# Reactions of Polarized Ketoketene *S,N*-Acetals with Thionyl Chloride: a Novel General Route to 1-Aroyl-(or -Acyl)-2-aryl-(or -ethoxycarbonyl)-4-alkylthiothiazoles by Direct Heterocyclization[1]

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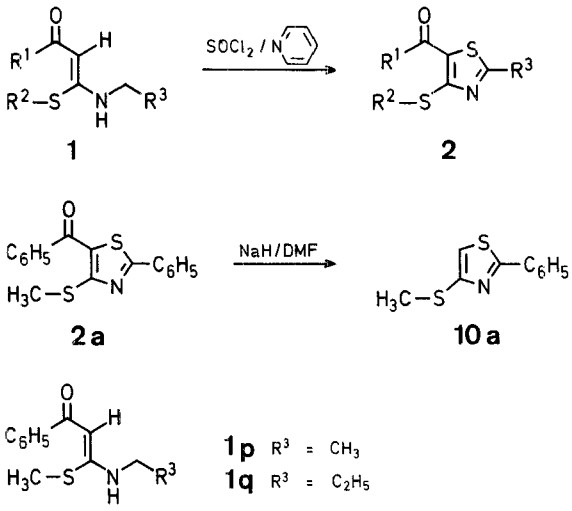
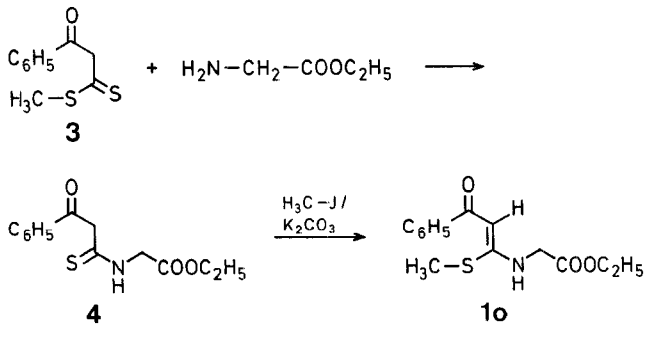
Extensive studies have been reported concerning the synthesis of 2-mercaptothiazoles and their *S*-alkyl or *S*-aryl derivatives[2]. The isomeric 5-mercaptothiazoles and their *S*-alkyl or aryl analogues have also been studied to some extent[2]. However, the chemistry of 4-mercaptothiazoles and their *S*-alkyl or *S*-aryl derivatives has received limited attention[2], i.e. the syntheses of 5-nitro-4-butylthio-2-acetylaminothiazole[3] and 4-phenylthiothiazole[4], which are obtained by nucleophilic displacement from the corresponding 4-halothiazoles by the appropriate anions. Although 2-, 4-, and 5-halothiazoles are known to undergo facile displacement reactions with appropriate nucleophiles[4], the 4-halothiazoles can only be obtained by partial dehalogenation of 2,4- or 4,5-dihalothiazoles[5]. Attempts to prepare 4-halothiazoles by direct halogenation are reported to yield either 5-halo- or 4,5-dihalothiazoles[6,7].

We now report a facile general route to the title thiazoles using ketoketene *S,N*-acetals[8,9] **1** as starting materials.




Scheme A

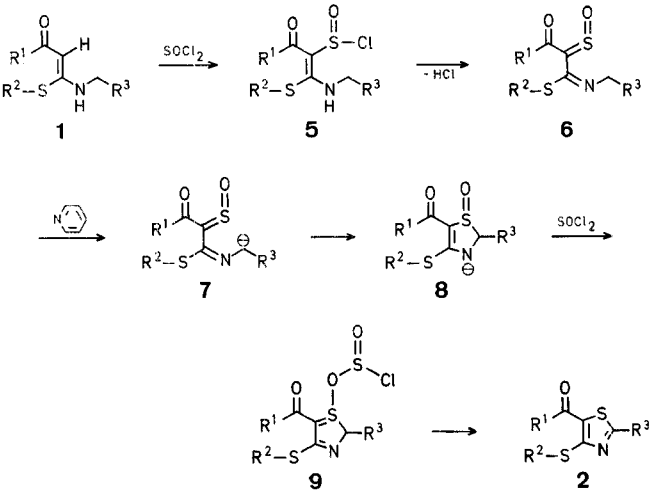
When **1a–m** were reacted with thionyl chloride in pyridine at 0–5 °C for 3 h the corresponding 2-phenyl-4-methylthio-5-benzoylthiazoles **2a–m** were obtained. The structures of **2a–m** were confirmed by analytical and spectral data (Table).




Scheme B

The *S,N*-acetal **1n** derived from acetone gave the corresponding **2n** only in 21% yield, while **1o** prepared as shown (Scheme **B**) gave the corresponding 2-ethoxycarbonylthiazole **(2o)** in 30% yield. The yield of **2n** and **2o** could not be improved further under various conditions. Compounds **1p** and **1q** failed to give the corresponding **2p** ($R^3 = H$) and **2q** ($R^3 = CH_3$), respectively. Only polymeric material was obtained in both cases.

The mechanism of the formation of **2** from **1** appears to be similar to that proposed[10] for the reaction of 6-*N*-substituted 1,3-dimethyluracils with thionyl chloride to give thiazolo[4,5-*d*]pyrimidines. The sulfene intermediate **6**, after proton abstraction undergoes cyclization via its anion **7** to form the corresponding thiazoline *S*-oxide **8**. Further reaction of **8** with thionyl chloride affords **2** via the Pummerer intermediate **9** (Scheme **C**).




Scheme C

Interestingly in one of the experiments, when **2a** was stirred with sodium hydride in dimethylformamide at room temperature the corresponding 5-unsubstituted-2-phenyl-4-methylthiothiazole **(10a)** was obtained in 70% yield. Similarly the thiazoles **10e, h, k** were prepared from the respective **2e, 2h,** and **2k** in 70–72% overall yields.

The method therefore provides hitherto inaccessible 2,5-disubstituted 4-alkylthiothiazoles as well as the corresponding 5-unsubstituted analogues starting from the same ketoketene *S,N*-acetals.

Freshly distilled thionyl chloride (E. Merck) was used in all reactions. All new *S,N*-acetals **1a–n, p, q** were prepared according to the previously reported procedures[11,12].

***N*-(α-Ethoxycarbonylmethyl)-β-benzoylthioacetamide (4):**

A solution of methyl β-benzoyldithioacetate (**3**; 4.2 g, 0.02 mol) and free ethyl glycinate [0.02 mol, generated from ethyl glycinate hydrochloride (2.80 g, 0.02 mol) and sodium ethoxide (0.02 mol)] in ethanol (50 ml) is refluxed for 8–10 h. After completion of the reaction (monitored by T.L.C.), the ethanol is removed under reduced pressure and the crude thioamide **4** is purified by passage through a silica gel column using benzene/hexane (1/4) as eluent; yield: 2.8 g (52%); pale needles; m.p. 95–96 °C.

| | | | | |
|---|---|---|---|---|
| $C_{13}H_{15}NO_3S$ | calc. | C 58.86 | H 5.66 | N 5.28 |
| (265.3) | found | 59.15 | 5.92 | 5.50 |

I.R. (KBr): $\nu = 3500$ (NH); 1730 (ester CO); 1665 $cm^{-1}$ (Ar—CO).

$^1$H-N.M.R. ($CCl_4$): $\delta = 1.30$ (t, 3H, $CH_3CH_2O$); 3.72 (s, 2H, $C_6H_5COCH_2$); 4.0–4.4 (m, 4H, $OCH_2CH_3$ and NH—$CH_2CO$); 7.1–7.3 (m, 3 $H_{arom}$); 7.82 ppm (m, 2 $H_{arom}$).

**Table.** 4-Alkylthiothiazoles **2a–o** and **10a, e, h, k** prepared

| Product No. | $R^1$ | $R^2$ | $R^3$ | Yield [%][a] | m.p. [°C][b] | Molecular formula[c] | I.R. $\nu$ [$cm^{-1}$] | $^1$H-N.M.R. ($CDCl_3$) $\delta$ [ppm] | M.S. $m/e$ ($M^+$) |
|---|---|---|---|---|---|---|---|---|---|
| **2a** | $C_6H_5$ | $CH_3$ | $C_6H_5$ | 60 | 95–96° | $C_{17}H_{13}NOS_2$ (311.4) | 1618 (CO)[d] | 2.70 (s, 3 H, $SCH_3$); 7.3–7.7 (m, 6 $H_{arom}$); 7.7–8.05 (m, 4 $H_{arom}$) | 311 |
| **2b** | 4-$H_3C$—$C_6H_4$ | $CH_3$ | $C_6H_5$ | 58 | 116–117° | $C_{18}H_{15}NOS_2$ (325.4) | 1621 (CO)[e] | 2.32 (s, 3 H, $CH_3$); 2.75 (s, 3 H, $SCH_3$); 7.05–8.0 (m, 9 $H_{arom}$) | 325 |
| **2c** | 4-$H_3CO$—$C_6H_4$ | $CH_3$ | $C_6H_5$ | 61 | 160° | $C_{18}H_{15}NO_2S_2$ (341.4) | 1620 (CO)[e] | 2.75 (s, 3 H, $SCH_3$); 3.90 (s, 3 H, $OCH_3$); 6.90 (d, 2 $H_{arom}$); 7.3–7.65 (m, 3 $H_{arom}$); 7.7–8.1 (m, 4 $H_{arom}$) | 341 |
| **2d** | 4-Cl—$C_6H_4$ | $CH_3$ | $C_6H_5$ | 60 | 143° | $C_{17}H_{12}ClNOS_2$ (345.8) | 1621 (CO)[d] | 2.68 (s, 3 H, $SCH_3$); 7.1–7.7 (m, 5 $H_{arom}$); 7.7–8.0 (m, 4 $H_{arom}$) | 347, 345 |
| **2e** | $C_6H_5$ | $CH_3$ | 4-Cl—$C_6H_4$ | 57 | 127–128° | $C_{17}H_{12}ClNOS_2$ (345.8) | 1626 (CO)[e] | 2.68 (s, 3 H, $SCH_3$); 7.2–7.55 (m, 5 $H_{arom}$); 7.65–8.0 (m, 4 $H_{arom}$) | 347, 345 |
| **2f** | 4-$H_3CO$—$C_6H_4$ | $CH_3$ | 4-Cl—$C_6H_4$ | 60 | 150° | $C_{18}H_{14}ClNO_2S_2$ (375.8) | 1615 (CO)[e] | 2.60 (s, 3 H, $SCH_3$); 3.79 (s, 3 H, $OCH_3$); 6.65–6.85 (m, 2 $H_{arom}$); 7.15–7.35 (m, 2 $H_{arom}$); 7.6–7.9 (m, 4 $H_{arom}$) | 377, 375 |
| **2g** | 4-Cl—$C_6H_4$ | $CH_3$ | 4-Cl—$C_6H_4$ | 61 | 157° | $C_{17}H_{11}Cl_2NOS_2$ (380.2) | 1610 (CO)[e] | 2.68 (s, 3 H, $SCH_3$); 7.3–7.5 (m, 4 $H_{arom}$); 7.6–7.9 (m, 4 $H_{arom}$) | 380 |
| **2h** | $C_6H_5$ | $CH_3$ | 4-$H_3CO$—$C_6H_4$ | 58 | 170–171° | $C_{18}H_{15}NO_2S_2$ (341.3) | 1615 (CO)[d] | 2.65 (s, 3 H, $SCH_3$); 3.80 (s, 3 H, $OCH_3$); 6.81 (d, 2 $H_{arom}$); 7.2–7.45 (m, 3 $H_{arom}$); 7.6–7.9 (m, 4 $H_{arom}$) | 341 |
| **2i** | 4-$H_3CO$—$C_6H_4$ | $CH_3$ | 4-$H_3CO$—$C_6H_4$ | 62 | 139–140° | $C_{19}H_{17}NO_3S_2$ (371.3) | 1610 (CO)[d] | 2.62 (s, 3 H, $SCH_3$); 3.80 (s, 3 H, $OCH_3$); 3.82 (s, 3 H, $OCH_3$); 6.83 (dd, 4 $H_{arom}$); 7.82 (dd, 4 $H_{arom}$) | 371 |
| **2j** | 4-Cl—$C_6H_4$ | $CH_3$ | 4-$H_3CO$—$C_6H_4$ | 60 | 199° | $C_{18}H_{14}ClNO_2S_2$ (375.8) | 1626 (CO)[e] | 2.65 (s, 3 H, $SCH_3$); 3.75 (s, 3 H, $OCH_3$); 6.7–6.9 (m, 2 $H_{arom}$); 7.0–7.4 (m, 2 $H_{arom}$); 7.6–8.0 (m, 4 $H_{arom}$) | 377, 375 |
| **2k** | $C_6H_5$ | $C_2H_5$ | $C_6H_5$ | 63 | 30–32° | $C_{18}H_{15}NOS_2$ (325.3) | 1612 (CO)[e] | 1.15 (t, 3 H, $CH_3$); 2.99 (q, 2 H, $CH_2S$); 6.85–7.2 (m, 6 $H_{arom}$); 7.3–7.7 (m, 4 $H_{arom}$) | 325 |
| **2l** | $C_6H_5$ | $C_6H_5CH_2$ | $C_6H_5$ | 60 | 128° | $C_{23}H_{17}NOS_2$ (387.4) | 1615 (CO)[e] | 4.40 (s, 2 H, $CH_2$); 7.0–7.5 (m, 11 $H_{arom}$); 7.5–7.95 (m, 4 $H_{arom}$) | 387 |
| **2m** | 4-$H_3CO$—$C_6H_4$ | $C_6H_5CH_2$ | $C_6H_5$ | 65 | 106–107° | $C_{24}H_{19}NO_2S_2$ (417.4) | 1610 (CO)[e] | 3.75 (s, 3 H, $OCH_3$); 2.49 (s, 2 H, $CH_2S$); 6.80 (d, 2 $H_{arom}$); 7.0–7.5 (m, 8 $H_{arom}$); 7.6–8.0 (m, 4 $H_{arom}$) | 417 |
| **2n** | $CH_3$ | $CH_3$ | $C_6H_5$ | 20 | 137–138° | $C_{12}H_{11}NOS_2$ (249.3) | 1670 (CO)[e] | 2.50 (s, 3 H, $CH_3$); 2.71 (s, 3 H, $SCH_3$); 7.2–7.5 (m, 3 $H_{arom}$); 7.8–8.1 (m, 2 $H_{arom}$) | 249 |
| **2o** | $C_6H_5$ | $CH_3$ | $COOC_2H_5$ | 30 | oil | $C_{14}H_{13}NO_3S_2$ (307.3) | 1724 (ester CO); 1660 (CO)[f] | 1.30 (t, 3 H, $OCH_2CH_3$); 2.01 (s, 3 H, $SCH_3$); 4.04 (q, 2 H, $OCH_2CH_3$); 7.2–7.5 (m, 3 $H_{arom}$); 7.5–7.7 (m, 2 $H_{arom}$) | 307 |
| **10a** | — | $CH_3$ | $C_6H_5$ | 70 | oil | $C_{10}H_9NS_2$ (207.2) | 1620 (s), 1500 (m), 1470 (s), 1250[f] | 2.55 (s, 3 H, $SCH_3$); 6.68 (s, 1 H, H-5); 7.1–7.5 (m, 3 $H_{arom}$); 7.65–8.1 (m, 2 $H_{arom}$) | 207 |
| **10e** | — | $CH_3$ | 4-Cl—$C_6H_4$ | 72 | 53–54° | $C_{10}H_8ClNS_2$ (241.7) | 1625 (s), 1505 (m), 1470 (s), 1265 (s)[e] | 2.38 (s, 3 H, $SCH_3$); 6.61 (s, 1 H, H-5); 7.0–7.8 (dd, 4 $H_{arom}$) | 243, 241 |
| **10h** | — | $CH_3$ | 4-$H_3CO$—$C_6H_4$ | 75 | 57–58° | $C_{11}H_{11}NOS_2$ (237.2) | 1615 (s), 1525 (m), 1470 (s), 1260 (s)[e] | 2.42 (s, 3 H, $SCH_3$); 3.65 (s, 3 H, $OCH_3$); 6.59 (s, 1 H, H-5); 6.70 (d, 2 $H_{arom}$); 7.75 (d, 2 $H_{arom}$) | 237 |
| **10k** | — | $C_2H_5$ | $C_6H_5$ | 72 | semi-solid | $C_{11}H_{11}NS_2$ (221.3) | 1615 (s), 1500 (m), 1462 (s), 1400 (s), 1265 (s)[f] | 0.90 (t, 3 H, $SCH_2CH_3$); 2.62 (q, 2 H, $SCH_2CH_3$); 6.45 (s, 1 H, H-5); 6.7–7.2 (m, 3 $H_{arom}$); 7.3–7.8 (m, 2 $H_{arom}$) | 221 |

[a] Yield of pure, isolated product.
[b] All products were recrystallized from benzene/hexane.
[c] Satisfactory microanalyses obtained: C ±0.40, H ±0.39, N ±0.37; exceptions: **2g, 2k, 2m, 2o, 10a, 10e, 10k** with H ±0.48, N ±0.54.
[d] In Nujol.
[e] In KBr.
[f] Neat.

**3-Methylthio-3-(α-ethoxycarbonylmethyl)-amino-1-phenyl-2-propen-1-one (1o):**

A suspension of thioamide **4** (1.0 g, 0.004 mol) and potassium carbonate (0.6 g, 0.004 mol) in acetone (30 ml) is refluxed for 3 h. The stirred solution is cooled, methyl iodide (0.8 g, 0.005 mol) is added, and the mixture is further stirred at room temperature for 3 h. It is poured onto crushed ice (100 ml), acidified with 20% acetic acid, extracted with chloroform (150 ml), dried with sodium sulfate, and the solvent evaporated to give a yellow viscous liquid; yield: 0.8 g (75%), T.L.C.: one spot.

| | | | | |
|---|---|---|---|---|
| $C_{14}H_{17}NO_3S$ | calc. | C 60.22 | H 6.11 | N 5.20 |
| (279.4) | found | 60.55 | 6.42 | 5.50 |

I.R. (KBr): $\nu = 3400$ (NH); 1730 (ester CO); 1620 $cm^{-1}$ (Ar—CO).

$^1$H-N.M.R. ($CDCl_3$): $\delta = 1.30$ (t, 3H, $CH_3CH_2$—); 2.34 (s, 3H, $SCH_3$); 3.82–4.30 (d and q, 4H, $OCH_2CH_3$ and NH—$CH_2$—); 7.2 (m, 3$H_{arom}$); 7.8 (m, 2$H_{arom}$); 11.0 ppm (br. s, 1H, NH, exchangeable with $D_2O$).

**2-Aryl-(or -Ethoxycarbonyl)-4-alkylthio-5-aroyl-(or -acyl)-thiazoles (2a–n) and (2o); General Procedure:**

To a stirred ice-cooled solution of *S,N*-acetal **1** (0.01 mol) in dry pyridine (8 ml), an excess of freshly distilled thionyl chloride (40 ml) is added slowly during 0.5 h and the mixture is further stirred for 2.5 h. The mixture is poured onto crushed ice (150 ml), slowly neutralized with solid sodium hydrogen carbonate, and the mixture is allowed to warm up to room temperature. It is then extracted with chloroform (3 × 100 ml), the extract is washed with water (3 × 150 ml), dried with sodium sulfate, and evaporated to give an orange yellow viscous residue, which is purified by column chromatography over neutral alumina. Elution with benzene/hexane (1/4) gives the pure thiazole as a bright yellow solid **(2a–n)** or as a viscous liquid **(2o)** (Table).

**2-Aryl-4-alkylthio-5-unsubstituted-thiazoles (10); General Procedure:**

To a stirred suspension of sodium hydride (0.3 g, 0.006 mol, 50% suspension) in dry dimethylformamide (20 ml), the respective thiazole **2a, 2e, 2h,** or **2k** (0.004 mol) in dry dimethylformamide (5 ml) is added slowly and the mixture is further stirred at 65–70°C for 5 h. It is then poured into ice-cold water (100 ml), neutralized with 20% acetic acid, and extracted with chloroform (2 × 100 ml). The chloroform layer, after drying and evaporation, yields the thiazoles as viscous liquids **(10a)** and **(10k)** or low melting solids **(10e)** and **(10h),** which are pure enough for spectroscopy. They are further purified for microanalysis by passing them through a small neutral alumina column using benzene/hexane (1/4) as eluent (Table).

*We thank the C. S. I. R. New Delhi for a Junior Research Fellowship (to A. R.) and special financial assistance under Career Award (to H. I.).*

Received: August 23, 1983

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