New reaction conditions using trifluoroethanol for the E-I Hofmann rearrangement

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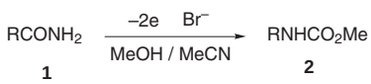
Received (in Cambridge) 24th May 1999, Accepted 11th June 1999

The Hofmann rearrangement of N^2-protected glutamine esters to N^2-protected (2*S*)-4-[(2,2,2-trifluoroethoxy)-carbonylamino]-2-aminobutyric acid esters was successfully achieved by an electrochemical method using a trifluoroethanol (TFE)–MeCN solvent system where the TFE may play an important role in controlling the basicity caused by electrochemically generated bases.

Introduction

It is worthwhile to investigate new reaction conditions that make it possible to achieve the Hofmann rearrangement (for example, the transformation of carboxamides **1** to methyl carbamates **2**) under non-basic conditions since the Hofmann rearrangement is in general carried out under strongly basic conditions,[1] and thus is not generally applicable to substrates which are unstable under such basic conditions. Recently several modified methods for the Hofmann rearrangement have appeared which can be carried out under non-basic conditions but all of them use more than an equimolar amount of an expensive or hazardous oxidizing reagent.[2] On the other hand, we have reported an electrochemical method (the E-I Hofmann rearrangement) which uses a catalytic amount of bromide ion in MeOH as solvent or in a mixed solvent consisting of MeOH and MeCN (Scheme 1).[3]



Scheme 1

One of the advantages of the E-I Hofmann rearrangement is its non-basic nature since the quantity of electrochemically generated base (EGB)[4] is theoretically equal to the quantity of protons generated in the rearrangement of **1** to **2** through *N*-brominated intermediates **3**, *N*-bromo anions **4**, and isocyanates **5** as schematically represented in Fig. 1. Hence, one equivalent of EGB plays the role of trapping the proton H^+ removed in the reaction of **1** with anodically generated $[Br]^+$ and the other EGB equivalent abstracts the proton H^+ from **3** to give **4**.

Accordingly, the reaction conditions for the E-I Hofmann rearrangement are neutral taken as a whole throughout the electrolysis, but a small amount of EGB may survive for a short time. Hence, if the substrate **1** and/or the rearranged product **2** are unstable under weakly basic conditions, the E-I Hofmann rearrangement may result in an unsatisfactory result. L-Glutamine esters are carboxamides unstable under such conditions, however the Hofmann rearranged products from L-glutamine are important in organic synthesis.[5]

We report herein new reaction conditions that allow us to efficiently achieve the E-I Hofmann rearrangement of L-glutamine esters without a loss of their optical purity.

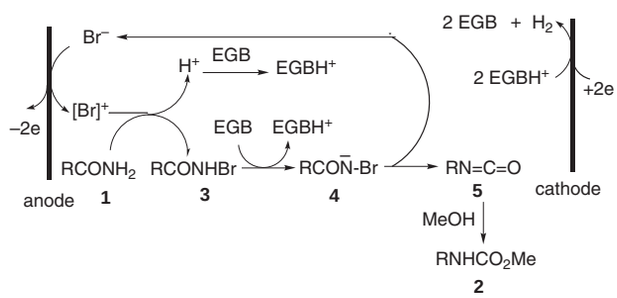
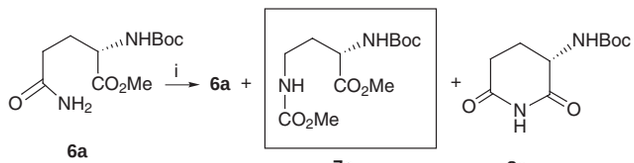


Fig. 1

Results and discussion

(2*S*)-N^2-Boc-Protected glutamine methyl ester **6a** is highly unstable under basic conditions. In fact, the E-I Hofmann rearrangement of (2*S*)-N^2-Boc-protected glutamine methyl ester **6a** in MeOH containing bromide ions[3] resulted in the formation of the desired product **7a** in low yield (Scheme 2).

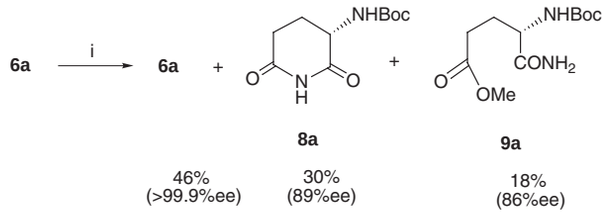


at 60 °C	2.2 F mol^{-1}	0%	28% (>99.9%ee)	14%(25%ee)
at ambient temp.	2.9 F mol^{-1}	20%	26% (>99.9%ee)	10%(47%ee)

Scheme 2 *Reagents and conditions*: i, Et_4NBr, MeOH–MeCN, Pt electrodes.

The by-product **8a** might be generated by a base-catalyzed cyclization of **6a**. Furthermore, the fact that **6a** was unstable under basic conditions was shown by the reaction of **6a** with sodium methoxide in MeOH even at a low temperature for a short time to give a mixture of recovered **6a** (46%, ~100% ee), **8a** (30%, 89% ee) and **9a** (18%, 86% ee) which was formed through **8a** (Scheme 3).[6]

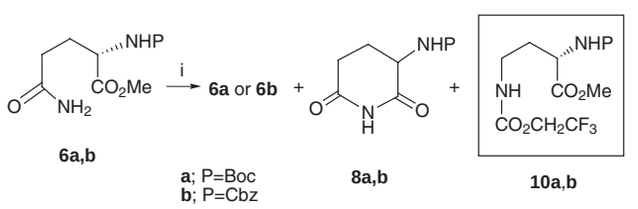
Because of the importance of the Hofmann rearranged products from L-glutamine in organic synthesis, there have been several attempts at the Hofmann rearrangement of L-glutamine derivatives,[2c,7] however it has not been possible to start from



Scheme 3 *Reagents and conditions*: i, NaOMe (0.5 equiv. with respect to **6a**), MeOH, 0 °C, 15 min.

glutamine esters. This may be due to the instability of such esters under basic conditions as shown in Scheme 3.

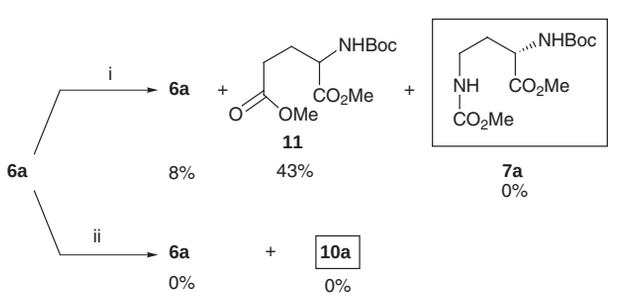
We report herein *new reaction conditions for the E-I Hofmann rearrangement in which N^2-protected glutamine methyl esters* **6a**,**b** *can be converted to the desired carbamates* **10a**,**b** *in good yields without any loss of the optical purity*. The key point in our method was the use of 2,2,2-trifluoroethanol (TFE) as a co-solvent. Namely, the E-I Hofmann rearrangement of **6a**,**b** in TFE–MeCN as solvent gave **10a**,**b** in good yield with ~100% ee, although a small amount of **8b**[8] was produced in the case of **6b** (Scheme 4). The use of MeOH containing an acid such as acetic acid instead of TFE did not afford any rearranged products.



at 60 °C	2.1 F mol^{-1}	**6a** 0%	**8a** 0%	**10a** 80% (>99.9%ee)
at ambient temp.	3.2 F mol^{-1}	**6a** 0%	**8a** 0%	**10a** 61% (>99.9%ee)
at 60 °C	2.1 F mol^{-1}	**6b** 0%	**8b** 15%	**10b** 75% (>99.9%ee)

Scheme 4 *Reagents and conditions*: i, Et_4NBr, TFE–MeCN, Pt electrodes.

The advantage of the E-I Hofmann rearrangement carried out under the new reaction conditions was clearly demonstrated by the fact that the reaction of **6a** with bromine and sodium methoxide (reaction conditions in the conventional Hofmann rearrangement) or the reaction of **6a** with bromine and NaH in TFE–MeCN did not afford any of the desired rearranged product **7a** or **10a** (Scheme 5),[9] and the E-I



Scheme 5 *Reagents and conditions*: i, Br_2 (2 equiv. with respect to **6a**), NaOMe (5 equiv. to **6a**), MeOH, reflux temp., 30 min; ii, Br_2 (2 equiv. with respect to **6a**), NaH (5 equiv. with respect to **6a**), TFE (5 equiv.)–MeCN, reflux temp., 30 min.

Hofmann rearrangement of **6a** in MeOH–MeCN as solvent gave **7a** in a low yield (Scheme 2).

Thus, we have for the first time succeeded in achieving the Hofmann rearrangement of N^2-protected glutamine esters **6a**,**b** by using a TFE–MeCN solvent system. TFE may play an important role in controlling the basicity which occurs for a short time by EGB on (or in the vicinity of) the cathode. TFE is known to be more acidic than MeOH.[10,11]

The application of these new reaction conditions to other carboxamides such as asparagine esters, which are more unstable to base than glutamine esters, is under investigation.

Experimental

Electrochemical reactions were carried out by using a DC Power Supply (GP 050-2) from Takasago Seisakusho, Inc. HPLC analyses were achieved by using an LC-10AT *VP* and an SPD-10A *VP* from Shimadzu Seisakusho Inc. Specific rotations, $[\alpha]_D$, were measured with using a Jasco DIP-1000 and are given in units of 10^{-1} deg cm^2 g^{-1}. ^{1}H NMR spectra were measured on a Varian Gemini 200 or 300 spectrometer with TMS as an internal standard. IR spectra were obtained on a Shimadzu FTIR-8100A. Elemental analyses were carried at the Center for Instrumental Analysis, Nagasaki University. Mass spectra were obtained on a JEOL JMS-DX 303 instrument. Since materials **6a**,[12] **6b**[13] and products **8a**,[14] **8b**,[8] **9a**,[15] **11**[16] are known compounds, their elemental analyses were not carried out.

N^2-Boc-L-Glutamine methyl ester 6a

A solution of di-*tert*-butyl dicarbonate in THF was added to a solution of L-glutamine (20 mmol) in 1 M sodium hydroxide by means of an addition funnel and cooling with ice–water. After stirring at rt for 5 h, the reaction mixture was acidified to pH 2–3 by slow addition of 1 M $KHSO_4$, and then extracted with ethyl acetate. The extract was dried over $MgSO_4$, and the solvent was evaporated *in vacuo* to give N^2-Boc-L-glutamine. To a solution of N^2-Boc-glutamine in DMF was added K_2CO_3 (24 mmol). Methyl iodide (30 mmol) was then added to the mixture and the resulting solution was stirred at rt for 6 h. The mixture was extracted with ethyl acetate. The extract was dried over $MgSO_4$, and the solvent was evaporated *in vacuo*. The residue was subjected to column chromatography (silica gel) with *n*-hexane–ethyl acetate to give pure **6a** in 60% overall yield. Mp 86–89 °C; $[\alpha]_D^{20}$ −24.9 (*c* 0.99, MeOH) (uncorrected); δ_H (200 MHz, $CDCl_3$) 1.45 (s, 9H), 1.80–2.03 (m, 1H), 2.21–2.39 (m, 3H), 3.75 (s, 3H), 4.26–4.41 (m, 1H), 5.30 (br d, J = 8.0 Hz, 1H), 5.35–5.56 (br s, 1H), 6.05–6.23 (br s, 1H); ν_{max} (KBr)/cm^{-1} 3352, 2979, 1740, 1671, 1528, 1165.

N^2-Cbz-L-Glutamine methyl ester 6b

A solution of Cbz-Cl in THF was added to a solution of L-glutamine (20 mmol) in 1 M sodium hydroxide by means of an addition funnel and cooling with ice–water. After stirring at rt for 5 h, the reaction mixture was acidified to pH 2–3 by slow addition of 1 M $KHSO_4$, and then extracted with ethyl acetate. The extracts were dried over $MgSO_4$, and the solvent was evaporated *in vacuo* to give N^2-Cbz-L-glutamine. To a solution of N^2-Cbz-L-glutamine in DMF was added K_2CO_3 (24 mmol). Methyl iodide (30 mmol) was added to the mixture and the resulting solution was stirred at rt for 6 h. The mixture was extracted with ethyl acetate. The extract was dried over $MgSO_4$, and the solvent was evaporated *in vacuo*. The residue was subjected to column chromatography (silica gel) with *n*-hexane–ethyl acetate to give pure **6b** in 60% overall yield. Mp 135–137 °C; $[\alpha]_D^{26}$ −21.2 (*c* 1.02, MeOH) (uncorrected); δ_H (200 MHz, $CDCl_3$) 1.87–2.09 (m, 1H), 2.15–2.39 (m, 3H), 3.76 (s, 3H), 4.30–4.48 (m, 1H), 5.11 (s, 1H), 5.19–5.40 (br s, 1H), 5.61 (br d, J = 7.4 Hz, 1H), 5.70–5.97 (br s, 1H), 7.36 (s, 5H); ν_{max} (KBr)/cm^{-1} 3156, 2984, 1794, 1717, 1682, 1562, 1096.

E-I Hofmann Rearrangement: typical procedure

A solution of **6a** (1.2 mmol) and Et_4NBr (0.6 mmol) in MeCN (6 mL) containing MeOH (6 mmol) was charged in a one-compartment cell equipped with platinum plate anode and cathode (1 cm × 2 cm), and a constant current (100 mA) was

passed through the cell at ambient temperature (30–40 °C) until 2.9 F mol^{-1} of electricity was passed. After the removal of MeCN, the residue was extracted with ethyl acetate. The extract was dried over $MgSO_4$, and the solvent was evaporated *in vacuo* to give a mixture of **7a**, **8a** and recovered **6a**, which was subjected to column chromatography (silica gel) with *n*-hexane–ethyl acetate to give pure **7a**, **8a** and recovered **6a**. The ees of **6a**, **7a**, and **8a** were determined by chiral HPLC.

Methyl (2*S*)-2-*tert*-butoxycarbonylamino-4-methoxycarbonylaminobutyrate 7a. Oil (Found: C, 49.5; H, 7.5; N, 9.6%; M^+, 290.1475. $C_{12}H_{22}N_2O_6$ requires C, 49.65; H, 7.64; N, 9.65%; *M*, 290.1477); $[\alpha]_D^{20}$ −19.3 (*c* 1.44, MeOH) (uncorrected), >99.9% ee (Chiralpak AS (0.46 cm id × 25 cm), *n*-hexane–ethanol 9:1, detected at 210 nm, retention times (t_r): (*R*) = 7.8 min, (*S*) = 8.5 min); δ_H (300 MHz, $CDCl_3$) 1.38 (s, 9H), 1.53–1.64 (m, 1H), 1.92–2.05 (m, 1H), 2.93–3.04 (m, 1H), 3.36–3.50 (m, 1H), 3.60 (s, 3H), 3.67 (s, 3H), 4.23–4.38 (m, 1H), 5.13–5.28 (br s, 1H), 5.36–5.49 (br s, 1H); ν_{max} (neat)/cm^{-1} 3347, 2978, 1740, 1539, 1167.

(3*S*)-3-*tert*-Butoxycarbonylamino-2,6-dioxopiperidine 8a. Mp 196–200 °C (Found: M^+, 228.1135. $C_{10}H_{16}N_2O_4$ requires *M*, 228.1109); $[\alpha]_D^{25}$ −55.5 (*c* 1.05, MeOH) (uncorrected), 89% ee (Chiralpak AS (0.46 cm id × 25 cm), *n*-hexane–ethanol 6:1, detected at 210 nm, retention times (t_r): (*R*) = 22 min, (*S*) = 28 min); δ_H (300 MHz, $CDCl_3$) 1.47 (s, 9H), 1.73–1.98 (m, 1H), 2.33–2.60 (m, 1H), 2.60–2.86 (m, 2H), 4.29–4.40 (m, 1H), 5.34–5.47 (br d, *J* = 5.4 Hz, 1H), 8.39–8.48 (br s, 1H); ν_{max} (KBr)/cm^{-1} 3357, 3235, 1725, 1690, 1534, 1358, 1190.

Methyl (2*S*)-2-*tert*-butoxycarbonylamino-4-[(2,2,2-trifluoroethoxy)carbonylamino]butyrate 10a. Mp 215–217 °C (Found: C, 43.8; H, 5.8; N, 7.8%; M^+, 358.1356. $C_{13}H_{21}F_3N_2O_6$ requires C, 43.58; H, 5.91; N, 7.82%; *M*, 358.1351); $[\alpha]_D^{22}$ −22.0 (*c* 1.11, MeOH) (uncorrected), >99.9% ee (Chiralpak AD (0.46 cm id × 75 cm), *n*-hexane–ethanol 15:1, detected at 210 nm, retention times (t_r): (*R*) = 11.5 min, (*S*) = 12.7 min); δ_H (200 MHz, $CDCl_3$) 1.45 (s, 9H), 1.62–1.81 (m, 1H), 2.00–2.20 (m, 1H), 3.02–3.22 (m, 1H), 3.47–3.61 (m, 1H), 3.76 (s, 3H), 4.30–4.55 (m, 3H), 5.32–5.44 (br d, *J* = 8.0 Hz, 1H), 5.86–6.00 (br s, 1H); ν_{max} (KBr)/cm^{-1} 3351, 2980, 1752, 1529, 1184.

Methyl (2*S*)-2-benzyloxycarbonylamino-4-[(2,2,2-trifluoroethoxy)carbonylamino]butyrate 10b. Mp 99–101 °C (Found: C, 49.1; H, 4.85; N, 7.2%; M^+, 392.1194. $C_{16}H_{19}F_3N_2O_6$ requires C, 48.98; H, 4.88; N, 7.14%; *M*, 392.1195); $[\alpha]_D^{18}$ −24.3 (*c* 1.10, MeOH) (uncorrected), >99.9% ee (Chiralcel OD (0.46 cm id × 25 cm), *n*-hexane–propan-2-ol 10:1, detected at 210 nm, retention times (t_r): (*R*) = 18 min, (*S*) = 25 min); δ_H (200 MHz, $CDCl_3$) 1.55–1.76 (m, 1H), 1.94–2.16 (m, 1H), 2.91–3.11 (m, 1H), 3.30–3.53 (m, 1H), 3.67 (s, 3H), 4.28–4.47 (m, 3H), 5.04 (s, 2H), 5.53 (br d, *J* = 3.7 Hz, 1H), 5.54–5.71 (br s, 1H), 7.28 (s, 5H); ν_{max} (KBr)/cm^{-1} 3341, 2959, 1747, 1537, 1289.

(3*S*)-3-Benzyloxycarbonylamino-2,6-dioxopiperidine 8b. $[\alpha]_D^{18}$ −16.0 (*c* 1.01, MeOH) (uncorrected), 24% ee (Chiralcel OD (0.46 cm id × 25 cm), *n*-hexane–ethanol 5:1, detected at 210 nm, retention times (t_r): (*S*) = 26 min, (*R*) = 31 min); δ_H (200 MHz, $CDCl_3$) 1.75–2.00 (m, 1H), 2.35–2.85 (m, 3H), 4.25–4.45 (m, 1H), 5.14 (s, 2H), 5.70 (br d, *J* = 6 Hz, 1H), 7.36 (s, 5H), 8.40 (br s, 1H).

Reaction of 6a with NaOMe in MeOH

To a solution of **6a** (0.5 mmol) in MeOH (6 ml) was added NaOMe (0.5 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 15 min, and then aqueous NH_4Cl was added to the mixture. After the removal of MeOH, the residue was extracted with ethyl acetate. The extract was dried over $MgSO_4$, and the solvent was evaporated *in vacuo* to give a residue which contained **6a**, **8a** and **9a**. The yields of **6a**, **8a** and **9a** were determined by integral intensity of the ^1H NMR spectrum.

Methyl (4*S*)-4-*tert*-butoxycarbonylamino-4-carbamoylbutyrate 9a. Mp 130–132 °C; $[\alpha]_D^{22}$ −6.2 (*c* 0.44, MeOH) (uncorrected), 86% ee (Chiralcel OD (0.46 cm id × 75 cm), *n*-hexane–ethanol 6:1, detected at 210 nm, retention times (t_r): (*R*) = 14 min, (*S*) = 15 min); δ_H (200 MHz, $CDCl_3$) 1.44 (s, 9H), 1.84–2.03 (m, 1H), 2.04–2.26 (m, 1H), 2.35–2.62 (m, 1H), 3.36–3.50 (m, 1H), 3.70 (s, 3H), 4.12–4.31 (m, 1H), 5.37–5.52 (br s, 1H), 5.79–5.98 (br s, 1H), 6.42–6.60 (br s, 1H); ν_{max} (KBr)/cm^{-1} 3056, 2988, 1735, 1696, 1595, 1422, 1273.

Reaction of 6a with Br_2: typical procedure

To a solution of NaOMe (5 mmol) in MeOH (12 ml) was added Br_2 (1.0 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 10 min. **6a** (1 mmol) was added to the mixture and the resulting reaction mixture was immediately refluxed for 30 min. After the removal of MeOH, aqueous $Na_2S_2O_3$ was added to the residue, and the organic portion was extracted with ethyl acetate. The extract was dried on $MgSO_4$, and the solvent was evaporated *in vacuo* to give a mixture of **11** and recovered **6a**, which was subjected to column chromatography (silica gel) with *n*-hexane–ethyl acetate to give pure **11** and recovered **6a**.

Dimethyl (2*S*)-N^2-Boc-glutamate 11. δ_H (200 MHz, $CDCl_3$) 1.43 (s, 9H), 1.90–2.50 (m, 5H), 3.68 (s, 3H), 3.74 (s, 3H), 4.20–4.40 (m, 1H), 5.37–5.52 (m, 1H).

Acknowledgements

One of the authors (Y. M.) is grateful for a Grant-in-Aid for Scientific Research on Priority Areas (No. 283, "Innovative Synthetic Reaction"), and Scientific Research (B) (No. 09450335) from the Ministry of Education, Science and Culture, Japan.

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Paper 9/04126E