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Phenylselenenyl Sulfate Induced Cyclization of Allylhydrazines. Synthesis of Pyrazole Derivatives

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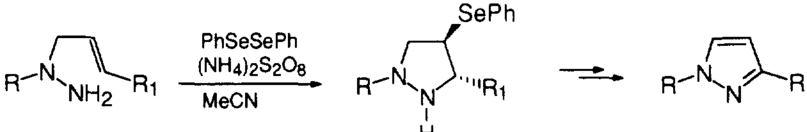
Abstract: Allylhydrazines react with phenylselenenyl sulfate, produced by diphenyl diselenide and ammonium persulfate in the presence of trifluoromethanesulfonic acid, to afford phenylseleno substituted pyrazolidines. Under the reaction conditions employed, these suffer dehydrogenation and oxidative deselenenylation to eventually give pyrazole derivatives. © 1997 Elsevier Science Ltd.

The interaction of an electrophilic selenium reagent with an alkene containing a suitably positioned nitrogen nucleophile evolves towards the production of a cyclic compound by formation of a carbon-nitrogen bond. These ring-closure reactions are very useful since they represent an easy access to a variety of nitrogen heterocyclic compounds.[1-3] Several new examples of these reactions have been described in recent years.[4-18] We have recently observed that N-allyl acethydrazides easily give rise to organoselenium-induced cyclization reactions to afford phenylseleno substituted 5,6-dihydro-4*H*-1,3,4-oxadiazines or N-acetyl pyrazolidines as the kinetically or the thermodynamically controlled products, respectively.[19]

We now report that similar cyclization reactions take place also in the case of simple N-allylhydrazines. Upon treatment with phenylselenenyl sulfate, N-allylhydrazines **1** (Scheme 1) are stereoselectively converted into the phenylseleno substituted pyrazolidines **2**. In most cases, however, under the experimental conditions employed, the pyrazolidines **2** suffer dehydrogenation and oxidative deselenenylation to eventually afford the pyrazole derivatives **4**.

Scheme 1

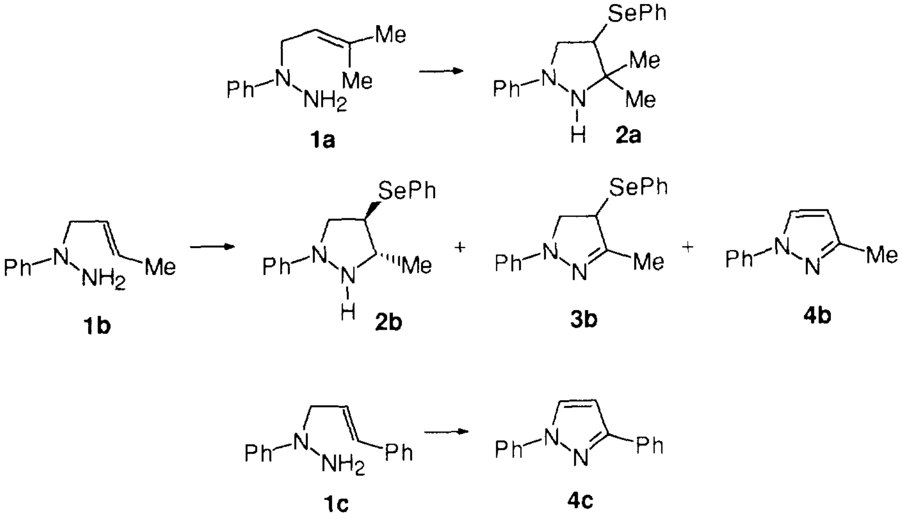


1 **2** **4**

The products **1**, necessary for the present investigation, were easily obtained by allylation of phenylhydrazine or of hydrazine. These were added to the solution of phenylselenenyl sulfate produced by oxidation of diphenyl diselenide with ammonium persulfate in the presence of trifluoromethanesulfonic acid in acetonitrile.[16]

The first experiment was carried out with the allylhydrazine **1a**. The reaction of **1a** (1 mmol) with a solution of diphenyl diselenide (1 mmol), ammonium persulfate (1.2 mmol) and trifluoromethanesulfonic acid (2.2 mmol) in acetonitrile (10 mL) proceeded smoothly at room temperature to afford, after the usual work-up and column chromatography, the 3,3-dimethyl-1-phenyl-4-(phenylseleno)pyrazolidine **2a** in 70% yield (Scheme 2). Under the same experimental conditions, the reaction of the allylhydrazine **1b** could not be stopped at the stage of the pyrazolidine **2b**. In fact, even at the early reaction stages two further products were also present in the reaction mixture. After 3h at room temperature the reaction was worked up. The three products were isolated by column chromatography and were identified as the 3-methyl-1-phenyl-4-(phenylseleno)pyrazolidine **2b** (30%), 3-methyl-1-phenyl-4-(phenylseleno)-4,5-dihydro-1*H*-pyrazole **3b** (16%) and 3-methyl-1-phenyl-1*H*-pyrazole **4b** (22%) (Scheme 2). Some diphenyl diselenide was also recovered. It seems reasonable to suggest that compound **3b** is produced from **2b** by dehydrogenation and that this suffers oxidative deselenenylation[19,20] producing the aromatic pyrazole **4b** and regenerating the selenenylating agent. Compound **4b** was obtained as the sole reaction product (76% yield) from an experiment in which **1b** (1 mmol) was allowed to react with a larger excess of phenylselenenyl sulfate (3 mmol). Diphenyl diselenide was almost quantitatively recovered from this reaction. In the case of the cinnamyl phenylhydrazine **1c** the reaction was much faster and the intermediate pyrazolidine and dihydropyrazole could not be isolated. The only product obtained from this reaction was the 1,3-diphenyl-1*H*-pyrazole **4c** (62%) (Scheme 2). Better yields of **4c** (75%) were obtained from a reaction carried out with an excess of phenylselenenyl sulfate.

Scheme 2

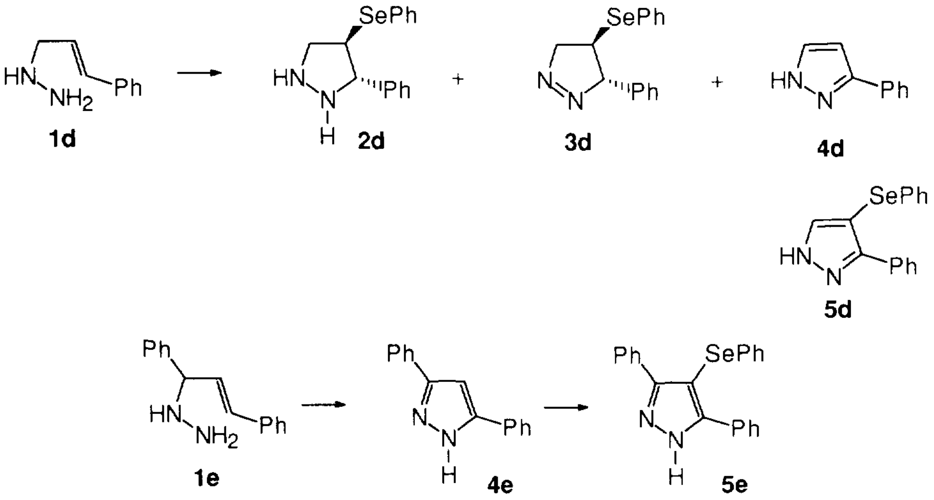


In the case of the allylhydrazines **1d** and **1e** the additions to the solution of phenylselenenyl sulfate were effected at -30 °C in every case. The reaction of the cinnamyl hydrazine **1d** with phenylselenenyl sulfate, after 2 h at -30 °C and column chromatography, gave a mixture of the 3-phenyl-4-(phenylseleno)pyrazolidine **2d** (10%), the 3-phenyl-4-(phenylseleno)-4,5-dihydro-3*H*-pyrazole **3d** (25%) and the 3-phenyl-1*H*-pyrazole **4d** (33%) (Scheme 3). As indicated by TLC and ^{1}H NMR, the amount of the pyrazolidine **2d** was considerably higher in the row reaction mixture. Clearly this compound suffered easy dehydrogenation during work-up and column chromatography. In a second experiment the reaction mixture was allowed to reach room temperature and then stirred for 24 h. The sole reaction product was the pyrazole **4d** which was isolated in very good yield (95%).

In a further experiment the cinnamyl hydrazine **1d** was allowed to react with an excess (3 mmol) of phenylselenenyl sulfate at room temperature. The only product obtained in this case, in 79% yield, was the 3-phenyl-4-(phenylseleno)-1*H*-pyrazole **5d**. Under these conditions the presence of the 3-phenyl-1*H*-pyrazole **4d** was indicated by TLC and GC-MS but the product could not be isolated because it gave rise to a rapid electrophilic aromatic phenylselenenylation reaction[21] to afford the 3-phenyl-4-(phenylseleno)-1*H*-pyrazole **5d**. A similar reaction was already observed in the selenium induced cyclization of N-cinnamyl acethydrazide.[19]

The reaction of the hydrazine **1e** with phenylselenenyl sulfate was very fast. Even at -30 °C the only product which could be detected by TLC and GC-MS was the 3,5-diphenyl-1*H*-pyrazole **4e** (Scheme 3). The reaction was then stirred at room temperature for 3h. After column chromatography compound **4e** was obtained in 48% yield. With an excess of phenylselenenyl sulfate the electrophilic aromatic phenylselenenylation reaction occurred also in this case. Under these conditions in fact the product obtained was the 3,5-diphenyl-4-(phenylseleno)-1*H*-pyrazole **5e** (52%).

Scheme 3



The presently described phenylselenium-induced cyclization reactions of allylhydrazines to pyrazole derivatives represent a new example of the utility of phenylselenenyl sulfate to produce nitrogen heterocycles from alkenes containing internal nitrogen nucleophiles. The starting materials are easily available and the procedure is extremely simple. Moreover, the diphenyl diselenide employed to produce the reactive selenenylating agent is almost completely recovered at the end of the reaction. The phenylselenenyl sulfate seems to be unique in promoting these ring-closure reactions. In fact, the reactions of allylhydrazines with phenylselenenyl bromide or chloride did not give any of the desired cyclization products.

EXPERIMENTAL

Melting points were determined on a capillary melting point apparatus and are uncorrected. GLC analyses and MS spectra were carried out with an HP 5890 gaschromatograph (dimethyl silicone column, 12.5 m) equipped with an HP 5971 Mass Selective Detector; for the ions containing selenium only the peak arising from the selenium-80 isotope is given. ^{1}H and ^{13}C NMR spectra were recorded at 200 and 50.32 MHz, respectively, on a Bruker AC 200 instrument; $CDCl_3$ was used as solvent and TMS as standard. Elemental analyses were carried out on a Carlo Erba 1106 Elemental Analyzer and were in good agreement with the calculated values.

Synthesis of N-Allylhydrazines. The allyl halides were commercially available or were prepared from the corresponding alcohols by treatment with $SOCl_2$.[22] The alkylation of hydrazine was effected according to the following procedure. The appropriate allyl halide (10 mmol) was added to phenylhydrazine hydrochloride (40 mmol) and K_2CO_3 (40 mmol) in EtOH (50 mL) and the mixture was stirred at reflux for 12 h. The alkylation of hydrazine hydrate (300 mmol) was instead effected at room temperature for 1 h. EtOH was evaporated under reduced pressure and water and CH_2Cl_2 were added to the residue. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The products **1a-c** were purified by silica gel column chromatography using petroleum ether/Et_2O (90/10) as eluant. The labile products **1d** and **1e** were not chromatographed and were used immediately as crude materials in the cyclization reactions. Physical and spectral data are reported below.

3-Methyl-2-butenyl(phenyl)hydrazine (1a):[23] oil; ^{1}H NMR δ 7.24 (dd, 2 H, *J* = 7.2, 8.8 Hz), 7.04 (dd, 2 H, *J* = 1.1, 8.8 Hz), 6.8 (tt, 1 H, *J* = 1.1, 7.2 Hz), 5.24 (tseptet, 1 H, *J* = 1.3, 6.7 Hz), 3.98 (d, 2 H, *J* = 6.7 Hz), 3.49 (br s, 2 H), 1.73 (d, 3 H, *J* = 1.3 Hz), 1.72 (d, 3 H, *J* = 1.3 Hz); ^{13}C NMR δ 151.6, 136.8, 128.7, 118.9, 118.3, 114.1, 53.6, 25.6, 17.9. MS *m/z* (relative intensity) 176 (M^+, 18), 121 (1), 108 (41), 107 (100), 91 (5), 77 (48), 41 (30).

(E)-2-Butenyl(phenyl)hydrazine (1b): oil; ^{1}H NMR δ 7.21 (dd, 2 H, *J* = 7.2, 8.9 Hz), 7.02 (dd, 2 H, *J* = 1.0, 8.9 Hz), 6.75 (tt, 1 H, *J* = 1.0, 7.2 Hz), 5.83-5.38 (m, 2 H), 3.9 (dd, 2 H, *J* = 1.1, 6.3 Hz), 3.43 (br s, 2 H), 1.68 (dd, 3 H, *J* = 1.2, 6.1 Hz); ^{13}C NMR δ 151.3, 129.9, 128.6, 124.9, 118.0, 113.7, 57.7, 17.5. MS *m/z* (relative intensity) 162 (M^+, 22), 107 (100), 79 (13), 77 (75), 51 (15). Anal. Calcd for $C_{10}H_{14}N_2$: C, 74.03; H, 8.70; N, 17.27. Found: C, 74.15; H, 8.61; N, 17.24.

Phenyl(3-phenyl-(E)-2-propenyl)hydrazine (1c): oil; ^{1}H NMR δ 7.48-7.1 (m, 7 H), 7.05 (d, 2 H, *J* = 7.8 Hz), 6.79 (t, 1 H, *J* = 7.0 Hz), 6.6 (d, 1 H, *J* = 15.9 Hz), 6.22 (dt, 1 H, *J* = 6.2, 15.9 Hz), 4.13 (d, 2 H, *J* = 6.2 Hz), 3.6 (br s, 2 H); ^{13}C NMR δ 151.1, 136.5, 133.7, 129.0, 128.5, 127.6, 126.3, 124.0, 118.5, 113.8, 58.3. MS *m/z* (relative intensity) 224 (M^+, 11), 206 (20), 117 (95), 107 (100), 91 (19), 77 (42), 51 (11). Anal. Calcd for $C_{15}H_{16}N_2$: C, 80.32; H, 7.19; N, 12.49. Found: C, 80.26; H, 7.21; N, 12.53.

3-Phenyl-(E)-2-propenylhydrazine (1d): oil; ^{1}H NMR δ 7.42-7.12 (m, 5 H), 6.55 (dt, 1 H, *J* = 1.0, 15.9 Hz), 6.16 (dt, 1 H, *J* = 6.6, 15.9 Hz), 3.85 (br s, 3 H), 3.45 (dd, 2 H, *J* = 1.0, 6.6 Hz); ^{13}C NMR δ 136.4, 133.4, 128.3, 127.4, 126.1, 125.4, 57.4.

1,3-Diphenyl-(E)-2-propenylhydrazine (1e): oil; ^{1}H NMR δ 7.5-7.1 (m, 10 H), 6.63 (d, 1 H, *J* = 15.8 Hz), 6.28 (dd, 1 H, *J* = 7.5, 15.8 Hz), 4.36 (d, 1 H, *J* = 7.5 Hz); ^{13}C NMR δ 140.5, 136.3, 132.0, 129.8, 128.6, 128.3, 127.5, 127.3, 126.6, 71.2.

Cyclization of N-Allylhydrazines. General Procedure. A solution of diphenyl diselenide (1 mmol or 1.5 mmol), ammonium persulfate (1.2 mmol or 2.5 mmol) and trifluoromethanesulfonic acid (2.2 mmol) in acetonitrile (10 mL) was stirred for 15 min at room temperature. The N-allylhydrazines (1 mmol) were added at room temperature or at -30 °C as reported above. The progress of the reaction was monitored by TLC and GC-MS. Reaction times ranged from 1 h to 24 h. The reaction mixture was poured into a 10% aqueous solution of Na_2CO_3 and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), evaporated and the residue was chromatographed through a silica gel column. Reaction yields are indicated above. Compounds **4b**,[24] **4c**,[24] **4d**,[25] **5d**,[19] and **4e**[26] have physical and spectral data identical to those reported in the literature. Physical and spectral data of the other compounds are reported below.

3,3-Dimethyl-1-phenyl-4-(phenylseleno)pyrazolidine (2a): oil; ^1H NMR δ 7.6-7.5 (m, 2 H), 7.3-7.2 (m, 3 H), 7.18 (dd, 2 H, *J* = 7.4, 8.4 Hz), 6.91 (dd, 2 H, *J* = 1.0, 8.4 Hz), 6.72 (tt, 1 H, *J* = 1.0, 7.4 Hz), 4.18-3.91 (m, 1 H), 3.82 (br s, 1 H), 3.56-3.38 (m, 2 H), 1.15 (s, 3 H), 0.99 (s, 3 H); ^{13}C NMR δ 152.0, 134.0, 129.6, 129.2, 128.6, 127.6, 117.9, 112.8, 61.8, 58.8, 53.6, 24.3, 21.9. MS *m/z* (relative intensity) 332 (M^+, 20), 175 (4), 159 (49), 148 (53), 107 (100), 77 (47), 69 (46), 51 (12). Anal. Calcd for $C_{17}H_{20}N_2Se$: C, 61.63; H, 6.08; N, 8.46. Found: C, 61.55; H, 6.15; N, 8.52.

3-Methyl-1-phenyl-4-(phenylseleno)pyrazolidine (2b): oil; ^1H NMR δ 7.6-7.45 (m, 2 H), 7.3-7.2 (m, 3 H), 7.2 (dd, 2 H, *J* = 7.2, 8.8 Hz), 6.93 (dd, 2 H, *J* = 1.1, 8.8 Hz), 6.76 (tt, 1 H, *J* = 1.1, 7.2 Hz), 3.99-3.78 (m, 2 H), 3.5-3.32 (m, 2 H), 3.14 (quintet, 1 H, *J* = 6.4 Hz), 1.14 (d, 3 H, *J* = 6.4 Hz); ^{13}C NMR δ 151.5, 134.5, 129.2, 128.8, 127.9, 118.4, 113.3, 60.1, 58.4, 48.6, 16.9. MS *m/z* (relative intensity) 318 (M^+, 36), 162 (37), 158 (26), 145 (38), 107 (100), 77 (92), 55 (55), 51 (29). Anal. Calcd for $C_{16}H_{18}N_2Se$: C, 60.57; H, 5.72; N, 8.83. Found: C, 60.45; H, 5.81; N, 8.77.

3-Methyl-1-phenyl-4-(phenylseleno)-4,5-dihydro-1*H*-pyrazole (3b): oil; ^1H NMR δ 7.6-7.47 (m, 2 H), 7.27-7.15 (m, 3 H), 7.2 (dd, 2 H, *J* = 7.3, 7.7 Hz), 6.88 (dd, 2 H, *J* = 1.0, 7.7 Hz), 6.78 (tt, 1 H, *J* = 1.0, 7.3 Hz), 4.39 (dd, 1 H, *J* = 4.1, 9.7 Hz), 4.06 (dd, 1 H, *J* = 4.1, 11.6 Hz), 3.95 (dd, 1 H, *J* = 9.7, 11.6 Hz), 2.11 (s, 3 H); ^{13}C NMR δ 149.0, 145.7, 135.0, 131.5, 129.2, 128.9, 128.3, 119.1, 112.8, 56.9, 48.0, 14.4. Anal. Calcd for $C_{16}H_{16}N_2Se$: C, 60.95; H, 5.12; N, 8.89. Found: C, 61.04; H, 5.18; N, 8.80.

3-Phenyl-4-(phenylseleno)pyrazolidine (2d): oil; ^1H NMR δ 7.5-7.0 (m, 10 H), 5.3 (br s, 2 H), 4.15 (d, 1 H, *J* = 6.1 Hz), 3.74 (ddd, 1 H, *J* = 5.6, 6.1, 7.3 Hz), 3.53 (dd, 1 H, *J* = 7.3, 11.9 Hz), 3.17 (dd, 1 H, *J* = 5.6, 11.9 Hz); ^{13}C NMR δ 138.7, 134.0, 131.4, 129.3, 129.1, 128.8, 127.6, 126.8, 70.2, 56.3, 48.4. Anal. Calcd for $C_{15}H_{16}N_2Se$: C, 59.41; H, 5.32; N, 9.24. Found: C, 59.34; H, 5.39; N, 9.33.

3-Phenyl-4-(phenylseleno)-4,5-dihydro-3*H*-pyrazole (3d): oil; ^1H NMR δ 7.5-7.42 (m, 2 H), 7.38-7.18 (m, 6 H), 6.99-6.88 (m, 2 H), 5.62 (dt, 1 H, *J* = 1.7, 5.3 Hz), 4.94 (ddd, 1 H, *J* = 2.2, 8.3, 18.6 Hz), 4.62 (ddd, 1 H, *J* = 1.5, 5.3, 18.6 Hz), 3.35 (dt, 1 H, *J* = 5.3, 8.3 Hz); ^{13}C NMR δ 138.5, 134.8, 134.0, 129.3, 128.8, 128.3, 128.0, 126.6, 97.2, 82.8, 37.5. Anal. Calcd for $C_{15}H_{14}N_2Se$: C, 59.81; H, 4.68; N, 9.30. Found: C, 59.89; H, 4.74; N, 9.21.

3,5-Diphenyl-4-(phenylseleno)-1*H*-pyrazole (5e): mp 168-170 °C; ^1H NMR δ 13.0 (br s, 1 H), 7.78-7.65 (m, 4 H), 7.42-7.28 (m, 6 H), 7.2-7.0 (m, 5 H); ^{13}C NMR δ 152.2, 133.8, 130.8, 128.8, 128.2, 128.0, 127.9, 125.4, 97.0. MS *m/z* (relative intensity) 376 (M^+, 84), 296 (97), 295 (100), 271 (9), 220 (18), 193 (18), 169 (14), 165 (24), 117 (10), 104 (17), 89 (10), 77 (26). Anal. Calcd for $C_{21}H_{16}N_2Se$: C, 67.20; H, 4.30; N, 7.46. Found: C, 67.16; H, 4.38; N, 7.53.

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