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SYNTHESIS OF 10-HYDROXY-3-METHYL-1*H*-PYRANO[4,3-*b*]-QUINOLINE DERIVATIVES

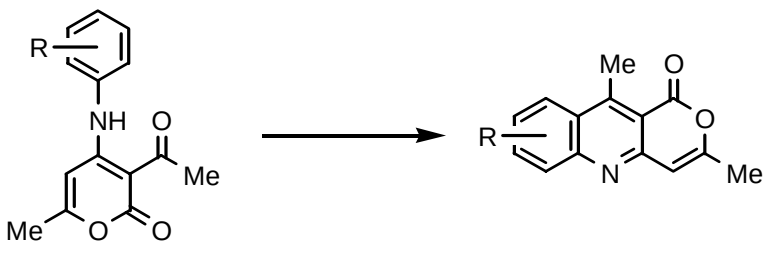
Mieko Morone, Atsuko Sato, and Yutaka Azuma*

Tohoku Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku, Sendai 981-8558, Japan

E-mail: y-azuma@tohoku-pharm.ac.jp

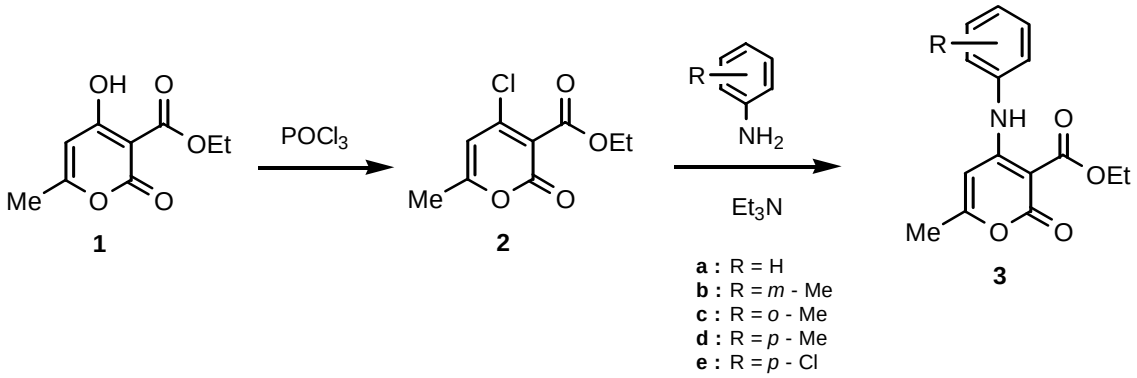
Abstract – Heating of 4-arylamino-3-ethoxycarbonyl-6-methyl-2*H*-pyran-2-one derivatives (**3**), which were obtained from the reaction between 4-chloro-3-ethoxycarbonyl-6-methyl-2*H*-pyran-2-one (**2**) and anilines, in PPA gave corresponding 10-hydroxy-3-methylpyrano[4,3-*b*]quinoline derivatives (**4**) and 1-(4-hydroxyquinolin-2-yl)propan-2-one (**5**).

There are a few reports on the preparations and pharmacological activities of the 9-aminoacridine derivatives and their analogues, which show inhibitory activity against acetylcholinesterase.[1-3] During the course of our investigation on the synthesis of the pyrane-fused heterocycles having biological activity, we reported the facile synthesis of the pyrano[4,3-*b*]quinoline ring system by the cyclization of 3-acetyl-4-arylamino-2*H*-pyran-2-one as shown in Scheme 1.[4] If the 4-arylamino-3-ethoxycarbonyl-2-pyrones are used instead of the 3-acetyl-4-arylaminopyrone in the method, one is able to prepare 10-hydroxypyranoquinolines, which could be used as the starting material for the 10-amino-pyranoquinoline derivatives. In this paper, we describe the synthesis and the cyclization of the 4-arylamino-3-ethoxycarbonylpyran-2-ones.



Scheme 1

4-Chloro-3-ethoxycarbonylpyran-2-one (**2**) as the starting material was obtained by the chlorination of 3-ethoxycarbonyl-4-hydroxypyran-2-one (**1**), which was prepared from diketene and diethyl malonate,[5] using a previously reported method.[6] A mixture of **2**, aniline, and Et_3N in EtOH was heated to give 3-ethoxycarbonyl-6-methyl-4-phenylamino-2*H*-pyran-2-one (**3a**) in 83 % yield. By a similar procedure, the reaction of **2** with various substituted anilines gave the corresponding 4-arylamino-2-pyrones (**3b**-**e**). The structures of the 4-arylamino-2-pyrones (**3a**-**e**) were determined by their spectral and analytical data.

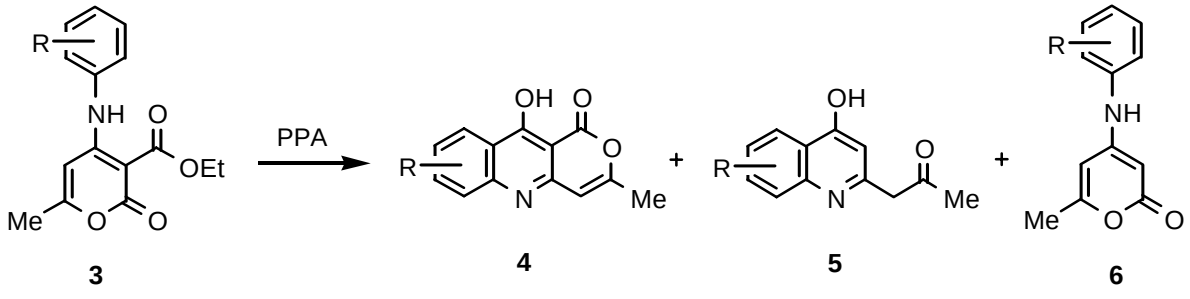


Scheme 2

Table 1. The Physical, Spectral, and Analytical Data of **3**

Compd No.	Yield (%) (solvent)	mp (°C)	Formula (*m/z* M^+)	*Anal.* (%) Calcd (Found) C	H	N	IR [KBr] (cm^{-1})	^{1}H-NMR δ(ppm) [$CDCl_3$]
3a	83 (Et_2O)	154-155	$C_{15}H_{15}NO_4$ (273)	65.92 (65.61	5.53 5.31	5.13 4.71)	1720 1655	1.41 (3H, t, *J* = 7 Hz), 2.13 (3H, s), 4.40 (2H, q, *J* = 7 Hz), 5.83 (1H, s), 7.14-7.50 (5H, m), 11.54 (1H, br s)
3b	85 (Et_2O)	118-120	$C_{16}H_{17}NO_4$ (287)	66.89 (66.60	5.96 5.75	4.88 4.43)	1730 1670	1.41 (3H, t, *J* = 7 Hz), 2.13 (3H, s), 2.39 (3H, s), 4.38 (2H, q, *J* = 7 Hz), 5.85 (1H, s), 6.93-7.49 (4H, m), 11.47 (1H, br s)
3c	77 (MeOH)	158	$C_{16}H_{17}NO_4$ (287)	66.89 (66.63	5.96 5.91	4.88 4.65)	1720 1655	1.42 (3H, t, *J* = 7 Hz), 2.10 (3H, s), 2.26 (3H, s), 4.40 (2H, q, *J* = 7 Hz), 5.59 (1H, s), 7.12-7.40 (4H, m), 11.35 (1H, br s)
3d	83 (Et_2O)	143-144	$C_{16}H_{17}NO_4$ (287)	66.89 (66.71	5.96 5.83	4.88 4.93)	1730 1660	1.41 (3H, t, *J* = 7 Hz), 2.11 (3H, s), 2.39 (3H, s), 4.39 (2H, q, *J* = 7 Hz), 5.80 (1H, s), 6.98-7.33 (4H, m), 11.43 (1H, br s)
3e	83 (EtOH)	148-149	$C_{15}H_{14}NO_4Cl$ (307)	58.55 (58.46	4.59 4.32	4.55 4.33)	1730 1660	1.41 (3H, t, *J* = 7 Hz), 2.13 (3H, s), 4.39 (2H, q, *J* = 7 Hz), 5.77 (1H, s), 7.06-7.52 (4H, m), 11.51 (1H, br s)

From the cyclization of **3a** by heating in PPA, three products (**4a**, **5a**, and **6a**) were isolated. The product (**4a**) was 10-hydroxy-3-methyl-1*H*-pyrano[4,3-*b*]quinolin-1-one, of which the structure was confirmed by comparison of its IR and NMR spectra and melting point with previous data.[7] The structure of **6a** as 6-methyl-4-phenylamino-2*H*-pyran-2-one was determined by comparison of the IR and NMR spectrum with the 4-arylaminopyrone derivatives which were obtained by the pyrolysis of 3-acetyl-4-arylaminopyrones.[4]



3 **4** **5** **6**

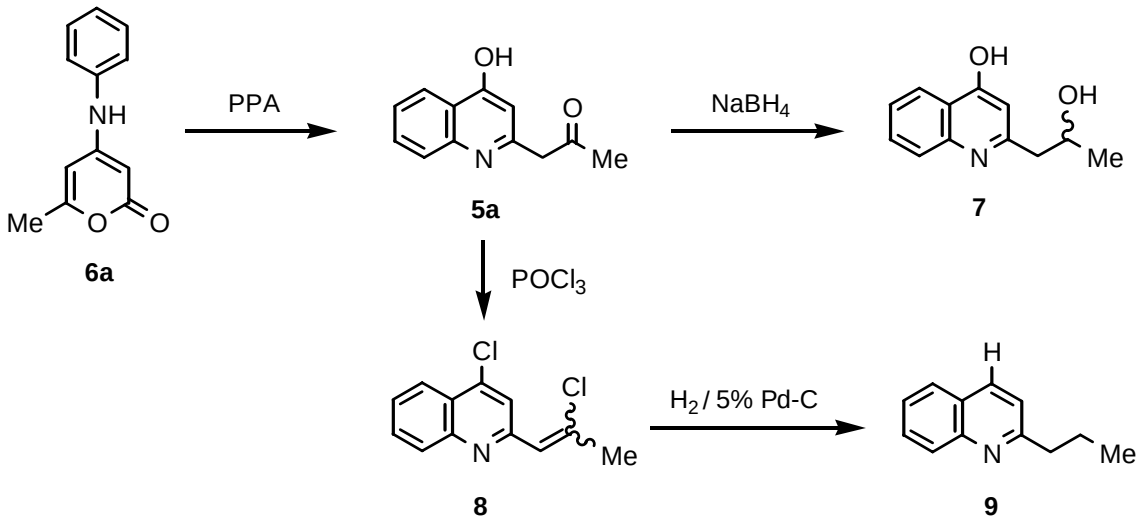
a : R = H
b : R = *m* - Me
c : R = *o* - Me
d : R = *p* - Me
e : R = *p* - Cl

Scheme 3

On the other hand, the structure of quinoline (**5a**) was determined by some chemical experiments as shown in Scheme 4 and its comparison with spectral and analytical data. Thus, the ^{1}H-NMR spectra of quinoline (**5a**) showed four ring protons arising from aniline at 7.14-8.21 ppm and four singlet peaks which are an olefin proton at 6.05 ppm, a methylene proton at 3.79 ppm, a methyl proton at 2.27 ppm, and a phenolic proton at 11.46 ppm. Especially, the irradiation of the methylene proton gave NOE on the olefin proton. Additionally, when **5a** was induced to compound (**7**) by the reduction with $NaBH_4$, the two singlet patterns of the methylene and methyl protons of **5a** were changed into the doublet patterns, and the C=O absorption in the 1720 cm^{-1} region of **5a** disappeared.

These spectral data and experimental evidence supported the fact that the product (**5a**) was 1-(4-hydroxyquinolin-2-yl)propan-2-one, and the structure of **5a** was further confirmed by converting it to 2-propylquinoline (**9**) [8] by chlorination followed by catalytic hydrogenation as shown in Scheme 4.

The yields of these products (**4a**, **5a** and **6a**) were influenced by the reaction time and reaction temperature as shown in Table 2. Thus, the yields of the pyranoquinoline (**4a**) were markedly increased by raising the temperature, but were slightly decreased by extension of the reaction time. On the other hand, the main factor which determines the rate of **5a** and **6a** is the reaction time. Thus, it seems that the extension of the reaction time promotes the pyrolysis of **6a**, and causes a decrease in the ratio of **5a**. Actually, the heating of **6a** in PPA for 30 min at 150℃ gave **5a** in 66 % yield.



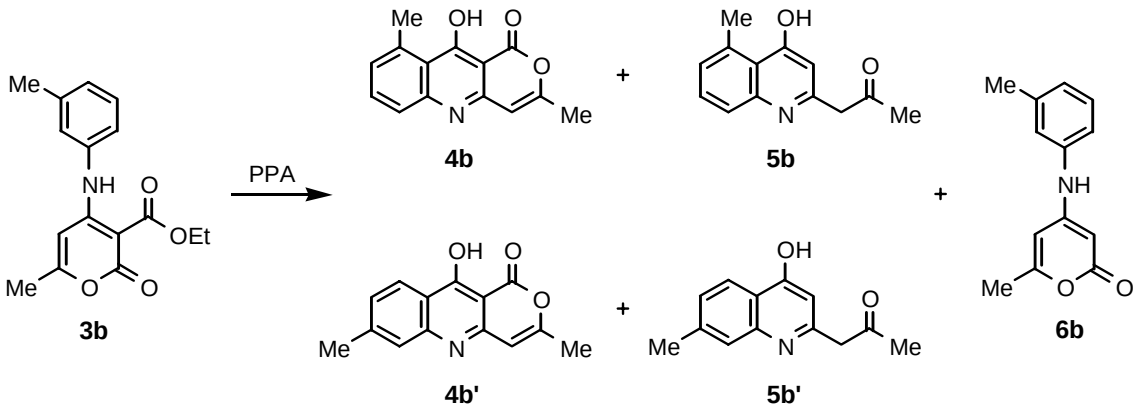
Scheme 4

Table 2. Reaction conditions for cyclization of **3a**

Run	Reaction Conditions		Yield (%)		
	Temp. (℃)	Time (min)	**4a**	**5a**	**6a**
1	100	120	19.3	—	47.5
2	130	30	26.4	2.7	57.0
3	130	10	27.5	1.6	42.7
4	150	30	42.1	25.8	1.6
5	150	10	45.7	5.9	12.5
6	180	10	46.9	27.2	1.6
7	200	10	55.3	27.2	—
8	220	10	62.5	10.9	—

When using 3-ethoxycarbonyl-6-methyl-4-(*m*-toluidino)-2*H*-pyran-2-one (**3b**) instead of **3a**, five products (**4b**, **4b'**, **5b**, **5b'**, and **6b**) were isolated as shown in Scheme 5.

The products (**4b** and **4b'**) were 10-hydroxypyranoquinoline derivatives, and were position isomers due to a methyl group on the benzene ring. The products (**5b** and **5b'**) were 4-hydroxyquinoline derivatives, and were position isomers as well as the relation between **4b** and **4b'**. The position of the methyl group on the benzene ring of these isomers were separately recognized by the split patterns of ring protons in the NMR spectra. It is considered that the differences between the yields of the isomers (**4b** and **4b'**, **5b** and **5b'**) arise from the electron-donating effect of the methyl group on the benzene ring. Additionally, the raising of the temperature improved the yields of the pyranoquinolines as shown in Table 3.



Scheme 5

Table 3. Reaction conditions for cyclization of **3b-e**

Pyrone	R	Reaction Conditions		Yield (%)		
		Temp. (℃)	Time (min)	**4**	**5**	**6**
3b	*m*-Me	150	30	42.5 [a)]	34.1 [b)]	1.2
〃	〃	220	10	57.1 [c)]	21.3 [d)]	—
3c	*o*-Me	150	30	32.3	32.4	3.8
〃	〃	220	10	57.2	26.7	—
3d	*p*-Me	150	30	47.6	43.9	1.5
〃	〃	220	10	54.8	21.4	—
3e	*p*-Cl	150	30	37.0	13.1	26.1
〃	〃	220	10	51.7	20.9	—

Yield (%) of the isomer ;
a) **4b** : **4b'** = 26.5 : 16.0 *b*) **5b** : **5b'** = 20.8 : 13.3 *c*) **4b** : **4b'** = 33.9 : 23.2 *d*) **5b** : **5b'** = 16.0 : 5.3

Although these experimental results show that the yields of the pyranoquinolines as a target compound increase at high temperature, the cyclization of the 4-arylamino-3-ethoxycarbonylpyrones (**3c-e**), which have a methyl group or chloro group at the 2- or 4-position of aniline, was carried out under the two conditions of 150℃ and 220℃ in order to confirm the effect on the yields. The yields of the pyranoquinolines and quinolines are shown in Table 3. Thus, the tendency for the yields in the cyclization of **3c-e** showed a similar to that in the reactions of **3a** and **3b**.

These results provide a new method of synthesizing 6, 7, 8 or 9-substituted 10-hydroxy-pyrano[4,3-*b*]quinoline derivatives as starting materials of 9-aminoacridine analogues. Additionally, the ring transformation of 4-arylaminopyrones (**6**) to 4-hydroxyquinoline (**5**) suggests that **6** serves as potential starting materials for a variety of quinolines.

Table 4. The Physical, Spectral, and Analytical Data of **4, 5,** and **6**

Compd No.	mp (°C)	Formula (*m/z* M^+)	Recryst. solvent	*Anal.* (%) Calcd (Found)			IR [KBr] (cm^{-1})	^{1}H-NMR [a] δ(ppm)
				C	H	N		
4a	>300 (lit.,[6] mp 300)	$C_{13}H_9NO_3$ (227)	EtOH	68.72 (68.38	3.99 3.80	6.16 6.07)	1730 1655	2.57 (3H, s), 6.92 (1H, s), 7.93 (1H, dd, *J* = 8 and 8 Hz), 8.02 (1H, d, *J* = 8 Hz), 8.24 (1H, dd, *J* = 8 and 8 Hz), 8.65 (1H, d, *J* = 8 Hz)
4b	>300	$C_{14}H_{11}NO_3$ (241)	EtOH	69.70 (69.56	4.60 4.37	5.81 5.67)	1720 1660	2.60 (3H, s), 3.11 (3H, s), 6.92 (1H, s), 7.73 (1H, d, *J* = 8 Hz), 7.85 (1H, d, *J* = 8 Hz), 8.09 (1H, dd, *J* = 8 and 8 Hz)
4b'	>300	$C_{14}H_{11}NO_3$ (241)	EtOH	69.70 (69.44	4.60 4.51	5.81 5.73)	1735 1660	2.60 (3H, s), 2.76 (3H, s), 6.94 (1H, s), 7.81(1H, dd, *J* = 8 and 1 Hz), 7.84 (1H, d, *J* = 1 Hz), 8.56 (1H, d, *J* = 8 Hz)
4c	>300	$C_{14}H_{11}NO_3$ (241)	MeOH	69.70 (69.54	4.60 4.35	5.81 5.60)	1710 1655	2.61 (3H, s), 2.84 (3H, s), 7.14 (1H, s), 7.88 (1H, dd, *J* = 8 and 7 Hz), 8.14 (1H, d, *J* = 7 Hz), 8.58 (1H, d, *J* = 8 Hz)
4d	>300	$C_{14}H_{11}NO_3$ (241)	MeOH	69.70 (69.01	4.60 4.39	5.81 5.64)	1725 1655	2.60 (3H, s), 2.72 (3H, s), 6.94 (1H, s), 7.97 (1H, d, *J* = 9 Hz), 8.14 (1H, dd, *J* = 9 and 2 Hz), 8.47 (1H, d, *J* = 2 Hz)
4e	>300	$C_{13}H_8NO_3Cl$ (261)	MeOH	59.67 (59.38	3.08 2.97	5.35 5.24)	1730 1660	2.61 (3H, s), 6.96 (1H, s), 8.04 (1H, d, *J* = 9 Hz), 8.20 (1H, dd, *J* = 9 and 2 Hz), 8.62 (1H, d, *J* = 2 Hz)
5a	225-227 (decomp)	$C_{12}H_{11}NO_2$ (201)	MeOH	71.63 (71.41	5.51 5.44	6.96 6.76)	1720 1640	2.27 (3H, s), 3.79 (2H, s), 6.05 (1H, s), 7.14-7.75 (3H, m), 8.21 (1H, dd, *J* = 7 and 1 Hz), 11.46 (1H, br)
5b	251	$C_{13}H_{13}NO_2$ (215)	EtOH	72.54 (72.46	6.09 6.14	6.51 6.72)	1720 1610	2.22 (3H, s), 2.79 (3H, s), 3.79 (2H, s), 5.83 (1H, s), 6.92-7.58 (3H, m), 11.25 (1H, br)
5b'	262	$C_{13}H_{13}NO_2$ (215)	EtOH	72.54 (72.62	6.09 6.13	6.51 6.52)	1730 1600	2.23 (3H, s), 2.42 (3H, s), 3.84 (2H, s), 5.88 (1H, s), 7.13 (1H, dd, *J* = 8 and 1 Hz), 7.26 (1H, d, *J* = 1 Hz), 7.95 (1H, d, *J* = 8 Hz), 11.39 (1H, br)
5c	229-231 (decomp)	$C_{13}H_{13}NO_2$ (215)	MeOH	72.54 (72.23	6.09 6.32	6.51 6.46)	1725 1630 1600	2.23 (3H, s), 2.49 (3H, s), 3.97 (2H, s), 5.94 (1H, s), 7.21 (1H, dd, *J* = 8 and 8 Hz), 7.48 (1H, dd, *J* = 1 and 8 Hz), 7.95 (1H, dd, *J* = 1 and 8 Hz), 10.42 (1H, br)
5d	251-252 (decomp)	$C_{13}H_{13}NO_2$ (215)	MeOH	72.54 (72.34	6.09 6.21	6.51 6.40)	1720 1600	2.23 (3H, s), 2.40 (3H, s), 3.85 (2H, s), 5.90 (1H, s), 7.41 (1H, d, *J* = 8 Hz), 7.46 (1H, dd, *J* = 2 and 8 Hz), 7.86 (1H, s), 11.50 (1H, br)
5e	270-272 (decomp)	$C_{12}H_{10}NO_2Cl$ (235)	MeOH	61.16 (60.68	4.28 4.17	5.94 5.75)	1725 1600	2.24 (3H, s), 3.89 (2H, s), 5.97 (1H, s), 7.54 (1H, d, *J* = 9 Hz), 7.66 (1H, dd, *J* = 2 and 9 Hz), 7.98 (1H, d, *J* = 2 Hz), 11.71 (1H, br)
6a	195-196	$C_{12}H_{11}NO_2$ (201)	MeOH	71.63 (71.66	5.51 5.60	6.96 6.80)	1680 1640	2.17 (3H, s), 5.19 (1H, d, *J* = 2 Hz), 5.95 (1H, m), 7.10-7.60 (5H, m), 9.23 (1H, br s)
6b	206-208	$C_{13}H_{13}NO_2$ (215)	CH_2Cl_2 - cyclohexane	72.54 (72.37	6.09 6.01	6.51 6.46)	1680 1640	2.19 (3H, s), 2.36 (3H, s), 5.22 (1H, d, *J* = 2 Hz), 6.01 (1H, m), 6.93-7.50 (4H, m), 9.20 (1H, br)

Table 4. continued

Compd No.	mp (°C)	Formula (*m/z* M^+)	Recryst. solvent	*Anal.* (%) Calcd (Found) C	H	N	IR [KBr] (cm^{-1})	^{1}H-NMR [a] δ(ppm)
6c	158	$C_{13}H_{13}NO_2$ (215)	EtOH	72.54 (72.37	6.09 6.23	6.51 6.35)	1680 1640	2.13 (3H, s), 2.22 (3H, s), 4.97 (1H, d, *J* = 2 Hz), 5.76 (1H, m), 6.60 (1H, br), 7.13-7.25 (4H, m)
6d	164-166	$C_{13}H_{13}NO_2$ (215)	MeOH	72.54 (72.38	6.09 6.07	6.51 6.40)	1680 1530	2.16 (3H, s), 2.35 (3H, s), 5.34 (1H, d, *J* = 2 Hz), 5.72 (1H, m), 6.50 (1H, br), 7.08-7.25 (4H, m)
6e	216-217	$C_{12}H_{10}NO_2Cl$ (235)	EtOH	61.16 (61.08	4.28 4.31	5.94 5.92)	1670 1635	2.18 (3H, s), 5.26 (1H, d, *J* = 2 Hz), 6.00 (1H, m), 7.17-7.60 (4H, m), 9.25 (1H, br s)

a) **4** in CF_3COOD, **5, 6** in DMSO (**6c** in $CDCl_3$, **6e** in $CDCl_3$-DMSO)

EXPERIMENTAL

All melting points are uncorrected. IR spectra were taken with a Hitachi Model 260-30 spectrophotometer. MS spectra were measured on a JEOL JMS-DX303/JMA-DA5000 instrument. ^{1}H-NMR spectra were recorded on JEOL JNM-LA600, JNM-GSX400, JNM-EX270, and JNM-PMX60$_{FT}$ spectrometers. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as the internal standard.

4-Chloro-3-ethoxycarbonyl-6-methyl-2*H*-pyran-2-one (2): Using the Hormi method,[6] **2** was prepared *via* the chlorination of 3-ethoxycarbonyl-4-hydroxy-6-methyl-2*H*-pyran-2-one (**1**): mp 86°C (lit.,[6] mp 85-86°C). 3-Ethoxycarbonyl-4-hydroxy-6-methyl-2*H*-pyran-2-one (**1**) was prepared *via* diketene and diethyl malonate using a literature procedure.[5]

4-Arylamino-3-ethoxycarbonyl-6-methyl-2*H*-pyran-2-ones (3); General procedure: A mixture of **2** (1 g, 4.6 mmol), arylamine (5.5 mmol), and Et_3N (0.7 g, 6.9 mmol) in 70 mL of EtOH was heated under reflux for 5 h. The precipitate was collected by filtration, washed with water, and then recrystallized from the solvent shown in Table 1. When there was little or no precipitate, the filtrate was concentrated *in vacuo*. The residue was diluted with 100 mL of $CHCl_3$, and the solution was washed with water, and then dried over Na_2SO_4. The solvent was removed *in vacuo*, and the residue was purified by column chromatography on silica gel with $CHCl_3$. The physical, spectral, and analytical data of the products are shown in Table 1.

Heating of 3 in PPA; General procedure: A mixture of **3** (1 g) in 15 g of PPA was heated under the

conditions shown in Table 2. The resulting mixture was slowly poured into ice-water. The formed precipitate was collected by filtration and washed with a saturated aqueous $NaHCO_3$ solution (10 mL×5) and water (10 mL×5). The precipitate was added to 30 mL of EtOH, and the suspension was stirred for 10 min at rt. The precipitate was collected by filtration and washed with EtOH (10 mL×3), and then purified by recrystallization to give **4**. The combined EtOH layers were concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of $CHCl_3$-MeOH (30:1, v:v) to give **6**. The aqueous filtrate was made alkaline with $NaHCO_3$ and the formed precipitate was collected by filtration. After washing with water, the precipitate was purified by recrystallization to give **5**. When there was little or no precipitate of **5**, the alkaline solution was extracted with $CHCl_3$. The combined $CHCl_3$ layer was washed with brine and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel with a mixture of $CHCl_3$-MeOH (30:1, v:v) to give **5**. The physical, spectral, and analytical data of the products are shown in Table 4.

Heating of 6a in PPA: A mixture of **6a** (0.5 g, 2.5 mmol) and 7 g of PPA was heated for 30 min at 150℃. The reaction mixture was treated by the same procedure described above to give **5a** (0.33 g, 66 %).

Reduction of 5a with $NaBH_4$: $NaBH_4$ (0.18 g, 5.0 mmol) was gradually added to a solution of **5a** (0.5 g, 2.5 mmol) in 50 mL of MeOH with stirring at rt. After stirring for 2 h, the reaction was quenched with 10 % HCl (10 mL) in an ice-water bath. The resulting mixture was condensed *in vacuo*. To the residue was added water (10 mL) and the solution was made alkaline with a saturated aqueous $NaHCO_3$ solution. The precipitate was collected by filtration and purified by column chromatography on silica gel with a mixture of $CHCl_3$-MeOH (3:1, v:v) to give **7** (0.4 g, 79 %); mp 209-210℃ (acetone-EtOH). IR (KBr): 3050, 2950, 1640, 1600 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 1.28 (3H, d, J = 6 Hz), 2.82 (2H, d, J = 6 Hz), 4.19 (1H, m), 6.29 (1H, s), 7.23-7.72 (3H, m), 8.14-8.31 (1H, m). MS *m/z*: 203 (M^+). *Anal*. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.80; H, 6.65; N, 6.79.

4-Chloro-2-(2-chloro-1-propenyl)quinoline (8): A mixture of **5a** (1 g, 5.0 mmol) and 12 mL (129 mmol) of $POCl_3$ was heated under reflux for 1 h. The reaction mixture was concentrated *in vacuo* and the residue was poured into ice-water. The aqueous mixture was neutralized with 20 % aqueous NH_3 solution and then extracted with $CHCl_3$. The combined $CHCl_3$ layer was washed with brine and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel with $CHCl_3$ to provide **8** (0.81 g, 68 %); mp 63-64℃ (EtOH-H_2O). IR (KBr): 1645, 1615 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.39 (3H, d, J = 1 Hz), 6.83 (1H, d, J = 1 Hz), 7.56-8.28 (5H, m). MS *m/z*: 237 (M^+). *Anal*. Calcd for $C_{12}H_9NCl_2$: C, 60.53; H, 3.81; N, 5.88. Found: C, 60.62; H, 3.75; N, 5.74.

2-Propylquinoline (9); Catalytic hydrogenation of 8: A mixture of **8** (0.5 g, 2.1 mmol), Et_3N (0.3 g, 3.1 mmol) and 5 % palladium carbon (0.15 g) in 50 mL of MeOH was shaken in an atmosphere of hydrogen at rt until a 3 mol eq. amount of hydrogen was absorbed. The reaction mixture was filtered, and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel with $CHCl_3$ to give **9** (0.32 g, 89 %) as an oil; bp 70°C/1.8 torr (lit.,[8] bp 136-139°C/13 mmHg). IR (KBr): 1620, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.02 (3H, t, *J* = 7 Hz), 1.82 (2H, m), 2.95 (2H, t, *J* = 8 Hz), 7.20-8.20 (6H, m). MS *m/z*: 171 (M^+). *Anal*. Calcd for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N, 8.18. Found: C, 83.98; H, 7.52; N, 8.02.

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