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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 thermal[2] and photolytic[3] 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**, $C_{10}H_9NO_2$, mp 92—93 °C

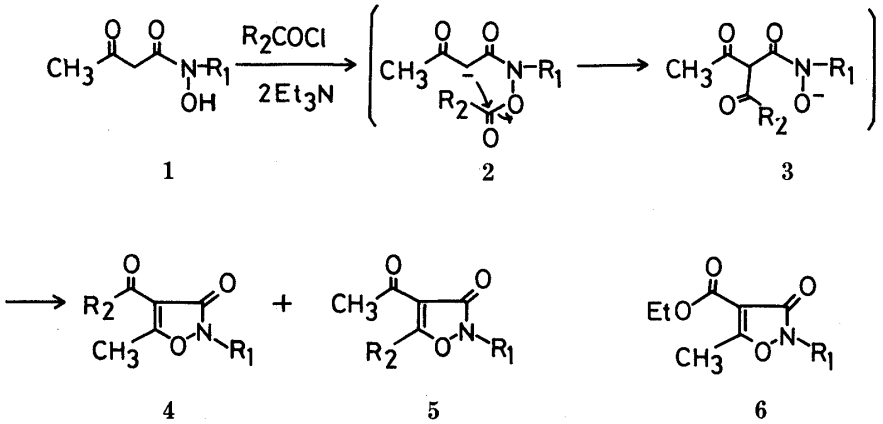


Fig. 1

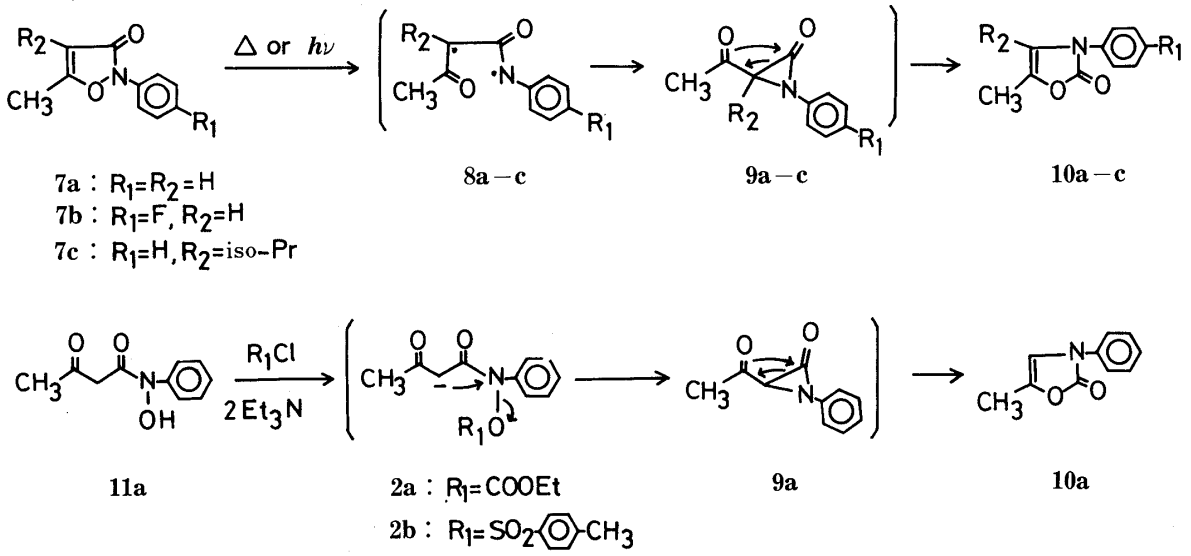


Fig. 2

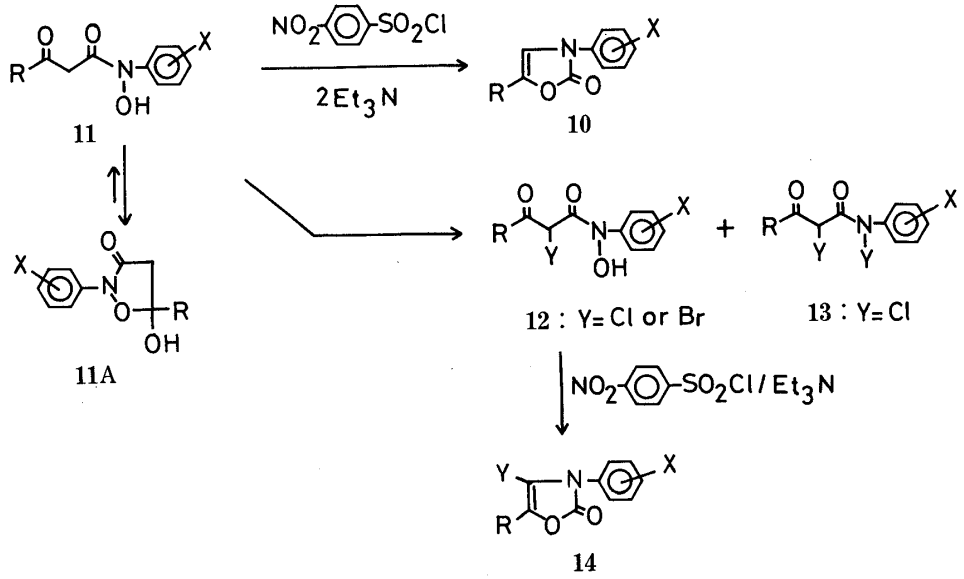
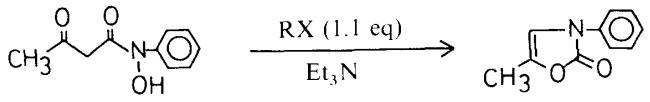


Fig. 3

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-CH_3), 6.63 ppm (1H, q, $J=1.5$ Hz, 4-H), and 7.2—7.7 ppm (5H, m, N–C_6H_5). 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**)

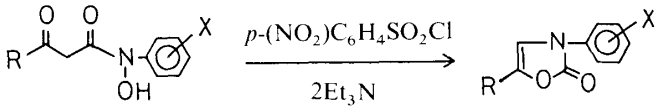


1a **10a**

RX	Et_3N (eq)	Conditions		Yield (%)
EtOCOCl	2.2	50 C	3 h	15.4
p-$(CH_3)C_6H_4SO_2Cl$	2.1	r.t.	12 h	70.0
CH_3SO_2Cl	2.2	r.t.	18 h	46.6
p-$(NO_2)C_6H_4SO_2Cl$[4]	2.1	r.t.	24 h	77.8
$(CF_3SO_2)_2O$	2.2	r.t.	17 h	12.1
CCl_3COCl[5]	2.2	r.t.	2 h	22.0

r.t. = room temperature.

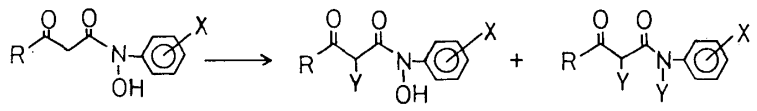
TABLE II. Synthesis of 5-Alkyl-3-aryl-4-oxazolin-2-ones (**10**)



11 **10**

10	R	X	Yield (%)	mp (C)	Formula	Analysis (%) Calcd (Found)			
						C	H	N	Halogen
b	Me	*p*-F	69.0	100—103	$C_{10}H_8FNO_2$	62.18	4.17	7.25	(F) 9.83
						(61.94	4.04	7.24	9.72)
d	Me	*p*-Me	66.3	136	$C_{11}H_{11}NO_2$	69.83	5.86	7.40	
						(69.51	5.89	7.55)	
e	Me	*p*-Cl	80.0	141—142	$C_{10}H_8ClNO_2$	57.30	3.85	6.68	(Cl) 16.91
						(57.04	3.75	6.79	17.21)
f	Me	*m*-Cl	64.5	109—110	$C_{10}H_8ClNO_2$	57.30	3.85	6.68	(Cl) 16.91
						(57.08	3.81	6.69	17.18)
g	Me	*p*-Br	74.5	132—133	$C_{10}H_8BrNO_2$	47.27	3.17	5.51	(Br) 31.45
						(47.35	3.15	5.53	31.70)
h	Me	*m*-Me	75.0	165—167	$C_{11}H_{11}NO_2$	69.83	5.86	7.40	
						(69.53	5.73	7.66)	
i	Et	H	57.6	82—84	$C_{11}H_{11}NO_2$	69.83	5.86	7.40	
						(69.55	5.81	7.36)	
j	Et	*p*-Cl	62.6	118—119	$C_{11}H_{10}ClNO_2$	59.07	4.51	6.26	(Cl) 15.85
						(58.91	4.26	6.14	15.92)
k	Et	*p*-Me	41.7	68—71	$C_{12}H_{13}NO_2$	70.92	6.45	6.89	
						(70.66	6.46	6.89)	
l	*n*-Pr	H	38.8	90—91	$C_{12}H_{13}NO_2$	70.92	6.45	6.89	
						(70.69	6.40	6.87)	
m	*n*-Pr	*p*-Cl	39.1	125—129	$C_{12}H_{12}ClNO_2$	60.64	5.09	5.89	(Cl) 14.92
						(69.39	4.97	5.86	14.68)

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



11 **12** **13**

Run	11	R	X	Reagent	Y	12:	Yield (%)	mp (°C)	13:	Yield (%)	mp (°C)
1	**a**	Me	H	CF_3SO_2Cl	Cl	**a**	56.0	91—94			
2	**a**	Me	H	Br_2	Br	**b**	72.1	90—93			
3	**b**	Me	*p*-F	CF_3SO_2Cl	Cl	**c**	77.2	122—124			
4	**b**	Me	*p*-F	Br_2	Br	**d**	60.6	114—116			
5	**d**	Me	*p*-Me	CF_3SO_2Cl	Cl	**e**	17.1	104—105	**e**	31.2	59—60
6	**d**	Me	*p*-Me	CCl_3SO_2Cl	Cl	**e**	21.0		**e**	32.0	
7	**e**	Me	*p*-Cl	CF_3SO_2Cl	Cl	**f**	84.9	98—100	**f**	8.0	98—99
8	**e**	Me	*p*-Cl	Br_2	Br	**g**	68.7	86—88			
9	**f**	Me	*m*-Cl	CF_3SO_2Cl	Cl	**h**	34.0	119—120	**h**	32.0	Oil
10	**g**	Me	*p*-Br	CF_3SO_2Cl	Cl	**i**	57.4	76—77		(Trace)	
11	**g**	Me	*p*-Br	Br_2	Br	**j**	63.6	111—112			
12	**j**	Et	*p*-Cl	CF_3SO_2Cl	Cl	**k**	67.1[a]	Oil	**k**	15.0	(Unstable)
13	**j**	Et	*p*-Cl	Br_2	Br	**l**	81.7[a]	82—84			
14	**m**	*n*-Pr	*p*-Cl	CCl_3SO_2Cl	Cl	**m**	70.5[a]	113—114		(Trace)	
15	**n**	iso-Pr	*p*-Cl	CCl_3SO_2Cl	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]

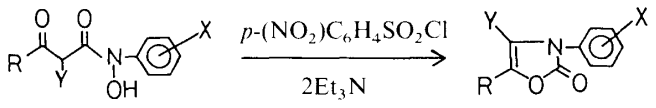
The synthesis of 4-chloro and 4-bromo derivatives of **10** was completed by the introduction of the halogen atom at the α-position of the starting materials **11**, followed by cyclization as described above. The bromination of **11** with bromine (1.1 eq) and triethylamine (1.1 eq) in benzene gave α-bromoacylacetamides **12** as the sole product (Table III). On the other hand, compounds **11** were chlorinated with trifluoromethanesulfonyl chloride[9] 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**)



12 **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	$C_{10}H_8ClNO_2$	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	$C_{10}H_8BrNO_2$	47.98 (47.77	3.57 3.27	5.72 5.41)		
3	**c**	Me	*p*-F	Cl	52.7	58—59	$C_{10}H_7ClFNO_2$	52.77 (52.48	3.10 3.15	6.15 5.97	(Cl) 15.58 15.28	(F) 8.35 8.40)
4	**d**	Me	*p*-F	Br	(Unstable)							
5	**f**	Me	*p*-Cl	Cl	56.2	58—61	$C_{10}H_7Cl_2NO_2$	49.21 (49.23	2.89 2.91	5.74 5.71	(Cl) 29.05 28.84)	
6	**g**	Me	*p*-Cl	Br	27.9	112—116	$C_{10}H_7BrClNO_2$	42.33 (42.03	2.60 2.45	5.00 4.85)		
7	**h**	Me	*m*-Cl	Cl	73.0	82—85	$C_{10}H_7Cl_2NO_2$	49.31 (49.21	2.76 2.89	5.58 5.74	(Cl) 29.20 29.05)	
8	**i**	Me	*p*-Br	Cl	60.0	101—103	$C_{10}H_7BrClNO_2$	41.63 (41.87	2.45 2.63	4.85 4.80	(Br) 27.69 27.61	(Cl) 12.29 12.34)
9	**j**	Me	*p*-Br	Br	(Unstable)							
10	**k**	Et	*p*-Cl	Cl	51.0	101—104	$C_{11}H_9Cl_2NO_2$	51.08 (51.19	3.39 3.51	5.41 5.43	(Cl) 27.43 27.47)	
11	**l**	Et	*p*-Cl	Br	40.0	131—132	$C_{11}H_9BrClNO_2$	43.67 (43.60	3.00 2.94	4.63 4.56	(Br) 26.41 26.60	(Cl) 11.72 11.84)
12	**m**	*n*-Pr	*p*-Cl	Cl	60.1	78—80	$C_{12}H_{11}Cl_2NO_2$	52.96 (52.83	4.07 4.16	5.15 5.14	(Cl) 26.06 25.73)	
13	**n**	iso-Pr	*p*-Cl	Cl	57.2	127—128	$C_{12}H_{10}Cl_2NO_2$	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 $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed over SiO_2 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 ν_{max}^{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 ν_{max}^{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 $C_{10}H_9Cl_2NO_3$: C, 45.83; H, 3.46; N, 5.34. Found: C, 46.12; H, 3.45; N, 5.34. IR ν_{max} 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 $C_{10}H_8Cl_3NO_3$: C, 42.81; H, 2.87; N, 4.99. Found: C, 42.52; H, 2.65; N, 5.23. IR ν_{max} 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 ν_{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 ν_{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 ν_{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 ν_{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 ν_{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 ν_{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 ν_{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 ν_{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 ν_{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 ν_{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 ν_{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 ν_{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 ν_{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 ν_{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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