REACTION OF THIOBENZOPHENONES WITH NORBORNADIENE: UNUSUAL FORMATION OF A SEVEN–MEMBERED CYCLIC SULFIDE

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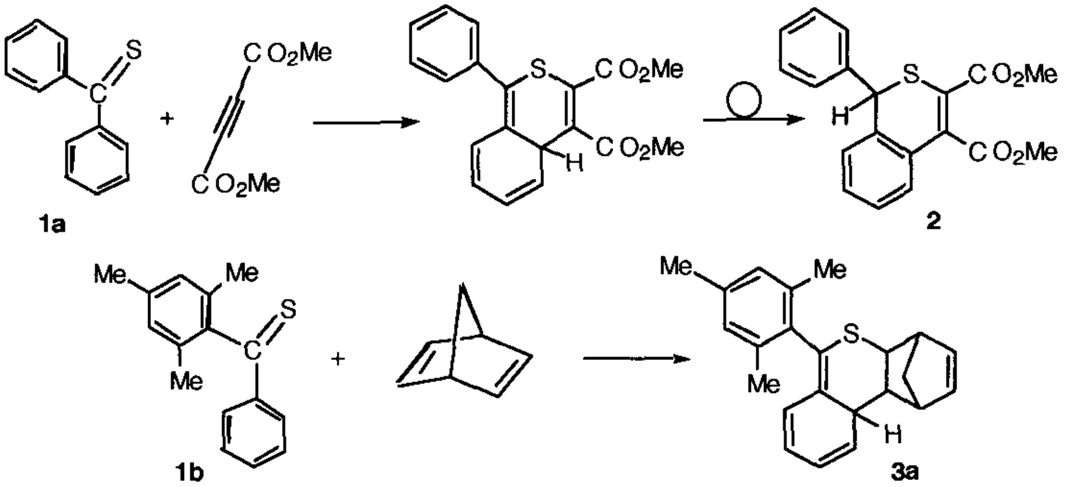
Abstract—Reaction of thiobenzophenone with 2,5-norbornadiene afforded an unusual seven-membered cyclic sulfide whereas 4,4'-dimethoxythiobenzophenone reacted with 2,5-norbornadiene to afford the corresponding quinone derivative *via* [4+2] type cycloaddition reaction. The mechanisms of these reactions are discussed.

Exocyclic methylenecyclohexadiene is a tautmeric form of toluene. Hasselman reported the isolation of exomethylenecylohexadiene (5-methylene-1,3-cyclohexadiene) by thermolysis of 5-methylenebicyclo-[2.2.0]hex-2-ene, which is easily converted into toluene.[1] Phenol-cyclohexadienone tautomerism generally lies well to the side of the phenol, since only on that side is there aromaticity.[2] Thiobenzophenone (**1a**) reacts with acetylenic compounds to afford the corresponding benzothiopyrane derivatives. For example, reaction of **1a** with dimethyl acetylenedicarboxylate (DMAD) at room temperature leads to a dimethyl 1*H*-benzothiopyrandicarboxylate (**2**) in 92% yield.[3] This is another example of toluene-exo–methylenecyclohexadiene tautomerism. Ohmura and Motoki found that the reaction of 2,4,6-trimethylthiobenzophenone (**1b**) with 2,5-norbornadiene afforded the corresponding Diels-Alder adduct (**3a**), which contains an exo–methylenecyclohexadiene structure.[4] While tautomerization (1,3-H shift) did not occur in this reaction, they did not discuss this unusual structure (Scheme 1).

In the course of investigating the reactivity of thiobenzophenones,[5] we became interested in a novel family of exo-methylenecyclohexadiene derivatives, because of their anomalous structure. We report herein the isolation of stable six-membered exo–methylene cyclic diene and an unusual seven-membered cyclic sulfide by the reaction of thiobenzophenones with 2,5-norbornadiene.

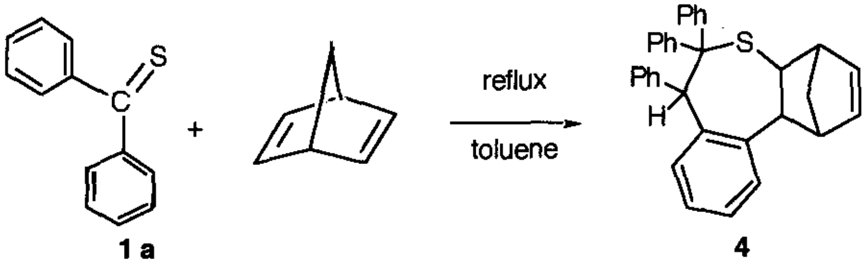
RESULTS AND DISCUSSION

We first tried the reaction of thiobenzophenone (**1a**) with 2,5-norbornadiene. Thiobenzophenone was prepared *in situ* by the reaction of diphenylmethylenetriphenylphosphorane with elemental sulfur (Staudinger chalcogenation).[6] A toluene solution of thiobenzophenone and 2,5-norbornadiene was heated



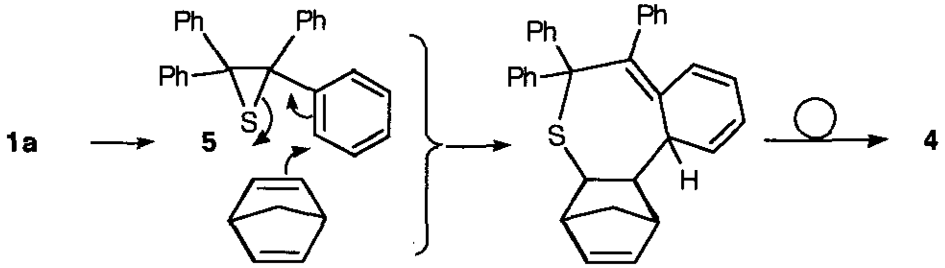
Scheme 1

under refluxing for 14 h to afford colorless crystals (mp 186-187°C) after chromatographic separation. Elemental analysis indicated the formula $C_{33}H_{28}S$, which was found to be 3-thia-4,4,5-triphenyl-6,7-benzotricyclo[7.2.1.$0^{2.8}$]-10-dodecene (**4**) in 21 % yield (Scheme 2). The structure was confirmed by its NMR spectrum. The ^{1}H NMR spectrum of **4** displayed signals at δ 1.27 and 1.87 (d, J=8.8 Hz, 2H) of bridge methylene protons, at δ 1.46, 2.60, 2.68, and 3.07 for four aliphatic methine protons, at δ 5.06 (s, 1H) of benzylic methine proton, at δ 5.95 and 6.22 (2H) of olefin protons, and 19 aromatic protons. The ^{13}C NMR spectrum of **4** showed seven aliphatic carbons and 20 olefinic and aromatic carbons.



Scheme 2

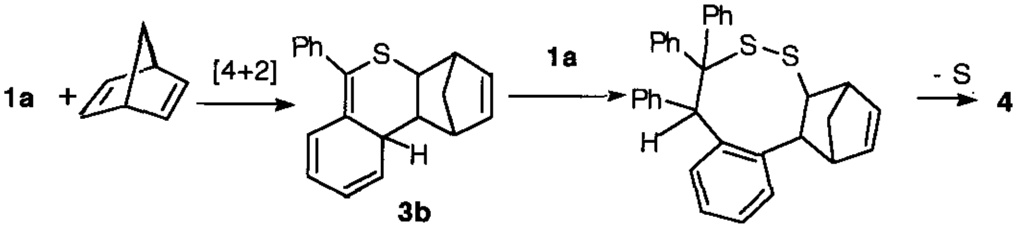
The formation of **4** may be reasonably explained by two mechanisms. We first thought that the reaction might proceed through tetraphenylethylene sulfide (**5**). The reaction of thiobenzophenone with phosphonium ylide (or thiobenzophenone itself) gave **5**, as stated by Vedejs *et al.*[7] This thiirane (**5**) further reacted with 2,5-norbornadiene to give **4** (Mechanism 1).



Mechanism 1

To confirm this possibility, the reaction of 2,5-norbornadiene with **5** was carried out. Thiirane (**5**) was prepared by the reaction of tetraphenylethylene oxide with triphenylphosphine sulfide.[8] Treatment of **5** with 2,5-norbornadiene was carried out under several conditions. However, the obtained products were tetraphenylethylene and the recovered 2,5-norbornadiene. Thus, the reaction does not proceed through a thiirane intermediate.

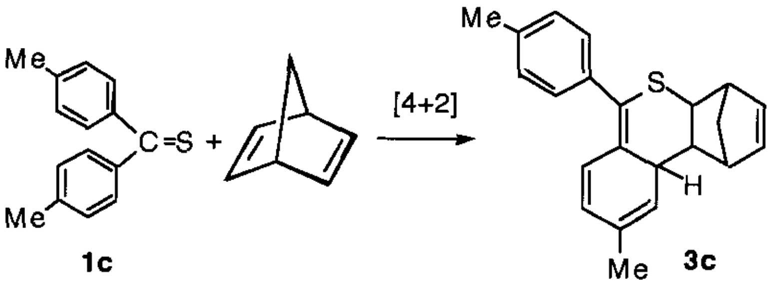
Another mechanism to explain the formation of **4** is as follows. If thermal ring-opening reaction of **3b** occurs in the present process, additional thiobenzophenone (or diphenylcarbene) would react with **3b** to give the eight-membered disulfide, which further desulfurized to afford the final product (**4**) (Mechanism 2).



Mechanism 2

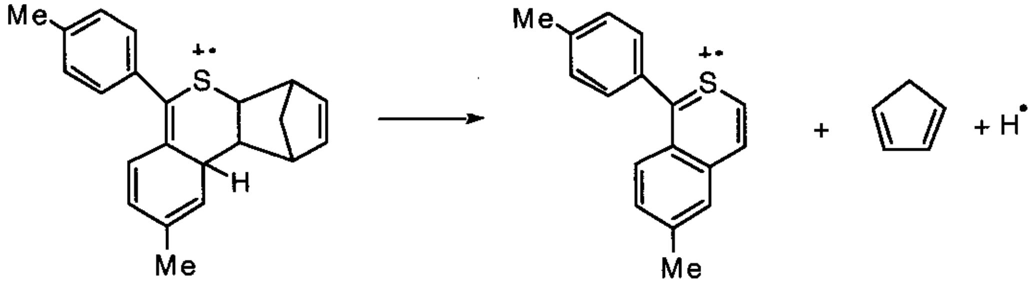
To confirm this mechanism, we then tried to isolate the six-membered cycloadduct (**3b**). Chromatographic separation of the reaction mixture resulted in a complex mixture of polymeric products. While isolation of [4+2] adduct (**3b**) is very difficult due to its unstability, a small amount of the product (**3b**) was finally isolated by gel-HPLC separation. Since the desired **3b** was in hand, the reaction with thiobenzophenone was carried out. Treatment of this adduct with thiobenzophenone in refluxing toluene gave a trace amount of **4**. At this temperature, the reaction might proceed very slowly. When the reaction was carried out in refluxing xylene, adduct (**4**) was obtained in 15% yield. At present, we believe that the reaction proceeded through the stepwise pathway (Mechanism 2).

The reaction of substituted benzophenones with norbornadiene was then tried. Treatment of 4,4'-dimethylthiobenzophenone (**1c**) with 2,5-norbornadiene in refluxing toluene afforded the corresponding normal cycloadduct (8-methyl-4-p-tolyl-3-thiatetracyclo-$[10.2.1.0^{2.11}.0^{5.10}]$pentadeca-4, 6, 8, 13-tetraene, **3c**) in 68% yield (Scheme 3). Interestingly, this adduct has an exo–methylenecyclohexadiene structure. In contrast to **3b**, this adduct **3c** is stable and isolation was accomplished by using silica gel chromatography.



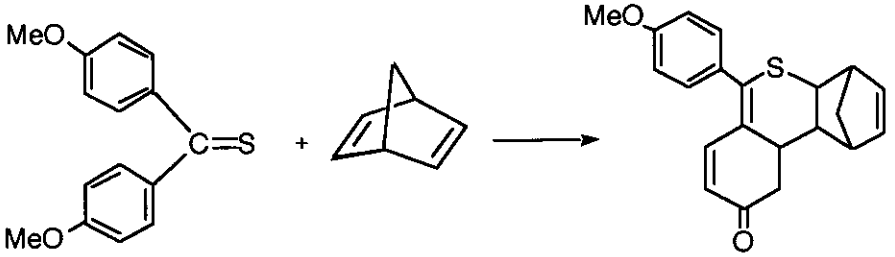
Scheme 3

Mass spectrum of this adduct exhibited a base peak at M^+–66, which is due to fragmentation of the molecular ion via a retro Diels-Alder manner as shown in Scheme 4.



Scheme 4

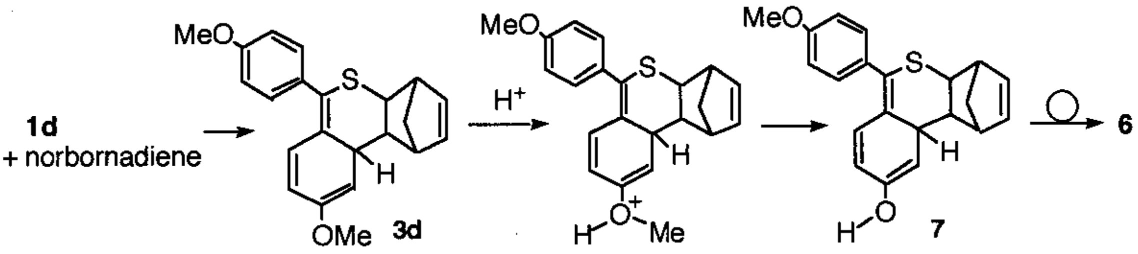
Since the reactivity of the two above reactions is quite different, we then tried the reaction of other substituted thiobenzophenones. A refluxing toluene solution of 4,4'-dimethoxythiobenzophenone (**1d**) and 2,5-norbornadiene afforded a stable colorless oil after chromatographic separation, in 56% yield. Elemental analysis and mass spectroscopy indicated the formula $C_{21}H_{20}O_2S$. The peak at 199 ppm in the ^{13}C NMR spectrum suggested the existence of a carbonyl carbon. Thus, the structure was found to be 4-(*p*-methoxyphenyl)-3-thiatetracyclo[10.2.1.$0^{2.11}$.$0^{5.10}$]pentadeca-4,6,13-trien-8-one (**6**) as shown in Scheme 5.



1d **6**

Scheme 5

Compound (**6**) would form as follows: Thione (**1d**) reacted with 2,5-norbornadiene to give the corresponding cycloadduct (**3d**), which might be sensitive to a small amount of acid in silica gel. In the work-up process, the acid attacks the methoxy oxygen of the adduct to give the corresponding hydroxide (**7**). Finally, the hydroxide (**7**) turned into a keto form to give the product (**6**) (Scheme 6).

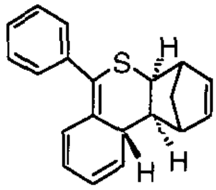
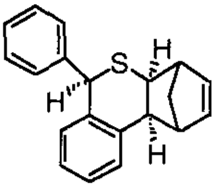
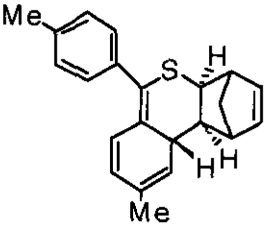
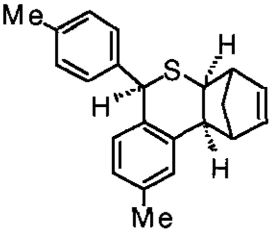


Scheme 6

The reaction of Michler's thioketone {4,4'-bis(dimethylamino)thiobenzophenone (**1e**)} with 2,5-norbornadiene was then tried. After refluxing for 3 days in toluene, this thione still remained in the reaction mixture. After usual work-up, **1e** was recovered in 86% yield. Thus, the reactivity of **1e** is quite different from those of other thiobenzophenones.

The first mechanistic question is why exo–methylene cyclohexadiene structures, **3b** and **3c** have been obtained. To clarify this point, the heats of formation of these compounds were calculated (Table 1). The energy difference between **3b** and **8b** (17 kcal/mol) is bigger than that between **3c** and **8c** (9 kcal/mol). Structure (**8b**) is found to be more stable than compound (**3b**).

Table 1. Heats of Formation of Compounds (**3b**, **8b**, **3c**, and **8c**).*

	 **3b**	 **8b**	 **3c**	 **8c**
kcal/mol	116	99	94	85

* Calculation was carried out by PM3.

Since **8b** and **8c** have aromatic structures, resonance energies of these compounds would be higher than those of **3b** and **3c**. The stability of the obtained compounds (**3b**) and (**3c**) might be due to the rigidity of norbornyl group. The PM3 optimized geometry of **3c** is shown in Figure 1. The rigid structure of the norbornyl group might prevent the conversion of **3c** into **8c** (1,3-H shift). Table 1 explains the energy difference between **3b** and **3c**, which suggests that compound (**3b**) is unstable compared to **3c**. Actually, **3c** is obtained in better yield than **3b**.

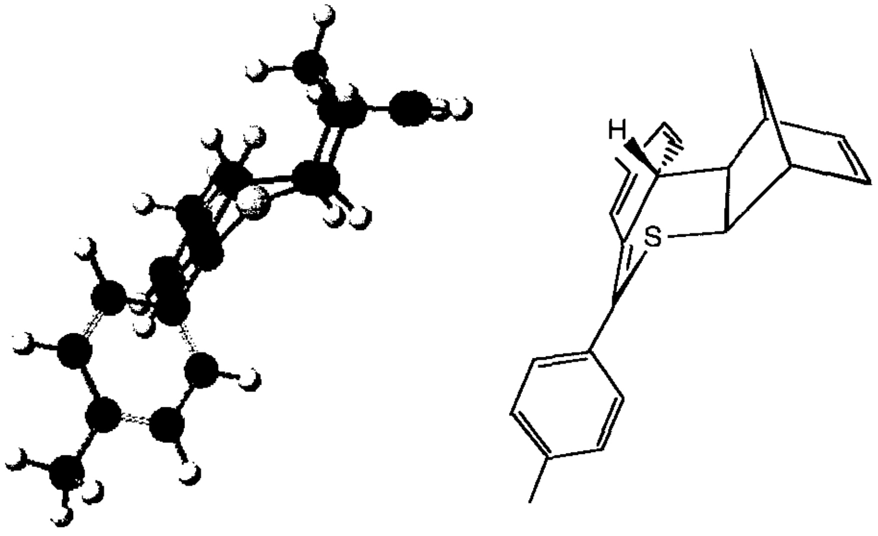


Figure 1. The optimized geometry of **3c**.

The second mechanistic question is why the difference in the reactivity of these thiones has occurred. An electron donating group, such as a dimethylamino, a methoxy, or a methyl group, elongates bond strength of the carbon-sulfur double bond. Substituted thiobenzophenones (**1b-e**) might be more stable than unsubstituted thiobenzophenone (**1a**). Thus, 2,5-norbornadiene reacts with thiobenzophenone more easily than thiobenzophenones containing electron-donating groups. This adduct **3b** further reacted with additional thiobenzophenone to afford **4**. It has been also found that 4,4'-bis(dimethylamino)-thiobenzophenone (**1e**) is too stable to react with 2,5-norbornadiene.

In summary, we have obtained the cycloadducts by the reaction of thiobenzophenones with 2,5-norbornadiene. When unsubstituted thiobenzophenone was used as a substrate, additional thiobenzophenone was further reacted with this adduct, which finally produced the seven-membered cycloadduct. Normal [4+2] cycloadduct was obtained by the use of 4,4'-dimethylthiobenzophenone as a substrate, which has an unusual exo–methylenecyclohexadiene structure. When 4,4-dimethoxythiobenzophenone was used as a substrate, demethylation of this adducts gave the corresponding quinone derivative (**6**).

EXPERIMENTAL

General Method: Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained with a JEOL GSX-400 spectrometer. Chemical shifts are given in ppm units downfield from tetramethylsilane. TLC analyses were performed using Merck Silica gel 60 F254 aluminum plates. MO calculation and geometry optimization were carried out with the PM3 method implemented in the MOPAC program package.

Material: Thiobenzophenone was prepared by Staudinger chalcogenation.[6] 4,4'-Dimethyl- and 4,4'-dimethoxythiobenzophenone were prepared by the reaction of the corresponding benzophenone with tetra–phosphorus decasulfide.[9] 4,4-Bis(dimethylamino)thiobenzophenone was purchased from Tokyo Kasei Co. Tetraphenylethylene was purchased from Aldrich.

Reaction of Thiobenzophenone with 2,5-Norbornadiene

To a solution of diphenylmethylenetriphenylphosphorane (2.14 g, 5 mmol) in toluene (40 mL) was added elemental sulfur (1.48 g, 15 mmol) in one portion. After refluxing for 1 h, the solution was turned to deep purple. 2,5-Norbornadiene (1.84 g, 20 mmol) was added to this deep purple solution. After refluxing for 14 h, the reaction mixture was evaporated to give a brown oil, which was chromatographed over silica gel by elution with hexane-dichloromethane (4:1) to give colorless crystals of **4** (0.479 g, 21%). mp 186-187 °C. ^{1}H NMR (CDCl$_3$) δ=1.27 (br d, 1H, J=8.8 Hz, C$\underline{H}$H), 1.46 (dd, 1H, J=14.8 and 7.2 Hz, norbornyl CH), 1.87 (br d, 1H, J=8.8 Hz, CH$\underline{H}$), 2.60 (br d, 1H, J=14 Hz, SCH), 2.68 (br s, 1H, CH), 3.07 (br s, 1H, CH), 5.06 (s, 1H, PhCH), 5.97 (dd, 1H, J=3.6 and 6.4 Hz, =CH), 6.23 (dd, 1H, J=2.8 and 6.4 Hz, =CH), 6.80 (br d, 2H, J=7.2 Hz, Ar), 6.80-7.30 (m, 13H, Ar), 7.55 (br d, 2H, Ar), 7.64 (br d, 2H). ^{13}C NMR (CDCl$_3$) δ=39.7, 39.8, 44.0, 49.7, 52.1, 58.4, 61.3. 124.6, 125.5, 125.9, 126.1, 127.0, 127.2, 127.3, 127.5, 127.6, 130.2, 130.4, 131.3, 132.1, 135.1, 138.3, 139.9, 141.9, 142.8, 143.2, 145.8. Anal. Calcd for $C_{33}H_{28}S$, C, 86.80; H, 6.18. Found: C, 86.51; H, 6.47.

Isolation of **3b** was carried out as follows. To a solution of isolated thiobenzophenone (0.99 g, 5 mmol) in toluene (30 mL) was added 2,5-norbornadiene (0.92 g, 10 mmol) in one portion. After refluxing for 8 h, the reaction mixture was evaporated to afford a pale brown oil, which was roughly chromatographed over silica gel by elution with hexane:dichloromethane (1:1) to give a pale yellow oil. The resulting mixture was separated by gel-HPLC by elution from chloroform to give a colorless oil of **3b** (0.087 g, 6 %). ^{1}H NMR (CDCl$_3$) δ=1.54 (d, 1H, J=8.4 Hz, CH$\underline{H}$), 1.78 (br d, 1H, J=8.4 Hz, CH), 2.40 (dt, 1H, J=3.2 and 8.8 Hz, C$\underline{H}$H), 2.80 (br m, 1H, CH), 2.90 (br s, 1H, CH), 3.15 (br s, 1H, CH), 3.22 (dd, 1H, *J*=3.2 and 8,8 Hz), 5.80 (dd, 1H, =CH), 6.05-6.40 (m, 4H, =CH), 6.45 (d, 1H, 9 Hz, =CH), 7.15-7.48 (m, 5H, Ph). HRMS: Found; 290.1125. Calcd for $C_{20}H_{18}S$; 290.1128.

Preparation of Tetraphenylethylene Sulfide

To a solution of tetraphenylethylene oxide (0.70 g, 2.0 mmol) and triphenylphosphine sulfide (0.59 g, 2 mmol) in benzene (20 mL) was added trifluoroacetic acid (0.16 mL, 2 mmol) in one portion. The reaction mixture was stirred for 24 h at 60 °C. The reaction mixture was washed with 10 % aq. sodium carbonate (5 mL x 3) and water (5 mL x 3), and dried over $MgSO_4$. The filtered solution was evaporated to give a pale orange oil, which was chromatographed over silica gel by elution with hexane:dichloromethane (4:1) to afford colorless needles of tetraphenylethylene sulfide (0.55 g, 75%). mp 174-176°C (lit.,[10] mp 178°C).

Reaction of Tetraphenylethylene Sulfide with 2,5-Norbornadiene

To a solution of tetraphenylethylene sulfide (0.182 g, 0.5 mmol) in toluene (15 mL) was added 2,5-norbornadiene (0.19 g, 2 mmol) in one portion. After refluxing for 20 h, the reaction mixture was evaporated to give pale yellow crystals, which was chromatographed over silica gel by elution with hexane to give tetraphenylethylene (0.12 g, 72%). mp 219-221°C This product is identical with the authentic sample (purchased from Aldrich, mp 222-224°C).

Reaction of 3b with Thiobenzophenone

To a solution of **3b** (0.058 g, 0.2 mmol) in xylene (5 mL) was added thiobenzophenone (0.060 g, 0.3 mmol) in xylene (2 mL) via syringe. After refluxing for 15 h, the resulting dark brown solution was evaporated to give a deep brown oil. This oil was chromatographed over silica gel by elution with hexane:dichloromethane (1:1) to give **4** (0.014 g, 15%).

Reaction of 4,4'-Dimethylthiobenzophenone (1c) with 2,5-Norbornadiene

To a solution of 4,4'-dimethylthiobenzophenone (0.45 g, 2 mmol) in toluene (15 mL) was added to 2,5-norbornadiene (0.92 g, 10 mmol) in one portion. After refluxing for 12 h, the reaction mixture was evaporated to give a yellow oil, which was chromatographed over silica gel by elution with hexane:dichloromethane (1:1) to afford a yellow oil of the adduct (**3c**, 0.464 g, 73 %). ^1H NMR ($CDCl_3$) δ=1.60 (d, 1H, *J*=9.2 Hz, C$\underline{H}$H), 1.81 (dd, 1H, *J*=9.6 and 7.6 Hz, CH), 1.86 (s, 3H, Me), 2.32 (s, 3H, ArMe), 2.56 (d, 1H, *J*=9.2 Hz, CH$\underline{H}$), 2.60 (d, 1H, *J*=8.0 Hz, CH), 2.88 (br s, 1H, CH), 3.04 (br d, 1H, *J*=7.6 Hz, CH), 3.17 (br s, 1H, CH), 5.68 (d, 1H, *J*=9.6 Hz, =CH), 6.00 (br d, 1H, *J*=1.0 Hz, =CH), 6.13 (dd, 1H, C$\underline{H}$=CH), 6.27 (dd, 1H, CH=C$\underline{H}$), 6.49 (br d, 1H, *J*=9.6 Hz, =CH), 7.14 (d, 2H, *J*=8.0 Hz, Ar), 7.35 (d, 2H, *J*=8.0 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ=21.3 (Tol-Me), 21.8 (Tol-Me), 42.8 (CH_2), 45.2 (CH), 45.9 (CH), 47.4 (CH), 59.8 (CH), 124.2 (=CH), 124.6 (=CH), 128.2, 128.4, 128.5, 128.6, 129.1, 130.6, 130.8, 136.3, 137.8, 139.6. HRMS: Found; 318.1148. Calcd for $C_{22}H_{22}S$; 318.1142.

Reaction of 4,4'-Dimethoxythiobenzophenone (1d) with 2,5-Norbornadiene

To a refluxing solution of 4,4'-dimethoxythiobenzophenone (0.258 g, 1.0 mmol) in toluene (10 mL) was added 2,5-norbornadiene (0.46 mL, 0.47 g, 5 mmol) in one portion. After refluxing for 12 h, the reaction mixture was evaporated to give a yellow oil, which was chromatographed over silica gel by elution with hexane:dichloromethane (1:1) to afford a yellow oil of **6** (0.175 g, 52 %). ^1H NMR ($CDCl_3$) δ=1.60 (br d, 1H *J*=9.4 Hz, CH$\underline{H}$), 1.96 (dd, 1H, J=7.2 and 10.8 Hz), 2.35 (d, 1H, *J*=9.4 Hz, CH$\underline{H}$), 2.70 (dd, 1H, *J*=3.6 and 17.2 Hz, C$\underline{H}$HC=O), 2.88 (m, 2H, CH and CH), 2.97 (br s, 2H, 2 xCH), 3.01 (dd, 1H, *J*=8.4 and 17.2 Hz, CHH̲C=O), 3.85 (s, 3H, MeO), 5.77 (d, 1H, *J*=10.4 Hz, CH̲=CHC=O), 6.11 (dd, 1H, *J*=2.8 and 6.0 Hz, CH̲=CH), 6.25 (dd, 1H, *J*=2.8 and 6.0 Hz), 6.91 (d, 2H, *J*=9.2 Hz, Ar), 7.15 (d, 1H, *J*=10.4 Hz, CH=CH̲C=O), 7.41 (d, 1H, *J*=9.2, Ar). ^{13}C NMR ($CDCl_3$) δ=40.6 (CH_2), 40.9 (CH), 43.0 (CH_2), 45.7 (CH), 47.4 (CH), 50.1 (CH), 54.6 (CH), 55.5 (MeO), 113.6, 122.1, 129.7, 131.6, 131.7, 132.8, 135.8, 139.3, 149.3, 160.6, 199.0 (C=O). HRMS: Found; 336.1184. Calcd for $C_{21}H_{20}O_2S$; 336.1184.

Reaction of 4,4'-Bis(dimethylamino)thiobenzophenone (1e) with 2,5-Norbornadiene

To a refluxing solution of 4,4'-bis(dimethylamino)thiobenzophenone (0.56 g, 2.0 mmol) in toluene (20 mL) was added 2,5-norbornadiene (0.46 mL, 0.47 g, 5 mmol) in one portion. After refluxing for 36 h, the reaction mixture was evaporated to give a dark brown oil, which was chromatographed over silica gel by elution with hexane:dichloromethane (1:1) to afford recovered 4,4'-bis(dimethylamino)thiobenzophenone (0.48 g, 86%).

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