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Syntheses of 2-Alkylthio-1,3-thiazine Derivatives from *S*-Alkyldithiocarbamates and α,β-Unsaturated Ketones

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ABSTRACT: *Various 2-alkylthio-1,3-thiazine derivatives were synthesized by the reactions of S-alkylthiocarbamates with α,β-unsaturated ketones in the presence of $BF_3 \cdot Et_2O$. The thiazine was converted into two isomeric dehydrated products in the presence of a Lewis acid.* © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:377–379, 2002; Published online in Wiley Interscience (www.interscience.wiley.com). DOI 10.1002/hc.10055

INTRODUCTION

The literature for heterocyclic pharmaceutical agents includes sulfur-containing compounds [1] that have been reported as antimalarial agents [2], HIV-1 inhibitors [3], and antimicrobial agents [4]. Syntheses of 1,3-thiazines have been realized by various methods [5]. For example, β-chlorovinyl ketones and thioamides in the presence of perchloric acid give rise to intermediate *S*-ketovinylthioimidium salts, which then cyclize to yield 1,3-thiazinium salts [6]. Recently, the selenium analogues, 1,3-selenazines, have also been reported [7]. In this article, we report a new synthesis of 2-alkylthio-1,3-thiazine derivatives **4** by the reaction of *S*-alkyldithiocarbamates **2** with α,β-unsaturated ketones **3** in the presence of $BF_3 \cdot Et_2O$, and the subsequent conversion into two isomeric dehydrated products from the thiazines by the reaction with Lewis acids.

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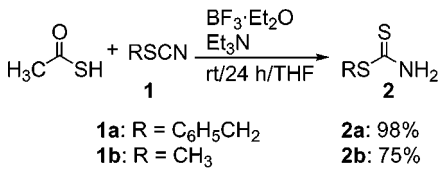
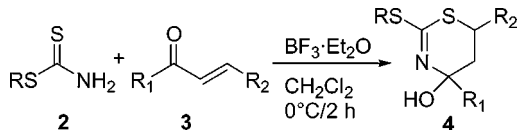
RESULTS AND DISCUSSION

Two dithiocarbamates **2** were prepared by the reaction of thioacetic acid with thiocyanates **1**, as shown in Scheme 1. Both **2a** and **2b**, respectively, were obtained in high yields. The reactions were thought to be initiated by the nucleophilic addition of the sulfur atom of thioacetate to the carbon atom of the cyano group of the thiocyanate, with subsequent elimination of acetic acid by hydrolysis, to give **2**. Previously, syntheses of the dithiocarbamate, such as *S*-methyl dithiocarbamate and *S*-phenyl dithiocarbamate, were reported by the reaction of a dithiophosphoric acid with a thiocyanate. However, the yields in these reactions were only around 40% [8]. The dithiocarbamates **2** were used for a synthesis of 2-alkylthio-4-hydroxy-4*H*-5,6-dihydro-1,3-thiazines **4** by reactions with α,β-unsaturated ketones **3**.

The results of the reactions of two dithiocarbamates **2** with various α,β-unsaturated ketones **3** are summarized in Table 1. All reactions gave 2-alkylthio-4-hydroxy-5,6-dihydro-4*H*-1,3-thiazines **4** in high yields. The typical procedure for the synthesis of **4** is shown in Scheme 2. Briefly, $BF_3 \cdot Et_2O$ (1 equiv.) was added to the *S*-benzyl dithiocarbamate **2a** (1 equiv.) in dry dichloromethane at 0°C under an argon atmosphere. Subsequently, methyl vinyl ketone (**3a**; 1 equiv.) was added at 0°C, and the mixture was stirred for 2 h. After workup, 2-benzylthio-4-hydroxy-4-methyl-5,6-dihydro-4*H*-1,3-thiazine (**4a**) was obtained as an orange liquid in 88% yield. Among the subsequently obtained thiazines, **4c, 4d, 4h**, and **4i** consist of diastereomers containing two asymmetric centers at the C4 and C6 positions of



SCHEME 1



SCHEME 2

the thiazine ring. The predominant diastereomer was confirmed to have a *cis* relationship between the OH group at C4 and the substituent at C6 by examination of the NOESY spectra.

Attempts to dehydrate the 2-benzylthio-4-hydroxy-5,6-dihydro-4*H*-1,3-thiazines **4a–c** were carried out by use of a series of Lewis acids such as $BF_3 \cdot Et_2O$, $AlCl_3$, $TiCl_4$, and $ZnCl_2$. The reactions of **4a** with $BF_3 \cdot Et_2O$ and $AlCl_3$ at room temperature in dichloromethane gave dehydrated products in 53 and 26% yields, respectively, while those with $TiCl_4$ and $ZnCl_2$ gave only recovered starting materials. The products obtained from the reaction were two isomeric dehydrated products, viz. 4,5-dihydro-4-methylene-6*H*-1,3-thiazine (**5a**) and 4-methyl-6*H*-1,3-thiazine (**6a**) (Scheme 3). The optimal conditions to obtain the products of highest yield were the reaction of **4a** with $BF_3 \cdot Et_2O$ under reflux for 2 h in chloroform, affording the mixture of **5a** and **6a** in the ratio of 16:84 (**5a**:**6a**) in 83% yield. Similarly, **4b** and **4c** were dehydrated under the reflux conditions, affording the corresponding two isomeric dehydrated products (Table 2). The ratio of the two isomers **5a** and **6a** depended on the reaction time. The amount of **5a** was decreased by applying a longer reaction time. This indicated that **5a** and **6a** of a certain ratio were formed first, and gradually isomerized to the more stable ratio favoring **6a**. In fact, when the reaction was refluxed for 24 h, an equilibrium mixture resulted at the ratio of 94:6 (**6a**:**5a**).

EXPERIMENTAL

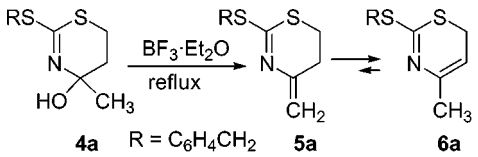
Spectral Data of Representative Compounds

*2-Benzylthio-4-hydroxy-4-methyl-5,6-dihydro-4H-1,3-thiazine (**4a**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 3H), 1.78–1.88 (m, 1H), 1.91–1.99 (m, 1H), 2.90–2.99 (m, 1H), 3.08–3.15 (m, 1H), 3.26 (br s, 1H), 4.17 (d, $J = 13.6$ Hz, 1H), 4.32 (d, $J = 13.6$ Hz, 1H), 7.17–7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1, 27.7, 31.2, 34.5, 82.3, 127.0, 128.2, 128.9, 137.1,

TABLE 1 Syntheses of Various 2-Alkylthio-1,3-thiazines **4**

*Ketone **3***	*Product **4***	*Yield[a] **4** (%) (cis/trans)[b]*	*Product **4***	*Yield[a] **4** (%) (cis/trans)[b]*
3a	**4a**	88	**4f**	74
3b	**4b**	90	**4g**	96
3c	**4c**	81 (51/49)	**4h**	89 (52/48)
3d	**4d**	88 (58/42)	**4i**	90 (65/35)
3e	**4e**	90	**4j**	78

R = $C_6H_5CH_2$, R′ = CH_3.
[a]Isolated yield.
[b]Calculated by ^{1}H NMR spectra.



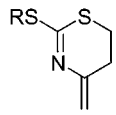
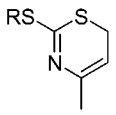
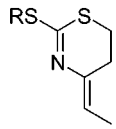
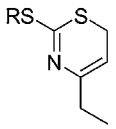
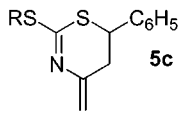
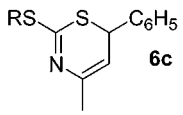
SCHEME 3

156.2; IR (neat) 3405, 1580 cm^{-1}; MS (CI) $m/z = 254$ ($M^+ + 1$); HRMS $m/z = 253.0953$ for $C_{12}H_{15}NOS_2$; found, 253.0974.

*2-Benzylthio-4-methylene-4,5-dihydro-6H-1,3-thiazine (**5a**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 (t, $J = 6.4$ Hz, 2H), 2.93 (t, $J = 6.4$ Hz, 2H), 4.32 (s, 2H), 4.67 (d, $J = 1.2$ Hz, 1H), 5.06 (d, $J = 1.2$ Hz, 1H), 7.17–7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.4, 27.3, 34.6, 109.1, 127.1, 128.4, 129.1, 137.2, 145.4, 157.1; MS (CI) $m/z = 236$ ($M^+ + 1$).

*2-Benzylthio-4-methyl-6H-1,3-thiazine (**6a**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98 (s, 3H), 3.20 (d, $J =$ 5.6 Hz, 2H), 4.33 (s, 2H), 4.96 (t, $J = 5.6$ Hz, 1H), 7.17–7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 25.6, 35.3, 98.4, 127.1, 128.4, 129.1, 137.2, 145.4, 158.8; MS (CI) $m/z = 236$ ($M^+ + 1$); Anal. Calcd. for $C_{12}H_{13}NS_2$: C, 61.24; H, 5.57; N, 5.95. Found: C, 61.33; H, 5.68; N, 5.92.

TABLE 2 Dehydration of 2-Benzylthio-1,3-thiazines **4a–c** with $BF_3 \cdot Et_2O$

Run	Thiazine	Products 5	Products 6	Yield[a] (%) (5/6)[b]
1	**4a**	 **5a**	 **6a**	83 (16/84)
2	**4b**	 **5b**	 **6b**	91 (24/76)
3	**4c**	 **5c**	 **6c**	56 (14/86)

$R = C_6H_5CH_2$.
[a] Total Isolated yield.
[b] The ratio of **5** and **6** was calculated by ^{1}H NMR spectra.

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