

Green synthesis of *N*-substituted-*N'*-aryl carbonyl bifunctional thioureas under solvent-free conditions

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

Keywords: Aryl dicarbonyl dithiourea, Ammonium thiocyanate, Aryldiamines, Acid chloride.

Introduction

Thioureas are important compounds as building blocks in the synthesis of heterocyclic compounds. For example thioureas condense with α -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 imino thiazolines [4], thiohydantoin [5,6], 1,3,5-triazines [7] and 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], aroylthiocyanates with amines followed by basic hydrolysis [10,11] and 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 (4 mmol) and an acid chloride (4 mmol) was stirred without solvent for 15 minutes. Then, an aryl diamine (2 mmol) was added and mixed for 60 minutes. The product was recrystallized from EtOH. The results obtained are shown in Scheme 1.

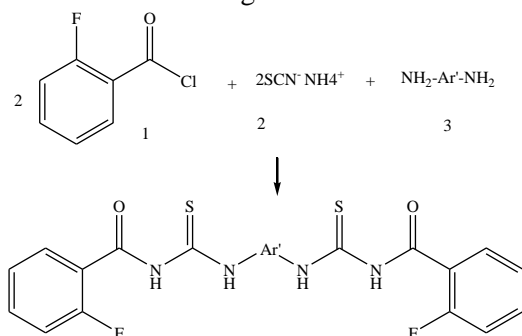
Results and discussion

Ammonium thiocyanate and acid chlorides are mixed and stirred at room temperature without a solvent to give the corresponding isothiocyanates which reacted smoothly with aryl amines to produce *N*-aryl-*N'*-aroyl(acyl)thioureas in good yields. The mechanism of reaction is shown below (Scheme 2).

The structures of compounds **4a-4e** were deduced from their elemental analyses and their ^1H - and ^{13}C -NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at appropriate m/z values. The ^1H -NMR spectrum of **4b** in CDCl_3 showed

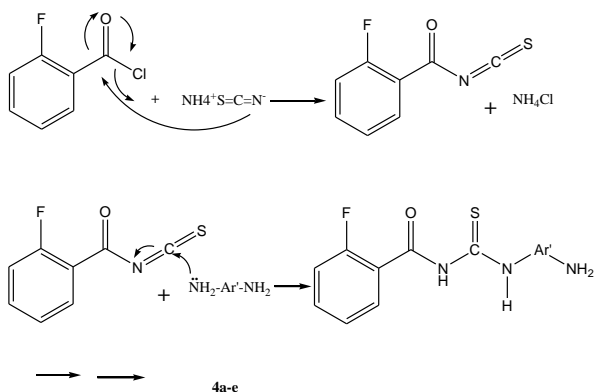
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two singlets for aromatic CH ($\delta = 8.29$), and NH ($\delta = 12.65$) protons, along with multiples for the aromatic ($\delta = 7.23-7.75$) protons. The NH between aromatic ring and C=S showed singlet at $\delta = 12.65$ and NH between C=O and C=S showed doublet in $\delta = 9.23$ with $^5J_{\text{HF}} = 15$ Hz. Hydrogen bonding formation for two NH is possible as shown in Figure 1.



4	Ar'	yield%
a	1,2-diamino benzene	90
b	1,3-diamino benzene	86
c	1,4-diamino benzene	85
d	1,8-diamino naphthalene	80
e	1,5-diamino naphthalene	87

Scheme 1: Synthesis of compounds 4a-e. Reagents and products



Scheme 2: Suggested mechanism of thioureas preparation

The ^{13}C -NMR spectrum of 4b showed twelve signals in agreement with the proposed structure. Partial assignments of these resonances are given in the experimental section. The ^1H and ^{13}C -NMR spectra of 4a-4e are similar to those for 4b, except for the aromatic moieties, which exhibited characteristic signals with appropriate chemical shifts.

Although the presence of ^{19}F nucleus complicates both the ^1H and ^{13}C -NMR spectra of 4a-4e, it helps in assignment of the signals by direct and long-range couplings with ^1H 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 $^5J = 12-15\text{Hz}$, which provides information about the Ar-C-N-H torsion (Figure 1). 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 (Figure 1), and would be expected to have a large through-space contribution to the coupling. The large observed coupling may thus be explained.

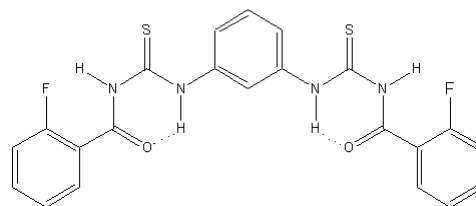


Figure 1. Structure of 1-(2-Fluorobenzoyl)-3-{3-[3-(2-fluorobenzoyl)-thioureido]-phenyl}-thiourea (4b)

Conclusion

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

Experimental

Chemical and instrumentation:

Compounds 1-3a-e were purchased 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 ^1H - and ^{13}C -NMR spectra, Bruker DRX-300 AVANCE instrument; in CDCl_3 or DMSO At 300MHz and 75MHz, respectively, δ in ppm, J in Hz; EI-MS(70eV): 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.

Synthesis:

NH₄SCN (4 mmol) was added to acid chloride (4 mmol). The mixture was stirred at 25 °C for 15 min, and then an aryl diamine (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 Na₂SO₄. The solvent was evaporated under reduced pressure to leave the crude product, which was purified by recrystallization (EtOH).

1-(2-Fluorobenzoyl)-3-[2-[3-(2-fluorobenzoyl)-thioureido]-phenyl] - thiourea (4a):

Yellow powder; yield: 0.85 g (90 %); mp 195-197 °C
IR (KBr): $\bar{\nu}$ = 3426, 3416 (2 NH), 1677 (C=O), 1146 (C=S) cm⁻¹; ¹H NMR: δ = 7.34(dd, ³J_{HF}=15, ³J_{HH}=4.1, 2 CH), 7.38 (t, ³J_{HH}=7.08, 2 CH), 7.44 (dd, ³J_{HH}=6, ⁴J_{HH}=3.5, 2 CH), 7.58-7.75 (m, 2 CH), 7.89 (dt, ³J_{HH}=7.96, ⁴J_{HH}=1.8, 2 CH), 8.06 (dd, ³J_{HH}=6, ³J_{HH}=3.5, 2 CH), 10.41 (d, ⁵J_{HF}=5.76, 2 NH), 12.42 (s, 2 NH) ppm; ¹³C NMR: δ = 117.09 (d, ²J_{CF}=24.4, 2 CH), 119.37 (d, ²J_{CF}=9.9, 2C), 125.75 (d, ³J_{CF}=3.2, 2 CH), 127.42 (2 CH), 128.60 (2 CH), 132.77(2CH), 133.58(2CH), 136.18 (d, ³J_{CF}=9.68, 2 C), 160.92(d, ¹J_{CF}=249.3, 2 C), 163.30(d, ³J_{CF}=3.15, 2C=O), 180.24 (2 C=S) ppm; EI-MS: *m/z* (%) = 470 (M⁺, 3.1), 450 (13.4), 383 (23.6), 253 (55.1), 150 (31.5), 123 (100), 95 (88.2), 75 (30.7). Anal. Calc. for C₂₂H₁₆F₂N₄O₂S₂ (470.51): C, 56.16; H, 3.43; N, 11.91. Found 56.63; H, 3.52; N, 12.07.

1-(2-Fluorobenzoyl)-3-[3-[3-(2-fluorobenzoyl)-thioureido]-phenyl] - thiourea (4b):

Yellow powder; yield: 0.81 g (86 %); mp 320 °C (decomposed); IR (KBr): $\bar{\nu}$ = 3423, 3412 (2 NH), 1673 (C=O), 1147 (C=S) cm⁻¹; ¹H NMR: δ = 7.27(dd, ³J_{HF}=12.78, ³J_{HH}=8.37, 2 CH), 7.39 (t, ³J_{HH}=7.8, 2 CH), 7.66-7.70(m, 4CH), 8.13 (dt, ³J_{HH}=6.9, ⁴J_{HH}= 1.7, 2 CH), 8.29 (S, CH), 9.23 (d, ⁵J_{HF}=15, 2 NH), 12.65 (S, 2 NH) ppm; ¹³C NMR: δ = 117.08 (d, ²J_{CF}=21.3, 2 CH), 120.66 (2 C), 122.96 (d, ²J_{CF}=12.6, 2C), 125.44 (d, ³J_{CF}=8.0, 2 CH), 129.76 (2 C), 131.27 (2 CH), 135.03 (d, ³J_{CF}=8.6, 2 C), 138.89 (2 CH), 160.12(d, ¹J_{CF}=249.38, 2 C), 166.15(d, ³J_{CF}=3.27, 2C=O), 179.25 (2 C=S) ppm; EI-MS: *m/z* (%) = 470 (M⁺, 4.6), 383 (27.6), 253 (56.3), 150 (31.5), 123 (100), 95 (85.2), 75 (29.7); Anal. Calc. for C₂₂H₁₆F₂N₄O₂S₂ (470.51): C, 56.16; H, 3.43; N, 11.91 found:C, 56.35; H, 3.59; N, 11.97..

1-(2-Fluorobenzoyl)-3-[4-[3-(2-fluorobenzoyl)-thioureido]-phenyl] - thiourea (4c):

Yellow powder; yield: 0.80 g (85 %); mp 245-247 °C
IR (KBr): $\bar{\nu}$ = 3424, 3410 (2 NH), 1685 (C=O), 1148 (C=S) cm⁻¹; ¹H NMR: δ = 7.28 (dd, ³J_{HF}=12.77, ³J_{HH}=8.25, 2 CH), 7.39 (t, ³J_{HH}=7.62, 2CH), 7.66-7.68 (m, 2 CH), 7.85(s, 4CH), 8.14 (t, ³J_{HH}=7.8, 2 CH), 9.19 (d, ⁵J_{HF}=14.76, 2 NH), 12.66 (S, 2 NH) ppm; ¹³C NMR: δ = 117.08 (d, ²J_{CF}=21.4, 2 CH), 122.89 (2 CH), 122.98(d, ²J_{CF}=13.8, 2C), 125.46 (bs, 6CH), 129.76 (2 C), 131.28 (2 CH), 135.08 (d, ³J_{CF}=8.7, 2 C), 136.62 (2 CH), 160.13(d, ¹J_{CF}=249.0, 2 C), 166.16(d, ³J_{CF}=3.08, 2C=O), 179.30(2 C=S) ppm; EI-MS: *m/z* (%) = 470 (M⁺, 3.3), 450 (13.4), 253 (54.5), 150 (31.5), 123 (100), 95 (88.1), 75 (32.3); Anal. Calc. for C₂₂H₁₆F₂N₄O₂S₂ (470.51): C, 56.16; H, 3.43; N, 11.91 found:C, 56.32; H, 3.49; N, 11.98..

1-(2-Fluorobenzoyl)-3-[8-[3-(2-fluorobenzoyl)-thioureido]-naphthalen-1-yl] - thiourea (4d):

Brown powder; yield: 0.42 g (80 %); mp 220-222 °C
IR (KBr): $\bar{\nu}$ = 3419, 3218 (2 NH), 1683 (C=O), 1150 (C=S) cm⁻¹; ¹H NMR: δ = 7.05 (t, ³J_{HH}=7.6, 2 CH), 7.16 (dd, ⁵J_{HF}=10.9, ³J_{HH}=8.4, 2CH), 7.47-7.54(m, 6CH), 7.62 (t, ³J_{HH}=7.5, 2 CH), 8.07(d, ³J_{HH}=7.99, 2CH), 11.53 (d, ⁵J_{HF}=2.4, 2 NH), 12.33 (S, 2 NH) ppm; ¹³C NMR: δ = 116.88 (d, ²J_{CF}=22.4, 2 CH), 121.85 (d, ²J_{CF}=13.5, 2C), 124.96(d, ³J_{CF}=7.6, 2CH), 126.76 (2CH), 127.46 (2C), 129.31 (2 CH), 130.19 (2 CH), 131.58(2CH), 133.69(2CH), 135.20 (d, ³J_{CF}=8.0, 2C), 136.26 (2 CH), 160.28(d, ¹J_{CF}=250.2, 2 C), 165.79(d, ³J_{CF}=3.46, 2C=O), 182.17(2 C=S) ppm. EI-MS: *m/z* (%) = 520 (M⁺, 3.9), 500 (13.8), 433 (22.3), 323 (16.6), 303 (52.3), 123 (100), 95 (87.4), 75 (31.7). Anal. Calc. for C₂₆H₁₈N₄O₂S₂F₂ (520.58): C, 59.99; H, 3.49; N, 10.76 found:C, 60.29; H, 3.59; N, 10.77.

1-(2-Fluorobenzoyl)-3-[5-[3-(2-fluorobenzoyl)-thioureido]-naphthalen-1-yl] - thiourea (4e)

Yellow powder; yield: 0.45 g (87 %); mp 270-272 °C
IR (KBr): $\bar{\nu}$ = 3415, 3154 (2 NH), 1669 (C=O), 1150 (C=S) cm⁻¹; ¹H NMR: δ = 7.34-7.41(m, 4CH), 7.65-7.71 (m, 4CH), 7.82-7.86 (m, 2CH), 7.93(d, ³J_{HH}=10.5, 2CH), 8.00 (d, ³J_{HH}=10.5, 2 CH), 11.55 (d, ⁵J_{HF}=2.4, 2 NH), 12.41 (S, 2 NH) ppm; ¹³C NMR: δ = 117.12 (d, ²J_{CF}=21.45, 2 CH), 122.94(d, ²J_{CF}=9.15, 2C), 125.45 (d, ³J_{CF}=7.3, 2CH), 126.30 (2CH), 127.15 (2 CH), 130.49 (2 C), 131.43(2CH), 135.02 (d, ³J_{CF}=8.0, 2C), 135.74 (2 CH), 160.24(d, ¹J_{CF}=249.3, 2 C), 166.31(d, ³J_{CF}=3.12, 2C=O), 181.51(2 C=S) ppm; EI-MS: *m/z*

(%) = 520 (M+, 4.1), 500 (11.8), 433 (20.1), 323 (15.7), 303 (50.1), 123 (100), 95 (88.2), 75 (30.7).
Anal. Calc. for C₂₆H₁₈N₄O₂S₂F₂ (520.58): C, 59.99; H, 3.49; N, 10.76 found: C, 60.19; H, 3.56; N, 10.70.

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