SYNTHESIS OF VARIOUS DITHIOCARBAMATE ESTERS THROUGH REGIOSELECTIVE THIOLATION OF 2-AMINOTHIAZOLE

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ABSTRACT

Dithiocarbamates are of significant importance as pesticides, vulcanizing agents and pharmaceuticals. In search of efficient regioselective strategy, the various dithiocarbamate esters were synthesized by regioselective thiolation at endo-cyclic nitrogen of 2-aminothiazole. The treatment of Boc-protected 2-aminothiazole with carbon disulphide and alkyl halide in the presence of potassium hydroxide in DMF afforded Boc-dithiocarbamate esters (3a-h). The removal of protecting group with TFA provided corresponding dithiocarbamate esters (4a-h). The formation of regioselective product was confirmed by spectral and molecular mechanical MM2 force field and PM3 approximation MOPAC energy minimization data. The strategy provides an important methodology for regioselective thiolation.

KEY WORDS: 2-Aminothiazole, Dithiocarbamate, Endo-cyclic, Regioselective, Thiolation.

1. INTRODUCTION

Salts and esters of dithiocarbamates (DTC) are of potential interest due to their wide utility as radical precursors and intermediates in organic synthesis.[1,2] They are of great importance in agriculture as pesticides and in the rubber industries as vulcanization accelerators.[3,4] They have been reported as linker in solid phase synthesis and in protection of amino group during peptide synthesis.[5,6] Because of strong metal binding capacity, they can act as inhibitors of various enzymes in biological systems.[7,8] Moreover, they have found application as antioxidant, antiradiation, antiparkinsonian, antifungal, antimicrobial, anticancer and anti-HIV agents.[9-15] Additionally, dithiocarbamates have also been reported as inhibitors of UV-induced p53 activation and hence may function as inhibitors of p53 mediated apoptosis.[16] Several methods have been reported for synthesis of variety of dithiocarbamates using NaOH, KOH, Triton-B, 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) and phosphate buffer.[17-21] Previously, we have reported regioselective mono- and di-alkylation at endo- cyclic nitrogen of L-histidine.[22] For further extension of our work, here we reported regioselective thiolation of 2-aminothiazole to obtain different types of dithiocarbamate esters.

2. MATERIAL AND METHODS

The ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 400 FT spectrometer in deuteriochloroform and deuteriodimethyl sulfoxide with tetramethysilane as internal standard. Chemical shifts were reported in parts per million. Mass spectra (MS) were measured by the EI method. Melting points are uncorrected. Silica gel (60-120 mesh) was used for column chromatography. All the reactions were monitored by TLC using 0.25 mm silica gel plates (Merck 60F-254) with or without UV indicator. *N*, *N*-Dimethylformamide was distilled from anhydrous magnesium sulfate prior to use. All other reagents were commercially available (Merck, Fluka) and were used without further purification. The energy minimization calculations were carried out using CS Chem3D Pro 6.0 (built in ChemOffice 6.0) software.

2.1. Synthesis of dithiocarbamate esters

*Thiazol-2-yl-carbamic acid tert-butyl ester (**2a**)*

To a suspension of **1** (200 mg, 2 mmole) in a mixture of 6 ml of THF and water, Boc-anhydride (436 mg, 2 mmole) was added. The mixture was allowed to cool at room temperature and pH was maintained at 10.5 by the addition of aqueous NaOH (2N). The reaction was followed by TLC until completion. The solution was concentrated to viscous oil and was triturated with dichloromethane (3×50 ml). The suspension was filtered and organic phase was dried over Na_2SO_4 and removal of solvent under vacuum afforded the product **2a** (92%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 1.32 (s, 9H, t-Bu), 12.34 (bs, 1H, NH), 7.25 (d, 1H, CH), 7.43 (d, 1H, CH) ppm; TOF-MS (ES^+) *m/z* = 201 (M+).

2-tert-Butoxycarbonylimino-thiazole-3-carbodithioic acid esters (**3a-h**)

To a ice cold mixture of carbon disulfide (6 mmol) and KOH (6 mmol) in dry DMF, a solution of compound **2a** (6 mmol) in dry DMF was added and stirred at 0 °C for 2 hrs, then warmed to room temperature and stirring was continued until KOH was dissolved completely. Then appropriate alkyl halide (6 mmol) was added and stirring was continued until reaction was complete (monitored by TLC). The solvent was removed under vacuo and mixture was quenched by addition of cold water and was extracted with EtOAc, dried over anhyd. Na_2SO_4. The product was purified by silica gel (60-120 mesh) column chromatography eluted with petroleum ether and ethyl acetate (20:80). Evaporation of the solvent afforded NMR pure product.

2-tert-Butoxycarbonylimino-thiazole-3-carbodithioic acid methyl ester (**3a**) Yield: 54%. Oil, ^{1}H-NMR ($CDCl_3$): δ 1.37 (s, 9H, t-Bu), 2.67 (s, 3H, CH_3), 7.16 (d, 1H, CH), 7.36 (d, 1H, CH); ^{13}C-NMR ($CDCl_3$): δ 21.5, 33.7, 71.2, 127.2, 128.2, 167.3, 171.1, 197.4; TOF-MS (ES^+) m/z= 291.9 (M+2).

2-tert-Butoxycarbonylimino-thiazole-3-carbodithioic acid ethyl ester (**3b**) Yield: 52%. Oil, ^{1}H-NMR ($CDCl_3$): δ 1.31 (t, 3H, CH_3), 1.40 (s, 9H, t-Bu), 2.81 (q, 2H, CH_2), 7.15 (d, 1H, CH), 7.24 (d, 1H, CH); ^{13}C-NMR ($CDCl_3$): δ 15.2, 28.3, 38.8, 70.8, 126.4, 132.1, 166.7, 170.8, 205.1; TOF-MS (ES^+) m/z= 306.1 (M+2).

2-tert-Butoxycarbonylimino-thiazole-3-carbodithioic acid propyl ester (**3c**) Yield: 41%. Oil, ^{1}H-NMR ($CDCl_3$): δ 0.98 (t, 3H, CH_3), 1.39 (s, 9H, t-Bu), 2.11 (m, 2H, CH_2), 2.87 (t, 2H, CH_2), 7.21 (d, 1H, CH), 7.26 (d, 1H, CH); ^{13}C-NMR ($CDCl_3$): δ 12.6, 24.3, 27.9, 39.9, 70.6, 129.1, 136.3,

164.9, 169.7, 199.2; TOF-MS (ES^+) m/z= 319.8 (M+2).

2-tert-Butoxycarbonylimino-thiazole-3-carbodithioic acid isopropyl ester (**3d**) Yield: 19%. Oil, ^{1}H-NMR ($CDCl_3$): δ 1.35 (d, 6H, $2CH_3$), 1.41 (s, 9H, t-Bu), 2.79 (m, 1H, CH), 7.19 (d, 1H, CH), 7.30 (d, 1H, CH); ^{13}C-NMR ($CDCl_3$): δ 21.6, 29.9, 41.2, 73.2, 128.7, 136.8, 166.1, 172.2, 196.7; TOF-MS (ES^+) m/z= 319.6 (M+2).

2-tert-Butoxycarbonylimino-thiazole-3-carbodithioic acid butyl ester (**3e**) Yield: 36%. Oil, ^{1}H-NMR ($CDCl_3$): δ 1.28 (m, 5H, CH_2 & CH_3), 1.45 (s, 9H, t-Bu), 1.96 (m, 2H, CH_2), 2.84 (t, 2H, CH_2), 6.97 (d, 1H, CH), 7.29 (d, 1H, CH); ^{13}C-NMR ($CDCl_3$): δ 13.7, 21.8, 28.5, 40.8, 72.1, 126.2, 135.5, 167.5, 172.4, 197.3; TOF-MS (ES^+) m/z= 333.7 (M+2).

2-tert-Butoxycarbonylimino-thiazole-3-carbodithioic acid isobutyl ester (**3f**) Yield: 21%. Oil, ^{1}H-NMR ($CDCl_3$): δ 1.06 (d, 6H, $2CH_3$), 1.40 (s, 9H, t-Bu), 2.16 (m, 1H, CH), 2.82 (d, 2H, CH_2), 7.21 (d, 1H, CH), 7.33 (d, 1H, CH); ^{13}C-NMR ($CDCl_3$): δ 20.8, 28.2, 31.1, 42.1, 71.5, 127.5, 136.3, 166.8, 171.3, 198.2; TOF-MS (ES^+) m/z= 334.2 (M+2).

2-*tert*-Butoxycarbonylimino-thiazole-3-carbodithioic acid pentyl ester (**3g**) Yield: 33%. Oil, ^{1}H-NMR ($CDCl_3$): δ 1.19 (m, 5H, CH_2 & CH_3), 1.39 (m, 11H, CH_2 & t-Bu), 1.92 (m, 2H, CH_2), 2.86 (t, 2H, CH_2), 6.99 (d, 1H, CH), 7.36 (d, 1H, CH); ^{13}C-NMR ($CDCl_3$): δ 14.0, 22.2, 29.1, 32.3, 41.6, 73.2, 128.1, 137.9, 168.5, 172.4, 196.9; TOF-MS (ES^+) m/z= 347.7 (M+2).

2-tert-Butoxycarbonylimino-thiazole-3-carbodithioic acid benzyl ester (**3h**) Yield: 43%. ^{1}H-NMR ($CDCl_3$): δ 1.42 (s, 9H, t-Bu), 3.83 (s, 2H, CH_2), 7.17 (d, 1H, CH), 7.21-7.53 (m, 6H, CH & C_6H_5); ^{13}C-NMR ($CDCl_3$): δ 30.2, 39.3, 70.7, 125.8, 126.7, 127.9, 128.6, 136.9, 142.3, 167.1, 171.5, 202.9; TOF-MS (ES^+) m/z= 367.8 (M+2).

2-Imino-thiazole-3-carbodithioic acid esters (**4a-h**)

Compound **4a-h** were synthesized using earlier reported method.[26] A solution of the compound **3a-h** (0.6 mmol) in CH_2Cl_2 (2 mL) and trifluoroacetic acid (2 mL) was stirred for 5 h at room temperature, and the solvent was evaporated under reduced pressure. To the residue an aqueous solution of saturated $NaHCO_3$ was added carefully, which was extracted with CH_2Cl_2. The organic layer was carefully washed with an aqueous solution of saturated $NaHCO_3$ and water, dried over Na_2SO_4, filtered, concentrated under reduced pressure. The product was purified by silica gel (60-120 mesh) column chromatography eluted with petroleum ether and ethyl acetate (40:60).

2-Imino-thiazole-3-carbodithioic acid methyl ester (**4a**) Yield: 58%. ^{1}H-NMR ($CDCl_3$): δ 2.81 (s, 3H, CH_3), 7.15 (d, 1H, CH), 7.29 (d, 1H, CH), 9.62 (s, 1H, NH); TOF-MS (ES^+) m/z= 191.8 (M+2).

2-Imino-thiazole-3-carbodithioic acid ethyl ester (**4b**) Yield: 59%. ^{1}H-NMR ($CDCl_3$): δ 1.36 (t, 3H, CH_3), 2.86 (q, 2H, CH_2), 7.21 (d, 1H, CH), 7.28 (d, 1H, CH), 9.51 (s, 1H, NH); TOF-MS (ES^+) m/z= 105.9 (M+2).

2-Imino-thiazole-3-carbodithioic acid propyl ester (**4c**) Yield: 56%. ^{1}H-NMR ($CDCl_3$): δ 0.97 (t, 3H, CH_3), 1.42 (m, 2H, CH_2) 2.78 (t, 2H, CH_2), 7.29 (d, 1H, CH), 7.36 (d, 1H, CH), 9.59 (s, 1H, NH); TOF-MS (ES^+) m/z= 219.8 (M+2).

2-Imino-thiazole-3-carbodithioic acid isopropyl ester (**4d**) Yield: 54%. ^{1}H-NMR ($CDCl_3$): δ 1.27 (d, 6H, $2CH_3$), 2.88 (m,

1H, CH), 7.25 (d, 1H, CH), 7.34 (d, 1H, CH), 9.63 (s, 1H, NH); TOF-MS (ES^+) m/z= 219.8 (M+2).

2-Imino-thiazole-3-carbodithioic acid butyl ester (**4e**) Yield: 46%. ^{1}H-NMR ($CDCl_3$): δ 1.19 (m, 5H, CH_2 & CH_3), 1.88 (m, 2H, CH_2), 2.82 (t, 2H, CH_2), 7.11 (d, 1H, CH), 7.32 (d, 1H, CH), 9.71 (s, 1H, NH); TOF-MS (ES^+) m/z= 233.9 (M+2).

2-Imino-thiazole-3-carbodithioic acid isobutyl ester (**4f**) Yield: 43%. ^{1}H-NMR ($CDCl_3$): δ 1.14 (d, 6H, $2CH_3$), 2.10 (m, 1H, CH), 2.91 (d, 2H, CH_2), 7.31 (d, 1H, CH), 7.38 (d, 1H, CH), 9.66 (s, 1H, NH); TOF-MS (ES^+) m/z= 233.8 (M+2).

2-Imino-thiazole-3-carbodithioic acid pentyl ester (**4g**) Yield: 41%. ^{1}H-NMR ($CDCl_3$): δ 1.16 (m, 5H, CH_2 & CH_3), 1.32 (m, 4H, $2CH_2$), 2.86 (t, 2H, CH_2), 7.25 (d, 1H, CH), 7.34 (d, 1H, CH), 9.72 (s, 1H, NH); TOF-MS (ES^+) m/z= 347.8 (M+2).

2-Imino-thiazole-3-carbodithioic acid benzyl ester (**4h**) Yield: 61%. ^{1}H-NMR ($CDCl_3$): δ 3.66 (s, 2H, CH_2), 7.14 (d, 1H, CH), 7.26 (d, 1H, CH), 7.32-7.58 (m, 5H, C_6H_5), 9.83 (s, 1H, NH); TOF-MS (ES^+) m/z= 267.8 (M+2).

2.2. Energy minimization

To find out global minimum for endo-cyclic (**3h**) and exo-cyclic (**7**) dithiocarbamate esters the energy minimization was carried out using Allinger's MM2 force field at minimum RMS gradient 0.100. Moreover, heat of formation (ΔH_f) was calculated using parameterized model revision 3 (PM3) approximation available in semiempirical MOPAC method of energy minimization. All calculations were carried out following the user's manual (provided).

3. RESULT AND DISCUSSION

Initially, Boc protected 2-aminothiazole (**2a**) was obtained by the treatment of compound (**1**) with Boc-anhydride in the presence of sodium hydroxide in mixture of THF and water. The treatment of Boc-protected 2-aminothiazole (**2a**) with alkyl halides in the presence of CS_2 and KOH in DMF afforded dithiocarbamate ester (**3a-h**) with thiolation exclusively at endo-cyclic nitrogen (Scheme 1).

The formation of dithiocarbamate esters (**3a-h**) was confirmed by spectral analysis of all obtained products. Additionally, molecular mechanical MM2 and semiempirical MOPAC methods of energy minimization also confirmed the formation of endo-N-thiolated product. The endo-cyclic nitrogen in Boc protected 2-aminothiazole functions as a secondary amine through the tautomerism and provides site for thiolation. Thus, dithiocarbamate esters (**3a-h**) may be regarded as product of α-substituted alicyclic secondary amine. Previously, Baikenova et al. have been reported formation dithiocarbamate salts of α-substituted alicyclic secondary amine, anabasine.[23] Similarly, Moghini and Mossalayi have also been reported dithiocarbamate salt of 2-propylpiperidine.[24]

Furthermore, deprotection of Boc using trifluoroacetic acid (TFA) in CH_2Cl_2 afforded endo-cyclic dithiocarbamate esters (**4a-4h**) (Scheme 2). Although, yield of the product decreased after deprotection but still satisfactory and sufficient for characterization of the products. This decreased yield may be expected to be due to degradation of the product in acidic media used during deprotection step.[25]

This strategy is highly efficient for synthesis of variety of Boc-protected as well as unprotected endo-cyclic dithiocarbamate esters. However, there may be formation of exo-cyclic dithiocarbamate ester (**7**) as a by product during thiolation of Boc protected 2-aminothizole (**2a**) (Scheme 1). Our data supported the formation of compound (**3h**), relatively, to a large extent than exo-cyclic dithiocarbamate ester (**7**). The preferential thiolation at endo-cyclic nitrogen can be explained on the basis of conversion of compound (**2a**) into a tautomeric intermediate (**2b**). Because sterically less hindered endo-cyclic nitrogen bears hydrogen in intermediate (**2b**) than compound (**2a)**, and reacts with CS_2 to generate *in situ* dithiocarbamate salt (**6**). The alkylation of salt (**6**) results in the formation of endo-cyclic dithiocarbamate ester (**3h**) rather than exo-cyclic ester (**7**) (Scheme 3).

The spectral (^{1}H-NMR and Mass) analysis provided little information about difference between endo-cyclic and exo-cyclic thiolation products. Thus, as a confirmatory data in the favour of endo-cyclic dithiocarbamate ester (**3h**), we carried out molecular mechanical MM2 force field energy minimization for two possible endo-cyclic (**3h**) and exo-cyclic (**7**). Both possible compounds are isomers but they will contain different total steric energies (TSEs).

The total steric energies (TSEs) for ompound (**3h**) and (**7**) were found to be 8.1604 and 21.5234 respectively. Thus, low steric energy indicated the higher stability of endo-cyclic N-thiolation product (**3h**) and confirmed the thiolation at endo-cyclic nitrogen. Similarly, MOPAC energy minimization indicated ΔH_f 5.87572 and 25.99264 kcal/mol for endo-cyclic (**3h**) and exo-cyclic (**7**) dithiocarbamate esters, respectively, and formation of compound **3h** (Figure 1).

4. CONCLUSION

The use of Boc protection-deprotection strategy provides an important approach for regioselective thiolation at endo-cyclic N-atom and producing various dithiocarbamate esters. However, there is need of further evaluation of reaction conditions to improve the yield of product.

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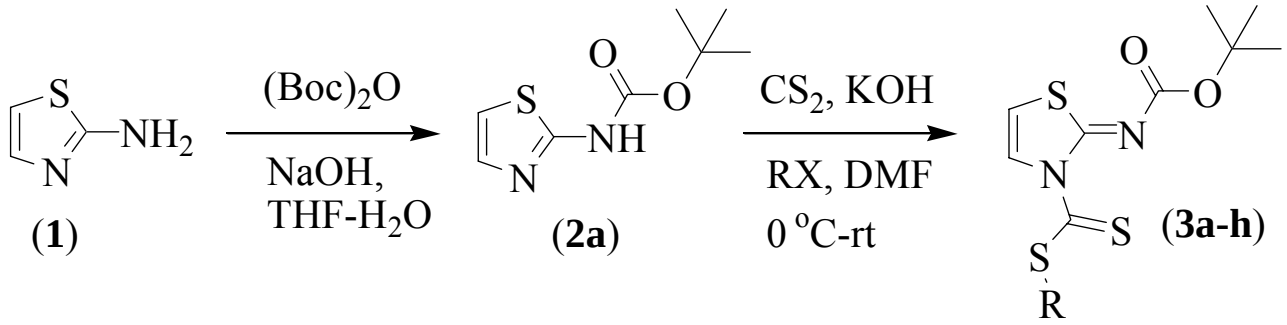
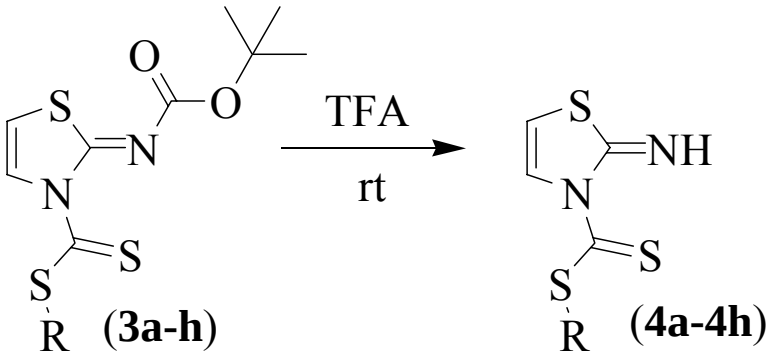
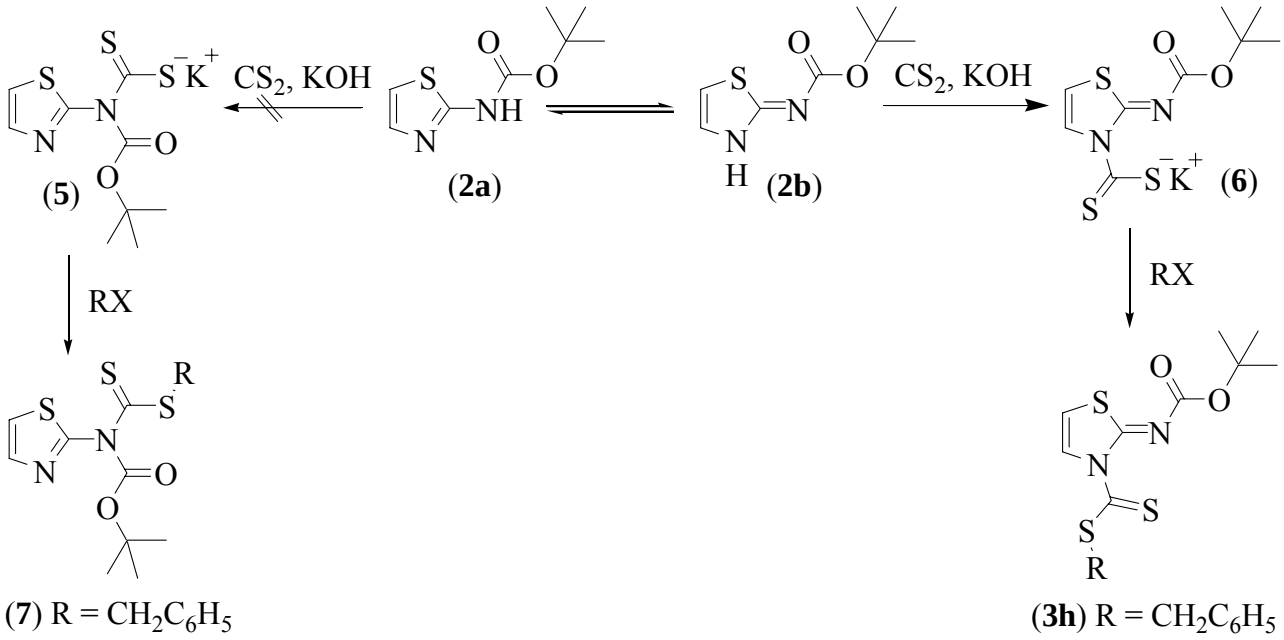


Scheme 1



Scheme 2



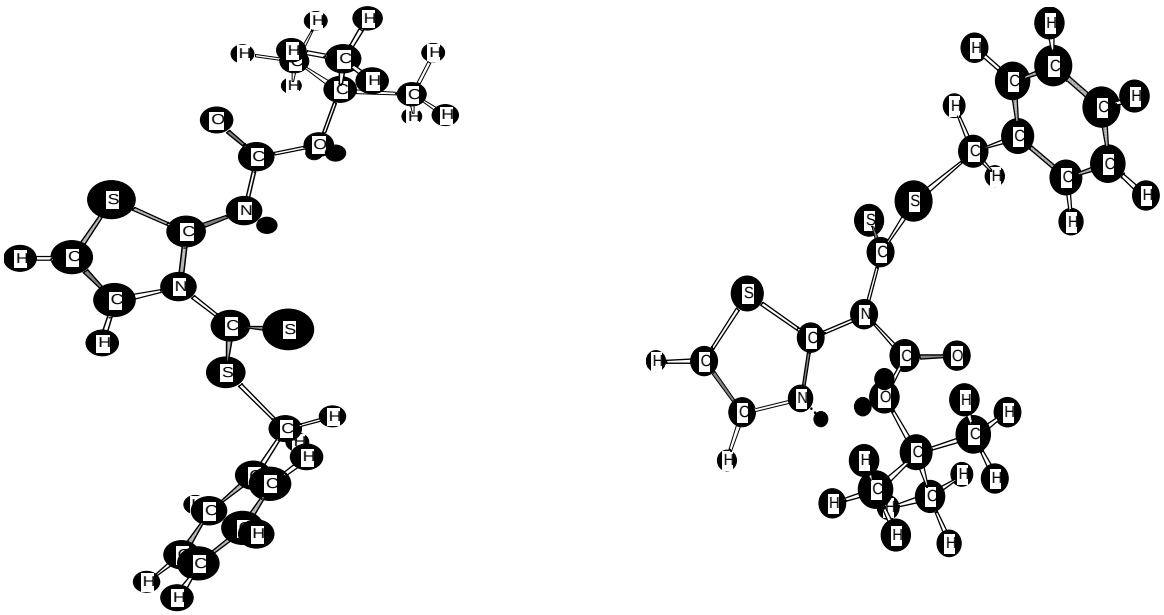
Scheme 3

Table 1 Synthesis of Boc protected endo-cyclic N-dithiocarbamate esters **3a-h**.

Product entry	R (alkyl)	Time (h)	% Yield
3a	CH_3	15	54
3b	CH_2CH_3	15	52
3c	$CH_2CH_2CH_3$	24	41
3d	$CH(CH_3)_2$	30	19
3e	$CH_2(CH_2)_2CH_3$	30	36
3f	$CH_2CH(CH_3)_2$	24	21
3g	$CH_2(CH_2)_3CH_3$	24	33
3h	$CH_2C_6H_5$	24	43

Table 2 Synthesis of endo-cyclic N-dithiocarbamate esters **4a-h**.

Product entry	R (alkyl)	Time (h)	% Yield
4a	CH_3	5	58
4b	CH_2CH_3	5	59
4c	$CH_2CH_2CH_3$	6	56
4d	$CH(CH_3)_2$	8	54
4e	$CH_2(CH_2)_2CH_3$	6	46
4f	$CH_2CH(CH_3)_2$	8	43
4g	$CH_2(CH_2)_3CH_3$	6	41
4h	$CH_2C_6H_5$	5	61



(**3h**) (**7**)

Figure 1. Energy minimized conformations of compound **3h** and **7**.