SELENIUM CATALYZED CONVERSION OF δ-PHENYL-γ-ALKENYL OXIMES INTO 2-PHENYLPYRIDINES

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Abstract - δ-Phenyl-γ-alkenyl oximes react with an excess of ammonium persulfate and catalytic amounts of diphenyl diselenide in the presence of trifluoromethanesulfonic acid in acetonitrile to afford 2-phenylpyridines and 2-phenylpyridine *N*-oxides in moderate yields.

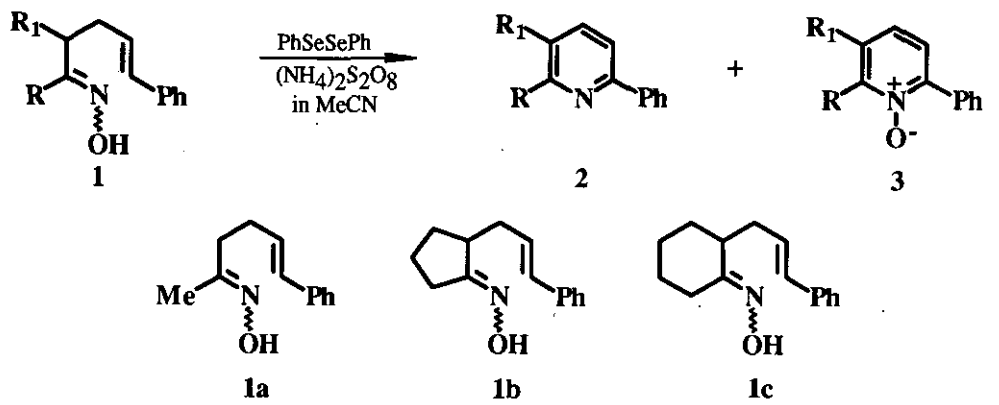
We have recently introduced a very simple and efficient selenium catalyzed multistep one-pot procedure to effect several conversions of functional groups. This procedure, which consists in the selenenylation of unsaturated compounds with benzeneselenenyl sulfate[1,2] followed by the deselenenylation of the addition products by ammonium persulfate, can be realized simply by using an excess of ammonium persulfate and only catalytic amounts of diphenyl diselenide. Depending on the solvent employed and on the structure of the starting unsaturated compounds, the deselenenylation process can evolve either towards the substitution[3] or the elimination products.[4,5] This procedure has also been used to convert β,γ-unsaturated ketones into substituted furans.[6]

We now report that, under the same experimental conditions, δ-phenyl-γ-alkenyl oximes (**1**) can be employed to effect the synthesis of 2-phenylpyridines (**2**) and of 2-phenylpyridine *N*-oxides (**3**) (Scheme 1).

The starting materials (**1a-1c**) necessary for the present investigation were easily obtained (70-80% yield) from the reaction of cinnamyl bromide with the dianion of acetone, cyclopentanone and cyclohexanone oxime, respectively, according to the procedure reported in the literature.[7] A 2:1 mixture of the *E* and *Z*

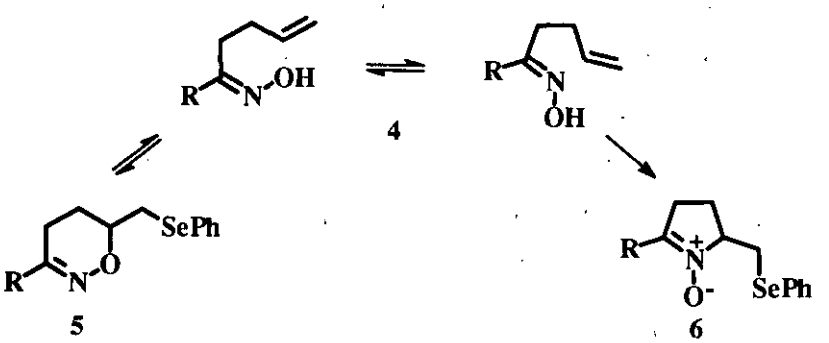
isomers was obtained in every case. The two stereoisomers could be separated by column chromatography and their configurations could be assigned on the basis of their ^{13}C nmr spectra.[8] Partial conversion of the *Z* into the *E* isomers was observed during column chromatography.

Scheme 1



In a previous investigation we observed that the benzeneselenenyl sulfate induced cyclization of terminal alkenyl oximes (**4**) was not influenced by the geometry of the starting oximes since it gave the five-membered cyclic nitrones (**6**) (Scheme 2) as the major and sometimes the sole reaction products. It was shown, in fact, that, under the experimental conditions employed, the starting oximes isomerized and the formation of the 1,2-oxazine (**5**) was a reversible process.[9]

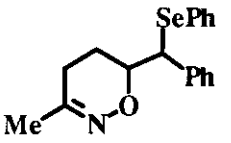
Scheme 2



On the basis of these observations, the presence of the phenyl group in the oximes (**1a-1c**) should control

the regiochemistry of the addition process and, owing to the easy isomerization of the oxime function, a six-membered nitrone should be formed as the sole cyclization product. This was confirmed by a preliminary experiment carried out on **1a** using a stoichiometric amount of benzeneselenenyl sulfate (*in* acetonitrile at 50°C for 4 h). Starting from the *E* isomer the nitrone (**7a**) was obtained in 90% yield. The same compound was also obtained from the reaction of the *Z* isomer. In this case, however, a small amount of the 1,2-oxazine (**8a**) was also isolated. This *anti*-Markovnikov addition product originates from the intramolecular capture of the seleniranium intermediate by the oxygen atom of the oxime. Compound (**8a**) was not present when longer reaction times were employed.

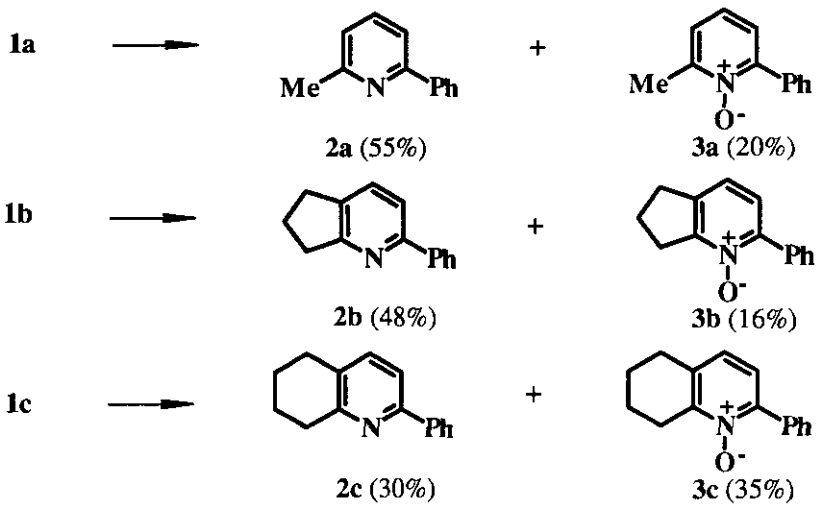
7a



8a

The other experiments were then carried out using the mixtures of the two stereoisomeric δ-phenyl-γ-alkenyl oximes (**1a-1c**).

Scheme 3

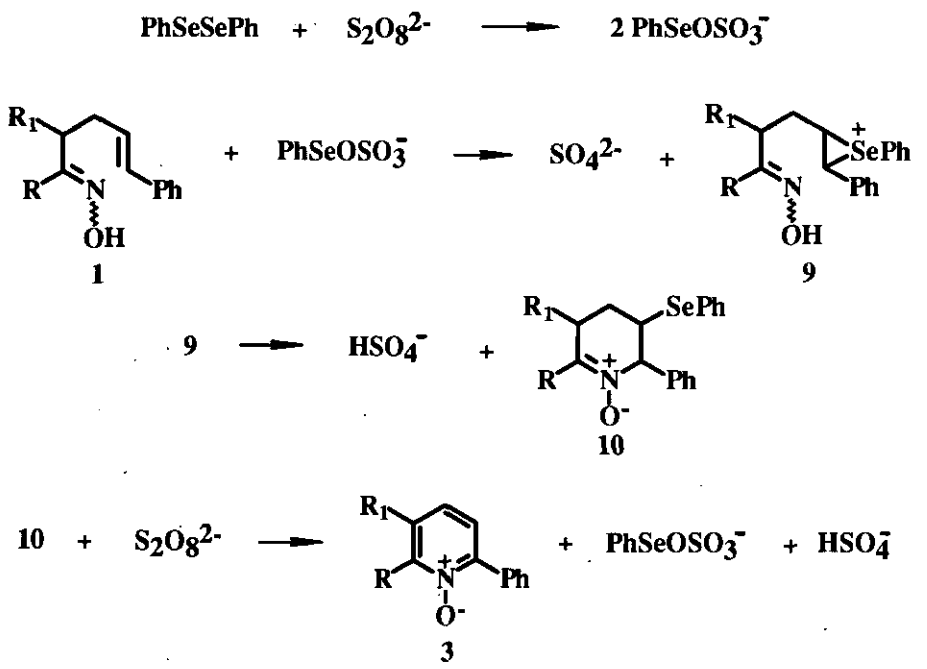


In a typical procedure trifluoromethanesulfonic acid (2.5 mmol) was added to a mixture of diphenyl

diselenide (0.25 mmol) and ammonium persulfate (7.5 mmol) in acetonitrile (30 ml). The oximes (**1a-1c**) (2.5 mmol) were added to the resulting red solution and the mixture was warmed at 50 °C for 4-5 h. The 2-phenylpyridines (**2a-2c**) and the 2-phenylpyridine *N*-oxides (**3a-3c**) obtained from these reactions are reported in Scheme 3. Reaction yields are also indicated.

The proposed course of this conversion of δ-phenyl-γ-alkenyl oximes (**1**) into the 2-phenylpyridine *N*-oxides (**3**) is indicated in Scheme 4. The benzeneselenenyl sulfate, produced from the reaction of the diphenyl diselenide with ammonium persulfate, reacts with the starting oximes to give the seleniranium intermediate (**9**) which is captured by the nitrogen atom of the oxime to afford the cyclization products (**10**). The persulfate promoted oxidative deselenenylation and the dehydrogenation of these compounds afford the observed reaction products (**3**) and regenerate the electrophilic reagent.

Scheme 4



Pyridine *N*-oxides are known to suffer deoxygenation under several different experimental conditions.[10] It has been reported that the deoxygenation can also be effected by benzenesulfenyl chloride.[11] It is suggested that this process could occur also in the present case with benzeneselenenyl sulfate and that it could be responsible for the formation of 2-phenylpyridines (**2**). Indeed, in a parallel experiment it was

observed that the pyridine *N*-oxide (**3b**) reacted with stoichiometric amounts of benzeneselenenyl sulfate to afford the pyridine (**2b**) quantitatively.

The presently described one-pot conversion of δ-phenyl-γ-alkenyl oximes into substituted 2-phenylpyridines and 2-phenylpyridine *N*-oxides represents a simple and convenient new synthetic method which can find general application. In principle, in fact, several kinds of substituents can be introduced in the various positions of the pyridine ring. Moreover, it represents a further example of the utility of benzeneselenenyl sulfate as a very versatile reagent easily available from diphenyl diselenide which is the simplest organoselenium compound.

EXPERIMENTAL SECTION

Mps were determined on a Kofler melting-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. ^1H 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.

Preparation of the Oximes (1a-c). Acetone oxime, cyclopentanone oxime and cyclohexanone oxime were commercial products. The described products (**1a-c**) were obtained by reaction of cinnamyl bromide with the dianion of the appropriate oxime according to the general procedure described in the literature.[7] The reactions were carried out on 20 mmol of the oxime. In every case the progress of the reaction was monitored by tlc and GC-ms.

The mixture was diluted with water and extracted with methylene chloride. The organic layer was washed with water, dried ($NaSO_4$), and evaporated. The reaction products were obtained in pure form by chromatography through a silica gel column with methylene chloride as eluent. Physical and spectral data are reported below.

6-Phenylhex-5-en-2-one oxime (1a). *(E)*-Isomer: mp 70-72 °C (petroleum ether); ^1H nmr δ 9.85 (br s, 1 H), 7.33-7.15 (m, 5 H), 6.38 (d, 1 H, *J* = 15.8 Hz), 6.15 (dt, 1 H, *J* = 6.2, 15.8 Hz), 2.45-2.25 (m, 4 H), 1.91 (s, 3 H); ^{13}C nmr δ 157.5, 137.4, 130.6, 128.9, 128.3, 127.0, 125.9, 35.4, 29.6, 13.6. Ms *m/z* (relative intensity) 189 (25), 172 (20), 131 (38), 117 (100), 91 (68), 83 (17), 42 (50). Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.09; H, 8.06; N, 7.48. *(Z)*-Isomer: viscous oil; ^1H

nmr δ 9.41 (br s, 1 H), 7.35-7.10 (m, 5 H), 6.42 (d, 1 H, *J* = 15.8 Hz), 6.19 (dt, 1 H, *J* = 6.4, 15.8 Hz), 2.60-2.35 (m, 4 H), 1.89 (s, 3 H); ^{13}C nmr δ 158.0, 137.5, 130.6, 129.2, 128.4, 127.0, 126.0, 28.8, 28.4, 20.0. Ms *m/z* (relative intensity) 189 (3), 130 (44), 117 (100), 91 (42), 70 (19), 42 (10). Found: C, 76.26; H, 7.91; N, 7.43.

2-Cinnamylcyclopentanone oxime (1b). *(E)*-Isomer: mp 76-78 °C (petroleum ether); ^{1}H nmr δ 9.45 (br s, 1 H), 7.40-7.10 (m, 5 H), 6.40 (d, 1 H, *J* = 15.6 Hz), 6.20 (dt, 1 H, *J* = 6.6, 15.6 Hz), 2.73-2.19 (m, 5 H), 2.10-1.40 (m, 4 H); ^{13}C nmr δ 168.0, 137.4, 131.3, 128.2, 128.0, 126.7, 125.9, 42.8, 35.5, 31.0, 27.3, 22.2. Ms *m/z* (relative intensity) 215 (10), 198 (17), 117 (100), 115 (36), 91 (25), 65 (5). Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.01; H, 7.87; N, 6.46. *(Z)*-Isomer: viscous oil; ^{1}H nmr δ 8.80 (br s, 1 H), 7.40-7.12 (m, 5 H), 6.41 (d, 1 H, *J* = 15.6 Hz), 6.18 (dt, 1 H, *J* = 7.0, 15.6 Hz), 3.21-3.12 (m, 1 H), 2.90-2.70 (m, 1 H), 2.48-2.25 (m, 3 H), 1.98-1.58 (m, 4 H); ^{13}C nmr δ 168.0, 137.5, 131.5, 128.3, 126.8, 125.9, 39.4, 33.8, 30.9, 30.1, 23.0. Ms *m/z* (relative intensity) 199 (8), 171 (20), 143 (10), 117 (100), 91 (33), 81 (13), 41 (6). Found: C, 78.13; H, 7.91; N, 6.58.

2-Cinnamylcyclohexanone oxime (1c). *(E)*-Isomer: mp 132-133 °C (petroleum ether); ^{1}H nmr δ 9.09 (br s, 1 H), 7.40-7.10 (m, 5 H), 6.40 (d, 1 H, *J* = 15.9 Hz), 6.18 (dt, 1 H, *J* = 7.4, 15.9 Hz), 3.01-2.83 (m, 1 H), 2.71-1.21 (m, 10 H); ^{13}C nmr δ 161.8, 137.5, 131.4, 128.4, 128.2, 126.7, 125.8, 42.1, 34.3, 32.2, 25.8, 23.8, 23.6. Ms *m/z* (relative intensity) 229 (13), 197 (4), 138 (15), 117 (100), 91 (29), 41 (5). Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.47; H, 8.29; N, 6.05. *(Z)*-Isomer: oil; ^{1}H nmr δ 9.00 (br s, 1 H), 7.40-7.10 (m, 5 H), 6.40 (d, 1 H, *J* = 15.8 Hz), 6.15 (dt, 1 H, *J* = 7.1, 15.8 Hz), 3.70-3.52 (m, 1 H), 2.50-2.00 (m, 3 H), 2.00-1.30 (m, 7 H); ^{13}C nmr δ 162.7, 137.8, 131.5, 128.4, 128.3, 127.0, 126.2, 33.9, 32.4, 28.8, 28.7, 26.7, 20.6. Ms *m/z* (relative intensity) 229 (1), 210 (5), 185 (9), 129 (12), 117 (100), 91 (21), 41 (5). Found: C, 78.63; H, 8.30; N, 6.16.

Selenium Induced Cyclization. General Procedure. To a mixture of diphenyl diselenide (0.08 g, 0.25 mmol) and ammonium persulfate (1.7 g, 7.5 mmol) in acetonitrile (30 ml) was added trifluoromethanesulfonic acid (0.4 g, 2.5 mmol) dropwise. To the resulting deep red solution was added the γ-alkenyl oxime (2.5 mmol). The progress of the reaction was monitored by tlc. The mixture was stirred at 50 °C for 4-5 h and was then poured onto water-methylene chloride. The organic layer was washed with water, dried ($NaSO_4$) and evaporated. The reaction products were obtained in pure form by

chromatography through a silica gel column with a 96:4 mixture of methylene chloride and methanol as eluent. The reaction products obtained and the reaction yields are summarized in Scheme 3. The reaction of **1a** (0.5 g, 2.5 mmol) with a stoichiometric amount of diphenyl diselenide (0.4 g, 1.25 mmol) and of ammonium persulfate (0.6 g, 2.5 mmol) was carried out as described above and afforded **7a** and **8a**. Physical and spectral data of isolated products are reported below.

2-Methyl-6-phenylpyridine (2a): bp 149-150 °C/15 mm Hg (lit.,[12] bp 138-139 °C/10 mm Hg).

6-Phenyl-2,3-cyclopentenopyridine (2b): mp 80-81 °C (petroleum ether) (lit.,[13] mp 82-83 °C).

2-Phenyl-5,6,7,8-tetrahydroquinoline (2c): bp 155-156 °C/1 mm Hg (lit.,[14] bp 118 °C/0.1 mm Hg).

2-Methyl-6-phenylpyridine-1-oxide (3a): viscous oil; ^{1}H nmr δ 7.82-7.72 (m, 2 H), 7.50-7.39 (m, 3 H), 7.33-7.15 (m, 3 H), 2.57 (s, 3 H); ^{13}C nmr δ 149.9, 149.4, 133.4, 129.4, 129.2, 128.1, 125.1, 125.0, 124.6, 18.4. Ms *m/z* (relative intensity) 185 (58), 184 (100), 169 (67), 131 (24), 115 (14), 84 (12), 77 (15), 51 (13).

6,7-Dihydro-2-phenyl-5*H*-1-pyrindine-1-oxide (3b): mp 129-130 °C (petroleum ether) (lit.,[15] mp 130-131 °C).

2-Phenyl-5,6,7,8-tetrahydroquinoline-1-oxide (3c): mp 142-143 °C (petroleum ether) (lit.,[15] mp 144-145 °C).

2-Phenyl-3-phenylseleno-6-methyl-2,3,4,5-tetrahydropyridine-1-oxide (7a): viscous oil; ^{1}H nmr δ 7.68-7.55 (m, 2 H), 7.38-7.20 (m, 6 H), 7.08-6.98 (m, 2 H), 5.11-5.05 (m, 1 H), 3.81-3.70 (m, 1 H), 2.92-2.47 (m, 2 H), 2.25 (s, 3 H), 2.10-1.65 (m, 2 H); ^{13}C nmr δ 146.0, 138.1, 135.2, 129.2, 128.5, 128.3, 127.6, 127.2, 126.0, 74.9, 44.7, 28.4, 19.9, 18.4. Ms *m/z* (relative intensity) 329 (7), 248 (3), 167 (67), 145 (15), 104 (100), 91 (42), 83 (22), 77 (19). Anal. Calcd for $C_{18}H_{19}NOSe$: C, 62.79; H, 5.56; N, 4.07. Found: C, 62.84; H, 5.48; N, 4.15.

5,6-Dihydro-3-methyl-6[phenyl(phenylseleno)methyl]-4*H*-1,2-oxazine (8a): mp 103-106 °C (petroleum ether); ^{1}H nmr δ 7.41-7.31 (m, 2 H), 7.29-7.05 (m, 8 H), 4.28 (d, 1 H, J = 6.4 Hz), 4.09 (ddd, 1 H, J = 1.9, 6.4, 8.3 Hz), 2.30-1.90 (m, 3 H), 1.85 (s, 3 H), 1.70-1.40 (m, 1 H); ^{13}C nmr δ 155.5, 139.2, 134.2, 128.8, 128.7, 127.9, 127.6, 126.9, 76.4, 51.9, 25.0, 23.3, 21.3. Ms *m/z* (relative intensity) 345 (9), 247 (13), 188 (31), 157 (20), 91 (100), 77 (13). Anal. Calcd for $C_{18}H_{19}NOSe$: C, 62.79; H, 5.56; N, 4.07. Found: C, 62.70; H, 5.59; N, 4.12.

ACKNOWLEDGEMENT

Financial support from the CNR, Rome, and Ministero dell'Università e della Ricerca Scientifica e Tecnologica, Italy, is gratefully acknowledged.

REFERENCES

1. M. Tiecco, L. Testaferri, M. Tingoli, D. Chianelli, and D. Bartoli, *Tetrahedron Lett.*, 1989, **30**, 1417.
2. M. Tiecco, L. Testaferri, M. Tingoli, D. Bartoli, and R. Balducci, *J. Org. Chem.*, 1990, **55**, 429 and references cited therein.
3. M. Tiecco, L. Testaferri, M. Tingoli, D. Bartoli, and F. Marini, *J. Org. Chem.*, 1991, **56**, 5207 and references cited therein.
4. M. Tiecco, L. Testaferri, M. Tingoli, L. Bagnoli, and C. Santi, *J. Chem. Soc., Chem. Commun.*, 1993, 637.
5. M. Tiecco, L. Testaferri, M. Tingoli, L. Bagnoli, and C. Santi, *Synlett*, 1993, 798.
6. M. Tiecco, L. Testaferri, M. Tingoli, and F. Marini, *Synlett*, 1994, 373.
7. M. E. Jung, P. A. Blair, and J. A. Lowe, *Tetrahedron Lett.*, 1976, 1439.
8. G. E. Hawkes, K. Herwig, and J. D. Roberts, *J. Org. Chem.*, 1974, **39**, 1017.
9. M. Tiecco, L. Testaferri, M. Tingoli, L. Bagnoli, and F. Marini, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1989.
10. R. A. Abramovitch and E. M. Smith, "The Chemistry of Heterocyclic Compounds: Pyridine and Its Derivatives", Vol. 14, Suppl. Part 2, ed. by R. A. Abramovitch, Interscience, New York, 1974, pp. 1-261.
11. (a) S. Oae and K. Ikura, *Bull. Chem. Soc. Jpn.*, 1965, **38**, 58; (b) S. Oae and K. Ikura, *Bull. Chem. Soc. Jpn.*, 1966, **39**, 1306; (c) S. Oae and K. Ikura, *Bull. Chem. Soc. Jpn.*, 1967, **40**, 1420.
12. (a) S. Kanemasa, Y. Asai, and J. Tanaka, *Bull. Chem. Soc. Jpn.*, 1991, **64**, 375; (b) J. Meisenheimer, E. Stratmann, and W. Theilacker, *Ber.*, 1932, **65**, 418.
13. E. C. Taylor, J. E. Macor, and L. G. French, *J. Org. Chem.*, 1991, **56**, 1807.
14. G. Chelucci, S. Cossu, and F. Soccolini, *J. Heterocycl. Chem.*, 1986, **23**, 1283.
15. W. E. Hahn and J. Epsztajn, *Roczniki Chem.*, 1963, **37**, 403 (*Chem. Abstr.*, 1963, **59**, 11412h).

Received, 5th August, 1996