An Acid-Catalyzed *O,N*-Acyl Migration and Application to the Synthesis of *N*-(4-Isopropyl-2,2-dimethyl-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazine-6-carbonyl) guanidine Methanesulfonate (KB-R9032), a Novel Na/H Exchange Inhibitor

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In the search for a practical synthesis of *N*-(4-isopropyl-2,2-dimethyl-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazine-6-carbonyl)guanidine methanesulfonate (KB-R9032), a potent Na/H exchange inhibitor, the acylation of methyl 4-hydroxy-3-isopropylaminobenzoate **6a** with 2-bromoisobutyryl bromide was carried out in order to prepare an *N*-acyl derivative, **8a**. However, an *O*-acyl derivative **7a** was obtained selectively. Acylations of derivatives of **6a** were examined. The results revealed that the *O*-acylation occurred because of the steric repulsion between the *N*-isopropyl moiety and the bulky acyl bromide. Then, we investigated the *O,N*-acyl migration of **7a**. We found that the migration was catalyzed by carboxylic acid and that **8a** was precipitated from a diisopropyl ether solution in good yield. Treatment of **8a** with potassium carbonate and subsequent guanidine gave the synthetic intermediate for KB-R9032 in high yield.

Key words *O,N*-acyl migration; rearrangement; practical synthesis; Na/H exchange inhibitor; KB-R9032

Recently, we have reported that *N*-(4-isopropyl-2,2-dimethyl-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazine-6-carbonyl) guanidine methanesulfonate (KB-R9032) is a novel, potent Na/H exchange inhibitor with high water-solubility, and that KB-R9032 is useful for the treatment of ischemia-reperfusion induced injury.¹⁾ KB-R9032 was originally synthesized by route A as shown in Chart 1. In route A, the *N*-isopropylation of methyl 2,2-dimethyl-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazine-6-carboxylate **3** proceeded in only 30% yield because of *O*-isopropylation. In our previous paper, we described the new *N*-selective isopropylation method, KF-alumina catalyzed repeated alkylation.²⁾ The yield of *N*-isopropylation of **3** was improved to 76%, but it took about 4 d to complete the reaction. Therefore, a more practical synthetic method was required for the large scale synthesis of KB-R9032. Thus, we designed an alternative synthetic route (route B). In route B, isopropylation was performed prior to the 2*H*-benzo[1,4]oxazine ring formation to avoid the *O*-isopropylation of the amide moiety. Methyl 4-hydroxy-3-isopropylaminobenzoate **6a** was allowed to react with 2-bromoisobutyryl bromide in order to obtain the *N*-acyl derivative **8a**. However, the ¹H-NMR spectrum of the product showed a signal of a methine proton of an isopropylamino moiety at δ 3.65–3.80 ppm. This value was almost equal to that (δ 3.61–3.76 ppm) of the corresponding signal of **6a**. Although **6a** showed the signals of both phenolic (δ 9.32 ppm) and anilinic (δ 4.07 ppm) protons, the product showed only a signal of the anilinic proton at δ 4.13 ppm. These NMR data indicated that the product was the *O*-acyl derivative **7a**, not the *N*-acyl derivative **8a** (route C).

In this study, we investigated the reason for the unusual *O*-acylation of methyl 4-hydroxy-3-isopropylaminobenzoate **6a**, and developed a carboxylic acid-catalyzed *O,N*-acyl migration to obtain the *N*-acyl derivative **8a** for the practical synthesis of KB-R9032.

Results and Discussion

Acylation of Methyl 4-Hydroxy-3-isopropylaminobenzoate **6a and Its Derivatives **6b–e**** Acylations of aminoalcohols or aminophenols in neutral to basic condition generally afford *N*-acyl derivatives, and do not yield *O*-acyl derivatives.³⁾ However, the acylation of methyl 4-hydroxy-3-isopropylaminobenzoate **6a** with 2-bromoisobutyryl bromide gave the *O*-acyl derivative **7a** selectively. The reason for the unusual *O*-acylation was thought to be the steric repulsion between the two bulky moieties, the isopropylamino and the bromoisobutyryl moieties.

In order to confirm the above hypothesis, acylations of the derivatives **6b–e** were investigated (Chart 2). *O*-Acylation also occurred in the regio-isomers **6b** and **6c** to afford **7b** and **7c**, respectively. Next, the acylation of methyl 3-ethylamino-4-hydroxybenzoate **6d** was examined. The product isolated by preparative TLC was the *O*-acyl derivative **7d**. However, **7d** gradually converted to the *N*-acyl derivative **8d** while standing overnight. The conversion of **7d** to **8d** was assured by a downfield shift of the methylene protons of the ethylamino moiety in ¹H-NMR spectrums (from δ 3.23 to 3.77 ppm). The conversion was also confirmed from the result that the *R_f* value lowered from 0.56 to 0.23 during the standing overnight (eluent: hexane–ethyl acetate (AcOEt) (2/1=v/v)). As shown in Table 3, the *R_f* value of *N*-acyl derivatives **8** is smaller than that of *O*-acyl derivatives **7**. The acylation of methyl 4-hydroxy-3-methylaminobenzoate **6e** occurred at the nitrogen atom, and **8e** was obtained, similar to the acylation of compound **1** (Chart 1). *N*-Acyl derivative **8f** was also obtained from **6a** with bromoacetyl bromide. However, the acylation of **6a** with 2-bromopropionyl bromide gave an interesting result. The ¹H-NMR spectrum showed a mixture of two acyl derivatives (the *O*-acyl derivative **7g**: the *N*-acyl derivative **8g**=about 2:3 in CDCl₃), but the CDCl₃ solution used for ¹H-NMR measurement showed only one spot on silica gel TLC. The *R_f* value was 0.18. From this value, we thought that **7g** was converted to **8g** on TLC.

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Chart 1. Synthetic Routes toward KB-R9032

Therefore, in order to confirm the conversion, we applied the solution on a preparative TLC plate. The obtained compound showed the $^1\text{H-NMR}$ spectrum of **8g**. And an elemental analysis agreed with the calculated value of **8g** within $\pm 0.4\%$. From these data, it was confirmed that the initially obtained product was a mixture of **7g** and **8g**, and that **7g** converted to **8g** on the TLC plate.

The above results revealed that the unusual O -acylation occurred in limited cases, such as in the acylations of methyl hydroxyisopropylaminobenzoate **6a–c** with 2-bromoisobutyl bromide because of the steric repulsion between two bulky groups. In less hindered derivatives, N -acylation occurred or O -acyl derivatives **7** converted to the N -acyl derivatives **8**, even if O -acylation occurred. Then, we investigated the O,N -acyl migration of **7a** considering the above results.

The Study on O,N -Acyl Migration of **7a–c** The O,N -acyl migration of O -acyl derivative **7a** was investigated in order to obtain the N -acyl derivative **8a** (Table 4). Considering the result that ethylamino derivative **7d** converted to **8d** during standing overnight at room temperature, **7a** was heated in N,N -dimethylformamide (DMF) at 50°C for 16 h. However, the O,N -acyl migration did not proceed (entry 1).

As described above, we confirmed that the O,N -acyl migration of **7g** to **8g** occurred on TLC. We considered that the acidity of silica gel affected the migration. Therefore, we ex-

amined an acid-catalyzed O,N -acyl migration. Hydrochloric acid was initially tested, but the hydrochloride of **7a** precipitated in 94% yield (entry 2). Then we examined more weak acids, carboxylic acids. As we expected, acetic acid (AcOH) catalyzed the O,N -migration. A new spot (**8a**, $R_f=0.28$) appeared in addition to the spot ($R_f=0.68$) of **7a**. But the ratio of **8a** to **7a** was about one by HPLC analysis (entry 3). The ratio of **8a/7a** was not improved by changing AcOH to formic acid (HCOOH) (entry 4). From these results, it was thought to be difficult to obtain **8a** selectively by changing carboxylic acids.

Therefore, we changed the solvent from AcOEt to diisopropyl ether (IPE) in order to precipitate **8a** from the reaction mixture, considering the difference in solubilities of **7a** and **8a** (entry 5). The N -acyl derivative **8a** was precipitated from the IPE solution in 67% yield. Then the reaction time was prolonged (16 h), and the yield of **8a** increased to 81% (entry 6).

In general, O,N -acyl migrations proceed in basic conditions and N,O -acyl migrations proceed in acidic conditions.^{4,5)} Therefore, we also tested basic conditions to obtain the N -acyl derivative **8a**. Potassium carbonate (K_2CO_3) was initially examined (entry 7). However, the product was a mixture of methyl 4-isopropyl-2,2-dimethyl-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazine-6-carboxylate **4** and a by-product, **9**.

Table 1. ¹H-NMR Spectral Data for Methyl Alkylaminohydroxybenzoates **6**

No.	Spectral data ^{a)} (250 MHz, CDCl ₃)
6a ^{b)}	δ: 1.24 (6H, d, <i>J</i> =6 Hz), <u>3.61—3.76</u> (1H, m), 3.84 (3H, s), 4.07 (1H, br), 6.77 (1H, d, <i>J</i> =8 Hz), 7.23—7.28 (2H, m), 9.32 (1H, br).
6b	δ: 1.26 (6H, d, <i>J</i> =6 Hz), <u>3.65—3.75</u> (1H, m), 3.86 (3H, s), 4.50 (1H, br), 6.18 (1H, br), 6.55 (1H, d, <i>J</i> =9 Hz), 7.56—7.59 (2H, m).
6c	δ: 1.19 (6H, d, <i>J</i> =6 Hz), 3.11 (1H, br), <u>3.50—3.70</u> (1H, m), 3.92 (3H, s), 6.77—6.86 (2H, m), 7.04 (1H, d, <i>J</i> =2 Hz), 10.14 (1H, br).
6d	δ: 1.27 (3H, t, <i>J</i> =7 Hz), <u>3.19</u> (2H, q, <i>J</i> =7 Hz), 3.88 (3H, s), 4.82 (2H, br), 6.73 (1H, d, <i>J</i> =8 Hz), 7.26 (1H, s), 7.31 (1H, d, <i>J</i> =8 Hz).
6e	δ: <u>2.90</u> (3H, s), 3.88 (3H, s), 4.82 (2H, br), 6.72 (1H, d, <i>J</i> =8 Hz), 7.32 (1H, s), 7.36 (1H, d, <i>J</i> =8 Hz).

a) Underlined signals are proton(s) at the α-position to the nitrogen atom of the anilino moiety. b) in DMSO-*d*₆.

Table 2. ¹H-NMR Spectral Data for the *O*- and *N*-Acyl Derivatives **7** and **8**

No.	Spectral data ^{a)} (250 MHz, CDCl ₃)
7a	δ: 1.24 (6H, d, <i>J</i> =6 Hz), 2.09 (6H, s), <u>3.65—3.80</u> (1H, m), 3.90 (3H, s), 4.13 (1H, br), 7.01 (1H, d, <i>J</i> =8 Hz), 7.35 (1H, dd, <i>J</i> =8, 2 Hz), 7.39 (1H, d, <i>J</i> =2 Hz).
7a ·HCl ^{b)}	δ: 1.27 (6H, d, <i>J</i> =6 Hz), 2.00 (6H, s), <u>3.65—3.80</u> (1H, m), 3.95 (3H, s), 4.50 (1H, br), 7.33 (1H, d, <i>J</i> =8 Hz), 8.06 (1H, dd, <i>J</i> =2, 8 Hz), 8.43 (1H, d, <i>J</i> =2 Hz).
7b	δ: 1.25 (6H, d, <i>J</i> =6 Hz), 2.10 (6H, s), <u>3.63—3.77</u> (1H, m), 3.84 (3H, s), 4.50 (1H, br), 6.67 (1H, d, <i>J</i> =9 Hz), 7.63 (1H, d, <i>J</i> =2 Hz), 7.83 (1H, dd, <i>J</i> =9, 2 Hz).
7c	δ: 1.21 (6H, d, <i>J</i> =6 Hz), 2.09 (6H, s), <u>3.58—3.68</u> (1H, m), 3.83 (3H, s), 6.72 (1H, dd, <i>J</i> =9, 3 Hz), 6.93 (1H, d, <i>J</i> =9 Hz), 7.16 (1H, d, <i>J</i> =3 Hz).
7d	δ: 1.29 (3H, t, <i>J</i> =7 Hz), 1.62 (1H, br), 2.09 (6H, s), <u>3.23</u> (2H, q, <i>J</i> =7 Hz), 3.90 (3H, s), 7.02 (1H, d, <i>J</i> =9 Hz), 7.35—7.80 (2H, m).
7g ^{c)}	δ: 1.07 (3H, d, <i>J</i> =7 Hz), 1.20 (3H, d, <i>J</i> =7 Hz), 1.68 (3H, d, <i>J</i> =8 Hz), 3.08—3.11 (1H, m), 3.91 (3H, s), <u>4.17—4.29</u> (1H, m), 6.60 (1H, br), 7.16 (1H, d, <i>J</i> =9 Hz), 7.67 (1H, d, <i>J</i> =2 Hz), 8.04 (1H, dd, <i>J</i> =9, 2 Hz).
8a	δ: 1.01 (3H, d, <i>J</i> =7 Hz), 1.25 (3H, d, <i>J</i> =7 Hz), 1.80 (3H, s), 1.83 (3H, s), 3.90 (3H, s), <u>4.81—4.92</u> (1H, m), 5.91 (1H, br), 7.04 (1H, d, <i>J</i> =9 Hz), 7.91 (1H, d, <i>J</i> =2 Hz), 8.02 (1H, dd, <i>J</i> =9, 2 Hz).
8d	δ: 1.15 (3H, t, <i>J</i> =7 Hz), 1.85 (6H, s), <u>3.77</u> (2H, br), 3.90 (3H, s), 6.48 (1H, br), 7.34 (1H, d, <i>J</i> =9 Hz), 7.97 (1H, d, <i>J</i> =2 Hz), 7.97 (1H, dd, <i>J</i> =9, 2 Hz).
8e	δ: 1.89 (6H, s), <u>3.36</u> (3H, s), 3.89 (3H, s), 6.85 (1H, br), 7.03 (1H, d, <i>J</i> =9 Hz), 7.94 (1H, dd, <i>J</i> =9, 2 Hz), 7.99 (1H, d, <i>J</i> =2 Hz).
8f	δ: 1.04 (3H, d, <i>J</i> =7 Hz), 1.26 (3H, d, <i>J</i> =7 Hz), 3.59 (1H, d, <i>J</i> =12 Hz), 3.70 (1H, d, <i>J</i> =12 Hz), 3.92 (3H, s), <u>4.83—4.93</u> (1H, m), 7.18 (1H, d, <i>J</i> =9 Hz), 7.84 (1H, d, <i>J</i> =2 Hz), 8.02 (1H, dd, <i>J</i> =9, 2 Hz), 8.61 (1H, br).
8g	δ: 0.99 (3H, d, <i>J</i> =7 Hz), 1.26 (3H, d, <i>J</i> =7 Hz), 1.73 (3H, d, <i>J</i> =7 Hz), 3.91 (3H, s), 3.95—4.08 (1H, m), <u>4.79—4.92</u> (1H, m), 7.13 (1H, d, <i>J</i> =9 Hz), 7.68 (1H, br), 7.94 (1H, d, <i>J</i> =2 Hz), 8.02 (1H, dd, <i>J</i> =9, 2 Hz).

a) Underlined signals are proton(s) at the α-position to the nitrogen atom of the anilino moiety. b) In DMSO-*d*₆. c) Spectrum for **7g** in a mixture of **7g** and **8g** (about 2:3).

Table 3. Physical Data for Methyl Alkylaminohydroxybenzoates **6** and the *O*- and *N*-Acyl Derivatives **7** and **8**

No.	Yield (%)	<i>R</i> _f ^{a)}	mp (°C)	Recryst. solvent	Formula	Analysis			Found		
						Calcd			Calcd		
						C	H	N	C	H	N
6a	72	0.37	139—140	Toluene	C ₁₁ H ₁₅ NO ₃	63.14	7.23	6.69	63.17	7.26	6.64
6b	72	0.41	105—107	—	C ₁₁ H ₁₅ NO ₃	63.14	7.23	6.69	63.07	7.27	6.69
6c	71	0.37	Oil	—	C ₁₁ H ₁₅ NO ₃	63.14	7.23	6.69	62.99	7.33	6.61
6d	36	0.49	153—156	Toluene	C ₁₀ H ₁₃ NO ₃	61.53	6.17	7.17	61.42	6.57	7.13
6e	46	0.28	154—156	IPE-AcOEt	C ₉ H ₁₁ NO ₃	59.60	6.12	7.73	59.60	6.12	7.73
7a	92	0.68	57—58	Hexane	C ₁₅ H ₂₀ BrNO ₄	50.29	5.63	3.91	50.03	5.65	3.82
7a ·HCl	94	0.68	175—176	MeCN	C ₁₅ H ₂₀ BrNO ₄ ·HCl	45.65	5.36	3.55	45.58	5.31	3.64
7b	98	0.66	Oil	—	C ₁₅ H ₂₀ BrNO ₄	50.29	5.63	3.91	50.27	5.62	3.96
7c	73	0.61	Oil	—	C ₁₅ H ₂₀ BrNO ₄	50.29	5.63	3.91	50.28	5.62	3.89
8a	67	0.28	178—179	MeCN	C ₁₅ H ₂₀ BrNO ₄	50.29	5.63	3.91	50.24	5.52	3.85
8d	36	0.23	133—135	IPE-hexane	C ₁₄ H ₁₈ BrNO ₄	48.85	5.27	4.07	48.79	5.31	4.07
8e	56	0.18	159—161	IPE-AcOEt	C ₁₃ H ₁₆ BrNO ₄	47.29	4.88	4.24	47.23	5.04	4.03
8f	24	0.14	176—178	IPE-AcOEt	C ₁₃ H ₁₆ BrNO ₄	47.29	4.88	4.24	47.09	4.90	3.86
8g	38	0.18	—	—	C ₁₄ H ₁₈ BrNO ₄	48.85	5.27	4.07	48.53	5.49	4.13

a) *R*_f value on silica gel TLC (eluent: hexane-AcOEt (2/1=v/v)).

The ratio of **9/4** was about one. The compound **4** was considered to be formed by cyclization of **8a** via *O,N*-acyl migration (Chart 3). The ¹H-NMR spectrum of **9** showed signals of six aromatic protons at δ 6.65—7.75 ppm and two methoxycarbonyl protons at δ 3.56 and 3.81 ppm in addition to a sig-

nal assigned to two methyl groups of the isobutyryl moiety (δ 1.48). These signals indicated that **9** has two aromatic moieties and one acyl moiety. In addition, there are signals corresponding to methine protons of isopropylamino and isopropylamido moieties at δ 3.20—3.34 ppm and δ 4.66—

Chart 2. Acylation of **6** and *O,N*-Acyl Migration of **7**

4.80 ppm, respectively. Furthermore, broad signals at δ 3.31 and 10.74 suggested that **9** has both anilinic and phenolic protons. From these data, the structure of the by-product **9** was confirmed as shown in Chart 3. The ratio of **9/4** increased to about five when a mixture of **7a** and **6a** was treated with K_2CO_3 , although the reaction of **8a** in a presence of **6a** gave only **4**. From these results, **9** was considered to be formed from **7a** and **6a**, which was thought to be produced by the hydrolysis of **7a** with moisture of the reaction medium. In order to avoid hydrolysis, a weaker base (triethylamine (NEt_3)) was examined, but **9** was also formed (entry 8). When IPE was used as a solvent in a basic condition, lit-

tle *O,N*-acyl migration was observed (entry 9).

We succeeded in the preparation of **8a** from **7a** by the carboxylic acid-catalyzed *O,N*-acyl migration. Then we investigated the *O,N*-acyl migration of regio-isomers **7b** and **7c** (Chart 2). However, **7b** and **7c** were not converted to the *N*-acyl derivatives by HCOOH . The amino group of **7b** was at the *para*-position of the methoxycarbonyl group, thus the nucleophilicity was weaker than that of **7a**. Also, the distance between the amino and acyloxy moieties in **7c** was thought to be too far for the *O,N*-migration.

The *N*-acyl derivative **8a** was easily cyclized by treatment with K_2CO_3 to give methyl 4-isopropyl-2,2-dimethyl-3-oxo-

Table 4. *O,N*-Acyl Migration of the *O*-Acyl Derivative **7a**

Entry	Reagent	Solvent	Time (h) ^{a)}	HPLC peak ratio (%) of the reaction solution ^{b)}				Isolated yield of 8a (%)
				7a	8a	4	9	
1	—	DMF	16	91	2	7	0	—
2	HCl 1 eq	AcOEt	3	98	1	1	0	—
3	AcOH 1 eq	AcOEt	4	45	54	1	0	—
4	HCOOH 1 eq	AcOEt	4	52	47	1	0	—
5	HCOOH 0.3 eq	IPE	4	63	35	2	0	67
6	HCOOH 0.3 eq	IPE	16	42	57	1	0	81
7	K ₂ CO ₃ 1 eq	DMF	0.5	2	0	51	47	—
8	NEt ₃ 1 eq	DMF	24	1	0	77	22	—
9	NEt ₃ 1 eq	IPE	4	91	1	8	0	—

a) Temperature at 50 °C. b) HPLC conditions: see Experimental section.

Chart 3. Possible Mechanism for the Formation of **4** and **9**

3,4-dihydro-2*H*-benzo[1,4]oxazine-6-carboxylate **4**, which was converted to KB-R9032 in high yield.

In conclusion, methyl 4-hydroxy-3-isopropylaminobenzoate **6a** was acylated with 2-bromoisobutyryl bromide, but the product was the undesired *O*-acyl derivative **7a**. Carboxylic acids were found to catalyze the *O,N*-acyl migration to give the *N*-acyl derivative **8a**, which was easily converted to a synthetic intermediate, **4**, of KB-R9032. In this way, we established a new practical synthetic method (Chart 1, route C) of KB-R9032, a novel Na/H exchange inhibitor.

Experimental

Melting points were measured with a capillary melting point apparatus

(Yamato MP-21) and are uncorrected. ¹H-NMR spectra were taken on Bruker DPX-250 NMR (250 MHz) and Hitachi R-24B NMR (60 MHz) spectrometers with tetramethylsilane (TMS) as an internal standard. Chemical shifts are given as δ values (ppm).

Elemental analysis was performed with a Yanagimoto CHN-Corder MT-5. HPLC was performed under the following conditions: column (Inertsil ODS-2, 4.6 mm i.d. $\times$ 150 mm, GL Science Inc.), eluent (50 mM KH₂PO₄ (pH 3.5)–acetonitrile (40 : 60, v/v)), UV detector (248 nm), 35 °C. Analytical and preparative TLCs were conducted on 0.25 and 2 mm pre-coated silica gel plates (60GF₂₅₄, Merck).

General Procedure for the Synthesis of Methyl Alkylamino-hydroxybenzoates (6a–d) A mixture of methyl aminohydroxybenzoate (10.0 g, 60 mmol), alkyl iodide (20.0 g, 120 mmol) and NaHCO₃ (7.5 g, 90 mmol) in acetonitrile (MeCN) (50 ml) was refluxed for 5 h. Water was added to the mixture. The precipitates were collected or the reaction mixture was ex-

tracted with AcOEt. The extract was dried over anhydrous magnesium sulfate (MgSO_4) and the solvent was removed under reduced pressure. Then, the crude product was recrystallized or purified by silica gel column chromatography with hexane–AcOEt as an eluent to give **6a–d**. $^1\text{H-NMR}$ spectral and physical data are listed in Tables 1 and 3.

Methyl 4-Hydroxy-3-methylaminobenzoate (6e) Acetyl chloride (3.5 ml) was added to methanol (35 ml). Then, 4-hydroxy-3-methylaminobenzoic acid (3.50 g, 20.9 mmol) was added to the mixture. The mixture was refluxed for 2 d and the solvent was removed under reduced pressure. Aqueous sodium hydroxide was added to the residue. The precipitates were collected by filtration and washed with water, then recrystallized to give **6e**. $^1\text{H-NMR}$ spectral and physical data are listed in Tables 1 and 3.

Acylation of Methyl Alkylaminohydroxybenzoates 6a–e. General Procedure 2-Bromoisobutyl bromide (30 g, 130 mmol) was added dropwise to a stirring mixture of methyl 4-hydroxy-3-isopropylaminobenzoate **6a** (25 g, 120 mmol), NEt_3 (18 g, 180 mmol) and AcOEt (250 ml) at 0°C over 10 min. After the mixture was stirred for 10 min, water was added. The mixture was extracted with AcOEt. The extract was washed with 5% NaHCO_3 , water, then brine, and dried over anhydrous MgSO_4 . The solvent was removed under reduced pressure to give **7a** (41 g, 110 mmol, yield 92%) as a colorless solid. A small portion was recrystallized from hexane for analysis. $^1\text{H-NMR}$ spectral and physical data are listed in Tables 2 and 3. A procedure similar to that described for **7a** was carried out using **6b–e** and **6a**.

Methyl 3-Hydroxy-4-isopropylaminobenzoate 6b and 2-Bromoisobutyl Bromide: The crude product was purified by silica gel column chromatography with hexane–AcOEt (5/1 = v/v) as an eluent to give **7b** as a colorless oil.

Methyl 2-Hydroxy-5-isopropylaminobenzoate 6c and 2-Bromoisobutyl Bromide: The crude product was purified by silica gel column chromatography with hexane–AcOEt (7/1 = v/v) as an eluent to give **7c** as a colorless oil.

Methyl 4-Hydroxy-3-ethylaminobenzoate 6d and 2-Bromoisobutyl Bromide: The oily product was purified by preparative TLC and was found to be the *O*-acyl derivative **7d** by TLC and $^1\text{H-NMR}$ analysis. It solidified while standing overnight at room temperature, and the *R_f* value on TLC lowered from 0.56 to 0.23. The resulting solid was recrystallized from IPE–hexane, and was confirmed to be the *N*-acyl derivative **8d** by TLC, $^1\text{H-NMR}$ and elemental analysis.

Methyl 4-Hydroxy-3-methylaminobenzoate 6e and 2-Bromoisobutyl Bromide: The crude product was recrystallized from IPE–AcOEt to give **8e** as a colorless solid.

Methyl 4-Hydroxy-3-isopropylaminobenzoate 6a and Bromoacetyl Bromide: The crude product was triturated with IPE–AcOEt to give **8f** as a colorless solid.

Methyl 4-Hydroxy-3-isopropylaminobenzoate 6a and 2-Bromopropionyl Bromide: The crude oily product was triturated with IPE–AcOEt as a colorless solid. The $^1\text{H-NMR}$ spectrum of the product showed signals of a mixture of the *O*- and *N*-acyl derivatives **7g** and **8g** in a ratio of about 2 to 3. But, the CDCl_3 solution used for $^1\text{H-NMR}$ analysis gave only one spot (*R_f* = 0.18) on TLC. The product obtained from preparative TLC was deter-

mined to be **8g** by $^1\text{H-NMR}$ analysis.

A Base Catalyzed Reaction of 7a A mixture of **7a** (5.00 g, 14.0 mmol), K_2CO_3 (1.93 g, 14.0 mmol) and DMF (10 ml) was stirred at 50°C for 0.5 h. After cooling, water was added to the reaction mixture. The mixture was extracted with AcOEt. The extract was washed with water and brine, and dried over anhydrous MgSO_4 . The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography with hexane–AcOEt (7/1 = v/v) as an eluent to give **4** (1.09 g, 3.92 mmol, yield 28%) and **9** (1.16 g, 2.38 mmol, yield 17%). **9**; mp: $192\text{--}194^\circ\text{C}$. $^1\text{H-NMR}$ (250 MHz, $\text{DMSO}-d_6$) δ : 0.86 (3H, d, $J=7$ Hz), 0.97 (3H, d, $J=7$ Hz), 1.01 (3H, d, $J=7$ Hz), 1.04 (3H, d, $J=7$ Hz), 1.48 (6H, s), 3.20–3.34 (1H, m), 3.31 (1H, br), 3.56 (3H, s), 3.81 (3H, s), 4.66–4.80 (1H, m), 6.65 (1H, d, $J=8$ Hz), 6.89 (1H, d, $J=2$ Hz), 6.98 (1H, d, $J=8$ Hz), 6.99 (1H, s), 7.21 (1H, d, $J=8$ Hz), 7.75 (1H, dd, $J=2, 8$ Hz), 10.74 (1H, br). *Anal.* Calcd for $\text{C}_{26}\text{H}_{34}\text{N}_2\text{O}_7$: C, 64.18; H, 7.04; N, 5.76. Found, C, 64.12; H, 7.05; N, 5.68. **4**; mp: $75\text{--}77^\circ\text{C}$. $^1\text{H-NMR}$ (60 MHz, CDCl_3) δ : 1.50 (6H, s), 1.60 (6H, d, $J=6$ Hz), 3.98 (3H, s), 4.50–5.10 (1H, m), 7.06 (1H, d, $J=7$ Hz), 7.82 (1H, dd, $J=7, 1$ Hz), 7.87 (1H, d, $J=1$ Hz). *Anal.* Calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_4$: C, 64.97; H, 6.91; N, 5.05. Found, C, 64.90; H, 6.99; N, 5.06.

Hydrochloric Acid Catalyzed Reaction of 7a A mixture of **7a** (0.50 g, 1.4 mmol), 4N HCl /AcOEt (0.5 ml) and AcOEt (2 ml) was stirred at room temperature for 2 h. The precipitates were collected by filtration to give **7a**·HCl (0.52 g, 1.3 mmol, yield 94%). $^1\text{H-NMR}$ spectral and physical data are listed in Tables 3 and 4.

A Carboxylic Acid Catalyzed *O,N*-Acyl Migration A mixture of **7a** (15 g, 42 mmol), HCOOH (0.50 ml, 13 mmol) and IPE (10 ml) was stirred at 50°C for 4 h. After cooling, the precipitates were collected by filtration to give **8a** (10 g, 27 mmol, yield 67%) and were recrystallized from MeCN. $^1\text{H-NMR}$ spectral and physical data are listed in Tables 2 and 3.

Cyclization of 8a to Methyl 4-isopropyl-2,2-dimethyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-carboxylate (4) A mixture of **8a** (49 g, 140 mmol), K_2CO_3 (21 g, 150 mmol) and DMF (300 ml) was stirred at 50°C for 5 h. After cooling, water was added to the mixture. The precipitates were collected and recrystallized from 80% aqueous MeOH to give **4** (35 g, 43 mmol, yield 93%) as colorless crystals.

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