Reactions of Monoprotic Thioureas with Ethyl α-Chloroacetoacetate, Ethyl Bromomalonate, and Ethyl Bromocyanoacetate †

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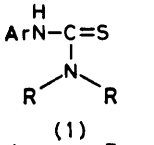
N,N,-Dialkyl-*N'*-arylthioureas (1) with ethyl α-chloroacetoacetate, furnished dialkylamine hydrochlorides, aryl isothiocyanates, 2-arylimino-1,3-oxathioles (2), 2-arylimino-3-aryl-Δ^4-thiazolines (3), diarylthioureas (9), and carbonyl sulphide. With ethyl bromomalonate the products were dialkylamine hydrobromides, aryl isothiocyanates, 2-arylimino-3-arylthiazolidin-4-ones (11), and diarylthioureas (9). Ethyl bromocyanoacetate gave an ethyl cyano{[dimethylamino(phenylimino)methyl]thio}acetate (13). Compound (13) with triethylamine gave the starting thiourea (1) and diethyl dicyanofumarate.

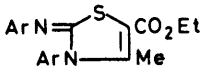
THE condensation products from *N*-mono- or *N,N*-disubstituted thiocarboxamides and α-electron-withdrawing-functionalised halides undergo sulphur extrusion reactions in the presence of phosphines,[2] NaOEt–DMF,[3] H_2SO_4,[4] Zn–acetic acid,[5] *etc.* or simply during their formation;[6-8] this reaction constitutes a versatile approach to carbon–carbon double bond formation.[9-12] However, in some cases ring formation involving the thiocarboxamide nitrogen and the electrophilic carbon atom of the electron-withdrawing group has been observed.[7,8] Similarly obtained condensation products from *N,N,N'N'*-tetrasubstituted thioureas, on reaction with a base, provide push–pull-stabilized thiocarbonyl ylides, which undergo transformations other than sulphur extrusion.[13,14] These reports prompted us to investigate the behaviour of monoprotic thioureas with α-electron-withdrawing-functionalised halides.

The condensation of *N,N*-diethyl-*N'*-*p*-tolylthiourea (1d) with ethyl α-chloroacetoacetate in acetone furnished

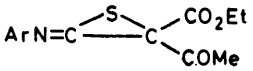


(1)

Ar	R
a; Ph	Me
b; Ph	Et
c; *p*-tolyl	Me
d; *p*-tolyl	Et



(3)

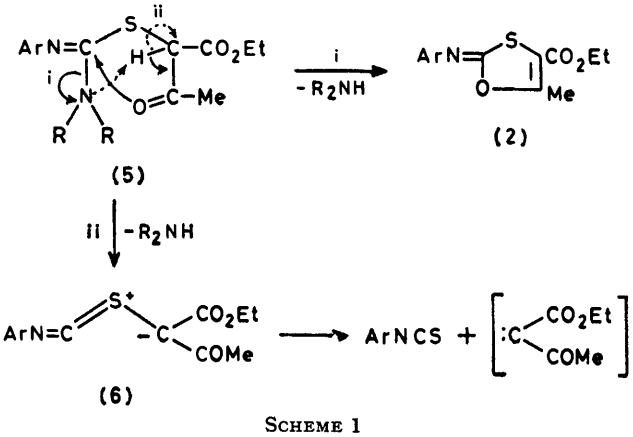


(4)

diethylamine hydrochloride (55%), *p*-tolyl isothiocyanate (6%), *N,N'*-di-*p*-tolylthiourea (9; Ar = *p*-tolyl) (7%), ethyl 4-methyl-2-*p*-tolylimino-Δ^4-thiazoline-5-carboxylate (3; Ar = *p*-tolyl)[15] (20%), and ethyl 5-methyl-2-*p*-tolylimino-1,3-oxathiole-4-carboxylate (2; Ar = *p*-tolyl) (15%). Assignment of structure (2) rather than the isomer (4) was made on the basis of the ^{13}C n.m.r. spectrum, which showed four rather than five sp^3 carbon signals. The isomeric thiocarbonyl ylide structure (6) was ruled out by the i.r. EtO_2C frequency.[16]

Similar results were obtained with the thioureas (1a—c). In DMF solution these reactions proceeded similarly, but in NaOEt–EtOH the number of products was increased (t.l.c.).

The mechanism of the reactions was clarified as follows. T.l.c. showed that the isothiocyanates and oxathioles were formed first; the formation of thiazolines and thioureas started later and at this stage the ethyl α-chloroacetoacetate had been consumed. I.r. spectral studies confirmed this, in that the intensity of the NCS absorption band at 2 200 cm^{-1}, which appeared after 10 min, increased for 1 h and thereafter decreased. These observations indicated that the thiazolines were not formed from diarylthioureas and ethyl α-chloroacetoacetate, but might have arisen from the isothiocyanates and oxathioles (2) formed first. Thus an initially formed intermediate (5) could give the oxathiole (2) in a straightforward manner (Scheme 1) by attack of



SCHEME 1

carbonyl oxygen at electrophilic carbon followed by elimination of dialkylamine (path i). Aryl isothiocyanate could be formed as shown in path ii; however the carbene could not be trapped with cyclohexene.

In order to clarify the formation of the thiazolines (3) and diarylthioureas (9), we investigated the reaction of phenyl isothiocyanate with 1,3-oxathiole (2; Ar = Ph): compounds (3; Ar = Ph) and (9; Ar = Ph) were produced and COS was eliminated.‡ Wishing to discover

† This paper is considered as Part 5 of the Series, Sulphur Extrusion Reactions.[1]

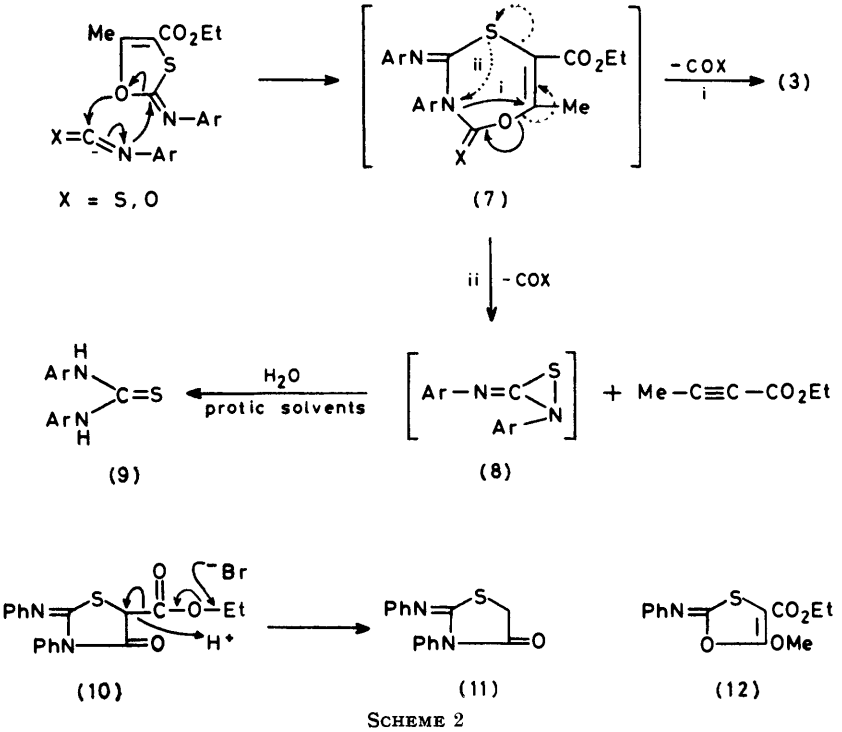
‡ Here, ethyl propiolate was not detected, but arylacetylene was detected by n.m.r. in the condensation of *N,N*-dialkyl-*N'*-arylthiourea and α-halogeno-ketones, as given in ref. 17.

which of the two sulphur atoms of the reactants (oxathiole or phenyl isothiocyanate) was retained in which product (thiazoline or thiourea or COS), we then studied the reaction of phenyl isocyanate with (2; Ar = Ph). Again (3; Ar = Ph) and (9; Ar = Ph) were formed, along with carbon dioxide, indicating that the structural units Ar–N=C–S– of (2; Ar = Ph) and Ar–N= of the heterocumulenes were responsible for the formation of the thiazoline and the thiourea, and that the structural unit =C=X, of the heterocumulenes and the O of the oxathiole gave rise to the COS or CO_2. These observations parallel those reported for the reactions of thioureas with α-halogeno-ketones.[17]

Consequently, a probable mechanism (Scheme 2) involves a 1,2-cycloaddition[18,19] of the heterocumulene to the C–O bond of (2; Ar = Ph), followed by the generation of an oxathiazepine intermediate (7), which could collapse either by extrusion of COX (path i) to give the thiazoline (3; Ar = Ph) or by the extrusion of COX and an acetylene * (path ii) to form thiaziridine (8; Ar = Ph), which in turn in the presence of moisture or a protic solvent could be cleaved to provide the thiourea (9). The thiourea could also be formed by the interaction of phenyl isothiocyanate with moisture[20] present in the solvent; indeed the reaction in anhydrous THF or xylene gave only the thiazoline (3; Ar = Ph); no thiourea (9; Ar = Ph) was formed.

Recently, 2-arylimino-4-cyano-1,3-oxathioles have been shown to behave as masked 1,3-dipoles towards dialkyl acetylene dicarboxylates.[21,22] However, in the present investigation 2-arylimino-1,3-oxathioles (2) react with heterocumulenes in a different manner, *via* initial 1,2-cycloaddition.

Condensation of ethyl bromomalonate with *N,N*-dimethyl-*N'*-phenylthiourea (1a) in acetone gave dimethylamine hydrobromide (50%), phenyl isothiocyanate (5%), 3-phenyl-2-phenyliminothiazolidin-4-one (11)[23] (28%) and the thiourea (9; Ar = Ph) (7%). For the formation of the thiazolidone (11) the initially produced ester (10) could have undergone de-ethoxycarbonylation;[24] indeed the condensation of (9; Ar = Ph) and ethyl bromomalonate in refluxing CH_2Cl_2, performed for procuring the ester (10), also gave (11).



SCHEME 2

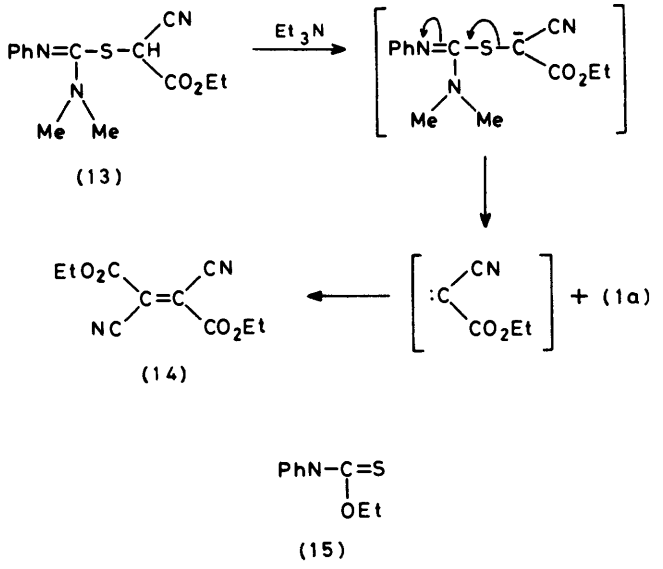
Here again, t.l.c. showed that phenyl isothiocyanate was formed first (along with an oily product which could not be isolated in sufficient amount for structure elucidation), followed by (11) and (9; Ar = Ph). The route to (11) probably involves the formation of the ester (12) (not isolated) and its reaction with phenyl isothiocyanate to form (10).

The thiourea (1b) with ethyl bromomalonate furnished diethylamine hydrobromide (50%), phenyl isothiocyanate (6%), the thiazolidine (11) (30%), and the thiourea (9; Ar = Ph) (5%).

Condensation of ethyl bromocyanoacetate with the thiourea (1a) in acetone gave ethyl cyano{[dimethylamino(phenylimino)methyl]thio}acetate (13), which on treatment with triethylamine afforded diethyl dicyanofumarate (14)[25] and the starting thiourea (1a); no sulphur extrusion was observed.

Ethyl bromocyanoacetate and (1a) in ethanol or DMF

* Here, ethyl propiolate was not detected, but arylacetylene was detected by n.m.r. in the condensation of *N,N*-dialkyl-*N'*-arylthiourea and α-halogeno-ketones, as given in ref. 17.



SCHEME 3

containing NaOEt afforded *O*-ethyl (*N*-phenyl)thiocarbamate (15).[26] Heating (1a) with sodium ethoxide in ethanol also gave (15). Thus in the above condensation, (15) might also have been formed from (1a).

EXPERIMENTAL

For general experimental details see ref. 1.

General Procedure for the Reactions of the Thioureas (1a—d) *with Ethyl α-Chloroacetoacetate, Ethyl Bromomalonate, and Ethyl Bromocyanoacetate.*—Equimolar amounts (0.01 mol) of the reactants in acetone (50 ml) were refluxed for 28—30 h. The mixture was cooled and the dimethyl- or diethyl-amine hydrohalide which had separated was collected. The solvent was removed from the filtrate, and the residue, taken up in ethyl acetate, was repeatedly washed with water to remove any dialkylamine. The solution was dried (Na_2SO_4) and the solvent distilled off. The residue was chromatographed over silica gel with, in sequence, light petroleum (b.p. 40—60 °C), benzene, chloroform, and chloroform–methanol (18 : 1), as eluants. Phenyl isothiocyanate, *p*-tolyl isothiocyanate, and *N,N'*-di-*p*-tolylthiourea isolated from the product mixtures were identical with authentic samples. The reported yields of the various products are based on the amounts of thioureas (1) used.

(a) *The thiourea* (1d) *with ethyl α-chloroacetoacetate.* This furnished (i) diethylamine hydrochloride (55%), m.p. 222°; (ii) *p*-tolyl isothiocyanate (6%), $\nu_{max.}$ (neat) 2 200 cm^{-1}; (iii) the thiourea (9; Ar = *p*-tolyl) (7%); (iv) ethyl 5-methyl-2-*p*-tolylimino-1,3-oxathiole-4-carboxylate (2; Ar = *p*-tolyl) (15%), m.p. 62—63°; *m/z* 277 (M^+), 204 (272—CO_2Et), and 149 (*p*-tolyl isothiocyanate cation); $\nu_{max.}$ ($CHCl_3$) 1 725 cm^{-1}; δ_H($CDCl_3$) 1.25 (3 H, t) and 4.19 (2 H, q) (Et), 2.32 (3 H, s, CH_3), 2.50 (3 H, s, CH_3), and 6.75—7.37 (4 H, m, ArH); δ_C($CDCl_3$) * 14.18 (q), 14.44 (q), 21.22 (q), 61.73 (t), 105.6 (d), 120.6 (d), 130.2, 134.4, 145.1, 156.7, 159.7, and 160.7; and (v) ethyl 2-*p*-tolylimino-4-methyl-Δ^4-thiazoline-5-carboxylate [15] (3; Ar = *p*-tolyl) (20%), m.p. 110—112°.

* The multiplicities of ^{13}C n.m.r. signals refer to the off-resonance proton-decoupled spectra.

(b) *The thiourea* (1b) *and ethyl α-chloroacetoacetate.* This gave (i) diethylamine hydrochloride (50%); (ii) phenyl isothiocyanate (7%); (iii) ethyl 5-methyl-2-phenyl-1,3-oxathiole-4-carboxylate (2; Ar = Ph) (12%), an oil, $\nu_{max.}$ (neat) 1 700 cm^{-1}; δ_H($CDCl_3$) 1.22 (3 H, t) and 4.17 (2 H, q) (Et), 2.46 (3 H, s, CH_3), and 6.81—7.52 (5 H, m, ArH); *m/z* 263 (M^+), 151 (263 − $MeC{\equiv}CCO_2Et$), and 135 (PhNCS cation); (iv) ethyl 4-methyl-2-phenyl-Δ^4-thiazoline-5-carboxylate (3; Ar = Ph) [15] (16%), m.p. 151—152°; $\nu_{max.}$ ($CHCl_3$) 1 708 cm^{-1}; δ_H 1.28 (3 H, t) and 4.23 (2 H, q) (Et), 2.26 (3 H, s, CH_3), and 6.97—7.54 (10 H, m, ArH); *m/z* 338 (M^+), 265 (338 − CO_2Et), and 112 (338 − diphenylthiourea); δ_C ($CDCl_3$) * 14.35 (2 closely spaced q), 60.73 (t), 100.9 (s), 121.3 (s), 123.6 (t), 129.1 (q), 129.3 (q), 129.8 (q), 137.0, 146.7 (s), 151.1 (s), 158.6 (s), and 162.6 (s); and (v) the thiourea (9; Ar = Ph).

(c) *The thiourea* (1a) *with ethyl bromomalonate.* This afforded (i) dimethylamine hydrobromide (50%), m.p. 131—132°; (ii) phenyl isothiocyanate (5%); (iii) 2-phenylimino-3-phenylthiazolidin-4-one [23] (11) (28%), m.p. 172°; δ_H ($CDCl_3$) 4.25 (2 H, s, CH_2) and 7.05—7.55 (10 H, m, ArH); *m/z* 268 (M^+), 267 (268 − H), 133 (268 − PhNCS), and 149 (268 − PhNCO); δ_C ($CDCl_3$) 32.97, 76.57, 77.04, 77.53, 121.0, 124.7, 128.1, 128.9, 129.2, 129.3, 135.1, 148.2, 154.6, and 171.2; and (iv) the thiourea (9; Ar = Ph) (7%).

(d) *The thiourea* (1a) *with ethyl bromocyanoacetate.* This furnished ethyl cyano{[dimethylamino(phenylimino)-methyl]thio}acetate (13), m.p. 107°; δ_H ($CDCl_3$) 1.3 (3 H, t) and 4.27 (2 H, q) (*J* 7 Hz, Et), 3.12 (6 H, s, NMe_2), 6.67 (1 H, s, CH), and 7.75 (5 H, m, ArH); *m/z* 291 (M^+), 219 (291 − CO_2Et), and 180 [291 − $CH(CN)CO_2Et$].

Reaction of the Oxathiole (2; Ar = Ph) *with Phenyl Isothiocyanate.*—A solution of (2; Ar = Ph) (2.6 g, 0.01 mol) and phenyl isothiocyanate (1.35 g, 0.01 mol) in acetone (50 ml) was refluxed on a water-bath. The evolved gas was trapped in a solution of piperidine in n-hexane. After the completion of the reaction (t.l.c.), the solvent was removed and the residue on chromatography over silica gel with light petroleum (b.p. 40—60 °C) as eluant gave starting material (2; Ar = Ph) (3%), the thiazoline (3; Ar = Ph) (25%), and the thiourea (9; Ar = Ph) (4%). The n-hexane solution, after concentration, showed $\lambda_{max.}$ 228 nm, characteristic of piperidinium oxythiocarbamate [27] (formed from COS and piperidine).

A similar reaction of equimolar quantities of (2; Ar = Ph) and phenyl isocyanate gave (2; Ar = Ph) (5%), (3; Ar = Ph) (20%), and (9; Ar = Ph) (6%), and the evolution of carbon dioxide was detected.

Reaction of N,N'-Diphenylthiourea with Ethyl Bromomalonate.—A solution of *N,N'*-diphenylthiourea (2.28 g, 0.01 mol) and ethyl bromomalonate (2.39 g, 0.01 mol) in CH_2Cl_2 (50 ml) was refluxed for 20 h. The solvent was removed and the residue after crystallisation from methanol gave the thiazolidone (11) [23] (60%).

Reaction of Compound (13) *with Triethylamine.*—A solution of (13) (0.58 g, 0.002 mol) and triethylamine (0.20 g, 0.002 mol) in CH_2Cl_2 (50 ml) was stirred for 48—50 h. The solvent was distilled off and the residue after washing with ether gave the thiourea (1a) (0.10 g, 17%). The ethereal washings after the removal of ether gave the dicyanofumarate (14) [26] (0.06 g, 10%), m.p. 114°; $\nu_{max.}$ ($CHCl_3$) 1 750 (CO_2Et) and 2 250 cm^{-1} (CN); δ($CDCl_3$) 1.48 (3 H, t) and 4.62 (2 H, q) (Et).

Reaction of the Thiourea (1a) *with Ethyl Bromocyanoacetate in Ethanol–Sodium Ethoxide.*—To a stirred solution

of (1a) (0.1 mol) and ethyl bromocyanoacetate (0.01 mol) in ethanol (50 ml) was added sodium ethoxide (0.02 mol). After the completion of the reaction (t.l.c.), the solvent was removed and the residue, after treatment with water and neutralisation with acetic acid, was extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and the solvent was distilled off. The residue after crystallisation from methanol gave *O*-ethyl(*N*-phenyl)thiocarbamate (15),[26] m.p. 73°; δ(CD-Cl_3) 2.2 (3 H, t) and 4.62 (2 H, q) (Et), 7.3 (5 H, m, ArH), and 9.5 (1 H, br, exch. NH); *m/z* 181.

Alternatively, (15) (50%) was formed by refluxing a solution of (1a) (0.01 mol) and sodium ethoxide (0.02 mol) in ethanol (50 ml).

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