Hypervalent Iodine in Synthesis; 60: A Novel Method for the Synthesis of 2-Mercaptothiazoles by Cyclocondensation of Alkynyl(phenyl)iodonium Salts and Ammonium Dithiocarbamate

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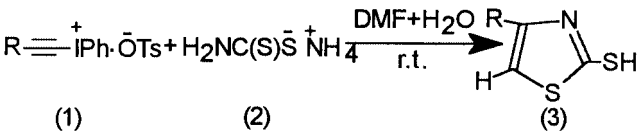
Abstract: A novel method for the synthesis of 2-mercaptothiazoles is achieved by cyclocondensation of alkynyl(phenyl)iodonium salts with ammonium dithiocarbamate. A reaction mechanism is proposed.

Key words: cyclocondensation, 2-mercaptothiazoles, alkynyl(phenyl)iodonium salts, ammonium dithiocarbamate, iodine, sulfur, heterocycles

Thiazoles, in particular, 2-mercaptothiazoles have become increasingly important in pharmaceutical, biochemical, and technical fields.[1] Recently, Prakash and Saini[2] reported a useful synthesis of 2-mercaptothiazoles. The approach involves hypervalent iodine oxidation of acetophenones with [hydroxy(tosyloxy)iodo]benzene, followed by treatment with potassium thiocyanate to afford the corresponding α-thiocyanatoacetophenones and their cyclization using $NH_2C(S)NH_2$/HCl. Although it offers a superior and general alternative of existing synthesis,[3] which involves the use of lachrymatory and toxic α-halogenoketones, the overall yield is low. For example, the yield of 2-mercapto-4-(*p*-chlorophenyl)thiazole is only 20%.

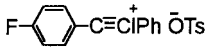
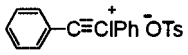
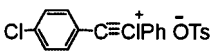
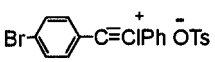
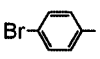
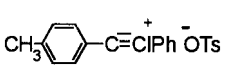
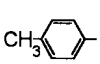
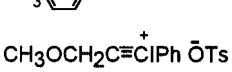
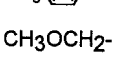
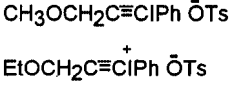
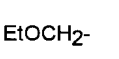
In our earlier reports dealing with hypervalent iodine in organic synthesis, it has been observed that alkynyl(phenyl)iodonium salts are highly reactive towards a variety of nucleophilic species of heteroatoms.[4] These encouraging results coupled with the ready availability and high reactivity of alkynyl(phenyl)iodonium salts prompted us to examine their reaction with nucleophilic ammonium dithiocarbamate. Herein we report a new effective method for the synthesis of 2-mercaptothiazoles by cyclocondensation of alkynyl(phenyl)iodonium salts with ammonium dithiocarbamate.

Simple stirring of the alkynyl(phenyl)iodonium salts **1** with the ammonium dithiocarbamate (**2**) in DMF and water at room temperature gave after workup the 2-mercaptothiazoles **3** in good yield (Scheme 1). The results are summarized in the Table.

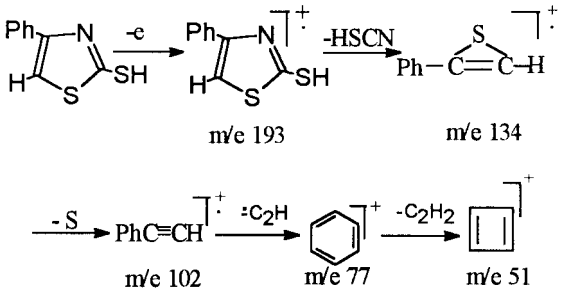


Scheme 1

Table Yields of 2-Mercaptothiazoles **3** Prepared from the Reaction of Alkynyl(phenyl)iodonium Salts and Ammonium Dithiocarbamates

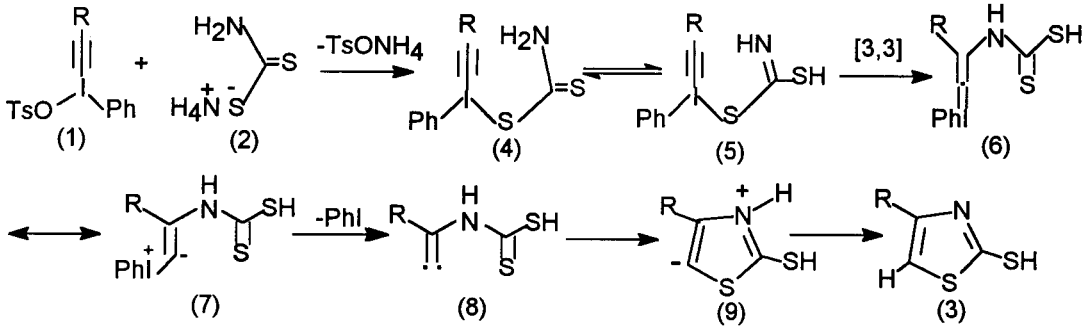
Entry	Alkynyl(phenyl)iodonium Salts	Product		Yield (%)
1			**3a**	73
2			**3b**	63
3			**3c**	57
4			**3d**	66
5			**3e**	61
6			**3f**	45
7			**3g**	51

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



Scheme 2

The reaction was found to be general and applicable to alkylethynyl(phenyl)iodonium salts or arylethynyl(phenyl)iodonium salts. Several arylethynyl(phenyl)iodonium



Scheme 3

salts containing various substituents, such as fluoro, chloro, bromo and methyl groups were successfully reacted.

A plausible mechanism for the formation of 2-mercaptothiazoles **3** is analogous to the synthesis of thiazoles from alkynyl(phenyl)iodoniuin salts and thioamides[5] and is shown in Scheme 3. lt involves the attack of the iodonium ion of alkynyl(phenyl)iodonium salts **1** on the sulfur of the ammonium dithiocarbamate (**2**) to form the primary addition products **4** followed by a polyhetero-Claisen rearrangement[6] and 1,1-elimination of iodobenzene to generate the carbene **8**, and cycloaromatization of **8** to give 2-mercaptothiazoles **3**.

In conclusion , the present study provides a novel method of synthesis of 2-mercaptothiazoles which has some advantages over the existing ones such as avoiding the use of lachrymatory and toxic α-halogenoketones, mild reaction conditions, simplicity of the procedure and higher yields. Furthermore, the range of useful applications of alkynyl(phenyl)iodonium salts in organic chemistry has been extended.

Melting points were determined on a X_4-Data microscopic melting point apparatus and were uncorrected. Microanalyses were obtained using Carlo-Erba 1106. ^{1}HNMR spectra were obtained at 500 MHz or 60 MHz (Avance DMX 500 or Jeol PMX 60$_{SI}$) in DMSO-d_6 or acetone-d_6 using TMS as an interal standard. IR spectra were recorded on a Perkin-Elmer 683 spectrometer at r.t. Mass spectra were obtained by electron inipact at 70eV (HP5989B).

4-(*p*-Fluorophenyl)-2-mercaptothiazole (3a); Typical Procedure

To solid ammonium dithiocarbamate (220 mg, 2 mmol) was added a solution of *p*-fluorophenylethynyl(phenyl)iodonium salt (**la**; 493 mg, 1 mmol) in DMF (10 mL) and H_2O (5 mL) and the resulting mixture was stirred for 30 min at r.t. H_2O (30 mL) was added and the solution was extracted with Et_2O (2 × 10 mL). The combined organic extracts were dried (Na_2SO_4), concentrated and chromatographed on a silica gel plate using mixtures of petroleum ether (bp 60−90 °C)/Et_2O (4:1) as eluent to afford **3a**; yield: 0.15 g (73%); mp 190−192 °C.

IR (KBr): ν = 3120 (m, sharp), 1510 (s), 1450 (s), 1060 (vs), 840 cm^{-1} (vs).

^{1}H NMR (DMSO-d_6, 500 MHz): δ = 8.29 (1 H, s), 8.00−8.03 (2 H, m), 7.32−7.34 (2 H, m), 7.30 (1 H, s).

^{13}C NMR (DMSO-d_6, 500 MHz): δ = 163.782, 163.097 ($^1J_{CF}$ = 253.8 Hz), 155.416, 130.504, 128.785 ($^3J_{CF}$ = 7.8 Hz), 118.728, 116.445 ($^2J_{CF}$ = 20.7 Hz).

MS: *m*/*z* = 211 (M$^+$, 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, 51.55; H, 2.48; N, 6.37.

2-Mercapto-4-phenylthiazole (3b)

Yield: 63%; mp 171−173 °C (Lit.[3h] mp 172−173 °C).

IR (KBr): ν = 3100 (m, sharp), 1490 (s), 1460 (s), 1060 (vs), 690 cm^{-1} (vs).

^{1}H NMR (acetone-d_6, 60 MHz): δ = 7.20−8.20 (1 H, br), 7.20−7.62 (5 H, m), 6.90 (1 H, s).

MS: *m*/*z* = 193 (M$^+$, 100), 134 (55.80), 102 (7.16), 89 (16.42), 77 (7.75), 51 (7.03).

4-(*p*-Chlorophenyl)-2-mercaptothiazole (3c)

Yield: 57%; mp 208−210 °C (Lit.[3h] mp 210−212 °C).

IR (KBr): ν = 3105 (m, sharp), 1470 (s), 1355 (s), 1070 (vs), 880 cm^{-1} (vs).

^{1}H NMR (acetone-d_6 60 MHz): δ = 7.92 (1 H, br), 7.45−7.85 (4 H, m), 6.85 (1 H, s).

MS: *m*/*z* = 229 (M$^+$ + 2, 44.73), 227 (M$^+$, 100), 170 (13.97), 168 (33.39), 134 (20.08), 133 (20.33), 102 (3.09), 89 (21.69).

4-(*p*-Bromophenyl)-2-mercaptothiazole (3d)

Yield: 66%; mp 219−221 °C (Lit.[3h] mp 220−222 °C).

IR (KBr): n = 3100 (m, sharp). 1530 (s), 1375 (s), 1050 (vs), 820 cm^{-1} (vs).

^{1}H NMR (acetone-d_6, 60 MHz): δ = 8.00 (1 H, br), 7.47−7.95 (4 H, m), 7.15 (1 H, s).

MS: *m*/*z* = 273 (M$^+$ + 2, 36.45), 271 (M$^+$, 34.11), 214 (4.71), 212 (4.73), 193 (100), 134 (54.40), 102 (5.50), 89 (20.56).

2-Mercapto-4-(*p*-methylphenyl)thiazole (3e)

Yield: 61%; mp 188−190 °C (Lit.[3h] mp 190 °C).

IR (KBr): ν = 3110 (m, sharp), 2980 (s), 2950 (s), 1545 (s), 1455 (s), 1060 (vs), 840 cm^{-1} (vs).

^{1}HNMR (acetone-d_6, 60 MHz): δ = 8.02 (1 H, br), 7.18−7,66 (4 H, m), 7.03 (1 H s), 2.20 (3 H, s).

MS: *m*/*z* = 207 (M$^+$, 100), 192 (11.88), 134 (31.67), 102 (3.20), 89 (25.12).

2-Mercapto-4-methoxymethylthiazole (3f)

Yield: 45%; mp 108−110 °C.

IR (KBr): ν = 3108 (m, sharp), 1455 (s), 1370 cm^{-1} (s).

^{1}H NMR (acetone-d_6, 500 MHz): δ = 7.30−7.81 (1 H, br), 7.00 (1 H, s), 4.25 (2 H, s), 3.31 (3 H, s).

MS: *m*/*z* = 161 (M^+, 100), 102 (23.32), 70 (18.73).

Anal. calcd for $C_5H_7NOS_2$: C, 37.24; H, 4.38; N, 8.69; Found: C, 37.62, H, 4.05; N, 8.31.

4-Ethoxymethyl-2-mercaptothiazole (3g)
Yield: 51%; mp 116−118 °C.

IR (KBr): ν = 3105 (m, sharp), 1455 (s), 1375 cm^{-1} (s).

^{1}H NMR (acetone-d_6, 500 MHz): δ = 7.31−7.80 (1 H, br), 6.83 (1 H, s), 4.05 (1 H, s), 3.45 (2 H, q, *J* = 6.6 Hz), 1.18 (3 H, t, *J* = 6.6 Hz).

MS: *m*/*z* = 175 (M^+, 100), 116 (15.87), 84 (13.69).

Anal. calcd for $C_6H_9NOS_2$: C, 41.12; H, 5.18; N, 7.99; Found: C, 41.51; H, 5.04; N, 7.61.

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