Original Article: An Environmentally Friendly Strategy for One-pot Synthesis of Dithiocarbamates Using Ceric Ammonium Nitrate (CAN) and PEG: H_2O Solvent System

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ABSTRACT

It is reported that dithiocarbamates can be produced effectively, conveniently, simply, and selectively in a single reaction vessel. Accordingly, aryl/alkyl halides are coupled to the *in situ* produced dithiocarbamate anion utilizing a highly inventive catalytic system consisting of ceric ammonium nitrate (CAN) and polyethylene glycol (PEG-400: H_2O) in a favourable reaction medium. The advantages of this new technology over previously reported methods include low costs, high product yields, rapid reaction times, easy access to an ecologically friendly catalytic system, and PEG's capacity to be recycled. All synthesized dithiocarbamates were characterized by FT-IR, ^{1}H-NMR, ^{13}C-NMR, and ESI-MS Mass spectra.

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Introduction

Organo-medicinal chemists are now paying a lot of attention to green synthesis. One of the most significant functions of green chemistry is the design, creation, and application of chemical reactions while avoiding the use of dangerous solvents [1]. Polyethylene glycol (PEG) is a less toxic, user-friendly, thermally stable, and recyclable medium for specific organic processes as compared to organic solvents [2-4]. In addition, PEG chemistry and its use in medicinal chemistry have been addressed in numerous reviews [5-7]. Due to the hydrophobic nature of the reactants and the sensitivity of many catalysts to aqueous reaction conditions, water, while a safe option, is not always practical to utilise as a solvent medium [8, 9]. These characteristics, together with the network of H-bonds, high polarity, and significant surface tension, make it both cost-effective and ecologically benign, making it an appropriate replacement eco-friendly medium to carry out organic synthesis over volatile and hazardous solvents [10].

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Multicomponent reactions (MCRs) have become an effective synthetic method for creating physiologically active molecules [11-14]. Due to the characteristics like atom economy, operational simplicity, easy reaction design, minimum workups, and methods of purification with no by-product, these sorts of reactions are very appealing. From an economic and environmental standpoint, the use of green chemistry with multicomponent reactions is a very appealing methodology that produces a high yield of products in a shorter amount of time [15-19].

Due to their extensive spectrum of biological and pharmacological attributes, dithiocarbamates (DTCs), a type of heterocycles containing sulphur, have drawn a lot of attention [20-26]. DTCs play a ligands role for the complex production of soft metals in a variety of ways described in the literature. These are made by mixing an amine with carbon disulfide, halides, or compounds that are α,β-unsaturated with the desired products [27-34]. Despite the potential usefulness of these procedures, the majority of them have a number of flaws, including demanding conditions for formation of catalyst, the use of costly, dangerous catalysts that can produce side products with low product yields, excessive catalyst loading, corrosiveness, and the use of harmful solvents.

To address these issues, we chose to use a novel catalyst to synthesise DTCs more efficiently and cleanly, with a wide range of potential biological features, including anti-mycobacterial activity (OCT-313) [23], antibacterial [35-38], and antifungal activity [39, 40]. Cerium (IV) ammonium nitrate [$(NH_2)_2Ce(NO_3)_6$ or CAN] has emerged as an important catalyst for the construction of various heteroatom and C-C bonds [41]. This is also a powerful catalyst for organic synthesis due to its various benefits, including its high reactivity, low toxicity, easy handling, and great solubility in water. In recent investigations, protocols for mild circumstances, quick conversions, and practical work-up techniques have also been revealed, making ceric (IV) ammonium nitrate as an effective tool in chemistry when employing green and safer methods. In addition, the Lewis acid feature of CAN as well as its electron transfer capacity allows it to catalyse various organic reactions [42-47].

The value of PEG polymers is mostly due to their low toxicity under CAN and PEG-H_2O as a green medium, which is reflected in the rapid rise of published work about PEG with CAN in the medical field. Due to its wide application results in many interesting field, a facile, rapid, and synthetic innovative strategy for the formation of biologically active DTCs with different substituted groups is desirable. On the basis of our best knowledge, we are first time reported a MCRs using an amines, CS_2, and halides with a new catalytic system.

Experimental

Instruments and reagents

All chemicals were purchased from Sigma-Aldrich and were used as follow. All reactions and purity of dithaiocarbamates were monitored by thin-layer chromatography (TLC) using aluminium plates coated with silica gel F 254 plates, (Merck) using 15% ethyl acetate and 85% hexane as an eluent. The spots were detected either under the UV light or by placing in iodine chamber. The melting point of compounds was determined using a Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR-1710 spectrophotometer using Nujol film or KBr pellet, ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a JEOL JNM-ECX 400P FT NMR system using TMS as an internal standard. ESI-MS mass spectra were recorded on waters LCT Micromass.

*General procedure for the synthesis of dithiocarbamate derivatives **4a-4n** and **6a-6l***

In a 50 mL round bottom flask, the required amount of carbon disulphide (2.5 mmol) was added dropwise to a stirred mixture of amines (1.2 mmol) in 3 ml PEG-400: H_2O system at 0-5 °C. After 5 min to this stirred mixture, ceric ammonium nitrate (CAN) (5 mol%) and alkyl/aryl halides or Michael acceptors (1 mmol) were added, mixed, and stirred at 50 °C for an appropriate time. The progress of reaction was monitored by TLC. After

completion of reaction, the reaction mixture was cooled in dry ice-acetone bath to precipitate the PEG-400 and extracted with diethyl ether (3 x 10 mL) (PEG being insoluble in ether). The upper organic layer was washed with water, brine, and dried over anhydrous sodium sulfate (Na_2SO_4). The solvent was removed under reduced pressure to afford the crude products, which were further purified by column chromatography on silica gel (60-120 mesh size) using ehtyl acetate in hexane (80:20) as eluent to yield pure products (**4a-4n** & **6a-6l**). The structures of all products were established on the basis of their spectral analysis (IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectral data) and melting point determination.

*Spectral data of synthesized dithiocarbamates **4a-4n** and **6a-6l***

*Diethyl-1-dithiocarbamic acid-n-phenyl ester (**4a**)*

White solid, M.Pt. 44-46 °C [48]. IR (KBr, ν_{max}, cm^{-1}): 2978, 1501, 1421, 1271, 1065, 732, and 686. ^{1}H-NMR ($CDCl_3$, 400 MHz): *δ* 7.24-7.69 (m, 5H), 3.83 (q, *J* = 6.92 Hz, 2H), 3.71 (q, *J* = 6.92 Hz, 2H), and 1.22-1.66 (m, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 196.4, 137.3, 130.2, 130.1, 129.4, 129.3, 127.4, 52.3, 52.5, 12.6, and 12.5. m/z (ESI-MS): 226.0679 (M+1, $C_{11}H_{15}NS_2$ requires 225.0646).

*Piperidine-1-carbodithioic acid-n-phenyl ester (**4b**)*

White solid, M.Pt. 116-118 °C [48]. IR (KBr, ν_{max}, cm^{-1}): 2918, 1459, 1252, 740, and 650. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.05-7.65 (m, 5H), 3.97 (br, 2H), 3.91 (br, 2H), 1.99 (br, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 198.8, 135.2, 129.6, 129.5, 129.2, 129.1, 125.6, 50.7, 50.6, 24.5, 24.4, and 24.1. m/z (ESI-MS): 238.0679 (M+1, $C_{12}H_{15}NS_2$ requires 237.0646).

*Morpholine-1-carbodithioic acid-n-phenyl ester (**4c**)*

White solid, M.Pt. 140-142 °C [49]. IR (KBr, ν_{max}, cm^{-1}): 2918, 1466, 1267, 1216, 1113, 756, and 667; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.49-6.70 (m, 5H), 3.99 (br, 4H), 3.74-3.88 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.2, 136.3, 131.2, 131.1, 130.6, 130.4, 125.2, 66.5, 66.3, 51.7, and 51.6. m/z (ESI-MS): 240.0472 (M+1, $C_{11}H_{13}NOS_2$ requires 239.0439).

*Pyrrolidine-1-carbodithioic acid-n-phenyl ester (**4d**)*

Colorless oil. IR (Film, ν_{max}, cm^{-1}): 2920, 1441, 1217, 756, and 667. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.57-7.80 (m, 5H), 3.95 (t, J = 6.8 Hz, 2H), 3.92 (t, J = 6.7 Hz, 2H), 2.55-2.56 (m, 2H), and 1.58-1.83 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 197.0, 135.7, 131.85, 129.8, 128.2, 56.9, 50.9, 26.5, and 24.2. m/z (ESI-MS): 224.0523 (M+1, $C_{11}H_{13}NS_2$ requires 223.0489).

*Piperidine-1-carbodithioic acid-4-methyl-phenyl ester (**4e**)*

White solid, M.Pt. 118-120 ° C [48]. IR (KBr, ν_{max}, cm^{-1}): 2945, 1480, 1279, 1134, 948, 851, 755, and 666. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23-7.48 (m, 4H), 4.10 (br, 2H), 3.29 (br, 2H), 2.38 (s, 3H), and 1.50 (br, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 195.9, 135.2, 131.6, 131.4, 131.3, 129.2, 129.1, 50.5, 50.4, 25.7, 24.3, 24.2, and 22.1; m/z (ESI-MS): 252.0836 (M+1, $C_{13}H_{17}NS_2$ requires 251.0802).

*Piperidine-1-carbodithioic acid-4-methoxy-phenyl ester (**4f**)*

White solid, M.Pt. 102-104 °C [48]. IR (KBr, ν_{max}, cm^{-1}): 2960, 1486, 1458, 1286, 913, 819, 744, and 670. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.55 (d, J = 8.8 Hz, 2H), 6.68 (d, J = 8.7 Hz, 2H), 4.22 (br, 2H), 3.76 (s, 2H), 2.16 (br, 2H), and 1.75 (br, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 196.8, 159.3, 138.3, 138.1, 126.3, 116.3, 116.2, 55.2, 52.5, 52.3, 24.8, 24.5, and 24.0. m/z (ESI-MS): 268.0785 (M+1, $C_{13}H_{17}NOS_2$ requires 267.0752).

*Pyrrolidine-1-carbodithioic acid-4-acetyl-phenyl ester (**4g**)*

White Solid, M.Pt. 78-80 °C [50]. IR (KBr, ν_{max}, cm^{-1}): 2953, 2865, 1685, 1438, 1264, 1153, 1009, 955, 820, 748, and 607. ^{1}H- NMR ($CDCl_3$, 400 MHz): δ 7.80 (d, J = 8.7 Hz, 2H), 7.59 (d, J = 8.1 Hz, 2H), 3.93 (br, 2H), 3.75 (br, 2H), 2.56 (s, 3H), 2.14-2.18 (m, 2H), 1.97-2.01 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 197.5, 195.2, 135.8, 131.9, 129.8, 129.7, 128.3, 128.2, 54.2, 52.6, 52.5, 24.6, and 24.2. m/z (ESI-MS): 266.0629 (M+1, $C_{13}H_{15}NOS_2$ requires 265.0595).

*Piperidine-1-carbodithioic acid-benzyl ester (**4h**)*

White solid, M.Pt. 52-54 °C [51]. IR (KBr, ν_{max}, cm^{-1}): 2919, 1426, 1292, 1180, 934, 809, and 709. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.47-7.60 (m, 5H), 4.55 (s, 2H), 4.16 (br, 2H), 3.65 (br, 2H),

and 1.76 (br, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 197.5, 136.4, 130.1, 129.2, 128.4, 127.4, 52.1, 51.5, 43.2, 29.6, 24.7, and 24.1. m/z (ESI-MS): 252.0836 (M+1, $C_{13}H_{17}NS_2$ requires 251.0802).

*Pyrrolidine-1-carbodithioic acid-4-hydroxy-phenyl ester (**4i**)*

Colorless oil. IR (Film, ν_{max}, cm^{-1}): 3441, 2953, 1436, 1250, 1154, 1038, 957, 856, 753, and 683. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.12 (d, J = 8.6 Hz, 2H), 7.64 (d, J = 8.0 Hz, 2H), 4.14 (s, 1H), 3.76 (br, 2H), 3.61 (br, 2H), 1.72-1.79 (m, 2H), and 1.23-1.55 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 197.1, 189.5, 136.7, 133.3, 127.2, 123.7, 122.6, 56.9, 50.9, 26.5, and 24.1. m/z (ESI-MS): 240.0473 (M+1, $C_{11}H_{13}NOS_2$ requires 239.0440).

*Piperidine-1-carbodithioic acid-n-ethyl ester (**4j**)*

Colorless oil. IR (Film, ν_{max}, cm^{-1}): 2917, 1431, 1243, 1108, 1006, 908, 851, and 731. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.21 (br, 2H), 3.85 (br, 2H), 3.14 (q, J = 7.0 Hz, 2H), 1.74 (br, 6H), and 1.22 (t, J = 2.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 192.6, 55.7, 52.4, 29.6, 26.6, 25.4, 24.1, and 14.8; m/z (ESI-MS): 190.0679 (M+1, $C_8H_{15}NS_2$ requires 189.0646).

*Pyrrolidine-1-carbodithioic acid-n-ethyl ester (**4k**)*

Colorless oil. IR (Film, ν_{max}, cm^{-1}): 2918, 1435, 1251, 1155, 1002, 910, 731, and 646. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.97 (br, 2H), 3.61 (t, J = 6.8 Hz, 2H), 3.27 (q, J = 7.3 Hz, 2H), 2.01-2.13 (m, 2H), 1.99-1.95 (m, 2H), and 1.32 (t, J = 9.8 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 192.6, 50.9, 50.4, 30.6, 26.5, 24.1, and 13.9. m/z (ESI-MS): 177.0447 (M+1, $C_7H_{13}NS_2$ requires 175.0489).

*Diethyl-1-dithiocarbamic acid-n-butyl ester (**4l**)*

Colorless oil. IR (Film, ν_{max}, cm^{-1}): 2932, 1418, 1270, 1143, 1007, 914, 732, and 646. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.04 (br, 2H), 3.75 (br, 2H), 3.28 (t, J = 7.3 Hz, 2H), 1.64-1.72 (m, 2H), 1.42-1.48 (m, 2H), 1.27-1.30 (m, 6H), and 0.92 (t, J = 7.4 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 195.9, 51.9, 49.1, 36.8, 30.5, 22.0, 13.6, 11.5, and 11.3. m/z (ESI-MS): 206.0992 (M+1, $C_9H_{19}NS_2$ requires 205.0959).

*Benzylamine-1-carbodithioic acid-n-ethyl ester (**4m**)*

Colorless viscous oil. IR (Film, ν_{max}, cm^{-1}): 3263, 2927, 2093, 1638, 1506, 1454, 1383, 1329, 1253, 1073, 1002, 912, 740, 699, and 648. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.82 (br, 1H, NH), 7.33-7.36 (m, 5H), 4.93 (d, J = 5.1 Hz, 2H, $PhCH_2N$), 3.26 (q, J = 6.8 Hz, 2H), and 1.22 (t, J = 6.8 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 198.1, 137.4, 128.9, 128.8, 128.2, 127.9, 126.7, 33.5, 26.3, and 14.3. m/z (ESI-MS): 212.0523 (M+1, $C_{10}H_{13}NS_2$ requires 211.0489).

*Benzylamine-1-carbodithioic acid-n-butyl ester (**4n**)*

Colorless viscous oil. IR (Film, ν_{max}, cm^{-1}): 3246, 2959, 2093, 1601, 1508, 1455, 1347, 1278, 1127, 1028, 909, 733, 698, and 648. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.90 (br, 1H, NH), 7.40-7.55 (m, 5H), 4.21 (d, J = 6.2 Hz, 2H, $PhCH_2N$), 3.64 (t, J = 6.9 Hz, 2H), 1.98-2.30 (m, 2H), 1.61-1.93 (m, 2H), and 1.24 (t, J = 7.6 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 199.2, 134.0, 128.9, 128.5, 128.4, 122.1, 118.9, 45.1, 38.4, 31.4, 24.1, and 15.4. m/z (ESI-MS): 240.0836 (M+1, $C_{12}H_{17}NS_2$ requires 239.0802).

*3-Diethylthiocarbamoylsulfanyl-propionic acid methyl ester (**6a**)*

Colorless oil. IR (Film, ν_{max}, cm^{-1}): 2935, 1735, 1421, 1355, 1202, 1147, 1008, 909, 732, and 648. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.0 (br, 2H, CH_2N), 3.68 (br, 2H, CH_2N), 3.65 (s, 3H), 3.53 (t, J = 6.9 Hz, 2H), 2.78 (t, J = 6.9 Hz, 2H), and 1.22-1.45 (m, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 194.6, 172.5, 51.9, 51.7, 49.3, 33.8, 31.5, 12.3, and 11.4. m/z (ESI-MS): 236.0736 (M+1, $C_9H_{17}NO_2S_2$ requires 235.0702).

*3-(Piperidine-1-carbothiosulfanyl)-propionic acid methyl ester (**6b**)*

Colorless oil. IR (Film, ν_{max}, cm^{-1}): 2919, 1654, 1439, 1217, 1020, 953, and 709. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.98 (br, 2H), 3.92 (br, 2H), 3.63 (s, 3H), 3.57 (t, J = 7.1 Hz, 2H), 2.84 (t, J = 7.1 Hz, 2H), and 1.61 (br, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 191.9, 172.4, 54.9, 51.9, 50.9, 33.8, 30.9, 26.5, 25.9, and 24.1. m/z (ESI-MS): 248.0734 (M+1, $C_{10}H_{17}NO_2S_2$ requires 247.0701).

*3-(Pyrrolidine-1-carbothiosulfanyl)-propionic acid methyl ester (**6c**)*

White solid, M.Pt. 46-48 °C [52]. IR (KBr, ν_{max}, cm^{-1}): 2917, 1735, 1437, 1221, 1156, 1007, 909, 732, and 647. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.98 (t, J = 6.8 Hz, 2H, CH_2N), 3.70 (s, 3H), 3.63 (t, J = 7.2 Hz, 2H, CH_2N), 3.57 (t, J = 6.9 Hz, 2H), 2.82 (t, J = 7.2 Hz, 2H), and 1.96-2.16 (m, 4H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 191.9, 172.4, 54.9,

51.7, 50.9, 33.8, 30.9, 26.5, and 24.1. m/z (ESI-MS): 234.0578 (M+1, $C_9H_{15}NO_2S_2$ requires 233.0544).

*3-(4-Phenylpiperazine-1-carbothiosulfanyl)-propionic acid methyl ester (**6d**)*

Colorless oil. IR (Film, ν_{max}, cm^{-1}): 3017, 2917, 2850, 1734, 1599, 1492, 1420, 1215, 1145, 1015, 925, 755, and 667. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.24-7.29 (m, 2H), 6.84-6.93 (m, 3H), 4.54 (br, 2H), 4.45 (br, 2H), 3.38 (s, 3H), 3.18 (t, J = 6.5 Hz, 2H), 3.09-3.10 (m, 4H), and 2.85 (t, J = 6.5 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 193.4, 172.5, 151.1, 129.3, 129.1, 120.3, 116.2, 52.4, 51.3, 49.1, 45.2, 31.8, and 29.6. m/z (ESI-MS):325.1245 (M+1, $C_{15}H_{20}N_2O_2S_2$ requires 324.0976).

*3-Diethylcarbamodithioic acid-3-amino-3-oxopropyl ester (**6e**)*

White solid, M.Pt. 104-106 °C [53]. IR (KBr, ν_{max}, cm^{-1}): 3411, 2920, 1667, 1271, 1202, 1147, 1006, 908, 733, and 649. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 5.70 and 5.34 (together, br, 2H, NH_2), 4.06 (br, 2H, CH_2N), 3.72 (q, J = 7.3 Hz, 2H, CH_2N), 3.56 (t, J = 6.5 Hz, 2H), 2.68 (t, J = 6.9 Hz, 2H), 1.25 (t, J = 7.3 Hz, 3H), and 0.85 (t, J = 7.3 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 196.2, 172.1, 53.8, 52.3, 34.1, 33.5, 13.6, and 12.8; m/z (ESI-MS): 221.0738 (M+1, $C_8H_{16}N_2OS_2$ requires 220.0704).

*3-(Piperidine-1-carbodithioic acid)-3-amino-3-oxopropyl ester (**6f**)*

White solid, M.Pt. 115-117 °C [53]. IR (KBr, ν_{max}, cm^{-1}): 3340, 2917, 1645, 1208, 1154, 1042, 913, and 744. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.23 (br, 2H, NH_2), 4.21 (br, 2H, CH_2N), 3.75 (br, 2H, CH_2N), 3.58 (t, J = 7.1 Hz, 2H), 2.68 (t, J = 7.2 Hz, 2H), and 0.85-1.73 (m, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 194.3, 173.5, 52.6, 52.2, 34.7, 33.2, 24.3, 24.1, and 21.3. m/z (ESI-MS): 233.0738 (M+1, $C_9H_{16}N_2OS_2$ requires 232.0704).

*3-(Pyrrolidine-1-carbodithioic acid)-3-amino-3-oxopropyl ester (**6g**)*

White solid, M.Pt. 76-78 °C [51]. IR (KBr, ν_{max}, cm^{-1}): 3431, 2979, 1647, 1442, 1216, 1154, 1038, 955, 757, and 667. ^{1}H- NMR ($CDCl_3$, 400 MHz): δ 4.13 and 4.11 (together, br, 2H, NH_2), 3.93 (t, J = 6.8 Hz, 2H, CH_2N), 3.63 (t, J = 6.9 Hz, 2H, CH_2N), 3.54 (t, J = 6.6 Hz, 2H), 2.13 (t, J = 6.6 Hz, 2H), and 1.98-2.03 (m, 4H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 206.5, 189.1, 56.9, 50.9, 32.1, 30.9, 26.5, and 24.2. m/z (ESI-MS): 219.0581 (M+1, $C_8H_{14}N_2OS_2$ requires 218.0548).

*Diethyl-1-carbamodithioic acid-3-oxo-1,3-diphenylpropyl ester (**6h**)*

Colorless oil. IR (Film, ν_{max}, cm^{-1}): 3017, 2981, 1663, 1578, 1450, 1216, 1178, 1018, 916, 754, and 689. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.00-8.03 (m, 2H), 7.40-7.55 (m, 8H), 4.89 (dd, J = 4.4, 4.4 Hz, 1H), 3.57-4.09 (m, 6H), and 1.25-1.45 (m, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 192.3, 190.2, 144.6, 137.9, 134.6, 132.6, 130.4, 129.6, 129.1, 128.8, 128.4, 128.3, 128.2, 52.1, 47.2, 29.5, 13.2, and 11.2. m/z (ESI-MS): 358.1255 (M+1, $C_{20}H_{23}NOS_2$ requires 357.1221).

*Piperidine-1-carbodithioic acid-3-oxo-1,3-diphenylpropyl ester (**6i**)*

Colorless oil. IR (Film, ν_{max}, cm^{-1}): 3060, 2940, 1664, 1606, 1576, 1449, 1216, 1134, 1016, 748, and 689. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.00-8.02 (m, 4H), 7.39-7.54 (m, 8H), 4.65 (dd, J = 4.4 Hz, 4.4 Hz, 1H), 4.21 (br, 2H, CH_2N), 3.85 (br, 2H, CH_2N), 3.57-3.60 (m, 2H), and 1.23-2.15 (m, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 202.4, 198.9, 144.8, 134.8, 132.7, 130.5, 128.9, 128.6, 128.5, 128.4, 128.3, 128.0, 127.8, 127.6, 48.2, 43.5, 38.7, 25.3, 24.8, and 24.9. m/z (ESI-MS): 370.1255 (M+1, $C_{21}H_{23}NOS_2$ requires 369.1221).

*Pyrrolidine-1-carbodithioic acid-3-oxo-1,3-diphenylpropyl ester (**6j**)*

White solid, M.Pt. 117-119 °C [54]. IR (KBr, νmax, cm^{-1}): 3062, 2923, 1664, 1577, 1440, 1215, 1178, 1017, 909, 753, and 689. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.26 -8.03 (m, 10H), 5.75 (dd, J = 4.5, 4.5 Hz, 1H), 3.59-4.15 (m, 6H), and 2.01-2.17 (m, 4H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 197.2, 190.3, 137.6, 134.6, 130.4, 128.8, 128.6, 128.4 128.3, 128.2, 128.1, 126.5, 126.3, 126.1, 52.9, 52.8, 48.5, 38.7, 26.3, and 24.1. m/z (ESI-MS): 356.1098 (M+1, $C_{20}H_{21}NOS_2$ requires 355.1065).

*Benzyl-1-carbamodithioic acid-3-oxo-1,3-diphenylpropyl ester (**6k**)*

Colorless oil. IR (Film, ν_{max}, cm^{-1}): 3018, 2918, 2850, 1638, 1664, 1605, 1450, 1336, 1215, 1177, 1016, and 747. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.02 (d, J = 7.3 Hz, 2H), 7.82-7.91 (m, 3H), 7.22-7.65 (m, 10H), 6.20 (br, 1H, NH), 4.86 (dd, J = 5.8, 5.8 Hz, 1H), 4.70 (s, 2H), and 3.74-3.86 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 196.2, 190.1, 144.8, 138.0, 134.7, 133.7, 132.7,

130.5, 128.9, 128.8, 128.5, 128.4, 128.2, 128.0, 121.9, 50.9, 50.1, 48.5, 43.6, 42.5, 37.8, and 29.6. m/z (ESI-MS): 392.1099 (M+1, $C_{23}H_{21}NOS_2$ requires 391.1067).

*Butyl-1-carbamodithioic acid-3-oxo-1,3-diphenylpropyl ester (**6l**)*

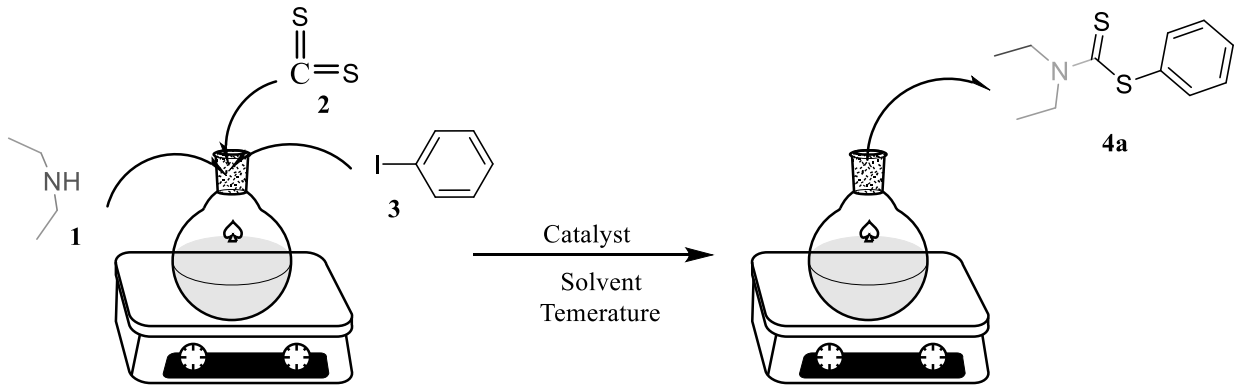
Colorless oil. IR (Film, ν_{max}, cm^{-1}): 3065, 2918, 2850, 1663, 1605, 1577, 1450, 1336, 1216, 1178, 1017, and 908; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.0 (d, J = 7.3 Hz, 2H), 7.30-7.37 (m, 8H), 4.70 (dd, J = 6.6, 6.6 Hz, 1H), 4.45 (br, 1H, NH), 3.17-3.46 (m, 2H), 3.17 (t, J = 6.8 Hz, 2H), 1.41-1.58 (m, 2H), 1.23-1.39 (m, 2H), and 0.92 (t, J = 7.3 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 202.0, 198.9, 138.1, 134.8, 128.9, 128.6, 128.4, 126.8, 48.6, 39.1, 38.1, 35.2, 31.8, 31.3, 30.8, 30.1, 23.5, 21.6, and 13.3; m/z (ESI-MS): 357.7302 (M+1, $C_{20}H_{23}NOS_2$ requires 357.1221).

Results and Discussion

The review of literature indicated that there are no studies on the use of CAN as a catalyst for the three-component synthesis of dithiocarbamate derivatives without the use of any harmful solvents. This approach uses CAN as a Lewis acid catalyst in PEG to combine the reactions of amines, carbon disulfide, and alkyl/aryl halides in a single reaction vessel. Amines are a key ingredient in the reaction that creates antibacterial and anti-cancer medications. In the intended products, this agent provided the C-N bond while the alkyl/aryl halides provided the C-S bond. The dithiocarbamate formation is stabilised by the inductive impact of the alkyl group, which also alters the polarity of the S-H bond by increasing the electron density on the nitrogen atom.

Diethylamine **1a**, carbon disulfide **2**, and iodobenzene **3a** were used in combination with varied amounts of the catalyst and temperatures to optimise the reaction conditions to increase yield (**Scheme 1**). **Table 1** provides a summary of the findings.

The ideal CAN dosage was assessed. The catalyst concentration of 5 mol% produced the maximum yield. Motivated by this outcome, we continued to investigate the optimal reaction conditions using CAN at varying concentrations from 2 to 5 mol%, which not only reduced the reaction time from 4 to 2 h, but also boosted the product yield from 90% to 94%. This demonstrated that a key factor in the optimization of product yields is the catalyst concentration. Although using 10 mol% of CAN allowed for a 1-hour reaction time reduction, the yield surprisingly dropped to 86%. When an excessive amount (10 mol%) of CAN was employed in the reaction, it is likely that the starting material or product was destroyed during the reaction, which might account for the low product yield. A reaction of diethyamine, carbon disulphide, and iodobenzene was carried out at 50 °C in PEG-400:H_2O without any catalyst to determine the catalyst's genuine efficacy. After 5 hours of heating, it turned out that just a little amount of dithiocarbamate was produced (**Table 1**, Entry **3**).



Scheme 1. Synthesis of diethyl-1-dithiocarbamic acid-*n*-phenyl ester as a model reaction

Table 1. One-pot synthesis of the modal reaction: temperature and CAN quantity screening[a]

Entry	CAN (mol%)	Temperature (°C)	Time (h)	Yield (%)[b]
1	10	50	1	86
2	7	50	1.5	89
3	**5**	**50**	**2**	**95**
4	2	50	4	90
5	-	50	5	Trace
6	5	30	3	72
7	5	40	2.5	86
8	5	60	2	92

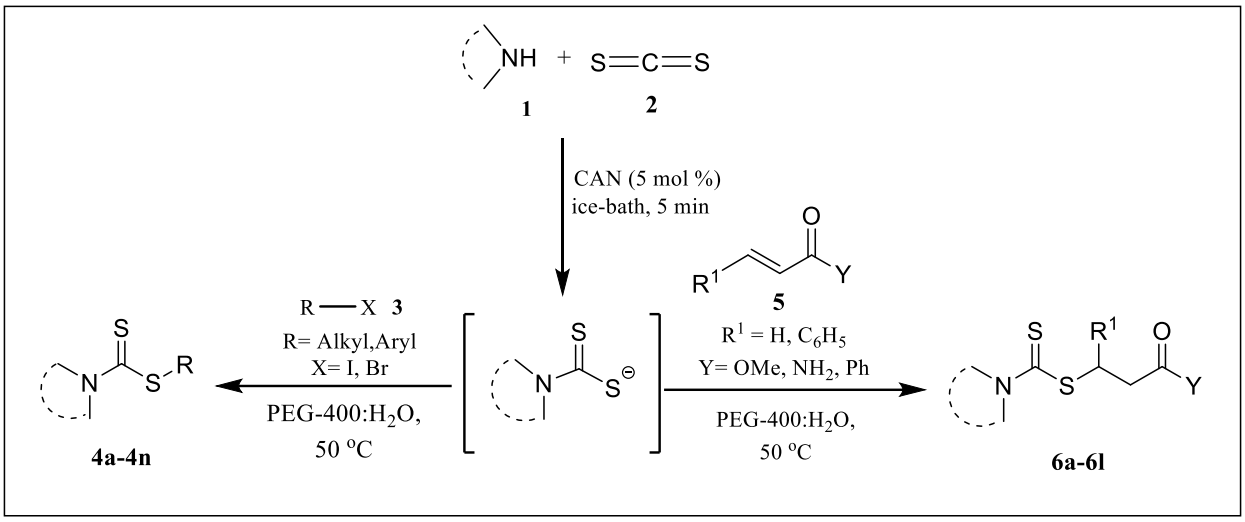
[a]Reaction conditions: diethylamine (1.2 mmol), CS_2 (2.5 mmol), iodobenzene (1 mmol), catalyst CAN (x mol%); solvent PEG-400: H_2O (1:1, 3 mL), and temperature 50 °C
[b]Product yields

In the majority of MCRs, solvent selection is significant. Different solvents, including non-polar solvents like n-hexane, protic solvents like water, ethanol, and ethanol: H_2O, polyethylene glycol (PEG), and PEG-400: H_2O, as well as aprotic polar solvents like acetonitrile, were examined to compare the solvent efficiency. The outcomes shown in **Table 2** show that solvents had an impact on the catalyst's effectiveness. Acetonitrile and *n*-hexane had lower yields (**Table 2**, Entries **6** and 7). Due to the lack of strong interactions between the starting components, the yield was low (30%) when the reaction was carried out without the use of a solvent. However, after only 2 hours of stirring the combination at 50 °C, a non-toxic, recyclable, and thermally stable PEG-400 was discovered to deliver the good product yield increase of up to 86% (**Table 2**, Entry **9**). We were encouraged by these encouraging results and used various PEG-400:H2O solvent system ratios to optimize the reaction conditions. The product yield increased from 87% to 95% when PEG-400 was reduced from 100% to 50% (**Table 2**, Entries **10**–**14**). However, a further reduction in the PEG-400 ratio reduced the product yield, which is attributable to the loss of the reactants' water solubility. The best solvent, PEG 400: H_2O, is thought to have the best catalytic activity

Table 2. Solvent effects[a]

Entry	Solvents	Temperature (°C)	Yields (%)[b]
1	Solvent-free	90	30
2	C_2H_5OH	Reflux	68
3	CH_3OH	Reflux	70
4	EtOH:H_2O	90	75
5	H_2O	100	80
6	*n*-Hexene	Reflux	Trace
7	CH_3CN	Reflux	50
9	PEG 400	50	86
	PEG-400:H_2O[c]	**Temperature (°C)**	
10	90:10	50	87
11	80:20	50	89
12	70:30	50	90
13	60:40	50	92
14	**50:50**	**50**	**95**
15	40:60	50	82

[a]Reaction conditions: diethylamine (1.2 mmol), CS_2 (2.5 mmol), iodobenzene (1 mmol), solvents (3 mL), and catalyst CAN (5 mol%) for 2 h
[b]Product Yields
[c]A mixture of 1.5 mL of PEG-400 and 1.5 ml of water was used as solvent



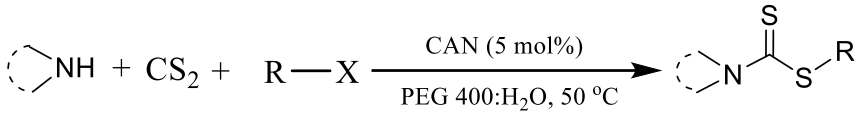
Scheme 2. Ceric ammonium nitrate (CAN) catalyze synthesis of dithiocarbamates

because "PEG-400 is a prominent solvent that may increase the solubility of substrates and other reagents with water." PEG also has the ability to remove the hydrogen atom from amine. This might be because the oxygen in the PEG hydroxyl group and hydrogen in diethyl amine $(C_2H_5)_2NH$ are attracted to one another. By weakening the N-H bond, this increases the carbon's nucleophilicity. To complete the synthesis of desired dithiocarbamate products, we can therefore anticipate that PEG-400: H_2O can provide a better reaction medium. As a result, this solvent system can significantly contribute to the achievement of green chemistry's objectives.

We tested the generality of this protocol after refining the reaction conditions by coupling alkyl or aryl halides (iodide and bromide groups) with the dithiocarbamate anion, which was produced in situ by the reaction of carbon disulfide and a number of amines to produce the corresponding dithiocarbamate derivatives (**Scheme 2**). **Table 1** provides a summary of the findings. We used various primary and secondary amines when dealing with amines. Due to the strong reactivity of 2°-amines (**Table 3**, Entries **13** and **14**), the secondary amines such diethyl amine, piperidine, morpholine, and pyrrolidine typically delivered larger yields of products in shorter reaction times as compared to primary amines (**Table 3**, Entries **1–12**). There is no discernible difference between alkyl iodides and bromides in terms of reaction time and product yields. In general, all of the syntheses were carried out using standard reaction conditions, including speedier reaction durations, high selectivity, and no by-products.

The viability of using the existing method for the other new one-pot three-component coupling was then evaluated, and we looked at various amines and Michael acceptors under the same reaction circumstances (**Scheme 2**). A wide variety of amines with different structural characteristics, including the primary and secondary amines, were utilised in this technique with great success. This procedure is also quite generic. In general, the secondary amines like piperidine, pyrrolidine, and diethylamine have better yields than primary amines. Michael acceptors are effectively added to primary amines like benzylamine and *n*-butylamine to produce the corresponding dithiocarbamate with great outcomes. Michael acceptors were produced in high to outstanding yields by reactions that went smoothly with electron-deficient olefins including methyl acrylate, acrylamide, and chalcone (**Table 4**). In addition, we discovered that using 1-phenylpiperazine produced the equivalent Michael adducts in high quantities as well. (**Table 4**, Entry **18**).

Table 3. Dithiocarbamate anions are coupled to alkyl/aryl halides *via* CAN[a]

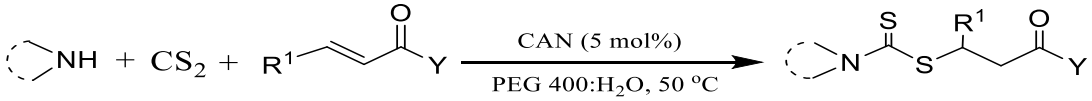


1 2 3 4a-n

Entry	R	X	Amines	Time (h)	Product	Yield (%)[b]	M.Pt. (°C)[c]
1	C_6H_5	I	$(C_2H_5)_2NH$	2	**4a**	95	44-46 [48]
2	C_6H_5	I	Piperidine	2	**4b**	92	116-118 [48]
3	C_6H_5	I	Morpholine	2.5	**4c**	89	140-142 [49]
4	C_6H_5	I	Pyrrolidine	2	**4d**	88	Colorless oil
5	4-$H_3CC_6H_4$	I	Piperidine	3	**4e**	82	118-120 [48]
6	4-$H_3COC_6H_4$	I	Piperidine	3.5	**4f**	79	102-104 [48]
7	4-$H_3COCC_6H_4$	I	Pyrrolidine	3	**4g**	81	70-80 [50]
8	$C_6H_5CH_2$	I	Piperidine	2.5	**4h**	92	52-54 [51]
9	4-HOC_6H_4	I	Pyrrolidine	3.5	**4i**	78	Colorless oil
10	C_2H_5	I	Piperidine	2	**4j**	96	Colorless oil
11	C_2H_5	Br	Pyrrolidine	3	**4k**	95	Colorless oil
12	C_4H_9	Br	$(C_2H_5)_2NH$	3.5	**4l**	91	Colorless oil
13	C_2H_5	I	Benzylamine	4	**4m**	75	Colorless oil
14	C_4H_9	I	Benzylamine	4.5	**4n**	72	Colorless oil

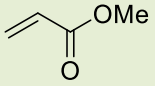
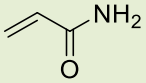
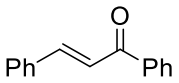
[a]Reaction conditions: amines (1.2 mmol), CS_2 (2.5 mmol), aryl/alkyl halides (1 mmol), catalyst CAN (5 mol%), solvent PEG-400:H_2O (1:1, 3 mL), and temperature 50 °C
[b]Product yields
[c]Melting Points

Table 4. Dithiocarbamate anions' nucleophilic addition to the Michael acceptor under CAN catalysis[a]



1 2 5 6a-6l

R^1 = H, C_6H_5; Y = OMe, NH_2, Ph

Entry	Michael acceptor	Amines	Time (h)	Product	Yield (%)[b]	M.Pt. (°C)[c]
15		$(C_2H_5)_2NH$	2	**6a**	92	Colorless oil
16		Piperidine	2.5	**6b**	81	Colorless oil
17		Pyrrolidine	2.5	**6c**	94	46-48 [52]
18		1-Phenylpiperazine	3.5	**6d**	82	Colorless oil
19		$(C_2H_5)_2NH$	3	**6e**	88	104-106 [53]
20		Piperidine	3	**6f**	86	115-117 [53]
21		Pyrrolidine	3.5	**6g**	81	76-78 [51]
22		$(C_2H_5)_2NH$	2.5	**6h**	95	Colorless oil
23		Piperidine	2.5	**6i**	93	Colorless oil
24		Pyrrolidine	3	**6j**	92	117-119 [54]
25		Benzylamine	4	**6k**	81	Colorless oil
26		*n*-Butylamine	4.5	**6l**	83	Colorless oil

[a]Reaction conditions: amines (1.2 mmol), CS_2(2.5 mmol), Michael acceptor (1 mmol), catalyst CAN (5 mol%), solvent PEG-400:H_2O (1:1, 3 mL), and temperature 50 °C
[b]Product yields
[c]Melting Points

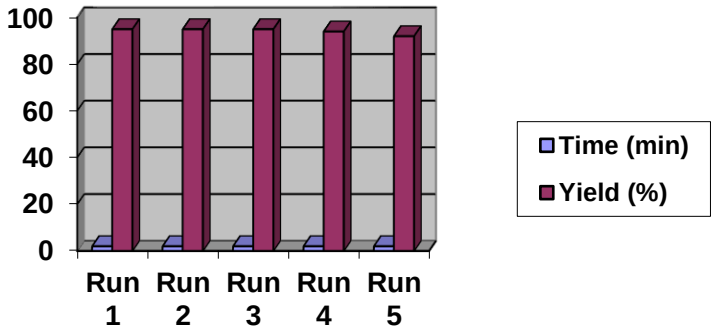
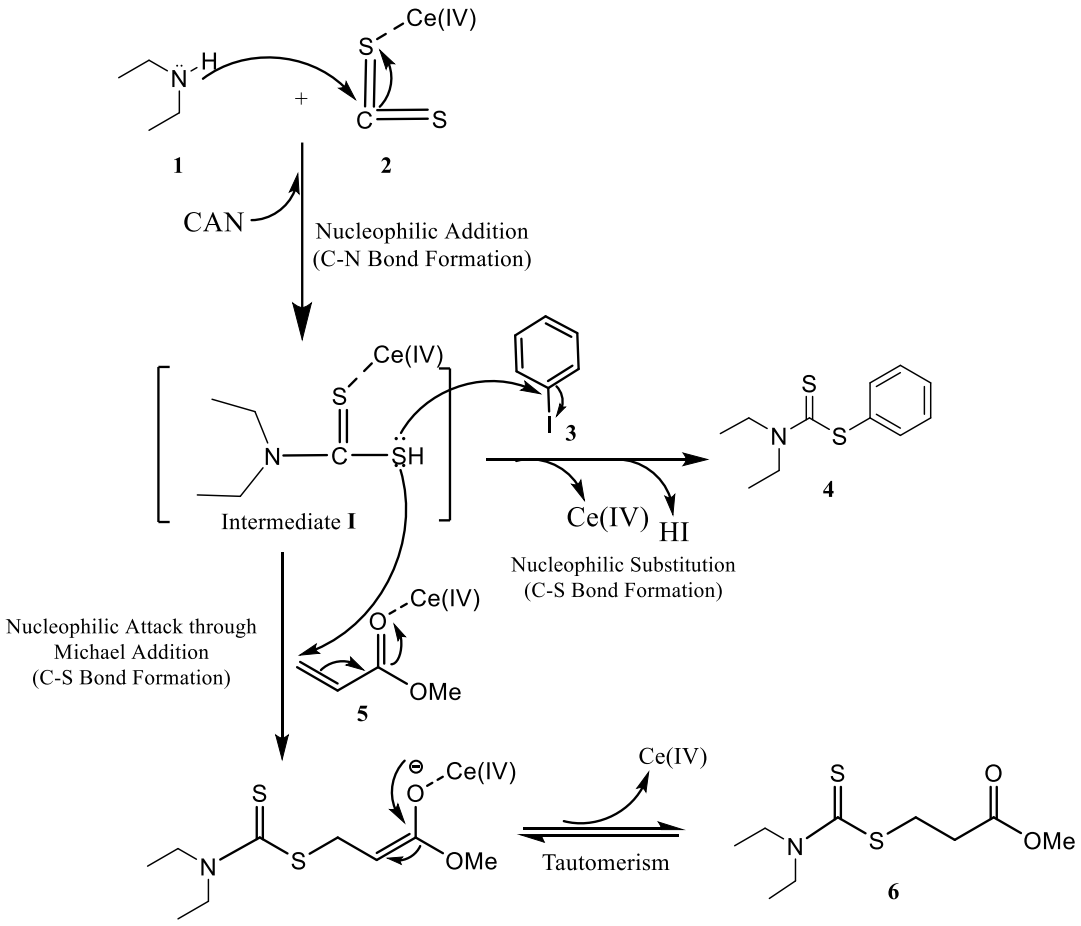


Figure 1. Recyclable ability of green solvent



Scheme 3. Intriguing pathway for the formation of dithiocarbamate using CAN as a catalyst

Recovery of the Solvent

After the reaction is finished, polyethylene glycol (PEG) should be easily recycled with little loss and degradation to demonstrate that using it as a reusable solvent is also feasible. Diethyl ether and PEG-400 are immiscible. Therefore, the desired product can be extracted using it while the PEG-400 phase is still present. Although there was a clean start to the reaction and consistent results up to three cycles, there was a 5% mechanical loss in the weight of PEG-400 from cycle to cycle (**Figure 1**).

The proposed mechanism for this formation of dithiocarbamate is depicted in **Scheme 3** under the Lewis acidic nature of CAN, carbon disulfide (CS_2) **2** become actively participated in nucleophilic addition reaction with diethyl amine $(C_2H_5)_2NH$ **1** to give dithiocarbamic acid (*in situ*) **I**. Furthermore, the properly activated *in situ* produced intermediate I quickly goes through, a) A nucleophilic substitution reaction with iodobenzene **3** to form dithiocarbamate **4**, b) Immediately Michael-type addition with conjugated alkene **5** to give the adduct **6**. We believe that Lewis acid catalyst (CAN) and formation of dithiocarbamic acid is essential for the progress of the reaction in forward direction. The plausible mechanism is cited in the article.

Conclusion

In conclusion, using ceric ammonium nitrate (CAN) as an Lewis acid catalyst in a PEG-400: H_2O green solvent system, we have devised a simple, efficient, and unique synthesis of bioactive dithiocarbamates using carbon disulfide, amines, and halides. The novel points of the proposed protocol include an eco-friendly nature, cost-effectiveness, simple purification, recovery of solvent, high yields of desired products, and an easy procedure. In addition, minimum loading of catalyst, clean reaction, and less chemical waste generation gives promising opportunities for generating a diversity-oriented library of molecules related to dithiocarbamates and green chemistry.

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Conflict of interest

The authors declare no potential conflict of interest.

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