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SYNTHESIS OF ISOCHROMANS BY HYDRIODIC ACID OR IODINE MEDIATED CYCLIZATION REACTIONS OF 1-(2-VINYLPHENYL)PROPAN-2-OLS

Kazuhiro Kobayashi,* Kazuaki Shikata, Hiroki Maegawa, Shuhei Fukamachi, Miyuki Tanmatsu, and Hisatoshi Konishi

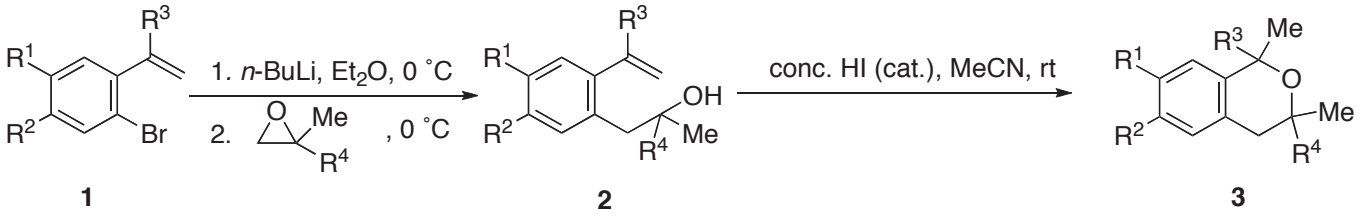
Division of Applied Chemistry, Department of Chemistry and Biotechnology, Graduate School of Engineering, Tottori University, 4-101 Koyama-minami, Tottori 680-8552, Japan; E-mail: kkoba@chem.tottori-u.ac.jp

Abstract – Treatment of 1-(2-vinylphenyl)propan-2-ols, which can be easily prepared from 2-bromostyrenes and epoxides, with hydriodic acid in acetonitrile yields the corresponding isochromans (1*H*-3,4-dihydro-2-benzopyrans). When the above alcohols are treated with iodine in acetonitrile in the presence of sodium hydrogencarbonate, the corresponding 1-iodomethylisochromans are obtained, which can be easily converted into the corresponding 1-alkyl(or aryl)sulfanylmethylisochromans on treatment with sodium thiolates in DMF.

As part of our studies on heterocycle syntheses utilizing hydriodic acid or iodine mediated cyclization of appropriately *o*-substituted styrenes,[1] we have previously reported on the preparation of phthalanes (1,3-dihydroisobenzofurans) using cyclization reactions of 2-vinylbenzyl alcohols, which are easily prepared from 2-bromostyrenes and carbonyl compounds, mediated by iodine[2a] or hydriodic acid.[2b] In this paper, we wish to describe a convenient synthesis of isochromans from 2-bromostyrenes and epoxides. We have found that 1-(2-vinylphenyl)propan-2-ols can be prepared by reacting 2-lithiostyrene, generated from 2-bromostyrenes and butyllithium, with epoxides and that these alcohols are treated with hydriodic acid or iodine to afford the corresponding isochroman derivatives in reasonable yields. Isochroman derivatives are an important class of molecules in medicinal chemistry,[3] because of their biological activities, such as antimicrobialy[3a] and neurokinin-1 receptor antagonistic activity.[3b] Moreover, some molecules having the isochroman skeleton have been found in nature and most of them exhibit biological activities.[4] Several excellent methods for the preparation of isochroman derivatives have recently been reported.[5] These are mainly based on the oxa-Pictet-Spengler cyclization[5b,c,g,i] or the [2+2+2]-cyclotrimerization approach.[5d,h] The formation of a 1,1-disubstituted isochroman derivative by TBAF-mediated intramolecular conjugate addition of TBDMS-protected methyl

3-[2-(2-hydroxyethyl)phenyl]but-2-enoate has also been reported.[5a]

We first explored the possibility of the synthesis of 1,1,3-trisubstituted and 1,1,3,3-tetrasubstituted isochromans (**3**) by hydriodic acid catalyzed cyclization of 1-[2-(1-alkyl(or aryl)vinyl)phenyl]propan-2-ols (**2**). Transformation of α-substituted 2-bromostyrenes (**1**) into **3**, via **2**, was conducted as illustrated in Scheme 1. The respective 2-lithiostyrenes were generated by the bromine-lithium exchange between **1** and butyllithium, and were allowed to react with epoxides, such as isobutene oxide and propylene oxide, to give **2** in moderate-to-fair yields as listed in the Table 1. Treatment of **2** with a catalytic amount of hydriodic acid in acetonitrile at room temperature resulted in the formation of the corresponding isochromans **3** in moderate-to-fair yields as summarized in Table 1. The mechanism is assumed to involve the protolytic formation of benzyl cation intermediates, which are intramolecularly trapped with hydroxy oxygen. When 1-(2-isopropenylphenyl)propan-2-ols (**2b-i**) and (**2b-ii**) were used as the substrates (Entries 2 and 3), we found slight drops in yields compared to those of the others. In order to investigate the scope of the present sequence, we attempted the reaction of the respective adduct, derived from 1-bromo-2-(1-phenylpropen-1-yl)benzene and isobutene oxide, with hydriodic acid to obtain 1-ethyl-3,3-dimethyl-1-phenylisochroman. Unfortunately, however, it proceeded very sluggishly under the conditions described above to give only a trace amount of the desired product. The β-methyl group of the vinyl moiety may make difficult in cyclization.



1 **2** **3**

Scheme 1

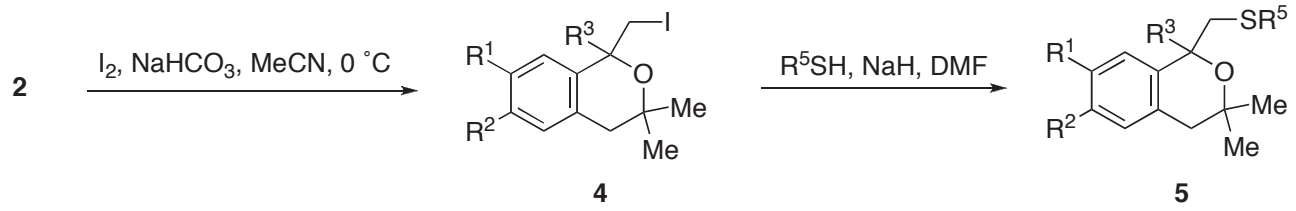
Table 1. Preparation of isochromans **3** via **2**

Entry	**1**	R^4	**2** (Yield/%)[a]	**3** (Yield/%)[a]
1	**1a** ($R^1 = R^2 = H$, $R^3 = Ph$)	Me	**2a** (54)	**3a** (61)
2	**1b** ($R^1 = R^2 = H$, $R^3 = Me$)	Me	**2b-i** (55)	**3b-i** (57)
3	**1b**	H	**2b-ii** (59)	**3b-ii** (55)
4	**1c** ($R^1 = OMe$, $R^2 = H$, $R^3 = Ph$)	Me	**2c** (51)	**3c** (63)
5	**1d** ($R^1 = OMe$, $R^2 = H$, $R^3 = Me$)	Me	**2d-i** (58)	**3d-i** (65)
6	**1d**	H	**2d-ii** (53)	**3d-ii** (54)
7	**1e** ($R^1 = R^2 = OMe$, $R^3 = Me$)	Me	**2e** (50)	**3e** (66)

[a] Isolated yields.

The iodine-mediated cyclization of 1-(2-vinylphenyl)propan-2-ols (**2**) for the synthesis of 1-iodomethylisochramans (**4**) was then investigated. Intramolecular iodoetheration proceeded

immediately and cleanly at 0 ˚C in acetonitrile in the presence of sodium hydrogencarbonate to afford the desired products, as shown in Scheme 2. The yields of the products are good-to-excellent as summarized in Table 2. Replacement of the iodo group with alkyl(or aryl)sulfanyl groups was achieved using sodium thiolates in DMF. Reaction times, reaction conditions, and yields of the products, 1-alkyl(or aryl)sulfanylmethylisochromans (**5**), are summarized in Table 2 as well.



Scheme 2

Table 2. Preparation of 1-(iodomethyl)isochromans **4** and 1-(sulfenylmethyl)isochromans **5**

Entry	**2**	**4** (Yield/%)[a]	R^5 in R^5SH	Temp	Time/h	**5** (Yield/%)[a]
1	**2a**	**4a** (94)	4,6-dimethylpyrimidin-2-yl	120 ˚C	3	**5a** (72)
2	**2b-i**	**4b** (80)	4-chlorophenyl	80 ˚C	4	**5b** (70)
3	**2c**	**4c** (92)	Bn	rt	3	**5c** (70)
4	**2d-i**	**4d** (80)	Ph	80 ˚C	4	**5d** (76)

[a] Isolated yields.

In conclusion, we have demonstrated that hydriodic acid or iodine mediated cyclization reactions of 1-(2-vinylphenyl)propan-2-ols provides easy routes to isochromans, which are hard to prepare by the previous methods. The present methods may find some value in organic synthesis, because the reactions are experimentally very simple and the starting materials are readily available.

EXPERIMENTAL

The melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were determined with a Shimadzu FTIR-8300 spectrophotometer. The ^1H NMR spectra were determined in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz. The ^{13}C NMR spectra were determined in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz. Low-resolution MS spectra (EI, 70 eV) m were measured by a JEOL JMS AX505 HA spectrometer. TLC was carried out on a Merck Kieselgel 60 PF_{254}. Column chromatography was performed using Merck Kieselgel 60 (0.063–0.200 mm). All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

Starting Materials. 2-Bromostyrenes (**1a**),[6] (**1b**),[7] (**1c**),[8] (**1d**),[8] and (**1e**)[9] were prepared by the appropriate

reported methods. All other chemicals used in this study were commercially available.

General Procedure for the Preparation of 1-(2-vinylphenyl)propan-2-ols 2. 2-Methyl-1-[2-(1-phenylethenyl)phenyl]propan-2-ol (2a). To a stirred solution of **1a** (0.43 g, 1.7 mmol) in Et_2O (5 mL) at 0 ˚C was added *n*-BuLi (1.6 M in hexane; 1.7 mmol) dropwise. After 1 h 2,2-dimethyloxiran (0.12 g, 1.7 mmol) was added and the mixture was stirred for an additional 3 h at the same temperature before addition of saturated aqueous NH_4Cl (10 mL). The mixture was extracted with Et_2O twice (10 mL each), and the combined extracts were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel to afford **2a** (0.23 g, 54%); a yellow oil; R_f 0.17 (1:9 AcOEt–hexane); IR (neat) 3402, 1612 cm^{-1}; ^1H NMR δ 1.09 (s, 6H), 1.42 (s, 1H), 2.54 (s, 2H), 5.27 (d, *J* = 1.4 Hz, 1H), 5.79 (d, *J* = 1.4 Hz, 1H), 7.23–7.36 (m, 9H). Anal. Calcd for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.64; H, 7.85.

2-Methyl-1-[2-(1-methylethenyl)phenyl]propan-2-ol (2b-i): a pale-yellow oil; R_f 0.15 (1:5 C_6H_6–hexane); IR (neat) 3403, 1640 cm^{-1}; ^1H NMR δ 1.20 (s, 6H), 1.48 (s, 1H), 2.06 (s, 3H), 2.90 (s, 2H), 4.89 (d, *J* = 0.9 Hz, 1H), 5.22 (d, *J* = 0.9 Hz, 1H), 7.15 (dd, *J* = 6.9, 2.3 Hz, 1H), 7.19–7.21 (m, 2H), 7.32 (dd, *J* = 7.3, 1.4 Hz, 1H). Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.84; H, 9.56.

1-[2-(1-Methylethenyl)phenyl]propan-2-ol (2b-ii): a pale-yellow oil; R_f 0.28 (1:10 AcOEt–hexane); IR (neat) 3364, 1640 cm^{-1}; ^1H NMR δ 1.23 (d, *J* = 6.4 Hz, 3H), 1.50 (s, 1H), 2.05 (d, *J* = 0.9 Hz, 3H), 2.75 (dd, *J* = 13.7, 8.2 Hz, 1H), 2.84 (dd, *J* = 13.7, 5.0 Hz, 1H), 4.03–4.04 (m, 1H), 4.85 (quint, *J* = 0.9 Hz, 1H), 5.21 (quint, *J* = 0.9 Hz, 1H), 7.14 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.18–7.25 (m, 3H). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.51; H, 9.30.

1-[4-Methoxy-2-(1-phenylethenyl)phenyl]-2-methylpropan-2-ol (2c): a pale-yellow oil; R_f 0.19 (1:5 AcOEt–hexane); IR (neat) 3441, 1607 cm^{-1}; ^1H NMR δ 1.08 (s, 6H), 1.61 (s, 1H), 2.46 (s, 2H), 3.83 (s, 3H), 5.28 (d, *J* = 1.4 Hz, 1H), 5.78 (d, *J* = 1.4 Hz, 1H), 6.85 (d, *J* = 2.7 Hz, 1H), 6.88 (dd, *J* = 8.2, 2.7 Hz, 1H), 7.24–7.30 (m, 6H). Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.82; H, 7.85. Found: C, 80.53; H, 8.14.

1-[4-Methoxy-2-(1-methylethenyl)phenyl]-2-methylpropan-2-ol (2d-i): a colorless oil; R_f 0.25 (1:5 AcOEt–hexane); IR (neat) 3414, 1640, 1607 cm^{-1}; ^1H NMR δ 1.18 (s, 6H), 1.57 (s, 1H), 2.05 (s, 3H), 2.83 (s, 2H), 3.80 (s, 3H), 4.89 (s, 1H), 5.21 (q, *J* = 1.4 Hz, 1H), 6.70 (d, *J* = 2.7 Hz, 1H), 6.77 (dd, *J* = 8.2, 2.7 Hz, 1H), 7.23 (d, *J* = 8.2 Hz, 1H). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.06; H, 9.35.

1-[4-Methoxy-2-(1-methylethenyl)phenyl]propan-2-ol (2d-ii): a colorless oil; R_f 0.20 (1:8 AcOEt–hexane); IR (neat) 3406, 1607 cm^{-1}; ^1H NMR δ 1.21 (d, *J* = 6.4 Hz, 3H), 1.48 (s, 1H), 2.04 (d, *J* = 1.4 Hz, 3H), 2.67 (dd, *J* = 13.7, 8.2 Hz, 1H), 2.77 (dd, *J* = 13.7, 5.0 Hz, 1H), 3.80 (s, 3H), 3.96–4.01 (m, 1H), 4.85 (d, *J* = 0.9 Hz, 1H), 5.20 (d, *J* = 0.9 Hz, 1H), 6.69 (d, *J* = 2.7 Hz, 1H), 6.78 (dd, *J* = 8.7, 2.7 Hz, 1H), 7.15 (d, *J* = 8.7 Hz, 1H). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.63; H, 8.80.

1-[4,5-Dimethoxy-2-(1-methylethenyl)phenyl]-2-methylpropan-2-ol (2e): a pale-yellow oil; R_f 0.08 (1:5 Et_2O–hexane); IR (neat) 3447, 1640, 1607 cm^{-1}; ^1H NMR δ 1.20 (s, 6H), 1.45 (s, 1H), 2.04 (s, 3H),

2.83 (s, 2H), 3.866 (s, 3H), 3.870 (s, 3H), 4,88 (d, *J* = 0.9 Hz, 1H), 5.20 (d, *J* = 0.9 Hz, 1H), 6.65 (s, 1H), 6.86 (s, 1H). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.96; H, 8.92.

Typical Procedure for Preparation of 1*H*-3,4-dihydro-2-benzopyrans 3. 1,3,3-Trimethyl-1-phenyl-1*H*-3,4-dihydro-2-benzopyran (3a). To a stirred solution of **2a** (0.16 g, 0.65 mmol) in MeCN (5 mL) at 0 ˚C was added a drop of concentrated HI; the mixture was then stirred for 1 h at rt before addition of saturated aqueous $NaHCO_3$ (10 mL). After evaporation of MeCN, the mixture was extracted with Et_2O three times (10 mL each), and the combined extracts were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by preparative TLC on silica gel to afford **3a** (0.10 g, 61%); a pale-yellow oil; R_f 0.59 (1:9 AcOEt–hexane); IR (neat) 1599 cm^{-1}; ^1H NMR δ 1.06 (s, 3H), 1.32 (s, 3H), 1.82 (s, 3H), 2.56 (s, 2H), 7.12 (d, *J* = 7.3 Hz, 1H), 7.17 (tt, *J* = 7.3, 1.4 Hz, 1H), 7.20–7.35 (m, 3H), 7.27–7.31 (m, 3H), 7.36 (d, *J* = 7.8 Hz, 1H); MS *m/z* 252 (M^+, 2.9), 237 (100). Anal. Calcd for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.53; H, 8.13.

1,1,3,3-Tetramethyl-1*H*-3,4-dihydro-2-benzopyran (3b-i): a pale-yellow oil; R_f 0.59 (C_6H_6); IR (neat) 1163, 1018, 758 cm^{-1}; ^1H NMR δ 1.23 (s, 6H), 1.51 (s, 6H), 2.72 (s, 2H), 7.05 (d, *J* = 7.3 Hz, 1H), 7.14–7.23 (m, 3H); ^{13}C NMR δ 28.99, 32.58, 41.61, 71.00, 74.05, 124.75, 126.02, 126.37, 128.66, 132.56, 142.44. Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.02; H, 9.50.

1,1,3-Trimethyl-1*H*-3,4-dihydro-2-benzopyran (3b-ii): a pale-yellow oil; R_f 0.24 (1:2 C_6H_6–hexane); IR (neat) 1121, 1065, 758 cm^{-1}; ^1H NMR δ 1.33 (d, *J* = 6.0 Hz, 3H), 1.52 (s, 3H), 1.53 (s, 3H), 2.63 (dd, *J* = 16.0, 3.2 Hz, 1H), 2.68 (dd, *J* = 16.0, 10.5 Hz, 1H), 3.93–4.00 (m, 1H), 7.05 (d, *J* = 7.8 Hz, 1H), 7.10–7.14 (m, 2H), 7.17 (t, *J* = 7.3 Hz, 1H); ^{13}C NMR δ 21.98, 28.77, 31.59, 37.15, 64.68, 75.24, 125.26, 125.88, 126.07, 128.61, 133.25, 142.85. Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.79; H, 9.23.

7-Methoxy-1,3,3-trimethyl-1-phenyl-1*H*-3,4-dihydro-2-benzopyran (3c): a colorless oil; R_f 0.31 (1:20 Et_2O–hexane); IR (neat) 1614 cm^{-1}; ^1H NMR δ 1.04 (s, 3H), 1.30 (s, 3H), 1.80 (s, 3H), 2.48 (s, 2H), 3.83 (s, 3H), 6.81 (dd, *J* = 8.2, 2.7 Hz, 1H), 6.93 (d, *J* = 2.7 Hz, 1H), 7.04 (d, *J* = 8.2 Hz, 1H), 7.17 (tt, *J* = 7.3, 1.4 Hz, 1H), 7.22 (d, *J* = 7.3 Hz, 2H), 7.31 (dd, *J* = 7.3, 1.4 Hz, 2H); ^{13}C NMR δ 29.36, 30.19, 31.37, 40.34, 55.31, 73.32, 78.03, 111.62, 112.27, 126.05, 126.54, 126.90, 127.73, 129.22, 142.24, 148.46, 158.00. Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.82; H, 7.85. Found: C, 80.74; H, 8.06.

7-Methoxy-1,1,3,3-tetramethyl-1*H*-3,4-dihydro-2-benzopyran (3d-i): a pale-yellow oil; R_f 0.56 (1:10 AcOEt–hexane); IR (neat) 1614 cm^{-1}; ^1H NMR δ 1.22 (s, 6H), 1.50 (s, 6H), 2.65 (s, 2H), 3.82 (s, 3H), 6.71–6.74 (m, 2H), 6.98 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR δ 28.93, 32.53, 40.77, 55.26, 71.18, 74.12, 110.81, 111.20, 124.89, 129.44, 143.62, 158.13. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.26; H, 9.19.

7-Methoxy-1,1,3-trimethyl-1*H*-3,4-dihydro-2-benzopyran (3d-ii): a pale-yellow oil; R_f 0.33 (1:15 AcOEt–hexane); IR (neat) 1614 cm^{-1}; ^1H NMR δ 1.31 (d, *J* = 6.0 Hz, 3H), 1.51 (s, 3H), 1.53 (s, 3H), 2.59

(d, *J* = 13.7 Hz, 1H), 2.61 (d, *J* = 13.7 Hz, 1H), 3.79 (s, 3H), 3.89–3.96 (m, 1H), 6.64 (d, *J* = 2.7 Hz, 1H), 6.71 (d, *J* = 8.2, 2.7 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR δ 21.95, 28.72, 31.57, 36.33, 55.26, 64.91, 75.28, 110.94, 111.52, 125.46, 129.40, 143.97, 157.81. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.63; H, 8.95.

6,7-Dimethoxy-1,1,3,3-tetramethyl-1*H*-3,4-dihydro-2-benzopyran (3e): a pale-yellow oil; R_f 0.28 (1:10 AcOEt–hexane); IR (neat) 1613 cm^{-1}; ^{1}H NMR δ 1.23 (s, 6H), 1.49 (s, 6H), 2.64 (s, 2H), 3.866 (s, 3H), 3.872 (s, 3H), 6.55 (s, 1H), 6.65 (s, 1H); ^{13}C NMR δ 28.97, 32.55, 41.11, 55.84, 56.11, 71.04, 73.86, 108.39, 111.50, 124.75, 134.18, 147.33, 147.51. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.85; H, 8.82.

Typical Procedure for the Preparation of 1-Iodomethyl-1*H*-3,4-dihydro-2-benzopyrans 4. 1-Iodomethyl-3,3-dimethyl-1-phenyl-1*H*-3,4-dihydro-2-benzopyran (4a). To a stirred solution of **3a** (0.19 g, 0.74 mmol) in MeCN containing $NaHCO_3$ (0.19 g, 2.2 mmol) at 0 ˚C was added I_2 (0.57 g, 2.2 mmol) in portions; the mixture was stirred for 30 min at the same temperature. Ten percent aqueous $Na_2S_2O_3$ was added until the color of I_2 disappeared. The mixture was extracted with Et_2O three times (10 mL each), and the combined extracts were washed with saturated aqueous $NaHCO_3$ and brine and then dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residual solid was recrystallized to give **4a** (0.26 g, 94%); a white solid; mp 134–135 ˚C (hexane–Et_2O); IR (KBr) 1265, 1065, 1015 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (s, 3H), 1.28 (s, 3H), 2.46 (d, *J* = 14.7 Hz, 1H), 2.62 (d, *J* = 14.7 Hz, 1H), 3.73 (d, *J* = 11.0 Hz, 1H), 3.76 (d, *J* = 11.0 Hz, 1H), 7.13 (d, *J* = 7.3 Hz, 1H), 7.22–7.26 (m, 3H), 7.30–7.37 (m, 5H); MS *m*/*z* 378 (M^+, 0.9), 251 (8.1), 237 (100). Anal. Calcd for $C_{18}H_{19}IO$: C, 57.16; H, 5.06. Found: C, 56.92; H, 5.05.

1-Iodomethyl-1,3,3-trimethyl-1*H*-3,4-dihydro-2-benzopyran (4b): a pale-yellow oil; R_f 0.37 (1:5 AcOEt–hexane); IR (neat) 1159, 1041 cm^{-1}; ^{1}H NMR δ 1.16 (s, 3H), 1.38 (s, 3H), 1.69 (s, 3H), 2.63 (d, *J* = 15.4 Hz, 1H), 2.97 (d, *J* = 15.4 Hz, 1H), 3.44 (d, *J* = 10.3 Hz, 1H), 3.51 (dd, *J* = 10.3, 1.4 Hz, 1H), 7.08 (d, *J* = 7.3 Hz, 1H), 7.13 (d, *J* = 7.3 Hz, 1H), 7.18–7.28 (m, 2H). Anal. Calcd for $C_{13}H_{17}IO$: C, 49.38; H, 5.42. Found: C, 49.15; H, 5.55.

1-Iodomethyl-7-methoxy-3,3-dimethyl-1-phenyl-1*H*-3,4-dihydro-2-benzopyran (4c): a pale-yellow solid; mp 82–85 ˚C (hexane); IR (KBr) 1614, 1231, 1041 cm^{-1}; ^{1}H NMR δ 1.16 (s, 3H), 1.28 (s, 3H), 2.38 (d, *J* = 15.1 Hz, 1H), 2.55 (d, *J* = 15.1 Hz, 1H), 3.68 (d, *J* = 11.0 Hz, 1H), 3.74 (d, *J* = 11.0 Hz, 1H), 3.87 (s, 3H), 6.87 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.92 (d, *J* = 2.3 Hz, 1H), 7.04 (d, *J* = 8.2 Hz, 1H), 7.22–7.25 (m, 3H), 7.37 (dd, *J* = 7.3, 1.4 Hz, 2H). Anal. Calcd for $C_{19}H_{21}IO_2$: C, 55.89; H, 5.18. Found: C, 55.85; H, 4.99.

1-Iodomethyl-7-methoxy-1,3,3-trimethyl-1*H*-3,4-dihydro-2-benzopyran (4d): a pale-yellow oil; R_f 0.26 (1:15 AcOEt–hexane); IR (neat) 1612, 1282, 1041 cm^{-1}; ^{1}H NMR δ 1.14 (s, 3H), 1.37 (s, 3H), 1.67 (s, 3H), 2.56 (d, *J* = 15.1 Hz, 1H), 2.89 (d, *J* = 15.1 Hz, 1H), 3.43 (d, *J* = 10.1 Hz, 1H), 3.49 (d, *J* = 10.1 Hz,

1H), 3.81 (s, 3H), 6.68 (d, *J* = 2.7 Hz, 1H), 6.78 (dd, *J* = 8.2, 2.7 Hz, 1H), 7.00 (d, *J* = 8.2 Hz, 1H). Anal. Calcd for $C_{14}H_{19}IO_2$: C, 48.57; H, 5.53. Found: C, 48.53; H, 5.50.

Typical Procedure for the Preparation of 1-Sulfenylmethyl-1*H*-3,4-dihydro-2-benzopyrans 5. 1-[(4,6-Dimethylpyrimidin-2-yl)sulfanylmehtyl]-3,3-dimethyl-1-phenyl-1*H*-3,4-dihydro-2-benzopyran (5a). To a stirred suspension of NaH (60% in oil; 21 mg, 0.53 mmol) in DMF (1 mL) at 0 ˚C was added a solution of 4,6-dimethyl-2-sulfanylpyrimidine (67 mg, 0.48 mmol) in DMF (2 mL). After evolution of H_2 ceased, a solution of **4a** (0.17 g, 0.44 mmol) in DMF (2 mL) was added. Then the mixture was heated at 120 ˚C for 3 h. After cooling saturated aqueous NH_4Cl (10 mL) was added and the organic materials were extracted with Et_2O three times (10 mL each). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated by evaporation. The residue was purified by preparative TLC on silica gel to give **5a** (0.11 g, 62%); white crystals; mp 143–144 ˚C (hexane–Et_2O); IR (KBr) 1580, 1263, 1063 cm^{-1}; ^1H NMR δ 1.09 (s, 3H), 1.30 (s, 3H), 2.36 (s, 6H), 2.47 (d, *J* = 15.1 Hz, 1H), 2.60 (d, *J* = 15.1 Hz, 1H), 3.84 (d, *J* = 13.0 Hz, 1H), 4.22 (d, *J* = 13.0 Hz, 1H), 6.62 (s, 1H), 7.09 (d, *J* = 7.3 Hz, 1H), 7.19–7.27 (m, 5H), 7.41 (dd, *J* = 7.3, 1.4 Hz, 2H), 7.47 (dd, *J* = 7.3, 1.8 Hz, 1H); MS *m/z* 390 (M^+, 1.7), 237 (100). Anal. Calcd for $C_{24}H_{26}N_2OS$: C, 73.81; H, 6.71; N, 7.17. Found: C, 73.71; H, 6.68; N, 7.12.

1-[(4-Chlorophenyl)sulfanylmethyl]-1,3,3-trimethyl-1*H*-3,4-dihydro-2-benzopyran (5b): a beige solid; mp 68–70 ˚C (hexane); IR (KBr) 1096, 1011 cm^{-1}; ^1H NMR δ 1.13 (s, 3H), 1.27 (s, 3H), 1.66 (s, 3H), 2.59 (d, *J* = 15.1 Hz, 1H), 2.95 (d, *J* = 15.1 Hz, 1H), 3.22 (d, *J* = 12.8 Hz, 1H), 3.35 (d, *J* = 12.8 Hz, 1H), 7.06–7.19 (m, 8H); ^{13}C NMR δ 27.23, 29.53, 30.14, 41.46, 50.82, 71.58, 76.30, 124.88, 126.47, 126.76, 128.53, 128.72, 130.63, 131.36, 134.05, 136.81, 139.21; MS *m/z* 332 (M^+, 0.3), 175 (100). Anal. Calcd for $C_{19}H_{21}ClOS$: C, 68.55; H, 6.36. Found: C, 68.50; H, 6.37.

1-(Benzylsulfanylmethyl)-7-methoxy-3,3-dimethyl-1-phenyl-1*H*-3,4-dihydro-2-benzopyran (5c): a yellow oil; R_f 0.11 (1:20 Et_2O–hexane); IR (neat) 1614, 1232, 1040 cm^{-1}; ^1H NMR δ 1.12 (s, 3H), 1.27 (s, 3H), 2.39 (d, *J* = 14.7 Hz, 1H), 2.53 (d, *J* = 14.7 Hz, 1H), 3.01 (d, *J* = 13.7 Hz, 1H), 3.10 (d, *J* = 13.7 Hz, 1H), 3.70 (d, *J* = 13.3 Hz, 1H), 3.78 (d, *J* = 13.3 Hz, 1H), 3.79 (s, 3H), 6.80 (d, *J* = 2.7 Hz, 1H), 6.83 (dd, *J* = 8.2, 2.7 Hz, 1H), 7.03 (d, *J* = 8.2 Hz, 1H), 7.18 (t, *J* = 7.3 Hz, 1H), 7.21 (dd, *J* = 7.8, 7.3 Hz, 2H), 7.27–7.31 (m, 7H); ^{13}C NMR δ 29.37, 29.74, 37.86, 40.28, 44.03, 55.33, 73.69, 81.38, 112.29, 112.89, 126.68, 126.78, 126.99, 127.73, 127.82, 128.35, 129.12, 129.45, 138.84, 138.95, 146.57, 157.68. Anal. Calcd for $C_{26}H_{28}O_2S$: C, 77.19; H, 6.98. Found: C, 77.15; H, 7.27.

7-Methoxy-1,3,3-trimethyl-1-(phenylsulfanylmethyl)-1*H*-3,4-dihydro-2-benzopyran (5d): a beige solid; mp 187 ˚C (decomp) (hexane); IR (KBr) 1616, 1296, 1030 cm^{-1}; ^1H NMR δ 1.12 (s, 3H), 1.26 (s, 3H), 1.65 (s, 3H), 2.53 (d, *J* = 14.7 Hz, 1H), 2.88 (d, *J* = 14.7 Hz, 1H), 3.26 (d, *J* = 13.3 Hz, 1H), 3.36 (d, *J* = 13.3 Hz, 1H), 3.75 (s, 3H), 6.67 (d, *J* = 2.7 Hz, 1H), 6.73 (dd, *J* = 8.2, 2.7 Hz, 1H), 6.99 (d, *J* = 8.2 Hz, 1H), 7.09 (tt, *J* = 7.3, 1.4 Hz, 1H), 7.17 (dd, *J* = 7.8, 7.3 Hz, 2H), 7.25 (dd, *J* = 7.8, 1.4 Hz, 2H); ^{13}C NMR δ 27.27, 29.48, 29.96, 40.65, 50.33, 55.25, 71.75, 76.35, 111.06, 111.93, 125.46, 128.48, 129.35 (2C),

129.45, 138.24, 140.50, 158.11. Anal. Calcd for $C_{20}H_{24}O_2S$: C, 73.13; H, 7.36. Found: C, 72.91; H, 7.41.

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