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Journal of Organometallic Chemistry 485 (1995) 19–24

Journal of Organometallic Chemistry

First example of selenium transfer reaction of primary selenoamides and selenourea. Novel synthesis of dialkyl diselenides from alkyl halides

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Received 16 December 1993; in revised form 26 April 1994

Abstract

As selenium transfer reagents, arylselenoamides react with a variety of alkyl halides in ethanol under mild conditions to give dialkyl diselenides in excellent yields. Similarly, alkyl halides treated with selenourea form dialkyl diselenides. The possible mechanism is discussed.

Keywords: Selenium; Selenoamides; Diselenides; Selenourea; Alkyl halide

1. Introduction

Thiocarboamides, especially thioacetamide (**1**), have been used as sulphur transfer reagents in the synthesis of symmetrical sulphides (**2**) from reactive halides (Scheme 1). For instance, benzyl bromide [1], α-halogenated ketones, esters and nitriles [2] β-functionalized halides [3] and hydrazonyl halides [4] all give the corresponding thioethers or the cyclization products [1]. Thioacetamide has also been utilized in the preparation of sulphur-containing heterocycles [5]. However, to our knowledge, no analogous selenium transfer reaction of selenoamides has been reported. Primary selenoamides, particularly aliphatic selenoamides, are far less stable than the corresponding thioamides and few reactions of selenoamides have been well studied [6]. All previously reported reactions of selenoamides with the reactive alkyl halides led to the Se-alkylated products or the subsequently cyclized selenium-containing heterocycles (Scheme 2). Treatment of selenobenzanilide (**3**) with α-bromophenylacetic acid and triethylamine gives α-seleno acid [7]. Recently Lai and Reid [8] have reported the conversion of primary alkyl selenocarboxamides (**5**) into selenazoles (**7**) by reaction with phenacyl bromide via the intermediate **6**. It is also known that *N*-methyl selenoacetamide (**8**) undergoes methylation at the selenium atom on treatment with methyl iodide to yield the selenoimidate **9** [9]. Similarly, β-aminovinyl selenoketones (**10**) react with a variety of electrophiles to give the *Se*-alkylated products (cf. **11** in Scheme 3) [10,11].

We have now discovered a novel selenium transfer reaction of selenocarboxamides: treatment of alkyl halides in ethanol with aromatic primary selenoamides or *N*-phenylselenourea gives the corresponding dialkyl diselenides. The alkyl halides used here do not have the α- or β-functional group, so no subsequent ring closure reaction can occur. In these reactions the selenoamide or selenourea acts as a selenium transfer reagent (see Scheme 4).

2. Results and discussion

Primary aryl selenoamides (**12**) were prepared from the corresponding nitriles and sodium hydrogenselenide as described previously [8,12]. When alkyl halides (**13a–h**) were treated with selenoamides (**12a**, **b** or **c**) in ethanol at 70°C under nitrogen for 3–8 h, the diselenides **14** were obtained after workup (Scheme 4). Benzyl halides (**13a** and **b**) and long-chain alkyl halides (**13c–h**) were employed and yields were all high (84–91%, Table 1). The symmetrical dialkyl diselenides **14a–14g**, all known compounds, were characterized by

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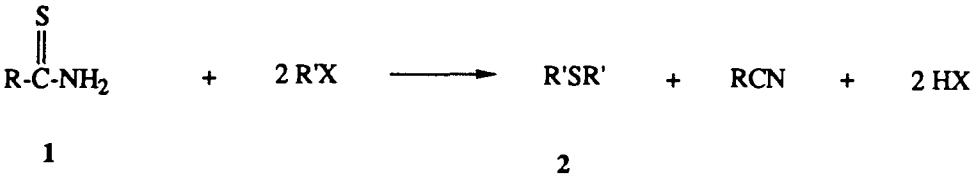
SSDI 0022-328X(94)24765-B

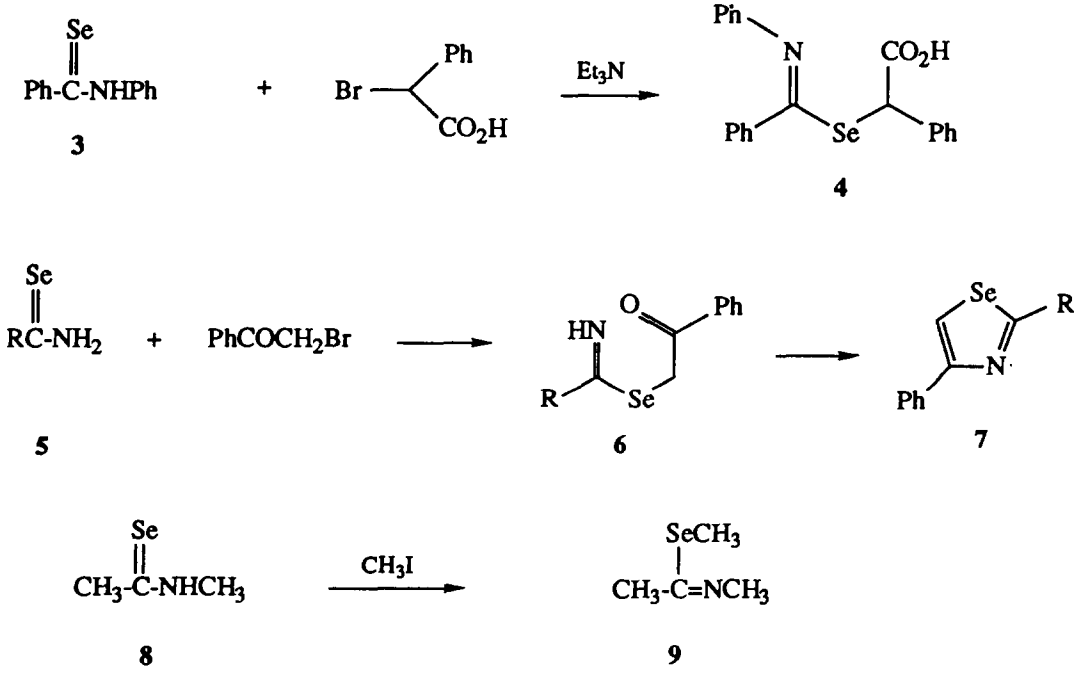


Scheme 1.

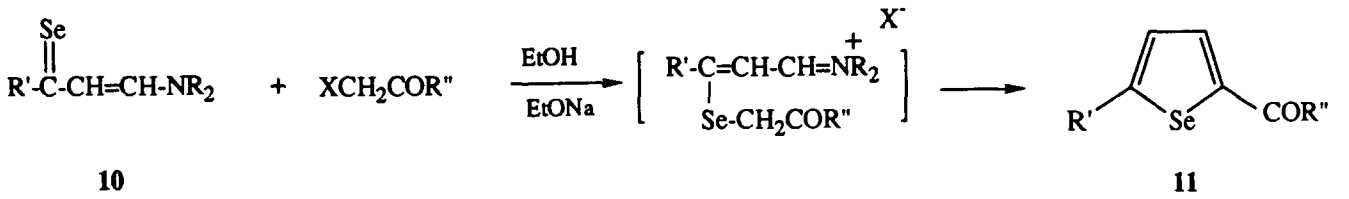
IR and NMR spectra (Tables 1 and 2). The structure of dialkyl selenide is ruled out by comparison with the previously reported melting points and ^{1}H NMR spectra. For example, the melting point of dibenzyl diselenide is 90–91°C [13], whereas that of dibenzyl selenide is 44–45°C [14]. In the ^{1}H NMR spectra, the chemical shifts of the CH_2 groups adjacent to selenium for **14b–g** are 2.90–2.95 ppm and that for **14a** is 3.79 ppm, which are in agreement with the diselenide structure. It has been reported that the CH_2 protons of $-CH_2SeSe-$ in di-*n*-hexyl diselenide appear at 2.92 ppm and that of $-CH_2Se-$ in di-*n*-hexyl selenide at 2.53 ppm [15]. It is generally true that the protons adjacent to selenium in dialkyl diselenides resonate at about 0.5 ppm lower field than that of the corresponding dialkyl selenides [15–18]. Selenobenzamide (**12a**) and substituted phenyl selenoamides (**12b** and **c**) gave essentially the same results. The by-products, ethyl benzoate (in the case of selenobenzamide) and ammonium halide, were isolated and identified by IR and the proton NMR spectra.

Dialkyl diselenides were similarly obtained in good yields (80–92%) when alkyl halides were treated with *N*-phenylselenourea (**15**) (Scheme 4 and Table 1). In these cases, *N*-phenylselenourea (**15**), prepared in situ from *N*-phenyl-*S*-methylthiopseudourea, elemental selenium and sodium borohydride [19], was directly used to convert alkyl halides into dialkyl diselenides in a one-pot procedure.

The previously reported reactions of thioacetamide and reactive halides [1,2] were generally carried out in a 1 : 1 molar ratio and in the presence of a strong base (KOH, EtONa or ^{t}BuOK). The initial *S*-alkylated intermediate undergoes the second nucleophilic attack on the C–X carbon to give the thionium adduct which then cleaved into the sulphide and nitrile [2]. In the present work, however, the selenoamide was treated with an equimolar amount of alkyl halides in the absence of base. The formation of the selenide was not observed. Considering the by-products ethyl benzoate and ammonium halide, a mechanism is proposed to rationalize this selenium transfer reaction as shown in Scheme 5. Nucleophilic attack on RX by Se of selenoamides gives the selenoimidate **16**. The SeR group is then replaced by OEt from the solvent via addition–elimination as shown in Scheme 5 to yield intermediate **17** and selenol **18**. The air-sensitive selenols **18** were rapidly converted into dialkyl diselenides (**14**) on expo-



Scheme 2.



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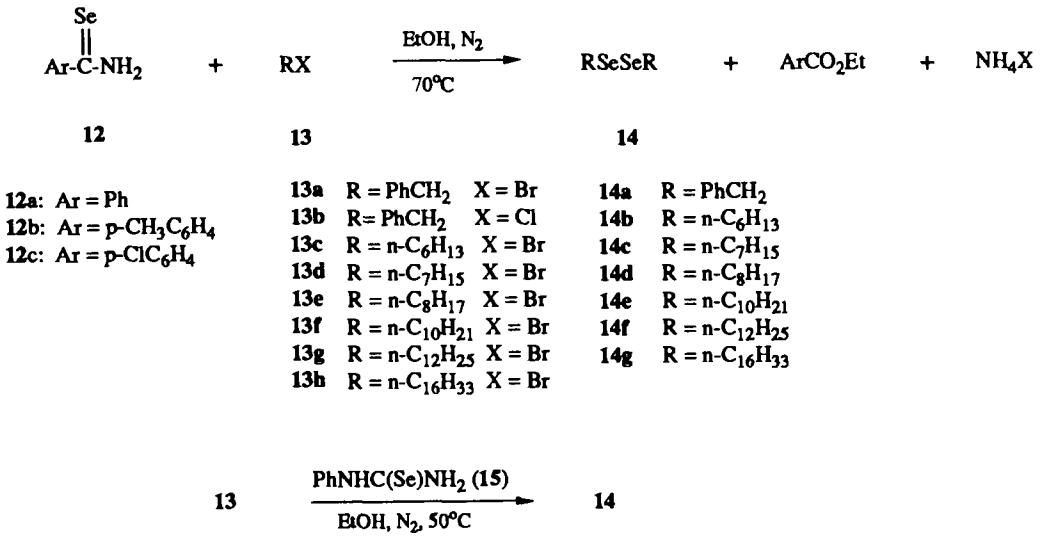
Scheme 3.



12 13 14

12a: Ar = Ph
12b: Ar = p-$CH_3C_6H_4$
12c: Ar = p-ClC_6H_4

13a R = $PhCH_2$ X = Br
13b R = $PhCH_2$ X = Cl
13c R = n-C_6H_{13} X = Br
13d R = n-C_7H_{15} X = Br
13e R = n-C_8H_{17} X = Br
13f R = n-$C_{10}H_{21}$ X = Br
13g R = n-$C_{12}H_{25}$ X = Br
13h R = n-$C_{16}H_{33}$ X = Br

14a R = $PhCH_2$
14b R = n-C_6H_{13}
14c R = n-C_7H_{15}
14d R = n-C_8H_{17}
14e R = n-$C_{10}H_{21}$
14f R = n-$C_{12}H_{25}$
14g R = n-$C_{16}H_{33}$

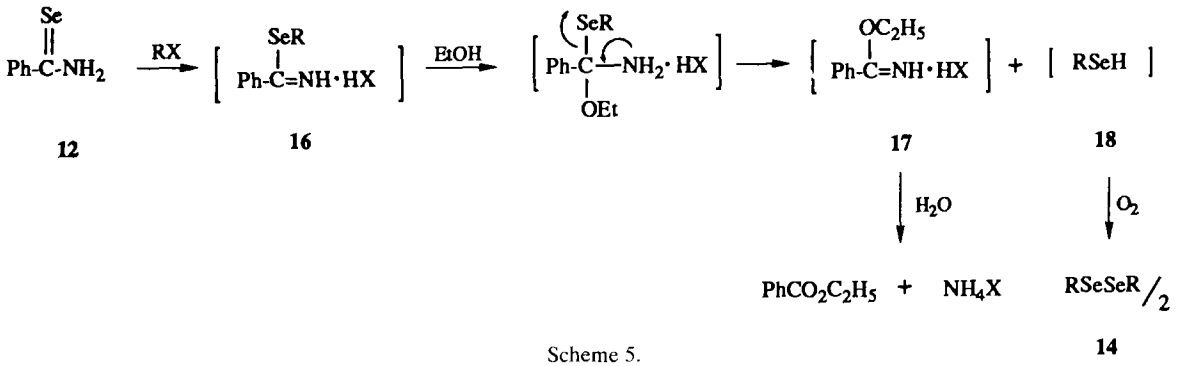
Scheme 4.

Table 1
Preparations of dialkyl diselenides (**14**)

Entry	RX	Reagent	Product	Reaction time (h)	Yield (%)	M.p. (°C)	Lit m.p. or b.p. (°C/Torr)
1	$PhCH_2Cl$	**12a**	$(PhCH_2Se)_2$	4	91	88–89.5	90–91 [13]
2	$PhCH_2Cl$	**12b**	$(PhCH_2Se)_2$	4	88	88–89.5	90–91 [13]
3	$PhCH_2Br$	**12c**	$(PhCH_2Se)_2$	3	90	88–89.5	90–91 [13]
4	n-$C_6H_{13}Br$	**12a**	(n-$C_6H_{13}Se)_2$	7	85	Oil	158/3 [26]
5	n-$C_6H_{13}Br$	**15**	(n-$C_6H_{13}Se)_2$	3	88	Oil	158/3 [26]
6	n-$C_7H_{15}Br$	**12a**	(n-$C_7H_{15}Se)_2$	8	86	Oil	Oil [22]
7	n-$C_8H_{17}Br$	**12a**	(n-$C_8H_{17}Se)_2$	8	89	Oil	85–90/0.01 [24]
8	n-$C_8H_{17}Br$	**15**	(n-$C_8H_{17}Se)_2$	6	90	Oil	85–90/0.01 [24]
9	n-$C_{10}H_{21}Br$	**12a**	(n-$C_{10}H_{21}Se)_2$	8	86	Oil	185–193/0.26 [23]
10	n-$C_{10}H_{21}Br$	**12b**	(n-$C_{10}H_{21}Se)_2$	8	84	Oil	185–193/0.26 [23]
11	n-$C_{12}H_{25}Br$	**12a**	(n-$C_{12}H_{25}Se)_2$	5	87	30–31	30.5–31 [27]
12	n-$C_{12}H_{25}Br$	**15**	(n-$C_{12}H_{25}Se)_2$	6	80	30–31	30.5–31 [27]
13	n-$C_{16}H_{33}Br$	**12a**	(n-$C_{16}H_{33}Se)_2$	8	89	50–51	52–52.5 [27]
14	n-$C_{16}H_{33}Br$	**15**	(n-$C_{16}H_{33}Se)_2$	7	92	50–51	52–52.5 [27]

Table 2
IR and ^1H NMR spectral data for dialkyl diselenide (**14**)

R in $(RSe)_2$	IR (KBr), ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS), δ (ppm)
$PhCH_2$	3040, 2930, 1605, 1495, 1460, 820, 760, 690	3.79 (s, 4H), 7.18 (s, 10H)
n-C_6H_{13}	2900, 2850, 1460, 1375, 1240, 1180, 720	0.89 (t, 6H), 1.33 (m, 12H), 1.73 (m, 4H), 2.92 (t, 4H)
n-C_7H_{15}	2900, 2850, 1460, 1375, 1235, 1175, 720	0.90 (t, 6H), 1.32 (m, 16H), 1.74 (m, 4H), 2.91 (t, 4H)
n-C_8H_{17}	2900, 2850, 1460, 1375, 1240, 1175, 715	0.91 (t, 6H), 1.32 (m, 20H), 1.73 (m, 4H), 2.93 (t, 4H)
n-$C_{10}H_{21}$	2900, 2850, 1460, 1370, 1240, 1170, 720	0.92 (t, 6H), 1.34 (m, 28H), 1.72 (m, 4H), 2.95 (t, 4H)
n-$C_{12}H_{25}$	2900, 2850, 1465, 1370, 1235, 1170, 710	0.90 (t, 6H), 1.34 (m, 36H), 1.73 (m, 4H), 2.93 (t, 4H)
n-$C_{16}H_{33}$	2900, 2850, 1460, 1380, 1220, 1170, 720	0.92 (t, 6H), 1.33 (m, 52H), 1.73 (m, 4H), 2.92 (t, 4H)



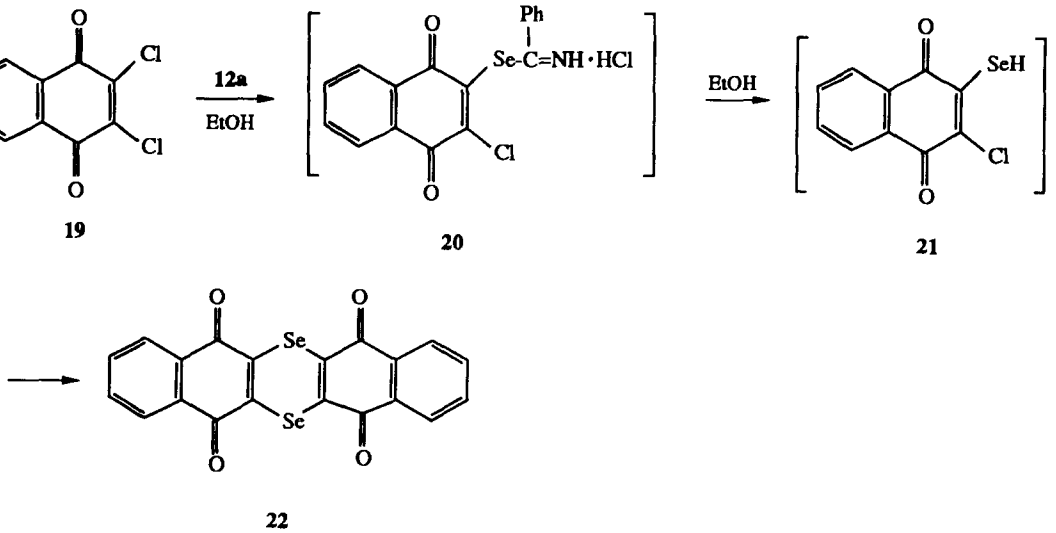
Scheme 5.

sure to air during the workup. The ethoxyimidate **17** is hydrolysed to ethyl benzoate and ammonium halide. The absence of base and extra amounts of RX suppressed the possible formation of selenide through the selenonium intermediate (by attack of **16** on RX). The reaction of *N*-phenylselenourea (**15**) with alkyl halides is believed to proceed in a similar way. It is known that *Se*-alkylselenopseudoureas (free base) when heated in air give diselenides [13].

The reaction of selenoamides with two equivalents of alkyl halides is currently under investigation to determine the possible formation of dialkyl selenide.

When 2,3-dichloro-1,4-naphthoquinone (**19**) which contains two reactive chlorine atoms, was treated with selenobenzamide (**12a**) (1 : 1 ratio) in ethanol, dibenzo [*b*,*i*]selenothrene-5,7,12,14-tetraone (**22**) was given in 70% yield. Compound **22** is a red solid with high melting point (319–320°C) and not soluble in common NMR solvents. It was therefore identified by elemental analysis. We believe that it was formed by the coupling reaction of the intermediate 2-chloro-3-hydroseleno-1,4-naphthoquinone (**21**) as shown in Scheme 6. Dibenzo[*b*,*i*]selenothrene-5,7,12,14-tetraone (**22**) was the only isolated product in this case, although the cyclized product selenoazole might also be formed from the reaction in small amount.

Dialkyl diselenides are the key intermediates in the organic chemistry of selenium [20], and much effort has been devoted to the synthesis of this type of compound [21]. One of the most general approach for diselenides is the alkylation of diselenide anion Se_2^{2-}, which can be prepared by the reduction of selenium with a number of reducing agents [22]. Most recently, dialkyl diselenides have been synthesized by the controlling reduction of selenium with carbon monoxide and water in the presence of tertiary amine followed by subsequent alkylation [18]. Diselenides were also prepared from selenocyanates [23] and from Grignard reagents or organolithiums [24]. All these methods suffer from some disadvantages: the reducing agents are often expensive, the starting materials are not readily available and sometimes relatively severe reaction conditions are needed. The selenium transfer reaction described in this paper has provided a general and convenient ac-



Scheme 6.

cess to dialkyl diselenides. Selenobenzamide can be easily prepared on a large scale and is stable on storage. The reaction is carried out under neutral conditions. Moreover, the method has other advantages such as mild reaction conditions, simple procedures and high yields of products.

3. Experimental

Melting points were determined on an electrothermal micro melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 683 spectrophotometer. The ^1H NMR spectra were obtained on an AC-80 (80 MHz) instrument with TMS as an internal standard. Elemental analysis was performed on a Carlo Erba 1106 elemental analyser.

3.1. Reaction of selenobenzamide with benzyl chloride: typical procedure

Selenobenzamide (0.40 g, 2 mmol) was added to benzyl chloride (0.26 g, 2 mmol) in anhydrous ethanol (10 ml) under nitrogen. The mixture was stirred at room temperature for 30 min and then at 70°C for 4 h. Ethanol was removed under reduced pressure and CH_2Cl_2 (15 ml) was added to the residue. The white precipitate (NH_4Cl) was filtered off and washed with CH_2Cl_2 (15 ml). The combined organic solution was washed with water (15 ml) and dried over $MgSO_4$. After removal of solvent, the product mixture was separated by column chromatography (silica gel, cyclohexane) to give dibenzyl diselenide as yellow crystals (0.31 g, 91%, m.p. 88–89.5°C, lit.[13] 90–91°C) and ethyl benzoate, which was identified by IR and NMR spectra.

Other dialkyl diselenides were prepared by the same procedure except for different heating times (see Table 1).

3.2. Reaction of N-phenylselenourea with dodecyl bromide: typical procedure

N-Phenyl-*S*-methylthiopseudourea hydroiodide (1.47 g, 5 mmol), prepared from phenylthiourea and methyl iodide [25], was added to NaSeH which was made in situ from elemental selenium (0.40 g, 5 mmol) and $NaBH_4$ (0.23 g, 6 mmol) in ethanol (20 ml) [26]. The mixture was refluxed for 4 h. Acetic acid (glacial, 0.8 ml) was added and refluxing continued for 30 min. To this *N*-phenylselenourea solution was added *n*-dodecyl bromide (1.0 g, 4 mmol), followed by stirring at room temperature for 30 min and then at 55°C for 6 h. After cooling and filtration, water (20 ml) was added. The mixture was extracted with CH_2Cl_2 (3×15 ml) and dried over $MgSO_4$. Evaporation of solvent gave a crude product, which was purified by column chromatography (silica gel, cyclohexane) to yield didodecyl diselenide as a yellow solid (0.80 g, 80%, m.p. 30–31°C).

3.3. Dibenzo[b,i]selenothrene-5,7,12,14-tetraone (22)

A mixture of selenobenzamide (0.40 g, 2 mmol) and 2,3-dichloro-1,4-naphthoquinone (0.46 g, 2 mmol) in ethanol was stirred at 70°C under nitrogen for 1 h. Ethanol was distilled off and the residue dissolved in $CHCl_3$ (20 ml), washed with water (2×10 ml) and dried over $MgSO_4$. Evaporation of solvent gave a crude product, which was purified by recrystallization from $CHCl_3$ (red crystals, 0.31 g, 70%, m.p. 319–320°C). IR (KBr) ν: 2935, 1665, 1550, 1290, 1140, 700, 615 cm^{-1}. Calcd. for $C_{20}H_8O_4Se_2$: C, 51.10; H, 1.72. Found: C, 51.13; H, 1.60%.

Acknowledgement

This work was financially supported by the National Natural Science Foundation of China.

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