The Synthesis of Novel Polycyclic Heterocyclic Ring Systems. [1]. Benzo[*e*][1]benzothieno[3,2-*g*][1]benzothiophenes

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The novel polycyclic heterocyclic ring system compound, methyl 3-chlorobenzo[*e*][1]benzothieno-[3,2-*g*][1]benzothiophene-2-carboxylate was synthesized. The assignment of its ^{1}H and ^{13}C nmr spectra was also accomplished by utilizing two-dimensional nmr methods.

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We have been interested in the synthesis of novel polycyclic heterocyclic ring systems *via* photocyclization of the appropriate enamide and their spectroscopic properties [1]. In our continuing study of the synthesis *via* oxidative photocyclization, we usually employed 3-chloro[1]benzothiophene-2-carbonyl chloride [1,3] as a requisite key compound which was allowed to react with an aromatic amine to prepare a starting amide for photocyclization. In this paper we describe the synthesis of a novel polycyclic fused benzothiophene derivative, 3-chlorobenzo[*e*][1]benzothieno[3,2-*g*][1]benzothiophene-2-carbonyl chloride (**8**), which will be used for preparing further novel polycyclic heterocyclic compounds. Furthermore compound **8** was converted to the corresponding methyl ester, methyl 3-chlorobenzo[*e*][1]benzothieno[3,2-*g*][1]benzothiophene-2-carboxylate (**9**) because of its stability and convenience for measurement of the nmr. The total assignments of the ^{1}H and ^{13}C nmr spectra of compound **9** were also determined.

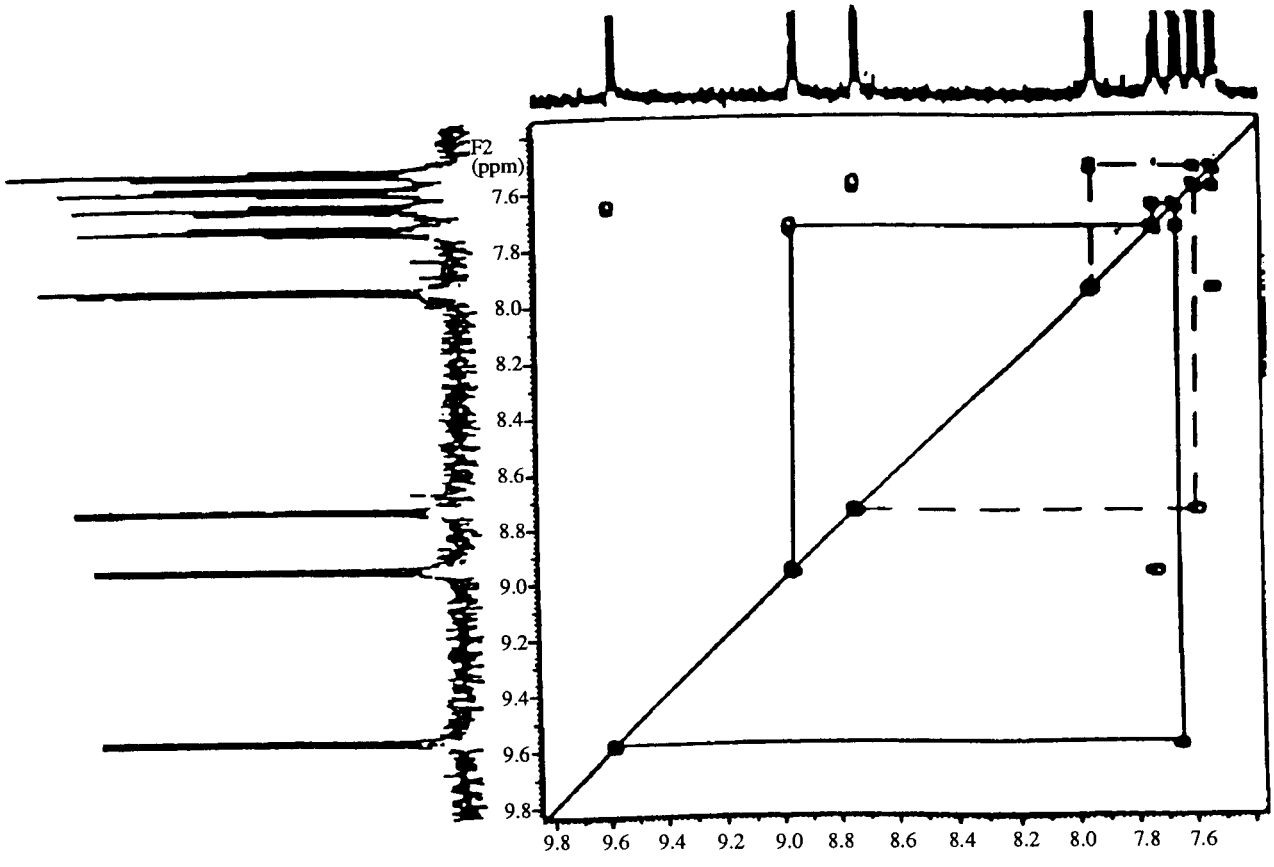
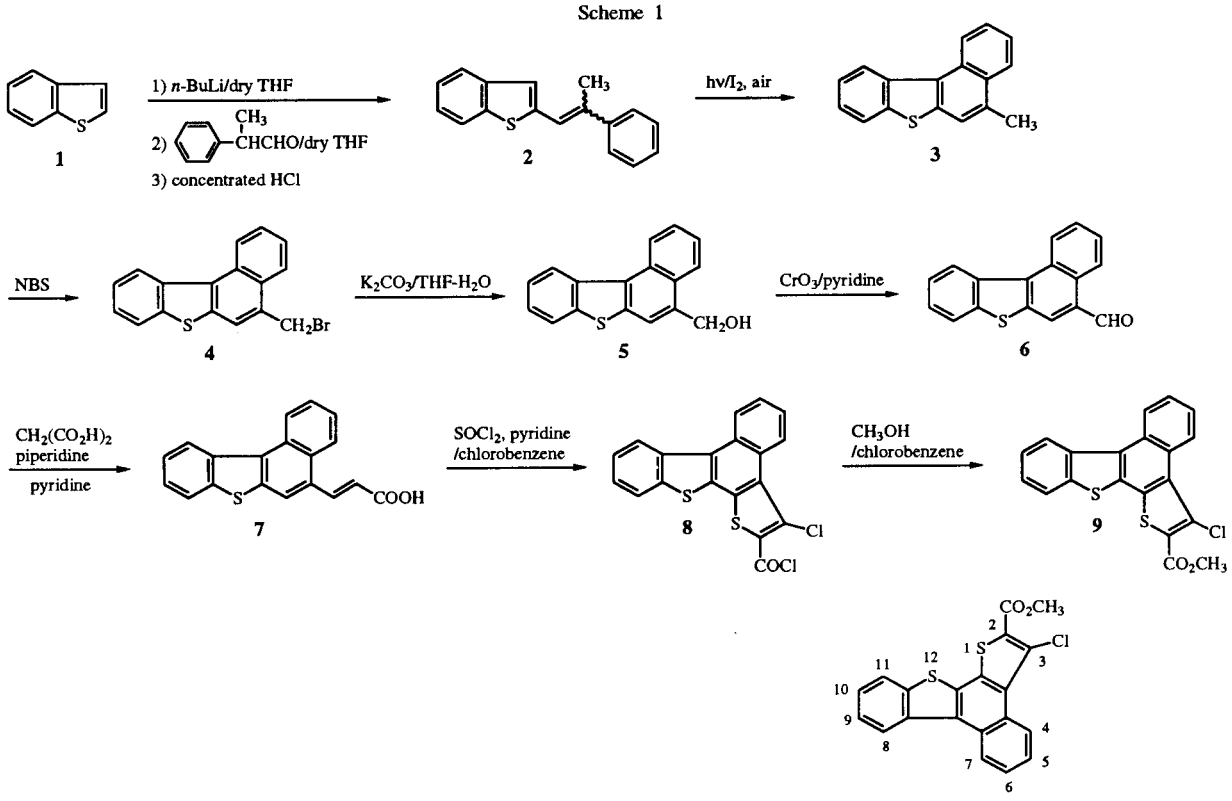


Figure 1. ^{1}H-^{1}H COSY Spectrum of **9**.

Scheme 1



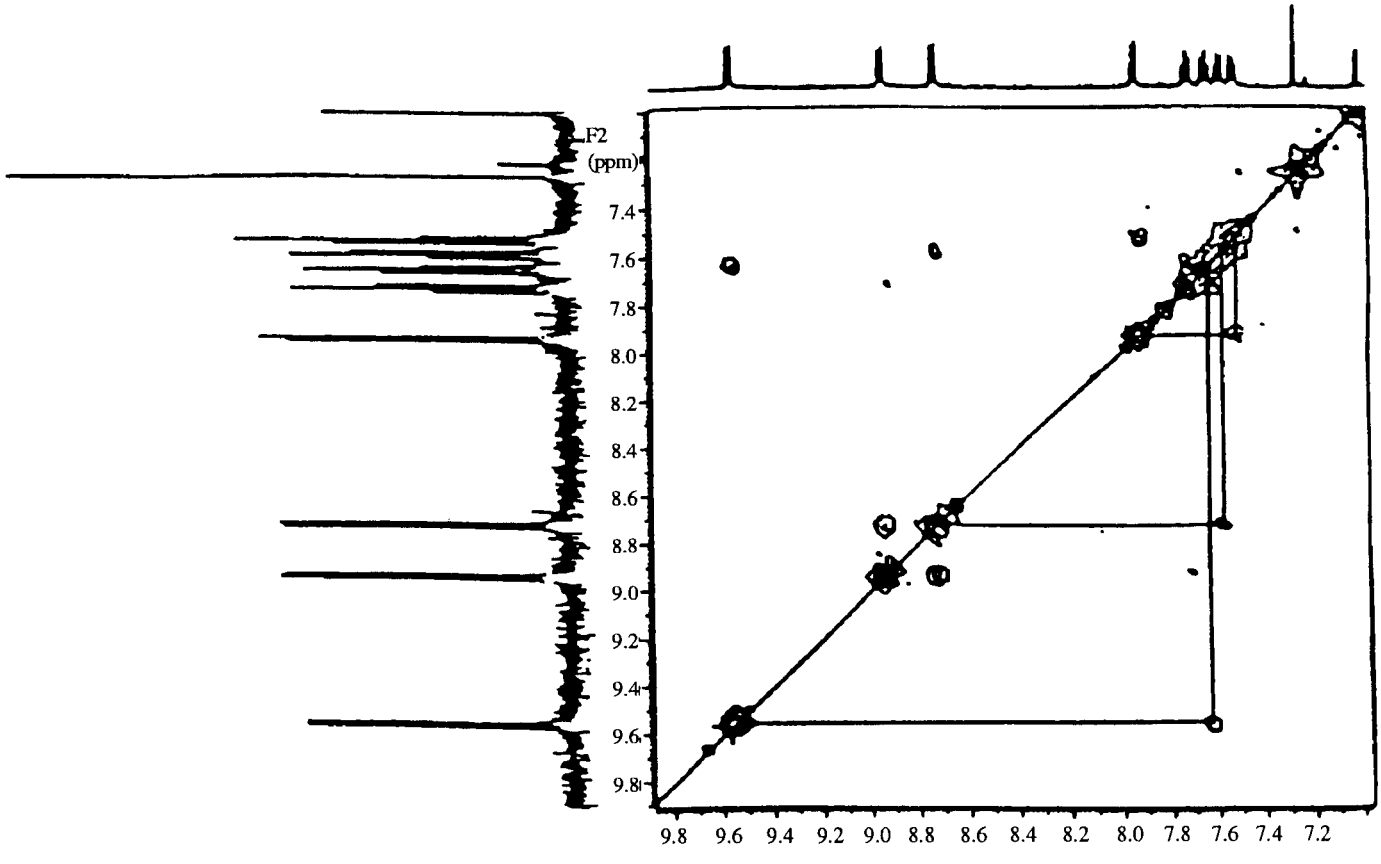


Figure 2. ^1H-^1H NOESY Spectrum of **9**.

The synthetic pathway to compound **9** is illustrated in Scheme 1. 5-Methylnaphtho[2,1-*b*][1]benzothiophene (**3**) was obtained by the methods of Tominaga *et al.* [4] from [1]benzothiophene. Bromination of **3** with *N*-bromosuccinimide and benzoyl peroxide in benzene gave 5-bromomethylnaphtho[1,2-*b*][1]benzothiophene (**4**), which was hydrolyzed with potassium carbonate to afford the corresponding 5-hydroxymethyl derivative **5**. Sarret oxidation of **5** with chromium trioxide in pyridine gave 5-carbaldehyde **6** in 99% yield. Reaction of aldehyde **6** with malonic acid under Knoevenagel-Doebner condensation conditions [5] gave the *E*-isomer of naphtho[2,1-*b*][1]benzothiophen-5-acrylic acid (**7**) in 62% yield, which was used in the next step without purification because it behaved as a single spot on tlc. Compound **8** was obtained by refluxing **7** with thionyl chloride in chlorobenzene in the presence of pyridine [6,7]. After treatment of **8** with methanol in chlorobenzene, the desired methyl ester **9** was obtained in 61% yield.

NMR Spectroscopy.

The well resolved ^{1}H nmr spectrum of **9** shows two four-spin systems which can be unambiguously assigned from the COSY spectrum (Figure 1) and NOESY spectrum (Figure 2). The well resolved ^{13}C nmr spectrum established direct heteronuclear correlations from the one-bond HETCOR spectrum, but unequivocal assignment of the spectrum was not possible without concerted use of one-bond and long-range HETCOR techniques.

From the ^{1}H-^{1}H COSY spectrum, one can see two four-spin systems. One of them included protons resonating at 9.58, 7.65, 7.73, and 8.96 ppm. The other four-spin system included protons at 8.74, 7.58, 7.52, and 7.94 ppm. In the NOESY spectrum of **9**, one proton doublet resonating at 8.74 ppm was correlated with a proton doublet resonating at 8.96 ppm, and these protons are included in different four-spin systems, independently. These protons are H7 and H8 by examining the structure of **9**. However, at this stage, it is impossible to assign which resonance is which proton. It is clear that the remaining two doublets resonating at 7.94 ppm and 9.58 ppm are the terminal H4 and H11 protons from their coupling patterns. The proton at the 11 position of compound **9** should resonate around 8 ppm because H7 of the non-substituted benzo[*b*]thiophene usually resonates around 8 ppm [8] and there is no factor to change the chemical shift of the proton at the same site (H11) except for the solvent effect in the case of **9**. Therefore, the upper proton at 7.94 ppm is assigned as H11 of the two proton doublets resonating at 7.94 ppm and 9.58 ppm. The other terminal proton res-

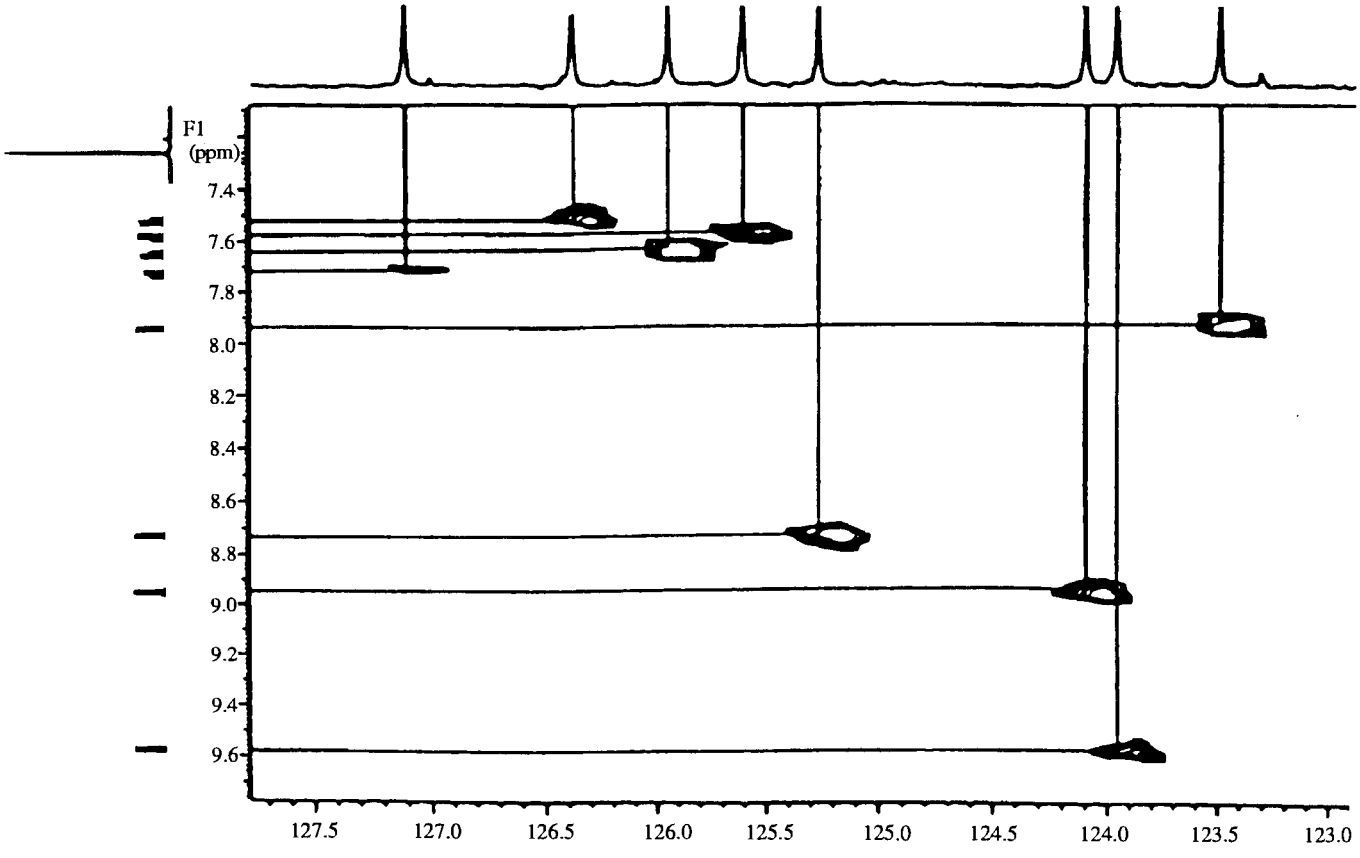


Figure 3. ^{1}H-^{13}C One Bond HETCOR Spectrum of **9**.

onating at 8.74 ppm in the same four-spin system including H11 is therefore assigned as H8. As mentioned above, protons at 8.96 ppm and 8.74 ppm are H7 and H8, therefore, the proton at 8.96 ppm is assigned as H7. Finally, the remaining terminal proton at 9.58 ppm in the four-spin system which includes H7 can be assigned as H4. The reason why H4 is strongly shifted to lower field can be explained by the fact that this proton is a bay-region proton and effected by the anisotropy of the chloro group at the 3-position. At this point one can complete the assignment of the ^{1}H nmr spectrum using the data from the COSY and NOESY spectra.

As shown in Figure 3, all protonated carbons were easily assigned from the one-bond HETCOR spectrum. For assignment of the quaternary carbons, we use the quaternary carbon which has the lowest resonance at 139.6 ppm. This carbon has correlations with both H8 and H10 in the long-range HETCOR spectrum shown in Figure 4. Therefore, one can assign this carbon as C11a. The carbon resonating at 136.3 ppm is assigned to C7c on the basis of both correlations with H9 and H11. The carbon resonating at 130.8 ppm which is correlated with H7 and H8 should be assigned as C7b. Similarly, one can see two quaternary carbons at 129.7 ppm and 129.5 ppm, both of which have correlations with H4. Between these two signals, only the signal resonating at 129.7 ppm has a correlation with H6, therefore, this quaternary carbon can be assigned as C7a, and the other quaternary carbon as C3a. C3b (128.6 ppm) is assigned on the basis of both correlations with H5 and H7. In the upper field one can see two quaternary carbons resonating at 115.5 ppm and 113.3 ppm. In these resonances, the carbon at 115.5 ppm has a correlation only with H5 and the carbon at 113.3 ppm has a correlation only with H7. The distances between C12b and H5, and C12b and H7 are both five bonds, however there is a zigzag relationship between C12b and H5. Thus the carbon at 115.5 ppm appears to be C12b and the remaining carbon at 113.3 ppm can be assigned as C12a. At this point, the remaining unassigned carbons are C2 and C3. Normally C2 and C3 of benzo[*b*]thiophene resonate at 126.4 ppm and 124.0 ppm, respectively [8]. Usually, ^{13}C-chemical shifts in multiple-substituted compounds can be estimated using data of that for a mono substituted compound. The effect of the introduction of the chloro group to the ^{13}C-chemical shifts of the adjacent carbon in monosubstituted benzene is +6.3 ppm (down field) and +0.4 ppm to the α-carbon. On the other hand, the chemical shift of the methyl ester group for the adjacent carbon is +2.0 ppm and +1.2 ppm for the α-carbon. On the basis of these data and the chemical shifts of the unsubstituted benzo[*b*]thiophene, the chemical shift of C3 of compound **9** which is adjacent to the chloro group should resonate at a lower field than that of C2 which is adjacent to

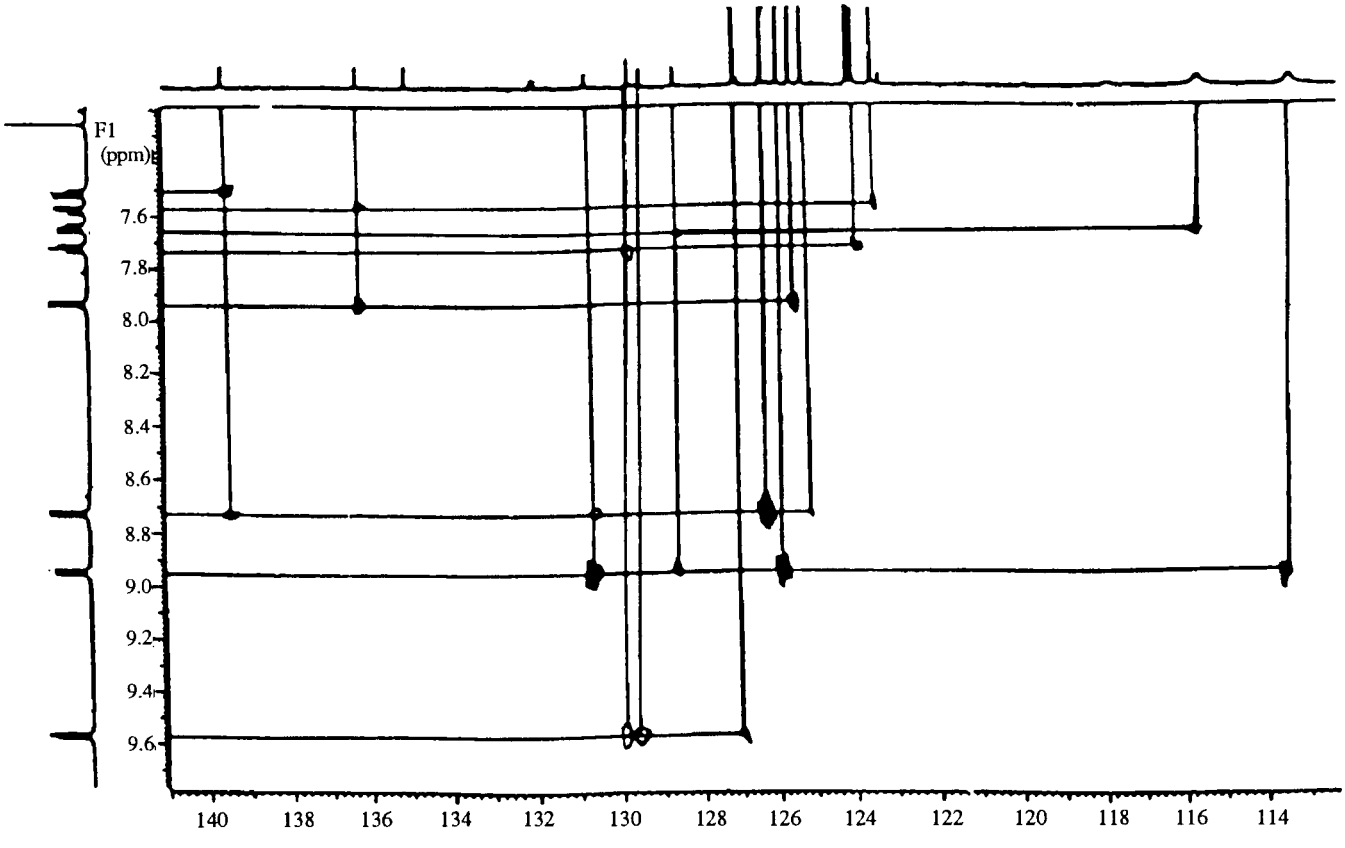


Figure 4. ^{1}H-^{13}C Long Range HETCOR Spectrum of **9**.

a methyl ester group. Therefore, the carbon resonating at 132.0 ppm can be assigned as C2, and the carbon at lower field (135.1 ppm) as C3. Proton and ^{13}C chemical shifts of **9** are listed in Table 1.

Table 1

^{1}H and ^{13}C Chemical Shifts of Methyl 3-Chlorobenzo[*e*][1]-benzothieno[3,2-*g*][1]benzothiophene-2-carboxylate (**9**)

Position	δH	δC	Long-Range Correlation
2		132.0	
3		135.1	
3a		129.5	H4
3b		128.6	H5, H7
4	9.58	124.0	H6
5	7.65	125.9	H7
6	7.73	127.1	H4
7	8.96	124.1	
7a		129.7	H4, H6
7b		130.8	H7, H8
7c		136.3	H9, H11
8	8.74	125.3	H8
9	7.58	125.6	H11
10	7.52	126.4	H8
11	7.94	123.5	H9
11a		139.6	H8, H10
12a		113.3	H7
12b		115.5	H5

In conclusion, we have synthesized the novel heterocyclic ring system compound, methyl 3-chlorobenzo[*e*]-[1]benzothieno[3,2-*g*][1]benzothiophene-2-carboxylate (**9**). The complete assignments of ^{1}H and ^{13}C spectra of **9** were determined by concerted usage of COSY, NOESY, and HETCOR two-dimensional nmr techniques.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro-melting point apparatus, and are uncorrected. The ir spectra were recorded on a Japan Spectroscopic IRA-102 diffraction grating infrared spectrophotometer and frequencies are expressed in cm^{-1}. Unless otherwise stated, the ^{1}H nmr spectra were recorded on a Varian VXR-200 instrument working at 200 MHz in the solvent indicated with tetramethylsilane as the internal standard. Chemical shifts are given in ppm (δ) and J values in Hz. The signals are designated as follow; s, singlet; d, doublet; t, triplet; quin; quintet, m, multiplet; br, broad. The ^{1}H and ^{13}C spectra of **9** were acquired on a Varian VXR-500 instrument operating at an observation frequency of 499.01 MHz for ^{1}H and 125.69 MHz for ^{13}C. The mass spectra (EI, FAB), and the high-resolution mass spectra were measured on a VG 70 mass spectrometer. In the case of FAB mass spectroscopy, glycerol or *m*-nitrobenzyl alcohol was used as the matrix agent. Elemental analyses were performed on a Yanagimoto MT-5 CHN Corder elemental analyzer.

2-(β-Methylstyryl)benzo[*b*]thiophene (**2**).

This compound was prepared by the method of Tominaga *et al.* [4] in 38% as colorless needles, mp 123°, mp 123° [4].

5-Methylnaphtho[2,1-*b*][1]benzothiophene (**3**).

This compound was prepared by the method of Tominaga *et al.* [4] in 77% as colorless needles, mp 123-124°, mp 128° [4].

5-Bromomethylnaphtho[2,1-*b*][1]benzothiophene (**4**).

A mixture of compound **3** (21 g, 85 mmoles), *N*-bromosuccinimide (18 g, 101 mmoles), benzoyl peroxide (0.05 g), and dry benzene (750 ml) was refluxed for 3 hours. The reaction mixture was cooled in an ice bath and succinimide was removed by suction filtration and then the filtrate was washed with water. The organic layer was dried over anhydrous sodium sulfate and evaporated to give 28 g (quantitative) of compound **4**. An aliquot of the resulting compound was recrystallized from acetone to give pale brown plates as the analytical sample, mp 172-174°; ^{1}H nmr (deuteriochloroform): 5.07 (s, 2H, CH_2), 7.48-7.82 (m, 4H, H2, H3, H9, and H10), 8.00 and 8.33 (each dd, J = 1.8 and 7.4, each 1H, H4 and H8), 8.02 (s, 1H, H6), 8.85 and 9.07 (each dd, J = 1.8 and 7.4, each 1H, H1 and H11); ms: FAB m/z 328 (MH^+ + 2), 326 (MH^+).

Anal. Calcd. for $C_{17}H_{11}BrS$: C, 62.40; H, 3.39. Found: C, 62.49; H, 3.61.

This compound was used in the next step without further purification because it behaved as a single spot on tlc.

5-Hydroxymethylnaphtho[2,1-*b*][1]benzothiophene (**5**).

To a solution of compound **4** (28 g, 85 mmoles) in tetrahydrofuran (500 ml) was added potassium carbonate (94 g, 680 mmoles) in water (600 ml), and the solution was refluxed for 72 hours. After cooling, the mixture was extracted with diethyl ether. The organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was subjected to column-chromatography on silica gel using a mixture of *n*-hexane-ethyl acetate (9:1, v/v) as the eluting agent to give 15 g (44%) of compound **5** as colorless needles after recrystallization from benzene, mp 175-179°; ir: 3350 (OH); ^{1}H nmr (500 MHz, DMSO-d_6): 5.11 (d, J = 6, 2H, CH_2), 5.54 (t, J = 6, 1H, exchangeable with deuterium oxide, OH), 7.57 (m, 1H, HAr), 7.64-7.70 (m, 2H, HAr), 7.81 (m, 1H, HAr), 8.17 (s, 1H, H6), 8.19 and 8.25 (each d, J = 8, each 1H, H4 and H8), 8.96 and 9.12 (each d, J = 8, each 1H, H1 and H11); ms: FAB m/z 265 (MH^+).

Anal. Calcd. for $C_{17}H_{12}OS$: C, 77.24; H, 4.58. Found: C, 77.47; H, 4.86.

Naphtho[2,1-*b*][1]benzothiophene-5-carbaldehyde (**6**).

Chromium trioxide (13 g, 0.13 mole) was carefully added in small portions to pyridine (100 ml). After all of the chromium trioxide had dissolved, compound **5** (7.0 g, 27 mmoles) in pyridine (160 ml) was added to the above suspension. After stirring at room temperature for 1 hour, the reaction mixture was poured into water (*ca.* 500 ml) and then the resulting mixture was extracted with a mixture of ethyl acetate-diethyl ether (4:1, v/v). The organic layer was washed with 10% hydrochloric acid, 10% aqueous sodium bicarbonate solution and then water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was subjected to column chromatography on silica gel using a mixture of *n*-hexane-ethyl acetate (9:1, v/v) as the eluting agent to give 6.6 g (92%) of compound **6** as a yellow crystalline solid. Recrystallization of an aliquot of **6** from benzene for preparing an analytical sample afforded pale yellow needles, mp 145-148°; ir: 1690 (C=O); ^{1}H nmr (deuteriochloroform): 7.60-7.88 (m, 4H, HAr), 8.07 and 8.94 (each d, J = 8.6, each 1H,

H4 and H8), 9.11 and 9.47 (each d, J = 8.6, each 1H, H1 and H11), 10.49 (s, 1H, CHO); ms: El m/z 262 (M^+, 100%), 233 (M^+-CHO, 40%).

Anal. Calcd. for $C_{17}H_{10}OS$: C, 77.86; H, 3.82. Found: C, 77.81; H, 4.11.

β-(Naphtho[2,1-*b*][1]benzothiophen-5-yl)acrylic Acid (**7**).

A mixture of compound **6** (6.9 g, 26 mmoles), malonic acid (3.3 g, 32 mmoles), piperidine (1.7 ml) and pyridine (150 ml) was refluxed for 48 hours. The reaction mixture was poured into ice-water (*ca.* 600 ml) and then the mixture was acidified with 20% hydrochloric acid. The precipitated solid was collected by filtration. This yellow solid was triturated with tetrahydrofuran and the undissolved solid was collected by filtration and dried *in vacuo* to give 4.9 g (62%) of **7** as a yellow crystalline solid. Recrystallization of an aliquot of **7** from toluene for preparing an analytical sample gave yellow granules, mp 282-285° (sublimed from 233°); ir: 3420 (OH), 1690 (C=O); ^{1}H nmr (DMSO-d_6): 6.76 (d, J = 16, 1H, Hα of acrylic acid), 7.58-7.91 (m, 4H, HAr), 8.23 and 8.40 (each d, J = 7.8, each 1H, H4 and H8), 8.49 (d, J = 16, 1H, Hβ of acrylic acid), 8.64 (s, 1H, H6), 9.01 and 9.17 (each d, J = 7.8, each 1H, H1 and H11), 12.66 (br s, 1H, exchangeable with deuterium oxide, OH); ms: FAB m/z 305 (MH^+).

Anal. Calcd. for $C_{19}H_{12}O_2S$: C, 74.98; H, 3.93. Found: C, 75.06; H, 3.93.

This compound was used in the next step without further purification because it behaved as a single spot on tlc.

3-Chlorobenzo[*e*][1]benzothieno[3,2-*g*][1]benzothiophene-2-carbonyl Chloride (**8**).

To a solution of compound **7** (1.5 g, 4.9 mmoles) in dry chlorobenzene (25 ml) was added thionyl chloride (2.4 g, 20 mmoles) and the resulting suspension was stirred at room temperature for 30 minutes. Pyridine (0.1 ml) was added dropwise to the suspension and then the mixture was refluxed for 72 hours. After cooling the mixture, the precipitated crystalline solid was collected by filtration and dried *in vacuo* to give 0.69 g (36%) of **8**, mp >300°.

This compound was used in the next step without further purification because of its low stability.

Methyl 3-Chlorobenzo[*e*][1]benzothieno[3,2-*g*][1]benzothiophene-2-carboxylate (**9**).

A mixture of compound **8** (110 mg, 0.28 mmole), methanol (20 ml) and chlorobenzene (20 ml) was refluxed for 1 hour. After cooling, the mixture was evaporated to dryness and the resulting residue was subjected to column chromatography on silica gel using chloroform as an eluting agent to afford 66 mg (61%) of **9** as colorless needles after recrystallization from chloroform, mp 239-241°; ir: 1715 (C=O); ^{1}H nmr [deuteriochloroform-trifluoroacetic acid-d (9:1, v/v)]: 4.02 (s, 3H, CH_3), 7.51-7.85 (m, 4H, HAr), 8.01 (dd, J = 1.5 and 8.0, 1H, H11), 8.84, 9.09 and 9.77 (each dd, J = 1.5 and 8.0, each 1H, H4, H7, and H8); ms: FAB m/z 385 (MH^+ + 2), 383 (MH^+).

Anal. Calcd. for $C_{20}H_{11}ClO_2S_2$: C, 62.74; H, 2.90. Found: C, 62.72; H, 3.10.

REFERENCES AND NOTES

[1] For the most recent report, see: J.-K. Luo, R. F. Federspiel, and R. N. Castle, *J. Heterocyclic Chem.*, **32**, 659 (1995) and references cited therein.

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