A VERSATILE NEW METHOD FOR SYNTHESIS OF ISOQUINOLINES;[1] 6,8-DIHYDROXYISOQUINOLINE DERIVATIVES FROM 6-METHYL-1,3-OXAZIN-4-ONES

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Abstract — A versatile method for synthesis of isoquinolone derivatives (**4a-h**) from 2-substituted 6-methyl-4*H*-1,3-oxazin-4-ones (**1a-h**) is described. Transformation of **1a-h** with diethyl acetonedicarboxylate (**2**) in the presence of potassium *tert*-butoxide afforded 6-substituted 3-acetyl-5-ethoxycarbonyl-4-ethoxycarbonylmethylene-2-pyridones (**3a-h**) in excellent yields. Dieckmann-type cyclization of **3a-h** with sodium ethoxide in ethanol produced the corresponding isoquinolone derivatives (**4a-h**) in good yields, respectively.

1,3-Oxazin-4-ones are potentially useful as building blocks for the synthesis and functionalization of various *N*-heterocyclic ring systems. [2] In the previous papers of this series, [2a,f] we have described the ring transformation of 4*H* -1,3-oxazin- 4-ones into polyfunctionalized pyridine derivatives with carbanions derived from nitriles and carbonyl compounds such as ketones and esters including β-diketones, β-keto esters, and lactones to provide 3-acetyl-4,5,6-trisubstituted 2-pyridone derivatives. Herein we describe a versatile new method for synthesis of isoquinoline derivatives as an application of the ring transformation of the 1,3-oxazines, that is, the ring transformation of the 1,3-oxazines with a tricarbonyl compound [diethyl acetonedicarboxylate (**2**)] into 3-acetyl-4-ethoxycarbonylmethylene-2-pyridone (**3**) which undergoes Dieckmann type condensation to produce isoquinoline derivatives (**4**).

First, reaction of 2-substituted 6-methyl-4*H*-1,3-oxazin-4-one (**1a-h**) with diethyl acetonedicarboxylate (**2**) was carried out: To a suspension of potassium *tert*-butoxide (1.1 g) in tetrahydrofuran (THF, 20 ml) was added successively, THF(20 ml) solutions of dicarboxylate **2** (2.0 g) and 1,3-oxazine **1a** (1.87 g) with stirring. The reaction mixture was stirred overnight at room temperature. After quenching the reaction mixture with 10% HCl, the formed precipitate was collected and recrystallized from methanol to afford 3-acetyl-5-ethoxycarbonyl-4-ethoxycarbonylmethylene-6-phenyl-2-pyridone (**3a**), mp 182-183°C, in 90% yield. Analogously, 2-substituted 6-methyl-1,3-oxazin-4-one (**1b-h**) were reacted with **2** to give 2-pyridone derivatives (**3b-h**) in good yields. Structural assignment of these products (**3a-h**) was accomplished on the basis of elemental analysis and spectroscopic data [infrared (ir), proton nuclear magnetic resonance (^{1}H-nmr), and mass spectra

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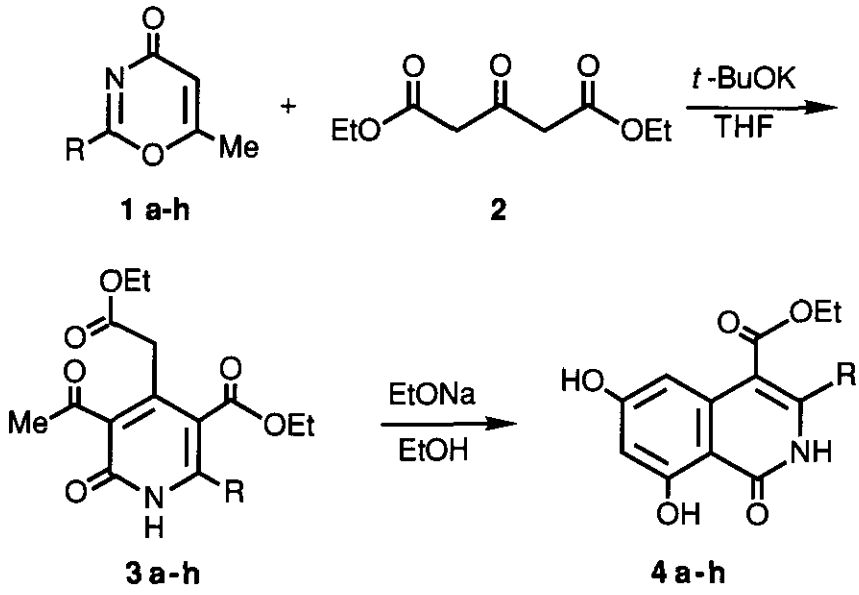
This paper is dedicated to the 75th birthday of Dr. Masatomo Hamana.

(ms)](Table I).

Thus formed pyridones (**3a-h**) readily underwent intramolecular condensation to cyclize into the isoquinolone (**4**): For example, pyridone (**3a**) was treated with sodium ethoxide in absolute ethanol overnight at room temperature, followed by quenching with 10% HCl to give 6,8-dihydroxy-4-ethoxycarbonyl-3-phenyl-1-isoquinolone (**4a**), mp 245-246 °C, in 96% yield. Similar treatment of 2-pyridones (**3b-h**) with sodium ethoxide gave the corresponding isoquinolones (**4b-h**) in good yields. The structural determination of isoquinolone **4** was based on their ir, nmr, and ms spectra together with elemental analysis. These data and yields are summarized in Table II.

Further development of the isoquinoline synthesis by means of ring transformation of 1,3-oxazin-4-one derivatives (**1**) with tricarbonyl compounds such as 1,3,5-triketones and β,δ-diketoesters is under investigation.



Scheme

Table I. Analytical and Spectral Data for **3a-h**

Product No.	Yield (%)	mp(°C) (Solvent)	Formula [3]	Ir(KBr) [4] cm^{-1}	^{1}H-Nmr($CDCl_3$) δ [5]
3a	90	182-183 (MeOH)	$C_{20}H_{21}NO_6$	1715 1695	0.83(3H,t,*J* =7Hz), 1.24(3H,t,*J* =7Hz), 2.36(3H,s), 3.88(2H,s), 3.94(2H,q,*J* =7Hz), 4.13(2H,q,*J* =7Hz), 7.44(5H,s), 12.50-13.50(1H,br)
3b	83	136 (Et_2O)	$C_{16}H_{21}NO_6$	1725 1695	1.27(3H,t,*J* =7Hz), 1.37(6H,t,*J* =7Hz), 2.60(3H,s), 2.78(2H,q,*J* =7Hz), 3.83(2H,s), 4.18(2H,q,*J* =7Hz), 4.35(2H,q,*J* =7Hz), 13.30-14.20(1H,br)
3c	86	162-163 (MeOH)	$C_{21}H_{23}NO_6$	1715 1695	1.27(6H,t,*J* =7Hz), 2.56(3H,s), 3.83(2H,s), 4.17(2H,s), 4.20(2H,q,*J* =7Hz), 4.32(2H,q, *J*=7Hz), 7.30(5H,s), 12.50-13.60(1H,br)
3d	86	187-189 (MeOH)	$C_{20}H_{20}NO_6F$	1740 1715 1695	0.93(3H,t,*J* =7Hz), 1.27(3H,t,*J* =7Hz), 2.40(3H,s), 3.88(2H,s), 4.03(2H,q,*J* =7Hz), 4.20(2H,q,*J* =7Hz), 7.03-7.67 (4H,m), 12.50-14.00(1H,br)
3e	83	175-176 (MeOH)	$C_{20}H_{20}NO_6Br$	1735 1715 1690	0.93(3H,t,*J* =7Hz), 1.27(3H,t,*J* =7Hz), 2.40(3H,s), 3.88(2H,s), 4.03(2H,q,*J* =7Hz), 4.20(2H,q,*J* =7Hz), 7.27-7.33(5H,m), 12.30-13.60(1H,br)
3f	85	138-140 (EtOH)	$C_{18}H_{19}NO_7$	1735 1720 1700	1.27(6H,t,*J* =7Hz), 2.60(3H,s), 3.83(2H,s), 4.20(2H,q,*J* =7Hz), 4.33(2H,q,*J* =7Hz), 6.53-6.63(1H,m), 7.40-7.60(2H,m), 12.00-13.80(1H,br)
3g	87	175-176 (MeOH)	$C_{19}H_{20}N_2O_6$	1735 1715 1685	1.02(3H,t,*J* =7Hz), 1.27(3H,t,*J* =7Hz), 2.53(3H,s), 3.95(2H,s), 4.16(2H,q,*J* =7Hz), 4.22(2H,q,*J* =7Hz), 7.37-8.03(3H,m), 8.70-8.83(1H,m), 12.00-13.90(1H,br)
3h	72	120-122 (MeOH)	$C_{18}H_{23}NO_8$	1735 1710 1700	1.27(6H,t,*J* =7Hz), 1.35(3H,t,*J* =7Hz), 2.58(3H,s), 3.93(4H,s), 4.15(2H,q,*J* =7Hz), 4.18(2H,q,*J* =7Hz), 4.27(2H,q,*J* =7Hz), 13.00-14.50(1H,br)

Table II. Analytical and Spectral Data for **4a-h**

Product No.	Yield (%)	mp(°C) (Solvent)	Formula [3]	Ir(KBr) [4] cm^{-1}	^{1}H-Nmr($CDCl_3$+ DMSO-d_6) δ [5]
4a	96	280-282 (AcOEt)	$C_{18}H_{15}NO_5$	1715 1690	0.94(3H,t,*J* =7Hz), 4.07(2H,q,*J* =7Hz), 6.40(1H,d,*J* =2Hz), 6.70(1H,d,*J* =2Hz), 7.53(5H,s), 10.30-12.30(2H,br), 13.20(1H,s)

Table II. (continued)

4b	94	245-246 (AcOEt)	$C_{14}H_{15}NO_5$	1700	1.30(3H,t,*J* =7Hz), 1.42(3H,t,*J* =7Hz), 2.67(2H,q,*J* =7Hz), 4.43(2H,q, *J* =7Hz), 6.35(1H,d,*J* =2Hz), 6.63(1H,d,*J* =2Hz), 9.60-10.50(1H,br), 11.20-12.00(1H,br), 12.60-13.60(1H,br)
4c	87	238-239 (MeOH)	$C_{19}H_{17}NO_5$	1690	1.30(3H,t,*J* =7Hz), 4.03(2H,s), 4.34(2H,q, *J* =7Hz), 6.33(1H,d,*J* =2Hz), 6.58(1H,d,*J* =2Hz), 7.30(5H,s), 10.17(1H,br), 11.50-11.80(1H,br), 13.03(1H,br)
4d	90	303-307 (AcOEt)	$C_{18}H_{14}NO_5F$	1690	0.93(3H,t,*J* =7Hz), 4.03(2H,q,*J*=7Hz), 6.35(1H,d,*J* =2Hz), 6.63(1H,d,*J* =2Hz), 7.03-7.63(4H,m), 10.10-12.10(1H,br), 11.60(1H,br), 13.07(1H,s),
4e	77	314-317 (AcOEt)	$C_{18}H_{14}NO_5Br$	1690	0.93(3H,t,*J* =7Hz), 4.05(2H,q,*J* =7Hz), 6.37(1H,d,*J* =2Hz), 6.65(1H,d,*J* =2Hz), 7.33-7.77(4H,m), 10.25(1H,s), 11.50-12.10(1H,br), 13.07(1H,s)
4f	76	274-276 (AcOEt)	$C_{16}H_{13}NO_5$	1685	1.27(3H,t,*J* =7Hz), 4.37(2H,q,*J* =7Hz), 6.38(1H,d,*J* =2Hz), 6.50(1H,d,*J* =2Hz), 6.57-6.67(1H,m), 7.18-7.29(1H,m), 7.62-7.70(1H,m), 10.23(1H,s), 10.30-10.80(1H,br), 13.03(1H,s)
4g	91	245-246 (AcOEt)	$C_{17}H_{14}N_2O_5$	1685	1.03(3H,t,*J* =7Hz), 4.14(2H,q,*J* =7Hz), 6.42(1H,d,*J* =2Hz), 6.72(1H,q,*J* =2Hz), 7.33-8.12(3H,m), 8.66-8.77(1H,m), 10.33 (1H,s), 11.30-12.00(1H,br), 13.07(1H,s)
4h	75	210-212 (AcOEt)	$C_{16}H_{17}NO_7$	1725 1705	1.26(3H,t,*J* =7Hz), 1.37(3H,t,*J* =7Hz), 3.77 (2H,s), 4.22(2H,q,*J* =7Hz), 4.35(2H,q,*J* =7Hz), 6.32(1H,d,*J* =2Hz), 6.85(1H,d,*J* =2Hz), 9.50-11.00(1H,br), 11.53-11.94(1H,br), 12.67-13.29(1H,br)

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3. All new compounds gave satisfactory microanalysis.
4. Ir spectra were taken on a Shimadzu IR-430 spectrophotometer.
5. ^{1}H-Nmr spectra were measured on a JEOL JNM-PMX 60 instrument.

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