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The electrochemically induced Hofmann rearrangement and its comparison with the classic Hofmann rearrangement

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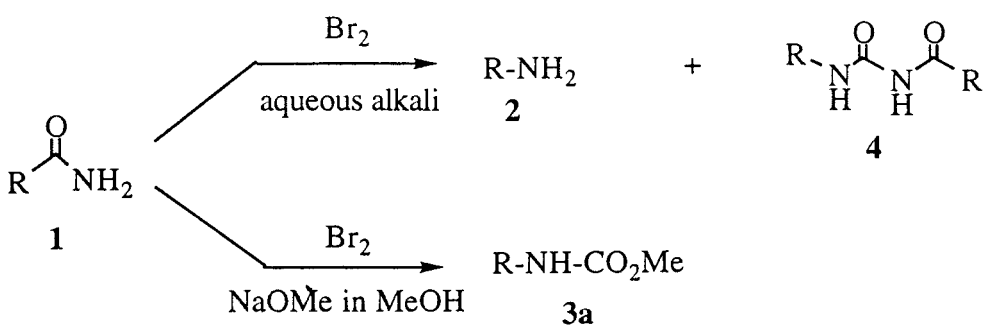
Abstract

The conditions suitable for the electrochemically induced (E-I) Hofmann rearrangement were scrutinized, and the E-I Hofmann rearrangement was compared with the classic Hofmann rearrangement. The E-I Hofmann rearrangement usually afforded reliable results with respect to the yields of the desired carbamates and the side products. Furthermore, by utilizing the advantage of the E-I Hofmann rearrangement which could be carried out in new solvent systems containing a variety of alcohols under mild conditions (neutral), a variety of carbamates possessing various functional groups were prepared.

Keywords: Hofmann rearrangement; Carbamate; *N*-Acylurea; Solvent effect

1. Introduction

The Hofmann rearrangement is a well-known reaction useful in organic synthesis in which primary carboxamides **1** are converted to amines **2** possessing a one-carbon-shortened structure by treatment with bromine and alkali, while a modified procedure using bromine and sodium methoxide in methanol is recommended for higher aliphatic carbamates **3a** (Eq. 1) since use of aqueous conditions for those amides results in a formation of large amount of serious side product, *N*-alkyl-*N′*-acylureas **4**, leading to poor yields of **2** [1,2].



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The recommended procedure, however, is not always applicable to all kinds of higher aliphatic carboxamides in terms of satisfactory and reliable results [3]. Thus, a

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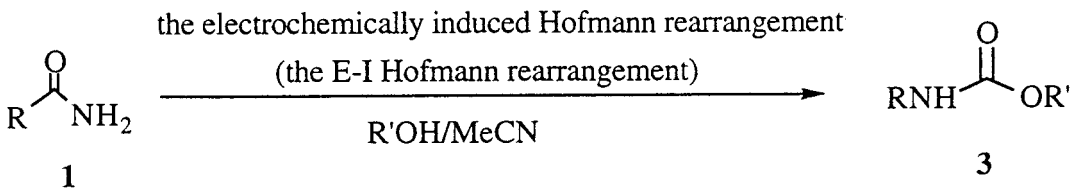
variety of further modified methods using other oxidizing reagents such as MeOBr [3], $Pb(OAc)_4$ [4], $PhI(OCOCF_3)_2$ [5–8], $NaBrO_2$–NaBr [9], $PhCH_2Me_3N^+Br_3^-$ [10], $Hg(OAc)_2$ [11], $PhI(OAc)_2$ [12], NBS–KOH [2], and NBS–MeONa [13] have been reported. Those modified methods, however, essentially require more than one equivalent or an excess amount of the oxidizing reagent which is undesirable from an environmental viewpoint. On the other hand, we have already developed an electrochemically induced Hofmann rearrangement (the E-I Hofmann rearrangement) in which bromonium ion electrochemically generated from a catalytic amount of bromide ion in methanol mediated the rearrangement of **1** to methyl carbamates **3a** [14], and furthermore we recently communicated a new reaction system for the E-I Hofmann rearrangement, which is convenient for the transformation of **1** to a variety of alkyl carbamates **3** (Eq. 2) [15].

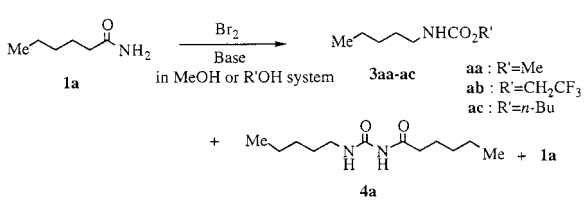


1 **3** (2)

This report describes the detail of the E-I Hofmann rearrangement and also its comparison with the classic Hofmann rearrangement to show the advantage of the E-I Hofmann rearrangement.

2. Results and discussion

The conditions using bromine and sodium methoxide in methanol with heating are commonly recommended for the classic Hofmann rearrangement of the higher aliphatic carboxamides [1]. However, there has been little information on the formation of undesirable side products **4** in those reaction conditions. Thus, in order to exactly compare the classic and E-I Hofmann rearrangements, we first examined the classic reaction of hexanoamide **1a** as a representative of aliphatic amides under several reaction conditions (Eq. 3). As being supposed, the results obtained for **1a** by the classic method were not reliable in our hand in terms of the yields of the rearranged products **3aa**–**ac** and the side product **4a** as shown in Table 1.



(3)

Namely, the yields of **3aa–ac** were dependent on the amount of bromine, the reaction temperature, and the presence of acetonitrile as a co-solvent. The use of one equivalent of bromine, which was recommended in a literature [1], did not give good results, even though the reaction was carried out at elevated temperatures (runs 1–3). On the other hand, the use of two equivalents of bromine in the presence of excess amount of base (5 equiv. to **1a**) with heating afforded **3aa–ac** in improved yields (runs 5, 7, 9, 11, and 13), while those yields were decreased in cases of the reactions carried out without heating (runs 4, 6, 8, 10, and 12). Furthermore, a system of a mixture of acetonitrile and trifluoroethanol gave better results than a system consisting of only trifluoroethanol (compare run 8 with run 10, run 9 with run 11).

Having these data on the classic Hofmann rearrangement in our hand, we then tried the E-I Hofmann rearrangement of **1a**. The result of an effect of halide ion on this reaction is shown in Table 2, which indicates that bromide ion (run 3) gave the best result among those examined.

Next, we surveyed co-solvents suitable for electrolysis of **1a** to **3ac** (runs 1–4, Table 3) since a higher alcohol such as *n*-butanol was difficult to be used as a solvent for electrolysis. As the result, acetonitrile was found to be a suitable solvent (run 1). Use of methylene chloride, dimethyl sulfoxide and dimethylformamide resulted in lower yields of **3ac** than that of acetonitrile. A co-solvent system using acetonitrile was also suitable for methanol (run 5).

We furthermore scrutinized the effect of reaction temperature and amount of *n*-butanol on the E-I Hofmann rearrangement of **1a** to a carbamate **3ac**. The results are summarized in Table 4, which shows that the E-I Hofmann rearrangement usually gives satisfactory yields of **3ac** when the reaction was carried out at ambient temperature (compare run 2 with runs 1 and 3) and more than 5 equivalent of *n*-butanol in acetonitrile (compare runs 2 and 5 with run 4).

On the bases of these results, we can make a comparison of the classic and E-I Hofmann rearrangements (Table 5), which clearly shows the advantage of the E-I Hofmann rearrangement over the classic one. The former method always gives better yields than the classic

Table 1
The classic Hofmann rearrangement of **1a**[a,b]

Run	**1a** (mmol)	Solvent system (ml)	Br_2 (equiv.)[c]	Method[d]	Reaction temperature (°C)	Reaction time	Yield[e] (%)			Recovery[e] of **1a** (%)
							3aa–ac		**4a**	
1	3.0	MeOH (7)	1.0	B	Reflux	10 min	**3aa**	4	44	4
2	3.0	MeOH (7)	1.0	C	Reflux	10 min	**3aa**	15	39	10
3	3.0	MeOH (21)	1.0	B	Reflux	10 min	**3aa**	7	36	14
4	1.0	MeOH (12)	2.0	A	Ambient	5 h	**3aa**	45–48	5–10	20–29
5	1.0	MeOH (12)	2.0	B	Reflux	10 min	**3aa**	63–84	2–5	4–10
6	1.0	Me0H/MeCN[f]	2.0	A	Ambient	5 h	**3aa**	30	20	4
7	1.0	Me0H/MeCN[f]	2.0	B	Reflux	10 min	**3aa**	42	6	12
8	1.0	CF_3CH_2OH[g] (10)	2.0	A	Ambient	5 h	**3ab**	17	2	17
9	1.0	CF_3CH_2OH[g] (10)	2.0	B	Reflux	10 min	**3ab**	42	3	0
10	1.0	CF_3CH_2OH/MeCN[g,h]	2.0	A	Ambient	5 h	**3ab**	56	2	1
11	1.0	CF_3CH_2OH/MeCN[g,h]	2.0	B	Reflux	10 min	**3ab**	73	2	1
12	1.0	*n*-BuOH/MeCN[g,h]	2.0	A	Ambient	5 h	**3ac**	33	25	10
13	1.0	*n*-BuOH/MeCN[g,h]	2.0	B	Reflux	10 min	**3ac**	63	14	0

[a] The amount of **1a** used was 1 mmol.
[b] The amount of NaOMe was 5.0 mmol (5 equiv. to **1a**).
[c] Equivalent to **1a**.
[d] A, B, C: The mode of addition of bromine. See Section 3.
[e] Yields based on the amount of starting **1a**.
[f] MeOH (5 equiv. to **1a**) in MeCN (10 ml).
[g] R′OH (5 equiv. to **1a**) in MeCN (10 ml).
[h] Sodium hydride (10 equiv. to **1a**) was used as a base.

Table 2
Effect of halide ion on the E-I Hofmann rearrangement of **1a** in *n*-BuOH[a]

Run	X (Et_4NX[b])	Electricity (F/mol)	Yield[c] (%)		Recovery[d] (%) of **1a**
			3ac	**4a**	
1	BF_4	5.0	0	0	~100
2	Cl	5.0	24	Trace	38
3	Br	2.9	82	Trace	0
4	I	4.0	20	20	34

[a] The reaction condition was as follows: **1a** (2.5 mmol); Et_4NX (1.25 mmol); *n*-BuOH (12.5 mmol); MeCN (10 ml); Pt electrodes without a diaphragm; 100 mA constant current electrolysis at ambient temperature.
[b] The amount was 0.5 equiv. to **1a**.
[c] Determined by GC with *o*-chloro-nitrobenzene as an internal standard.
[d] Determined by integral intensity of ^1H NMR spectrum.

Table 3
Effect of co-solvent for the E-I Hofmann rearrangement of **la**[a]

Run	Co-solvent/alcohol	F/mol	Yield[c] (%)		
			3aa, ac		**4a**[d]
1	MeCN/*n*-BuOH	2.9	**3ac**	82	Trace
2	CH_2Cl_2/*n*-BuOH[b]	5.3	**3ac**	28	8
3	DMSO/*n*-BuOH	2.0	**3ac**	Trace	0
4	DNF/*n*-BuOH	2.6	**3ac**	62	NI[e]
5	MeCN/MeOH	2.2	**3aa**	98[d]	0

[a] The reaction condition was as follows: **1a** (2.5 mmol); Et_4NBr (1.25 mmol); alcohol (12.5 mmol); co-solvent (10 ml); Pt electrodes without a diaphragm; 100 mA constant current electrolysis at ambient temperature.
[b] *n*-Bu_4NBr (1.25 mmol) was used.
[c] Determined by GC with *o*-chloro-nitrobenzene as an internal standard.
[d] Deterniined by integral intensity of ^1H NMR spectrum.
[e] NI, not identified.

Table 4
The E-I Hofmann rearrangement of **1a**[a,b,c]

Run	Amount of *n*-BuOH (equiv.)[d]	Reaction temperature[e] (°C)	F/mol	Yield[f] (%)		Recovery[f] (%) of **1a**
				3ac	**4a**	
1	5.0	–15	3.6	29	20	0
2	5.0	Ambient	2.9	82	Trace	0
3	5.0	60	3.5	74	Trace	Trace
4	1.0	Ambient	3.0	48	32	Trace
5	10.0	Ambient	3.5	90	Trace	0

[a] The amount of **1a** was 2.5 mmol.
[b] Solvent system; *n*-BuOH/MeCN (10 ml).
[c] Supporting electrolyte was Et_4NBr (1.25 mmol; 0.5 equiv. to **1a**).
[d] Equiv. to **1a**.
[e] The ambient temperature means 30–40°C through electrolysis.
[f] Yields were obtained based on the amount of starting **1a**.

Table 5
Comparison of the classic and E-I Hofinann rearrangements of **1a**[a]

Run	Classic or E-I	Solvent system	Br_2 (equiv.)[b]	Base (equiv.)[b]	Supporting electrolyte (equiv.)[b]	Reaction temperature[c]	F/mol	Yield[d] (%)			Recovery[d] of **1a**
								3aa–ac		**4a**	
1	E-I	MeOH/MeCN[g]	–	–	Et_4NBr (0.5)	Ambient	2.2	**3aa**	98	Trace	0
2	Classic[e]	MeOH/MeCN[g]	2.0	NaOMe (5.0)	–	Ambient	–	**3ap**	30	20	4
3	Classic[f]	MeOH	2.0	NaOMe (5.0)	–	Reflux	–	**3ap**	63–84	2–5	4–10
4	Classic[f]	MeOH/MeCN[g]	2.0	NaOMe (5.0)	–	Reflux	–	**3ap**	42	6	12
5	E-I	CF_3CH_2OH/MeCN[h]	–	–	Et_4NBr (0.5)	Ambient	2.2	**3ab**	83	Trace	0
6	Classic[f]	CF_3CH_2OH/MeCN[h]	2.0	NaH (5.0)	–	Reflux	–	**3aq**	73	2	1
7	E-I	*n*-BuOH/MeCN[g]	–	–	Et_4NBr (0.5)	Ambient	2.9	**3ac**	82	Trace	0
8	Classic[f]	*n*-BuOH/MeCN[h]	2.0	NaH (5.0)	–	Reflux	–	**3ac**	63	14	0

[a] The classic or E-I Hofmann rearrangement.
[b] Equiv. to **1a**.
[c] The ambient temperature means 30–40°C through electrolysis.
[d] Yields were obtained based on the amount of starting **1a**.
[e] The mode of addition of bromine was method A (see Section 3).
[f] The mode of addition of bromine was method B (see Section 3).
[g] A mixture of R′OH (5 equiv. to **1a**) and MeCN (10 ml).
[h] A mixture of R′OH (10 eq iv. to **1a**) and MeCN (10 ml).

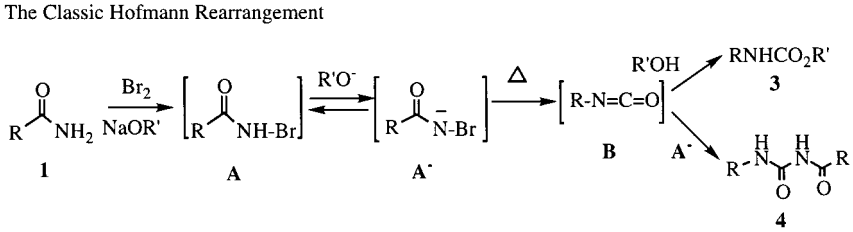


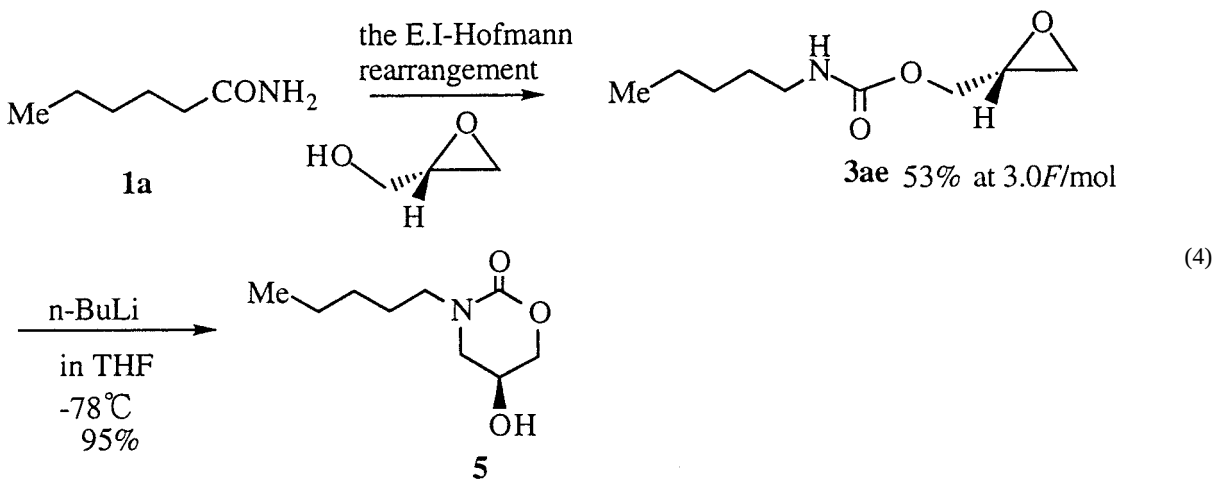
Fig. 1. The classic Hofmann rearrangement.

method with a less formation of an undesired side product **4a** and can be achieved at ambient temperature under neutral conditions (runs 1, 5, and 7), while the classic method must be carried out at elevated temperature under strongly basic conditions (runs 2–4, 6, and 8).

The advantages of the E-I Hofmann rearrangement over the classic one is explainable by taking their reaction mechanisms into consideration. Namely, the classic Hofmann rearrangement has been considered to proceed as follows; a carboxamide **1** is converted to a carbamate **3** through *N*-brominated carboxamide **A**, its anion form $\mathbf{A}^-$ and an isocyanate **B** as intermediates, and the side product **4** is generated by the reaction of **B** with $\mathbf{A}^-$ (Fig. 1). Accordingly, the formation of an undesired **4** may depend on the concentration of $\mathbf{A}^-$ which may also depend on the concentration of **A**, the pH of the system, and the degradation rate of $\mathbf{A}^-$ to **B**. On the other hand, a plausible mechanism in the E-I Hofmann rearrangement is schematically represented as shown in Fig. 2 in which **A**, $\mathbf{A}^-$ and **B** are also involved as intermediates. The large difference between the conditions of the classic and the E-I Hofmann rearrangements may be in the concentration of **A** and $\mathbf{A}^-$ which may be very low in the latter reaction. Furthermore, the latter reaction proceeded under neutral conditions which might also make the concentration of $\mathbf{A}^-$ low. A decrease of a concentration of $\mathbf{A}^-$ in the classic Hofmann rearrangement is achieved by heating to accelerate the degradation rate of $\mathbf{A}^-$ to **B** (run 5 in Table 1), whereas the E-I Hofmann rearrangement generally gives satisfactory results even though it is carried out at ambient temperature since **A** is gradually generated depending on electricity.

In view of these findings and consideration, a variety of alkyl carbamates **3** were prepared from carboxamides **1** by the E-I Hofmann rearrangement. The results are summarized in Table 6, which involves carbamates possessing an epoxy group prepared by utilizing the neutral reaction conditions characteristic to the E-I Hofmann rearrangement (runs 5, 11, and 12).

Those products can be utilized in organic synthesis as exemplified by the conversion of epoxy ester **3ae** to optically active **5** (Eq. 4).



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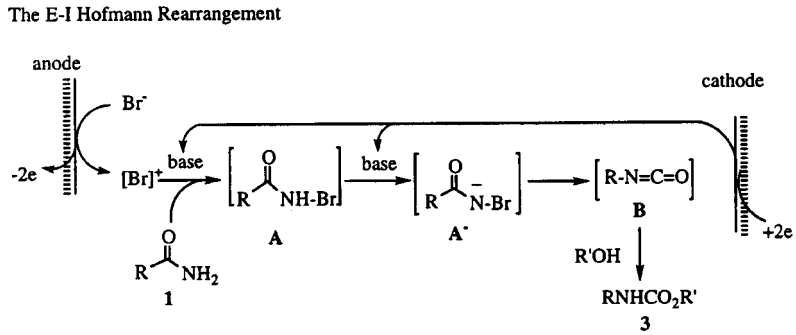
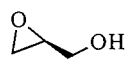
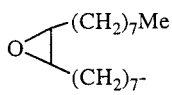


Fig. 2. The E-I Hofmann rearrangement.

Table 6
The E-I Hofmann rearrangement of **1** in the presence of a variety of alcohols[a]

Run	R, carboxamides (R–$CONH_2$ **1**[b])	Alcohols (R′OH)	Equiv.[c]	F/mol[d]	Yields (%) of alkyl carbarnates **3**[e]
1	$Me(CH_2)_4$- **1a**	MeOH	(5.0)	2.2	**3aa** 98
2	**1a**	CF_3CH_2OH	(5.0)	2.2	**3ab** 83
3	**1a**	*n*-BuOH	(5.0)	2.9	**3ac** 82
4	**1a**	$PhCH_2OH$	(5.0)	3.0	**3ad** 80
5	**1a**		(1.0)	3.0	**3ae** 53
6	$PhCH_2$- **1b**	MeOH	(5.0)	3.2	**3ba** 79
7	**1b**	CF_3CH_2OH	(5.0)	2.0	**3bb** 66
8	 **1c**	CF_3CH_2OH	(5.0)	2.1	**3cb** 95
9	**1c**	*n*-BuOH	(5.0)	2.4	**3cc** 40
10	*t*-Bu- **1d**	CF_3CH_2OH	(5.0)	2.2	**3db** 63
11	 **1e**	CF_3CH_2OH	(5.0)	2.0	**3eb** 50
12	**1e**	*n*-BuOH	(5.0)	3.0	**3ec** 41
13	Ph- **1f**	CF_3CH_2OH	(5.0)	2.0	**3fb** 58
14	*p*-MeOPh- **1g**	MeOH	(5.0)	2.6	**3ga** 67
15	**1g**	CF_3CH_2OH	(5.0)	4.0	**3gb** 50
16	$PhCH_2OCH_2CH_2$- **1h**	CF_3CH_2OH	(5.0)	3.8	**3hb** 77

[a] A mixed solvent with MeCN (10 ml) was used.
[b] The amount of carboxamide was 2.5 mmol.
[c] Equiv. to starting **1**.
[d] Pt electrodes were used, and direct current (100 rnA) was passed.
[e] Isolated yields.

In conclusion, this study clearly shows a variety of advantages of the E-I Hofmann rearrangement in comparison with the classic Hofmann rearrangement. Namely, the former method usually gives better yields of carbamates with a less formation of side products under mild reaction conditions (ambient temperature, and neutral). These advantages may be useful for fine organic synthesis as well as for a purpose of large scale preparation.

3. Experimental

3.1. General

All solvents were dried by standard techniques. Et_4NBr, methanol, 2,2,2-trifluoroethanol, *n*-butanol, benzyl alcohol, optically active (*S*)-glycidol, hexanoamide (**1a**), phenylacetamide (**1b**), cyclohexanecarboxamide (**1c**), trimethylacetamide (**1d**), benzamide (**12**), and 4-methoxybenzamide (**1f**) were commercially available. The other starting compounds **1e**, **1h** were prepared according to conventional known methods.

3.2. Preparation of 9,10-epoxyoleamide (*1e*)

Oleamide (6 mmol) was epoxidated by *m*-CPBA (12 mmol) in methylene chloride (30 ml) to afford 9,10–epoxyoleamide (**1e**) in 83% yield. m.p. 64–65°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, $J=6.8$ Hz, 3H), 1.20–1.85 (m, 28H), 2.23 (t, $J=7.8$ Hz, 2H), 3.85–3.96 (m, 2H), 5.21–5.71 (br s, 2H); IR (neat) 3360, 2923, 1634, 1468, 1422 cm^{-1}; HRMS Calcd. for $C_{18}H_{35}NO_2$ 297.2667. Found 297.2662.

3.3. 3-Benzyloxypropanoxamide (*1h*)

Into a solution of sodium hydride (63 mmol), washed with hexane, in dry THF (150 ml), benzyl carbamate (60 mmol) was added at 0°C under a nitrogen atmosphere and the resulting solution was stirred at the room temperature for 2 h. Then, a solution of acrylamide (30 mmol) in THF (50 ml) was dropwise added into the solution at 0°C. After being stirred overnight at rt, the solution was worked up with an aqueous NH_4Cl, the organic portion was extracted with methylene chloride. Evaporation of the solvent in vacuo gave a residue which was subjected on a column chromatography (silica gel, *n*-hexane: AcoEt = 2: 1) to afford **1h** in 50% yield. m.p. 46°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.53 (t, $J=5.8$ Hz, 2H), 3.75 (t, $J=5.8$ Hz, 2H), 4.56 (s, 2H), 5.35–5.60 (br s, 1H), 6.18–6.40 (br s, 1H), 7.23–7.40 (m, 5H); IR (neat) 3500–3300, 1674, 1660, 1453, 1098 cm^{-1}; Anal. Calcd. for $C_{10}H_{13}NO_2$ C; 67.02, H; 7.31, N; 7.82. Found: C; 67.07, H; 7.31, Ni; 7.83.

3.4. The classic Hofmann rearangement; typical procedure

The Hofmann rearrangement was carried out according to the methods A–C described below. After the reaction, the resulting solution was worked up with 10% $Na_2S_2O_3$ and aqueous NH_4Cl, and then the organic portion was extracted with ethyl acetate. Evaporation of the solvent *in vacuo* gave a residue. Yields of **3aa**, **3ab**, **3ac**, **4a**, and recovery of **1a** were determined by integral intensity of ^{1}H NMR spectrum.

3.4.1. Method A

Bromine was added to a solution of **1a** in methanol (the amount shown in Table 1) or methanol (5 mmol)/acetonitrile (10 ml) system containing sodium methoxide (5 equiv. to **1a**) at ambient temperature (30–32°C). The reaction solution was stirred for 5 h.

3.4.2. Method B

Bromine was added to a solution of **1a** in methanol (the amount shown in Table 1) or methanol (5 mmol)/acetonitrile (10 ml) system containing sodium methoxide (5 equiv. to **1a**) at ambient temperature, and then the resulting solution was heated at the reflux temperature (bath temp. 100°C) for 10 min.

3.4.3. Method C

Bromine (1 equiv. to **1a**) was added into a solution of **1a** (2.0 mmol) in methanol (7 ml) containing sodium methoxide (2 equiv. to **1a**) at the reflux temperature (bath temp.100°C) for 10 min.

3.5. The E-I Hofmann rearrangement; typical procedure

A solution of **1a** (2.5 mmol) and Et_4NBr (1.25 mmol) in acetonitrile (10 ml) containing an alcohol R'OH (2.5 ~ 25 mmol (1.0 ~ 10.0 equiv. to amide)) was charged in a one-compartment cell equipped with platinum plate anode and cathode (1×2 cm), and a constant current (100 mA) was passed through the cell at ambient temperature (30–40°C) until 2.0–4.0 F/mol of electricity was passed. After the removal of acetonitrile, the residue was extracted with methylene chloride. The extract was dried on $MgSO_4$, and the solvent was evaporated in vacuo to give a mixture of carbamate **3aa**, **4a**, and recovered **1a**. The mixture was subjected to column chromatography (silica gel) with *n*-hexane/ethyl acetate to give pure **3aa** and **4a**.

3.6. N-Methoxycarbonylpentylamine (*3aa*)

Oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.90 (t, $J=6.8$ Hz, 3H), 1.20–1.65 (m, 6H), 3.17 (q, $J=6.5$ Hz, 2H), 3.67 (s, 3H), 4.60–4.81 (br s, 1H); IR (neat) 3337, 2964,

1716, 1545, 1266 cm^{-1}; HRMS Calcd. for $C_7H_{15}NO_2$ 145.1102. Found 145.1100.

3.7. N-Hexanoyl-N′-pentylurea (**4a**)

m.p. 86°C; ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (t, $J = 6.6$ Hz, 3H), 1.21–1.73 (m, 12H), 2.34 (t, $J = 7.6$ Hz, 2H), 3.28 (q, $J = 7.6$ Hz, 2H), 8.45–8.59 (br s, 1H), 9.60–9.73 (br s, 1H). IR (neat) 3318, 3235, 2930, 1686, 1561, 1266, 747 cm^{-1}; HRMS Calcd. for $C_{12}H_{24}N_2O_2$ 228.1837. Found 228.1831.

Other products **3ab–hb** were formed by similar procedures. The products **3ba** [16] and **3ga** [17] were known compounds.

3.8. N-2,2,2-Trifluoroethoxycarbonylpentylamine (**3ab**)

Oil; ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (t, $J = 6.7$ Hz, 3H), 1.23–1.65 (m, 6H), 3.21 (q, $J = 6.8$ Hz, 2H), 4.45 (q, $J = 8.5$ Hz, 2H), 4.79–4.98 (br s, 1H); IR (neat) 3361, 2963, 1750, 1550 cm^{-1}; HRMS Calcd. for $C_8H_{14}F_3NO_2$ 213.0976. Found 213.0977.

3.9. N-Butoxycarbonylpentylamine (**3ac**)

Oil; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, $J = 6.9$ Hz, 3H), 0.93 (t, $J = 7.5$ Hz, 3H), 1.25–1.65 (m, 10H), 3.18 (q, $J = 5.7$ Hz, 2H), 4.05 (t, $J = 6.0$ Hz, 2H), 4.40–4.72 (br s, 1H); IR(neat) 3335, 2959, 2934, 2847, 1698, 1538, 1258 cm^{-1}; HRMS Calcd. for $C_{10}H_{21}NO_2$ 187.1572, found 187.1572.

3.10. N-Benzyloxycarbonylpentylamine (**3ad**)

Oil; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, $J = 6.4$ Hz, 3H), 1.21–1.38 (m, 4H), 1.39–1.55 (m, 2H), 3.16 (q, $J = 6.5$ Hz, 2H), 5.08 (s, 2H), 4.80–4.98 (br s, 1H), 7.25–7.43 (m, 5H); IR (neat) 2361, 2342, 1719, 1260, 750 cm^{-1}; HRMS Calcd. for $C_{13}H_{19}NO_2$ 221.1415. Found 221.1416.

3.11. N-Glycidylcarbonylpentylamine (**3ae**)

Oil; $[\alpha]_D^{18}$ 21.2° (c 1.01, MeOH) (uncorrected); ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, $J = 6.4$ Hz, 3H), 1.26–1.36 (m, 4H), 1.45–1.56 (m, 2H), 2.64 (q, $J = 4.8$ Hz, 1H), 2.84 (t, $J = 4.5$ Hz, 1H), 3.12–3.24 (m, 3H), 3.88 (dd, $J = 6.1$, 12.2 Hz, 1H), 4.43 (dd, $J = 2.7$, 12.2 Hz, 1H), 4.65–4.81 (br s, 1H); IR (neat) 3337, 2932, 1701, 1536, 1256, 1038, 912 cm^{-1}; HRMS Calcd. for $C_9H_{17}NO_3$ 187.1208. Found 187.1208.

3.12. N-2,2,2-Trifluoroethoxycarbonylbenzylamine (**3bb**)

m.p. 59°C; ^1H NMR (200 MHz, $CDCl_3$) δ 4.45 (q, $J = 8.5$ Hz, 2H), 3.35 (d, $J = 5.9$ Hz, 2H) 7.19–7.41 (m, 5H); IR (neat) 3326, 1701, 1673, 1549, 1279, 1254, 1183, 963, 775, 698 cm^{-1}; HRMS Calcd. for $C_{10}H_{10}F_3NO_2$ 233.0663. Found 233.0682.

3.13. N-2,2,2-Trifluoroethoxycarbonylcyclohexylamine (**3cb**)

m.p. 73°C; ^1H NMR (200 MHz, $CDCl_3$) δ 1.03–1.48 (m, 4H), 1.56–1.82 (m, 4H), 1.85–2.03 (m, 2H), 3.37–3.60 (m, 1H), 4.44 (q, $J = 8.5$ Hz, 2H), 4.63–4.85 (br s, 1H); IR (neat) 3440, 1794, 1748, 1472, 1383, 1095 cm^{-1}; HRMS Calcd. for $C_9H_{14}F_3NO_2$ 225.0976. Found 225.0977.

3.14. N-Buthoxycarbonylcyclohexylamine (**3cc**)

m.p. 42–43°C; ^1HNMR (200 MHz, $CDCl_3$) δ 0.93 (t, $J = 7.1$ Hz, 3H), 0.99–1.48 (m, 7H), 1.51–2.00 (m, 7H), 3.35–3.48 (m, 1H), 4.04 (t, $J = 6.6$ Hz, 2H), 4.46–4.68 (br s, 1H); IR (KBr) 2934, 2857, 1694, 1534, 1233 cm^{-1}; Anal. Calcd. for $C_{11}H_{21}NO_2$ C; 66.28, H; 10.63, N; 7.03. Found: C; 66.18, H; 10.52, N; 6.93.

3.15. N-2,2,2-Trifluoroethoxycarbonyl-1,1-dimethylethylamine (**3db**)

Oil; ^1H NMR (200 MHz, $CDCl_3$) δ 1.34 (s, 9H), 4.39 (q, $J = 8.5$ Hz, 2H), 4.72–4.98 (br s, 1H); IR (KBr) 3054, 2932, 1748, 1543, 1277, 1171, 1100, 749 cm^{-1}; HRMS Calcd. for $C_7H_{12}F_3NO_2$ 199.0820. Found 199.0820.

3.16. N-2,2,2-Trifluoroethoxycarbonyl-cis-8,9-epoxyheptadecylamine (**3eb**)

m.p. 37°C; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, $J = 4.5$ Hz, 3H), 1.19–1.65 (m, 26H), 2.85–2.95 (m, 2H), 3.21 (q, $J = 4.6$ Hz, 2H), 4.45 (q, $J = 5.7$ Hz, 2H), 4.89–5.03 (br s, 1H); IR (neat) 3420, 2928, 1747, 1541, 1281, 1165 cm^{-1}; HRMS Calcd. for $C_{20}H_{36}F_3NO_3$ 395.2647. Found 395.2647.

3.17. N-Butoxycarbonyl-cis-8,9-epoxyheptadecylamine (**3ec**)

m.p. 30°C; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, $J = 6.9$ Hz, 3H), 0.93 (t, $J = 7.2$ Hz, 3H), 1.17–1.73 (m, 26H), 2.85–2.96 (m, 2H), 3.16 (q, $J = 6.8$ Hz, 2H), 4.05 (t, $J = 6.6$ Hz, 2H), 4.54–4.73 (br s, 1H). IR (neat) 3350, 2957, 1725, 1530, 1466, 1250 cm^{-1}; HRMS Calcd. for $C_{22}H_{43}NO_3$ 369.3242. Found 369.3243.

3.18. N-2,2,2-Trifluoroethoxycarbonylaniline (**3fb**)

m.p. 57°C; ^1H NMR (200 MHz, $CDCl_3$) δ 4.56 (q, $J = 8.4$ Hz, 2H), 6.78–6.93 (br s, 1H), 7.20–7.48 (m,

5H); IR (KBr) 3058, 2982, 1748, 1543, 1447, 1277, 1171, 1100, 912, 749 cm^{-1}; HRMS Calcd. for $C_9H_8F_3NO_2$ 219.0507. Found 219.0521

3.19. N-2,2,2-Trifluoroethoxycarbonyl-p-methoxyaniline (3gb)

m.p. 71°C; ^1H NMR (200 MHz, $CDCl_3$) δ 3.79 (s, 3H), 4.54 (q, $J = 8.4$ Hz, 2H), 6.65–6.81 (br s, 1H), 6.82–6.93 (m, 2H), 7.23–7.36 (m, 2H); IR (neat) 3318, 1709, 1549, 1173, 1030, 828 cm^{-1}; HRMS Calcd. for $C_{10}H_{10}F_3NO_3$ 249.0612. Found 249.0613.

3.20. N-2,2,2-Trifluoroethoxycarbonyl-2-benzyloxyethylamine (3hb)

Oil; ^1H NMR (200 MHz, $CDCl_3$) δ 3.43 (q, $J = 5.0$ Hz, 2H), 3.57 (t, $J = 5.0$ Hz, 2H), 4.45 (q, $J = 8.7$ Hz, 2H), 4.53 (s, 2H), 5.23–5.33 (br s, 1H), 7.23–7.42 (m, 5H); IR (neat) 3400, 1720, 1523, 1163 cm^{-1}; HRMS Calcd. for $C_{13}H_{15}F_3N_2O_4$ 277.0799. Found 277.0773.

3.21. Conversion of 3ae to 1-pentyl-5-(S)-hydroxy-3,4,5,6-tetrahydro-2H-1,3-oxazin-2-one (5)

Into the solution of THF (13 ml) containing **3ae** (0.38 mmol), a solution of *n*-BuLi (0.38 mmol) in hexane was added at -78°C under a nitrogen atmosphere, and the resulting solution was stirred at room temperature for 2 h. The solution was worked up with an aqueous NH_4Cl, and then the organic portion was extracted with diethyl ether. Evaporation of the solvent *in vacuo* gave a residue which was subjected on a column chromatography (silica gel, *n*-hexane: AcOEt = 4:1) to afford **5** in 95% yield. The ee (84%) of **5** was determined on the basis of the ^1H NMR spectrum of its Mosher's ester. Since the ee of starting (*S*)-glycidol was 84%, the transformation of **1a** to **3ae** and of **3ae** to **5** was found to proceed with complete stereoselectivity. oil; $[\alpha]_D^{18}$ -1.1° (c 1.23, MeOH) (uncorrected); ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 3H, $J = 6.9$ Hz), 1.23–1.42 (m, 4H), 1.45–1.64 (m, 2H), 2.55–2.80 (br s, 1H), 3.07 (ddd, $J = 1.8$, 5.6, 8.8 Hz, 1H), 3.39–3.52 (m, 1H), 3.65 (dd, $J = 3.0$, 11.7 Hz, 1H), 3.79 (dd, $J = 4.2$, 11.7 Hz, 1H), 3.84–3.92 (m, 1H), 4.27 (dd, $J = 5.4$, 8.7 Hz, 1H), 4.36 (t, $J = 8.7$ Hz, 1H); IR (neat) 3730–3100, 1748, 1448, 1256 cm^{-1}; HRMS Calcd. for $C_9H_{17}NO_3$ 187.1208. Found 187.1209.

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