# Synthesis of Indeno[2,1-*b*][1,4]benzothiazine Derivatives from 2-Bromoinden-1-ones



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2-Bromoinden-1-ones **2** were condensed with 6-substituted 3-aminopyridine-2(1*H*)-thiones to produce a new type of 4-azaindeno[2,1-*b*][1,4]benzothiazine derivatives **3**. Substituted 6-phenylindeno[2,1-*b*][1,4]benzothiazines **4** were also prepared by reacting 2-bromo-5-methoxy- and 2,6-dibromo-5-methoxyinden-1-ones with *o*-aminobenzenethiol.

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The importance of 1,4-benzothiazine derivatives in dyestuffs [1] as well as in medicinal chemistry [2] has attracted a lot of attention. Armensie *et al* [3] reported pyrrolo[1,2,3-*de*][1,4]benzothiazine derivatives as biologically active compounds. In view of these findings it is interesting to synthesize compounds containing the 1,4-benzothiazine systems.

The present work represents the preparation of a new type of azabenzothiazine derivatives by the reaction of 2-bromoinden-1-ones **2** with 6-substituted 3-aminopyridine-2(1*H*)-thiones. The bromination of *o*-diacylbenzene with *N*-bromosuccinimide in acetic acid at 50-55° produced 2-bromo-3-methylinden-1-one **2** [4]. However, 2-bromo-3-phenylinden-1-one **2b** was obtained quantitatively by reacting an equimolar amounts of bromine and *o*-acetylbenzophenone in ice bath [4]. The reaction of **1c** under similar conditions yielded, after chromatographic separation, an orange product, 2,6-dibromo-5-methoxyinden-1-one **2d** (10%) and a yellow product 2-bromo-5-methoxyinden-1-one **2c** (66%). By use of bromine and **1c** in a molar ratio of 2:1, **2d** was isolated in 92% yield. The reaction between **2a-d** and 6-substituted 3-aminopyridine-2(1*H*)-thiones in ethanol at reflux temperature produces substituted indeno[2,1-*b*][1,4]benzothiazines **3a-h** in good yields.

In our previous paper we have reported the condensation products of 2-bromo-3-methyl- and 2-bromo-3-phenylinden-1-ones with *o*-aminobenzenethiol [4]. Now we have investigated analogous reactions with other substituted 2-bromoinden-1-ones.

In the nmr spectra of **2d**, **3d**, **3h**, and **4d** the characteristic signal in the lowest magnetic field was assigned to the proton on the adjacement carbon to the bromine substitution on the indene nucleus. The uv spectrum of the compounds having bromine substitution on the indene nucleus shows absorption at the longest wave-

Scheme 1

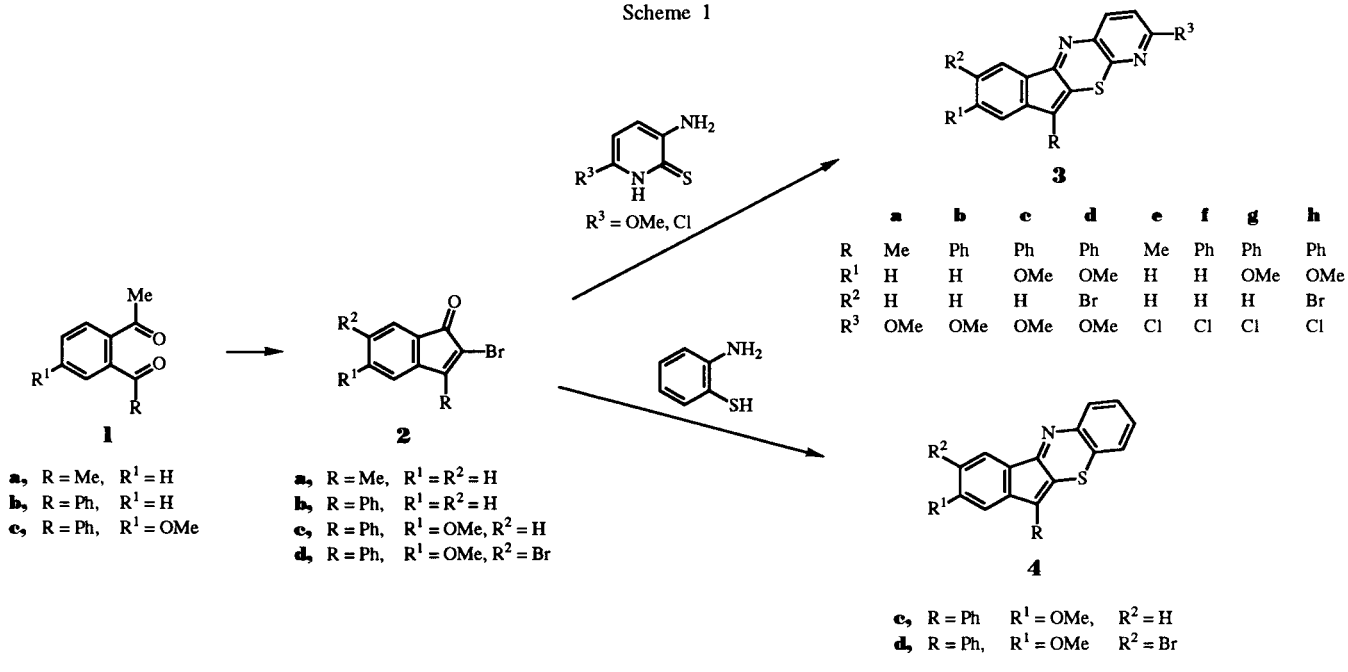

Table 1
Physical and Analytical Data for **2**, **3** and **4**

| Compound | R | $R_1$ | $R_2$ | $R_3$ | Yield (%) | Mp (°C) (Recrystallized from) | Molecular Formula | Elemental Analyses (%) Calcd./Found C | H | N | Br |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **2c** | Ph | OMe | H | – | 66 [a] | 134-136 | $C_{16}H_{11}BrO_2$ | 60.72 | 3.79 | – | 24.63 |
| | | | | | | Ethanol | •1/5 $C_2H_5OH$ (324.3) | 60.42 | 3.41 | – | 24.23 |
| **2d** | Ph | OMe | Br | – | 10 [a] | 195 | $C_{16}H_{10}Br_2O_2$ | 48.77 | 2.56 | – | 40.55 |
| | | | | | 92 [b] | Methanol | (394.1) | 48.99 | 2.53 | – | 40.48 |
| **3a** | Me | H | H | OMe | 22 | 198-201 | $C_{16}H_{12}N_2OS$ | 68.55 | 4.31 | 9.99 | |
| | | | | | | Methanol | (280.3) | 68.71 | 4.31 | 9.86 | |
| **3b** | Ph | H | H | OMe | 85 | 208-211 | $C_{21}H_{14}N_2OS$ | 73.66 | 4.12 | 8.18 | |
| | | | | | | Methanol | (342.4) | 73.71 | 4.03 | 8.04 | |
| **3c** | Ph | OMe | H | OMe | 81 | 231-233 | $C_{22}H_{16}N_2O_2S$ | 70.95 | 4.33 | 7.52 | |
| | | | | | | Methanol | (372.4) | 71.01 | 4.24 | 7.47 | |
| **3d** | Ph | OMe | Br | OMe | 76 | 282-285 | $C_{22}H_{15}BrN_2O_2S$ | 58.55 | 3.35 | 6.21 | |
| | | | | | | Benzene | (451.3) | 58.57 | 3.32 | 6.06 | |
| **3e** | Me | H | H | Cl | 47 | 202-204 | $C_{15}H_9ClN_2S$ | 62.92 | 3.50 | 9.53 | |
| | | | | | | Ethanol | •1/5 $C_2H_5OH$ (293.9) | 62.55 | 2.95 | 9.68 | |
| **3f** | Ph | H | H | Cl | 77 | 277-278 | $C_{20}H_{11}ClN_2S$ | 69.26 | 3.20 | 8.08 | |
| | | | | | | Benzene | (346.8) | 68.97 | 3.49 | 7.85 | |
| **3g** | Ph | OMe | H | Cl | 81 | 286-288 | $C_{21}H_{13}ClN_2OS$ | 66.93 | 3.48 | 7.43 | |
| | | | | | | Benzene | (376.9) | 66.92 | 3.42 | 7.29 | |
| **3h** | Ph | OMe | Br | Cl | 83 | 316-317 | $C_{21}H_{12}BrClN_2OS$ | 55.34 | 2.65 | 6.15 | |
| | | | | | | Benzene | (455.8) | 55.22 | 2.65 | 6.01 | |
| **4c** | Ph | OMe | H | – | 75 | 187-189 | $C_{22}H_{15}NOS$ | 77.39 | 4.43 | 4.10 | |
| | | | | | | Ethanol | (341.4) | 77.25 | 4.24 | 3.88 | |
| **4d** | Ph | OMe | Br | – | 82 | 261-262 | $C_{22}H_{14}BrNOS$ | 62.87 | 3.36 | 3.33 | |
| | | | | | | Ethanol | (420.3) | 63.20 | 3.25 | 3.19 | |

[a] Compounds **2c** and **2d** were obtained by the use of a 1:1 molar ratio of **1c** and bromine. [b] Molar ratio of **1c** and bromine of 1:2 was used.

length compared to the unsubstituted and the methoxy substituted compounds.

The structures of the new compounds were determined by elemental analyses and their spectroscopic data. The reactions investigated are summarized in Scheme 1. The analytical and spectral data for the compounds obtained in these reactions are listed in Tables 1 and 2.

## EXPERIMENTAL

Melting points were determined on a Yanaco micromelting point apparatus and are uncorrected. The infrared spectra were taken on a JASCO A-102 spectrometer using potassium bromide pellets and ultraviolet spectra were recorded with a JASCO UVI-DEC-505 in methanol solution unless otherwise noted. The nuclear magnetic resonance spectra were measured on Varian Gemini-200 and Hitachi R-90 spectrometers in deuteriochloroform, using tetramethylsilane as the internal standard. Mass spectra were obtained with a Hitachi M-2000 spectrometer. For column chromatography silica gel (kiesel gel 60, Merck, 70-230 mesh) was used. Elemental analyses were performed at the Elemental Analyses Center in Kyoto University.

Preparation of 2-Bromo-5-methoxy-3-phenylinden-1-one **2c** and 2,6-Dibromo-5-methoxyinden-1-one **2d**.

To a suspension of 20 mmoles of **1c** in acetic acid was added 2 drops of hydrobromic acid (47%), the reaction mixture was cooled in ice bath, and 20 mmoles of bromine was added dropwise with constant stirring. After the complete addition of bromine stirring was continued for a further 2 hours in an ice bath. The solid was collected by filtration, washed with aqueous ethanol (v/v). The mixture was chromatographed on a silica gel column using benzene as the eluent. From the first fraction **2d** and from the next subsequent fraction **2c** was obtained. Using a 2:1 molar ratio of bromine and **1c**, 92% of **2d** was obtained.

General Procedure for the Preparation of Substituted 4-Azaindeno[2,1-*b*][1,4]benzothiazines **3a-h**.

Table 2

Spectroscopic Data for **2**, **3** and **4**

| Compound | Mass (relatative intensity) | IR ($cm^{-1}$) | UV λ max (nm) (log ε) | H-NMR δ (ppm) [a] [c] |
|---|---|---|---|---|
| **2c** | 314/316 (100/100) | 1705 (C=O) 1218, 1020 | 410 (2.90), 340 (3.76) 292 (4.06), 260 (4.53) | 3.83 (*s*, 3H, OMe), 6.48-6.68 (m, 2H, arom), 7 .46-7.60 (m, 6H, arom) |
| **2d** | 392/394/396 (15/41/10) | 1718 (C=O) 1260, 1022 | 430 (2.94), 304 (4.07) 268 (4.62) | 3.90 (*s*, 3H, OMe), 6.68 (*s*, 1H, arom), 7.46-7.69 (m, 5H, arom), 7.73 (*s*, 1H, arom) |
| **3a** | 280 (100) | 1618 (C=N), 1260, 1015 | 505 (3.58), 377 (3.99), 330 (4.32), 282 (4.39), 246 (4.38) | 2.23 (*s*, 3H, Me), 3.99 (*s*, 3H, OMe), 6.71 (m, 1H, arom), 7.25-7.36 (m, 2H, arom), 7.46-7.56 (m, 1H, arom), 7.96 (m, 1H, arom), 8.08 (m, 1H, arom) |
| **3b** | 342 (100) | 1605 (C=N), 1260, 1020 | 519 (3.68), 388 (4.03), 368 (4.14), 333 (4.34), 287 (4.44), 276 (4.48), 248 (4.49) | 3.98 (*s*, 3H, OMe), 6.76 (*s*, 1H, arom), 7.32-7.82 (m, 8H, arom), 8.02 (m, 1H, arom), 8.20 (m, 1H, arom) |
| **3c** | 372 (100) | 1615 (C=N), 1255, 1025 | 504 (3.59), 396 (4.26), 332 (4.34), 266 (4.67) | 3.90 (*s*, 3H, OMe), 3.95 (*s*, 3H, OMe), 6.68-7.13 (m, 3H, arom), 7.35-7.81 (m, 5H, arom), 7.99 (m, 1H, arom), 8.11 (m, 1H, arom) |
| **3d** | 450/452 (96/100) | 1600 (C=N), 1265, 1020 | 524 (3.57), 414 (4.07), 397 (4.11), 334 (4.25), 272 (4.50) | 3.95 (*s*, 3H, OMe), 3.99 (*s*, 3H, OMe), 6.78 (m, 1H, arom), 7.10-8.10 (m, 7H, arom), 8.38 (*s*, 1H, arom), |
| **3e** | 284/286 (100/40) | 1605 (C=N) | 504 (3.45), 365 (3.92), 347 (4.21), 334 (4.22), 280 (4.57), 248 (4.34) | 2.21 (*s*, 3H, Me), 7.19-7.32 (m, 4H, arom), 7.89-7.99 (m, 2H, arom) |
| **3f** | 346/348 (100/40) | 1610 (C=N) | 525 (3.42), 377 (3.77), 354 (4.01), 338 (4.06), 278 (4.47), 271 (4.47) 254 (4.38) | 7.30-7.65 (m, 7H, arom), 7.73-7.75 (m, 2H, arom), 8.06-8.24 (m, 2H, arom) |
| **3g** [b] | 376/378 (100/45) | 1590 (C=N) 1235, 1035 | 514 (3.51), 412 (4.17), 393 (4.23), 295 (4.48), 270 (4.61) | 3.93 (*s*, 3H, OMe), 6.87-6.92 (m, 1H, arom), 7.14-7.15 (m, 1H, arom), 7.30-7.62 (m, 4H, arom), 7.72-7.77 (m, 2H, arom), 8.03-8.16 (m, 2H, arom) |
| **3h** [b] | 454/456/458 (74/100/32) | 1590 (C=N) 1245, 1040 | 533 (3.49), 409 (4.18), 390 (4.23), 299 (4.56), 278 (4.63) | 3.98 (*s*, 3H, OMe), 7.11 (*s*, 1H, arom), 7.32-7.75 (m, 6H, arom), 8.07 (m, 1H, arom), 8.35 (*s*, 1H, arom) |
| **4c** | 341 (100) | 1605 (C=N) 1240, 1015 | 520 (3.48), 387 (4.30), 294 (4.60), 269 (4.64), 240 (4.30) | 3.90 (*s*, 3H, OMe), 6.84 (m, 1H, arom), 7.10-7.98 (m, 10H, arom), 8.17 (m, 1H, arom) |
| **4d** | 419/421 (26/25) | 1598 (C=N), 1255, 1045 | 538 (3.44), 400 (4.17), 385 (4.22), 300 (4.64), 272 (4.70) | 3.98 (*s*, 3H, OMe), 7.12 (*s*, 1H, arom), 7.35-8.02 (m, 9H, arom), 8.40 (*s*, 1H, arom) |

[a] Deuteriochloroform was used as the solvent. [b] The uv spectra were recorded in chloroform solution. [c] *s* = singlet, m = multiplet.

A reaction mixture of **2a-d**, 1 mmole and 6-substituted 3-aminopyridine-2(1*H*)-thione, 1.2 mmoles was stirred under reflux for 2-5 hours in ethanol. After the mixture was evaporated *in vacuo* the residue was chromatographed on a silica gel column using benzene as the eluent. In some cases, the products were precipitated during the course of the reaction. They were filtered and recrystallized from the appropriate solvent.

Preparation of Substituted Indeno[2,1-*b*][1,4]benzothiazines **4c-d**.

To a suspension of **2c** or **2d** (1 mmole) in ethanol *o*-aminobenzenethiol (1 mmole) was added and the resulting mixture was stirred at room temperature for 3 hours. The precipitated product was collected by filtration and column chromatography on silica gel using benzene as the eluent.

## REFERENCES AND NOTES

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