A SIMPLE ROUTE TO 2,3-DIHYDRONAPHTHO[1,2-b]THIOPHENES AND NAPHTHO[1,2-b]THIOPHENES BEARING TRIFLUOROMETHYL GROUPS BY AROMATIC NUCLEOPHILIC SUBSTITUTION OF N,N-DIMETHYL-2,4-BIS(TRIFLUOROACETYL)-1-NAPHTHYLAMINE

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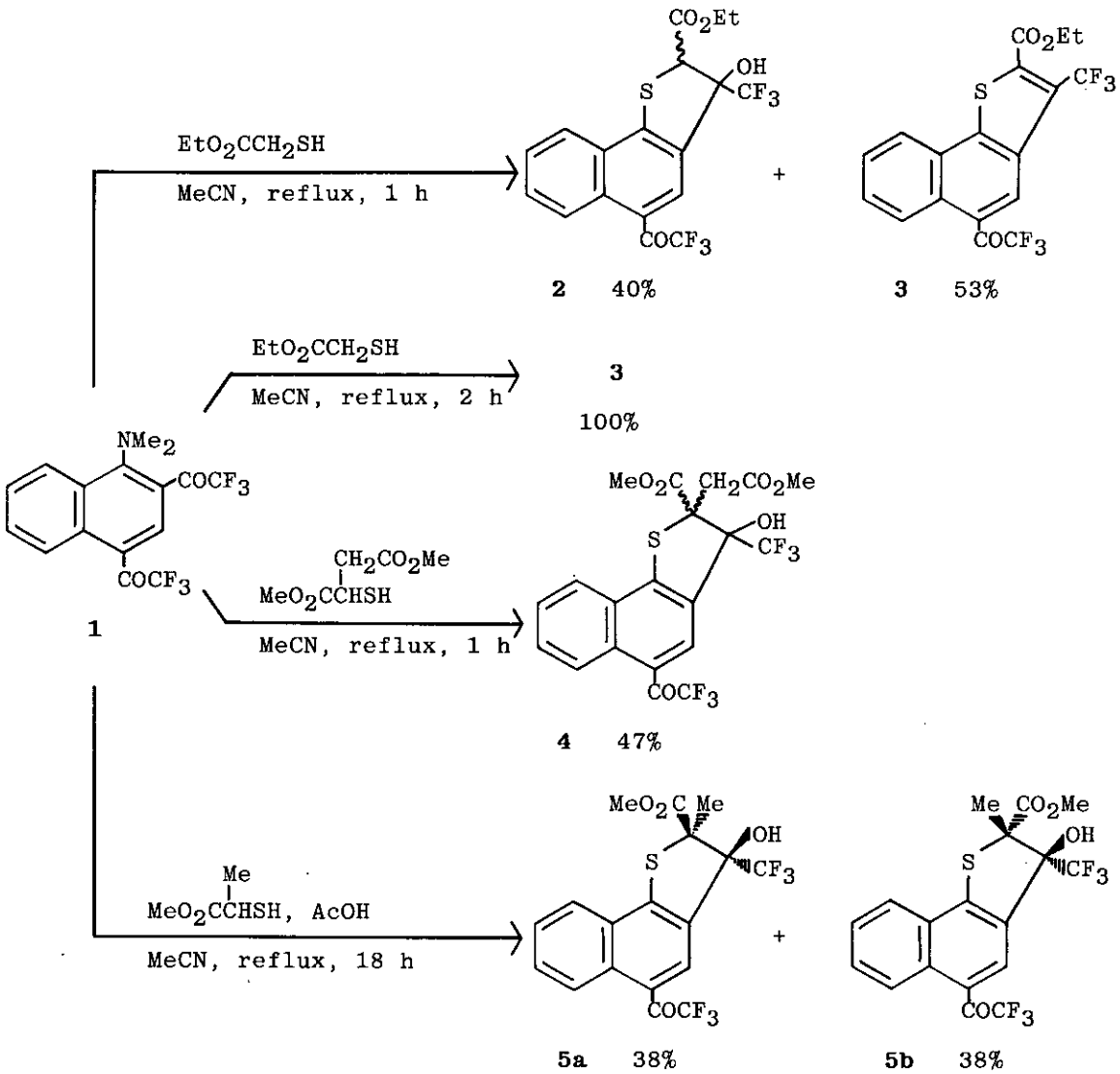
Abstract - 2,3-Dihydronaphtho[1,2-b]thiophenes (**2**, **4**, **5**, and **7**) and naphtho[1,2-b]thiophenes (**3** and **8**) bearing trifluoromethyl groups were easily synthesized by aromatic nucleophilic nitrogen-sulfur exchange reaction of N,N-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine (**1**) with thioglycolic acids and with benzyl mercaptan, followed by cyclization (cyclodehydration).

Activated aromatic compounds bearing good leaving groups such as halo, alkoxy, nitro, etc., are well known to undergo aromatic nucleophilic substitution with various nucleophiles.[1-3] However, amino groups attached to aromatic rings are seldom replaced by nucleophiles. Recently we reported that a dimethylamino group of N,N-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine (**1**) is easily exchanged by various amines,[4,5,6] thiols,[6,7] and alcohols[6,7] to give the corresponding 2,4-bis(trifluoroacetyl)-1-naphthylamines, sulfides, and ethers in excellent yields. Later, **1** was actually shown to be a useful building block for construction of naphthalene-fused heterocyclic compounds bearing trifluoromethyl groups, such as benzindoles,[8] benzindazoles,[9] naphthoisoxazoles,[9] benzacridines,[10] and naphthoxazines[11] using this type of aromatic nucleophilic

substitution and the related reactions. As an extension and generalization of these works, we now describe a synthetic method for 2,3-dihydronaphtho[1,2-b]thiophenes and naphtho[1,2-b]thiophenes bearing trifluoromethyl groups by the new aromatic nucleophilic substitution of **1** with thioglycolic acids and with benzyl mercaptan. These fluorine-containing heterocycles are expected to show interesting biological activities [12-14]

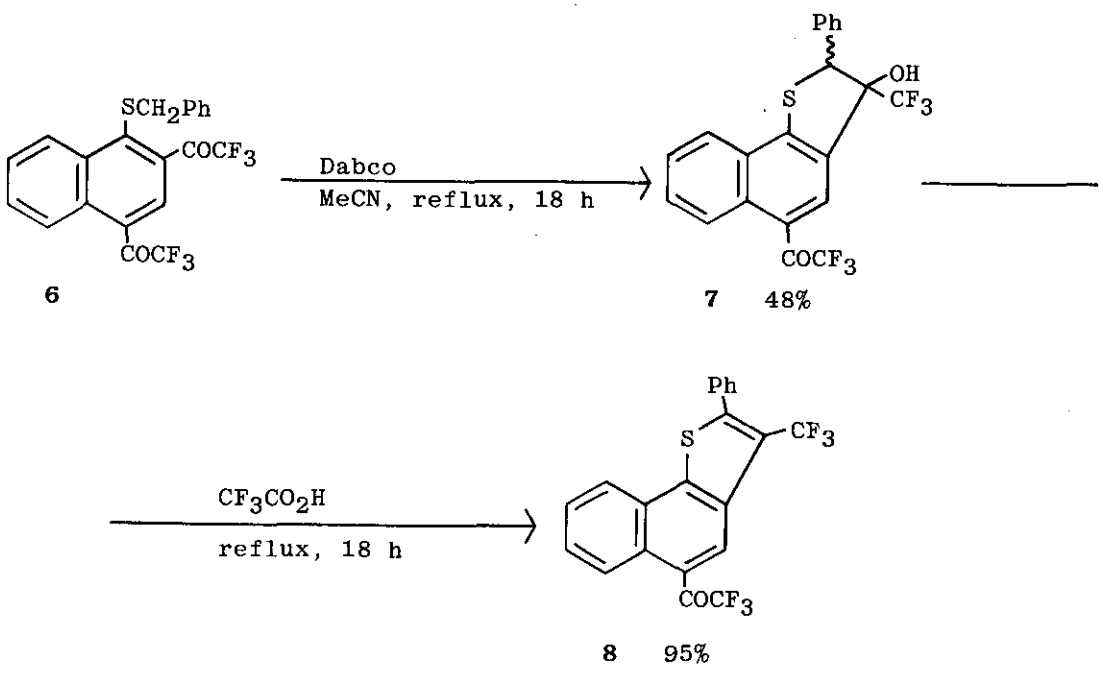


Scheme 1

and are hardly accessible by other methods.

Reaction of **1**, which is easily prepared by bistrifluoroacetylation of N,N-dimethyl-1-naphthylamine,[4] with ethyl thioglycolate in refluxing acetonitrile for 1 h gave 2,3-dihydronaphtho[1,2-b]thiophene (**2**) and naphtho[1,2-b]thiophene (**3**) in 40 and 53% yields, respectively (Scheme 1). Prolonged (2 h) heating in this reaction afforded **3** as a sole product in a quantitative yield. A possible reaction course is as follows. Aromatic nucleophilic Me_2N-SCH_2CO_2Et exchange reaction of **1** with ethyl thioglycolate takes place to give an intermediate 2,4-bis(trifluoroacetyl)-1-naphthyl ethoxycarbonylmethyl sulfide which undergoes intramolecular nucleophilic attack of its active S-methylene carbon onto the carbonyl carbon of the trifluoroacetyl group to afford dihydronaphthothiophene (**2**). Dehydration of **2** by heating provides naphthothiophene (**3**). Dimethyl thiomalate also reacted to give the corresponding dihydronaphthothiophene (**4**) in 47% yield. Similarly, **1** underwent the present exchange and cyclization reactions with methyl thiolactate in the presence of acetic acid in refluxing acetonitrile for 18 h to afford a mixture of dihydronaphthothiophene (**5a**) and its stereoisomer (**5b**) in 76% total yield (**5a**:**5b** =1:1). Although this reaction proceeded without using acetic acid as a catalyst, some unreacted starting material was recovered. This synthetic strategy is applicable to the case of 2,4-bis(trifluoroacetyl)-1-naphthyl benzyl sulfide (**6**), which can be easily obtained in an almost quantitative yield by N-S exchange reaction of **1** with benzyl mercaptan (Scheme 2).[5] Base-catalyzed cyclization of **6** with 1,4-diazabicyclo[2.2.2]octane (Dabco) proceeded in refluxing acetonitrile for 18 h to yield the desired dihydronaphthothiophene (**7**) in 48% yield. Treatment of **7** with trifluoroacetic acid at reflux temperature for 18 h caused dehydration to provide naphthothiophene (**8**) in 95% yield.

Stereochemistry of **5a** and **5b** was determined on the basis of their ^{1}H-nmr spectra. The signal of methyl proton at the 2-position of **5a** appeared as quartet (J=2 Hz) owing to through-space coupling with fluorine nuclei



6 7 48% 8 95%

Scheme 2

of a trifluoromethyl group at the 3-position, in contrast to the case of **5b** where it appeared as singlet. These observations show that **5a** has a cis configuration with respect to the methyl and the trifluoromethyl groups. The nmr signal for each hydrogen of **2**, **4**, and **7** appeared as a single peak, exhibiting the presence of a single stereoisomer in each case. However, their stereochemistries are not determined yet.
In conclusion, aromatic nucleophilic substitution of **1** with thioglycolic acid derivatives and benzyl mercaptan, followed by cyclization (cyclodehydration) provides a simple synthetic approach to naphthalene-fused dihydrothiophenes and thiophenes bearing trifluoromethyl groups.

EXPERIMENTAL

Melting points were determined on an Electrothermal digital melting point apparatus and are uncorrected. Ir spectra were recorded on a Hitachi

EPI-G3 spectrophotometer. ^{1}H-Nmr spectra were obtained with a JEOL PMX-60SI spectrometer using $CDCl_3$ as a solvent. All chemical shifts are reported in ppm downfield from internal tetrametylsilane; coupling constants (J) are given in Hz. ^{19}F-Nmr spectra were obtained with a JEOL FX-90Q spectrometer. All chemical shifts are reported in ppm upfield from trichlorofluoromethane as internal standard in $CDCl_3$; coupling constants (J) are given in Hz. Elemental analyses were performed by the Microanalyses Center of Kyoto University. Chromatographic separations were carried out on silica gel column (Wakogel C-200; 100-200 mesh). Dimethyl thiomalate and methyl thiolactate were prepared by esterification of thiomalic and thiolactic acids, respectively. All other reagents and solvents were obtained commercially, dried over molecular sieves, and used without further purification.

2-Ethoxycarbonyl-5-trifluoroacetyl-3-trifluoromethyl-3-hydroxy-2,3-dihydronaphtho[1,2-b]thiophene (2) and 2-Ethoxycarbonyl-5-trifluoroacetyl-3-trifluoromethylnaphtho[1,2-b]thiophene (3). A mixture of **1**[4] (200 mg, 0.55 mmol) and ethyl thioglycolate (72 mg, 0.6 mmol) in MeCN (2 ml) was heated at reflux for 1 h. Evaporation of the solvent and chromatography using benzene and hexane/benzene (1:1) gave **2** (96 mg, 40%) and **3** (123 mg, 53%), respectively. **2**: mp 110-111 °C (hexane/$CHCl_3$); ir (KBr) 3413, 1726, 1704 cm^{-1}; ^{1}H-nmr 8.93-8.70 (1H, m, H-6), 8.13 (1H, s, H-4), 7.82-7.33 (3H, m, H-7, -8, -9), 5.60-5.36 (1H, br, OH), 4.72 (1H, s, H-2), 4.23 (2H, q, J=7, $OC\underline{H}_2CH_3$), 1.32 (3H, t, J=7, $OCH_2C\underline{H}_3$). Anal. Calcd for $C_{18}H_{12}O_4F_6S$: C, 49.32; H, 2.76; F, 26.00. Found: C, 48.88; H, 2.86; F, 25.56. **3**: mp 144-145 °C (hexane/$CHCl_3$); ir (KBr) 1713 cm^{-1}; ^{1}H-nmr 8.75-8.48 (2H, m, H-4, -6), 8.07-7.90 (1H, m, H-9), 7.88-7.42 (2H, m, H-7, -8), 4.45 (2H, q, J=7, $OC\underline{H}_2CH_3$), 1.47 (3H, t, J=7, $OCH_2C\underline{H}_3$). Anal. Calcd for $C_{18}H_{10}O_3F_6S$: C, 51.44; H, 2.40; F, 27.12. Found: C, 51.28; H, 2.55; F, 27.34.

5-Trifluoroacetyl-3-trifluoromethyl-3-hydroxy-2-methoxycarbonyl-2-methoxycarbonylmethyl-2,3-dihydronaphtho[1,2-b]thiophene (4). Following the procedure described for the preparation of **2** and **3**, the reaction of **1** (200 mg, 0.55 mmol) with dimethyl thiomalate (290 mg, 1.63 mmol) in refluxing MeCN (2 ml) for 1 h afforded a crude mixture which was purified by chromatography with benzene/EtOAc (19:1) to give **4** (128 mg, 47%): mp 190-191 °C ($CHCl_3$/EtOAc); ir (KBr) 3388, 1749, 1725, 1708 cm^{-1}; ^{1}H-nmr 8.93-8.72 (1H, m, H-6), 8.07 (1H, s, H-4), 7.80-7.45 (3H, m, H-7, -8, -9), 5.73-5.33 (1H, br, OH), 3.75 (3H, s, OCH_3), 3.60 (3H, s, OCH_3), 3.47 (2H, s, CH_2). Anal. Calcd for $C_{20}H_{14}O_6F_6S$: C, 48.39; H, 2.84; F, 22.96. Found: C, 47.68; H, 2.88; F, 22.67.

5-Trifluoroacetyl-3-trifluoromethyl-3-hydroxy-2-methoxycarbonyl-2-methyl-2,3-dihydronaphtho[1,2-b]thiophene (5a and 5b). To a solution of **1** (200 mg, 0.55 mmol) in MeCN (2 ml) were added methyl thiolactate (66 mg, 0.55 mmol) and acetic acid (37 mg, 0.61 mmol). The solution was then stirred at reflux temperature for 18 h, diluted with CH_2Cl_2, washed with aqueous solution of 20% Na_2CO_3, and dried (Na_2SO_4) and the solvent was evaporated. Chromatography of the residue with benzene and benzene/EtOAc (19:1) afforded **5a** (92 mg, 38%) and **5b** (91 mg, 38%), respectively. **5a**: mp 151-152 °C ($CHCl_3$); ir (KBr) 3412, 1716, 1697 cm^{-1}; ^{1}H-nmr 9.00-8.75 (1H, m, H-6), 8.15 (1H, s, H-4), 7.80-7.53 (3H, m, H-7, -8, -9), 5.40-5.10 (1H, br, OH), 3.75 (3H, s, OCH_3), 2.03 (3H, q, J=2, CCH_3); ^{19}F-nmr 69.9 (3F, d, J=1.7, $COCF_3$), 75.8-76.0 (3F, m, CF_3-3). Anal. Calcd for $C_{18}H_{12}O_4F_6S$: C, 49.32; H, 2.76; F, 26.00. Found: C, 48.82; H, 2.81; F, 25.93. **5b**: mp 169-170 °C ($CHCl_3$); ir (KBr) 3488, 1727, 1698 cm^{-1}; ^{1}H-nmr 8.95-8.78 (1H, m, H-6), 8.08 (1H, s, H-4), 7.88-7.48 (3H, m, H-7, -8, -9), 3.88 (3H, s, OCH_3), 4.10-3.72 (1H, br, OH), 1.90 (3H, s, CCH_3); ^{19}F-nmr 69.9 (3F, d, J=1.7, $COCF_3$), 76.2 (3F, s, CF_3-3). Anal. Calcd for $C_{18}H_{12}O_4F_6S$: C, 49.32; H, 2.76; F, 26.00. Found: C, 49.12; H, 2.73; F, 26.01.

5-Trifluoroacetyl-3-trifluoromethyl-3-hydroxy-2-phenyl-2,3-dihydronaphtho-[1,2-b]thiophene (7). To a solution of **6**[7] (600 mg, 1.36 mmol) in MeCN (6 ml) was added Dabco (456 mg, 4.06 mmol), and the mixture was stirred at reflux temperature for 18 h. Most of the solvent was evaporated and CH_2Cl_2 was then added. The whole mixture was washed with 1N HCl and water, and the organic layer was separated and dried (Na_2SO_4). The solvent was evaporated and the crude mixture was chromatographed with benzene to give **7** (289 mg, 48%): bp 200 °C/5 mmHg; ir (film) 3513, 1696 cm^{-1}; ^{1}H-nmr 9.02-8.85 (1H, m, H-6), 8.25 (1H, s, H-4), 7.92-7.10 (3H, m, H-7, -8, -9), 7.38 (5H, s, C_6H_5), 5.40 (1H, s, H-2), 2.85-2.50 (1H, br, OH). Anal. Calcd for $C_{21}H_{12}O_2F_6S$: C, 57.02; H, 2.73; F, 25.77. Found: C, 57.31; H, 2.66; F, 25.76.

5-Trifluoroacetyl-3-trifluoromethyl-2-phenylnaphtho[1,2-b]thiophene (8). A solution of **7** (1240 mg, 2.8 mmol) in CF_3CO_2H (20 ml) was heated at reflux for 18 h with stirring. The mixture was washed with aq. 20% Na_2CO_3, extracted with CH_2Cl_2, and dried (Na_2SO_4). The solvent was evaporated to afford practically pure **8** (1130 mg, 95%): mp 133-134 °C (hexane); ir (KBr) 1709 cm^{-1}; ^{1}H-nmr 8.76-8.49 (2H, m, H-4, -6), 8.09-7.89 (1H, m, H-9), 7.66-7.36 (7H, m, H-7, -8, C_6H_5). Anal. Calcd for $C_{21}H_{10}OF_6S$: C, 59.44; H, 2.38; F, 26.86. Found: C, 59.31; H, 2.33; F, 27.00.

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