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Studies of Heterocyclic Compounds. XVII.[1] Synthesis of 3-(Substituted-phenyl)-thiazolo[2,3-*b*]benzothiazolium Perchlorates

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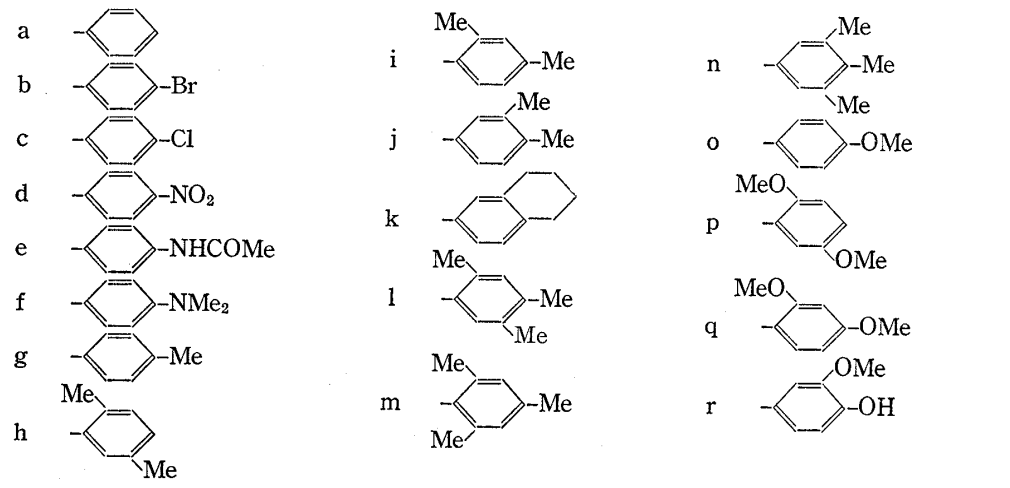
Seventeen 3-(substituted-phenyl)thiazolo[2,3-*b*]benzothiazolium perchlorates (**3**) were synthesized by acid-cyclization of the ketosulfides (**2**), which were prepared by alkylation of 2-mercaptobenzothiazole sodium salt with substituted phenacyl halides (**1**). Some of the phenacyl halides were prepared by chloroacetylation of substituted benzenes, and the others by bromination of the corresponding substituted acetophenones.

Keywords——phenacyl halide; 2-phenacylthiobenzothiazole; thiazolo[2,3-*b*]benzothiazolium salt; acid-cyclization; pi-deficient thiazolium salt; Friedel-Crafts reaction; quarternary salt; bridge-headed carbonium ion

In connection of our research on the reactivity of *pi* deficient thiazoles and thiazolium salts[3,4] needs and interests in thiazolo[2,3-*b*]benzothiazolium salts[1,5] which have a carbonium ion adjacent to three heteroatoms, S, S and N[6] have led us to prepare thiazolo[2,3-*b*]benzothiazolium perchlorates. The reactivity of these salts toward carbon-nucleophiles such as malononitrile and 1-morpholino-1-cyclohexene have been examined by us and some of newly prepared pyrrolo[2,1-*b*]benzothiazole systems have exhibited physiological activity related to antiflammatory drugs. In this article is presented the preparation of thiazolo[2,3-*b*]benzothiazolium perchlorates which have at the 3 position a phenyl group substituted with various functional groups. (Table. I)

Table I. Substitituents Y for Compounds **2** and **3**



1) Part XVI: K. Arakawa, T. Miyasaka, and S. Sawada, *Chem. Pharm. Bull.* (Tokyo), "submitted."
2) Location: *1-5-8, Hatanodai, Shinagawa-ku, Tokyo, 142, Japan.*
3) *a*) H. Ohtsuka, H. Toyofuku, T. Miyasaka, and K. Arakawa, *Chem. Pharm. Bull.* (Tokyo), **23**, 3234 (1975); *b*) H. Ohtsuka, T. Miyasaka, and K. Arakawa, *ibid.*, **23**, 3243 (1975); *c*) H. Ohtsuka, T. Miyasaka, and K. Arakawa, *ibid.*, **23**, 3254 (1975).
4) *a*) K. Arakawa, T. Miyasaka, and K. Satoh, *Chem. Pharm. Bull.* (Tokyo), **25**, 299 (1977); *b*) K. Satoh, T. Miyasaka, and K. Arakawa, *ibid.*, **25**, 307 (1977).
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As shown in Chart 1 phenacyl halides (**1**) were prepared either by chloroacetylation of substituted benzenes by Friedel-Crafts reaction or bromination of acetophenones with bromine. Alkylation of 2-mercaptobenzothiazole sodium salt with the halides (**1**) afforded 2-(substituted-phenacylthio)benzothiazoles (**2**), which were heated in mineral acids to give 3-(substituted-phenyl)thiazolo[2,3-*b*]benzothiazolium salts (**3**) in good yield.

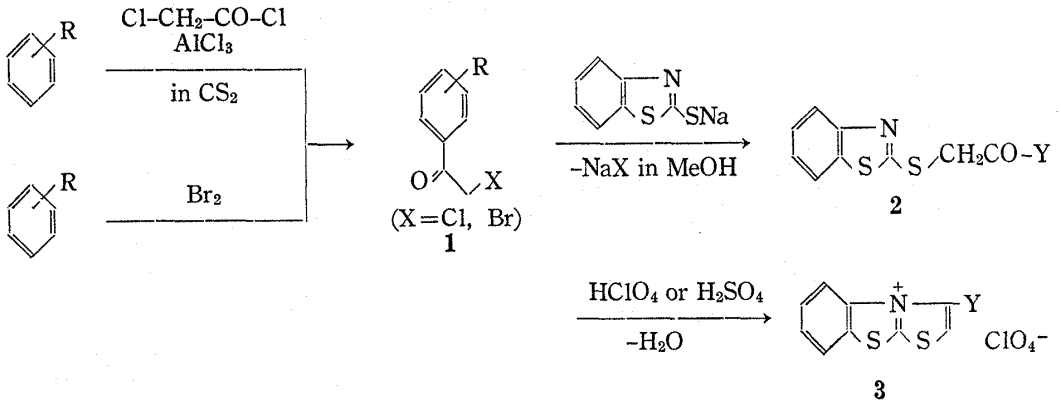

Chart 1

p-Nitrophenacyl bromide[7] (**1d**) and *p*-N,N-dimethylaminophenacyl bromide[8] (**1f**) were prepared by bromination of corresponding acetophenones with bromine according to the literature. Phenacyl chloride (**1a**) and *p*-chlorophenacyl bromide (**1c**) were commercially available. The other phenacyl chlorides (**1**) were synthesized from substituted benzenes by Friedel-Crafts reaction with chloroacetyl chloride or bromoacetyl bromide in the presence of $AlCl_3$. By heating a mixture of *p*-dimethoxybenzene and chloroacetyl chloride in CS_2 in the presence of 1.2 molar equivalent of $AlCl_3$, 51% of reaction product (71.6% isolated yield) was 2-hydroxy-5-methoxy-phenacyl chloride (I), which seemingly formed by demethylation during the reaction.[9] In the case of chloroacetylation of *m*-dimethoxybenzene, 2,4-dimethoxyphenacyl chloride (**1q**) was prepared in good yield without contamination of demethylated product. In the case of chloroacetylation of *o*-dimethoxybenzene, even though the reaction was conducted under nitrogen-stream,[9] considerable amount of brown tar was formed, from which small amount of 3,4-dimethoxyphenacyl chloride[10](II)(3.1% yield) and 4-hydroxy-3-methoxyphenacyl chloride[11](III)(2.5% yield) were isolated by separation through silica gel column chromatography. Friedel-Crafts reaction of guaiacol with bromoacetyl bromide[12] was carried out according to the literature to give the corresponding phenacyl bromide (**1r**) in good yield (Table II).

The phenacyl halides (**1**) were then combined with mercaptobenzothaizole into 2-phenacylthiobenzothiazoles (**2**). Into methanolic solution of 2-mercaptobenzothiazole sodium salt (1.4 molar equivalent) there was added dropwise a MeOH–$CHCl_3$ solution of the phenacyl halide (**1**) and the solution was stirred at room temperature for an hour and then heated under reflux for an hour. The physical constants and the yield of the thioether (**2**) are summarized in Table III.

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Table II. Phenacyl Halides (1)

Compound No.	Appearance	mp (°C) [recryst. solvt.]	Reaction time rt.[ii]	Reaction time rf.[iii]	Yield (%)
1b	Colorless needles	113.5—115 [MeOH][a]	4 hr	1 hr	78.4
1e	Yellow flakes	208—209 [MeOH–$CHCl_3$][b]	4 hr	1 hr	78.5
1g	Brown flakes	58.5—59 [EtOH–H_2O][c]	1 hr	1 hr	72.6
1h	Yellow oil	—[d] i)	1 hr	1 hr	81.5
1i	Colorless needles	62—63 [*n*-hexane][e]	1 hr	1 hr	61.7
1j	Colorless needles	70—71 [*n*-hexane][f]	1 hr	1 hr	68.7
1k	Yellow needles	57—59 [*n*-hexane][g]	1 hr	1 hr	75.8
1l	Colorless needles	72—73 [*n*-hexane][h]	16 hr	—	50.0
1m	Colorless prisms	65—66 [*n*-hexane][i]	16 hr	—	73.0
1n	Colorless prisms	104—107 [*n*-hexane]	16 hr	—	72.7
1o	Pale yellow powder	96—99 [EtOH][j]	2 hr	40 min	76.4
1p	Colorless needles	81—82.5 [*n*-hexane][k]	2 hr	40 min	34.7
1q	Colorless needles	112—114 [EtOH][l]	2 hr	20 min	68.7

a) 117—118°[9] *b*) 212°[13] *c*) 54.5—55°[14] *d*) 31—32°[15] *e*) 62—63°[15] *f*) 73—74°[16]
g) 63—64°[17] *h*) 76°[16] *i*) 71—72°[18] *j*) 102°[19] *k*) 87—88°[20] *l*) 114—115°[21]
i) Purified by silica gel column chromatography with $CHCl_3$ as an eluent.
ii) Stirred at room temperature.
iii) Heated under reflux.

Table III. 2-Phenacylthiobenzothiazoles (2)

Compound No.	Appearance	mp (°C) [recryst. solvt.]	Yield (%)	IR cm^{-1}: C=O	NMR ($CDCl_3$) δ: $-CH_2-$
2a	Colorless needles	109.5—111 [MeOH][a]	71.3	1690	4.92
2b	Colorless needles	142—143 [MeOH][b]	83.0	1705	4.90
2c	Colorless needles	128—129 [MeOH][c]	75.0	1705	4.87
2d	Yellow needles	141.5—143 [$CHCl_3$]	75.1	1700	5.05
2e	Pale yellow needles	179—181 [DMF–MeOH]	79.0	1675	4.95
2f	Yellow needles	110—113 [MeOH]	69.4	1660	4.93
2g	Colorless needles	78—79 [MeOH][d]	74.0	1685	4.91
2h	Yellow prisms	83—84 [MeOH]	61.4	1675	4.79
2i	Pale yellow needles	67—69 [EtOH]	68.2	1675	4.87
2j	Pale yellow needles	106—107 [EtOH]	67.8	1675	4.95
2k	Yellow prisms	81—82 [MeOH]	83.9	1705	4.95
2l	Colorless needles	109—111 [MeOH]	82.0	1715	4.63
2m	Colorless flakes	85—86 [MeOH]	72.7	1680	4.82
2n	Colorless needles	111—112 [MeOH]	88.8	1680	4.89
2o	Pale yellow needles	109—110 [MeOH–$CHCl_3$]	84.3	1690	4.94
2p	Colorless needles	88—89 [MeOH]	68.0	1655	4.82
2q	Colorless needles	138—140 [MeOH]	84.0	1675	4.81
2r	Colorless needles	146.5—148 [MeOH–$CHCl_3$]	74.8	1680	4.94

a) 111.5—113°[22] *b*) 150—150.5°[23] *c*) 132.5—133.5°[23] *d*) 80—81°[23]

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Cyclization of the phenacylthioether (**2a, 2g—k, 2n—r**) was carried out in 70% $HClO_4$[22,23] on a boiling water-bath. The starting material gradually dissolved into the solution and finally the reaction mixture turned dark brown after heating for half an hour to 2 hours. The reaction mixture was poured into ice-water and the quaternary ammonium perchlorate separated as crystals. Treatment of *p*-halo-, *p*-nitro-, *p*-acetamino-, *p*-dimethylamino-, and polymethylphenacylthioethers (**2b—f, 21, m**) in the same manner was not effective for cyclization. By heating in conc. H_2SO_4 on a boiling water-bath these thioethers smoothly dissolved into the solution and the cyclized quarternary salts were isolated as water-insoluble perchlorates by pouring the mixture into ice-water together with 70% $HClO_4$. Cyclization of 2,4,6-tri-methylphenacylthioether (**2m**) was not successful even in conc.H_2SO_4. The starting material was completely recovered unchanged after heating in a mixture of P_2O_5 and 85% H_3PO_4[23] at 100° for 16 hours. The steric compression of *o,o'*-dimethylphenyl moiety and the hydrogen atom at C-4 position of the benzothiazole conceivably effected unfavorably for the cyclization reaction.

The 3-phenylthiazolo[2,3-*b*]benzothiazolium perchlorates (**3**) were purified by recrystallization. The elemental analysis data were in good agreement with the assigned structure. (Table IV). In the IR spectra the carbonyl band of the phenacyl group of the thioether

Table IV. 3-Subst. Phenylthiazolo[2,3-*b*]benzothiazolium Perchlorates (3)

Compd. No.	Appearance	mp (°C) [MeOH–Et_2O]	Formula	Analysis (%) Calcd. (Found) C	H	N	λ_{max}^{EtOH} (log ε)
3a	Colorless needles	243.5—246[a]	$C_{15}H_{10}ClNO_4S_2$	48.97 (48.80)	2.74 (2.80)	3.80 (4.16)	257(3.77), 268(sh, 3.56), 312(3.97)
3b	Colorless flakes	270 (dec.)[b]	$C_{15}H_9BrClNO_4S_2$	40.32 (40.35)	2.03 (1.99)	3.13 (3.05)	254(4.01), 310(4.02)
3c	Colorless needles	277.5 (dec.)[c]	$C_{15}H_9Cl_2NO_4S_2$	44.78 (44.74)	2.25 (2.06)	3.48 (3.78)	255(3.85), 312(3.97)
3d	Colorless prisms	300[e]	$C_{15}H_9ClN_2O_6S_2$	43.64 (43.75)	2.20 (2.32)	6.79 (6.30)	257(3.99), 312(3.95)
3e	Pale yellow flakes	300[e]	$C_{17}H_{13}ClN_2O_5S_2$	48.05 (48.07)	3.08 (3.02)	6.59 (6.57)	261(4.02), 312(3.69)
3f	Yellow prisms	252 (dec.)	$C_{17}H_{15}ClN_2O_4S_2$	49.68 (49.93)	3.67 (3.67)	6.81 (6.78)	262(sh, 3.94), 268(3.97), 305(3.92)
3g	Colorless prisms	238 (dec.)[d]	$C_{16}H_{12}ClNO_4S_2$	50.32 (50.38)	3.16 (3.16)	3.66 (3.88)	256(3.90), 312(4.02)
3h	Colorless prisms	269—271	$C_{17}H_{14}ClNO_4S_2$	51.57 (51.65)	3.56 (3.57)	3.53 (3.47)	261(3.82), 269(sh, 3.72), 280(3.62), 312(4.04)
3i	Yellow prisms	259—269	$C_{17}H_{14}ClNO_4S_2$	51.57 (51.71)	3.56 (3.65)	3.53 (3.48)	260(3.83), 296(sh, 3.66), 313(4.01)
3j	Pale yellow prisms	251—252	$C_{17}H_{14}ClNO_4S_2$	51.57 (51.60)	3.56 (3.56)	3.53 (3.51)	255(3.91), 313(3.98)
3k	Colorless powder	208—213	$C_{19}H_{16}ClNO_4S_2$	54.08 (53.80)	3.82 (4.21)	3.31 (3.19)	252(3.92), 312(3.99)
3l	Colorless prisms	251—254	$C_{18}H_{16}ClNO_4S_2$	52.74 (52.90)	3.93 (4.03)	3.41 (3.34)	255(3.83), 282(3.60), 312(3.98)
3n	Colorless prisms	258—259.5	$C_{18}H_{16}ClNO_4S_2$	52.74 (52.92)	3.93 (4.05)	3.41 (3.33)	252(3.90), 312(3.97)
3o	Pale yellow needles	255—256	$C_{16}H_{12}ClNO_5S_2$	48.30 (48.01)	3.01 (3.06)	3.51 (3.47)	256(4.01), 281(3.63), 313(3.97)
3p	Colorless needles	174—176	$C_{17}H_{14}ClNO_6S_2$	47.71 (47.78)	3.29 (3.29)	3.27 (3.15)	255(sh, 3.78), 260(3.83), 309(4.03)
3q	Colorless needles	184—186	$C_{17}H_{14}ClNO_6S_2$	47.71 (47.58)	3.29 (3.19)	3.27 (3.52)	260(4.02), 280(sh, 3.79), 285(3.82), 313(3.92)
3r	Colorless prisms	251—252	$C_{16}H_{12}ClNO_6S_2$	46.43 (46.76)	2.92 (3.28)	3.38 (3.58)	244(sh, 4.02), 255(3.97), 260(3.99), 310(3.96)

a) 252—254°[22] *b*) 270° (dec.)[23] *c*) 269° (dec.)[23] *d*) 242° (dec.)[23]
e) Recrystallized from DMF–MeOH–Et_2O

(2) were observed intensely at around 1700 cm^{-1}, however, the quaternary salts exhibited characteristic band at around 1460 cm^{-1} ($>\overset{+}{N}=C<$) and at 1100 cm^{-1} (very strong, ClO^-_4). The methylene signal (2H, s, S–CH_2–CO) of thioether (2) was not observed any more in the NMR spectra of the thiazolobenzothiazolium salts (3). The aromatic methine signal of C-2 proton of 3 was observed by overlapping with the other aromatic signals of the protons at C-5,6,7 and 8 positions. In the UV spectra the thiazolo[2,3-*b*]benzothiazolium salts exhibited typical pattern of the maximum absorption at around 260 and 310 nm.

Of further interest is the reactivity of these thiazolium salts (3) toward nucleophilic reagents. The reaction of 3 with 1-morpholino-1-cyclohexene into tetracyclic pyrrolo[2,1-*b*]-benzothiazole system will be reported in the forthcoming article.

Experimental[24]

The General Procedure for the Preparation of the Phenacyl Chlorides (I) listed in Table II——Into an ice-cooled vigorously stirred solution of substituted benzene and chloroacetyl chloride in CS_2 there was added portion wise finely powdered $AlCl_3$ (1.2 mol equivalent to the benzene). After addition was completed, stirring was continued at room temperature and finally the mixture was heated under reflux. After cooling the supernatant CS_2–layer was removed by decantation and the residual precipitated complex was decomposed by addition of conc. HCl and water. The separated crystals of chloride were collected by filtration, washed with ice-water and purified by recrystallization.

Friedel-Crafts Reaction of *p*-Dimethoxybenzene. The Formation of 2-Hydroxy-5-methoxyphenacyl Chloride (I)——Treatment of *p*-dimethoxybenzene (14.35 g, 0.104 mol) with $AlCl_3$ (16.59 g, 0.124 mol) in CS_2 (100 ml) afforded brown solid (17.58 g), which was separated by recrystallization from *n*-hexane into 2,5-dimethoxyphenacyl chloride (**1p**) and 2-hydroxy-5-methoxyphenacyl chloride (**I**) as yellow prisms, mp 77—78° (lit. 81—81.5°),[25] *Anal.* Calcd. for $C_9H_9ClO_3$: C, 53.88; H, 4.52; Cl, 17.45. Found: C, 54.08; H, 4.66; Cl, 17.67.

Friedel-Crafts Reaction of *o*-Dimethoxybenzene. The Formation of 3,4-Dimethoxyphenacyl Chloride (II) and 4-Hydroxy-3-methoxyphenacyl Chloride (III)——Treatment of *o*-dimethoxybenzene (10.00 g, 0.0723 mol) with $AlCl_3$ (11.54 g, 0.0867 mol) in CS_2 (100 ml) afforded light brown solid (1.43 g, 9.2% yield), which was separated by column-chromatography by silica gel into 3,4-dimethoxyphenacyl chloride (**1I**) (0.47 g, 3.1% yield) as colorless needles, mp 99.5—103° [from *n*-hexane] (lit. 100—102°)[10] and 4-hydroxy-3-methoxyphenacyl chloride (**III**) (0.35 g, 2.5% yield), as pale yellow needles, mp 100—102° [from *n*-hexane] (lit. 102—104°[11]), UV λ_{max}^{EtOH} nm (log ε): 233 (3.89), 273 (3.75), 301 (3.75). The UV spectrum of the demethylated chloride (**III**) was almost superimposable with that of the corresponding bromide (**1r**),[25a] which was prepared according to the literature from guaiacol and bromoacetyl bromide.

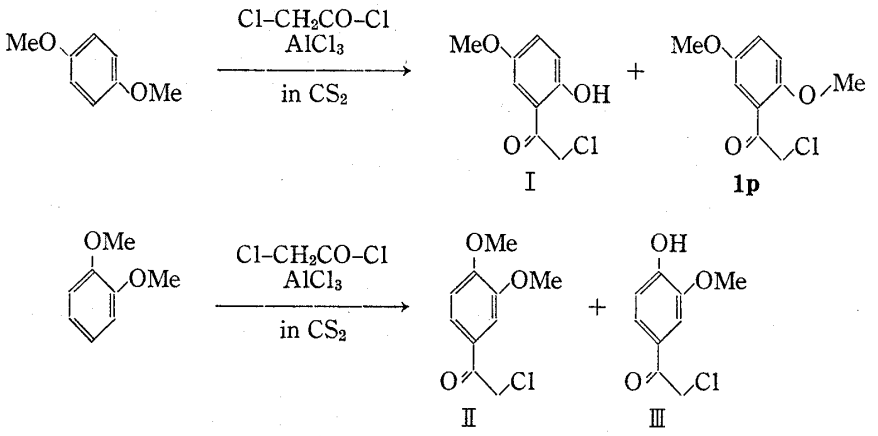

Chart 2

24) All melting points were measured in capillary tubes and were uncorrected. Nuclear magnetic resonance (NMR) spectra were measured by HITACHI R-20 60 MC and R-22 90 MC spectrophotometers using tetramethylsilane as an internal reference. The infrared (IR) and the ultraviolet (UV) spectra were measured on a JASCO IRS spectrophotometer and on a HITACHI ESP-3 spectrophotometer, respectively.

25) A. Sonn, *Chem. Ber.*, **50**, 1268 (1917); *a*) UV λ_{max}^{EtOH} nm (log ε): 234 (3.87), 275 (3.75), 305 (3.08).

The General Procedure for the Preparation of the 2-Phenacylthiobenzothiazoles (2)——Into a methanolic solution of 2-mercaptobenzothiazole sodium salt (1.4 mol equivalent to the phenacyl chloride) there was added dropwise a solution of phenacyl chloride (**1**) in MeOH–$CHCl_3$. After stirring at room temperature for an hour the reaction mixture was heated under reflux for an additional hour. The solvent was evaporated *in vacuo* and the residue was extracted with $CHCl_3$ and water. The chloroform layer was dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by recrystallization to give 2-phenacylthiobenzothiazole (**2**), listed in Table III.

The General Procedure for the Preparation of the 3-(Substituted-phenyl)thiazolo[2,3-b]benzothiazolium perchlorates (3) listed in Table IV and V——(1) Cyclization by Heating in 70% $HClO_4$: The 2-phenacylthiobenzothiazole (**2**) was suspended in 70% $HClO_4$ (20 times the weight of the thiazole) and the mixture was heated at 90—95°. The suspended thiazole (**2**) dissolved into the solution and the mixture turned dark-brown. After cooling the reaction mixture was poured onto ice-water and the precipitated crystals were collected by filtration, washed with water and purified by recrystallization.

(2) Cyclization by Heating in conc. H_2SO_4: A suspension of 2-phenacylthiobenzothiazole (**2**) in conc. H_2SO_4 (5 times the weight of **2**) was heated at 90—95°. The suspended starting material soon dissolved into the solution and the reaction mixture turned gradually dark-brown. After cooling 70% $HClO_4$ (twice the weight of conc. H_2SO_4) was added into the solution. The mixture was poured onto ice-water with stirring and the precipitated crystals were collected by filtration, washed with water and purified by recrystallization.

Table V. Cyclization of Thioethers (**2**)

Compound No.	Reagent	Reaction time	Yield (%)
3a	$HClO_4$	1 hr	78.5
3b	H_2SO_4	30 min	75.2
3c	H_2SO_4	1 hr	64.8
3d	H_2SO_4	1 hr	67.2
3e	H_2SO_4	1 hr	89.0
3f	H_2SO_4	20 min	75.8
3g	$HClO_4$	1 hr	71.4
3h	$HClO_4$	1.5 hr	75.9
3i	$HClO_4$	1.5 hr	82.3
3j	$HClO_4$	2.5 hr	85.0
3k	$HClO_4$	1.5 hr	63.8
3l	H_2SO_4	30 min	57.8
3n	$HClO_4$	1 hr	71.8
3o	$HClO_4$	30 min	88.6
3p	$HClO_4$	1 hr	57.8
3q	$HClO_4$	2 hr	60.0
3r	$HClO_4$	2 hr	61.5

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