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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) Utilizing Potassium Fluoride–Alumina Catalyzed *N*-Alkylation

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N-Isopropylation of methyl 2,2-dimethyl-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazine-6-carboxylate (2a) with various reagents was examined in order to prepare 3a, the key intermediate in the synthesis of *N*-(4-isopropyl-2,2-dimethyl-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazine-6-carbonyl)guanidine methanesulfonate (1, KB-R9032), a novel, potent Na/H exchange inhibitor. When a base such as sodium hydride, potassium carbonate or potassium *tert*-butoxide was used, the undesired *O*-isopropyl derivative 4a was produced as the main product. Among the hydrogen bond assisted mild bases examined, potassium fluoride (KF)–alumina afforded the best *N*-/*O*-selectivity with a ratio of about four. The undesired *O*-isopropyl derivative 4a could be easily converted to the starting 2a under non-aqueous acidic conditions. Combination of the above two processes increased the *N*-/*O*-ratio (to about 42). Consequently, the *N*-isopropyl derivative 3a was isolated without column chromatography in more than 70% yield. This KF–alumina catalyzed repeated isopropylation was applicable to *N*-selective alkylation of other hindered cyclic amides to afford *N*-alkyl derivatives in high yields.

Key words potassium fluoride–alumina; *N*-alkylation; repeated alkylation; *N*-/*O*-selectivity; methyl 2,2-dimethyl-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazine-6-carboxylate

In the course of our study on Na/H exchange inhibitors, we found *N*-(4-isopropyl-2,2-dimethyl-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazine-6-carbonyl)guanidine methanesulfonate (KB-R9032, **1**).[1)] As a potent and highly water-soluble Na/H exchange inhibitor, **1** is under investigation as a drug for ischemia-reperfusion induced injury. The key intermediate for the synthesis of **1** is methyl 4-isopropyl-2,2-dimethyl-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazine-6-carboxylate (**3a**), which can be prepared by *N*-isopropylation of methyl 2,2-dimethyl-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazine-6-carboxylate (**2a**) (Chart 1). But isopropylation using sodium hydride (NaH) gave the undesired *O*-isopropyl derivative **4a** as the main product. The starting material **2a** was recovered in about 20% yield, and the isolated yield of the desired *N*-isopropyl derivative **3a** was less than 30%.

NaH, potassium carbonate (K_2CO_3) or potassium *tert*-butoxide (*tert*-BuOK) have classically been used for *N*-alkylation of carboxamides. About two decades ago, hydrogen bond assisted mild bases such as tetrabutylammonium fluoride (TBAF),[2)] potassium fluoride (KF)[3)] and solid supported KF (KF-supports)[4)] were developed. These reagents were originally developed for *N*-alkylation using *n*-alkyl halides such as methyl iodide, butyl bromide and benzyl halide, and *N*-*n*-alkylated compounds were obtained in more than 80% yield in most cases. However, there were few reports on *N*-*sec*-alkylation.[5)] In this paper, we report a practical *N*-*sec*-alkylation of **2a** and an alternative cyclic amide **2b** using a KF–alumina catalyzed repeated alkylation.

Results and Discussion

Examination of *N*-Alkylation of 2a At first, we examined general bases such as NaH, K_2CO_3, *tert*-BuOK, or, KOH for *N*-isopropylation of **2a**. The results are summarized in Table 1. The ratios of **3a**/**4a** were estimated by HPLC analysis and are not corrected. All of the conventional bases gave predominately the *O*-isomer with a **3a**/**4a** ratio of less than one, and unconsumed starting material **2a** was generally recovered in more than 10% yield (entries 1—5). The reason for the remaining **2a** was thought to be the competitive dehydroiodidation of the isopropyl iodide. The dehydroiodidation was suggested by evolution of gas from the reaction mixture,[5,6)] and the slow isopropylation was due to the steric repulsion between isopropyl iodide and the hindered amide moiety of **2a**.

Next, hydrogen-bond assisted bases, such as TBAF, KF and KF–supports were examined. The starting com-

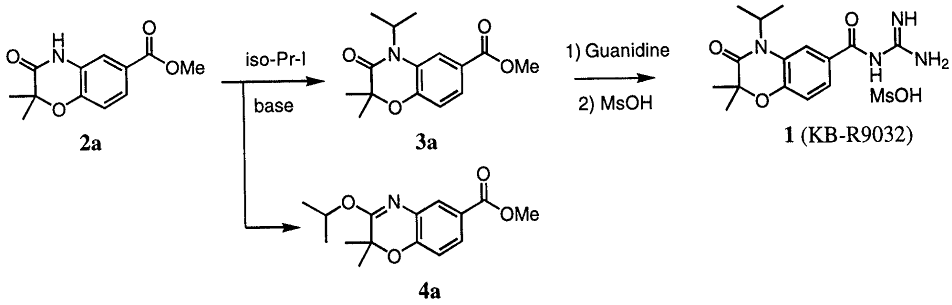

Chart 1. Synthetic Route for the Potent Na/H Exchange Inhibitor KB-R9032 (1)

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Table 1. Isopropylation of **2a** by Isopropyl Iodide under Various Conditions

Entry	Base	Solvent	Time (h)	HPLC anal. (%)*a*)			Ratio of **3a**/**4a***b*)	Yield (%) of **3a***c*)
				2a	**3a**	**4a**		
1	NaH	DMF	5	17	29	45	0.64	24
2	NaH	DME	5	23	30	36	0.83	—*d*)
3	K_2CO_3	DMF	3	29	24	36	0.67	—*d*)
4	*tert*-BuOK	DMF	17	10	22	34	0.65	—*d*)
5	KOH	DMSO	5	4	39	45	0.87	—*d*)
6	TBAF	THF	16	60	10	16	0.63	—*d*)
7	KF	DME	21	82	2	1	2	—*d*)
8	KF–silica gel	DME	70	85	2	ND*e*)	—*d*)	—*d*)
9	KF–celite	DME	21	71	3	1	3	—*d*)
10	KF–alumina	DME	30	4	62	15	4.1	60

a) HPLC condition: see experimental section. *b*) The ratios are the ratios of peak areas and are uncorrected. *c*) Isolated yield using column chromatography operation. *d*) Not determined. *e*) Not detected.

pound **2a** was recovered in 60% and 82% yield, respectively when TBAF and KF were used (entries 6 and 7). Among commercially available KF–silica gel, KF–celite and KF–alumina as KF–supports tested in 1,2-dimethoxyethane (DME), KF–alumina catalyzed the isopropylation (entry 10), while no isopropylation occurred with KF–silica gel and KF–celite (entries 8 and 9). Furthermore, KF–alumina showed a better *N*-/*O*-selectivity than NaH, K_2CO_3 and *tert*-BuOK. The predominance of KF–alumina for the above *N*-*sec*-alkylation coincided with Yamawaki's results that KF–alumina was more efficient for *n*-alkylation than other KF–supports.4) The basicity of KF was strengthened by supporting with alumina.7)

However, the ratio of *N*-/*O*-isopropylation (**3a**/**4a**) by KF–alumina was not so high (about four), and a column chromatography operation was needed for isolation of **3a**. Therefore, a more selective *N*-*sec*-alkylation method of **2a** was required for the practical synthesis of **1**.

Development of KF–Alumina Catalyzed Repeated Alkylation Imidates are generally unstable against acids which cause them to decompose into amides. As expected, treatment of a solution of **4a** in *N*,*N*-dimethylformamide (DMF)–water with conc. HCl yielded the starting compound **2a** (Chart 2). The regeneration of **2a** also proceeded under non-aqueous conditions with a catalytic amount of 4 N HCl–1,4-dioxane in DME. The compound **2a** was obtained in a quantitative yield by simple evaporation of the solvent.

KF–Alumina was considered to be the most promising reagent for *N*-selective isopropylation. Thus, we developed a convenient *N*-selective isopropylation method, by combination of repeated KF–alumina catalyzed alkylation and HCl catalyzed decomposition of the undesired *O*-alkyl product (Chart 3).

$$\mathbf{4a} \xrightarrow{\text{HCl}} \mathbf{2a}$$

Chart 2. Regeneration of **2a** by Decomposition of **4a**

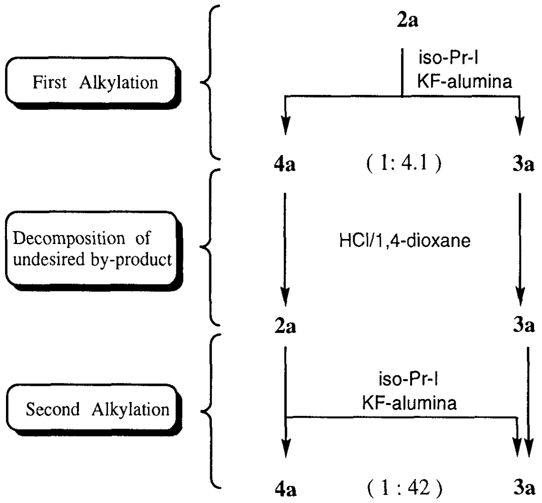


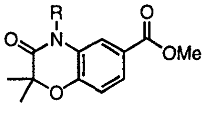
Chart 3. Scheme for the KF–Alumina Catalyzed Repeated Alkylation

A general procedure of KF–alumina catalyzed repeated alkylation is as follows: A mixture of the starting carboxamide, 3 eq of an alkyl halide and 3 eq of KF–alumina in DME is stirred at 50 °C until the starting carboxamide is consumed (about 1—2 d). 4 N HCl–1,4-dioxane is added to the reaction mixture until the pH becomes about three. The mixture is stirred at 50 °C until the undesired *O*-alkyl product is completely decomposed (about 1 h). Then, KF–alumina (3 eq) is added to the reaction mixture. After the regenerated starting carboxamide is consumed (about 1—2 d), the insoluble materials are filtered off. Evaporation of the filtrate affords the almost pure *N*-alkylated carboxamide (Table 2).

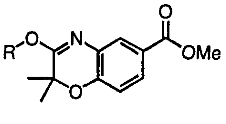
By application of this alkylation to **2a**, the ratio of **3a**/**4a** increased to about 10 (entry 1). The isolated yield of **3a** was 76% without column chromatography, and this provided a practical synthesis of KB-R9032. *N*-*sec*-Butylation of **2a** also gave a good result (entry 2). The initial *N*-/*O*-selectivity of cyclopentylation of **2a** was low (2.3), but the final ratio was highly improved. The isolated yield was 70% (entry 3). The KF–alumina catalyzed repeated alkylation was also useful for *N*-isopropylation of the amide **2b**8) (entry 4).

In conclusion, we developed a KF–alumina catalyzed repeated alkylation of carboxamides by combination of KF–alumina catalyzed alkylation and non-aqueous decomposition of an undesired *O*-alkyl derivative, leading to a practical synthesis of the key intermediate **3a** of KB-R9032 (**1**), a potent Na/H exchange inhibitor. Although the total reaction time was long, the work-up

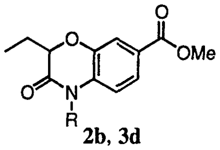
Table 2. N-Alkylation of **2** by KF–Alumina Catalyzed Repeated Alkylation



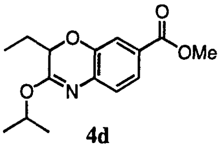
2a, 3a–c



4a–c



2b, 3d



4d

Entry	Starting amide **2** (R=H)	R^1-X	N-Alkyl amide **3** (R=R^1)	O-Alkyl imidate **4** (R=R^1)	Ratio of **3**/**4**[a)] First[b)]	(NaH condition)[d)]	Second[c)]	Yield (%)[e)]
1	**2a**	Iso-PrI	**3a**	**4a**	4.1	(0.64)	42	76
2	**2a**	*sec*-ButylI	**3b**	**4b**	5.6	(1.2)	62	73
3	**2a**	CyclopentylBr	**3c**	**4c**	2.3	(0.32)	11	70
4	**2b**	Iso-PrI	**3d**	**4d**	9.8	(1.0)	120	78

a) HPLC condition: see experimental section. The ratios are the ratios of peak areas and are uncorrected. *b)* Result of the first alkylation. *c)* Result of the second alkylation. *d)* The ratio obtained by using NaH (in condition of Table 1 entry 1). *e)* Isolated yield.

procedure required only filtration and evaporation.

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 in $CDCl_3$ 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 i.d. × 150 mm, GL Science Inc.), eluent (20 mM KH_2PO_4 (pH 6.8)–acetonitrile (40 : 60, v/v)), UV detector (254 nm). KF–alumina, KF–celite and KF–silica gel were purchased from Aldrich Inc.

General Procedure for Alkylation of 2a or 2b (Table 1, Entries 1—7 and Table 2, NaH Condition) A mixture of **2a**[1)] or **2b**[8)] (10 mmol), a base (15 mmol), an alkyl halide (15 mmol) and a solvent (20 ml) was stirred at 50 °C for the reported number of hours. Then, water was added to the mixture and the whole was extracted with ethyl acetate (AcOEt). The extract was washed with water, and dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo*. The residue was chromatographed on silica gel (hexane–AcOEt) to give **3** and **4**.

Methyl 4-Isopropyl-2,2-dimethyl-3-oxo-3,4-dihydro-2*H*-benzo[1,4]-oxazine-6-carboxylate (**3a**): mp 75—77 °C (60% MeOH). ^{1}H-NMR (60 MHz) 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, 64.86; H, 6.88; N, 4.91.

Methyl 3-Isopropyloxy-2,2-dimethyl-2*H*-benzo[1,4]oxazine-6-carboxylate (**4a**): mp 50—52 °C. ^{1}H-NMR (60 MHz) δ: 1.36 (6H, d, $J=6$ Hz), 1.42 (6H, s), 3.89 (3H, s), 5.15—5.68 (1H, m), 6.88 (1H, d, $J=9$ Hz), 7.78 (1H, dd, $J=9$, 2 Hz), 7.89 (1H, d, $J=2$ Hz). *Anal.* Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.01; H, 6.88; N, 4.96.

Methyl 4-Isobutyl-2,2-dimethyl-3-oxo-3,4-dihydro-2*H*-benzo[1,4]-oxazine-6-carboxylate (**3b**): Colorless oil. ^{1}H-NMR (250 MHz) δ: 0.86 (3H, t, $J=7$ Hz), 1.43 (3H, s), 1.47 (3H, s), 1.49 (3H, d, $J=7$ Hz), 1.75—1.92 (1H, m), 2.03—2.21 (1H, m), 3.89 (3H, s), 4.49—4.63 (1H, m), 6.97 (1H, d, $J=8$ Hz), 7.68 (1H, dd, $J=8$, 2 Hz), 7.81 (1H, d, $J=2$ Hz). *Anal.* Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.26; N, 4.81. Found: C, 65.92; H, 7.27; N, 4.77.

Methyl 3-Isobutyloxy-2,2-dimethyl-2*H*-benzo[1,4]oxazine-6-carboxylate (**4b**): Colorless oil. ^{1}H-NMR (250 MHz) δ: 0.96 (3H, t, $J=7$ Hz), 1.30 (3H, d, $J=6$ Hz), 1.46 (3H, s), 1.47 (3H, s), 1.58—1.77 (2H, m), 3.88 (3H, s), 5.11—5.24 (1H, m), 6.86 (1H, d, $J=8$ Hz), 7.72 (1H, dd, $J=8$, 2 Hz), 7.82 (1H, d, $J=2$ Hz). *Anal.* Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.26; N, 4.81. Found: C, 66.06; H, 7.27; N, 4.71.

Methyl 4-Cyclopentyl-2,2-dimethyl-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazine-6-carboxylate (**3c**): mp 58—60 °C. ^{1}H-NMR (250 MHz) δ: 1.49 (6H, s), 1.67—1.77 (2H, m), 1.93—2.22 (6H, m), 3.93 (3H, s), 4.86—5.00 (1H, m), 7.01 (1H, d, $J=8$ Hz), 7.72 (1H, dd, $J=8$, 2 Hz), 7.79 (1H, d, $J=2$ Hz). *Anal.* Calcd for $C_{17}H_{21}NO_4$: C, 63.71; H, 6.98; N, 4.62. Found: C, 67.45; H, 7.05; N, 4.56.

Methyl 3-Cyclopentyloxy-2,2-dimethyl-2*H*-benzo[1,4]oxazine-6-carboxylate (**4c**): mp 32—34 °C. ^{1}H-NMR (250 MHz) δ: 1.45 (6H, s), 1.60—1.84 (6H, m), 1.86—2.04 (2H, m), 3.90 (3H, s), 5.43—5.50 (1H, m), 6.87 (1H, d, $J=8$ Hz), 7.72 (1H, dd, $J=8$, 2 Hz), 7.84 (1H, d, $J=2$ Hz). *Anal.* Calcd for $C_{17}H_{21}NO_4$: C, 63.71; H, 6.98; N, 4.62. Found: C, 67.45; H, 7.00; N, 4.58.

Methyl 2-Ethyl-4-isopropyl-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazine-7-carboxylate (**3d**): Colorless oil. ^{1}H-NMR (60 MHz) δ: 1.02 (3H, t, $J=7$ Hz), 1.52 (6H, d, $J=6$ Hz), 1.60—2.20 (2H, m), 3.90 (3H, s), 4.37 (1H, dd, $J=8$, 5 Hz), 4.50—5.00 (1H, m), 7.18(1H, d, $J=9$ Hz), 7.65 (1H, d, $J=1$ Hz), 7.78 (1H, dd, $J=9$, 1 Hz). *Anal.* Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.88; H, 6.98; N, 5.00.

Methyl 2-Ethyl-3-isopropyloxy-2*H*-benzo[1,4]oxazine-7-carboxylate (**4d**): Colorless oil. ^{1}H-NMR (60 MHz) δ: 1.00 (3H, t, $J=7$ Hz), 1.40 (6H, d, $J=6$ Hz), 1.50—2.00 (2H, m), 3.91 (3H, s), 4.48 (1H, t, $J=6$ Hz), 5.11—5.73 (1H, m), 7.15 (1H, d, $J=9$ Hz), 7.58 (1H, d, $J=1$ Hz), 7.67 (1H, dd, $J=9$, 1 Hz). *Anal.* Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.95; H, 7.05; N, 5.00.

General Procedure for Isopropylation of 2a (Table 1, Entries 8—10) A mixture of **2a** (10 mmol), a KF–support (KF, 30 mmol), isopropyl iodide (30 mmol) and a solvent (30 ml) was stirred at 50 °C. Then, the mixture was filtered and the filtrate was concentrated *in vacuo* to give **3a** and **4a**.

Decomposition of 4a to Regeneration of 2a Several drops of 4 N HCl–1,4-dioxane was added to a solution of **4a** (10 mmol) in DME (30 ml) (pH about 3, checked by wet pH test paper). The mixture was stirred at 50 °C for 1 h, and was evaporated *in vacuo* to give **2a** (yield 100%).

General Procedure for KF–Alumina Catalyzed Repeated Alkylation (Table 2) A mixture of **2** (10 mmol), KF–alumina (KF, 30 mmol), an alkyl halide (30 mmol) and DME (30 ml) was stirred at 50 °C. After the alkylation was complete, 4 N HCl–1,4-dioxane was added to the mixture until the pH became about 3, and the mixture was stirred at 50 °C until the O-alkyl derivative **4** was decomposed (about 1 h). Then KF–alumina (KF, 30 mmol) was added to the reaction mixture. The mixture was stirred at 50 °C and filtered. The filtrate was evaporated *in vacuo* to give **3**.

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