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N-(2-ALKOXYCARBONYLBENZENESULFENYL)BENZIMIDAZOLES AS NITROGEN-, SULFUR-, AND CARBON-SULFENYLATION REAGENTS

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Abstract – *N*-(2-Alkoxycarbonylbenzenesulfenyl)benzimidazoles reacted with nucleophiles such as amides, imidates, thiols, Grignard reagents, and active methylene compounds to yield the corresponding sulfenylated products: *N*-acylsulfenamides, *N*-sulfenylimidates, disulfides, sulfides, and sulfenylated active methylene compounds, respectively.

Sulfenylation is usually carried out with sulfenyl chlorides,[1] which must sometimes be purified before use because they are unstable compounds that decompose to the corresponding disulfides.[2] Sulfenyl chlorides are prepared by reaction of thiols or disulfides with chlorine gas.[3] The use of chlorine is to be avoided, especially in laboratories, because it is a hazardous, poisonous, and corrosive gas. Therefore, alternative sulfenylation methods involving compounds with leaving groups other than chloride have been studied: amine exchange reactions of *N*-unsubstituted sulfenamides have been used to prepare substituted ones,[4] and *N*-sulfenyl heterocycles have been used as sulfenylation reagents.[2,5] However, the *N*-sulfenyl heterocycles are usually synthesized by reaction of heterocycles with sulfenyl chlorides.

In previous papers, we reported that *N*-acylsulfenamides[6] and *N*-sulfenyl-1,2-benzisothiazolin-3-ones,[7] which were prepared without using sulfenyl chlorides, react with various nucleophiles.[8,9] Although these compounds showed potential for use as sulfenylation reagents, there were some problems with reactivity and selectivity: for example, *N*-acylsulfenamides form salts with some amines,[8] and the reaction of *N*-sulfenyl-1,2-benzisothiazolin-3-ones with thiols produces ring-opened disulfide derivatives.[9] Therefore, we have been working on developing *N*-sulfenyl heterocycles as new sulfenylating reagents. We compared the reactivities of various *N*-sulfenyl heterocycles with *para*-substituted anilines and found

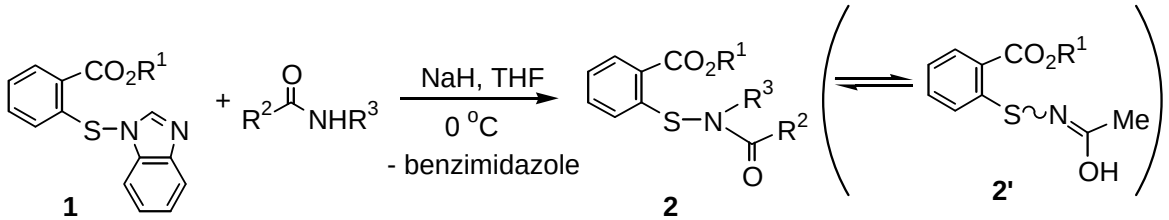
that *N*-(2-alkoxycarbonylbenzenesulfenyl)benzimidazoles are the most effective sulfenylating reagents. They react with various amines to afford the corresponding sulfenamides in good yields.[10] In this paper, we report on the reactions of *N*-sulfenylbenzimidazoles with other types of nucleophiles.

RESULTS AND DISCUSSION

(1) Reactions with nitrogen nucleophiles

In this study, we attempted to synthesize *N*-acylsulfenamides by sulfenylation with *N*-sulfenylbenzimidazoles. When *N*-(2-methoxycarbonylbenzenesulfenyl)benzimidazole (**1a**) was heated with benzamide in toluene at 100 ºC for 5 h, no substitution reaction occurred, owing to the weak nucleophilicity of the amide nitrogen; starting material was recovered. In contrast, treatment of **1a** with benzamide in the presence of sodium hydride as a base in THF for 10 min at 0 ºC afforded the substitution product, *N*-benzoylsulfenamide (**2a**), in 62% yield. The structure of **2a** was confirmed by comparison of mp and NMR spectral data with **2a** prepared by acylation of a sulfenamide.[6] Other amides were subjected to the same sulfenylation conditions, and the results are summarized in Table 1. All the sulfenylation reactions proceeded within 10–30 min. An *N*-substituted amide also underwent sulfenylation to afford *N*-sulfenylamide (**2f**) (Entry 6). As reported in previous papers,[6,11] *N*-acetylsulfenamides **2b** and **2e** exist as mixtures of two isomers, acetyl forms (**2**) and imidic acid forms (**2′**), in $CDCl_3$. The structures of the imidic acid forms were deduced by the comparison of the spectral data of **2′** with data for the corresponding *N*-sulfenylimidates (**3**), as described in a previous paper.[6] The *N*-sulfenylimidates were synthesized by sulfenylation of imidic acid ester hydrochlorides with *N*-sulfenylbenzimidazoles (**1**) in the presence of triethylamine (Table 2). *N*-Sulfenamides are usually

Table 1. The reaction of **1** with amides

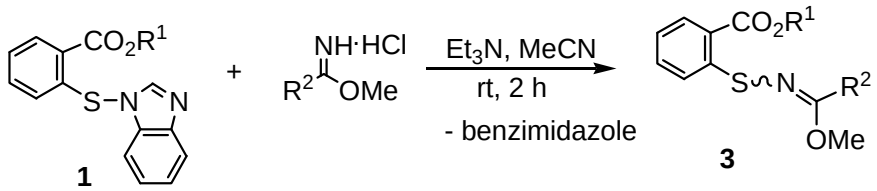


(R^2 = Me, R^3 = H)

Entry	**1**	R^1	R^2	R^3	Time (min)	Product	Yield[a] (%)
1	**1a**	Me	Ph	H	10	**2a**	62
2	**1a**	Me	Me	H	30	**2b**+**2'b**	42
3	**1b**	Et	Ph	H	10	**2c**	70
4	**1b**	Et	*p*-Tol	H	10	**2d**	90
5	**1b**	Et	Me	H	10	**2e**+**2'e**	78
6	**1b**	Et	Me	Me	10	**2f**	60

[a]Isolated product.

Table 2. The reaction of **1** with methyl imidates



Entry	**1**	R^1	R^2	Product	Yield[a] (%)
1	**1a**	Me	Me	**3a**	90
2	**1b**	Et	Me	**3b**	94
3	**1b**	Et	Ph	**3c**	86

[a]Isolated product.

prepared by sulfenylation of imidic acid esters with sulfenyl chlorides.[6]

Thus, *N*-sulfenylbenzimidazoles (**1**) acted as good sulfenylation reagents for amides and imidates to form nitrogen–sulfur bonds in good yields.

(2) Reactions with sulfur nucleophiles

Asymmetrical disulfides are sometimes difficult to prepare because equilibration between starting materials and products can afford mixtures of symmetrical disulfides.[12] The *N*-acylsulfenamide sulfenylating reagents that we developed afford unsymmetrical disulfides,[8] and *N*-sulfenyl-1,2-benzisothiazolin-3-ones react with thiols at the sulfur atom on the heterocycles to yield ring-opened products.[9]

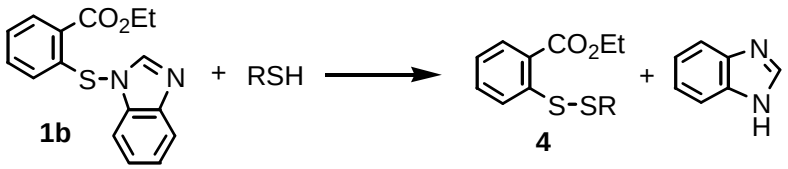
In this study, we attempted to prepare unsymmetrical disulfides by sulfenylation of thiols with *N*-sulfenylbenzimidazoles. The reactions of **1b** with various kinds of thiols were carried out, and the results are listed in Table 3. Sulfenylation of thiols with long alkyl chains with *N*-sulfenylbenzimidazole (**1b**) proceeded at room temperature, and alkyl aryl disulfides were isolated in good yields (Entries 1–4). The reaction was rapid in protic solvents such as methanol. However, the reaction of **1b** with *p*-chlorobenzenethiol in methanol afforded unsymmetrical disulfide (**4c**) in a low yield, and ethyl thiosalicylate (**5**) was isolated in 60% yield as the main product (Entry 5). It is likely that a thiol exchange reaction between the initially formed unsymmetrical disulfide and *p*-chlorobenzenethiol proceeded easily. When a mixture of disulfide (**4c**) and *p*-chlorobenzenethiol was allowed to react in methanol for 1 h at room temperature, a thiol exchange reaction occurred, and **5** was formed in 18% yield (82% of **4c** was recovered). When benzimidazole was added to the reaction system, the yield of **5** increased to 75%, and only 16% of **4c** was recovered. This result indicates that the benzimidazole formed by the initial substitution reaction accelerated the thiol exchange reaction. To minimize this undesired side reaction, we shortened the reaction time for the sulfenyl reaction and removed the formed benzimidazole from the reaction system. Thus, after confirming that starting material (**1b**) had

disappeared, we quenched the reaction mixture containing **1b** and *p*-chlorobenzenethiol with water after 30 min. Extraction of the reaction mixture with an organic solvent afforded unsymmetrical disulfide **4c** in 78% yield (Entry 6). The same reaction in dichloromethane proceeded rather slowly, and the thiol exchange reaction was not observed (Entry 7).

The reactions of *N*-sulfenylbenzimidazole (**1b**) with arenethiols proceeded more rapidly than the reactions with alkanethiols. To obtain the desired products in good yield, we quenched the reaction mixture with water and extracted the products with dichloromethane. From the reactions of **1b** with *o*-aminobenzenethiol and 2-mercaptopyridine, sulfenamide derivatives resulting from reaction at the nitrogen atoms were not obtained, and disulfides formed selectively (Entries 12 and 13).

Thus, *N*-sulfenylbenzimidazoles reacted with thiols to afford unsymmetrical disulfides in good yields. The benzimidazole that formed during the reaction sometimes accelerated disulfide exchange reactions, and therefore the benzimidazole had to be removed from the reaction system.

Table 3. The reaction of **1b** with thiols



Entry	R	Solvent	Time	Product	Yield[a] (%)
1	$CH_3(CH_2)_7$	MeOH	45 min	**4a**	80
2	$CH_3(CH_2)_7$	MeCN	3 h	**4a**	79
3	$CH_3(CH_2)_7$	CH_2Cl_2	5 h	**4a**	91
4	$CH_3(CH_2)_{11}$	MeOH	1.5 h	**4b**	84
5	*p*-$ClC_6H_4CH_2$	MeOH	30 min	**4c**	31[b]
6	*p*-$ClC_6H_4CH_2$	MeOH	30 min	**4c**	78[c]
7	*p*-$ClC_6H_4CH_2$	CH_2Cl_2	3 h	**4c**	88
8	*p*-$Bu^tC_6H_4$	MeOH	10 min	**4d**	81[c]
9	*o*-$MeOCOC_6H_4$	MeOH	10 min	**4e**	82[c]
10	Ph	MeOH	10 min	**4f**	85[c]
11	Ph	CH_2Cl_2	60 min	**4f**	91[c]
12	*o*-$NH_2C_6H_4$	CH_2Cl_2	30 min	**4g**	83
13	2-Pyridyl	CH_2Cl_2	10 min	**4h**	89

[a] Isolated product.

[b] Ethyl thiosalicylate (**5**) was obtained in 60% yield.

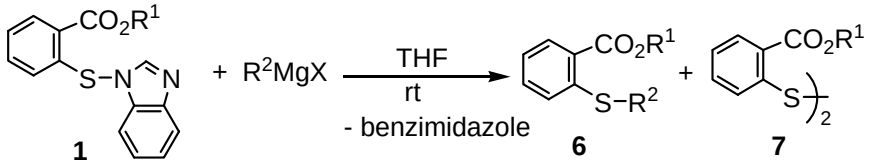
[c] Benzimidazole and remaining thiols were removed with water.

(3) Reactions with carbon nucleophiles

In a previous paper, we reported that *N*-sulfenyl-1,2-benzisothiazolin-3-ones react with Grignard reagents and active methylene compounds.[9] Grignard reagents react at the sulfur atoms of both the sulfenamide and the 1,2-benzisothiazolin-3-one moieties, whereas active methylene compounds react only at the sulfur

atom of the sulfenamide moiety to afford sulfide derivatives in good yields. In this study, we investigated the reactivity of carbon nucleophiles with *N*-sulfenylbenzimidazoles.

Table 4. The reaction of **1** with Grignard reagents



1 **6** **7**

Entry	**1**	R^1	R^2	X	Time (h)	Products			
						6	Yield[a] (%)	**7**	Yield[a] (%)
1	**1a**	Me	Me	Br	0.5	**6a**	74		
2	**1a**	Me	Me	I	0.5	**6a**	8	**7a**	71
3	**1a**	Me	Ph	Br	0.5	**6b**	91		
4	**1b**	Et	Me	Cl	2	**6c**	83		
5	**1b**	Et	Me	Br	2	**6c**	68		
6	**1b**	Et	Me	I	1	**6c**	22	**7b**	63
7	**1b**	Et	Me	Br	2	**6d**	85		
8	**1b**	Et	Ph	Cl	3	**6e**	86		
			$PhCH_2$						

[a] Isolated product.

The reactions of various Grignard reagents with *N*-sulfenylbenzimidazoles (**1**) were carried out, and the results are listed in Table 4. The carbon atoms of Grignard reagents with chloride or bromide anions attacked the sulfur atom of **1** and displaced benzimidazole to yield sulfide compounds (**6**) in good yields. However, when **1** was treated with methylmagnesium iodide, the yields of 2-methylthiobenzoates (**6**) were low, and the main products were disulfide derivatives (**7**) (Entries 2 and 6). These results can be explained in terms of the nucleophilicities of the anions of the Grignard reagents. When *N*-sulfenylbenzimidazole (**1b**) was treated with tetrabutylammonium iodide in THF for 30 min, disulfide (**7b**) was obtained in 45% yield. When **1b** was treated with tetrabutylammonium bromide in THF, the yield of **7b** was only 2%, and **1b** was recovered unchanged. These results clearly indicate that iodide anions accelerated the formation of **7b** from **1b**. Because sulfenyl iodides are easily converted to disulfides,[1] it is likely that iodide anions attacked the sulfur atom of **1** to form sulfenyl iodides, which were converted to the disulfides. These results indicate that Grignard reagents containing iodide anions cannot be used for reaction with *N*-sulfenylbenzimidazoles.

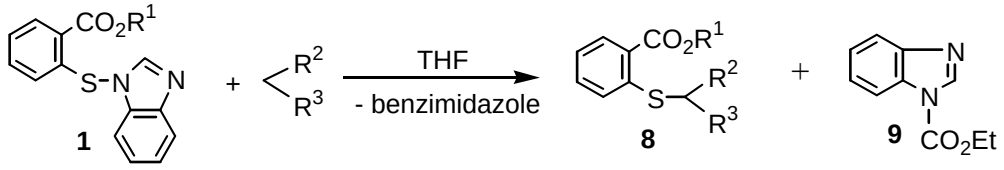
The reactions of **1a** with active methylene compounds were investigated, and the results are summarized in Table 5. The reaction of **1a** with ethyl cyanoacetate was carried out in THF in the presence of sodium hydride as a base. After the reaction mixture was quenched with aqueous ammonium chloride, sulfenylated ethyl cyanoacetate (**8a**) was obtained in 54% yield (Entry 1). When triethylamine was employed as a base instead of sodium hydride, the reaction was slow, and the starting material disappeared only after 5 h at reflux. After purification of the product by silica gel column chromatography without quenching with water, **8a** was obtained in 72% yield (Entry 2). When the

reaction was carried out at 80 ºC in toluene, 1-(ethoxycarbonyl)benzimidazole (**9**) was the main product (Entry 3). The structure of **9** was confirmed by comparison with the compound prepared by reaction of benzimidazole with ethyl chloroformate.[13] To determine the reaction mechanism for the formation of **9**, we isolated **8a** and treated it with benzimidazole in toluene at 80 ºC for 7 h; **9** was isolated in 83% yield. Under the same reaction conditions, ethyl cyanoacetate did not react with benzimidazole. These results indicate that sulfenylated ethyl cyanoacetate (**8a**) reacted with the formed benzimidazole. Benzimidazole attacked the carbonyl group of **8a** and the C-C bond cleaved to form **9**.

The reaction of **1a** with diethyl malonate afforded **8c** in 55% yield in the presence of sodium hydride (Entry 5). Although the reaction of **1a** with acetylacetone gave a sulfenylated product, which existed as an enol isomer (**8'd**),[9] the yields were low under both reaction conditions that we tried (Entries 6 and 7).

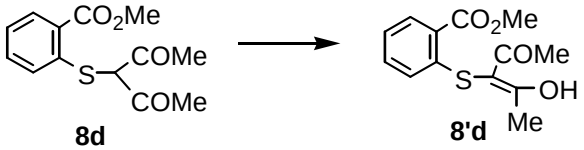
Thus, *N*-sulfenylbenzimidazoles sulfenylated active methylene compounds, but the yields of the reactions were lower than those of the reactions of *N*-sulfenyl-1,2-benzisothiazolin-3-ones, because the formed benzimidazole reacted with the sulfenylated products.

Table 5. The reaction of **1** with active methylene compounds



Entry	**1**	R^1	R^2	R^3	Base	Temp. (°C)	Time	Product	Yield[a] (%)
1	**1a**	Me	CN	CO_2Et	NaH	0	5 min	**8a**	54
2	**1a**	Me	CN	CO_2Et	Et_3N	reflux	5 h	**8a**	72
3	**1a**	Me	CN	CO_2Et	Et_3N	80[b]	7 h	**9**	57
4	**1b**	Et	CN	CO_2Et	Et_3N	80[b]	7 h	**8b**	41
								9	23
5	**1a**	Me	CO_2Et	CO_2Et	NaH	0	5 min	**8c**	55
6	**1a**	Me	COMe	COMe	NaH	rt	0.5 h	**8d**[c]	26
7	**1a**	Me	COMe	COMe	Et_3N	reflux	10 h	**8d**[c]	20
								7a	11

[a] Isolated product.
[b] Reaction was carried out in toluene.
[c] The structure of the product was observed as an enol isomer (**8'd**) in the ^{1}H NMR spectrum.



Our results indicate that *N*-sulfenylbenzimidazoles are good sulfenylating reagents for amides, imidates, thiols, and Grignard reagents, affording *N*-acylsulfenamides, *N*-sulfenylimidates, unsymmetrical disulfides, and sulfides, respectively. The formed benzimidazole sometimes interfered with the

formation of the desired products: thiol exchange reactions of asymmetrical disulfides were accelerated, and sulfenylated cyanoacetate derivatives were decomposed.

EXPERIMENTAL

Melting points were determined on a Mettler FP90 microscopic plate and are uncorrected. ^{1}H (500 MHz) and ^{13}C NMR spectra (125 MHz) were obtained with a JEOL LA-500 spectrometer, and chemical shifts (δ) are reported in parts per million relative to internal tetramethylsilane and $CDCl_3$, respectively. IR spectra were recorded on a JASCO FT IR-5300 spectrophotometer. Silica gel column chromatography was carried out on Merck silica gel 60 (0.063–0.200 mm). Elemental analysis and high-resolution mass spectral analysis were performed by the Analytical Center at the National Institute of Advanced Industrial Science and Technology. *N*-Sulfenylbenzimidazoles (**1**) were prepared by the method described in our previous paper.[10]

General procedure for the reaction of **1** with amides

To a solution of an amide (1.0 mmol) in THF (4 mL) cooled in an ice bath was added a solution of NaH (2.0 mmol) in THF (2 mL) under a nitrogen atmosphere. After 30 min, a solution of an *N*-sulfenylbenzimidazole (**1**, 0.35 mmol) in THF (1 mL) was added to the mixture at 0 °C. The reaction mixture was stirred for 10–30 min, and then water was added. The product was extracted with CH_2Cl_2, and the organic layer was washed with water and dried over magnesium sulfate. The solvent was removed under reduced pressure, and the crude product was purified by silica gel column chromatography (eluent: 10:1 CH_2Cl_2:EtOAc). The structures of **2a** and **2b** were determined by comparison with data from our previous paper.[6]

N-(2-Ethoxycarbonylbenzenesulfenyl)benzamide (**2c**).

mp 146.0-147.0 °C (from EtOAc-hexane); ^{1}H NMR ($CDCl_3$) δ 1.40 (3H, t, J = 7.0 Hz), 4.38 (2H, q, J = 7.0 Hz), 7.16 (1H, td, J = 8.2, 1.2 Hz), 7.30 (1H, d, J = 8.2 Hz), 7.41-7.45 (3H, m), 7.55 (1H, t, J = 7.6 Hz), 7.61 (1H, brs), 7.92 (2H, d, J = 7.6 Hz), 8.01 (1H, dd, J = 7.6, 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.3, 61.6, 122.1, 124.6, 127.7, 128.8, 131.1, 132.5, 133.1, 133.1, 144.8, 166.7, 169.1; IR (KBr) ν_{max} 3281, 1688, 1661, 1453, 1426, 1256, 1150, 1105, 1057, 1020, 756, 689 cm^{-1}; Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02; N, 4.65. Found: C, 63.79; H, 4.89; N, 4.56.

N-(2-Ethoxycarbonylbenzenesulfenyl)-4-methylbenzamide (**2d**).

mp 138.4-139.5 °C (from EtOAc-hexane); ^{1}H NMR ($CDCl_3$) δ 1.40 (3H, t, J = 7.3 Hz), 2.41 (3H, s), 4.39 (2H, q, J = 7.3 Hz), 7.16 (1H, ddd, J = 7.9, 7.0, 1.2 Hz), 7.24 (2H, d, J = 7.9 Hz), 7.29 (1H, d, J = 7.9 Hz), 7.42 (1H, brs), 7.42 (1H, ddd, J = 7.9, 7.0, 1.5 Hz), 7.82 (2H, d, J = 8.2 Hz), 8.01 (1H, dd, J = 7.9, 1.2

Hz); ^{13}C NMR ($CDCl_3$) δ 14.3, 21.6, 61.5, 122.1, 124.5, 124.6, 127.7, 129.4, 130.3, 131.1, 133.0, 143.1, 145.0, 166.7, 168.8; IR (KBr) ν_{max} 3227, 2978, 1696, 1657, 1437, 1254, 1148, 1101, 1059, 748 cm^{-1}; Anal. Calcd for $C_{17}H_{17}NO_3S$: C, 64.74; H, 5.43; N, 4.44. Found: C, 64.51; H, 5.29; N, 4.32.

N-(2-Ethoxycarbonylbenzenesulfenyl)acetamide (**2e**).

mp 122.0-123.0 °C (from EtOAc-hexane); ^{1}H NMR (CD_3OD) δ 1.39 (3H, t, *J* = 7.0 Hz), 2.21 (3H, s), 4.37 (2H, q, *J* = 7.0 Hz), 7.23 (1H, ddd, *J* = 7.9, 7.3, 1.2 Hz), 7.28 (1H, d, *J* = 7.9 Hz), 7.54 (1H, ddd, *J* = 7.9, 7.3, 1.5 Hz), 8.02 (1H, dd, *J* = 7.9, 1.2 Hz); ^{13}C NMR (CD_3OD) δ 14.6, 23.0, 62.6, 123.1, 125.5, 125.6, 132.1, 134.1, 146.5, 167.9, 175.8; IR (KBr) ν_{max} 3231, 2986, 1682, 1439, 1370, 1277, 1240, 1148, 1107, 1059, 1011, 752 cm^{-1}; Anal. Calcd for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48; N, 5.85. Found: C, 55.57; H, 5.39; N, 5.73.

Mixture of **2e** and **2e'**. Compound (**2e**): ^{1}H NMR ($CDCl_3$) δ 1.38-1.48 (3H, m), 2.28 (3H, s), 4.36-4.48 (2H, m), 6.89 (1H, brs), 7.19 (1H, t, *J* = 7.3 Hz), 7.22-7.28 (1H, m), 7.47 (1H, t, *J* = 6.7 Hz), 8.02 (1H, d, *J* = 7.3 Hz). Compound (**2e'**): ^{1}H NMR ($CDCl_3$) δ 1.38-1.48 (3H, m), 2.16 (3H, s), 4.36-4.48 (2H, m), 6.42 (1H, brs), 7.22-7.28 (1H, m), 7.41 (1H, d, *J* = 7.9 Hz), 7.57 (1H, t, *J* = 7.6 Hz), 8.08 (1H, d, *J* = 7.6 Hz).

N-(2-Ethoxycarbonylbenzenesulfenyl)-*N*-methylacetamide (**2f**).

mp 81.2-82.2 °C (from hexane); ^{1}H NMR ($CDCl_3$) δ 1.43 (3H, t, *J* = 7.0 Hz), 2.29 (3H, s), 3.29 (3H, s), 4.42 (2H, q, *J* = 7.0 Hz), 7.07 (1H, d, *J* = 7.9 Hz), 7.27 (1H, td, *J* = 7.6, 1.2 Hz), 7.57 (1H, td, *J* = 8.2, 1.2 Hz), 8.12 (1H, dd, *J* = 7.6, 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.2, 21.5, 38.8, 61.6, 121.0, 124.2, 124.9, 131.5, 133.5, 144.3, 166.6, 176.7; IR (KBr) ν_{max} 1678, 1368, 1308, 1148, 1101, 965, 918, 748, 509 cm^{-1}; Anal. Calcd for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.97; N, 5.53. Found: C, 57.32; H, 5.99; N, 5.35.

General procedure for the reaction of **1** with methyl imidates

To a solution of **1** (0.35 mmol) in MeCN (20 mL) were added a methyl imidate hydrochloride (2.0 mmol) and Et_3N (0.55 mmol) at rt. The mixture was stirred for 2 h, the solvent was removed under reduced pressure, and the crude product was purified by neutral silica gel column chromatography (eluent: CH_2Cl_2).

Methyl *N*-(2-methoxycarbonylsulfenyl)acetimidate (**3a**).

mp 71.5-72.3 °C (from hexane); ^{1}H NMR ($CDCl_3$) δ 2.21 (3H, s), 3.85 (3H, s), 3.93 (3H, s), 7.16 (1H, ddd, *J* = 7.9, 7.3, 0.9 Hz), 7.55 (1H, ddd, *J* = 8.5, 7.3, 1.2 Hz), 8.03 (1H, dd, *J* = 7.9, 1.2 Hz), 8.20 (1H, dd, *J* = 8.5, 0.9 Hz); ^{13}C NMR ($CDCl_3$) δ 18.4, 52.2, 53.4, 122.8, 123.4, 123.7, 130.8, 132.9, 145.8, 161.6, 167.0; IR (KBr) ν_{max} 1699, 1645, 1267, 1047, 743 cm^{-1}; Anal. Calcd for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48;

N, 5.85. Found: C, 55.29; H, 5.38; N, 5.78.

Methyl *N*-(2-ethoxycarbonylsulfenyl)acetimidate (**3b**).

mp 51.3-52.6 °C (from hexane); ^{1}H NMR ($CDCl_3$) δ 1.40 (3H, t, *J* = 7.0 Hz), 2.21 (3H, s), 3.85 (3H, s), 4.39 (2H, q, *J* = 7.3 Hz), 7.15 (1H, d, *J* = 7.6, 7.3, 0.9 Hz), 7.54 (1H, ddd, *J* = 8.2, 7.3, 1.5 Hz), 8.05 (1H, dd, *J* = 7.3, 1.5 Hz), 8.20 (1H, dd, *J* = 8.2, 0.9 Hz); ^{13}C NMR ($CDCl_3$) 14.3, 18.3, 53.3, 61.1, 123.1, 123.2, 123.6, 130.6, 132.7, 145.6, 161.4, 166.4; IR (KBr) ν_{max} 3002, 2982, 1696, 1638, 1453, 1433, 1265, 1140, 1100, 1044, 743 cm^{-1}; Anal. Calcd for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.97; N, 5.53. Found: C, 57.34; H, 5.91; N, 5.36. HRMS Calcd for $C_{12}H_{15}NO_3S$: 253.0773. Found: 253.0743.

Methyl *N*-(2-ethoxycarbonylsulfenyl)benzimidate (**3c**).

Oil; NMR ($CDCl_3$) δ 1.37 (3H, t, *J* = 7.1 Hz), 4.04 (3H, s), 4.35 (2H, q, *J* = 7.1 Hz), 7.17 (1H, td, *J* = 7.6, 1.2 Hz), 7.43-7.51 (3H, m), 7.59 (1H, t, *J* = 7.6 Hz), 7.77 (2H, d, *J*=5.8 Hz), 8.04 (1H, d, *J* = 7.9 Hz), 8.38 (1H, d, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$) 14.3, 54.0, 61.1, 123.4, 123.5, 123.5, 128.1, 128.4, 130.4, 130.8, 132.2, 132.7, 146.3, 158.3, 166.4; IR (neat) ν_{max} 1699, 1623, 1668, 1103, 1056, 744, 696 cm^{-1}; HRMS Calcd for $C_{17}H_{17}NO_3S$: 315.0929. Found: 315.0899.

General procedure for the reaction of **1** with thiols

To a solution of **1** (0.35 mmol) in MeOH or CH_2Cl_2 (10 mL) was added a thiol (0.35 mmol) at rt. The mixture was stirred for 2 h, the solvent was removed under reduced pressure, and the crude product was purified by silica gel column chromatography (eluent: 2:1 CH_2Cl_2:hexane). For the reactions in which thiol exchange reactions occurred readily, water was added to the reaction mixture. The product was extracted with CH_2Cl_2, and the organic layer was washed with water and dried over magnesium sulfate. The solvent was removed under reduced pressure at room temperature, and the crude product was purified by silica gel column chromatography.

2-Ethoxycarbonylphenyl octyl disulfide (**4a**).

Oil: ^{1}H NMR ($CDCl_3$) δ 0.87 (3H, t, *J* = 7.0 Hz), 1.25-1.26 (8H, m), 1.28-1.38 (2H, m), 1.41 (3H, t, *J* = 7.0 Hz), 1.66 (2H, quint, *J* = 7.3 Hz), 2.70 (2H, t, *J* = 7.3 Hz), 4.39 (2H, q, *J* = 7.0 Hz), 7.22 (1H, td, *J* = 7.6, 1.2 Hz), 7.54 (1H, td, *J* = 7.6, 1.5 Hz), 8.02 (1H, dd, *J* = 7.6, 1.5 Hz), 8.18 (1H, dd, *J* = 7.6, 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0, 14.2, 22.5, 28.5, 28.9, 29.1, 29.1, 31.7, 38.4, 61.2, 124.8, 125.5, 127.3, 131.3, 132.5, 142.0, 166.3; IR (neat) ν_{max} 2928, 2854, 1707, 1458, 1267, 1252, 1144, 1101, 1053, 745 cm^{-1}; HRMS Calcd for $C_{17}H_{26}O_2S_2$: 326.1374. Found: 326.1322.

Dodecyl 2-ethoxycarbonylphenyl disulfide (**4b**).Oil; ^{1}H NMR ($CDCl_3$) δ 0.88 (3H, t, *J* = 7.0 Hz), 1.24-1.31 (16H, m), 1.35-1.38 (2H, m), 1.41 (3H, t, *J* = 7.0 Hz) 1.66 (2H, quint, *J* = 7.6 Hz), 2.70 (2H, t, *J*

= 7.6 Hz), 4.40 (2H, q, *J* = 7.0 Hz), 7.22 (1H, m), 7.54 (1H, ddd, *J* = 8.2, 7.0, 1.5 Hz), 8.02 (1H, dd, *J* = 7.9, 1.5 Hz), 8.18 (1H, dd, *J* = 8.2, 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0, 14.2, 22.6, 28.5, 28.9, 29.1, 29.3, 29.4, 29.5, 29.6, 29.6, 31.8, 38.4, 61.2, 124.8, 125.6, 127.3, 131.3, 132.5, 142.0, 166.3; IR (neat) ν_{max} 2926, 2853, 1709, 1267, 1252, 1144, 1101, 1053, 745 cm^{-1}; HRMS Calcd for $C_{21}H_{34}O_2S_2$: 382.2000. Found: 382.1984.

4-Chlorobenzyl 2'-ethoxycarbonylphenyl disulfide (**4c**).

Oil; ^{1}H NMR ($CDCl_3$) δ 1.41 (3H, t, *J* = 7.0 Hz), 3.87 (2H, s), 4.39 (2H, q, *J* = 7.0 Hz), 7.18-7.21 (5H, m), 7.42 (1H, ddd, *J* = 7.3, 5.8, 0.9 Hz), 7.94 (1H, dd, *J* = 8.2, 0.9 Hz), 7.98 (1H, dd, *J* = 7.9, 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.3, 42.4, 61.3, 125.1, 125.6, 127.4, 128.6, 130.5, 131.2, 132.4, 133.3, 135.1, 140.9, 166.3; IR (neat) ν_{max} 2982, 1703, 1491, 1458, 1267, 1098, 1053, 1017, 745 cm^{-1}; HRMS Calcd for $C_{16}H_{15}ClO_2S_2$: 338.0202. Found: 338.0203.

4-*tert*-Butylphenyl 2'-ethoxycarbonylphenyl disulfide (**4d**).

Oil; ^{1}H NMR ($CDCl_3$) δ 1.27 (9H, s), 1.41 (3H, t, *J* = 7.3 Hz), 4.42 (2H, q, *J* = 7.3 Hz), 7.22 (1H, td, *J* = 7.6, 0.9 Hz), 7.29 (2H, d, *J* = 8.5 Hz), 7.40 (2H, d, *J* = 8.2 Hz), 7.48 (1H, td, *J* = 8.2, 1.5 Hz), 8.04 (1H, dd, *J* = 8.2, 1.5 Hz), 8.06 (1H, dd, *J* = 8.5, 0.9 Hz); ^{13}C NMR ($CDCl_3$) δ 14.3, 31.2, 34.5, 61.5, 125.3, 125.8, 126.2, 126.2, 127.2, 127.3, 131.3, 132.9, 141.5, 150.3, 166.4; IR (neat) ν_{max} 2963, 1705, 1460, 1269, 1254, 1144, 1101, 1053, 824, 745 cm^{-1}; HRMS Calcd for $C_{19}H_{22}O_2S_2$: 346.1061. Found: 346.1045.

2-Ethoxycarbonylphenyl 2'-methoxycarbonylphenyl disulfide (**4e**).

mp 105.5-107.0 (from hexane); ^{1}H NMR ($CDCl_3$) δ 1.45 (3H, t, *J* = 7.3 Hz), 3.98 (3H, s), 4.45 (2H, q, *J* = 7.3 Hz), 7.23 (2H, td, *J* = 7.6, 0.6 Hz), 7.38-7.42 (2H, m), 7.75 (1H, dd, *J* = 5.8, 0.9 Hz), 7.76 (1H, dd, *J* = 5.8, 0.9 Hz), 8.07 (2H, td, *J* = 7.6, 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 14.3, 52.3, 61.5, 125.4, 125.4, 125.8, 125.8, 127.2, 127.6, 131.4, 131.4, 132.9, 133.0, 140.2, 140.4, 166.4, 166.9; IR (KBr) ν_{max} 1699, 1460, 1435, 1254, 1144, 1103, 1057, 1036, 737 cm^{-1}; Anal. Calcd for $C_{17}H_{16}O_4S_2$: C, 58.60; H, 4.63. Found: C, 58.61; H, 4.47.

2-Ethoxycarbonylphenyl phenyl disulfide (**4f**).

Oil; ^{1}H NMR ($CDCl_3$) δ 1.42 (3H, t, *J* = 7.0 Hz), 4.42 (2H, q, *J* = 7.0 Hz), 7.17-7.29 (4H,m), 7.45-7.48 (3H, m), 7.99 (1H, dd, *J* = 8.2, 1.2 Hz), 8.05 (1H, dd, *J* = 7.6, 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 14.3, 61.5, 125.4, 125.7, 126.8, 127.0, 127.3, 129.1, 131.3, 132.9, 136.2, 141.1, 166.4; IR (neat) ν_{max} 2980, 1703, 1586, 1460, 1437, 1368, 1269, 1144, 1103, 741, 689 cm^{-1}; HRMS Calcd for $C_{15}H_{14}O_2S_2$: 290.0435. Found: 290.0411.

2-Aminophenyl 2'-ethoxycarbonylphenyl disulfide (**4g**).

mp 89.3-90.3 °C (from hexane); ^{1}H NMR ($CDCl_3$) δ 1.38 (3H, t, *J* = 7.0 Hz), 4.34 (2H, brs), 4.37 (2H, q, *J* = 7.0 Hz), 6.62 (1H, td, *J* = 7.6, 1.2 Hz), 6.69 (1H, dd, *J* = 7.6, 1.2 Hz), 7.09 (1H, td, *J* = 7.6, 1.5 Hz), 7.24 (1H, td, *J* = 7.6, 1.2 Hz), 7.42 (1H, dd, *J* = 7.9, 1.5 Hz), 7.56 (1H, ddd, *J* = 7.9, 7.6, 1.5 Hz), 7.99 (1H, dd, *J* = 7.6, 1.5 Hz), 8.28 (1H, dd, *J* = 7.9, 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.3, 61.4, 115.7, 118.4, 118.6, 125.4, 126.5, 127.7, 130.5, 131.3, 132.6, 133.8, 141.4, 147.6, 166.3; IR (KBr) ν_{max} 3422, 3318, 1696, 1616, 1476, 1250, 1146, 1101, 741 cm^{-1}; Anal. Calcd for $C_{15}H_{15}NO_2S_2$: C, 58.99; H, 4.95; N, 4.59. Found: C, 59.43; H, 4.84; N, 4.51.

2-Ethoxycarbonylphenyl 2'-pyridyl disulfide (**4h**).

mp 105.0-106.0 °C (from hexane); ^{1}H NMR ($CDCl_3$) δ 1.45 (3H, t, *J* = 7.0 Hz), 4.45 (2H, q, *J* = 7.0 Hz), 7.07-7.10 (1H, m), 7.24-7.26 (1H, m), 7.46 (1H, td, *J* = 8.5, 1.5 Hz), 7.52-7.58 (2H, m), 7.91 (1H, d, *J* = 8.2 Hz), 8.08 (1H, dd, *J* = 7.6, 1.2 Hz), 8.46 (1H, dd, *J* = 4.6, 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.3, 61.6, 119.7, 120.9, 125.7, 125.8, 127.5, 131.4, 133.0, 137.3, 140.2, 149.6, 159.3, 166.4; IR (KBr) ν_{max} 2986, 1698, 1562, 1443, 1416, 1368, 1292, 1150, 1117, 1053, 768, 747 cm^{-1}; Anal. Calcd for $C_{14}H_{13}NO_2S_2$: C, 57.71; H, 4.50; N, 4.81. Found: C, 57.65; H, 4.24; N, 4.70.

General procedure for the reaction of **1** with Grignard reagents

To a solution of **1** (0.5 mmol) in THF (10 mL) was added a Grignard reagent (1 M in THF, 1.0 mL) at rt under a nitrogen atmosphere. The mixture was stirred for 0.5–3 h, and then aqueous NH_4Cl solution was added to the reaction mixture. Products were extracted with CH_2Cl_2, and the organic layer was washed with water and dried over magnesium sulfate. The solvent was removed under reduced pressure, and the crude product was purified by silica gel column chromatography (eluent: 1:1 CH_2Cl_2:hexane). The structures of compounds (**6b**–**e**)[9] and (**7a**)[14] were determined by comparison with data from our previous papers.

Methyl 2-(methylthio)benzoate (**6a**).

mp 65.6-66.4 °C (lit.,[15] 64-66 °C, from hexane); ^{1}H NMR ($CDCl_3$) δ 2.45 (3H, s), 3.91 (3H, s), 7.15 (1H, ddd, *J* = 8.5, 7.6, 0.9 Hz), 7.27 (2H, d, *J* = 7.9 Hz), 7.47 (1H, ddd, *J* = 8.5, 7.9, 1.5 Hz), 8.00 (1H, dd, *J* = 7.6, 1.5 Hz) ; IR (KBr) ν_{max} 2952, 1710, 1560, 1435, 1250, 1146, 1061, 956, 749, 690 cm^{-1}.

Bis(2-ethoxycarbonyphenyl) disulfide (**7b**).

mp 117.0-118.0 °C (lit.,[16] 118-119 °C, from EtOH); ^{1}H NMR ($CDCl_3$) δ 1.45 (6H, t, *J* = 7.2 Hz), 4.46 (4H, q, *J* = 7.2 Hz), 7.23 (2H, ddd, *J* = 7.9, 7.6, 1.2 Hz), 7.41 (2H, ddd, *J* = 8.5, 7.6, 1.5 Hz), 7.76 (2H, dd, *J* = 8.5, 1.2 Hz), 8.07 (2H, dd, *J* = 7.9, 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 14.2, 61.6, 125.5, 125.9, 127.8,

131.5, 133.0, 140.4, 166.6; IR (KBr) ν_{max} 2979, 1698, 1459, 1270, 1148, 1057, 742 cm^{-1};.

General procedure for the reaction of **1a** with active methylene compounds

To a suspension of NaH (0.75 mmol, 18.0 mg) in THF (5 mL) at rt under a nitrogen atmosphere was added a solution of an active methylene compound (0.75 mmol) in THF (5 mL). The mixture was stirred for 0.5 h. A solution of **1a** (0.50 mmol) in THF (5 mL) was then added; and after the reaction mixture was stirred for 0.5 h, water was added. Product was extracted with CH_2Cl_2, and the organic layer was washed with water and dried over magnesium sulfate. The solvent was removed under reduced pressure, and the crude product was purified by silica gel column chromatography (eluent: CH_2Cl_2). The structures of compounds (**8a,c,d**) were determined by comparison with data from a previous paper.[9]

Ethyl 2-cyano-2-(2-ethoxycarbonylbenzenesulfenyl)acetate (**8b**).

mp 77.3-78.3 °C (from EtOAc-hexane); ^{1}H NMR ($CDCl_3$) δ 1.31 (3H, t, *J* = 7.3 Hz), 1.42 (3H, t, *J* = 7.3 Hz), 4.28-4.33 (2H, m), 4.41 (2H, q, *J* = 7.3 Hz), 4.87 (1H, s), 7.41 (1H, td, *J* = 7.6, 1.2 Hz), 7.56 (1H, td, *J* = 7.6, 1.5 Hz), 7.61 (1H, dd, *J* = 7.6, 1.2 Hz), 7.98 (1H, dd, *J* = 7.6, 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0, 14.4, 39.1, 62.0, 64.1, 114.3, 128.1, 131.4, 131.4, 132.0, 132.9, 133.6, 166.4, 166.6; IR (KBr) ν_{max} 2984, 2874, 2247, 1752, 1699, 1264, 1233, 1150, 1111, 1069, 1019, 748 cm^{-1}; Anal. Calcd for $C_{14}H_{15}NO_4S$: C, 57.32; H, 5.15; N, 4.77. Found: C, 57.37; H, 5.02; N, 4.67.

1-Ethoxycarbonylbenzimidazole (**9**).[13]

^{1}H NMR ($CDCl_3$) δ 1.51 (3H, t, *J* = 7.0 Hz), 4.57 (2H, q, *J* = 7.0 Hz), 7.36-7.43 (2H, m), 7.80 (1H, d, *J* = 7.6 Hz), 8.03 (1H, d, *J* = 7.9 Hz), 8.49 (1H, s); ^{13}C NMR ($CDCl_3$) δ 14.3, 64.2, 114.4, 120.7, 124.5, 125.5, 131.3, 141.7, 144.0, 149.5; IR (neat) ν_{max} 2984, 1753, 1453, 1379, 1287, 1242, 1208, 1065, 766, 747 cm^{-1}.

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