One-pot synthesis and crystal structure of *N*-acyl-*N*′-[1-(2,6-dichloro-4-trifluoromethyl)phenyl-3-cyano-1*H*-pyrazol-5-yl]thioureas

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Nine novel thiourea derivatives containing pyrazole rings have been prepared in good yields by the reaction of 5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)pyrazole with acylisothiocyanates, which were generated in situ by potassium thiocyanate and different acyl chlorides in one pot. *N*-Benzoyl-*N*′-[1-(2,6-dichloro-4-trifluoromethyl)phenyl-3-cyano-1H-pyrazol-5-yl]thiourea was characterised by a single crystal X-ray diffraction study.

Keywords: 5-amino-3-cyano-1-arylpyrazole, acylthiourea, one-pot, crystal structure

Acylthiourea derivatives have attracted much attention due to their chemical properties[1–2] and their biological activities. For example, some thiourea derivatives have been found to be useful as insecticides,[3] herbicides,[4] inhibitors,[5] anti-HIV agents,[6] antimicrobial and anticancer agents[7] and plant-growth regulators.[8] Furthermore, acylthioureas are important compounds as building blocks in the synthesis of heterocycles with special biological activities, such as thiadiazolo pyrimidine,[5] triazoles[9] and benzothiazoles.[10]

In recent years, close attention has been paid to pyrazole derivatives owing to their biological activities.[11–13] Pyrazole derivatives possessing fluorine-containing groups, for example, fipronil (**1a**) [5-amino-1-[2,6-dichloro-4-(trifluoromethyl)-phenyl]-4-trifluoromethylsulfinyl-lH-pyrazole-3-carbonitrile] is effective against a host of agricultural and household pests including grass hoppers, boll weevils, rice insects, termites, houseflies, fruitflies and thrips.[14–16] So we surmised that the acylthiourea derivatives bearing a pyrazole moiety might have high biological activities.

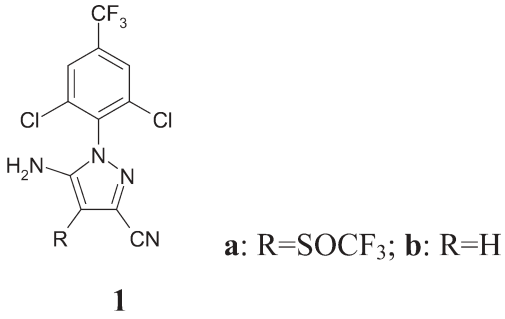
Here a series of new *N*-Aroyl-*N*′-[1-(2,6-dichloro-4-trifluoromethyl)phenyl-3-cyano-1H-pyrazol-5-yl] thioureas (**2a–i**) were synthesised based on the reaction of 5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-1H-pyrazole (**1b**), the parent of fipronil, with potassium thiocyanate and different acyl chlorides in one pot. They were characterised by elemental analysis, IR, ^{1}H NMR and ^{13}C NMR spectroscopy and compound **3a** was also characterised by a single crystal X-ray diffraction study.

Results and discussion

The starting material, 5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-1H-pyrazole (**1b**) was prepared adopting the reported procedures.[17]

The experimental procedures were simple. An acyl chloride (7 mmol) in dry acetonitrile (10 mL) was added to dry potassium thiocyanate (10 mmol) and the mixture refluxed for 2 h to get the corresponding isothiocyanate. 5-Amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-1H-pyrazole (5 mmol) was added, and was reacted until complete consumption of amine, as monitored by TLC. This gave the compounds **2a–i** in good yields (Scheme 1 and Table 1).

From Table 1, it can be seen that when the acyl chloride was an aromatic chloride, the yields were higher than for an aliphatic chloride. Moreover, owing to steric hindrance, the yields



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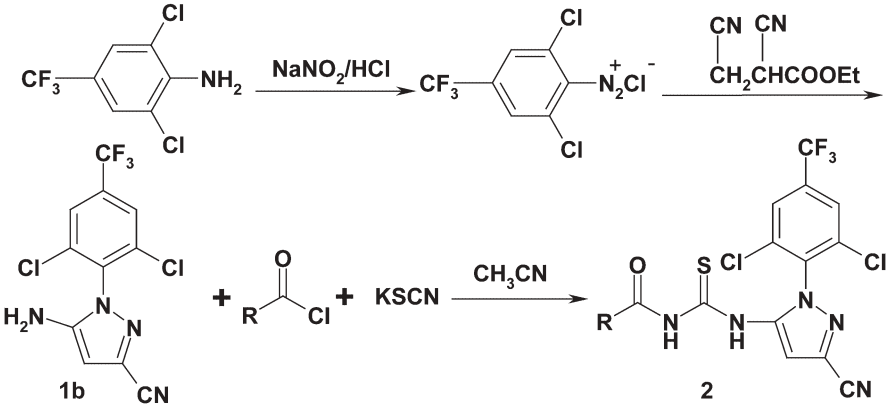

R: **2a** = C_6H_5; **2b** = $C_6H_5CH_2$; **2c** = 4-$OCH_3C_6H_4$; **2d** = 2,4-$Cl_2C_6H_3$; **2e** = CH_3; **2f** = 4-$CH_3C_6H_4$; **2g** = 4-ClC_6H_4; **2h** = 2-$CH_3C_6H_4$; **2i** = 4-FC_6H_4.

Scheme 1 Synthesis of *N*-acyl-*N*′-[1-(2, 6-dichloro-4-trifluoromethyl)phenyl-3-cyano-1H-pyrazol-5-yl] thioureas.

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Table 1 The yields of compounds **2a–i**

Entry	R	Yield/%
2a	C_6H_5	85
2b	$C_6H_5CH_2$	70
2c	4-$OCH_3C_6H_4$	83
2d	2,4-$Cl_2C_6H_3$	73
2e	CH_3	50
2f	4-$CH_3C_6H_4$	85
2g	4-ClC_6H_4	86
2h	2-$CH_3C_6H_4$	75
2i	4-FC_6H_4	80

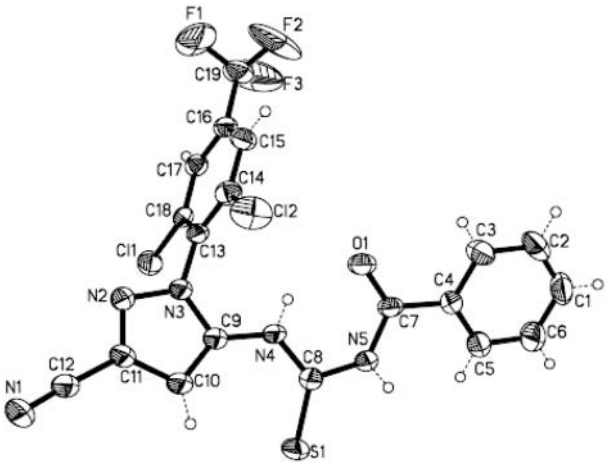

Fig. 1 Molecular structure of **2a**.

from *ortho* substituted acyl chlorides were lower than from the *para* substituted compounds.

The IR spectra of **2a–i** revealed, in each case, four characteristic absorptions near 3400, 2245, 1680 and 1311cm^{-1} due to NH, nitrile (CN), C=O and C=S groups. The ^{1}H NMR spectrum of **2c** for example, displayed singlets at δ 13.54 and δ 10.68 due to the NH groups (two protons), a singlet signal at δ 8.21 due to the benzyl ring bearing CF_3 (two protons), a singlet signal at δ 7.76 due to the pyrazolyl ring (one proton), two double signals at δ 7.96 and δ 7.05 due to the benzyl ring bearing OCH_3 (four protons), and a singlet signal at δ 3.89 due to OCH_3 (three protons).

A single crystal of *N*-Benzoyl-*N′*-[1-(2,6-dichloro-4-trifluoromethyl)phenyl-3-cyano-1h-pyrazol-5-yl]thiourea (**2a**) was grown from a mixed solution of alcohol and ethyl acetate. The molecular structure is shown in Fig.1. All H atoms were placed in geometrically idealised positions and constrained to bond to their parent atoms, with C—H = 0.93–0.96Å, and U_{iso} (H) = 1.2U_{eq}(C) for aryl H atoms. The CF_3 group may be subject to unresolved disorder, which could account for the weak diffracting ability of the crystal, leading to a rather high *R* value. Selected crystal data and structure refinement details are presented in Table 2.

CCDC 802496 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, via www.ccdc.cam.ac.uk/data_request.cif.

Experimental

All the melting points were determined with a Thomas–Hoover melting point apparatus; the thermometer was not standardised. ^{1}H and ^{13}C NMR spectra were recorded at a 300 MHz and 75 MHz respectively, using CD_3COCD_3 as a solvent with TMS as the internal standard. IR spectra were measured on a FT-IR spectrophotometer as KBr disks. Silicagel 60 GF254 was used for analytical and preparative TLC. The elemental analysis values were determined on EA-1112 instrument from Italy CarloErba; The crystal was mounted on a Bruker APEX area-detector diffractometer equipped with a graphite-monochromatic MoKα (λ=0.71073Å) radiation. The structures were solved by direct methods using the SHELXLS-97 program and refined by using the SHELXL-97 program.[18] All products were characterised using elemental analysis, IR, ^{1}H, and ^{13}C NMR.

Preparation of N-acyl-N′-[1-(2,6-dichloro-4-trifluoromethyl)phenyl-3-cyano-1H-pyrazol-5-yl]thioureas (**2a–i**)

A solution of an appropriate acyl chloride (7 mmol) in dry acetonitrile (10 mL) was added to dry potassium thiocyanate (10 mmol) and the mixture was refluxed for 2h. Then 5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-1H-pyrazole (5 mmol) was added and, reflux continued for an additional 5–6 h until complete consumption of the starting material, as monitored by TLC. After the reaction was finished, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography to give one of the title compounds. Single crystals suitable for X-ray analysis were obtained by slow evaporation of the mixed solution in alcohol and ethyl acetate of **2a**.

N-Benzoyl-N′-[1-(2,6-dichloro-4-trifluoromethyl)phenyl-3-cyano-1H-pyrazol-5-yl]thiourea (**2a**): White solid. m.p. 157–158 °C; ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 13.37 (s, 1H), 10.84 (s, 1H), 8.20 (s, 2H), 7.93(dd, *J* = 7.28, 1.26 Hz, 2H), 7.76(s, 1H), 7.67 (dt, *J* = 7.70, 1.26Hz, 1H), 7.52 (dd, *J* = 7.28, 7.70 Hz, 2H); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ: 179.1, 170.0, 141.1, 136.9, 135.9 (q, *J* = 33.7Hz), 135.2, 134.6, 132.1, 129.6, 129.3, 128.6, 128.0, 123.2 (q, *J* = 271Hz), 113.9, 104.5; IR (KBr) ν: 3403 (NH), 2245 (CN), 1681 (C=O), 1649 (pyrazole ring), 1517 (phenyl), 1311(C=S) cm^{-1}. Anal. Calcd for $C_{19}H_{10}Cl_2F_3N_5OS$: C, 47.12; H, 2.08. Found: C, 47.00; H, 2.05%.

N-Phenylacetyl-N′-[1-(2,6-dichloro-4-trifluoromethyl)phenyl-3-cyano-1H-pyrazol-5-yl]thiourea (**2b**): White solid. m.p. 160–162 °C; ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 13.0 (s, 1H), 10.95 (s, 1H), 8.10 (s, 2H), 7.60 (s, 1H),7.31(m,5H), 3.81(2H); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ: 179.3, 175.0, 172.3, 140.9, 136.8, 135.2 (q, *J* = 33,5Hz),

Table 2 Crystal parameters data collections and structure refinements for **2a**

	2a		2a
Formula	$C_{19}H_{10}Cl_2F_3N_5OS$	*D*c/(Mg m^{-3})	1.528
Molecula weight	484.28	*F*(000)	976
Temperature/*K*	298(2)	μ/mm^{-1}	0.455
Crystal size/mm^3	0.28 x 0.27 x 0.15	Scan mode	φ and ω
Crystal system	Monoclinic	θ range of data collection/(°)	1.74 to 25.08
Space group	P 21/n	Total reflections collected	10761
a/nm	1.60963(13)	Independent reflection	3714 (R_{int}= 0.0338)
b/nm	0.77108(6)	Index ranges	–19<=*h*<=19, –9<=*k*<=8, –12<=*l*<=20
c/nm	1.69650(13)	Max. and min. transmission	0.9348 and 0.8831
α/(°)	90	Data/restraints/parameters	3714/2/286
β/(°)	90.322(2)	Refine method	Full-matrix least-squares on *F*2
γ/(°)	90	Final R indices [*I*>2σ(**1a**)]	R = 0.0778, wR = 0.1726
V/nm^3	2.1056(3)	R indices (all data)	R= 0.1057, wR = 0.1883
Z	4	Goodness of fit	1.071

130.4, 130.1, 129.3, 129.1, 128.1, 127.6, 123.1 (q, *J*=272Hz), 113.8, 104.8, 44.2; IR (KBr) ν: 3168 (NH), 2245 (CN), 1695 (C=O), 1576, 1527 (phenyl), 1308 (C=S) cm^{-1}; Anal. Calcd for $C_{20}H_{12}Cl_2F_3N_5OS$: C, 48.21; H, 2.43. Found: C, 48.10; H, 2.40%.

N-4-Methoxylacyl-N′-[1-(2,6-dichloro-4-trifluoromethyl)phenyl-3-cyano-1H-pyrazol-5-yl]thiourea (**2c**): White solid. m.p. 185–187 °C; ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 13.54 (s, 1H), 10.68 (s, 1H), 8.21 (s, 2H), 7.96 (d, *J* = 8.91 Hz, 2H), 7.76 (s, 1H), 7.05 (d, *J* = 8.91 Hz, 2H)，3.89 (s, 3H); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ: 179.3, 169.2, 162.3, 141.2, 137.0, 135.7, 135.4(q, *J* = 34.3 Hz), 131.6, 127.9, 127.7, 123.7, 123.2(q, *J* = 272Hz), 114.9, 113.9, 104.4, 56.1; IR (KBr) ν: 3332 (NH), 2243 (CN), 1671 (C=O), 1575(phenyl), 1311(C=S), 1173 cm^{-1}; Anal. Calcd for $C_{20}H_{12}Cl_2F_3N_5O_2$ S: C, 46.71; H, 2.35. Found: C, 46.65; H, 2.30%.

N-2,4-Dichloroacyl-N′-[1-(2,6-dichloro-4-trifluoromethyl)phenyl-3-cyano-1H-pyrazol-5-yl]thiourea (**2d**): White solid. m.p. 150–152 °C; ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 12.85 (s, 1H), 11.26 (s, 1H), 8.21 (s, 2H), 7.75 (s,1H), 7.67 (s,1H), 7.64 (d, *J* = 7.98Hz 1H), 7.50 (d, *J* = 7.98Hz 1H); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ: 178.6, 168.6, 140.7, 138.4, 136.9, 135.2 (q, *J* = 33.3 Hz), 135.0, 132.8, 132.7, 131.6, 130.5, 128.4, 128.0, 127.8, 123.3(q, *J* = 272Hz), 113.8, 104.9; IR (KBr) ν: 3369 (NH), 2246 (CN), 1675 (C=O), 1574 (phenyl), 1315 (C=S), 1173 cm^{-1}; Anal. Calcd for $C_{19}H_8Cl_4F_3N_5OS$: C, 41.25; H, 1.46. Found: C, 41.20; H, 1.43%.

N-Acetyl-N′-[1-(2,6-dichloro-4-trifluoromethyl)phenyl-3-cyano-1H-pyrazol-5-yl]thiourea (**2e**): White solid. 199–200 °C. ^{1}H NMR (CD_3COCD_3, 300 MHz)：δ: 13.19 (s,1H), 10.87 (s, 1H), 8.21 (S, 2H), 7.74 (s, 1H), 2.16 (s, 3H); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ: 178.0, 173.9,140.2, 136.1, 135.9 (q, 1 C, *J*= 33.7 Hz), 134.8, 127.0, 126.9, 123.2 (q, 1 C, *J*= 271 Hz), 113.0, 103.2, 23.0. IR (KBr) ν: 3253, 2244, 1698 (C=O), 1610 (phenyl), 1530, 1310 (C=S) cm^{-1}; Anal. Calcd for $C_{14}H_8Cl_2F_3N_5OS$: C, 39.83; H, 1.91. Found: C, 39.80; H, 1.89%.

N-4-Methylacyl-N′-[1-(2,6-dichloro-4-trifluoromethyl)phenyl-3-cyano-1H-pyrazol-5-yl]thiourea (**2f**): White solid. 169–171 °C. ^{1}H NMR (CD_3COCD_3, 300 MHz)：δ: 13.21(s,1H), 10.8(s, 1H), 8.31(S, 2H), 7.94(d, *J* = 7.97 Hz 2H), 7.86(s, 1H), 7.44(d, *J* = 7.97 Hz 2H), 2.50(s, 3H); ^{13}C NMR (CD_3COCD_3, 125 MHz) δ: 179.2, 169.9, 145.8, 141.2, 136.9, 135.7, 135.6(q, 1 C, *J*=34.8 Hz), 130.2, 129.4, 129.2, 127.9, 127.8, 123.2 (q, 1 C, *J*= 270.8 Hz), 113.9, 104.4, 21.5; IR (KBr) ν: 3250, 2240, 1699(C=O), 1578 (phenyl), 1492, 1305 (C=S) cm^{-1}; Anal. Calcd for $C_{20}H_{12}Cl_2F_3N_5OS$: C, 48.21; H, 2.43. Found: C, 48.19; H, 2.40%.

N-4-Chloroacyl-N′-[1-(2,6-dichloro-4-trifluoromethyl)phenyl-3-cyano-1H-pyrazol-5-yl]thiourea (**2g**): White solid. m.p. 209–210 °C; ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 13.30 (s, 1H), 11.00 (s, 1H), 8.22 (s, 2H), 7.96 (d, *J* = 8.22 Hz 2H), 7.77 (s,1H), 7.57 (d, *J* = 8.22 Hz 2H); ^{13}C NMR (CD_3COCD_3, 125 MHz) δ: 179.1, 169.2, 141.0, 140.4, 137.0, 135.8, 135.5 (q, *J* = 35 Hz), 131.2, 131.0, 129.8, 127.9, 127.8, 123.2 (q, *J* = 271.2Hz), 113.9, 104.7; IR (KBr) ν: 3370 (NH), 2241 (CN), 1699 (C=O), 1583 (phenyl), 1310 (C=S), 1181cm^{-1}; Anal. Calcd for $C_{19}H_9Cl_3F_3N_5OS$: C, 43.99; H, 1.75. Found: C, 43.95; H, 1.72%.

N-2-Methylacyl-N′-[1-(2,6-dichloro-4-trifluoromethyl)phenyl-3-cyano-1H-pyrazol-5-yl]thiourea (**2h**): White solid. m.p. 151–152 °C; ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 13.18 (s, 1H), 10.94 (s, 1H), 8.11 (s, 2H), 7.66 (s, 1H), 7.42 (d, *J*=7.7 Hz 1H), 7.32 (d, *J*=7.5 Hz 1H), 7.18–7.73 (m, 2H); ^{13}C NMR (CD_3COCD_3, 125 MHz) δ: 179.0, 172.5, 141.1, 138.2, 137.0, 135.7, 135.5(q, *J* = 33.8 Hz), 133.4, 132.7, 132.1, 128.9, 128.0, 127.8, 126.6, 123.2(q, *J* = 271.3Hz), 114.0, 104.2, 19.8; IR (KBr) ν: 3365(NH), 2241 (CN), 1699 (C=O), 1580 (phenyl), 1308 (C=S), 1177 cm^{-1}; Anal. Calcd for $C_{20}H_{12}Cl_2F_3N_5OS$: C, 48.21; H, 2.43. Found: C, 48.19; H, 2.40%.

N-4-fluoroacyl-N′-[1-(2,6-dichloro-4-trifluoromethyl)phenyl-3-cyano-1H-pyrazol-5-yl]thiourea (**2i**): White solid. m.p. 201–203°C; ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 13.20 (s, 1H), 10.82 (s, 1H), 8.08 (s, 2H), 7.90(d, *J*=9.45Hz 2H), 7.63(s, 1H), 7.16(d, *J*=9.45Hz 2H); ^{13}C NMR (CD_3COCD_3, 125 MHz) δ: 179.0, 169.0, 166.8(d, 1C, *J*=252.5Hz), 141.0, 136.9, 135.7, 135.4(q, *J* = 34.1 Hz), 132.4, 128.6, 127.9, 127.7, 123.2 (q, *J* = 272.3Hz), 116.6, 113.9, 104.2; IR (KBr) ν: 3362(NH), 2241 (CN), 1698 (C=O), 1580 (phenyl), 1309 (C=S), 1178 cm^{-1}; Anal. Calcd for $C_{19}H_9Cl_2F_4N_5OS$: C, 45.44; H, 1.81. Found: C, 45.43; H, 1.80%.

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