Reaction of 3-Aryl-2-cyanothioacrylamides with Electron-deficient Alkynes: Synthesis of 4-Aryl-4*H*-thiopyrans

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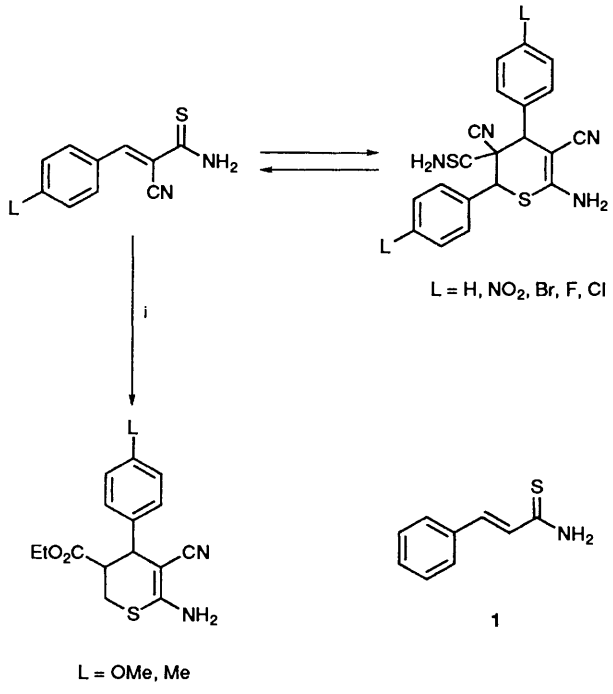
The 3-aryl-2-cyanothioacrylamides **2–4** react well with methyl propiolate and dimethyl acetylenedicarboxylate yielding the thiopyrans **8–13**. Reactions with less activated alkynes proceed sluggishly, if at all.

Our interest in the synthesis of a range of 2-amino-4-aryl-4*H*-5,6-dihydronaphtho[1,2-*b*]pyran-3-carbonitriles[1] for biological testing[2] has prompted us to examine routes to simplified analogues, including those in which the pyran is replaced by a thiopyran nucleus. Thiocarbonyl compounds, including unsaturated thioketones[3–8] and enaminothiones[9–14] (vinylogous thioamides) are well known to react in a formal hetero-Diels–Alder sense with electron-deficient species yielding a variety of thiopyrans. Our major concern has been to maintain the enaminonitrile functionality in our target compounds. Particularly relevant to this aim are the observations[15,16] that 3-aryl-2-cyanothioacrylamides react well with ethyl acrylate, acrylonitrile, ω-nitrostyrene and *N*-arylmaleimides providing 4-aryldihydrothiopyrans with an integral enaminonitrile portion (Scheme 1). Indeed, it has been indicated[17] that in some cases

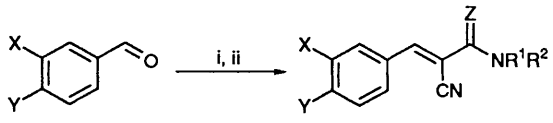


Scheme 1 *Reagents and conditions:* i, ethyl acrylate, AcOH, heat

these thioacrylamides undergo [4 + 2] dimerisation, yielding dihydrothiopyrans (Scheme 1). It is of note that in compounds lacking the 2-cyano functionality, such as **1**, hetero-Diels–Alder reaction either with itself or with an added dienophile does not proceed until the thioamide is activated by *in situ* acylation.[18–21] Our intention was to exploit the described reactivity of 3-aryl-2-cyanothioacrylamides in a series of reactions with electron-deficient alkynes.

Results and Discussion

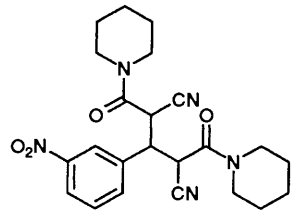
Synthesis of the starting primary 3-aryl-2-cyanothioacrylamides **2–4** was performed using a Knoevenagel condensation between the appropriate aromatic aldehyde and 2-cyanothioacetamide (Scheme 2).[17] Fresh 2-cyanothioacetamide appeared to be



2–6

	X	Y	Z	R^1	R^2
2	NO_2	H	S	H	H
3	OMe	OMe	S	H	H
4	Cl	Cl	S	H	H
5*	NO_2	H	O	$-[CH_2]_5-$	
6*	NO_2	H	S	$-[CH_2]_5-$	

*Mixture of *E* and *Z* isomers at the carbon–carbon double bond



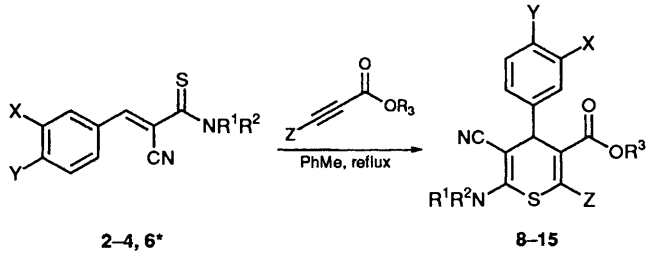
7

Scheme 2 *Reagents:* i, $R^1R^2NC(=Z)CH_2CN$, EtOH, piperidine; ii, (for Z = O→Z = S) Lawesson's reagent, toluene

crucial for the success of this reacton. Only in the instance of the 3-nitrophenyl compound **2** was there any evidence for the [4 + 2] dimer; two thiocarbonyl resonances were seen at δ 191 and 195 in the ^{13}C NMR spectrum, as well as a diagnostic resonance for the 4*H*-thiopyran proton at δ 5.60 in the ^1H NMR spectrum. In a variable temperature ^1H NMR experiment, it was noted that when the monomer–dimer mixture was warmed to *ca.* 85 °C in [$^2H_6$]dimethyl sulfoxide, only signals for the monomeric 3-aryl-2-cyanothioacrylamide **2** were seen. On cooling to room temperature, the dimer did not reform. The unsaturated tertiary thioamide **6** was prepared by Knoevenagel condensation of 1-cyanoacetylpiperidine with 3-nitrobenzaldehyde (yielding **5** as a mixture of *E* and *Z* unsaturated amides), followed by thionation of the amide carbonyl with Lawesson's reagent (Scheme 2).[22,23] Normally in these Knoevenagel

condensations, the desired product precipitates from the reaction medium. In the case of the amide **5**, the initial precipitate was the bis-adduct **7** in which a second molecule of 1-cyanoacetylpiperidine has added in a Michael sense to the desired product. This structure was confirmed by the spectral data; in the ^{1}H NMR spectrum, four aromatic proton resonances were visible, together with a 2 H resonance at δ 4.52, a 1 H signal at δ 4.05 and multiplets for the piperidine ring resonances at δ 3.5–3.7 and 1.6–1.8. The ^{13}C NMR showed only one carbonyl (δ 160.3) and one nitrile (δ 114.9) resonance, three new CH resonances (δ 44.3, 44.2 and 39.2) plus six aromatic ring resonances and three signals for the piperidine rings. The mass spectrum gave a strong ion at 438, corresponding to $(M + H)^+$. When the precipitate of **7** was removed and the solution was stirred for longer, the desired unsaturated amide **5** was precipitated.

Reaction of the unsaturated thioamide **2** with methyl propiolate in toluene at reflux proceeded very quickly; within 2 h, the starting thioamide had been consumed. As the solution cooled to room temperature, a solid was precipitated. The ^{1}H NMR of this material displayed the four aromatic proton resonances of the 3-nitrophenyl group, an olefinic 1 H singlet resonance at δ 7.89, a 2 H exchangeable singlet resonance at δ 4.79 and a 3 H singlet resonance at δ 3.64. This is consistent with the product being the desired 4*H*-thiopyran **8** (see Scheme 3). Evidence for the regiochemistry of the addition



2–4, 6*

8–15

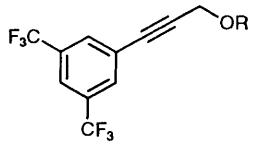
*Mixture of E and Z isomers at the carbon–carbon double bond

	X	Y	Z	R^1	R^2	R^3
8	NO_2	H	H	H	H	Me
9	NO_2	H	CO_2Me	H	H	Me
10	OMe	OMe	H	H	H	Me
11	OMe	OMe	CO_2Me	H	H	Me
12	Cl	Cl	H	H	H	Me
13	Cl	Cl	CO_2Me	H	H	Me
14	NO_2	H	Ph	H	H	Et
15	NO_2	H	CO_2Me	$-[CH_2]_5-$		Me

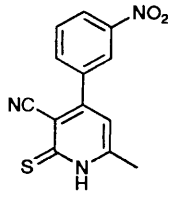
Scheme 3

being as shown is derived from the two new 1 H resonances in the NMR spectrum being singlets. This argument was further enhanced by the use of an NOE difference experiment; irradiation of the thiopyran 4-H proton resonance produced strong enhancements of the signals for the aromatic 2′ and 6′ protons yet only a weak enhancement of the olefinic singlet resonance at δ 7.89. Further corroboration of the gross structure were the stretches seen for the NH_2 (3378, 3323 and 3220 cm^{-1}), CN (2189 cm^{-1}) and ester groups (1700 cm^{-1}) in the IR spectrum and the presence of a base peak at 335 in the mass spectrum corresponding to $(M + NH_4)^+$. The unsaturated thioamide **2** similarly reacted well with dimethyl acetylenedicarboxylate providing the thiopyran **9**. Spectral data were similar to those of the methyl propiolate adduct **8**, with the olefinic proton being replaced by a 3 H singlet resonance at δ 3.80 for the additional methyl ester group. The thioamides **3** and **4** also reacted well with methyl propiolate and dimethyl acetylenedicarboxylate yielding the analogous adducts **10–13**. The tertiary thioamide **6** reacted similarly with dimethyl acetylenedicarboxylate. However, in this case the adduct **15**, although identified by diagnostic signals in the ^{1}H NMR of the crude reaction product, proved to be very labile, decomposing upon chromatography. As indicated earlier, the unsaturated tertiary thioamide **6** was obtained as a mixture of geometrical isomers. It was of interest that by TLC only one of these geometrical isomers participated in the cycloaddition, with the other isomer appearing to remain unchanged throughout the course of the reaction. One might predict that the *E*-isomer should react whilst the *Z*-isomer should not, as the aryl group may hinder approach of the alkyne to the heterodiene moiety.

Returning to the primary thioacrylamides, we wished to examine the scope of the reaction between the thioamide **2** and a variety of other alkynes. Reaction with ethyl phenylpropiolate proceeded sluggishly (48 h at reflux in glacial acetic acid) yielding the thiopyran **14** in modest yield after chromatography (these thiopyrans do not chromatograph well; large losses can easily be incurred on silica, alumina or Florisil). However, phenylacetylene, diphenylacetylene, 3-phenylprop-2-yn-1-ol and 3-phenylpropynal all failed to provide thiopyran adducts with **2** under a variety of conditions (toluene, xylene or acetic acid at reflux). In an attempt to make the phenyl group of the acetylene more electron deficient to promote reaction, the 3,5-bis(trifluoromethyl)phenyl substituted alkyne **16** was allowed to



16 R = H
17 R = Ac



18

react with **2** in acetic acid at reflux (no reaction occurred in toluene). In this instance, the alcohol was rapidly consumed but the product obtained was the solvolysis product **17** with the thioamide remaining unchanged. Structural assignment for compound **17** was facilitated by direct comparison with spectra of the starting alcohol **16**. Finally in this series of reactions, the thioamide **2** was allowed to react with 3-phenylpropynal diethyl acetal in toluene at reflux. After 6 h, a large amount of **2** still remained undissolved, so acetone was added as a cosolvent. As the mixture cooled to room temperature after 48 h at reflux, a precipitate appeared. This was obviously not a thiopyran since its spectral characteristics were simple; the ^{1}H NMR showed an exchangeable 1 H singlet resonance at δ 14.29, a 1 H singlet resonance at δ 6.97 and a 3 H singlet resonance at δ 2.46, as well as the characteristic 4 H signal pattern of the 3-nitrophenyl group. In the ^{13}C NMR, thirteen signals were seen. Three signals were of particular note, at δ 177.9, 116.0 and 18.6. The first of these was thought to represent a thiocarbonyl group, the second indicated the retention of the nitrile and the third a new methyl group. The mass spectrum showed a base peak at 272, suggesting that the isolated material was the pyridinethione **18** resulting from the condensation of acetone with the thioamide. Whilst the addition of ketones (and the enamines derived from them) to unsaturated thioamides is known to yield pyridinethiones, this normally proceeds in the presence of a basic catalyst.[24]

Further work on the reactions of unsaturated thioamides

with compounds that function as alkyne equivalents is currently underway in these laboratories.

Experimental

Melting points were determined on a Reichert hot-stage apparatus and are uncorrected. IR spectra were recorded on a Bruker IFS 48 instrument as KBr discs. UV spectra were determined on a Philips PU 8725 instrument as methanol solutions. Mass spectra were recorded using a VG7070E instrument. NMR spectra were obtained on dilute solutions in [$^2H_6$]dimethyl sulfoxide, except where indicated otherwise, on a Bruker AM300 or AC300 instrument (300 MHz). Signals are reported downfield from tetramethylsilane (TMS). Coupling constants are in Hz. Microanalyses were carried out by the molecular structure research group at Eli Lilly and Company, Indianapolis. Ether refers to diethyl ether.

Preparation of 2-*Cyano*-3-(3-*nitrophenyl*)*thioacrylamide* **2**.—A mixture of 2-cyanothioacetamide (4.81 g, 48 mmol) and 3-nitrobenzaldehyde (7.26 g, 48 mmol) in ethanol (25 cm^3) was stirred in an oil bath maintained at 50 °C. After 5 min, piperidine (8 drops) was added. A red colour developed in the suspension and the solids slowly went into solution. After 35 min, a copious yellow precipitate appeared. The mixture was removed from the oil bath and stirring continued for 15 min. The solid was then filtered off, washed with ethanol and then ether and dried *in vacuo* at 60 °C, providing the *title compound* **2** as a yellow powder (6.8 g, 61%). We found that the melting point of different batches of **2** varied, depending on the proportion of dimer, *e.g.* 159–162, 174, 192 °C. Russian literature[25] gives a figure of 204–205 °C. The correct identity of our product was indicated by the following data (Found: C, 51.8; H, 3.2; N, 17.75; S, 13.5. $C_{10}H_7N_3O_2S$ requires C, 51.5; H, 3.0; N, 18.0; S, 13.75%); δ_H(360 K, monomeric form) 9.90 (1 H, br s), 9.42 (1 H, br s), 8.85 (1 H, d, *J* 2), 8.38 (1 H, dd, *J* 8 and 2), 8.30 (1 H, dd, *J* 8 and 2), 8.08 (1 H, s) and 7.82 (1 H, t, *J* 8); *m*/*z* 251 [(M + NH_4)$^+$, 100%], 233 (18), 216 (13), 202 (28), 187 (8), 170 (5) and 86 (24).

Prepared in a similar manner were 2-*cyano*-3-(3,4-*dimethoxyphenyl*)*thioacrylamide* **3** (90% yield) and 2-*cyano*-3-(3,4-*dichlorophenyl*)*thioacrylamide* **4** (73% yield). Compound **3**: M.p. 197–201 °C (Found: C, 58.2; H, 5.0; N, 11.3; S, 12.9. $C_{12}H_{12}N_2O_2S$ requires C, 58.05; H, 4.9; N, 11.3; S, 12.9%); ν_{max}/cm^{-1} 3330, 2205 and 1620; λ_{max}/nm 249 and 362; δ_H 10.01 (1 H, br s), 9.48 (1 H, br s), 8.08 (1 H, br s), 7.69 (1 H, d, *J* 2), 7.58 (1 H, dd, *J* 8 and 2), 7.17 (1 H, d, *J* 8), 3.87 (3 H, s) and 3.81 (3 H, s); *m*/*z* 249 (100%), 233 (6) and 217 (9). **4**: M.p. 174–177 °C (Found: C, 46.6; H, 2.5; Cl, 27.9; N, 11.0; S, 12.3. $C_{10}H_6Cl_2N_2S$ requires C, 46.7; H, 2.35; Cl, 27.6; N, 10.9; S, 12.5%); ν_{max}/cm^{-1} 3376, 3356, 3306, 3219, 2225, 1642 and 1624; λ_{max}/nm 254 and 324; δ_H 10.22 (1 H, br s), 9.74 (1 H, br s), 8.15 (1 H, d, *J* 2), 8.03 (1 H, s) and 7.90 (2 H, m); *m*/*z* 274 (19%), 257 (100) and 221 (21).

Representative Preparation of a Tertiary Thioamide.—A mixture of 1-cyanoacetylpiperidine (12.0 g, 78.8 mmol) and 3-nitrobenzaldehyde (11.2 g, 78.7 mmol) was suspended in ethanol (70 cm^3) and warmed in an oil bath. To this was added piperidine (6 drops) and the solution warmed to reflux. After 2 h at reflux, the solution was stirred at room temperature for a further 16 h. The precipitated white solid **7** was filtered off and dried *in vacuo* (13.0 g, 38%), m.p. 163 °C (Found: C, 63.4; H, 6.2; N, 16.2. $C_{23}H_{27}N_5O_4$ requires C, 63.1; H, 6.2; N, 16.0%); δ_H($CDCl_3$) 8.29 (2 H, m), 7.83 (1 H, d, *J* 8), 7.64 (1 H, t, *J* 8), 4.52 (2 H, d, *J* 8), 4.05 (1 H, t, *J* 8), 3.7–3.5 (8 H, m) and 1.8–1.6 (12 H, m); δ_C($CDCl_3$) 160.3, 148.2, 136.0, 134.5, 130.2, 124.4, 124.0, 114.9, 47.4, 44.3, 44.2, 39.2, 26.2 and 25.4; *m*/*z* 438 (66%), 303 (13), 286 (37), 170 (100) and 153 (42). With time, the mother liquor provided further crystals. These were collected and dried *in vacuo*, yielding the desired unsaturated amide **5** as a mixture of *E* and *Z* isomers (3.6 g, 16%), m.p. 127 °C (Found: C, 63.0; H, 5.3; N, 14.4. $C_{15}H_{15}N_3O_3$ requires C, 63.15; H, 5.3; N, 14.7%). Combined batches of this amide from a number of experiments (4.50 g, 15.8 mmol) and Lawesson's reagent (3.49 g, 7.9 mmol) in toluene (60 cm^3) were stirred and heated to reflux. After 3 h, the solution was allowed to cool, concentrated under reduced pressure and the residue passed down a column of silica, eluting with chloroform–ether (1:3). The resulting oil was triturated with ether to yield a yellow–orange solid which was dried *in vacuo*, providing the thioamide **6** (4.20 g, 88%) as a 3:2 mixture of *E* and *Z* isomers, m.p. 95 °C (Found: C, 59.7; H, 5.2; N, 13.7; S, 10.7. $C_{15}H_{15}N_3O_2S$ requires C, 59.8; H, 5.0; N, 13.9; S, 10.6%); ν_{max}/cm^{-1} 1539, 1532, 1522, 1355 and 1250; δ_H($CDCl_3$, *E* isomer) 8.56 (1 H, s), 8.28 (1 H, d, *J* 8), 8.26 (1 H, d, *J* 8), 7.67 (1 H, t, *J* 8), 7.48 (1 H, s), 4.40 (2 H, m), 3.85 (2 H, m) and 1.7 (6 H, m); δ_H($CDCl_3$, *Z* isomer) 8.39 (1 H, s), 8.23 (1 H, d, *J* 8), 7.81 (1 H, d, *J* 8), 7.59 (1 H, t, *J* 8), 7.00 (1 H, s), 4.40 (2 H, m), 3.65 (2 H, m) and 1.7 (6 H, m); partial δ_C($CDCl_3$, *E* isomer) 188.7 (C=S), 143.8 [Ar*C*=C(CN)], 115.0 (CN); partial δ_C($CDCl_3$, *Z* isomer) 186.1 (C=S), 136.6 [Ar*C*=C(CN)] and 116.2 (CN); *m*/*z* 301 (100%), 284 (24), 254 (26), 179 (41) and 83 (80).

Representative Reactions Between Thioamides and Alkynes.—*Methyl* 6-*amino*-5-*cyano*-4-(3-*nitrophenyl*)-4H-*thiopyran*-3-*carboxylate* **8**.—To a stirred suspension of the thioacrylamide **2** (1.0 g, 4.29 mmol) in toluene (60 cm^3) was added methyl propiolate (0.40 g, 4.75 mmol). The mixture was warmed to reflux during which time the solid **2** dissolved and the solution became red. After 2 h at reflux, the solution was allowed to cool to room temperature. From this, precipitated a solid that was filtered off, washed well with toluene and dried *in vacuo* providing the title compound **8** as a microanalytically pure pale yellow powder (0.99 g, 73%). For microanalytical and spectroscopic data, see Tables 1 and 2. Thiopyrans **10** and **12** were prepared and isolated in similar fashion in 65 and 75% yields, respectively.

Dimethyl 6-*amino*-5-*cyano*-4-(3,4-*dichlorophenyl*)-4H-*thiopyran*-2,3-*dicarboxylate* **13**. To a stirred suspension of the thioacrylamide **4** (4.23 g, 16.45 mmol) in toluene (125 cm^3) was added dimethyl acetylenedicarboxylate (2.57 g, 18.1 mmol). The mixture was brought to reflux whereupon the solid dissolved forming a red solution. After 3 h at reflux, the black solution was cooled to room temperature and concentrated under reduced pressure. The resulting gum was triturated with dichloromethane–hexane producing a solid which was stirred with methanol to remove trace impurities. The collected tan solid, the *title compound* **13**, was dried *in vacuo* (4.02 g, 62%). Data are presented in Tables 1 and 2. Note that chromatography of crude **13** on Florisil gave poor recovery of pure material. The thiopyrans **9** and **11** were prepared and isolated in similar fashion in 70 and 65% yields, respectively.

Preparation of Ethyl 6-*Amino*-5-*cyano*-4-(3-*nitrophenyl*)-2-*phenyl*-4H-*thiopyran*-3-*carboxylate* **14**.—A mixture of compound **2** (1.21 g, 5.19 mmol) and ethyl phenylpropiolate (0.90 g, 5.19 mmol) in glacial acetic acid (60 cm^3) was stirred and brought to reflux. After 24 h, a further portion (0.60 g, 3.46 mmol) of ethyl phenylpropiolate was added and heating at reflux continued for a further 24 h. The solution was allowed to cool and then concentrated under reduced pressure. The resulting gum was taken up in dichloromethane (50 cm^3), and the solution washed with water (2 × 20 cm^3), dried ($MgSO_4$), filtered and reconcentrated. The brown gum was taken up in toluene and diluted with hexane to precipitate a brown solid. This was collected and dried (1.1 g of almost pure **14**, 52% yield). A portion of this (600 mg) was taken, dissolved in a small

Table 1 Microanalytical and spectral data

	M.p. (°C)	Found (%) (Required) C	H	N	S	ν_{max}/cm^{-1}	λ_{max}/nm
8	235–236	53.2 (53.0)	3.5 (3.5)	13.1 (13.2)	10.0 (10.1)	3378, 3323, 3220, 2189, 1700, 1653	255
9	122–124	51.4 (51.2)	3.4 (3.5)	11.0 (11.2)	8.3 (8.5)	3410, 3215, 2190, 1737, 1730, 1643	259
10	149–150	57.8 (57.8)	4.8 (4.85)	8.3 (8.4)	9.9 (9.65)	3393, 3325, 3229, 2187, 1695, 1646	254
11	154–155	55.5 (55.4)	4.7 (4.65)	6.9 (7.2)	8.0 (8.2)	3390, 3321, 2193, 1737, 1715, 1647	259
12	215–217	49.6 (49.3)	3.1 (2.95)	8.1 (8.2)	9.5 (9.4)	3397, 3329, 3232, 2191, 1698, 1650	255
13	158	48.4 (48.1)	3.3 (3.0)	7.0 (7.0)	8.0 (8.0)	3416, 3316, 3220, 2191, 1745, 1707, 1635	259
14	201–203	61.9 (61.9)	4.5 (4.2)	10.0 (10.3)	8.0 (7.9)	3397, 3324, 3219, 2191, 1677	260
18	279–283	57.5 (57.5)	3.3 (3.3)	15.5 (15.5)	11.7 (11.8)	2220	312, 254

Table 2 Spectroscopic data

	m/z (%)	δ_H/ppm
8	335 (100), 318 (7), 300 (7), 288 (10) and 195 (16)	8.13 (1 H, d, *J* 7), 8.04 (1 H, br s), 7.89 (1 H, s), 7.68 (2 H, m), 7.10 (2 H, s), 4.79 (1 H, s) and 3.64 (3 H, s)
9	393 (100), 376 (11), 358 (4), 343 (9), 327 (4), 316 (15) and 253 (14)	8.17 (1 H, dd, *J* 7 and 2), 8.11 (1 H, br s), 7.73 (1 H, d, *J* 7), 7.69 (1 H, t, *J* 7), 7.34 (2 H, s), 4.96 (1 H, s), 3.80 (3 H, s) and 3.68 (3 H, s)
10	350 (81), 333 (100), 301 (3), 273 (6) and 195 (43)	7.73 (1 H, s), 6.89 (1 H, br s), 6.88 (2 H, s), 6.80 (1 H, d, *J* 2), 6.72 (1 H, d, *J* 8), 4.53 (1 H, s), 3.72 (3 H, s), 3.70 (3 H, s) and 3.65 (3 H, s)
11	408 (46), 391 (100), 359 (9), 331 (33) and 253 (54)	7.12 (2 H, s), 6.93 (1 H, d, *J* 8), 6.81 (1 H, br s), 6.75 (1 H, d, *J* 8), 4.60 (1 H, s), 3.78 (3 H, s), 3.73 (3 H, s), 3.71 (3 H, s) and 3.66 (3 H, s)
12	358 (100), 341 (23) and 195 (41)	7.83 (1 H, s), 7.62 (1 H, d, *J* 8), 7.40 (1 H, *J* 2), 7.22 (1 H, dd, *J* 8 and 2), 7.06 (2 H, s), 4.63 (1 H, s) and 3.65 (3 H, s)
13	399 (100)	7.66 (1 H, d, *J* 8), 7.45 (1 H, br s), 7.29 (2 H, s), 7.25 (1 H, m), 4.79 (1 H, s), 3.79 (3 H, s) and 3.67 (3 H, s)
14	425 (100), 408 (39), 378 (29), 359 (10), 342 (32), 312 (8) and 278 (8)	8.22 (1 H, br s), 8.18 (1 H, d, *J* 8), 7.85 (1 H, d, *J* 8), 7.71 (1 H, t, *J* 8), 7.47–7.43 (3 H, m), 7.34–7.31 (2 H, m), 7.24 (2 H, s), 4.94 (1 H, s), 3.80 (2 H, q, *J* 7) and 0.70 (3 H, t, *J* 7)
18	289 (22), 272 (100), 242 (34) and 225 (9)	14.29 (1 H, br s), 8.49 (1 H, d, *J* 2), 8.43 (1 H, dd, *J* 8 and 2), 8.12 (1 H, dd, *J* 8 and 2), 7.88 (1 H, t), 6.97 (1 H, s) and 2.46 (3 H, s)

quantity of dichloromethane and subjected to flash chromatography on Florisil eluting with ethyl acetate–hexane (2:3). Fractions containing **14** were combined and concentrated, yielding the title compound as a cream solid (70 mg). Spectral data are presented in Tables 1 and 2. Additional data: δ_C 164.9, 154.4, 148.0, 144.4, 143.0, 136.3, 133.5, 130.4, 129.6, 128.6, 128.1, 123.2, 122.2, 121.2, 118.9, 70.2, 60.6, 43.7 and 13.0.

Reaction between **6** *and Dimethyl Acetylenedicarboxylate.*—A stirred solution of the tertiary thioamide **6** (800 mg, 2.5 mmol) and dimethyl acetylenedicarboxylate (520 mg, 3.7 mmol) in xylene (20 cm^3) was heated at reflux for 15 h. The black solution was cooled to room temperature and concentrated. The oily residue was passed down a column of Florisil eluting with chloroform–ether (1:3) yielding a yellow oil (500 mg) that appeared to be a mixture of the desired thiopyran **15** and xylene. The presence of **15** was indicated particularly by a singlet resonance for the 4-H proton at δ 4.97 in the ^{1}H NMR spectrum. A second column destroyed this product.

Reaction between Thioamide **2** *and Alkyne* **16**.—A mixture of the thioacrylamide **2** (1.16 g, 5.0 mmol) and 3-[3,5-bis(trifluoromethyl)]phenylprop-2-ynol **16** (available from Maybridge Chemicals, 1.45 g, 5.4 mmol) in toluene (60 cm^3) was stirred and brought to reflux. Within 1 h the yellow suspension had become a red solution. After 24 h at reflux, no reaction had occurred (TLC). The solution was cooled, concentrated under reduced pressure and the residue taken up in glacial acetic acid (60 cm^3). After 48 h at reflux in acetic acid, the black solution was cooled and concentrated. The residue was triturated with toluene–hexane. The insoluble solids contained no thiopyran by ^{1}H NMR. The soluble material was subjected to flash chromatography on silica, eluting with ethyl acetate–hexane (1:4) yielding in the first fractions 3-[3,5-*bis*(*trifluoromethyl*)]*phenylprop*-2-*ynyl acetate* **17** as a colourless oil (1.0 g, 60%), ν_{max}(film)/cm^{-1} 1751; δ_H($CDCl_3$) 7.90 (2 H, br s), 7.82 (1 H, br s), 4.92 (2 H, s) and 2.08 (3 H, s); m/z 328 (100%), 311 (68), 310 (95), 268 (47) and 250 (71) [M (accurate mass), 311.0500. $C_{13}H_8F_6O_2$ requires *M*, 311.0507].

Reaction between Thioamide **2** *and* 3-*Phenylpropynal Diethyl Acetal.*—To a suspension of the thioacrylamide **2** (2.45 g, 10.5 mmol) in toluene (125 cm^3) was added 3-phenylpropynal diethyl acetal (2.36 g, 11.55 mmol). The mixture was stirred and brought to reflux. After 6 h, a considerable quantity of **2** remained undissolved so acetone (10 cm^3) was added as a cosolvent. After 48 h at reflux, the solution was allowed to cool to room temperature. The deposited tan solid was collected, washed with toluene and hexane, and dried *in vacuo*, providing 3-*cyano*-6-*methyl*-4-(3-*nitrophenyl*)-2(1H)-*pyridinethione* **18** as a yellow solid (450 mg, 16%). Data on this are presented in

Tables 1 and 2. Additional data: δ_C 177.9, 153.8, 153.6, 147.3, 137.0, 134.3, 130.0, 124.6, 122.7, 116.0, 113.5, 111.4 and 18.6.

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