Preparations of diversely substituted thiosemicarbazides and *N*-hydroxythioureas

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Dedicated to Prof. James Coxon on his 65th birthday

Abstract
Thiosemicarbazides **5** (yields 50-97%) and *N*-hydroxythioureas **6** (yields 71-99%) of variable substitution patterns are prepared efficiently by reactions of 1-(thiocarbamoyl)benzotriazoles **4a–i** with hydrazines or hydroxylamines, respectively.

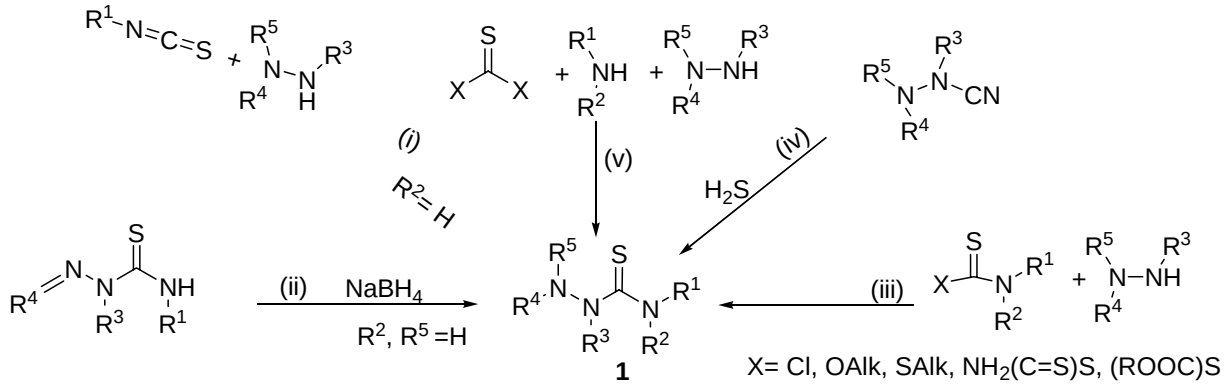
Keywords: Thiosemicarbazides, *N*-hydroxythioureas, isothiocyanates

Introduction

Thiosemicarbazides

Thiosemicarbazides are valuable building blocks for the synthesis of five-membered heterocycles.[1] Biologically active thiosemicarbazide derivatives include 1,3,4-thiadiazoles, as antibacterial[2]and antifungal[3]agents, and 1,3,4-thiadiazolium-2-amidines as anticonvulsant,[4] antimicrobial,[5] and antitumor agents.[6]

Published preparations of thiosemicarbazides **1** (Scheme 1) include (i) reactions of isothiocyanates with hydrazines, the method most frequently used,[7a-e] but isothiocyanates are difficult to handle and store;[8a-b] (ii) reduction of thiosemicarbazones by sodium borohydride is used for the preparation of and only applicable if R^2=H mono-, di-, and tri- substituted **1** (but not tetra- or pentasubstituted);[9] (iii) reactions of hydrazines with reactive thiocarbamic acid derivatives; the yields (66-73%) were affected by side reactions;[10-12] (iv) reactions of cyanohydrazines with hydrogen sulfide can yield mono or disubstituted thiosemicarbazides **1** (R^1=R^2=H);[13] and (v) reactions of 1,2,4-triazolyl or bis(imidazolyl)methanethiones with amines then with hydrazines to give di- and trisubstituted thiosemicarbazides **1**.[14-15]



Scheme 1

Seventeen classes of *N*-substituted thiosemicarbazides can exist as shown in Table 1: three of mono (A, B, C), five of di (D through H), five of tri (I through M), three of tetra (N, O, P), and one of penta (Q) substitution). Of these seventeen, nine have previously been reported in the literature (Table 1 classes A, B, C, D, E, F, G, H, M).While most of the other classes could potentially be made by one or more of the existing methods; a literature sub-structural search showed no known examples of compounds of classes I, J, K, L, N, O, P, Q.

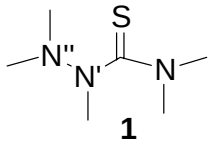
Method i is convenient for the preparation of classes A, E, F. Methods ii and iii are mainly used for the preparation of class F with a single example of class D using iii. Classes B, C, G, H, M are easily prepared using methods iv and v (Table 1). The work now presented provides an efficient route to the hither to unexplored classes J and L together with alternative access or potential access to classes A, B, C, E, F, G, H, M, P.

N-Hydroxythioureas

N-Hydroxythioureas are toxic to *Lactobacillus arabinosus*, *Leuconostoc dextranicum* and *Streptococcus Faecalis*,[16] and some derivatives, e.g. *S*-methyl-*N*-hydroxyisothiourea, inhibit nitrous oxide synthase (NOS).[17]

Methods of preparation of *N*-hydroxythioureas **2** (Scheme 2) include (i) reactions of isothiocyanates with hydroxylamine to give **2** (23-66%);[16-20] (ii) the reduction of unstable *N*, *N*`-dihydroxythioureas.[21]

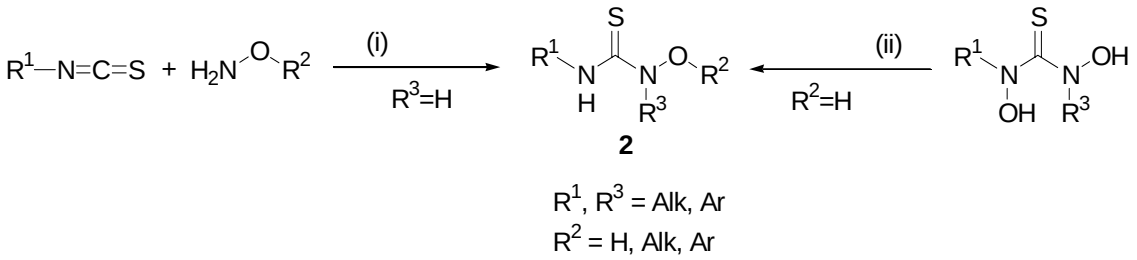
Table 1. The possible classes of substituted thiosemicarbazides **1** and reported methods of preparation



1

N-Substituents		Class	Literature Methods (Scheme 1)					This work
Number	**Position**		**i**	**ii**	**iii**	**iv**	**v**	
	N	**A**	R	P	P	-	P	R
Mono	**N'**	**B**	-	P	-	R	R	P
	N''	**C**	-	P	-	R	R	P
	NN	**D**	-	-	P	-	-	-
	NN'	**E**	R	P	P	-	P	P
Di	**NN''**	**F**	R	R	R	-	P	R
	N'N''	**G**	-	P	-	R	R	P
	N''N''	**H**	-	P	-	R	R	P
	NNN'	**I**	-	-	P	-	-	-
	NN'N''	**J**	P	P	P	-	P	R
Tri	**NNN''**	**K**	-	-	P	-	-	-
	NN''N''	**L**	P	P	P	-	P	R
	N'N''N''	**M**	-	P	-	R	R	P
	NNN'N''	**N**	-	-	P	-	-	-
Tetra	**NNN''N''**	**O**	-	-	P	-	-	-
	NN'N''N''	**P**	P	P	P	-	P	P
Penta	**NNN'N''N''**	**Q**	-	-	P	-	-	-

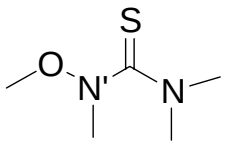
R: Reported; P: Possible, but no example reported; -: Not possible



Scheme 2

Eleven classes of *N*,*O* substituted hydroxythioureas **2** can exist as shown in Table 2 (three Mono, four Di, three Tri, and one Tetra). The two existing literature methods (i and ii) , provide preparative methods for classes A', E', G' (Table 2). The present work affords an easy access to novel classes C', F', H' in addition to A', B', E', G'. However, classes D', I', J', K', not previously reported, could not be prepared via our proposed procedure because although reacting **3** (Scheme 3) with secondary amines was successful, further reactions with hydrazines and hydroxylamines failed.

Table 2. The possible classes of substituted *N*-hydroxythioureas **2** and reported methods of preparation



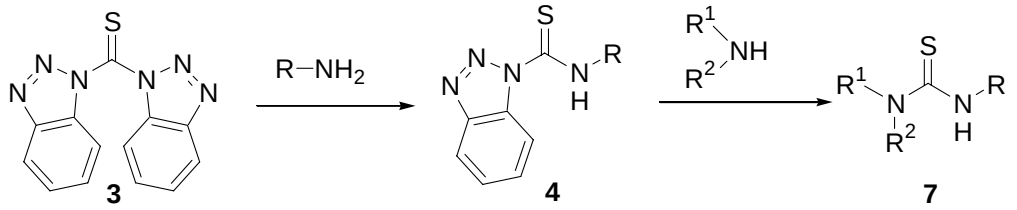
2

		Mono-subst.			Di-subst.				Tri-subst.			Tetra-subst.
		N	**N'**	**O**	**NN**	**NO**	**N'O**	**NN'**	**NN'O**	**NNN'**	**NNO**	**NNN'O**
	Class	**A'**	**B'**	**C'**	**D'**	**E'**	**F'**	**G'**	**H'**	**I'**	**J'**	**K'**
Literature Methods	**i**	R	-	-	-	R	-	-	-	-	-	-
	ii	R	P	-	-	-	-	R	-	-	-	-
	This work	R	P	P	-	R	P	R	R	-	-	-

R: Reported; P: Possible but no example reported; -: not possible by this method

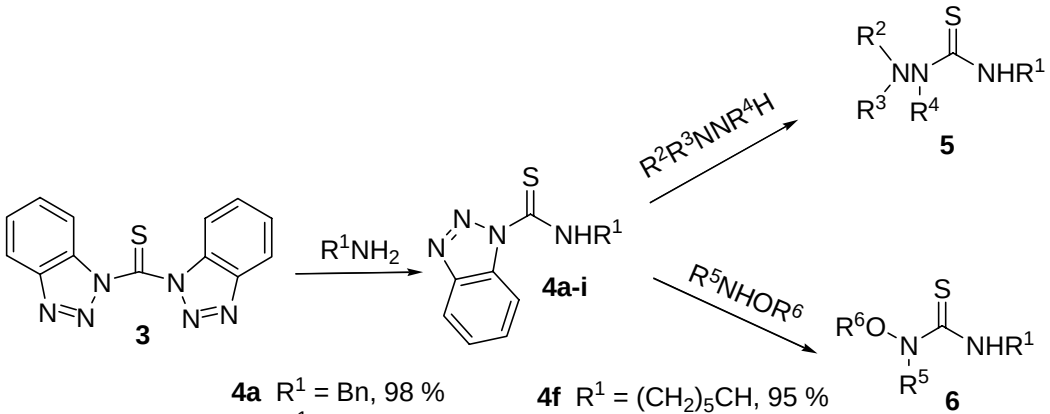
Results and Discussion

Recently, we reported efficient synthesis of di- and trisubstituted thioureas **7** utilizing 1-(alkyl-or-arylthiocarbamoyl)benzotriazoles **4** (Scheme 3).[22] We have now expanded this methodology to include the synthesis of thiosemicarbazides **5** and *N*-hydroxythioureas **6**.



Scheme 3

Bis(benzotriazolyl)methanethione **3**, a thiophosgene equivalent, is easily prepared from 1-trimethylsilylbenzotriazole and thiophosgene in quantitative yield.[23] As previously described, treatment of **3** with various primary amines in methylene chloride at room temperature followed by a 5% Na_2CO_3 wash and recrystallization afforded 1-(alkyl-or-arylthiocarbamoyl)benzotriazoles **4a–i** in 90-98% yields (Scheme 4).[22] Only primary amines were used in the preparation of **4a–i.**



4a R^1 = Bn, 98 %
4b R^1 = *i*-Pr, 95 %
4c R^1 = Ph, 90 %
4d R^1 = *n*-Bu, 98 %
4e R^1 = $(CH_2)_2$Ph, 93 %
4f R^1 = $(CH_2)_5CH$, 95 %
4g R^1 = $C(CH_3)$Bn, 97 %
4h R^1 = 2-Furfuryl, 93 %
4i R^1 = allyl, 95 %

Structures **5** and **6** are fully defined in Tables 3 and 4 respectively

Scheme 4

Substituted thiosemicarbazides **5** were prepared via a single step reaction of 1-(alkyl-or-arylthiocarbamoyl)benzotriazoles **4a–i** with the appropriate hydrazine (Scheme 4, Table 3). Stirring 1 equiv. of **4** in methylene chloride at room temperature with 1.1 equiv. of the hydrazine and 2 equiv. of triethylamine followed by a 5% Na_2CO_3 wash afforded **5** in excellent yields (Table 3). The reaction reached completion after 2 h. as monitored by TLC. Substituted thiosemicarbazides **5** were purified using column chromatography (EtOAc/Hex) and characterized using NMR (^1H, ^{13}C). Melting points for known **5** agreed with reported values (see the Experimental Section). Novel **5** were characterized by ^1H, ^{13}C NMR spectra and elemental analyses (see the Experimental Section).

N-Hydroxythioureas **6** were prepared from the reaction of 1-(alkyl-or-arylthiocarbamoyl)benzotriazoles **4a–i** in methylene chloride at room temperature with 1.5 equiv. of the corresponding hydroxylamine and 3 equiv. of triethylamine (Scheme 4, Table 4). Starting materials disappeared completely after 5-12 h. as monitored by TLC. Formation of a white precipitate (benzotriazole triethylamine salt) marked the completion of the reaction. The precipitate was filtered and the filtrate washed with 5% Na_2CO_3. The organic layer was extracted with methylene chloride (3 times), evaporated under vacuum, and chromatographed (EtOAc/Hex) to give *N*-hydroxythioureas **6** in excellent yields (Table 4). *N*-Hydroxythioureas **6** were fully characterized using NMR (^1H, ^{13}C) and elemental analysis. Melting points for known **6** agreed with reported values (see the Experimental Section). Novel **6** were characterized by ^1H, ^{13}C NMR spectra and elemental analyses (see the Experimental Section).

Table 3. Preparation of substituted and unsubstituted thiosemicarbazides

R^1	R^2	R^3	R^4	Product	Yield%
Cy	Ph	H	H	**5f–a**	88
n-Bu	Ph	H	H	**5d–a**	85
Phenethyl	H	H	H	**5e–a**	85
Cy	H	H	H	**5f–b**	91
Bn	H	H	H	**5a–a**	97
Allyl	H	H	H	**5i–a**	74
DL-alpha-Methylbenzyl	Me	Me	H	**5g–a**	50
n-Bu	Me	Me	H	**5d–b**	85
Furfuryl	Me	Me	H	**5h–a**	83
i-Pr	Me	H	Me	**5b–a**	78
Bn	Me	H	Me	**5a–b**	97

* Solvent: CH_2Cl_2, Temp.: 25˚C, Time: 2h.

Table 4. Preparation of substituted and unsubstituted *N*-hydroxythioureas

R^1	R^5	R^6	Product	Yield%
Bn	H	H	**6a–a**	90
n-Bu	H	H	**6d–a**	77
Cy	H	H	**6f–a**	83
Ph	H	H	**6c–a**	99
i-Pr	Me	Me	**6b–a**	99
n-Bu	Me	H	**6d–b**	87
DL-alpha-Methylbenzyl	Me	Me	**6g–a**	89
i-Pr	H	Bn	**6b–b**	75
Phenethyl	H	Bn	**6e–a**	71

* Solvent: CH_2Cl_2, Temp.: 25˚C, Time: 5-12h.

Conclusion

A new route providing easy access to thiosemicarbazides and *N*-hydroxythioureas of diverse substitution patterns in excellent yields has been established. Tables 1 and 2 compare our method to already reported routes of preparation of thiosemicarbazides and *N*-hydroxythioureas. Our method is particularly advantageous for the preparation of trisubstituted thiosemicarbazides (Table 1) and mono and disubstituted *N*-hydroxythioureas (Table 2). It is efficient with relatively short reaction time, and avoids the use of unstable isothiocyanates which are the classical starting materials for preparation of thiosemicarbazides and *N*-hydroxythioureas.

Experimental Section

General Procedures. Melting points were determined on a hot-stage apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$, or DMSO-d_6 with TMS as the internal standard for ^{1}H (300 MHz) or a solvent as the internal standard for ^{13}C NMR (75 MHz). Column chromatography was conducted on silica gel (200–425 mesh). *Bis*-benzotriazol-1-yl-methanethione **3** was prepared according to a previously reported procedure; Mp 171-172°C, yield 98%, (Lit. Mp 170-171 °C, yield 90%).[23]

General procedure for the preparation of 4a–i. 1-Thiocarbamoyl benzotriazoles **4a–i** were synthesized by the reaction of compound **3** (2 mmol) and the appropriate primary amine (2 mmol) in methylene chloride at room temperature for 2 h according to reported procedure.[22] Melting points and spectral data were used to characterize known **4a-f, h-i** and were found to be identical to reported values: **4a** mp 108-109 °C (Lit. mp 108-109 °C);[22] **4b** mp 107-108 °C (Lit. mp 107.7°C);[24] **4c** mp 98-99 °C (Lit. mp 98.5°C);[24] **4d** mp 92-93 °C (Lit. mp 92.3°C);[24] **4e** mp

110.5 °C (Lit. mp 110.2°C);[24] **4f** mp 72 °C (Lit. mp 72-73 °C);[22] **4h** mp 117 °C (Lit. mp 117-119 °C);[22] **4i** mp 56.4 °C (Lit. mp 56-57 °C).[22] Known **4g** was isolated as a yellow oil;[22] spectral data and elemental analysis were used for characterization.

General procedure for the preparation of compounds 5. To a stirred solution of (1.15 mmol) **4a–i** in 12ml of dichloromethane, was added (1.27mmol) of the corresponding hydrazine hydrate followed by (2.5 mmol) of triethylamine. The mixture was stirred for 3 hours at room temperature, then 10 ml of 5% Na_2CO_3 were added to remove excess benzotriazole. The solution was extracted with dichloromethane (3x50ml) and the organic layer was dried over magnesium sulfate. Evaporating the solvent under reduced pressure followed by column chromatography (EtOAc/Hex gradient) afforded pure **5** in 50-97% yield.

***N*-Cyclohexyl-2-phenyl-1-hydrazinecarbothioamide (5f–a).** [25] Recrystallized from EtOAc/Hex to give pink crystals (88%), mp 165 °C (lit. 163°C); ^{1}H NMR δ 7.32–7.26 (m, 2H), 7.19 (br s, 1H), 7.12–7.10 (m, 1H), 6.97-7.02 (m, 1H), 6.81-6.86 (m, 2H), 5.71 (br s, 1H), 4.27– 4.24 (m, 1H), 2.06–2.03 (m, 2H), 1.72–1.61 (m, 3H), 1.42–1.34 (m, 2H), 1.23–1.11 (m, 3H); ^{13}C NMR δ 146.1, 134.8, 129.6, 122.4, 113.5, 53.0, 32.7, 25.4, 24.8.

***N*-Butyl-2-phenyl-1-hydrazinecarbothioamide (5d–a).** [12] Oil (85%); ^{1}H NMR δ 7.48 (br s, 1H), 7.30–7.23 (m, 3H), 6.95-7.01 (m, 1H), 6.92-6.86 (m, 2H), 5.89 (br s, 1H), 3.63 (q, J = 7.1 Hz,2H), 1.59–1.54 (m, 2H), 1.37–1.29 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR δ 146.1, 129.5, 129.3, 122.3, 113.5, 44.1, 31.1, 19.9, 13.7.

***N*-Phenethyl-1-hydrazinecarbothioamide (5e–a).** [12] Recrystallized from EtOAc/Hex to give white prisms (85%), mp 115 °C (lit. 113 °C); ^{1}H NMR δ 8.13 (s, 1H), 7.49 (br s, 1H), 7.33– 7.27 (m, 2H), 7.24–7.22 (m, 3H), 3.89–3.83 (m, 2H), 3.77 (s, 2H), 2.94–2.89 (m, 2H) ; ^{13}C NMR (DMSO) δ 158.7, 128.7, 128.4, 128.3, 126.1, 36.2, 34.9.

***N*-Cyclohexyl-1-hydrazinecarbothioamide (5f–b).** [27] Recrystallized from EtOAc/Hex to give white crystals (91%), mp 142 °C (lit. 143 °C); ^{1}H NMR δ 7.34 (br s, 1H), 7.19 (br s, 1H), 4.26–4.20 (m, 1H), 3.71 (s, 2H), 2.08–2.03 (m, 2H), 1.77–1.71 (m, 2H), 1.66–1.60 (m, 2H), 1.46–1.36 (m, 2H), 1.30–1.18 (m, 2H); ^{13}C NMR δ 152.4, 52.6, 32.9, 25.5, 24.8.

***N*-Benzyl-1-hydrazinecarbothioamide (5a–a).** [27] Recrystallized from CH_2Cl_2//Hex to give colorless plates (97%), mp 125–127 °C (lit. 126–128 °C); ^{1}H NMR δ 7.97 (s, 1H), 7.73 (br s, 1H), 7.35–7.28 (m, 5H), 4.84 (d, J = 5.8 Hz, 2H), 3.78 (br s, 2H); ^{13}C NMR δ 182.3, 137.8, 128.6, 127.7, 127.6, 47.8.

***N*-Allyl-1-hydrazinecarbothioamide (5i–a).** [28] Recrystallized from CH_2Cl_2//Hex to give colorless microcrystals (74%), mp 93– 94 °C (lit. 90– 94 °C); ^{1}H NMR δ 8.07 (s, 1H), 7.54 (br s, 1H), 5.99–5.86 (m, 1H), 5.27 (d, J=1.4Hz, 0.5H), 5.22–5.20 (m, 1H), 5.16 (d, J=1.4Hz, 0.5H), 4.29 (t, J= 5.9Hz, 2H), 3.87 (br s, 2H) ; ^{13}C NMR δ 182.0, 133.7, 116.6, 46.3.

2,2-Dimethyl-N-(DL-alpha-methylbenzyl)-1-hydrazinecarbothioamide (5g–a). [12] Recrystallized from EtOAc/Hex to give white crystals (50%), mp 105–107 °C (lit. 105 °C); ^{1}H NMR δ 7.6 (br s, 1H), 7.36–7.35 (m, 4H), 7.30–7.26 (m, 1H), 6.59 (br s, 1H), 5.69–5.64 (m, 1H), 2.56 (s, 3H), 2.53 (s, 3H), 1.59 (s, 1H), 1.61 (s, 1H); ^{13}C NMR δ 142.8, 135.5, 128.6, 127.3, 126.2, 52.6, 47.3, 47.1, 21.6.

***N*-Butyl-2,2-dimethyl-1-hydrazinecarbothioamide (5d–b).**[12] Oil (85%); ^{1}H NMR δ 7.23 (br s, 1H), 6.25 (br s, 1H), 3.67–3.60 (m, 2H), 2.53 (s, 6H), 1.66–1.57 (m, 2H), 1.43–1.35 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR δ 158.0, 47.2, 43.8, 31.3, 20.1, 13.8.

***N*- (2-Furylmethyl)-2,2-dimethyl-1-hydrazinecarbothioamide (5h–a).** Recrystallized from EtOAc/Hex to give colorless rods (83%), mp 106 °C; ^{1}H NMR δ 7.57 (br s, 1H), 7.39 (s, 1H), 7.02 (br s, 1H), 6.36–6.34 (m, 1H), 6.31–6.30 (m, 1H), 4.84 (d, *J* = 5.5 Hz, 2H), 2.54 (s, 6H); ^{13}C NMR δ 150.7, 142.2, 138.0, 110.4, 107.8, 47.0, 40.8. Anal. Calcd for $C_8H_{13}N_3OS$: C, 48.22; H, 6.58; N, 21.09. Found: C, 48.55; H, 6.77; N, 21.34.

***N*-Isopropyl-1,2-dimethyl-1-hydrazinecarbothioamide (5b–a).** [29] Recrystallized from CH_2Cl_2/Hex to give colorless needles (78%), mp 64– 65 °C (lit. 64.0 - 65.0°C); ^{1}H NMR δ 7.65 (s, 1H), 4.52–4.41 (m, 1H), 3.53 (s, 3H), 3.36 (q, *J* = 5.6 Hz, 1H), 2.59 (d, *J* = 5.6 Hz, 3H), 1.22 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR δ 180.0, 46.2, 36.6, 34.4, 22.6.

***N*-Benzyl-1,2-dimethyl-1-hydrazinecarbothioamide (5a–b).** [30] Recrystallized from CH_2Cl_2/ / Hex to give colorless cubes (97%), mp 116–117 °C (lit. 115–116°C); ^{1}H NMR δ 8.06 (s, 1H), 7.33–7.24 (m, 5H), 4.80 (d, *J* = 5.6 Hz, 2H), 3.55 (s, 3H), 3.40–3.39 (m, 1H), 2.57 (d, *J* = 5.6 Hz, 3H); ^{13}C NMR δ 181.5, 138.3, 128.5, 127.5, 127.3, 48.8, 36.9, 34.5.

General procedure for the preparation of compounds 6. To a stirred solution of (2.0 mmol) **4a–i** in 15ml of dichloromethane, was added (3.0 mmol) of the corresponding hydroxylamine hydrochloride followed by (9.0 mmol) of triethylamine. The mixture was stirred for 5 hours at room temperature. Completion of the reaction is marked by the formation of a white precipitate (benzotriazole triethylamine salt). The reaction mixture was evaporated under reduced pressure then redissolved in diethyl ether. The precipitate formed was filtered, followed by addition of 10 ml of 5% Na_2CO_3 to remove excess benzotriazole. The solution was extracted with dichloromethane (3x50ml) and the organic layer was dried over magnesium sulfate. Evaporating the solvent under reduced pressure followed by column chromatography (EtOAc/Hex gradient) afforded pure **6** in 71–99% yield.

***N*-Benzyl-*N*-hydroxythiourea (6a–a).** [16] Recrystallized from EtOAc/Hex to give white powder (90%), mp 156 °C (lit. 155–157 °C); ^{1}H NMR δ 7.26–7.22 (m, 3H), 7.19–7.15 (m, 2H), 6.05 (br s, 1H), 4.56 (s, 2H), 1.54 (br s, 1H); ^{13}C NMR δ 153.7, 136.5, 128.9, 128.0, 127.5, 48.6.

***N*-Butyl-*N*-hydroxythiourea (6d–a).** [16] Recrystallized from CH_2Cl_2//Hex to give colorless plates (77%), mp 107 °C (lit. 107–108 °C); ^{1}H NMR δ 5.90 (br s, 1H), 3.42 (br s, 2H), 1.64–1.55 (m, 2H), 1.45–1.33 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR δ 181.3, 44.0, 31.0, 20.0, 13.7.

***N*-Cyclohexyl-*N*-hydroxythiourea (6f–a).** [16] Recrystallized from EtOAc/Hex to give brown powder (83%), mp 116 °C (lit 116–118 °C); ^{1}H NMR δ 6.01 (br s, 1H), 4.53 (br s, 1H), 3.49–3.45 (m, 1H), 2.00–1.92 (m, 2H), 1.74–1.60 (m, 3H), 142– 1.06 (m, 5H); ^{13}C NMR δ 158.2, 49.4, 33.6, 25.5, 24.8.

***N*-Hydroxy-*N*-phenylthiourea (6c–a).** [16] Recrystallized from CH_2Cl_2//Hex to give white microcrystals (99%), mp 103 °C (lit. 103 °C); ^{1}H NMR δ 8.13 (s, 1H), 7.43–7.36 (m, 5H), 7.30–7.25 (m, 1H); ^{13}C NMR δ 179.7, 137.0, 129.5, 127.0, 125.2.

***N′*-Isopropyl-*N*-methoxy-*N*-methylthiourea (6b–a).** Colorless liquid (99%); ^{1}H NMR δ 6.74 (s, 1H), 4.59–4.43 (m, 1H), 3.70 (s, 3H), 3.55 (s, 3H), 1.26 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR δ 180.0, 60.4, 46.2, 38.0, 22.2. Anal. Calcd for $C_6H_{14}N_2OS$: C, 44.42; H, 8.70; N, 17.27. Found: C, 44.79; H, 8.74; N, 17.13.

***N`*-Butyl-*N*-hydroxy-*N*-methylthiourea (6d–b).** Oil (87%); ^{1}H NMR δ 7.90 (br s, 1H), 6.99 (br s, 1H), 3.61 (s, 3H), 3.55 (q, *J* = 7.1 Hz, 2H), 1.62–1.54 (m, 2H), 1.42–1.35 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR δ 157.3, 44.9, 42.0, 31.3, 20.0, 13.8. Anal. Calcd for $C_6H_{14}N_2OS$: C, 44.42; H, 8.70; N, 17.27. Found: C, 44.75; H, 9.17; N, 17.52.

***N*-Methoxy-*N*-methyl-*N'*-(DL-alpha-methylbenzyl)thiourea (6g–a).** Colorless oil (89%); ^{1}H NMR δ 7.36–7.34 (m, 4H), 7.29–7.25 (m, 1H), 7.08 (d, *J* = 7.3 Hz, 1H), 5.68–5.58 (m, 1H), 3.67 (s, 3H), 3.56 (s, 3H), 1.59 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR δ 180.2, 142.6, 128.5, 127.3, 126.1, 60.7, 53.3, 38.1, 21.3. Anal. Calcd for $C_{11}H_{16}N_2OS$: C, 58.90; H, 7.19; N, 12.49. Found: C, 59.27; H, 7.35; N, 12.74.

***N*- (Benzyloxy)-*N*-isopropylthiourea (6b–b).** Recrystallized from CH_2Cl_2//Hex to give white microcrystals (75%), mp 60 °C; ^{1}H NMR δ 7.94 (br s, 1H), 7.387.44 (m, 5H), 6.46 (br s, 1H), 4.82 (s, 2H), 4.46–4.35 (m, 1H), 1.10 (d, *J* = 6.6 Hz, 6H) ; ^{13}C NMR δ 181.4 , 134.9, 129.4, 129.3, 129.0, 78.5, 46.0, 22.0. Anal. Calcd for $C_{11}H_{16}N_2OS$: C, 58.90; H, 7.19; N, 12.49. Found: C, 59.10; H, 7.39; N, 12.83.

***N*- (Benzyloxy)-*N*-phenethylthiourea (6e–a).** Recrystallized from CH_2Cl_2//Hex to give white microcrystals (71%), mp 79– 80 °C; ^{1}H NMR δ 8.34 (s, 1H), 7.37–7.30 (m, 5H), 7.27–7.19 (m, 5H), 6.79 (s, 1H), 4.71 (s, 2H), 3.83 (q, *J* = 6.9 Hz, 2H), 2.85 (t, *J* = 6.9 Hz, 2H); ^{13}C NMR δ 182.0, 138.2, 134.5, 129.2, 129.1, 128.8, 128.7, 126.7, 78.4, 44.9, 34.8. Anal. Calcd for $C_{16}H_{18}N_2OS$: C, 67.10; H, 6.33; N, 9.78. Found: C, 66.96; H, 6.41; N, 9.71.

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