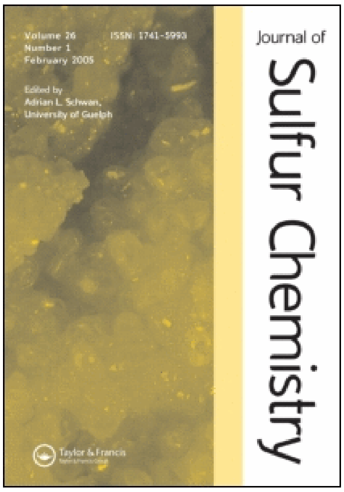

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RESEARCH ARTICLE

Efficient synthesis of *N*-substituted-*N'*-arylcarbonylthioureas under solvent-free conditions

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A convenient method for the synthesis of *N*-substituted-*N'*-arylcarbonylthioureas under solvent-free conditions has been developed. Ammonium thiocyanate and acid chlorides were mixed, and stirred at room temperature without a solvent, to give the corresponding isothiocyanates, which reacted smoothly with arylamines to produce the aryl(alkyl)carbonylthioureas in good yields. Unusually large values of $^5J_{FH} = 12.2$–15.1 Hz are observed for 1-(2-fluorobenzoyl)-thiourea derivatives, which provide information about the Ar-C-N-H torsions in these compounds.

Keywords: Arylcarbonylthiourea; Ammonium thiocyanate; Arylamines; Acid chlorides

1. Introduction

Thioureas are important compounds as building blocks in the synthesis of heterocycles. For example, thioureas condense with *a*-halocarbonyl compounds to afford 2-amino-1,3-thiazoles [1,2]. Benzothiazoles can be prepared from arylthioureas in the presence of bromine [3]. The use of thioureas to make iminothiazolines [4], thiohydantoins [5, 6], 1,3,5-triazines [7], and 2-amino-oxazolidines [8] was also described recently. Many methods for the synthesis of thioureas have been reported, for example, *N*-substituted thioureas are commonly prepared from the reaction of amines with alkali metal thiocyanates in the presence of a strong acid [9], aroyl isothiocyanates with amines followed by basic hydrolysis [10, 11], isothiocyanates with ammonia or amines [12].

Several new methods for the preparation of substituted thioureas have been recently reported [13–15]. However, these methods have several drawbacks, namely, the need for a high reaction temperature, long reaction time, the use of noxious reagents, and special starting materials. The development of mild, efficient, and environmentally friendly methods is still desired.

We present here a mild and efficient method under solvent-free conditions to give *N*-aryl-*N'*-aroyl(acyl)thioureas in good yields. Thus, a mixture of ammonium thiocyanate (2 mmol)

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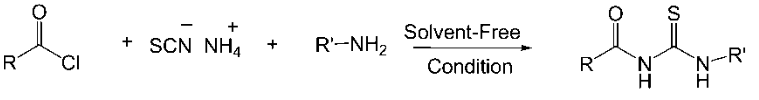


1	R
a	2-F-C_6H_4
b	4-Cl-C_6H_4
c	4-$NO_2C_6H_4$
d	CMe_3

2

3	R'
a	Ph
b	2-Me-C_6H_4
c	4-Et-C_6H_4
d	Bn
e	1-Naphthyl

4	R	R'	Yield (%)
a	2-F-C_6H_4	Bn	90
b	2-F-C_6H_4	4-Et-C_6H_4	79
c	2-F-C_6H_4	1-Naphthyl	82
d	2-F-C_6H_4	2-Me-C_6H_4	92
e	2-F-C_6H_4	Ph	96
f	4-Cl-C_6H_4	Bn	79
g	4-NO_2-C_6H_4	Bn	91
h	CMe_3	1-Naphthyl	84
i	CMe_3	2-Me-C_6H_4	80

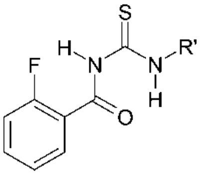
SCHEME 1

and an acid chloride (2 mmol) was stirred without solvent for 5 minutes. Then, an arylamine (2 mmol) was added and mixed for 30 minutes. The product was recrystallized from EtOH. The results obtained are shown in scheme 1.

The structures of compounds **4a–4i** were deduced from their elemental analyses and their IR, ^{1}H- and ^{13}C-NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at appropriate *m/z* values. The ^{1}H-NMR spectrum of **4i** in $CDCl_3$ showed four singlets for *tert*-butyl ($\delta = 1.34$), methyl ($\delta = 2.33$), and NH ($\delta = 8.62$ and 12.15) protons, along with multiplets for the aromatic ($\delta = 7.24$–7.75) protons. The ^{13}C-NMR spectrum of **4i** showed eleven signals in agreement with the proposed structure. Partial assignments of these resonances are given in the Experimental section. The ^{1}H- and ^{13}C-NMR spectra of **4a–4 h** are similar to those for **4i**, except for the aromatic moieties, which exhibited characteristic signals with appropriate chemical shifts.

Although the presence of ^{19}F nucleus complicates both the ^{1}H- and ^{13}C-NMR spectra of **4a–4e**, it helps in assignment of the signals by direct and long-range couplings with ^{1}H and ^{13}C nuclei (see Experimental section). Of particular interest is the observation of an unusually high value for the five-bond fluorine-proton coupling constants, $^5J_{FH} = 12.2$–15.1 Hz, which provides information about the Ar-C-N-H torsion (see scheme 2). It has been suggested [16] that F-H spin coupling can operate not only through the bonds in a molecule but also through space, provided the interacting fluorine and proton nuclei are in close proximity. In compounds **4a–4e**, the fluorine and the NH proton can come into fairly close proximity in certain conformations (scheme 2), and would be expected to have a large through-space contribution to the coupling. The large observed coupling may thus be explained.

In conclusion, we have developed a mild, simple, and efficient method for the synthesis of *N*-substituted-*N*'-arylcarbonylthioureas from the reaction of ammonium thiocyanate, acid chlorides, and arylamines in high yields under solvent-free conditions.



SCHEME 2

2. Experimental

2.1 *General*

Compounds **1–3** were obtained from Fluka and were used without further purification. The following instruments were used: M.p., Electrothermal-9100 apparatus, uncorrected; IR spectra, Shimadzu IR-460 spectrometer; ^{1}H- and ^{13}C-NMR spectra, Bruker DRX-300 AVANCE instrument; in $CDCl_3$ at 300 MHz and 75 MHz, respectively, δ in ppm, J in Hz; EI-MS (70 eV): Finnigan-MAT-8430 mass spectrometer, in m/z. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyzer. The mass and elemental analyses data were in agreement with the proposed structures.

2.2 *Typical procedure for the preparation of N-substituted-N'-benzoylthioureas*

To NH_4SCN (2 mmol) was added an acid chloride (2 mmol). The mixture was stirred at 25 °C for 10 min, and then an arylamine (2 mmol) was added to it and stirred for an additional 1 h. Dichloromethane (10 mL) was added to the reaction mixture, and the solution was filtered to remove the insoluble material. The filtrate was washed with 5% HCl, brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to leave the crude product, which was purified by recrystallization (EtOH).

2.3 *3-Benzyl-1-(2-fluorobenzoyl)-thiourea (4a)*

Pale yellow powder; yield: 0.53 g (90%); mp 81–82 °C. IR (KBr): 3413, 3208 (NH); 1670 (C=O). ^{1}H-NMR: 4.94 (d, $^{3}J_{HH} = 6.0$, CH_2); 6.99–7.70 (m, 7 CH arom); 7.81–8.41 (m, CH arom); 9.62 (d, $^{5}J_{HF} = 12.2$, NH); 10.97 (t, $^{3}J_{HH} = 6.0$, NH). ^{13}C-NMR: 50.3 (CH_2); 117.3 (d, $^{2}J_{CF} = 24.0$, CH); 119.5 (d, $^{2}J_{CF} = 20.5$, C); 121.2 (CH); 125.8 (d, $^{4}J_{CF} = 3.2$, CH); 128.3, 129.3 (2 CH); 132.4 (d, $^{3}J_{CF} = 9.9$, CH); 136.1 (d, $^{3}J_{CF} = 9.7$, CH); 136.6 (CH); 160.9 (d, $^{1}J_{CF} = 249.0$, C-F); 163.3 (d, $^{3}J_{CF} = 4.1$, C=O); 180.3 (C=S). EI-MS: 288 (7, M^{+}), 123 (34), 105 (56), 91 (100), 32 (13), 28 (30), 19 (27). Anal. calcd. for $C_{15}H_{13}FN_2OS$ (288.35): C, 62.48; H, 6.59; N, 9.72; found: C, 62.68; H, 6.42; N, 9.84.

2.4 *3-(4-Ethylphenyl)-1-(2-fluorobenzoyl)-thiourea (4b)*

Pale yellow powder; yield: 0.48 g (79%); mp 79–81 °C. IR (KBr): 3422 (NH); 1668 (C=O). ^{1}H-NMR: 1.27 (t, $^{3}J_{HH} = 7.0$, Me); 2.69 (d, $^{3}J_{HH} = 7.0$, CH_2); 7.23–8.14 (8 H, m, arom); 9.66 (d, $^{5}J_{HF} = 15.0$, NH); 12.46 (s, NH). ^{13}C-NMR: 15.8 (Me); 28.9 (CH_2); 117.2 (d, $^{2}J_{CF} = 21.1$, CH); 119.5 (d, $^{2}J_{CF} = 20.7$, CH); 124.5, 125.8 (2 CH); 128.7 (d, $^{4}J_{CF} = 3.3$, CH); 132.5 (d, $^{3}J_{CF} = 9.6$, CH); 135.6 (CH); 136.2 (d, $^{3}J_{CF} = 9.6$, CH); 143.6 (CH); 161.0 (d, $^{1}J_{CF} = 264.7$, C-F); 163.4 (d, $^{3}J_{CF} = 3.9$, C=O); 178.5 (C=S). EI-MS: 302 (9, M^{+}), 123 (28), 106 (43), 105 (76), 91 (100), 32 (31), 28 (17), 19 (10). Anal. calcd. for $C_{16}H_{15}FN_2OS$ (302.37): C, 63.56; H, 5.00; N, 9.26; found: C, 63.69; H, 5.19; N, 9.37.

2.5 *1-(2-Fluorobenzoyl)-3-(naphthalen-1-yl)-thiourea (4c)*

Pale yellow powder; yield: 0.53 g (82%); mp 168–170 °C. IR (KBr): 3423 (NH); 1671 (C=O); 1179 (C=S). ^{1}H-NMR: 7.22–8.20 (13 H, m, arom); 9.86 (d, $^{5}J_{HF} = 15.1$, NH); 12.71 (s, NH). ^{13}C-NMR: 117.2 (d, $^{2}J_{CF} = 24.0$, CH); 119.4 (d, $^{2}J_{CF} = 19.7$, C); 122.1, 124.3, 125.7 (3 CH); 125.9 (d, $^{4}J_{CF} = 3.0$, CH); 126.8 (CH); 127.4 (CH); 128.9 (CH); 129.1 (CH); 132.7 (d,

$^3J_{CF}$ = 9.6, CH); 134.0 (CH); 134.6 (CH); 136.3 (*d*, $^3J_{CF}$ = 9.0, CH); 161.0 (*d*, $^1J_{CF}$ = 249.7, C-F); 163.7 (*d*, $^3J_{CF}$ = 3.7, C=O); 180.2 (C=S). EI-MS: 324 (7, M^+), 127 (24), 123 (56), 105 (100), 32 (17), 28 (22), 19 (20). Anal. calcd. for $C_{18}H_{13}FN_2OS$ (324.38): C, 66.65; H, 4.04; N, 8.64; found: C, 66.88; H, 3.98; N, 8.71.

2.6 *1-(2-Fluorobenzoyl)-3-(2-methylphenyl)-thiourea (4d)*

Pale yellow powder; yield: 0.53 g (92%); mp 68–70 °C. IR (KBr): 3413, 3225 (NH); 1678 (C=O); 1155 (C=S). ^{1}H-NMR: 2.39 (*s*, Me); 7.23–7.34 (*m*, 4 CH arom); 7.39 (*m*, CH arom); 7.62–7.79 (*m*, 2 CH arom); 8.15 (*m*, CH arom); 9.75 (*d*, $^5J_{HF}$ = 13.6, NH); 12.21 (*s*, NH). ^{13}C-NMR: 18.4 (Me); 117.2 (*d*, $^2J_{CF}$ = 24.2, CH); 119.4 (*d*, $^2J_{CF}$ = 19.8, C); 125.9 (*d*, $^4J_{CF}$ = 3.4, CH); 126.6 (CH); 126.9 (CH); 128.1 (CH); 131.2 (CH); 132.6 (*d*, $^3J_{CF}$ = 9.4, CH); 133.7 (CH); 136.3 (d, $^3J_{CF}$ = 9.7, CH); 136.8 (CH); 161.0 (*d*, $^1J_{CF}$ = 249.4, C-F); 163.5 (*d*, $^3J_{CF}$ = 3.3, C=O); 179.5 (C=S). EI-MS: 288 (5, M^+), 188 (34), 123 (65), 105 (100), 32 (19), 28 (32), 19 (21). Anal. calcd. for $C_{15}H_{13}FN_2OS$ (288.35): C, 62.48; H, 6.59; N, 9.72; found: C, 62.66; H, 6.39; N, 9.79.

2.7 *1-(2-Fluorobenzoyl)-3-phenyl-thiourea (4e)*

Pale yellow powder; yield: 0.52 g (96%); mp 89–91 °C. IR (KBr): 3414, 3368 (NH); 1675 (C=O); 1143 (C=S). ^{1}H-NMR: 7.30–7.80 (8 H, *m*, CH arom); 8.13–8.15 (1 H, *m*, CH arom); 9.65 (*d*, $^5J_{HF}$ = 13.5, NH); 12.50 (*s*, NH). ^{13}C-NMR: 117.2 (*d*, $^2J_{CF}$ = 24.1, CH); 119.4 (*d*, $^2J_{CF}$ = 9.9, C); 124.5 (CH); 125.9 (*d*, $^4J_{CF}$ = 3.1, CH); 127.3 (CH); 129.3 (CH); 132.6 (*d*, $^3J_{CF}$ = 9.4, CH); 136.3 (*d*, $^3J_{CF}$ = 9.7, CH); 138.0 (CH); 161.0 (*d*, $^1J_{CF}$ = 248.1, C-F); 163.5 (*d*, $^3J_{CF}$ = 3.4, C=O); 178.5 (C=S). EI-MS: 274 (6, M^+), 197 (58), 123 (100), 105 (87), 32 (17), 28 (24), 19 (22). Anal. calcd. for $C_{14}H_{11}FN_2OS$ (274.32): C, 61.30; H, 4.04; N, 10.21; found: C, 61.41; H, 4.09; N, 10.34.

2.8 *3-Benzyl-1-(4-chlorobenzoyl)-thiourea (4f)*

Pale yellow powder; yield: 0.48 g (79%); mp 214–216 °C. IR (KBr): 3260 (NH); 1634 (C=O); 1167 (C=S). ^{1}H-NMR: 4.93 (*d*, $^3J_{HH}$ = 6.0, CH_2); 7.33–7.40 (*m*, C_6H_5); 7.50 (2 H, *d*, $^3J_{HH}$ = 7.7, C_6H_4); 7.79 (2 H, *d*, $^3J_{HH}$ = 7.7, C_6H_4); 9.06 (*s*, NH); 10.96 (*t*, $^3J_{HH}$ = 6.0, NH). ^{13}C-NMR: 50.3 (CH_2); 128.3, 128.4, 129.27, 129.3, 129.9, 130.5, 136.4, 140.6 (C_6H_4, C_6H_5); 166.1 (C=O); 180.3 (C=S). EI-MS: 304 (4, M^+), 140 (18), 139 (23), 105 (78), 91 (100), 32 (21), 28 (17). Anal. calcd. for $C_{15}H_{13}ClN_2OS$ (304.80): C 59.11, H 4.30, N 9.19; found: C, 59.38; H, 4.42; N, 9.35.

2.9 *3-Benzyl-1-(4-nitrobenzoyl)-thiourea (4g)*

Yellow powder; yield: 0.57 g (91%); mp 222–224 °C. IR (KBr): 3168, 3116 (NH); 1671 (C=O); 1447 (NO_2). ^{1}H-NMR: 4.93 (*d*, $^3J_{HH}$ = 6.0, CH_2); 7.40–7.41 (*m*, C_6H_5); 8.04 (2 H, *d*, $^3J_{HH}$ = 8.0, C_6H_4); 8.37 (2 H, *d*, $^3J_{HH}$ = 8.0, C_6H_4); 9.20 (*s*, NH); 10.85 (*t*, $^3J_{HH}$ = 6.0, NH). ^{13}C-NMR: 50.4 (CH_2); 124.7, 128.3, 128.5, 129.2, 129.4, 136.2, 137.6, 151.1 (C_6H_4, C_6H_5); 165.3 (C=O); 179.8 (C=S). EI-MS: 315 (7, M^+), 145 (100), 91 (43), 76 (56), 32 (18), 28 (23). Anal. calcd. for $C_{15}H_{13}N_3O_3S$ (315.35): C, 57.13; H, 4.16; N, 13.32; found: C, 57.37; H, 4.25; N, 13.44.

2.10 *1-(2,2-Dimethylpropionyl)-3-(naphthalen-1-yl)-thiourea (4h)*

Pale yellow powder; yield: 0.45 g (84%); mp 156–160 °C. IR (KBr): 3303, 3142, (2 NH); 1678 (C=O); 1152 (C=S). ^{1}H-NMR: 1.40 (*s*, CMe_3); 7.53–8.04 (*m*, $C_{10}H_7$); 8.74 (*s*, NH); 12.67 (*s*, NH). ^{13}C-NMR: 27.5 (CMe_3); 40.5 ($\mathit{C}Me_3$); 122.0, 124.1, 125.6, 126.8, 127.3, 128.4, 128.8, 129.0, 133.9, 134.6 (Naph); 180.0, 180.6 (C=O, C=S). EI-MS: 286 (8, M^+), 143 (38), 127 (73), 85 (100), 32 (19), 28 (20). Anal. calcd. for $C_{16}H_{18}N_2OS$ (286.40): C, 67.10; H, 6.34; N, 9.78; found: C, 67.41; H, 6.43; N, 9.73.

2.11 *1-(2,2-Dimethylpropionyl)-3-(2-methylphenyl)-thiourea (4i)*

Pale yellow powder; yield: 0.40 g (80%); mp 108–110 °C. IR (KBr): 3303, 3220 (2 NH); 1648 (C=O); 1150 (C=S). ^{1}H-NMR: 1.34 (*s*, CMe_3); 2.33 (*s*, Me); 7.24–7.29 (1 H, *m*, C_6H_4); 7.22–7.75 (3 H, *m*, C_6H_4); 8.62 (*s*, NH); 12.15 (*s*, NH). ^{13}C-NMR: 18.4 (Me); 27.4 (CMe_3); 40.4 ($\mathit{C}Me_3$) 126.4, 126.8, 128.0, 131.1 (4 CH); 133.6, 136.8 (2 C); 179.8, 179.9 (C=O, C=S). EI-MS: 250 (3, M^+), 143 (38), 105 (76), 85 (100), 32 (18), 28 (26). Anal. calcd. for $C_{13}H_{18}N_2OS$ (250.37): C, 62.37; H, 7.25; N, 11.19; found: C, 62.68; H, 7.42; N, 11.34.

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