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THE HOFMANN REARRANGEMENT INDUCED BY ELECTROORGANIC METHOD[1)]

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The Hofmann rearrangement has been induced by the electroorganic method using potassium bromide as a mediator, of which role in the reaction is really catalytic.

The electroorganic reaction involving mediators in the reaction system has been attracting much attention from mechanistic and synthetic points of view, since the oxidation or reduction of substrates proceeds in this system at lower potentials than those required for the direct anodic oxidation or cathodic reduction of substrates. One of our interests in the study on electroorganic chemistry has been devoted to the finding and development of new systems involving mediators.[2a-c)]

We describe herein an electrochemical mediatory system in which the Hofmann rearrangement[3,4)] of primary amides **1** to carbamates **3** is easily accomplished under mild conditions (eq. 1).

$$\underset{\mathbf{1}}{RCONH_2} \xrightarrow[KBr/CH_3OH]{-\ 2e} \underset{\mathbf{2}}{RNCO} \xrightarrow{CH_3OH} \underset{\mathbf{3}}{RNHCO_2CH_3} \qquad (1)$$

This electroorganic Hofmann rearrangement is schematically represented in Fig. 1, which comprises the regeneration of bromonium ion from bromide ion on the anode and of potassium from potassium cation on the cathode, and the reaction system involving the reaction of **1** with bromine and potassium methoxide which are formed *in situ* from bromonium ion and potassium, respectively.

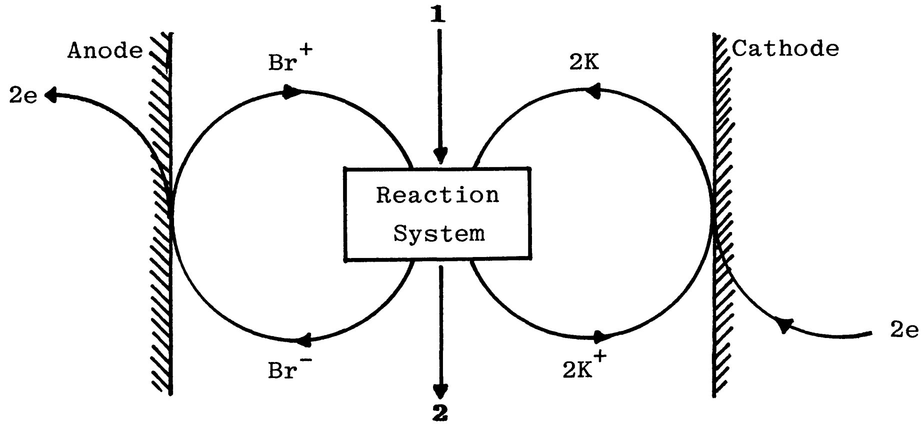


Fig. 1. Schematic Representation of Electroorganic Hofmann Rearrangement

The overall process is the transformation of **1** to **2** without consuming potassium bromide, though **3** will be formed as the final product through the reaction of **2** with methanol. Although the transformation of **1** to **3** has been well known as the Hofmann rearrangement, the advantages of this electroorganic method are in the following points:

(1) In the electroorganic method, a catalytic amount of potassium bromide is enough in theory to forward the reaction. On the other hand, the usual Hofmann rearrangement consumes 1 equivalent of bromine and 2 equivalents of base.

(2) The usual Hofmann rearrangement has to be carried out under strongly basic conditions, whereas in the electroorganic method, the generated bromine and potassium methoxide react rapidly with **1**, so that the reaction medium is always kept neutral. Accordingly, the electroorganic method is applicable to the Hofmann rearrangement of amides bearing groups which are unstable under basic conditions.

A general procedure is as follwos. A solution of potassium bromide (0.75 mmol) and an amide (2.5 mmol) in 10 ml of methanol was added into a cell (50 ml, Φ 3.2 cm X 6 cm) equipped with platinum anode (2 cm X 2 cm) and cathode (2 cm X 2 cm). The cell was cooled with a water jacket and a constant current (0.1 - 0.4 A) was passed with stirring. After 3 - 30 *F*/mol of electricity was passed, methanol was removed *in vacuo*, and the products were isolated from the residue by column chromatography (silica gel). In some cases, the yields were determined by glc. The results are shown in Table I.

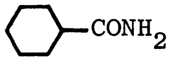
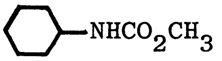
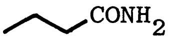
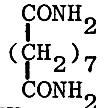
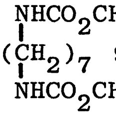
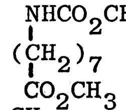
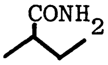
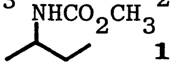
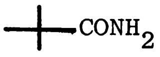
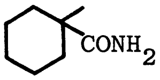
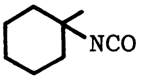
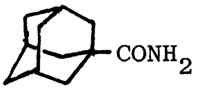
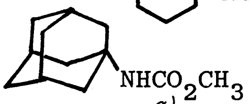
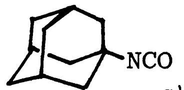
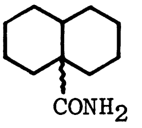
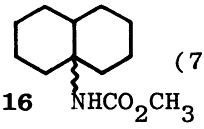
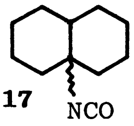
In this electroorganic Hofmann rearrangement, that the oxidation of bromide ion (Br^-) to bromonium ion (Br^+) is one of the initiation reactions is supported by the fact that the yield of **5** was highly dependent on the anode potential, and satisfactory yields were obtained at higher anode potential than the oxidation potential[2c] of bromide ion (Table II).

The regeneration of bromide ion is clearly demonstrated in the relationship between the yield of **5** and the amount of potassium bromide shown in Table III, in which the yield of **5** based on potassium bromide was always higher than 100%, the highest yield being 570%.

The use of potassium chloride instead of bromide was also effective in the transformation of **1** to **2**, whereas the yield and the current efficiency decreased (run 2 in Table I). The electroorganic Hofmann rearrangement did not take place when potassium iodide was used as a mediator.

As described above, the electroorganic Hofmann rearrangement is achievable under very mild reaction conditions, so that isocyanate7) can be obtained as a sole product (run 9 in Table I), or as a mixture with carbamate (runs 10 and 11). Also, the electroorganic reaction of epoxyamide **18** yielded the desired product **19** in which the epoxyl group remained intact (eq. 2), whereas the treatment of **18** under the usual reaction conditions of the Hofmann rearrangement gave unidentified products which did not possess the epoxyl group.

Table I. Electroorganic Hofmann Rearrangement

Run	Amide	Mediator $(\frac{\text{Mediator}}{\text{Amide}})$	Passed Electricity (*F*/mol)	Yield of Carbamate and/or Isocyanate (%)[c]
1.	 **4**	KBr (0.1)	7.5	 **5** (71)[b]
2.	**4**	KCl (0.1)	8.3	**5** (62)[b]
3.		KBr (0.3)	8.2	 **6** (53)[b]
4.		KBr (0.3)	9.0	 **7** (73)[b]
5.	$PhCH_2CONH_2$	KBr (0.3)	4.8	$PhCH_2NHCO_2CH_3$ **8** (61)[b]
6.	 $\begin{array}{c}CONH_2\\ (CH_2)_7\\ CONH_2\end{array}$	KBr (0.3)	29.9	 $\begin{array}{c}NHCO_2CH_3\\ (CH_2)_7\\ NHCO_2CH_3\end{array}$ **9**(40)[a]  $\begin{array}{c}NHCO_2CH_3\\ (CH_2)_7\\ CO_2CH_3\end{array}$ **10**(22)[a]
7.		KBr (0.1)	3.3	 **11** (64)[b]
8.		KBr (0.3)	6.7	 **12** (92)[b]
9.		KBr (0.3)	3.3	 **13** (80)[b]
10.		KBr (0.3)	3.7	 **14** (14)[a]  **15** (58)[a]
11.		KBr (0.3)	3.7	 (76)[a] **16**  (22)[a] **17**

[a] Isolated yields. [b] The yields were determined by glc method. [c] See ref. 9.

Table II. Electroorganic Hofmann Rearrangement of Cyclohexanecarboxamide (**4**) at a Controlled Potential[a]

Anode Potential (V *vs*. SCE)	Yield (%)[b] of **5**
0.8	30
0.9	70
1.0	72
1.3	80

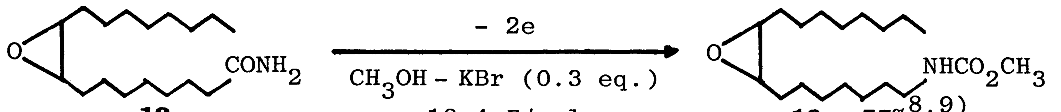
[a] The mediator was potassium bromide.

[b] The yield was determined by glc method after 3 *F*/mol of electricity was passed.

Table III. Electroorganic Hofmann Rearrangement of Cyclohexanecarboxamide (**4**) to **5**

KBr/**4**[a]	Yield (%) of **5**[b, c]
0.05	220 (11)
0.1	570 (57)
0.3	270 (81)
0.5	186 (93)
0.7	137 (96)

[a] Molar ratio.
[b] Based on potassium bromide.
[c] See ref. 10.



18 **19**, 77%[8,9] (2)

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2) a) T. Shono, Y. Matsumura, J. Hayashi, and M. Mizoguchi, *Tetrahedron Lett.*, **1979**, 165. b) *Idem, ibid.*, **1979**, 3861. c) *Idem, ibid.*, **21**, 1867 (1980).
3) a) E. S. Wallis and J. F. Lave, *Org. React.*, **3**, 267 (1946). b) P. Radlick and L. R. Brown, *Synthesis*, **1974**, 290.
4) The Hofmann rearrangement with lead tetraacetate: H. E. Baumgarten, H. L. Smith, and A. Staklis, *J. Org. Chem.*, **40**, 3554 (1975).
5) The electrochemical transformation of acetamide to *N*-acetyl-*N*-methylurea in the presence of sodium bromide and sodium hydroxide has been reported.[6] The reaction conditions are, however, extremely different from our mediatory system, and the result does not seem to indicate the regeneration of bromonium ion. Furthermore, no further development as tools for organic synthesis has been described in the report.
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7) Recently, a method to isolate isocyanates in the Hofmann rearrangement has been exploited: A. O. Sy and J. W. Raksis, *Tetrahedron Lett.*, **21**, 2223 (1980).
8) The yield was based on the consumed epoxyamide.
9) Identification of methyl carbamates (**5**,[3b,11] **6**,[12] **7**,[13] **8**,[11] **9**,[14] **10**,[15] **11**,[16] **12**,[17] and **14**[18]) and an isocyanate (**15**)[18] was carried out by comparison of their spectroscopic data with authentic samples prepared by the reaction of the corresponding amines with methyl chloroformate or by comparison of their physical data with those in literatures. Spectroscopic and physical data of compounds (**13**, **16**, **17**, and **19**) are as follows. **13**: oil; IR (film) 2925, 2240, 1443, 1162 cm^{-1}; NMR (CCl_4) δ 0.85-2.20 (m, 10H), 1.33 (s, 3H). **16**: *cis* and *trans* mixture; IR (KBr) 3345, 2925, 1690, 1535, 1250, 1103 cm^{-1}; NMR (CCl_4) δ 1.10-2.20 (m, 17H), 3.50 (s, 3H), 4.40-4.90 (br, 1H). **17**: oil; *cis* and *trans* mixture; IR (film) 2930, 2250, 1450, 1150 cm^{-1}; NMR (CCl_4) δ 1.05-2.30 (m, 17H). **19**: mp 81-83 °C; IR (KBr) 3325, 2915, 1693, 1518, 1450, 1250, 770 cm^{-1}; NMR (CCl_4) δ 0.65-1.15 (m, 3H), 1.10-2.00 (m, 26H), 2.90 (m, 2H), 3.04-3.48 (m, 2H), 3.63 (s, 3H), 5.05-5.60 (br, 1H).
10) The yield shown in parentheses is based on the starting cyclohexanecarboxamide, and it was determined by glc method after 5 *F*/mol of electricity was passed.
11) B. Acott, A. L. J. Beckwith, and A. Hassanali, *Aust. J. Chem.*, **21**, 197 (1968).
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