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IODINE-INDUCED IMINOTHIOLACTONIZATION OF γ,δ-UNSATURATED SECONDARY THIOAMIDES. NEW ENTRY TO 2-ACETOAMIDOTHIOPHENES

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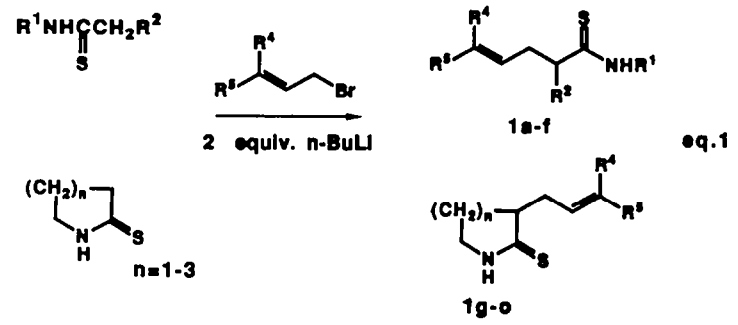
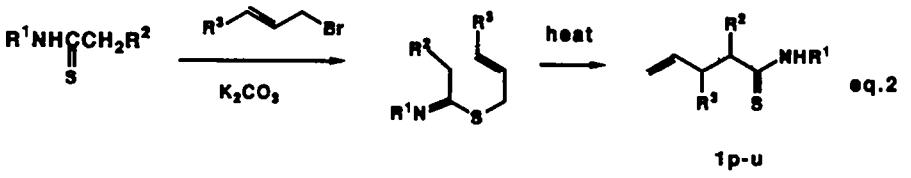
Abstract: Iodine-induced cyclization of γ,δ-unsaturated secondary thioamides **1** proceeded regio- (5-exo-trigonal) and chemo- (sulfur-carbon bond formation)selectively, providing iminothiolactones **2**, which were converted in two-step sequences (dehydroiodination and N-acetylation) into 2-acetoamidothiophenes **4**. This procedure was performed in one flask to afford polysubstituted 2-aminothiophenes.

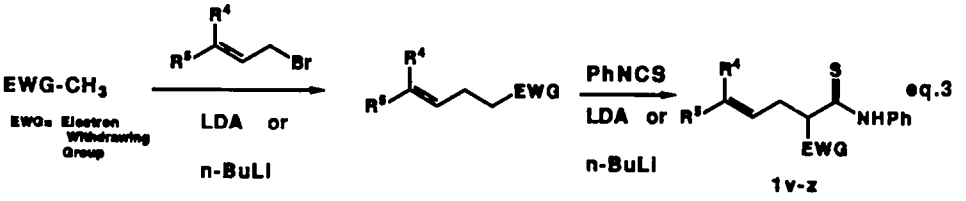
Electrophilic olefin cyclization leading to carbon-heteroatom bonding is an important process, particulary in the regio- and stereo-selective synthesis of heterocycles leading to biologically active compounds.[1] Sulfur cyclization has been less studied[2] than oxygen or nitrogen heterocyclization,[3] In the course of our studies using thioamides as synthetic intermediates for heterocycles,[4] we have found a novel iodoiminothiolactonization of γ,δ-unsaturated thioamides. Preliminary results have been reported;[5] in this paper, we report the scope and the details of a novel synthesis of 2-acetoamidothiophenes *via* iodine-induced intramolecular S-C bond formation with γ,δ-unsaturated ambident secondary thioamides.

Results and Discussion

Preparation of γ,δ-unsaturated secondary thioamides. The γ,δ-unsaturated secondary thioamides were readily accessible by three procedures described. A) Treatment of secondary thioamides with 2 equiv. of n-butyllithium (n-BuLi) in tetrahydrofuran (THF) provided dianions as metalloenamines which reacted with allyl halides to give γ,δ-unsaturated secondary thioamides **1a-o** (Table I, runs 1-14) (eq. 1).[6] B) α- or/and β-substituted γ,δ-unsaturated secondary thioamides **1p-u** were obtained by chemoselective (S→C) thio-Claisen rearrangement of the corresponding thioimidates (eq. 2) (Table I, runs 15-21).[7] The temperature required for reaction is dependent on the nature of the α-substituents (R^2) of the precursor thioamides. As the acidity of α-position increases, the reaction temperature may be lower. C) Methyl compounds substituted by electron-withdrawing groups were treated with n-BuLi or lithium diisopropylamide (LDA) to give anions, which were then allylated. The anions of the so-derived allyl compounds were reacted with phenylisothiocyanate to afford substituted unsaturated secondary thioamides **1v-z** (eq. 3) (Table I, runs 22-26).







Iodine-induced iminothiolactonization of γ,δ-unsaturated thioamides and Synthesis of 2-acetoamidothiophenes (Scheme 1). The thioamide **1a** with iodine in THF at ambient temperature for 1 day underwent iodoiminothiolactonization to furnish 5-iodomethyliminothiolactone **2a** in good yield. However, it was difficult to purify **2a** due to reaction between the imine group and the iodomethyl group. Accordingly, without isolation of **2a**, hydroiodide salt of **2a** was treated with 2.2 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) for dehydroiodination in the same flask to give the exo-olefin **3a** in 67% overall yield from **1a**. N-Acetylation of **3a** with acetyl chloride in the presence of DBU in methylene chloride followed by spontaneous aromatization afforded 2-acetylamino-5-methylthiophene **4a** in 73% yield. The structure of **4a** was easily determined by ^{1}H-NMR (see Experimental). The use of THF in place of methylene chloride resulted in lower yield. The three-step sequences (iminothiolactonization, dehydroiodination, and N-acetylation) for the synthesis of 2-acetoamidothiophenes could be carried out in the same flask. However, an attempted one-pot synthesis of **4** using methylene chloride as solvent instead of THF failed.

In the synthesis of 3-substituted 2-acetoamidothiophene such as **4f**, most of the exo-olefin **3f** was recovered unchanged together with a small amount of the desired compound. Deprotonation at the 3-position on N-acetylation would scarcely proceed, presumably due to steric hindrance of alkyl substituent. We found that the addition of 4,4-dimethylaminopyridine (DMAP) as a catalyst promoted N-acetylation reaction so that no exo-olefin was recovered. With this result in hand, DMAP was added to all reactions.

Table I. Preparation of γ,δ-Unsaturated Secondary Thioamides 1a-z

run	product	R^1	R^2	R^3	R^4	R^5	yield, %[a]	method[b]
1	**1a**	Bn	H	H	H	H	67	A
2	**1b**	Ph	H	H	H	H	79	A
3	**1c**	Bn	H	H	H	Me	62	A
4	**1d**	Bn	H	H	H	Ph	61	A
5	**1e**	Bn	H	H	Me	Me	52	A
6	**1f**	Ph	Me	H	H	H	42	A
7	**1g**	$-(CH_2)_3-$		H	H	H	63	A
8	**1h**	$-(CH_2)_3-$		H	H	Me	51	A
9	**1i**	$-(CH_2)_3-$		H	Me	Me	87	A
10	**1j**	$-(CH_2)_4-$		H	H	H	99	A
11	**1k**	$-(CH_2)_4-$		H	H	Me	42	A
12	**1l**	$-(CH_2)_4-$		H	Me	Me	75	A
13	**1m**	$-(CH_2)_5-$		H	H	H	48	A
14	**1n**	$-(CH_2)_5-$		H	H	Me	29	A
15	**1o**	$-(CH_2)_5-$		H	Me	Me	23	A
16	**1p**	Bn	cyclohexyl	H	H	H	56	B
17	**1q**	Bn	Ph	H	H	H	63	B
18	**1r**	Bn	H	Me	H	H	54	B
19	**1s**[c]	Bn	Me	Me	H	H	17	B
20	**1t**[c]	Bn	$PhSO_2$	Me	H	H	40	B
21	**1u**[c]	Bn	Ph	Me	H	H	49	B
22	**1v**	Ph	$PhSO_2$	H	H	H	27	C
23	**1w**	Ph	$PhSO_2$	H	H	Me	19	C
24	**1x**	Ph	$PhSO_2$	H	Me	Me	45	C
25	**1y**	Ph	CN	H	H	H	16	C
26	**1z**	Ph	PhNHCO	H	H	H	29	C

[a] Yields of runs (16-21) are those of two-steps from secondary thioamides. Yields of runs (22-26) are those of three-steps from methyl compounds.

[b] Reaction temperatures of method B are as follows. Runs (16, 18, and 19) are 170-180 °C. Runs (17 and 21) are 120 °C. Run 20 is 80 °C. In method C, LDA as base was used except for run 26 (n-BuLi).

[c] A mixture of diastereomers. A signal of Me (R^3) was detected as a mixture of doublets (ratio was about 1:1) by ^1H NMR spectroscopy.

3-Allylthiolactams **1j-o** except for the pyrrolidinethiones **1g-i** underwent iodocyclization smoothly to afford, after elaboration described above, azacycloalkano[2,3-b]thiophenes **4j-o** in good yields (Table II, runs 10-15). The reaction of **1g-i** provided thiophenes **4 g-i** in low yields with **1g-i** recovered (Table II, runs 7-9). This result revealed the step of iodocyclization was incomplete.

Reaction of the substrate possessing thioamide and amide functions at allyl position was carried out to give thiophene **4z** as the sole compound isolated in low yield (Table II, run 26). S-Cyclization proceeds in preference to O-cyclization. Therefore, we examined iodocyclization using γ,δ-unsaturated secondary amide **5** (eq. 4). In spite of prolonged reaction times (3 days), the reaction did not proceed smoothly, giving unchanged material (73%) and 4-iodomethyl-γ-

Table II. Preparation of 2-Acetoamidothiophenes 4a-x and 4z

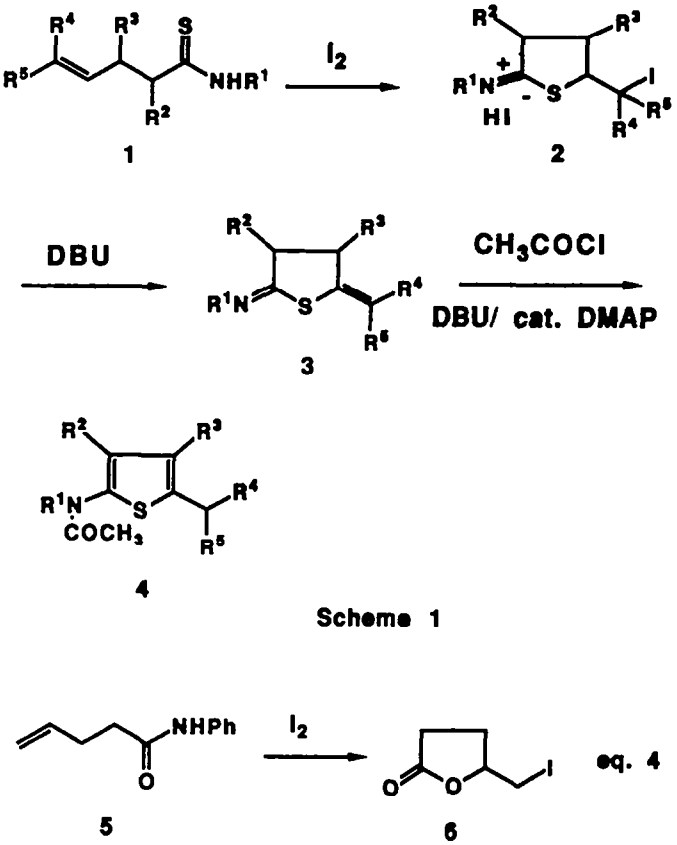
run	product	yield, %[a]
1	**4a**	57
2	**4b**	53
3	**4c**	25
4	**4d**	50
5	**4e**	47
6	**4f**	23
7	**4g**	36[b]
8	**4h**	13[c]
9	**4i**	20[d]
10	**4j**	64
11	**4k**	54
12	**4l**	85
13	**4m**	83
14	**4n**	82
15	**4o**	86
16	**4p**	25
17	**4q**	23
18	**4r**	49
19	**4s**	37
20	**4t**	19
21	**4u**	35
22	**4v**	38
23	**4w**	35
24	**4x**	18
25	**4y**	--
26	**4z**	12

[a] Overall yields of three-step sequences are shown.

[b] **1g** was recovered in 45%.

[c] **1h** was recovered in 35%.

[d] **1i** was recovered in 39%.



1 **2** **3** **4**

Scheme 1

5 **6** eq. 4

butyrolactone **6** (15%) after chromatography. Presumably the iminolactone was converted to the lactone **6** by hydrolysis during work up. It was found that iodine-induced cyclization of γ,δ-unsaturated secondary amides scarcely occurred. Reaction of substrate **1y** bearing cyano group at α position gave no thiophene **4y**, presumably due to dehydrocyanation with DBU.

In these reactions, no trace of other compounds such as nitrogen- and six-membered heterocycles was isolated. Accordingly, although the secondary thioamide is an ambident nucleophile, these heterocyclization reactions proceeded chemoselectively (sulfur-carbon bond formation) together with regioselective cyclization (5-exo-trigonal).[9]

In summary, the novel synthesis of 2-acetoamidothiophenes *via* iodine-promoted iminothiolactonization of γ,δ-unsaturated secondary thioamides followed by dehydroiodination and N-acetylation was expediently performed in one flask reaction. This method should be applicable to the preparation[10] of multifunctionalized 2-aminothiophenes with pharmacological interests.[11]

Experimental

^{1}H NMR spectra were determined on a JEOL PMX-60 or FX-270 spectrometer using tetramethylsilane as internal standard. Mass spectra were recorded on a JEOL JMS-D200 machine. Infrared spectra were recorded on a JASCO A-102 spectrophotometer. Melting points were determined on a Yanaco micro melting point apparatus and are uncorrected. THF was dried by distillation under nitrogen from sodium benzophenone ketyl. Column chromatography was performed on silica gel (Merck-9385 230-400 mesh), under medium pressure using a mixture of n-hexane - ethyl acetate as eluent.

General Procedure for Preparation of γ,δ-Unsaturated secondary thioamides 1a-o. Method A: A 15% solution of n-BuLi in hexane (7.1 ml, 11 mmol) was added to a stirred solution of N-alkylthioacetoamides or azacycloalkane-2-thiones (5 mmol) in THF (10 ml) at 0 °C. After stirring for 1 h at the same temperature, a solution of allyl halides (10 mmol) in THF (10 ml) was added to the reaction mixture at -78 °C. The mixture was gradually warmed to room temperature, quenched with ammonium chloride solution, and extracted with ethyl acetate. The extracts were dried, and evaporated. Column chromatography of the residue yielded γ,δ-unsaturated thioamides 1a-o in yields shown in Table I.

Method B: A mixture of N-benzylthioamides (5 mmol) with allyl bromides (6 mmol) in acetone (30 ml) in the presence of potassium carbonate (6 mmol) was stirred at room temperature overnight, filtrated through celite, and washed with acetone. Combined solvents were evaporated to give the residue, to which was added water. The mixture was extracted with ether. The extracts were washed with brine, dried over potassium carbonate, and evaporated to yield S-allylthioimidates. Without further purification, the S-allylthioimidates were heated in a Kuhgelrohr apparatus under reduced pressure (50-60 mmHg) at the temperature described in Table I for 2 h. Column chromatography of the mixture afforded γ,δ-unsaturated secondary thioamides 1p-u in yields shown in Table I.

Method C: To LDA (11 mmol) prepared from diisopropylamine (22 mmol) and n-BuLi (11 mmol) in THF (10 ml) was added a solution of electron withdrawing substituted methyl compounds (10 mmol) in THF (5 ml) at -78 °C. The mixture was stirred at the same temperature for 1 h. Allyl bromide (11 mmol) was injected to the mixture, which was gradually warmed to room temperature, quenched with aqueous ammonium chloride, and extracted with ethyl acetate. The extracts were dried with magnesium sulfate and evaporated. The residue was distilled to yield allyl substituted compounds, which were similarly treated with LDA as described above. Phenylisothiocyanate was injected to the mixture at -78 °C. The mixture was gradually warmed at 0 °C, quenched with aqueous ammonium chloride, and extracted with ethyl acetate. The extracts were dried with magnesium sulfate, and evaporated. Column chromatography of the residue yielded 1v-y in two-step yields shown in Table I. In a similar, 1z was prepared by using n-BuLi in place of LDA in the presence of hexamethylphosphoric triamide as cosolvent.

N-Benzyl 4-Pentenethioamide (1a): mp 37-39 °C (diisopropyl ether/pet. ether) as colorless fine needles; IR (Nujol) 3200, 1640, 1520 cm^{-1}; ^{1}H NMR ($CDCl_3$)δ 2.65 (m, 4H), 4.80 (d, J=5 Hz, 2H), 4.90-5.29 (m, 2H), 5.47-6.21 (m, 1H). Anal. Calcd for $C_{12}H_{15}NS$: C, 70.20; H, 7.36; N, 6.82. Found: C, 70.05; H, 7.42; N, 6.72.

N-Phenyl 4-Pentenethioamide (1b): mp 42-44 °C (n-hexane/ethyl acetate) as colorless fine needles; IR (Neat) 3200, 1530 cm^{-1}; ^{1}H NMR ($CDCl_3$)δ 2.50 (m, 2H), 4.90-5.17 (m, 2H), 5.50-6.17 (m, 1H). Anal. Calcd for $C_{11}H_{13}NS$: C, 69.07; H, 6.85; N, 7.32. Found: C, 68.93; H, 6.73; N, 7.18.

N-Benzyl 4-Hexenethioamide (1c): mp 32-34 °C (diisopropyl ether/pet. ether) as colorless fine needles; IR (Nujol) 3220, 1530 cm^{-1}; ^1H NMR ($CDCl_3$)δ1.60 (d, J=4.5 Hz, 3H), 2.13-2.95 (m, 4H), 4.85 (d, J=5.2 Hz, 2H), 5.45 (m, 2H). Anal. Calcd for $C_{13}H_{17}NS$: C, 71.18; H, 7.81; N, 6.39. Found: C, 71.31; H, 7.75; N, 6.32.

N-Benzyl (E)-5-Phenyl-4-pentenethioamide (1d): mp 110-111 °C (methylene chloride/pet.ether) as colorless fine needles; IR (Nujol) 3210, 1545 cm^{-1}; ^1H NMR ($CDCl_3$)δ 2.80 (m, 2H), 4.78 (d, J=5.4 Hz, 2H), 6.35 (m, 2H). Anal. Calcd for $C_{18}H_{20}NS$: C, 76.82; H, 6.81; N, 4.98. Found: C, 76.56; H, 6.77; N, 4.79.

N-Benzyl 5-Methyl-4-hexenethioamide (1e): mp 45-47 °C (diisopropyl ether/ pet. ether) as colorless fine needles; IR (Nujol) 3175, 1540 cm^{-1}; ^1H NMR ($CDCl_3$)δ 1.57 (s, 3H), 1.64 (s, 3H), 2.15-3.00 (m, 4H), 4.80 (d, J=5.4 Hz, 2H), 4.93-5.20 (m, 1H). Anal. Calcd for $C_{14}H_{19}NS$: C, 72.05; H, 8.21; N, 6.00. Found: C, 71.85; H, 8.33; N, 5.83.

N-Phenyl 2-Methyl-4-pentenethioamide (1f): mp 54-57 °C (n-hexane/ethyl acetate) as colorless fine needles; IR (Nujol) 3200, 1530 cm^{-1}; ^1H NMR ($CDCl_3$)δ 1.33 (d, J=, 3H), 2.30-3.00 (m, 3H). Anal. Calcd for $C_{12}H_{15}NS$: C, 70.20; H, 7.36; N, 6.82. Found: C, 70.28; H, 7.50; N, 6.64.

3-(2-Propenyl)pyrrolidine-2-thione (1g): mp 58-60 °C (methylene chloride/diisopropyl ether) (lit.[12] mp 65.5-67 °C) as colorless fine needles; IR (Nujol) 1540 cm^{-1}; ^1H NMR ($CDCl_3$)δ 3.40-3.70 (t, J=7Hz, 2H), 4.90-5.30 (m, 2H), 5.50-6.20 (m, 1H).

3-(2-Butenyl)pyrrolidine-2-thione (1h): mp 76-80 °C (methylene chloride/pet. ether) as colorless fine needles; IR (Nujol) 3150, 1535 cm^{-1}; ^1H NMR ($CDCl_3$)δ 1.66 (d, J=3Hz, 3H), 5.40-5.50 (m, 2H). Anal. Calcd for $C_8H_{13}NS$: C, 61.89; H, 8.44; N, 9.02. Found: C, 61.82; H, 8.46; N, 8.81.

3-(3-Methyl-2-butenyl)pyrrolidine-2-thione (1i): mp 64-70 °C (methylene chloride/diisopropyl ether) as colorless fine needles; IR (Nujol) 3170, 1530 cm^{-1}; ^1H NMR ($CDCl_3$)δ 1.15, 1.17 (each s, 6H), 4.40-4.90 (m, 1H). Anal. Calcd for $C_9H_{15}NS$: C, 63.85; H, 8.93; N, 8.27. Found: C, 63.71; H, 8.89; N, 8.02.

3-(2-Propenyl)piperidine-2-thione (1j): mp 76-79 °C (diisopropylether/pet. ether) as colorless fine needles; IR (Nujol) 1565 cm^{-1}; ^1H NMR ($CDCl_3$)δ 4.80-5.30 (m, 2H), 5.50-6.20 (m, 1H). Anal. Calcd for $C_8H_{13}NS$: C, 61.89; H, 8.44; N, 9.02. Found: C, 61.56; H, 8.18; N, 8.95.

3-(2-Butenyl)piperidine-2-thione (1k): mp 90-95 °C (diisopropyl ether/pet. ether) as colorless fine needles; IR (Nujol) 3160, 1560 cm^{-1}; ^1H NMR ($CDCl_3$)δ 5.30-5.60 (m, 2H). Anal. Calcd for $C_9H_{15}NS$: C, 63.85; H, 8.93; N, 8.27. Found: C, 64.19; H, 9.23; N, 8.09.

3-(3-Methyl-2-butenyl)piperidine-2-thione (1l): mp 42-47 °C (methylene chloride/diisopropyl ether) as colorless fine needles; IR 3160, 1565 cm^{-1}; ^1H NMR ($CDCl_3$)δ 1.70, 173 (each s, 6H), 4.93-5.40 (m, 1H). Anal. Calcd for $C_{10}H_{17}NS$: C, 65.52; H, 9.35; N, 7.64. Found: C, 65.49; H, 9.45; N, 7.73.

3-(2-Propenyl)-1,3,4,5,6,7-hexahydro-2H-azepine-2-thione (1m): mp 58-60 °C (diisopropyl ether/pet. ether) (Lit.[12] 60-60.5 °C) as colorless fine needles; IR (NUjol) 3200, 1550 cm^{-1}; ^1H NMR ($CDCl_3$)δ 4.80-5.20 (m, 2H), 5.30-6.20 (m, 1H).

3-(2-Butenyl)-1,3,4,5,6,7-hexahydro-2H-azepine-2-thione (1n): mp 97-104 °C (methylene chloride/pet. ether) as colorless fine needles; IR (Nujol) 3200, 1550 cm^{-1}; ^1H NMR ($CDCl_3$)δ 1.65 (d, J=4Hz, 3H), 5.30-5.50 (m, 2H). Anal. Calcd for $C_{10}H_{17}NS$: C, 65.52, H, 9.34: N, 7.64. Found: 65.46; H, 9.38; N, 7.48

3-(3-Methyl-2-bytenyl)-1,3,4,5,6,7-hexahydro-2H-azepine-2-thione (1o): mp 91-94 °C (methylene chloride/ pet. ether) as colorless fine needles; IR (Nujol) 3150, 1535 cm^{-1}; ^1H NMR ($CDCl_3$)δ 1.60, 170 (each s, 6H), 5.40-5.50 (m, 1H). Anal. Calcd for $C_{11}H_{19}NS$: C, 66.95; H, 9.70; N, 7.10. Found: C, 67.24; H, 9.82; N, 7.28.

N-Benzyl 2-Cyclohexyl-4-pentenethioamide (1p): bp 127-135 °C/0.25 mmHg; IR (Neat) 3175, 1530 cm^{-1}; ^1H NMR ($CDCl_3$)δ 1.07-2.08 (m, 13H), 4.85 (d, J=6Hz, 2H), 5.05-5.27 (m, 2H), 5.47-6.12 (m,

1H). High resolution mass spectrum (HRMS) $C_{18}H_{25}NS$: 287.1706. found: 287.1705.

N-Benzyl 2-Phenyl-4-pentenethioamide (1q): mp 80–82.5 °C (ethyl acetate/n-hexane) as colorless fine needles; IR (Nujol) 3175, 1535 cm^{-1}; ^1H NMR ($CDCl_3$)δ 4.74 (d, J=5Hz, 2H), 4.85-5.16 (m, 2H), 5.43-6.05 (m, 1H), 7.23-7.33 (m, 10H). Anal. Calcd for $C_{18}H_{19}NS$: C, 76.82; H, 6.81; N, 4.98. Found: C,76.57; H, 6.80; N, 5.02.

N-Benzyl 3-Methyl-4-pentenethioamide (1r): oil; IR (Neat) 3230, 1530 cm^{-1}; ^1H NMR ($CDCl_3$)δ 1.25 (d, J=6.4 Hz, 3H), 4.79 (d, J=5.0 Hz, 2H), 4.78-5.32 (m, 2H), 5.40-6.06 (m, 1H). HRMS $C_{13}H_{17}NS$: 219.1072. found: 219.1092.

N-Benzyl 2,3-Dimethyl-4-pentenethioamide (1s): oil; IR 3250, 1540 cm^{-1}; ^1H NMR ($CDCl_3$)δ 0.95-1.10 (m, 3H), 1.20-1.30 (m, 3H), 4.76-5.20 (m, 2H), 5.42-6.02 (m, 1H). HRMS $C_{14}H_{19}NS$: 233.1237. found: 233.1231.

N-Benzyl 2-Benzenesulfonyl-3-methyl-4-pentenethioamide (1t): mp 133-144 °C (methylene chloride/diisopropyl ether) as yellow fine needles; IR (Nujol) 3230, 1530 cm^{-1}; ^1H NMR ($CDCl_3$)δ 1.25-145 (m, 3H), 3.08-3.55 (m, 1H), 4.50-4.77 (m, 1H), 5.00-5.25 (m, 2H), 5.73-6.30 (m, 1H). Anal. Calcd for $C_{19}H_{21}NO_2S_2$: C, 63.48; H, 5.89; N, 3.90. Found: C, 63.48; H, 5.92; N, 4.09.

N-Benzyl 3-Methyl-2-phenyl-4-pentenethioamide (1u): oil; IR (Neat) 3250, 1530 cm^{-1}; ^1H NMR ($CDCl_3$)δ 0.80-1.20 (m, 3H), 4.98-5.40 (m, 2H), 5.50-6.27 (m, 1H). HRMS $C_{19}H_{21}NS$: 295.1394. found: 295.1393.

N-Phenyl 2-Benzenesulfonyl-4-pentenethioamide (1v): mp 107-111 °C (methylene chloride/diisopropyl ether) as yellow fine needles; mp (Nujol) 3250, 1530 cm^{-1}; ^1H NMR ($CDCl_3$)δ 4.62 (m, 1H), 4.90-5.22 (m, 2H), 5.43-6.00 (m, 1H). Anal. Calcd for $C_{17}H_{17}NO_2S_2$: Found: C, 61.45; H, 5.20; N, 4.26.

N-Phenyl 2-Benzenesulfonyl-4-hexenethioamide (E,Z mixture) (1w): oil; IR (Neat) 3300, 1530 cm^{-1}; ^1H NMR ($CDCl_3$)δ 1.55, 1.62 (d, J=4.2 Hz, 3H), 4.58 (m, 1H), 5.12-5.83 (m, 2H). HRMS $C_{18}H_{19}NO_2S_2$: 345.0856. found: 345.0857.

N-Phenyl 2-Benzenesulfonyl-5-methyl-4-hexenethioamide (1x): oil; IR (Neat) 3250, 1530 cm^{-1}; ^1H NMR ($CDCl_3$)δ 1.60 (s, 6H), 4.57 (t, J=7.2 Hz, 1H), 5.15 (t, J=6 Hz). HRMS $C_{19}H_{21}NO_2S_2$: 359.1013. found: 359.1010.

N-Phenyl 2-Cyano-4-pentenethioamide (1y): mp 95-97 °C (methylene chloride/diisopropyl ether) as pale yellow fine needles; IR (Nujol) 3275, 2240, 1550 cm^{-1}; ^1H NMR ($CDCl_3$)δ 4.05 (t, J=7.2 Hz, 1H), 5.07-5.40 (m, 2H), 5.53-6.20 (m, 1H). Anal. Calcd for $C_{12}H_{12}N_2S$: C, 66.63; H, 5.59; N, 12.95. Found: C, 66.36; H, 5.53; N, 13.20.

N-Phenyl 2-Phenylcarbamoyl-4-pentenethioamide (1z): mp 91-93 °C (diisopropyl ether/n-hexane) as pale yellow fine needles; IR (Nujol) 3250, 1670, 1530 cm^{-1}; ^1H NMR ($CDCl_3$)δ 4.20 (t, J=7.2 Hz, 1H), 4.93-5.25 (m, 2H), 5.52-6.30 (m, 1H). Anal. Calcd for $C_{18}H_{18}N_2OS$: C, 69.65; H, 5.86; N, 9.02. Found: C, 69.55; H, 5.82; N, 8.88.

General Procedure for Preparation of 2-Aminothiophenes 4a-x,z. To a solution of γ,δ-unsaturated secondary thioamide **1** (1 mmol) in THF (10 ml) was added a solution of iodine (1.2 mmol) in THF (10 ml) at 0 °C. After addition, the reaction mixture was stirred for 15 h at room temperature. DBU (2.2 mmol) was then added to the mixture with ice cooling and the mixture was stirred for 2 h at ambient temperature. After evaporation of the solvent, methylene chloride (10 ml), DBU (1.2 mmol) and DMAP (0.1 mmol) were successively added to the residue (crude of **3**). To the mixture was added by syringe acetyl chloride (1.2 mmol) at 0 °C. The reaction mixture was stirred for 15 h at room temperature and poured into cold water. The mixture was extracted with methylene chloride. The extract was washed with 5% HCl, water, saturated sodium bicarbonate, and brine, dried with magnesium sulfate, and evaporated to yield an oil, which was purified by column chromatography to give **4** in yields shown in Table II.

2-(N-Acetyl-N-benzylamino)-5-methylthiophene (4a): mp 85–88 °C (n-hexane/ethyl acetate) as colorless fine needles; IR (Nujol) 1645 cm^{-1}; ^1H NMR ($CDCl_3$)δ 2.03 (s, 3H), 2.36 (s, 3H), 4.80 (s, 2H). Anal. Calcd for $C_{14}H_{15}NOS$: C, 68.54; H, 6.16; N, 5.71. Found: C, 68.83; H, 6.13; N, 5.65.

2-(N-Acetyl-N-phenylamino)-5-methylthiophene (4b): mp 58–61 °C (n-hexane/ethyl acetate) as colorless fine needles; IR (Nujol) 1645 cm^{-1}; ^1H NMR ($CDCl_3$)δ 2.03 (s, 3H), 2.36 (s, 3H). Anal. Calcd for $C_{13}H_{13}NOS$: C, 67.50; H, 5.66; N, 6.06. Found: C, 67.84; H, 5.74; N, 5.59.

2-(N-Acetyl-N-benzylamino)-5-ethylthiophene (4c): a pale yellow oil; IR (Neat) 1660 cm^{-1}; ^1H NMR ($CDCl_3$)δ 1.27 (t, 3H), 2.03 (s, 3H), 2.73 (q, 2H). HRMS $C_{15}H_{17}NOS$: 259.1031. found: 259.1033.

2-(N-Acetyl-N-benzylamino)-5-benzylthiophene (4d): a viscous oil; IR (Neat) 1650 cm^{-1}; ^1H NMR ($CDCl_3$)δ 2.03 (s, 3H), 4.10 (s, 2H), 4.88 (s, 2H). HRMS $C_{20}H_{19}NOS$: 321.1186. found: 321.1188.

2-(N-Acetyl-N-benzylamino)-5-isopropylthiophene (4e): a viscous oil; IR (Neat) 1670 cm^{-1}; ^1H NMR ($CDCl_3$)δ1.30 (d, J=6Hz, 6H), 2.10 (s, 3H), 2.95 (m, 1H), 4.85 (s, 2H), 6.45–6.65 (m, 2H). HRMS $C_{16}H_{19}NOS$: 273.1186. found: 273.1187.

2-(N-Acetyl-N-phenylamino)-3-methyl-5-methylthiophene (4f): a viscous oil; IR (Neat) 1660 cm^{-1}; ^1H NMR ($CDCl_3$)δ 2.10 (s, 3H), 2.36 (s, 3H). HRMS $C_{14}H_{15}NOS$: 245.0875. found: 245.0875.

1-Acetyl-2,3-dihydro-5-methylthieno[2,3-b]pyrrole (4g): mp 133 °C (methylene chloride/diisopropyl ether) as colorless fine needles; IR (Nujol) 1630 cm^{-1}; ^1H NMR ($CDCl_3$)δ 2.16 (s, 3H), 2.43 (s, 3H), 6.45 (s, 1H). Anal. Calcd for $C_9H_{11}NOS$: C, 59.64; H, 6.12; N, 7.73. Found: C, 59.70; H, 6.12; N, 7.43.

1-Acetyl-2,3-dihydro-5-ethylthieno[2,3-b]pyrrole (4h): mp 106–108 °C (methylene chloride/diisopropyl ether) as colorless fine needles; IR (Nujol) 1635 cm^{-1}; ^1H NMR ($CDCl_3$)δ 1.30 (t, J=7Hz, 3H), 2.25 (s, 3H), 6.35 (s, 1H). Anal. Calcd for $C_{10}H_{13}NOS$: C, 61.51; H, 6.71; N, 7.17. Found: C, 61.63; H, 6.70; N, 6.83.

1-Acetyl-2,3-dihydro-5-isopropylthieno[2,3-b]pyrrole (4i): mp 139–144 °C (methylene chloride/diisopropyl ether) as colorless fine needles; IR (Nujol) 1630 cm^{-1}; ^1H NMR ($CDCl_3$)δ 1.33 (d, J=7Hz, 6H), 2.26 (s, 3H), 6.48 (s, 1H). Anal. Calcd for $C_{11}H_{15}NOS$: C, 63.12; H, 7.22; N, 6.69. Found: C, 63.32; H, 7.14; N, 6.29.

1-Acetyl-6-methyl-1,2,3,4-tetrahydrothieno[2,3-b]pyridine (4j): mp 114–116 °C (methylene chloride/diisopropyl ether) as colorless fine needles; IR (Nujol) 1640 cm^{-1}; ^1H NMR ($CDCl_3$)δ 2.23 (s, 3H), 2.33 (s, 3H), 6.35 (s, 1H). Anal. Calcd for $C_{10}H_{13}NOS$: C, 61.51; H, 6.71; N, 7.17. Found: C, 61.80; H, 6.76; N, 7.00.

1-Acetyl-6-ethyl-1,2,3,4-tetrahydrothieno[2,3-b]pyridine (4k): mp 70–72 °C (pet. ether/diisopropyl ether) as colorless fine needles; IR (Nujol) 1635 cm^{-1}; ^1H NMR ($CDCl_3$)δ 1.26 (s, 3H, 2.26 (s, 3H), 6.45 (s, 1H). Anal. Calcd for $C_{11}H_{15}NOS$: C, 63.12; H, 7.22; N, 6.69. Found: C, 62.87; H, 7.30; N, 6.39.

1-Acetyl-6-isopropyl-1,2,3,4-tetrahydrothieno[2,3-b]pyridine (4l): mp 92–93 °C (methylene chloride/pet. ether) as colorless fine needles; IR (Nujol) 1630 cm^{-1}; ^1H NMR ($CDCl_3$)δ 1.25 (s, 3H), 2.20 (s, 3H), 6.45 (s, 1H). Anal. Calcd for $C_{12}H_{17}NOS$: C, 64.54; H, 7.67; N, 6.27. Found: C, 64.58; H, 7.52; N, 5.97.

8-Acetyl-2-methyl-4,5,6,7-tetrahydro-8H-azepino[2,3-b]thiophene (4m): a viscous oil; IR (Neat) 1670 cm^{-1}; ^1H NMR ($CDCl_3$)δ 2.09 (s, 3H), 2.36 (s, 3H), 6.37 (s, 1H). HRMS $C_{11}H_{13}NOS$: 209.0875. found: 209.0903.

8-Acetyl-2-ethyl-4,5,6,7-tetrahydro-8H-azepino[2,3-b]thiophene (4n): a viscous oil; IR (Neat) 1670 cm^{-1}; ^1H NMR ($CDCl_3$)δ 1.28 (t, J=7Hz, 3H), 2.12 (s, 3H), 6.45 (s, 1H). HRMS $C_{12}H_{17}NOS$: 223.1030. found: 223.1030.

8-Acetyl-2-isopropyl-4,5,6,7-tetrahydro-8H-azepino[2,3-b]thiophene (4o): a viscous oil; IR

(Neat) 1670 cm^{-1}; ^1H NMR ($CDCl_3$)δ 1.36 (d, J=7Hz, 6H), 2.10 (s, 3H), 6.45 (s, 1H). HRMS $C_{13}H_{19}NOS$: 237.1187. found: 237.1232.

2-(N-Acetyl-N-benzylamino)-3-cyclohexyl-5-methylthiophene (4p): a viscous oil; IR (Neat) 1670 cm^{-1}; ^1H NMR ($CDCl_3$) 0.83-1.77 (m, 11H), 1.98 (s, 3H), 2.37 (s, 3H), 4.80 (d, J=5Hz, 2H), 6.42 (s, 1H). HRMS $C_{20}H_{25}NOS$: 372.1656. found: 327.1657.

2-(N-Acetyl-N-benzylamino)-5-methyl-3-phenylthiophene (4q): a viscous oil; IR (Neat) 1670 cm^{-1}; ^1H NMR ($CDCl_3$)δ1.94 (s, 3H), 2.39 (s, 3H), 6.75 (s, 1H). HRMS $C_{20}H_{19}NOS$: 321.1186. found: 321.1187.

2-(N-Acetyl-N-benzylamino)-4,5-dimethylthiophene (4r): a viscous oil; IR (Neat) 1660 cm^{-1}; ^1H NMR ($CDCl_3$)δ2.00 (s, 3H), 2.06 (s, 3H), 2.23 (s, 3H). HRMS $C_{15}H_{17}NOS$: 259.1031. found: 259.1031.

2-(N-Acetyl-N-benzylamino)-3,4,5-trimethylthiophene (4s): a viscous oil; IR (Neat) 1640 cm^{-1}; ^1H NMR ($CDCl_3$)δ 1.60 (s, 3H), 1.94 (s, 6H), 2.29 (s, 3H), 4.8 (s, 2H). HRMS $C_{16}H_{19}NOS$: 273.1186. found: 273.1185.

2-(N-Acetyl-N-benzylamino)-3-benzenesulfonyl-4,5-dimethylthiophene (4t): mp 128-133 °C (pet. ether/ ethyl acetate) as colorless fine needles; IR (Nujol) 1670 cm^{-1}; ^1H NMR ($CDCl_3$)δ1.91 (s, 3H), 2.35, (s, 3H), 2.45 (s, 3H), 3.94, 5.62 (ABq, J=14 Hz, each 1H). Anal. Calcd for $C_{21}H_{21}NO_2S_2$: C, 62.13; H, 5.30; N, 3.51. Found: C, 62.13; H, 5.34; N, 3.38.

2-(N-Acetyl-N-benzylamino)-4,5-dimethyl-3-phenylthiophene (4u): a viscous oil; IR (Neat) 1670 cm^{-1}; ^1H NMR ($CDCl_3$)δ 1.92 (s, 3H), 1.97 (s, 3H), 2.29 (s, 3H) 4.10 (br s, 1H), 5.18 (br s, 1H). HRMS $C_{21}H_{21}NOS$: 335.1343. found: 335.1342.

2-(N-Acetyl-N-phenylamino)-3-benzenesulfonyl-5-methylthiophene (4v): a viscous oil; IR (Neat) 1690 cm^{-1}; ^1H NMR ($CDCl_3$)δ 2.10 (s, 3H), 2.35 (s, 3H), 6.84 (s, 1H). HRMS $C_{19}H_{17}NO_3S_2$: 371.0649. found: 371.0648.

2-(N-Acetyl-N-phenylamino)-3-benzenesulfonyl-5-ethylthiophene (4w): mp 107-108 °C (pet. ether/ethyl acetate) as colorless fine needles; IR (Nujol) 1680 cm^{-1}; ^1H NMR ($CDCl_3$)δ 1.28 (t, J=8.4 Hz, 3H), 2.60 (q, J=8.4 Hz, 2H), 6.65 (s, 1H). Anal. Calcd for $C_{20}H_{19}NO_3S_2$: C, 62.95; H, 4.99; N, 4.08. Found: C, 62.93; H, 5.07; N, 4.06.

2-(N-Acetyl-N-phenyamino)-3-benzenesulfonyl-5-isopropylthiophene (4x): a viscous oil; IR (Neat) 1690 cm^{-1}; ^1H NMR ($CDCl_3$)δ 1.57 (s, 6H), 2.06 (s, 3H), 7.09 (s, 1H). HRMS $C_{21}H_{21}NO_3S_2$: 399.0962. found: 399.0963.

2-(N-Acetyl-N-phenylamino)-5-methyl-3-phenylcarbamoylthiophene (4z): a viscous oil; IR (Neat) 3325, 1680 cm^{-1}; ^1H NMR ($CDCl_3$)δ 2.10 (s, 3H), 2.42 (s, 3H), 6.90 (s, 1H). HRMS $C_{20}H_{18}N_2O_2S$: 350.1088. found: 350.1089.

4-Iodomethyl-γ-butyrolactone (6). To a solution of N-phenyl-4-pentenamide (**5**) (2 mmol) in THF (20 ml) was added iodine (1.5 mmol) in THF (20 ml) at an ambient temperature. The reaction mixture was stirred for 3 days and then was treated with saturated $Na_2S_2O_3$. After evaporation of THF, the residue was extracted with methylene chloride. The extracts was washed with brine, dried, and evaporated to provide an oil, which was chromatographed to **6** (15%) and **5** (73%). **6**; bp 90-100 °C/8 mmHg (Lit.[13] bp 150 °C/15 mmHg); IR (Neat) 1770 cm^{-1}; ^1H NMR ($CDCl_3$)δ 1.70-2.82 (m, 4H), 3.37 (m, 2H), 4.38-4.80 (m, 1H).

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