Synthesis of Heterocycles using a new Immonium Salt derived from *NN*-Dimethylthiourea

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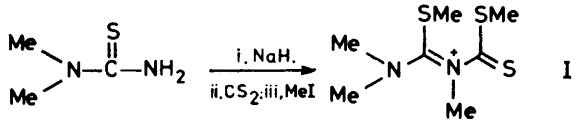
The preparation of a new immonium salt (2) by the reaction of *NN*-dimethylthiourea with carbon disulphide, followed by methylation with an excess of methyl iodide, is reported. The reaction of compound (2) with nucleophiles affords several useful heterocycles such as the mesoionic triazolines (3), the triazolines (4), an oxadiazole (5), a thiazole (6), a triazine (7), a benzoxadiazepine (9), and a benzothiadiazepine (11).

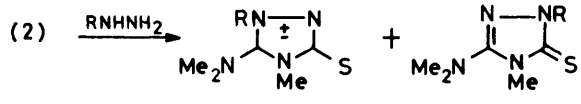
OUR recent work[1-6] has emphasized the versatility of thioureas in the formation of heterocycles and has prompted the investigation of the reaction of *NN*-dimethylthiourea (1) with carbon disulphide. The reaction of compound (1) with carbon disulphide in the presence of NaH, followed by methylation with an excess of methyl iodide afforded a new immonium salt, the methylimmonium iodide (2).[7] We found that compound (2) reacts with nucleophiles, such as hydrazines, hydroxylamine, the dianion of ethyl thioglycolate, guanidine, *o*-aminophenol, and *o*-aminothiophenol, to give several useful heterocycles.



(1) (2) I

RESULTS AND DISCUSSION

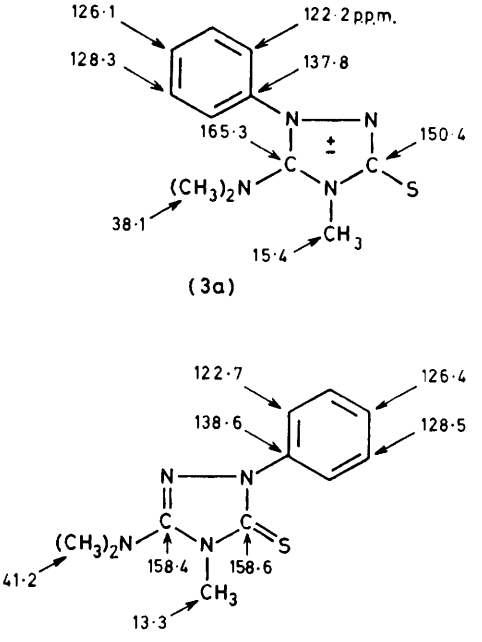
Compound (2) was treated with hydrazine hydrate in ethanol at reflux to give the cyclic, five-membered product (4c) in 74% yield with the loss of two molecules of methanethiol. Treatment of compound (2) with hydroxylamine led to the formation of the oxadiazole (5) in 55% yield.



(3) (4)

a; R = Ph
b; R = Me
c; R = H [(3c) was not obtained]

Similarly, compound (2) was treated with phenylhydrazine to produce two isomeric heterocycles, which were separated by thin layer chromatography (t.l.c.) on silica gel using benzene–diethyl ether (9 : 1) as eluant. The structures were determined as the mesoionic compound (3a) and the triazoline-thione (4a) on the basis of their spectroscopic data. Analysis of the fragmentation patterns in the high resolution mass spectra was crucial for the elucidation of the structures;[8] a characteristic peak (*m/e* 164.040), which corresponds to the ion $[MeN{-}C(:S){-}NPh]^{+\cdot}$, appeared in the spectrum of compound (4a), while the same peak was not observed in that of compound (3a). ^{13}C N.m.r. spectra of both compounds (in CCl_4) also support the structures given. Our assignments are depicted in the Figure (values in p.p.m.).



FIGURE

It is noteworthy that the regioselectivity of the reaction, which leads to the mesoionic isomer, greatly depends on the reaction conditions, especially temperature. As is shown in the Table compound (3a) is formed predominantly at low temperatures (0 °C).

Next, the reaction of compound (2) with methylhydrazine was carried out under various conditions. The results are also given in the Table. In contrast to the results of the reaction with phenylhydrazine, the mesoionic compound (3b) was preferentially formed at higher temperatures and the triazoline-3-thione (4b) was selectively produced at lower temperatures.

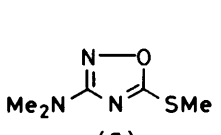
Mesoionic compounds form a class of heterocycles of theoretical interest and practical utility.[9-11] Thus, many preparative methods for such heterocycles have been reported. The present reaction of compound (2)

Reaction of compound (2) with $RNHNH_2$

R	Solvent	T (°C)	t (h)	Yield (%)	Ratio (3) : (4)
Ph	EtOH	(Reflux)	0.5	73	46 : 54
		0	1	81	96 : 4
	n-C_6H_{14}	(Reflux)	0.5	27	81 : 19
		0	1	43	96 : 4
		−50	3	40	100 : 0
Me	EtOH	(Reflux)	1	63	62 : 38
		0	2	85	22 : 78
		−60	2.5	74	14 : 86
	n-C_6H_{14}	(Reflux)	1	74	52 : 48
		0	2	87	7 : 93
		−60	3	86	0 : 100
	C_6H_6	(Reflux)	1	60	82 : 18

with hydrazines may promise a useful tool in the preparation of mesoionic compounds such as (3a) and (3b).

The reaction of compound (2) with the dianion of ethyl thioglycolate afforded the ethyl carboxylate (6) in 47% yield.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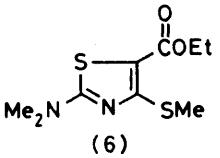
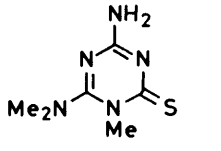

(6)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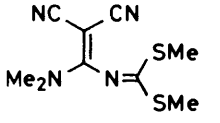
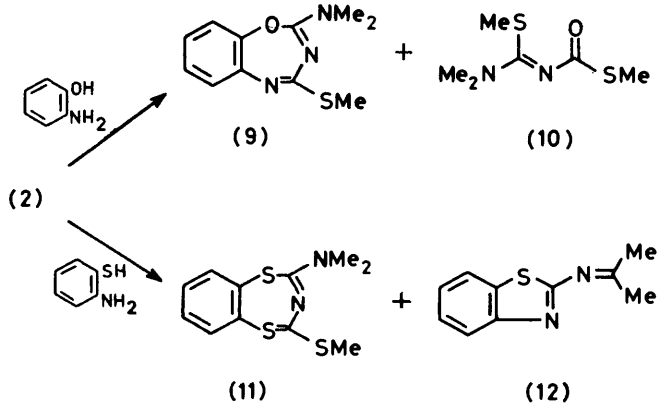

(8)

In order to synthesize six-membered heterocycles, compound (2) was treated with guanidine to form the expected triazine-2-thione (7) in 78% yield.

Further, this reaction was extended to *o*-aminophenol and *o*-aminothiophenol. That is, the former afforded the seven-membered heterocycle (9) and the isothiourea (10) in 31 and 17% yields, respectively, and the latter afforded the two cyclic products (11) and (12) in 35 and 42% yields, respectively.

Compound (2) was treated with malononitrile in the presence of base and formed the nitrile (8) instead of the expected four-membered heterocycle. The structures of compounds (5)—(12) were tentatively assigned on the basis of their spectroscopic data, especially the mass fragmentation patterns together with elemental analyses.


(2) (9) (10) (11) (12)

From these results it is concluded that compound (2) is a useful starting material for the synthesis of heterocycles.

EXPERIMENTAL

Microanalyses were performed at the Analytical Center of Chiba University. I.r., u.v., mass, ^1H n.m.r., and ^{13}C n.m.r. spectra were measured with Hitachi 215, EPS-3T, RMU-6MC, Japan Electron Optics Lab. Co. C-60 HL and FX-100 instrument, respectively. *NN*-Dimethylthiourea (1) was prepared by the method of Wallach.[12]

[*Dimethylamino*(*methylthio*)*methylene*](*dithiomethoxycarbonyl*)*methylimmonium Iodide* (2).—To a suspension of NaH (1 g, 42 mmol) in 50 ml of dry tetrahydrofuran (THF) was added compound (1) (2 g, 19 mmol) under nitrogen. After being refluxed for 1 h, the reaction mixture was cooled and then a solution of CS_2 (6 ml, 100 mmol) in dry THF (30 ml) was added and cooled with ice. The resulting mixture was allowed to warm to the ambient temperature and then treated with MeI (7 ml, 112 mmol) and stirred for a further hour. The reaction mixture was condensed to give a white solid, which was extracted with chloroform. The chloroform extract was evaporated to give compound (2) in 65% yield. Recrystallization from CH_2Cl_2–Et_2O gave white *prisms*, m.p. 155 °C (decomp.); $\nu_{max.}$ (KBr) 2 950, 2 880, 1 590, and 1 550 cm^{-1}; $\lambda_{max.}$ (EtOH) 219 (log ε 4.48) and 250 nm (4.43); δ($CDCl_3$) 3.62 (s, 3 H), 3.47 (s, 3 H), 2.77 (s, 6 H), and 2.57 (s, 3 H); *m/e* 208 (M^+ −MeI) (Found: C, 23.8; H, 4.4; N, 8.05. $C_7H_{15}N_2S_3$ requires C, 24.00; H, 4.32; N, 8.00%).

5-*Dimethylamino*-4-*methyl*-1-*phenyl*-1,2,4-*triazolinylium*-3-*thiolate* (3a) *and* 5-*Dimethylamino*-4-*methyl*-2-*phenyl*-1,2,4-*triazoline*-3-*thione* (4a).—Compound (2) (0.35 g, 1 mmol) was dissolved in various solvents (10 ml, see the Table) and phenylhydrazine (0.3 ml, 3 mmol) was added to the solution. The mixture was allowed to react under various conditions (see the Table). The reaction mixture was evaporated to give a red oil, which was acidified with 0.1N HCl. The resulting solution was extracted with diethyl ether. Work-up of the diethyl ether extract by preparative t.l.c. with silica gel (diethyl ether–benzene, 1 : 9) gave compound (3a) as white *prisms*, m.p. 52—53 °C (from diethyl ether); $\nu_{max.}$ (KBr) 3 050, 3 000, 2 920—2 800, and 1 580 cm^{-1}; $\lambda_{max.}$ (EtOH) 228sh and 289 nm (log ε 3.76); δ(CCl_4) 7.4 (m, 5 H, Ph), 3.00 (s, 6 H, NMe_2), and 2.65 (s, 3 H, Me); *m/e* 234 (M^+) (Found: C, 56.45; H, 6.05; N, 23.9. $C_{11}H_{14}N_4S$ requires C, 56.39; H, 6.02; N, 23.91%); and compound (4a) as white *plates*, m.p. 77—78 °C (from diethyl ether); $\nu_{max.}$ (KBr) 3 040, 3 000, 2 920—2 800, and 1 600 cm^{-1}; $\lambda_{max.}$ (EtOH) 272 nm (log ε 3.79); δ(CCl_4) 7.4 (m, 5 H, Ph), 2.76 (s, 6 H, NMe_2), and 2.50 (s, 3 H, Me); *m/e* 234 (M^+) (Found: C, 56.45; H, 6.05; N, 24.0. $C_{11}H_{14}N_4S$ requires C, 56.39; H, 6.02; N, 23.91%).

5-*Dimethylamino*-1,4-*dimethyl*-1,2,4-*triazolinylium*-3-*thiolate* (3b) *and* 5-*Dimethylamino*-2,4-*dimethyl*-1,2,4-*triazoline*-3-*thione* (4b).—Work-up was as described for compounds (3a) and (4a). Purification was performed successively by preparative t.l.c. with silica gel (diethyl ether) and Kugelrohr distillation. Compound (3b) was obtained as a *liquid*, b.p. 93 °C/0.3 Torr; $\nu_{max.}$ (neat) 2 920—2 790 and 1 560 cm^{-1}; $\lambda_{max.}$ (EtOH) 240sh and 266sh nm; δ(CCl_4)

3.54 (s, 3 H), 2.88 (s, 6 H), and 2.61 (s, 3 H) (Found: M^+, 172.0789. $C_6H_{12}N_4S$ requires M, 172.0783). Compound (4b) was obtained as a *liquid*, b.p. 105 °C/0.3 Torr; $\nu_{max.}$ (neat) 2 920—2 800 and 1 550 cm^{-1}; $\lambda_{max.}$ (EtOH) 238sh nm; $\delta(CCl_4)$ 3.64 (s, 3 H), 2.84 (s, 6 H), and 2.47 (s, 3 H) (Found: M^+, 172.0771. $C_6H_{12}N_4S$ requires M, 172.0783).

5-Dimethylamino-4-methyl-2H-1,2,4-triazoline-3-thione (4c).—To a solution of compound (2) (0.35 g, 1 mmol) in ethanol (10 ml) was added hydrazine hydrate (0.4 ml, 8.2 mmol). The mixture was refluxed for 4 h and then condensed, acidified by 0.1N HCl, and extracted with dichloromethane. The extract was evaporated to give compound (4c) in 74% yield as white *prisms*, m.p. 200—201 °C (from MeOH); $\nu_{max.}$ (KBr) 3 000—2 800 and 1 620 cm^{-1}; $\lambda_{max.}$ (EtOH) 227sh nm; $\delta([^2H_5]$pyridine) 9.8br (1 H, NH), 3.03 (s, 6 H, NMe_2), and 2.68 (s, 3 H, Me); *m/e* 158 (M^+) (Found: C, 37.95; H, 6.4; N, 35.65. $C_5H_{10}N_4S$ requires C, 37.96; H, 6.37; N, 35.41%).

3-Dimethylamino-5-methylthio-1,2,4-oxadiazole (5).—To a solution of compound (2) (0.35 g, 1 mmol) in ethanol (20 ml) was added successively hydroxylamine hydrochloride (0.21 g, 3.0 mmol) and tributylamine (0.72 ml, 3.0 mmol). After being stirred for 4 h under nitrogen at ambient temperature, the reaction mixture was evaporated to leave an oil. To this oil was added water and chloroform, and the chloroform extract was concentrated to afford a yellow liquid. Purification was performed successively by preparative t.l.c. with silica gel (diethyl ether–benzene, 1 : 4) and Kugelrohr distillation to give compound (5) in 55% yield as an *oil*, b.p. 100 °C/1 Torr; $\nu_{max.}$ (neat) 2 930—2 800 and 1 590 cm^{-1}; $\lambda_{max.}$ (EtOH) 219 nm (log ε 4.44); $\delta(CCl_4)$ 2.98 (s, 6 H, NMe_2) and 2.67 (s, 3 H, Me); *m/e* 159 (M^+), 112 (M^+ − SMe), and 83 (M^+ − MeSCO, H) (Found: C, 37.55; H, 5.65; N, 26.25. $C_5H_9N_3OS$ requires C, 37.96; H, 6.37; N, 35.41%).

Ethyl 2-Dimethylamino-4-methylthiothiazole-5-carboxylate (6).—To a solution of ethyl thioglycolate (0.18 ml, 1.5 mmol) in THF (10 ml) was added, as drops lithium diisopropylamide (LDA) (1.5 mmol) in THF (5 ml) at −70 °C under a nitrogen atmosphere. The resultant suspension was stirred for 1 h and compound (2) (0.35 g, 1 mmol) was added. The mixture was stirred for 1 h at −70 °C and then at room temperature for 1 h. The reaction mixture was poured into water and extracted with diethyl ether. The diethyl ether extract was condensed to give a red oil, which was purified by preparative t.l.c. with silica gel (diethyl ether–benzene, 1 : 9) and then by Kugelrohr distillation to yield (47%) a light yellow *oil*, b.p. 165 °C/0.3 Torr; $\nu_{max.}$ (neat) 2 970—2 800, 1 690, 1 550, and 1 090 cm^{-1}; $\lambda_{max.}$ (EtOH) 266 (log ε 4.47) and 347 nm (4.39); $\delta(CCl_4)$ 4.15 (q, 2 H, CH_2, J 7 Hz), 3.17 (s, 6 H, NMe_2), 2.63 (s, 3 H, SMe), and 1.32 (t, 3 H, Me, J 7 Hz); *m/e* 246 (M^+), 185 [(M^+ + H) − Me, SMe], 145 [(M^+ + H) − S–N=C–NMe_2] (Found: C, 43.8; H, 5.7; N, 11.25. $C_9H_{14}N_2O_2S_2$ requires C, 43.88; H, 5.73; N, 11.37%).

4-Amino-6-dimethylamino-1-methyl-1,2-dihydro-1,3,5-triazine-2-thione (7).—To a solution of compound (2) (0.35 g, 1 mmol) in ethanol (10 ml) was added guanidine hydrochloride (0.24 g, 2.5 mmol) and KOH (0.18 g, 3.2 mmol). The mixture was refluxed for 2 h and then condensed to give a white solid, to which was added water. The resultant mixture was acidified with 0.1N HCl and extracted with dichloromethane. The extract was evaporated to give white crystals of compound (7) in 78% yield. Recrystallization from $CHCl_3$ gave white *prisms*, m.p. 207—208 °C; $\nu_{max.}$ (KBr) 3 360, 3 300, 3 130, 2 920, and 1 500 cm^{-1}; $\lambda_{max.}$ (EtOH) 215 (log ε 4.23), 235 (4.25), and 270sh nm; $\delta(CDCl_3)$ 5.0br (2 H, NH_2), 3.14 (s, 6 H, NMe_2), and 2.48 (s, 3 H, Me); *m/e* 185 (M^+) (Found: C, 38.8; H, 5.9; N, 37.85. $C_6H_{11}N_5S$ requires C, 38.90; H, 5.98; N, 37.81%).

2-Dimethylamino-4-methylthio-1,3,5-benzoxadiazepine (9) *and 1,1,2-Trimethyl-3-methylthiocarbonylisothiourea* (10).—To a solution of compound (2) (0.35 g, 1 mmol) in ethanol (10 ml) was added *o*-aminophenol (0.16 g, 1.5 mmol) and triethylamine (0.15 ml, 1.1 mmol) under nitrogen. The mixture was heated to reflux for 5.5 h. Work-up of the reaction mixture was as described for compound (7). Separation of compounds (9) and (10) was carried out by preparative t.l.c. with silica gel (diethyl ether–ethyl acetate, 4 : 1). Compound (9) was obtained as white *prisms*, m.p. 89—90 °C (from diethyl ether), yield 31%; $\nu_{max.}$ (KBr) 3 040, 2 980, 2 910, and 1 540 cm^{-1}; $\lambda_{max.}$ (EtOH) 241 (log ε 4.26) and 307 nm (4.35); $\delta(CCl_4)$ 7.2 (m, 4 H, ArH), 3.21 (s, 6 H, NMe_2), and 2.22 (s, 3 H, SMe); *m/e* 235 (M^+), 188 (M^+ − SMe), and 149 [M^+ − O–N=C–NMe_2] (Found: C, 55.7; H, 5.55; N, 17.8. $C_{11}H_{13}N_3OS$ requires C, 56.15; H, 5.57; N, 17.86%). Compound (10) was obtained as an *oil*, b.p. 165 °C/0.3 Torr (Kugelrohr), yield 17%; $\nu_{max.}$ (neat) 2 920 and 1 630 cm^{-1}; $\lambda_{max.}$ (EtOH) 254 nm (log ε 3.83); $\delta(CCl_4)$ 3.07 (s, 3 H, SMe), 2.48 (s, 6 H, NMe_2), and 2.98 (s, 3 H, SMe); *m/e* 192 (M^+) (Found: C, 37.5; H, 6.2; N, 14.45. $C_6H_{12}N_2OS_2$ requires C, 37.48; H, 6.29; N, 14.57%).

2-Dimethylamino-4-methylthio-1,3,5-benzothiadiazepine (11) *and 2-[Bis(methylthio)methyleneamino]benzothiazole* (12).—Compounds (11) and (12) were prepared by the same method as above ($CHCl_3$ was used as the development solvent for preparative t.l.c.). Compound (11) was obtained as a yellow *oil*, b.p. 233 °C/0.3 Torr (Kugelrohr), yield 35%; $\nu_{max.}$ (neat) 3 040, 2 900, and 1 550 cm^{-1}; $\lambda_{max.}$ (EtOH) 224sh, 258sh, and 322 nm (log ε 4.38); $\delta(CCl_4)$ 7.4 (m, 4 H, ArH), 3.19 (s, 6 H, NMe_2), and 2.24 (s, 3 H, SMe); *m/e* 241 (M^+), 204 (M^+ − SMe), and 149 [M^+ − S–N=C–NMe_2] (Found: C, 52.5; H, 5.3; N, 16.7. $C_{11}H_{13}N_3S_2$ requires C, 52.51; H, 5.21; N, 16.72%). Compound (12) was obtained as white *needles*, m.p. 75—76 °C (from EtOH), yield 42%; $\nu_{max.}$ (KBr) 3 050, 2 980, 2 910, and 1 515 cm^{-1}; $\lambda_{max.}$ (EtOH) 237sh, 264 (log ε 3.97), and 331 nm (3.95); $\delta(CCl_4)$ 7.5 (m, 4 H, ArH), and 2.58 (s, 6 H, 2 × SMe); *m/e* 254 (M^+) (Found: C, 47.3; H, 4.05; N, 10.95. $C_{10}H_{10}N_2S_3$ requires C, 47.22; H, 3.96; N, 11.01%).

[Bis(methylthio)methyleneamino]dimethylaminomethylenemalononitrile (8).—To a solution of compound (2) (0.1 g, 0.29 mmol) in dichloromethane (5 ml) was added malononitrile (0.019 g, 0.29 mmol) and triethylamine (0.1 ml, 0.7 mmol). The mixture was stirred at −60 °C for 3 h and then evaporated to give an oil. Purification was performed by preparative t.l.c. with silica gel (diethyl ether) to give compound (8) as white *needles*, m.p. 131—132 °C (from EtOH), yield 37%; $\nu_{max.}$ (KBr) 2 920, 2 205, 2 195, and 1 560 cm^{-1}; $\lambda_{max.}$ (EtOH) 258 nm (log ε 4.38); $\delta(CDCl_3)$ 3.20 (s, 6 H, NMe_2), and 2.62 (s, 6 H, 2 × SMe); *m/e* 240 (M^+) (Found: C, 44.9; H, 5.0; N, 23.35. $C_8H_{12}N_4S_2$ requires C, 44.98; H, 5.03; N, 23.31%).

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