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A simple method removing 2-oxazolidinone and 2-hydroxyethylamine auxiliaries in methoxide–carbonate systems for synthesis of planar-chiral nicotinate

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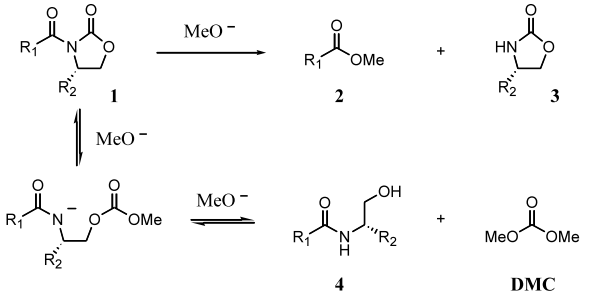
Abstract—A facile and practical removal of 2-oxazolidinone and 2-hydroxyethylamine auxiliaries was accomplished by treating the corresponding *N*-acyl-2-oxazolidinone and *N*-(2-hydroxyethyl)amide derivatives in simple methoxide–carbonate systems. The presence of excess DMC (dimethyl carbonate) accelerates the *N*-acyl bond cleavage for those substrates under mild reaction conditions, and the present method was found to be useful especially for the synthesis of planar-chiral nicotinate.

2-Oxazolidinone derivatives have been widely used as chiral auxiliaries for a number of asymmetric reactions and for resolution in synthetic organic chemistry.[1] Several useful methods have been reported on non-destructive removal of those auxiliaries by cleaving their *N*-acyl bonds with hydrolytic reagents such as alkoxides,[2] thiolate,[3] amine,[4] hydroxide,[2c,5] hydroperoxide,[6] etc., or with hydride reagents[7] for reductive removal. Among them, the methoxide ion is obviously one of the most convenient reagents in terms of its commercial availability and technical simplicity in that the corresponding esters produced are easily separable from the co-produced 2-oxazolidinone derivatives. However, *exo*-carbonyl selectivity leading to the desired *N*-acyl bond cleavage depends on the steric and electronic properties surrounding the carbonyl group, and undesired *endo*-carbonyl alcoholysis often takes place to give ring-opening 2-hydroxyethylamide as by-products.[6a,8,9] We have been studying, on the other hand, the synthetic utility of the 2-hydroxyethylamide derivatives and have recently reported that chiral *N*-(2-hydroxyethyl)carbamoyl groups play an important role in the stereocontrol of planar-chiral nicotinamides,[10,11] which are key synthetic intermediates of chiral bridged NADH models effecting biomimetic reduction with high enantioselectivity.[12] We report here a simple method removing 2-oxazolidinone and its related 2-hydroxyethylamine auxiliaries in common methoxide–carbonate systems from the corresponding *N*-acyl-2-oxazolidinones and *N*-(2-hydroxyethyl)amides, respectively. We also describe its application to the synthesis of enantiomerically pure bridged nicotinate with single planar-chirality.



Scheme 1. Reaction pathways for the reaction of **1** with methoxide.

Our method simply runs the removal of those chiral auxiliaries in methoxide–carbonate systems instead of methoxide alone, where an excess amount of DMC (dimethyl carbonate) remarkably accelerates the reactions to improve the yields of ester products. Scheme 1 depicts the reaction pathways for the formation of the desired esters **2** and undesired amides **4**, the latter of which is initiated by methoxide attack onto the endocyclic carbonyl of *N*-acyl-2-oxazolidinones **1**. These unfavorable reactions causing the formation of the

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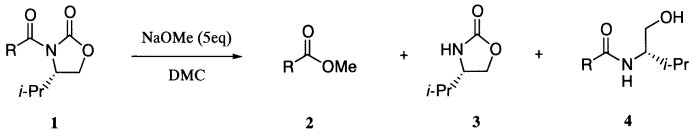
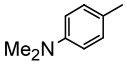
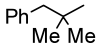
amides **4** usually become more problematic for such substrates where R_1 is an aromatic or sterically demanding alkyl group making their exocyclic carbonyl groups less reactive. We then focused on the side-reaction pathway simultaneously releasing an equimolecular amount of DMC after the second methoxide substitution. Therefore, further addition of DMC should shift the equilibrium toward the starting oxazolidinone **1** to improve the yield of the desired ester **2**. Based on this simple strategy, we treated various *N*-acyl-2-oxazolidinones **1** with NaOMe in the presence of excess DMC.

Table 1 summarizes the results of transesterfication of *N*-acyl-2-oxazolidinones **1**.[13] Initially, we investigated the reactions of benzoate derivative **1a** in the absence or presence of DMC at room temperature. The reactions of **1a** with NaOMe alone afforded significant amounts of undesired **4a** in 8–30% yields as well as the desired ester **2a** even in the standard solvents such as THF and MeOH (entries 1–3). On the contrary, compound **1a** readily reacted with NaOMe in the presence of DMC to form both **2a** and **4a** in 76% and 10% yields, respectively (entry 4), and the further conversion of **4a** to **2a** was complete within an additional hour to result in the formation of **2a** in 98% yield (entry 5). Similarly, DMC affected the reaction of a benzoate derivative having an electron-donating amino group on its aromatic moiety. The reaction of **1b** gave the desired **2b** in 97% yield within 4 h, although the reaction with methoxide alone co-produced the 2-hydroxyethylamide **4b** in 8–34% yields (entries 6–9). Compounds **1c**,**d** with alkenyl and phenethyl groups readily reacted to afford the corresponding esters **2c**,**d** in high yields (entries 10, 11). The reaction of **1e**,**f**[14] and **1g**,**h** having another alkyl group on the α-position was also readily complete within 2.5–5 h to give optically active esters **2e**–**h** in 93–96% yields (entries 12–15). Though the esters (*S*)-**2e**, (*R*)-**2f** and (*S*)-(+)-**2g**[15] were obtained without signifi-

Table 1. Transesterification of 2-oxazolidinones **1** in methoxide–carbonate systems[a]



Entry	1	R	Conditions				Yield [%]		
			DMC	Solvent	*T* [°C]	*t*	**2** (Stereoselectivity)[b,c]	**3**	**4**
1	**a**		none	THF	RT	2 h	89	76	8
2[d]	**a**		none	MeOH	RT	20 m	70	70	30
3	**a**		none	CH_2Cl_2	RT	1 h	69	71	25
4	**a**		5 eq	CH_2Cl_2	RT	1 h	76	83	10
5	**a**		5 eq	CH_2Cl_2	RT	2 h	98	95	0
6	**b**		none	THF	RT	4 h	88	89	8
7	**b**		none	MeOH	RT	4 h	66	63	34
8[e]	**b**		none	CH_2Cl_2	RT	4 h	61	60	8
9	**b**		5 eq	CH_2Cl_2	RT	4 h	97	95	0
10	**c**		5 eq	CH_2Cl_2	RT	2 h	95	91	0
11	**d**		5 eq	CH_2Cl_2	RT	45 m	97	92	0
12	**e**		5 eq	CH_2Cl_2	RT	2.5 h	94 (99)	96	0
13	**f**		5 eq	CH_2Cl_2	RT	4 h	93 (98)	96	0
14	**g**		5 eq	CH_2Cl_2	RT	5 h	96 (>99)	94	0
15	**h**		5 eq	CH_2Cl_2	RT	5 h	96 (94)	97	0
16	**h**		5 eq	DMC	RT	4 h	92 (98)	97	0
17	**i**		none	Toluene	50	10 h	58	60	32
18	**i**		5 eq	Toluene	110	8 h	78	75	14
19[f,g]	**i**		excess	DMC	50	24 h	87	82	0

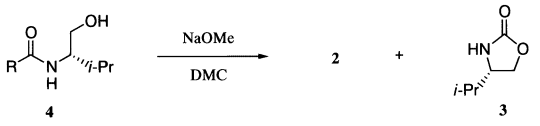
[a]5 eq of NaOMe was used in all reactions unless otherwise specified. [b]Calculated by [100 x (% ee of **2e-h**)/(% de of **1e-h**)]. The diastereomeric purities of **1e-h** used were in a rage of 99.0 to 99.8%de. [c]Enantiomeric excesses of **2e-h** were determined by HPLC by using Chiralcel OD column (Dicel Chemical Industries Ltd.) with 1% isopropanol in hexane at 15 °C. [d]Monitored by using ^{1}H NMR in methanol-d_4. [e]*N*-acyl-2-oxazolidinone **1b** was recovered in 22% yield. [f]10eq of NaOMe was used. [g]Oxazoline derivative was obtained in 12% yield.

cant racemization (entries 12–14), a decrease of enantiomeric purity was observed in case of (*R*)-(–)-**2h**[15] (entry 15). This problem was overcome efficiently by running the reaction in large excess DMC as solvent to give (*R*)-(–)-**2h** with 98% selectivity (entry 16). On the other hand, conversion of compound **1i** incorporating a more sterically demanding dimethyl group required much higher temperature and longer reaction times for its completion (entries 17–19). However, the DMC effect is still evident in these reactions so that removal of the oxazolidinone moiety proceeded in DMC at 50°C to increase the yield of **2i** to 87% (entry 19). In each reaction, oxazolidinone **3** was isolated in almost identical yields as those for the esters obtained, which is compatible with the proposed reaction mechanism depicted in Scheme 1.

The postulated reaction pathways were further rationalized by the following results: (1) the *N*-(2-hydroxyethyl)amide derivatives **4** also afforded the corresponding ester **2** in excellent yields under similar reaction conditions as those employed for *N*-acyl-2-oxazolidinones **1** (vide infra), (2) methoxide alone did not cleave the *N*-acyl bond of the compounds **4** without addition of DMC, and (3) *N*-propyl phenethylcarboxamide, a simple secondary amide, is completely inert in the methoxide–carbonate systems.

An efficient transesterification of compounds **4**[16] proceeds also in methoxide–carbonate systems to remove chiral hydroxyethylamine auxiliaries with a clean *N*-acyl bond cleavage (Table 2). The transesterification of **4d** underwent in excellent yields with 3–5 equiv. of NaOMe though the less amount of methoxide required longer reaction times (entries 1–3). Aprotic solvents are compatible with this system (entries 4–6), but no reaction took place in methanol, a common solvent with methoxide for the conventional method removing 2-oxazolidinone auxiliaries (entry 7). Reaction of diastereomerically pure compounds **4e–h** also proceeded smoothly to give the corresponding chiral esters **2e–h** in excellent yields (entries 8–12). For compound **4i** with fully substituted quaternary carbon as R, *N*-acyl cleavage was less efficient and the ester **2i** was obtained in modest yields (entries 13 and 14). The formation of the oxazolidinone intermediate is apparently less favorable due to steric repulsion between the substituents on R and the isopropyl group on the 2-oxazolidinone moiety, and the relatively acidic protons generating methanol in situ also decrease the reactivity of methoxide toward **4i** (see entry 7).

Table 2. Transesterification of *N*-hydroxyethylamides **4** in methoxide–carbonate systems[a]

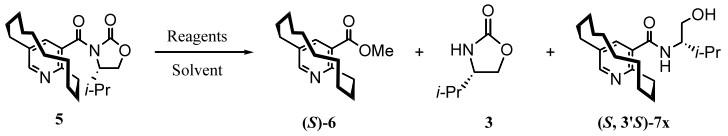


4 3

Entry	4	R	Conditions					Yield [%]		
			NaOMe	DMC	Solvent	*T*	*t*	**2** (Stereoselectivity)[b,c]	**3**	**4**
1	**d**		2 eq	5 eq	CH_2Cl_2	RT	6 h	85	85	8
2	**d**		3 eq	5 eq	CH_2Cl_2	RT	1 h	97	95	0
3[d]	**d**		5 eq	5 eq	CH_2Cl_2	RT	20 m	93	94	0
4	**d**	Ph	5 eq	5 eq	CH_3CN	RT	10 m	95	97	0
5	**d**		5 eq	5 eq	Toluene	RT	10 m	97	96	0
6	**d**		5 eq	5 eq	THF	RT	10 m	85	98	0
7	**d**		5 eq	5 eq	MeOH	RT	72 h	0	0	98
8	**e**	Ph, Me	5 eq	5 eq	CH_2Cl_2	RT	40 m	92 (>99)	96	0
9	**f**	Ph, Me	5 eq	5 eq	CH_2Cl_2	RT	40 m	92 (99)	97	0
10	**g**	Ph, Et	5 eq	5 eq	CH_2Cl_2	RT	9 h	90 (99)	92	0
11	**h**	Ph, Et	5 eq	5 eq	CH_2Cl_2	RT	9 h	94 (95)	96	0
12	**h**		5 eq	excess	DMC	RT	1 h	95 (96)	99	0
13	**i**	Ph, Me, Me	5 eq	5 eq	Toluene	50 °C	48 h	47	43	11
14[e]	**i**		10 eq	excess	DMC	50 °C	48 h	63	66	7[f]

[a]Phenyl and alkenyl derivatives such as **4a,c** also gave the corresponding esters **2a,c** in 97% yield each. [b]Calculated by [100 x (% ee of **2e-h**)/(% de of **4e-h**)]. The diastereomeric purities of **4e-h** used were in a range of 98.5-99.9%ee. [c]Enantiomeric excesses were determined by HPLC (see footnote c in Table 1). [d]The reaction in the absence of DMC recovered **4d** in 92% yield after 3 h. [e]Oxazoline derivative was obtained in 14% yield. [f]Methoxycarbonyl derivative was isolated instead of alcohol **4i**.

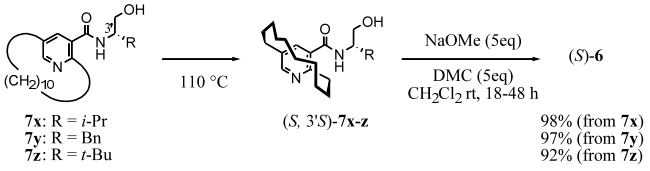
Table 3. Transesterification of **5** having a chiral oxazolidinone auxiliary



5 (*S*)-**6** **3** (*S*, 3'*S*)-**7x**

Entry	Conditions				Yield [%]			Recovery [%]
	Reagents	Solvent	*T*	*t*	**6**	**3**	**7x**	**5**
1	NaOMe (5 eq), DMC	DMC	RT	2 h	92	92	0	0
2	NaOMe (5 eq)	CH_2Cl_2	RT	8 h	52	55	33	0
3	NaOMe (5 eq)	THF	RT	2 h	35	35	61	0
4	NaOMe (5 eq)	MeOH	RT	2 h	16	15	83	0
5	Ti(O*i*-Pr)$_4$ (0.1 eq)	MeOH-Toluene	80 °C	21 h	< 1[a]	< 1[a]	0	93[b]
6	LaI_3 (1 eq), MeOH (3 eq)	THF	RT	2 h	3	n/a[a]	23[c]	64
7	Sc(OTf)$_3$ (0.1 eq)	MeOH	Ref.	18 h	5	6	5[c,d]	89[e]

[a]Detected by ^{1}H NMR. [b]Recoverd with 90% de. [c]Methoxycarbonyl derivative was isolated instead of alcohol (*S*, 3'*S*)-**7x**. [d]Obtained with 47% de. [e]Recovered with 95% de.



7x: R = *i*-Pr
7y: R = Bn
7z: R = *t*-Bu

(*S*, 3'*S*)-**7x-z**

98% (from **7x**)
97% (from **7y**)
92% (from **7z**)

Scheme 2. Synthesis of bridged nicotinate (*S*)-**6** with single planar-chirality.

These efficient transesterification developed here was best applied to the synthesis of the enantiomerically pure nicotinate **6** having a planar-chiral [10]parapyridinophane structure (Table 3 and Scheme 2). Table 3 indicates the results of transesterification of bridged nicotinimide **5** incorporating a chiral 2-oxazolidinone moiety. The methoxide–carbonate reactions effected a clean removal of 2-oxazolidinone **3** within 2 h to give the ester (*S*)-**6** in 92% yield (entry 1).[17] This is in good contrast with the results attained by using methoxide alone where undesired (*S*,3′*S*)-**7x** still remains in 33–83% yields (entries 2–4). Common Lewis acid catalysts such as Ti(O*i*-Pr)$_4$,[9b] LaI_3[9a] and Sc(OTf)$_3$[9b] were incompetent for synthesizing chiral bridged nicotinates **6** (entries 5–7). Hydrolysis with widely used LiOOH is already known to exhibit solvent-dependent selectivity for **6** and **7x**.[12b] Further important application is certainly to the efficient *N*-acyl cleavage of planar-chiral (*S*,3′*S*)-**7x**–**z**, which are available with single planar-chirality via crystallization-induced asymmetric transformation of their 1/1 diastereomeric mixtures.[10] The reactions proceeded without atropisomerization of their planar-chiral unit[18] to afford the chiral nicotinate (*S*)-**6** in 92–98% yields (Scheme 2).[19] These transformations provide not only the enantioselective synthesis of a potentially useful planar-chiral source for synthetic organic chemistry[20] but also a practical method for thermodynamically less stable molecules with planar, axial, or herical chirality, which might face a risk of isomerization at higher temperatures. Further synthetic application of planar-chiral pyridines is now under way.

Acknowledgements

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13. *N*-Acyl-2-oxazolidinones **1** were prepared from the corresponding acid chlorides and deprotonated (*S*)-4-isopropyl-2-oxazolidinone **3** based on the known procedure. See: Gage, J. R.; Evans, D. A. *Org. Synth. Coll. VIII* **1993**, 339–343.
14. Stereochemistry of **1e**,**f** was assigned as shown in Table 1 by comparison with ^{1}H NMR spectral data of **1f** reported in literature. See: Miyata, O.; Shinada, T.; Ninomiya, I.; Naito, T. *Tetrahedron* **1997**, *53*, 2421–2438.
15. To determine absolute configuration of (*S*)-(+)-**2f** and (*R*)-(−)-**2h**, the latter ester was hydrolyzed to (*R*)-(−)-2-benzylbutanoic acid whose specific rotation is known in literature. See: Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 567–576.
16. *N*-(2-Hydroxyethyl)carboxamides **4** were prepared in excellent yields from the corresponding acid chlorides and 2-hydroxethylamines (1.5 equiv.) in the presence of Et_3N (1.5 equiv.) in CH_2Cl_2 at room temperature.
17. The diastereomeric isomer of **5** afforded (*R*)-**6** in 95% yield by the reaction with NaOMe in DMC within 1 h at room temperature.
18. Enantiomeric excess of **6** (>99% ee) was determined by HPLC with Daicel CHIRALCEL OD column (1% IPA in hexane).
19. *Experimental procedures*: A solution of bridged nicotinamide (*S*,3′*S*)-**7x** (357 mg, 1.03 mmol), sodium methoxide (278 mg, 5.15 mmol), and dimethyl carbonate (0.42 ml, 5.15 mmol) in CH_2Cl_2 (5 ml) was stirred at room temperature for 18 h. After the reaction was complete, water (5 ml) was added and the organic layer was separated. The aqueous layer was acidified to ca. pH 7 with hydrochloric acid and was extracted with CH_2Cl_2 (3×). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The mixture was chromatographed on silica gel by ether–hexane (1/2) to give (*S*)-**6** (278 mg, 98%) and by ether to give 4-isopropyl-2-oxazolidinone (**3**) (128 mg, 96%).
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