The Synthesis of 5-(*p*-Bromophenacylthio)- and 5-(Carbamoylthio)isothiazoles

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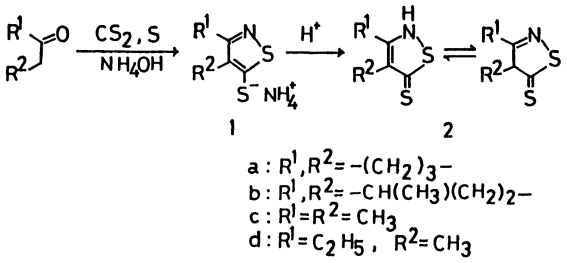
Synopsis. The reaction of the ammonium salts of 5(2*H*)-isothiazolethiones with *p*-bromophenacyl bromide, and methyl and phenyl isocyanates afforded 5-(*p*-bromophenacylthio)-, and 5-(carbamoylthio)isothiazoles. From phenyl isothiocyanate and hydrazine, 2,4-pyrimidinedithione, and 3*H*-pyrazole-3-thione derivatives were obtained, respectively.

Previously, we have reported on a new zwitterion, *N*-(1-ammoniocyclohexyl)-1,4,5,6-tetrahydro-2,1-benzisothiazole-3-thiolate, obtained through a reaction of cyclohexanone with carbon disulfide in the presence of aqueous ammonia and sulfur.[1] Under similar conditions, cyclopentanone gave 1,4,5,6-tetrahydro-3*H*-cyclopent[*c*]isothiazole-3-thione(**2a**),[1] which was the cyclo-oxidation product of 2-iminocyclopentanecarbodithioic acid.[2] Although many 5-substituted isothiazole derivatives have been reported, there are few 5(2*H*)- and 5(4*H*)-isothiazolethiones, and 5-alkylthioisothiazoles mentioned in the literature.[3] In this note, we wish to report on a new synthesis of 5-(*p*-bromophenacylthio)- (**3**), and 5-(carbamoylthio)isothiazoles (**4** and **5**) by a reaction of ammonium salts



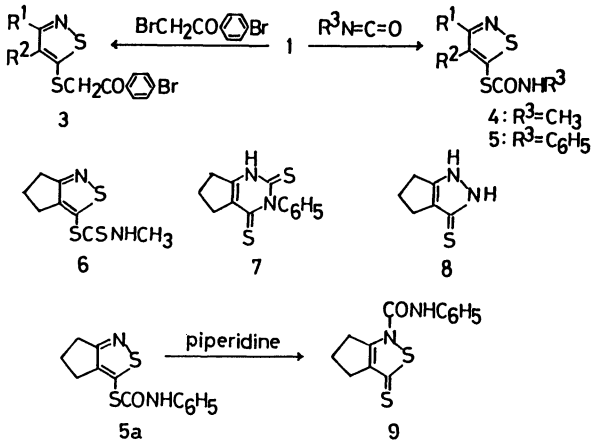
Scheme 1.

1a—d with *p*-bromophenacyl bromide, and methyl and phenyl isocyanates.

Salts **1b—d** were obtained from 2-methylcyclopentanone, ethyl methyl ketone, and diethyl ketone, respectively, in lower yields in a similar manner as described for the preparation of **1a**.[1] A treatment of **1** with hydrochloric acid gave 5(2*H*)-isothiazolethiones **2**. Salts **1** reacted with *p*-bromophenacyl bromide to give 5-(*p*-bromophenacylthio)isothiazoles **3**, whereas it was difficult to obtain crystalline products by a reac-

Table 1. Physical Properties and Spectral Data

Compd	Yield %	Mp θ_m/°C	IR spectra in KBr(cm^{-1})	UV spectra in EtOH (nm) (log ε)	Molecular formula	Found(Calcd)(%) C	H	N	S
2b	79	123—125	3250—3180(s) 1615(vs)	279(3.74), 298sh(3.72), 395(4.13)	$C_7H_9NS_2$	48.89 (49.12)	5.23 (5.30)	7.90 (8.18)	37.00 (37.39)
2c	94	113—115 (decomp)	1515(vs)	256(3.80), 307(3.70), 357(3.75)	$C_5H_7NS_2$	41.57 (41.38)	4.79 (4.86)	9.71 (9.65)	44.15 (44.10)
3a	83	123—125	1688(vs)	263(4.36)	$C_{14}H_{12}NOS_2Br$	47.57 (47.46)	3.45 (3.41)	3.73 (3.95)	17.90 (18.10)
3b	23	95—97	1680(vs)	263(4.69)	$C_{15}H_{14}NOS_2Br$	48.99 (48.92)	3.72 (3.83)	4.05 (3.80)	17.81 (17.41)
4a	85	149	3180(s) 1695(vs)	270(3.99), 311sh(2.97)	$C_8H_{10}N_2OS_2$	44.99 (44.86)	4.70 (4.71)	12.95 (13.08)	29.72 (29.88)
4b	26	96—97	3160(s) 1695(vs)	269(4.28), 310sh(3.33)	$C_9H_{12}N_2OS_2$	47.22 (47.37)	5.29 (5.30)	12.26 (12.28)	28.10 (28.05)
4c	70	143—145	3205(s) 1680(vs)	259(3.88), 266(3.88), 306(3.57)	$C_7H_{10}N_2OS_2$	41.85 (41.58)	4.99 (4.99)	13.97 (13.86)	31.90 (31.66)
4d	42	103—104	3212(s) 1685(vs)	258(3.85), 264(3.84), 306(3.60)	$C_8H_{12}N_2OS_2$	44.18 (44.44)	5.44 (5.60)	12.87 (12.96)	29.60 (29.60)
5a	59	166	3155(m) 1688(vs)	245(4.17), 277(4.14), 310sh(3.39)	$C_{13}H_{12}N_2OS_2$	56.57 (56.52)	4.55 (4.38)	9.97 (10.14)	23.54 (23.17)
5b	48	143—144	3175(m) 1690(vs)	246(4.16), 255sh(4.14), 277(4.11), 308sh(3.67)	$C_{14}H_{14}N_2OS_2$	58.19 (57.93)	4.83 (4.86)	9.67 (9.65)	21.88 (22.05)
5c	86	180—184	3200(m) 1695(vs)	236(3.90), 253sh(3.44), 306(3.62)	$C_{12}H_{12}N_2OS_2$	54.32 (54.54)	4.41 (4.58)	10.49 (10.60)	24.02 24.22)
5d	35	140—141	3200(m) 1702(vs)	239(4.23), 255sh(4.07), 276(3.99), 306(3.77)	$C_{13}H_{14}N_2OS_2$	56.11 (56.11)	5.10 (5.07)	10.07 (10.07)	23.38 (23.00)
6	35	116	3220(vs)	230sh(3.98), 268(4.23)	$C_8H_{10}N_2S_3$	41.95 (41.74)	4.48 (4.38)	12.21 (12.17)	41.55 (41.71)
7	32	ca. 190 (decomp)	3230—3150(m) 1610(vs)	264(4.38), 295sh(4.00), 432(4.32)	$C_{13}H_{12}N_2S_2$	59.95 (59.99)	4.58 (4.65)	10.79 (10.77)	24.59 (24.59)
9	83	ca. 190	3250—3170(m) 1715(vs)	240(4.06), 271(3.73), 337(3.69), 415(4.19)	$C_{13}H_{12}N_2OS_2$	56.80 (56.52)	4.66 (4.38)	10.32 (10.14)	23.59 (23.17)



Scheme 2.

tion with methyl iodide.

Reaction of **1** with methyl and phenyl isocyanates gave the corresponding addition compounds, 5-(carbamoylthio)isothiazoles **4** and **5**. Although the expected adduct, 5-(thiocarbamoylthio)isothiazole **6**, was obtained from methyl isothiocyanate, the reaction of **1a** with phenyl isothiocyanate afforded a ring-expanded compound **7**. The structure of **7** was judged from the microanalysis, and mass (M^+ 260) and UV spectra (432 nm). Salt **1a** reacted with hydrazine hydrate to give the pyrazole derivative **8**, which we had previously prepared from 2-imino-[4] or 2-oxocyclopentanecarbodithioic acid.[5] Perhaps the mechanism of the reaction leading to **7** or **8** involves a replacement of either the sulfur atom of **1a** by a nitrogen atom of isothiocyanate or hydrazine. It is of interest that a treatment of **5a** with piperidine afforded isomer **9**. The UV spectrum of **9** showed a red shift due to the thione-type structure (Table 1). A rearrangement, however, did not occur in **5b—d**.

Experimental

The Ammonium Salts (1) and 5(2*H*)-Isothiazolethiones (2). General Procedure. A mixture of ketone (0.25 mol), carbon disulfide (38 g, 0.5 mol), aqueous ammonia (28%; 70 ml), and sulfur (10 g, 0.31 mol) was stirred for 6 h—2 days at 0 °C. The mixture was kept for 2—7 days at 0—4 °C. The solid product was collected, and washed with carbon disulfide and ether. The crude salt was dissolved in water; the solution was then filtered and saturated with ammonium chloride to give practically pure crystals for use in reactions. The yields and melting points (from ethanol-hexane) of the salts were: **1a**, 61%, 145—146 °C;[1] **1b**, 30%, 93—95 °C; **1c**, 6%, 158—159 °C (decomp); **1d**, 3%, 97—99 °C. The salt **1** was dissolved in water and acidified with dilute hydrochloric acid to give yellow crystals, 1,4,5,6-tetrahydro-3*H*-cyclopent-[*c*]isothiazole-3-thione (**2a**),[1] 6-methyl-1,4,5,6-tetrahydro-3*H*-cyclopent[*c*]isothiazole-3-thione (**2b**), or 3,4-dimethyl-5(2*H*)-isothiazole-5-thione (**2c**). Compound **2d**, an oil, was not analyzed.

3-(*p*-Bromophenacylthio)-5,6-dihydro-4*H*-cyclopent[*c*]isothiazole (3a) and 3-(*p*-Bromophenacylthio)-6-methyl-5,6-dihydro-4*H*-cyclopent[*c*]isothiazole (3b). To a solution of **1** (0.003 mol) in ethanol (3 ml) was added a solution of *p*-bromophenacyl bromide (1.3 g, 0.005 mol) in ethanol (2 ml) with stirring at room temperature. The solid product was collected, washed with ether, and recrystallized from ethanol.

3-(Methylcarbamoylthio)-5,6-dihydro-4*H*-cyclopent[*c*]isothiazole (4a), 6-Methyl-3-(methylcarbamoylthio)-5,6-dihydro-4*H*-cyclopent[*c*]isothiazole (4b), 3,4-Dimethyl-5-(methylcarbamoylthio)isothiazole (4c), and 3-Ethyl-4-methyl-5-(methylcarbamoylthio)isothiazole (4d). To a solution or suspension of **1** (0.002 mol) in ethanol (2 ml) was added an excess of methyl isocyanate (0.004—0.005 mol); the mixture was kept for 2 days at 4—20 °C. In the case of **4a** or **4b**, the mixture was warmed at 60 °C for 20 min, and then kept for 3 days at 4 °C. The solid product was collected, washed with carbon disulfide and ethanol, and recrystallized from ethanol.

3-(Phenylcarbamoylthio)-5,6-dihydro-4*H*-cyclopent[*c*]isothiazole (5a), 6-Methyl-3-(phenylcarbamoylthio)-5,6-dihydro-4*H*-cyclopent[*c*]isothiazole (5b), 3,4-Dimethyl-5-(phenylcarbamoylthio)isothiazole (5c), and 3-Ethyl-4-methyl-5-(phenylcarbamoylthio)isothiazole (5d). Compounds **5b—d** were prepared by the method used for **4c** and **4d**, and recrystallized from methanol. In the case of **5a**, **1a** (0.35 g, 0.002 mol) was dissolved in ethanol (3.5 ml) at 50 °C, and to the warm solution was added phenyl isocyanate (0.6 g, 0.005 mol). When a large excess of phenyl isocyante was used, needles of *N,N'*-diphenylurea (mp 238 °C) were obtained together with **5**.

3-(Methylthiocarbamoylthio)-5,6-dihydro-4*H*-cyclopent[*c*]-isothiazole (6). To a suspension of **1a** (0.5 g, 0.0029 mol) in ethanol (3 ml) were added methyl isothiocyanate (0.4 g, 0.0055 mol) and acetic acid (0.12 ml), and the mixture was warmed for 10 min at 60 °C. The solid product was collected and washed with ethanol and carbon disulfide.

3-Phenyl-6,7-dihydro-1*H*-cyclopentapyrimidine-2,4(3*H*, 5*H*)-dithione (7). A mixture of **1a** (0.5 g, 0.0029 mol) and phenyl isothiocyanate (0.8 g, 0.0059 mol) was kept for 4 days at room temperature. The solid product was collected, washed with ethanol and carbon disulfide, and recrystallized from methanol.

1,4,5,6-Tetrahydrocyclopenta[*c*]pyrazole-3(2*H*)-thione (8). To a suspension of **1a**(0.5 g, 0.0029 mol) in ethanol (3 ml) was added 80% hydrazine hydrate (0.5 g, 0.008 mol). The mixture was warmed for 3 min at 60 °C and cooled to room temperature. Acetic acid (1 ml) was then added dropwise, and the solid product was collected, washed with water and ethanol, and recrystallized from ethylene glycol; mp 230 °C (decomp). The IR spectrum was identical with that reported.[4,5]

1-(Phenylcarbamoyl)-1,4,5,6-tetrahydro-3*H*-cyclopent[*c*]isothiazole-3-thione (9). A mixture of **5a** (0.1 g, 0.00036 mol), ethanol (3 ml), and piperidine (0.04 ml) was warmed for 10 min at 60 °C and kept overnight at room temperature. The solid product was collected and recrystallized from ethanol-pyridine.

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