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A one-pot conversion of di-substituted thiourea to O-organyl arylthiocarbamate using $FeCl_3$

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A one-pot conversion of di-substituted thiourea to *O*-organyl arylthiocarbamate using $FeCl_3$

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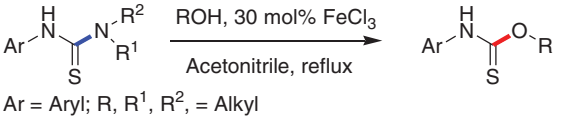
Unsymmetrical thiourea, which on demand can generate isothiocyanate in the presence of $FeCl_3$, can serve as a latent isothiocyanate functionality and circumvent the difficulties associated with the direct use of reactive isothiocyanate functionality. An unusual and unorthodox reactivity has been achieved during a one-pot reaction of an unsymmetrically di-substituted thiourea with an alcohol in the presence of $FeCl_3$ leading to an expeditious synthesis of *O*-organyl arylthiocarbamates. In this reaction, a thiono-ester (C−O) bond is formed at the expense of a thioamidic (C−N) bond and works over a wide range of structurally diverse thioureas and alcohols without affecting the other functional groups.



Ar = Aryl; R, R^1, R^2, = Alkyl

Keywords: green chemistry; thiourea; Fe-catalyst; arylthiocarbamate; C−O bond

1. Introduction

In synthetic methodology, interconversion of one functional group to another without isolating any intermediate is highly attractive because of higher yields of the desired product and reduced reaction time. Recently, the focus of organic chemistry has shifted toward the development of clean, fast, efficient, and selective processes for organic transformations and this has increased the demand for metal-based "reaction-promoters", especially ones that can be applied in catalytic amount and/or are recyclable. Many heavy and rare earth-metal-based catalysts have been devised with varied efficiencies for synthetic purposes and have some degree of general applicability but suffer from one or more common drawbacks, including moisture sensitivity, toxicity, high cost, harsh reaction conditions, or incompatibility with acid- or base-sensitive functional groups. In addition, handling these catalysts often requires the use of special and expensive instrumental techniques. Consequently, new atom-efficient, cost-effective, environmentally benign, and

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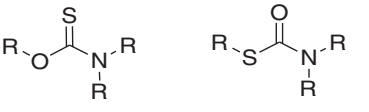
broad functional-group-compatible catalysts are of utmost importance from a green chemistry perspective. Iron exactly fits into this role. It is one of the most abundant metals on earth and consequently one of the most inexpensive and environmentally friendly one (*1*). In addition, many iron salts and complexes are commercially available and their reactivities are well documented in the literature (*2*). Iron (III) chloride and other iron (III) salts are generally strong and hard Lewis acids. They also behave as BrØnsted acids in the presence of various alcohols. These properties make iron (III) salts extraordinary catalysts in the presence of carbonyl and thiocarbonyl compounds. Consequently, a variety of iron (III) species are formed when iron (III) salts coordinate with hard Lewis bases, viz. simple adduct with donors, for example, $FeCl_3(THF)_3$, basic carboxylates of the type $[Fe_3O(O_2CR)_6L_3]^+$, bent bridged species, like $[(sal_2en)Fe]_2(\mu O)$, and linear bridged species of the type $(porph\ Fe)_2(\mu\text{-}X)$ (X = O, N, and C) (*1*, *3*). Also, polymeric oxo species such as $Fe_{11}O_6(PhCO_2)_{15}(OH)_6$ are well documented in the literature (*3c*).

In the last decade, iron (III) chloride and other iron (III) salts have emerged as a very important catalyst of choice for various synthetically useful organic transformations (*4*). Recently, Bolm and co-workers presented mild and practical inter- and intramolecular cross-coupling reactions that formed aryl–heteroatom bonds (e.g. C−N, C−S, and C−O) utilizing $FeCl_3$ (*5*). Kerr and co-workers reported the use of $FeCl_3$ for the nucleophilic displacement of azide by dimethyl hydrazide (*6*).

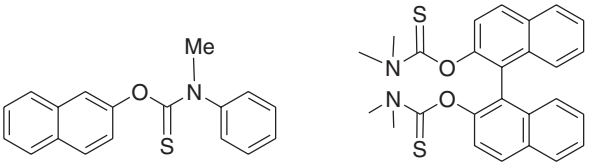
Thiocarbamates, which exist in two isomeric forms viz. *O*-Organyl thiocarbamate and *S*-organyl thiocarbamate (Figure 1), are a very important class of organo-sulfur compounds. The *O*-organyl thiocarbamates can isomerize to *S*-organyl thiocarbamates via different types of thione-thiol rearrangements. For example, the Miyazaki–Newman–Kwart rearrangement (*7*) is a type of rearrangement in which the aryl group of *O*-aryl thiocarbamate migrates from the oxygen to the sulfur atom, forming an *S*-aryl thiocarbamate. The rearrangement can be viewed as an intramolecular aromatic nucleophilic substitution favored both kinetically as well as thermodynamically. Kinetically, the stronger nucleophilicity of sulfur compared with oxygen and thermodynamically, formation of the more stable C=O bond from the C=S bond ($\Delta H \sim 13$ kcal/mol) are the impetus for this transformation (*8*).

Recently, there has been an increasing interest in thiocarbamates due to their newly found ability to act as inhibitors in various biological processes (*9*). Alkyl-*N*-phenyl thiocarbamates represent a biologically important subclass of thiocarbamates. Lu *et al.* described alkyl-*N*-phenyl thiocarbamates as active site-binding inhibitors that are probably alkyl-chain binding-site-directed inhibitors for enzymes such as porcine pancreatic cholesterol esterase and *Pseudomonas* species lipase (*10*). The inhibitory effect of alkyl-*N*-phenylthiocarbamates (alkyl = methyl–butyl) on the photosynthetic electron transport in plants were studied by Macho and co-workers (*11*) and were found to be quite effective. One very useful drug of this thiocarbamate family is Tolnaftate (Figure 2), which is an effective anti-fungal drug, used to treat jock itch, athlete's foot, and ringworm (*12*). Use of thiocarbamates as pesticides and insect repellent is also well known (*13*). A synthetically important compound of this class is the BINOL analog (Dimethyl-thiocarbamic acid-O-(2′-dimethylthiocarbamoyloxy-[1,1′]binapthaleryl-2-yl)ester), which is used as a chiral ligand for various asymmetric syntheses (*14*).



O-organyl thiocarbamate **S-organyl thiocarbamate**

Figure 1. Two isomeric thiocarbamates.



Tolnaflate
O-2-napthyl methyl(3-methylphenyl) thiocarbamate

DTAB
Dimethyl-thiocarbamic acid-O-(2'-dimethylthio carbamoyloxy-[1,1']binapthaleryl-2-yl)ester

Figure 2. Synthetically important thiocarbamates.

A number of methods have been reported for the preparation of *O*-organyl aryl thiocarbamates. Among those, the most convenient procedures utilize the reaction between aryl isothiocyanates and the corresponding alcohols under various conditions, viz. in the presence of a strong base (by generating alkoxide anion) at an elevated temperature, under microwave irradiation and neutral conditions using a large excess of alcohol (*15*). One major drawback of using neutral conditions is that symmetrical 1,3-disubstituted thioureas are formed as byproducts when small chain alcohols react with *N*-aryl-*O*-alkyl thiocarbamates. In another approach, treatment of thiocarbamic acid chloride with alcohols under strongly alkaline conditions generate thiocarbamate adducts (*16*). In contrast to thiocarbamic acid chlorides, unsymmetrical di-substituted thioureas with one side substituted with a secondary amine are not expected to undergo a similar reaction with loss of the secondary amine because of the poor leaving ability of its corresponding anion compared to chloride.

In an earlier study, Konig and co-workers (*17a*) developed a method for the direct single-step conversion of di-substituted thioureas to *O*-organyl thiocarbamates. The transformation was done in an unconventional way using the corresponding ether of an alcohol in the presence of concentrated mineral acid at an elevated temperature. Similarly, *N*-arylthiocarbamates in trichlorosilane in the presence of triethylamine is directly converted to a thiourea adduct via an isothiocyanate intermediate (*17b*). The reported methods are useful but have limited substrate scope and utilize harsh reaction conditions which can easily lead to other major side reactions. The use of anhydrous iron (III) chloride as a reagent of choice in place of mineral acids in Friedel–Crafts alkylation and acylation reactions are well known in the literature (*18*). In another instance, Weng *et al.* (*19*) described a mild but expedient transesterification technique using Fe (III) chloride in the presence of β-diketonate ligands. Taking cues from the reported use of $FeCl_3$ in place of mineral acids in a number of transformations, we envisaged the development of a one-pot strategy to synthesize thiocarbamates from di-substituted thioureas. The potential advantage of this strategy would be to use less reactive thioureas as a dormant isothiocyanate functionality that could be introduced early in a synthesis and carried forward through subsequent steps prior to the liberation of isothiocyanate in a penultimate step. In this context, the thiourea acts as a stable protected isothiocyanate functionality that can liberate isothiocyanate if desired and thus reactions directly using reactive isothiocyanate can be minimized.

2. Results and discussion

In a typical reaction, di-substituted thiourea *N*-phenylpiperidine-1-carbothioamide (**1a**) (2 mmol) was dissolved in ethanol (2.5 ml) to which was added $FeCl_3$ (30 mol%), under stirring at room temperature. After a prolonged reaction time (24 h), the product was obtained in 10% yield leaving much of the starting material unreacted. From subsequent temperature optimization studies, it was found that the reaction gave the best yield when performed at 80 °C using a shorter reaction time of

6 h. To find out the role of $FeCl_3$, the reaction was performed with different concentrations of $FeCl_3$ (e.g. 5%, 10%, 15%, 20%, 25%, 30%, and 40%). Although the use of both 25 mol% and 30 mol% of $FeCl_3$ afforded identical yields (75% and 77%, respectively), the reaction with the smaller amount of $FeCl_3$ took longer (12 h versus 6 h) and in the absence of $FeCl_3$ the thiocarbamate product did not form at all. The reaction was found to be less effective using other iron salts such as $Fe(NO_3)_2.9H_2O$ and Fe_3O_4 giving 57% and 51% yield, respectively. Control experiments using an equivalent amount of HCl revealed the role of acid in the reaction but the yield was poor (22%), thus confirming that Fe has a role other than just liberating HCl in the medium. According to previous studies, ligands improve the efficiency of iron-catalyzed carbon–heteroatom bond forming reactions (*5*). We were interested to find out if the same is true for our reactions as well. A study combining 30 mol% $FeCl_3$ and two different ligands methylacetoacetate (30 mol%) and 1,10-phenanthroline (30 mol%) were conducted. To our surprise, the ligands failed to show the expected efficacy and both gave messy reactions mixtures giving undesirable side products and only 42% and 46% of the desired product (**1a**).

The use of neat alcohol, as described above, when more expensive alcohols are needed, is not economically feasible. Consequently, we have also explored the use of co-solvents. Among the five different polar aprotic solvents tested, acetonitrile was found to be the most effective giving a 77% yield of (**1a**). Very low conversions were obtained using THF and acetone (14% and 31% respectively), while in polar solvents such as DMF and DMSO moderate yields of 45% and 41% were obtained, respectively.

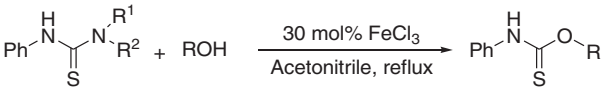
With the optimum protocol in hand, different types of alcohols as the nucleophiles and different secondary amines attached to the thiourea were explored, while keeping the aryl side of the thiourea constant. As shown in Table 1, a variety of aliphatic primary and secondary alcohols react efficiently giving moderate to good yields of the product. The bulky alcohol, cyclohexanol, afforded lower yields compared with linear primary alcohols. The structure *O*-cyclohexyl *N*-phenylcarbamothioate (**1d**) has been confirmed by X-ray crystallography as shown in Figure 3. Piperidine-derived thiourea (**1**) gave better yields compared with morpholine (**2**) and *N*, *N*′-diethylamine (**3**) derived thioureas. Thus, the reactivity order follows the trend piperidine $\gg$ *N*, *N*′-diethylamine > morpholine. The lower reactivity of morpholine may be due to its low donor and coordination ability, especially in the presence of alcohols.

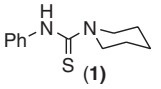
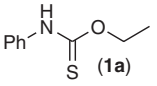
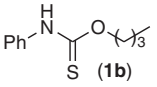
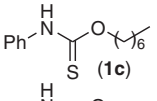
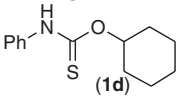
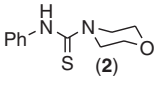
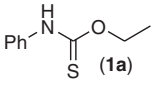
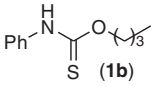
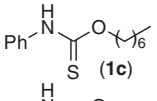
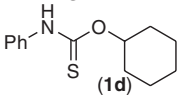
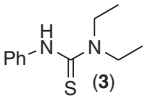
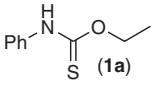
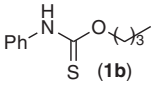
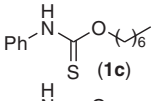
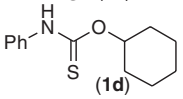
Various unsymmetrical 1,3-di-substituted thioureas with diverse functionality on the aryl ring were subjected to the optimized reaction conditions in order to understand the effect of various substituents. For all of these reactions, piperidine-derived thioureas (**4**–**9**) were chosen as the outgoing secondary amine and heptanol as the incoming alcohol. As summarized in Table 2, all the substrates possessing weakly electron-donating group −Me (**4**), −OMe (**5**), −*n*-Bu (**6**) react efficiently giving the corresponding products (**4c**), (**5c**), and (**6c**), respectively. Similarly, substrates bearing weakly deactivating substituents −Cl (**7**), −F (**8**), and 4-bromo-2-fluoro (**9**), all gave the expected products in moderate yield under the optimized reaction conditions (Table 2). It was observed that electron-donating substituents in the aryl ring gave somewhat better yield (ranging from 72% to 92%) compared with substrates possessing electron-withdrawing substituents (ranging from 61% to 73%). The aryl ring containing two electron-withdrawing groups (4-bromo-2-fluoro) (**9**) gave the lowest yield.

Recently, we have synthesized an interesting class of thiourea having an aryl group on one side and a cyclic guanidine moiety (as secondary amine) on the other side, called imidazolidenecarbothioamides (*20*). We were interested to see whether a cyclic guanidine containing secondary amine can be displaced with primary alcohols. It is heartening to note that thioureas (**10**)–(**12**) containing a cyclic guanidine underwent smooth transformations to give the corresponding thiocarbamates (**1c**), (**4c**), and (**8c**), respectively, demonstrating the power of the methodology (Table 3).

We suggest the mechanism shown in Scheme 1 for this new reaction. This suggestion is based upon the previous report that iron (III) species tend to hydrolyze in the presence of water or

Table 1. Synthesis of thiocarbamates from disubstituted thioureas.[a]



Substrate	Alcohol	Product[b]	Time (h)	Yield (%)[c]
 (**1**)	Ethanol	 (**1a**)	6	77
	Butanol	 (**1b**)	6.5	82
	Heptanol	 (**1c**)	6	95
	Cyclohexanol	 (**1d**)	7	65
 (**2**)	Ethanol	 (**1a**)	8.5	51
	Butanol	 (**1b**)	8	59
	Heptanol	 (**1c**)	9	64
	Cyclohexanol	 (**1d**)	9	49
 (**3**)	Ethanol	 (**1a**)	7	61
	Butanol	 (**1b**)	6.5	71
	Heptanol	 (**1c**)	8	81
	Cyclohexanol	 (**1d**)	7.5	55

Notes: [a]Reactions were performed in presence of excess (5 equiv.) alcohol and were monitored by TLC; [b]Confirmed by ^{1}H and ^{13}C NMR; [c]Yield after column chromatography.

alcohols into oxophilic doubly μ-hydroxo or μ-alkoxy species (*21*) and on other mechanistic studies of iron alkoxide-catalyzed reactions (*19*) and on the observation of the formation of trace amount of aryl isothiocyanate in the reaction mixture (confirmed by checking GC and IR). According to this mechanistic speculation, the main species that serves as the active reaction promoter is not the monomeric iron (III) chloride but the dimeric iron (III) μ-alkoxy species.

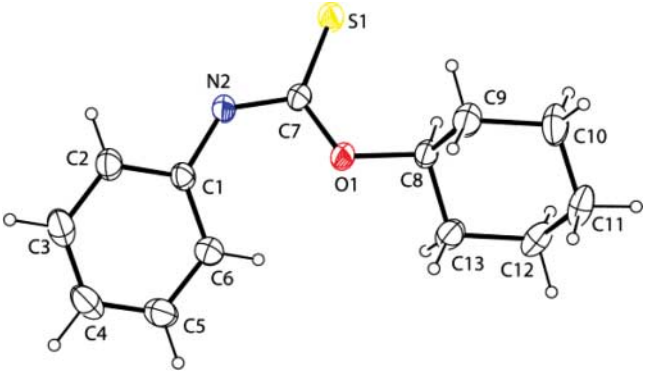
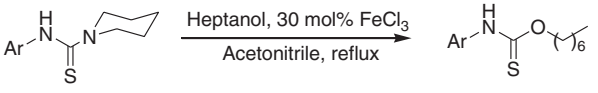
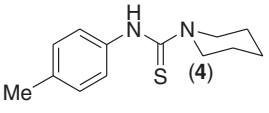
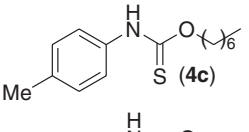
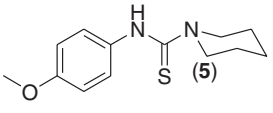
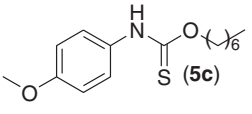
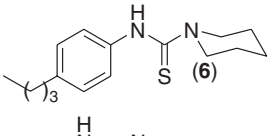
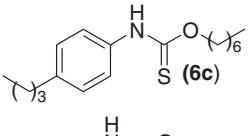
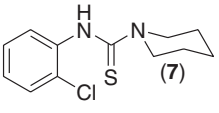
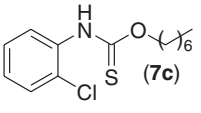
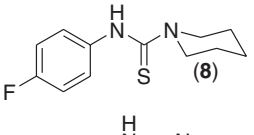
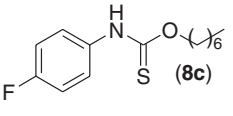
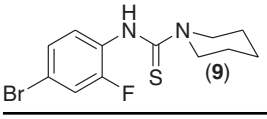
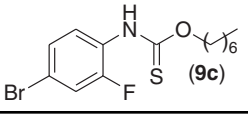


Figure 3. ORTEP view of (**11d**).

Table 2. Synthesis of thiocarbamates from disubstituted thioureas.[a]

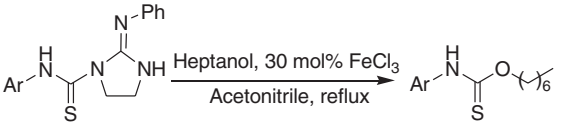


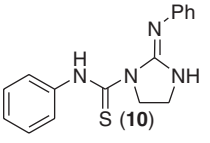
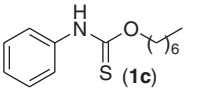
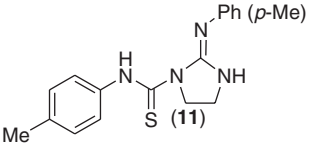
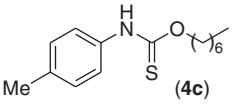
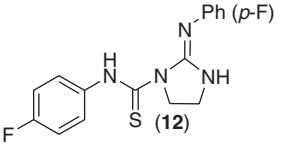
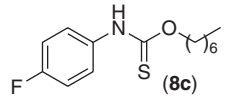
Substrate	Product	Time (h)	Yield (%)[c]
 (**4**)	 (**4c**)	8	72
 (**5**)	 (**5c**)	6	84
 (**6**)	 (**6c**)	6.5	92
 (**7**)	 (**7c**)	8	73
 (**8**)	 (**8c**)	8	70
 (**9**)	 (**9c**)	10	61

Notes: [a]Reactions were performed in the presence of excess (5 equiv.) alcohol and were monitored by TLC; [b]Confirmed by ^{1}H and ^{13}C NMR; [c]Yield after column chromatography.

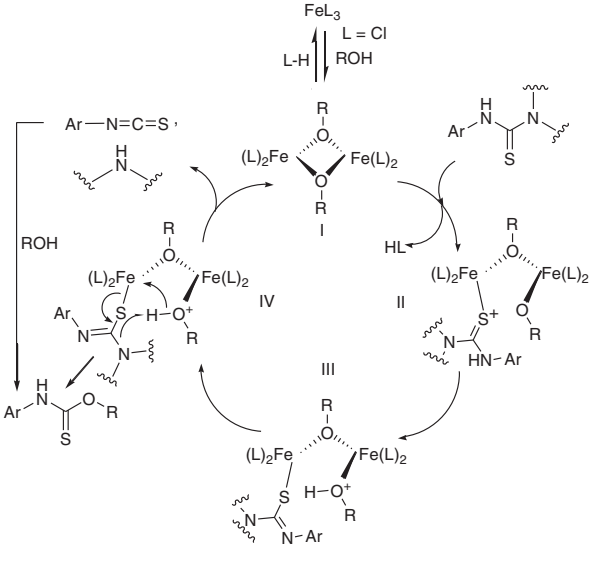
Initial dissociation of the monomeric iron (III) chloride driven by nucleophilic substitution of the alcohol leads to the formation of the μ-alkoxy dimer (I) that serves as the active reaction promoter and activates the di-substituted thiourea to generate the cationic adduct (II). Proton transfer, either intra or intermolecular, then leads to the formation of species (III). In the next step, intramolecular nucleophilic attack of the coordinated alcohol to the sterically congested iron

Table 3. Synthesis of thiocarbamates from imidazolidenecarbothioamides.[a]



Substrate	Product	Time (h)	Yield (%)[c]
		10	72
		10.5	69
		12	64

Notes: [a]Reactions were performed in the presence of excess (5 equiv.) alcohol and were monitored by TLC.
[b]Confirmed by ^{1}H and ^{13}C NMR.
[c]Yield after column chromatography.



Scheme 1. Proposed catalytic cycle for the $FeCl_3$ promoted synthesis of thiocarbamate.

center and concomitant elimination of secondary amine from the coordinated thiourea lead to the formation of arylisothiocyanate. This then reacts with the free alcohol to afford the thiocarbamate adduct.

On the basis of this proposed mechanism, we can interpret our previous observation that the reaction efficiency drastically changes with the identity of the secondary amine substituents in

the order piperidine $\gg$ N,N'-diethylamine > morpholine. In the case of N,N'-diethylamine, the free rotation of two ethyl groups destabilizes the cationic species (IV) (as in Scheme 1) due to steric congestion. This effect of steric hindrance is less prominent in the piperidine ring system that can be considered as a diethyl substituent with the two ethyl groups tied together to prevent rotation. Among all the three secondary amines, morpholine showed the least efficiency in the reaction. This can be explained by considering the high oxophilicity of iron (III), which promotes coordination with the oxygen atom of morpholine, thus preventing the formation of an effective reaction promoter iron (III) μ-alkoxy species (I).

3. Conclusion

In conclusion thiourea serves as latent isothiocyanate functionality which can be converted to *O*-organyl arylthiocarbamates under mildly acidic conditions; thus, the problem associated with the direct use of reactive isothiocyanate functionality can be avoided. The iron (III) catalyst system has several exciting features, including a high tolerance for diverse functional groups, cost-effectiveness, high yields and environmental-friendliness compared with the other conventional approaches.

4. Experimental

All the reagents were of commercial grade and purified according to established procedures. Organic extracts were dried over anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Reactions were monitored by TLC on silica gel 60 F_{254} (0.25 mm). Column chromatography was performed using silica gel (60–120 meshes). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz); the chemical shifts are expressed as δ values (ppm). HRMS spectra were recorded using WATERS MS system, Q-Tof premier and data analyzed using Mass Lynx 4.1. Melting points were recorded in a Buchi B-545 melting point apparatus and are uncorrected. IR spectra were recorded in KBr or neat on a Nicolet Impact 410 spectrophotometer.

4.1. *General procedure for the preparation of phenyl-thiocarbamic acid O-heptyl ester from piperidine-1-carbothioic acid phenylamide*

To a solution of piperidine-1-carbothioic acid phenylamide (**1**) (0.44 g, 2 mmol) in acetonitrile, heptanol (1.16 g, 10 mmol) and anhydrous $FeCl_3$ (0.10 g, 0.6 mmol) was added and the reaction mixture was stirred constantly under open atmosphere. After 6 h, the mixture was mixed with water (1 ml) and the product extracted with ethyl acetate (2 × 10 ml). The ethyl acetate layer was washed with saturated sodium bicarbonate solution (2 × 2 ml). The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), filtered, and evaporated under reduced pressure. The product so obtained was sufficiently pure but for analytical data it was purified through a short column of silica gel using hexane/ethyl acetate (9 : 1) as the eluent to yield the pure product phenyl-thiocarbamic acid *O*-heptyl ester (**1c**) (0.477 g, 95%). White solid; m.p. 39–40 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3H, J = 6.8 Hz), 1.28–139 (m, 7H), 1.77 (t, 3H, J = 6.8 Hz), 4.56 (s, 2H), 7.16–7.33 (m, 5H), 8.72 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 22.6, 26.0, 28.5, 28.9, 31.7, 73.1, 121.6, 125.4, 129.1, 137.2, 188.8; IR (KBr): 3224 (m), 3120 (m), 3054 (m), 2956 (m), 2922(m), 2851(m), 1598 (s), 1548 (s), 1492 (m), 1413 (m), 1348 (m), 1192 (s), 1036 (s), 747 (s) cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{21}NOS$ ($M + H^+$) 252.1482; found 252.1478.

4.1.1. *O-Ethyl N-phenylcarbamothioate (**1a**)*

White solid; m.p. 78–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (t, 3H, $J = 6.4$ Hz), 4.64 (s, 2H) 7.16 (s, 1H), 7.32 (d, 4H., $J = 6.8$ Hz), 9.21 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 4.2, 68.8, 121.6, 125.3, 129.0, 137.2, 188.5; IR (KBr): 3223 (s), 3106 (m), 3042 (m), 2989 (m), 2931 (m), 2864 (m), 2731 (m), 1594 (s), 1539 (s), 1462 (m), 1403 (m), 1372 (m), 1320 (m), 1291 (m), 1214 (m), 1203 (m), 1100 (m), 1041 (s), 814 (s), 742 (m) cm^{-1}; HRMS (ESI) calcd for $C_9H_{11}NOS$ ($M + H^+$) 182.0667; found 180.0670.

4.1.2. *O-Butyl N-phenylcarbamothioate (**1b**)*

Oily; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87–0.97 (m, 3H), 1.40–1.44 (m, 2H), 1.73–1.78 (m, 2H), 4.58 (s, 2H), 7.21 (d, 2H, $J = 7.2$ Hz), 7.28 (d, 2H, $J = 7.2$ Hz), 7.34 (t, 1H, $J = 7.6$ Hz; ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 19.2, 30.5, 72.7, 125.7, 127.3, 129.0, 129.5, 188.6; IR (KBr): 3231 (s), 3036 (m), 2958 (s), 2930 (s), 2872 (m), 1596 (s), 1538 (s), 1445 (m), 1404 (m), 1335 (m), 1188 (m), 1028 (m), 750 (m), 690 (m) cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{12}N_2S$ (209.09): ($M + H^+$) 210.0972; found 210.0978.

4.1.3. *O-Cyclohexyl N-phenylcarbamothioate (**1d**)*

White solid; m.p. 76–78 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25–1.79 (m, 8H), 2.00–2.03 (M, 2H), 5.45 (s, 1H), 7.16 (d, 1H, $J = 6.0$ Hz), 7.26–7.35 (m, 4H), 8.83 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.7, 24.8, 25.3, 31.3, 31.7, 81.7, 121.6, 125.2, 129.0, 137.3, 187.7; IR (KBr): 3228 (s), 3121 (m), 3036 (m), 2935 (s), 2858 (s), 1712 (s), 1597 (s), 1538 (s), 1446 (m), 1391 (m), 1359 (m), 1193 (m), 1145 (m), 1044 (m), 1019 (m), 986 (m), 749 (m), 690 (m) cm^{-1}. Anal. Calcd for $C_{13}H_{17}NOS$ (235.10): C 66.34, H 7.28, N 5.95, S 13.62; found C 66.44, H 7.35, N 5.91, S 13.53.

4.1.4. *O-Heptyl N-p-tolylcarbamothioate (**4c**)*

Oily; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, 3H, $J = 6.8$ Hz), 1.27–1.34 (m, 4H), 1.71–1.76 (m, 2H), 2.30–1.32 (m, 6H), 4.54 (s, 2H), 7.06–7.12 (m, 4H), 8.60 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 21.3, 22.6, 25.9, 28.6, 31.8, 73.1, 125.6, 129.6, 130.2, 137.6, 188.7; IR (KBr): 3327 (m), 3026 (m), 2928 (s), 2856 (s), 1709 (s), 1583 (s), 1526 (s), 1453 (m), 1405 (m), 1365 (m), 1226 (m), 1208 (m), 1123 (m), 1071 (m), 816 (s) cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{23}NOS$ ($M + H^+$) 266.1615; found 266.1618.

4.1.5. *O-Heptyl N-4-methoxyphenylcarbamothioate (**5c**)*

Oily; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (t, 3H, $J = 6.8$ Hz), 1.24 (m, 8H), 1.68–1.74 (m, 2H), 3.76 (s, 3H), 4.51 (s, 2H) 6.82 (d, 2H, $J = 8.0$ Hz), 8.86 (brs, 1H) ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.6, 25.9, 28.5, 28.9, 31.7, 55.5, 72.9, 114.2, 123.7, 126.1, 130.3, 157.3, 188.6; IR (KBr): 3231 (m), 2954 (s), 2929 (s), 2856 (m), 1596 (m), 1514 (s), 1463 (m), 1404 (m), 1366 (m), 1298 (m), 1249 (s), 1171 (s), 1037 (s), 828 (s), 735 (m) cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{23}NO_2S$ ($M + H^+$) 282.1615; found 266.1614.

4.1.6. *O-Heptyl N-4-butylphenylcarbamothioate (**6c**)*

Oily; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86–0.93 (m, 8H), 1.19–1.36 (m, 10H), 1.52–1.60(m, 4H), 1.73–1.75 (m, 2H), 2.56 (t, 3H, $J = 7.6$ Hz), 4.55 (s, 2H), 7.02–7.25 (m, 4H), 9.21 (brs, 1H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 14.0, 22.3, 25.9, 28.5, 28.9, 31.7, 33.5, 35.0, 49.4, 72.8, 121.6, 128.8, 134.9, 140.0, 188.5; IR (KBr): 3395 (m), 3235 (m), 3029 (m), 2955 (m), 2928 (s), 2857 (s), 1714 (m), 1592 (s), 1536 (s), 1520 (s), 1465 (m), 1403 (m), 1360 (m), 1341 (m), 1176 (s), 1042 (m), 831 (m), 725 (m) cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{29}NOS$ ($M + H^+$) 308.2106; found 308.2109.

4.1.7. *O-Heptyl N-2-chlorophenylcarbamothioate (**7c**)*

Oily; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, 3H, $J = 6.0$ Hz), 1.26–1.32 (m, 8H), 1.73 (t, 2H, $J = 7.2$ Hz), 4.50 (t, 2H, $J = 6.8$ Hz), 7.06 (t, 1H, $J = 7.6$ Hz), 7.34 (d, 2H, $J = 8.0$ Hz), 8.46 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.4, 25.7, 28.3, 28.7, 31.6, 72.2, 124.3, 125.4, 126.1, 127.1, 129.3, 134.0, 188.6; IR (KBr): 3397 (s), 2950 (s), 2928 (s), 2856 (s), 1592 (m), 1519 (s), 1442 (m), 1397 (m), 1360 (m), 1333 (m), 1179 (m), 1033 (m), 750 (m) cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{20}NOSCl$ ($M + H^+$) 286.1074; found 286.1079.

4.1.8. *O-Heptyl N-4-fluorophenylcarbamothioate (**8c**)*

Oily; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82–0.92 (m, 2H), 1.27 (s, 9H) 1.62–1.74 (m, 2H), 4.14 (s, 2H) 6.90–7.02 (m, 2H), 7.23–7.32 (m, 2H),9.18 (brs, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.6, 25.9, 28.5, 29.0, 73.1, 115.7 (d, $^2J_{CF} = 88.4$ Hz), 115.9 (d, $^2J_{CF} = 88.4$ Hz), 120.6, 123.9, 134.1, 160.2 (d, $^1J_{CF} = 964$ Hz), 188.9; IR (KBr): 3434 (s), 2961 (m), 2928 (s), 2857 (m), 1704 (m), 1613 (s), 1531 (m), 1410 (m), 1300 (m), 1211 (s), 1068 (m), 833 (s), 768 (m), 725 (m), 511 (m) cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{20}NOSF$ ($M + H^+$) 270.1330; found 270.1335.

4.1.9. *O-Heptyl N-4-bromo-2-fluorophenylcarbamothioate (**9c**)*

Oily; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83–0.90 (m, 3H), 1.25–1.35(m, 8H), 1.65–1.78 (m, 2H), 4.11–4.18 (m, 2H), 7.20–7.29 (m, 3H), 7.99 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.6, 25.9, 28.5, 28.9, 31.7, 72.7, 118.5 ($^2J_{CF} = 88.4$ Hz), 119.2 (d, $^2J_{CF} = 91.6$ Hz), 121.3, 125.0, 127.6, 153.3, 188.7; IR (KBr): 3426 (s), 2955 (s), 2928 (s), 2856 (s), 1737 (m), 1614 (m), 1591 (m), 1519 (s), 1396 (m), 1338 (m), 1231 (s), 1183 (m), 1069 (m), 881 (m), 855 (m), 811 (m) cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{19}NOSBrF$ ($M + H^+$) 348.0505; found 348.0505.

Acknowledgements

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(22) CCDC numbers for compound **1d**: CCDC 828383. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif. Crystallographic description of **1d**: Crystal dimension (mm): $0.43 \times 0.35 \times 0.26$. $C_{13}H_{16}N_1O_1S_1$, $M_r = 234.34$. Monoclinic, space group $P_2(1)/n$; $a = 10.1039(19)$ Å, $b = 18.054(4)$ Å, $c = 14.444(3)$ Å; $\alpha = 90.00°$, $\beta = 99.687(10)$, $\gamma = 90.00°$, $V = 2597.2(9)$ Å^3; $Z = 8$; $\rho_{cal} = 2.26\,mg/m^3$; $\mu\,mm^{-1}) = 1.199$; $F\ (000) = 1000$; reflection collected/unique = 6538/3452; refinement method = full-matrix least-squares on F^2; final R indices $[I > 2\sigma_l]\ R_1 = 0.1325$, $wR_2 = 0.2032$, R indices (all data) $R_1 = 0.0724$, $wR_2 = 0.1741$; goodness of fit = 0.997.