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A Convenient Synthesis of α-(2-Benzothiazolylthio)alkanoates by Cleavage of β-Keto Esters with 2-Benzothiazolesulfenamides

Sigeru TORII,* Hideo TANAKA, and Hiroshi OKUMOTO

Department of Industrial Chemistry, School of Engineering, Okayama University, Okayama 700

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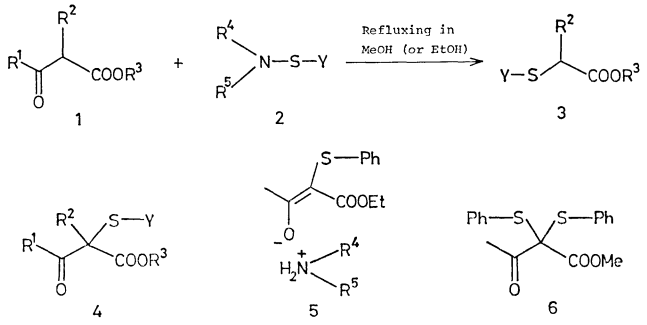
Synopsis. α-(2-Benzothiazolylthio)alkanoates were prepared by the reaction of β-keto esters with 2-(morpholinothio)benzothiazole in refluxing alcohols. Sulfenylating cleavage of α-methoxycarbonylcycloalkanones afforded the corresponding ω-alkoxycarbonyl- and/or ω-carbamoyl-α-(2-benzothiazolylthio)alkanoates.

In a previous paper, it has been shown that the direct cross-coupling reaction of disulfides with amines by an electrochemical procedure provides a variety of sulfenamides **2** in high yields.[1] Several investigations demonstrate that the sulfenamides **2** and their related compounds can be used for sulfenylation of active hydrogen compounds.[2,3] It was previously reported that sulfenylation of ethyl acetoacetate (**1**, R^1=Me, R^2=H, R^3=Et) with sulfenamides **2** (Y=Ph, R^4, R^5=alkyl) in CH_2Cl_2 gives ethyl α-(phenylthio)acetoacetate (**4**, R^1=Me, R^2=H, R^3=Et, Y=Ph) *via* the intermediate **5**.[3] However, sulfenylating cleavage of β-keto esters **1** with **2** into the corresponding α-sulfenyl esters **3** has not yet been realized. In this paper, we wish to report an efficient synthesis of α-sulfenylalkanoates **3** from β-keto esters **1** by the action of 2-benzothiazolesulfenamides **2**.



The reaction of equimolar amounts of methyl acetoacetate (**1a**, R^1=R^3=Me, R^2=H) with sulfenamide **2a** (Y=Ph, R^4, R^5=$(CH_2CH_2)_2O$) in refluxing methanol for 7 h afforded methyl (phenylthio)acetate (**3a**) along with disulfenylated product **6** (8%) (Table 1, entry 1). On the other hand, the reaction of **1a**

TABLE 1. REACTION OF METHYL ACETOACETATE WITH SULFENAMIDES **2**

Entry		Sulfenamide **2**			Product **3**		Yield[a]
		Y[b]	R^4	R^5		Y[b] (R^3=Me)	%
1	**2a**	Ph	$-CH_2CH_2OCH_2CH_2-$		**3a**	Ph	61[c]
2	**2b**	BT	$-CH_2CH_2OCH_2CH_2-$		**3b**	BT	92
3	**2c**	BT	$-(CH_2)_5-$		**3b**	BT	81
4	**2d**	BT	H	Cyclohexyl	**3b**	BT	73
5	**2e**	T	$-(CH_2)_5-$		**3c**	T	21
6	**2f**	(*N*-(Phenylthio)phthalimide)					—

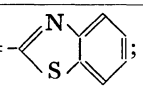
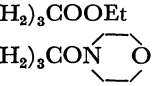
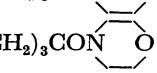
a) Isolated yield. b) BT=  ; T=  . c) Disulfenylated compound **6** was also produced in 8% yield.

TABLE 2. REACTION OF β-KETO ESTERS WITH (2-BENZOTHIAZOLE)SULFENAMIDE **2b**

Entry		β-Keto ester **1**			Solvent		Product **3** (Y=BT)		Yield[a]
		R^1	R^2	R^3			R^2	R^3	%
7	**1b**	Me,	n-C_6H_{13},	Me	MeOH	**3d**	n-C_6H_{13}	Me	98
8	**1c**	$-(CH_2)_3-$		Me	MeOH	**3e**	$(CH_2)_3COOMe$	Me	99
9	**1c**	$-(CH_2)_3-$		Me	EtOH	**3f**	$(CH_2)_3COOEt$	Me	73
10	**1c**	$-(CH_2)_3-$		Me	Benzene	**3g**		Me	97
11	**1c**	$-(CH_2)_3-$		Me	CH_2Cl_2	**3g**		Me	87
12	**1d**	$-(CH_2)_3-$		Et	MeOH	**3h**	$(CH_2)_3COOMe$	Et	92
13	**1d**	$-(CH_2)_3-$		Et	EtOH	**3i**	$(CH_2)_3COOEt$	Et	58
14	**1e**	$-(CH_2)_4-$		Me	MeOH	**3j**	$(CH_2)_4COOMe$	Me	99

a) Isolated yield.

with various 2-benzothiazolesulfenamides **2b—d** (Y= 2-benzothiazolyl (BT)) furnished **3b** (Y=BT, R^2=H) as a sole product in high yields (entries 2—4). In contrast, thiocarbamoylsulfenamide **2e** (entry 5) afforded only 21% of the desired α-sulfenyl ester **3c** as well as complex materials. In entry 6, most of *N*-(phenylthio)phthalimide (**2f**) was recovered.

Above all, it was found that 2-benzothiazolesulfenamide **2b** is the most effective reagent for the conversion of **1a** into the corresponding α-sulfenylacetates **3**. The results of sulfenylation of α-substituted β-keto esters **1** (R^1, R^2=alkyl) with **2b** in refluxing alcohols are shown in Table 2. Thus, α-alkoxycarbonylcycloalkanones **1** afforded the corresponding ω-alkoxycarbonyl-α-sulfenylalkanoates **3** ($R^2=(CH_2)_nCOOMe$ (or COOEt)) (entries 8, 9, 12, 13, and 14), indicating that regioselective nucleophilic attack with alcohols, providing the ω-ester groups, was encountered.

When the reaction of 2-methoxycarbonylcyclopentanone (**1c**) with **2b** was carried out in benzene or CH_2Cl_2, the corresponding methyl 5-morpholinocarbonyl-2-sulfenylpentanoate **3g** was isolated in good yields (entries 10 and 11). This result demonstrates that nucleophilic attack of morpholine provided by the sulfenylation to the ketonic carbonyl of **4** [Y=BT, R^1, $R^2=(CH_2)_3$, R^3=Me] would occur preferentially in aprotic solvent.

Experimental

All the melting and boiling points are uncorrected. IR spectra were determined with a JASCO IRA-I infrared spectrometer. NMR spectra were obtained at 100 MHz with a JEOL MH-100 spectrometer.

*Methyl (Phenylthio)acetate (**3a**).* A MeOH solution (3 ml) of $AcCH_2COOMe$ (70 mg, 0.6 mmol) and **2a** (110 mg, 0.6 mmol) was heated to reflux for 7 h. The solution was concentrated *in vacuo* and the residue was chromatographed (SiO_2, benzene–hexane–AcOEt, 10/10/1). The first coming elute gave **6** (16 mg, 8%): bp 119—123 °C/0.003 Torr; IR (neat) 3060, 3030 (HC=C), 1723, 1712 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.30 (s, 3, CH_3), 3.59 (s, 3, CH_3O), 7.10—7.82 (m, 10, HC=C). Found: C, 61.50; H, 4.99%. Calcd for $C_{17}H_{16}O_3S_2$: C, 61.42; H, 4.85%.

The second fraction afforded **3a** (67 mg, 61%): bp 38—40 °C/0.007 Torr (lit,[4a] bp 87—90 °C/0.3 Torr); IR (neat) 3046 (HC=C), 1734 cm^{-1}; NMR ($CDCl_3$) δ 3.70 (s, 2, CH_2), 3.76 (s, 3, CH_3O), 7.30—7.72 (m, 5, HC=C).

*Methyl (2-Benzothiazolylthio)acetate (**3b**).* A MeOH solution (3 ml) of $AcCH_2COOMe$ (116 mg, 1.0 mmol) and **2b** (252 mg, 1.0 mmol) was heated to reflux for 7 h. Evaporation of the solvent followed by column chromatography (SiO_2, benzene–hexane–AcOEt, 10/10/1) gave **3b** (219 mg, 92%): mp 74—75 °C (Et_2O–hexane, 1/2); IR (Nujol) 3050 (HC=C), 1743 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.70 (s, 3, CH_3O), 4.12 (s, 2, CH_2), 7.06—7.86 (m, 4, HC=C). Found: C, 50.20; H, 3.81%. Calcd for $C_{10}H_9NO_2S_2$: C, 50.19; H, 3.79%.

The reaction of β-keto esters **1** with **2b—c** was carried out in a similar manner to that above (Tables 1 and 2). Physical properties and spectral data of the products **3c—j** are as follows.

*Compound **3c**:* Bp 64—68 °C/0.006 Torr; IR (neat) 1734 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.72 (br, 6, CH_2), 3.75 (s, 3, CH_3O). 3.92—4.40 (m, 4, CH_2N), 4.18 (s, 2, CH_2S). Found: C, 46.14; H, 6.23%. Calcd for $C_9H_{15}NO_2S_2$: C, 46.32; H, 6.48%.

*Compound **3d**:* Bp 123—126 °C/0.005 Torr; IR (neat) 3053 (HC=C), 1739 cm^{-1}; NMR ($CDCl_3$) δ 0.87 (t, 3, J=6 Hz, CH_3), 1.05—2.19 (m, 10, CH_2), 3.72 (s, 3, CH_3), 4.61 (t, 1, J=7 Hz, CH), 7.11—7.91 (m, 4, HC=C). Found: C, 59.38; H, 6.42%. Calcd for $C_{16}H_{21}NO_2S_2$: C, 59.41; H, 6.54%.

*Compound **3e**:* Bp 124—126 °C/0.008 Torr; IR (neat) 3050 (HC=C), 1732 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.58—2.27 (m, 4, CH_2), 2.35 (t, 2, J=7 Hz, CH_2CO), 3.61 (s, 3, CH_3O), 3.72 (s, 3, CH_3O), 4.66 (t, 1, J=7 Hz, CH), 7.14—7.90 (m, 4, HC=C). Found: C, 53.03; H, 4.87%. Calcd for $C_{15}H_{17}NO_4S_2$: C, 53.08; H, 5.05%.

*Compound **3f**:* Bp 121—123 °C/0.009 Torr; IR (neat) 3050 (HC=C), 1732 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.22 (t, 3, CH_3), 1.62—2.26 (m, 4, CH_2), 2.35 (t, 2, J=7 Hz, CH_2CO), 3.73 (s, 3, CH_3O), 4.07 (q, 2, CH_2O), 4.66 (t, 1, J=7 Hz, CH), 7.09—7.94 (m, 4, HC=C). Found: C, 54.32; H, 5.41%. Calcd for $C_{16}H_{19}NO_4S_2$: C, 54.37; H, 5.42%.

*Compound **3g**:* Bp 147—150 °C/0.006 Torr; IR (neat) 3060 (HC=C), 1733, 1640 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.65—2.31 (m, 4, CH_2), 2.40 (t, 2, J=7 Hz, CH_2CO), 3.28—3.78 (m, 8, NCH_2CH_2O), 3.79 (s, 3, CH_3O), 4.76 (t, 1, J=7 Hz, CH), 7.24—8.06 (m, 4, HC=C). Found: C, 54.64; H, 5.52%. Calcd for $C_{18}H_{22}N_2O_4S_2$: C, 54.80; H, 5.62%.

*Compound **3h**:* Bp 124—126 °C/0.009 Torr; IR (neat) 3065 (HC=C), 1735 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.25 (t, 3, CH_3), 1.63—2.25 (m, 4, CH_2), 2.37 (t, 2, J=7 Hz, CH_2CO), 3.62 (s, 3, CH_3O), 4.19 (q, 2, CH_2O), 4.63 (t, 1, J=7 Hz, CH), 7.11—7.95 (m, 4, HC=C). Found: C, 54.24; H, 5.59%. Calcd for $C_{16}H_{19}NO_4S_2$: C, 54.37; H, 5.42%.

*Compound **3i**:* Bp 124—126 °C/0.006 Torr; IR (neat) 3050 (HC=C), 1730 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.24 (t, 3, CH_3), 1.26 (t, 3, CH_3), 1.67—2.28 (m, 4, CH_2), 2.38 (t, 2, J=7 Hz, CH_2CO), 4.14 (q, 2, CH_2O), 4.26 (q, 2, CH_2O), 4.70 (t, 1, J=7 Hz, CH), 7.24—8.03 (m, 4, HC=C). Found: C, 55.65; H, 5.86%. Calcd for $C_{17}H_{21}NO_4S_2$: C, 55.56; H, 5.76%.

*Compound **3j**:* Bp 125—128 °C/0.006 Torr; IR (neat) 3058 (HC=C), 1739 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.32—2.22 (m, 6, CH_2), 2.31 (t, 2, J=7 Hz, CH_2CO), 3.63 (s, 3, CH_3O), 3.73 (s, 3, CH_3O), 4.64 (t, 1, J=7 Hz, CH), 7.08—8.04 (m, 4, HC=C). Found: C, 54.20; H, 5.43%. Calcd for $C_{16}H_{19}NO_4S_2$: C, 54.37; H, 5.42%.

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