Phenylselenyl Halide Induced Formation of Cyclic Nitrones from Alkenyl Oximes

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Oximes possessing alk-γ- or -δ-enyl substituents are cyclised by phenylselenyl bromide, or by phenylselenyl chloride and an appropriate silver salt, to the corresponding cyclic nitrones; the seleno nitrones undergo facially specific cycloadditions with *N*-methylmaleimide, bis(alk-γ,δ-enyl) and bis(alk-δ,δ-enyl) ketones undergo regiospecific cyclisation and stereospecific cycloaddition to furnish spirocyclic products.

Inter- and intra-molecular cycloaddition reactions of nitrones have attracted much attention because they provide a potentially flexible entry into the complex molecular frameworks of natural products.[1] Utilising oximes as nitrone precursors in tandem nitrone generation–cycloaddition protocols substantially enhances this flexibility. We have recently introduced a range of such protocols[2] most of which have four distinct synthetic variants. Further novel developments in this area are now reported.

We have been exploring the generality of electrophile induced oxime–olefin (alkyne) reactions as a source of novel tandem nitrone formation–cycloaddition protocols and in our preceding communication[2] we reported reactions in which mercuric acetate functioned as the electrophile. This paper is concerned with the application of phenylselenyl halides[3] to such processes.

In a preliminary evaluation of phenylselenyl halides it became clear that phenylselenyl bromide, or phenylselenyl chloride in combination with silver triflate (trifluoromethanesulfonate), usually gave rise to cleaner reactions and improved yields compared with phenylselenyl chloride alone or phenylselenyl chloride in combination with silver tetrafluoroborate.

Oxime **1a** which comprised a 2 : 1 mixture of *syn* (Me/OH)- and *anti*-isomers reacted (CH_2Cl_2, 25 °C, 0.5 h) with phenylselenyl bromide (1 mol) to give a quantitative yield of the adduct **2a**.† Treatment of **2a** with anhydrous potassium carbonate (1.1 mol) (CH_2Cl_2, 25 °C, 16 h) afforded the nitrone **3a** together with a trace of oxazine **4a**.‡ Heating the nitrone **3a** in acetonitrile (80 °C, 9 h) with *N*-methylmaleimide (1 mol) afforded cycloadduct **5a** (70% overall from **1a**) as a 3:2 mixture of *endo*- and *exo*-isomers. It is apparent from this result that the ratio of nitrone **3a** to oxazine **4a** does not reflect the *syn* : *anti* ratio of the oxime. The nitrone : oxazine ratio is sensitive to the reagents/conditions used as shown by reaction of **1a** with PhSeCl–AgOTf (CH_2Cl_2, 0 °C) to give **2b**† followed

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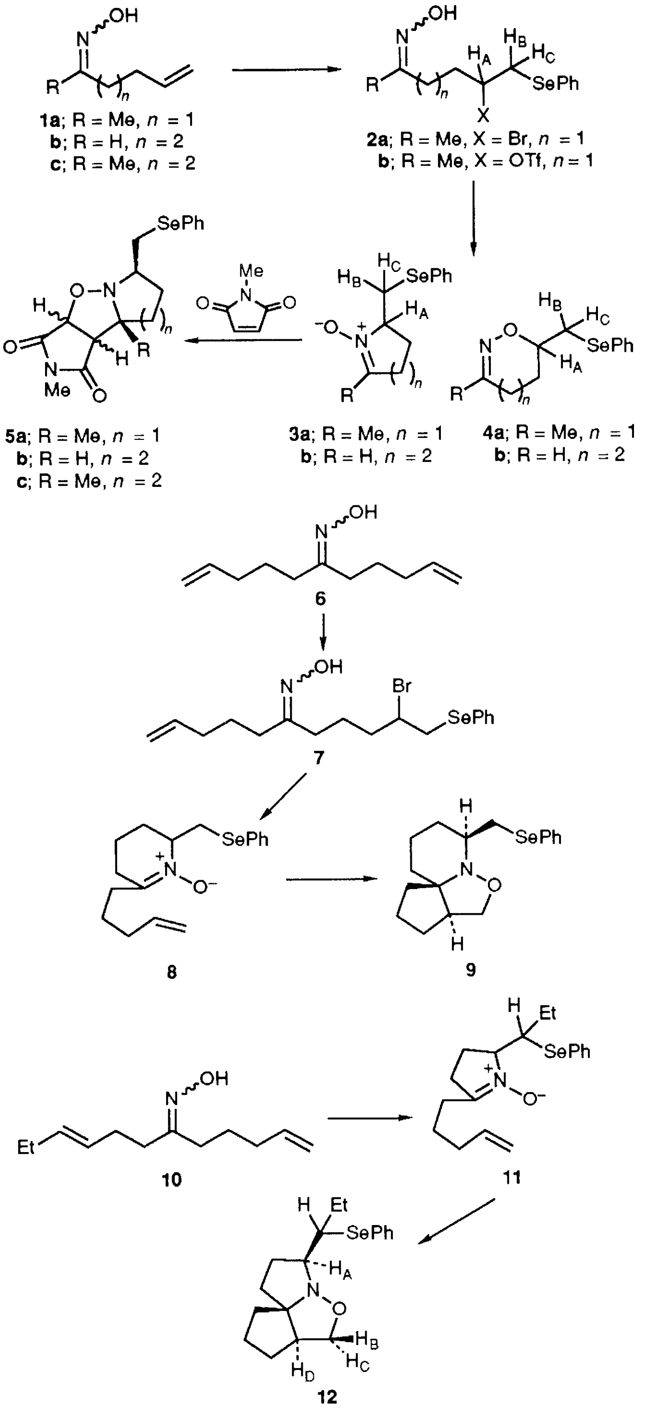
† The ^1H NMR spectrum ($CDCl_3$) of **2a** exhibited a broad singlet at δ 5.1 (H_A) and two double doublets at δ 3.6 and 3.34 (H_B, H_C); **2b** δ 5.0 (br s, 1H, H_A) and 3.55 and 3.45 (2 × dd, 2 × 1H, H_B, H_C).

‡ ^1H NMR data ($CDCl_3$): **3a** δ 4.3 (br s, 1H, H_A), 3.62 and 3.22 (2 × dd, 2 × 1H, H_B, H_C) and 2.0 (s, 3H, Me); **4a** δ 3.8 (m, 1 H, H_A), 3.25 and 2.9 (2 × dd, 2 × 1H, H_B, H_C) and 1.9 (s, 2H, Me).



by treatment with potassium carbonate (CH_2Cl_2, 25 °C), which affords a 2.5 : 1 mixture of **3a** and **4a** in 76% combined yield. The diastereofacially specific cycloaddition of this and all the nitrones in this paper accords with our observations on related cases.[2,4]

Oxime **1b** (1 : 1 mixture of *syn*- and *anti*-isomers) reacted under analogous conditions to give the nitrone **3b** and subsequently the cycloadducts **5b** (61% overall from **1b**). In this case none of the corresponding oxazine **4b** was observed and only the *endo*-cycloadduct **5b** was obtained. The oxime **1c** reacted under the same conditions to give cycloadduct **5c** as a 3 : 2 mixture of *endo*- and *exo*-cycloadducts but again no oxazine was detected. The conversion of oximes **1a–c** into cycloadducts **5a–c** constitute examples of Class 3 processes according to our classification.[2]

Class 4 processes[2] have been explored with both symmetrical and unsymmetrical substrates. Thus, **6** reacts (MeCN, 25 °C, 0.5 h) with phenylselenyl bromide to afford **7**, which on treatment with anhydrous potassium carbonate (1.1 mol) (MeCN, 25 °C, 16 h) affords nitrone **8**. The nitrone on heating (MeCN, 80 °C, 5 h) affords a single spirocyclic cycloadduct **9** (65% overall from **6**).

A similar sequence of reactions was performed on the unsymmetrical dialk-γ,δ-enyl oximes **10**. Regiospecific cyclisation (MeCN, 25 °C) to nitrone **11** occurred on treatment of **10** sequentially with phenylselenyl bromide and potassium carbonate. Heating of **11** in acetonitrile (80 °C, 4 h) afforded a single cycloadduct **12** (61%) *via* the anticipated diastereofacially specific cycloaddition.

The stereochemistry of the cycloadducts reported herein was established by PMR decoupling experiments and NOE studies. A typical example is provided by **12** in which irradiation of H_C caused enhancements of the signals for H_B, H_A and H_D.

Further work on these and related electrophile induced conversion of oximes to nitrones is underway.

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