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One-Pot Synthetic Method of Unsymmetrical Diorganyl Selenides: Reaction of Diphenyl Diselenide with Alkyl Halides in the Presence of Lanthanum Metal

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Abstract: A convenient synthetic method of unsymmetrical selenides has been developed. When diphenyl diselenide was allowed to react with two equimolar amounts of primary alkyl iodides and bromides in the presence of an equimolar amount of lanthanum metal, alkyl phenyl selenides were formed in moderate to good yields. For the reaction of primary alkyl chlorides and secondary alkyl iodides, the yields of the selenides were low; however, the yields were dramatically improved by the addition of TMEDA or HMPA. A reaction pathway involving the generation of a lanthanum phenylselenolate intermediate was suggested.

Organic selenides are widely accepted as key intermediates in organic synthesis, and much effort is being devoted to accomplishing the synthesis of these compounds.[1] Although numerous reports on the synthesis of organoselenium compounds have already been published, it usually requires the handling of unstable reagents, strongly basic or acidic reaction conditions, and two-step procedures. Therefore, the development of a one-step synthetic method using stable reagents under neutral conditions has attracted much attention. In this paper, we show a novel one-step synthetic method of unsymmetrical selenides by the reaction of diselenide with alkyl halides in the presence of lanthanum metal (Scheme 1).[2]

When diphenyl diselenide (**1**) (1.0 mmol) was allowed to react with two equimolar amounts of iodododecane (2.0 mmol) in the presence of an equimolar amount of lanthanum metal (1.0 mmol) and a catalytic amount of iodine at 67 °C for 5 h, dodecyl phenyl selenide was obtained in 1.56 mmol (156% yield based on lanthanum metal) (entry 1 in Table 1).[5] Table 1 shows the results on the synthesis of various alkyl phenyl selenides using lanthanum metal-assisted reaction of **1** with alkyl halides. Dodecyl and benzyl phenyl selenides were also formed by the reaction of dodecyl and benzyl bromides in moderate yields (entries 2 and 5). In contrast, for the alkyl chloride, the yield of alkyl phenyl selenide was low under the same reaction conditions as that of the primary alkyl iodides and bromides; however, the reaction of alkyl chloride was accelerated by the addition of HMPA (entries 3 and 4). The similar treatment of PhSeSePh with 3-iodopropene produced 3-phenylselenopropene in 72% yield (entry 6). In the case of crotylbromide, allylic phenyl selenides were formed in 73% yield with a mixture of regioisomers (entry 7). Although the synthesis of unsymmetrical selenide having a branched alkyl chain and cyclic ring was successfully achieved by the elevation

SCHEME 1

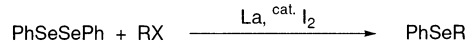
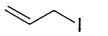
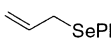
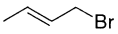
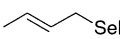
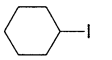
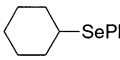
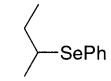
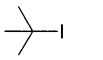
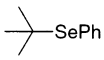


TABLE 1. Synthesis of Organoselenium Compounds[a]

entry	RX	RSePh	yield (%)[b]
1	$C_{11}H_{23}I$	$C_{11}H_{23}SePh$	78 (156)[c]
2	$C_{11}H_{23}Br$	$C_{11}H_{23}SePh$	77
3	$C_{11}H_{23}Cl$	$C_{11}H_{23}SePh$	34
4[d]	$C_{11}H_{23}Cl$	$C_{11}H_{23}SePh$	78
5	PhBr	PhSePh	73
6			72
7			61(12)[e]
8[f,g]			68
9[f,g]			54
10[f,g]			trace
11	PhCOCl	PhCOSePh	43

[a] Reaction conditions: RX (2.0 mmol), PhSeSePh (1.0 mmol), La (1.0 mmol), I_2 (0.2 mmol), and THF (5 mL) at 67 °C for 5 h. [b] GC yield based on RX. [c] GC yield based on lanthanum metal. [d] HMPA (1 mL) was added. [e] Yield of 3-phenylseleno-1-butene. [f] TMEDA (1 mL) was added. [g] At 110 °C for 13 h.

(1) For recent reviews: (a) Krief, A.; Hevesi, L. In *Organoselenium Chemistry*; Springer-Verlag: Berlin, 1988; Vol. 1. (b) Paulmier, C. In *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon Press: Oxford, 1986. (c) Patai, S.; Rappoport, Z. In *The Chemistry of Organic Selenium and Tellurium Compounds*; Wiley & Sons: New York, 1986 and 1987; Vols. 1 and 2. (d) Krief, A. In *Comprehensive Organometallic Chemistry*; Trost, B. M., Eds.; Pergamon Press: Oxford, 1991; pp 85−192 and references therein.

(2) Recently, there have been some reports on methods for generating lanthanoid selenolate anion species via the reductive cleavage of the Se−Se bond with samarium compounds such as $Sm/HgCl_2$[3] and SmI_2.[4] However, these methods required the handling of reagents unstable toward air and/or moisture and the poisonous reagents. Furthermore, to the best of our knowledge, there are no examples of methods for generating lanthanoid selenolate anion by use of other lanthanoid metals.

(3) Wang, L.; Zhang, Y. *Heteroat. Chem.* **1999**, *10*, 203.

(4) (a) Fukuzawa, S.; Niimoto, Y.; Fujinami, T.; Sakai, S. *Heteroat. Chem.* **1990**, *1*, 491. (b) Sekiguchi, M.; Tanaka, H.; Takemi, N.; Ogawa, A.; Ryu, I.; Sonoda, N. *Heteroat. Chem.* **1991**, *2*, 427. (c) Zhang, Y.; Yu, Y.; Lin, R. *Synth. Commun.* **1993**, *23*, 189.

(5) We have already shown that the addition of a catalytic amount of iodine dramatically enhanced the reductive dimerization of carbonyl compounds,[6] imines,[7] and alkyl halides.[8]

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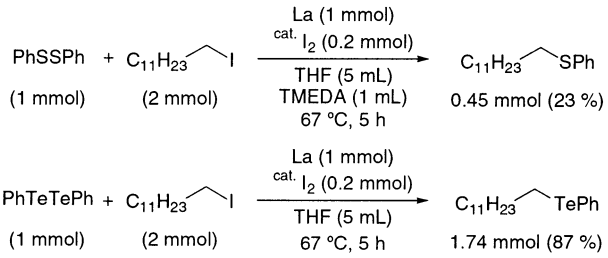
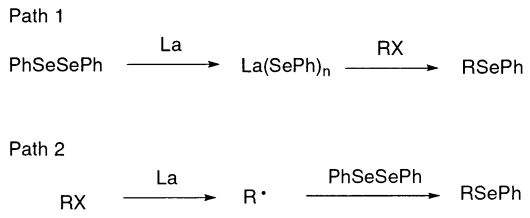
SCHEME 2



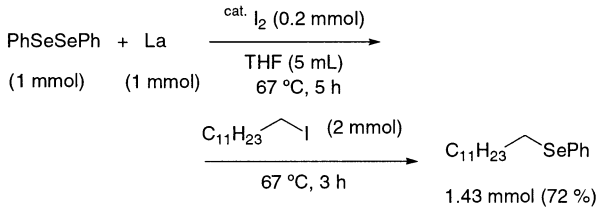
SCHEME 3



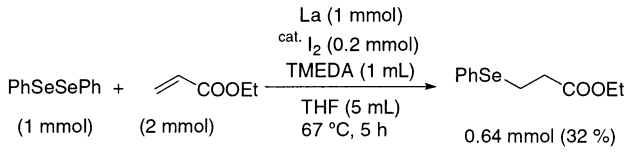
of the reaction temperature and extension of the reaction time, tertiary alkyl phenyl selenide was not formed even under harsh reaction conditions (entries 8−10). The treatment of diphenyl diselenide with benzoyl chloride gave *Se*-phenyl selenobenzoate in 43% yield (entry 11). This reaction can be applicable to the synthesis of alkyl phenyl sulfide and telluride. When diphenyl disulfide or ditelluride instead of the diselenide was used as diphenyl dichalcogenide, alky phenyl sulfide and telluride were formed in 23 and 87% yields, respectively (Scheme 2).

Nakamura and Mashima et al. have shown a direct synthetic method toward lanthanoid thiolate complexes (Ln = Sm and Eu) via the reaction of diaryl disulfide with samarium and europium metal in the presence of a catalytic amount of iodine.[9] We have recently found that alkyl radicals were easily generated by the reduction of alkyl halides with lanthanum metal and coupled to form the corresponding dimerization products.[8] On the basis of both results, two reaction pathways for the formation of alkyl phenyl selenides were shown in Scheme 3. One was the alkylation pathway of lanthanum phenylselenolate prepared by the reduction of diphenyl diselenide with lanthanum metal with alkyl halides to form alkyl phenyl selenides (Path 1). Another pathway including the S_H2 reaction of alkyl radicals, which was generated by the reduction of alkyl halides with lanthanum metal, with PhSeSePh was suggested (Path 2). To better understand the reaction pathway, we carried out some experiments and obtained the following results. When PhSeSePh was treated with lanthanum metal at 67 °C for 5 h, lanthanum metal was gradually dissolved to give a brown solution. Subsequently, an addition of 1-iodododecane to the solution provided dodecyl phenyl selenide in 72% yield (Scheme 4). By quenching the brown solution with aqueous HCl, the formation of benzeneselenol was certified by GC. The treatment of diphenyl diselenide with

SCHEME 4



SCHEME 5



ethyl acrylate in the presence of lanthanum metal gave the Michael addition product, ethyl 3-phenylseleno propionate, in 32% yield (Scheme 5).[10] In addition, even when alkyl phenyl selenides were not obtained, reductive dimerization, reduction, and/or dehydroiodination products of alkyl halide were not formed in the reaction of PhSeSePh with alkyl halide. Furthermore, the addition of TMEDA and HMPA to the reaction solution caused an increase in the yield of the alkyl phenyl selenides.[11,12] On the basis of these results, at the present time, while the preparation pathway of alkyl phenyl selenides is not clearly shown, the reaction pathway including the alkylation of lanthanum phenyl selenolate, generated by the reduction of diphenyl diselenide with lanthanum metal, with alkyl halides was strongly suggested.

In summary, a one-pot synthetic method of unsymmetrical selenides by the treatment of diphenyl diselenide with alkyl halides in the presence of lanthanum metal has been developed. The present method has the following noteworthy features: (1) the high and moderate yield preparation method of alkyl phenyl selenides; (2) a simple operation; (3) neutral reaction conditions; and (4) the efficient transfer of electrons of the lanthanum metal. A wide range of diorganyl selenides were synthesized successfully by employing this reaction system.

Experimental Section

Instruments. ^1H and ^{13}C NMR spectra were recorded on a 400 and 99.5 MHz spectrometer using $CDCl_3$ as a solvent with tetramethylsilane as the internal standard. IR spectra were recorded on a FT-IR spectrophotometer. Gas chromatography (GC) was carried out on a flame ionizing detector-equipped instrument and using a capillary column (0.25 mm × 25 m). HPLC separation was

(6) Nishino, T.; Nishiyama, Y.; Sonoda, N. *Heteroat. Chem*. **2000**, *11*, 81.

(7) Nishino, T.; Nishiyama, Y.; Sonoda, N. *Heteroat. Chem*. **2002**, *13*, 131.

(8) Nishino, T.; Watanabe, T.; Okada, M.; Nishiyama, Y.; Sonoda, N. *J. Org. Chem*. **2002**, *67*, 966.

(9) Mashima, K.; Nakayama, Y.; Fukumoto, H.; Kanehisa, N.; Kai, Y.; Nakamura, A. *J. Chem. Soc., Chem. Commun*. **1994**, 2523.

(10) Fujiwara et al. reported that the reaction of diaryl and dialkyl disulfide with ytterbium metal was activated by benzophenone to afford ytterbium(III) thiolates. The thiolates thus formed in situ were reacted with enones to give Michael adducts. See: Taniguchi, Y.; Maruo, M.; Takaki, K.; Fujiwara, Y. *Tetrahedron Lett*. **1994**, *35*, 7789.

(11) It was known that the reduction of organic compounds with samarium(II) iodide was promoted by the addition of HMPA.[13] However, the reductive coupling of carbonyl compounds with lanthanum metal was not accelerated by the addition of HMPA.[6]

(12) It is well-known that the nucleophilic addition of organometallic compounds such as alkyllithium compounds is promoted by the addition of HMPA and TMEDA due to the deaggregation of organometallic compound by these reagents. From the background, we suggested that the deaggregation of lanthanum selenolate with HMPA or TMEDA raised the nucleophilicity of selenolate.

performed on recycling preparative HPLC equipped with GPC columns (20 × 1200 mm).

Reagents. Organic halides and iodine were commercially available high-grade products and used without purification. Lanthanum metal was commercially available high-grade products and used after powderization. Diphenyl diselenide was synthesized by the literature method.[14] The other reagents and solvents were purified by the usual mehods before use.

General Procedure for the Reaction of Organic Halides and Diphenyl Diselenide with Lanthanum Metal. Lanthanum powder (1.0 mmol, 139 mg), iodine (0.2 mmol, 51 mg), and diphenyl diselenide (1.0 mmol, 312 mg) were placed in a two-necked flask. THF (5 mL) and organic halide (2.0 mmol) were added to the flask, and the mixture was stirred at 67 °C for 5 h under a nitrogen atmosphere. The color of the solution gradually changed to dark gray. After the reaction, aqueous HCl (1 M) was added to the reaction mixture, and the mixture was extracted with diisopropyl ether (three times). The organic layer was dried over $MgSO_4$. The resulting mixture was filtered, and the organic solvent was removed under the reduced pressure. Purification of the residue by HPLC afforded the corresponding alkyl phenyl selenide. Products were characterized by comparison of their spectra data with those of authentic samples. The structures of the products were assigned by their ^1H and ^{13}C NMR and IR spectra.

General Procedure for the Reaction of Organic Halides and Diphenyl Diselenide with Lanthanum Metal in the Presence of TMEDA. Lanthanum powder (1.0 mmol, 139 mg), iodine (0.2 mmol, 51 mg), diphenyl diselenide (1.0 mmol, 312 mg), organic halide (2.0 mmol), TMEDA (1 mL), and THF (5 mL) were added to the autoclave, and the mixture was stirred at 110 °C for 13 h under a nitrogen atmosphere. After the reaction, the same workup as described in the general procedure for the reaction of organic halides with diphenyl diselenide with lanthanum metal was carried out to give the corresponding alkyl phenyl selenides. The product was characterized by comparison of its spectra data with those of authentic samples. The structures of the products were assigned by their ^1H and ^{13}C NMR and IR spectra.

Two Step Procedure for Synthesis of Alkyl Phenyl Selenide. A THF (5 mL) solution of lanthanum powder (1.0 mmol, 139 mg), iodine (0.2 mmol, 51 mg), and diphenyl diselenide (1.0 mmol, 312 mg) were stirred at 67 °C for 5 h under a nitrogen atmosphere. Iodododecane (2.0 mmol, 592 mg) was added to the resulting solution, and the mixture was stirred at 67 °C for 3 h. After the reaction, the same workup as described in the general procedure for the reaction of organic halides with diphenyl diselenide with lanthanum metal was carried out to give the corresponding alkyl phenyl selenides. The product was characterized by comparison of its spectra data with those of authentic samples. The structures of the products were assigned by their ^1H and ^{13}C NMR and IR spectra.

Acknowledgment. We thank the Santoku Co. for supplying the lanthanum metal.

Supporting Information Available: Copies of spectra (^1H and ^{13}C NMR and IR) for all coupling products. This material is available free of charge via the Internet at http://pubs.acs.org.

JO026032H

(13) (a) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 5763. (b) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28*, 4437. (c) Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485. (d) Hou, Z.; Wakatuki, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 1205. (e) Hou, Z.; Zhang, Y.; Wakatuki, Y. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 149.

(14) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.