REACTION OF HALOACETOACETATE WITH L-CYSTEINE ETHYL ESTER —SYNTHESIS OF 1,4-THIAZINE DERIVATIVES—

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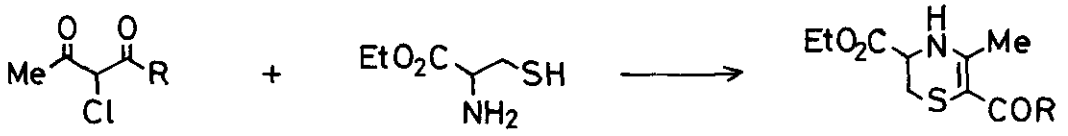
Abstract —— Reaction of ethyl 2-chloroacetoacetate (2a) with L-cysteine ethyl ester (1) gave 3,6-diethoxycarbonyl-5-methyl-3,4-dihydro-2*H*-1,4-thiazine (3a). Similarly, 2-chloroacetoacetanilides 2b-2d reacted with 1 to give 6-carbamoyl-5-methyl-3,4-dihydro-2*H*-1,4-thiazines 3b-3d.
Ethyl 4-bromoacetoacetate (4a) reacted with L-cysteine ethyl ester (1) to give 3-ethoxycarbonyl-5-(ethoxycarbonylmethylene)-tetrahydro-2*H*-1,4-thiazine (5a) in 62% yield. Reaction of 4-bromoacetoacetanilides 4b and 4c with 1 gave 5-(carbamoylmethylene)tetrahydro-2*H*-1,4-thiazines 5b and 5c, respectively.

The reaction of L-cysteine methyl ester with α-haloketones represents an important synthetic route to dihydrothiazines.[1-4] However, there is no report concerning such a reaction using haloacetoacetic acid derivatives.
Previously, we have reported that ethyl 4-haloacetoacetate reacted with thioacetanilides and 2-cyanoethene-1,1-dithiols to give thiazolidine-4-acetates and 1,3-dithiolane-4-acetates, respectively.[5,6]
In a continuation of our study on the synthesis of sulfur containing heterocycles using haloacetoacetic acid derivatives, we now wish to report the reaction of L-cysteine ethyl ester with haloacetoacetic acid derivatives, which were easily prepared from diketene.[7]

When ethyl 2-chloroacetoacetate (2a) was allowed to react with L-cysteine ethyl ester (1), 3,6-diethoxycarbonyl-5-methyl-3,4-dihydro-2*H*-1,4-thiazine (3a) was obtained in 30% yield. Similarly, reaction of 2-chloroacetoacetanilides 2b-2d with 1 gave rise to the corresponding 3,4-dihydro-2*H*-1,4-thiazines 3b-3d in 44-68% yields.



2a: R=OEt
2b: R=NHC$_6$H$_4$-*o*-CO$_2$Me
2c: R=NHC$_6$H$_4$-*o*-Cl
2d: R=NHC$_6$H$_4$-*p*-Cl

1

3a: R=OEt (30%)
3b: R=NHC$_6$H$_4$-*o*-CO$_2$Me (68%)
3c: R=NHC$_6$H$_4$-*o*-Cl (44%)
3d: R=NHC$_6$H$_4$-*p*-Cl (53%)

4a: R=OEt
4b: R=NHC$_6$H$_4$-*o*-CO$_2$Me
4c: R=NHC$_6$H$_4$-*o*-Cl

5a: R=OEt (62%)
5b: R=NHC$_6$H$_4$-*o*-CO$_2$Me (63%)
5c: R=NHC$_6$H$_4$-*o*-Cl (23%)

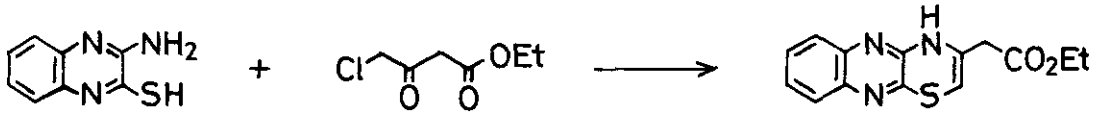


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Chart 1

On the other hand, reaction of ethyl 4-bromoacetoacetate (4a) with 1 gave 3-ethoxycarbonyl-5-(ethoxycarbonylmethylene)tetrahydro-2*H*-1,4-thiazine (5a)[8] in 62% yield. Its structure was confirmed by elemental analyses and spectral measurements. Safonova *et al.*[9] reported that reaction of 2-amino-3-mercaptoquinoxaline (6) with ethyl 4-chloroacetoacetate (7) afforded ethyl 4*H*-quinoxalino[2,3-*b*][1,4]thiazine-3-acetate (8). They concluded that compound 8 has the structure containing the C=C double bond in the ring.

Infrared (ir) spectrum of compound 5a indicated the band due to α,β-unsaturated ester carbonyl absorption at 1655 cm^{-1}. Nuclear magnetic resonance (nmr) spectrum of 5a showed the signal due to an N_4 proton at lower field (8.82-9.01 ppm) than that of compound 3a (4.70-5.00 ppm).

These spectral data showed the structure of compound 5a to be 5-(ethoxycarbonylmethylene)tetrahydro-2*H*-1,4-thiazine.

Similarly, 4-bromoacetoacetanilide derivatives 4b and 4c reacted with 1 to give the corresponding 5-(carbamoylmethylene)tetrahydro-2*H*-1,4-thiazines 5b and 5c.

Table I. Melting Points, ir Spectra and Specific Rotations for 3a-d and 5a-c

No.	mp (°C)	$\nu_{max.}$ ($CHCl_3$) cm^{-1} C=O	$[\alpha]_D^{19}$ (c=0.2, MeOH)
3a	56-57	1735, 1675	+135°
3b	111-112	1735, 1690, 1650	+19°
3c	105-106	1735, 1650	+41°
3d	114-116	1735, 1650	+90°
5a	94.5-95.5	1740, 1655	-50°
5b	112	1740, 1690, 1645	-58°
5c	83-84	1740, 1640	-14°

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8. 3-Ethoxycarbonyl-5-(ethoxycarbonylmethylene)tetrahydro-2*H*-1,4-thiazine (5a) — A solution of ethyl 4-bromoacetoacetate (4a) (2.1 g, 0.01 mol) in ethanol (10 ml) was added dropwise to a solution of L-cysteine ethyl ester hydrochloride (1) (1.85 g, 0.01 mol) in ethanol (10 ml) under stirring at 0-10°C. After being stirred at room temperature for 3.5 h, the mixture was concentrated *in vacuo*. The residue was neutralized with saturated sodium carbonate, and the mixture was extracted with chloroform (50 ml). The chloroform layer was dried over sodium sulfate and concentrated *in vacuo*. Crystals thus obtained were recrystallized from ethanol to give the product 5a as colorless needles, mp 94.5-95.5°C. Yield, 1.6 g (62 %). Found: C, 51.03; H, 6.63; N, 5.28; S, 12.21. $C_{11}H_{17}NO_4S$ requires C, 50.95; H, 6.61; N, 5.40; S, 12.36%; $\nu_{max.}$ ($CHCl_3$) 3300, 1740, 1655, and 1610 cm^{-1}. δ ($CDCl_3$) 1.25 (3H, t, *J* 7 Hz, $CH_2\underline{CH_3}$), 1.30 (3H, t, *J* 7 Hz, $CH_2\underline{CH_3}$), 3.01 (1H, dd, *J* 8 Hz, 12 Hz, 2-$H_{ax.}$), 3.22 (1H, dd, *J* 4 Hz, 12 Hz, 2-$H_{eq.}$), 3.15 and 3.36 (2H, ABq, *J* 15 Hz, SCH_2C=), 4.12 (2H, q, *J* 7 Hz, $O\underline{CH_2}CH_3$), 4.20 (1H, dd, *J* 4 Hz, 8 Hz, 3-H), 4.23 (2H, q, *J* 7 Hz, $O\underline{CH_2}CH_3$), 4.60 (1H, s, CH=), and 8.82-9.01 (1H, br, NH). $[\alpha]_D^{22}$ -116.5 (c=0.4, MeOH).
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