**Molar Ratio.** 11 (2.0 g, 7.5 mmol) with 1,3,5-trimethoxybenzene (2.5 g, 15 mmol) produced a 100% yield of $N_2$ and, nearly quantitatively, a mixture of mono- and diadducts, in an 87:13 ratio. Chromatography gave *N*-(2,4,6-trimethoxyphenyl)-*N'*-(methylsulfonyl)-*O*-(2,6-dimethylphenyl)isourea (**32**), mp 209–10 °C. $^1$H NMR: 2.15 (s, 6 H), 2.96 (s, 3 H), 3.80 (s, 3 H), 3.85 (s, 6 H), 6.19 (s, 2 H), 7.00 (s, 3 H), 8.39 (br, 1 H). $^{13}$C NMR: 15.76, 41.86, 55.48, 55.74, 90.39, 125.84, 128.40, 130.10, 130.24, 148.43, 156.89, 157.25, 160.85. Anal. Calcd for $C_{19}H_{24}N_2O_6S$: C, 55.87; H, 59.92; N, 6.86. Found: C, 55.19; H, 6.00; N, 6.97. The diadduct *N,N'*-bis(*N''*-(methylsulfonyl)(2,6-dimethylphenoxy)carbimidoyl)-1,3-diamino-2,4,6-trimethoxybenzene (**33**) has mp 285 ° dec. $^1$H NMR (DMSO-$d_6$): 2.18 (s, 12 H), 2.95 (s, 8 H), 3.96 (s, 6 H), 4.04 (s, 3 H), 6.60 (s, 1 H), 7.00 (s, 6 H), 8.80 (br, 2 H). Anal. Calcd for $C_{29}H_{36}N_4O_9S$: C, 53.69; H, 5.59; N, 8.64. Found: C, 53.69; H, 5.60; N, 8.54.

**Attempt To Trap Azepine. Thermolysis of *N'*-Cyanomethoxycarbimidoyl Azide[2] in the Presence of *p*-Xylene and Tetracyanoethylene.** The azide (1.5 g, 12 mmol), *p*-xylene (120 mmol), and tetracyanoethylene (5 mmol) produced a 99% yield of $N_2$. Chromatography produced 1.46 g (61%) of *N*-(2,5-dimethylphenyl)-*N'*-cyano-*O*-methylisourea (**35**), but no TCNE adduct. Recrystallization from dichloromethane–hexane gave **35**, mp 172–3 °C. $^1$H NMR: 2.21 (s, 3 H), 2.31 (s, 3 H), 3.81 (s, 3 H), 7.00–7.20 (m, 3 H), 7.80 (br, 1 H). $^{13}$C NMR: 17.31, 20.85, 58.41, 115.55, 127.17, 128.69, 130.68, 130.89, 133.17, 136.54, 163.48. $M^+$ = 203. Anal. Calcd for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.67. Found: C, 64.94; H, 6.44; N, 20.81.

# Strong Participation of Selenium Substituents in Decomposition of Pyrazolines Formed by 1,3-Dipolar Cycloaddition of Appropriate Vinyl Selenides with Diazoalkanes

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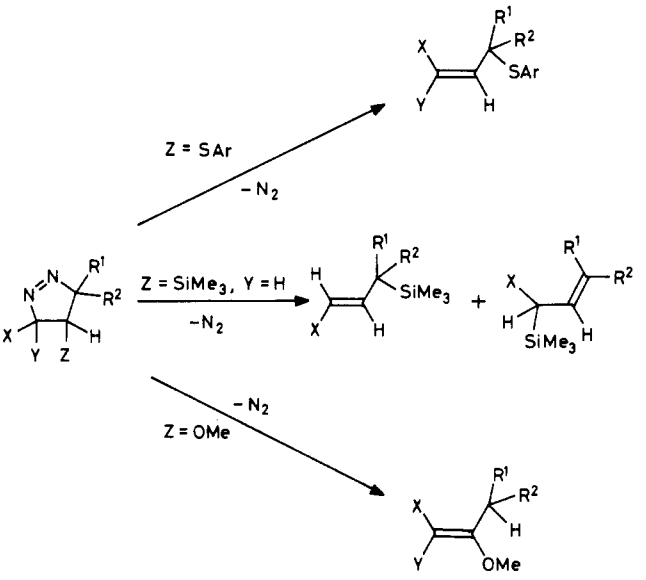
*Received November 17, 1988*

Decomposition of 4-(arylseleno)pyrazolines (**3**) bearing two electron-withdrawing groups such as COOMe, COMe, and CN at C-3, which were prepared in situ by reaction of the corresponding aryl vinyl selenides (**2**) with diazoalkanes, are reported. The pyrazolines decompose below 0 °C to give allyl aryl selenide derivatives (**4**) by migration of 4-arylseleno group to C-5 concerted with extrusion of nitrogen. Facile decomposition of the pyrazolines with migration of the selenium substituent is explained by strong contribution of intramolecular diazonium salt resonance structure, within which arylseleno groups strongly participate in the decomposition. Most reactions of **2** with 2 mol of diazoalkanes gave the pyrazolines **5**, whereas reaction of **2c** with 2 mol of 2-diazopropane gave a reverse orientation adduct, the pyrazoline **9**.

There is continuing interest in the decomposition of pyrazolines from synthetic, mechanistic, and theoretical points of view.[1] We have been interested in effects of heteroatoms on decomposition of 4-heteroatom-substituted pyrazolines bearing two geminal electron-withdrawing groups at C-3. Three types of the effects of heteroatom substituents on the decomposition of pyrazolines have been reported. We have found that 4-(arylthio)pyrazolines, geminally substituted with two electron-withdrawing groups at C-3, decompose quantitatively to allyl sulfide derivatives by concerted migration of 4-arylthio group to C-5 with loss of nitrogen under mild conditions.[2] However, decomposition of a 4-trimethylsilyl group substituted pyrazoline bearing an electron-withdrawing group at C-3 leads to migration of the 4-trimethylsilyl group to C-3 or to C-5, depending on the bulkiness of the substituent at C-5;[3] the mechanism seems to be different from the case of 4-(arylthio)pyrazolines in the sense that the trimethylsilyl group has positive character opposing the nucleophilic sulfur group (Scheme I). On the other hand, analogous 4-alkoxypyrazolines generally cause predominant 4-hydride migration to C-5 with elimination of nitrogen.[4] This observation prompted us to investigate the

**Scheme I**




effect of the 4-arylseleno group on decomposition of the 4-(arylseleno)pyrazolines: how the 4-arylseleno group behaves on decomposition (like arylthio or trimethylsilyl group) because a seleno group is also able to eliminate reductively.[5] We have found that 4-(arylseleno)-substi-

(1) Wulfman, D. S.; Linstrumelle, G.; Copper, C. F. Synthetic Applications of Diazoalkanes. In *The Chemistry of Diazonium and Diazo Groups*; Patai, S., Ed.; Wiley: New York, 1978; p 821.

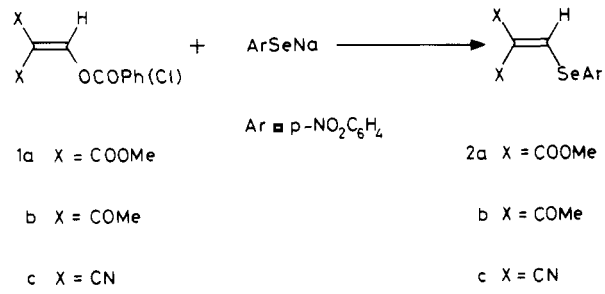
(2) Hamaguchi, M.; Miyazaki, S.; Nagai, T. *J. Chem. Soc., Chem. Commun.* **1983**, 12.

(3) (a) Cunico, R. F.; Lee, H. M. *J. Am. Chem. Soc.* **1977**, *99*, 7613. (b) Himbert, G. *J. Chem. Res.* **1978**, (s) 88; (m) 1201. (c) Himbert, G. *Ibid.* **1978**, (s) 442; (m) 5240. (d) Birkofer, L.; Kuhn, T. *Chem. Ber.* **1981**, *114*, 2293.

(4) (a) Hamaguchi, M.; Furusawa, T.; Nagai, T. *Heterocycles* **1986**, *24*, 2111. (b) Popp, F. D.; Catala, A. *J. Org. Chem.* **1960**, *26*, 2738.

0022-3263/89/1954-3957$01.50/0 

**Scheme II**




tuted pyrazolines bearing two electron-withdrawing groups at C-3 undergo facile decomposition at low temperature accompanied with 4-arylseleno group migration to C-5, giving rise to allyl selenide derivatives. Thus the 4-arylseleno group participates in decomposition more strongly than the 4-arylthio group in the arylthio analogues. These results and studies concerning the steric effects of substituents on the reaction pathway are reported.

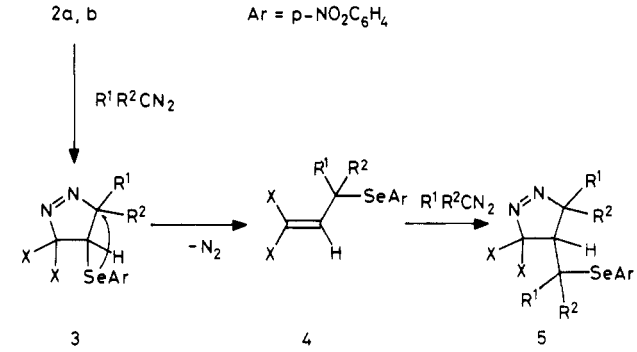
## Results and Discussion

Aryl vinyl selenides (**2a–c**) bearing two electron-withdrawing groups at the β-position were prepared by reaction of the corresponding vinyl chloride or vinyl benzoate derivatives (**1a–c**) with sodium aryl selenolate (Scheme II).

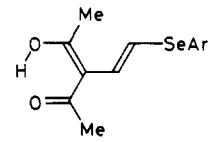
Dimethyl (((*p*-nitrophenyl)seleno)methylene)malonate (**2a**) was allowed to react with an equimolar amount of diazomethane at −30 °C in dichloromethane to give 3,3-bis(methoxycarbonyl)allyl *p*-nitrophenyl selenide (**4a**) in 94% yield. Treatment of **2a** with a large excess of diazomethane gave in high yield the pyrazoline **5a**, which is an adduct of diazomethane with **4a**. Treatment of **2a** with an equimolar amount of diazoethane at −30 °C afforded 3,3-bis(methoxycarbonyl)-1-methylallyl *p*-nitrophenyl selenide (**4b**). Similar results were obtained when **2a** was treated with isopropyldiazomethane and 2-diazopropane, giving allyl selenide derivatives **4c** and **4e**, respectively. Superficially, these transformations into allyl selenides are formally carbene insertions into carbon selenium bonds. Although we could not detect the pyrazolines **3a**, **3b**, **3c**, and **3e** by the NMR spectra of the reaction mixtures after evaporation of solvent in vacuo, we can exclude a carbene mechanism on the basis of the following results. Evidence for the intermediacy of pyrazolines was obtained from the NMR spectrum of the reaction mixture between **2a** and diazoneopentane, which showed the existence of the pyrazoline **3d**, (δ 1.10 (s, 9 H), 3.77 (s, 3 H), 3.95 (s, 3 H), 3.98 (d, 1 H, $J$ = 7.5 Hz), 4.65 (d, 1 H, $J$ = 7.5 Hz), and 7.72, 8.12 (AB q, 4 H)) together with **4d** in a ratio of 7:3. While the NMR signals corresponding to **3d** gradually disappeared with evolution of nitrogen, the signals of **4d** increased. In the reaction of the corresponding vinyl sulfides with diazoalkanes, the 4-(arylthio)pyrazolines corresponding to **3a**, **3b**, **3c**, and **3e** were isolated and were observed to undergo decomposition under mild conditions to give the corresponding allyl sulfide derivatives, quantitatively.[2] Therefore, it is reasonable that the compounds **4a**, **4b**, **4c**, and **4e** are products arising not from carbene insertion into the C–Se bond but from formation of the unstable pyrazolines **3a**, **3b**, **3c**, and **3e** by 1,3-dipolar cycloaddition of diazoalkanes with **2a**, followed by concerted nitrogen extrusion and 4-arylseleno group migration to C-5 within **3** (Scheme III).

2,2-Diacetylvinyl *p*-nitrophenyl selenide (**2b**) was allowed to react with diazomethane at −30 °C. The NMR

**Scheme III**

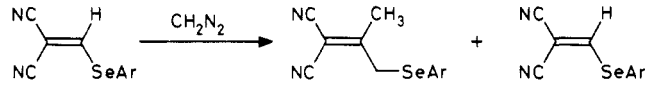



a X = COOMe, R¹ = R² = H
b X = COOMe, R¹ = H, R² = Me
c X = COOMe, R¹ = H, R² = i-Pr
d X = COOMe, R¹ = H, R² = t-Bu
e X = COOMe, R¹ = R² = Me
f X = COMe, R¹ = R² = H
g X = COMe, R¹ = H, R² = Me
h X = COMe, R¹ = H, R² = i-Pr
i X = COMe, R¹ = H, R² = t-Bu
j X = COMe, R¹ = R² = Me




6

**Scheme IV**




2c 7k

spectrum of the reaction mixture showed the presence of the enol ketone **6**, a tautomer of the allyl selenide **4f**[6] (the enol proton appeared at 16.7 ppm), together with an equal amount of **4f**. The isomerization of initially formed **4f** to **6** might occur via [1,5]-sigmatropic migration of a proton of **4f**. However, when **2b** was reacted with excess of diazomethane, the initially formed **4f** was trapped by diazomethane before isomerization, giving the pyrazoline **5f**. The reaction of **2b** with an equimolar amount of diazoethane, isopropyldiazomethane, diazoneopentane, and 2-diazopropane gave only the allyl selenide derivatives **4g–j**, respectively, without formation of any enols. Isolation of **4g–j** without enolization seems reasonable by the analogy of the fact that bulky substituents at C-2 in 1,3-diketones decrease the stability of the enol form relative to that of the keto form, presumably due to steric interactions between the substituents.[7]

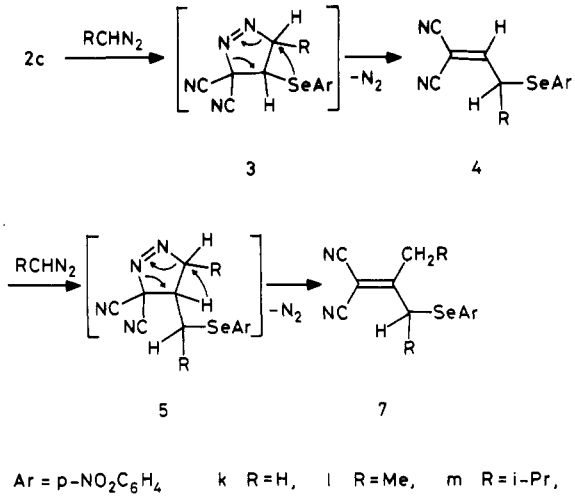
The reaction of (((*p*-nitrophenyl)seleno)methylene)-malononitrile (**2c**), bearing strong electron-withdrawing groups in comparison with **2a** and **2b**, with diazomethane was carried out. When solutions of **2c** and diazomethane were mixed at −10 °C, evolution of nitrogen was observed immediately. Evaporation of the volatile component left

(5) Reich, H. J. *Acc. Chem.Res.* **1979**, *12*, 22.

(6) The enol ketone **6** was not isolated, but the NMR spectrum of **6** quite resemble the NMR spectrum of the thio analogue of **6**, which was isolated (unpublished results).

(7) Forsen, S.; Nillson, M. Enolization. In *The Chemistry of Carbonyl Group*; Patai, S., Ed.; Wiley: New York, 1970; Vol. 2, p 203.

**Scheme V**



Ar = p-$NO_2C_6H_4$ k R=H, l R=Me, m R=i-Pr,

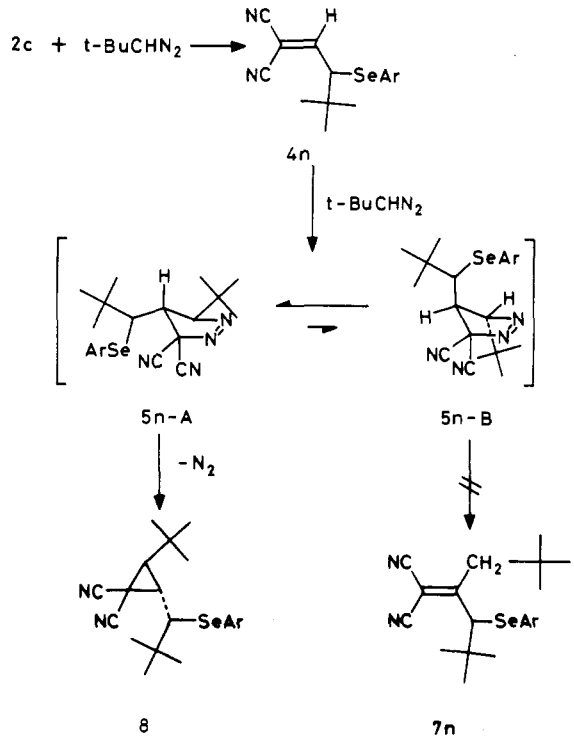
**Table I. Product Distribution in the Reaction between 2c and an Equimolar Amount of Diazoalkanes[a]**

| diazoalkane | 1:1 products,[b] % | 1:2 products,[c] % |
|---|---|---|
| $CH_2N_2$ | 0 | 100 |
| $MeCHN_2$ | 75 | 25 |
| *i*-$PrCHN_2$ | 100 | 0 |
| *t*-$BuCHN_2$ | 100 | 0 |
| $Me_2CN_2$ | 100 | 0 |

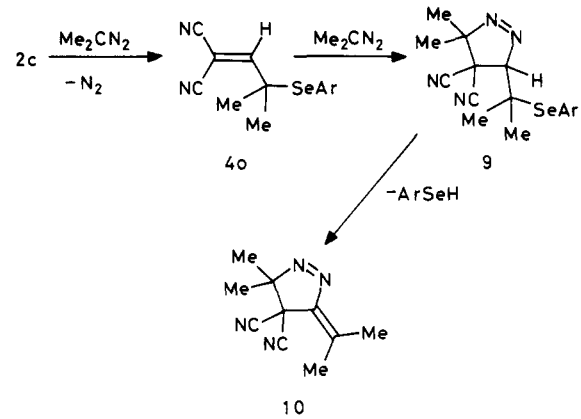
[a] The reactions were carried out in $CH_2Cl_2$/ether at −10 °C. [b] 1:1 products formed are 1-alkyl-3,3-dicyanoallyl *p*-nitrophenyl selenide derivatives (4). [c] 1:2 products formed are 1,2-dialkyl-3,3-dicyanoallyl *p*-nitrophenyl selenide derivatives (7).

a solid residue, the NMR spectrum of which showed a 1:1 mixture of the starting material **2c** and the 3,3-dicyano-2-methylallyl selenide derivative (**7k**), arising from the reaction of **2c** with 2 mol of diazomethane (Schemes IV and V). The 1:1 product **4k** was not detected in the reaction mixture even under conditions which allowed the recovery of a large amount of the starting material. This indicates that the rate of decomposition for the initially formed pyrazoline **3k** is much faster than the rate of addition of diazomethane to **2c**, that the allyl selenide **4k**, formed by nitrogen extrusion with arylseleno migration to C-5 within **3k**, is much more reactive toward diazomethane than **2c**, and that the pyrazoline **5k**, a cycloadduct between **4k** and diazomethane, decomposed with concerted 4-hydride migration to C-5 and nitrogen extrusion to give **7k**. However, the reaction of **2c** with diazoethane gave the 1:1 product **4l** as a major product with a small amount of the 1:2 product **7l**. Furthermore, the reaction of **2c** with an equimolar amount of isopropyldiazomethane, diazoneopentane, and 2-diazopropane gave only the 1:1 products (**4m–o**, respectively). These product distributions are summarized in Table I. These observations indicate that the reactivity of the initially formed 1:1 adducts **4** toward the corresponding diazoalkanes decreases with increasing bulkiness of the C-1 substituents of **4** owing to the steric hindrance in comparison with that of **2c**, resulting in the isolation of the 1:1 products **4**. Detardation was also observed in the reaction of **2a** and **2b** with diazoalkanes. Although the allyl selenides (**4a–c,f–h**), formed from the reaction of **2a** and **2b** with diazomethane, diazoethane, and isopropyldiazomethane, were observed to undergo further reaction with excess of the corresponding diazoalkanes to give the pyrazoline **5**, the allyl selenides (**4d,e,i,j**) formed from the reaction with diazoneopentane and 2-diazopropane did not react further with an excess of the corresponding diazoalkanes because of the steric

**Scheme VI**



**Scheme VII**



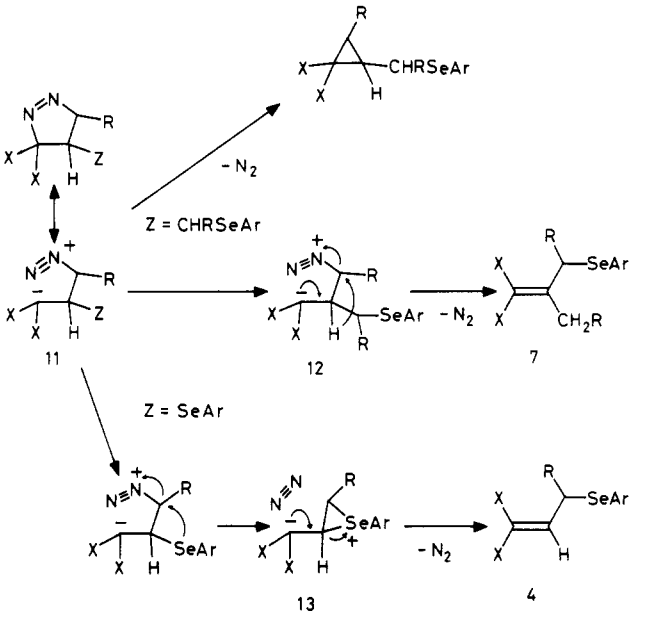
hindrance of the bulky substituents of the allyl selenide derivatives **4**. When **2c** was reacted with 2 mol of diazoethane and isopropyldiazomethane, the alkenes **7** were obtained as 1:2 products, arising from decomposition of the intermediary pyrazolines **5**, cycloadducts between **4** and the diazoalkanes, with concerted hydrogen migration to C-5 and nitrogen extrusion. It is known that 4-monosubstituted pyrazolines bearing two electron-withdrawing groups at C-3 decompose to give 4-hydride migration products, quantitatively.[8] However, the reaction of **2c** with 2 mol of diazoneopentane and 2-diazopropane gave different types of 1:2 products from the alkenes **7**. Unusually, the pyrazoline **5n**, formed in the reaction of **2c** with an excess of diazoneopentane, did not afford the hydrogen migration product **7n**, but the cyclopropane **8**, quantitatively (Scheme VI). The reaction of **2c** with excess of 2-diazopropane gave the pyrazoline **9** (four methyl singlets at 1.50, 1.83, 1.87, and 2.00 and a methine singlet at 4.97 ppm), which was formed by the reverse orientation

(8) (a) Hamelin, J.; Carrie, R. *Bull. Soc. Chim. Fr.* **1968**, 3000. (b) Clinging, R.; Dean, F. M.; Houghton, L. E.; Park, B. K. *Tetrahedron Lett.* **1976**, 1227. (c) Clinging, R.; Dean, F. M.; Houghton, L. E. *J. Chem. Soc. C* **1970**, 897. Also see ref 1.

addition of 2-diazopropane to **4o** (Scheme VII). The reverse orientation addition of 2-diazopropane to some acrylates bearing a β-bulky group has been observed due to steric hindrance of the β-bulky substituent.[9] In the transition state for the normal orientation addition, a steric interaction between the bulky substituent of **4o** and the methyl group of 2-diazopropane increases the energy of activation for the normal orientation addition. Owing to this steric repulsive interaction, the electronically unfavorable, but sterically favorable, reverse orientation addition occurred. The pyrazoline **9** was not stable and gradually eliminated (*p*-nitrophenyl)selenol to produce the 3-methylenepyrazoline derivative **10** and bis(*p*-nitrophenyl) diselenide. The formation of **8** and **9** indicates that steric factors are strongly operating in determining reaction paths in decomposition of pyrazoline and 1,3-dipolar cycloaddition.

Formation of allyl selenide derivatives in the reaction of the electron-deficient vinyl selenides with diazoalkanes, as described above, can reasonablly be explained by the mechanism involving 4-(arylseleno)pyrazolines, though the pyrazolines **3** were not detected except in the case of the reaction between **2a** and diazoneopentane. We believe that the pyrazolines bearing two geminal electron-withdrawing groups have a large contribution from the intramolecular diazonium salt **11** as a resonance form owing to stabilization of the anion at C-3 by the two electron-withdrawing groups. In the structure of **11**, the large arylseleno group assumes the pseudoequatorial position in a folded conformation of the pyrazolines. A preference for a folded conformation has been shown for 1-pyrazoline itself,[10] as well as for numerous substituted derivatives.[11] Work carried out by McGreer and collaborators on pyrazolines bearing an electron-withdrawing group at C-3 indicates that for these species migration of a C-4 hydrogen is concerted with nitrogen extrusion. These pyrazolines are predicted to undergo thermolysis preferentially from the conformer which places a migrating group, a C-4 hydrogen, in the pseudoequatorial position, thus orienting it in an anti relationship to the breaking C–N bond.[12] The ability of selenium and sulfur substituents to accelerate the decomposition by migration and the reluctance of an oxygen substituent to migrate could be explained by the mechanism shown in Scheme VIII. The arylselenium or sulfur group at the pseudoequatorial position participates (by backside approach) in the breaking of the C–N bond through episelenonium or episulfonium-like transition state **13** with elimination of nitrogen, as in the behavior of β-arylthio group observed in the $S_N1$ reaction of β-(arylthio)alkyl halides.[13] But the oxygen group cannot participate as effectively as the selenium or sulfur group: the oxygen substituent preferentially promotes a hydride shift to the neighbor cationic center as in the Pinacol rearrangement or Tiffeneau reaction.[14] The participation of

**Scheme VIII**

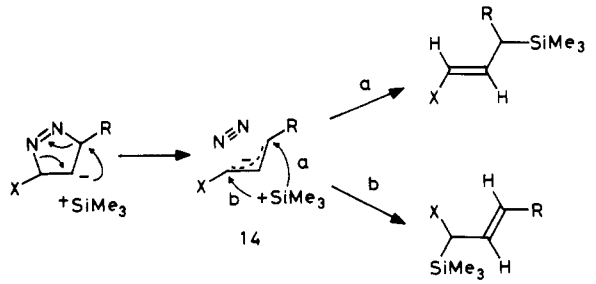



the selenium group in decomposition is stronger than the sulfur group probably due to the higher nucleophilicity and greater polarizability of selenium compared with sulfur,[15] as indicated by the fact that 4-(arylthio)pyrazolines are isolable, while the corresponding 4-(arylseleno)pyrazolines are quite unstable. In the selenium participation step **13**, the participation of selenium could be partly hindered by a bulky substituent at C-5, such as a *tert*-butyl group, which allowed the detection of only the pyrazoline **3d** among all studied pyrazolines. Migration of the C-4 hydrogen to C-5 on decomposition of **5n** is also hindered. Based on steric control of the orientation of the "two plane" complex leading to a cycloadduct, the structure of **5n** is predicted to have the C-4 substituent trans to the *tert*-butyl group at C-5. Both bulky ring substituents at C-4 and C-5 are located at the pseudoequatorial positions in a preferred folded conformation **5n-A** which should be quite favorable in comparison with the other conformation **5n-B**, in which the two bulky C-4 and C-5 substituents are located at the axial positions. To undergo the C-4 hydrogen migration to C-5, the pyrazoline **5n** should take the quite unfavorable conformation **5n-B** which place a C-4 hydrogen in the pseudoequatorial position. Even if the conformation **5n-B** is allowed, migration of 4-hydride to C-5 might be hindered by the bulky *tert*-butyl group at C-5, and migration of the C-4 substituent at the pseudoequatorial position in the preferred conformation **5n-A** should also be hindered by the bulky C-5 substituent, resulting in an alternative path leading to the cyclopropane **8**. Although arylthio migration within the pyrazoline formed from the reaction of the thio analogue of **2c** with diazoneopentane is somewhat hindered by the bulky 5-*tert*-butyl group, resulting in the formation of an arylthio migration product and a cyclopropane in a ratio of 3:1,[16] the stronger migration ability of the arylseleno group allows quantitative formation of the arylseleno migration product **4n** in the reaction of **2c** with diazoneopentane. This also indicates that selenium participates in decomposition more strongly than sulfur.

In contrast to the case just discussed, in which the 4-arylseleno group migrated predominantly to C-5 regardless

(9) Andrews, S. D.; Day, A. C.; McDonald, A. N. *J. Chem. Soc. C* **1969**, 787.
(10) During, J. R.; Karrier, J. M.; Harris, W. C. *J. Chem. Phys.* **1970**, *52*, 6090.
(11) McGreer, D. E.; Wu, W. S. *Can. J. Chem.* **1967**, *45*, 461.
(12) (a) McGreer, D. E.; Masters, I. M. E. *Can. J. Chem.* **1969**, *47*, 3975. (b) Hamelin, J.; Carrie, R. *Bull. Soc. Chim.* **1968**, 3000.
(13) It has been shown that a 2-sulfur substituent accelerates a $S_N1$ reaction to give an episulfonium intermediate owing to strong participation of sulfur. Oxygen substituents do not seem to participate so strongly as those of sulfur. See: Bohme, H.; Sell, K. *Chem. Ber.* **1948**, *81*, 123. It was suggested that reductive elimination of a seleno group proceeds via a pathway involving an episelenonium ion. See: Reich, H. J.; Chow, F.; Shah, S. K. *J. Am. Chem. Soc.* **1979**, *101*, 6638.
(14) Smith, P. A. S.; Baer, D. R. Demjanov and Tiffeneau-Demjanov Ring Expansion. In *Organic Reaction*; Wiley: New York, 1960; Vol. 11, p 157.
(15) Pearson, R. G.; Sabel, H.; Songsted, J. *J. Am. Chem. Soc.* **1968**, *90*, 319.
(16) Hamagushi, M.; Nagai, T., unpublished results.

**Scheme IX**



of the bulkiness of the C-5 substituents, in the decomposition of 4-(trimethylsilyl)pyrazoline migration of the 4-trimethylsilyl group to C-3 as well as to C-5 occurred, depending on the bulkiness of the C-5 substituents.[3] Considering the knowledge that a trimethylsilyl group has metallic properties contrary to nucleophilic properties of selenium and sulfur, the decomposition of 4-(trimethylsilyl)pyrazolines may proceed via an allyl anion complex **14** in a similar manner to the decomposition of 4-metalopyrazolines[17] (Scheme IX).

## Experimental Section

Proton nuclear magnetic resonance spectra were recorded on a Varian EM-390 (90 MHz) instrument, and chemical shifts are reported relative to internal tetramethylsilane (0.00 ppm). Infrared spectra were recorded on a Perkin-Elmer 983G infrared spectrometer. All melting points were uncorrected. Diazomethane, diazoethane,[18] isopropyldiazomethane,[19] and diazoneopentane[20] were prepared by alkali treatment of *N*-alkyl-*N*-nitrosoureas and *N*-neopentyl-*N*-nitrosourethane. 2-Diazopropane was prepared by oxidation of acetone hydrazone.[21]

**2,2-Bis(methoxycarbonyl)vinyl *p*-Nitrophenyl Selenide (2a).** An ethereal solution (30 mL) of 7.5 g of benzoyl chloride was added to a mixture of 7.2 g of dimethyl (hydroxymethylene)malonate and 5.5 g of triethylamine in 50 mL of ether. After 1 h the reaction mixture was washed with water and dilute aqueous sulfuric acid and dried over $MgSO_4$. The product was purified by recrystallization from ether, giving 5.5 g of dimethyl ((benzoyloxy)methylene)malonate (**1a**): mp 85–6 °C; NMR ($CDCl_3$) $\delta$ 3.87 (s, 3 H), 3.93 (s, 3 H), 7.35–7.75 (m, 3 H), 8.0–8.2 (m, 2 H), 8.67 (s, 1 H); IR (KBr) 1757, 1730, 1712, 1639, 1252, 1149, 1103 $cm^{-1}$.

Anal. Calcd for $C_{13}H_{12}O_6$: C, 59.09; H, 4.58. Found: C, 59.04; H, 4.58.

A dichloromethane solution (5 mL) of 1.32 g of **1a** was added to a methanol solution of sodium *p*-nitrophenyl selenolate, which was prepared by reduction of 1.005 g of the finely powdered bis(*p*-nitrophenyl) diselenide with 0.281 g of $NaBH_4$. The reaction mixture was poured into water and extracted with $CH_2Cl_2$. The extract was washed with water and dried over $MgSO_4$. After evaporation of $CH_2Cl_2$, the crude product was crystallized from $CH_2Cl_2$/ether to give 1.52 g of **2a** (88%): mp 181–182 °C; NMR ($CDCl_3$) $\delta$ 3.78 (s, 3 H), 3.90 (s, 3 H), 7.75 and 8.18 (AB q, $J$ = 9.0 Hz, 4 H), 8.80 (s, 1 H); IR (KBr) 1735, 1679, 1517, 1347 $cm^{-1}$.

Anal. Calcd for $C_{12}H_{11}O_6NSe$: C, 41.87; H, 3.22; N, 4.07. Found: C, 41.89; H, 3.22; N, 4.28.

**2,2-Diacetylvinyl *p*-Nitrophenyl Selenide (2b).** A dichloromethane solution of 2.32 g of 2,2-diacetylvinyl benzoate (**1b**), synthesized by the reaction between benzoyl chloride and 2,2-diacetylvinyl alcohol in the presence of triethylamine in $CH_2Cl_2$, was added to a methanol solution of sodium *p*-nitrophenyl selenolate prepared from 2.01 g of bis(*p*-nitrophenyl) diselenide and 0.563 g of $NaBH_4$. The reaction mixture was worked up as described in the preparation of **2a**. Recrystallization from $CH_2Cl_2$/ether gave 2.49 g of a yellow crystalline solid **2b**: mp 146–7 °C; NMR ($CDCl_3$) $\delta$ 2.42 (s, 3 H), 2.56 (s, 3 H), 7.77 and 8.20 (AB q, $J$ = 9.0 Hz, 4 H), 8.77 (s, 1 H); IR (KBr) 1671, 1635, 1511, 1343 $cm^{-1}$.

Anal. Calcd for $C_{12}H_{11}O_4NSe$: C, 46.17; H, 3.55; N, 4.49. Found: C, 46.24; H, 3.60; N, 4.72.

**2,2-Dicyanovinyl *p*-Nitrophenyl Selenide (2c).** An ethereal solution of 1.12 g of 2,2-dicyanovinyl chloride (**1c**) was added to an ethanol solution of 10 mmol of sodium *p*-nitrophenyl selenolate prepared from bis(*p*-nitrophenyl) diselenide and $NaBH_4$. The reaction mixture was poured into water, giving 2.5 g of solid. Recrystallization from $CH_2Cl_2$/ether gave a yellow crystalline solid **2c**: mp 150–151 °C; NMR ($CDCl_3$) $\delta$ 7.78 and 8.28 (AB q, $J$ = 9.0 Hz, 4 H), 8.63 (s, 1 H); IR (KBr) 2227, 1597, 1522, 1348 $cm^{-1}$.

Anal. Calcd for $C_{10}H_5O_2N_3Se$: C, 43.18; H, 1.81; N, 15.11. Found: C, 43.35; H, 1.86; N, 15.13.

**Reaction of 2a with Diazomethane.** To a solution of 344 mg of **2a** in 25 mL of $CH_2Cl_2$ at −30 °C was added an ethereal solution of an equimolar amount of diazomethane (1.5 mL). The reaction mixture was allowed to stand at −30 °C overnight. After solvent was removed, the residue was treated with ether, giving 83 mg of **2a** and 254 mg of 3,3-bis(methoxycarbonyl)allyl *p*-nitrophenyl selenide (**4a**) (94% yield on the basis of the unrecovered **2a**): mp 55–56 °C; NMR ($CDCl_3$) $\delta$ 3.76 (s, 6 H), 3.90 (d, $J$ = 8.6 Hz, 2 H), 7.13 (t, $J$ = 8.6 Hz, 1 H), 7.60 and 8.07 (AB q, $J$ = 9.0 Hz, 4 H); IR (KBr) 1720, 1706, 1519, 1354, 1266, 1231 $cm^{-1}$.

Anal. Calcd for $C_{13}H_{13}O_6NSe$: C, 43.59; H, 3.66; N, 3.91. Found: C, 43.66; H, 3.67; N, 4.24.

A dichloromethane solution of 344 mg of **2a** was treated with a 2-fold excess of diazomethane in ether. Evaporation of solvent gave an oil, NMR of which showed quantitative formation of 3,3-bis(methoxycarbonyl)-4-(((*p*-nitrophenyl)seleno)methyl)-$\Delta^1$-pyrazoline (**5a**): NMR ($CDCl_3$) $\delta$ 2.62 (t, $J$ = 10.8 Hz, 1 H), 2.98 (dddd, $J$ = 3.6, 7.2, 7.8, 10.8 Hz, 1 H), 3.92 (dd, $J$ = 3.6, 10.8 Hz, 1 H), 3.87 (s, 3 H), 3.90 (s, 3 H), 4.40 (dd, $J$ = 7.2, 17.7 Hz, 1 H), 4.97 (dd, $J$ = 7.8, 17.7 Hz, 1 H), 7.53 and 8.03 (AB q, $J$ = 9.0 Hz, 4 H).

**Reaction of 2a with Diazoethane.** To 344 mg of **2a** in 25 mL of $CH_2Cl_2$ at −30 °C was added an ether solution of about an equimolar amount of diazoethane. Evaporation of the solvent gave an oil, NMR of which showed a mixture of 3,3-bis(methoxycarbonyl)-1-methylallyl *p*-nitrophenyl selenide (**4b**) and **5b** in a ratio of 5:1: NMR ($CDCl_3$) $\delta$ 1.57 (d, $J$ = 6.6 Hz, 3 H), 3.63 (s, 3 H), 3.75 (s, 3 H), 4.57 (dq, $J$ = 11.4, 6.6 Hz, 1 H), 6.93 (d, $J$ = 11.4 Hz, 1 H), 7.62 and 8.05 (AB q, $J$ = 9.0 Hz, 4 H); IR (film) 1724, 1631, 1517, 1348 $cm^{-1}$.

A dichloromethane solution of 344 mg of **2a** was reacted with a 2-fold excess of diazoethane. After solvent was removed, NMR spectrum of the residue showed formation of 3,3-bis(methoxycarbonyl)-5-methyl-4-(1-((*p*-nitrophenyl)seleno)ethyl)-$\Delta^1$-pyrazoline (**5b**): NMR ($CDCl_3$) $\delta$ 1.38 (d, $J$ = 6.6 Hz, 3 H), 1.55 (d, $J$ = 6.6 Hz, 3 H), 2.70 (t, $J$ = 6.6 Hz, 1 H), 3.73 (quintet, $J$ = 6.6 Hz, 1 H), 3.83 (s, 3 H), 3.91 (s, 3 H), 4.77 (quintet, $J$ = 6.6 Hz, 1 H), 7.50 and 8.08 (AB q, $J$ = 9.0 Hz, 4 H); IR (film) 1735, 1517, 1347 $cm^{-1}$.

**Reaction of 2a with Isopropyldiazomethane.** An ethereal solution (2.5 mL) containing 1 mmol of isopropyldiazomethane was added to 344 mg of **2a** in 30 mL of $CH_2Cl_2$ at −30 °C. After workup the reaction mixture was treated with ether, giving 333 mg of 3,3-bis(methoxycarbonyl)-1-isopropylallyl *p*-nitrophenyl selenide (**4c**); mp 73–74 °C; NMR ($CDCl_3$) $\delta$ 1.08 (d, $J$ = 6.6 Hz, 3 H), 1.17 (d, $J$ = 6.6 Hz, 3 H), 2.07 (octet, $J$ = 6.6 Hz, 1 H), 3.57 (s, 3 H), 3.73 (s, 3 H), 4.30 (dd, $J$ = 6.8, 12.0 Hz, 1 H), 7.03 (d, $J$ = 12.0 Hz, 1 H), 7.65 and 8.05 (AB q, $J$ = 9.0, 4 H); IR (KBr) 1719, 1597, 1526, 1369, 1349 $cm^{-1}$.

Anal. Calcd for $C_{16}H_{18}O_6SeN$: C, 48.12; H, 4.54; N, 3.51. Found: C, 48.19; H, 4.83; N, 3.59.

**Reaction of 2a with Diazoneopentane.** An ethereal solution containing 1 mmol of diazoneopentane was added to 1 mmol of **2a** in $CH_2Cl_2$ at −10 °C. After standing at −10 °C overnight and evaporation of the solvent, the NMR spectrum of the residue showed a mixture of *trans*-5-*tert*-butyl-3,3-bis(methoxycarbonyl)-4-((*p*-nitrophenyl)seleno)-$\Delta^1$-pyrazoline (**3d**) and 3,3-bis(methoxycarbonyl)-1-*tert*-butylallyl *p*-nitrophenyl selenide (**4d**)

(17) Eberhard, P.; Huisgen, R. *J. Am. Chem. Soc.* **1972**, *94*, 1345.
(18) Diazoethane was prepared by a similar procedure to the synthetic method of diazomethane described in *Organic Syntheses*. See: *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. II, p 165.
(19) von Bruchhausen, F.; Hoffmann, H. *Chem. Ber.* **1941**, *74*, 1584.
(20) Curtin, D. Y.; Gerber, S. M. *J. Am. Chem. Soc.* **1952**, *74*, 4052.
(21) *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 392.

in a ratio of 7:3: NMR ($CDCl_3$) of **3d** $\delta$ 1.10 (s, 9 H), 3.77 (s, 3 H), 3.95 (s, 3 H), 3.98 (d, $J$ = 7.5 Hz, 1 H), 4.65 (d, $J$ = 7.5 Hz, 1 H), 7.72 and 8.12 (AB q, $J$ = 9.0 Hz, 4 H). Fractional precipitation of the residue extended over many days gave 35 mg of **2a** and 336 mg of **4d** (90%): mp 103–104 °C; NMR ($CDCl_3$) $\delta$ 1.17 (s, 9 H), 3.50 (s, 3 H), 3.78 (s, 3 H), 4.28 (d, $J$ = 12.0 Hz, 1 H), 7.17 (d, $J$ = 12.0 Hz, 1 H), 7.67 and 8.07 (AB q, $J$ = 9.0 Hz, 4 H); IR (KBr) 1722, 1598, 1528, 1368, 1348 $cm^{-1}$.

Anal. Calcd for $C_{17}H_{21}O_6NSe$: C, 49.28; H, 5.11; N, 3.38. Found: C, 49.37; H, 5.08; N, 3.26.

Treatment of **2a** with a 2-fold excess of diazoneopentane at room temperature gave **4d** together with trace of **3d**.

**Reaction of 2a with 2-Diazopropane.** A $CH_2Cl_2$ solution of 1 mmol of **2a** was mixed with an ethereal solution of 2-diazopropane at room temperature for 10 min. Evaporation of the solvent gave an oil, the NMR spectrum of which showed quantitative formation of 3,3-bis(methoxycarbonyl)-1,1-dimethylallyl *p*-nitrophenyl selenide (**4e**): NMR ($CDCl_3$) $\delta$ 1.62 (s, 6 H), 3.57 (s, 3 H), 3.77 (s, 3 H), 7.03 (s, 1 H), 7.70 and 8.10 (AB q, $J$ = 9.0 Hz, 4 H); IR (film) 1741, 1629, 1517, 1350 $cm^{-1}$.

**Reaction of 2b with Diazomethane.** To a $CH_2Cl_2$ solution of **2b** at −30 °C was added an ethereal solution of an equimolar amount of diazomethane (1.7 mL). NMR of the reaction mixture showed a mixture of 3,3-diacetylallyl *p*-nitrophenyl selenide (**4f**), the enol of 3-(2-((*p*-nitrophenyl)seleno)vinyl)-3-acetylacetone (**6**), 3,3-diacetyl-4-(((*p*-nitrophenyl)seleno)methyl)-$\Delta^1$-pyrazoline (**5f**), and **2b** in a ratio of 3:3:2:1. The products were not separated in a pure state: NMR ($CDCl_3$) of **4f** $\delta$ 2.33 (s, 3 H), 2.45 (s, 3 H), 3.83 (d, $J$ = 8.4 Hz, 2 H), 6.87 (t, $J$ = 8.4 Hz, 1 H); NMR ($CDCl_3$) of **6** $\delta$ 2.28 (s, 6 H), 6.52 (d, $J$ = 15.6 Hz, 1 H), 6.87 (d, $J$ = 15.6 Hz, 1 H), 16.78 (s, 1 H). The aromatic region was not characterized. Treatment of **2b** with a large excess of diazomethane gave the pyrazoline (**5f**) (78%): mp 108–110 °C; NMR ($CDCl_3$) $\delta$ 2.43 (s, 3 H), 2.46 (s, 3 H), 2.4–2.6 (m, 1 H), 2.85–3.30 (m, 2 H), 4.45 (dd, $J$ = 6.0, 18.0 Hz, 1 H), 4.72 (dd, $J$ = 7.8, 18.0 Hz, 1 H), 7.50 and 8.10 (AB q, $J$ = 9.0 Hz, 4 H); IR (KBr) 1728, 1704, 1595, 1574, 1507, 1343 $cm^{-1}$.

Anal. Calcd for $C_{14}H_{15}O_4N_3Se$: C, 45.66; H, 4.11; N, 11.41. Found: C, 45.60; H, 4.10; N, 11.40.

**Reaction of 2b with Diazoethane.** An ethereal solution of 1 mmol of diazoethane was added to 1 mmol of **2b** in $CH_2Cl_2$ at −30 °C. Fractional recrystallization of the reaction mixture from ether/pentane gave 160 mg of **2b** and 126 mg of 3,3-diacetyl-1-methylallyl *p*-nitrophenyl selenide (**4g**) (76% yield on the basis of the unrecovered **2b**): mp 59–60 °C; NMR ($CDCl_3$) $\delta$ 1.58 (d, $J$ = 6.9 Hz, 3 H), 2.07 (s, 3 H), 2.30 (s, 3 H), 4.48 (d, $J$ = 11.1 Hz, q, $J$ = 6.9 Hz, 1 H), 6.63 (d, $J$ = 11.1 Hz, 1 H), 7.65 and 8.07 (AB q, $J$ = 9.0 Hz, 4 H); IR (KBr) 1701, 1664, 1512, and 1345 $cm^{-1}$.

Anal. Calcd for $C_{14}H_{15}O_4NSe$: C, 49.42; H, 4.44; N, 4.12. Found: C, 49.28; H, 4.37; N, 4.14.

Treatment of 312 mg of **2b** with an excess of diazoethane gave 273 mg of 3,3-diacetyl-5-methyl-4-(1-((*p*-nitrophenyl)seleno)-ethyl)-$\Delta^1$-pyrazoline (**5g**): mp 104 °C dec; NMR ($CDCl_3$) $\delta$ 1.08 (d, $J$ = 7.0 Hz, 3 H), 1.28 (d, $J$ = 7.2 Hz, 3 H), 2.43 (s, 3 H), 2.62 (s, 3 H), 2.80 (t, $J$ = 4.5 Hz, 1 H), 3.78 (d, $J$ = 4.5, q, $J$ = 7.0, 1 H), 4.83 (d, $J$ = 4.5, q, $J$ = 7.2, 1 H), 7.55 and 8.12 (AB q, $J$ = 9.0 Hz, 4 H); IR (KBr) 1727, 1695, 1595, 1571, 1507, 1341 $cm^{-1}$.

Anal. Calcd for $C_{16}H_{18}N_3O_4Se$: C, 48.61; H, 4.59; N, 10.63. Found: C, 48.64; H, 4.84; N, 10.52.

**Reaction of 2b with Isopropyldiazomethane.** A dichloromethane solution of 1 mmol of **2b** was allowed to react with 1 mmol of isopropyldiazomethane in ether at −30 °C overnight. After the solvent was removed, the product was purified by recrystallization from ether/pentane, giving 300 mg of 3,3-diacetyl-1-isopropylallyl *p*-nitrophenyl selenide (**4h**) (82%) as a yellow crystalline solid: mp 86.0–86.5 °C; NMR ($CDCl_3$) $\delta$ 1.10 (d, $J$ = 6.6 Hz, 3 H), 1.15 (d, $J$ = 6.6 Hz, 3 H), 1.98 (s, 3 H), 2.00 (octet, $J$ = 6.6 Hz, 1 H), 2.30 (s, 3 H), 4.22 (dd, $J$ = 6.8, 11.4 Hz, 1 H), 6.70 (d, $J$ = 11.4 Hz, 1 H), 7.67 and 8.07 (AB q, $J$ = 9.0 Hz, 4 H); IR (KBr) 1692, 1665, 1600, 1517, 1351 $cm^{-1}$.

Anal. Calcd for $C_{16}H_{19}O_4NSe$: C, 52.18; H, 5.20; N, 3.80. Found: C, 52.36; H, 5.25; N, 3.94.

**Reaction of 2b with Diazoneopentane.** A dichloromethane solution of 312 mg of **2b** was treated with an ethereal solution of 1 mmol of diazoneopentane at −25 to −10 °C overnight. After evaporation of the solvent, recrystallization of the residue from ether/pentane gave 355 mg of 3,3-diacetyl-1-*tert*-butylallyl *p*-nitrophenyl selenide (**4i**): mp 96–97 °C; NMR ($CDCl_3$) $\delta$ 1.17 (s, 9 H), 1.88 (s, 3 H), 2.32 (s, 3 H), 4.27 (d, $J$ = 12.0 Hz, 1 H), 6.83 (d, $J$ = 12.0 Hz, 1 H), 7.68 and 8.07 (AB q, $J$ = 9.0 Hz, 4 H); IR (KBr) 1695, 1662, 1599, 1517, 1351 $cm^{-1}$.

Anal. Calcd for $C_{17}H_{21}O_4NSe$: C, 53.40; H, 5.54; N, 3.66. Found: C, 53.41; H, 5.51; N, 3.40.

**Reaction of 2b with 2-Diazopropane.** The vinyl selenide **2b** (1 mmol) in $CH_2Cl_2$ was allowed to react with an equimolar amount of 2-diazopropane in ether at room temperature. Recrystallization gave 308 mg of 3,3-diacetyl-1,1-dimethylallyl *p*-nitrophenyl selenide (**4j**) as a yellow crystalline solid: mp 100 °C; NMR ($CDCl_3$) $\delta$ 1.60 (s, 6 H), 2.07 (s, 3 H), 2.30 (s, 3 H), 6.63 (s, 1 H), 7.73 and 8.15 (AB q, $J$ = 9.0 Hz, 4 H); IR (KBr) 1707, 1655, 1614, 1596, 1524, 1351 $cm^{-1}$.

Anal. Calcd for $C_{15}H_{17}O_4NSe$: C, 50.85; H, 4.84; N, 3.95. Found: C, 50.91; H, 4.88; N, 3.73.

**Reaction of 2c with Diazomethane.** When a 0.7 M ethereal solution of diazomethane (1.5 mL) was added to a 10 mL of $CH_2Cl_2$ solution containing 278 mg of **2c** at −30 °C, evolution of nitrogen was observed. After evaporation of solvent NMR of the residue showed a 1:1 mixture of **2c** and 3,3-dicyano-2-methylallyl *p*-nitrophenyl selenide (**7k**). Reaction of 1 mmol of **2c** with 2 molar equiv of diazomethane gave 264 mg of **7k**: mp 121–122 °C; NMR ($CDCl_3$) $\delta$ 2.40 (s, 3 H), 3.98 (s, 2 H), 7.73 and 8.12 (AB q, $J$ = 9.0 Hz, 4 H); IR (KBr) 2233, 1597, 1512, 1351 $cm^{-1}$.

Anal. Calcd for $C_{12}H_9O_2N_3Se$: C, 47.07; H, 2.96; N, 13.73. Found: C, 47.16; H, 2.93; N, 13.51.

**Reaction of 2c with Diazoethane.** A dichloromethane solution of 1 mmol of **2c** was treated with 1 mmol of diazoethane in ether at −30 °C. NMR of the reaction mixture showed a mixture of **2c**, 3,3-dicyano-1-methylallyl *p*-nitrophenyl selenide (**4l**), and 3,3-dicyano-2-ethyl-1-methylallyl *p*-nitrophenyl selenide (**7l**) in a ratio of 1:3:1. Fractional precipitation separated **4l** and **7l**.

**4l**: mp 132.5–133.5 °C; NMR ($CDCl_3$) $\delta$ 1.63 (d, $J$ = 6.9 Hz, 3 H), 4.43 (dq, $J$ = 11.2, 6.9 Hz, 1 H), 7.10 (d, $J$ = 11.2 Hz, 1 H), 7.73 and 8.18 (AB q, $J$ = 9.0 Hz, 4 H); IR (KBr) 2233, 1598, 1584, 1520, 1353 $cm^{-1}$.

Anal. Calcd for $C_{12}H_9O_2N_3Se$: C, 47.07; H, 2.96; N, 13.73. Found: C, 47.07; H, 2.96; N, 13.74.

**7l**: mp 108–109 °C; NMR ($CDCl_3$) $\delta$ 1.32 (t, $J$ = 7.2 Hz, 3 H), 1.68 (d, $J$ = 7.2 Hz, 3 H), 2.45–2.80 (m, 2 H), 4.75 (q, $J$ = 6.9 Hz, 1 H), 7.73 and 8.17 (AB q, $J$ = 9.0 Hz, 4 H); IR (KBr) 2231, 1598, 1572, 1515, 1347 $cm^{-1}$.

Anal. Calcd for $C_{14}H_{13}O_2N_3Se$: C, 50.31; H, 3.92; N, 12.57. Found: C, 50.52; H, 3.91; N, 12.64.

**Reaction of 2c with Isopropyldiazomethane.** The vinyl selenide **2c** (1 mmol) in $CH_2Cl_2$ was allowed to react with 1 mmol of isopropyldiazomethane in ether. Recrystallization of the reaction mixture from ether/pentane gave 248 mg of yellow crystalline 3,3-dicyano-1-isopropylallyl *p*-nitrophenyl selenide (**4m**): mp 99.5–101 °C; NMR ($CDCl_3$) $\delta$ 1.13 (d, $J$ = 6.6 Hz, 3 H), 1.20 (br septet, $J$ = 6.6 Hz, 1 H), 4.13 (dd, $J$ = 7.0, 12.0 Hz, 1 H), 7.27 (d, $J$ = 12.0 Hz, 1 H), 7.73 and 8.17 (AB q, $J$ = 9.0 Hz, 4 H); IR (KBr) 2231, 1595, 1515, 1353 $cm^{-1}$.

Anal. Calcd for $C_{14}H_{13}O_2N_3Se$: C, 50.31; H, 3.92; N, 12.57. Found: C, 50.23; H, 3.93; N, 12.23.

Treatment of **2c** with an excess of isopropyldiazomethane gave 3,3-dicyano-2-isobutyl-1-isopropylallyl *p*-nitrophenyl selenide (**7m**): NMR ($CDCl_3$) $\delta$ 1.03 (d, $J$ = 6.4 Hz, 6 H), 1.07 (d, $J$ = 6.3 Hz, 3 H), 1.33 (d, $J$ = 6.5 Hz, 3 H), 1.95–2.90 (m, 4 H), 4.17 (d, $J$ = 10.8 Hz, 1 H), 7.73 and 8.17 (AB q, $J$ = 9.0 Hz, 4 H).

**Reaction of 2c with Diazoneopentane.** To a dichloromethane solution of **2c** (139 mg) was added 0.5 mmol of diazoneopentane in ether at room temperature for 10 min. The reaction mixture was shown to contain only 1-*tert*-butyl-3,3-dicyanoallyl *p*-nitrophenyl selenide (**4n**) by the NMR spectrum. Recrystallization from ether/pentane yielded a yellowish crystalline solid **4n**: mp 154–155 °C; NMR ($CDCl_3$) $\delta$ 1.18 (s, 9 H), 4.07 (d, $J$ = 12.0 Hz, 1 H), 7.33 (d, $J$ = 12.0 Hz, 1 H), 7.72 and 8.15 (AB q, $J$ = 9.0 Hz, 4 H); IR (KBr) 2237, 1596, 1515, 1351 $cm^{-1}$.

Anal. Calcd for $C_{15}H_{15}O_2N_3Se$: C, 51.73; H, 4.34; N, 12.07. Found: C, 51.55; H, 4.27; N, 11.98.

When **2c** was treated with a large excess of diazoneopentane, quantitative formation of *trans*-3-*tert*-butyl-1,1-dicyano-2-(2,2-

dimethyl-1-((p-nitrophenyl)seleno)propyl)cyclopropane (8) was shown by NMR of the reaction mixture, which was purified by recrystallization, giving a yellow crystalline solid 8: mp 176-177 °C; NMR ($CDCl_3$) δ 1.10 (s, 9 H), 1.18 (s, 9 H), 2.03 (d, J = 8.7 Hz, 1 H), 2.18 (dd, J = 8.7, 10.2 Hz, 1 H), 3.00 (d, J = 10.2 Hz, 1 H), 7.78 and 8.08 (AB q, J = 9.0 Hz, 4 H); IR (KBr) 2241, 1597, 1571, 1511, 1348 $cm^{-1}$.

Anal. Calcd for $C_{20}H_{25}O_2N_3Se$: C, 57.41; H, 6.02; N, 10.04. Found: C, 57.41; H, 5.99; N, 9.82.

**Reaction of 2c with 2-Diazopropane.** To 1 mmol of **2c** in $CH_2Cl_2$ at -20 °C was added an ethereal solution containing 1 mmol of 2-diazopropane. Quantitative formation of 3,3-dicyano-1,1-dimethylallyl p-nitrophenyl selenide (**4o**) was shown by the NMR of the reaction mixture, which was purified by recrystallization, giving a yellow crystalline solid **4o**: mp 149-150 °C; NMR ($CDCl_3$) δ 1.80 (s, 6 H), 7.08 (s, 1 H), 7.73 and 8.25 (AB q, J = 9.0 Hz, 4 H); IR (KBr) 2232, 1595, 1579, 1516, 1350 $cm^{-1}$.

Anal. Calcd for $C_{13}H_{11}O_2N_3Se$: C, 48.76; H, 3.46; N, 13.12. Found: C, 48.86; H, 3.47; N, 12.94.

Compound **2c** was treated with a large excess of 2-diazopropane. After the solvent was removed, NMR analysis of the reaction mixture showed formation of 4,4-dicyano-3,3-dimethyl-5-(2-((p-nitrophenyl)seleno)-2-methylpropyl)-$\Delta^1$-pyrazoline (**9**): NMR ($CDCl_3$) δ 1.50 (s, 3 H), 1.83 (s, 3 H), 1.87 (s, 3 H), 2.00 (s, 3 H), 4.97 (s, 1 H), 7.29 and 8.15 (AB q, J = 9.0 Hz, 4 H). The reaction mixture was chromatographed over silica gel using benzene as an eluent, giving bis(p-nitrophenyl) diselenide and 4,4-dicyano-5,5-dimethyl-3-isopropylidene-$\Delta^1$-pyrazoline (**10**): mp 61.5-62.0 °C; NMR ($CDCl_3$) δ 1.67 (s, 6 H), 2.30 (s, 3 H), 2.48 (s, 3 H); IR (KBr) 2246, 1663, 1501 $cm^{-1}$.

Anal. Calcd for $C_{10}H_{12}N_4$: C, 63.81; H, 6.43; N, 29.77. Found: C, 63.79; H, 6.39; N, 29.52.

# Resolution and Determination of the Absolute Stereochemistry of α- and β-Aryl-Substituted γ-Methylenevalerolactones, Alternate Substrate Inhibitors for Serine Proteases

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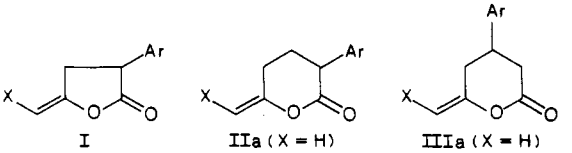
*Received January 18, 1989*

To study the enantioselectivity of alternate substrate inhibition of chymotrypsin by chiral α- and β-aryl-substituted enol lactones, we have prepared four of these lactones in homochiral form: 3-phenyl-6-methylenetetrahydro-2-pyranone (αPh6H, IIa), 3-(1-naphthyl)-6-methylenetetrahydro-2-pyranone (αNp6H, IIb), 4-phenyl-6-methylenetetrahydro-2-pyranone (βPh6H, IIIa), and 4-(1-naphthyl)-6-methylenetetrahydro-2-pyranone (βNp6H, IIIb). Their resolution was carried out on the acetylenic acid precursors α- and β-aryl-5-hexynoic acids (**2ab** and **7ab**, respectively) by silica gel chromatographic separation of the corresponding (R)-phenylglycinol amide derivatives. The homochiral acids, obtained by acid hydrolysis of the amides, have enantiomeric excesses of 94-100% and are readily converted to the enol lactones by mercury-catalyzed lactonization. The absolute configuration of the β-aryl-substituted lactones was established by X-ray crystallographic analysis of one of the phenylglycinol amide diastereomers, cocrystallized with triphenylphosphine oxide; the configuration of the α-aryl-substituted lactones is based on a stereochemical correlation. In all cases, the assigned stereochemistry of the amides is consistent with their chromatographic elution order and the chemical shift of diagnostic resonances in the $^1H$ NMR spectra. Both enantiomers of the IIIa hydrolysis product β-phenyl-substituted 5-oxohexanoic acid **10a** were prepared by an asymmetric synthesis using the RAMP and SAMP hydrazones; their stereochemistry was correlated with that of the corresponding acetylenic acids.

## Introduction

Serine proteases play a major role in the regulation of many normal physiological and pathological processes,[1] and recently, major efforts have been directed toward the development of effective and selective serine protease inhibitors as agents of therapeutic promise.[2]

We have investigated the activity of halo enol lactones as enzyme-activated irreversible inhibitors of serine proteases and found that the α-aryl-substituted (halomethylene)butyrolactone and -valerolactone systems I and II are effective mechanism-based inhibitors of α-chymotrypsin.[3,4] Reaction proceeds by acylation of the active site serine-195, with concomitant unmasking of a latent alkylating agent, a halomethyl ketone; inactivation then results from subsequent alkylation of an active site residue (presumed to be histidine-57), a process that competes with deacylation. In further studies on the β-phenyl-substituted systems (III, X = Br, I), only transient inhibition, characteristic of a stable acyl enzyme, but not alkylation, was observed.[5] Such stable acyl enzymes were also noted with the corresponding protio enol lactones (IIIa, X = H), which do not have the latent alkylating function. In some cases, extremely stable acyl enzymes, having half-lives of several hours at pH 7.2, 25 °C, were obtained.[5]




I IIa (X = H) IIb (X = H) IIIa (X = H) IIIb (X = H)

Ar = phenyl (a); 1-naphthyl (b); X = H, Br, I

Questions arose concerning enantioselectivity in the three steps of enzymatic lactone hydrolysis—substrate

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