The Synthesis of Novel Polycyclic Heterocyclic Ring Systems. 3 [1]. Synthesis and NMR Spectroscopy of 15-Chloro[1]benzothieno[2",3":3',4']naphtho[1',2':4,5]thieno[2,3-*c*]quinoline

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The polycyclic heterocyclic compound with a novel ring system, 15-chloro[1]benzothieno[2",3":3',4']naphtho[1',2':4,5]thieno[2,3-*c*]quinoline was synthesized *via* photocyclization of 3-chloro-*N*-phenyl[1]benzothieno[2',3':3,4]naphtho[2,1-*b*]thiophene-2-carboxamide followed by chlorination with phosphorus oxychloride. The assignment of its ^{1}H and ^{13}C nmr spectra was 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 enamides and to study their nmr spectroscopic properties [3]. In our continuing study of the synthesis *via* oxidative photocyclization, we employed 3-chlorobenzo[*b*]thiophene-2-carbonyl chloride [4] as a requisite key intermediate, which was allowed to react with an aromatic amine to prepare a starting enamide for photocyclization. In a search of the literature we found that there are few reports in which an enamide containing two thiophene rings was employed as the starting material for photocyclization [3,5].

In this paper we describe the synthesis of a novel polycyclic heterocyclic compound, 15-chloro[1]benzothieno[2",3":3',4']naphtho[1',2':4,5]thieno[2,3-*c*]quinoline (**4**), *via* photocyclization of 3-chloro-*N*-phenyl[1]benzothieno[2',3':3,4]naphtho[2,1-*b*]thiophene-2-carboxamide (**2**), which contains two thiophene rings in the molecule. The total assignment of the ^{1}H and ^{13}C nmr spectra of compound **4** was also determined.

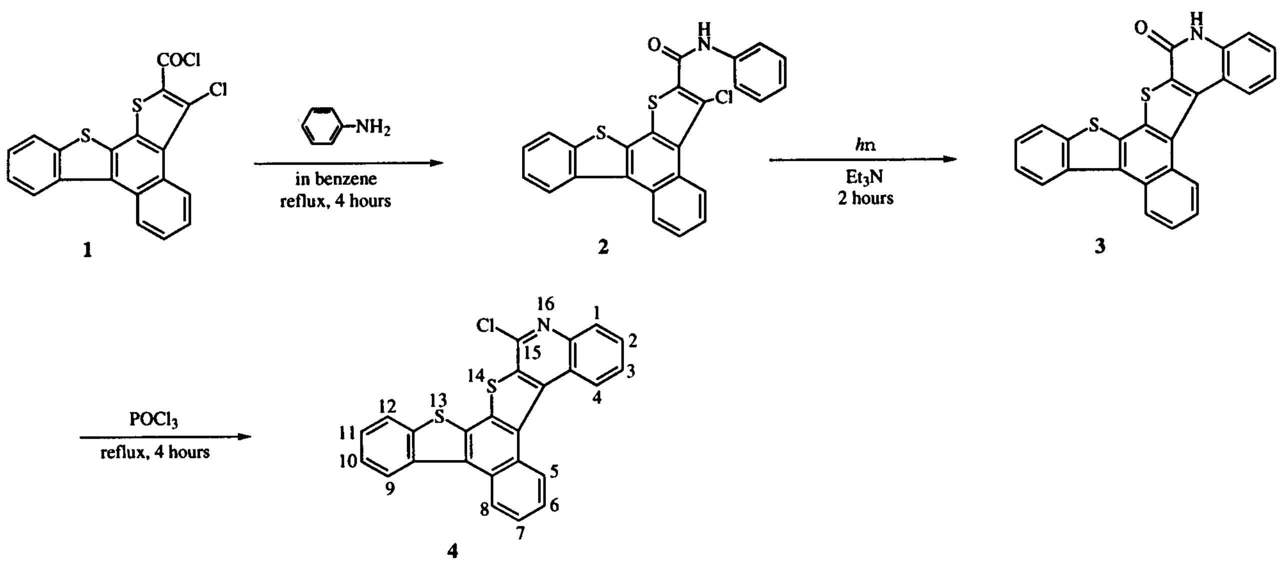
The synthetic pathway to compound **4** is illustrated in Scheme 1.

When 3-chloro[1]benzothieno[2',3':3,4]naphtho[2,1-*b*]thiophene-2-carbonyl chloride (**1**) was allowed to react with aniline, compound **2** was obtained in 80% yield. Absorptions at 3300 cm^{-1} (NH) and 1630 cm^{-1} (C=O) in the ir spectrum of **2** as well as a broad singlet at 10.47 ppm which is exchangeable with deuterium oxide in its nmr spectrum indicated the formation of the amide bond. Irradiation of **2** in benzene solution containing triethylamine with a 500 watt high pressure mercury vapor lamp gave the desired cyclization product, [1]benzothieno[2",3":3',4']naphtho[1',2':4,5]thieno[2,3-*c*]quinolin-15(16*H*)-one (**3**), in 22% yield. Four downfield shifted doublets resonating at 8.86, 8.91, 8.94 and 9.16 ppm in its nmr spectrum were collectively assigned as H4, H9, H8 and H5 located in two bay regions and these observations are anticipated when the cyclization of **2** takes place. Chlorination of **3** with phosphorus oxychloride afforded compound **4** in 29% yield. The FAB-mass spectrum of **4** showed an isotopic peak (MH$^+$ + 2, 8%) of the parent peak (MH$^+$, 16%). The structural confirmation was further established by its ^{1}H and ^{13}C nmr spectra as well as its elemental analysis.

NMR Spectroscopy of 4.

From simple inspection of the structure of the molecule, it should be clear that compound **4** consists of three four-spin systems. The connectivity of these four-spin systems could be established by the COSY spectrum [6], but the differentiation among them and the orientation in each spin system could not be accomplished without further experiments. The NOESY spectrum [7] of **4** showed two long-range nOe's indicating the proximity between H4/H5 and H8/H9 in addition to the vicinal protons such as H1/H2, H2/H3, H3/H4, H5/H6, H6/H7, H7/H8, H9/H10 and H11/H12 [8]. However, the differentiation of these two long-range nOe's cannot be made without the identification of these four protons, *i.e.* H4/H5 and H8/H9. Moreover, the congestion of the proton and the carbon-13 spectra prevented us from identifying several protonated carbons through the HMQC spectrum [9]. Upon examination of the HMBC spectrum [10] several expected long-range correlations are not observable and several quaternary carbons show no correlations. Thus, a complete assignment of the ^{1}H and ^{13}C spectra of **4** appears to be very challenging with the lack of a convenient starting point.

Scheme 1



In the HMBC spectrum of **4** the most downfield quaternary carbon resonating at 145.6 ppm has to be either C16a or C15 from the consideration of chemical shift due to their proximity to a deshielding nitrogen atom. Since this quaternary carbon displays a long-range correlation with a proton appearing as a doublet resonating at 9.10 ppm, it is tentatively assigned as C16a rather than C15, which should show no long-range correlations. It is not clear why an expected additional long-range correlation from H2 to C16a is not observed. Thus, the quaternary carbon resonating at 143.9 ppm is assigned as C15. This assignment is supported by our recent report [11] which indicated that the chlorine atom exerts very little change in the chemical shift of C15. Accordingly, the doublet resonating at 9.10 ppm can be unmistakably assigned to H4 upon consideration of chemical shift, split pattern, and most importantly its long-range correlations to C2, C16a and C4b (*vide infra*). This contention is supported by the observation of its long-range nOe with the proton resonance at 8.88 ppm shown in the NOESY spectrum. Hence, the proton resonance at 8.88 ppm is assigned as H5 because of its proximity to H4 in the bay region.

Having identified H4 and H5, the assignment of the remaining protons can be achieved through the concerted use of the COSY and NOESY spectra. For instance, from the COSY spectrum the identification of H4 and H5 leads to the identities of two four-spin systems, *i.e.*, H1-H4 and H5-H8, and their orientation relative to one another in the molecular framework. Consequently, the NOESY spectrum of **4** provides the clue for the assignment of H9 *via* a long-range nOe with H8 (*vide supra*) and thus establishes the identification and orientation of the components of the remaining four-spin system, H9-H12. With all protons accounted for, some of the protonated carbons could thus be established by the HMQC spectrum except C2/C12, C3/C7, C6/C10 and C5/C9 owing to the congestion of the proton and carbon-13 spectra.

Given the location of H4, we note that H4 exhibits three long-range correlations, a protonated carbon resonating at 133.7 ppm, and two quaternary carbons at 137.1 and 145.6 ppm, respectively, in the HMBC spectrum. Clearly, the protonated carbon must be C2 and the most downfield quaternary carbon is C16a (*vide supra*). Hence, the remaining quaternary carbon at 137.1 ppm is denoted as C4b. Also using the HMQC spectrum, by elimination the carbon resonating at 124.1 ppm is assigned as C12, which is further confirmed by its long-range coupling to H10 shown in the HMBC spectrum. The differentiation of C3 and C7 is based on the long-range correlation to H5 by C7 resonating at 129.2 ppm. The carbon resonating at 128.9 ppm is thus assigned as C3. Although a long-range coupling between H1 and C3 is expected, there are no carbons coupling to H1 observable. Again, it is not clear why the long-range coupling to C3 and C4a from H1 are not observable. Fortunately, C4a resonating at 122.5 ppm could be elucidated by its long-range correlation with H3. At this point, we have dispensed with the assignment of the quinoline moiety except the quaternary carbon C14a, which displays no correlations as expected.

Continuing to the long-range coupling of H5, we observe couplings to carbons resonating at 129.2, 129.4 and 130.2 ppm. The protonated carbon resonating at 129.2 ppm was previously assigned as C7 (*vide supra*). The quaternary carbon resonating at 130.2 ppm also exhibits response to H7 and is thus assigned as C8a. Consequently, the quaternary carbon resonating at 129.4 ppm is identified as C4c by elimination. The proton resonating at 9.17 ppm, previously identified as H8, is long-range coupled to three carbons resonating at 126.3, 128.6, and 135.2 ppm. The furthest upfield carbon resonating at 126.3 ppm is a protonated carbon, which must be C6. The quaternary carbon resonating at 128.6 ppm displaying a long-range correlation to H6 has to be C4d, whereas the carbon resonating at 135.2 ppm exhibiting long-range responses to H8 and H9 is assigned as C8b. To this point, we have accounted for the naphthalene moiety with the exception of two quaternary carbons, *i.e.*, C13a and C13b.

Turning to the benzo[*b*]thiophene moiety, while the long-range coupling of C9 to H11 leads us to the identification of the quaternary carbon C12a resonating at 141.3 ppm, the previously assigned C12 (*vide supra*) provides us the assignment of C8c resonating at 135.5 ppm. At this point, with the exception of the quaternary C13a, C13b and C14a we have accomplished the assignment of proton and carbon-13 spectra of **4**. Among these uncharacterized quaternary carbons, C13b could be deduced as the most downfield carbon resonating at 142.1 ppm, and C14a at 131.6 ppm based on our previous reports [3,5b,11,12]. Finally, the carbon resonating at 130.7 ppm is assigned as C13a and the assignment is supported by our recent report [12j]. Final chemical shift assignments are presented in Table 1.

Table 1

^{1}H and ^{13}C NMR Chemical Shift Assignments and Observed Proton-Carbon Multiple-Bond Correlations for Compound 4 in Deuteriochloroform in the Presence of Deuterated Trifluoroacetic Acid at 298° K at Observation Frequencies of 360.13 and 90.56 MHz, Respectively

Position	δ H	δ C	Long-Range Correlation
1	8.37	121.3	H3
2	8.10	133.7	H4
3	7.93	128.9	H1 (Not Observed)
4	9.10	126.5	H2
4a		122.5	H3, H1 (Not Observed)
4b		137.1	H4
4c		129.4	H5
4d		128.6	H6, H8
5	8.88	126.5	H7
6	7.75	126.3	H8
7	7.93	129.2	H5
8	9.17	125.2	H6
8a		130.2	H5, H7
8b		135.2	H8, H9
8c		135.5	H10, H12
9	8.92	126.2	H10
10	7.71	126.6	H12
11	7.69	128.3	H9
12	8.10	124.1	H10
12a		141.3	H9, H11
13a	130.7	126.3	
13b		142.1	
14a		131.6	
15		143.9	
16a		145.6	H4, H2 (Not Observed)

EXPERIMENTAL

All melting points were determined on a Yanagimoto micromelting 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}. The FAB-mass and high resolution FAB and EI-mass spectra were measured on a VG 70 mass spectrometer. Elemental analyses were performed on a Yanagimoto MT-5 CHN Corder elemental analyzer. The ^{1}H nmr spectra at 200 MHz and 500 MHz were acquired on a Varian VXR-200 and -500 instruments in the solvent indicated with tetramethylsilane as the internal standard. The ^{1}H and ^{13}C spectra of **4** were acquired on a Bruker AMX 360 MHz NMR spectrometer at an observation frequency of 360.13 MHz for ^{1}H and 90.56 MHz for ^{13}C. These experiments were performed using an inverse-geometry 5 mm broad band probe. Pulse widths (90°) for ^{1}H and ^{13}C were 7.8 and 15.6 μsec, respectively. The COSY spectrum was recorded using the Bruker pulse program (*COSY90*) [6]. The NOESY experiment was performed using the Bruker pulse program (*noesytp*) [7]. The HMQC spectrum was acquired using the Bruker pulse program (*invbdgtp*) with the BIRD sequence optimized for direct couplings (165 Hz $^1J_{CH}$) [9]. The HMBC spectrum was obtained using the Bruker pulse program (*inv4lplrnd*) [10] optimized for 10 Hz $^3J_{CH}$ couplings.

3-Chloro-*N*-phenyl[1]benzothieno[2',3':3,4]naphtho[2,1-*b*]thiophene-2-carboxamide (**2**).

A solution of 3-chloro[1]benzothieno[2',3':3,4]naphtho[2,1-*b*]thiophene-2-carbonyl chloride **1** (1.0 g, 2.6 mmoles) and aniline (0.31 g, 3.3 mmoles) in dry chlorobenzene (40 ml) was refluxed for 4 hours. The reaction mixture was cooled and a crystalline precipitate was collected by filtration *in vacuo*. The solid thus obtained was recrystallized from benzene to give 0.92 g (80%) of **2** as colorless needles, mp 274-276°, sublimes 266°; ir: cm^{-1} 3300 (NH stretching), 1630 (C=O stretching); ^{1}H nmr (200 MHz, dimethyl-d$_6$ sulfoxide): δ 7.17 (t, J = 7.6 Hz, 1H, ArH), 7.40 (t, J = 7.6 Hz, 2H, ArH), 7.60-7.97 (m, 6H, ArH), 8.24 (d, J = 8.2 Hz, 1H, H11), 9.01, 9.24 and 9.65 (three d, J = 8.2 Hz, 3H, H4, H7 and H8), 10.47 (br s, 1H, exchangeable with deuterium oxide, NH); ms: (FAB) m/z 446 (MH$^+$ + 2, 1%), 444 (MH$^+$, 2%).

Anal. Calcd. for $C_{25}H_{14}ClNOS_2$: C, 67.64; H, 3.18; N, 3.16. Found: C, 67.40; H, 3.26; N, 3.41.

[1]Benzothieno[2",3":3',4']naphtho[1',2':4,5]thieno[2,3-*c*]quinolin-15(16*H*)-one (**3**).

A solution of **2** (100 mg, 0.22 mmole) in benzene (500 ml) containing triethylamine (*ca.* 0.5 ml) was irradiated for 2 hours with a 500 watt high pressure mercury vapor lamp. The solvent was evaporated *in vacuo* and the residue was triturated with methanol. After filtration the methanol insoluble solid was chromatographed on silica gel using chloroform as the eluting agent to give a yellow residue, which was recrystallized from chloroform to afford 20 mg (22%) of **3** as pale yellow granules, mp >300°; ir: cm^{-1} 3135, 3040 (NH stretching), 1650 (C=O stretching);

^{1}H nmr (500 MHz, a mixture of 0.7 ml of deuteriochloroform and 0.3 ml of deuterated trifluoroacetic acid): δ 7.54 (m, 1H, ArH), 7.62 (t, J = 8.1 Hz, 1H, ArH), 7.67-7.75 (m, 4H, ArH), 7.86 (t, J = 8.1 Hz, 1H, ArH), 8.09 (d, J = 8.1 Hz, 1H, ArH), 8.86, 8.91, 8.94 and 9.16 (four d, J = 8.1 Hz, 4H, H4, H9, H8 and H5); ms: (FAB) m/z 408 (MH$^+$, 4%); hrms: (FAB) m/z Calcd. for $C_{25}H_{14}NOS_2$: 408.0517. Found: 408.0557.

15-Chloro[1]benzothieno[2",3":3',4']naphtho[1',2':4,5]thieno-[2,3-*c*]quinoline (**4**).

A solution of **3** (100 mg, 0.25 mmole) in phosphorus oxychloride (3 ml) was refluxed for 4 hours. After refluxing, the reaction mixture was evaporated and ice-water (20 g) was poured onto the residue. The resulting mixture was basified with sodium carbonate and the precipitate was collected by filtration. The precipitate thus obtained was chromatographed on silica gel using a mixture of *n*-hexane and chloroform (1:1, v/v) as the eluting agent to give a yellow residue, which was recrystallized from a mixture of *n*-hexane and chloroform to afford 30 mg (29%) of **4** as pale yellow needles, mp >300°; ms: (FAB) m/z 428 (MH$^+$ + 2, 8%), 426 (MH$^+$, 16%); hrms: (EI) m/z Calcd. for $C_{25}H_{12}ClNS_2$: 425.0100. Found 425.0075 [13].

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