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Article

Tf_2O: A Desulfurating Reagent in the Synthesis of Isothiocyanates

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ABSTRACT

Isothiocyanates are ubiquitous building blocks used across fields. Nevertheless, their classical syntheses very often rely on the use of toxic and expensive reagents. Herein, we report a new practical and mild protocol for the preparation of isothiocyanates starting from amine and carbon disulfide employing triflic anhydride (Tf_2O) as a desulfurating reagent. The resulting isothiocyanates on reaction with an amine gave thioureas with a good to excellent yield.

Key words: Carbon disulfide, Dithiocarbamate, Isothiocyanates, Triflic anhydride

1. INTRODUCTION

Isothiocyanates are an important class of compounds with a wide range of biological activities. They are indeed commonly encountered in various fields, and one notable example of their occurrence is in natural products, particularly cruciferous vegetables and mustard oils. The synthesis of isothiocyanates in these natural products occurs through the enzymatic conversion of glucosinolates [1]. They serve as potential precursors for accessing thioamides [2], thioureas [3], and various heterocyclic compounds. [4] Thioureas have commonly been encountered across the fields of pharmaceuticals and agriculture [5-7]. Numerous thiourea and its derivatives serve as anticancer [8,9], antimicrobial [10,11], anti-fungal agents [12], are useful in the preparation of pesticides [13], fungicides, and herbicides [14,15]. The synthesis of thioureas involves a reaction between an isothiocyanate and a primary or secondary amine. Several protocols have been developed to convert amines into isothiocyanates. A common protocol for the synthesis of isothiocyanates involves the treatment of primary amine with thiophosgene [16]. In recent years, several new methods have been developed for the synthesis of ITCs using fluorine-containing reagents such as Langlois reagent (F_3CSO_2Na) [17], $Ph_3P+CF_3CO_2$ (PDFA)/S8 [18], (Me_4N) SCF_3 [19], CF_3SiMe_3/S_8 or $AgSCF_3$ [20], and $BrCF_2CO_2Na/S_8$ [21]. However, three methods still predominate. Besides numerous desulfurating agents available for the synthesis of isothiocyanates, there is still a desirable reagent in the synthesis of isothiocyanates [22-29]. It is worth noting that the Staudinger/Aza-Wittig tandem reaction is just one of several methods for synthesizing isothiocyanates [28], but it is known to have few concerns. These methods are also very often limited in scope and, in some cases, involve harsh reaction conditions [30]. A simple route for the synthesis of isothiocyanates through desulfurization and application in the synthesis of thioureido peptides is described.

2. EXPERIMENTAL

2.1. Material and Methods

Instrumentation: All the chemicals used were purchased from Sigma Aldrich, USA. The solvents were freshly distilled and dried. TLC analysis was carried out using Merck aluminum TLC sheets (silica gel 60 F254). The chromatograms were observed by ultraviolet light and by the iodine chamber whenever it was necessary. High-resolution mass spectrometry spectra were recorded in the Micromass Q-TOF mass spectrometer. ^1H and ^{13}C nuclear magnetic resonance (NMR) was determined in a Brucker AV NMR (400 MHz, 100 MHz) spectrometer.

2.2. General Procedure: Synthesis of Isothiocyanates and Thioureas

Triethylamine (Et_3N) (3.0 equiv) and CS_2 (2.0 equiv) were added dropwise to an amine (1.5 equiv) in anhyd CH_2Cl_2 (10 mL) at 0°C. The solution was stirred for 15 min. Triflic anhydride (Tf_2O) (1.0 equiv) was added over 5 min in three portions, and the solution was stirred for another 30-40 min. Next, the mixture was hydrolyzed with H_2O (10 mL) and diluted with CH_2Cl_2 (50 mL). The organic layer was separated and washed successively with H_2O (2 × 5 mL), 1 M HCl (2 × 5 mL), H_2O (2 × 5 mL), saturated $NaHCO_3$ (2 × 5 mL), H_2O (5 mL), and brine (5 mL) and then dried over anhydrous Na_2SO_4. The crude products were purified by flash chromatography on silica gel using hexane or pentane as eluents. Pure isothiocyanates were isolated after the evaporation of the solvent under reduced pressure. The isolated isothiocyanates were then treated with amines (1.5 equiv) at rt for 2–3 h. The reaction mixture was concentrated to dryness under reduced pressure. The residue was extracted into ethyl acetate (EtOAc). The organic layer was washed with a 10% citric acid solution, brine, and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo, and the crude product was purified by flash chromatography using hexane-EtOAc to get a pure product.

2.3. Compound Name

(Isothiocyanatomethyl)benzene **(3a):** Colorless oil; yield 81%.

Fourier-transform infrared spectroscopy: 2162 (NCS), 2087 (NCS), 1453, 1396, 1170, 705 cm^{-1}.

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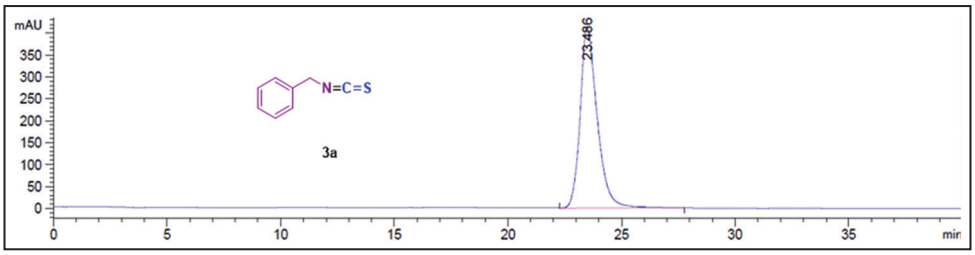


Figure 1: Reversed-phase high-performance liquid chromatography of 3a for determining purity.

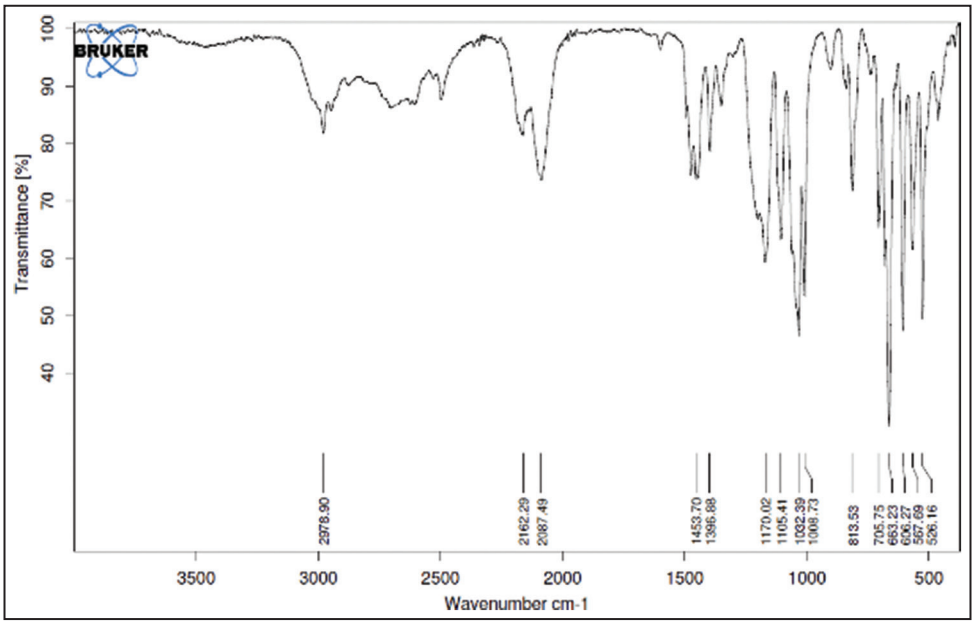
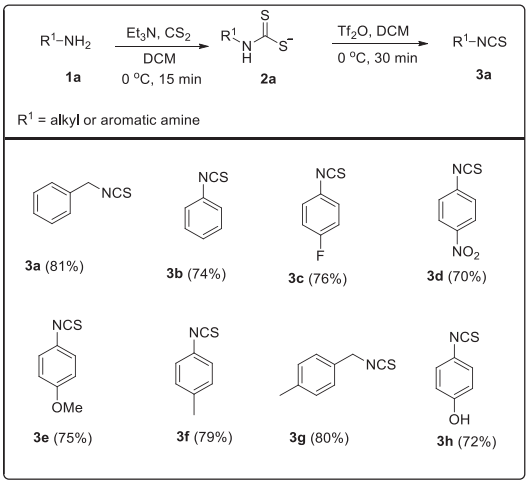


Figure 2: Fourier-transform infrared spectroscopy spectrum of compound 3a.



Scheme 1: List of isothiocyanates prepared.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46−7.34 (m, 5H), 4.73 (s, 2H).

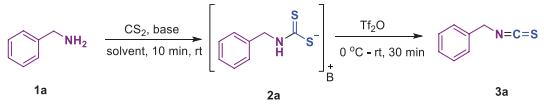
^{13}C NMR (101 MHz, DMSO-d_6) δ 136.6, 128.9 (2), 127.9 (2), 127.5, 48.6.

High resolution mass spectra (HRMS) (ESI-TOF) m/z: $[M]^+$ Calcd for C_8H_7NS 149.0299, found 149.0291.

3. RESULTS AND DISCUSSION

We initiated the study by optimizing the reaction at room temperature involving the conversion of amine to dithiocarbamate further treated with Tf_2O in the synthesis of isothiocyanates. Screening of a variety of bases was performed with the equivalents of the base gradually increased from 1.5 eq to 2.0 eq and 3.0 eq. The product was obtained in 42%, 58%, and 81% yields (Table 1 entry 1,5,6) [Figures 1 and 2] in the presence of Tf_2O as a desulfurating agent. Next, screening of different solvents was also carried out; the best

Table 1: Optimization of the reaction conditions.



Entry	Solvent	Base (equiv)	Time (min)	Yield (%)
1	DCM	Et_3N (2.0)	60	58
2	DCM	DIPEA (3.0)	30	61
3	DCM	NMM (3.0)	30	72
4	DCM	DBU (3.0)	30	45
5	DCM	Et_3N (3.0)	30	81
6	MeCN	Et_3N (1.5)	30	42
7	1,4 dioxane	Et_3N (3.0)	30	68
8	DMF	Et_3N (3.0)	30	38

DCM: Dichloromethane, DMF: Dimethylformamide, Et_3N: Triethylamine, DIPEA: Diisopropylethylamine

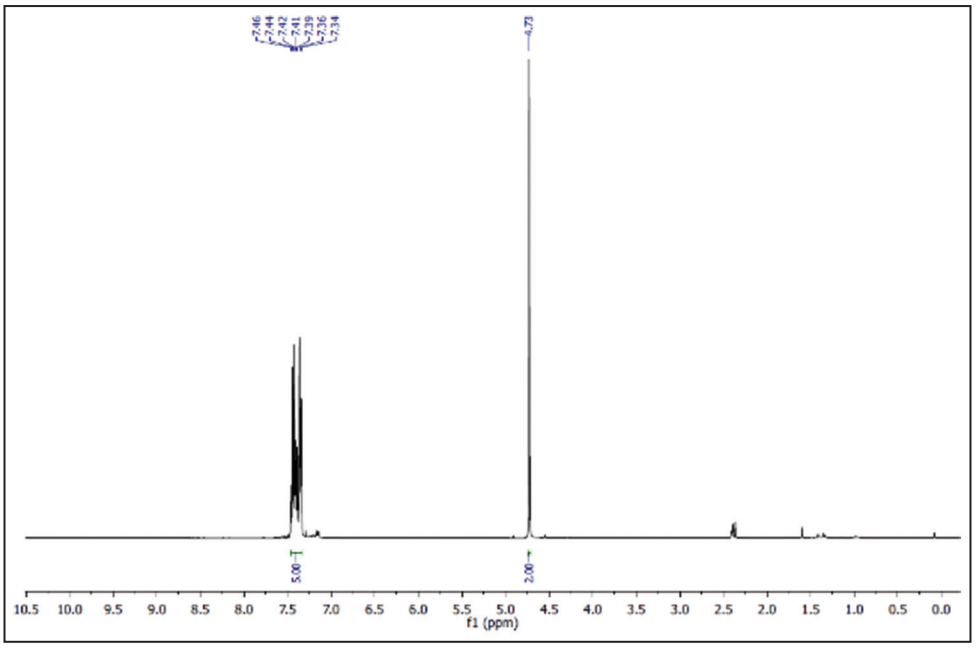


Figure 3: ^{1}H Nuclear magnetic resonance spectrum of compound 3a.

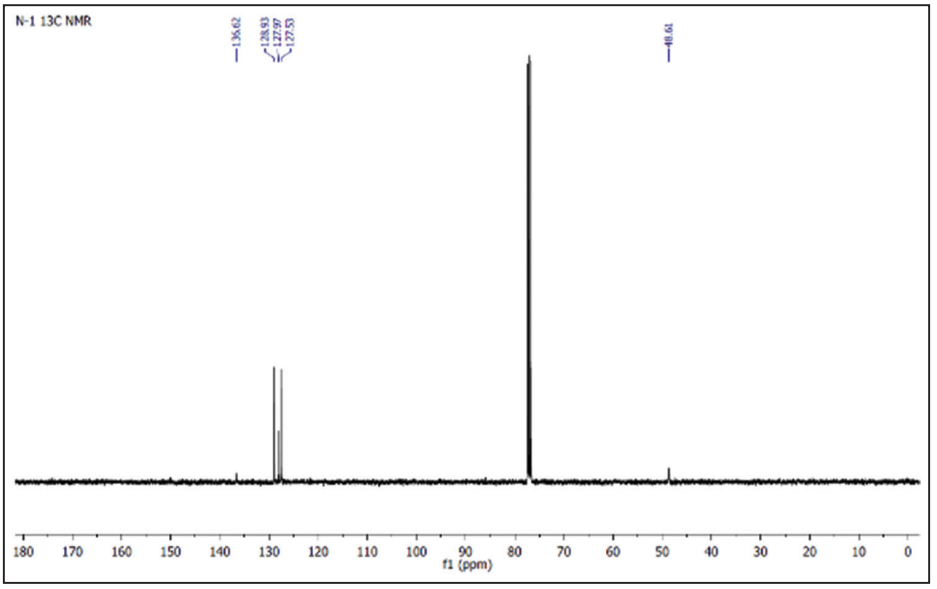
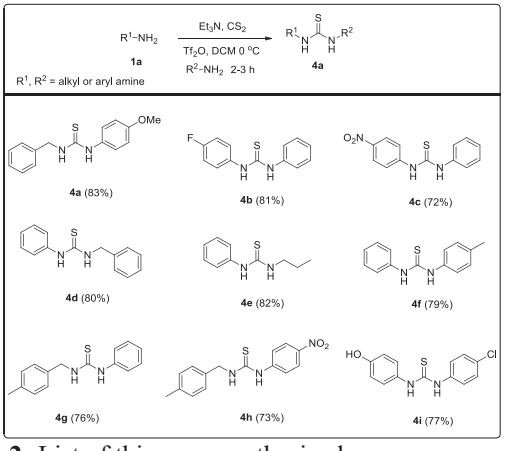


Figure 4: ^{13}C nuclear magnetic resonance spectrum of compound 3a.



Scheme 2: List of thioureas synthesized.

obtained 3a was under dichloromethane as a solvent and Et_3N as a base (Table 1, entry 5).

In a typical experiment, a solution of benzyl amine (1a) in THF was treated with CS_2 in the presence of Et_3N at 0°C for 15 min, and the *in situ* generated benzyl dithiocarbamate (2a) was treated with Tf_2O at 0°C to room temperature. Upon completion of the reaction (monitored by TLC), isothiocyanates (3a) [Figures 3-5] were isolated by a simple workup and then purified by flash chromatography with a good yield [Scheme 1]. All the isothiocyanates obtained were characterized by NMR and mass spectra [Supplementary information].

The obtained isothiocyanates was treated with amine nucleophile. Thioureas (4a-i) were isolated by simple workup and purified by flash chromatography. A series of thioureas was obtained with a good yield [Scheme 2] and characterized by NMR and mass spectra.

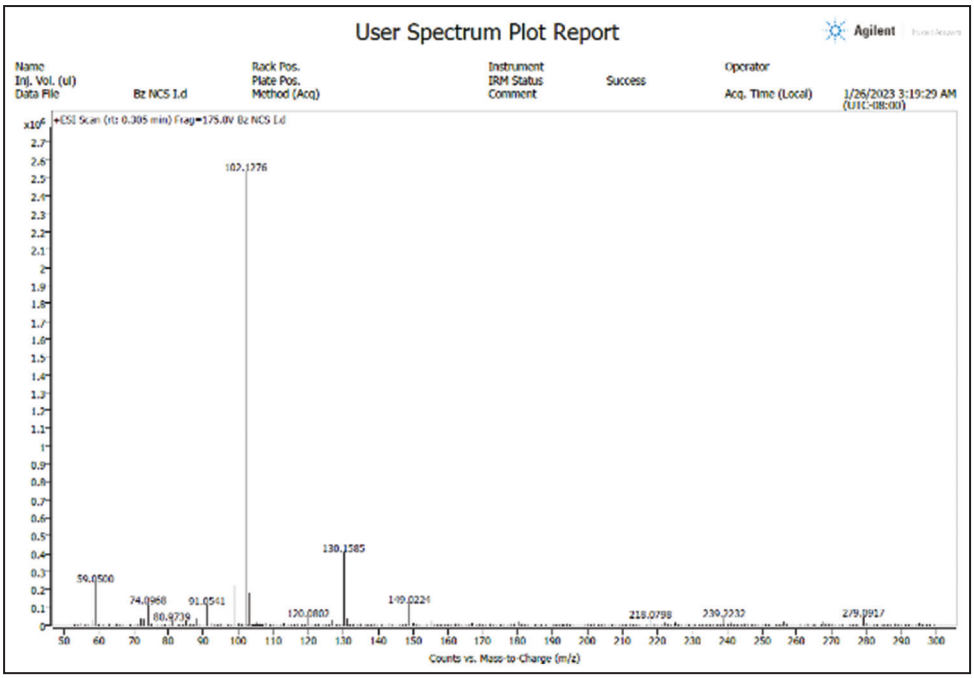


Figure 5: High resolution mass spectra spectrum of compound 3a.

4. CONCLUSION

This one-pot protocol appears to be a robust and efficient method for the synthesis of structurally diverse alkyl, aryl, and bifunctional isothiocyanates. It appears to be a valuable and efficient method with several noteworthy features offering advantages in terms of yield, compatibility with protecting groups, enantioselectivity, and the use of a low-cost reagent. This kind of innovation is crucial in synthetic chemistry for expanding the toolkit available to researchers in various fields. We have synthesized isothiocyanates and substituted thioureas with a simple experimental protocol in a short duration of reaction. Moreover, all the synthesized compounds were purified and characterized by NMR data.

5. ACKNOWLEDGMENTS

The inclusion of an acknowledgements section is optional. It may include credit for technical assistance, financial support, and other appropriate recognition and should be brief and placed after the experimental section.

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***Bibliographical Sketch**

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SUPPLEMENTARY INFORMATION

Isothiocyanatobenzene (3b): colorless oil; Yield 74%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.35 (dd, J = 8Hz, J = 4Hz, 2H), 6.99–7.18 (m, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 136.7, 130.8, 129.8 (2), 127.1, 126.3 (2). HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for C_7H_5NS 135.0143, found 135.0101.

1-Fluoro-4-isothiocyanatobenzene (3c): colorless oil; Yield 76%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.32 (dd, J = 16Hz, J = 16Hz, 2H), 7.11 (dd, J = 8Hz, J = 4Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.1, 137.0, 127.7 (2), 127.0, 118.1 (2). HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for C_7H_4FNS 153.0048, found 153.0013.

1-Isothiocyanato-4-nitrobenzene (3d): colorless oil; Yield 70%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07–8.34 (m, 2H), 6.87 (dd, J = 16Hz, J = 4Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ147.6, 137.2, 136.4, 126.8 (2), 125.3, 124.7. HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for $C_7H_4N_2O_2S$ 179.9993, found 179.9987.

1-Isothiocyanato-4-methoxybenzene (3e): colorless oil; Yield 75%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.37 (dd, J = 8Hz, J = 4Hz, 2H), 7.12 (dd, J = 8Hz, J = 4Hz, 2H), 3.92 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.4, 137.1, 125.9 (2), 123.5, 115.6, 113.9, 55.8. HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for C_8H_7NOS 165.0248, found 165.0212.

1-Isothiocyanato-4-methylbenzene (3f): colorless oil; Yield 79%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.18–7.28 (m, 2H), 7.05 (dd, J = 4Hz, J = 4Hz, 2H), 2.32 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 137.5, 136.9, 130.3, 130.1, 128.1, 126.0 (2), 21.1. HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for C_8H_7NS 149.0299, found 149.0128.

1-(Isothiocyanatomethyl)-4-methylbenzene (3g): colorless oil; Yield 80%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.20 (dd, J = 8Hz, J = 4Hz, 2H), 7.01 (dd, J = 8Hz, J = 4Hz, 2H), 4.88 (s, 2H), 2.15 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 135.9, 135.3, 129.0, 128.6, 128.2, 127.9 (2), 47.1, 21.1. HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for C_9H_9NS 163.0456, found 163.0487.

4-Isothiocyanatophenol (3h): colorless oil; Yield 72%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 (s, 1H), 7.17–7.31 (m, 2H), 6.88 (dd, J = 8Hz, J = 4Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.1, 138.3, 127.2, 126.9, 124.1, 118.3, 117.9. HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for C_7H_5NOS 151.0092, found 151.0199.

1-Benzyl-3-(4-methoxyphenyl)thiourea (4a): White solid; Yield 92%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 (s, 1H), 8.14 (s, 1H), 7.44 (dd, J = 8Hz, J = 4Hz, 2H), 7.23–7.30 (m, 5H), 6.88 (dd, J = 8Hz, J = 4Hz, 2H), 4.68 (s, 2H), 3.92 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 177.2, 159.1, 136.8, 130.7, 128.0, 127.6, 127.0, 126.3, 125.3, 112.0, 65.6, 51.7. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{17}N_2OS$ 273.1062, found 273.1066.

1-(4-Fluorophenyl)-3-phenylthiourea (4b): White solid; Yield 89%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.81 (s, 1H), 8.93 (s, 1H), 7.83 (dd, J = 16Hz, J = 4Hz, 2H), 7.29–7.62 (m, 5H), 6.62 (dd, J = 8Hz, J = 4Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 178.2, 164.1, 137.4, 134.2, 131.9, 129.0, 127.9, 125.9, 115.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{12}FN_2S$ 247.0705, found 247.0786.

1-(4-Nitrophenyl)-3-phenylthiourea (4c): White solid; Yield 81%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.46 (s, 1H), 8.99 (s, 1H), 8.11 (dd, J = 16Hz, J = 4Hz, 2H), 7.69–7.87 (m, 4H), 7.14–7.44 (m, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 177.7, 146.7, 145.1, 139.8, 131.2, 131.1, 129.7, 127.8 (2), 124.9 (2), 124.0, 123.9. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{12}N_3O_2S$ 274.0650, found 274.0688.

1-Benzyl-3-phenylthiourea (4d): White solid; Yield 91%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (s, 1H), 8.22 (s, 1H), 7.90 (dd, J = 4Hz, J = 4Hz, 2H), 7.09–7.57 (m, 8H), 4.99 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 181.1, 141.3, 138.9, 129.0 (2), 127.4 (2), 126.8, 51.1. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{15}N_2S$ 243.0956, found 243.0941.

1-Phenyl-3-propylthiourea (4e): White solid; Yield 90%; ^{1}H NMR (400 MHz, DMSO-d_6) δ9.76 (s, 1H), 7.88 (dd, J = 8Hz, J = 4Hz, 2H), 7.07–7.48 (m, 4H), 3.67 (t, J = 8Hz, 2H), 1.39–1.57 (m, 2H), 0.88 (dd, J = 16Hz, J = 8Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 177.9, 138.8, 127.6 (2), 128.8, 127.0, 126.4, 47.1, 23.2, 11.7. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{10}H_{14}N_2NaS$ 217.0775, found 217.0689.

1-Phenyl-3-(p-tolyl)thiourea (4f): White solid; Yield 84%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.99 (s, 1H), 8.26, (s, 1H), 7.39–7.69 (m, 5H), 7.01–7.22 (m, 1H), 2.32 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ180.0, 140.1, 138.4, 136.1, 129.5 (2), 129.1 (2), 128.4, 127.1, 126.5, 126.3, 126.1, 21.2. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{15}N_2S$ 243.0956, found 243.0957.

1-(4-Methylbenzyl)-3-phenylthiourea (4g): White solid; Yield 88%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (s, 1H),8.21 (s, 1H), 7.47–7.21 (m, 8H), 4.79 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 179.4,137.6, 135.9, 135.0, 133.3, 131.1, 129.6, 128.7, 128.2, 51.2, 21.7. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{17}N_2S$ 257.1112, found 257.1121.

1-(4-Methylbenzyl)-3-(4-nitrophenyl)thiourea (4h): White solid; Yield 79%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.87 (s, 1H),8.21 (s, 1H), 7.47–7.11 (m, 8H), 4.73 (s, 2H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 184.3,138.7, 135.9, 134.7, 132.8, 130.4, 129.1. 128.9, 128.0, 127.7, 122.9, 53.5, 22.3. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{16}N_3O_2S$ 302.0963, found 302.0961.

1-(4-Chlorophenyl)-3-(4-hydroxyphenyl)thiourea (4i): White solid; Yield 85%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (s, 1H), 8.01 (s, 1H), 7.48–7.33 (m, 5H), 3.66 (q, J = 4Hz, 2H), 1.67–1.55 (m, 2H), 1.38–1.27 (m, 2H), 0.97 (t, J = 8 Hz, 3H): ^{13}C NMR (101 MHz, DMSO-d_6) δ 183.5, 139.3, 133.8, 128.4, 125.2, 45.7, 32.7, 22.9, 14.1. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{12}ClN_2OS$ 279.0359, found 279.0344.