NOVEL SYNTHESES OF 2,3-DISUBSTITUTED BENZOTHIOPHENES*

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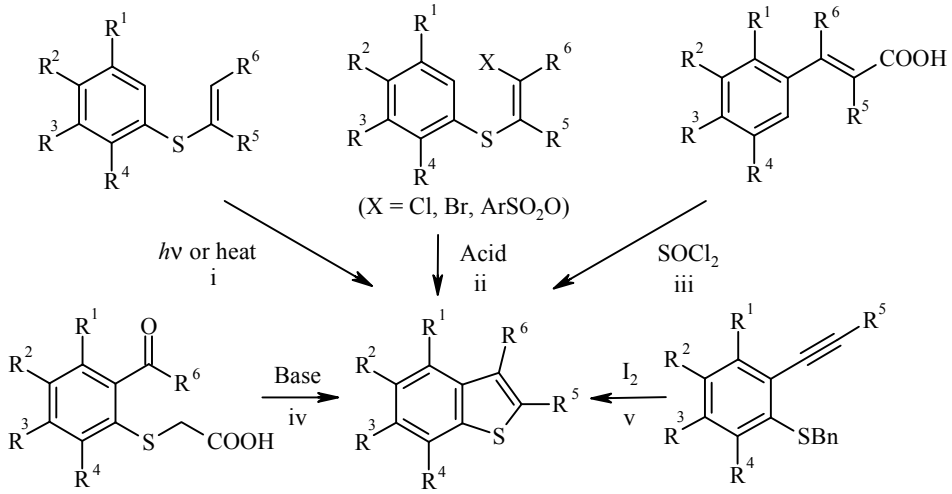
*The sodium salts of o-sulfanylphenyl ketones **3a-g** were treated with α-benzotriazol-1-ylalkyl chlorides **4a,b** to give intermediates **5a-k** in good yields. Compounds **5a-k**, on treatment successively with LDA and Ti (0), gave benzothiophenes **7a-k**.*

Keywords: benzothiophenes, *o*-sulfanylphenyl ketones.

Benzothiophenes [1-3] possess a broad range of biological activities and have many pharmaceutical applications [4-6]. Major synthetic strategies utilized include (Scheme 1): (i) intramolecular cyclizations of phenylsulfanylethenes upon irradiation [7-10], (ii) from β-aryl(thio)vinyl cations [11-13]; (iii) from cinnamic acids, hydrocinnamic acids, or certain ketones with thionyl chloride and pyridine [14, 15]; (iv) by cyclodehydrogenation of aryl sulfides [16]; (v) formation of benzothiophenes *via* palladium-mediated coupling [17].

Scheme 1



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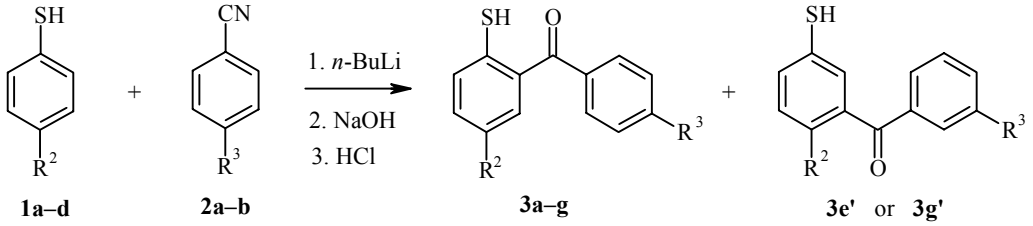
Scheme 2



1a–d **2a–b** **3a–g** **3e'** or **3g'**

1a: R^2 = H
1b: R^2 = Me
1c: R^2 = OMe
1d: R^2 = Cl

2a: R^3 = H
2b: R^3 = Me

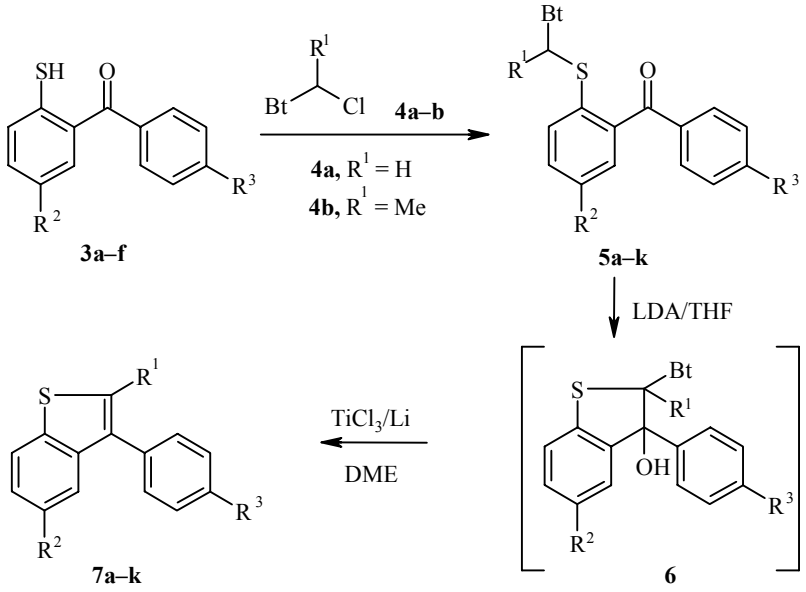
3a: $R^2 = R^3$ = H, 80% [21]
3b: R^2 = H, R^3 = Me, 67% [22]
3c: R^2 = Me, R^3 = H, 32% [23]
3d: $R^2 = R^3$ = Me, 71%
3e: R^2 = OMe, R^3 = H, 15%
3f: R^2 = Cl, R^3 = Me, 49%
3g: R^2 = OMe, R^3 = Me, 9%

3e' : 8%

3g' : 5%

We now disclose the preparation of 2,3-disubstituted benzothiophenes from *o*-sulfanylphenyl ketones **3a-f** (Scheme 2) and α-benzotriazol-1-ylalkyl chlorides **4a-b** in three steps (Scheme 3). This modification of approach (iv) broadens the variety of benzothiophenes readily available by simple procedures and in good overall yields. An analogous approach has recently been demonstrated for benzofurans [18].

Scheme 3



Results and Discussion

Benzenethiols **1a-d** were treated with 2.5 equivalents of *n*-BuLi in cyclohexane in the presence of 2 equivalents of tetramethyl-1,2-ethanediamine at 0-5°C for 17-20 h. To the suspension thus formed, a solution of benzonitrile **2a-b** (1.0 equivalent) in cyclohexane was added dropwise at 0°C. The reaction mixture was

stirred at 20°C for 4-5 h to give the corresponding *o*-sulfanylphenyl ketones **3a-g** (Scheme 2). The reaction yields depend greatly on the substitutions of the starting benzenethiols **1a-d**. Compound **1c** on treatment with benzonitriles **2a** gave two regioisomers: (5-methoxy-2-sulfanylphenyl)phenylmethanone **3e** (15%), and (2-methoxy-5-sulfanylphenyl)phenylmethanone **3e'** (8%). Similarly **1c** and **2b** gave both (5-methoxy-2-sulfanylphenyl)(4-methylphenyl)methanone **3g** and (2-methoxy-5-sulfanylphenyl)(4-methylphenyl)methanone **3g'** in 9% and 5% yields respectively. The small difference in the directing ability of the thiol and methoxy groups led to lithiation with no regioselectivity. Structures **3a-g** are supported by their ^{1}H NMR and ^{13}C NMR spectra.

Compounds **3a-f** were treated with sodium hydroxide in ethanol to afford the corresponding sodium salts of *o*-sulfanylphenyl ketones, which were treated with compounds **4a-b** (available from aldehydes, benzotriazole, and thionyl chloride in 90% and 95% yields [19]) to afford the corresponding intermediates **5a-k** in good yields (Scheme 3). The structures of **5a-k** are supported by their ^{1}H NMR and ^{13}C NMR spectra.

Intermediates **5a-k** were treated with an equivalent amount of LDA in THF at temperatures ranging from -78°C to 20°C to give the corresponding 2-(benzotriazol-1-yl)-3-substituted 2,3-dihydro-1-benzothiophen-3-ols (**6**) as diastereomeric mixtures. Compounds **6** without separation or further purification were treated with a low-valence titanium reagent (prepared by heating $TiCl_3$ and Li under reflux in DME for 5 h under argon protection[20]) in DME under reflux for 100 h to give the corresponding benzothiophenes **7a-k**.

We isolated and characterized intermediates **6a** and **6d**. The structure of **6a** (one isomer) was deduced from its ^{1}H NMR, ^{13}C NMR, and DEPT spectra. The ^{1}H NMR spectrum of **6a** showed changes compared to that of compound **5a** in the aromatic region (7.00-8.10 ppm), and the characteristic singlet of the methylene protons (5.92 ppm) of **5a** had disappeared. The disappearance of the signal at 3.94 ppm present in the spectrum of **6a** after adding D_2O suggested the existence of an OH group. In the ^{13}C NMR spectrum of **6a**, the signals corresponding to the carbonyl (196.2 ppm) and methylene (52.1 ppm) fragments of **5a** vanished. Two new signals (at 75.3 and 87.9 ppm) in the ^{13}C NMR spectrum of **6a** are assigned to the two aliphatic carbons connected to the OH and the benzotriazole groups. Intermediate **6d** was isolated as two isomers, and structures **6d**-*syn* and **6d**-*anti* are supported by their ^{1}H and ^{13}C NMR using similar reasoning. However, the pairs of diastereomers **6** each gave the same olefin on low-valence Ti treatment in the next step.

The structures of benzothiophenes **7a-k** were assigned by their ^{1}H and ^{13}C NMR.

In summary, an efficient and simple route to benzothiophenes was developed from α-benzotriazolylalkyl chlorides and *o*-sulfanylphenyl ketones. The sequence works well for 3-arylbenzothiophenes but could not be extended to 3-alkyl analogs.

TABLE 1. Preparative yields of *ortho*-Sulfanylphenyl Ketones **5a-k** and Benzothiophenes **7a-k**

Compound	R^1	R^2	R^3	Yield, %	
				5	**7**
a	H	H	H	90	55 [24]
b	H	H	Me	84	63 [25]
c	H	Me	H	90	55 [26]
d	H	Me	Me	69	52
e	H	MeO	H	79	56 [27]
f	H	Cl	Me	87	55
g	Me	H	H	68	59 [7]
h	Me	H	Me	76	55
i	Me	Me	H	71	61 [28]
j	Me	Me	Me	75	60 [29]
k	Me	Cl	Me	68	65

EXPERIMENTAL

General. Melting points were determined on a hot-stage apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 with TMS as the internal standard for ^1H (300 MHz) or a solvent as the internal standard for ^{13}C (75 MHz). Microanalyses were performed on a Carlo Erba-1106 elemental analyzer. Benzene and toluene were dried over molecular sieves. Column chromatography was conducted with silica gel 200-425 mesh.

1-Benzotriazol-1-ylalkyl chlorides **4a,b** were synthesized according to the previously published procedure [19].

General Procedure for the Preparation of *o*-Sulfanylphenyl Ketones 3a-g. A solution of TMEDA (1.05 g, 9 mmol) in cyclohexane (20 ml) was cooled to 0°C and *n*-BuLi (1.5 M, 6 ml, 9 mmol) was added. To this solution, thiophenol (4.5 mmol) in cyclohexane (5 ml) was slowly added and the reaction was allowed to warm and was then stirred at room temperature for 18 h. To the resulting slurry, benzonitrile **2a,b** (4.5 mmol) in cyclohexane (5 ml) was added and the mixture stirred for 4 h at room temperature; then water (5 ml) was added and the mixture stirred for an additional 0.5 h. The aqueous layer was separated, basified with sodium hydroxide to a pH of 14, and then warmed at 60°C for 1 h. The mixture was cooled to room temperature, acidified with concentrated hydrochloric acid, and extracted with ether. The organic layer was separated and concentrated *in vacuo* to give a crude product, which was purified by column chromatography on silica gel.

Phenyl(2-sulfanylphenyl)methanone (3a). White powder (hexane–ethyl acetate, 10:1); mp 50-52°C (mp 54-55°C [21]) (80%). ^1H NMR, δ, ppm: 4.21 (1H, s); 7.17 (1H, t, *J* = 7.5 Hz); 7.33 (1H, t, *J* = 7.5 Hz); 7.39-7.48 (4H, m); 7.58 (1H, t, *J* = 7.5 Hz); 7.76 (2H, d, *J* = 6.9 Hz). ^{13}C NMR, δ, ppm: 124.5, 128.3, 130.1, 131.2, 131.4, 131.6, 132.8, 134.4, 135.3, 137.4, 196.7.

(4-Methylphenyl)(2-sulfanylphenyl)methanone (3b). White needles (hexane–ethyl acetate, 10:1); mp 78-79°C [22] (32%). ^1H NMR, δ, ppm: 2.43 (3H, s); 4.16 (1H, s); 7.15-7.20 (1H, m); 7.26 (2H, d, *J* = 8.1 Hz); 7.30-7.35 (1H, m); 7.39-7.44 (2H, m); 7.69 (2H, d, *J* = 8.1 Hz). ^{13}C NMR, δ, ppm: 21.7, 124.6, 129.1, 130.4, 131.0, 131.2, 131.4, 133.7, 134.7, 136.0, 143.9, 196.5

(5-Methyl-2-sulfanylphenyl)(phenyl)methanone (3c). Yellow plates (benzene–hexane); mp 73-74°C [23] (67%). ^1H NMR, δ, ppm: 2.27 (3H, s); 5.15 (1H, s); 7.23 (1H, s); 7.27 (1H, d, *J* = 7.8 Hz); 7.49 (1H, d, *J* = 7.8 Hz); 7.53-7.60 (2H, m); 7.66-7.72 (3H, m). ^{13}C NMR, δ, ppm: 20.2, 128.7, 129.6, 129.9, 130.7, 131.3, 132.12, 133.2, 134.2, 135.8, 136.8, 196.0. Found, %: C 73.81; H 5.56. $C_{14}H_{12}OS$. Calculated, %: C 73.65; H 5.30.

(4-Methylphenyl)(5-methyl-2-sulfanylphenyl)methanone (3d). Yellow plates (ethyl acetate–hexane); mp 92-93°C (71%). ^1H NMR, δ, ppm: 2.27 (3H, s); 2.40 (3H, s); 5.19 (1H, s); 7.17 (1H, s); 7.23 (1H, d, *J* = 8.0 Hz); 7.35 (2H, d, *J* = 7.8 Hz); 7.44 (1H, d, *J* = 8.0 Hz); 7.59 (2H, d, *J* = 7.8 Hz). ^{13}C NMR, δ, ppm: 20.7, 21.7, 129.1, 129.3, 130.3, 131.3, 131.5, 131.8, 134.7, 134.8, 136.7, 143.9, 196.7. Found, %: C 74.10; H 6.12. $C_{15}H_{14}OS$. Calculated, %: C 74.34; H 5.82.

(5-Methoxy-2-sulfanylphenyl)(phenyl)methanone (3e). Yellow oil (15%). ^1H NMR, δ, ppm: 3.76 (3H, s); 3.82 (1H, s); 6.93-6.98 (2H, m); 7.36 (1H, d, *J* = 8.7 Hz); 7.47 (2H, t, *J* = 7.5 Hz); 7.60 (1H, t, *J* = 7.5 Hz); 7.80 (2H, d, *J* = 7.2 Hz). ^{13}C NMR, δ, ppm: 55.5, 115.8, 117.2, 122.0, 128.5, 130.1, 133.2, 133.5, 137.0, 138.7, 157.4, 196.6. Found, %: C 68.86; H 4.06. $C_{14}H_{12}O_2S$. Calculated, %: C 68.83; H 4.95.

(2-Methoxy-5-sulfanylphenyl)(phenyl)methanone (3e'). Yellow powder (hexane–benzene); mp 72-73°C (8%). ^1H NMR, δ, ppm: 3.43 (1H, s); 3.67 (3H, s); 6.88 (1H, d, *J* = 8.6 Hz,); 7.31-7.45 (4H, m); 7.55 (1H, t, *J* = 7.2 Hz); 7.77-7.80 (2H, m). ^{13}C NMR, δ, ppm: 55.7, 112.3, 120.6, 128.2, 129.6, 129.7, 131.6, 133.1, 134.1, 137.3, 156.0, 195.4. Found, %: C 68.75; H 4.96. $C_{14}H_{12}O_2S$. Calculated, %: C 68.83; H 4.95.

(5-Chloro-2-sulfanylphenyl)(4-methylphenyl)methanone (3f). Yellow powder (benzene–hexane); mp 86-87°C (49%). ^1H NMR, δ, ppm: 2.44 (3H, s); 4.11 (1H, s); 7.29 (2H, d, *J* = 8.1 Hz); 7.32 (1H, d, *J* = 2.0 Hz); 7.34 (1H, s,); 7.40 (1H, d, *J* = 2.0 Hz); 7.68 (2H, d, *J* = 8.1 Hz). ^{13}C NMR, δ, ppm: 21.7, 129.3,

130.3, 130.5, 130.7, 130.9, 131.7, 132.6, 134.0, 137.7, 144.5, 195.2. HRMS (EI). Found: 261.0136. $C_{14}H_{10}ClOS$ (M-1). Calculated: 261.0149.

(5-Methoxy-2-sulfanylphenyl)(4-methylphenyl)methanone (3g). Yellow powder (benzene–hexane); mp 98-99°C (9%). ^{1}H NMR, δ, ppm: 2.43 (3H, s); 3.76 (3H, s); 3.78 (1H, s, SH); 6.90-6.94 (2H, m); 7.27 (2H, d, *J* = 8.1 Hz); 7.33-7.37 (1H, m); 7.71 (2H, d, *J* = 8.1 Hz). ^{13}C NMR, δ, ppm: 21.7, 55.5, 115.4, 117.0, 121.4, 129.2, 130.3, 133.5, 134.3, 139.3, 144.3, 157.5, 196.3. Found, %: C 69.67; H 5.59. $C_{15}H_{14}O_2S$. Calculated, %: C 69.74; H 5.46.

(2-Methoxy-5-sulfanylphenyl)(4-methylphenyl)methanone (3g'). Yellow powder (benzene–hexane); mp 107-108°C (5%). ^{1}H NMR, δ, ppm: 2.41 (3H, s); 3.42 (1H, s); 3.70 (3H, s); 6.88 (1H, d, *J* = 8.7 Hz); 7.23 (2H, d, *J* = 8.1 Hz); 7.29 (1H, d, *J* = 2.1 Hz); 7.41 (1H, dd, *J* = 8.7, 2.1 Hz); 7.70 (2H, d, *J* = 8.1 Hz). ^{13}C NMR, δ, ppm: 21.7, 55.8, 112.3, 120.5, 129.0, 130.0, 131.6, 133.9, 134.7, 134.8, 144.1, 155.9, 195.1. Found, %: C 69.67; H 5.57. $C_{15}H_{14}O_2S$. Calculated, %: C 69.74; H 5.46.

General Procedure for the Preparation of *o*-Sulfanylphenyl Ketones 5a-k. To a stirred solution of *o*-sulfanylphenyl ketones **3** (3 mmol) in ethanol (20 ml), a solution of NaOH in ethanol (3 ml, 1 N, 3 mmol) was added at room temperature and the reaction mixture was stirred for 0.5 h. Ethanol was removed from the reaction mixture *in vacuo*. The residue was dissolved in DMF. To the solution obtained the corresponding 1-benzotriazol-1-ylalkyl chloride (**4**) (3 mmol) was added, and the reaction mixture was stirred at 70°C for 12 h. After the starting materials were consumed, the reaction mixture was poured into iced water and extracted with diethyl ether. Ether was removed *in vacuo*, and the residue was purified by column chromatography on silica gel.

[2-(1-Benzotriazol-1-ylmethylsulfanyl)phenyl](phenyl)methanone (5a). White plates (hexane–ethyl acetate, 4:1); mp 114-115°C (90%). ^{1}H NMR, δ, ppm: 5.92 (2H, s); 7.25-7.37 (9H, m); 7.51 (1H, t, *J* = 6.9 Hz); 7.61 (2H, d, *J* = 7.5 Hz); 7.96 (1H, d, *J* = 8.1 Hz). ^{13}C NMR, δ, ppm: 52.1, 109.8, 119.5, 123.8, 127.1, 128.0, 128.2, 128.4, 129.7, 129.8, 130.3, 132.1,133.2,134.4, 136.4, 142.8, 145.7, 196.2. Found, %: C 69.37; H 4.15; N 12.27. $C_{20}H_{15}N_3OS$. Calculated, %: C 69.54; H 4.38; N 12.16.

[2-(1-Benzotriazol-1-ylmethylsulfanyl)phenyl](4-methylphenyl)methanone (5b). White plates (ethyl ether); mp 96-97°C (84%). ^{1}H NMR, δ, ppm: 2.41 (3H, s); 5.93 (2H, s); 7.17-7.35 (9H, m); 7.53-7.57 (2H, m); 7.97-8.01 (1H, m). ^{13}C NMR, δ, ppm: 21.7, 52.5, 110.0, 119.8, 124.0, 127.3, 128.4, 128.4, 129.2, 129.6, 130.2, 130.3, 132.4, 134.2, 135.0, 143.7, 144.6, 146.0, 196.2. Found, %: C 69.91; H 4.72; N 11.70. $C_{21}H_{17}N_3OS$. Calculated, %: C 70.17; H 4.77; N 11.69.

[2-(1-Benzotriazol-1-ylmethylsulfanyl)-5-methylphenyl](phenyl)methanone (5c). White powder (methylene chloride–hexane, 1:5); mp 66-68°C (90%). ^{1}H NMR, δ, ppm: 2.31 (3H, s); 5.87 (2H, s); 7.02 (2H, s); 7.12 (1H, s); 7.27-7.42 (5H, m); 7.55 (1H, t, *J* = 7.5 Hz); 7.64-7.67 (2H, m); 7.95-8.03 (1H, m). ^{13}C NMR, δ, ppm: 21.0, 52.8, 110.0, 119.8, 124.0, 125.9, 127.3, 128.5, 129.0, 130.0, 131.2, 132.4, 133.4, 135.5, 136.8, 139.2, 143.8, 146.0, 196.8. Found, %: C 70.13; H 4.81; N 11.75. $C_{21}H_{17}N_3OS$. Calculated, %: C 70.17; H 4.77; N 11.69.

[2-(1-Benzotriazol-1-ylmethylsulfanyl)-5-methylphenyl](4-methylphenyl)methanone (5d). White powder (methylene chloride–hexane, 1:4); mp 91-92°C (69%). ^{1}H NMR, δ, ppm: 2.30 (3H, s); 2.40 (3H, s); 5.86 (2H, s); 6.96-7.03 (2H, m); 7.11 (1H, s); 7.18 (2H, d, *J* = 8.1 Hz); 7.27-7.38 (3H, m); 7.56 (2H, d, *J* = 8.1 Hz); 7.95-8.00 (1H, m). ^{13}C NMR, δ, ppm: 21.0, 21.7, 52.9, 110.1, 119.8, 123.9, 125.6, 127.2, 128.8, 129.2, 130.1, 131.0, 132.4, 134.2, 135.5, 139.2, 144.2, 144.5, 146.0, 196.5. Found, %: C 71.10; H 5.46; N 11.31. $C_{22}H_{19}N_3OS$. Calculated, %: C 70.75; H 5.13; N 11.25.

[2-(1-Benzotriazol-1-ylmethylsulfanyl)-5-methoxyphenyl](phenyl)methanone (5e). Colorless plates (diethyl ether); mp 97-98°C (79%). ^{1}H NMR, δ, ppm: 3.74 (3H, s); 5.79 (2H, s); 6.66 (1H, dd, *J* = 8.7, 2.6 Hz); 6.83 (1H, d, *J* = 2.6 Hz); 6.88 (1H, d, *J* = 8.7 Hz); 7.25-7.36 (3H, m); 7.41 (2H, t, *J* = 7.5 Hz); 7.56 (1H, t, *J* = 7.5 Hz); 7.71 (2H, d, *J* = 7.8 Hz); 7.94-8.04 (1H, m). ^{13}C NMR, δ, ppm: 53.4, 55.6, 110.0, 114.0, 115.7, 119.1, 119.9, 124.0, 127.4, 128.6, 130.1, 132.6, 133.7, 136.5, 138.3, 146.0, 146.1, 160.3, 196.4. Found, %: C 67.04; H 4.43; N 11.21. $C_{21}H_{17}N_3O_2S$. C 67.18; H 4.56; N 11.19.

[2-[(1-Benzotriazol-1-ylmethylsulfanyl)-5-chlorophenyl](4-methylphenyl)methanone (5f). White powder (DMF–water), 106-107°C (87%). ^{1}H NMR, δ, ppm: 2.41 (3H, s); 5.89 (2H, s); 7.08 (1H, d, *J* = 8.4 Hz); 7.16-7.21 (3H, m,); 7.28-7.36 (4H, m); 7.55 (2H, d, *J* = 8.1 Hz); 7.99-8.02 (1H, m). ^{13}C NMR, δ, ppm: 21.8, 52.5, 109.8, 120.0, 124.1, 127.5, 127.7, 128.2, 129.4, 130.2, 130.3, 132.3, 133.6, 135.2, 136.5, 145.1, 145.4, 146.0, 194.7. Found, %: C 64.17; H 4.18; N 10.53. $C_{21}H_{16}ClN_3OS$. Calculated, %: C 64.03; H 4.09; N 10.67.

{2-[1-(1-Benzotriazol-1-yl)ethylsulfanyl]phenyl}(phenyl)methanone (5g). White plates (benzene–hexane); mp 135-136°C (68%). ^{1}H NMR, δ, ppm: 2.03-2.04 (3H, d, *J* = 6.9 Hz); 6.46 (1H, q, *J* = 6.9 Hz); 6.98 (1H, d, *J* = 7.7 Hz); 7.07-7.11 (1H, m); 7.22-7.27 (4H, m); 7.40 (2H, t, *J* = 7.5 Hz); 7.49-7.64 (4H, m); 7.95-7.98 (1H, m). ^{13}C NMR, δ, ppm: 20.5, 62.9, 110.7, 119.8, 123.9, 127.0, 128.3, 128.4, 128.5, 129.8, 130.0, 130.3, 131.8, 133.5, 135.3, 136.7, 143.5, 146.1, 196.6. Found, %: C 70.55; H 4.92; N 11.53. $C_{21}H_{17}N_3OS$. Calculated, %: C 70.17; H 4.77; N 11.69.

{2-[1-(1-Benzotriazol-1-yl)ethylsulfanyl]phenyl}(4-methylphenyl)methanone (5h). Colorless oil (76%). ^{1}H NMR, δ, ppm: 2.02 (3H, d, *J* = 6.9 Hz); 2.42 (3H, s); 6.45 (1H, q, *J* = 6.9 Hz); 6.95 (1H, d, *J* = 7.5 Hz); 7.03-7.09 (1H, m); 7.18-7.29 (6H, m); 7.47-7.55 (3H, m); 7.94-7.97 (1H, m). ^{13}C NMR, δ, ppm: 20.6, 21.7, 62.9, 110.7, 119.8, 123.8, 127.0, 128.1, 128.4, 129.2, 129.5, 130.1, 130.2, 131.9, 134.2, 135.4, 144.0, 144.5, 146.0, 196.3. Found, %: C 70.73; H 5.44; N 11.22. $C_{22}H_{19}N_3OS$. Calculated, %: C 70.75; H 5.13; N 11.25.

{2-[1-(1-Benzotriazol-1-yl)ethylsulfanyl]-5-methylphenyl}(phenyl)methanone (5i). White plates (methylene chloride–hexane); mp 109-111°C (71%). ^{1}H NMR, δ, ppm: 2.00 (3H, d, *J* = 6.9 Hz); 2.24 (3H, s); 6.38 (1H, q, *J* = 6.9 Hz); 6.79 (1H, d, *J* = 8.1 Hz); 6.88 (1H, d, *J* = 7.8 Hz); 7.05 (1H, s); 7.23-7.27 (2H, m); 7.40 (2H, t, *J* = 7.5 Hz); 7.49-7.59 (2H, m); 7.64 (2H, d, *J* = 7.2 Hz); 7.95-7.98 (1H, m). ^{13}C NMR, δ, ppm: 20.4, 21.0, 63.2, 110.8, 119.8, 123.8, 125.9, 126.9, 128.4, 128.8, 130.0, 131.0, 131.8, 133.4, 135.7, 136.8, 139.1, 144.0, 146.1, 196.8. Found, %: C 70.51; H 5.23; N 11.73. $C_{22}H_{19}N_3OS$. Calculated, %: C 70.75; H 5.13; N 11.25.

{2-[1-(1-Benzotriazol-1-yl)ethylsulfanyl]-5-methylphenyl}(4-methylphenyl)methanone (5j). White powder (ethyl acetate–hexane); mp 75-76°C (75%). ^{1}H NMR, δ, ppm: 2.00 (3H, d, *J* = 7.2 Hz); 2.24 (3H, s); 2.42 (3H, s); 6.37 (1H, q, *J* = 7.2 Hz,); 6.76 (1H, d, *J* = 7.8 Hz); 6.85 (1H, d, *J* = 7.8 Hz); 7.04 (1H, s); 7.18-7.28 (4H, m); 7.48-7.51 (1H, m); 7.54 (2H, d, *J* = 8.1 Hz,); 7.95-7.98 (1H, m). ^{13}C NMR, δ, 20.4, 21.0, 21.7, 63.2, 110.8, 119.7, 123.7, 125.6, 126.9, 128.6, 129.2, 130.2, 130.8, 131.9, 134.3, 135.8, 139.1, 144.4, 144.4, 146.0, 196.6. Found, %: C 71.38; H 5.56; N 10.90. $C_{23}H_{21}N_3OS$. Calculated, %: C 71.29; H 5.46; N 10.84.

{2-[1-(1-Benzotriazol-1-yl)ethylsulfanyl]-5-chlorophenyl}(4-methylphenyl)methanone (5k). Colorless plates (methylene chloride); mp 99-101°C (68%). ^{1}H NMR, δ, ppm: 2.03 (3H, d, *J* = 7.0 Hz); 2.43 (3H, s,); 6.39 (1H, q, *J* = 7.0 Hz); 6.81 (1H, d, *J* = 8.4 Hz); 7.01 (1H, dd, *J* = 8.4, 2.1 Hz); 7.21-7.29 (5H, m); 7.47-7.50 (1H, m); 7.53 (2H, d, *J* = 8.1 Hz); 7.97-7.99 (1H, m). ^{13}C NMR, δ, ppm: 20.5, 21.8, 63.0, 110.6, 120.0, 123.9, 127.2, 127.7, 128.0, 129.4, 130.1, 130.2, 131.8, 133.7, 135.2, 136.9, 145.1, 145.7, 146.1, 194.8. Found, %: C 64.69; H 4.47; N 10.22. $C_{22}H_{18}ClN_3OS$. Calculated, %: C 64.78; H 4.45; N 10.30.

General Procedure for the Preparation of 2-(Benzotriazol-1-yl)-3-substituted-2,3-dihydro-1-benzothiophen-3-ols of 6. To a stirred solution of *o*-sulfanylphenyl ketones **5** (1.5 mmol) in THF was added LDA (2.0 M, 0.85 ml, 1.7 mmol) at -78°C. The reaction mixture was stirred at the same temperature overnight and then quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel.

2-(1-Benzotriazol-1-yl)-3-phenyl-2,3-dihydro-1-benzothiophen-3-ol (6a). White plates; mp 153-156°C (85%). ^{1}H NMR, δ, ppm: 3.94 (1H, s); 6.76 (1H, s); 7.11 (1H, d, *J* = 8.4 Hz); 7.26-7.43 (11H, m); 7.89 (1H, d, *J* = 8.4 Hz). ^{13}C NMR, δ, ppm: 75.3, 87.9, 111.0, 120.0, 122.5, 124.2, 125.7, 126.1, 126.4, 127.8, 128.5, 128.6, 130.4, 132.8, 137.7, 141.5, 142.7, 146.0. Found, %: C 69.04; H 4.73; N 11.91. $C_{20}H_{15}N_3OS$. Calculated, %: C 69.54; H 4.38; N 12.16.

(2S,3S)-2-(1-Benzotriazol-1-yl)-2,5-dimethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzothiophen-3-ol (6d-*anti*). White powder (methylene chloride–hexane); mp 177-178°C (37%). ^{1}H NMR, δ, ppm: 2.08 (s, 3H); 2.24 (3H, s); 2.54 (3H, s); 3.31 (1H, s); 6.63 (2H, d, *J* = 8.2 Hz); 6.68 (2H, d, *J* = 8.2 Hz); 6.91 (1H, s); 7.10-7.18 (2H, m); 7.21-7.25 (1H, m); 7.30-7.38 (2H, m); 7.77-7.80 (1H, m). ^{13}C NMR, δ, ppm: 20.8, 21.0, 23.9, 87.1, 90.6, 113.1, 119.4, 122.1, 123.0, 126.3, 126.6, 127.3, 128.1, 131.2, 132.9, 134.7, 135.9, 136.2, 137.9, 142.6, 146.1. Found, %: C 70.84; H 5.64; N 10.70. $C_{23}H_{21}N_3OS$. Calculated, %: C 71.29; H 5.46; N 10.84.

(2R,3S)-2-(1-Benzotriazol-1-yl)-2,5-dimethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzothiophen-3-ol (6d-*syn*). White powder (methylene chloride–hexane); mp 162-163°C (54%). ^{1}H NMR, δ, ppm: 2.03 (3H, s); 2.30 (3H, s); 2.36 (3H, s); 4.74 (1H, s); 7.12-7.22 (7H, m); 7.32-7.45 (2H, m); 7.81 (1H, d, *J* = 8.2 Hz); 8.02 (1H, d, *J* = 8.0 Hz). ^{13}C NMR, δ, ppm: 21.1, 21.2, 25.0, 86.5, 90.8, 114.3, 120.1, 122.7, 124.0, 126.9, 127.1, 128.0, 128.6, 130.6, 133.5, 133.9, 135.5, 136.3, 138.2, 143.1, 145.9. Found, %: C 71.43; H 5.61; N 10.85. $C_{23}H_{21}N_3OS$. Calculated, %: C 71.29; H 5.46; N 10.84.

General Procedure for the Preparation of Benzothiophenes 7a-k. To a stirred solution of *o*-sulfanylphenyl ketones **5** (1.5 mmol) in THF was added LDA (2.0 M, 0.85 ml, 1.7 mmol) at -78°C, and the reaction mixture was stirred at the same temperature overnight. The reaction mixture was quenched by 10% aqueous HCl and extracted with diethyl ether. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was used directly in the next step for which $TiCl_3$ (277 mg, 1.8 mmol), Li (38 mg, 5.4 mmol), and DME (15 ml) were loaded in a three-necked round bottom flask under argon. The reaction mixture was heated under reflux for 12 h to generate the Ti(0) species. A solution of the crude product in DME (10 ml) was added to the Ti(0) solution and heated under reflux for 100 h. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl and extracted with diethyl ether. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed in *vacuo*. The residue was purified by column chromatography on silica gel.

3-Phenylbenzothiophene (7a). Colorless oil [24] (55%). ^{1}H NMR, δ, ppm: 7.37-7.42 (4H, m); 7.48 (2H, t, *J* = 7.5 Hz); 7.58 (2H, d, *J* = 7.8 Hz); 7.90-7.92 (2H, m). ^{13}C NMR, δ, ppm: 122.9, 123.4, 124.3, 124.4, 127.5, 128.7, 136.0, 137.9, 138.1, 140.7.

3-(4-Methylphenyl)benzothiophene (7b). Colorless oil [25] (63%). ^{1}H NMR, δ, ppm: 2.41 (3H, s,); 7.27 (2H, d, *J* = 7.7 Hz); 7.34-7.37 (3H, m); 7.46 (2H, d, *J* = 7.7 Hz); 7.86-7.92 (2H, m). ^{13}C NMR, δ, ppm: 21.2, 122.9, 122.9, 122.9, 124.2, 124.3, 128.5, 129.4, 133.1, 137.3, 138.0, 138.0, 140.6.

5-Methyl-3-phenylbenzothiophene (7c). Colorless oil [26] (55%). ^{1}H NMR, δ, ppm: 2.45 (3H, s); 7.19-7.21 (1H, m); 7.34 (1H, s); 7.36-7.41 (1H, m); 7.47 (2H, t, *J* = 7.2 Hz); 7.57 (2H, d, *J* = 7.2 Hz); 7.69 (1H, s); 7.77 (1H, d, *J* = 8.4 Hz). ^{13}C NMR, δ, ppm: 21.5, 122.5, 122.8, 123.6, 126.2, 127.4, 128.7, 128.7, 134.1, 136.2, 137.7, 137.8, 138.2.

5-Methyl-3-(4-methylphenyl)benzothiophene (7d). Colorless oil (52%). ^{1}H NMR, δ, ppm: 2.44 (3H, s); 2.46 (3H, s); 7.21 (1H, d, *J* = 7.8 Hz); 7.30 (2H, d, *J* = 8.1 Hz); 7.33 (1H, s); 7.48 (2H, d, *J* = 8.1 Hz); 7.69 (1H, s); 7.79 (1H, d, *J* = 8.2 Hz). ^{13}C NMR, δ, ppm: 21.3, 21.5, 122.5, 122.8, 123.1, 126.1, 128.6, 129.4, 133.2, 134.0, 137.2, 137.7, 137.8, 138.3. Found, %: C 80.51; H 6.31. $C_{16}H_{14}S$. Calculated, %: C 80.63; H 5.92.

5-Methoxy-3-phenylbenzothiophene (7e). Colorless oil [27] (56%); ^{1}H NMR, δ, ppm: 3.81 (3H, s); 7.03 (1H, dd, *J* = 8.8, 2.3 Hz,); 7.35-7.41 (3H, m); 7.48 (2H, t, *J* = 7.2 Hz); 7.56-7.59 (2H, m); 7.75 (1H, d, *J* = 9.0 Hz). ^{13}C NMR, δ, ppm: 55.5, 105.2, 114.6, 123.5, 124.7, 127.5, 128.5, 128.8, 133.0, 136.1, 137.7, 139.0, 157.7.

5-Chloro-3-(4-methylphenyl)benzothiophene (7f). Yellow needles (hexane); mp 77-78°C (55%). ^{1}H NMR, δ, ppm: 2.42 (3H, s); 7.29 (2H, d, *J* = 8.1 Hz); 7.34 (1H, d, *J* = 1.8 Hz); 7.40 (2H, d, *J* = 8.7 Hz,); 7.44 (1H, s); 7.78 (1H, d, *J* = 8.7 Hz); 7.86 (1H, d, *J* = 1.8 Hz). ^{13}C NMR, δ, ppm: 21.2, 122.6, 123.8, 124.7, 124.8, 128.5, 129.5, 130.8, 132.4, 137.6, 137.6, 138.7, 139.3. Found, %: C 69.81; H 4.48. $C_{15}H_{11}ClS$. Calculated, %: C 69.62; H 4.28.

2-Methyl-3-phenylbenzothiophene (7g). Colorless oil [7] (59%). ^{1}H NMR, δ, ppm: 2.49 (3H, s); 7.24-7.32 (2H, m); 7.37-7.41 (3H, m); 7.45-7.51 (3H, m); 7.76-7.80 (1H, m). ^{13}C NMR, δ, ppm: 14.5, 121.9, 122.4, 123.7, 124.1, 127.26, 128.5, 130.0, 133.8, 135.3, 136.1, 138.2, 140.3. Found, %: C 80.75; H 5.42. $C_{15}H_{12}S$. Calculated, %: C 80.31; H 5.39.

2-Methyl-3-(4-methylphenyl)benzothiophene (7h). Colorless oil (55%). ^{1}H NMR, δ, ppm: 2.38 (3H, s); 2.44 (3H, s); 7.19-7.24 (6H, m); 7.46-7.51 (1H, m); 7.70-7.75 (1H, m). ^{13}C NMR, δ, ppm: 14.4, 21.2, 121.9, 122.4, 123.6, 124.0, 129.2, 129.8, 132.2, 133.7, 135.7, 136.8, 138.2, 140.4. Found, %: C 80.80; H 6.26. $C_{16}H_{14}S$. Calculated, %: C 80.63; H 5.92.

2,5-Dimethyl-3-phenylbenzothiophene (7i). Colorless needles (hexane); mp 84-85°C (mp 88-88°C [28]) (61%). ^{1}H NMR, δ, ppm: 2.37 (3H, s); 2.46 (3H, s); 7.10 (1H, d, J = 8.1 Hz); 7.28 (1H, s); 7.34-7.41 (3H, m); 7.46-7.52 (2H, m); 7.65 (1H, d, J = 8. 1 Hz). ^{13}C NMR, δ, ppm: 14.5, 21.4, 121.6, 122.4, 125.4, 127.2, 128.5, 130.0, 133.5, 133.8, 135.3, 135.5, 136.2, 140.6.

2,5-Dimethyl-3-(4-methylphenyl)benzothiophene (7j). Yellow oil [29] (60%); ^{1}H NMR, δ, ppm: 2.36 (3H, s); 2.41 (3H, s); 2.44 (3H, s); 7.08 (1H, d, J = 8.1 Hz); 7.22-7.28 (5H, m); 7.63 (1H, d, J = 8.1 Hz). ^{13}C NMR, δ, ppm: 14.5, 21.3, 21.4, 121.6, 122.4, 125.3, 129.2, 129.9, 132.4, 133.4, 133.7, 135.3, 135.9, 136.8, 140.7.

5-Chloro-2-methyl-3-(4-methylphenyl)benzothiophene (7k). Yellow oil (65%). ^{1}H NMR, δ, ppm: 2.40 (3H, s); 2.44 (3H, s); 7.18-7.28 (5H, m); 7.46 (1H, d, J = 2.0 Hz); 7.62 (1H, d, J = 8.5 Hz). ^{13}C NMR, δ, ppm: 14.5, 21.2, 122.0, 122.9, 124.0, 129.4, 129.7, 130.5, 131.5, 133.3, 136.2, 137.2, 137.9, 141.7. Found, %: C 70.84; H 5.12. $C_{16}H_{13}ClS$. Calculated, %: C 70.45; H 4.80.

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