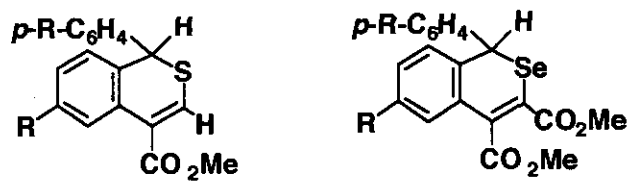
REGIOSELECTIVE SYNTHESIS OF 1*H*-2-BENZOSELENOPYRANS. REACTION OF 4,4'-DIMETHOXYSELENOBENZOPHENONE WITH ACETYLENES

Kentaro Okuma,* Yuji Koga, Yayoi Furunushi, Kazuki Kojima, and Kosei Shioji
Department of Chemistry, Faculty of Science, Fukuoka University, Jonan-ku, Fukuoka 814-0180, Japan

Abstract—4,4'-Dimethoxyselenobenzophenone combines as a diene with methyl propiolate, ethyl propiolate, and phenylacetylene furnishing 1*H*-2-benzoselenopyrans; the primary [4+2] cycloaddition is followed by 1,3-proton shift. The reaction proceeds regioselectively. On the other hand, a nonaromatic ketone was obtained by using propiolic acid as a substrate.

The reaction of selenocarbonyl compounds is of current interest.[1] We have succeeded the isolation of selenobenzophenones by the reaction of phosphorus ylides with elemental selenium.[2] The complete determination of the structure of 4,4'-dimethoxyselenobenzophenone (**1**) was carried out by X-Ray diffraction analysis.[3] Recently, Rapp and Huisgen reported the regioselective Diels-Alder reaction of thiobenzophenones with methyl propiolate and related compounds.[4] We have also reported the reaction of selenobenzophenones with dimethyl acetylenedicarboxylate (DMAD), which afforded normal [4+2] cycloadducts and unusual cycloadducts of dihydro-3-benzoselenepins (Scheme 1).[5] However, there is no report on the investigation concerning the regioselectivity of selenobenzophenones toward alkenes for cycloaddition.



R=H, Cl R=Me, MeO,

Scheme 1. Cycloadducts of Thio- and Selenobenzophenones with Propiolate or DMAD.

The reaction of **1** with other olefins such as tetracyanoethylene afforded a novel type of cycloadducts.[6] Recently, the stereoselectivity of selones with dienes was extensively investigated by many researchers.[1,7,8] These results prompted us to investigate the regiochemistry of another type of [4+2] cycloaddition of **1** with acetylenes. We report herein the regioselective reaction of **1** with acetylene (**2**).

The reaction of **1** with methyl propiolate (**2a**) proceeded regioselectively through [4+2] type cycloaddition reaction. The analytical data indicated the formation of a single cycloadduct, suggesting that a highly regioselective reaction proceeded. The structure of the cycloadduct was determined by ^{1}H and ^{13}C NMR spectra along with its MS spectrum. The regiochemistry of the cycloaddition of thiobenzophenone to propiolates is not as unequivocal for the concerted pathway as it would be for the formation of a zwitterion or a biradical intermediate. Rapp and Huisgen carefully studied the regiochemistry of the cycloaddition by checking the ^{13}C NMR spectra of the 1*H*-benzothiopyran formed.[4] On the other hand, determination of regiochemistry of cycloadducts of **1** with propiolates is easier than that of thiobenzophenones. As shown in Figure 1, ^{77}Se satellite was clearly observed in its proton and carbon NMR spectra, which indicated that vinylic proton was located on the carbon adjacent to selenium. Thus, the structure of **3a** was determined as shown in Scheme 2.

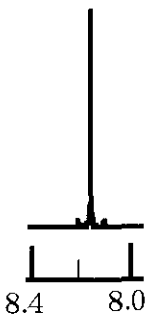
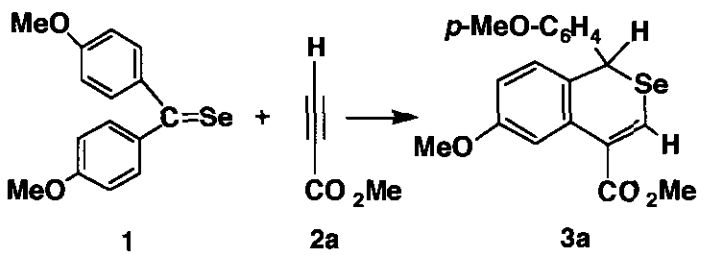
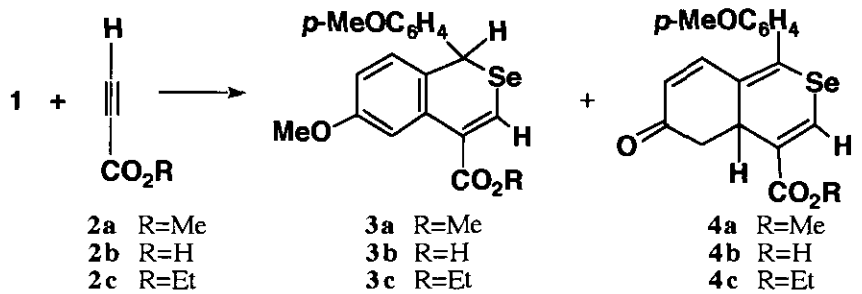


Figure 1. Vinylic proton of **3a**



Scheme 2. Regioselective cycloaddition of **1** with **2a**.

Interestingly, the reaction of **1** with propiolic acid gave 4a,5-dihydro-1-(*p*-methoxyphenyl)-6-oxo-2-selenanaphthalene-4-carboxylic acid (**4b**) in 62 % yield as a major product. When the cycloaddition of **1** with **4a** was carried out in refluxing toluene for 16 h, a related compound **4a** was obtained in 16%. (Scheme 3). Table 1 summarizes the experimental results.



Scheme 3. Reaction of **1** with **2**.

In 1971, Ohno *et al.* described the photocycloadditions of thiobenzophenone to acetylene, which furnishes 1*H*-2-benzothiopyran derivatives.[9] The authors assumed that addition of the π,π^* triplet state of thiobenzophenone to the acetylenic bond proceeded and was followed by intramolecular hydrogen migration. In 1980, Gotthardt and Nieberl discovered the cycloaddition of thiobenzophenone to DMAD proceeds in the dark at room temperature giving rise to 92% yield of 1*H*-2-benzothiopyran derivative.[10]

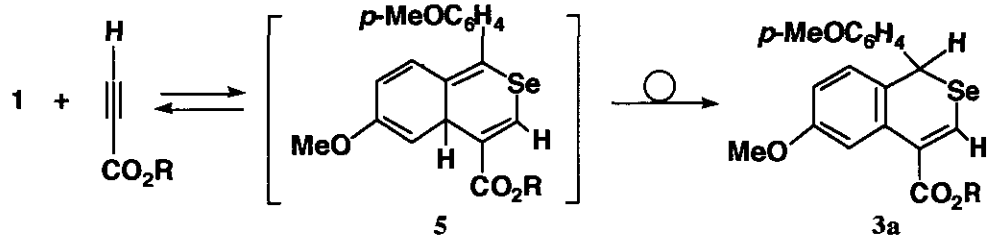
Recently, Erker and coworkers reported the cycloaddition of selenobenzophenones with *cis*- and *trans*-hexadienes.[8] They have shown that the reaction proceeds stereoselectively via a [4+2] process,

Table 1. Reaction of **1a** with **2**.

1	2[a]	Conditions Temp./°C	Solvent	Time	Products (Yield/%) 3	4
1	**2a**	50	Toluene	3	**3a**: 81	**4a**: 0
1	**2a**	reflux	Toluene	16	**3a**: 55	**4a**: 16
1	**2b**	50	Benzene	4	**3b**: 15	**4b**: 62
1	**2c**	reflux	Benzene	1	**3c**: 80	**4c**: 0

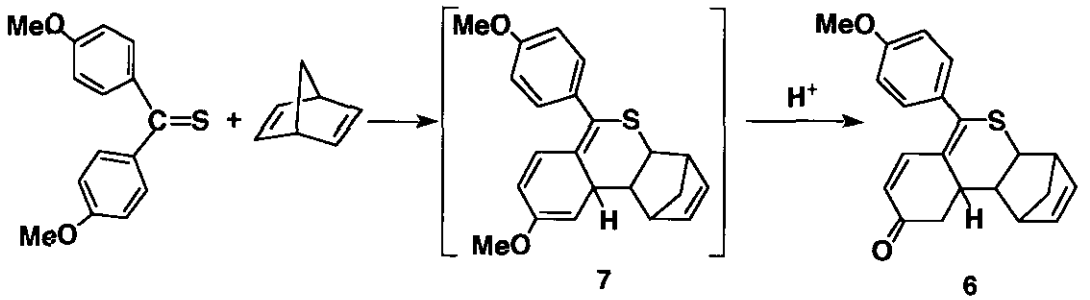
a) Three mol eq of propiolates were used in all cases.

whereas a biradical process was observed at a pressure of 12 k bar. Since only one regioisomer is obtained in all cases and the reaction completed within 3 h, the present reaction would proceed through [4+2] cycloaddition mechanism (Scheme 4). Huisgen and Rapp also suggested a similar mechanism in the reaction of thiobenzophenones with propiolates.[4]



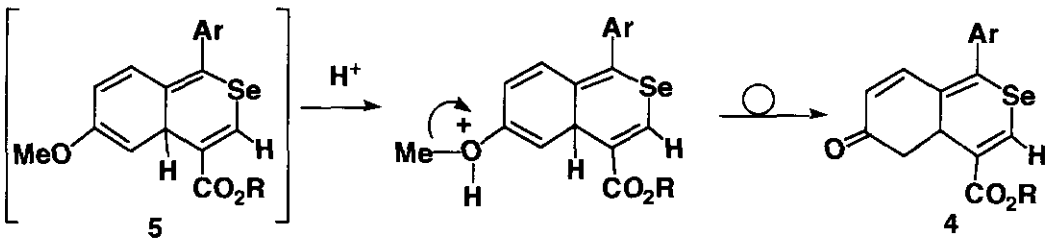
Scheme 4.

The nonaromatic [4+2] cycloadduct (**5**) was not observed in the reaction mixture by ^{1}H NMR analysis. How do we account for the formation of ketones (**4**)? Acid might play an important role in the formation of **4**. When cycloadducts (**5**) were treated with propiolic acid, the oxonium intermediates were further demethylated to give the corresponding hydroxides which tautomerized to afford the final products, ketones (**4**). To confirm this reaction mechanism, the reaction of **3b** with excess amount of propiolic acid (10 eq) was carried out in refluxing toluene. After refluxing for 20 h, compound **3b** was recovered quantitatively. Thus, the rearranged products (**3**) do not tautomerize to give the keto compounds (**4**). Recently, we have reported the reaction of 4,4'-dimethoxythiobenzophenones with 2,5-norbornadiene.[11] The obtained product was 4-(*p*-methoxyphenyl)-3-thiatetracyclo[10.2.1.$0^{2.11}$.$0^{5.10}$]pentadeca-4,6,13-trien-8-one (**6**). The reaction might proceed through the cycloaddition product containing exomethylenecyclohexadiene structure (**7**), which was further demethylated to afford **6** (Scheme 5).



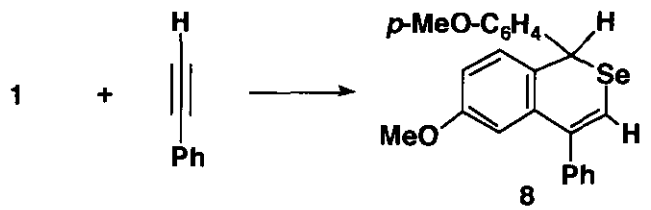
Scheme 5. Reaction of 4,4'-Dimethoxythiobenzophenone with 2,5-Norbornadiene.

These two results are unequivocal evidence for the formation of **4** from nonaromatized cycloadducts (**5**) (Scheme 6).



Scheme 6.

We then tried the reaction of **1** with other acetylenes. Diphenylacetylene did not react with **1** due to its low reactivity, whereas the reaction of **1** with phenylacetylene afforded the corresponding [4+2] cycloadduct (**8**) (26%) with the same regiochemistry as **3**.



Scheme 7. Reaction of **1** with Phenylacetylene.

In summary, we have succeeded the regioselective reaction of **1** with propiolates; 4,4'-dimethoxyselenobenzophenone reacted with propiolates to give the corresponding [4+2] cycloadducts with carboxy groups at 4-position. Other regioisomers could not be obtained.

ACKNOWLEDGMENT

This work was partly supported by Grants-in-Aid for Scientific Research (06640706 and 07804046) from the Ministry of Education, Science, Culture, and Sports of Japan.

EXPERIMENTAL

Material: 4,4'-Dimethoxyselenobenzophenone was obtained by the reaction of 4,4'-diphenylmethylene-triphenylphosphorane with elemental selenium.[3]

Reaction of 1 with Methyl Propiolate (2a)

To a solution of **1** (0.094 g, 0.308 mmol) in toluene (10 mL) was added methyl propiolate (0.084 mL, 1.0 mmol) in one portion. After being stirred for 3 h at 50 °C, the reaction mixture was concentrated to afford a pale brown oil, which was chromatographed over silica gel by elution of hexane-ethyl acetate

(4:1). Colorless crystals of **3a** was obtained in 81 % yield (0.13 g, 0.25 mmol). **3a**: mp 126-128 °C (MeOH). ^{1}H NMR ($CDCl_3$) δ=3.73 (s, 3 H, OMe), 3.81 (s, 3 H, OMe), 3.83 (s, 3 H, OMe), 5.20 (s, 1 H, CH with Se-H satellite, J_{Se-H}=23.4 Hz), 6.78 (d, 2 H, *J*=8.8 Hz, Ar), 6.83 (dd, 1 H, *J*=2.8 and 8.0 Hz Ar), 6.94 (d, 1 H, *J*=8.0 Hz, Ar), 7.08 (d, 2 H, *J*=8.8 Hz, Ar), 7.41 (s, 1 H, Ar), 8.16 (s, 1 H, with Se-H satellite J_{Se-H}=41.1 Hz). ^{13}C NMR ($CDCl_3$) δ=41.54 (CH), 51.98 (OMe), 55.13 (OMe), 55.27 (OMe), 113.50, 113.76, 114.36, 125.23, 127.73, 129.27, 129.85, 132.52, 133.14, 134.53 (CH), 158.64, 158.75, 164.87 (COO). ^{77}Se NMR ($CDCl_3$) δ=375.20. Anal. Calcd for $C_{19}H_{18}O_4Se$: C, 58.62. H, 4.66. Found: C, 58.94; H, 4.58.

When the reaction was carried out in refluxing toluene for 16 h, ketone (**4a**) was obtained in 16 % along with **3a** (55 %). **4a**: orange oil. ^{1}H NMR ($CDCl_3$) δ=2.73 (dd, 1 H, *J*=12.4 and 16.0 Hz CH_2), 3.00 (dd, 1 H, *J*=4.4 and 16.0 Hz, CH_2), 3.78 (s, 3 H, COOMe), 3.84 (s, 3 H, OMe), 4.05 (dd, 1 H, *J*=4.4 and 12.4 Hz, CH), 5.90 (d, 1 H, *J*=10.0 Hz, CH=), 6.92 (d, 2 H, *J*=8.4 Hz, Ar), 7.11 (d, 1 H, *J*=10.0 Hz, CH=), 7.25 (d, 2 H, *J*=8.4 Hz, Ar), 7.87 (s, 1 H, SeCH=, with Se-H satellite, J_{Se-H}=50.8 Hz). ^{13}C NMR ($CDCl_3$) δ=38.47 (CH), 43.22 (CH_2), 52.27 (COOMe), 55.35 (OMe), 114.16 (ArH), 125.30 (olefinic), 126.52, 1237.62, 128.90, 130.22 (ArH). 130.88 (SeCH=), 133.25, 143.70 (olefinic), 160.36 (COO), 164.27, 196.77 (CO). HRMS. Found: m/z 376.0173. Calcd for $C_{18}H_{16}O_4{}^{80}Se$ (M^+): 376.0213.

Reaction of 1 with propiolic acid (2b)

To a solution of **1** (0.086 g, 0.28 mmol) in benzene (10 mL) was added **2b** (0.062 mL, 1.0 mmol) in one portion. After being stirred for 4 h at 50 °C, the reaction mixture was concentrated to afford pale brown crystals, which was chromatographed over silica gel by elution of hexane-ethyl acetate (4:1). Colorless crystals of **3b** was obtained in 15 % yield (0.014 g, 0.042 mmol). **3b**: mp 129-130 °C (MeOH). ^{1}H NMR ($CDCl_3$) δ=3.77 (s, 3 H, OMe), 3.84 (s, 3H, OMe), 5.27 (s, 1 H, CH with Se-H satellite J_{Se-H}=22.7 Hz), 6.82 (d, 2 H, *J*=8.8 Hz, Ar), 6.87 (dd, 1 H, *J*=2.4 and 8.4 Hz, Ar), 6.99 (d, 1 H, *J*=8.4 Hz, Ar), 7.11 (d, 2 H, *J*=8.8 Hz Ar), 7.51 (d, 1 H, *J*=2.4 Hz, Ar), 8.45 (s, 1 H, =CH with Se-C satellite, J_{Se-H}=41.2 Hz). ^{13}C NMR ($CDCl_3$) δ= 42.34 (CH with Se-C satellite), 55.59 (OMe), 55.73 (OMe), 114.11, 114.23, 114.80, 125.66, 128.17, 129.18, 129.69, 132.71, 133.18, 138.72, (=CH with Se-C satellite), 159.10, 159.24 (Ar), 169.24 (C=O). Anal. Calcd for $C_{18}H_{16}O_4Se$: C, 57.61; H, 4.30. Found: C, 57.79; H, 4.60.

4b was obtained in 62 % yield. **4b**: colorless crystals. mp 223-224 °C (MeOH). ^{1}H NMR ($CDCl_3$) δ=2.75 (dd, 1 H, *J*=13.2 and 16.4 Hz, CHH), 3.12 (dd, 1 H, *J*=3.6 and 16.4 Hz, CHH), 3.85 (s, 3 H, OMe), 4.10 (dd, 1 H, *J*=3.6 and 13.2 Hz, CH), 5.93 (d, 1 H, *J*=9.6 Hz, =CH), 6.93 (d, 2 H, *J*=8.6 Hz, Ar), 7.13 (d, 1H, *J*=9.6 Hz, =CH), 7.26 (d, 2 H, *J*=8.6 Hz, Ar), 8.05 (s, 1 H, =CH with Se-H satellite, J_{Se-H}=50.1 Hz). ^{13}C NMR ($CDCl_3$) δ= 38.01 (CH), 43.30 (CH_2), 55.40 (OMe), 114.25 (ArH), 125.60, 126.49, 127.80, 130.18, 133.73, 144.04, 160.43 (COO), 167.60, 197.10. Anal. Calcd for $C_{17}H_{14}O_4Se$: C, 56.52; H, 3.91. Found: C, 56.76; H, 4.31.

Reaction of 1 with Ethyl Propiolate (2c)

To a solution of **1** (0.078 g, 0.26 mmol) in benzene (10 mL) was added **2c** (0.05 mL, 0.6 mmol) in one portion. After being stirred for 5 h at 50 °C, the reaction mixture was concentrated to afford pale brown

crystals, which were chromatographed over silica gel by elution of hexane-ethyl acetate (4:1). Colorless crystals of **3c** was obtained in 80 % yield (0.084 g, 0.21 mmol). **3c**: mp 157-158 °C (MeOH). ^{1}H NMR ($CDCl_3$) δ=1.35 (t, 3 H, J=7.2 Hz, Et), 3.75 (s, 3 H, OMe), 3.86 (s, 3H, OMe), 4.31 (m, 2H, Et), 5.21 ((s, 1 H, with Se-H satellite J_{Se-H}=22.0 Hz, CH), 6.79 (d, 2 H, *J*=8.8 Hz, Ar), 6.83 (dd, 1 H, *J*=2.4 and 8.0 Hz, Ar), 6.94 (d, 1 H, *J*=8.0 Hz, Ar), 7.09 (d, 2 H, *J*=8.8 Hz, Ar), 7.40 (d, 1 H, *J*=8.0 Hz, Ar), 8.16 (s, 1 H, =CH with Se-H satellite J_{Se-H}=41.1 Hz). ^{13}C NMR ($CDCl_3$) δ=14.25 (Et), 41.59 (CH with Se-C satellite), 55.16 (OMe), 55.27 (OMe), 60.89 (CH_2), 113.43, 113.78, 114.45, 125.30, 127.69, 129.32, 130.22, 132.54, 133.25, 134.13 (=CH with Se-C satellite), 158.64, 158.78, 164.49 (C=O). Anal. Calcd for $C_{20}H_{20}O_4Se$: C, 59.26; H, 5.00. Found: C, 59.60; H, 5.12.

Reaction of 1 with Phenylacetylene

To a solution of **1** (0.049 g, 0.16 mmol) in benzene (10 mL) was added phenylacetylene (0.066 mL, 0.6 mmol) in one portion. After refluxing for 12 h, the reaction mixture was concentrated to afford a pale brown oil, which was chromatographed over silica gel by elution of hexane-dichloromethane (5:1). The adduct **8** was obtained in 26 % yield (0.017 g, 42 %). **8**: orange oil. ^{1}H NMR ($CDCl_3$) δ=3.68 (s, 3 H, OMe), 3.78 (s, 3 H, OMe), 5.25 (s, 1 H, =CH with Se-H satellite, J_{Se-H} =24.1 Hz), 6.70 (d, 1 H, Ar), 6.81 (m, 3 H, Ar), 7.04 (d, 1 H, Ar), 7.20 (d, 2 H, Ar), 7.26-7.55 (m, 6 H, Ar). HRMS. Found: m/z: 408.0634 . Calcd for $C_{23}H_{20}O_2{}^{80}Se$ (M^+): 408.0628.

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Received, 14th August, 1998