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 ^{1}H-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

Acylations 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*-Acylations 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 ^{1}H-NMR spectrums (from δ 3.23 to 3.77 ppm). The conversion was also confirmed from the result that the *Rf* 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 *Rf* 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 ^{1}H-NMR spectrum showed a mixture of two acyl derivatives (the *O*-acyl derivative **7g** : the *N*-acyl derivative **8g**=about 2 : 3 in $CDCl_3$), but the $CDCl_3$ solution used for ^{1}H-NMR measurement showed only one spot on silica gel TLC. The *Rf* value was 0.18. From this value, we thought that **7g** was converted to **8g** on TLC.

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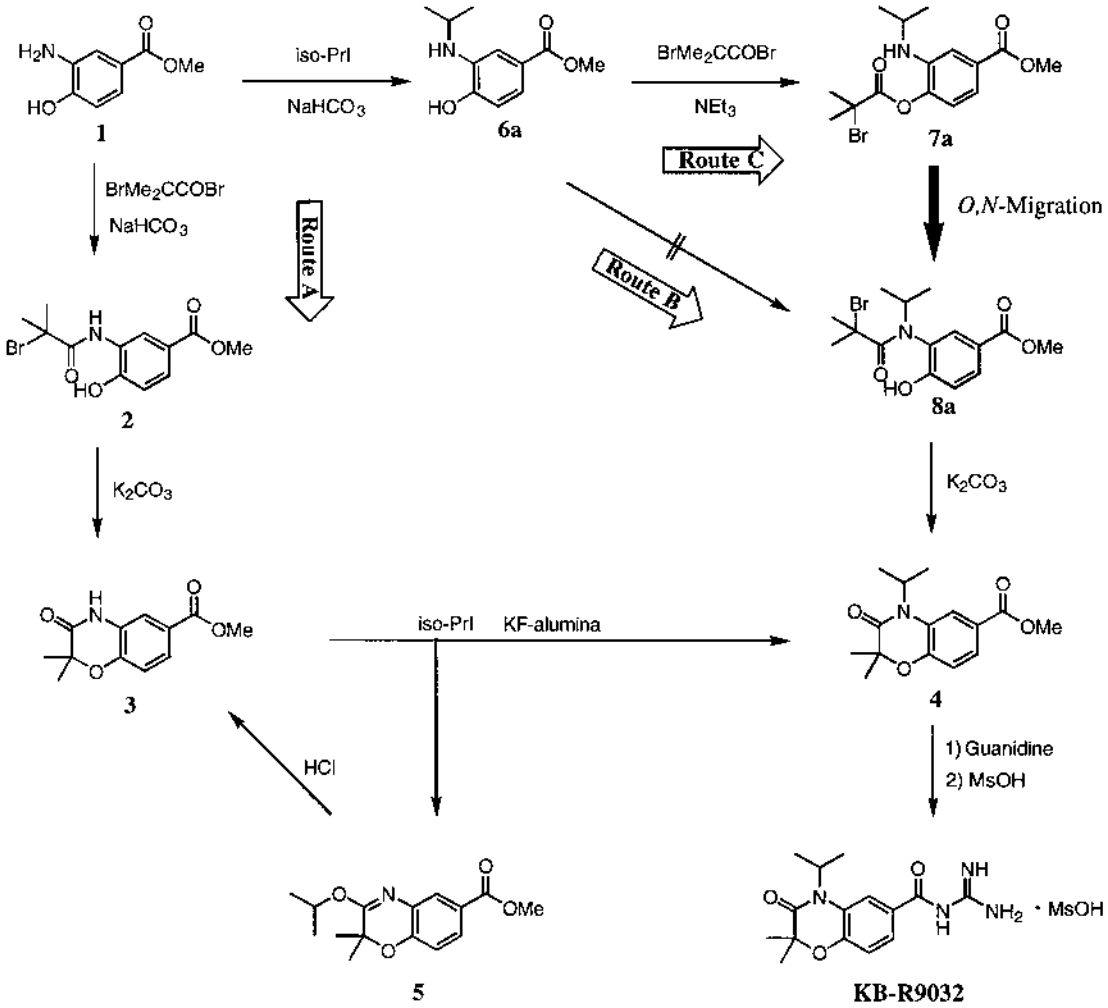


Chart 1. Synthetic Routes toward KB-R9032

Therefore, in order to confirm the conversion, we applied the solution on a preparative TLC plate. The obtained compound showed the ^{1}H-NMR spectrum of **8g**. And an elemental analysis agreed with the calculated value of **8g** within ±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-bromoisobutyryl 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 examined 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**, *Rf*=0.28) appeared in addition to the spot (*Rf*=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. ^{1}H-NMR Spectral Data for Methyl Alkylaminohydroxybenzoates **6**

No.	Spectral data[a] (250 MHz, $CDCl_3$)
6a[b]	δ; 1.24 (6H, d, J=6 Hz), 3.61—3.76 (1H, m), 3.84 (3H, s), 4.07 (1H, br), 6.77 (1H, d, J=8 Hz), 7.23—7.28 (2H, m), 9.32 (1H, br).
6b	δ; 1.26 (6H, d, J=6 Hz), 3.65—3.75 (1H, m), 3.86 (3H, s), 4.50 (1H, br), 6.18 (1H, br), 6.55 (1H, d, J=9 Hz), 7.56—7.59 (2H, m).
6c	δ; 1.19 (6H, d, J=6 Hz), 3.11 (1H, br), 3.50—3.70 (1H, m), 3.92 (3H, s), 6.77—6.86 (2H, m), 7.04 (1H, d, J=2 Hz), 10.14 (1H, br).
6d	δ; 1.27 (3H, t, J=7 Hz), 3.19 (2H, q, J=7 Hz), 3.88 (3H, s), 4.82 (2H, br), 6.73 (1H, d, J=8 Hz), 7.26 (1H, s), 7.31 (1H, d, J=8 Hz).
6e	δ; 2.90 (3H, s), 3.88 (3H, s), 4.82 (2H, br), 6.72 (1H, d, J=8 Hz), 7.32 (1H, s), 7.36 (1H, d, J=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. ^{1}H-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, J=6 Hz), 2.09 (6H, s), 3.65—3.80 (1H, m), 3.90 (3H, s), 4.13 (1H, br), 7.01 (1H, d, J=8 Hz), 7.35 (1H, dd, J=8, 2 Hz), 7.39 (1H, d, J=2 Hz).
7a ·HCl[b]	δ; 1.27 (6H, d, J=6 Hz), 2.00 (6H, s), 3.65—3.80 (1H, m), 3.95 (3H, s), 4.50 (1H, br), 7.33 (1H, d, J=8 Hz), 8.06 (1H, dd, J=2, 8 Hz), 8.43 (1H, d, J=2 Hz).
7b	δ; 1.25 (6H, d, J=6 Hz), 2.10 (6H, s), 3.63—3.77 (1H, m), 3.84 (3H, s), 4.50 (1H, br), 6.67 (1H, d, J=9 Hz), 7.63 (1H, d, J=2 Hz), 7.83 (1H, dd, J=9, 2 Hz).
7c	δ; 1.21 (6H, d, J=6 Hz), 2.09 (6H, s), 3.53 (1H, br), 3.58—3.68 (1H, m), 3.83 (3H, s), 6.72 (1H, dd, J=9, 3 Hz), 6.93 (1H, d, J=9 Hz), 7.16 (1H, d, J=3 Hz).
7d	δ; 1.29 (3H, t, J=7 Hz), 1.62 (1H, br), 2.09 (6H, s), 3.23 (2H, q, J=7 Hz), 3.90 (3H, s), 7.02 (1H, d, J=9 Hz), 7.35—7.80 (2H, m).
7g[c]	δ; 1.07 (3H, d, J=7 Hz), 1.20 (3H, d, J=7 Hz), 1.68 (3H, d, J=8 Hz), 3.08—3.11 (1H, m), 3.91 (3H, s), 4.17—4.29 (1H, m), 6.60 (1H, br), 7.16 (1H, d, J=9 Hz), 7.67 (1H, d, J=2 Hz), 8.04 (1H, dd, J=9, 2 Hz).
8a	δ; 1.01 (3H, d, J=7 Hz), 1.25 (3H, d, J=7 Hz), 1.80 (3H, s), 1.83 (3H, s), 3.90 (3H, s), 4.81—4.92 (1H, m), 5.91 (1H, br), 7.04 (1H, d, J=9 Hz), 7.91 (1H, d, J=2 Hz), 8.02 (1H, dd, J=9, 2 Hz).
8d	δ; 1.15 (3H, t, J=7 Hz), 1.85 (6H, s), 3.77 (2H, br), 3.90 (3H, s), 6.48 (1H, br), 7.34 (1H, d, J=9 Hz), 7.97 (1H, d, J=2 Hz), 7.97 (1H, dd, J=9, 2 Hz).
8e	δ; 1.89 (6H, s), 3.36 (3H, s), 3.89 (3H, s), 6.85 (1H, br), 7.03 (1H, d, J=9 Hz), 7.94 (1H, dd, J=9, 2 Hz), 7.99 (1H, d, J=2 Hz).
8f	δ; 1.04 (3H, d, J=7 Hz), 1.26 (3H, d, J=7 Hz), 3.59 (1H, d, J=12 Hz), 3.70 (1H, d, J=12 Hz), 3.92 (3H, s), 4.83—4.93 (1H, m), 7.18 (1H, d, J=9 Hz), 7.84 (1H, d, J=2 Hz), 8.02 (1H, dd, J=9, 2 Hz), 8.61 (1H, br).
8g	δ; 0.99 (3H, d, J=7 Hz), 1.26 (3H, d, J=7 Hz), 1.73 (3H, d, J=7 Hz), 3.91 (3H, s), 3.95—4.08 (1H, m), 4.79—4.92 (1H, m), 7.13 (1H, d, J=9 Hz), 7.68 (1H, br), 7.94 (1H, d, J=2 Hz), 8.02 (1H, dd, J=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 (%)	*Rf*[a]	mp (°C)	Recryst. solvent	Formula	Analysis					
						Calcd			Found		
						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	$C_9H_{11}NO_3$	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) *Rf* 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 ^{1}H-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 signal 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—

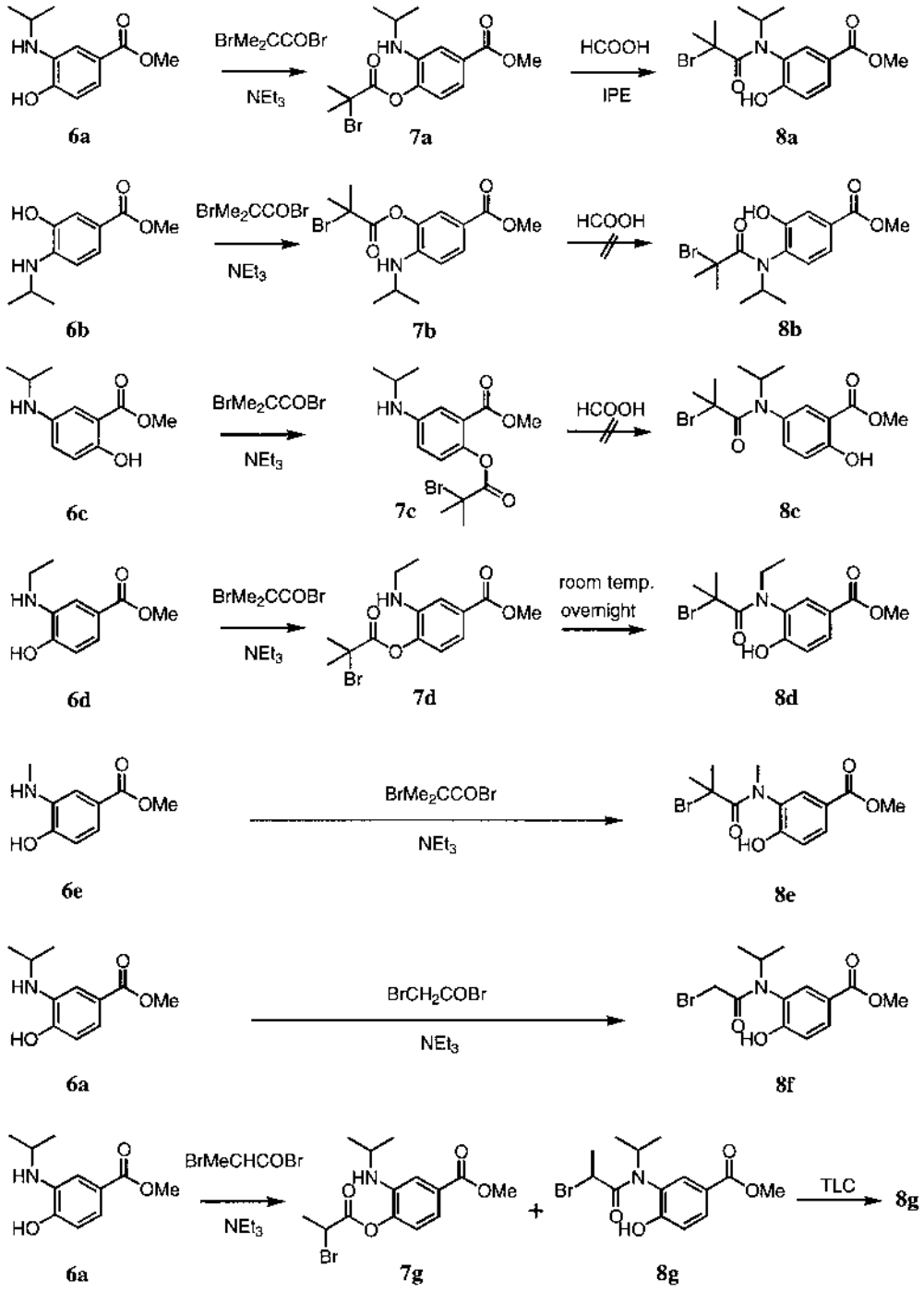


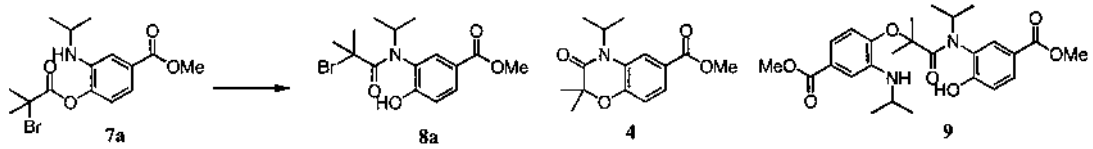
Chart 2. Acylation of **6** and *O*,*N*-Acyl Migration of **7**

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, little *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_2CO_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.

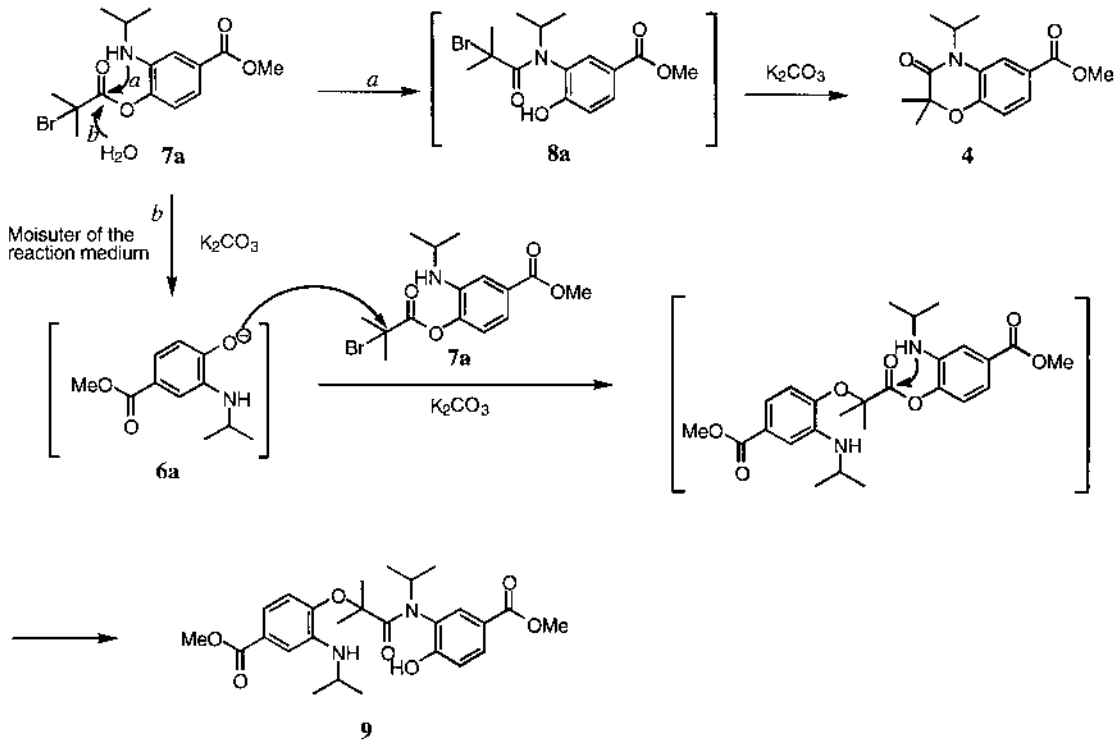


Chart 3. Possible Mechanism for the Formation of **4** and **9**

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. ^{1}H-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.×150 mm, GL Science Inc.), eluent (50 mM KH_2PO_4 (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 ($60GF_{254}$, 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 $NaHCO_3$ (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}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}H-NMR spectral and physical data are listed in Tables 1 and 3.

Acylations of Methyl Alkylaminohydroxybenzoates 6a—e. General Procedure 2-Bromoisobutyryl 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}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-Bromoisobutyryl 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-Bromoisobutyryl 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-Bromoisobutyryl Bromide: The oily product was purified by preparative TLC and was found to be the *O*-acyl derivative **7d** by TLC and ^{1}H-NMR analysis. It solidified while standing overnight at room temperature, and the *Rf* 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}H-NMR and elemental analysis.

Methyl 4-Hydroxy-3-methylaminobenzoate **6e** and 2-Bromoisobutyryl 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}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}H-NMR analysis gave only one spot (*Rf*=0.18) on TLC. The product obtained from preparative TLC was determined to be **8g** by ^{1}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—194 °C. ^{1}H-NMR (250 MHz, 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 $C_{26}H_{34}N_2O_7$: C, 64.18; H, 7.04; N, 5.76. Found, C, 64.12; H, 7.05; N, 5.68. **4**: mp: 75—77 °C. ^{1}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 $C_{15}H_{19}NO_4$: 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), 4 N 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}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}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-2*H*-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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