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A New Synthesis of 5-Alkyl-3-aryl-4-oxazolin-2-ones

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The reaction of (*N*-aryl-*N*-hydroxy)acylacetamides **11** with *p*-nitrobenzenesulfonyl chloride in the presence of 2 eq of triethylamine gave 5-alkyl-3-aryl-4-oxazolin-2-ones **10**. In the same manner, 5-alkyl-3-aryl-4-halogeno-4-oxazolin-2-ones **14** were synthesized from the corresponding *N*-aryl-*N*-hydroxy- α -halogeno-acylacetamides **12**, which were prepared by chlorination or bromination of (*N*-aryl-*N*-hydroxy)acylacetamides **11**.

Keywords—*N*-phenyl-*N*-hydroxyacetoacetamide; 5-methyl-3-phenyl-4-oxazolin-2-one; cyclization; *p*-nitrobenzenesulfonyl chloride; chlorination; bromination; α -lactam

In the previous paper,¹⁾ we reported that the reaction of *N*-substituted *N*-hydroxyacetoacetamides **1** with acyl chlorides in the presence of 2 eq of triethylamine gave 2-substituted 4-acyl-5-methyl-4-isoxazolin-3-ones **4** as the major product together with a regio isomer **5** through acyl rearrangement as shown in Fig. 1. As an extension of this work, we tested the applicability of this reaction for the purpose of preparing 4-ethoxycarbonyl derivatives **6** by using ethyl chloroformate as an acyl halide. However, contrary to our expectation, 5-methyl-3-phenyl-4-oxazolin-2-one (**10a**) was obtained from the reaction of *N*-phenyl-*N*-hydroxyacetoacetamide (**11a**) and ethyl chloroformate. In this paper, we wish to present a plausible mechanism for the unexpected formation of **10a**, and to describe a new synthesis of 5-alkyl-3-aryl-4-oxazolin-2-ones **10** and **14** starting from (*N*-aryl-*N*-hydroxy)acylacetamides **11** and **12**.

4-Oxazolin-2-ones **10a—c** have been synthesized by thermal²⁾ and photolytic³⁾ rearrangement of the corresponding 4-isoxazolin-3-ones **7a—c**. The three-membered α -lactams **9a—c** were reported to be intermediates in the transformation.

Firstly, for the purpose of preparing **6**, **11a** was treated with ethyl chloroformate in the presence of 2.2 eq of triethylamine to give a crystalline product **10a**, C₁₀H₉NO₂, mp 92—93 °C

Fig. 1

Fig. 2

Fig. 3

in 15.4% yield, and the unreacted **11a** (50%) was recovered. Compound **10a** was identified as 5-methyl-3-phenyl-4-oxazolin-2-one by comparison of its spectral data with those reported in the literature.²⁾ The nuclear magnetic resonance (NMR) spectrum of **10a** showed signals at 2.12 ppm (3H, d, $J=1.5$ Hz, 5-CH₃), 6.63 ppm (1H, q, $J=1.5$ Hz, 4-H), and 7.2–7.7 ppm (5H, m, N-C₆H₅). The mass spectrum (MS) of **10a** showed the molecular ion peak at m/z 175.

The reaction mechanism is proposed to be as follows: the carbanion **2a**, initially generated by triethylamine, attacks the nitrogen atom of the hydroxamate with the elimination of ethoxycarbonate to give the α -lactam **9a**, which is isomerized to the 4-oxazolin-2-one **10a**. The α -lactam **9a** is the same intermediate as proposed in the isoxazoline-oxazoline transformation.²⁾ Therefore, a good leaving group on the nitrogen atom of **2a** was expected to accelerate the formation of the 4-oxazolin-2-one **10a**. When *p*-toluenesulfonyl chloride was used in place of ethyl chloroformate, **11a** gave a 70% yield of **10a** in the presence of triethylamine (2.1 eq) in benzene at room temperature for 12 h. This result supported our hypothesis. Several leaving groups were examined, as shown in Table I. As a result, the *p*-nitrobenzenesulfonyloxy group was found to be the most suitable leaving group, and was

TABLE I. Yield of 5-Methyl-3-phenyl-4-oxazolin-2-one (**10a**)

RX	Et ₃ N (eq)	Conditions		Yield (%)
EtOCOC ₂ H ₅	2.2	50 °C	3 h	15.4
<i>p</i> -(CH ₃)C ₆ H ₄ SO ₂ Cl	2.1	r.t.	12 h	70.0
CH ₃ SO ₂ Cl	2.2	r.t.	18 h	46.6
<i>p</i> -(NO ₂)C ₆ H ₄ SO ₂ Cl ⁽¹⁾	2.1	r.t.	24 h	77.8
(CF ₃ SO ₂) ₂ O	2.2	r.t.	17 h	12.1
CCl ₃ COCl ⁽⁵⁾	2.2	r.t.	2 h	22.0

r.t. = room temperature.

TABLE II. Synthesis of 5-Alkyl-3-aryl-4-oxazolin-2-ones (**10**)

10	R	X	Yield (%)	mp (°C)	Formula	Analysis (%)			
						Calcd	(Found)		
						C	H	N	Halogen
b	Me	<i>p</i> -F	69.0	100—103	C ₁₀ H ₈ FNO ₂	62.18 (61.94)	4.17 4.04	7.25 7.24	(F) 9.83 9.72)
d	Me	<i>p</i> -Me	66.3	136	C ₁₁ H ₁₁ NO ₂	69.83 (69.51)	5.86 5.89	7.40 7.55)	
e	Me	<i>p</i> -Cl	80.0	141—142	C ₁₀ H ₈ ClNO ₂	57.30 (57.04)	3.85 3.75	6.68 6.79	(Cl) 16.91 17.21)
f	Me	<i>m</i> -Cl	64.5	109—110	C ₁₀ H ₈ ClNO ₂	57.30 (57.08)	3.85 3.81	6.68 6.69	(Cl) 16.91 17.18)
g	Me	<i>p</i> -Br	74.5	132—133	C ₁₀ H ₈ BrNO ₂	47.27 (47.35)	3.17 3.15	5.51 5.53	(Br) 31.45 31.70)
h	Me	<i>m</i> -Me	75.0	165—167	C ₁₁ H ₁₁ NO ₂	69.83 (69.53)	5.86 5.73	7.40 7.66)	
i	Et	H	57.6	82—84	C ₁₁ H ₁₁ NO ₂	69.83 (69.55)	5.86 5.81	7.40 7.36)	
j	Et	<i>p</i> -Cl	62.6	118—119	C ₁₁ H ₁₀ ClNO ₂	59.07 (58.91)	4.51 4.26	6.26 6.14	(Cl) 15.85 15.92)
k	Et	<i>p</i> -Me	41.7	68—71	C ₁₂ H ₁₃ NO ₂	70.92 (70.66)	6.45 6.46	6.89 6.89)	
l	<i>n</i> -Pr	H	38.8	90—91	C ₁₂ H ₁₃ NO ₂	70.92 (70.69)	6.45 6.40	6.89 6.87)	
m	<i>n</i> -Pr	<i>p</i> -Cl	39.1	125—129	C ₁₂ H ₁₂ ClNO ₂	60.64 (69.39)	5.09 4.97	5.89 5.86	(Cl) 14.92 14.68)

TABLE III. Halogenation of **11** to **12** and **13**

Run	11	R	X	Reagent	Y	12 :	Yield (%)	mp (°C)	13 :	Yield (%)	mp (°C)
1	a	Me	H	CF ₃ SO ₂ Cl	Cl	a	56.0	91—94			
2	a	Me	H	Br ₂	Br	b	72.1	90—93			
3	b	Me	<i>p</i> -F	CF ₃ SO ₂ Cl	Cl	c	77.2	122—124			
4	b	Me	<i>p</i> -F	Br ₂	Br	d	60.6	114—116			
5	d	Me	<i>p</i> -Me	CF ₃ SO ₂ Cl	Cl	e	17.1	104—105	e	31.2	59—60
6	d	Me	<i>p</i> -Me	CCl ₃ SO ₂ Cl	Cl	e	21.0		e	32.0	
7	e	Me	<i>p</i> -Cl	CF ₃ SO ₂ Cl	Cl	f	84.9	98—100	f	8.0	98—99
8	e	Me	<i>p</i> -Cl	Br ₂	Br	g	68.7	86—88			
9	f	Me	<i>m</i> -Cl	CF ₃ SO ₂ Cl	Cl	h	34.0	119—120	h	32.0	Oil
10	g	Me	<i>p</i> -Br	CF ₃ SO ₂ Cl	Cl	i	57.4	76—77		(Trace)	
11	g	Me	<i>p</i> -Br	Br ₂	Br	j	63.6	111—112			
12	j	Et	<i>p</i> -Cl	CF ₃ SO ₂ Cl	Cl	k	67.1 ^{a)}	Oil	k	15.0	(Unstable)
13	j	Et	<i>p</i> -Cl	Br ₂	Br	l	81.7 ^{a)}	82—84			
14	m	<i>n</i> -Pr	<i>p</i> -Cl	CCl ₃ SO ₂ Cl	Cl	m	70.5 ^{a)}	113—114		(Trace)	
15	n	iso-Pr	<i>p</i> -Cl	CCl ₃ SO ₂ Cl	Cl	n	74.6	96—97			

^{a)} Starting materials (runs 12, 13, and 14) were recovered in 16.1%, 10.0%, and 11.3% yields, respectively.

employed in the following cyclizations.

A variety of (*N*-aryl-*N*-hydroxy)acylacetamides **11** reacted with *p*-nitrobenzenesulfonyl chloride (1.1 eq) in the presence of triethylamine (2.2 eq) and cyclized smoothly into the corresponding 4-oxazolin-2-ones **10** in moderate to good yields as shown in Table II. Following the procedures described in the literature, the starting materials, (*N*-aryl-*N*-hydroxy)acetoacetamides **11a**, **11b**, and **11d—h**, and (*N*-aryl-*N*-hydroxy)acylacetamides **11i—m** were easily prepared from *N*-arylhydroxylamines and diketene,⁶⁾ and from *N*-arylhydroxylamines and acyl Meldrum's acids (5-acyl-2,2-dimethyl-1,3-dioxane-4,6-diones),⁷⁾ respectively. An NMR analysis indicated that **11** existed mainly as a cyclic form **11A**, as reported by Perronnet *et al.*⁸⁾

The synthesis of 4-chloro and 4-bromo derivatives of **10** was completed by the introduction of the halogen atom at the α -position of the starting materials **11**, followed by cyclization as described above. The bromination of **11** with bromine (1.1 eq) and triethylamine (1.1 eq) in benzene gave α -bromoacylacetamides **12** as the sole product (Table III). On the other hand, compounds **11** were chlorinated with trifluoromethanesulfonyl chloride⁹⁾ or trichloromethanesulfonyl chloride in the presence of triethylamine (1.1 eq) to give α -chloro compounds **12**, accompanied with *N*, α -dichloro compounds **13** in some runs (Table III). The cyclization of **12** into **14** was successfully performed under the above conditions, as shown in Table IV. However, the prepared 4-bromo derivatives were generally too unstable to be isolated, and decomposed quickly.

In conclusion, a new synthesis of 4-oxazolin-2-ones **10** and **14** was achieved by the cyclization of (*N*-aryl-*N*-hydroxy)acylacetamides **11** and **12** with the aid of *p*-nitrobenzenesulfonyl chloride and triethylamine.

Experimental

All melting points are uncorrected. Infrared (IR) spectra (determined on a Jasco A-102 spectrometer) refer to

TABLE IV. Synthesis of 5-Alkyl-3-aryl-4-halogeno-4-oxazolin-2-ones (**14**)

Run	14	R	X	Y	Yield (%)	mp (°C)	Formula	Analysis (%)			
								Calcd (Found)			
								C	H	N	Halogen
1	a	Me	H	Cl	36.5	30—34	C ₁₀ H ₈ ClNO ₂	57.30 (57.01)	3.85 3.92	6.68 6.35	(Cl) 16.91 16.25
2	b	Me	H	Br	40.0	130—134	C ₁₀ H ₈ BrNO ₂	47.98 (47.77)	3.57 3.27	5.72 5.41	
3	c	Me	<i>p</i> -F	Cl	52.7	58—59	C ₁₀ H ₇ ClFNO ₂	52.77 (52.48)	3.10 3.15	6.15 5.97	(Cl) (F) 15.58 8.35 15.28 8.40
4	d	Me	<i>p</i> -F	Br	(Unstable)						
5	f	Me	<i>p</i> -Cl	Cl	56.2	58—61	C ₁₀ H ₇ Cl ₂ NO ₂	49.21 (49.23)	2.89 2.91	5.74 5.71	(Cl) 29.05 28.84
6	g	Me	<i>p</i> -Cl	Br	27.9	112—116	C ₁₀ H ₇ BrClNO ₂	42.33 (42.03)	2.60 2.45	5.00 4.85	
7	h	Me	<i>m</i> -Cl	Cl	73.0	82—85	C ₁₀ H ₇ Cl ₂ NO ₂	49.31 (49.21)	2.76 2.89	5.58 5.74	(Cl) 29.20 29.05
8	i	Me	<i>p</i> -Br	Cl	60.0	101—103	C ₁₀ H ₇ BrClNO ₂	41.63 (41.87)	2.45 2.63	4.85 4.80	(Br) (Cl) 27.69 12.29 27.61 12.34
9	j	Me	<i>p</i> -Br	Br	(Unstable)						
10	k	Et	<i>p</i> -Cl	Cl	51.0	101—104	C ₁₁ H ₉ Cl ₂ NO ₂	51.08 (51.19)	3.39 3.51	5.41 5.43	(Cl) 27.43 27.47
11	l	Et	<i>p</i> -Cl	Br	40.0	131—132	C ₁₁ H ₉ BrClNO ₂	43.67 (43.60)	3.00 2.94	4.63 4.56	(Br) (Cl) 26.41 11.72 26.60 11.84
12	m	<i>n</i> -Pr	<i>p</i> -Cl	Cl	60.1	78—80	C ₁₂ H ₁₁ Cl ₂ NO ₂	52.96 (52.83)	4.07 4.16	5.15 5.14	(Cl) 26.06 25.73
13	n	iso-Pr	<i>p</i> -Cl	Cl	57.2	127—128	C ₁₂ H ₁₀ Cl ₂ NO ₂	52.96 (52.61)	4.07 4.06	5.15 5.02	(Cl) 26.06 26.27

Nujol mulls. NMR spectra were recorded at 60 MHz on a Varian 360A spectrometer with tetramethylsilane as an internal standard.

3-Phenyl-5-methyl-4-oxazolin-2-one (10a)—*p*-Nitrobenzenesulfonyl chloride (0.60 g, 2.73 mmol) and triethylamine (0.55 g, 5.4 mmol) were added to a solution of *N*-phenyl-*N*-hydroxyacetoacetamide (**11a**) (0.50 g, 2.6 mmol) in dry benzene (20 ml) under ice-cooling. After stirring at room temperature for 12 h, the reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The residue was chromatographed over SiO₂ to give 0.35 g (77.8%) of **10a** as crystals.

Compounds **10** and **14** were synthesized in the same manner as above. Details and spectral data are given in Tables II, IV, V, and VI.

***N*-(*p*-Chlorophenyl)-*N*-hydroxy- α -chloroacetoacetamide (12f) and *N*-(*p*-Chlorophenyl)-*N*, α -dichloroacetoacetamide (13f)**—Triethylamine (1.50 g, 14.8 mmol) was added to a solution of *N*-(*p*-chlorophenyl)-*N*-hydroxyacetoacetamide (**11e**) (3.0 g, 13.2 mmol) and trifluoromethanesulfonyl chloride (2.4 g, 15.4 mmol) in dry benzene

TABLE V. Spectral Data for **10b** and **10d—m**

10	IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} (C=O)	NMR (CDCl_3) δ^a ppm
b	1750	2.15 (3H, d, $J=1.5$), 6.53 (1H, q, $J=1.5$), 7.1 (2H, d, d, $J=8, 9$), 7.5 (2H, d, d, $J=5, 9$)
d	1745	2.13 (3H, d, $J=1.5$), 2.35 (3H, s), 6.62 (1H, q, $J=1.5$), 7.25 (2H, d, $J=9$), 7.51 (2H, d, $J=9$)
e	1745	2.13 (3H, d, $J=1.5$), 6.64 (1H, q, $J=1.5$), 7.37 (2H, d, $J=9$), 7.58 (2H, d, $J=9$)
f	1740	2.14 (3H, d, $J=1.5$), 6.68 (1H, q, $J=1.5$), 7.1—7.8 (4H, m)
g	1750	2.15 (3H, d, $J=1.5$), 6.63 (1H, q, $J=1.5$), 7.55 (4H, m)
h	1745	2.12 (3H, d, $J=1.5$), 2.37 (3H, s), 6.63 (1H, q, $J=1.5$), 7.0—7.5 (4H, m)
i	1725	1.21 (3H, d, $J=7.5$), 2.52 (2H, dq, $J=1.2, 7.5$), 6.57 (1H, t, $J=1.2$), 7.2—7.6 (5H, m)
j	1735	1.23 (3H, t, $J=7.5$), 2.54 (2H, dq, $J=1.2, 7.5$), 6.57 (1H, t, $J=1.2$), 7.35 (2H, d, $J=9$), 7.58 (2H, d, $J=9$)
k	1735	1.21 (1H, t, $J=7.5$), 2.35 (3H, s), 2.50 (2H, dq, $J=1.2, 7.5$), 6.57 (1H, t, $J=1.1$), 7.18 (2H, d, $J=9$), 7.42 (2H, d, $J=9$)
l	1750	1.0 (3H, t, $J=7.5$), 1.65 (2H, tq, $J=7.5, 7.5$), 2.45 (2H, dt, $J=1.1, 7.5$), 6.56 (1H, t, $J=1.1$), 7.2—7.6 (5H, m)
m	1735	0.99 (3H, t, $J=7.5$), 1.67 (2H, tq, $J=7.5, 7.5$), 2.48 (2H, dt, $J=1.2, 7.5$), 6.57 (1H, t, $J=7.5$), 7.35 (2H, d, $J=9$), 7.55 (2H, d, $J=9$)

^a) J is the coupling constant in Hz.

TABLE VI. Spectral Data for **14a—n**

14	IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}	NMR (CDCl_3) δ^a ppm
a	1780, 1750, 1690	2.17 (3H, s), 7.43 (5H, s)
b	1760, 1670	2.15 (3H, s), 7.37 (5H, s)
c	1785, 1770, 1690	2.17 (3H, s), 7.0—7.5 (4H, m)
f	1780, 1685	2.18 (3H, s), 7.2—7.7 (4H, m)
g	1765, 1675	2.14 (3H, s), 7.20 (2H, d, $J=9$), 7.42 (2H, d, $J=9$)
h	1770, 1680	2.17 (3H, s), 7.15—7.4 (4H, m)
i	1780, 1765, 1695	2.17 (3H, s), 7.25 (2H, d, $J=9$), 7.62 (2H, d, $J=9$)
k	1760, 1680	1.32 (3H, t, $J=7$), 2.60 (2H, q, $J=7$), 7.15—7.55 (4H, m)
l	1740	1.22 (3H, t, $J=7$), 2.51 (2H, q, $J=7$), 7.19 (2H, d, $J=9$)
m	1790, 1755	0.99 (3H, t, $J=9$), 1.45—1.85 (2H, m), 2.51 (2H, t, $J=7$), 7.35 (2H, d, $J=9$), 7.55 (2H, d, $J=9$)
n	1755	1.28 (6H, d, $J=7$), 3.01 (1H, qq, $J=7, 7$), 7.38 (2H, d, $J=9$), 7.57 (2H, d, $J=9$)

^a) J is the coupling constant in Hz.

(40 ml) under ice-cooling. After stirring at room temperature for 1.5 h, the reaction mixture was poured into water and extracted with ether. The extract was washed with water and brine, dried over MgSO_4 , and concentrated *in vacuo*. The residue was chromatographed over SiO_2 to give 0.293 g (84.9%) of **12f** and 0.30 g (8.0%) of **13f** as the less polar fraction.

12f: *Anal.* Calcd for $\text{C}_{10}\text{H}_9\text{Cl}_2\text{NO}_3$: C, 45.83; H, 3.46; N, 5.34. Found: C, 46.12; H, 3.45; N, 5.34. IR $\nu_{\max} \text{cm}^{-1}$: 3340 (OH), 1680 (C=O). NMR (CDCl_3) δ : 1.80 (3H, s), 4.4—4.7 (2H, m), 7.33 (2H, d, $J=8$ Hz), 7.65 (2H, d, $J=8$ Hz).

13f: *Anal.* Calcd for $\text{C}_{10}\text{H}_8\text{Cl}_3\text{NO}_3$: C, 42.81; H, 2.87; N, 4.99. Found: C, 42.52; H, 2.65; N, 5.23. IR $\nu_{\max} \text{cm}^{-1}$: 3260 (m, OH), 1735 (m), 1700 (s), 1665 (s, C=O). NMR (CDCl_3) δ : 2.16 (0.9H, s), 2.53 (2.1H, s), 6.06 (0.7H, s), 7.2—7.65 (4H, m), 8.4 (0.3H, br s).

Compounds **12a**, **12c**, **12e**, **12h**, **12i**, **12k**, **13e**, and **13h** were synthesized in the same manner as above. Under the same reaction conditions as above, **12e**, **12m**, **12n**, and **13e** were synthesized with trichloromethanesulfonyl chloride in place of trifluoromethanesulfonyl chloride (Table III).

12a: Anal. Calcd for $C_{10}H_{10}ClNO_3$: C, 52.76; H, 4.42; Cl, 15.75; N, 6.15. Found: C, 52.47; H, 4.19; Cl, 15.62; N, 6.18. IR $\nu_{\max}$ cm^{-1} : 3300 (OH), 1690 (C=O). NMR ($CDCl_3$) δ : 1.77 (3H, s), 4.37 (0.5H, s), 4.66 (0.5H, s), 4.83 (0.5H, s), 7.1–7.8 (5H, m).

12c: Anal. Calcd for $C_{10}H_9ClFNO_3$: C, 48.90; H, 3.69; N, 5.70. Found: C, 48.86; H, 3.69; N, 5.63. IR $\nu_{\max}$ cm^{-1} : 3350 (OH), 1680 (C=O). NMR ($CDCl_3$) δ : 1.79 (3H, s), 4.35 (0.5H, s), 4.4 (1H, s), 4.66 (0.5H, s), 6.8–7.7 (4H, m).

12e: Anal. Calcd for $C_{11}H_{12}ClNO_3$: C, 54.66; H, 4.59; Cl, 14.67; N, 5.79. Found: C, 54.93; H, 4.96; Cl, 14.48; N, 5.74. IR $\nu_{\max}$ cm^{-1} : 3330 (OH), 1685 (C=O). NMR ($CDCl_3$) δ : 1.75 (3H, s), 2.31 (3H, s), 4.34 (0.5H, s), 4.63 (0.5H, s), 7.10 (2H, d, $J=9$ Hz), 7.42 (1H, br s), 7.58 (2H, d, $J=9$ Hz).

13e: Anal. Calcd for $C_{11}H_{11}Cl_2NO_2$: C, 50.76; H, 3.46; Cl, 27.31; N, 5.38. Found: C, 50.44; H, 3.37; Cl, 27.30; N, 5.28. IR $\nu_{\max}$ cm^{-1} : 3300 (m, OH), 1760 (m), 1740 (m), 1670 (s, C=O). NMR ($CDCl_3$) δ : 2.32 (3H, s), 2.51 (3H, s), 7.16 (2H, d, $J=9$ Hz), 7.46 (2H, d, $J=9$ Hz), 8.3 (1H, br s).

12h: Anal. Calcd for $C_{10}H_9Cl_2NO_3$: C, 45.83; H, 3.46; Cl, 27.05; N, 5.34. Found: C, 45.57; H, 3.35; Cl, 27.34; N, 5.25. IR $\nu_{\max}$ cm^{-1} : 3310 (OH), 1695 (C=O). NMR ($CDCl_3$) δ : 1.78 (3H, s), 4.39 (0.5H, s), 4.71 (0.5H, s), 5.0 (0.5H, br s), 5.25 (0.5H, br s), 7.1–7.8 (4H, m).

13h: MS m/z : 259 (M^+). NMR ($CDCl_3$) δ : 2.03 (0.3H, s), 2.56 (2.7H, s), 6.05 (0.1H, s), 7.0–7.4 (3H, m), 7.6–7.7 (1H, m), 8.6 (0.9H, br s).

12i: Anal. Calcd for $C_{10}H_9BrClNO_3$: C, 39.18; H, 2.96; N, 4.57; Found: C, 39.16; H, 2.89; N, 4.47. IR $\nu_{\max}$ cm^{-1} : 3330 (OH), 1695 (C=O). NMR ($CDCl_3$) δ : 1.80 (3H, s), 4.35 (0.5H, s), 4.45 (1H, br s), 4.65 (0.5H, s), 7.48 (4H, s).

12k: Anal. Calcd for $C_{11}H_{11}Cl_2NO_3$: C, 47.85; H, 4.02; N, 5.07. Found: C, 47.65; H, 3.95; N, 4.82. IR $\nu_{\max}$ cm^{-1} : 3350 (OH), 1695 (C=O). NMR ($CDCl_3$) δ : 0.8–1.3 (3H, m), 1.7–2.2 (2H, m), 4.30 (0.5H, s), 4.70 (0.5H, s), 4.85 (0.5H, br s), 5.05 (0.5H, br s), 7.18 (2H, d, $J=8$ Hz), 7.55 (2H, d, $J=8$ Hz).

12m: Anal. Calcd for $C_{12}H_{13}Cl_2NO_3$: C, 49.68; H, 4.52; N, 4.83. Found: C, 49.58; H, 4.43; N, 4.65. IR $\nu_{\max}$ cm^{-1} : 3340 (OH), 1695 (C=O). NMR δ ppm ($CDCl_3$): 1.05 (3H, t, $J=7$ Hz), 1.4–2.3 (4H, m), 4.2 (1H, br s), 4.40 (0.5H, s), 4.80 (0.5H, s), 7.40 (2H, d, $J=9$ Hz), 7.74 (2H, d, $J=9$ Hz).

12n: Anal. Calcd for $C_{12}H_{13}Cl_2NO_3$: C, 49.68; H, 4.52; Cl, 24.44; N, 4.83. Found: C, 49.58; H, 4.50; Cl, 24.05; N, 4.76. IR $\nu_{\max}$ cm^{-1} : 3330 (OH), 1675 (C=O). NMR ($CDCl_3$) δ : 1.15 (1.8H, d, $J=7$ Hz), 1.17 (1.2H, d, $J=7$ Hz), 2.25 (0.6H, qq, $J=7$, 7 Hz), 2.54 (0.4H, qq, $J=7$, 7 Hz), 4.31 (0.6H, s), 4.79 (0.4H, s), 7.25 (0.8H, d, $J=8.5$ Hz), 7.29 (1.2H, d, $J=8.5$ Hz), 7.62 (0.8H, d, $J=8.5$ Hz), 7.69 (1.2H, d, $J=8.5$ Hz).

***N*-(*p*-Chlorophenyl)-*N*-hydroxy- α -bromoacetoacetamide (**12g**)**—Bromine (0.53 g, 3.3 ml) was added dropwise to a solution of *N*-(*p*-chlorophenyl)-*N*-hydroxyacetoacetate (**11e**) (0.681 g, 3.0 mmol) and triethylamine (0.334 g, 3.3 mmol) in dry benzene (30 ml) under ice-cooling. After stirring at room temperature for 30 min, the reaction mixture was poured into water, and extracted with ether. The extract was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed over SiO_2 to give 0.63 g (68.7%) of **12g**. Anal. Calcd for $C_{10}H_9BrClNO_3$: C, 39.18; H, 2.96; Br, 26.07; Cl, 11.57; N, 4.57. Found: C, 39.26; H, 2.96; Br, 26.02; Cl, 11.57; N, 4.56. IR $\nu_{\max}$ cm^{-1} : 3340 (OH), 1680 (C=O). NMR ($CDCl_3$) δ : 1.78 (1.5H, s), 1.84 (1.5H, s), 4.40 (0.5H, s), 4.70 (0.5H, s), 4.4–4.9 (1H, br s), 7.20 (2H, d, $J=9$ Hz), 7.55 (2H, d, $J=9$ Hz).

Compounds **12b**, **12d**, **12j**, and **12l** were prepared in the same manner as above (Table III).

12b: Anal. Calcd for $C_{10}H_{10}BrNO_3$: C, 44.14; H, 3.70; Br, 29.37; N, 5.15. Found: C, 43.86; H, 3.52; Br, 29.66; N, 5.14. IR $\nu_{\max}$ cm^{-1} : 3310 (OH), 1690 (C=O). NMR ($CDCl_3$) δ : 1.65 (1.5H, s), 1.84 (1.5H, s), 4.45 (0.5H, s), 4.75 (0.5H, s), 5.35 (1H, br s), 7.1–7.7 (5H, m).

12d: Anal. Calcd for $C_{10}H_9BrFNO_3$: C, 41.40; H, 3.13; Br, 27.55; F, 6.55; N, 4.83. Found: C, 41.52; H, 3.15; Br, 27.84; F, 6.46; N, 4.91. IR $\nu_{\max}$ cm^{-1} : 3350 (OH), 1690 (C=O). NMR ($CDCl_3$) δ : 1.80 (1.5H, s), 1.88 (1.5H, s), 4.22 (1H, br s), 4.41 (0.5H, s), 4.71 (0.5H, s), 6.9–7.3 (2H, m), 7.5–7.8 (2H, m).

12j: Anal. Calcd for $C_{10}H_9Br_2NO_3$: C, 34.22; H, 2.58; Br, 45.53; N, 3.99. Found: C, 34.14; H, 2.43; Br, 45.79; N, 4.20. IR $\nu_{\max}$ cm^{-1} : 3310 (OH), 1690 (C=O). NMR ($CDCl_3$) δ : 1.79 (1.5H, s), 1.86 (1.5H, s), 4.25 (0.5H, br s), 4.42 (0.5H, s), 4.50 (0.5H, br s), 4.72 (0.5H, s), 7.53 (4H, s).

12l: Anal. Calcd for $C_{11}H_{11}BrClNO_3$: C, 41.21; H, 3.46; Br, 24.93; Cl, 11.06; N, 4.37. Found: C, 40.98; H, 3.31; Br, 25.19; Cl, 11.19; N, 4.30. IR $\nu_{\max}$ cm^{-1} : 3300 (OH), 1685 (C=O). NMR ($CDCl_3$) δ : 1.11 (3H, t, $J=7$ Hz), 1.8–2.2 (2H, m), 4.40 (0.5H, s), 4.80 (0.5H, s), 7.36 (2H, d, $J=7$ Hz), 7.71 (2H, d, $J=7$ Hz), OH was not observed.

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