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New Mild Methodology for the Synthesis of α-Phenylthio and α-Phenylseleno Ketones

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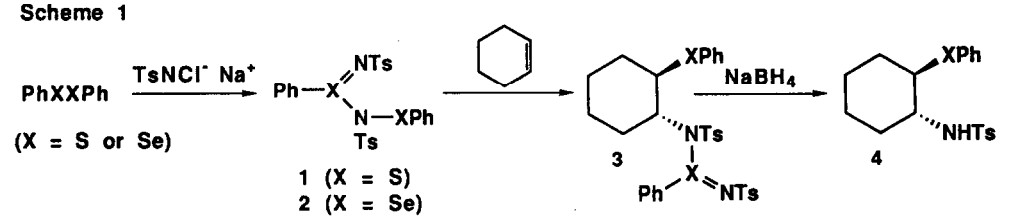
Abstract: Treatment of trimethylsilyl enol ethers with the adduct **1**, derived from chloramine-T and $(PhS)_2$, gave good yields of α-phenylthioketones. The selenium version of this reagent **2** gave α-phenylselenoketones.

The sulfenylation and selenenylation of ketones is an important transformation because the resulting α-functionalized derivatives can be used to great advantage in a variety of synthetically useful reactions. For example oxidation to the corresponding sulfoxide/selenoxide followed by syn-elimination leads to the α,β-unsaturated ketone. The increased acidity of the α-protons allows regiospecific monoalkylation. Pummerer reaction of sulfoxide/selenoxide provides a convenient route to carbonyl compounds. There are a number of sulfenylation and selenenylation methods for the conversion of ketones into α-thio/seleno derivatives that utilize ketone enol or enolate derivatives and electrophilic sulfenylating and selenenylating reagents.[1] Our recent interest in new trialkylsilyl enol ether methodology prompted the examination of mild electrophilic methods for functionalizing trialkylsilyl enol ethers.[2]

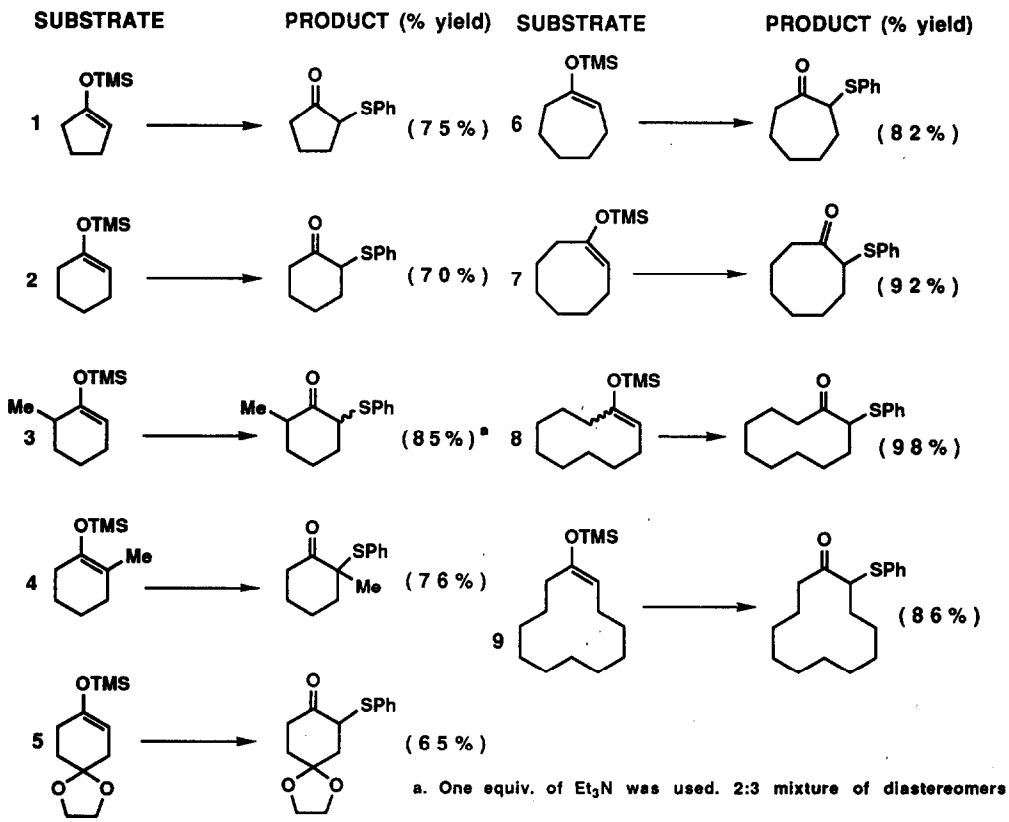
In 1978 Barton reported that the reagent **1** derived from treatment of diphenyl disulfide with chloramine-T (p-$MeC_6H_4SO_2NCl^-$ Na^+) reacted with alkenes to give *trans*-vicinal thiophenyl N-tosyl amines.[3] The selenium version of this reagent **2**, behaves in analogous manner.

Scheme 1



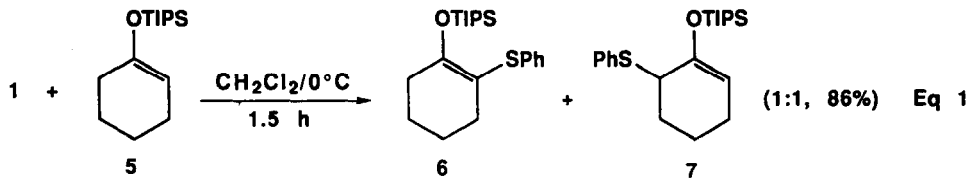
Presumably these transformations proceed through the intermediacy of an *epi*-sulfonium/selenonium ion followed by nucleophilic opening by the anion $PhX(NTs)_2^-$ to give **3** and reductive work-up to give **4**. The exceptionally mild conditions (no electrophilic catalysis) prompted us to see whether or not the reagents **1** and **2** would function as sulfenylating and selenenylating agents respectively, towards trialkyl silyl enol ethers.

TABLE 1



a. One equiv. of Et_3N was used. 2:3 mixture of diastereomers

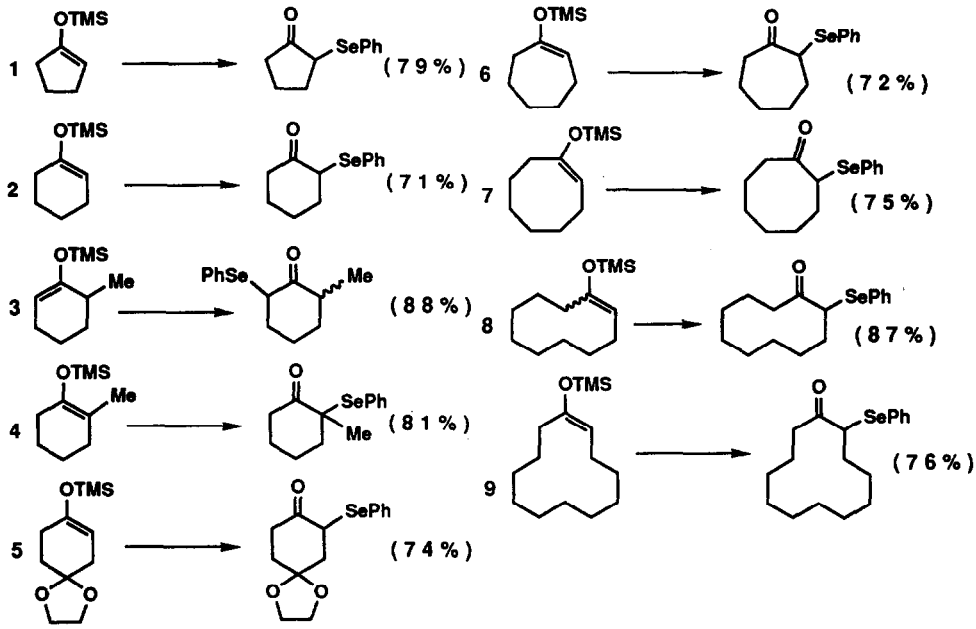
A suspension of **1** in CH_2Cl_2 was treated with 1-triisopropylsilyl(oxy)-cyclohexene **5** to afford a 1:1 mixture of the sulfenylated products **6** and **7** (Eq 1). Under a variety of reaction conditions we could not significantly alter the ratio of **6** and **7**. Consequently, it was decided to examine trimethylsilyl enol ethers with the expectation that the problem of regiochemistry would disappear, since the trimethylsilyl group should be removed *in situ*.



The various trimethylsilyl enol ethers (Table 1) were treated with reagent **1** in dichloromethane at 0° C. All of the reactions went to completion in 15-30 minutes, except *entry 5* which required 3 additional hours at 25° C.[4]

Addition of diphenyldiselenide to a suspension of anhydrous chloramine-T in CH_2Cl_2 at -12° C, followed by cooling to -25° C gave a solution of **2** which was directly treated with the trimethylsilyl enol ethers for 30 mins to give 2-(phenylseleno) ketones in good yield (Table 2).[5]

TABLE 2



These exceptionally mild sulfenylating and selenenylating procedures operate under neutral conditions and do not lead to the introduction of more than one α-SPh/α-SePh group.[6]

References and Footnotes.

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4. **2-(Thiophenyl)-cyclooctanone.** A stirred suspension of 0.668 g (1.2 mmol) of adduct **1** in CH_2Cl_2 (10 ml) at 0° C was treated with 0.198 g (1.0 mmol) of 1-(trimethylsilyloxy)-cyclooctene. After completion of the reaction (ca. 20 min) the solution was concentrated *in vacuo* and the residue was partitioned between Et_2O (50 ml) and water (15 ml). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The resulting solids were applied to a short column of silica gel (hexanes/ethyl acetate, 7:3) to give 0.20 g (92% yield) of 2-(thiophenyl)-cyclooctanone as an oil. ^1H NMR (C_6D_6) δ 7.43 (d, J = 7.1 Hz, 2 H), 7.0 (t, J = 7.3 Hz, 3 H), 6.93 (d, J = 7.1 Hz, 1 H), 3.60 (dd, J = 11.4 Hz, J = 4.3 Hz, 1 H), 2.60 (td, J = 12.3 Hz, J = 3.9 Hz, 1 H), 2.03 (m, 1 H), 1.7-1.9 (m, 2 H), 0.8-1.7 (m, 8 H) ppm; ^{13}C NMR ($CDCl_3$) δ 210.8, 133.0, 132.2, 128.7, 127.6, 57.4, 36.9, 28.6, 28.3, 26.6, 25.5, 24.2 ppm.
5. **2-(Phenylseleno)-cyclodecanone.** A stirred suspension of 0.592 g (2.6 mmol) of anhydrous chloramine-T in CH_2Cl_2 (10 ml) at -12° C was treated with 0.406 g (1.3 mmol) of phenyldiselenide. After 1 hour at -12° C, the suspension has turned into an almost clear yellow solution. It is cooled to -25° C and slowly treated with 0.226 g (1.0 mmol) of 1-trimethylsilyloxy-cyclodecene in CH_2Cl_2 (1 ml). Upon completion (ca. 1 hour), the solution was concentrated *in vacuo* and the residue was chromatographed on silica gel (hexanes/ethylacetate, 9:1 vol) to give 0.27 g (87% yield) of 2-(phenylseleno)-cyclodecanone (**2e**) as an oil. ^1H NMR (C_6D_6) δ 7.51 (m, 2 H), 6.96 (m, 3 H), 3.91 (dd, J = 12.1 Hz, J = 3.6 Hz, 1 H), 2.3-2.6 (m, 2 H), 2.22 (m, 1 H), 1.80 (m, 1 H), 1.0-1.7 (m, 12 H) ppm; ^{13}C NMR ($CDCl_3$) δ 208.2, 135.4, 128.9, 128.4, 127.5, 49.8, 39.4, 30.8, 25.3, 25.3, 24.8, 24.2, 23.9, 23.5 ppm.
6. The NSF and NIH are thanked for their support of this research.

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