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Syntheses and reactivity of alkyl 1-[*N*-(2-chloro-5-nitro-phenyl)-benzimidoyl] thioureas†

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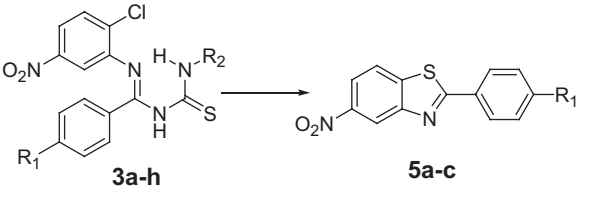
A series of new alkyl 1-[*N*-(2-chloro-5-nitro-phenyl)-benzimidoyl] thioureas **3a**–**h** were prepared from benzamides **1a**–**c**. Benzimidoyl thioureas **3a**–**e** afforded 5-nitro-2-phenyl-benzothiazole **5a**–**c** under basic conditions via thiourea–isothiourea rearrangement and S_NAr. A mechanistic rationalization supported by the direct formation of benzothioamide **8** and bis-benzimidoyl sulfide **9** derivatives from the reaction of imidoyl isothiocyanate **2** with bulky amines was supported.



Keywords: thiourea–isothiourea rearrangement; S_NAr reaction; benzimidoyl thiourea; benzothiazole

1. Introduction

Several heterocyclic thioureas have been reported as a new class of potent non-nucleoside inhibitors of human immunodeficiency virus type 1 reverse transcriptase (NNRTIs) such as phenethylthiazolyl-thiourea derivatives (*1–4*).

Thiourea is an important building block of a number of heterocycles such as pyrimidines (*5*), pyridines (*6*) and thiazoles (*7, 8*). Compounds containing the benzothiazole nucleus belong to an important class of heterocycles which are known to possess important pharmaceutical antitumor (*9, 10*) and anticancer activities (*11–13*). A variety of methods for the syntheses of

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†Dedicated to Professor El-Said Ismail Faculty of Science, Suez Canal University, for his 65th birthday

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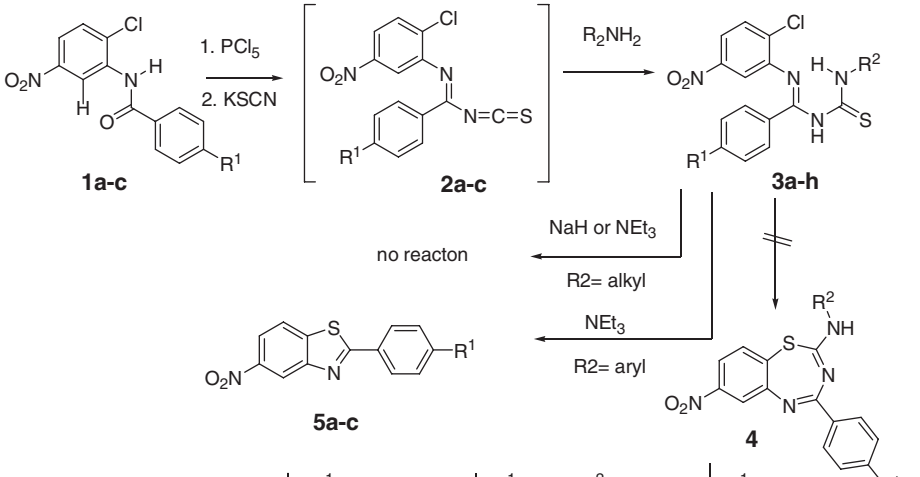
2-arylbenzothiazoles have been developed (*14–16*). The most common methods for syntheses involve direct condensation of aldehydes with 2-aminothiophenol in the presence of various catalysts or the oxidation of thiobenzanilides (*17*). Recently, we have explored the reactivity of *N*-(2-cyanophenyl)benzimidoyl isothiocyanate with primary amines, secondary amines, anilines, amino heterocycles and amino acids. These studies have led to a number of interesting quinazoline derivatives (*18–23*). The formation of these compounds was tentatively explained by a multi-step domino reaction.

2. Results and discussion

In view of these facts, we have found it desirable to synthesize a series of alkyl 1-[*N*-(2-chloro-5-nitro-phenyl)-benzimidoyl] thioureas **3** containing alkyl or aryl substituents and to induce *S*-chemoselective intramolecular nucleophilic aromatic substitution to afford benzothiadiazepine derivatives **4** (Scheme 1) (*24*). The very reactive starting compound **3** was successfully prepared from *N*-(2-chloro-5-nitro-phenyl)-benzamide (**1**) in a *one-pot* strategy. The amide **1** was transformed by the action of phosphorous pentachloride into benzimidoyl chloride that subsequently reacted with potassium thiocyanate to give *N*-(2-chloro-5-nitro-phenyl)-benzimidoyl isothio-cyanate (**2**). The isothiocyanate **2** was used without further isolation or purification (to avoid polymerization and destruction of this very reactive compound). The *in situ*-generated imidoyl isothiocyanate **2** reacted with one equivalent of amines and anilines in *one-pot* strategy to furnish the desired benzimidoyl thioureas **3** in very good yields. We further explored the possibility of intramolecular cyclization under basic conditions to benzothiadiazepine derivative **4**. Heating benzimidoyl thiourea **3a**–**c** (R=Ar) in DMF in the presence of triethyl amine gave 5-nitro-2-phenyl-benzothiazole **5**a instead. The use of benzimidoyl thiourea **3a**–**c** (R=Ar) with an aromatic side chain proved to be mandatory since employment of benzimidoyl thiourea **3f**–**h**



1, 2, 5	R^1
a	H
b	CH_3
c	Cl

3	R^1	R^2	3	R^1	R^2
a	H	$C_6H_5^-$	e	Cl	C_6H_5
b	H	$4\text{-}CH_3C_6H_4^-$	f	H	$C_6H_5CH_2^-$
c	H	$4\text{-}CH_3OC_6H_4^-$	g	H	$CH_3(CH_2)_3^-$
d	CH_3	$C_6H_5^-$	h	H	$(CH_3)_2CHCH_2^-$

Scheme 1. Sequential syntheses of benzothiazole **5a–c** from the corresponding benzamide **1a–c**.

with aliphatic side chain gave no reaction or poor yields. Consequently, we used this new method to synthesize benzothiazole **5a–c** from the corresponding benzamide **1a–c** (R^1 = H, CH_3, Cl) (*25*, *26*). The synthetic procedures for the formation of **3a-h** and **5a–c** reported herein have the advantage of *one-pot* synthesis in addition to operational simplicity and availability giving a series of very interesting compounds with promising biological activities.

The structures of compounds **3a–h** were assigned by ^{1}H NMR, ^{13}C NMR and mass spectral data. The mass spectrum of **3b** displayed its molecular ion peak at $m/z = 424$. The ^{1}H-NMR spectrum of **3b** in $CDCl_3$ showed three singlets for CH_3 ($\delta = 2.36$ ppm) and NH ($\delta = 13.35$ and 8.21 ppm) groups along with multiplets for the aromatic protons. The significant downfield shifts of the NH protons are due to intra- and intermolecular hydrogen bond interactions (*18–20, 27*). All the isolated thioureas **3a–h** exhibited similar ^{1}H NMR spectral pattern with the NH protons at similar chemical shifts and they adopt a rather interesting folded conformation (vide infra). The ^{13}C NMR spectrum of **3b** reveals carbon signals at $\delta = 178.49$ and 21.31 ppm assigned to C=S and CH_3 groups, respectively.

A single-crystal X-ray diffraction study confirmed the identities of compounds **3a–h**. ORTEP diagrams of **3g** and **3h** are shown in Figures 1 and 3, respectively. The hydrogen bond interactions and the folded conformation of benzimidoyl thiourea derivatives alluded to above are also evident from an examination of these X-ray crystal structures shown in Figures 1 and 2.

The crystallographic analysis of **3g** suggests that the crystal packing is determined by N–H. . .N=C and N–H. . .S=C interactions. These intra- and intermolecular hydrogen bond interactions show a bond distance of 2.01 and 2.67 Å, respectively (Figures 1–4 and Appendix 1).

The structures of compounds **5a–c** were assigned by ^{1}H NMR, ^{13}C NMR and physicochemical analysis. Thus, the ^{1}H NMR spectrum of **5a** exhibited signals at δ 8.90, 8.26, 8.19–8.09, 8.00 and 7.55–7.39 ppm, respectively, due to aromatic protons. The ^{13}C NMR spectrum of **5a** exhibited quaternary carbon signals at 171.76, 154.21, 147.27, 141.85 and 132.92, respectively. The structural assignment of 5-nitro-2-phenyl-benzothiazole (**5a**) was corroborated by X-ray crystallographic analysis. The molecular structure and labeling scheme used for **5a** are shown in Figure 5. The structure of **5a** shows that the phenyl ring bonded at C2 is almost coplanar with the C_2–N_3

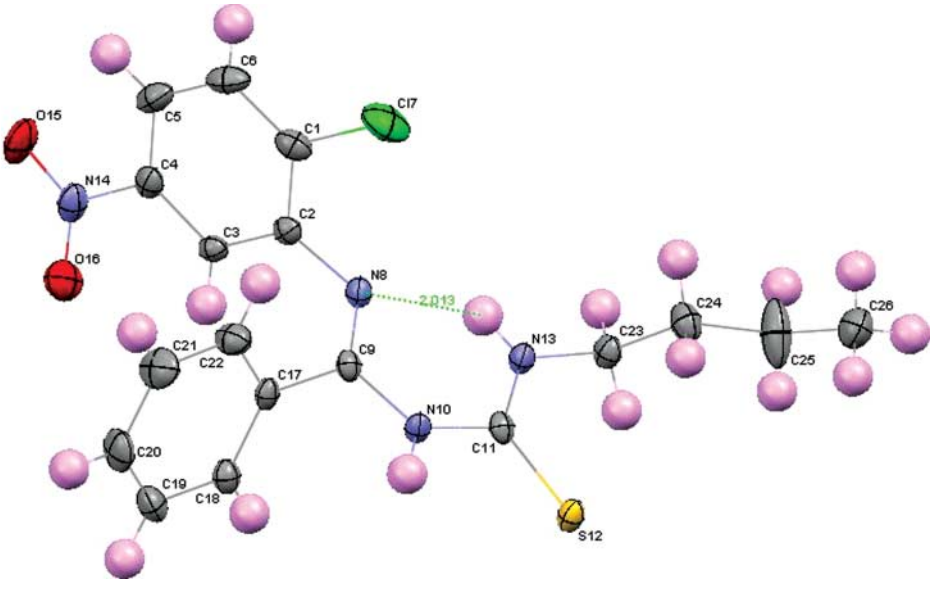


Figure 1. ORTEP plot of **3g** from the X-ray crystal structure.

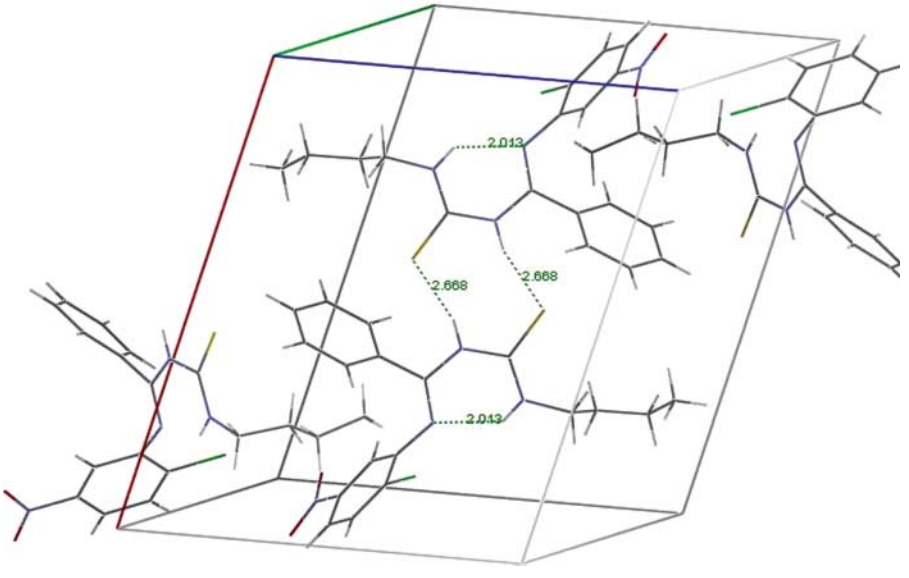


Figure 2. ORTEP plot of **3h** from the X-ray crystal structure.

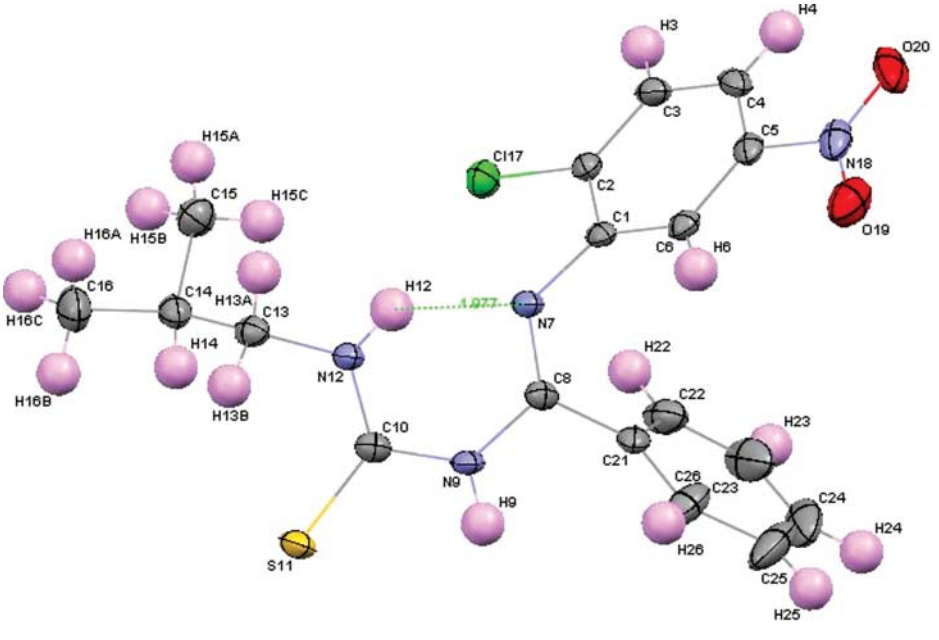


Figure 3. ORTEP plot of **5a** from the X-ray crystal structure.

bond as verified by torsion angle values and the crystal packing pattern (Appendix 1, Table 12 and Figures 6 and 7).

The reaction of *N*-(2-chloro-5-nitro-phenyl)-benzimidoyl isothiocyanate (**2**) with bulk amines: *tert*-butyl amine, *iso*-propyl amine, *sec*-butyl amine and cyclohexyl amine were principally expected to give the thioureas **3**. We found now that the reaction of isothiocyanate **2** with the above-mentioned nucleophiles gave different products, *i.e.* thioamide **8** (NH_2R^2 = *iso*-propyl

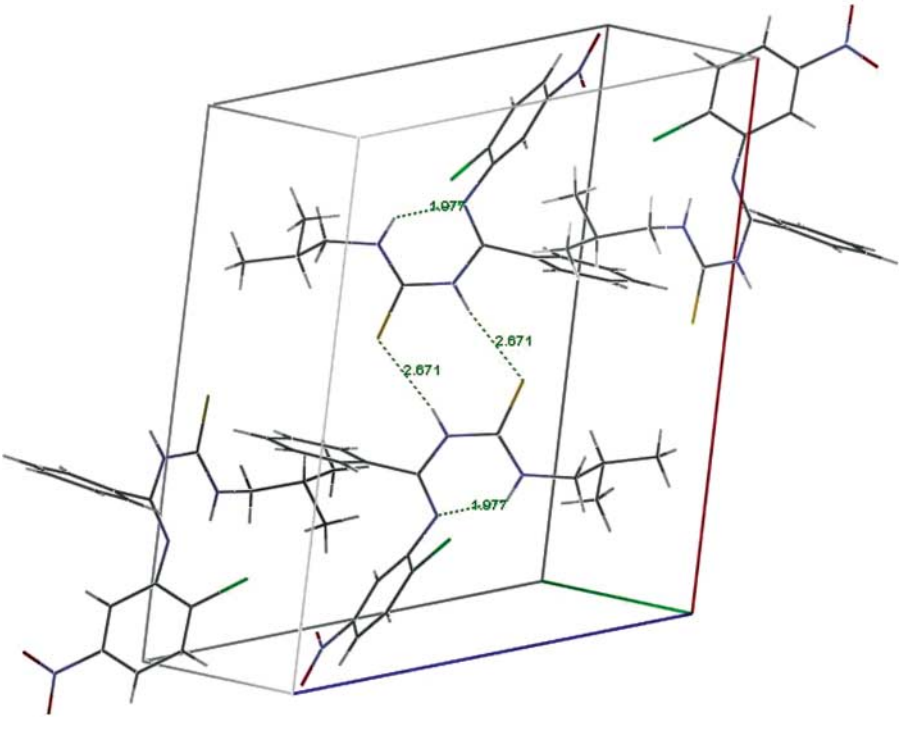


Figure 4. ORTEP plot of **9** from the X-ray crystal structure.

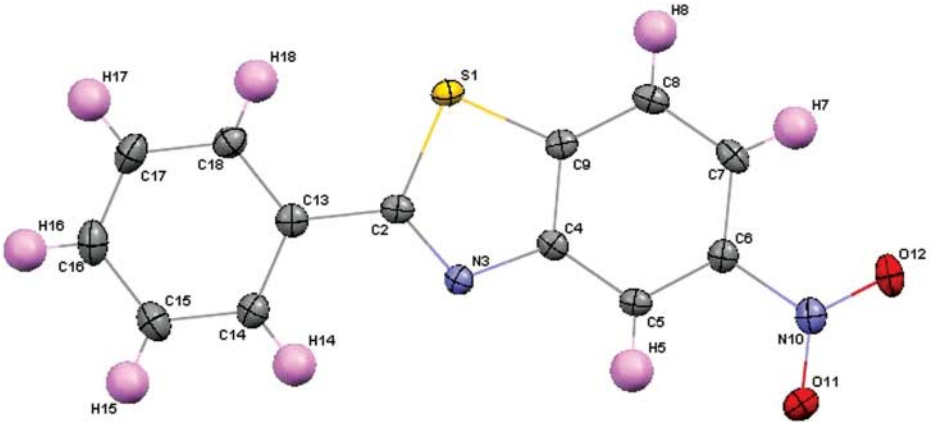


Figure 5. ORTEP plot of **5a** from the X-ray crystal structure.

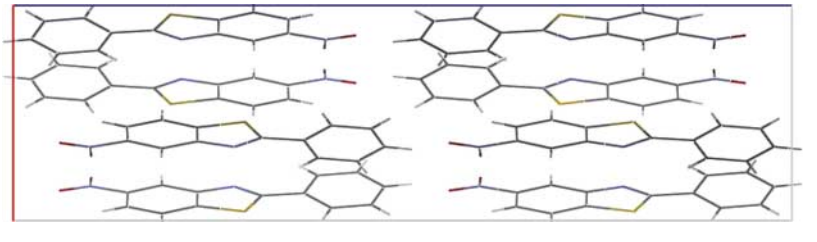


Figure 6. Packing diagram pattern of **5a**.

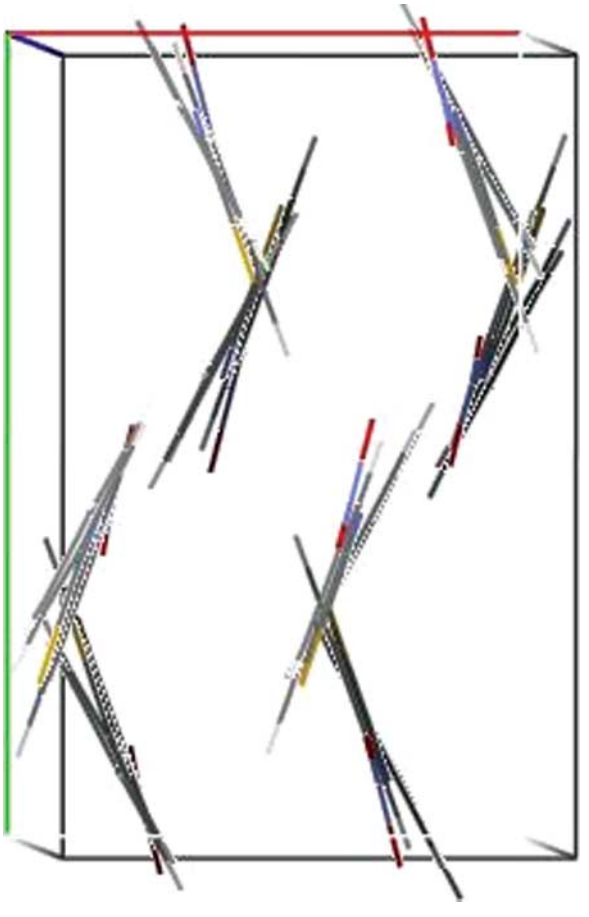


Figure 7. Packing diagram pattern of **5a**.

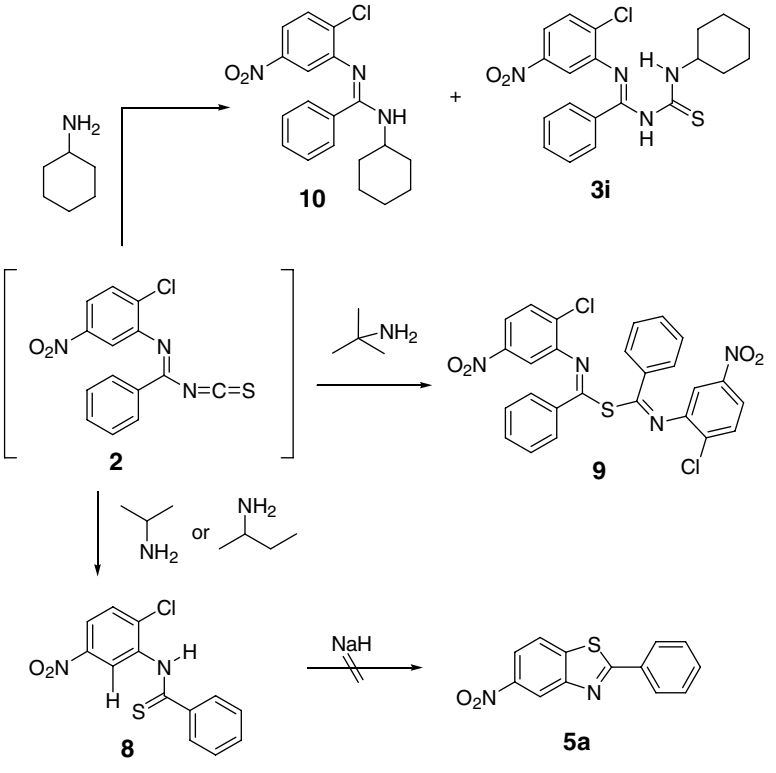
amine or *sec*-butyl amine), bis benzimidoyl sulfide **9** (NH_2R^2 = *tert*-butyl amine), benzamidine **10** and the expected thiourea **3i** (NH_2R^2 = cyclohexyl amine) by different reaction pathways (Scheme 2). The attempted intramolecular cyclization of thioamide **8** in the presence of NaH failed to give the benzothiazole **5**.

The structure of compound **8** was assigned by ^{1}H NMR, ^{13}C NMR and physicochemical analysis. The ^{1}H NMR spectrum of **8** exhibited an aromatic proton at at δ 9.51 ppm attributed to proton H6 of the phenyl ring, which implies an anisotropy caused by the adjacent thiocarbonyl group (*28*, *29*). The ^{1}H NMR spectrum of **8** also shows an exchangeable signal at δ 8.54 ppm corresponding to the NH group.

The ^{1}H and ^{13}C NMR spectra of **9**, **3i** and **10** showed distinct resonances in agreement with the proposed structure as expressed in the experiment part. The structural assignment of **9** was corroborated by X-ray crystallographic analysis. An ORTEP diagram and packing diagram pattern of **9** are shown in Figures 8–10, respectively.

A mechanistic rationalization for the benzimidoyl thiourea reactivity and the resulting rearrangement is given in Scheme 3.

A first step: N3-deprotonation of the thiourea **3** and the subsequent sulfur attack at the electrophilic imidoyl carbon atom afforded the four-membered ring intermediate **11** (*30*). The intramolecular hydrogen atom transfer in the first step provides a rationale for why R^2 must



Scheme 2. Reaction of *N*-(2-chloro-5-nitro-phenyl)-benzimidoyl isothiocyanate (**2**) with bulk amines.

be aromatic not aliphatic. The hydrogen atom migration together with the four-membered ring opening afforded the isothiourea intermediate **12**. Thioureas are normally characterized by a high reluctance to undergo alterations to isothioureas (*24, 31, 32*). This thiourea–isothiourea conversion is promoted by a remarkable electrophilic activity at the imidoyl carbon atom induced by the electron-withdrawing groups on the aromatic ring. In the next step, a base-assisted deprotonation of another proton from N3 followed by sulfur–carbon bond rupture gives the intermediate **13**. Finally, sulfur attack at the C–Cl bond via S_NAr reaction gives the product **5** (Scheme 3).

The reaction of benzimidoyl isothiocyanate **2** with bulk amines gave good evidence for our rational mechanism by tracking the reaction intermediates. The reaction of *N*-(2-chloro-5-nitro-phenyl)-benzimidoyl isothiocyanate (**2**) with bulk amines were principally expected to give the thioureas **3**, which subsequently was converted to intermediate **11**. The formation of the four-membered ring intermediate **11** provides an excellent branching point for the formation of all products. Its conceivable that as the size of R^2 gets larger (NH_2R^2 = *iso*-propyl amine or *sec*-butyl amine), it promotes the $-[2+2]$ reaction to give the thioamide derivative **8** as an alternative reaction pathway. This happens to reduce the steric interactions between R^2 and either the NH or S atom on **11** (*30*).

Thioamide **8** is capable of nucleophilic attack at the imidoyl carbon of isothiourea **12**. This result was obtained by the reaction of benzimidoyl isothiocyanate **2** with *tert*-butyl amine. Similarly, cyclohexyl amine reacted with intermediate **12** to afford benzamidine **10**.

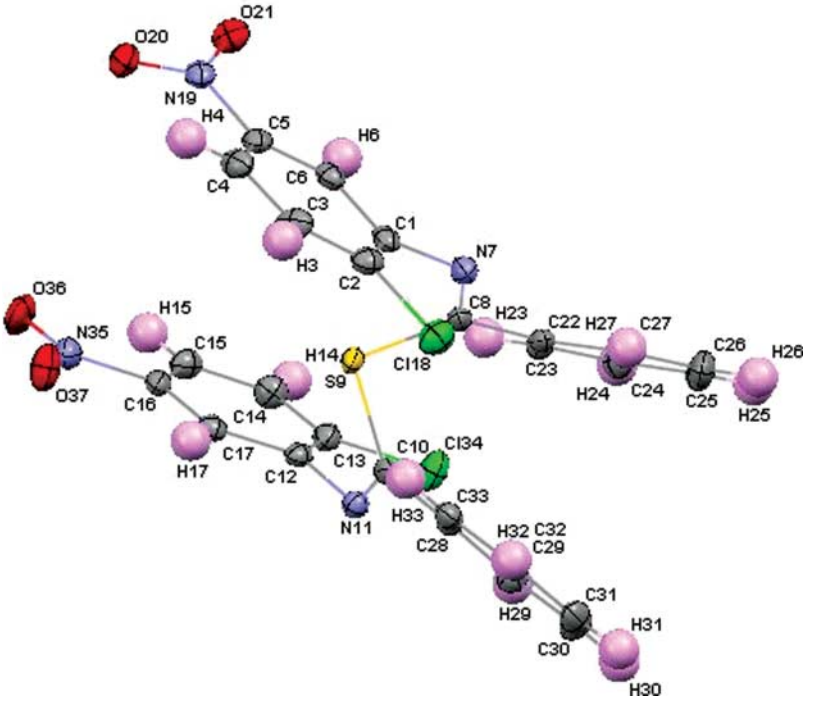


Figure 8. ORTEP plot of **5a** from the X-ray crystal structure **9**.

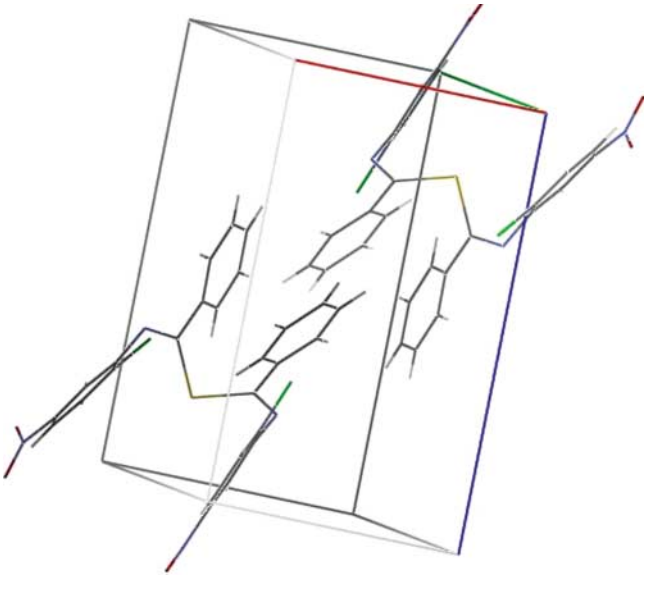


Figure 9. Packing diagram pattern of **9**.

3. Conclusion

We reported herein the formation and reactivity of a series of benzimidoyl thiourea derivatives. Benzimidoyl thioureas **3** were prepared by the reaction of *N*-(2-chloro-5-nitro-phenyl)-benzimidoyl isothiocyanate with amines and anilines. Moreover, we have presented a facile novel

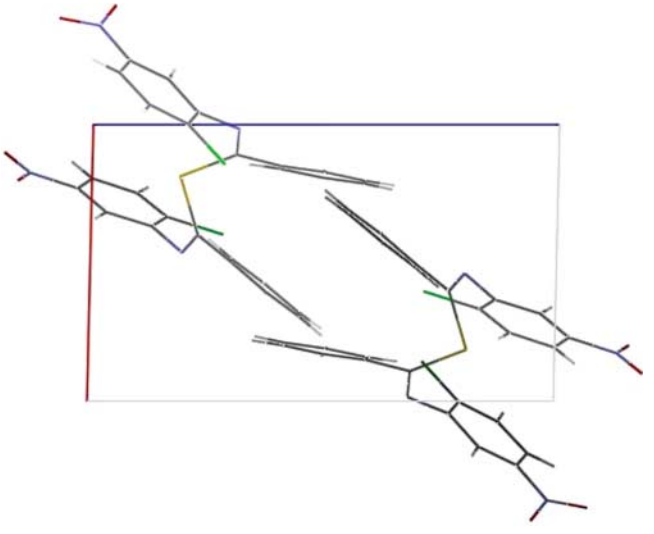
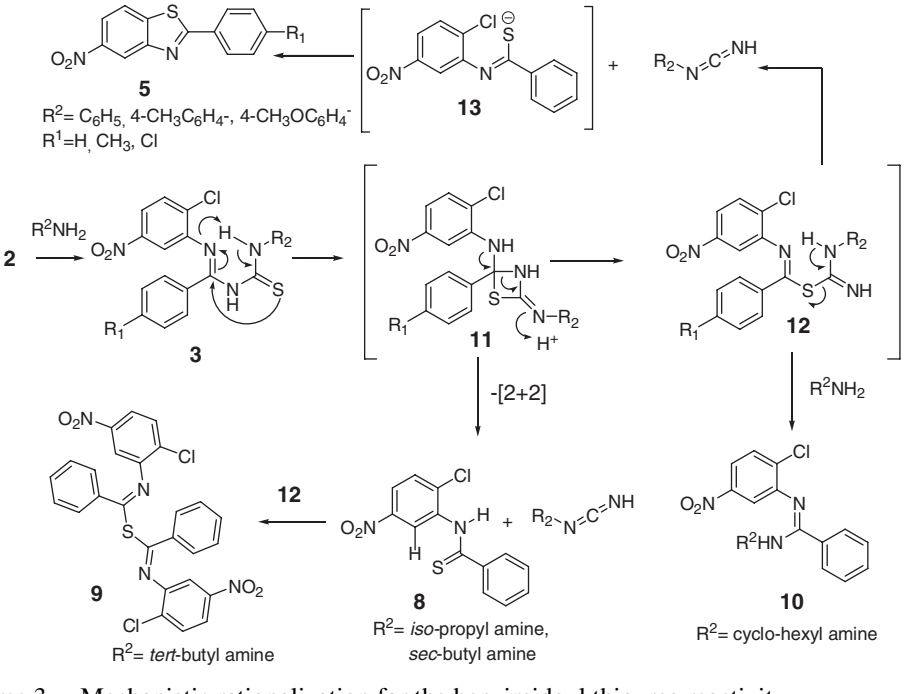


Figure 10. Packing diagram pattern of **9**.



Scheme 3. Mechanistic rationalization for the benzimidoyl thiourea reactivity.

route for the formation of benzothiazole by heating benzimidoyl thiourea derivatives containing an aryl substituent under basic conditions. Benzothiazole was formed due to the capability of benzimidoyl thiourea to rearrange and subsequent intramolecular cyclization via nucleophilic aromatic substitution reaction.

4. Experimental

4.1. *General procedures*

Solvent were purified and dried in the usual way. The boiling range of the petroleum ether used was 40–60°C. Analysis of the reaction mixtures and purity control of the products were carried out by TLC on Silufole UV-254. Elemental analyses were performed on a *Flash EA-1112* instrument at the Microanalytical Laboratory, Faculty of Science, Suez Canal University, Ismailia, Egypt. Melting points were determined on a Buchi 510 melting-point apparatus and the values are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively (DRX 500 Avance Bruker) in $CDCl_3$ solution with tetramethylsilane as an internal standard. X-ray crystal data and structure refinement of compounds **3g**, **3h**, **5a** and **9** were collected with a KUMA KM-4 kappa four-circle diffractometer. The structure was solved by direct methods using SHELXS86 (*33*) and refined on $F2$ for all reflections using SHELXl93 (*34*). Crystals suitable for X-ray determination were obtained in the form of white prisms by recrystallization from $CHCl_3$/petroleum ether at room temperature. The crystallographic data for **3g**, **3h**, **5a** and **9** have been deposited with the Cambridge Crystallographic Data Center as supplementary publications number CCDC 815032-815034 and 815036. The molecular structure, bond lengths, angles, packing diagrams and crystal structure refinement data can be found in Supplementary data, Appendix 1. Mass spectra were determined (electron impact, 70 eV) with a Fisons TRIO 1000 and GC 8000 series instrument.

The starting compounds **1** were prepared according to the described methods (*35*).

4.2. *Synthesis of N-(2-chloro-5-nitro-phenyl)-benzimidoyl isothiocyanate (2)*

A mixture of *N*-(2-chloro-5-nitro-phenyl)-benzamide (**1**) (0.5 g, 2.25 mmol) and phosphorous pentachloride (0.5 g, 2.4 mmol) was refluxed in dry toluene for 8 h. The solvent was removed under reduced pressure to give a brownish colored oil of *N*-(2-chloro-5-nitro-phenyl)-benzimidoyl chloride which was not further purified. To a solution of this crude oil in dry acetone, a solution of potassium thiocyanate (0.22 g, 2.25 mmol) in dry acetone was added portion-wise with stirring and cooling at −5°C for 2 h. The precipitated potassium chloride was filtered off, thus leaving an acetone solution of *N*-(2-chloro-5-nitro-phenyl)-benzimidoyl isothiocyanate (**2**).

4.3. *General procedure for the synthesis of alkyl 1-[N-(2-chloro-5-nitro-phenyl)-3-benzimidoyl] thioureas 3*

The appropriate aromatic and non-bulky aliphatic primary amine (2.25 mmol) solution in acetone was added portion-wise to an *in situ*-generated benzimidoyl isothiocyanate (**2**, 2.25 mmol) solution in acetone. The reaction mixture was stirred at room temperature for 24 h. The precipitated benzimidoyl thiourea **3** was filtered off and recrystallized from ethyl alcohol. Spectral data are given below.

4.3.1. *1-[N-(2-Chloro-5-nitro-phenyl)-benzimidoyl]-3-phenyl thiourea (**3a**)*

From aniline and **1a**. Colorless crystals (0.62 g, 67%); mp 155–156°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.44 (1H, s, N-H), 8.31 (1H, s, N-H), 7.69–7.85 (1H, m, Ar-H), 7.78–7.61 (3H, m, Ar-H), 7.45–7.33 (8H, m, Ar-H), 7.16–7.04 (1H, m, Ar-H). ^{13}C-NMR ($CDCl_3$): δ 178.56 (C9S), 159.18 (C_q), 156.07 (C_q), 144..39 (C_q) , 138.15 (C_q), 135.81 (C_q), 131.85 (CHAr), 131.67 (C_q), 134.78 (CHAr), 129.59 (CHAr), 129.14 (CHAr), 127.51 (CHAr), 124.35 (CHAr), 121.16 (CHAr), 120.31 (CHAr). Anal. Calcd. For $C_{20}H_{15}ClN_4O_2S$ (410.9): C, 58.46; H, 3.68, Cl, 8.63, N, 13.64, S, 7.80; Found: C, 58.39; H, 3.61, N, 13.57.

4.3.2. *1-[N-(2-Chloro-5-nitro-phenyl)-benzimidoyl] 3-(4-methyl phenyl) thiourea (**3b**)*

From *p*-toluidine and **1a**. Colorless crystals (0.79 g, 83%); mp 170–171°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.35 (1H, s, N-H), 8.21 (1H, s, N-H), 7.71 (1H, d, $J = 8.0$ Hz, Ar-H), 7.77 (2H, d, $J = 8.0$ Hz, Ar-H), 7.51–7.18 (9H, m, Ar-H), 2.36 (3H, s, CH_3). ^{13}C-NMR ($CDCl_3$): δ 178.49 (C9S), 158.01 (C_q), 146.85 (C_q), 145.29 (C_q), 136.89 (C_q), 135.63 (C_q), 134.55 (C_q), 131.39 (CHAr), 130.54 (C_q), 129.69 (CHAr), 129.61 (CHAr), 127.56 (CHAr), 124.25 (CHAr), 119.75 (CHAr), 118.48 (CHAr), 21.31 (CH_3). MS, *m/z* (Ir/%): 427 (0.1), 424 (2), 391 (1), 317 (2), 277 (18), 276 (31), 275 (11), 261 (31), 259 (36), 240 (13), 228 (11), 219 (8), 194 (12), 166 (7), 151 (8), 152 (23), 149 (100), 121 (4), 109 (18), 104 (83), 91 (88), 77 (39), 62 (25), 51 (23). Anal. Calcd. For $C_{21}H_{17}ClN_4O_2S$ (424.9): C, 59.36; H, 4.03, Cl, 8.34, N, 13.19, S, 7.55; Found: C, 59.31; H, 4.03, N, 13.11.

4.3.3. *1-[N-(2-Chloro-5-nitro-phenyl)-benzimidoyl] 3-(4-methoxy phenyl) thiourea (**3c**)*

From *p*-anisdine and **1a**. Colorless crystals (0.73 g, 74%); mp 158–159°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.44 (1H, s, N-H), 8.32 (1H, s, N-H), 7.85 (1H, d, $J = 8.0$ Hz, Ar-H), 7.81–7.59 (4H, m, Ar-H), 7.46–7.25 (7H, m, Ar-H), 3.86 (3H, s, OCH_3). ^{13}C-NMR ($CDCl_3$): δ 178.56 (C9S), 159.47 (C_q), 156.07 (C_q), 144.39 (C_q), 138.15 (C_q), 135.81 (C_q), 134.55 (C_q), 131.85 (CHAr), 131.67 (C_q), 129.59 (CHAr), 129.14 (CHAr), 127.13 (CHAr), 124.35 (CHAr), 121.02 (CHAr), 116.56 (CHAr), 114.48 (CHAr), 55.75 (OCH_3). Anal. Calcd. For $C_{21}H_{17}ClN_4O_3S$ (440.9): C, 57.21; H, 3.89, Cl, 8.04, N, 12.71, S, 7.27; Found: C, 57.09; H, 3.74, N, 12.48.

4.3.4. *3-Phenyl-1-[N-(2-chloro-5-nitro-phenyl)-4-methylbenzimidoyl] thiourea (**3d**)*

From aniline and **1b**. Colorless crystals (0.58g, 61%); mp 176–177°C. δ 13.24 (1H, s, N-H), 8.22 (1H, s, N-H), 7.79 (1H, d, $J = 8.0$ Hz, Ar-H), 7.63–6.99 (11H, m, Ar-H), 2.29 (3H, s, CH_3). ^{13}C-NMR ($CDCl_3$): δ 178.59 (C=S), 159.47 (C_q), 156.07 (C_q), 145.31 (C_q), 136.97 (C_q), 135.89 (C_q), 134.55 (C_q), 131.81 (CHAr), 129.70 (C_q), 129.34 (CHAr), 129.66 (CHAr), 127.51 (CHAr), 124.22 (CHAr), 119.35 (CHAr), 116.99 (CHAr), 21.38 (CH_3). Anal. Calcd. For $C_{21}H_{17}ClN_4O_2S$ (424.9): C, 59.36; H, 4.03; Cl, 8.34; N, 13.19; S, 7.55; Found: C, 59.16; H, 3.84; N, 12.88.

4.3.5. *3-Phenyl-1-[N-(2-chloro-5-nitro-phenyl)-4-chlorobenzimidoyl] thiourea (**3e**)*

From aniline and **1c**. Colorless crystals (0.72 g, 72%); mp 184–185°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.59 (1H, s, N-H), 8.29 (1H, s, N-H), 7.79 (1H, d, $J = 8.0$ Hz, Ar-H), 7.57–7.45 (4H, d, $J = 8.0$ Hz, Ar-H), 7.38–7.08 (7H, m, Ar-H). ^{13}C-NMR ($CDCl_3$): δ 179.09 (C9S), 159.12 (C_q), 146.85 (C_q), 145.13 (C_q), 137.22 (C_q), 135.91 (C_q), 131.39 (CHAr), 130.58 (C_q), 130.31 (C_q), 129.69 (CHAr), 129.23 (CHAr), 127.84 (CHAr), 125.84 (CHAr), 119.75 (CHAr), 117.98 (CHAr). Anal. Calcd. For $C_{20}H_{14}Cl_2N_4O_2S$ (445.3): C, 53.94; H, 3.17; Cl, 15.92; N, 12.58; S, 7.20; Found C, 53.63; H, 2.82; N, 12.11.

4.3.6. *3-Benzyl-1-[N-(2-chloro-5-nitro-phenyl)-benzimidoyl] thiourea (**3f**)*

From benzyl amine and **1a**. Colorless crystals (0.82 g, 86%); mp 215–216°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.53 (1H, s, N–H), 8.33 (1H, s, N–H), 7.74 (1H, d, $J = 8.0$ Hz, Ar–H), 7.45–7.23 (12H, m, Ar–H), 4.97 (2H, d, $J = 4.8$ Hz, CH_2). ^{13}C-NMR ($CDCl_3$): δ 180.20 (C9S), 157.89 (C_q), 146.64 (C_q), 145.40 (C_q), 136.57 (C_q), 134.42 (C_q), 134.55 (C_q), 131.69 (CHAr), 131.29 (C_q), 130.39 (CHAr), 129.47 (CHAr), 128.70 (CHAr), 119.54 (CHAr), 118.36 (CHAr), 50.18

(CH_2). Anal. Calcd. For $C_{21}H_{17}ClN_4O_2S$ (424.9): C, 59.36; H, 4.03; Cl, 8.34; N, 13.19; S, 7.55; Found: C, 59.21; H, 3.97; N, 13.01.

4.3.7. *3-Butyl-1-[N-(2-chloro-5-nitro-phenyl)-benzimidoyl] thiourea (**3g**)*

From *n*-butyl amine and **1a**. Colorless crystals (0.38 g, 43%); mp 182–183°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.43 (1H, s, N-H), 8.12 (1H, s, N-H), 7.47 (1H, d, *J*=8.0 Hz, Ar-H), 7.40–7.16 (7H, m, Ar-H), 3.65 (2H, q, $J = 6.7$ Hz, CH_2), 1.68–1.54 (2H, m, CH_2), 1.42–1.31 (2H, m, CH_2), 0.91 (3H, t, $J = 6.7$ Hz, CH_3). ^{13}C-NMR ($CDCl_3$): δ 179.77 (C9S), 157.89 (C_q), 146.78 (C_q), 145.64 (C_q), 136.57 (C_q), 134.30 (C_q), 134.55 (C_q), 131.59 (CHAr), 131.45 (C_q), 130.39 (CHAr), 129.69 (CHAr), 128.68 (CHAr), 119.44 (CHAr), 118.35 (CHAr), 45.99 (CH_2), 30.46 (CH_2) 20.36 (CH_2) 13.84 (CH_3). Anal. Calcd. For $C_{18}H_{19}ClN_4O_2S$ (390.9): C, 55.31; H, 4.90; Cl, 9.07; N, 14.33; S, 8.20; Found: C, 55.13; H, 4.87; N, 14.26.

4.3.8. *3-Isobutyl 1-[N-(2-chloro-5-nitro-phenyl)-benzimidoyl] thiourea (**3h**)*

From *iso*-butyl amine and **1a**. Colorless crystals (0.50 g, 57%); mp 158–159°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.56 (1H, s, N-H), 8.20 (1H, s, N-H), 7.76 (1H, d, $J = 8.0$ Hz, Ar-H), 7.40–7.16 (7H, m, Ar-H), 3.75 (2H, q, $J = 6.6$ Hz, CH_2), 2.14–2.02 (1H, m, CH), 1.03 (6H, t, $J = 6.7$ Hz, $2CH_3$). ^{13}C-NMR ($CDCl_3$): δ 179.98 (C9S), 157.85 (C_q), 146.63 (C_q), 145.64 (C_q), 136.55 (C_q), 134.55 (C_q), 131.79 (CHAr), 131.45 (C_q), 130.41 (CHAr), 129.69 (CHAr), 128.68 (CHAr), 119.94 (CHAr), 118.45 (CHAr), 53.88 (CH_2), 28.16 (CH), 19.75 (CH_3). Anal. Calcd. For $C_{18}H_{19}ClN_4O_2S$ (390.9): C, 55.31; H, 4.90; Cl, 9.07; N, 14.33; S, 8.20; Found: C, 55.28; H, 4.81; N, 14.27.

4.4. *Preparation of 5-nitro-2-aryl-benzothiazole*

A mixture of the appropriate aryl 1-[*N*-(2-chloro-5-nitro-phenyl)-benzimidoyl] thioureas **3** (2.25 mmol) and triethyl amine (2.50 mmol) was refluxed in dry DMF for 4 h. The reaction mixture was evaporated and poured over cold water, extracted with CH_2Cl_2 and washed with $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered evaporated and the residue was crystallized from ethanol.

4.4.1. *5-Nitro-2-phenyl-benzothiazole (**5a**)*

From **3a**. Colorless crystals (0.49 g, 86%); mp 201–202°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.90 (1H, s, Ar-H), 8.26 (1H, d, $J = 8.0$ Hz, Ar-H), 8.19–8.09 (2H, m, Ar-H), 8.00 (1H, d, $J = 8.0$ Hz, Ar-H), 7.55–7.39 (3H, m, Ar-H). ^{13}C-NMR ($CDCl_3$): δ 171.76 (C_q), 154.21 (C_q), 147.27 (C_q), 141.85 (C_q), 132.92 (C_q), 132.22 (CHAr), 129.49 (CHAr), 128.06 (CHAr), 122.21 (CHAr), 119.85 (CHAr), 118.82 (CHAr). Anal. Calcd. For $C_{13}H_8N_2O_2S$ (256.3): C, 60.93; H, 3.15; N, 10.93; S, 12.51 Found: C, 60.84; H, 3.01; N, 10.78.

From **3b**. Colorless crystals (0.40 g, 69%).

From **3c**. Colorless crystals (0.36 g, 64%).

4.4.2. *5-Nitro-2-(4-methylphenyl)-benzothiazole (**5b**)*

From **3d**. Colorless crystals (0.38 g, 62%); mp 185–186°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.78 (1H, s, Ar-H), 8.23 (1H, d, *J*=8.0 Hz, Ar-H), 8.19–8.97 (5H, m, Ar-H), 2.48 (3H, s, CH_3). ^{13}C-NMR ($CDCl_3$): δ 169.87 (C_q), 154.38 (C_q), 146.13 (C_q), 141.84 (C_q), 132.31 (CHAr), 131.48

(C_q), 129.49 (CHAr), 127.21 (CHAr), 122.07 (CHAr), 119.97 (CHAr), 118.62 (CHAr), 21.43 (CH_3). Anal. Calcd. For $C_{14}H_{10}N_2O_2S$ (270.3): C, 62.21; H, 3.73; N, 10.36; S, 11.86; Found: C, 62.15; H, 3.69; N, 10.44

4.4.3. *5-Nitro-2-(4-chlorophenyl)-benzothiazole (**5c**)*

From **3e**. Colorless crystals (0.31 g, 53%); mp 213–214°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.91 (1H, s, Ar-H), 8.24 (1H, d, $J = 8.0$ Hz, Ar-H), 8.14–8.01 (5H, m, Ar-H). ^{13}C-NMR ($CDCl_3$): δ 168.45 (C_q), 154.01 (C_q), 135.85 (C_q), 132.92 (C_q), 131.22 (CHAr), 129.23 (CHAr), 127.19 (CHAr), 122.85 (CHAr), 118.97 (CHAr). Anal. Calcd. For $C_{13}H_7ClN_2O_2S$ (290.7): C, 53.71; H, 2.43; Cl, 12.19; N, 9.64; S, 11.03 Found: C, 53.65; H, 2.36; N, 9.60.

4.5. *Reaction of benzimidoyl isothiocyanate 2 with bulk primary amines*

The appropriate amine (*tert*-butyl amine, *iso*-propyl amine, *sec*-butyl amine) (2.25 mmol) solution in acetone was added portion-wise to an *in situ*-generated benzimidoyl isothiocyanate (**2**, 2.25 mmol) solution in acetone. The reaction mixture was stirred at room temperature for 24 h, poured over H_2O and extracted with CH_2Cl_2, dried over Na_2SO_4 and evaporated. The resultant residue was crystallized from ethyl alcohol.

4.6. *N-(2-Chloro-5-nitro-phenyl)-thiobenzamide (8)*

From *iso*-propyl amine. Colorless crystals (0.58 g, 88%); mp 131–132°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.51 (1H, s, Ar-H), 8.54 (1H, s, N-H), 8.03–7.92 (3H, m, Ar-H), 7.68–7.46 (4H, d, $J = 8.0$ Hz, Ar-H). ^{13}C-NMR ($CDCl_3$): δ 165.48 (C_q), 147.55 (C_q), 135.93 (C_q), 133.91 (C_q), 133.03 (CHAr), 129.74 (CHAr), 129.34 (CHAr), 129.10 (C_q), 127.38 (CHAr), 119.30 (CHAr), 116.46 (CHAr). MS, m/z (Ir/%): 294 (1), 261 (31), 259 (100), 257 (4), 215 (18), 213 (31), 210 (3), 126 (2), 121 (6), 109 (13), 105 (6), 90 (15), 77 (12), 51 (25). Anal. Calcd. For $C_{13}H_9ClN_2O_2S$ (292.7): C, 53.34; H, 3.10; Cl, 12.11; N, 9.57; S, 10.95; Found: C, 53.24; H, 2.91; N, 9.38.

From *sec*-butyl amine. 0.43 g, 65%.

4.7. *Bis-[N′-(2-chloro-5-nitrophenyl)benzimidoyl] sulfide (9)*

From *tert*-butyl amine. Colorless crystals (0.61 g, 47%); mp 135–136°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98 (2H, d, $J = 8.0$ Hz, Ar-H), 7.63–7.30 (14H, d, $J = 8.0$ Hz, Ar-H). ^{13}C-NMR ($CDCl_3$): δ 155.08 (C_q), 147.06 (C_q), 136.45 (C_q), 133.91 (C_q), 132.04 (CHAr), 130.99 (CHAr), 128.96 (CHAr), 129.56 (C_q), 128.75 (CHAr), 120.60 (CHAr), 116.09 (CHAr). Anal. Calcd. For $C_{26}H_{16}Cl_2N_4O_4S$ (551.4): C, 56.63; H, 2.92; Cl, 12.86; N, 10.16; S, 5.82; Found: C, 56.56; H, 2.84; N, 10.03.

4.8. *Reaction of benzimidoyl isothiocyanate 2 with cyclohexyl amine*

Cyclohexyl amine (2.25 mmol) solution in acetone was added portion-wise to an *in situ*-generated benzimidoyl isothiocyanate (**2**, 2.25 mmol) solution in acetone. The reaction mixture was stirred at room temperature for 24 h, poured over H_2O and extracted with CH_2Cl_2, dried over Na_2SO_4 and evaporated. The resultant residue was separated by column chromatography (ethyl acetate: petroleum ether 1:3 eluent) to give 3-cyclohexyl *N*-(2-chloro-5-nitro-phenyl)-benzimidoyl] thiourea (**3g**) and *N*-(2-chloro-5-nitro-phenyl)-*N′*-cyclohexyl-benzamidine (**10**). Spectral data are given below.

4.9. *3-Cyclohexyl 1-[N-(2-chloro-5-nitro-phenyl)-benzimidoyl] thiourea (3i)*

Colorless crystals (0.42 g, 45%); mp 168–169°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.41 (1H, s, N-H), 8.24 (1H, s, N-H), 7.48 (1H, d, $J = 8.0$ Hz, Ar-H), 7.47–7.16 (7H, m, Ar-H), 4.64–4.57 (1H, m, CH), 2.44–2.27 (2H, m, CH2), 1.91–1.71 (4H, m, 2CH2), 1.59–1.33 (4H, m, 2CH2). ^{13}C-NMR ($CDCl_3$): δ 178.34 (C9S), 157.90 (C_q), 146.82 (C_q), 145.65 (C_q), 134.47 (C_q), 133.01 (C_q), 131.65 (CHAr), 131.49 (C_q), 130.41 (CHAr), 129.52 (CHAr), 128.95 (CHAr), 127.48 (CHAr), 119.47 (CHAr), 118.41 (CHAr), 54.73 (CH), 31.86 (CH_2), 25.71 (CH_2), 24.48 (CH_2). Anal. Calcd. For $C_{20}H_{21}ClN_4O_2S$ (416.9): C, 57.62; H, 5.08; Cl, 8.50; N, 13.44; S, 7.69; Found: C, 57.45; H, 4.93; N, 13.36.

4.10. *N-(2-Chloro-5-nitro-phenyl)-N′-cyclohexyl-benzamidine (10)*

Yellowish crystals (0.41 g, 51%); mp 122–123°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (1H, d, $J = 8.0$ Hz, Ar-H), 7.66–7.45 (3H, m, Ar-H), 7.32–7.18 (4H, m, Ar-H), 4.78–4.67 (1H, m, CH), 4.01 (1H, s, N-H), 2.34–2.08 (1H, m, CH_2), 2.34–2.08 (1H, m, CH_2), 2.34–2.08 (2H, m, CH2), 1.74–1.22 (8H, m, 2CH2). ^{13}C-NMR ($CDCl_3$): δ 158.39 (C_q), 150.23 (C_q), 146.85 (C_q), 135.95 (C_q), 134.75 (C_q), 133.94 (CHAr), 130.01 (CHAr), 129.80 (CHAr), 129.36 (CHAr), 128.82 (CHAr), 119.31 (CHAr), 116.76 (CHAr), 50.61(CH), 33.24 (CH_2), 26.19 (CH_2), 25.21 (CH_2). Anal. Calcd. For $C_{19}H_{20}ClN_3O_2$ (357.8): C, 63.77; H, 5.63; Cl, 9.91; N, 11.74; Found: C, 63.68; H, 5.47; N, 11.51.

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