenadiazine

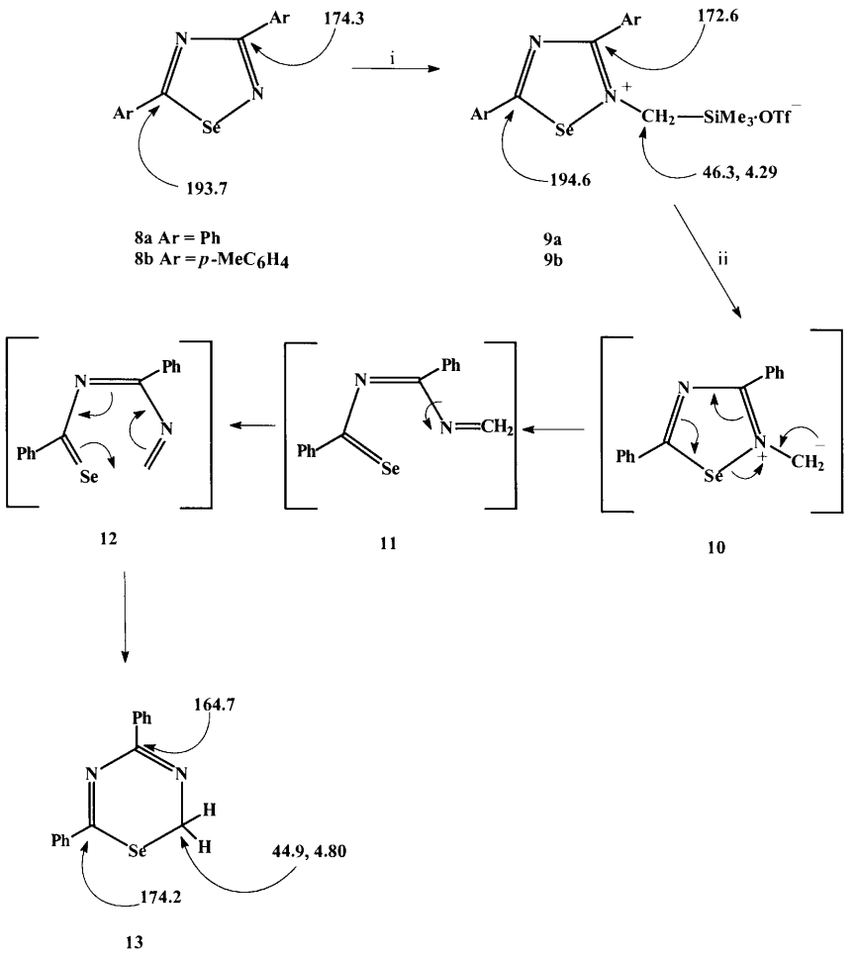
Quaternisation of the 1,2,4-selenadiazole **8** with trimethylsilylmethyl trifluoromethanesulfonate in dichloromethane at 40 °C occurred at N-2 giving the unstable salt **9** as a gum (Scheme 2). This was characterised by proton and carbon-13 NMR spectra but due to its propensity for decomposition it was not purified other than by washing with diethyl ether. Desilylation with CsF in CH_2Cl_2 at ambient temperature generated the ylide **10** for which, unlike the species **3**, a valency-allowed ring-opening to a conjugated triene **11** is possible. The intramolecular rearrangement occurred more rapidly than a cycloaddition and no trapping was achieved with up to 20 mol excess of dimethyl acetylenedicarboxylate. The rearrangement gave 4,6-diphenyl-2*H*-1,3,5-selenadiazine **13**, mp 110–112 °C (79%). The structure of compound **13**, which was stable, was readily established from microanalysis, IR, proton and carbon-13 NMR spectra which showed all of the expected signals and multiplicities. We have previously established this class of valency-allowed ring-expansion of azolium-unsubstituted methanide species with both oxygen[21] and sulfur[12] azoles. This is the first example of such a ring-expansion for a selenium azole system and it extends the general reaction in the azole series to selenium systems. However, the successful use of the reaction is limited by the instability of the 1,2,4-selenadiazole ring. We could not achieve the reaction with the 3,5-di(*p*-tolyl) derivative **8b**. These systems have a propensity for collapsing to aryl nitriles with loss of Se and although quaternisation was achieved with **8b** to give **9b**, treatment of this with CsF gave decomposition to *p*-toluonitrile (*p*-methylbenzonitrile) and gums.

Conclusion

The reaction sequences which had previously been established for oxadiazoliumyl- and thiadiazoliumyl-*N*-methanide 1,3-dipoles have been found to occur also with some derivatives of 1,2,3- and 1,2,4-selenadiazoles, thereby establishing that the chemistry is the same deeper into Group VI. However, unlike the earlier cases, relatively minor changes in the substituents on the selenadiazole showed major effects on the stability of the compounds and the synthetic usefulness may be limited.

Experimental

Mps were measured on an electrothermal apparatus. The 4,5-



Scheme 2 *Reagents*: (i) $Me_3SiCH_2OSO_2CF_3$; (ii) CsF. Shown are some ^1H and ^{13}C NMR shifts.

diaryl-1,2,3-selenadiazoles were prepared from the reaction of selenium(IV) oxide with the semicarbazone of the appropriate ketone.[22] The 3,5-diaryl-1,2,4-selenadiazoles were prepared by treating selenocarboxamides with *N*-bromosuccinimide following a literature procedure.[4] NMR spectra were measured on a JEOL LAMBDA 400 MHz instrument with tetramethylsilane as reference for ^{13}C and proton shifts and nitromethane for ^{15}N shifts (measured at natural abundance level). IR spectra were measured on a Perkin-Elmer 983G spectrometer and microanalyses were measured on a Perkin-Elmer model 240 CHN analyser. The following examples show typical experimental procedures.

4,5-Diphenyl-3-trimethylsilylmethyl-1,2,3-selenadiazol-3-ium triflate, 2

A mixture of 4,5-diphenyl-1,2,3-selenadiazole (0.25 g, 0.9 mmol) and trimethylsilylmethyl trifluoromethanesulfonate (0.4 cm^3, 1.8 mmol) was heated at 80 °C for 12 h, under a reflux condenser. The resultant mixture was cooled to ambient temperature giving compound **2** in the form of a black gum. ν_{max} (mull) 1605.2 cm^{-1} (C=N); δ_H ($CDCl_3$) 0.10 (s, 9H, $SiMe_3$), 4.02 (s, 2H, CH_2-N), 6.99–7.11 (m, 6H, $H_{meta,para}$, Ph), 7.22–7.26 (m, 4H, H_{ortho}, Ph); δ_C ($CDCl_3$) −2.4 ($SiMe_3$), 51.7 (N-CH_2), 158.2 (C-4), 154.6 (C-5), 123.6, 126.8 (C-1′ of 4-C-Ph and 5-C-Ph), 128.3, 129.8 (C-3′ of 4-C-Ph and 5-C-Ph), 130.6, 131.2 (C-2′ of 4-C-Ph and 5-C-Ph), 132.4, 133.0 (C-4′ of 4-C-Ph and 5-C-Ph); δ_{is_N} ($CDCl_3$) 51.2 (N-2), −88.0 (N-3). The compound was used directly as the residue and not purified further.

Dimethyl 1-{(*Z*)-2-[(*Z*)-1,2-bis(methoxycarbonyl)vinylseleno]-1,2-diphenylethenyl}-1*H*-pyrazole-3,4-dicarboxylate, 6

A solution of compound **2** (400 mg, crude) in dry methylene chloride (4 cm^3) was treated with dimethyl acetylenedicarboxylate (0.43 cm^3, 3.5 mmol) followed by CsF (600 mg, 3.9 mmol), stirred at ambient temperature for 24 h, filtered to remove insoluble salts and evaporated under reduced pressure. The residue in dichloromethane (2 cm^3) was placed on a silica gel-60 column (70–230 mesh ASTM). Elution with a gradient mixture of dichloromethane–diethyl ether (1:0–30:1 v/v) gave the product **6** (*ca.* 61% yield) (*ca.* 40% overall yield from 1,2,3-selenadiazole **1**) as a yellow solid, mp 77–79 °C (from CH_2Cl_2–hexane) (Found: C, 56.1; H, 4.2; N, 4.5. $C_{27}H_{24}N_2O_8Se$ requires C, 55.6; H, 4.1; N, 4.8%); ν_{max} (mull)/cm^{-1} 1748, 1720, 1703 (C=O); δ_H ($CDCl_3$) (2.5:1 mixture of *Z*,*Z* and *E*,*Z* isomers) 3.38, 3.39, 3.63, 3.66, 3.67, 3.73, 3.77, 3.80 (s, 3H each, OMe), 6.57, 6.58 (s, 1H each β-vinyl 10-CH), 6.75, 6.77 (m, 2H, Ph), 6.97–7.03 (m, 1H, Ph), 7.04–7.11 (m, 10H, Ph), 7.16–7.17 (m, 1H, Ph), 7.25–7.26 (m, 3H, Ph), 7.25–7.32 (m, 3H, Ph), 7.52 (s, 1H, 5-CH, *ZZ* form), 8.80 (s, 1H, 5-CH, *EZ* form); δ_C ($CDCl_3$) 51.7, 52.2, 52.3, 52.5, 53.1 (each OMe, overlap of some signals from both isomers), 166.1, 166.0, 165.1, 164.9, 162.0, 161.9, 161.6 (each C=O), 115.2, 114.9 (C-4), 146.4, 145.7, 144.3, 143.7 (C-3 and C-9), 124.6, 124.0 (C-10), 138.9, 138.0 (C-5), 137.7, 137.4, 136.8, 136.4, 135.1, 134.2, 133.8, 131.4, 129.7, 129.5, 128.8, 128.5, 128.3, 128.2 (aromatic C–H), overlap of some signals from both isomers.

Methyl 1-{(*Z*)-2-[(*Z*)-2-methoxycarbonylvinylseleno]-1,2-diphenylethenyl}-1*H*-pyrazole-3-carboxylate, 7

A solution of **2** (400 mg, crude) in dry methylene chloride (4 cm^3) was treated with methyl propiolate (4.24 cm^3, 47.6 mmol) followed by CsF (450 mg, 3.0 mmol), stirred at ambient temperature for 24 h, filtered to remove insoluble salts and evaporated under reduced pressure. The liquid was placed on a

silica gel-60 column (70–230 mesh ASTM) using dichloromethane (2 cm^3) for complete transfer. Excess methyl propiolate was first eluted with CH_2Cl_2 (*ca.* 800 cm^3) and elution with a mixture of methylene chloride–diethyl ether (30 : 1 v/v) gave the product **7** (*ca*. 51% yield) (*ca*. 34% overall yield from 1,2,3-selenadiazole **1**), mp 193–195 °C (from CH_2Cl_2–hexane 1 : 1) (Found: C, 58.9; H, 4.3; N, 5.7. $C_{23}H_{20}N_2O_4Se$ requires C, 59.1; H, 4.3; N; 6.0%); ν_{max} (mull)/cm^{-1} 1724, 1679 (ester C=O); δ_H ($CDCl_3$) (3 : 1 mixture of *ZZ* and *EZ* isomers) 3.71, 3.95 (s, each 3H, OMe, *ZZ*-isomer), 3.75, 3.98 (s, each, 3H, *EZ* isomer), 6.13 (d, 1H, *J* 12 Hz, 9-CH, NOEDS, enhancement from 10-CH), 6.90 (d, 1H, 10-CH, NOEDS, enhancement from 9-CH), 6.97 (d, *J* 2.5 Hz, 1H, 4-CH, NOEDS, enhancement from 5-CH *ZZ*-isomer), 7.63 (d, *J* 2.5 Hz, 1H, 5-CH, *ZZ*-isomer), 7.05–7.09 and 7.10–7.13 (m, 6H, $H_{meta,\ para}$, Ph), 7.27–7.33 (m, 4H, H_{ortho}, Ph), 8.87 (weak d, $J < 2$ Hz, 5-CH, *EZ*-isomer); δ_C 51.7, 52.1 (OMe), 165.6, 162.1 (C=O), 109.7 (C-4), 116.5 (C-10), 144.5 and 145.7 (C-9, of both stereoisomers), 137.5, 136.7, 135.7, 134.5 (C-3, C-6, C-7, C-1′ Ph), 132.8 (C-5), 130.6, 130.5, 129.3, 128.9, 128.7, 128.6, 128.3, 128.0, 127.9 (Ar, CH), overlap of some signals from both isomers.

3,5-Diphenyl-2-trimethylsilylmethyl-1,2,4-selenadiazol-2-ium trifluoromethanesulfonate, 9a

A solution of 3,5-diphenyl-1,2,4-selenadiazole (0.2 g, 0.7 mmol) and trimethylsilylmethyl trifluoromethanesulfonate (0.3 ml, 1.5 mmol) in dry methylene chloride (1 cm^3) was stirred at 40 °C under a reflux condenser for 24 h, evaporated under reduced pressure and the residue washed with ether to give compound **9a** as a gum. ν_{max} 1602.3 cm^{-1} (C=N); δ_H ($CDCl_3$) 0.15 (s, 9H, $SiMe_3$), 4.29 (s, 2H, CH_2-N), 7.44–7.69 (m, 6H, $H_{meta,\ para}$, Ph), 7.91–7.99 (m, 2H, H_{ortho}, Ph), 8.21–8.23 (m, 2H, H_{ortho}, Ph); δ_C ($CDCl_3$) −2.9 ($SiMe_3$), 46.3 (N-CH_2), 194.6, 172.6 (C-5 and C-3), 127.3, 133.1 (C-1′ of 3-C-Ph and 5-C-Ph), 130.3, 129.6 (C-3′ of 3-C-Ph and 5-C-Ph), 130.0, 129.3 (C-2′ of 3-C-Ph and 5-C-Ph), 136.4, 134.8 (C-4′ of 3-C-Ph and 5-C-Ph).

4,6-Diphenyl-2*H*-1,3,5-selenadiazine, 13

A solution of **9a** (0.15 g, 0.4 mmol) in dry dichloromethane (3.2 cm^3) was treated with CsF (120 mg, 0.8 mmol), stirred at ambient temperature for 14 h, filtered to remove salts and then evaporated under reduced pressure. The residue in dichloromethane (1 cm^3) was placed on a silica gel-60 column (70–230 mesh ASTM). Elution with methylene chloride gave compound **13** (79%) (52% overall yield from 1,2,4-selenadiazole **8**), mp 110–112 °C (from CH_2Cl_2–hexane 1 : 1 v/v) (Found: C, 59.9; H, 3.9; N, 9.2. $C_{15}H_{12}N_2Se$ requires C, 60.2; H, 4.0; N, 9.4%). ν_{max} (mull) 1604.3, 1575.1 cm^{-1} (C=N); δ_H ($CDCl_3$) 4.8 (s, 2H, $SeCH_2N$), 7.3–7.5 (m, 6H, $H_{meta,\ para}$, Ph), 8.0–8.1 (m, 4H, H_{ortho}, Ph); δ_C ($CDCl_3$) 44.9 ($SeCH_2N$), 164.7 (C-4), 174.2 (C-6), 138.8, 136.5 (C-1′ of 4-Ph and 6-Ph), 128.8, 128.7 (C-2′ of 4-Ph and 6-Ph), 128.3, 127.9 (C-3′ of 4-Ph and 6-Ph), 133.2, 130.0 (C-4′ of 4-Ph and 6-Ph). Similar results were obtained in the presence of various quantities of dimethyl acetylenedicarboxylate up to a 20 molar excess. When this reaction was attempted with the 3,5-di(*p*-tolyl)-1,2,4-selenadiazol-2-ium-2-yl(trimethylsilyl)methyl triflate salt **9b** decomposition to *p*-toluonitrile and gums occurred.

References

1 T. P. Coultate, *Food, The Chemistry of the Components*, Royal Society of Chemistry, London, 1984, p. 174.
2 A. Shafier, I. Lalezari, S. Yazdani and A. Pournorouz, *J. Pharm. Sci.*, 1973, **62**, 839; I. Lalezari, A. Shafier and S. Yazdani, *J. Pharm. Sci.*, 1974, **63**, 628.
3 F. T. Burling and B. M. Goldenstein, *J. Am. Chem. Soc.*, 1992, **114**, 2313; *Organic Selenium Compounds: Their Chemistry and Biology*, eds. D. L. Klayman and W. H. H. Günter, John Wiley and Sons, New York, 1973.
4 K. Shimada, Y. Matsuda, S. Hikage, Y. Takeishi and Y. Takikawa, *Bull. Chem. Soc. Jpn.*, 1991, **64**, 1037.
5 Y. Zhou and H. Heimgartner, *Helv. Chim. Acta*, 2000, **83**, 539.
6 M. Yokoyama, K. Kumata, H. Hatanaka and T. Shiraishi, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 2909.
7 T. Ueda, S. Kawai and J. Sakakibara, *Chem. Pharm. Bull.*, 1987, **35**, 398.
8 M. Renson, *The Chemistry of Organic Selenium and Tellurium Compounds*, eds. S. Patai and Z. Rappoport, John Wiley and Sons, Chichester, 1986, vol. 1, p. 399.
9 V. Bertini, A. De Munno, N. Picci, F. Lucchesini and M. Pocci, *Heterocycles*, 1987, **26**, 2153.
10 A. Shafiee, M. A. Ebrahimzadeh and A. Maleki, *J. Heterocycl. Chem.*, 1999, **36**, 901.
11 R. N. Butler, M. O. Cloonan, P. McArdle and D. Cunningham, *J. Chem. Soc.*, *Perkin Trans. 1*, 1999, 1415.
12 R. N. Butler, M. O. Cloonan, J. M. McMahon and L. A. Burke, *J. Chem. Soc.*, *Perkin Trans. 1*, 1999, 1705.
13 R. N. Butler, E. C. McKenna, J. M. McMahon, K. M. Daly, D. Cunningham and P. McArdle, *J. Chem. Soc.*, *Perkin Trans. 1*, 1997, 2919; R. N. Butler and M. O. Cloonan, *Bull. Soc. Chim. Belg.*, 1997, **106**, 515.
14 P. N. Gaponik, O. A. Ivashkevish, V. N. Naumenko, T. B. Kovalyova, T. N. Andreeva and O. A. Koren, *Spectrochim. Acta*, *Part A*, 1993, **49**, 135.
15 R. N. Butler, in *Comprehensive Heterocyclic Chemistry II*, Series ed. A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Pergamon Press, Oxford, 1996, vol. 4, vol. ed. R. C. Storr, pp. 628–630.
16 G. L'abbé, P. Delberke, L. Bastin, W. Dehaen and S. Toppet, *J. Heterocycl. Chem.*, 1993, **30**, 301.
17 E. Vedejs, S. Larsen and F. G. West, *J. Org. Chem.*, 1985, **50**, 2170.
18 R. C. F. Jones, J. R. Nichols and M. T. Cox, *Tetrahedron Lett.*, 1990, **31**, 2333.
19 J. J. Batterham, *NMR Spectra of Simple Heterocycles*, John Wiley and Sons, New York, 1973, pp. 173–179.
20 J. Elguero, *Comprehensive Heterocyclic Chemistry*, Series ed. A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, vol. 5, vol. ed. K. T. Potts, pp. 184–186.
21 R. N. Butler, J. P. Duffy, D. Cunningham, P. McArdle and L. A. Burke, *J. Chem. Soc.*, *Perkin Trans. 1*, 1992, 147.
22 T. L. Gilchrist, P. G. Mente and C. W. Rees, *J. Chem. Soc.*, *Perkin Trans. 1*, 1972, 2165.