

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

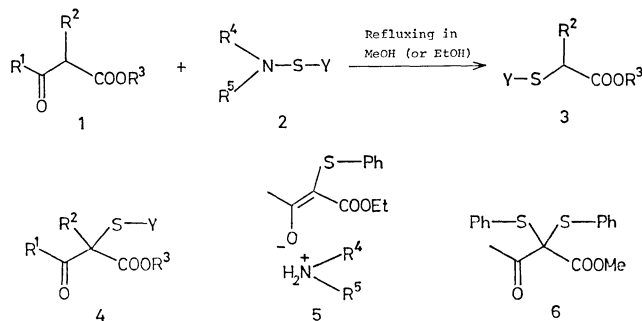
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Synopsis. α -(2-Benzothiazolylthio)alkanoates were prepared by the reaction of β -keto esters with 2-(morpholinio-thio)benzothiazole in refluxing alcohols. Sulfenylating cleavage of α -methoxycarbonylcycloalkanones afforded the corresponding ω -alkoxycarbonyl- 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 ₂ CH ₂ OCH ₂ CH ₂ -		3a	Ph	61 ^{c)}
2	2b	BT	-CH ₂ CH ₂ OCH ₂ CH 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)					—

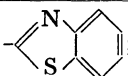
a) Isolated yield. b) BT = ; T = -CS-N . c) Disulfenylated compound **6** was also produced in 8% yield.

TABLE 2. REACTION OF β -KETO ESTERS WITH (2-BENZOTHAZOLE)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,	<i>n</i> -C ₆ H ₁₃ ,	Me	MeOH	3d	<i>n</i> -C ₆ H ₁₃	Me	98
8	1c	-(CH ₂) ₃ -		Me	MeOH	3e	(CH ₂) ₃ COOMe	Me	99
9	1c	-(CH ₂) ₃ -		Me	EtOH	3f	(CH ₂) ₃ COOEt	Me	73
10	1c	-(CH ₂) ₃ -		Me	Benzene	3g	(CH ₂) ₃ CON 	Me	97
11	1c	-(CH ₂) ₃ -		Me	CH ₂ Cl ₂	3g	(CH ₂) ₃ CON 	Me	87
12	1d	-(CH ₂) ₃ -		Et	MeOH	3h	(CH ₂) ₃ COOMe	Et	92
13	1d	-(CH ₂) ₃ -		Et	EtOH	3i	(CH ₂) ₃ COOEt	Et	58
14	1e	-(CH ₂) ₄ -		Me	MeOH	3j	(CH ₂) ₄ COOMe	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 , $R^2 = \text{alkyl}$) with **2b** in refluxing alcohols are shown in Table 2. Thus, α -alkoxycarbonylcycloalkanones **1** afforded the corresponding ω -alkoxycarbonyl- α -sulfenylalkanoates **3** ($R^2 = (CH_2)_n COOMe$ (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 $C_{18}H_{25}N_2O_4S_2$: 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%.

References

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