

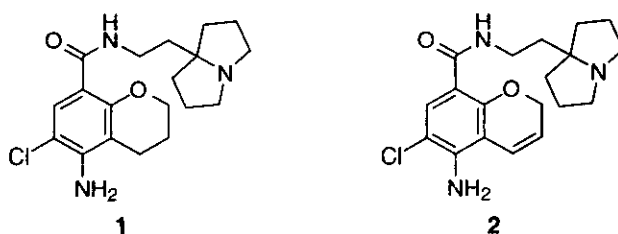
A FACILE SYNTHESIS OF METHYL 5-AMINO-6-CHLORO-2*H*-1-BENZOPYRAN-8-CARBOXYLATE DERIVATIVES

Takuji Kakigami*, Kunihisa Baba, and Toshinao Usui¹

General Research Park, Sanwa Kagaku Kenkyusho Co., Ltd., 363, Shiosaki, Hokusei-cho, Inabe-gun, Mie 511-0406, Japan

Abstract - Methyl 6-chloro-5-pivaloylamino-2*H*-1-benzopyran-8-carboxylate (**4d**) was prepared in good yield as a result of the thermal cyclization of methyl 5-chloro-4-pivaloylamino-2-propargyloxybenzoate (**3d**) using *N,N*-diethylaniline as a solvent.

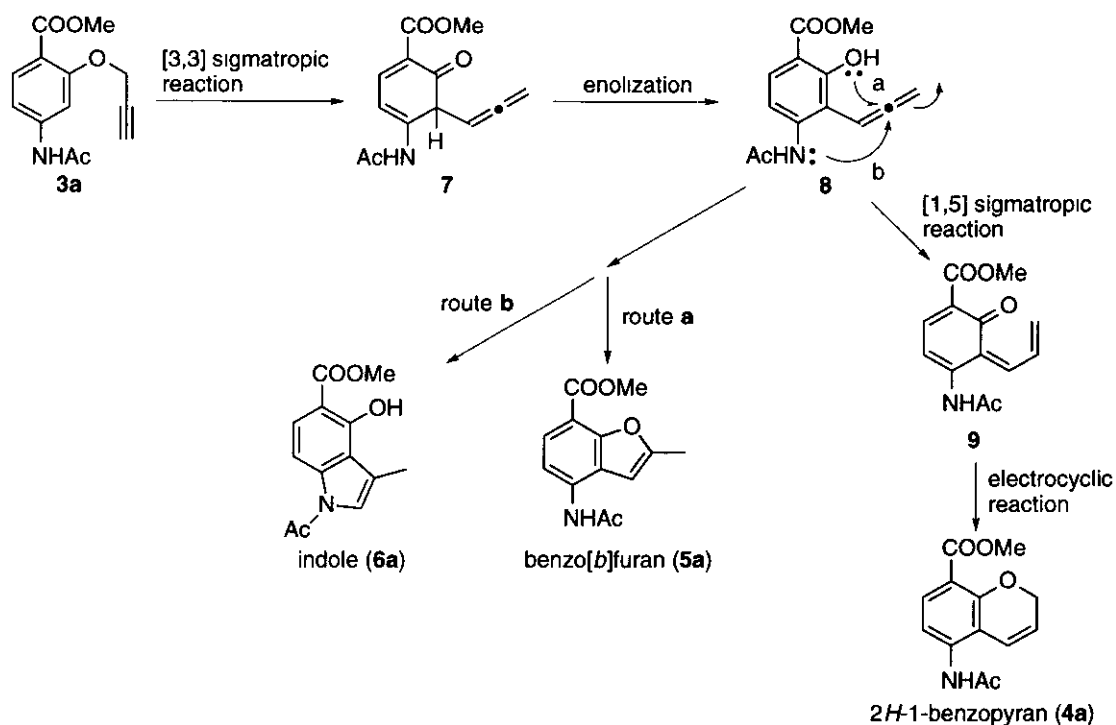
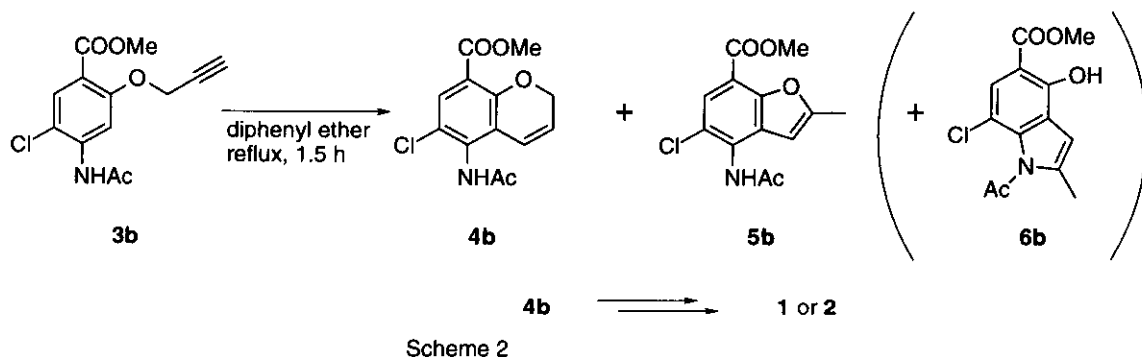
In our previous paper, we reported the synthesis of 5-amino-*N*-[2-(1-azabicyclo[3.3.0]octan-5-yl)ethyl]-6-chloro-2*H*-1-benzopyran-8-carboxamide derivatives (**1**, **2**), which showed potent serotonin 5-HT₄ agonistic activity. However, a benzopyran derivative (**4b**), the key intermediate of **1** and **2**, was prepared only in low yields (25 - 30 %) *via* the Claisen rearrangement of the methyl 2-propargyloxybenzoate derivatives (**3b**) (Scheme 2). It is necessary to synthesize the methyl 2*H*-1-benzopyran-8-carboxylate derivatives (**4**) in good yields in order to develop the efficacious synthesis method of **1** and **2**. We examined the cyclization reactions of methyl 2-propargyloxybenzoates.



Scheme 1

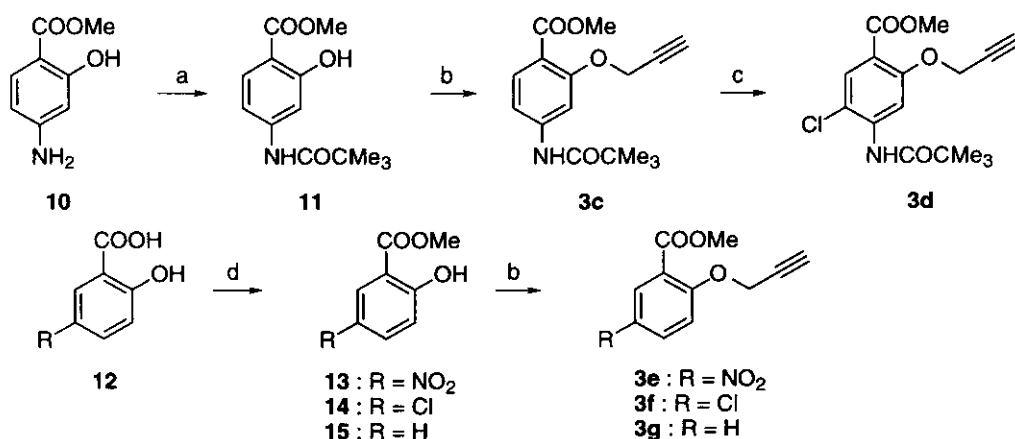
This paper describes the thermal cyclization of methyl 2-propargyloxybenzoates to methyl 2*H*-1-benzopyran-8-carboxylates. The mechanism for formation of 2*H*-1-benzopyran and benzo[*b*]furan can be

proposed in Scheme 3.² A Claisen-like [3,3] sigmatropic rearrangement of a phenyl propargyl ether (**3a**) gives an allenylated cyclohexadienone (**7**), which aromatizes to form an *o*-allenylphenol (**8**). A [1,5] hydrogen shift of **8** followed by the electrocyclic reaction of **9** yields a 2*H*-1-benzopyran (**4a**). When the hydroxy group attacks at the allenic carbon *via* route **a**, a 2-methylbenzo[*b*]furan (**5a**) is formed. If the amide nitrogen combined with the allenic carbon *via* route **b**, an indole derivative (**6a**) would be produced.



It is reported that the cyclization process is influenced by the solvent or a property of the substituent at

the aryl group, and the product ratio of the 2*H*-1-benzopyran ring (4) or 2-methylbenzo[*b*]furan ring (5) depends on these factors.³ However, the standardized condition has not been established, and we examined the reaction conditions for the thermal cyclization of some methyl 2-propargyloxybenzoates. Methyl 4-acetylamino-2-propargyloxybenzoate (3a) and 5-chloro derivative (3b) were prepared by the method reported in our previous paper.⁴ and other congeners (3c–g) were synthesized by the methods shown in Scheme 4. The cyclization reactions of 3a–g were performed using diphenyl ether or *N,N*-diethylaniline as a solvent.



Reagents: a Me_3CCOCl , Et_3N ; b $\text{BrCH}_2\text{C}\equiv\text{CH}$, K_2CO_3 ; c NCS ; d MeOH , 97% H_2SO_4 ; e *N*-carbethoxyphthalimide

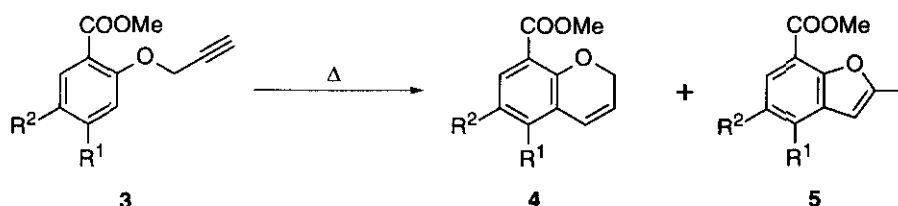
Scheme 4

The results are summarized in Table 1. *N,N*-Diethylaniline (method B) was a better solvent than diphenyl ether (method A) for the cyclization reaction of 3a–g. Compounds (3e–g) without an acylamino group gave the cyclized products (4) and (5) in lower yields than other amides (3c,d). It is thought that the cyclization of 3e–g was slow because the allene group turned to the opposite side as a result of steric hindrance with the hydroxyl group.

In the case of the *N*-acetyl derivatives (3a,b), the yield of both the 2*H*-1-benzopyran (4) and benzo[*b*]furan (5) derivatives is low. In our previous report,⁴ the cyclization of 3a in 1,2-dichlorobenzene (bp : 180 °C) gave methyl 4-acetylamino-2-methylbenzo[*b*]furan-7-carboxylate (5a) in 45% yield and methyl 1-acetyl-4-hydroxy-2-methylindol-5-carboxylate (6a) in 4% yield. But, the yield of methyl 5-acetylamino-2*H*-1-benzopyran-8-carboxylate (4a) was very low (< 8%). In this report, the cyclization of

3a and **3b** in diphenyl ether (bp : 259 °C) gave methyl 5-acetylamino-2*H*-1-benzopyran-8-carboxylate (**4a**) and methyl 5-acetylamino-6-chloro-2*H*-1-benzopyran-8-carboxylate (**4b**) in 13% and 27% yields. This implies that the high temperature is necessary for the formation of 2*H*-1-benzopyran ring, and the decrease of yield is caused by the creation of indole derivatives together with benzo[*b*]furan and 2*H*-1-benzopyran derivatives because of the competition with cyclization at the *N*-atom (route **b**) (Scheme 3). On the other hand, in the case of the *N*-pivaloyl derivatives (**3c,d**), 2*H*-1-benzopyran (**4**) or benzo[*b*]furan (**5**) derivatives were obtained in good yield. It is conceived for the reason that the allene group turns to the hydroxy group side, and the cyclization between the allene and the *N*-atom is restricted because of the bulkiness of the *N*-pivaloyl group. Furthermore, it is possible to prepare 2*H*-1-benzopyran (**4**) or benzo[*b*]furan (**5**) derivatives separately by introducing a chlorine atom at the 5-position of *N*-pivaloyl derivatives. It is proved that the electron-attractiveness of chlorine atom at the 5-position controls the precedence [1.5] sigmatropic reaction and nucleophilic cyclization.

Table 1. Cyclization of Methyl 2-Propargyloxybenzoate Derivatives



Compd.	R ¹	R ²	Yield (%) ^{a)}			
			Method A ^{b)}		Method B ^{c)}	
			4	5	4	5
3a	NHAc	H	13	15	— ^{d)}	— ^{d)}
3b	NHAc	Cl	27	0	29	0
3c	NHCOCMe ₃	H	15	49	6.5	68
3d	NHCOCMe ₃	Cl	53	0	74	0
3e	H	NO ²	11	6	30	20
3f	H	Cl	— ^{d)}	— ^{d)}	42	10
3g	H	H	— ^{d)}	— ^{d)}	56	0

a) Isolated yield.

b) A mixture of a substrate and diphenyl ether [5.0 mL/g (substrate)] was refluxed for 2 h.

c) A mixture of a substrate and *N,N*-diethylaniline [5.0 mL/g (substrate)] was refluxed for 2 h.

d) Not tested.

In conclusion, methyl 6-chloro-5-pivaloylamino-2*H*-1-benzopyran-8-carboxylate (**4d**) was prepared in high yield as a result of thermal cyclization of methyl 5-chloro-4-pivaloylamino-2-propargyloxybenzoate (**3d**) using *N,N*-diethylaniline as a solvent.

EXPERIMENTAL SECTION

All melting points were determined using a Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were recorded using a Perkin Elmer 1600. MS spectra were obtained on a JEOL JMS-SX 120A spectrometer. ¹H-NMR(270MHz) spectra were recorded using a JEOL JNM-GSX 270 in CDCl₃ or DMSO-*d*₆. Chemical shifts are expressed as δ values (ppm) with tetramethylsilane as an internal standard, and coupling constants (*J* values) are given in Hertz (Hz).

Methyl 2-Hydroxy-4-pivaroylamino-2-hydroxybenzoate (**11**).

The solution of pivaloyl chloride (0.361 g, 2.99 mmol) in CH₂Cl₂ (3.0 mL) was added to a solution of methyl 4-amino-2-hydroxybenzoate (**7**) (0.500 g, 2.99 mmol) and triethylamine (0.00361 g, 3.29 mmol) in CH₂Cl₂ (7.0 mL) at 0-5 °C, and then stirred for 3 h at 20 °C. The reaction mixture was washed with saturated NaHCO₃ and then water, dried over Na₂SO₄, and thereafter, the solvent was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (CHCl₃) to give 0.613 g (81.6%) of **11** as a powder. mp 141-142 °C. ¹H-NMR (CDCl₃) δ : 1.32 (9H, s, CH₃), 3.93 (3H, s, COOCH₃), 7.13 (1H, dd, *J*=2.5, 8.8 Hz, C5-H), 7.18 (1H, d, *J*=2.5 Hz, C3-H), 7.37 (1H, br s, NH), 7.78 (1H, d, *J*=8.8 Hz, C6-H), 10.8 (1H, s, OH). IR (KBr)cm⁻¹: 3303 (NH), 1683, 1661 (C=O). EI-MS *m/z* : 251 (M⁺). *Anal.* Calcd for C₁₃H₁₇NO₄: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.25; H, 6.68; N, 5.48.

Methyl 4-Pyvaroylamino-2-propargyloxybenzoate (**3c**).

A mixture of **11** (0.300 g, 1.20 mmol), propargyl bromide (0.156 g, 1.31 mmol), and potassium carbonate (0.181 g, 1.31 mmol) in *N,N*-dimethylformamide (5.0 mL) was stirred for 4 h at 70 °C. The reaction mixture was poured into ice-water (80 mL), and extracted with CHCl₃. The extract was washed with water, dried over Na₂SO₄, and thereafter, the solvent was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt : hexane = 1 : 2) to give 0.309 g (89.6%) of **3c** as a powder. mp 142-143 °C. ¹H-NMR (CDCl₃) δ : 1.33 (9H, s, CH₃), 2.54 (1H, t, *J*=2.4 Hz, CH), 3.87 (3H, s, COOCH₃), 4.81 (2H, d, *J*=2.4 Hz, CH₂), 6.94 (1H, dd, *J*=2.0, 8.3 Hz, C5-H), 7.42 (1H, br s, NH), 7.75 (1H, d, *J*=2.0 Hz, C3-H), 7.84 (1H, d, *J*=8.3 Hz, C6-H). IR (KBr)cm⁻¹: 3374 (NH), 1707, 1681 (C=O). EI-MS *m/z* : 289 (M⁺). *Anal.* Calcd for C₁₆H₁₉NO₄: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.35; H, 6.69;

N, 4.76.

Methyl 5-Chloro-4-pivaroylamino-2-propargyloxybenzoate (3d).

A mixture of **3c** (0.0700 g, 0.242 mmol) and *N*-chlorosuccinimide (0.0323 g, 0.242 mmol) in *N,N*-dimethylformamide (1.0 mL) was stirred for 5 h at 70 °C. The cooled reaction mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt : hexane = 1 : 3) to give 0.0620 g (79.1%) of **3d** as a powder. mp 89-90 °C. ¹H-NMR (CDCl₃) δ: 1.36 (9H, s, CH₃), 2.56 (1H, t, *J*=2.4 Hz, CH), 3.88 (3H, s, COOCH₃), 4.82 (2H, d, *J*=2.4 Hz, CH₂), 7.92 (1H, s, C3-H), 8.19 (1H, br s, NH), 8.48 (1H, s, C6-H). IR (KBr)cm⁻¹: 3419 (NH), 1727, 1686 (C=O). EI-MS *m/z* : 323 (M⁺). *Anal.* Calcd for C₁₆H₁₈NO₄Cl: C, 59.35; H, 5.60; N, 4.33. Found: C, 59.32; H, 5.75; N, 4.12.

Methyl 2-Hydroxy-5-nitrobenzoate (13).

A mixture of 2-hydroxy-5-nitrobenzoic acid (**12**:R=NO₂) (2.50 g, 13.7 mmol) and 97% H₂SO₄ (1.00g) in methanol (10 mL) was refluxed for 20 h. The cooled reaction mixture was poured into ice-water (40 mL). The resultant precipitate was collected by filtration to give 2.55 g (95.0%) of **13** as a powder. mp 109-110 °C. ¹H-NMR (CDCl₃) δ: 3.99 (3H, s, COOCH₃), 7.09 (1H, d, *J*=9.3 Hz, C3-H), 8.34 (1H, dd, *J*=2.9, 9.3 Hz, C4-H), 8.80 (1H, d, *J*=2.9 Hz, C6-H), 11.4 (1H, s, OH). IR (KBr)cm⁻¹: 1680 (C=O).⁵

Methyl 5-Nitro-2-propargyloxybenzoate (3e).

A mixture of **13** (5.00 g, 25.4 mmol), propargyl bromide (3.32 g, 27.9 mmol), and potassium carbonate (7.01 g, 50.8 mmol) in *N,N*-dimethylformamide (50 mL) was stirred for 2 h at 70 °C. The cooled reaction mixture was poured into ice-water (800 mL). The resultant precipitate was collected by filtration to give 5.54 g (93.0%) of **3e** as a powder. mp 90-91 °C. ¹H-NMR (CDCl₃) δ: 2.61 (1H, t, *J*=2.4 Hz, CH), 3.94 (3H, s, COOCH₃), 4.92 (2H, d, *J*=2.4 Hz, CH₂), 7.25 (1H, d, *J*=8.8 Hz, C4-H), 8.38 (1H, dd, *J*=2.9, 8.8 Hz, C4-H), 7.82 (1H, d, *J*=2.9 Hz, C6-H). IR (KBr)cm⁻¹: 1739 (C=O). EI-MS *m/z* : 235 (M⁺). *Anal.* Calcd for C₁₁H₉NO₅: C, 56.17; H, 3.86; N, 5.96. Found: C, 56.32; H, 3.91; N, 5.78.

Methyl 5-Chloro-2-propargyloxybenzoate (3f).

Methyl 2-hydroxy-5-chlorobenzoate (**14**) (5.00 g, 26.8 mmol) was converted to 5.54 g (98.7%) of **3f** in a similar procedure as employed in the synthesis of **3e** as a powder. mp 54-55 °C. ¹H-NMR (CDCl₃) δ: 2.54 (1H, t, *J*=2.4 Hz, CH), 3.90 (3H, s, COOCH₃), 4.78 (2H, d, *J*=2.4 Hz, CH₂), 7.10 (1H, d, *J*=8.8 Hz, C4-H), 7.43 (1H, dd, *J*=2.9, 8.8 Hz, C4-H), 7.79 (1H, d, *J*=2.9 Hz, C6-H). IR (KBr)cm⁻¹: 1726 (C=O). EI-MS *m/z* : 224 (M⁺). *Anal.* Calcd for C₁₁H₉O₃Cl: C, 58.81; H, 4.04. Found: C, 58.92; H, 3.92.

Methyl 2-Propargyloxybenzoate (3g).

A mixture of methyl 2-hydroxybenzoate (**15**) (2.50 g, 16.4 mmol), propargyl bromide (2.15 g, 18.1 mmol), and potassium carbonate (2.50 g, 18.1 mmol) in CH₃CN (10 mL) was refluxed for 24 h. After having filtered the insolubles, the filtrate was concentrated *in vacuo*. The residue was dissolved in CHCl₃, washed with water, dried over Na₂SO₄, and concentrated *in vacuo* to give 3.52 g (100 %) of **3g** as a syrup. ¹H-NMR (CDCl₃) δ: 2.52 (1H, t, J=2.4 Hz, CH), 3.89 (3H, s, COOCH₃), 4.80 (2H, d, J=2.4 Hz, CH₂), 7.05 (1H, m, C3-H), 7.13 (1H, d, J=8.3 Hz, C4-H), 7.48 (1H, m, C5-H), 7.82 (1H, dd, J=2.0, 4.8 Hz, C6-H).⁶

Cyclization method A

A mixture of a substrate and diphenyl ether [5.0 mL/g (substrate)] was refluxed for 2 h. The cooled reaction mixture was refined by silica gel column chromatography (AcOEt : hexane = 1 : 2) to give the methyl 2*H*-1-benzopyran-8-carboxylate derivative and the methyl 2-methylbenzo[*b*]furan-7-carboxylate derivative.

Cyclization method B

A mixture of a substrate and *N,N*-diethylaniline [5.0 mL/g (substrate)] was refluxed for 2 h. The cooled reaction mixture was dissolved in chloroform (30 mL), washed with water, 1N HCl, and then water, and thereafter, the solvent was concentrated *in vacuo*. The residue was refined by silica gel column chromatography (AcOEt : hexane = 1 : 2) to give the methyl 2*H*-1-benzopyran-8-carboxylate derivative and the methyl 2-methylbenzo[*b*]furan-7-carboxylate derivative.

Methyl 5-Pivaloylamino-2*H*-1-benzopyran-8-carboxylate (**4c**)

A syrup. ¹H-NMR (CDCl₃) δ: 1.34 (9H, s, CH₃), 3.86 (3H, s, COOCH₃), 4.82 (2H, dd, J=1.5, 3.9 Hz, CH₂), 5.95 (1H, dt, J=3.9, 9.8 Hz, CH), 6.37 (1H, dt, J=1.5, 9.8 Hz, CH), 7.38 (1H, s, NH), 7.40 (1H, d, J=9.8 Hz, C6-H), 7.68 (1H, d, J=9.8 Hz, C7-H). EI-MS *m/z* : 289 (M⁺). *Anal.* Calcd for C₁₆H₁₉NO₄: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.65; H, 6.51; N, 4.87.

Methyl 2-Methyl-4-pivaloylamino-2*H*-1-benzopyran-8-carboxylate (**5c**)

A powder. mp 139-141 °C. ¹H-NMR (CDCl₃) δ: 1.37 (9H, s, CH₃), 2.52 (3H, s, CH₃), 3.97 (3H, s, COOCH₃), 6.34 (1H, d, J=0.98 Hz, CH), 7.63 (1H, s, NH), 7.84 (2H, s, C5,6-H). EI-MS *m/z* : 289 (M⁺). *Anal.* Calcd for C₁₆H₁₉NO₄: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.63; H, 6.48; N, 4.85.

Methyl 6-Chloro-5-pivaloylamino-2*H*-1-benzopyran-8-carboxylate (**4d**)

A amorphous mass. ¹H-NMR (CDCl₃) δ: 1.38 (9H, s, CH₃), 3.88 (3H, s, COOCH₃), 4.90 (2H, dd, J=2.0, 3.9 Hz, CH₂), 5.91 (1H, dt, J=3.9, 9.8 Hz, CH), 6.21 (1H, dt, J=2.0, 9.8 Hz, CH), 7.35 (1H, s, NH), 7.73 (1H, s, J=9.8 Hz, C7-H). IR (KBr)cm⁻¹: 3376 (NH), 1718, 1678 (C=O). EI-MS *m/z* : 323 (M⁺). *Anal.*

Calcd for $C_{16}H_{18}NO_4Cl$: C, 59.35; H, 5.60; N, 4.33. Found: C, 59.14; H, 5.58; N, 4.52.

Methyl 6-Nitro-2H-1-benzopyran-8-carboxylate (4e)

A powder. mp 122-124 °C. 1H -NMR ($CDCl_3$) δ : 3.86 (3H, s, $COOCH_3$), 5.13 (2H, dd, $J=2.0, 3.4$ Hz, CH_2), 5.95 (1H, dt, $J=3.4, 9.8$ Hz, CH), 6.21 (1H, dt, $J=2.0, 9.8$ Hz, CH), 7.92 (1H, d, $J=2.4$ Hz, C5-H), 7.73 (1H, d, $J=2.4$ Hz, C7-H). IR (KBr) cm^{-1} : 1706 (C=O), 1520 (NO). EI-MS m/z : 235 (M^+). *Anal.* Calcd for $C_{11}H_9NO_5$: C, 56.17; H, 3.86; N, 5.96. Found: C, 56.06; H, 3.79; N, 5.86.

Methyl 5-Nitro-2-methylbenzo[b]furan-7-carboxylate (5e)

A powder. mp 121-123 °C. 1H -NMR ($CDCl_3$) δ : 2.59 (3H, s, CH_3), 4.04 (3H, s, $COOCH_3$), 6.60 (1H, s, C3-H), 8.55 (1H, d, $J=2.5$ Hz, C4-H), 8.77 (2H, d, $J=2.5$ Hz, C6-H). IR (KBr) cm^{-1} : 1714 (C=O), 1534 (NO). EI-MS m/z : 235 (M^+). *Anal.* Calcd for $C_{11}H_9NO_5$: C, 56.17; H, 3.86; N, 5.96. Found: C, 56.11; H, 3.71; N, 5.82.

Methyl 6-Chloro-2H-1-benzopyran-8-carboxylate (4f)

A amorphous mass. 1H -NMR ($CDCl_3$) δ : 3.88 (3H, s, $COOCH_3$), 4.94 (2H, dd, $J=2.0, 3.9$ Hz, CH_2), 5.88 (1H, dt, $J=3.9, 9.8$ Hz, CH), 6.36 (1H, dt, $J=2.0, 9.8$ Hz, CH), 7.05 (1H, d, $J=2.5$ Hz, C5-H), 7.58 (1H, d, $J=2.5$ Hz, C7-H). IR (KBr) cm^{-1} : 1702 (C=O). EI-MS m/z : 224 (M^+). *Anal.* Calcd for $C_{11}H_9O_3Cl$: C, 58.81; H, 4.04. Found: C, 58.74; H, 3.99.

Methyl 5-Chloro-2-methylbenzo[b]furan-7-carboxylate (5f)

A powder. mp 68-70 °C. 1H -NMR ($CDCl_3$) δ : 2.52 (3H, s, CH_3), 3.99 (3H, s, $COOCH_3$), 6.38 (1H, s, C3-H), 7.60 (1H, d, $J=2.5$ Hz, C4-H), 7.81 (2H, d, $J=2.5$ Hz, C6-H). IR (KBr) cm^{-1} : 1716 (C=O). EI-MS m/z : 224 (M^+). *Anal.* Calcd for $C_{11}H_9O_3Cl$: C, 58.81; H, 4.04. Found: C, 58.69; H, 3.15.

Methyl 2H-1-Benzopyran-8-carboxylate (4g)

A syrup. 1H -NMR ($CDCl_3$) δ : 3.87 (3H, s, $COOCH_3$), 4.93 (2H, dd, $J=1.9, 3.9$ Hz, CH_2), 5.82 (1H, dt, $J=3.9, 10.3$ Hz, CH), 6.36 (1H, dt, $J=1.9, 10.3$ Hz, CH), 6.86 (1H, t, $J=7.8$ Hz, C6-H), 7.05 (1H, dd, $J=1.5, 7.8$ Hz, C5-H), 7.60 (1H, dd, $J=1.5, 7.8$ Hz, C7-H). IR (KBr) cm^{-1} : 1711 (C=O).⁶

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