HETEROCYCLES, Vol. 75, No. 12, 2008, pp. 3025 - 3033. © The Japan Institute of Heterocyclic Chemistry
Received, 25th June, 2008, Accepted, 28th July, 2008, Published online, 31st July, 2008. COM-08-11473

SYNTHESIS OF 1-IMINOISOTHIOCHROMAN DERIVATIVES BASED ON REACTIONS OF 2-LITHIO-β-METHOXYSTYRENE DERIVATIVES WITH ISOTHIOCYANATES FOLLOWED BY ACID-MEDIATED CYCLIZATION

Kazuhiro Kobayashi,* Daisuke Nakai, Kazutaka Hayashi, and Hisatoshi Konishi

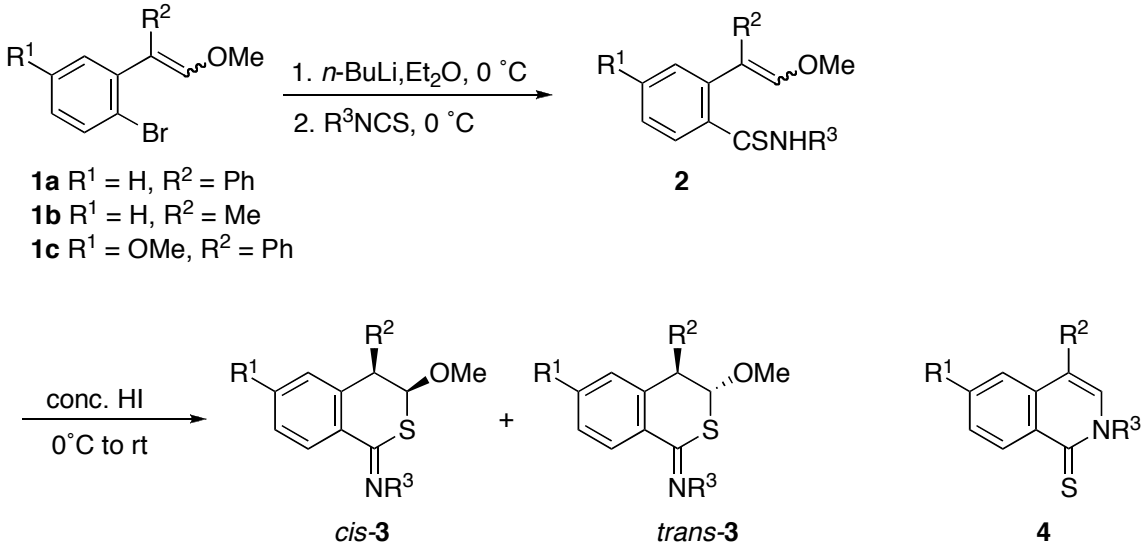
Division of Applied Chemistry, Department of Chemistry and Biotechnology, Graduate School of Engineering, Tottori University, 4-101 Koyama-minami, Tottori 680-8552, Japan

Abstract - The reaction of 2-lithio-β-methoxystyrene derivatives with isothiocyanates yields the corresponding 2-(2-methoxyvinyl)thiobenzamide derivatives. Treatment of these thiobenzamides with concentrated hydriodic acid affords 1-imino-3-methoxyisothiochroman (1-imino-3-methoxy-3,4-dihydro-1*H*-2-benzothiopyran) derivatives.

In the course of our studies on the synthesis of heterocyclic compounds utilizing 2-lithio-β-methoxystyrene derivatives,[1] we reported that these lithium compounds reacted with isocyanates to give 2-(2-methoxyvinyl)benzamide derivatives, which in turn were treated with a catalytic amount of concentrated hydriodic acid to give isoquinolin-1(2*H*)-one derivatives.[2] In continuation of this study, we became interested in investigating a similar reaction sequence using isothiocyanates in place of isocyanates, which should lead to the formation of isoquinoline-1(2*H*)-thione derivatives (**4**). However, we found that the sequence gave 1-imino-3-methoxyisothiochroman (1-imino-3-methoxy-3,4-dihydro-1*H*-2-benzothiopyran) derivatives (**3**) in practice. In this paper, we wish to describe the results of our study on the reactions of 2-lithio-β-methoxystyrene derivatives, derived from 2-bromo-β-methoxystyrene derivatives (**1**), with isothiocyanates and subsequent treatment of the resulting 2-(2-methoxyvinyl)thiobenzamide derivatives (**2**) with concentrated hydriodic acid, affording **3**. So far, few methods have been known for the preparation of 1-iminoisothiochroman derivatives,[3] though several methods are available for the preparation of isothiochroman derivatives,[4] and some of these derivatives have been reported to exhibit biological activities.[4b]

The preparation of 1-imino-3-methoxyisothiochroman derivatives (**3**) from 2-bromo-β-methoxystyrene derivatives (**1**) was conducted as illustrated in Scheme 1. Thus, the reaction of 2-lithio-β-methoxystyrene

derivatives, easily generated from **1** and butyllithium,[1] with isothiocyanates afforded the corresponding thiobenzamide derivatives (**2**). The yields of **2** were generally fair, though benzyl isothiocyanates bearing acidic α-hydrogens provided the corresponding product (**2j**) in rather lower yield (Table 1, Entry 10). Although the products **2** were obtained as inseparable mixtures of stereoisomers in general, the stereoisomeric products from cyclohexyl isothiocyanate (*E*- and *Z*-**2e**) were easily separable by preparative TLC on silica gel (Entry 5). The stereochemistries of the products were determined by their ^{1}H NMR spectra. Each of the *E*-isomers exhibits the signal assignable to the α-vinyl proton of methoxyvinyl moiety at downfield compared to that of each of *Z*-isomers.



Scheme 1

Table 1. Preparation of 1-Iminoisothiochromane Derivatives (**3**) *via* **2**

Entry	**1**	R	**2** (Yield/%;[a,b] *E*:*Z*)	Temp	Time	**3** (Yield/%)[a]
1	**1a**	Ph	**2a** (71; 5:5)	0 ˚C	1.5 h	*cis*-**3a** (31), *trans*-**3a** (53)[c]
2	**1a**	*m*-Tol	**2b** (69; 6:4)	0 ˚C	3 h	*cis*-**3b** (23), *trans*-**3b** (59)[c]
3	**1a**	4-BrC_6H_4	**2c** (64; 6:4)	0 ˚C	20 min	*cis*-**3c** (22), *trans*-**3c** (56)[c]
4	**1a**	2-MeOC_6H_4	**2d** (59; 5:5)	rt	1 d	*trans*-**3d** (52)[d]
5	**1a**	*c*-Hex	**2e** (52; 5:5)[c]	0 ˚C	5 min	*cis*-**3e** (19), *trans*-**3e** (31)[c,e]
6	**1b**	Ph	**2f** (62; 7:3)	rt	1 d	*cis*-**3f** (29), *trans*-**3f** (46)[c]
7	**1b**	*m*-Tol	**2g** (64; 6:4)	rt	18 h	*cis*-**3g** (23), *trans*-**3g** (51)[c]
8	**1b**	4-BrC_6H_4	**2h** (66; 7:3)	rt	5 h	*cis*-**3h** (21), *trans*-**3h** (47)[c]
9	**1c**	*m*-Tol	**2i** (64; 8:2)	0 ˚C	45 min	*cis*-**3i** (11), *trans*-**3i** (47)[c]
10	**1c**	Bn	**2j** (37; 8:2)	0 ˚C	10 min	*trans*-**3j** (55)[d]

[a]Isolated yields. [b]Obtained as mixtures of stereoisomers unless otherwise stated. The ratios were determined by ^{1}H NMR spectra. [c]Separable by preparative TLC on silica gel. [d]Only trace amounts of *cis*-isomers were obtained. [e]The same result was obtained with each isomer of **2e**.

Initially, compounds (**2**) were reacted with a catalytic amount of hydriodic acid in a manner similar to that

for the preparation of isoquinolin-1(2*H*)-ones from 2-(β-methoxyvinyl)benzamide derivatives.[3b] However, the reactions did not complete and these gave rather lower yields of 1-imino-3-methoxyisothiochroman derivatives (**3**), and considerable amounts of the starting materials were recovered. Further investigation revealed that the reactions proceeded in appropriate extent by treating **2** with a stoichiometric amount of concentrated hydriodic acid in acetonitrile to afford satisfactory yields of **3**, as summarized in Table 1. The *N*-(alkyl)thiobenzamides (**2e**) and (**2j**) reacted immediately to give the corresponding products **3e** and **3j** (Entries 5 and 10), respectively, but the yields were somewhat lower than those using *N*-(aryl)thiobenzamides. *N*-(2-Methoxyphenyl)-2-(2-methoxy-1-phenylethenyl)thiobenzamide (**2d**) and the 2-(2-methylethenyl)thiobenzamides (**2f–h**) did not undergo cyclization so smoothly at 0 ˚C, and required longer reaction times at an higher temperature, thus leading to somewhat diminished yields of the desired products (Entries 4 and 6–8). Separate experiments using stereoisomers (*E*)- and (*Z*)-(**2e**) gave the same result (Entry 5). The uses of **2d** and **2j** provided the corresponding *trans*-isomers almost exclusively, and only trace amounts of *cis*-isomers were obtained as mixtures with not fully identified products (Entries 4 and 10). The stereochemistry between 3- and 4-substituents of the products (**3**) could not be determined unambiguously. We determined tentatively the major isomers to be *trans* and the minor isomers to be *cis*. The stereochemistry of the imino moiety is probably *E*, but this determination is only tentative.

The iminoisothiochroman structure of products (**3**) was confirmed by the spectral data. For example, the ^{13}C NMR spectra for compound (**3b**) revealed the signals assignable to the imino carbon at δ 157.38 (*cis* isomer) and 158.10 (*trans* isomer), the IR spectra exhibited absorption bands at 1589 and 1582 cm^{-1}, respectively, due to imine functions. No signals were observed at δ ~ 200 assignable to thiocarbonyl carbon in the ^{13}C NMR spectra. Although the IR spectra for **2b** exhibited a strong absorption band at 1364 cm^{-1} probably due to a thiocarbonyl function, no absorption bands ~ 1350 cm^{-1} were observed in the IR spectra for **3b**. These results can exclude the possibility of the thiolactam structure (**4**). The preferable formation of **3** may be attributable to the higher nucleophilicity of sulfur atom than that of nitrogen atom, as explained for the formation of related systems in our previous reports.[5]

The foregoing results indicate that preparation of 1-iminoisothiochroman derivatives can be achieved using 2-bromo-β-methoxystyrene derivatives and isothiocyanates in two steps. To the best of our knowledge, this is the first method for the general preparation of this class of derivatives. The ease of operations as well as readily availability of the starting materials make this method attractive.

EXPERIMENTAL

The melting points were determined on a Laboratory Devices MEL-TEMP II melting-point apparatus and are uncorrected. The IR spectra were recorded on a Shimadzu FTIR-8300 spectrometer. ^{1}H NMR spectra were determined using $SiMe_4$ as an internal reference in $CDCl_3$ with a JEOL ECP500 FT NMR

spectrometer operating at 500 MHz. ^{13}C NMR spectra were determined using $SiMe_4$ as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz in $CDCl_3$. Low-resolution mass spectra (EI, 70 eV) were recorded on a JEOL JMS-AX505 HA spectrometer. Thin-layer chromatography (TLC) was carried out using Merck Kieselgel 60 PF_{254}. Column chromatography was performed using Merck Kieselgel 60 (0.063–0.200 mm). All of the solvents used were dried over the appropriate drying agents and distilled under argon prior to use.

Starting Materials. 1-Bromo-2-(2-methoxyvinyl)benzenes **1a**,[1a] **1b**,[6] and **1c**[1a] were prepared by appropriate previously reported procedures. All other chemicals used in this study were commercially available.

Typical Procedure for the Preparation of 2-(2-Methoxyvinyl)thiobenzamide Derivatives (2). *N*-Phenyl-2-(2-methoxy-1-phenylethenyl)thiobenzamide (2a). To a stirred solution of **1** (0.24 g, 0.83 mmol) in Et_2O (4 mL) at 0 °C was added dropwise *n*-BuLi (1.6 M in hexane; 0.83 mmol). After 1 h, PhNCS (0.12 g, 0.91 mmol) was added and stirring was continued for an additional 30 min. The mixture was quenched with saturated aqueous NH_4Cl (15 mL) and extracted with Et_2O three times (10 mL each). The combined extracts were dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel to afford **2a** (0.21 g, 71%): a yellow solid; mp 130–140 °C; a mixture of stereoisomers (*E*:*Z* = *ca.* 1:1); IR (neat) 3249, 3192, 1628, 1369 cm^{-1}; ^1H NMR δ 3.74 (1.5H, s), 3.75 (1.5H, s), 6.45 (0.5H, s), 6.68 (0.5H, s), 7.11–7.46 (12H, m), 7.57 (1H, d, *J* = 7.3 Hz), 7.86 (1H, dd, *J* = 7.3, 1.4 Hz), 8.73 (0.5H, br s), 9.23 (0.5H, br s). Anal. Calcd for $C_{22}H_{19}NOS$: C, 76.49; H, 5.54; N 4.05. Found: C, 76.28; H, 5.60; N, 4.02.

2-(2-Methoxy-1-phenylethenyl)-*N*-(3-methylphenyl)thiobenzamide (2b): a yellow viscous oil; R_f 0.27 (1:5 AcOEt–hexane); a mixture of stereoisomers (*E*:*Z* = *ca.* 6:4); IR (neat) 3312, 1634, 1367 cm^{-1}; ^1H NMR δ 2.28 (1.2H, s), 2.33 (1.8H, s), 3.73 (1.8H, s), 3.76 (1.2H, s), 6.44 (0.4H, s), 6.68 (0.6H, s), 6.95–7.46 (12H, m), 7.85 (1H, td, *J* = 7.3, 1.4 Hz), 8.67 (0.4H, br s), d 9.17 (0.6H, s). Anal. Calcd for $C_{23}H_{21}NOS$: C, 76.85; H, 5.89; N 3.90. Found: C, 76.74; H, 6.11; N, 3.75.

***N*-(4-Bromophenyl)-2-(2-methoxy-1-phenylethenyl)thiobenzamide (2c):** a yellow viscous oil; R_f 0.30 (1:5 AcOEt–hexane); a mixture of stereoisomers (*E*:*Z* = *ca.* 6:4); IR (neat) 3288, 3187, 1634, 1360 cm^{-1}; ^1H NMR δ 3.73 (1.8H, s), 3.75 (1.2H, s), 6.42 (0.4H, s), 6.66 (0.6H, s), 7.08–7.31 (6H, m), 7.37–7.48 (6H, m), 7.82–7.84 (1H, m), 8.67 (0.4H, br s), 9.15 (0.6H, s). Anal. Calcd for $C_{22}H_{18}BrNOS$: C, 62.27; H, 4.28; N 3.30. Found: C, 62.27; H, 4.47; N, 3.28.

***N*-(2-Methoxyphenyl)-2-(2-methoxy-1-phenylethenyl)thiobenzamide (2d):** a yellow solid; mp 94–103 °C; a mixture of stereoisomers (*E*:*Z* = *ca.* 5:5); IR (KBr) 3342, 1628, 1373 cm^{-1}; ^1H NMR δ 3.61 (1.5H, s), 3.65 (1.5H, s), 3.67 (1.5H, s), 3.70 (1.5H, s), 6.48 (0.5H, s), 6.54 (0.5H, s), 6.82–6.96 (2H, m), 7.11–7.25 (5H, m), 7.32–7.42 (4H, m), 7.80 (0.5H, dd, *J* = 7.3, 1.4 Hz), 7.84 (0.5H, dd, *J* = 7.3, 1.4 Hz), 8.91 (0.5H, dd, *J* = 7.8, 1.4 Hz), 8.93 (0.5H, dd, *J* = 7.3, 1.4 Hz), 9.42 (0.5H, br s), 9.58 (0.5H, br s). Anal. Calcd for

$C_{23}H_{21}NO_2S$: C, 73.57; H, 5.64; N 3.73. Found: C, 73.39; H, 5.90; N, 3.40.

***N*-Cyclohexyl-2-(2-methoxy-1-phenylethenyl)thiobenzamide (2e).** Although this product was obtained as a mixture of stereoisomers (*E*:*Z* = *ca.* 5:5), an analytical specimen of each isomer was isolated by fractional column chromatography on silica gel. *E*-**2e**: a yellow viscous oil; R_f 0.30 (1:7 AcOEt–hexane); IR (neat) 3323, 1636, 1386 cm^{-1}; ^1H NMR δ 1.02–1.18 (3H, m), 1.32–1.41 (2H, m), 1.61–1.68 (3H, m), 1.99–2.05 (2H, m), 3.75 (3H, s), 4.31–4.38 (1H, m), 6.69 (1H, s), 7.11–7.16 (4H, m), 7.22 (2H, dd, *J*= 7.8, 7.3 Hz), 7.33–7.39 (2H, m), 7.70 (1H, br d, *J*= 6.9 Hz), 7.77 (1H, dd, *J* = 7.8, 1.4 Hz). Anal. Calcd for $C_{22}H_{25}NOS$: C, 75.17; H, 7.17; N 3.98. Found: C, 75.04; H, 7.06; N, 3.82. *Z*-**2e**: a yellow viscous oil; R_f 0.36 (1:7 AcOEt–hexane); IR (neat) 3364, 1634, 1387 cm^{-1}; ^1H NMR δ 0.80–0.87 (2H, m), 0.99–1.06 (1H, m), 1.25–1.32 (2H, m), 1.50–1.55 (3H, m), 1.82–1.84 (2H, m), 3.78 (3H, s), 4.20–4.28 (1H, m), 6.35 (1H, s), 7.10 (1H, br d, *J*= 6.9 Hz), 7.16–7.21 (2H, m), 7.30 (2H, t, *J*= 7.3 Hz), 7.32–7.36 (2H, m), 7.45–7.48 (2H, m), 7.74 (1H, dd, *J*= 7.8, 1.4 Hz). Anal. $C_{22}H_{25}NOS$: C, 75.17; H, 7.17; N 3.98. Found: C, 74.96; H, 7.23; N, 3.77.

2-(2-Methoxy-1-methylethenyl)-*N*-(phenyl)thiobenzamide (2f): a yellow solid; mp 82–86 °C; a mixture of stereoisomers (*E*:*Z* = *ca.* 7:3); IR (KBr disk) 3219, 1655, 1362 cm^{-1}; ^1H NMR δ 1.83 (0.9H, s), 1.96 (2.1H, d, *J* = 1.4 Hz), 3.60 (0.9H, s), 3.70 (2.1H, s), 6.06 (0.3H, q, *J* = 1.4 Hz), 6.34 (0.7H, q, *J* = 1.4 Hz), 6.59 (0.3H, d, *J* = 7.3 Hz), 7.07–7.21 (1.7H, m), 7.27–7.46 (4.2H, m), 7.75 (1.4H, d, *J* = 7.8 Hz), 7.85 (1.4H, dd, *J* = 7.8, 7.3 Hz), 9.05 (0.7H, br s), 9.47 (0.3H, br s). Anal. Calcd for $C_{17}H_{17}NOS$: C, 72.05; H, 6.05; N 4.94. Found: C, 72.04; H, 6.06; N, 4.82.

2-(2-Methoxy-1-methylethenyl)-*N*-(3-methylphenyl)thiobenzamide (2g): a yellow oil; R_f 0.33 (1:5 AcOEt–hexane); a mixture of stereoisomers (*E*:*Z* = *ca.* 6:4); IR (neat) 3285, 1655, 1611, 1367 cm^{-1}; ^1H NMR δ 1.84 (1.2H, d, *J* = 1.4 Hz), 1.96 (1.8H, d, *J* = 1.4 Hz), 2.40 (3H, s), 3.60 (1.2H, s), 3.70 (1.8H, s), 6.06 (0.4H, q, *J* = 1.4 Hz), 6.33 (0.6H, q, *J* = 1.4 Hz), 7.08–7.20 (2H, m), 7.29–7.40 (4H, m), 7.52–7.59 (1H, m), 7.77 (0.4H, dd, *J* = 7.8, 1.4 Hz), 7.85 (0.6H, dd, *J* = 7.8, 1.4 Hz), 9.00 (0.6H, br s), 9.41 (0.4H, br s). Anal. Calcd for $C_{18}H_{19}NOS$: C, 72.69; H, 6.44; N 4.71. Found: C, 72.59; H, 6.70; N, 4.91.

***N*-(4-Bromophenyl)-2-(2-methoxy-1-methylethenyl)thiobenzamide (2h):** a yellow solid; mp 86–90 °C; a mixture of stereoisomers (*E*:*Z* = *ca.*7:3); IR (KBr) 3207, 1655, 1364 cm^{-1}; ^1H NMR δ 1.81 (0.9H, d, *J* = 1.4 Hz), 1.93 (2.1H, d, *J* = 1.4 Hz), 3.59 (0.9H, s), 3.70 (2.1H, s), 6.05 (0.3H, q, *J* = 1.4 Hz), 6.32 (0.7H, q, *J* = 1.4 Hz), 7.15 (0.3H, dd, *J* = 7.8, 1.4 Hz), 7.20 (0.7H, d, *J* = 7.8, 1.4 Hz), 7.29–7.41 (2H, m), 7.54 (0.6H, d, *J* = 9.2 Hz), 7.56 (1.4H, d, *J* = 8.7 Hz), 7.67 (1.4H, d, *J* = 8.7 Hz),7.75 (0.3H, dd, *J* = 7.8, 1.4 Hz), 7.76 (0.6H, d, *J* = 9.2 Hz), 7.84 (0.7H, dd, *J* = 7.8, 1.4 Hz), 9.02 (0.7H, br s), 9.46 (0.3H, br s). Anal. Calcd for $C_{17}H_{16}BrNOS$: C, 56.36; H, 4.45; N 3.87. Found: C, 56.33; H, 4.70; N, 3.87.

4-Methoxy-2-(2-methoxy-1-phenylethenyl)-*N*-(3-methylphenyl)thiobenzamide (2i): a yellow oil; R_f 0.33 (1:4 AcOEt–hexane); a mixture of stereoisomers (*E*:*Z* = *ca.* 8:2); IR (neat) 3317, 1639, 1362 cm^{-1}; ^1H NMR δ 2.27 (0.6H, s), 2.31 (2.4H, s), 3.75 (2.4H, s), 3.76 (0.6H, s), 3.84 (2.4H, s), 3.85 (0.6H, s), 6.45

(0.2H, s), 6.68 (0.8H, s), 6.74 (0.8H, d, *J* = 2.6 Hz), 6.79 (0.2H, d, *J* = 2.6 Hz), 6.92–7.06 (2H, m), 7.12–7.30 (8H, m), 7.47 (0.2H, d, *J* = 8.7 Hz), 7.92 (0.8H, d, *J* = 8.7 Hz), 8.75 (0.2H, br s), 9.14 (0.8H, br s). Anal. Calcd for $C_{24}H_{23}NO_2S$: C, 74.00; H, 5.95; N 3.60. Found: C, 73.98; H, 5.98; N, 3.72.

***N*-Benzyl-4-methoxy-2-(2-methoxy-1-phenylethenyl)thiobenzamide (2j):** a mixture of stereoisomers (*E*:*Z* = *ca*. 8:2); IR (neat) 3320, 1644, 1327 cm^{-1}; ^1H NMR δ 3.31 (2.4H, s), 3.71 (0.6H, s), 3.78 (2.4H, s), 3.81 (0.6H, s), 4.54 (0.4H, d, *J* = 5.0 Hz), 4.73 (1.6H, d, *J* = 5.0 Hz), 6.34 (0.2H, s), 6.35 (0.8H, s), 6.60 (0.8H, d, *J* = 2.3 Hz), 6.73 (0.2H, d, *J* = 2.7 Hz), 6.88–7.07 (3H, m), 7.14–7.23 (5H, m), 7.29–7.37 (3H, m), 7.52 (0.2H, br s), 7.84 (0.2H, d, *J* = 8.7 Hz), 7.90 (0.8H, d, *J* = 8.7 Hz), 8.05 (0.8H, br s). Anal. Calcd for $C_{24}H_{23}NO_2S$: C, 74.00; H, 5.95; N 3.60. Found: C, 73.82; H, 6.00; N, 3.54.

Typical Procedure for the Preparation of 1-Imino-3,4-dihydro-1*H*-2-benzothiopyran Derivatives (3).

3-Methoxy-4-phenyl-1-phenylimino-3,4-dihydro-1*H*-2-benzothiopyran (3a). To a stirred solution of **1a** (0.18 g, 0.53 mmol) in MeCN (4 mL) at 0 ˚C was added concentrated aqueous HI (69 mg, 0.53 mmol); the mixture was stirred for 1.5 h at the same temperature. Saturated aqueous $NaHCO_3$ (10 mL) was added, and MeCN was evaporated. The organic materials was extracted with Et_2O twice (10 mL each), and the combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was separated by preparative TLC on silica gel to give *cis*-**3a** (57 mg, 31%) and *trans*-**3a** (97 mg, 53%). *cis*-**3a**: a pale-yellow solid; mp 135–140 ˚C (hexane–Et_2O); IR (KBr) 1587 cm^{-1}; ^1H NMR δ 3.39 (3H, s), 4.76 (1H, d, *J* = 3.2 Hz), 4.94 (1H, d, *J* = 3.2 Hz), 6.87 (2H, dd, *J* = 7.3, 1.4 Hz), 7.10 (1H, t, *J* = 7.3 Hz), 7.14 (1H, dd, *J* = 7.8, 7.3 Hz), 7.22–7.34 (5H, m), 7.41–7.50 (4H, m), 8.40 (1H, dd, *J* = 7.8, 1.8 Hz); MS *m*/*z* 345 (M^+, 89), 271 (100). Anal. Calcd for $C_{22}H_{19}NOS$: C, 76.49; H, 5.54; N 4.05. Found: C, 76.48; H, 5.67; N, 3.99. *trans*-**3a**: a pale-yellow solid; mp 146–150 ˚C (hexane–Et_2O) IR (KBr) 1583 cm^{-1}; ^1H NMR δ 3.33 (3H, s), 4.74 (1H, s), 4.97 (1H, d, *J* = 1.8 Hz), 6.83 (1H, d, *J* = 7.3 Hz), 6.98 (2H, dd, *J* = 8.2, 0.9 Hz), 7.16 (1H, tt, *J* = 7.3, 0.9 Hz), 7.33–7.45 (9H, m), 8.31 (1H, dd, *J* = 7.8, 1.3 Hz); MS *m*/*z* 345 (M^+, 82), 271 (100). Anal. Calcd for $C_{22}H_{19}NOS$: C, 76.49; H, 5.54; N 4.05. Found: C, 76.39; H, 5.80; N, 3.99.

3-Methoxy-1-(3-methylphenyl)-4-phenyl-3,4-dihydro-1*H*-2-benzothiopyran (3b). *cis*-**3b**: a yellow solid; mp 162–166 ˚C (hexane–Et_2O); IR (KBr) 1589 cm^{-1}; ^1H NMR δ 2.33 (3H, s), 3.39 (3H, s), 4.76 (1H, d, *J* = 3.2 Hz), 4.94 (1H, d, *J* = 3.2 Hz), 6.66 (1H, d, *J* = 7.8 Hz), 6.69 (1H, s), 6.91 (1H, d, *J* = 7.8 Hz), 7.14 (2H, d, *J* = 7.3 Hz), 7.18–7.25 (2H, m), 7.31 (2H, dd, *J* = 7.8, 7.3 Hz), 7.40–7.52 (3H, m), 8.39 (1H, dd, *J* = 7.3, 1.8 Hz); ^{13}C NMR δ 21.50, 51.77, 56.83, 88.70, 116.44, 120.18, 120.24, 124.90, 126.83, 127.24, 127.82, 128.50, 128.58, 128.72, 130.86, 131.54, 132.70, 138.78, 139.13, 150.84, 157.38; MS *m*/*z* 359 (M^+, 100). Anal. Calcd for $C_{23}H_{21}NOS$: C, 76.85; H, 5.89; N 3.90. Found: C, 76.53; H, 6.13; N, 3.91. *trans*-**3b**: a yellow solid; mp 119–121 ˚C (hexane–Et_2O); IR (KBr) 1582 cm^{-1}; ^1H NMR δ 2.38 (3H, s), 3.33 (3H, s), 4.74 (1H, s), 4.97 (1H, d, *J* = 1.8 Hz), 6.78 (1H, d, *J* = 7.3 Hz), 6.79 (1H, s), 6.83 (1H, d, *J* = 7.3 Hz), 6.97 (1H, d, *J* = 7.3 Hz), 7.28 (1H, t, *J* = 7.3 Hz), 7.33–7.45 (7H, m), 8.29 (1H, dd, *J* = 7.8, 1.4 Hz); ^{13}C NMR δ 21.54, 52.75, 57.32, 86.10, 116.65, 120.34, 120.39, 125.02, 126.79, 127.12, 127.62,

128.60, 128.85, 130.20, 130.85, 132.87, 138.24, 138.91, 139.25, 150.91, 158.10; MS *m/z* 359 (M^+, 84), 283 (100). Anal. Calcd for $C_{23}H_{21}NOS$: C, 76.85; H, 5.89; N 3.90. Found: C, 76.62; H, 6.01; N, 3.61.

1-(4-Bromophenylimino)-3-methoxy-4-phenyl-3,4-dihydro-1*H*-2-benzothiopyran (3c). *cis*-**3c**: a white solid; mp 194–198 ˚C (hexane–Et_2O) IR (KBr) 1581 cm^{-1}; ^1H NMR δ 3.39 (3H, s), 4.77 (1H, d, *J* = 3.2 Hz), 4.96 (1H, d, *J* = 3.2 Hz), 6.74 (2H, d, *J* = 8.2 Hz), 7.11 (2H, d, *J* = 7.3 Hz), 7.22–7.27 (2H, m), 7.30 (2H, t, *J* = 7. 3 Hz), 7.42 (2H, d, *J* = 8.2 Hz), 7.45–7.50 (2H, m), 8.37 (1H, dd, *J* = 7.8, 1.4 Hz); MS *m/z* 423 (M^+, 85), 347 (100). Anal. Calcd for $C_{22}H_{18}BrNOS$: C, 62.27; H, 4.28; N 3.30. Found: C, 62.26; H, 4.50; N, 3.08. *trans*-**3c**: a pale-yellow solid; mp 156–158 ˚C (hexane–Et_2O); IR (KBr) 1580 cm^{-1}; ^1H NMR δ 3.33 (3H, s), 4.73 (1H, s), 4.98 (1H, d, *J* = 1.8 Hz), 6.83–6.87 (3H, m), 7.34–7.47 (6H, m), 7.48–7.51 (3H, m), 8.28 (1H, dd, *J* = 7.8, 1.4 Hz); MS *m/z* 423 (M^+, 81), 347 (100). Anal. Calcd for $C_{22}H_{18}BrNOS$: C, 62.27; H, 4.28; N 3.30. Found: C, 61.97; H, 4.35; N, 3.18 .

***trans*-3-Methoxy-1-(2-methoxyphenylimino)-4-phenyl-3,4-dihydro-1*H*-2-benzothiopyran (3d):** a yellow solid; mp 125–128 ˚C (hexane–CH_2Cl_2); IR (KBr) 1583 cm^{-1}; ^1H NMR δ 3.33 (3H, s), 3.84 (3H, s), 4.75 (1H, s), 4.97 (1H, d, *J* = 2.3 Hz), 6.84 (1H, d, *J* = 7.3 Hz), 6.90 (1H, dd, *J* = 7.8, 1.4 Hz), 6.97–7.01 (2H, m), 7.14 (1H, td, *J* = 7.8, 1.4 Hz), 7.32–7.41 (5H, m), 7.45 (2H, d, *J* = 7.3 Hz), 8.38 (1H, dd, *J* = 7.8, 1.4 Hz); ^{13}C NMR δ 52.71, 55.82, 57.20, 86.04, 111.92, 120.57, 120.89, 125.17, 127.07, 127.14, 127.55, 128.52, 128.72, 130.26, 130.85, 132.77, 138.23, 139.24, 139.95, 149.59, 159.76; MS *m/z* 375 (M^+, 100). Anal. Calcd for $C_{23}H_{21}NO_2S$: C, 73.57; H, 5.64; N 3.73. Found: C, 73.53; H, 5.70; N, 3.42.

1-Cyclohexylimino-3-methoxy-4-phenyl-3,4-dihydro-1*H*-2-benzothiopyran (3e). *cis*-**3e**: a pale-yellow solid; mp 135–138 ˚C (hexane–Et_2O); IR (KBr) 1589 cm^{-1}; ^1H NMR δ 1.26–1.87 (10H, m), 3.46 (3H, s), 3.53–3.58 (1H, m), 4.71 (1H, d, *J* = 3.2 Hz), 5.05 (1H, d, *J* = 3.2 Hz), 7.10 (2H, d, *J* = 7.3 Hz), 7.14–7.37 (5H, m), 7.45 (1H, td, *J* = 7.3, 1.8 Hz), 8.21 (1H, dd, *J* = 7.8, 1.4 Hz); MS *m/z* 351 (M^+, 40), 193 (100). Anal. Calcd for $C_{22}H_{25}NOS$: C, 75.17; H, 7.17; N 3.98. Found: C, 75.15; H, 7.31; N, 3.97. *trans*-**3e**: a pale-yellow solid; mp 88–92 ˚C (hexane–Et_2O); IR (KBr) 1585 cm^{-1}; ^1H NMR δ 1.30–1.45 (3H, m), 1.53–1.60 (2H, m), 1.67–1.70 (1H, m), 1.84–1.86 (4H, m), 3.40 (3H, s), 3.61–3.65 (1H, m), 4.65 (1H, s), 5.10 (1H, d, *J* = 1.8 Hz), 6.77 (1H, d, *J* = 7.3 Hz), 7.23–7.31 (2H, m), 7.33–7.43 (5H, m), 8.09 (1H, d, *J* = 7.8 Hz); ^{13}C NMR δ 24.72, 24.77, 25.86, 32.75, 32.92, 52.72, 57.24, 61.98, 86.03, 126.80, 127.13, 127.45, 128.43, 128.47, 129.82, 130.16, 133.77, 137.38, 139.35, 152.42; MS *m/z* 351 (M^+, 37), 193 (100). Anal. $C_{22}H_{25}NOS$: C, 75.17; H, 7.17; N 3.98. Found: C, 74.87; H, 7.31; N, 3.97.

3-Methoxy-4-methyl-1-phenylimino-3,4-dihydro-1*H*-2-benzothiopyran (3f). *cis*-**3f**: a yellow oil; R_f 0.49 (1:8 AcOEt–pentane); IR (neat) 1580 cm^{-1}; ^1H NMR δ 1.55 (3H, d, *J* = 6.9 Hz), 3.32 (3H, s), 3.48 (1H, qd, *J* = 6.9, 2.7 Hz), 4.87 (1H, d, *J* = 2.7 Hz), 6.95 (2H, dd, *J* = 7.3, 0.9 Hz), 7.15 (1H, tt, *J* = 7.3, 0.9 Hz), 7.33 (1H, d, *J* = 7.8 Hz), 7.37–7.40 (3H, m), 7.49 (1H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 8.20 (1H, dd, *J* = 7.8, 1.4 Hz); ^{13}C NMR δ 20.82, 41.20, 56.76, 88.43, 119.68, 124.11, 126.99, 127.24, 129.01, 129.44, 131.14, 131.36, 141.04, 151.10, 157.22; MS *m/z* 283 (M^+, 94), 206 (100). Anal. Calcd for Calcd for

$C_{17}H_{17}NOS$: C, 72.05; H, 6.05; N, 4.94. Found: C, 71.73; H, 6.10; N, 4.85. *trans*-**3f**: a white solid; mp 127–128 °C (hexane–Et_2O); IR (KBr) 1583 cm^{-1}; ^1H NMR δ 1.41 (3H, d, *J* = 6.9 Hz), 3.35 (3H, s), 3.43 (1H, qd, *J* = 6.9, 3.2 Hz), 4.75 (1H, d, *J* = 3.2 Hz), 6.95 (2H, dd, *J* = 7.3, 0.9 Hz), 7.15 (1H, tt, *J* = 7.3, 0.9 Hz), 7.22 (1H, d, *J* = 7.8, 1.4 Hz), 7.36 (1H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.39 (2H, t, *J* = 7.3 Hz), 7.43 (1H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 8.26 (1H, dd, *J* = 7.8, 1.4 Hz); MS *m*/*z* 283 (M^+, 96), 206 (100). Anal. Calcd for $C_{17}H_{17}NOS$: C, 72.05; H, 6.05; N, 4.94. Found: C, 71.99; H, 6.01; N, 4.78.

3-Methoxy-4-methyl-1-(3-methylphenyl)imino-3,4-dihydro-1*H*-2-benzothiopyran (3g). *cis*-**3g**: a yellow oil; R_f 0.43 (1:10 AcOEt–pentane); IR (neat) 1587 cm^{-1}; ^1H NMR δ 1.54 (3H, d, *J* = 6.9 Hz), 2.37 (3H, s), 3.33 (3H, s), 3.48 (1H, qd, *J* = 6.9, 2.3 Hz), 4.86 (1H, d, *J* = 2.3 Hz), 6.76 (1H, d, *J* = 7.8 Hz), 6.77 (1H, s), 6.96 (1H, d, *J* = 7.8 Hz), 7.27 (1H, dd, *J* = 7.8, 7.3 Hz), 7.33 (1H, d, *J* = 7.8 Hz), 7.38 (1H, t, *J* = 7.8 Hz), 7.49 (1H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 8.19 (1H, dd, *J* = 7.8, 1.4 Hz); MS *m*/*z* 297 (M^+, 100). Anal. Calcd for $C_{18}H_{19}NOS$: C, 72.69; H, 6.44; N 4.71. Found: C, 72.60; H, 6.49; N, 4.50. *trans*-**3g**: a white solid; mp 95–98 °C (hexane–Et_2O); IR (KBr) 1583 cm^{-1}; ^1H NMR δ 1.41 (3H, d, *J* = 7.3 Hz), 2.38 (3H, s), 3.35 (3H, s), 3.43 (1H, qd, *J* = 7.3, 3.2 Hz), 4.75 (1H, d, *J* = 3.2 Hz), 6.75 (1H, d, *J* = 7.8 Hz), 6.76 (1H, s), 6.97 (1H, d, *J* = 7.3 Hz), 7.21 (1H, dd, *J* = 7.8, 1.4 Hz), 7.27 (1H, dd, *J* = 7.8, 7.3 Hz), 7.35 (1H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.43 (1H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 8.24 (1H, d, *J* = 7.8 Hz); MS *m*/*z* 297 (M^+, 100). Anal. Calcd for $C_{18}H_{19}NOS$: C, 72.69; H, 6.44; N 4.71. Found: C, 72.57; H, 6.45; N, 4.68.

1-(4-Bromophenyl)imino-3-methoxy-4-methyl-3,4-dihydro-1*H*-2-benzothiopyran (3h). *cis*-**3h**: a white solid; mp 93–95 °C (hexane–Et_2O); IR (neat) 1580 cm^{-1}; ^1H NMR δ 1.54 (3H, d, *J* = 7.8 Hz), 3.33 (3H, s), 3.47 (1H, qd, *J* = 7.8, 2.3 Hz), 4.88 (1H, d, *J* = 2.3 Hz), 6.84 (2H, d, *J* = 8.7 Hz), 7.33 (1H, d, *J* = 7.8 Hz), 7.38 (1H, dd, *J* = 7.8, 7.3 Hz), 7.47–7.52 (3H, m), and 8.17 (1H, dd, *J* = 7.8, 1.4 Hz); ^{13}C NMR δ 16.30, 39.96, 57.68, 87.39, 117.16, 121.72, 126.92, 126.95, 127.10, 131.40, 132.11, 132.35, 139.57, 149.86, 159.75; MS *m*/*z* 361 (M^+, 100). Anal. Calcd for $C_{17}H_{16}BrNOS$: C, 56.36; H, 4.45; N 3.87. Found: C, 56.22; H, 4.41; N, 3.53. *trans*-**3h**: a pale-yellow solid; mp 127–130 °C (hexane–Et_2O); IR (KBr) 1568 cm^{-1}; ^1H NMR δ 1.40 (3H, d, *J* = 7.3 Hz), 3.35 (3H, s), 3.44 (1H, qd, *J* = 7.3, 3.2 Hz), 4.77 (1H, d, *J* = 3.2 Hz), 6.84 (2H, d, *J* = 8.7 Hz), 7.22 (1H, dd, *J* = 7.8, 1.4 Hz), 7.35 (1H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.45 (1H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.49 (2H, d, *J* = 8.7 Hz), 8.23 (1H, dd, *J* = 7.8, 1.4 Hz); ^{13}C NMR δ 20.82, 41.15, 56.83, 88.45, 117.13, 121.59, 126.96, 127.28, 129.52, 131.59, 132.10 (two overlapped C's), 140.70, 150.00, 157.99; MS *m*/*z* 361 (M^+, 100). Anal. Calcd for $C_{17}H_{16}BrNOS$: C, 56.36; H, 4.45; N 3.87. Found: C, 56.34; H, 4.60; N, 3.82.

3,5-Dimethoxy-1-(3-methylphenylimino)-4-phenyl-3,4-dihydro-1*H*-2-benzothiopyran (3i). *cis*-**3i**: a pale-yellow solid; mp 157–160 °C (hexane–Et_2O); IR (KBr) 1607, 1589 cm^{-1}; ^1H NMR δ 2.35 (3H, s), 3.39 (3H, s), 3.81 (3H, s), 4.68 (1H, d, *J* = 3.2 Hz), 4.90 (1H, d, *J* = 3.2 Hz), 6.66 (1H, d, *J* = 7.8 Hz), 6.69 (1H, s), 6.70 (1H, d, *J* = 2.7 Hz), 6.89 (1H, d, *J* = 7.3 Hz), 6.96 (1H, dd, *J* = 8.7, 2.7 Hz), 7.15 (2H, d, *J* = 7.3 Hz), 7.18 (1H, dd, *J* = 7.8, 7.3 Hz), 7.25 (1H, t, *J* = 7.3 Hz), 7.31 (2H, t, *J* = 7.3 Hz), 8.36 (1H, d, *J* =

8.7 Hz); MS *m/z* 389 (M^+, 90), 313 (100). Anal. Calcd for $C_{24}H_{23}NO_2S$: C, 74.00; H, 5.95; N 3.60. Found: C, 73.82; H, 6.11; N, 3.53. *trans*-**3i**: a pale-yellow solid; mp 113–116 ˚C (hexane–Et_2O); IR (KBr) 1612, 1578 cm^{-1}; ^1H NMR δ 2.38 (3H, s), 3.33 (3H, s), 3.70 (3H, s), 4.70 (1H, s), 4.95 (1H, d, *J* = 2.3 Hz), 6.34 (1H, d, *J* = 2.3 Hz), 6.76 (1H, d, *J* = 7.8 Hz), 6.78 (1H, d, *J* = 2.3 Hz), 6.88 (1H, dd, *J* = 8.7, 2.3 Hz), 6.96 (1H, d, *J* = 7.8 Hz), 7.26 (2H, dd, *J* = 7.8, 7.3 Hz), 7.35–7.45 (4H, m), 8.78 (1H, d, *J* = 8.7 Hz); MS *m/z* 389 (M^+, 76), 313 (100). Anal. Calcd for $C_{24}H_{23}NO_2S$: C, 74.00; H, 5.95; N 3.60. Found: C, 74.96; H, 6.24; N, 3.48.

***trans*-1-Benzylimino-3,5-dimethoxy-4-phenyl-3,4-dihydro-1*H*-2-benzothiopyran (3j):** a yellow oil; R_f 0.61 (1:4 AcOEt–hexane); IR (neat) 1580 cm^{-1}; ^1H NMR δ 3.42 (3H, s), 3.67 (3H, s), 4.69 (1H, s), 4.71 (1H, d, *J* = 17.0 Hz), 4.77 (1H, d, *J* = 17.0 Hz), 5.10 (1H, d, *J* = 1.8 Hz), 6.31 (1H, d, *J* = 2.3 Hz), 6.82 (1H, dd, *J* = 8.7, 2.3 Hz), 7.27 (1H, t, *J* = 7.3 Hz), 7.33–7.44 (7H, m), 7.49 (2H, d, *J* = 7.8 Hz), 8.23 (1H, d, *J* = 8.7 Hz); MS *m/z* 389 (M^+, 10), 355 (23), 222 (100). Anal. Calcd for $C_{24}H_{23}NO_2S$: C, 74.00; H, 5.95; N 3.60. Found: C, 74.02; H, 6.14; N, 3.54.

ACKNOWLEDGEMENTS

The authors wish to thank Mrs. Miyuki Tanmatsu of this University for determining mass spectra and performing combustion analyses.

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