Retro-Ene Reactions in Heterocyclic Synthesis. II. A Facile Synthetic Method for 4-Hydroxy-2-pyridones

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Schiff's bases **1** derived from ketones and *t*-butylamine reacted with diphenyl malonate, diphenyl methylmalonate and diphenyl phenylmalonate to give 4-hydroxy-2-pyridones **4-6**. Schiff's bases **1** on reaction with trimethyl methanetricarboxylate afforded 4-hydroxy-3-methoxycarbonyl-2-pyridones **12**.

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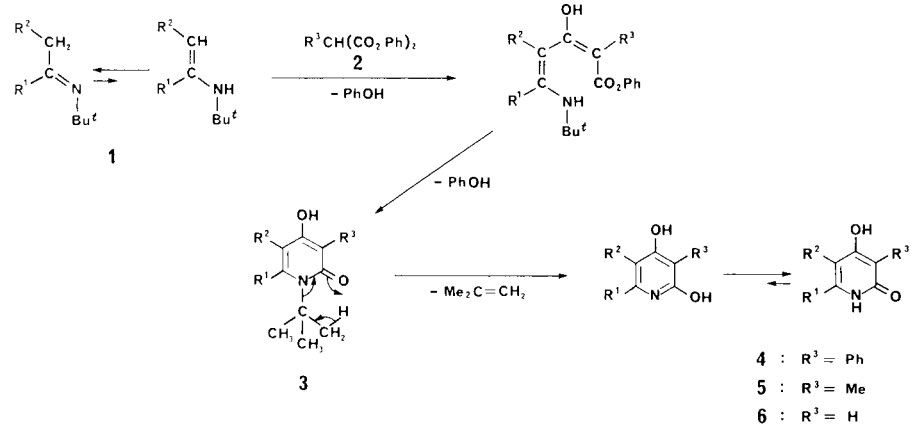
In the preceding paper [1], we reported on a sterically assisted retro-ene reaction which constituted the key step in a synthesis of 3-methoxycarbonyl-2-pyridones, 2-amino-3-cyanopyridines or 2-amino-3-ethoxycarbonylpyridines. Since the retro-ene reaction assisted by a steric effect has received little attention from synthetic chemists, its application to synthesis seems to deserve further investigation. The present paper deals with an extension of this reaction to the synthesis of 4-hydroxy-2-pyridones.

We first examined the behavior of *N*-(1-phenylethylidene)-*t*-butylamine (**1a**) toward diphenyl phenylmalonate (**2**, R^3 = Ph). When **1a** was heated with **2** (R^3 = Ph) at 100° and then at 130° in diglyme, condensation and subsequent cyclization took place and 1-*t*-butyl-4-hydroxy-3,6-diphenyl-2-pyridone (**3a**, R^3 = Ph) was obtained in 65% yield (Scheme 1). On heating at 200° in triglyme, **3a** (R^3 = Ph) underwent a retro-ene reaction with elimination of 2-methylpropene to afford 4-hydroxy-3,6-diphenyl-2-pyridone (**4a**) nearly quantitatively. The synthesis of **4a** was successfully carried out in a one-pot procedure. This procedure could be applied to the syntheses of a large number of 4-hydroxy-2-pyridones. Thus, Schiff's bases **1** derived from various ketones and *t*-butylamine were allowed to react with diphenyl phenylmalonate, diphenyl methylmalonate and diphenyl malonate. Addition of ether to the reaction mixtures followed by cooling gave the crystalline products **4-6**, which were characterized on the basis of their microanalyses and spectral data. The results obtained are summarized in Tables 1 and 2.

In contrast to diphenyl malonates **2**, the diethyl esters on reaction with **1** under the same conditions gave 4-hydroxy-2-pyridones in much lower yields. When diethyl phenylmalonate was allowed to react with **1a** and **1i**, **4a** and **4i** were obtained in 18 and 10% yield, respectively.

Scheme 1



	R^1	R^2		R^1	R^2
a	Ph	H	f	Ph	Me
b	p-Me-C_6H_4	H	g	p-Me-C_6H_4	Me
c	p-MeO-C_6H_4	H	h	Et	Me
d	p-NO_2-C_6H_4	H	i	$-(CH_2)_4-$	
e	p-Cl-C_6H_4	H	j	$-(CH_2)_3-$	

Table 1
Preparation of **4-6**

Product	R^1	R^2	R^3	Reaction Conditions [a]	Yield %	Mp °C	Molecular Formula	Analysis %, Calcd./Found C	H	N
4a	Ph	H	Ph	A	62	298-299 [c]	$C_{17}H_{13}NO_2$	77.55	4.98	5.32
								77.47	5.11	5.40
4b	*p*-Me-C_6H_4	H	Ph	A	68	260-260.5	$C_{18}H_{15}NO_2$	77.96	5.45	5.05
								78.11	5.43	5.14
4c	*p*-MeO-C_6H_4	H	Ph	A	63	264-265	$C_{18}H_{15}NO_3$	73.71	5.15	4.78
								73.69	5.16	4.93
4d	*p*-NO_2-C_6H_4	H	Ph	A	58	322-323	$C_{17}H_{12}N_2O_4$	66.23	3.92	9.09
								66.03	4.03	9.17
4e	*p*-Cl-C_6H_4	H	Ph	A	68	285-285.5	$C_{17}H_{12}ClNO_2$	68.58	4.06	4.70
								68.82	4.13	4.90
4f	Ph	Me	Ph	A	64	263-264	$C_{18}H_{15}NO_2$	77.96	5.45	5.05
								77.66	5.47	5.04
4g	*p*-Me-C_6H_4	Me	Ph	A	61	291-292	$C_{19}H_{17}NO_2$	78.33	5.88	4.81
								78.32	5.83	4.95
4h	Et	Me	Ph	A	59	280-280.5	$C_{14}H_{15}NO_2$	73.34	6.59	6.11
								73.12	6.56	6.11
4i	-$(CH_2)_4$-		Ph	A	64	361-362 [d]	$C_{15}H_{15}NO_2$	74.67	6.27	5.80
								74.46	6.35	5.96
4j	-$(CH_2)_3$-		Ph	A	60	323-324	$C_{14}H_{13}NO_2$	73.99	5.77	6.16
								73.77	5.75	6.14
5a	Ph	H	Me	B	64	329.5-330	$C_{12}H_{11}NO_2$	71.63	5.51	6.96
								71.55	5.45	7.01
5b	*p*-Me-C_6H_4	H	Me	B	64	314-315	$C_{13}H_{13}NO_2$	72.54	6.09	6.51
								72.25	6.03	6.37
5c	*p*-MeO-C_6H_4	H	Me	B	70	305-305.5	$C_{13}H_{13}NO_3$	67.52	5.67	6.06
								67.25	5.64	6.33
5d	*p*-NO_2-C_6H_4	H	Me	B	65	318.5 [b]	$C_{12}H_{10}N_2O_4$	58.54	4.09	11.38
								58.26	4.18	11.31
5e	*p*-Cl-C_6H_4	H	Me	B	76	332 [b]	$C_{12}H_{10}ClNO_2$	61.16	4.28	5.94
								60.94	4.38	5.89
5f	Ph	Me	Me	B	79	202.5-203	$C_{13}H_{13}NO_2$	72.54	6.09	6.51
								72.46	6.01	6.49
5g	*p*-Me-C_6H_4	Me	Me	B	75	227-227.5	$C_{14}H_{15}NO_2$	73.34	6.59	6.11
								73.16	6.50	6.21
5h	Et	Me	Me	B	67	203.5-204	$C_9H_{13}NO_2$	64.65	7.84	8.38
								64.47	7.78	8.67
5i	-$(CH_2)_4$-		Me	B	62	259-260	$C_{10}H_{13}NO_2$	67.02	7.31	7.82
								66.86	7.28	7.91
5j	-$(CH_2)_3$-		Me	B	62	259.5-260	$C_9H_{11}NO_2$	65.44	6.71	8.48
								65.42	6.85	8.52
6a	Ph	H	H	A	52	325 [b] [e]	$C_{11}H_9NO_2$	70.58	4.85	7.48
								70.67	4.97	7.50
6b	*p*-Me-C_6H_4	H	H	A	55	322 [b]	$C_{12}H_{11}NO_2$	71.63	5.51	6.96
								71.33	5.67	7.23
6c	*p*-MeO-C_6H_4	H	H	A	55	302 [b]	$C_{12}H_{11}NO_3$	66.35	5.10	6.45
								66.23	5.11	6.60
6d	*p*-NO_2-C_6H_4	H	H	A	60	300.5-301.5	$C_{11}H_8N_2O_4$	56.90	3.47	12.06
								56.74	3.50	11.76
6e	*p*-Cl-C_6H_4	H	H	A	57	326-327 [f]	$C_{11}H_8ClNO_2$	59.61	3.64	6.32
								59.31	3.86	6.49
6f	Ph	Me	H	A	71	365 [b]	$C_{12}H_{11}NO_2$	71.63	5.51	6.96
								71.42	5.62	7.20
6g	*p*-Me-C_6H_4	Me	H	A	66	371 [b]	$C_{13}H_{13}NO_2$	72.54	6.09	6.51
								72.31	6.18	6.76

Table 1 (Continued)

Product	R^1	R^2	R^3	Reaction Conditions [a]	Yield %	Mp °C	Molecular Formula	Analysis %, Calcd./Found C	H	N
6h	Et	Me	H	A	43	350-351	$C_8H_{11}NO_2$	62.73	7.24	9.14
								62.82	7.21	9.39
6i	-$(CH_2)_4$-		H	A	57	383-384 [g]	$C_9H_{11}NO_2$	65.44	6.71	8.48
								65.14	6.60	8.51
6j	-$(CH_2)_3$-		H	A	54	357 [b] [h]	$C_8H_9NO_2$	63.57	6.00	9.27
								63.28	5.91	9.29

[a] A: Temperature (time), 100° (2 hours) and then 200° (2 hours); solvent, triglyme. B: Temperature (time), 100° (2 hours) and then 230° (2 hours); solvent, tetraglyme. [b] Decomposition. [c] Reference [2], mp 298°. [d] Reference [2], mp 359°. [e] Reference [3], mp 317-318° dec. [f] Reference [4], mp 324° (decomposition). [g] Reference [5], mp >300°. [h] Reference [5], mp >310°.

Table 2
Spectral Data of **4-6**

Product	IR [a] cm^{-1}	^1H NMR [b] δ	MS [c] m/z (MH^+)
4a	1607, 1551	6.31 (1H, s, CH), 7.0-7.8 (10H, m, aromatic), 10.6 and 11.4 (each 1H, br, s, OH or NH)	264
4b	1605, 1590, 1545	2.36 (3H, s, CH_3), 6.27 (1H, s, CH), 7.1-7.7 (9H, m, aromatic), 10.4 and 11.4 (each 1H, br s, OH or NH)	278
4c	1605, 1590, 1560	3.82 (3H, s, OCH_3), 6.24 (1H, s, CH), 7.04 and 7.65 (each 2H, d, J = 8.6 Hz, aromatic), 7.15-7.55 (5H, m, aromatic), 10.4 and 11.3 (each 1H, br s, OH or NH)	294
4d	1612, 1590, 1571	6.51 (1H, s, CH), 7.1-7.55 (5H, m, aromatic), 7.99 and 8.32 (each 2H, d, J = 9.1 Hz, aromatic), 10.6 and 11.55 (each 1H, br s, OH or NH)	309
4e	1605, 1586, 1560	6.31 (1H, s, CH), 7.1-7.45 (5H, m, aromatic), 7.56 and 7.70 (each 2H, d, J = 8.7 Hz, aromatic), 10.5 and 11.4 (each 1H, br s, OH or NH)	298
4f	1623, 1595, 1572	1.87 (3H, s, CH_3), 7.2-7.6 (10H, m, aromatic), 9.35 and 11.1 (each 1H, br s, OH or NH)	278
4g	1616, 1593	1.87 and 2.37 (each 3H, s, CH_3), 7.1-7.5 (9H, m, aromatic), 9.4 and 11.0 (each 1H, br s, OH or NH)	292
4h	1624, 1595, 1547	1.10 (3H, t, J = 7.4 Hz, CH_2CH_3), 1.92 (3H, s, CH_3), 2.49 (2H, q, J = 7.4 Hz, CH_2CH_3), 7.1-7.4 (5H, m, aromatic), 9.0 and 11.0 (each 1H, br s, OH or NH)	230
4i	1631, 1605, 1596, 1545	1.5-1.9 and 2.2-2.6 (8H, m, $4CH_2$), 7.1-7.5 (5H, m, aromatic), 9.1 and 10.8 (each 1H, br s, OH or NH)	242
4j	1628, 1610, 1548	1.8-2.2 and 2.5-2.9 (6H, m, $3CH_2$), 7.1-7.4 (5H, m, aromatic), 9.6 and 11.25 (each 1H, br s, OH or NH)	228
5a	1648, 1610, 1543	1.83 (3H, s, CH_3), 6.17 (1H, s CH), 7.3-7.75 (5H, m, aromatic), 10.2 and 11.2 (each 1H, br s, OH or NH)	202
5b	1601, 1570	1.83 and 2.34 (each 3H, s, CH_3), 6.15 (1H, s, CH), 7.25 and 7.52 (each 2H, d, J = 8.8 Hz, aromatic), 10.15 and 11.15 (each 1H, br s, OH or NH)	216
5c	1601, 1564	1.82 (3H, s, CH_3), 3.81 (3H, s, OCH_3), 6.11 (1H, s, CH), 7.01 and 7.58 (each 2H, d, J = 8.8 Hz, aromatic), 10.15 and 11.05 (each 1H, br s, OH or NH)	232
5d	1652, 1628, 1594	1.87 (3H, s, CH_3), 6.41 (1H, s, CH), 7.94 and 8.28 (each 2H, d, J = 8.8 Hz, aromatic), 10.35 and 11.35 (each 1H, br s, OH or NH)	247
5e	1600, 1571, 1560	1.84 (3H, s, CH_3), 6.20 (1H, s, CH), 7.53 and 7.65 (each 2H, d, J = 8.8 Hz, aromatic), 10.35 and 11.2 (each 1H, br s, OH or NH)	236
5f	1629, 1600, 1555	1.82 and 1.90 (each 3H, s, CH_3), 7.2-7.55 (5H, m, aromatic), 9.5 and 10.9 (each 1H, br s, OH or NH)	216
5g	1598, 1560	1.81, 1.90 and 2.35 (each 3H, s, CH_3), 7.15-7.3 (5H, m, aromatic), 9.4 and 10.75 (each 1H, br s, OH or NH)	230
5h	1612, 1561	1.05 (3H, t, J = 7.4 Hz, CH_2CH_3), 1.82 and 1.87 (each 3H, s, CH_3), 2.43 (2H, q, J = 7.4 Hz, CH_2CH_3), 9.2 and 10.8 (each 1H, br s, OH or NH)	168
5i	1626, 1610, 1555	1.4-2.8 and 2.15-2.5 (8H, m, $4CH_2$), 1.82 (3H, s, CH_3), 9.1 and 10.7 (each 1H, br s, OH or NH)	180
5j	1635, 1614, 1448	1.7-2.15 and 2.4-2.8 (6H, m, $3CH_2$), 1.78 (3H, s, CH_3), 9.5 and 11.1 (each 1H, br s, OH or NH)	166
6a	1650, 1625, 1599, 1572	5.56 and 6.11 (each 1H, d, J = 2.1 Hz, CH), 7.3-7.8 (5H, m, aromatic), 10.6 and 11.15 (each 1H, br s, OH or NH)	188
6b	1611, 1591, 1563	2.34 (3H, s, CH_3), 5.53 and 6.08 (each 1H, d, J = 2.1 Hz, CH), 7.26 and 7.58 (each 2H, d, J = 8.2 Hz, aromatic), 10.55 and 11.1 (each 1H, br s, OH or NH)	202
6c	1610, 1575	3.80 (3H, s, OCH_3), 5.49 and 6.04 (each 1H, d, J = 2.1 Hz, CH), 7.00 and 7.64 (each 2H, d, J = 8.7 Hz, aromatic), 10.5 and 11.05 (each 1H, br s, OH or NH)	218

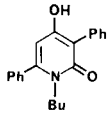
Table 2 (Continued)

Product	IR [a] cm^{-1}	^{1}H NMR [b] δ	MS [c] m/z (MH$^+$)
6d	1640, 1618, 1588	5.73 and 6.41 (each 1H, d, J = 2.0 Hz, CH), 8.02 and 8.28 (each 2H, d, J = 9.0 Hz, aromatic), 10.7 and 11.25 (each 1H, br s, OH or NH)	233
6e	1640, 1613, 1588, 1562	5.59 and 6.16 (each 1H, d, J = 2.1 Hz, CH), 7.52 and 7.71 (each 2H, d, J = 8.8 Hz, aromatic), 10.6 and 11.1 (each 1H, br s, OH or NH)	222
6f	1645, 1607, 1591, 1560	1.75 (3H, s, CH_3), 5.62 (1H, s, CH), 7.2-7.55 (5H, m, aromatic), 10.65 and 10.8 (each 1H, br s, OH or NH)	202
6g	1648, 1593, 1564	1.75 and 2.35 (each 3H, s, CH_3), 5.60 (1H, s, CH), 7.15-7.35 (4H, m, aromatic), 10.6 and 10.8 (each 1H, br s, OH or NH)	216
6h	1654, 1607, 1563	1.05 (3H, t, J = 7.5 Hz, CH_2CH_3), 1.81 (3H, s, CH_3), 2.42 (2H, q, J = 7.5 Hz, CH_2CH_3), 5.44 (1H, s, CH), 10.4 and 10.7 (each 1H, br s, OH or NH)	154
6i	1653, 1606, 1565	1.4-1.8 and 2.1-2.5 (8H, m, $4CH_2$), 5.40 (1H, s, CH), 10.4 and 10.7 (each 1H, br s, OH or NH)	166
6j	1647, 1612, 1569	1.75-2.15 and 2.4-2.8 (6H, m, $3CH_2$), 5.34 (1H, s, CH), 10.4 and 11.0 (each 1H, br s, OH or NH)	152

[a] Measured in potassium bromide. [b] Measured in dimethyl sulfoxide-d_6. [c] Measured by the CI method with isobutane.

Reaction of diethyl malonate with **1a** gave **6a** in 5% yield. Gas chromatographic analysis of the reaction mixtures revealed that large portions of the starting materials remained unaltered, indicating that the first step of the reaction sequence shown in Scheme 1 was retarded.

In order to examine the steric effect in the retro-ene reaction, 1-alkyl-4-hydroxy-2-pyridones **7-9**, prepared by reaction of the corresponding Schiff's bases with **2** (R^3 = Ph), were heated at 200° for 2 hours in triglyme. Compounds **7** and **8** were recovered unchanged (98 and 96%, respectively). Compound **9** was also recovered (78%), the retro-ene reaction product **10** being obtained in only 7% yield. These facts indicate that the easy elimination of



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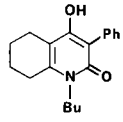

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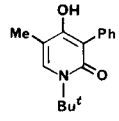

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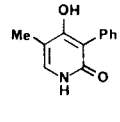

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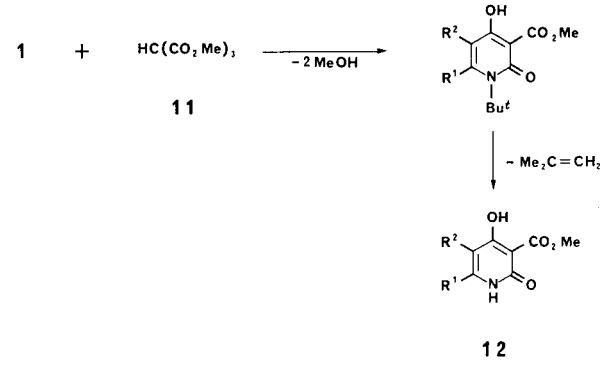
2-methylpropene from **3** is due to steric acceleration caused by relief of the steric strain between the *t*-butyl and R^1 groups at positions 1 and 6 in **3**.

The synthetic method described above for 4-hydroxy-2-pyridones **4-6** can be extended to the synthesis of 4-hydroxy-3-methoxycarbonyl-2-pyridones **12** (Scheme 2). Schiff's bases **1a-g** were heated with trimethyl methanetricarboxylate (**11**) at 150° for 25 hours in diglyme. On cooling, the crystalline products **12a-g** were separated out from the reaction mixtures. The results obtained are summarized in Tables 3 and 4. When the reaction was carried out at higher temperature, formation of a demethoxycarbonylation product was observed. Thus, Schiff's base **1a**, when heated with **11** at 200° for 5 hours in triglyme, gave a mixture of **12a** and **6a** in a molar ratio of 1:1 as determined by ^{1}H-nmr analysis. Reaction of **1h** with **11** at 150° in diglyme yielded, besides the expected 4-hydroxy-3-methoxycarbonyl-2-pyridone **12h**, 3-(*t*-butylaminocarbonyl)-4-hydroxy-2-pyridone **13**. Reaction of **1i** with **11** also gave a mixture of **12i** and **14**. These products were isolated by column chromatography.

Scheme 2



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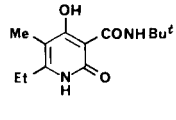

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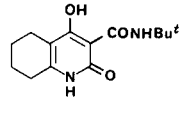

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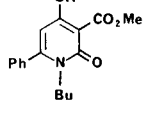

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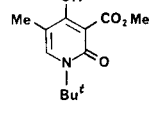

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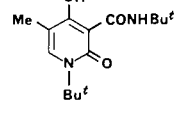

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Table 3

Preparation of **12** [a]

Product	R^1	R^2	Yield %	Mp °C	Molecular Formula	Analysis %, Calcd./Found C	H	N
12a	Ph	H	71	243 [b]	$C_{13}H_{11}NO_4$	63.67	4.52	5.71
						63.37	4.58	5.63
12b	*p*-Me-C_6H_4	H	69	253 [b]	$C_{14}H_{13}NO_4$	64.86	5.05	5.40
						64.81	5.09	5.48
12c	*p*-MeO-C_6H_4	H	71	250 [b]	$C_{14}H_{13}NO_5$	61.09	4.76	5.09
						60.84	4.81	5.13
12d	*p*-NO_2-C_6H_4	H	32	325 [b]	$C_{13}H_{10}N_2O_6$	53.80	3.47	9.65
						53.90	3.67	9.72
12e	*p*-Cl-C_6H_4	H	63	282.5 [b]	$C_{13}H_{10}ClNO_4$	55.83	3.60	5.01
						55.62	3.70	5.03
12f	Ph	Me	43	232.5 [b]	$C_{14}H_{13}NO_4$	64.86	5.05	5.40
						64.96	5.12	5.55
12g	*p*-Me-C_6H_4	Me	52	260.5 [b]	$C_{15}H_{15}NO_4$	65.92	5.53	5.13
						65.75	5.52	5.30
12h	Et	Me	51 [c]	172.5-173.5	$C_{10}H_{13}NO_4$	56.87	6.20	6.63
						56.89	6.30	6.92
12i	-$(CH_2)_4$-		45 [d]	234.5 [b]	$C_{11}H_{13}NO_4$	59.19	5.87	6.27
						58.98	5.85	6.56

[a] All reactions were carried out at 150° for 25 hours in diglyme. [b] Decomposition. [c] Compound **13** was also isolated (20% yield based on **11**). [d] Compound **14** was also isolated (16% yield based on **11**).

Table 4

Spectral Data of **12**

Product	IR [a] cm^{-1}	^1H NMR [b] δ	MS m/z (M^+)
12a	1675, 1661, 1634, 1562	3.81 (3H, s, CO_2CH_3), 6.27 (1H, s, CH), 7.4-7.9 (5H, m, aromatic), 11.7 and 12.5 (each 1H, br s, OH or NH)	245
12b	1640, 1611, 1562	2.36 (3H, s, CH_3), 3.80 (3H, s, CO_2CH_3), 6.25 (1H, s, CH), 7.30 and 7.65 (each 2H, d, J = 8.0 Hz, aromatic), 11.6 and 12.5 (each 1H, br s, OH or NH)	259
12c	1640, 1628, 1601, 1565	3.82 (6H, s, OCH_3 and CO_2CH_3), 6.24 (1H, s, CH), 7.04 and 7.75 (each 2H, d, J = 8.8 Hz, aromatic), 11.55 and 12.6 (each 1H, br s, OH or NH)	275
12d	1662, 1645, 1597, 1559	3.80 (3H, s, CO_2CH_3), 6.41 (1H, s, CH), 8.00 and 8.31 (each 2H, d, J = 8.9 Hz, aromatic), 11.9 and 12.3 (each 1H, br s, OH or NH)	290
12e	1653, 1645, 1593, 1562	3.80 (3H, s, CO_2CH_3), 6.28 (1H, s, CH), 7.56 and 7.77 (each 2H, d, J = 8.6 Hz, aromatic), 11.7 and 12.4 (each 1H, br s, OH or NH)	279
12f	1654, 1630, 1606, 1559	1.81 (3H, s, CH_3), 3.85 (3H, s, CO_2CH_3), 7.3-7.6 (5H, m, aromatic), 11.45 and 13.5 (each 1H, br s, OH or NH)	260 [c]
12g	1668, 1652, 1611, 1563	1.81 and 2.37 (each 3H, s, CH_3), 3.85 (3H, s, CO_2CH_3), 7.2-7.4 (4H, m, aromatic), 11.4 and 13.5 (each 1H, br s, OH or NH)	273
12h	1660, 1617, 1560	1.09 (3H, t, J = 7.5 Hz, CH_2CH_3), 1.88 (3H, s, CH_3), 2.50 (2H, q, J = 7.5 Hz, CH_2CH_3), 3.81 (3H, s, CO_2CH_3), 11.3 and 13.5 (each 1H, br s, OH or NH)	211
12i	1640, 1625, 1578	1.4-1.8 and 2.1-2.6 (8H, m, $4CH_2$), 3.81 (3H, s, CO_2CH_3), 11.2 and 13.4 (each 1H, br s, OH or NH)	223

[a] Measured in potassium bromide. [b] Measured in dimethyl sulfoxide-d_6. [c] MH^+ measured by the CI method with isobutane.

Contrary to our expectation, triphenyl methanetricarboxylate failed to react with Schiff's bases **1**. When triphenyl methanetricarboxylate was heated with **1a** at 150° in diglyme, the ester remained unchanged, whereas **1a** was gradually consumed presumably because of self-condensation, as observed by gas chromatography.

Reaction of *N*-(1-phenylethylidene)butylamine with **11** under the conditions used in the synthesis of **12** gave 1-butyl-4-hydroxy-3-methoxycarbonyl-6-phenyl-2-pyridone (**15**) in 54% yield. With *N*-propylidene-*t*-butylamine, compounds **16** (20%) and **17** (23% based on **11**) were obtained. No retro-ene reaction products could be isolated in these reactions.

The present method offers a facile synthetic route to a variety of 4-hydroxy-2-pyridone derivatives.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a Hitachi 260-50 spectrometer. The ^{1}H-nmr data were obtained with a JEOL JNM-FX90Q spectrometer at 90 MHz by using tetramethylsilane as an internal standard. Mass spectra were measured with a Shimadzu GCMS-QP1000 spectrometer at 70 eV of ionization energy by use of a direct-inlet system. Gas chromatographic measurements were carried out with a Hitachi 263-30 instrument by using an SE-30 column. Microanalyses were performed at the Microanalysis Laboratory, Department of Chemistry, Faculty of Science, the University of Tokyo.

Schiff's bases **1a-h** were prepared by the procedure of Weingarten *et al* [6]. Schiff's bases **1i,j** were prepared according to the method of Lai [7]. *N*-(1-Phenylethylidene)butylamine and *N*-cyclohexylidenebutylamine were obtained by the procedure of Norton *et al* [8]. *N*-Propylidene-*t*-butylamine was prepared by the procedure of Tiollais [9]. Esters **2** were prepared as described in the literature [10]. Diethyl malonate and diethyl phenylmalonate were commercially available and used without further purification. Ester **11** was prepared as described in the literature [11]. Triphenyl methanetricarboxylate was obtained according to the method of Lund and Voigt [12].

1-*t*-Butyl-4-hydroxy-3,6-diphenyl-2-pyridone (**3a**, R^3 = Ph).

A solution containing *N*-(1-phenylethylidene)-*t*-butylamine (**1a**) (3.51 g, 20.0 mmoles) and diphenyl phenylmalonate (**2**, R^3 = Ph) (6.65 g, 20.0 mmoles) in diglyme (40 ml) was heated at 100° for 2 hours and then at 130° for 1 hour. The solvent and the phenol formed were removed under reduced pressure and the residual solid was triturated with ether (15 ml) to give **3a** (R^3 = Ph) (4.14 g, 65%), mp 297.5-299°; mp 298-299° after recrystallization from dimethylformamide; ir (potassium bromide): 1621, 1586, 1501 cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 1.38 (9H, s, $C(CH_3)_3$), 5.80 (1H, s, CH), 7.1-7.5 (10H, m, aromatic), 10.25 (1H, br s, OH); ms: (CI) m/z 320 (MH^+).

Anal. Calcd. for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39. Found: C, 78.68; H, 6.61; N, 4.37.

Compound **3a** (R^3 = Ph) (1.60 g, 5.01 mmoles) was heated in triglyme (10 ml) at 200° for 2 hours. The triglyme was removed under reduced pressure and the residual solid was triturated with ether (10 ml) to give **4a** (1.30 g, 99%), mp 297-298.5°.

4-Hydroxy-2-pyridones **4-6**.

A solution containing **1** (20.0 mmoles) and **2** (20.0 mmoles) in triglyme or tetraglyme (40 ml) was heated at the temperature indicated in Table 1. Ether (200 ml) was added to the cooled reaction mixture. The mixture was left in a refrigerator overnight and the crystalline product (**4-6**) was collected. All the products obtained were of satisfactory purity as judged by ^{1}H-nmr spectroscopy. Samples for analysis were recrystallized from dimethylformamide. Yields, analytical data and physical properties of **4-6** are shown in Tables 1 and 2.

Reaction of **1a** with Diethyl Phenylmalonate.

A solution of **1a** (3.51 g, 20.0 mmoles) and diethyl phenylmalonate (4.73 g, 20.0 mmoles) in triglyme (40 ml) was heated at 100° for 2 hours and then at 200° for 2 hours in a distilling flask. The ethyl alcohol formed was allowed to escape from a condenser. Gas chromatographic analysis of the reaction mixture showed that 70% of the Schiff's base and 64% of the ester remained unchanged. Ether (200 ml) was added to the reaction mixture and then the mixture was left in a refrigerator overnight. Crystals of **4a** were collected (0.93 g, 18%), mp 297-298.5°.

Reaction of **1i** with Diethyl Phenylmalonate.

Schiff's base **1i** was allowed to react with diethyl phenylmalonate in the same manner as described in the reaction of **1a** with diethyl phenylmalonate. Gas chromatographic analysis of the reaction mixture showed that 60% of the Schiff's base and 48% of the ester remained unchanged. Working up the reaction mixture gave 0.47 g (10%) of **4i**, mp 359-360.5°.

Reaction of **1a** with Diethyl Malonate.

Schiff's base **1a** was allowed to react with diethyl malonate in the same manner as described in the reaction of **1a** with diethyl phenylmalonate. Gas chromatographic analysis of the reaction mixture showed that 73% of the Schiff's base and 55% of the ester remained unchanged. Working up the reaction mixture gave 0.17 g (5%) of **6a**, mp 325° dec.

1-Butyl-4-hydroxy-3,6-diphenyl-2-pyridone (**7**).

A solution containing *N*-(1-phenylethylidene)butylamine (3.51 g, 20.0 mmoles) and **2** (R^3 = Ph) (6.65 g, 20.0 mmoles) in diglyme (40 ml) was heated at 150° for 2 hours. Removal of the solvent and the phenol formed under reduced pressure and trituration of the residual solid with ether (15 ml) gave **7** (4.89 g, 77%), mp 273.5-275°, mp 275-276° after recrystallization from dimethylformamide; ir (potassium bromide): 1625, 1553 cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 0.64 (3H, t, J = 6.2 Hz, CH_3), 0.8-1.6 and 3.6-3.75 (6H, m, $3CH_2$), 5.91 (1H, s, CH), 7.1-7.6 (10H, m, aromatic), 10.4 (1H, br s, OH); ms: (CI) m/z 320 (MH^+).

Anal. Calcd. for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39. Found: C, 78.76; H, 6.60; N, 4.66.

Compound **7** (1.60 g, 5.01 mmoles) was heated in triglyme (10 ml) at 200° for 2 hours. The solvent was removed under reduced pressure and the residual solid was triturated with ether (10 ml) to give unchanged **7** (1.57 g, 98%), mp 274.5-275.5°.

1-Butyl-4-hydroxy-2-oxo-3-phenyl-1,2,5,6,7,8-hexahydroquinoline (**8**).

A solution containing *N*-cyclohexylidenebutylamine (3.07 g, 20.0 mmoles) and **2** (R^3 = Ph) (6.65 g, 20.0 mmoles) in diglyme (40 ml) was heated at 150° for 2 hours. Removal of the solvent and the phenol formed and trituration of the residual solid with carbon tetrachloride (10 ml) gave **8** (4.01 g, 67%), mp 182-185°, mp 185-185.5° after recrystallization from carbon tetrachloride; ir (potassium bromide): 1630, 1601, 1535 cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 0.90 (3H, t, J = 6.2 Hz, CH_3), 1.1-1.9, 2.3-2.8 and 3.8-4.0 (14H, m, $7CH_2$), 7.1-7.5 (5H, m, aromatic), 9.0 (1H, br s,

OH); ms: (CI) m/z 298 (MH^+).

Anal. Calcd. for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.79; N, 4.71. Found: C, 76.46; H, 7.75; N, 4.80.

Compound **8** (1.49 g, 5.01 mmoles) was heated in triglyme (10 ml) at 200° for 2 hours. Removal of the solvent under reduced pressure and trituration of the residual solid with carbon tetrachloride (5 ml) gave unchanged **8** (1.43 g, 96%), mp 182.5-185°.

1-*t*-Butyl-4-hydroxy-5-methyl-3-phenyl-2-pyridone (**9**).

To a stirred solution of **2** (R^3 = Ph) (6.65 g, 20.0 mmoles) in diglyme (20 ml) heated at 150° was added a solution of *N*-propylidene-*t*-butylamine (2.26 g, 20.0 mmoles) in diglyme (20 ml) during 0.5 hour. Stirring and heating were continued for an additional 2 hours. The solvent and the phenol formed were removed under reduced pressure and the residual solid was recrystallized from carbon tetrachloride to give **9** (3.18 g, 62%), mp 114.5-117.5°, mp 117.5-118.5° after further recrystallization; ir (potassium bromide): 1648, 1601, 1544 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.68 (9H, s, $C(CH_3)_3$), 2.05 (3H, d, J = 1.1 Hz, CH_3), 5.6 (1H, br s, OH), 7.2-7.6 (6H, m, CH and aromatic); ms: (CI) m/z 258 (MH^+).

Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.60; H, 7.36; N, 5.53.

Compound **9** (1.29 g, 5.01 mmoles) was heated in triglyme (10 ml) at 200° for 2 hours. After removal of the solvent under reduced pressure, the residual solid was heated with carbon tetrachloride (15 ml) to boiling. The insoluble material was collected by filtration and washed with carbon tetrachloride, giving 0.07 g (7%) of 4-hydroxy-5-methyl-3-phenyl-2-pyridone (**10**), mp 304.5-307.5°, mp 308.5-309.5° after recrystallization from dimethylformamide; ir (potassium bromide): 1645, 1632, 1616 cm^{-1}; ^{1}H-nmr (dimethylformamide-d_7): δ 2.02 (3H, s, CH_3), 7.20 (1H, s, CH), 7.1-7.5 (5H, m, aromatic), 10.4 (2H, br s, OH and NH); ms: (CI) m/z 202 (MH^+).

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.39; H, 5.65; N, 6.90.

Concentration of the filtrate, followed by cooling, gave crystals of unchanged **9** (1.01 g, 78%), mp 116.5-118°.

4-Hydroxy-3-methoxycarbonyl-2-pyridones **12**.

A solution containing **1a-g** (20.0 mmoles) and trimethyl methanetricarboxylate (**11**) (20.0 mmoles) in diglyme (30 ml) was heated at 150° for 25 hours in a distilling flask. The reaction mixture was cooled, and the crystalline product (**12a-g**) was collected and washed with hexane-ethyl acetate (2:1). Reaction of **1h** and **11** was carried out under the same conditions as described above. After removal of the solvent under reduced pressure, the residue was chromatographed on a silica gel column. Elution with chloroform gave compound **13**. Subsequent elution with ethyl acetate afforded **12h**. Compounds **14** and **12i** were obtained from **1i** and **11** by the same procedure. Yields, analytical data and physical properties of **12** are given in Tables 3 and 4. Analytical samples were prepared by recrystallization from dimethylformamide.

3-(*t*-Butylaminocarbonyl)-6-ethyl-4-hydroxy-5-methyl-2-pyridone (**13**).

This compound was obtained in a yield of 1.00 g (20% based on **11**), mp 229.5-231°; mp 230.5-231° after recrystallization from ethyl acetate; ir (potassium bromide): 1635, 1623, 1575 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.25 (3H, t, J = 7.5 Hz, CH_2CH_3), 1.45 (9H, s, $C(CH_3)_3$), 1.99 (3H, s, CH_3), 2.63 (2H, q, J = 7.5 Hz, CH_2CH_3), 10.15 and 12.5 (each 1H, br s, OH or NH), 16.44 (1H, s, CONH); ms: m/z 252 (M^+).

Anal. Calcd. for $C_{13}H_{20}N_2O_3$: C, 61.88; H, 7.99; N, 11.10. Found: C, 61.58; H, 7.80; N, 11.36.

3-(*t*-Butylaminocarbonyl)-4-hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline (**14**).

This compound was obtained in a yield of 0.85 g (16% based on **11**), mp 273-274.5°, mp 274.5-275° after recrystallization from dimethylformamide; ir (potassium bromide): 1638, 1631, 1578 cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 1.37 (9H, s, $C(CH_3)_3$), 1.5-1.8 and 2.2-2.5 (8H, m, $4CH_2$), 10.35 and 11.45 (each 1H, br s, OH or NH, 16.3 (1H, s, CONH); ms: m/z 164 (M^+).

Anal. Calcd. for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63; N, 10.60. Found: C, 63.69; H, 7.57; N, 10.75.

Reaction of **1a** with **11** at 200°.

A solution of **1a** (3.51 g, 20.0 mmoles) and **11** (3.80 g, 20.0 mmoles) in triglyme (30 ml) was heated at 200° for 5 hours in a distilling flask. Removal of the solvent under reduced pressure and trituration of the residue with ether (15 ml) gave 1.79 g of a solid. The ^{1}H-nmr analysis revealed that this was a mixture of **12a** and **6a** in a molar ratio of 1:1.

Reaction of *N*-(1-Phenylethylidene)butylamine with **11**.

A solution of *N*-(1-phenylethylidene)butylamine (3.51 g, 20.0 mmoles) and **11** (3.80 g, 20.0 mmoles) in diglyme (30 ml) was heated at 150° for 25 hours in a distilling flask. After removal of the solvent, the residue was chromatographed on a silica gel column using chloroform as an eluent to give 3.27 g (54%) of 1-butyl-4-hydroxy-3-methoxycarbonyl-6-phenyl-2-pyridone (**15**), mp 86.5-88°, mp 88-88.5° after recrystallization from carbon tetrachloride; ir (potassium bromide): 1661, 1655, 1628, 1564 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 0.72 (3H, t, J = 6.5 Hz, CH_3), 0.9-1.7 and 3.6-3.9 (6H, m, $3CH_2$), 4.00 (3H, s, CO_2CH_3), 5.87 (1H, s, CH), 7.2-7.6 (5H, m, aromatic), 13.2 (1H, s, OH); ms: (CI) m/z 302 (MH^+).

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.35; N, 4.65. Found: C, 67.69; H, 6.22; N, 4.80.

Reaction of *N*-Propylidene-*t*-butylamine with **11**.

To a stirred solution of **11** (3.80 g, 20.0 mmoles) in diglyme (20 ml) heated at 150° was added a solution of *N*-propylidene-*t*-butylamine (2.26 g, 20.0 mmoles) in diglyme (10 ml) during 15 minutes. The reaction flask was equipped with a condenser and the contents were heated at 150° for 25 hours. The methyl alcohol formed was allowed to escape from the condenser. After removal of the solvent and the unchanged starting materials under reduced pressure, the residual solid was chromatographed on a silica gel column. Elution with carbon tetrachloride gave compound **17**. Subsequent elution with chloroform afforded compound **16**.

1-*t*-Butyl-4-hydroxy-3-methoxycarbonyl-5-methyl-2-pyridone (**16**).

This compound was obtained in a yield of 0.94 g (20%), mp 159.5-162°, mp 162.5-163° after recrystallization from carbon tetrachloride; ir (potassium bromide): 1663, 1615, 1540 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.67 (9H, s, $C(CH_3)_3$), 2.01 (3H, d, J = 0.9 Hz, CH_3), 3.98 (3H, s, CO_2CH_3), 7.4-7.5 (1H, m, CH), 13.55 (1H, s, OH); ms: m/z 239 (M^+).

Anal. Calcd. for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.37; H, 7.05; N, 5.91.

1-*t*-Butyl-3-(*t*-butylaminocarbonyl)-4-hydroxy-5-methyl-2-pyridone (**17**).

This compound was obtained in a yield of 1.30 g (23% based on **11**), mp 154-157.5°, mp 158.5-159° after recrystallization from carbon tetrachloride; ir (potassium bromide): 1655, 1560 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 1.46 and 1.66 (each 9H, s, $C(CH_3)_3$), 1.99 (3H, d, J = 0.9 Hz, CH_3), 7.25-7.4 (1H, m, CH), 10.5 (1H, br s, OH), 16.7 (1H, s, CONH); ms: m/z 280 (M^+).

Anal. Calcd. for $C_{15}H_{24}N_2O_3$: C, 64.26; H, 8.63; N, 9.99. Found: C, 63.98; H, 8.46; N, 9.96.

Attempted Reaction of **1a** with Triphenyl Methanetricarboxylate.

A solution of **1a** (1.75 g, 10.0 mmoles) and triphenyl methanetricarboxylate (3.76 g, 10.0 mmoles) in diglyme (15 ml) was heated at 150° for 25 hours. Gas chromatographic analysis showed that 86% of the Schiff's base was consumed, whereas 89% of the ester remained unchanged. The ester was recovered by distillation (3.21 g, 85%).

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