Isothiocyanate Transposition through a Retro-ene Reaction: Pyrolysis of Acylthioureas

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Pyrolysis of *N*-aryl-*N'*-benzoylthioureas produces aryl isothiocyanates as the major product. This reaction has been used to prepare 4-isothiocyanato-4'-nitrodiphenylamine (7), a potent anthelmintic.

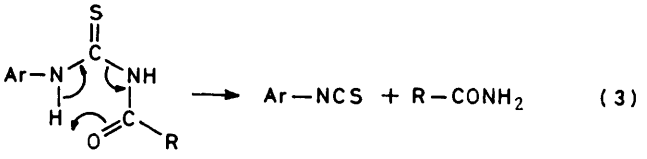
ONE of the possible methods of converting an aromatic amine to the isothiocyanate is through *trans*-isothiocyanation. The process involves two separate steps, equations (1) and (2). In (1) a readily available isothiocyanate, RNCS, reacts with the aromatic amine

$$Ar\text{-}NH_2 + R\text{-}NCS \longrightarrow Ar\text{-}NH\text{-}CS\text{-}NH\text{-}R \quad (1)$$

$$Ar\text{-}NH\text{-}CS\text{-}NH\text{-}R \xrightarrow{heat} Ar\text{-}NCS + R\text{-}NH_2 \quad (2)$$

to form a thiourea; subsequent pyrolysis of this is expected to lead to the aromatic isothiocyanate. The obvious disadvantage in this scheme is that on pyrolysis, the thiourea is equally likely to revert to the aromatic amine [reverse of equation (1)]. It is necessary therefore, to look for a way of forcing the thiourea to fragment exclusively in the desired direction.

We felt that this objective might be achieved if one were to start with *N*-acyl-*N'*-aryl thioureas. Here the desired mode of fragmentation would be favoured because of participation by the carbonyl group as shown in equation (3). This constitutes a retro-ene reaction [1] involving a cyclic six-electron process, which might proceed in concerted fashion. The unwanted fragmentation [equation (4)] would presumably require higher energy. Further, the decomposition to aryl isothiocyanate and amide [equation (3)] is likely to be irreversible, thus obviating the necessity of removing the products from the reaction as it progresses.



(3)

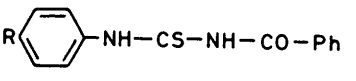
$$Ar\text{-}NH\text{-}CS\text{-}NH\text{-}CO\text{-}R \longrightarrow Ar\text{-}NH_2 + R\text{-}CO\text{-}NCS \quad (4)$$

The necessary acylthioureas are prepared [2] by the addition of aromatic amines to acyl isothiocyanates [reverse of equation (4)]; the latter are derived from acid chlorides and inorganic thiocyanates. The starting materials for the pyrolysis are thus easily accessible.

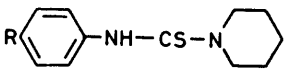
To our knowledge, there has been no report in the literature on any attempt to use acylthioureas as precursors for isothiocyanates. We therefore decided to study first, the pyrolysis of the simple benzoylthioureas (1) in order to establish the feasibility of the reaction. Ultimately our aim was to extend this reaction to the synthesis of the potent anthelmintic, 4-isothiocyanato-4'-nitrodiphenylamine (7).[3]

RESULTS AND DISCUSSION

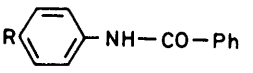
Preliminary experiments on *N*-benzoyl-*N'*-phenylthiourea (1a) established that the pyrolysis was best conducted in refluxing *o*-dichlorobenzene (ODCB); the decomposition was complete in 4 h as shown by the absence of a t.l.c. spot corresponding to the starting material.



(1)

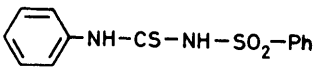


(2)



(3)

a: R = H
b: R = OMe
c: R = NO_2



(4)

Distillation of the ODCB after pyrolysis of a 10% solution of *N*-benzoyl-*N'*-phenylthiourea (1a) carried the product phenyl isothiocyanate in the distillate. This was converted to the piperidine adduct (2a) and identified by comparison with an authentic specimen. Based on the isolated yield of this thiourea, the yield of phenyl isothiocyanate in the pyrolysis was 47%. From the residue after distillation of the ODCB, benzamide (*ca.* 20%) and benzanilide (3a) (*ca.* 10%) could be isolated by fractional crystallisation. Theoretically, phenyl isothiocyanate and benzamide should be produced in equimolar amounts. We ascribe the lower isolated yield of benzamide to loss on crystallisation and possibly to some dehydration under the pyrolytic conditions.

Under the same conditions of pyrolysis, *N*-benzoyl-*N'*-(*p*-methoxyphenyl)thiourea (1b) gave *p*-methoxyphenyl isothiocyanate in 57% yield [isolated and identified as the thiourea (2b)] and the benzanilide (3b) in about 12% yield. *N*-Benzoyl-*N'*-(*p*-nitrophenyl)thio-

urea (1c) on pyrolysis gave *p*-nitrophenyl isothiocyanate [isolated and characterised as its piperidine adduct (2c)] in 37% yield. In this case, we were unable to isolate any benzanilide (3c). A very small quantity of a high-melting compound of unknown structure was obtained as a by-product.

The products obtained on pyrolysis of the benzoylthiourea (1a) were also identified and quantified by g.l.c. The estimation was carried out by using the internal standardisation technique. *p*-Methoxyphenyl isothiocyanate was chosen as the internal standard. The values obtained (mean of three estimations) for the product yields on pyrolysis of a 10% solution of the benzoylthiourea (1a) were phenyl isothiocyanate 74%, and benzanilide 15.9%. Benzamide could not be determined quantitatively due to poor peak symmetry in the column employed.

Two modes of fragmentation of the benzoylthioureas thus became evident. Phenyl isothiocyanate and benzamide obviously resulted from reaction (3), whereas benzanilide could have arisen from a four-centre reaction with loss of thiocyanic acid. The former was the major pathway of decomposition in the three examples studied. Apart from these two processes, there must be other minor reactions also taking place, which became evident in the following study on the effect of dilution on product yields.

Solutions of the benzoylthiourea (1a) in ODCB at different concentrations were refluxed for 4 h and the product yields determined in each case both by g.l.c. and by actual isolation of the derived thiourea (2a). The results are shown in Table 1. The increase in

TABLE 1

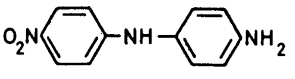
Effect of dilution on product yield in the pyrolysis of (1a)

Concentration of (1a) in ODCB (w/v)	Isolated yield of (2a) (%)	Yield by g.l.c. (%)	
		Ph–NCS	(3a)
20	29	59	21.7
10	47	74	15.9
5	58	85	11.8
1	70	96.5	6.7
0.2		102	2.9

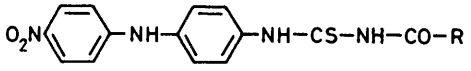
yield of the isothiocyanate with increasing dilution is ascribed to the suppression of intermolecular reactions involving either the starting benzoylthiourea or the product isothiocyanate. The reason for the consistent decrease in yield of the anilide with increasing dilution is not clear. These two together account for all the starting material at concentrations of $\leqslant 1\%$, but at 20% concentration, they add up to only about 80%. The rest of the material must therefore be involved in other side-reactions.

The role of the carbonyl group in promoting the desired fragmentation was further highlighted by studying the effect of replacing it by a sulphone. Under the same conditions of pyrolysis as before (concentration 10%), the sulphonylthiourea (4) underwent extensive resinification and gave only an 8% yield of phenyl isothiocyanate. This parallels the behaviour of β-sulphonylacetic acids, which on pyrolysis, require higher temperatures for decarboxylation than do the β-ketoacids, and also produce much resinous material.[4]

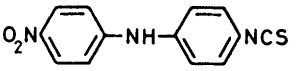
We were now in a position to attempt the synthesis of 4-isothiocyanato-4′-nitrodiphenylamine (7) from the amine (5) *via* the acylthiourea (6). Initially, using the



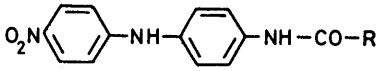
(5)



(6)



(7)



(8)

a; R = Ph b; R = C_6H_4OMe-*p*

c; R = $C_6H_4NO_2$-*p* d; R = Me

benzoylthiourea (6a), temperature and duration of the reaction were varied to establish the optimum conditions. A range of solvents with b.p.s varying from 132 to 210 °C was investigated. The results are given in Table 2. As expected from our previous model studies,

TABLE 2

Effect of temperature on the decomposition of (6a)

Solvent	B.p. (°C)	Reaction time/h	Result
Chlorobenzene	132	20	Starting material recovered
Chlorobenzene + ODCB (1 : 2)	148—150	4	
Diglyme	162	4	(7) + (8a)
ODCB	180—183	4	
Tetralin	207	4	Extensive decomposition, very low yield of (7)
Nitrobenzene	210	0.5	

the anilide (8a) was the chief contaminant of the isothiocyanate. These two were clearly separated on t.l.c. The product from diglyme appeared to contain more of the by-product anilide (8a) than that from ODCB (t.l.c.). ODCB thus emerged as the best solvent for the pyrolysis of the acylthiourea (6a).

At this stage we decided to vary the acyl residue R in (6) to see if the isothiocyanate could be obtained free of the contaminating anilide. The *p*-methoxybenzoylthiourea (6b) gave only about 15% yield of the crude isothiocyanate which was reasonably pure on t.l.c. The *p*-nitrobenzoylthiourea (6c) on pyrolysis gave a 48% yield of crude isothiocyanate, contaminated by three minor impurities (t.l.c.). The acetylthiourea (6d) gave only about 20% of crude isothiocyanate, which on t.l.c. showed a second spot corresponding to the *N*-acetyl derivative (8d). Thus no particular advantage accrued from changing the acyl residue.

The only way to improve the purity and yield of the isothiocyanate (7) would seem to be by taking advantage of the results on the effect of dilution (see above). Table 3 presents our results on the pyrolysis (4 h in refluxing ODCB) of the benzoylthiourea (6a) at two different concentrations (10 and 1%). Preparative t.l.c. using a weighed amount of the crude product, followed by extraction and estimation by spectrophotometry, enabled us to determine the percentage of the isothiocyanate (7) and anilide (8a) in the product mixture, and hence the yield of these two in the reaction. Two conclusions emerge from this: (*i*) in the partially purified products on which the preparative t.l.c. was carried out, there is little variation in the proportion of the anilide; and (*ii*) there are apparently side-reactions, possibly intermolecular, taking place in the more concentrated solution. These are suppressed as the solution is diluted, and thus the isothiocyanate obtained is much purer, in agreement with the pilot studies on *N*-benzoyl-*N'*-phenylthiourea.

TABLE 3

Effect of dilution on the pyrolysis of (6a)

	Isothiocyanate		Anilide	
Concentration	Amount in product mixture (%)	Yield in reaction (%)	Amount in product mixture (%)	Yield in reaction (%)
10% w/v	76	39.9	3.6	1.5
1% w/v	103 *	63.0	3.5 *	1.75

* The recovery of >100% is due to inherent errors in the analytical methodology (±5—10%); we consider the isothiocyanate here to be 96.5% pure.

Conclusion.—Pyrolysis of acylthioureas provides a route for the preparation of isothiocyanates, if it is carried out on a sufficiently dilute solution. The significance of this method of preparation lies in the fact that the source of the thiocarbonyl unit is an inexpensive and ecologically acceptable inorganic thiocyanate.

EXPERIMENTAL

G.l.c. Conditions.—Gas chromatography was carried out with a Varian model 2740 instrument equipped with a flame ionisation detector, using a 5 ft × 4 mm (i.d.) glass column packed with 3% OV-225 on 80—100 mesh Gas-chrom Q (Applied Science Labs, State College, Pa., U.S.A.). The temperature settings were as follows: Column oven, 135 °C; injection port, 240 °C; and detector, 300 °C. The gas pressures were: nitrogen, 16 lb in^{-2} (column head pressure); hydrogen, 34 ml min^{-1}; and air, 300 ml min^{-1}. The recorder was run at 40 in h^{-1} for the quantitation of the anilide and 80 in h^{-1} for the phenyl isothiocyanate. The column was operated isothermally at 135 °C for 3 min and then programmed at the rate of 8 °C min^{-1} up to 230 °C, where it was held for 5 min. The peak areas were integrated by the height × half-height-width method.

Using *p*-methoxyphenyl isothiocyanate as the internal standard, standard calibration curves were prepared for both phenyl isothiocyanate and benzanilide, covering the weight ratio range of 0.5—2.5, where the response was found to be linear. Concentrations of the phenyl isothiocyanate and benzanilide in the pyrolysis solution were calculated by diluting an aliquot of the reaction mixture with a solution of the internal standard (concentration 1 mg ml^{-1}) in ODCB. Aliquots (2 μl) of this solution were injected in triplicate and the peak areas were measured. The concentrations of the isothiocyanate and anilide were calculated from the calibration curve.

T.l.c.—This was carried out using silica gel GF_{254} plates (0.5 mm) in the solvent system n-hexane–acetone (3 : 2). The regions corresponding to the reference standards [isothiocyanate (7) and anilide (8a)] were scraped off and the silica gel was extracted with methanol. The concentrations of the isothiocyanate and anilide were calculated from the calibration graphs which had been prepared previously for each compound, using the optical density at 390 nm. From control experiments the recovery of the isothiocyanate after t.l.c. and subsequent extraction was found to be 87%, and this was used as a scaling factor to correct the value obtained by spectrophotometry.

Synthesis of N-*Aryl*-N'-*benzoylthioureas* (1).—The aniline and benzoyl isothiocyanate were mixed in ether and set aside at room temperature until precipitation was complete. The product was filtered off, washed with ether, and recrystallised from a suitable solvent. The following thioureas were prepared: *N*-benzoyl-*N'*-phenylthiourea (1a),[2] m.p. 148—151 °C (from isopropanol) (Found: C, 65.7; H, 4.95; N, 10.7. Calc. for $C_{14}H_{12}N_2OS$: C, 65.6; H, 4.7; N, 10.9%); *N*-benzoyl-*N'*-(*p*-methoxyphenyl)thiourea (1b),[2] m.p. 151—154 °C (from ethyl acetate–hexane) (Found: C, 63.2; H, 5.1; N, 10.0. Calc. for $C_{15}H_{14}N_2O_2S$: C, 62.9; H, 4.9; N, 9.8%); and N-*benzoyl*-N'-(p-*nitrophenyl*)*thiourea* (1c), m.p. 187—189 °C (from acetonitrile) (Found: C, 55.6; H, 4.0; N, 14.1. $C_{14}H_{11}N_3O_3S$ requires C, 55.8; H, 3.7; N, 13.95%).

Pyrolysis of N-*Benzoyl*-N'-*phenylthiourea* (1a).—(*i*) The benzoylthiourea (1a) (1.0 g) in ODCB (10 ml) was refluxed for 4 h. The solvent was then distilled off *in vacuo*. More ODCB (5 ml) was added to the residue and again distilled off, leaving residue (A). The combined distillate was treated with piperidine (0.4 g) and set aside at room temperature for 1 h. The ODCB was again distilled off *in vacuo*, leaving behind crude thiourea (2a). This was digested with hexane, cooled, and filtered to give (2a) (0.4 g), m.p. and mixed m.p. with an authentic sample,[5] 99—101 °C (Found: C, 65.6; H, 7.5; N, 12.4. Calc. for $C_{12}H_{16}N_2S$: C, 65.4; H, 7.3; N, 12.7%). The residue (A) above was extracted twice with boiling water, leaving a residue (B). The combined water filtrate was concentrated, cooled, and filtered, to give benzamide (0.1 g), m.p. and mixed m.p. 126—129 °C. The residue (B) was crystallised from aqueous ethanol to give benzanilide (*ca.* 0.1 g), m.p. and mixed m.p. 160—162 °C.

(*ii*) The first part of the experiment was repeated with the benzoylthiourea (1a) (1.0 g) in ODCB (5 ml). Work-up as before gave the thiourea (2a) (0.25 g).

(*iii*) The pyrolysis was carried out as before with the benzoylthiourea (1a) (1.0 g) in ODCB (20 ml). Work-up as before gave the thiourea (2a) (0.51 g).

(*iv*) Pyrolysis of the benzoylthiourea (1a) (2.0 g) in ODCB (200 ml) gave the thiourea (2a) (1.2 g) after the usual work-up.

Pyrolysis of N-*benzoyl*-N'-(p-*methoxyphenyl*)*thiourea* (1b).—The benzoylthiourea (1b) (1.0 g) in ODCB (10 ml) was refluxed for 4 h, after which the ODCB was distilled off *in vacuo*. The residue was extracted twice with ether, leaving behind an ether-insoluble residue (A). The com-

bined ether extracts were treated with piperidine (0.3 g) and set aside at room temperature overnight. Evaporation of the ether left a solid which was first digested with boiling water and then crystallised from ethyl acetate–hexane to give the thiourea (2b) (0.5 g), m.p. 141—144 °C. This was identical (mixed m.p.) with an authentic sample [5] prepared by addition of piperidine to *p*-methoxyphenyl isothiocyanate (Found: C, 62.4; H, 7.5; N, 11.0. Calc. for $C_{13}H_{18}N_2OS$: C, 62.4; H, 7.25; N, 11.2%). The ODCB distillate was similarly treated with piperidine and worked up, but this gave only traces of the thiourea (2b).

The ether-insoluble residue (A) above was digested with hot water to remove benzamide, dissolved in ethanol, filtered, and the product precipitated by addition of water to the filtrate. Recrystallisation of this from ethyl acetate–hexane gave the *p*-methoxybenzanilide (3b) (0.1 g), m.p. 155—156 °C. Mixed m.p. with an authentic sample (m.p. 157—160 °C) prepared from benzoyl chloride and *p*-anisidine was 155—159 °C. The two samples had identical i.r. spectra.

Pyrolysis of N-*Benzoyl*-N′-(p-*nitrophenyl*)*thiourea* (1c).—The benzoylthiourea (1c) (1.0 g) in ODCB (10 ml) was refluxed for 4 h, the solvent then removed *in vacuo*, and the residue extracted twice with ether. The ether extract was reacted with piperidine (0.4 g) at room temperature for 15 h and the thiourea (2c) (0.325 g), m.p. 164—167 °C, obtained after crystallisation from ethyl acetate–hexane (2c), m.p. 170—171 °C, undepressed on admixture with an authentic sample prepared by adding piperidine to *p*-nitrophenyl isothiocyanate (Found: C, 54.3; H, 5.95; N, 16.0. $C_{12}H_{15}N_3O_2S$ requires C, 54.3; H, 5.7; N, 15.8%).

The ether-insoluble residue from the pyrolysis was processed as before, by first digesting with hot water to remove benzamide and then crystallising from ethyl acetate–hexane. A small quantity (*ca.* 25 mg) of material was obtained, m.p. 250—255 °C, which did not correspond to the benzanilide (3c).

Pyrolysis of N-*Phenylsulphonyl*-N′-*phenylthiourea* (4).—The sulphonylthiourea (4) [6] was prepared from *N*-phenylsulphonyldithiocarbamic acid methyl ester [7] and aniline. This (2.0 g) in ODCB (20 ml) was refluxed for 4 h and then worked up as described for the pyrolysis of the benzoylthiourea (1a). The piperidino-thiourea (2a) (125 mg) was obtained as before, m.p. and mixed m.p. 99—102 °C.

Synthesis of the N-*Acylthioureas* (6).—4-Amino-4′-nitrodiphenylamine (5) [8] (10.0 g) dissolved in warm dioxan was treated with benzoyl isothiocyanate [9] (8.0 g) and set aside at 30 °C for 16 h. The solid was filtered off, washed with dioxan, and recrystallised from acetone to give the benzoylthiourea (6a) (16.0 g), m.p. 218—220 °C (Found: C, 61.4; H, 4.4; N, 14.0. $C_{20}H_{16}N_4O_3S$ requires C, 61.2; H, 4.1; N, 14.3%).

Similarly, the amine (5) (4.6 g) and *p*-methoxybenzoyl isothiocyanate [9] (3.8 g) gave the *p*-methoxybenzoylthiourea (6b) (3.1 g), m.p. 192—194 °C (from 1,2-dimethoxyethane–hexane) (Found: C, 59.4; H, 4.6; N, 13.05. $C_{21}H_{18}N_4O_4S$ requires C, 59.7; H, 4.3; N, 13.3%).

The amine (5) (6.9 g) and *p*-nitrobenzoyl isothiocyanate [9] (6.3 g) gave the *p*-nitrobenzoylthiourea (6c) (8.0 g), m.p. 224—226 °C (from acetic acid) (Found: C, 55.3; H, 3.7; N, 15.8. $C_{20}H_{15}N_5O_5S$ requires C, 54.9; H, 3.5; N, 16.0%).

The amine (5) (4.6 g) and acetyl isothiocyanate (2.0 g) gave the acetylthiourea (6d) (3.1 g), m.p. 230—232 °C (from acetic acid) (Found: C, 54.85; H, 4.6; N, 17.15. $C_{15}H_{14}N_4O_3S$ requires C, 54.5; H, 4.3; N, 17.0%).

4-N-*Benzoylamino*-4′-*nitrodiphenylamine* (8a).—The amine (5) (1.1 g) in dioxan was treated with benzoyl chloride (0.7 g) and triethylamine (0.5 g). After 30 min at 30 °C, the solvent was removed *in vacuo*, the residue digested with water, filtered, and recrystallised from isopropanol–water to give the anilide (8a) (1.0 g), m.p. 211—213 °C (Found: C, 68.7; H, 4.5; N, 12.4. $C_{19}H_{15}N_3O_3$ requires C, 68.5: H, 4.5; N, 12.6%).

Pyrolysis of the Benzoylthiourea (6a).—(*i*) The benzoylthiourea (6a) (2.0 g) in ODCB (20 ml) was refluxed for 4 h. The solvent was then distilled off *in vacuo*. The residue was digested with cold acetonitrile, set aside at 0 °C for 15 h, filtered, and washed with cold acetonitrile to give the product (0.725 g), m.p. 130—160 °C, which was used for t.l.c. estimation.

(*ii*) The benzoylthiourea (6a) (1.0 g) in ODCB (100 ml) was pyrolysed and worked up as above to give the product (0.425 g), m.p. 190—194 °C, which was used for t.l.c. estimation. One crystallisation of this from acetone gave the isothiocyanate (7), m.p. 196—198 °C, which was at least 98% pure (t.l.c.) (Found: C, 57.45; H, 3.3; N, 15.3. Calc. for $C_{13}H_9N_3O_2S$: C, 57.6; H, 3.3; N, 15.5%).

We thank Dr. S. Selvavinayakam and his associates for the analytical data.

[8/1231 *Received*, 4*th July* 1978]

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