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An Efficient and Eco-Friendly Procedure for Electrophilic Thiocyanation of Anilines and 1-(Substituted benzylidene)-2-phenyl Hydrazines

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Abstract: Thiocyanates form an important class of organic compounds commonly found in natural products that exhibit excellent antimicrobial activity. The electrophilic thiocyanation is one of the most effective methods of introducing a -SCN functional group to the parent organic molecule. In this work, we explored an eco-friendly and highly efficient method for thiocyanation of anilines and 1-(substituted benzylidene)-2-phenylhydrazines using commercially available N-bromoscuccinimide (NBS) and potassium thiocyanate (KSCN). The optimized protocol afforded thiocyanates with good regioselectivity and excellent yields in comparison to the available methods.

Keywords: N-bromosuccinimide; KSCN; aromatic amines; schiff bases; electrophilic thiocyanation

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1. Introduction

The thiocyanation of both aromatic and heteroaromatic compounds represents a crucial transformation with implications for both organic synthesis and pharmaceuticals [1,2]. In recent years, there has been a significant attraction to sulphur-containing aromatic compounds due to their diverse biological activities. Among these compounds, thiocyanates are a prominent class, serving as key building blocks in the synthesis of pharmacologically active compounds. Thiocyanates exhibit versatile reactivity, leading to the formation of thiols [3], sulfonyl chlorides [4], sulphides [5], trifluoromethyl (or difluoromethyl) sulphides [6,7], disulphides [8], phosphonothioates [9], and other sulphur-containing heterocycles [10,11]. This functional group is well-established in numerous biologically active natural products [12–17] and synthetic compounds featuring them as potential enzyme inhibitors (Figure 1), with applications ranging from treating Chagas disease [18,19] and cancer [20,21] to the more recent considerations for COVID-19 [22].

Various methods have been employed for the thiocyanation of aromatic systems using different reagents. For instance, thiocyanation of indoles and carbazoles was achieved using ammonium thiocyanate by montmorillonite K 10 clay-mediated reactions [23]. Thiocyanation of alcohols, trimethyl silyl, and tetrahydropyranyl ethers was carried out using a diphenyl phosphinite ionic liquid [24]. Peroxydisulfate-Cu(II), as an oxidant, was employed for the α-thiocyanation of carbonyl and β-dicarbonyl compounds [25]. Thiocyanation of aromatic compounds was carried out by anodic oxidation of thiocyanate anion to SCN radical [26]. Indoles and pyrrole undergo a reaction with ammonium thiocyanate in the

presence of o-iodoxy benzoic acid [27]. Indoles were converted to corresponding thiocyanato derivatives on treatment with ammonium thiocyanate in the presence of *p*-toluene sulfonic acid [28]. An NBS-mediated procedure was developed for the thiocyanation of cyclohexene-fused isoxazoline N-oxides under mild conditions [29].

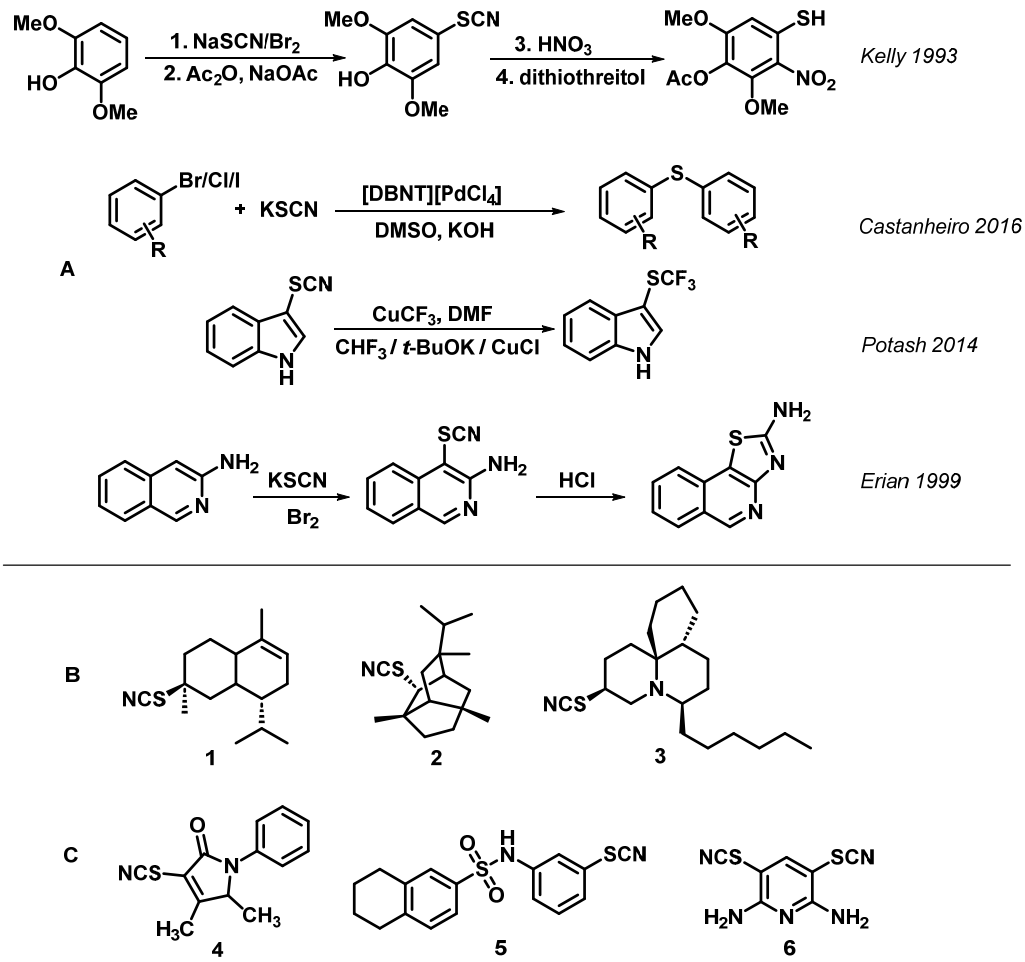


Figure 1. (**A**) Representative conversions of thiocyanate into different functional moieties [3,5,6,10]; A few thiocyanates as (**B**) natural products and (**C**) enzyme inhibitors.

Several methods have been tried for the synthesis of thiocyanatoaniline. Reaction with ammonium thiocyanate, trichloroisocyanuric acid, and wet SiO_2 yielded the product by in situ generation of hypochlorous acid in a heterogeneous system and subsequent oxidation of the thiocyanate anion in dichloromethane solvent [30]. Among the other oxidants employed with ammonium thiocyanate, cerium (IV) ammonium nitrate in methanol afforded unsatisfactory yield of the product [31]. A significant improvement could be observed when the reaction was performed with iodine [32]. Sodium perborate also facilitates the transformation but under acidic conditions employing glacial acetic acid [33]. A free radical process for the transformation could be invoked using oxone in a methanol medium [34] or manganese acetate in acetic acid [35] with modest yields. The conversion was also achieved using diethyl azodicarboxylate in an acetonitrile medium [36]. A milder condition was attempted using anhydrous ferric chloride in dichloromethane but took a longer time to achieve an appreciable yield [37]. Microwave irradiation was explored on a solid surface by employing acidic alumina [38]. DDQ mediation thiocyanation of the substrates depends on the electron donor ability of the aromatic nucleus [39]. Attempts to obtain the product with iodine pentoxide were not encouraging [40]. Thiocyanation in iodic acid afforded good yields, but chloroform was used as the solvent [41]. With hydrogen peroxide or periodic

acid, the reaction was performed in aqueous medium [42]. Dichloroidodo benzene promotes the reaction at 0 °C in a dichloromethane medium [43]. Despite these advancements, the methods employed have one or more limitations, such as poor yield, narrow substrate scope, halogenated or toxic solvent, need for an excessive amount of strong oxidizing reagent, acidic conditions, heterogeneous reaction phase, poor performance, anhydrous medium, long reaction time, inert atmosphere, and stringent reaction conditions with difficultly in scalability. Therefore, there is an unmet need to develop an efficient process for synthesizing thiocyanate derivatives of anilines. A simple procedure for thiocyanation was demonstrated on arene substrates using N-thiocyanatosuccinimide (NTS) [44]. However, the scope of this strategy was not widely explored for aniline derivatives and 1-(substituted benzylidene)-2-phenylhydrazines. We, therefore, decided to investigate the electrophilic thiocyanation reactions of these substrates under eco-friendly conditions by using N-bromosuccinimide and potassium thiocyanate in an ethanol medium.

2. Experimental Section

2.1. Materials and Methods

All the chemicals were obtained from commercial suppliers and used without further purification. The reactions were conducted in oven-dried glassware and maintained under the appropriate atmospheric conditions. To monitor the progress of the reactions, thin-layer chromatography (TLC) was employed, specifically, 0.25 mm Merck Silica gel 60 F254 plates were used, and visualization was achieved using UV light. In column chromatography, 60–120 mesh silica gel was used as the stationary phase. Elution was carried out using a mixture of hexane and ethyl acetate as the mobile phase. Nuclear magnetic resonance (NMR) spectra were recorded using a Jeol ECZ 400R spectrometer operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. $CDCl_3$ was used as the solvent, and tetramethyl silane (TMS) served as the internal standard. Chemical shifts (δ) were reported relative to residual solvent signals, specifically 7.25 ppm for ^{1}H NMR and a triplet centred at 77.00 ppm for ^{13}C NMR. Mass spectrometry analysis was conducted using an ESI (electrospray ionization) quadrupole time-of-flight Agilent mass spectrometer. IR spectra were recorded on a Bruker Alpha II FTIR spectrophotometer.

(i) *General procedure for the synthesis of thiocyanatoaniline analogues*

To a solution of N-bromosuccinimide (1.0 mmol) in EtOH (10 mL), KSCN (2.1 mmol) was added and stirred at room temperature (27 °C) for 5 min. To this solution, substituted aniline (1.0 mmol) was added and the reaction mixture was stirred at room temperature (27 °C) for 20 min. The reaction mixture was concentrated, diluted with water, and extracted thrice with EtOAc. The combined organic extracts were concentrated under vacuum, and the resultant crude was subjected to purification by column chromatography on silica gel (60–120 mesh) using a hexane-ethyl acetate mixture (10:1) as the mobile phase to obtain the desired product.

4-thiocyanatoaniline (**1a**) [30]: Pale brown solid; Yield 98%; m.p. = 52–53 °C; IR (ν_{max}, cm^{-1}): 3374.27, 2152.01, 1707.83 1625.05, 1594.80, 1495.78, 1428.12, 1361.05, 1301.37, 1221.64, 1179.07, 1129.30, 1085.54, 824.74, 676.97; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.31–7.34 (m, 2H, Ar), 6.63–6.66 (m, 2H, Ar), 3.97 (s, 2H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 148.9, 134.6, 116.2, 112.5, 109.6; HRMS (ESI): *m*/*z* calcd. for $C_7H_6N_2S$ $[M + H]^+$: 151.0252; found: 151.0486.

2-chloro-4-thiocyanatoaniline (**1b**) [39]: White solid; Yield 96%; m.p. = 64–66 °C; IR (ν_{max}, cm^{-1}): 3474.59, 3372.59, 3233.14, 2925.76, 2154.54, 2054.68, 1623.93, 1591.81, 1476.32, 1420.75, 1315.22, 1239.46, 1123.23, 1020.23, 902.03, 849.96, 813.39; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.48 (d, 1H, Ar), 7.25–7.28 (m, 1H, Ar), 6.75 (d, 1H, Ar), 4.38 (s, 2H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 145.4, 133.9, 132.7, 119.8, 116.5, 111.7, 110.1; HRMS (ESI): *m*/*z* calcd. for $C_7H_5ClN_2S$ $[M + H]^+$: 184.9864; found: 184.9975.

2-methyl-4-thiocyanatoaniline (**1c**) [42]: Creamy white solid; Yield 96%; m.p. = 68–70 °C; IR (ν_{max}, cm^{-1}): 3449.59, 3368.62, 3246.89, 2924.89, 2150.60, 1628.89, 1592.12, 1568.60, 1491.02, 1454.53, 1402.63, 1296.51, 1153.92, 1091.96, 1032.18, 995.58, 885.14, 814.70, 719.01; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.24–7.26 (m, 1H, Ar), 7.20–7.23 (m, 1H, Ar), 6.59–6.68 (m, 1H, Ar), 3.90 (s, 2H, NH_2), 2.13 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 147.2, 135.1, 132.2, 124.0, 115.8, 112.7, 109.3, 17.3; HRMS (ESI): *m*/*z* calcd. for $C_8H_8N_2S$ $[M + H]^+$: 165.0408; found: 165.0509.

4-methyl-2-thiocyanatoaniline (**1d**): White solid; Yield 97%; m.p. = 80–82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.34 (d, 1H, Ar), 6.56–6.58 (m, 1H, Ar), 6.46–6.50 (m, 1H, Ar), 3.91 (s, 2H, NH_2), 2.43 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 149.5, 143.1, 136.4, 117.4, 113.8, 112.2, 109.1, 21.0; HRMS (ESI): *m*/*z* calcd. for $C_8H_8N_2S$ $[M + H]^+$: 165.0408; found: 165.641.

2,3-dichloro-4-thiocyanatoaniline (**1e**): Yellow solid; Yield 96%; m.p. = 75–77 °C; IR (ν_{max}, cm^{-1}): 3333.01, 3226.89, 2925.74, 2161.17, 1708.24, 1629.63, 1577.77, 1539.59, 1466.44, 1393.56, 1359.26, 1323.83, 1294.70, 1220.32, 1181.86, 1109.75, 1056.51, 919.81, 813.47, 773.60; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.39 (d, 1H, Ar), 6.70 (d, 1H, Ar), 4.50 (s, 2H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 146.5, 135.5, 132.0, 118.9, 114.1, 110.6, 110.5; HRMS (ESI): *m*/*z* calcd. for $C_7H_4Cl_2N_2S$ $[M + H]^+$: 217.9472; found: 217.0195.

2-fluoro-4-thiocyanatoaniline (**1f**): Pale yellow solid; Yield 95%; m.p. = 61–63 °C; IR (ν_{max}, cm^{-1}): 3474.59, 3372.59, 3233.14, 2925.76, 2154.54, 2054.68, 1623.93, 1591.81, 1476.32, 1420.75, 1315.22, 1239.46, 1123.23, 1020.23, 902.03, 849.96, 813.39; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.19–7.23 (m, 1H, Ar), 7.12–7.16 (m, 1H, Ar), 6.73–6.78 (m, 1H, Ar), 4.09 (s, 2H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 152.2, 149.8, 137.6, 129.9, 120.0, 117.4, 111.8; HRMS (ESI): *m*/*z* calcd. for $C_7H_5FN_2S$ $[M + H]^+$: 169.0157; found: 169.0281.

4-fluoro-2-thiocyanatoaniline (**1g**): Pale yellow solid; Yield 96%; m.p. = 76–78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.44–7.48 (m, 1H, Ar), 7.26–7.30 (m, 1H, Ar), 6.99–7.05 (m, 1H, Ar), 5.42 (s, 2H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 160.0, 119.8, 119.7, 114.0, 113.7, 107.9, 107.6; HRMS (ESI): *m*/*z* calcd. for $C_7H_5FN_2S$ $[M + H]^+$: 169.0157; found: 169.0281.

3-chloro-4-thiocyanatoaniline (**1h**): Yellow solid; Yield 97%; m.p. = 70–72 °C; IR (ν_{max}, cm^{-1}): 3474.59, 3372.59, 3233.14, 2925.76, 2154.54, 2054.68, 1623.93, 1591.81, 1476.32, 1420.75, 1315.22, 1239.46, 1123.23, 1020.23, 902.03, 849.96, 813.39; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.39–7.40 (m, 1H, Ar), 6.75–6.77 (m, 1H, Ar), 6.54–6.57 (m, 1H, Ar), 4.08 (s, 2H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 150.0, 137.8, 135.4, 116.2, 114.6, 111.2, 108.7; HRMS (ESI): *m*/*z* calcd. for $C_7H_5ClN_2S$ $[M + H]^+$: 184.9862; found: 184.9978.

3,5-dichloro-4-thiocyanatoaniline (**1i**): Creamy white solid; Yield 96%; m.p. = 65–67 °C; IR (ν_{max}, cm^{-1}): 3408.88, 3333.01, 3226.89, 2925.74, 2161.17, 1708.24, 1629.63, 1577.77, 1539.59, 1466.44, 1393.56, 1359.26, 1323.83, 1294.70, 1220.32, 1181.86, 1109.75, 1056.51, 919.81, 813.47, 773.60; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.71–6.73 (m, 2H, Ar), 4.15 (s, 2H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 150.4, 141.7, 114.9, 110.0, 107.9; HRMS (ESI): *m*/*z* calcd. for $C_7H_4Cl_2N_2S$ $[M + H]^+$: 218.9472; found: 218.9472.

3-methyl-4-thiocyanatoaniline (**1j**) [42]: Yellow solid; Yield 96%; m.p. = 81–83 °C; IR (ν_{max}, cm^{-1}): 3427.48, 3339.89, 3213.03, 2920.65, 2146.96, 1708.08, 1625.62, 1592.74, 1481.86, 1453.57, 1360.12, 1325.91, 1254.65, 1221.13, 1139.17, 1034.00, 858.95, 817.13, 739.36, 671.84; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.34 (d, 1H, Ar), 6.56–6.59 (m, 1H, Ar), 6.46–6.50 (m, 1H, Ar), 3.91 (s, 2H, NH_2), 2.44 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 149.5, 143.1, 136.4, 117.4, 113.8, 112.2, 109.1, 21.0; HRMS (ESI): *m*/*z* calcd. for $C_8H_8N_2S$ $[M + H]^+$: 165.0408; found: 165.0754.

2-methoxy-4-thiocyanatoaniline (**1k**): White solid; Yield 96%; m.p. = 52–54 °C; IR (ν_{max}, cm^{-1}): 3449.59, 3368.62, 3246.89, 2924.89, 2150.60, 1628.89, 1592.12, 1568.60, 1491.02, 1454.53, 1402.63, 1296.51, 1153.92, 1091.96, 1032.18, 995.58, 885.14, 814.70, 719.01; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.99– 7.02 (m, 1H, Ar), 6.94 (d, 1H, Ar), 6.64–6.68 (m, 1H, Ar), 4.08 (s, 2H, NH_2), 3.86 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 147.7, 139.1, 126.9, 115.0, 114.6, 112.5, 109.0, 55.8; HRMS (ESI): *m*/*z* calcd. for $C_8H_8N_2OS$ $[M + H]^+$: 181.0352; found: 181.0760.

2,6-dimethyl-4-thiocyanatoaniline (**1l**) [30]: White solid; Yield 97%; m.p. = 85–87 °C; IR (ν_{max}, cm^{-1}): 3412.21, 3343.82, 2971.60, 2151.47, 1709.41, 1636.90, 1582.66, 1465.66, 1438.27, 1360.04, 1284.95, 1221.05, 1113.24, 1027.29, 867.69, 746.19, 731.58; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.15–7.16 (m, 2H, Ar), 3.82 (s, 2H, NH_2), 2.15 (m, 6H, 2 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 145.3, 132.9, 123.2, 112.8, 108.6, 17.5; HRMS (ESI): m/z calcd. for $C_9H_{10}N_2S$ $[M + H]^+$: 179.0565; found: 179.095.

4-bromo-2-thiocyanatoaniline (**1m**): Yellow solid; Yield 98%; m.p. = 73–75 °C; IR (ν_{max}, cm^{-1}): 3474.59, 3372.59, 3233.14, 2925.76, 2154.54, 2054.68, 1623.93, 1591.81, 1476.32, 1420.75, 1315.22, 1239.46, 1123.23, 1020.23, 902.03, 849.96, 813.39; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.44–7.48 (m, 1H, Ar), 7.26–7.30 (m, 1H, Ar), 6.99–7.05 (m, 1H, Ar), 5.49 (s, 2H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 160.0, 119.8, 119.7, 114.0, 113.7, 107.9, 107.6; HRMS (ESI): m/z calcd. for $C_7H_5BrN_2S$ $[M + H]^+$: 230.9357; found: 230.9581.

4-methoxy-2-thiocyanatoaniline (**1n**): Pale yellow solid; Yield 96%; m.p. = 100–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.99–7.02 (m, 1H, Ar), 6.94 (d, 1H, Ar), 6.65–6.67 (m, 1H, Ar), 4.08 (s, 2H, NH_2), 3.86 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 147.7, 139.1, 126.9, 115.0, 114.6, 112.5, 109.0, 55.8; HRMS (ESI): m/z calcd. for $C_8H_8N_2OS$ $[M + H]^+$: 181.0357; found: 181.0557.

2,4-dimethyl-6-thiocyanatoaniline (**1o**): White solid; Yield 96%; m.p. = 75–76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.21–7.23 (m, 1H, Ar), 6.92–6.94 (m, 1H, Ar), 5.65 (s, 2H, NH_2), 2.50 (s, 3H, CH_3), 2.35 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 164.8, 148.9, 132.0, 131.3, 128.4, 128.3, 118.5, 21.3, 18.5; HRMS (ESI): m/z calcd. for $C_9H_{10}N_2S$ $[M + H]^+$: 179.0565; found: 179.0882.

4-chloro-2-thiocyanatoaniline (**1p**): Yellow solid; Yield 98%; m.p. = 69–71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.44–7.48 (m, 1H, Ar), 7.26–7.30 (m, 1H, Ar), 6.99–7.05 (m, 1H, Ar), 5.40 (s, 2H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 160.0, 119.8, 119.7, 114.0, 113.7, 107.9, 107.6; HRMS (ESI): m/z calcd. for $C_7H_5ClN_2S$ $[M + H]^+$: 184.9862; found: 185.0111.

(ii) *General procedure for the synthesis of substituted (E)-1-benzylidene-2-(4-thiocyanatophenyl) hydrazine analogues.*

To a solution of N-bromosuccinimide (1.0 mmol) in EtOH (10 mL), KSCN (2.1 mmol) was added and stirred at room temperature (27 °C) for 5 min. To this solution, 1-(substituted benzylidene)-2-phenylhydrazine (1.0 mmol) was added and the reaction mixture was stirred at room temperature (27 °C) for 20 min. The reaction mixture was concentrated, diluted with water, and extracted thrice with EtOAc. The combined organic extracts were concentrated under vacuum, and the resultant crude was subjected to purification by column chromatography on silica gel (60–120 mesh) using a hexane-ethyl acetate mixture (10:1) as the mobile phase to obtain the desired product.

1-benzylidene-2-(4-thiocyanatophenyl)hydrazine (**2a**): Yellow solid; Yield 95%; m.p. = 112–114 °C; IR (ν_{max}, cm^{-1}): 3479.12, 3373.20, 2155.30, 1707.64, 1625.34, 1589.70, 1544.17, 1494.36, 1444.08, 1422.36, 1358.39, 1304.85, 1259.80, 1220.69, 1191.30, 1138.59, 1067.28, 1026.73, 953.13, 928.58, 842.48, 802.17, 755.39; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.80 (s, 1H, NH), 7.71 (s, 1H, CH), 7.64–7.66 (m, 2H, Ar), 7.44–7.47 (m, 2H, Ar), 7.31–7.40 (m, 3H, Ar), 7.11–7.14 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 146.6, 139.4, 134.7, 134.2, 129.2, 128.8, 126.6, 114.2, 112.2, 111.6; HRMS (ESI): m/z calcd. for $C_{14}H_{11}N_3S$ $[M + H]^+$: 254.0674; found: 254.0794.

1-(2-bromobenzylidene)-2-(4-thiocyanatophenyl)hydrazine (**2b**): White solid; Yield 80%; m.p. = 146–148 °C; IR (ν_{max}, cm^{-1}): 3477.89, 3372.94, 2926.24, 2155.71, 1708.75, 1625.84, 1590.34, 1544.08, 1494.31, 1443.82, 1422.32, 1358.46, 1304.64, 1259.70, 1220.31, 1191.54, 1133.84, 1092.93, 1067.24, 1026.65, 928.31, 842.62, 802.07, 755.02, 693.91; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.11 (s, 1H, NH), 8.03 (s, 1H, CH), 8.01 (s, 1H, Ar), 7.52–7.56 (m, 1H, Ar), 7.46–7.48 (m, 2H, Ar), 7.31–7.34 (m, 1H, Ar), 7.13–7.18 (m, 3H, Ar), ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 146.2, 138.1, 134.1, 133.6, 133.1, 130.2, 127.7, 127.2, 123.16, 114.3, 112.3, 112.0; HRMS (ESI): m/z calcd. for $C_{14}H_{10}BrN_3S$ $[M + H]^+$: 333.9779; found: 333.9846.

1-(2-chlorobenzylidene)-2-(4-thiocyanatophenyl)hydrazine (**2c**): Pale brown solid; Yield 90%; m.p. = 113–114 °C; IR (ν_{max}, cm^{-1}): 3480.27, 3374.88, 2926.24, 2155.25, 1707.39, 1625.72, 1590.60, 1544.19, 1494.22, 1444.23, 1422.36, 1358.23, 1303.22, 1259.94, 1221.15, 1191.24, 1135.16, 1067.31, 1026.67, 928.27, 842.70, 802.17, 754.81; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.14 (s, 1H, NH), 8.05 (s, 1H, CH), 8.01–8.03 (m, 1H, Ar), 7.47–7.48 (m, 1H, Ar), 7.45–7.46 (m, 1H, Ar), 7.34–7.36 (m, 1H, Ar), 7.25–7.29 (m, 2H, Ar), 7.13–7.15 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 146.2, 135.8, 135.7, 134.1, 133.1, 132.1, 129.9, 127.1, 126.8, 114.3, 112.2, 112.1; HRMS (ESI): *m*/*z* calcd. for $C_{14}H_{10}ClN_3S$ $[M + H]^+$: 288.0284; found: 288.0384.

1-(3-bromobenzylidene)-2-(4-thiocyanatophenyl)hydrazine (**2d**): White solid; Yield 83%; m.p. = 119–121 °C; IR (ν_{max}, cm^{-1}): 3474.59, 3372.59, 3233.14, 2925.76, 2154.54, 2054.68, 1623.93, 1591.81, 1476.32, 1420.75, 1315.22, 1239.46, 1123.23, 1020.23, 902.03, 849.96, 813.39; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.86 (s, 1H, NH), 7.81 (s, 1H, CH), 7.63 (s, 1H, Ar), 7.53 (d, 1H, Ar), 7.41–7.50 (m, 3H, Ar), 7.25 (s, 1H, Ar), 7.12 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 146.1, 137.4, 136.8, 134.1, 131.9, 130.3, 129.1, 125.2, 123.0, 114.3, 112.3, 112.0; HRMS (ESI): *m*/*z* calcd. for $C_{14}H_{10}BrN_3S$ $[M + H]^+$: 333.9779; found: 333.9831.

1-(4-chlorobenzylidene)-2-(4-thiocyanatophenyl)hydrazine (**2e**): Pale yellow solid; Yield 90%; m.p. = 120–122 °C; IR (ν_{max}, cm^{-1}): 3449.59, 3368.62, 3246.89, 2924.89, 2150.60, 1628.89, 1592.12, 1568.60, 1491.02, 1454.53, 1402.63, 1296.51, 1153.92, 1091.96, 1032.18, 995.58, 885.14, 814.70, 719.01, 671.25; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.81 (s, 1H, NH), 7.67 (s, 1H, CH), 7.56–7.59 (m, 2H, Ar), 7.45–7.48 (m, 2H, Ar), 7.33–7.36 (m, 2H, Ar), 7.11–7.14 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 146.3, 138.0, 134.9, 134.1, 133.2, 129.0, 127.6, 114.2, 112.1, 112.0; HRMS (ESI): *m*/*z* calcd. for $C_{14}H_{10}ClN_3S$ $[M + H]^+$: 288.0284; found: 288.0461.

1-(4-fluorobenzylidene)-2-(4-thiocyanatophenyl)hydrazine (**2f**): White solid; Yield 87%; m.p. = 125–127 °C; IR (ν_{max}, cm^{-1}): 3477.89, 3372.94, 2926.24, 2155.71, 1708.75, 1625.84, 1590.34, 1544.08, 1494.31, 1443.82, 1422.32, 1358.46, 1304.64, 1259.70, 1220.31, 1191.54, 1133.84, 1092.93, 1067.24, 1026.65, 928.31, 842.62, 802.07, 755.02, 693.91; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.78 (s, 1H, NH), 7.69 (s, 1H, CH), 7.61–7.65 (m, 2H, Ar), 7.44–7.47 (m, 2H, Ar), 7.05–7.13 (m, 4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 146.5, 138.2, 134.2, 128.3, 128.2, 116.0, 115.8, 114.1, 112.1, 111.7; HRMS (ESI): *m*/*z* calcd. for $C_{14}H_{10}FN_3S$ $[M + H]^+$: 272.0579; found: 272.0639.

1-(4-nitrobenzylidene)-2-(4-thiocyanatophenyl)hydrazine (**2g**): Orange solid; Yield 93%; m.p. = 143–145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.25 (s, 1H, NH), 8.23 (s, 1H, CH), 8.09 (s, 1H, Ar), 7.74–7.81 (m, 3H, Ar), 7.50 (d, 2H, Ar), 7.18 (d, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 146.3, 138.0, 134.9, 134.1, 133.2, 129.0, 127.6, 114.2, 112.1, 112.0; HRMS (ESI): *m*/*z* calcd. for $C_{14}H_{10}N_4O_2S$ $[M + H]^+$: 299.0524; found: 299.0602.

1-(4-bromobenzylidene)-2-(4-thiocyanatophenyl)hydrazine (**2h**): Yellow solid; Yield 83%; m.p. = 111–113 °C; IR (ν_{max}, cm^{-1}): 3427.48, 3339.89, 3213.03, 2920.65, 2146.96, 1708.08, 1625.62, 1592.74, 1481.86, 1453.57, 1360.12, 1325.91, 1254.65, 1221.13, 1139.17, 1034.00, 858.95, 817.13, 739.36, 671.84; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.80 (s, 1H, NH), 7.66 (s, 1H, CH), 7.51 (m, 4H, Ar), 7.45–7.48 (m, 2H, Ar), 7.11–7.14 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 146.2, 138.0, 134.1, 133.7, 132.0, 127.9, 123.1, 114.2, 112.2, 112.1; HRMS (ESI): *m*/*z* calcd. for $C_{14}H_{10}BrN_3S$ $[M + H]^+$: 333.9844; found: 333.9779.

2.2. X-ray Diffraction Analysis

A good quality single crystal of compound **1l** was obtained by slow evaporation from a solution using ethanol solvent. The crystal was mounted along its largest dimension and used for data collection. The intensity data were collected on a Bruker Smart CCD Area Detector System using MoKα (0.71073 Å) radiation in ω–ϕ scan mode. The data were reduced using SAINT-Plus [45]. The structure was solved by Direct Methods and refined on F^2 using the SHELX-97 [46] package. All the non-hydrogen atoms were refined anisotropically. As the hydrogens were not readily revealed from difference Fourier maps, they were included in the ideal positions with fixed isotropic U values, and they were riding with their respective non-hydrogen atoms. The difference Fourier map, after the refinement,

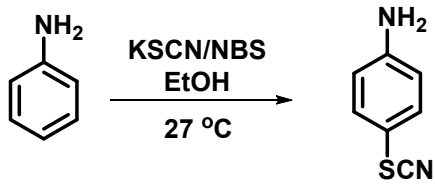
was essentially featureless in all cases. The mean plane calculations were conducted using the program PARST [47]. Diagrams and publication material were generated using ORTEP-3 [48] PLATON [49], CAMERON [50] and DIAMOND [51]. The CIF files are deposited at the Cambridge Crystallographic Data Centre, the deposition number for compound **1l** is CCDC-2251369. This data can be obtained free of charge at https://www.ccdc.cam.ac.uk/ (accessed on 8 January 2024) [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033; email: deposit@ccdc.cam.ac.uk].

3. Results and Discussion

Attempts to thiocyanate the aromatic nucleus have been tried under several conditions. An examination of the numerous reagents employed indicates that the strategies for thiocyanation can be generalised mechanistically. The more common approach is to generate an SCN^+ electrophile from the thiocyanate anion, followed by the addition of the electrophile to the aryl ring and a proton abstraction [32,36,44]. The second approach involves the oxidation of substrate to form a radical cation that will facilitate a direct attack by SCN^- anion. This resulting species can undergo hydrogen radical abstraction to form the product [34]. Yet another approach would be the oxidation of thiocyanate anion to the SCN radical and the addition of the radical on the substrate to generate a thiocyanated carbon radical. Transfer of an electron from the carbon radical would result in the formation of a carbocation that undergoes a proton loss [35]. The π-complex or ion pair formed between substrate and oxidant can undergo attack by the SCN^- anion to form a thiocyanated carbon radical and subsequent transfer of an electron transfer generates a carbocation that forms the product by a proton loss [39]. Among these strategies, the formation and reaction of electrophilic SCN^+ would be a simpler and more convenient process that can take advantage of the nucleophilic character of the substrates such as anilines. With this background, we decided to investigate the electrophilic thiocyanation of aniline using the SCN^+ electrophile.

In our pursuit of a milder and more convenient procedure for thiocyanation, we have explored various reaction conditions involving the interaction of NBS with an alkali metal thiocyanate. Our findings indicate that NBS, in conjunction with potassium thiocyanate in ethanol as solvent, yields optimal results. To study the efficiency of this reaction, aniline was chosen as the model substrate, and various experiments were conducted to assess reagent concentration and potential solvent. The results summarized in Table 1 indicate that ethanol would be the most effective solvent. Considering the attributes of green chemistry and environmental friendliness, ethanol was selected as the solvent for the thiocyanation reactions. Through optimization studies, we determined that a 1:2:1 mole ratio of aniline/KSCN/NBS in ethanol at room temperature (27 °C) provided the best condition for complete conversion in a short reaction time, resulting in the highest yield of 4-thiocyanatoaniline product. Based on this, the thiocyanation of substituted anilines and 1-(substituted benzylidene)-2-phenylhydrazine derivatives was achieved using the in situ-generated N-thiocyanatosuccinimide (NTS).

Table 1. Optimization of the reaction conditions for thiocyanation of aniline.



Entry	Solvent	KSCN (Eq)	NBS (Eq)	Time h/min	Yield [a] (%)
1	DMSO	2	1	2 h	60
2	DCE	2	1	1.5 h	50
3	DCM	2	1	1.5 h	70
4	DMF	2	1	2 h	50
5	THF	2	1	1 h	60
6	Dioxane	2	1	1.5 h	40
7	Acetonitrile	2	1	1 h	80
8	MeOH	2	1	45 min	85
9	EtOH	2	0.25	1 h	70
10	EtOH	2	0.50	1 h	85
11	EtOH	2	0.75	1 h	90
12	EtOH	2	1	20 min	98

Aniline (1.0 mmol), N-bromosuccinimide (1.0 mmol), KSCN (2.1 mmol); [a] Isolated yields.

The reaction mechanism involves the initial reaction of N-bromosuccinimide with potassium thiocyanate to produce N-thiocyanatosuccinimide. This intermediate serves as an electrophilic thiocyanate precursor in the reaction. The amino nitrogen facilitates the donation of a lone pair of electrons to the aromatic ring, resulting in the formation of a nucleophile at the para position, and concurrently a positive charge develops on the nitrogen. The nucleophile attacks N-thiocyanatosuccinimide, leading to thiocyanate substitution at the para position while eliminating the succinimide ion. Subsequently, the succinimide ion abstracts the proton at the para position, culminating in the formation of the desired product (Figure 2). To extend the scope of this methodology, we employed substituted aniline derivatives for the reaction with the in situ-generated N-thiocyanatosuccinimide in ethanol at room temperature (27 °C). Interestingly, both electron-donating and electron-withdrawing compounds gave satisfactory results in terms of good yields and a short reaction time. An intriguing observation was made regarding the regioselectivity of the thiocyanation reactions. For ortho- and meta-substituted aromatic compounds, the reaction exclusively occurred at the para position. Conversely, para-substituted compounds resulted in ortho-thiocyanated products (Figure 3). Subsequently, we investigated the reactions of 1-benzylidene-2-phenylhydrazine and its analogues. Thiocyanation of 1-benzylidene-2-phenylhydrazine under the described conditions afforded the desired product, 1-benzylidene-2-(4-thiocyanatophenyl)hydrazine, with an impressive yield of 95%. Various 1-(substituted benzylidene)-2-phenylhydrazine derivatives bearing electron-withdrawing substituents such as bromo, chloro, fluoro, and nitro groups exhibited good yields with high regioselectivity. However, the investigated electron-donating groups did not yield the thiocyanated products (Figure 4). The synthesized compounds were characterized by IR, NMR, and Mass spectrometric techniques, and finally, the structure was convincingly established by single crystal X-ray diffraction analysis of **1l** (Figure 5 and Figures S1–S91, Supplementary Materials).

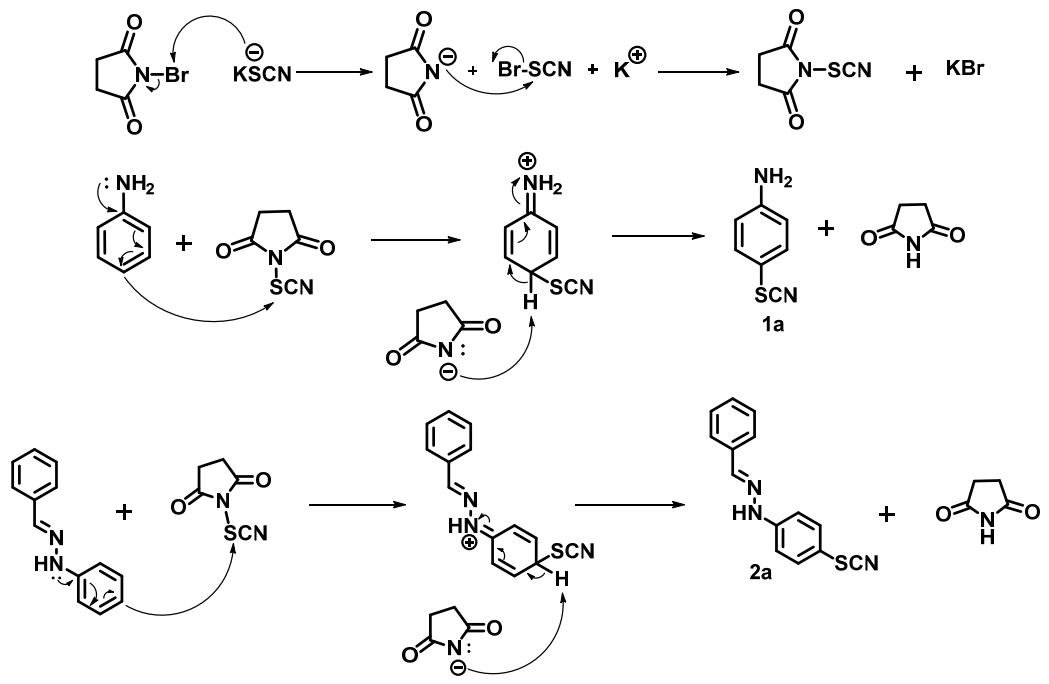


Figure 2. Suggested reaction mechanism for thiocyanation. Arrows denote the movement of the electrons, and also the transformation of the substrate to the intermediate or product.

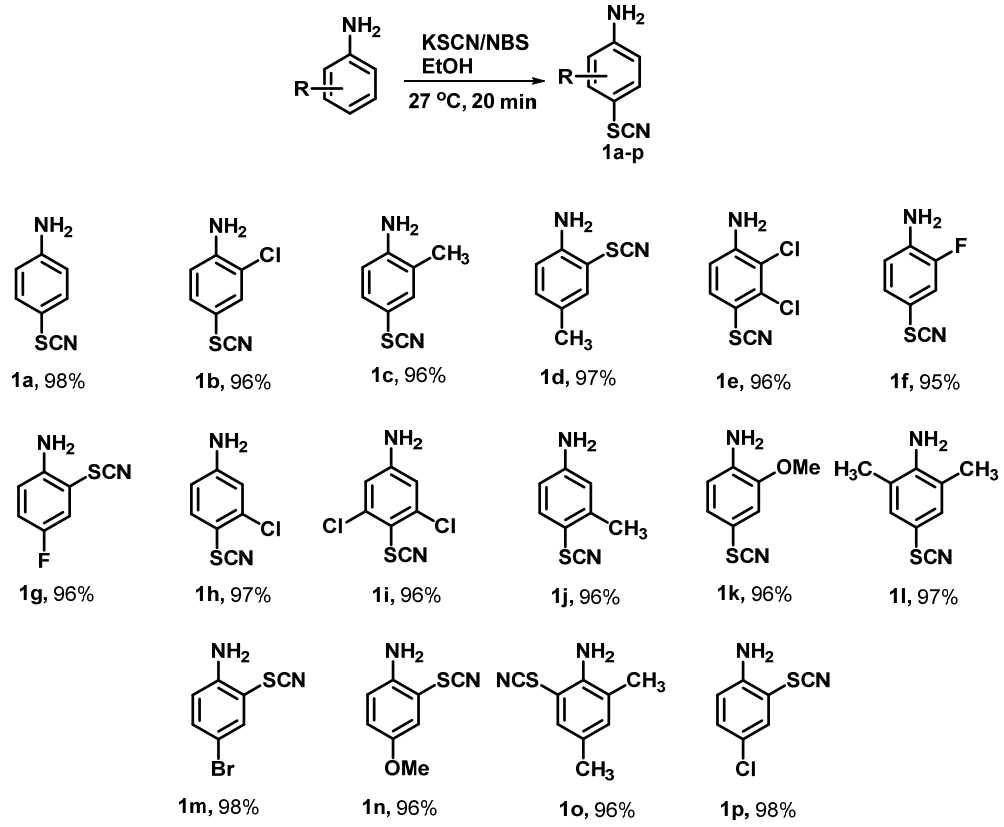


Figure 3. Synthesized substituted thiocyanatoanilines.

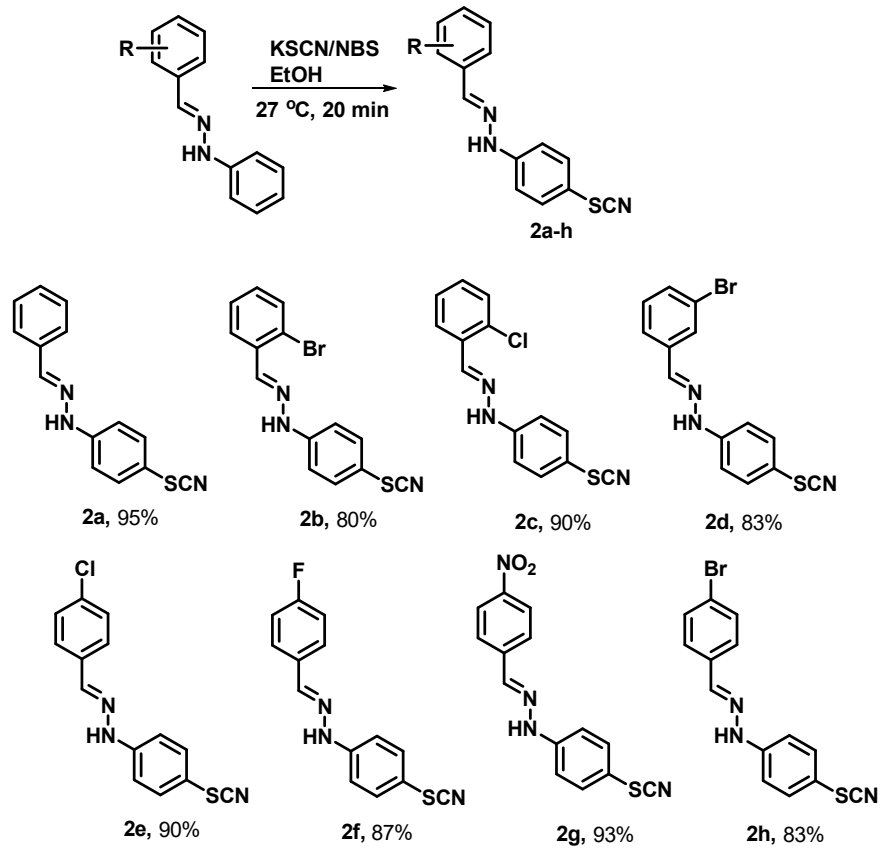


Figure 4. Synthesized 1-(substituted benzylidene)-2-(thiocyanatophenyl)hydrazines.

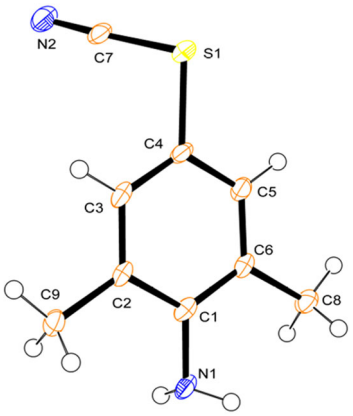


Figure 5. ORTEP view of the molecule **1l** with atomic labelling (thermal ellipsoids drawn at 50% probability).

Based on the thiocyanation experiments on 1-(substituted benzylidene)-2-(phenyl) hydrazines (Ar-CH=N-NH-Ph), it was obvious that though the substrate has two aryl rings that could undergo thiocyanation, the reaction happens only on the phenyl ring attached to the -NH group. The reason could be attributed to the electron-donating ability of the -NH group, which increases the electron density on the phenyl ring and therefore makes it highly nucleophilic to undergo an electrophilic substitution reaction. In comparison, the aryl ring of the imine is a poorer nucleophile and therefore hesitant to attack the electrophile.

4. Conclusions

In conclusion, we report an efficient, eco-friendly, and experimentally simple method for the selective thiocyanation of substituted anilines and 1-(substituted benzylidene)-2-

phenylhydrazines. The protocol, employing NBS and KSCN at room temperature (27 °C), has demonstrated excellent yields across all derivatives, highlighting its practicality and effectiveness. The environment-friendly nature of the protocol for thiocyanation opens up avenues for diverse applications in medicinal chemistry and related fields. The present findings would not only advance the methodology of selective thiocyanation but also pave the way for the development of novel compounds, offering exciting prospects for future research and practical applications.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/chemistry6030027/s1, Figures S1–S91: ^{1}H and ^{13}C NMR spectra, high-resolution mass spectra of all the synthesized compounds along with IR Spectra of representative compounds, and X-ray diffraction analysis of compound **1l** can be found in the Electronic Supplementary Content of this article. Table S1: Crystal data and refinement parameters for compound **1l**. Table S2: Non-bonded interactions and possible hydrogen bonds (Å, °) for compound **1** (D-donor; A-acceptor; H-hydrogen).

Author Contributions: A.M.M.M., Experiments; G.K., Compilation; K.S., Reviewing; V.D.R., Analysis; V.A.N., Conceptualization. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The original contributions presented in the study are included in the article/Supplementary Materials, further inquiries can be directed to the corresponding author/s.

Conflicts of Interest: The authors declare no conflicts of interest, either of a financial or personal nature.

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