Sustainable synthesis of substituted thioureas and their potential applications

Km. Divya[1], Nitin Srivastava[2*], Amit K. Chaturvedi[3],

Abstract:
The synthesis of thiourea has been done employing strong bases. In this synthesis we have employed choline hydroxide for the synthesis of the unsymmetrical thioureas. We explored the synthesis of thiourea using one aromatic and one aliphatic amine in the presence of the carbon disulfide in the aqueous medium. For this we need the basic catalyst which is water soluble and ecofriendly. After searching for several catalysts, we focused on the choline hydroxide which is water soluble and biodegradable. cleaner, greener, and effective synthesis for the substituted thioureas has been reported.

Keyword: Thioureas, carbon disulfide, choline hydroxide, anticancer activty

[1,3]Department of Chemistry, J. S. University Shikohabad, Firozabad, U.P. -283135, India.
[2*]Department of Chemistry Amity University Uttar Pradesh Lucknow Campus, Lucknow226028, India.

***Corresponding Authors:** Nitin Srivastava
Email Address: nitinsriv5@gmail.com; achaturvedi794@gmail.com

Doi: 10.53555/ecb/2022.11.12.443

Introduction:

Diversified applications of biologically potent thioureas have drawn the attention of the organic research community. The derivatives of the thiourea have exhibited promising anti-inflammatory, anticancer, analgesic, antimicrobial activities [1-4]. These have been used clinically as sedative [1], hyperthyroidism [2]. The thioureas have been employed in the agricultural sectors as fungicide, rodenticides, herbicides, insecticides [5]. Organic synthesis makes use of thioureas for the synthesis of prominent compounds like sulfur containing heterocycles, amides, guanidine [68]. They have also been employed for the catalyzing the reaction [9-11].

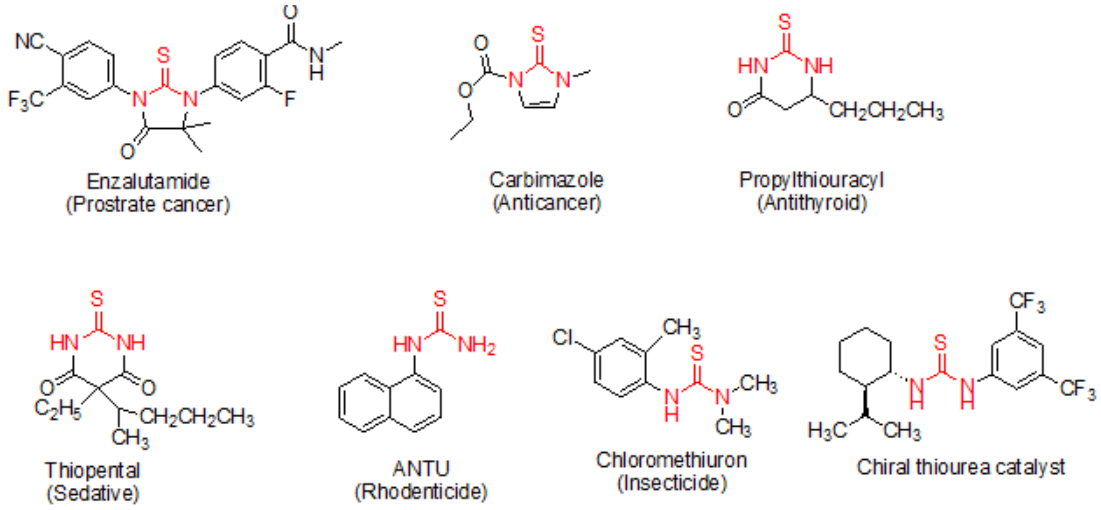
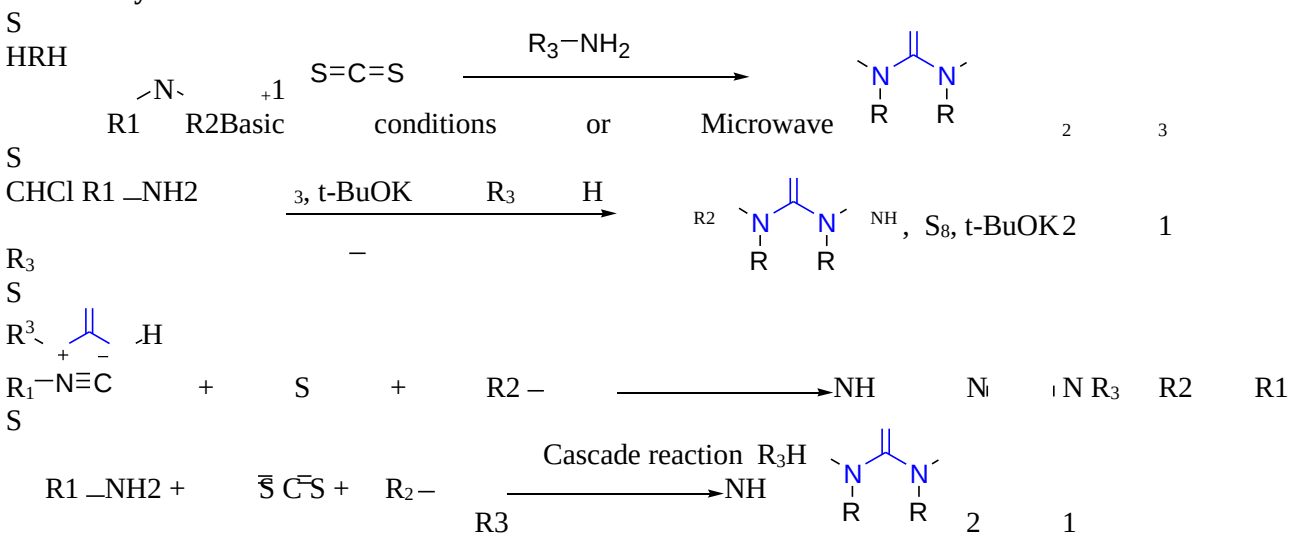


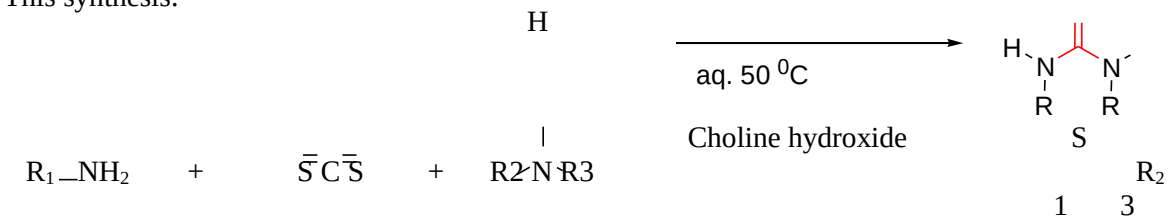
Figure 1. Structurally diverse biologically potent thiourea scaffolds

Several synthetic strategies have been employed for the synthesis of such important class of compounds [12-22, 26]. Various strategies include transformation of carbonyl to thiocarbonyl [14,15], and condensation of amines with isothiocyanate, substituted imidazoles, benzotriazoles etc. [1, 16-18]. These two basic strategies lead to many reported protocols for the synthesis of the thioureas either symmetric or unsymmetric. The reported protocols suffer constraints like extras synthetic steps which deviate the yield and make the process exhaustive. There is another way which focusses on the direct reaction of carbon disulfide with amines. This method has also been explored for the synthesis of the symmetrical and unsymmetrical thioureas. Here two kinds of amines are mixed under the basic condition at high temperature [19-23]. Such protocol a have limited application [24]. Cascade reaction has also been proposed for the synthesis of the thioureas but here too the organic solvent has been used which is hider the cleaner greener approach for the synthesis of biologically potent molecules [25].

Previous synthesis:



This synthesis:



Scheme 1 Synthesis of unsymmetrical thiourea employing Choline hydroxide

In pursuit to the cleaner and greener chemistry we have working for ten years in the field of carbon disulfide mediated synthesis of biologically potent scaffolds involving novel protocols [26-36]. In the present communication, we are reporting the cleaner greener and efficient synthesis of thioureas employing the choline hydroxide as a cleaner greener sustainable organic base which is water soluble, and biodegradable.

Results and Discussion

The synthesis of thiourea has been done employing strong bases. In this synthesis we have employed choline hydroxide for the synthesis of the unsymmetrical thioureas. We explored the synthesis of thiourea using one aromatic and one aliphatic amine in the presence of the carbon disulfide in the aqueous medium. For this we need the basic catalyst which is water soluble and ecofriendly. After searching for several catalysts, we focused on the choline hydroxide which is water soluble and biodegradable. The reaction between 2-fluoroaniline (**1**) and carbon disulfide (**2**) was carried out in the presence of the basic medium choline hydroxide (ChOH) (**3**). This led to the formation of thiocarbamic acid salt (**4**) which causes the release of H_2S in the presence of base choline hydroxide leading to the formation of isothiocyanate (**5**). Reaction of this isothiocyanate with other amine (**6**) lead to the formation of isothiourea (**7**) This thiourea on rearrangement gives thiourea (**8**). It was found that the continued stirring for 2 minutes leads to the entire starting material getting converted to thiocarbamic acid the addition of the other amine i.e. diethyl amine and constant stirring the reaction mixture for the another 5 minutes lead to the formation of the desired unsymmetrical thiourea. The completion of both these steps of the reaction were assured with the help of the thin layer chromatography. The synthesized thiourea was extracted and purified for the characterization. The IR characterization of the synthesized compound revealed the presence of the C-H (2976 cm^{-1}), C=S (1261 cm^{-1}),N-H (3295 cm^{-1}), C-F (756 cm^{-1}), bonds in it. The ^1H NMR characterization of the synthesized compound revealed the presence of the ethyl and phenyl moiety in the synthesized compounds. Similarly, the elemental analysis and Mass spectra (ES) of the synthesized compound established the identity of the synthesized compound as 1,1 Diethyl 3-(2-fluoro phenyl) thiourea.

Further this protocol was explored in the presence of the various solvents and the promoters for optimizing the yield of the proposed reaction and the results are given in table 1. The bases were screened in the presence of the several solvents like DMSO, DMF, ethyl alcohol, water. But as tabulated in the table 1 the model reaction did well in the choline hydroxide (ChOH) both as a solvent and the mild base. The ChOH performed the reaction well at a little higher than room temperature which added another feature to the clean and green process for the synthesis of the thioureas.

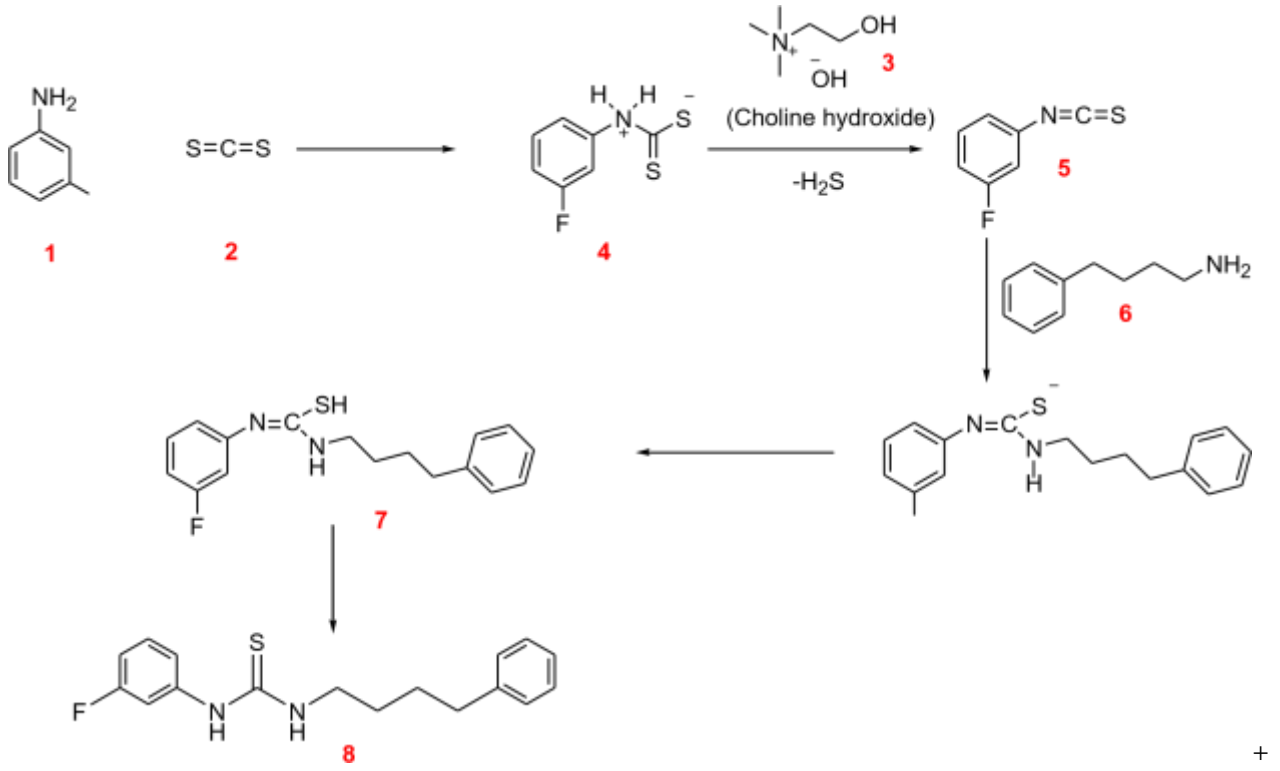
Table 1. Reaction yield in the presence of the various solvent and the bases

S. No	Solvent	Base	Yield in %
1	ChOH	ChOH	96
2	H_2O	Et_3N	74
3	EtOH	Et_3N	74
4	DMF	Et_3N	70
5	DMSO	Et_3N	78
6	EtOH	DBU	70
7	EtOH	DABCO	62
8	EtOH	NaOH	60

After the optimization several substituted unsymmetrical thiourea were synthesized as given in table 2. The protocol did well for the aliphatic as well as the aromatic constituents of the thiourea with good to excellent yields.

Another task of the reaction was to recover the choline hydroxide which is basically an ionic liquid to prove cleaner, greener, and sustainable synthesis. For this we considered the model reaction and after the synthesis of the product which was filtered in the solid form from the reaction mixture. The filtrate containing choline hydroxide was evaporated at very low pressure in the rotatory evaporator in which it was left as solid after the evaporation of the water. The ChOH was found to be regenerated 5 consecutive times after the conduct of the reaction. But after each cycle the efficiency of the catalyst was found to be decreased.

It was found that the electron repelling groups attached to the amines gave higher yield which was due to the fact that the electron repelling groups enhanced the nucleophilicity of the nitrogen atom in the amines. Primary amines reacted easily with higher yield and lesser time than the aromatic amines which is due to the higher nucleophilicity of the aliphatic amines than the aromatic amines.



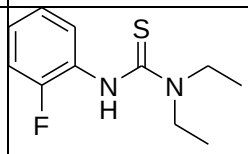
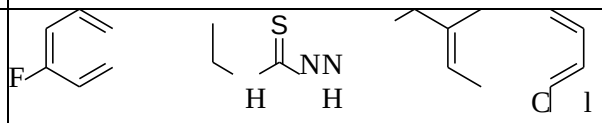
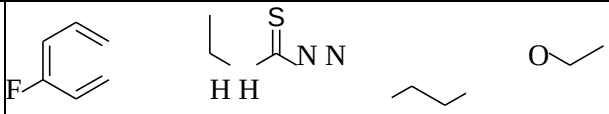
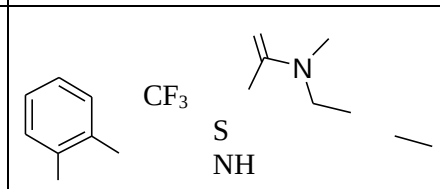
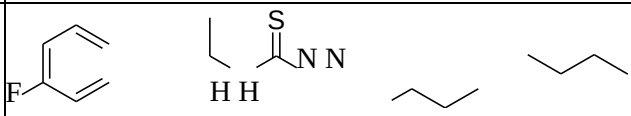
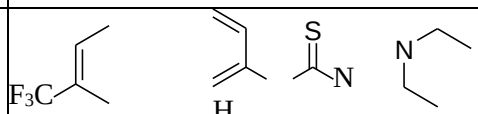
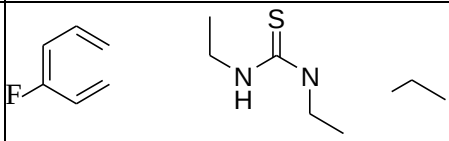
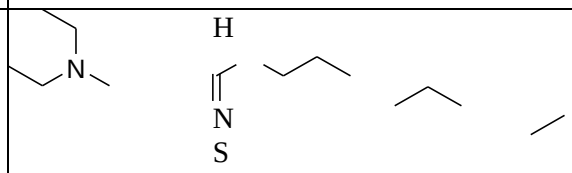
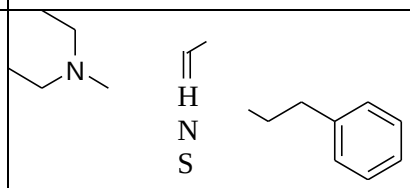
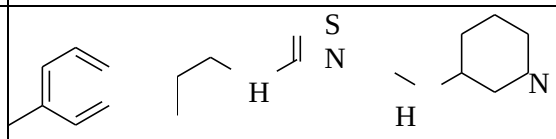
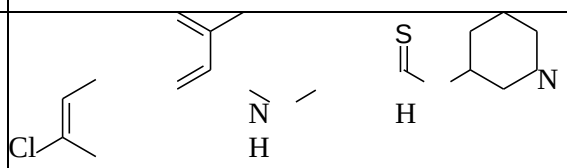
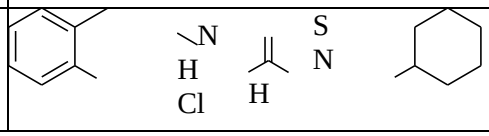
Scheme 2. Proposed mechanism of the synthesis of unsymmetrical thiourea

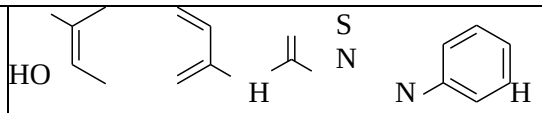
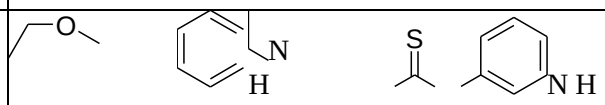
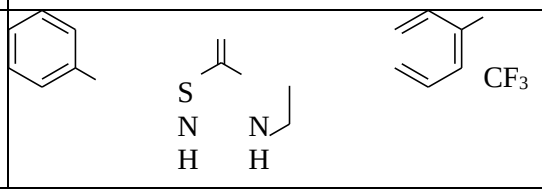
Experimental

Reagents employed in the research were purchased form companies like Fluka, Merck, Alfa Aesar and were used without further purification. The synthesized compound were characterized by comparing the data obtained from spectral, elemental analysis and were compared with the data of the compound available in literature. Infra-Red spectroscopy (4000-450cm^{-1}) of the compounds were done on Perkin Elmer spectrophotometer using KBr pallets and NMR spectroscopy was done on Brooker Advance DPX instrument spectrophotometer (400 MHz) with usual standards. Elements in the compounds were analysed on Carlo-Erba EA 1110 CHNOS analyser. Compounds were related with the data obtained and data for the existing compounds in literature.

General Procedure: **1** mmols of aromatic amine (**1**) was taken in 5.0 mL of water in a clean round bottom flask fitted with magnetic stirrer and added with 1 mmols of carbon disulphide (**2**) and 1 mmols of choline hydroxide (**3**). This mixture was stirred for 10 minutes and then added with 1.0 mmols of diethyl amine (**6**) and the mixture was stirred for next 20 minutes. The advancement of the reaction was evaluated using TLC in both the first and second step for the formation of isothiocyanate (**5**) from dithiocarbamic acid (**4**) and substituted thiourea (**8**). The product formed was filtered, washed, and purified with the help of column chromatography. The filtrate was vaporized in vacuum for the regeneration of the choline hydroxide.

Table 2. Substituted thiourea synthesis using Choline hydroxide

S.No	Compound	Time in min.	Yield	Ref
1		30	70	26
2		30	75	26
3		30	76	26
4		30	68	26
5		30	70	26
6		30	75	26
7		30	74	26
8		30	90	19
9		30	84	19
10		30	80	24
11		30	75	24
12		30	70	24

13		30	91%	37
14		30	91%	37
15		30	94%	37

Data analysis of Synthesized compounds

1. 1,1 Diethyl 3-(2-fluoro phenyl) thiourea (8a)

Solid, greyish melting range=70-73 ^{0}C; IR (cm^{-1}): C-H (2980), C-F(756), C=S (1261), N-H (3260); ^{1}HNMR: δ 1.29(t, 6H), 3.80 (q, 4H), 7.10-7.89 (4H, aromatic), 7.00 (NH, broad); ^{13}C NMR: δ= 13.4, 47.4, 115.9, 124.4, 126.0, 126.5, 127.0, 157.0, 180.1; Elemental analysis: %Element, found(calcd.); %C, 60.01(58.38); %H, 6.30(6.28); %N, 12.20(12.39); %S 14.10(14.14); %F, 8.08(8.42).Molecular weight calculated for $C_{11}H_{15}FN_2S$= 226.31, Found (MS), m/z =226.28

2. 1-(3-chlorobenzyl)-3-fluoro phenyl thiourea (8b)

White solid, melting range= 71-74 ^{0}C; IR(cm^{-1}): N-H (3208), C-H (2979), C=S (1218), C-F (759); ^{1}H NMR:δ 4.90(2H), 6.98-7.06 (4H, aromatic), 7.19-7.38(4H aromatic), 6.39 (NH), 8.40 (NH); ^{13}C NMR: δ 111.6, 112.4, 121.0, 125.2, 127.0, 129.7, 130.5, 133.7, 141.0, 143.9, 162.5, 179.6; Elemental analysis: %Element, found(calcd.); %C, 57.09(57.06); %H, 3.99(4.01); %N, 9.44(9.49); %S 10.59(10.63); %F, 6.30(6.39), %Cl, 11.90.(11.92).Molecular weight calculated for $C_{14}H_{12}N_2SFCl$ =294.755, Found (MS), m/z = 294.72

3. 1-(2-ethoxyethyl)-3-(3-fluorophenyl) thiourea (8c)

White solid,melting range=86-88 ^{0}C; IR (cm^{-1}): C-F(760), (C-O) 970, 2975 (C-H), (N-H), 3266 (N-H);^{1}HNMR: δ= 1.19 (t, 3H), 3.34-3.81(m, 6H,), 6.7(NH, s), 6.93-7.34 (m, 4H), 8.47 (s, NH); ^{13}C NMR: 14.8, 49.9, 62.8, 71.6, 112.4, 111.6, 120.9, 130.5, 139.9, 162.5, 180.0; Elemental analysis: %Element, found(calcd.); %C, 54.20(54.32); %H, 6.36(6.32); %N, 11.40(11.36); %O, 6.48(6.58); %S, 13.31(13.25); %F, 7.74(7.78);Molecular weight calculated for $C_{11}H_{15}N_2OSF$ = 242.31, found (MS), m/z = 242.1

4. 1,1Diethyl-3-(2-trifluoromethyl-phenyl)-thiourea (8d)

Yellow solid, melting range=68-71 ^{0}C; IR (cm^{-1}): C-F (760), C=S (1215), C-H (2980), N-H (3210); ^{1}H NMR: δ 1.35 (t, 6H), 3.80 (q, 4H), 7.10 (N-H), 7.28-7.65 (m, 4H); ^{13}C NMR: δ 14.8, 62.8, 70.9, 51.7, 111.1, 112.0, 120.3, 130.7, 141.6, 162.3, 180.0; Elemental analysis: %Element, found(calcd.); %C, 52.08 (52.15); %H, 5.44(5.47); %N, 10.05(10.14); %S 11.56(11.60); %F, 20.49(20.62).Molecular weight calculated for $C_{12}H_{15}N_2SF_3$= 276.31. MS: m/z = 276.32

5. 1-(3-fluoro phenyl)-3-hexyl thiourea (8e)

Pale yellow solid, melting range= 73-75 ^{0}C; IR (cm^{-1}): C-F (760), C=S (1216), C-H (2980), NH (3210); ^{1}H NMR: 0.86 (t, 3H), 1.28 (q, 8H), 1.60 (q, 2H), 6.10 (N-H), 6.93-7.42 (m, 4H), 7.90 (1H, NH-CH_2); ^{13}C NMR δ 14.0, 23.5, 22.0, 28.7, 29.8, 31.1, 50.6, 120.2, 112.0, 111.1, 130.6, 141.1, 162.3, 179.5,; Elemental analysis: %Element, found(calcd.); %C, 61.42(61.38); %H, 7.48(7.52); %N, 11.04(11.02); %S 12.58(12.60); %F, 7.45(7.46).Molecular weight calculated for $C_{13}H_{19}N_2SF$ =254.364, found (MS), m/z = 254.34

6. 1,1Diethyl-3(3-trifluoromethylphenyl) thiourea (8f)

Cream solid, melting range= 69-71 ^{0}C; IR (cm^{-1}): C-F (760), C=S (1216), C-H (2979), N-H (3210); ^{1}HNMR: δ 1.31 (t, 6H), 3.76 (q, 4H), 7.05 (s, NH), 7.41-7.60 (m, 4H); ^{13}C NMR: δ 13.5, 47.6, 180.0, 125.6, 127.0; Elemental analysis: %Element, found(calcd.); %C, 52.15(52.17); %H, 5.45(5.48); %N, 10.16(10.14); %S 11.54(11.58); %F, 20.56(20.62); Molecular weight calculated for $C_{12}H_{15}N_2SF_3$= 276.318, found (MS), m/z =276.41

7. 1,1 Diethyl 3-(3-fluoro phenyl) thiourea (8g)

Grey solid, melting range=72-74 ^{0}C; IR (cm^{-1}): C-F (759), C=S (1216), N-H (3210); ^{1}HNMR: δ 1.31(t, 6H), 3.76 (q, 4H), 7.00 (N-H, broad), 7.05-7.30 (m, 4H); ^{13}C NMR: δ 13.4, 47.6, 112.5, 121.0, 140.9, 162.5, 179.6; Elemental analysis: %Element, found(calcd.); %C, 58.32(58.38); %H,

6.62(6.66); %N, 12.40(12.38); %S 14.18(14.17); %F, 8.37(8.40).Molecular weight calculated for $C_{11}H_{15}N_2SF$ = 226.3117, found (MS), m/z =226.3

8. 1,1-Diethyl-3-hexyl-thiourea (8h)

Pale brown viscous liquid; yield 90%; IR (cm^{-1}): 1529, 3310; ^{1}HNMR: δ 0.929 (t, 3H, J = 6.6 Hz), 1.25 (t, 6H, J = 7.2 Hz), 1.29-1.39 (m, 6H), 1.61-1.70 (m, 2H), 3.59-3.72 (m, 6H), 5.40 (br, 1H); ^{13}C NMR: δ 12.8, 14.0, 22.5, 26.5, 30.0, 31.6, 45.0, 46.2, 179.8; Molecular weight calculated for $C_{11}H_{24}N_2S$ (M + Na) 240.0060, found (HR-MS), (m/z) (M + Na)= 240.0059.

9. 1,1-Diethyl-3-(2-phenylethyl)thiourea ((8i)

Colorless solid; melting range= 68-70 C; IR (cm^{-1}): 1529, 3320; ^{1}H NMR: δ 1.10 (t, 6H, J = 7.4 Hz), 3.01 (t, 2H, J = 6.8 Hz), 3.60 (q, 4H, J = 7.5 Hz), 3.90-3.98 (m, 2H), 5.30 (br, 1H), 7.191-7.40 (m, 5H); ^{13}C NMR: δ 12.5, 34.8, 45.0, 46.5, 126.5, 130.2, 129.0, 140.8, 179.9; Molecular weight calculated for $C_{13}H_{20}N_2S$ (M + Na)= 260.0286, found (HRMS), (m/z) (M + Na) 260.0284.

10. 1-Cyclohexyl-3-(4-methyl-benzyl)-thiourea (8j)

Colorless solid; melting range= 68-70 C; IR (cm^{-1}): 1529, 3320; ^{1}H NMR: δ 1.44 (m, 6H, J = 6.4 Hz), 1.66 (q, 4H, J = 6.6 Hz), 2.57 (q, 1H, J = 4.5 Hz), 4.71 (s, 2H), 5.04 (br, 1H), 7.01-7.40 (m, 4H), 2.35 (s, 3H); ^{13}C NMR: δ 20.9, 127.0, 129.0, 135.7, 139.4, 55.8, 184.0, 22.6, 27.1; Molecular weight calculated for $C_{15}H_{22}N_2S$ (M + H)= 263.1504, found (HRMS), (m/z) (M + H) 263.1508.

11. 1-(4-Chloro-benzyl)-3-cyclohexyl-thiourea (8k)

Colorless solid; melting range= 68-70 C; IR (cm^{-1}): 1532, 3330; ^{1}H NMR: δ 1.44 (m, 6H, J = 6.5 Hz), 1.66 (q, 4H, J = 6.8 Hz), 2.57 (quin, 1H, J = 4.5 Hz), 4.71 (s, 2H), 5.04 (br, 1H), 7.00 (dd, 2H, J=7.8), 7.32 (dd, 2H, J= 7.6); ^{13}C NMR: δ 128.5, 128.7, 140.5, 55.8, 184.1, 22.6, 27.1, 33.4, 52.3; Molecular weight calculated for $C_{14}H_{19}ClN_2S$ (M + H)= 283.0958, found (HRMS), (m/z) (M + H) 283.0950.

12. 1-(2-Chloro-benzyl)-3-cyclohexyl-thiourea (8l)

Colorless solid; melting range= 68-70 C; IR (cm^{-1}): 1532, 3330; ^{1}H NMR: δ 1.44 (m, 6H, J = 6.5 Hz), 1.66 (q, 4H, J = 6.8 Hz), 2.57 (quin, 1H, J = 4.5 Hz), 4.71 (s, 2H), 5.04 (br, 1H), 7.00-7.20 (m, 4H); ^{13}C NMR: δ 128.5, 128.7, 140.5, 55.8, 184.1, 22.6, 27.1, 33.4, 52.3; Molecular weight calculated for $C_{14}H_{19}ClN_2S$ (M + H)= 283.0958, found (HRMS), (m/z) (M + H) 283.0946

13. 1-(4-Hydroxy-phenyl)-3-phenyl-thiourea (8m)

Whitish solid; melting range= 68-70 C; IR (cm^{-1}): 1528, 3327; ^{1}H NMR: δ 6.29-6.48 (dd, 4H, J = 7.2 Hz, 7.4Hz), 6.46 (d, 2H, J= 7.2), 7.01 (d, 2H, J=7.4), 6.62 (m, 1H), 5.04 (br, 1H), 5.0 (br, 1H); ^{13}C NMR: δ 116.0, 126.7, 132.0, 179.6, 124.5, 125.3, 128.8, 139.4; Molecular weight calculated for $C_{13}H_{12}N_2OS$ (M + H)= 245.0670, found (HRMS), (m/z) (M + H) 245.0770

14. 1-(4-Ethoxy-phenyl)-3-phenyl-thiourea (8n)

Whitish solid; melting range= 68-70 C; IR (cm^{-1}): 1532, 3334; ^{1}H NMR: δ 1.33 (t, 3H), 4.02 (q, 2H), 6.52 (dd, 2H, J = 7.2 Hz), 6.35 (dd, 2H, J= 7.4), 7.01 (dd, 2H, J=7.4), 6.46 (dd, 2H), 5.04 (br, 1H), 6.63 (m, 1H); ^{13}C NMR: δ 14.3, 65.1, 154.8, 114.5, 125.9, 131.0, 180.0, 124.5, 125.3, 128.8, 139.4; Molecular weight calculated for $C_{16}H_{16}N_2OS$ (M + H)= 273.0983, found (HRMS), (m/z) (M + H) 273.0990

15. 1-Phenyl-3-(4-trifluoromethyl-phenyl)-thiourea (8o)

Whitish solid, melting range= 68-70 ^{0}C; IR (cm^{-1}): C-F (760), C=S (1216), C-H (2979), N-H (3210); ^{1}HNMR: δ 6.46 (dd, 2H, J=7.6 Hz), 7.01 (dd, 2H, J= 7.6 Hz), 6.62 (m, 1H), 6.39 (dd, 2H, J= 7.8 Hz), 7.20 (dd, 2H, J=7.6 Hz), 7.05 (s, NH); ^{13}C NMR: δ 124.5, 125.3, 128.8, 139.4, 119.3, 125.6, 127.0, 142.7; Elemental analysis: %Element, found(calcd.); %C, 56.18(56.75); %H, 3.72(3.74); %N, 9.52(9.45); %S 10.75(10.82); %F, 19.36(19.23); Molecular weight calculated for $C_{14}H_{11}N_2SF_3$= 296.06, found (MS), m/z =296.10

Conflict of Interest

The authors declare absence of conflict of interest.

References

1. S. Begum, M.I. Choudhary, K.M. Khan, Synthesis, phytotoxic, cytotoxic, acetylcholinesterase and butrylcholinesterase activities of N,N'-diaryl unsymmetrically substituted thioureas Nat Prod Res. 23 (2009)1719-30. https://doi.org/10.1080/14786410802223778
2. I. Van Daele, H. Munier-Lehmann, M. Froeyen, J. Balzarini, S. Van Calenbergh, Rational design of 5'-thiourea-substituted alpha-thymidine analogues as thymidine monophosphate kinase inhibitors capable of inhibiting mycobacterial growth,J Med Chem. 50 (2007) 5281-92. https://doi.org/10.1021/jm0706158

3. Y. Touati- Jallabe, E. Bojnik, B. Legrand, E. Mauchauff´ee, N.N. Chung, P.W. Schiller, S. Benyhe, M.C. Averlant-Petit, J. Martinez and J.F. Hernandez, Cyclic Enkephalins with a Diversely Substituted Guanidine Bridge or a Thiourea Bridge: Synthesis, Biological and Structural Evaluations, J. Med. Chem. 56 (2013) 5964-5973. https://doi.org/10.1021/jm4008592
4. L.Y. Ma, Y.C. Zheng, S.Q. Wang, B. Wang, Z.R. Wang, L.P. Pang, M. Zhang, J.W. Wang, L. Ding, J. Li, C. Wang, B. Hu, Y. Liu, X.D. Zhang, J. J. Wang, Z.J. Wang, W.Zhao, H.M. Liu, Design, Synthesis, and Structure–Activity Relationship of Novel LSD1 Inhibitors Based on Pyrimidine–Thiourea Hybrids As Potent, Orally Active Antitumor Agents,J. Med. Chem. 58 (2015) 1705-1716. https://doi.org/10.1021/acs.jmedchem.5b00037
5. B.L. Wang, H.W. Zhu, Y. Ma, L.X. Xiong, Y.Q. Li, Y. Zhao, J.F. Zhang, Y.W. Chen, S. Zhou, Z.M. Li, Synthesis, insecticidal activities, and SAR studies of novel pyridylpyrazole acid derivatives based on amide bridge modification of anthranilic diamide insecticides,J Agric Food Chem. 61 (2013) 5483-93. https://doi.org/10.1021/jf4012467
6. R. Yella, H. Ghosh, B. K. Patel, It is "2-imino-4-thiazolidinones" and not thiohydantoins as the reaction product of 1,3-disubstituted thioureas and chloroacetylchloride,Green Chem. 10 (2008) 1307-1312. https://doi.org/10.1039/B807775D
7. I. Cano, E. Gómez-Bengoa, A. Landa, M. Maestro, A. Mielgo, I. Olaizola, M. Oiarbide,C. Palomo, N-(Diazoacetyl)oxazolidin-2-thiones as sulfur-donor reagents: asymmetric synthesis of thiiranes from aldehydes,Angew Chem Int Ed Engl. 51 (2012) 10856-60. https://doi.org/10.1002/anie.201204771
8. J. Zhao, H. Huang, W. Wu, H. Chen, H. Jiang H, Metal-free synthesis of 2aminobenzothiazoles via aerobic oxidative cyclization/dehydrogenation of cyclohexanones and thioureas,Org Lett. 15 (2013) 2604-7. https://doi.org/10.1021/ol400773k
9. T. Inokuma, Y. Hoashi and Y. Takemoto, Thiourea-Catalyzed Asymmetric Michael Addition of Activated Methylene Compounds to α,β-Unsaturated Imides: Dual Activation of Imide by Intra- and Intermolecular Hydrogen Bonding,J. Am. Chem. Soc. 128 (2006) 9413-9419. https://doi.org/10.1021/ja061364f
10. Y. Zhang, Y.K. Liu, T.R. Kang, Z.K. Hu, Y.C. Chen, Organocatalytic enantioselective Mannich-type reaction of phosphorus ylides: synthesis of chiral N-boc-beta-amino-alpha-methylene carboxylic esters,J Am hem Soc.130 (2008) 2456-7. https://doi.org/10.1021/ja7114844
11. A. Madar´asz, Z. D´osa, S. Varga, T. So´os, A. Cs´ampai and I. P´apai, Thiourea Derivatives as Brønsted Acid Organocatalysts,ACS Catal. 6 (2016) 4379-4387. https://doi.org/10.1021/acscatal.6b00618
12. M. Xian, X. Zhu, Q. Li and J. P. Cheng, Tetrahedron Lett., 40 (1999) 1957.
13. B. Yin, Z. Liu, M. Yi and J. Zhang, An efficient method for the synthesis of disubstituted thioureas via the reaction of N,N′-di-Boc-substituted thiourea with alkyl and aryl amines under mild conditions, Tetrahedron Lett. 49(2008) 3687-3690. https://doi.org/10.1016/j.tetlet.2008.03.158
14. T. Ozturk, E. Ertas and O. Mert, Use of Lawesson's reagent in organic syntheses,Chem Rev. 107 (2007)5210-78. https://doi.org/10.1021/cr040650b
15. T. Ozturk, E. Ertas and O. Mert, A Berzelius reagent, phosphorus decasulfide (P4S10), in organic syntheses,Chem Rev.110 (2010) 3419-78. https://doi.org/10.1021/cr900243d.
16. A. Ortiz and E. Sansinenea, The synthetic versatility of oxazolidinethiones,J. Sulfur Chem. 28 (2007) 109-147.https://doi.org/10.1080/17415990601139699
17. J. Li, Z. Tan, S. Tang, I. Hewlett, R. Pang, M. He, S. He, B. Tian, K. Chen and M. Yang, Discovery of dual inhibitors targeting both HIV-1 capsid and human cyclophilin A to inhibit the assembly and uncoating of the viral capsid,Bioorg Med Chem.17 (2009) 3177-88. https://doi.org/10.1016/j.bmc.2009.02.051
18. M. Đud, O. V. Magdysyuk, D. Margeti´ca and V. ˇStrukil, Synthesis of monosubstituted thioureas by vapour digestion and mechanochemical amination of thiocarbamoyl benzotriazoles,Green Chem. 18 (2016) 2666-2674. https://doi.org/10.1039/C6GC00089D
19. M. R. Maddani and K. R. Prabhu, A Concise Synthesis of Substituted Thiourea Derivatives in Aqueous Medium,J. Org. Chem. 75 (2010) 2327-2332. https://doi.org/10.1021/jo1001593

20. Z. Zhang, H. H. Wu and Y. J. Tan, A simple and straightforward synthesis of phenyl isothiocyanates, symmetrical and unsymmetrical thioureas under ball milling,RSC Adv. 3 (2013) 16940-16944. https://doi.org/10.1039/C3RA43252A
21. C. M. Chau, T. J. Chuan and K. M. Liu, A highly efficient one-pot method for the synthesis of thioureas and 2-imino-4-thiazolidinones under microwave conditions,RSC Adv. 4 (2014) 1276-1282. https://doi.org/10.1039/C3RA46270F
22. T. Haywood, S. Kealey, S. ´anchez-Cabezas, J. J. Hall, L. Allott, G. Smith, C. Plisson and P. W. Miller, Carbon-11 Radiolabelling of Organosulfur Compounds: 11C Synthesis of the Progesterone Receptor Agonist Tanaproget,Chem.–Eur. J.21 (2015) 9034-9038. https://doi.org/10.1002/chem.201501089
23. W. Tan, J. Wei and X. Jiang, Thiocarbonyl Surrogate via Combination of Sulfur and Chloroform for Thiocarbamide and Oxazolidinethione Construction,Org. Lett. 19 (2017) 2166-2169. https://doi.org/10.1021/acs.orglett.7b00819
24. T.B. Nguyen, L. Ermolenko, A. Al-Mourabit, Three-Component Reaction between Isocyanides, Aliphatic Amines and Elemental Sulfur: Preparation of Thioureas under Mild Conditions with Complete Atom Economy,Synthesis46 (2014) 3172-3179.https://doi.org/10.1055/s-0034-1379327
25. C. Ding, S. Wang, Y. Sheng, Q. Dai, Y. Zhao, G. Liang, Z. Song, One-step construction of unsymmetrical thioureas and oxazolidinethiones from amines and carbon disulfide via a cascade reaction sequence,RSC Adv. 9 (2019) 26768. https://doi.org/10.1039/c9ra04540f
26. N. Srivastava, D. Chaturvedi, R. Kishore, M. Kaur, R. Kaur, Triton-B/CS_2 mediated novel synthesis of substituted thioureas: A novel class of anti-cancer agents, Indian J. Chem.Sec B. 61 (2022), 870-877. https://doi.org/10.56042/ijc.v61i8.65053
27. N. Srivastava, Efficient TBAI-CS2 Promoted Synthesis of Substituted HydrazinecarbodithiolatesOrg. Prep.Proced. Int. 54 (2022) 569-577. https://doi.org/10.1080/00304948.2022.2111171
28. N. Srivastava, R. Kishore, Cleaner and greener synthesis of 3H-benzothiazole-2-thione and its derivatives, J Sulfur Chem.42 (2020) 29-39. https://doi.org/10.1080/17415993.2020.1803321
29. N. Srivastava, Tetrabutylammonium Iodide/I_2Mediated Convenient and Green Synthesis of Substituted Organic Isothiocyanates, Org. Prep.Proced. Int.53 (2021) 562-570. https://doi.org/10.1080/00304948.2021.1975487
30. N. Srivastava, M. Saxena, Novel Synthesis of Symmetrical Dialkyl/ Diaryl trithiocarbonates in Non-aqueous Medium at Room Temperature Using CS_2. CS_2CO_3 and Alkyl/aryl halide, Rasayan J. Chem.12 (2019) 333-337. ttp://dx.doi.org/10.31788/RJC.2019.1215038
31. N. Srivastava, R. Kishore, Cleaner, Greener Synthesis, Characterization, and Anticancer Evaluation of 2-Thioxo-1,3-Thiazolanes, Indian J.Heterocycl. Chem.31 (2021) 265-271. https://connectjournals.com/01951.2021.31.265
32. N. Srivastava, R. Kishore, Synthesis, Characterization, Anticancer, Antibacterial, Antifungal, and Antimalarial activity of (Aryl or Hetero Aryl) substituted-4-Methyl-2,3dihydro- 2-thioxo-1H-imidazol-5-yl) Ethanone Derivatives, Indian J.Heterocycl Chem.31 (2021) 347-355. https://connectjournals.com/01951.2021.31.347
33. R. Kishore, M. Kamboj, M. Shukla, D. Chaturvedi, N. Srivastava, Novel Strategy for Synthesis of Cyclic Dithiocarbamates Catalyzed by Triton-B, Asian J Chem.31 (2019) 1091-1094. http://dx.doi.org/10.14233/ajchem.2019.21830
34. N. Srivastava, M. Saxena, M. Shukla, Novel Synthesis of 5-Oxo-2-thioxo-2,5-dihydro-3thiophenecarboxylate Derivative in Non-aqueous Medium, Asian J Chem.31 (2019) 176-180. https://doi.org/10.14233/ajchem.2019.21622
35. R. K.Vishnoi, R. Kishore, D. Chaturvedi, M. Shukla, S. Bajpai, Nitin Srivastava, Synthesis and antimicrobial activity of cyclic dithiocarbamates employing Triton-B/CS_2 system, Asian J Chem. 33 (2021) 1133–1136. https://doi.org/10.14233/ajchem.2021.23173

36. N. Srivastava, R. Kishore, D. Chaturvedi, Novel and efficient method for the synthesis of cyclic trithiocarbonates employing Cs_2CO_3 and CS_2 system, Research J Chem Environ.25 (2021) 142-148. https://doi.org/10.25303/2512rjce142148
37. A.D.Karche, P. Kamalakannan, R. Powar, G.G. Shenoy, K.J. Padiya, On-Water" Reaction of (Thio)isocyanate: A Sustainable Process for the Synthesis of Unsymmetrical (Thio)ureas. Org. Process Res. Dev. 26 (2022) 3141–3152. https://doi.org/ 10.1021/acs.oprd.2c00266