Diphenyl Diselenide-Assisted α-Phenylthiolation of Carbonyl Compounds with Diphenyl Disulfide

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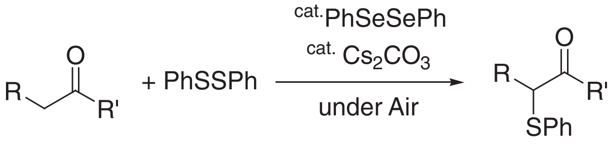
For the cesium carbonate-catalyzed α-phenylthiolation of carbonyl compounds with diphenyl disulfide, the yields of the α-phenylthio carbonyl compounds were dramatically improved by the addition of a catalytic amount of diphenyl diselenide.

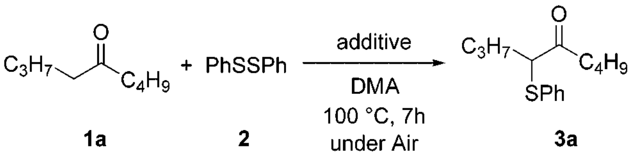
α-Phenylthio carbonyl compounds are useful synthetic intermediates in organic synthesis and many efforts are being devoted to accomplish the synthesis of α-phenylthio carbonyl compounds.[1] The most common methods for the synthesis of these compounds are the reaction of enolates with electrophilics, such as PhSX,[2] PhSSPh,[3] phenyl benzenethiosulfonate,[4] PhSH/NCS,[5] *N*-(phenylthio)amide,[6] *N*-(phenylthio)phthalimide,[7] *N*-(phenylthio)caprolactam,[8] or *N*-(phenylthio)succinimide,[9] and the S_N2 displacement of α-halogenated carbonyl derivatives with benzenethiol.[10] Generally, these methods require multistep sequences for the preparation of substrate, strongly basic and acidic conditions, and anhydrous conditions.

We have recently found that the cesium salt-catalyzed α-phenylselenation of carbonyl compounds with diphenyl diselenide gave the corresponding α-phenylseleno carbonyl compounds in moderate to good yields.[11] This method has some advantages: (i) the use of reagents which are stable toward air and moisture, (ii) under nearly neutral reaction conditions, (iii) moderate to good product yields, (iv) one-step procedure, (v) the efficient use of both phenylseleno groups of diphenyl diselenide, and (vi) catalytic use of a cesium salt. Thus, if diphenyl disulfide instead of diphenyl diselenide was used as a dichalcogenide, it is expected that the α-phenylthio carbonyl compounds could be conveniently synthesized by the cesium salt catalytic method. Although carbonyl compounds were treated with diphenyl disulfide in the presence of a catalytic amount of cesium carbonate, the yields of the α-phenylthio carbonyl compounds were low.[11] We now find that an α-phenylthiolation of carbonyl compounds with diphenyl disulfide proceeds successfully in the presence of a catalytic amount of diphenyl diselenide (Scheme 1).[12]



Scheme 1.

Table 1. α-Phenylthiolation of 5-Nonanone (**1a**) with Diphenyl Disulfide in the Presence of Various Additives[a)]



Entry	Additive (mmol)	Yield/mmol[b)]
1	none	0.00
2	Cs_2CO_3 (0.10)	0.62
3	PhSeSePh (0.10)/Cs_2CO_3 (0.10)	1.54
4	PhSeSePh (0.10)/CsF (0.10)	0.24
5	PhSeSePh (0.10)/CsCl (0.10)	0.00
6	PhSeSePh (0.10)/CsBr (0.10)	0.00
7	PhSeSePh (0.10)/Na_2CO_3 (0.10)	0.32
8	PhSeSePh (0.10)/K_2CO_3 (0.10)	0.50

a) Reaction conditions: **1a** (2.00 mmol), **2** (1.00 mmol), and DMA (2 mL) under air at 100 °C for 7 h. b) GLC yield.

When 5-nonanone (**1a**) (2.00 mmol) was allowed to react with PhSSPh (**2**) (1.00 mmol) in the presence of a catalytic amount of cesium carbonate (0.10 mmol) in DMA solvent under air at 100 °C for 7 h, the α-phenylthiolated product, 4-phenylthio-5-nonanone (**3a**), was formed in only 0.62 mmol (Table 1, Entry 2).[13] It is interesting to note that the addition of a small amount of PhSeSePh (0.10 mmol) led to an increase in the yield of **3a** (1.54 mmol) (Entry 3). The result showed that both phenylthio groups on PhSSPh are effectively introduced on the α-carbon of the 5-nonanone. In the absence of both Cs_2CO_3 and PhSeSePh, **3a** was not formed at all and **1a** was recovered (Entry 1). We next investigated the effect of the alkaline metal salts on the reaction and the results are shown in Table 1. In the case of other cesium salts such as cesium fluoride, chloride, and bromide, the reaction hardly proceeded (Entries 4–6). When using another alkaline metal carbonate, the α-phenylthiolation of 5-nonanone occurred, however, the product yield was lower than that of cesium carbonate (Entries 7 and 8).

The reaction of various carbonyl compounds with PhSSPh was carried out under the same reaction conditions as those of Entry 3 in Table 1 and these results are shown in Table 2. For the reaction of octanal, cyclohexanone, and acetophenone, the corresponding α-phenylthio carbonyl compounds, **3b**–**3d**, were formed in 0.94, 1.30, and 1.24 mmol, respectively (Entries 1–3). When 2-nonanone, which has primary and secondary carbon atoms at the α-position, was allowed to react with PhSSPh, the secondary carbon atom was predominantly phenylthiolated to give 3-phenylthio-2-nonanone (**3e**) (Entry 4). In the case of 3-methyl-2-butanone and 2-methyl-3-pentanone, the phenylthiolation on the tertiary carbon atom proceeded to give the corresponding α-phenylthio ketones **3f** and **3g** (Entries 5 and 6).

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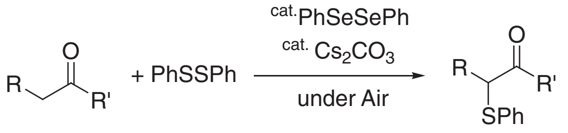
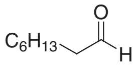
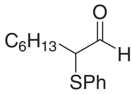
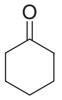
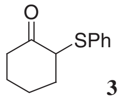
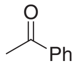
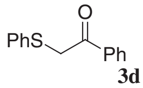
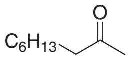
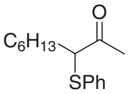
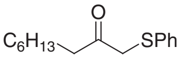
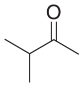
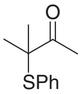
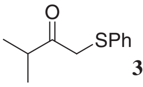
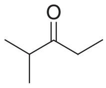
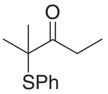
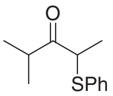
Table 2. Synthesis of Various α-Phenylthio Carbonyl Compounds[a)]



Entry	Substrate	Product	Yield[b)]/mmol
1		 **3b**	0.94 (0.11)
2		 **3c**	1.30 (0.62)
3		 **3d**	1.24 (0.34)
4		 **3e**	0.57 (0.08)
		 **3e′**	0.23 (0.04)
5		 **3f**	1.04 (0.30)
		 **3f′**	0.18 (0.10)
6		 **3g**	1.12 (0.86)
		 **3g′**	0.28 (0.10)

a) Reaction conditions: carbonyl compound (2.00 mmol), PhSSPh (1.00 mmol), PhSeSePh (0.10 mmol), Cs_2CO_3 (0.10 mmol), and DMA (2 mL) under air at 100 °C for 7 h. b) GLC yields. The numbers in parentheses show the yields in the absence of PhSeSePh.

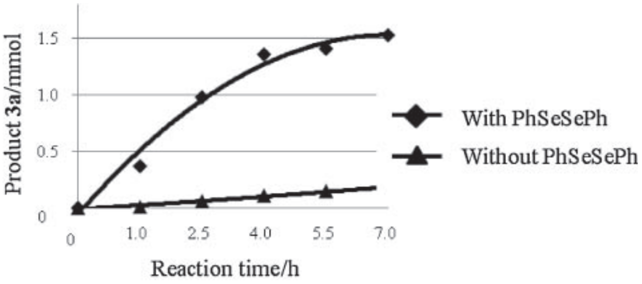
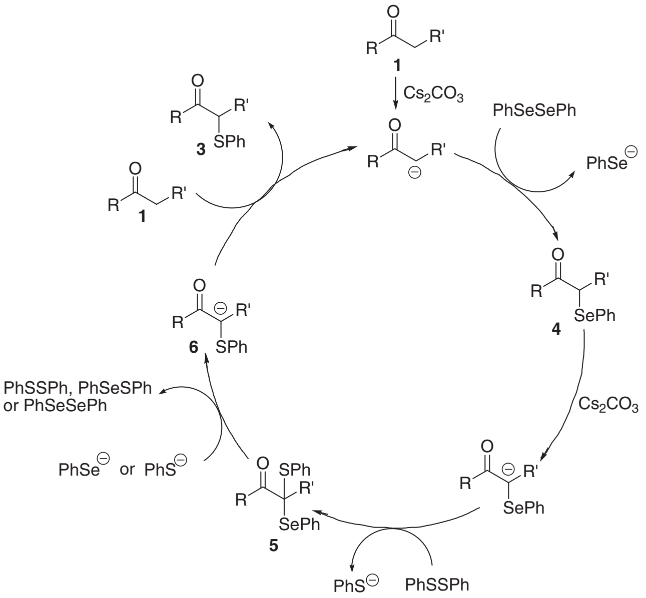


Figure 1. Time dependent curves for the reaction of **1a** and **2**.

Comparison of plots of the yield of α-phenylthio ketone, **3a**, vs. the reaction time in the presence of PhSeSePh-catalyst with those without PhSeSePh-catalyst are shown in Figure 1. It was clearly shown that good catalytic activity of PhSeSePh occurred during the reaction.



Scheme 2. A possible reaction pathway.

For the PhSeSePh-assisted reaction of **1** with PhSSPh, the formation of seleno sulfide (PhSSePh) and α-phenylseleno-α-phenylthio ketones were identified with GC mass analysis. To gain insight into the reaction pathway, the reaction of isolated 4-phenylseleno-5-nonanone (0.50 mmol) with diphenyl disulfide (0.50 mmol) in the presence of cesium carbonate at 100 °C for 7 h gave rise to 0.43 mmol 4-phenylthio-5-nonanone (**3a**).[14] From these results, we suggest that the α-phenylseleno ketone **4** was an intermediate in the reaction.

Although we cannot clearly determine the reaction pathway, one of the plausible reaction pathways is shown in Scheme 2. The removal of the α-proton with cesium carbonate to give the enolate anion is the first step for the reaction. The reaction of the enolate anion with diphenyl diselenide leads to the α-phenylseleno carbonyl compound **4** with phenylselenolate. The deprotonation of **4** with Cs_2CO_3 followed by quenching with PhSSPh gives α-phenylseleno-α-phenylthio ketone **5**.[15,16] **5** is reacted with selenolate or thiolate giving the enolate **6**. **6** abstracts an α-proton from the carbonyl compound to provide a thermodynamically more stable product, **3**, and regenerates the enolate anion.

We found a new synthetic method of α-phenylthio carbonyl compounds by the diphenyl diselenide-assisted reaction of carbonyl compounds with diphenyl disulfide in the presence of a catalytic amount of cesium carbonate.

Experimental

General Procedures. The ^{1}H and ^{13}C NMR spectra were recorded on 270 and 67.5 MHz spectrometers using $CDCl_3$ as the solvent with tetramethylsilane as the internal standard. The IR spectra were recorded by FT-IR spectrometry. ESI mass spectra were obtained by a triple quadrupole mass spectrometer in a positive ion mode. Gas chromatography (GC) was carried out using a flame-ionizing detector equipped instrument and a capillary column (0.25 mm × 1200 mm).

Reagents. Diphenyl disulfide, the carbonyl compounds, and Cs_2CO_3 were commercially available and were used without further purification. The diphenyl diselenide[17] and 4-phenylseleno-5-nonanone[11] were prepared by a literature method. DMA was commercially obtained and purified by distillation.

General Procedure for Reaction of Carbonyl Compounds with Diphenyl Disulfide in the Presence of a Catalytic Amount of Diphenyl Diselenide. A DMA (2 mL) solution of PhSSPh (218 mg, 1.00 mmol), carbonyl compound (2.00 mmol), PhSeSePh (31 mg, 0.10 mmol), and Cs_2CO_3 (32 mg, 0.10 mmol) was stirred at 100 °C for 7 h in air. After the reaction was complete, H_2O was added to the reaction mixture and then extracted with diisopropyl ether. The organic layer was dried over $MgSO_4$. The resulting mixture was filtered, and the filtrate concentrated. Purification of the residue by HPLC afforded the corresponding α-phenylthiolated product. The product was characterized by comparing its spectral data with those of an authentic sample or previous reports for **3a**,[18] **3b**,[7] **3c**,[10c] **3d**,[8] **3f**,[6] **3f′**,[19] **3g**,[20] and **3g′**.[21] The structure of the **3e** was assigned based on the ^{1}H and ^{13}C NMR, IR, and mass spectrum.

Mixture of 3-Phenylthio-2-nonanone (3e) and 1-Phenylthio-2-nonanone (3e′) (3e:3e′ = 71:29): ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.37–7.16 (m, 5H), 3.65 (s, 2×0.29H), 3.62 (t, $J = 7.2$ Hz, 1×0.71H), 2.56 (t, $J = 7.2$ Hz, 2×0.29H), 2.23 (s, 3×0.71H), 1.82–1.24 (m, 20H), 0.87 (t, $J = 7.2$ Hz, 3×0.71H), 0.85 (t, $J = 7.2$ Hz, 3×0.29H); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 205.7, 205.5, 134.9, 133.1, 132.1, 129.04, 129.02, 128.96, 128.93, 127.7, 57.7, 57.6, 43.9, 43.8, 40.5, 31.5, 31.5, 30.3, 28.8, 27.1, 26.3, 26.2, 22.5, 22.4, 14.0; IR (KBr): 2927, 2856, 1709, 1438, 1354, 740, 690 cm^{-1}; ESI: [M + Na$^+$] 272.67.

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14 In the absence of Cs_2CO_3, the reaction did not proceed and 4-phenylseleno-5-nonanone was recoverd in almost quantitatively yield.

15 R. M. Coates et al. have measured the position of equilibrium established between lithium enolate of cyclohexanone and 2-phenylthiocyclohexanone. See Ref. 3a.

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