Synthesis of 2-[1-(Alkoxycarbonyl)alkyl]-3-methylbenzothiazolines and 3-Methyl-2-(2-oxoalkyl)benzothiazolines by the Direct Alkylation of Lithium Enolates with 3-Methylbenzothiazolium Salts

Hidenori CHIKASHITA,* Naoto TAKEGAMI, Yoshiyuki YANASE, and Kazuyoshi ITOH
Department of Applied Chemistry, Faculty of Engineering, Kansai University, Suita, Osaka 564
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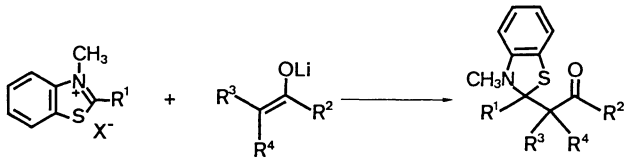
Synopsis. A variety of lithium enolates derived from esters and ketones could be readily alkylated with 3-methylbenzothiazolium salts to give the novel α-(benzothiazolinyl) esters and ketones, 2-[1-(alkoxycarbonyl)alkyl]-3-methylbenzothiazolines and 3-methyl-2-(2-oxoalkyl)benzothiazolines in good yields, respectively.

1,3-Dithienium tetrafluoroborates,[1] are well-known promising candidates of heterocyclic formyl or acyl cation equivalents. Although, up to now, the introduction of masked formyl and acyl groups at the α-position of carbonyl compounds has been achieved by the reaction of these salts with enol silyl ethers prepared from esters and ketones, a simpler and more direct method with lithium enolates have not been reported yet.[1] We have recently demonstrated that 3-methylbenzothiazolium salts can be used as useful formyl and acyl cation equivalents.[2,3] As an extension of our previous work[2] and as a requirement for the convenient preparation method of α-(benzothiazolinyl) carbonyl compounds in our study of enolate-transfer type aldol reaction,[4] we were interested in examining the direct reaction of lithium enolates with 3-methylbenzothiazolium salts. We now report that lithium enolates **2** and **3** derived from esters and ketones are readily alkylated under mild conditions with 3-methylbenzothiazolium salts **1**, leading to the introduction of the 3-methylbenzothiazoline unit at the α-position of carbonyl compounds.



1a : R^1=H , X=I
b : R^1=Ph, X=SO_3F
c : R^1=Me, X=I

2 : R^2=OEt
3 : R^2=alkyl, aryl

4 : R^2=OEt
5 : R^2=alkyl, aryl

The alkylation of ester enolates **2** was carried out by the enolization of esters with lithium diisopropylamide in THF followed by treatment with one equiv of the benzothiazolium salts **1a—c** at −78 °C to room temperature, with the results summarized in Table 1. Under these conditions, 3-methylbenzothiazolium iodide (**1a**), which has a very acidic hydrogen at the 2-position, reacted with a variety of ester enolates **2** without significant abstraction of that hydrogen as a proton[5] to give the corresponding 2-[1-(ethoxycarbonyl)alkyl]benzothiazolines **4a—e** in good yields (Entries 1—5). Diastereoselectivity on the reaction of **1a** with the enolates produced from ethyl propionate, ethyl butanoate, and ethyl 3-methylbutanoate was found to be roughly 1 : 1 in each case (Entries 3—5), although the relative stereochemistry of each diastereoisomers has been not clarified. On the other hand, 2-substituted benzothiazolium salts **1b, c** reacted more efficiently with ester enolates to give the corresponding 2,2-disubstituted 3-methylbenzothiazolines in high yields (Entries 6,7).

The alkylation of ketone enolates **3** was similarly and efficiently achieved with benzothiazolium salts **1a, b** at 0 °C to room temperature giving the corresponding 2-(2-oxoalkyl)benzothiazolines **5a—g** in good

Table 1. Preparation of 2-[1-(Ethoxycarbonyl)alkyl]-3-methylbenzothiazolines **4** by the Reaction of Benzothiazolium Salts **1** with Lithium Enolates **2** from Esters

Entry	Salt **1**	Enolate **2**		Benzothiazoline **4**	Yield/%[a]
		R^3	R^4		
1	**1a**	H	H	**4a**	50
2	**1a**	Me	Me	**4b**	75
3	**1a**	Me	H	**4c**	42[b]
4	**1a**	Et	H	**4d**	48[b]
5	**1a**	*i*-Pr	H	**4e**	67[b]
6	**1b**	H	H	**4f**	87
7	**1c**	Me	Me	**4g**	81

a) Yield of pure product isolated by MPLC. b) Unseparable diastereomeric mixture with the ratio of 55 : 45 (Entry 3), 50 : 50 (Entry 4), and 60 : 40 (Entry 5).

Table 2. Preparation of 3-Methyl-2-(2-oxoalkyl)benzothiazolines **5** by the Reaction of Benzothiazolium Salts **1** with Lithium Enolates **3** from Ketones

Entry	Salt **1**	Enolate **3**			Benzothiazoline **5**	Yield/%[a]
		R^2	R^3	R^4		
1	**1a**	Ph	H	H	**5a**	34
2	**1b**	Ph	H	H	**5b**	71
3	**1b**	Me	H	H	**5c**	34
4	**1b**	*n*-Pr	H	H	**5d**	69
5	**1b**	Ph	Me	H	**5e**	72[b]
6	**1b**	Ph	Et	H	**5f**	55[c]
7	**1b**	$-(CH_2)_4-$		H	**5g**	75[c]

a) Yield of pure product isolated by MPLC. b) Yield of major diastereoisomer (the minor isomer **5e'** was isolated in 3% yield). c) A single diastereoisomer was predominantly obtained.

yields. The results are listed in Table 2. In contrast to the case of ester enolates **2**, the diastereoselectivity on the reaction with ketone enolates **3** was very high, as seen in the results of reactions with the enolates produced from propiophenone, butyrophenone, and cyclohexanone (Entries 5—7). As shown in the successful conversion of the kinetic enolate of 2-pentanone to **5d**, the regiocontrolled introduction of a 3-methylbenzothiazoline unit at the α-position of ketones can be conveniently achieved by the present method (Entry 4).

The present study is the first example of the direct alkylation of lithium enolates with heterocyclic formyl and acyl cation equivalents and provides a useful procedure for introduction of masked formyl and acyl groups at the α-position of carbonyl compounds because of ready and diverse availability of benzothiazolium salts[2,3] and high operational conveniency. The alkylation products can be regarded as selectively protected 1,3-dicarbonyl compounds and potentially useful synthetic intermediates because, for example, the 3-methylbenzothiazoline unit could be, after desired synthetic transformation, hydrolyzed to a carbonyl group as shown in the previous work.[2,3] In addition the another unique functionalities of 3-methylbenzothiazoline ring system increases the value of the present alkylation products in organic synthesis.[4,6]

Experimental

Melting points were recorded on a Yanagimoto micro-melting-point apparatus and are uncorrected. ^{1}H NMR spectra were measured with a JEOL PMX-60 spectrometer at 60 MHz using tetramethylsilane as an internal reference. IR spectra were recorded on a JASCO A-202 spectrophotometer. Silica gel (Merck silica gel 60, 230—400 mesh ASTM) was used for medium-pressure liquid chromatography (MPLC).

Materials. 2,3-Dimethylbenzothiazolium iodide (**1c**) was prepared by methylation of commercially available 2-methylbenzothiazole with iodomethane according to the preparation method reported for 3-methylbenzothiazolium iodide (**1a**).[2] 3-Methyl-2-phenylbenzothiazolium fluorosulfate (**1b**) was prepared by the methylation of 2-phenylbenzothiazole with methyl fluorosulfate according to the preparation method reported for 3-methylbenzothiazolium fluorosulfate.[2]

The Reaction of Benzothiazolium Salts 1 with Lithium Enolates 2 from Esters; General Procedure. To a solution of diisopropylamine (1.21 g, 12 mmol) in THF (20 ml), a 1.6 M hexane solution (1M=1 mol dm^{-3}) of *n*-BuLi (6.9 ml, 11 mmol) was slowly added with stirring at −78 °C and the mixture was then stirred at 0 °C for 10 min. To this mixture, a THF (5 ml) solution of ester (10 mmol) was slowly added at −78 °C and the mixture was then stirred for 50 min. Benzothiazolium salts **1** (10 mmol) was added at −78 °C and the mixture was stirred for 1 h at −78 °C and for 2 h at room temperature. The mixture was quenched by the addition of water and the aqueous mixture was extracted with ether. The extract was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to MPLC to give pure product **4**. The results are summarized in Table 1. The spectral and physical data of the products **4** are as follows:

4a: pale yellow oil; IR (neat) 1720 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ=1.16 (t, 3H, J=7 Hz), 2.67 (s, 3H), 2.73 (m, 2H), 4.00 (q, 2H, J=7 Hz), 5.15 (dd, 1H, J=8, 5 Hz), and 6.05—6.87 (m, 4H). Calcd for $C_{12}H_{15}NO_2S$: C, 60.73; H, 6.37; N, 5.90%. Found: C, 60.12; H, 6.46; N, 6.04%.

4b: pale yellow oil; IR (neat) 1720 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ=1.13 (s, 3H), 1.17 (s, 3H), 1.20 (t, 3H, J=7 Hz), 2.82 (s, 3H), 4.04 (q, 2H, J=7 Hz), 5.23 (s, 1H), and 6.25—6.90 (m, 4H). Calcd for $C_{14}H_{19}NO_2S$: C, 63.36; H, 7.22; N, 5.28%. Found: C, 62.86; H, 7.30; N, 5.30%.

4c: pale yellow oil (diastereomeric mixture of 55 : 45 by ^{1}H NMR analysis); IR (neat) 1720 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ=1.17 (d, 3H, J=7 Hz), 1.23 (t, 3H, J=7 Hz), 2.74 and 2.82 (each s, 4H), 4.06 and 3.94 (each q, 2H, J=7 Hz), 5.13 and 5.29 (each d, 1H, J=5 Hz), and 6.10—6.93 (m, 4H). Calcd for $C_{13}H_{17}NO_2S$: C, 62.12; H, 6.82; N, 5.57%. Found: C, 61.86; H, 6.96; N, 5.52%.

4d: pale yellow oil (diastereomeric mixture of 50 : 50 by ^{1}H NMR analysis); IR (neat) 1710 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ=0.93 (t, 3H, J=7 Hz), 1.20 (t, 3H, J=7 Hz), 1.66 (q, 2H, J=7 Hz), 2.80 and 2.87 (each s, 4H), 4.05 (m, 2H), 4.97 and 5.08 (each d, 1H, J=2, 3 Hz), and 6.23—7.17 (m, 4H). Calcd for $C_{14}H_{19}NO_2S$: C, 63.36; H, 7.22; N, 5.28%. Found: C, 63.31; H, 7.21; N, 5.31%.

4e: pale yellow oil (diastereomeric mixture of 60 : 40 by ^{1}H NMR analysis); IR (neat) 1720 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ=0.93 and 0.96 (each d, 6H, J=7 Hz), 1.22 (t, 3H, J=7 Hz), 2.27 (m, 1H), 2.62 and 2.64 (each d, 1H, J=8, 6 Hz), 2.80 and 2.83 (each s, 3H), 3.95 and 4.08 (each q, 2H, J=7 Hz), 5.10 and 5.12 (each d, 1H, J=8, 6 Hz), and 6.25—7.00 (m, 4H). Calcd for $C_{15}H_{21}NO_2S$: C, 64.48; H, 7.58; N, 5.01%. Found: C, 64.03; H, 7.71; N, 5.06%.

4f: pale yellow oil; IR (neat) 1720 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ=1.00 (t, 3H, J=7 Hz), 2.53 (s, 3H), 3.27 (s, 2H), 3.84 (q, 2H, J=7 Hz), and 6.57—7.50 (m, 9H). Calcd for $C_{18}H_{19}NO_2S$: C, 68.98; H, 6.11; N, 4.47%. Found: C, 69.06; H, 6.09; N, 4.50%.

4g: pale yellow oil; IR (neat) 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.19 (t, 3H, J=8 Hz), 1.33 (s, 6H), 1.90 (s, 3H), 2.73 (s, 3H), 3.98 (q, 2H, J=8 Hz), and 6.00—6.92 (m, 4H). Calcd for $C_{15}H_{21}NO_2S$: C, 64.48; H, 7.58; N, 5.01%. Found: C, 64.16; H, 7.32; N, 4.91%.

The Reaction of Benzothiazolium Salts 1 with Lithium Enolates 3 from Ketones; General Procedure. A THF (5 ml) solution of ketone (10 mmol) was slowly added to a THF solution of LDA (11 mmol) at −78 °C and the mixture was allowed to gradually warm to room temperature. The mixture was stirred for 3 h and then cooled to 0 °C. Benzothiazolium salt **1** (10 mmol) was added to the mixture and the mixture was stirred for 1 h at 0 °C and for 1 h at room temperature. After a similar work-up to the reaction of ester enolates, the crude product was purified by MPLC to give pure product **5**. The results are summarized in Table 2. The spectral and physical data of the products **5** are as follows:

5a: pale yellow oil; IR (neat) 1680 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ=2.43 (s, 3H), 3.10 (m, 2H), 5.10 (dd, 1H, J=8, 6 Hz), and 5.76—7.57 (m, 9H). This compound was unstable at room temperature in air.

5b: pale yellow needles; mp 119—120 °C; IR (KBr) 1680 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ=2.55 (s, 3H), 3.83 (d, 1H, J=16 Hz), 4.33 (d, 1H, J=16 Hz), and 6.05—7.83 (m, 14H). Calcd for $C_{22}H_{19}NOS$: C, 76.49; H, 5.54; N, 4.05%. Found: C, 76.42; H, 5.53; N, 3.85%.

5c: pale yellow needles; mp 123—124 °C; IR (KBr) 1700 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ=2.10 (s, 3H), 2.55 (s, 3H), 3.21 (d, 1H, J=11 Hz), 3.47 (d, 1H, J=11 Hz), and 6.21—7.52 (m, 9H). Calcd for $C_{17}H_{17}NOS$: C, 72.05; H, 6.05; N, 4.94%. Found: C, 71.91; H, 5.96; N, 4.83%.

5d: pale yellow needles; mp 66—66.7 °C; IR (KBr) 1700

cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=0.80 (t, 3H, J=8 Hz), 1.50 (m, 2H), 2.33 (t, 2H, J=6 Hz), 2.50 (s, 3H), 3.28 (d, 1H, J=18 Hz), 3.72 (d, 1H, J=18 Hz), and 6.23—7.70 (m, 9H). Calcd for $C_{19}H_{21}NOS$: C, 73.28; H, 6.80; N, 4.50%. Found: C, 73.09; H, 6.80; N, 4.46%.

5e: pale yellow needles; mp 153—153.5 °C; IR (KBr) 1680 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=1.53 (d, 3H, J=8 Hz), 2.42 (m, 3H), 4.56 (q, 1H, J=8 Hz), and 6.43—7.33 (m, 14H). Calcd for $C_{23}H_{21}NOS$: C, 76.85; H, 5.89; N, 3.90%. Found: C, 76.75; H, 5.98; N, 3.69%.

5e′: pale yellow needles; mp 120.3—121.5 °C; IR (KBr) 1700 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=1.05 (d, 3H, J=6 Hz), 2.55 (s, 3H), 3.85 (q, 1H, J=6 Hz), and 6.31—7.40 (m, 14H). Calcd for $C_{23}H_{21}NOS$: C, 76.85; H, 5.89; N, 3.90%. Found: C, 76.41; H, 6.04; N, 4.55%.

5f: pale yellow needles; mp 150.5—152 °C; IR (KBr) 1680 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=0.96 (t, 3H, J=8 Hz), 2.03 (m, 2H), 2.50 (s, 3H), 4.41 (dd, 1H, J=4, 7 Hz), and 6.23—7.83 (m, 14H). Calcd for $C_{24}H_{23}NOS$: C, 77.17; H, 6.21; N, 3.75%. Found: C, 77.23; H, 6.17; N, 3.42%.

5g: colorless needles; mp 184.2—186 °C; IR (KBr) 1700 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=1.52—2.33 (bm, 9H), 2.40 (s, 3H), and 6.43—7.35 (m, 9H). Calcd for $C_{20}H_{21}NOS$: C, 74.27; H, 6.54; N, 4.33%. Found: C, 74.03; H, 6.49; N, 4.13%.

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