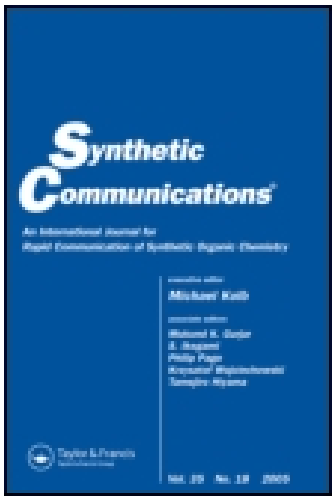

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HYPERVALENT IODINE IN SYNTHESIS. 48. A ONE-POT CONVENIENT PROCEDURE FOR THE SYNTHESIS OF 2-MERCAPTOTHIAZOLES BY CYCLOCONDENSATION OF KETONES WITH [HYDROXY(TOSYLOXY)IODO]-BENZENE AND AMMONIUM DITHIOCARBAMATE

Peng-Fei Zhang [a] & Zhen-Chu Chen [b]

[a] Department of Chemistry , Zhejiang University (Xi-Xi Campus) , Hangzhou, 310028, People's Republic of China

[b] Department of Chemistry , Zhejiang University (Xi-Xi Campus) , Hangzhou, 310028, People's Republic of China

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HYPERVALENT IODINE IN SYNTHESIS. 48. A ONE-POT CONVENIENT PROCEDURE FOR THE SYNTHESIS OF 2-MERCAPTOTHIAZOLES BY CYCLOCONDENSATION OF KETONES WITH [HYDROXY(TOSYLOXY)IODO]-BENZENE AND AMMONIUM DITHIOCARBAMATE

Peng-Fei Zhang and Zhen-Chu Chen*

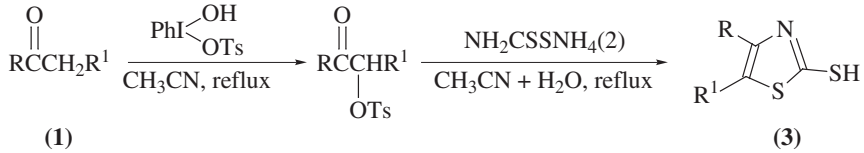
Department of Chemistry, Zhejiang University (Xi-Xi Campus), Hangzhou 310028, People's Republic of China

ABSTRACT

α-Tosyloxylation of ketones with [hydroxy(tosyloxy)iodo]-benzene (HTIB), followed by treatment with ammonium dithiocarbamate, provides a one-pot convenient procedure for the synthesis of 2-mercaptothiazoles with good yields.

Thiazoles, particularly 2-mercaptothiazoles, have become increasingly important in pharmaceutical, biochemical, and technical fields (1–6). Recently, Prakash and Saini (7) reported a useful synthesis of 2-mercaptothiazoles. The approach involves hypervalent iodine oxidation of acetophenones with

*Corresponding author.



(1) **(3)**

Scheme 1.

[hydroxy(tosyloxy)iodo]benzene, followed by treatment with potassium thiocyanate to offer corresponding α-thiocyanatoacetophenones and cyclization of α-thiocyanatoacetophenones using $NH_2C(S)NH_2$/HCl. Although it offers a superior alternative to the existing synthesis (8–21), which contain the use of lachrymatory and toxic α-halogenoketones, the overall yield is low. For example, the yield of 4-(*p*-chlorophenyl)-2-mercaptothiazole is only 20%.

In connection with our programs to utilize hypervalent iodine compounds in organic synthesis (22), we found that α-tosyloxyketones, generated from ketones by the oxidation with [hydroxy(tosyloxy)iodo]benzene, can react with ammonium dithiocarbamate directly to give 2-mercaptothiazoles. Now we would like to report our result, a one-pot procedure for the synthesis of 2-mercaptothiazoles starting from ketones. α-Tosyloxylation of ketones with [hydroxy(tosyloxy)iodo]benzene in acetonitrile, followed by treatment with ammonium dithiocarbamate, afforded 2-mercaptothiazoles in 40–58% overall yields without isolation of any intermediate (Sch. 1). The results are summarized in Table 1.

This one-pot methodology proved quite efficient irrespective of the ketones used; acetophenones, aliphatic ketones, and β-diketones were successfully employed. All acetophenones with different substituents in the para position of aromatic ring (Entries 2–5) gave the expected products.

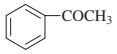
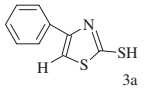
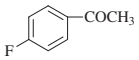
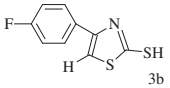
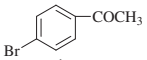
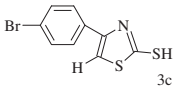
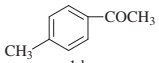
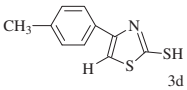
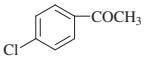
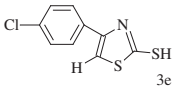
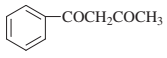
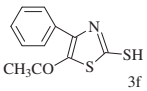
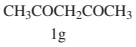
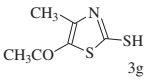
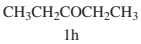
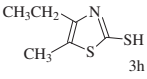
The structures of the products were confirmed by m.p., microanalysis, ^{1}H-NMR-spectral, IR-spectral, and mass-spectral data. The mass spectra showed the correct M^+ peaks and peaks of the fragments. Compound **3a** is taken as an example to describe the general fragmentation mechanism of the thiazole ring, which is proposed in Scheme 2.

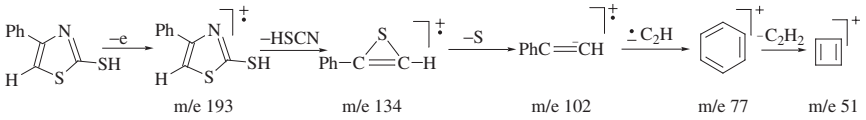
In conclusion, the present study provides a one-pot procedure for the synthesis of 2-mercaptothiazoles, which has the advantages of avoiding the use of lachrymatory and toxic α-halogenoketones, and higher yields than the method previously reported (7).

EXPERIMENTAL

All products were recrystallized by EtOH. The m.p. values were measured on a X_4-Data microscopic melting point apparatus and are uncorrected. Microanalyses

Table 1. One-Pot Synthesis of 2-Mercaptothiazoles

Entry	Ketones	Ammonium dithiocarbamate	2-Mercaptothiazoles	Yield (%)
1	 1a	 2	 3a	46
2	 1b	2	 3b	57
3	 1c	2	 3c	40
4	 1d	2	 3d	42
5	 1e	2	 3e	43
6	 1f	2	 3f	58
7	 1g	2	 3g	48
8	 1h	2	 3h	55



Scheme 2.

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were obtained using Carlo-Erba 1106. ^{1}HNMR spectra were measured on a JEOL $PMX60_{SI}$ spectrometer using TMS as an interal standard. IR spectra were recorded with a Perkin Elmer 683 spectrometer. MS spectra were measured on a HP5989B spectrometer.

Preparation of 2-Mercaptothiazoles 3a–h (General Procedure). To a solid of HTIB (0.392 g, 1 mmol) was added a solution of ketones 1(a–h, 1 mmol) in dry acetonitrile (10 mL). After the addition was completed, refluxing was continued for 45 min (suspended solution changes clear). Then water (10 mL) and ammonium dithiocarbamate (0.22 g, 2 mmol) were added to it. The mixture was refluxed for 2.5 hr. Diluting with water (10 mL) and HCl (1 mL), the solution was extracted with diethyl ether (10 mL × 2). The extracts were dried with Na_2SO_4 and the solvent was distilled off in vacuo. The residue was recrystallized using ethanol to give pure compound.

2-Mercapto-4-Phenylthiazole (**3a**): m.p. 170–172°C (lit. (9) 172–173°C); IR (KBr): 3100 cm^{-1} (m, sharp), 2530 cm^{-1} (vw), 1490 cm^{-1} (s), 1460 cm^{-1} (s), 1060 cm^{-1} (vs); ^{1}H NMR (CD_3COCD_3-d_6) δ 7.20–8.20 (1H, m), 7.20–7.62 (5H, m), 6.90 (1H, s). MS: 193 ($M^{+\cdot}$, 100), 134 (55.80), 102 (7.16), 89 (16.42), 77 (7.75), 51 (7.03).

4-(p-Fluorophenyl)-2-Mercaptothiazole (**3b**): m.p. 190–192°C; IR (KBr): 3120 cm^{-1} (m, sharpen), 2580 cm^{-1} (vw), 1510 cm^{-1} (s), 1450 cm^{-1} (s), 1060 cm^{-1} (vs); ^{1}H NMR (CD_3COCD_3-d_6) δ 7.92 (1H, s), 7.22–7.88 (4H,m), 6.98 (1H, s); MS: 211 ($M^{+\cdot}$, 100), 152 (60.20), 134 (13.23), 133 (10.89), 102 (2.77), 89 (20.66), Anal. calcd for $C_9H_6FNS_2$: C, 51.17; H, 2.86; N, 6.63. Found: C, 51.93; H, 2.48; N, 6.71.

4-(p-Bromophenyl)-2-Mercaptothiazole (**3c**): m.p. 219–221°C (lit. (15) 220–222°C); IR (KBr): 3100 cm^{-1} (m, sharpen), 2600 cm^{-1} (w), 1530 cm^{-1} (s), 1375 cm^{-1} (s), 1050 cm^{-1} (vs); ^{1}H NMR (CD_3COCD_3-d_6) δ 8.0 (1H, s), 7.47–7.95 (4H, m), 7.15 (1H, s); MS: 271 ($M^{+\cdot}$, 34.11), 273 (M + 2, 36.45), 212 (4.73), 214 (4.71), 193 (100), 134 (54.40), 102 (5.50), 89 (20.56).

2-Mercapto-4-(p-Methylphenyl)thiazole (**3d**): m.p. 188–190°C (lit. (15) 190°C); IR (KBr): 3110 cm^{-1} (m, sharp), 2980 cm^{-1}, 2950 cm^{-1} (s), 2610 cm^{-1} (vw), 1545 cm^{-1} (s), 1455 cm^{-1} (s), 1060 cm^{-1} (vs); ^{1}H NMR (CD_3COCD_3-d_6) δ 8.02 (1H, s), 7.18–7.66 (4H, m), 7.03 (1H, s), 2.20 (3H, s); MS: 207 ($M^{+\cdot}$, 100), 192 (11.88), 134 (31.67), 102 (3.20), 89 (25.12).

4-(p-Chlorophenyl)-2-Mercaptothiazole (**3e**): m.p. 208–210°C (lit. (15) 210–212°C); IR (KBr): 3105 cm^{-1} (m, sharp), 2540 cm^{-1} (vw), 1470 cm^{-1} (s), 1355 cm^{-1} (s), 1070 cm^{-1} vs); ^{1}H NMR (CD_3COCD_3-d_6) δ 7.92 (1H, s), 7.45–7.85 (4H, m), 6.85 (1H, s); MS: 229 (M+2, 44.73), 227 ($M^{+\cdot}$, 100), 170 (13.97), 169 (7.94), 168 (33.39), 134 (20.08), 133 (20.33), 102 (3.09), 89 (21.69).

5-Acetyl-2-Mercapto-4-Phenylthiazole (**3f**): m.p. 148–150°C; IR (KBr): 2980 cm^{-1} (s), 2685 cm^{-1} (vw), 1665 cm^{-1} (vs), 1580 cm^{-1} (s), 1475 cm^{-1} (s),

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1355 cm^{-1} (s), 1085 cm^{-1} (s), ^{1}H NMR (CD_3COCD_3-d_6) δ 7.80 (1H, s), 6.60–7.60 (4H, m), 2.72 (3H, s); MS: 235 ($M^{+\cdot}$, 100), 220 (59.32), 192 (21.23), 43 (77.11) Anal. calcd for $C_{11}H_9NOS_2$: C, 56.15; H, 3.86; N, 5.95. Found: C, 55.89; H, 3.57; N, 6.02.

5-Acetyl-2-Mercapto-4-Methylthiazole (**3g**): m.p. 209–211°C (lit. (21) 210–211°C); IR (KBr): 2990 cm^{-1} (s), 2620 cm^{-1} (vw), 1660 cm^{-1} (vs), 1460 cm^{-1} (s), 1355 cm^{-1} (s), 1090 cm^{-1} (s); ^{1}H NMR (CD_3COCD_3-d_6) δ 4.61 (1H, s), 2.55 ((3H, s), 2.33 (3H, s); MS: 173 ($M^{+\cdot}$, 100), 158 (51.65), 130 (19.19), 43 (86.39).

4-Ethyl-2-Mercapto-5-Methylthiazole (**3h**): m.p. 178–180°C; IR (KBr): 2970–2940 cm^{-1} (s), 2650 cm^{-1} (vw), 1495 cm^{-1} (s), 1390 cm^{-1} (s), 1035 cm^{-1} (vs); ^{1}H NMR (CD_3COCD_3-d_6) δ 3.10 (1H, s), 2.45 (2H, q), 2.04 (3H, s), 1.10 (3H, t); MS: 159 (M^+, 100), 144 (34.23), 100 (8.99), 85 (26.80), 53 (2.71), Anal. calcd for $C_6H_9NS_2$: C, 45.25; H, 5.69; N, 8.79. Found: C, 45.52; H, 5.34; N, 8.86.

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