Pergamon

Tetrahedron Letters, Vol. 38, No. 51, pp. 8879-8882, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10324-0

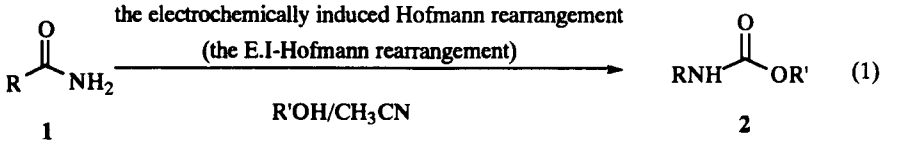
Electrochemically Induced Hofmann Rearrangement

Yoshihiro Matsumura,* Toshihide Maki, and Yuki Satoh

Faculty of Pharmaceutical Sciences, Nagasaki University
1-14 Bunkyo-machi, Nagasaki 852, Japan

Abstract: Electrochemically induced Hofmann rearrangement under new solvent systems containing a variety of alcohols was developed. Since the reaction proceeds under mild conditions (neutral), a variety of carbamates possessing various alkoxy moieties could be easily prepared by this method. An epoxy functional group in the amide and alcohol parts remained intact during the electrolysis.

The Hofmann rearrangement is well known as a useful reaction in organic synthesis to convert primary carboxamides to amines or carbamates possessing a one carbon-shortened structure,[1] while much effort has been so far devoted to the development of modified reagents to optimize the Hofmann rearrangement since the classical Hofmann rearrangement using an aqueous NaOH and Br_2 is not always effectively applicable to all kinds of substrates because of insufficient oxidizing power of the reagents or of the instability of the products under the reaction conditions. Such modified reagents are, for example, CH_3OBr,[2] $Pb(OAc)_4$,[3] $PhI(OCOCF_3)_2$,[4] $NaBrO_2$-NaBr,[5] $PhCH_2(CH_3)_3N^+Br_3^-$,[6] $Hg(OAc)_2$,[7] $PhI(OAc)_2$,[8] NBS-KOH,[1b] and NBS-CH_3ONa.[9] These modified methods, however, 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 already developed an electrochemically induced Hofmann rearrangement (the *E.I-Hofmann rearrangement*) in which the bromonium ion electrochemically generated from a catalytic amount of KBr in CH_3OH mediated the rearrangement to afford methyl carbamates.[10] We report herein a new solvent system for the E.I-Hofmann rearrangement, which effects the transformation of primary carboxamides **1** to a variety of alkyl carbamates **2** (eq 1). A general method to prepare a variety of alkyl carbamates **2** from **1** is unprecedented.

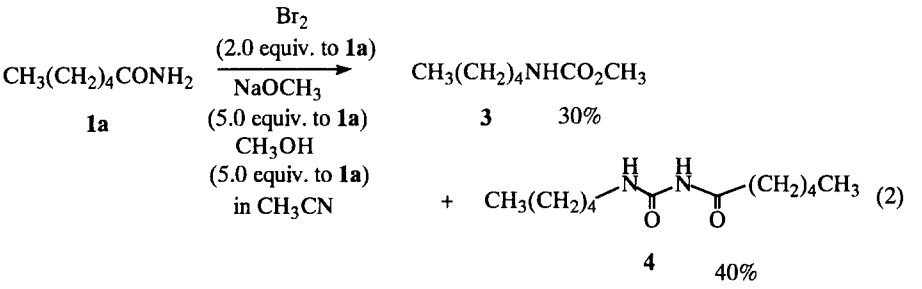


1 **2** (1)

A typical procedure is as follows: A solution of **1** (2.5mmol) and Et_4NBr (1.25mmol) in acetonitrile (10mL) containing an alcohol R'OH (1.0~10.0 equiv. to **1**) was charged in a one-compartment cell equipped with Pt plate anode and cathode (1cm x 2cm), and a constant current (100mA) was passed through the cell at room temperature until 2.0-4.0*F*/mol of electricity was passed. After usual work-up, the corresponding carbamates **2** were obtained in various yields. The results are summarized in Table 1.

Acetonitrile was selected as a suitable solvent for the E.I-Hofmann rearrangement on the basis of the result of the solvent effect. Use of methylene chloride, dimethyl sulfoxide and dimethylformamide resulted in lower yields of **2** than in acetonitrile (for R'=$CH_2(CH_2)_2CH_3$: 28% in CH_2Cl_2; trace in DMSO; 62% in DMF; 82% in CH_3CN).

The Hofmann rearrangement using Br_2-$NaOCH_3$ in acetonitrile containing methanol for **1a** was examined in order to compare with the E.I-Hofmann rearrangement, and it was found that the former yielded carbamate **3** in a low yield with a by-product **4** (eq 2), suggesting the advantages of the E.I-Hofmann rearrangement.

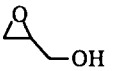
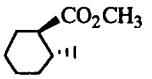
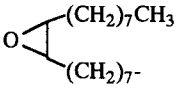


As shown in Table 1, the E.I-Hofmann rearrangement under conditions using acetonitrile as a solvent containing primary alcohols such as methanol, 1-butanol and 2,2,2-trifluoroethanol afforded the corresponding alkyl carbamates **2** in moderate to good yields (runs 1-4, 7-18), though secondary alcohol resulted in a lower yield of **2** (run 5 in Tab.1) and no *t*-butyl carbamate was obtained in the reaction with *t*-butyl alcohol (run 6).

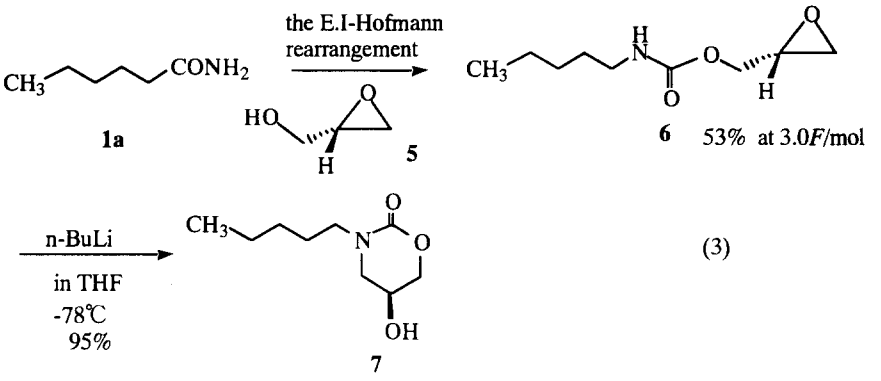
A significant feature of our reaction system is its neutral nature. During electrolysis, the reaction conditions did not become acidic or basic. Thus, carboxamide **1f** possessing an epoxy group gave esters keeping the epoxy group intact (run 14), and also epoxy alcohol could be used (run 7). As an application of this feature to organic synthesis, an optically active epoxy alcohol **5**[11] was treated with **1a** to give an optically active carbamate **6**,[12] which was converted to an optically active 1-pentyl-5-hydroxyoxazolidinone **7** without a loss of optical purity (eq 3).[13]

In conclusion, this new E.I-Hofmann rearrangement makes possible the preparation of a variety of alkyl carbamates **2**, useful intermediates in organic synthesis, from carboxamides **1**. The mechanism and further application of this new reaction are now under investigation.

Table 1. The E.I-Hofmann rearrangement in the presence of a variety of alcohols

Run	Carboxamides R-$CONH_2$ (**1a-h**)[a] R-	Alcohols R'OH	(equiv.to **1**)[b]	*F*/mol[c]	Yields (%) of Alkyl Carbamates **2**[d]
1	$CH_3(CH_2)_4$- **1a**	CH_3OH	(5.0)	2.2	98
2	**1a**	CF_3CH_2OH	(5.0)	2.2	83
3	**1a**	$CH_3(CH_2)_3OH$	(5.0)	2.9	82
4	**1a**	$PhCH_2OH$	(5.0)	3.0	80
5	**1a**	i-PrOH	(10.0)	3.0	44
6	**1a**	t-BuOH	(10.0)	2.7	0[e]
7	**1a**		(1.0)	3.0	53
8	$PhCH_2$- **1b**	CF_3CH_2OH	(5.0)	2.0	66
9	**1b**	CH_3OH	(5.0)	3.2	79
10	 **1c**	$CH_3(CH_2)_3OH$	(5.0)	2.4	40
11	**1c**	CF_3CH_2OH	(5.0)	2.1	95
12	t-Bu- **1d**	CF_3CH_2OH	(5.0)	2.2	63
13	 **1e**	$CH_3(CH_2)_3OH$	(5.0)	2.2	74
14	 **1f**	$CH_3(CH_2)_3OH$	(5.0)	3.0	41
15	**1f**	CF_3CH_2OH	(5.0)	2.0	50
16	Ph- **1g**	CF_3CH_2OH	(5.0)	2.0	58
17	*p*-CH_3OPh- **1h**	CH_3OH	(5.0)	2.6	67
18	**1h**	CF_3CH_2OH	(5.0)	4.0	50

[a] The amount of carboxamide was 2.5 mmol.
[b] A mixed solvent with CH_3CN (10mL) was used.
[c] Pt electrodes (1 cm x 2 cm) were used, and direct current (100mA) was passed.
[d] Isolated yields.
[e] **1a** was recovered.



Acknowledgment: This work was supported by Grant-in-Aid for Scientific Research on Priority Areas (No. 283 , "Innovative Synthetic Reactions") from the Ministry of Education, Science and Culture, Japan.

REFERENCES AND NOTES

1. (a) Wallis, E.F.; Lane, J.F. *"Organic Reaction"*, John Wiley & Sons, New York, **1946**, *3*, 267-306. (b) Senanayake, C.H.; Fredenburgh, L.E.; Reamer, R.A.; Larsen, R.D.; Verhoeven, T.R.; Reider, P.J. *J.Am.Chem.Soc.* **1994**, *116*, 7947-7948 and references cited therein.
2. Radlick, P.; Brown, L.R. *Synthesis* **1974**, 290-292.
3. Baumgarten, H.E.; Smith,H.L.; Staklis, A.J. *J.Org.Chem.* **1975**, *40*, 3554-3561.
4. (a) Radhakrishna, A.S.; Parham, M.E.; Riggs, R.M.; Loundon, G.M. *J.Org.Chem.* **1979**, *44*, 1746-1747. (b) Loundon, G.M.; Radhakrishna, A.S.; Almond, M.R.; Blodgett, J.K.;Boutin, R.H.*J.Org. Chem.* **1984**, *49*, 4272-4276. (c) Loundon, G.M.; Boutin, R.H. *J.Org.Chem.* **1984**,*49*, 4277-4284. (d) Tamura, M.; Jacyno, J.; Stammer, C.H. *Tetrahedron Lett.* **1986**, *27*, 5435-5436.
5. Kajigaeshi, S.; Nakagawa, T.; Fujisaki, S.; Nishida, A.; Noguchi, M. *Chem.Lett.* **1984**, 713-714.
6. Kajigaeshi, S.; Asano, K.; Fujisaki, S.; Kakinami, T.; Okamoto, T. *Chem.Lett.* **1989**, 463-464.
7. Jew, S.-s.; Park, H.G.; Park, H.-J.; Park, M.-s.; Cho, Y.-s. *Tetrahedron Lett.* **1990**, *31*, 1559-1562.
8. Moriarty, R.M.; Chany II, C.J.; Vaid, R.K.; Tuladhar, S.M. *J.Org.Chem.* **1993**, *58*, 2478-2482.
9. Huang, X.; Keilor, J.W. *Tetrahedron Lett.* **1997**, *38*, 313-316.
10. Shono, T.; Matsumura, Y.; Yamane, S.; Kashimura, S. *Chem. Lett.* **1982**, 565-568.
11. The ee of **5** was 84%.
12. Data for **6**: $[\alpha]_D^{18}$ 21.2° (c 1.01 CH_3OH); ^1H NMR (300MHz, $CDCl_3$) δ 0.90 (t, 3H, *J*=6.4Hz), 1.26 -1.36 (m, 4H), 1.45-1.56 (m, 2H), 2.64 (q, 2H,*J*=4.8,2.5), 2.84 (t, 3H, *J*=4.5Hz), 3.12-3.24 (m, 3H), 3.88 (dd, 1H,*J*=12.2, 6.1), 4.43 (dd, 1H,*J*=12.2, 2.7), 4.65-4.81 (br s, 1H). HRMS Calcd. for $C_9H_{17}NO_3$: 187.1208, found 187.1208.
13. Data for **7**: $[\alpha]_D^{18}$ -1.1° (c 1.23 CH_3OH); ^1H NMR (300MHz, $CDCl_3$) δ 0.90 (t, 3H, *J*=6.9Hz), 1.23 -1.42 (m, 4H), 1.45-1.64 (m, 2H), 3.07 (ddd, 1H,*J*=1.8, 8.8, 5.6), 2.55-2.80 (br s, 1H), 3.39-3.52 (m, 1H), 3.65 (dd,1H,*J*=11.7, 3.0), 3.79 (dd, 1H,*J*=11.7, 4.2), 3.84-3.92 (m, 1H), 4.27 (dd, 1H, *J*=8.7, 5.4), 4.36 (t, 1H,*J*=8.7). HRMS Calcd. for $C_9H_{17}NO_3$: 187.1208, found 187.1209. For determining the ee of **7**, the Mosher esters of **7** and of racemic **7** were prepared and the ee of **7** was determined on the basis of NMR spectra of the esters.

(*Received in Japan* 8 *September* 1997; *revised* 1 *October* 1997; *accepted* 3 *October* 1997)