Transformation of amides to thioamides using efficient and novel thiating reagent

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Abstract

Convenient protocol was developed for the transformation of *N*-aryl substituted benzamides to *N*-aryl substituted benzothioamides using *N*-isopropyldithiocarbamate isopropyl ammonium salt as a novel thiating reagent. The major advantages of this protocol are *one-pot* procedure, short reaction times, mild conditions, simple work up, high yields and pure products.

Introduction

Amides and their isosteres thioamides are very important biologically active compounds. [1] Benzothioamides are used as building blocks for the preparation of various compounds specially those containing sulfur.[2–4] Many methods have been reported for the synthesis of substituted thiobenzamides from various substrates and reagents. Typically, Beckmann rearrangement was applied to prepare thioamides using ketoxime substrates in the presence of $PSCl_3$ [5], *in situ* generated Appel's salt, Mitsunobu's zwitterionic adduct [6] or in the presence of *O*,*O*-diethyl dithiophosphoric acid [7] as the dehydrating agents. Another interesting method for the introduction of thioamides is the modified Willgerodt–Kindler reaction using a three-component reactions involving aniline, aldehydes, and elemental sulfur powder in the presence of sulfated tungstate catalyst as acidic catalyst [8], Na_2S as a basic catalyst [9], Sulfonic acid functionalized nano γ-Al_2O_3 [10] or in the absence of a catalyst [11, 12]. Other method was carried out using thioacyl dithiophosphates used for thioacylation of amines to afford thioamides and water soluble ammonium monothiophosphates [13, 14]. Other methods involve the *N*-substituted amide-thioamide transformation *via* thionation reagents such as Lawesson's reagent (2,4-bis(4-ethoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide) [15] and Berzelius reagent [16] (P_4S_{10}), in dry; toluene, xylene or pyridine under reflux condition. Some of these protocols are very interesting showing high yields but still have major drawbacks harsh reaction conditions, prolonged reaction times and expensive specific reagents, ultra-dry solvents and bad smell have limited their applications. New protocol for the thioamide preparation is highly appreciable. Our group developed the heterocyclic benzamide-thioamide transformation by chlorination then reaction with *N*-cyclohexyl dithiocarbamate cyclohexyl ammonium salt in chloroform for 12 h. at 61^{o}C to afford heteocyclic thioamides in excellent yields [17–20]. As a part of our continuous efforts towards the improvement of synthetic methods we now report highly efficient protocol for the open-chain amide-thioamide transformation using two steps *one-pot* sequential reactions: first chlorination of benzanilides, second the reaction with an efficient and novel thiating reagent; *N*-isopropyldithiocarbamate isopropyl ammonium salt in acetonitrile for 1h. This reagent is prepared from simple commercial substrates; isopropyl amine and carbon disulfide.

Discussion

N-cyclohexyl dithiocarbamate cyclohexyl ammonium salt **2** proved to be an interesting thiating reagent used in the preparation of a number of heterocyclic thioamides [17–20]. The thiating reagent *N*-

cyclohexyl dithiocarbamate cyclohexyl ammonium salt **2** was simply prepared from cyclohexyl amine reaction with carbon disulfide in water at room temperature for 2h., Scheme 1. [17]

Herein, we wish to examine the application of this thiating reagent to involve open chain amide-thioamide transformation. Thus, the reaction of benzoyl chloride **3** with *p*-toluidine **4** in benzene in the presence of triethyl amine for 6h. afforded the model precursor *N*-(*p*-tolyl)benzamide (**5**). The reaction of *N*-(*p*-tolyl)benzamide (**5**) with thionyl chloride at 70 ^{o}C for 8h. gave *N*-(*p*-tolyl)benzimidoyl chloride (**6**), thionyl chloride was then evaporated under reduced pressure. The imidoyl chloride **6** was kept under reduced pressure (6.7 KPa) at 120^{o}C for 2 h. and was used in *insitu* without further purification [21–23]. Finally, the *insitu* generated acetonitrile solution of imidoyl chloride **6** was refluxed with **2** to afford a mixture of the desired compound *N*-(*p*-tolyl)benzothioamide (**7**) cyclohexylcarbamothioic-*N*-(*p*-tolyl)benzimidic thioanhydride **(8)**, Scheme 2.

This behavior is most probably due steric hindrance of cyclohexyl moiety, which tangle the cyclohexyl amine proton abstraction by the imine nitrogen atom. Consequently, out of necessity we should modify the structure of the thiating reagent. Recently, we reported an interesting method for the preparation of 2-arylquinazolin-4-amines by the reaction of *N*-(2-cyanophenyl)substituted benzimidoyl isothiocyanates with isopropyl amine through 1-isopropyl-3-(2-(4-substitutedphenyl)-quinazolin-4-yl)thiourea. [24] Due to the previous facts, we designed *N*-isopropyldithiocarbamate isopropyl ammonium salt **10** as our novel thiating reagent to solve the mentioned discrete problem. The reaction of three molar equivalents of isopropylamine **9** with one molar equivalent of carbon disulfide in ethyl acetate for 2 h. precipitated pure *N*-isopropyldithiocarbamate isopropyl ammonium salt **10** in high yield, Scheme 3. Compound **10** is hygroscopic and should be tightly packed.

Indeed, our hypothesis related to applying *N*-isopropyldithiocarbamate isopropyl ammonium salt **10** as a novel thiating reagent gave remarkable results. Thus, *N*-aryl substituted benzamides **11–13(a-e)** were prepared by the reaction of carboxylic acid chlorides with anilines as described earlier. *N*-Aryl substituted benzamides **11–13(a-e)** were chlorinated with thionyl chloride at 70 ^{o}C for 8h. and the acetonitrile solution of the *insitu* generated benzimidoyl chloride **14–16(a-e)** were treated with *N*-isopropyldithiocarbamate isopropyl ammonium salt (**10**) at room temperature for 1h. (TLC monitored). The reaction mixture was evaporated and ethanol was added to give bright yellow crystals as only isolated products identified as *N*-aryl substituted benzothioamides **17–19(a-e)**. Scheme 4.

A total number of 15 *N*-aryl substituted benzothioamides **17–19(a-e)** were obtained from *N*-aryl substituted benzamides **11–13**(**a-e**) in a *one-pot* strategy and in excellent yields. This synthetic procedure using *N*-isopropyldithiocarbamate isopropyl ammonium salt **10** as the thiating reagent beside solving all previously mentioned problems have the advantage of applying the *one-pot* strategy for the amide-thioamide transformations beside the operational simplicity, availability of substrates, reaction at room temperature and high yields in short reaction time.

A rational mechanism is described for this interesting protocol is given in Scheme 5. The reaction of *N*-(*p*-tolyl)benzamide (**11b**) with thionyl chloride principally afforded *N*-(*p*-tolyl)benzimidoyl chloride (**14b**). The *insitu* generated **14b** solution in acetonitrile reacted with *N*-isopropyldithiocarbamate isopropyl ammonium salt **(10**) to principally afford *(E)-N*-(*p*-tolyl)benzimidic thioanhydride **I** as the most stable geometric isomer. Earlier results obtained by our group concerning similar structures showed that the reaction of *N*-(2-chloro-5-nitrophenyl)benzimidoyl isothiocyanate with *tert*-butyl amine afforded principally the intermediate (*E*)-*N*-(*tert*-butyl)carbamimidic-*N*-(2-chloro-5-nitrophenyl)benzimidic thioanhydride which subsequently converted to the stable bis-[*N*-(2-chloro-5-nitrophenyl)benzimidoyl] sulfide as Z-geometric isomer (structure assignment of this compound was corroborated by X-ray crystallographic analysis). [25] The tolyl residue directly attached to the imine nitrogen pushes electrons to it which enhances hydrogen bond acceptor character for this nitrogen atom of imine. This behavior cause the nitrogen atom of the imine group able to abstract isopropyl amine NH proton and the residual electrons will attack the thiocarbonyl group with the consequent cleavage of S-C bond and finally give our desired product **17b** and isopropyl isothiocyanate, Scheme 5. A similar result was obtained by our group for the rearrangement of 2-phenylquinazolin-4-yl cyclohexylcarbamodithioate to finally produce 2-phenylquinazoline-4(3*H*)-thione in the presence or absence of a base. [17] Also, similar explanation was given by our group for the 2-arylquinazolin-4-amines from 1-isopropyl-3-(2-(4-substitutedphenyl)-quinazolin-4-yl)thiourea in the presence of isopropyl amine. [24]

Conclusion

In this work, we successfully developed a facile and convenient general method for the conversion of *N*-aryl substituted benzamide to *N*-aryl substituted benzothioamide. This protocol consists of two steps in a *one-pot* strategy: first, we transformed *N*-aryl substituted benzamide to benzimidoyl chloride derivatives by the reaction with thionyl chloride. Second, the benzimidoyl chloride reacted with *N*-isopropyldithiocarbamate isopropyl ammonium salt as a novel thiating reagent to finally produce *N*-aryl substituted benzothioamide. This method have the advantage of applying the *one-pot* strategy for the amide-thioamide transformations beside the operational simplicity, availability of substrates, reaction at room temperature and high yields in short reaction time.

Experimental

General procedures. Solvent were purified and dried by standard procedures. The boiling range of the petroleum ether used was 40–60 ^{o}C. Thin layer chromatography (TLC): silica gel 60 F_{254} plastic plates (E. Merck, layer thickness 0.2 mm) detected by UV absorption. 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 400 MHz and 100 MHz, respectively (Bruker AC 400) in $CDCl_3$ and DMSO solution with tetramethylsilane as an internal standard. The NMR analyses were performed at Faculty of Science, Sohag University.

General method for the preparation of thiating reagent N-cyclohexyl dithiocarbamate cyclohexyl ammonium salt (2).

To a mixture of freshly distilled cyclohexyl amine (60 mmol) and water (50 mL) was added carbon disulfide (21 mmol) dropwise. The reaction mixture was stirred at room temperature for 2h. The white solid obtained was filtered, washed with water, dried and crystalized from ethanol to provide pure product of cyclohexyl amine cyclohexyl ammonium dithiocarbamate provided the pure compound.

Yield 98% (ethanol 95%) white crystals, mp 188–189°C. ^{1}H NMR spectrum, (400 MHz, DMSO), δ, ppm (*J*, Hz): 8.01 (3H, bs, 3NH); 4.15–3.95 (1H, m, CH); 3.05–2.96 (1H, m, CH); 1.98–0.96 (20H, m, 10CH_2). ^{13}C NMR spectrum, (100.0 MHz, DMSO), δ, ppm: 212.4 (C = S); 55.3 (CH); 50.0 (CH); 32.3 (2CH_2); 30.9 (2CH_2); 25.8 (CH_2); 25.5 (2CH_2); 25.1 (CH_2); 24.3 (2CH_2). Found, %: C, 56.88; H, 9.55; N, 10.21. For $C_{13}H_{26}N_2S_2$ (274.2). Calculated, %: C, 56.56; H, 9.43; N, 10.09.

Preparation of cyclohexylcarbamothioic- N -(p -tolyl)benzimidic thioanhydride (**8**).

A mixture of *N*-(*p*-tolyl)benzoamide (**5**) (2.5 mmol) and thionyl chloride (5 mL) were heated at 70^{o}C for 8 h. The thionyl chloride was removed under reduced pressure and was heated at 120^{o}C under reduced pressure 50 mmHg for 2 extra hrs. to give a yellowish clear colored oil of benzimidoyl chloride **6**, which was not further purified and was used directly in the next step. To a solution of benzimidoyl chloride **6** (2.5 mmol) in acetonitrile (10 mL) was added (0.69 g, 2.5 mmol) of *N*-cyclohexyl dithiocarbamate cyclohexyl ammonium salt (**2**). The reaction mixture was stirred at room temperature for 1 h. (TLC monitored), then heated for 2h.. The reaction mixture was evaporated under reduced pressure and 25 mL of ethanol was added to the solid residue. The yellowish precipitate was filtered to give **8**. The crude compound was purified by crsystalization from ethyl alcohol 95%.

Yield 84% yellow crystals, mp 138–139°C. ^{1}H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.89 (2H, d, *J* = 8.0, ArH); 7.82 (1H, bs, NH); 7.55–7.48 (5H, m, ArH); 7.19 (2H, d, *J* = 8.0, ArH); 3.87–3.67 (1H, m, CH); 2.36 (3H, s, CH_3); 2.06–1.59 (4H, m, 2CH_2); 1.44–1.20 (6H, m, 3CH_2). Found, %: C, 68.36; H, 6.48; N, 7.46. For $C_{21}H_{24}N_2S_2$ (368.6). Calculated, %: C, 68.44; H, 6.56; N, 7.60; S, 17.40.

General method for the preparation of thiating reagent N-isopropyldithiocarbamate isopropyl ammonium salt (10).

To a mixture of isopropyl amine (60 mmol) and ethyl acetate (50 mL) was added carbon disulfide (21 mmol) dropwise. The reaction mixture was stirred at room temperature for 2h. The white solid obtained was filtered, washed with ethyl acetate, dried and was packed tightly and was pure enough for further reactions.

Yield 95% (acetonitrile) white crystals, mp 85–86°C. ^{1}H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.19 (1H, bs, NH); 6.06–5.75 (3H, bs, 3NH); 3.88–3.75 (1H, m, CH); 3.72–3.51 (1H, m, CH); 1.43–1.08

(12H, m, $4CH_3$). ^{13}C NMR spectrum, (100.0 MHz, $CDCl_3$), δ, ppm: 211.8 (C = S); 52.7 (CH); 48.3 (CH); 24.5 ($2CH_3$); 22.3 ($2CH_3$). Found, %: C, 43.17; H, 9.23; N, 14.38. For $C_7H_{18}N_2S_2$ (194.4). Calculated, %: C, 43.26; H, 9.34; N, 14.41; S, 32.99.

General method for the preparation of N-aryl substituted benzthioamide 17–19(a-e)

A mixture of *N*-aryl substituted benzamide **11–13**(**a-e**) (2.5 mmol) and thionyl chloride (5 mL) were heated at 70°C for 8 h. The thionyl chloride was removed under reduced pressure and was heated at 120°C under reduced pressure 50 mmHg for 2 extra hrs. to give a yellowish clear colored oil of benzimidoyl chloride **14–16**(**a-e**), which was not further purified and was used directly in the next step. To a solution of benzimidoyl chloride **14–16**(**a-e**) (2.5 mmol) in acetonitrile (10 mL) was added (0.49 g, 2.5 mmol) of *N*-isopropyldithiocarbamate isopropyl ammonium salt (**10**). The reaction mixture was stirred at room temperature for 1 h. (TLC monitored). The reaction mixture was evaporated under reduced pressure and 25 mL of ethanol was added to the solid residue. The yellowish precipitate was filtered to give the desired *N*-aryl substituted benzothioamides **17–19**(**a-e**). The crude compounds were pure enough for analytical purposes. Purification of products for analysis was achieved by crystallization from the appropriate solvent.

N -Phenylbenzothioamide (17a).

Yield 89% (ethanol 95%) yellow crystals, mp 100–101°C (lit. [26] 102°C). ^1H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 9.06 (1H, bs, NH); 8.20–7.80 (4H, m, ArH); 7.64–7.29 (6H, m, ArH).^{13}C NMR spectrum, (100.0 MHz, $CDCl_3$), δ, ppm: 197.5 (C = S), 143.5, 139.6, 130.2, 129.3, 128.9, 127.6, 125.8, 124.7. Found, %: C, 73.15; H, 5.17; N, 6.53. For $C_{13}H_{11}NS$ (213.3). Calculated, %: C, 73.20; H, 5.20; N, 6.57; S, 15.03.

N -(p -Tolyl)benzothioamide (17b).

Yield 93% (ethanol 95%) yellow crystals, mp 126–127°C (lit. [8] 130°C). ^1H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.99 (1H, bs, NH); 7.88–7.77 (2H, m, ArH); 7.66 (2H, d, *J* = 8.0, ArH); 7.51 (2H, d, *J* = 8.0, ArH); 7.42–7.39 (3H, m, ArH); 2.37 (3H, s, CH_3).^{13}C NMR spectrum, (100.0 MHz, $CDCl_3$), δ, ppm: 198.8 (C = S), 143.7, 136.7, 135.1, 130.6, 129.9, 128.4, 127.6, 125.9, 124.3, 21.7 (CH_3). Found, %: C, 73.93; H, 5.74; N, 6.09. For $C_{14}H_{13}NS$ (227.3). Calculated, %: C, 73.97; H, 5.76; N, 6.16; S, 14.10.

N -(m -Tolyl)benzothioamide (17c).

Yield 76% (ethanol 95%) yellow crystals, mp 87–88°C (lit. [27] 81°C). ^1H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 9.00 (1H, bs, NH); 7.88–7.72 (2H, m, ArH); 7.67–7.54 (2H, m, ArH); 7.46–7.36 (3H, m, ArH); 7.31–7.18 (2H, m, ArH); 2.42 (3H, s, CH_3). Found, %: C, 73.89; H, 5.72; N, 6.11. For $C_{14}H_{13}NS$ (227.3). Calculated, %: C, 73.97; H, 5.76; N, 6.16; S, 14.10.

N -(o -Tolyl)benzothioamide (17d).

Yield 84% (ethanol 95%) yellow crystals, mp 148–150°C (lit. [26] 151°C). ^{1}H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.86 (1H, d, *J* = 6.0, ArH); 7.81 (2H, d, *J* = 6.0, ArH); 7.59 (1H, bs, NH); 7.59–7.41 (3H, m, ArH); 7.22–7.15 (2H, m, ArH); 7.13 (1H, t, *J* = 6.0, ArH) 2.27 (3H, s, CH_3).^{13}C NMR spectrum, (100.0 MHz, $CDCl_3$), δ, ppm: 198.2 (C = S), 142.9, 139.1, 133.6, 131.8, 131.3, 128.9,126.0, 125.6,125.1, 18.4 (CH_3). Found, %: C, 73.85; H, 5.70; N, 6.12. For $C_{14}H_{13}NS$ (227.3). Calculated, %: C, 73.97; H, 5.76; N, 6.16; S, 14.10.

N -(4-Methoxyphenyl)benzothioamide (17e).

Yield 96% (ethanol 95%) yellow crystals, mp 130–131°C (lit. [26] 127°C). ^{1}H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.89 (1H, bs, NH); 7.87–7.76 (2H, m, ArH); 7.54 (2H, d, *J* = 8.0, ArH); 7.53–7.42 (3H, m, ArH); 6.88 (2H, d, *J* = 8.0, ArH); 3.73 (3H, s, OCH_3).^{13}C NMR spectrum, (100.0 MHz, $CDCl_3$), δ, ppm: 199.6 (C = S), 158.6, 142.8, 131.4, 130.2, 128.3, 127.5, 125.3, 113.8, 55.3 (OCH_3). Found, %: C, 69.03; H, 5.36; N, 5.72. For $C_{14}H_{13}NOS$ (243.3). Calculated, %: C, 69.11; H, 5.39; N, 5.76; S, 13.18.

4-Methoxy- N -phenylbenzothioamide (**18a**).

Yield 82% (ethanol 95%) yellow crystals, mp 145–146°C (lit. [8] 150°C). ^{1}H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.86 (2H, d, *J* = 6.0, ArH); 7.71 (1H, bs, NH); 7.45–7.36 (2H, m, ArH); 7.34–7.29 (3H, m, ArH); 6.93 (2H, d, *J* = 6.0, ArH); 3.82 (3H, s, OCH_3).^{13}C NMR spectrum, (100.0 MHz, $CDCl_3$), δ, ppm: 199.4 (C = S), 158.4, 139.1, 134.5, 129.0, 127.2, 126.9, 123.4, 114.1, 55.5 (OCH_3). Found, %: C, 69.09; H, 5.38; N, 5.72. For $C_{14}H_{13}NOS$ (243.3). Calculated, %: C, 69.11; H, 5.39; N, 5.76; S, 13.18.

4-Methoxy- N -(p -tolyl)benzothioamide (18b).

Yield 93% (ethanol 95%) yellow crystals, mp 172–173°C (lit. [28] 174°C). ^{1}H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.85 (2H, d, *J* = 6.0, ArH); 7.73 (1H, bs, NH); 7.52 (2H, d, *J* = 6.0, ArH); 7.19 (2H, d, *J* = 6.0, ArH); 6.99 (2H, d, *J* = 6.0, ArH); 3.73 (3H, s, OCH_3); 2.36 (3H, s, CH_3).^{13}C NMR spectrum, (100.0 MHz, $CDCl_3$), δ, ppm: 200.5 (C = S), 158.7, 136.6, 135.8, 134.1, 129.9, 127.4 124.7, 113.8, 55.7 (OCH_3), 21.5 (CH_3). Found, %: C, 69.94; H, 5.76; N, 5.38. For $C_{15}H_{15}NOS$ (257.4). Calculated, %: C, 70.01; H, 5.88; N, 5.44; S, 12.46.

4-Methoxy N-(m-**tolyl)benzothioamide (18c).**

Yield 86% (ethanol 95%) yellow crystals, mp 132–133°C. ^{1}H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.82 (2H, d, *J* = 6.0, ArH); 7.67 (1H, bs, NH); 7.62–7.54 (2H, m, ArH); 7.31–7.11 (2H, m, ArH); 6.93 (2H, d, *J* = 6.0, ArH); 3.86 (3H, s, OCH_3); 2.39 (3H, s, CH_3).^{13}C NMR spectrum, (100.0 MHz, $CDCl_3$), δ, ppm: 200.2

(C = S), 158.5, 138.9, 136.3, 135.4, 134.4, 129.8, 127.6, 125.9, 124.5, 114.6, 21.2 (CH_3). Found, %: C, 69.87; H, 5.74; N, 5.36. For $C_{15}H_{15}NOS$ (257.4). Calculated, %: C, 70.01; H, 5.88; N, 5.44; S, 12.46.

4-Methoxy- N **-(**o **-tolyl)benzothioamide (18d).**

Yield 94% (ethanol 95%) yellow crystals, mp 125–126°C (lit. [29] 119°C). ^{1}H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.94 (1H, d, *J* = 6.0, ArH); 7.88 (2H, d, *J* = 6.0, ArH); 7.64 (1H, bs, NH); 7.29–7.24 (2H, m, ArH); 7.13 (1H, t, *J* = 6.0, ArH); 7.00 (2H, d, *J* = 6.0, ArH); 3.98 (3H, s, OCH_3); 2.36 (3H, s, CH_3).^{13}C NMR spectrum, (100.0 MHz, $CDCl_3$), δ, ppm: 199.1 (C = S), 159.3, 139.2, 136.5, 134.3, 133.6, 130.1, 127.4, 126.4, 125.6, 113.9, 55.5 (OCH_3), 18.9 (CH_3). Found, %: C, 69.92; H, 5.79; N, 5.41. For $C_{15}H_{15}NOS$ (257.4). Calculated, %: C, 70.01; H, 5.88; N, 5.44; S, 12.46.

4-Methoxy- N **-(4-methoxyphenyl)benzothioamide (18e).**

Yield 90% (ethanol 95%) yellow crystals, mp 149–150°C (lit. [8] 152°C). ^{1}H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.75 (2H, d, *J* = 6.0, ArH); 7.61 (1H, bs, NH); 7.44 (2H, d, *J* = 6.0, ArH); 6.89 (2H, d, *J* = 6.0, ArH); 6.82 (2H, d, *J* = 6.0, ArH); 3.82 (3H, s, OCH_3); 3.74 (3H, s, OCH_3). ^{13}C NMR spectrum, (100.0 MHz, $CDCl_3$), δ, ppm: 202.1 (C = S), 159.7, 157.6, 134.1, 131.3 127.8, 125.6, 114.4, 113.7, 55.6 (OCH_3), 55.2 (OCH_3). Found, %: C, 65.88; H, 5.51; N, 5.04. For $C_{15}H_{15}NO_2S$ (273.4). Calculated, %: C, 65.91; H, 5.53; N, 5.12; S, 11.73.

4-Chloro- N **-phenylbenzothioamide** (**19a**).

Yield 92% (ethanol 95%) yellow crystals, mp 157–158°C (lit. [30] 153°C). ^{1}H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 9.03 (1H, bs, NH); 7.67 (2H, d, *J* = 6.0, ArH); 7.45–7.36 (4H, m, ArH); 7.34–7.29 (3H, m, ArH).^{13}C NMR spectrum, (100.0 MHz, $CDCl_3$), δ, ppm: 198.6 (C = S), 140.3, 139.8, 135.3, 129.0, 128.5, 127.9, 127.3, 123.6. Found, %: C, 62.89; H, 4.05; N, 5.61. For $C_{13}H_{10}ClNS$ (247.7). Calculated, %: C, 63.03; H, 4.07; Cl, 14.31; N, 5.65; S, 12.94.

4-Chloro- N **-(**p **-tolyl)benzothioamide (19b).**

Yield 96% (ethanol 95%) yellow crystals, mp 150–151°C. ^{1}H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 9.03 (1H, bs, NH); 7.71 (2H, d, *J* = 6.0, ArH); 7.52 (2H, d, *J* = 6.0, ArH); 7.42 (2H, d, *J* = 6.0, ArH); 7.19 (2H, d, *J* = 6.0, ArH); 2.37 (3H, s, CH_3).^{13}C NMR spectrum, (100.0 MHz, $CDCl_3$), δ, ppm: 199.5 (C = S), 141.2, 136.3, 135.6, 134.7, 129.2, 128.9, 127.6, 124.5, 21.3 (CH_3). Found, %: C, 64.14; H, 4.59; N, 5.28. For $C_{14}H_{12}ClNS$ (261.8). Calculated, %: C, 64.24; H, 4.62; Cl, 13.54; N, 5.35; S, 12.25.

4-Chloro- N **-(**m **-tolyl)benzothioamide (19c).**

Yield 98% (ethanol 95%) yellow crystals, mp 136–137°C. ^{1}H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 9.01 (1H, bs, NH); 7.67–7.54 (4H, m, ArH); 7.39 (2H, d, *J* = 6.0, ArH); 5.31–7.13 (2H, m, ArH); 2.36 (3H,

s, CH_3).^{13}C NMR spectrum, (100.0 MHz, $CDCl_3$), δ, ppm: 199.6 (C = S), 141.5, 138.4, 136.7, 135.6, 134.9, 129.6, 129.0, 127.2, 125.8, 123.4. 21.5 (CH_3). Found, %: C, 64.18; H, 4.54; N, 5.29. For $C_{14}H_{12}ClNS$ (261.8). Calculated, %: C, 64.24; H, 4.62; Cl, 13.54; N, 5.35; S, 12.25.

4-Chloro- N **-(**o **-tolyl)benzothioamide (19d).**

Yield 73% (ethanol 95%) yellow crystals, mp 129–130°C. ^{1}H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 9.03 (1H, bs, NH); 7.94 (1H, d, *J* = 6.0, ArH); 7.67 (2H, d, *J* = 6.0, ArH); 7.39 (2H, d, *J* = 6.0, ArH); 7.31–7.24 (2H, m, ArH); 7.16 (1H, t, *J* = 6.0, ArH); 2.36 (3H, s, CH_3). ^{13}C NMR spectrum, (100.0 MHz, $CDCl_3$), δ, ppm: 199.3 (C = S), 140.5, 139.4, 136.5, 134.5, 133.8, 130.5, 128.8, 127.9, 127.3, 125.6, 18.5 (CH_3). Found, %: C, 64.12; H, 4.48; N, 5.31. For $C_{14}H_{12}ClNS$ (261.8). Calculated, %: C, 64.24; H, 4.62; Cl, 13.54; N, 5.35; S, 12.25.

4-Chloro- N **-(4-methoxyphenyl)benzothioamide (19e).**

Yield 85% (ethanol 95%) yellow crystals, mp 166–167°C (lit. [31] 172°C).. 1H NMR spectrum, (400 MHz, $CDCl_3$), δ, ppm (J, Hz): 8.89 (1H, bs, NH); 7.82 (2H, d, *J* = 6.0, ArH); 7.64 (2H, d, *J* = 6.0, ArH); 7.36 (2H, d, *J* = 6.0, ArH); 6.91 (2H, d, *J* = 6.0, ArH); 3.75 (3H, s, OCH_3).^{13}C NMR spectrum, (100.0 MHz, DMSO), δ, ppm: 199.8 (C = S), 158.9, 140.4, 134.2, 131.9, 128.6, 127.6, 126.3, 114.5, 55.4 (OCH_3). Found, %: C, 60.49; H, 4.32; N, 4.87. For $C_{14}H_{12}NClNOS$ (277.8). Calculated, %: C, 60.54; H, 4.35; Cl, 12.76; N, 5.04; S, 11.54.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

All data are already presented in details along the manuscript in each section and title has its corresponding data

Competing interests

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Authors' contributions

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Walid, Ibrahim and Samir substantial contribution to acquisition of data

Walid, Gaber, Ibrahim and Samir substantial contribution to analysis and interpretation of data

Walid, Gaber, Ibrahim and Samir drafting the article

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Schemes

Schemes 1 to 5 are available in the Supplemental Files section.

Supplementary Files

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- Scheme1.jpg
- Scheme2.jpg
- Scheme3.jpg
- Scheme4.png
- Scheme5.jpg