Anodic Fluorination and Cathodic Michael Addition of Schiff Bases Bearing Trifluoromethyl and Ester Groups

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ABSTRACT

Anodic fluorination of N-(diphenylmethyleneamino)-2,2,2-trifluoroethane and N-[bis(methylthio)methyleneamino]-2,2,2-triphenylethane in acetonitrile containing poly(HF) salt liquids afforded monofluorinated products in moderate to good yields. On the other hand, anodic fluorination of N-[bis(methylthio)methylene]glycine methyl ester provided mono- and difluoroproducts depending on the amount of electricity passed. This is the first successful electrochemical fluorination of open-chain α-amino acid derivatives. Cathodic Michael addition of N-(diphenylmethyleneamino)-2,2,2-trifluoroethane to activated olefins such as acrylate and acrylonitrile was also successfully carried out using a titanium cathode.

Keywords : Anodic Fluorination, Cathodic Michael Addition, Schiff Base, α-Fluoroglycine Ester Equivalent

1. Introduction

Organofluorine compounds are highly useful for development of new types of pharmaceuticals, agrochemicals, and functional materials. In recent years, a large number of organofluorine molecules and macromolecules have been developed. However, their synthesis is not so easy due to the unique nature of a fluorine atom. For example, selective fluorination of organic compounds under safe conditions and selective conversion of organofluorine compounds remain under-developed. Therefore, development of new methodology to solve such problems is highly important in modern synthetic organofluorine chemistry. From these points, we have developed selective electrochemical fluorination of various organic molecules and macromolecules under safe conditions. We have also achieved nucleophilic and electrophilic substitutions at α to a CF3 group by using electrochemical methodology although these substitution reactions have been quite difficult to accomplish by ordinary chemical methods. For instance, anodic methoxylation and acetoxylation of trifluoroethyl sulfides, selenides, and anilines have been achieved for the first time as shown in Scheme 1. It was demonstrated that the products were versatile building blocks bearing a CF3 group. We also reported the first examples of anodic α-acetoxylation of CF3-containing imine and imidate as shown in Scheme 2.

Fluorinated α-amino acids are biologically interesting and highly useful since they have various bio-organic medicinal applications. Although synthesis of side-chain-fluorinated amino acids and fluorinated β-amino acids has been well established, synthetic methods of α-fluoro-α-amino acids have been underdeveloped so far. Particularly, N-protected α-fluoro-α-amino acids are unstable because of facile elimination of HF as shown in Scheme 3.

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CF₃ group is quite difficult because of facile elimination of a fluoride ion. However, we successfully generated a stable enolate from (trifluoromethyl)malonate ester by using an electrogenerated base such as α-pyridolide anion with tetraethylammonium ion, followed by α-alkylation as shown in Scheme 8. With these facts in mind, we have studied anodic fluorination of Schiff bases of 2,2,2-trifluoroethylamine and glycine methyl ester. Furthermore, we have also studied the cathodic generation of α-anion of 2,2,2-trifluoroethylamine, which can be trapped by activated olefins as a Michael acceptor.

2. Experimental

2.1 General.

1H, 13C, and 19F NMR spectra were recorded on a JEOL JNM EX-270 (1H: 270 MHz, 13C: 67.8 MHz, 19F: 254.05 MHz) spectrometer in CDCl₃. The chemical shifts for 1H and 13C are given in δ (ppm) downfield from internal TMS and CDCl₃, respectively. 19F NMR chemical shifts are given in δ (ppm) upfield from external trifluoroacetic acid. All calculations were performed using Gaussian 16 software. Geometry optimizations, frequency calculations, and single point calculations were performed for all compounds at the B3LYP level of theory using 6-31G(d) basis set for all atoms. Oxidation potentials (E°) were measured in 0.1 M Bu₄NBF₄/MeCN at a scan rate of 100 mV/s by cyclic voltammetry using ALS Instruments model 600 A. A platinum disk electrode (φ = 1 mm) and a platinum plate (1 cm × 1 cm) were used as working and counter electrodes, respectively. A saturated calomel electrode (SCE) was used as a reference electrode. Preparative electrolysis...
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2.2 Materials.
Et3N-nHF (n = 2, 3) and Et4NF-nHF (n = 3, 4) were kindly supplied by Morita Chemical Industries Co. Ltd. Japan. N-(Diphenylmethyleneamino)-2,2,2-trifluoroethane (1a) was prepared similarly according to the literature.19 N-[Bis(methylthio)methylene]-2,2,2-trifluoroethane (1b), N-[bis(phenylthio)methylene]glycine methyl ester (1c), and N-[bis(phenylthio)methylene]glycine methyl ester (1d)20 were prepared according to the literature methods.

2.3 General procedure for electrochemical fluorinization.

Anodic oxidation of substrate (1 mmol) was carried out at a constant current (10 mA/cm²) with platinum plate electrodes (2 cm × 2 cm) in a single compartment glass cell containing 10 mL of 1 M Et3N-nHF (n = 2, 3) or Et4NF-nHF (n = 3, 4)/DME or MeCN. Consumption of the starting material was followed by 1H NMR using CHCl3 as an eluent to remove fluoride salts. Since the fluorinated products are readily decomposed by silica gel column chromatography, the products were purified by alumina column chromatography with hexane/ethyl acetate (7:1) as an eluent to remove fluoride salts. The resulting solution was extracted with ethyl acetate and the extracts were washed with brine, and then were dried over MgSO4. The solvent was evaporated under vacuum and the residue was purified by column chromatography on silica gel using a mixture of hexane/ethyl acetate (7:1) as an eluent to give 4a or 4b.

1-[(Diphenylmethylene)amino]-1 trifluoromethyl-3-methoxycarbonylpropane (4a) — Colorless oil; 1H NMR: δ = 7.66–7.15 (m, 10H), 3.94–3.85 (m, 1H), 3.55 (s, 3H), 2.37–2.08 (m, 4H); 13C NMR: δ = 173.00, 172.61, 138.58, 135.38, 130.83, 128.85, 128.79, 128.61, 128.03, 127.50, 125.34, 118.48, 62.51, 51.64, 29.68, 24.93, 13.43; 19F NMR: δ = 2.93 (d, J = 7 Hz, 3F); MS m/z 349 (M+), 348, 276 (M–CH3COOMe), 262 (M–MeOOC2H3); HRMS Calcd for C21H19NO3: 349.1290, found: 349.1298.

1-[(Diphenylmethylene)amino]-1 trifluoromethyl-3-cyanopropane (4b) — Colorless oil; 1H NMR: δ = 7.78–7.18 (m, 10H), 6.03 (d, J = 18 Hz, 1H); 13C NMR: δ = 165.72, 157.99, 153.27, 130.30, 128.92, 128.64, 128.57, 128.07, 96.59; 19F NMR: δ = 18.89 (d, J = 19 Hz, 1F), 8.93 (dd, J = 19, 18 Hz, 1F); MS m/z 243 (M+), 224 (M–F), 166 (M–Ph); HRMS Calcd for C21H18NO2: 349.1290, found: 349.1284.

3. Results and Discussion

3.1 Oxidation potentials of Schiff bases of 2,2,2-trifluoroethylymine and glycine methyl ester

At first, the oxidation potentials (E°) of various Schiff bases, 1a–1d were measured by cyclic voltammetry in Et4NBF4/MeCN using a platinum (Pt) disk electrode. The oxidation potentials are summarized in Table 1.

The oxidation potentials of sulfur-containing Schiff base derivatives 1b–1d are much less positive compared to that of imine 1a devoid of sulfur atoms. Schiff base 1c having MeS groups is more easily oxidized than that having PhS groups 1d. Since a CF3 group is a stronger electron-withdrawing group than an ester group, the oxidation potential of imine 1b bearing a CF3 group is more positive compared to that bearing an ester group 1c.

To theoretically determine the site of electron abstraction of imines 1a–1d, density functional theory (DFT) calculations were carried out (Fig. 2). The highest occupied molecular orbital (HOMO) of 1a was mainly located on one of the phenyl groups of the C=N bond while that of 1b and 1c is mainly located on one of the sulfur atoms and the C=N double bond. The HOMO of 1d is mainly located on one of the phenylthio groups and the C=N double bond as shown in Fig. 2.

3.2 Anodic fluorination of Schiff bases

At first, anodic fluorination of N-(diphenylmethyleneamino)-2,2,2-trifluoroethane (1a) was carried out at a Pt anode in DME and MeCN containing Et3N-nHF (n = 2, 3) or Et4NF-nHF (n = 3, 4) using an undivided cell. The results are summarized in Table 2.

Table 1. Oxidation potentials of Schiff bases 1a–1d.a)

| Substrate | Y | EWG | E° (V vs. SCE) |
|-----------|---|-----|---------------|
| 1a | Ph | CF3 | 2.30 |
| 1b | MeS | CF3 | 1.76 |
| 1c | MeS | COOMe | 1.62 |
| 1d | PhS | COOMe | 1.82 |

a) Pt disk electrode (φ = 1 mm), 0.1 M Et4NBF4/MeCN, scan rate: 100 mV/s.

Experiments were carried out with a Hokuto Denko HAFB 501 potentiostat/galvanostat. Mass spectra and high resolution-mass spectra were obtained with a Shimadzu GCMS-QP-2000A or JEOL JMS-700 mass spectrometer. 19F NMR yields were estimated with α,α,α-trifluorotoluene as an internal standard.
As shown in Table 2, electrolysis in Et₄NF-3HF/DME provided the desired α-monofluorinated product 2a; however, the yield was low (run 1). In this case, even a large excess amount of electricity was passed, the starting material 1 was not completely consumed and a considerable amount of 1 was recovered. When Et₄NF-4HF/DME was used, the conversion of 1 increased, but the yield of 2a was extremely low (run 2) because of formation of unidentified by-products. Since the oxidation potential of 1a is rather positive (E_f = 2.70 V vs. SCE), DME was more easily oxidized than the substrate 1a resulting in low current efficiency. Then, anodically stable MeCN was used as an electrolytic solvent. As expected, the yield increased to 18% when Et₃N-2HF/MeCN was employed (run 3), but a larger excess amount of electricity was necessary to consume 1a because of readily oxidizable Et₃N-2HF containing free Et₃N. Then, anodically more stable Et₄NF-3HF/MeCN was used. In this case, the starting material 1a was consumed by passing an amount of electricity slightly higher (2.5 F/mol) than the theoretical amount and the yield of 2a was increased significantly to 45% (run 4). However, the use of anodically stable Et₄NF-3HF/MeCN was found to be less effective (run 5). Since Et₃N-3HF contains free Et₃N, the deprotonation of 1a radical cation was presumably promoted to give the better yield in run 4.

Next, more easily oxidizable 2,2,2-trifluoroethylamine bearing two methylthio groups 1b was subjected to anodic fluorination. As shown in Scheme 9, anodic fluorination proceeded efficiently even in DME containing Et₄NF-3HF. When 3 F/mol of electricity was passed, starting 1b was consumed and the desired fluorinated product (2b) was formed in good yield as 78%. Next, anodic fluorination of N-[bis(methylthio)methylene]glycine methyl ester (1c) was carried out in Et₄NF-3HF/DME. The results are summarized in Table 3.

When the theoretical electricity (2 F/mol) was passed, the expected monofluoro product 2c was formed in moderate yield as 50% (run 1). When the electricity was increased to 3 F/mol, the yield also increased to 77%. However, the electricity was increased further to 4 F/mol, the yield decreased to 60%. In this case, difluoro product 3 was formed. The yield of 3 was increased with increasing electricity, and reached 34% at 8 F/mol. At a larger excess amount of electricity (10 F/mol), difluoro product 3 was formed predominantly in 35% yield. The relationship between the yields of 2c and 3 with electricity passed is shown in Fig. 3.

![Figure 2](image_url)  
**Figure 2.** Computationally simulated HOMO diagrams of 1a, 1b, 1c and 1d with a B3LYP/6-31G(d) level of theory (iso value = 0.04).

**Table 2.** Anodic fluorination of N-(diphenylmethyleneamino)-2,2,2-trifluoroethane (1a).

| Run | Supporting electrolyte | Solvent | Electricity (F/mol) | Yield of 2a (%) | Recovery of 1a (%) |
|-----|------------------------|---------|---------------------|-----------------|-------------------|
| 1   | Et₄NF-3HF              | DME     | 9.3                 | 11              | 63                |
| 2   | Et₄NF-4HF              | DME     | 7.2                 | 2               | 23                |
| 3   | Et₃N-2HF               | MeCN    | 10.0                | 18              | 0                 |
| 4   | Et₃N-3HF               | MeCN    | 2.5                 | 45              | 0                 |
| 5   | Et₄NF-3HF              | MeCN    | 5.2                 | 15              | 0                 |

a) Determined by ¹⁹F NMR.

**Scheme 9.** Anodic monofluorination of 1b.

**Table 3.** Anodic fluorination of N-[Bis(methylthio)methylene]glycine methyl ester (1c).

| Run | Electricity (F/mol) | Yield (%) | 2c | 3 |
|-----|---------------------|-----------|----|---|
| 1   | 2                   | 50        | 0  |   |
| 2   | 3                   | 77        | 0  |   |
| 3   | 4                   | 60        | 11 |   |
| 4   | 6                   | 33        | 17 |   |
| 5   | 8                   | 5         | 34 |   |
| 6   | 10                  | 0         | 35 | b |

a) Determined by ¹⁹F NMR. b) Isolated yield.
Next, we attempted anodic fluorination of Schiff base having bis(phenylthio) group 1d. However, fluorination did not proceed at all. In this case, decomposition of 1d took place during electrolysis and diphenyl disulfide was formed.

In consideration to the relationship between the yields of 2c and 3 with electricity passed shown in Fig. 3, anodic fluorination of imines seems to proceed as shown in Scheme 10. As already mentioned, electron transfer takes place from the (Ph)2C=N- (1a) or the (RS)2C=N- (1b–1d) portion to generate the delocated radical cation A followed by deprotonation, and further one electron oxidation to form cation intermediate B. The resulting cation reacts with a fluoride ion to give fluorinated products 2b and 2c. Product 2c undergoes two-electron oxidation and deprotonation followed by reaction with a fluoride ion to form gem-difluoro product 3.

3.3 Cathodic Michael addition of N-(diphenylmethyleneamino)-2,2,2-trifluoroethane (1a) to activated olefins

At first, the reduction potentials of 1a and activated olefins such as methyl acrylate, acrylonitrile, and acrylamide were measured by cyclic voltammetry. Their reduction onset and peak potentials (\(E_{\text{onset,red}}\) and \(E_{\text{p,red}}\)) are summarized in Table 4.

As shown in Table 4, the reduction onset potential (\(E_{\text{onset,red}}\)) and the reduction peak potential (\(E_{\text{p,red}}\)) of 1a are less negative than those of methyl acrylate and acrylonitrile, while \(E_{\text{onset,red}}\) of 1a is more negative than that of acrylamide and \(E_{\text{p,red}}\) of 1a is almost same as that of acrylamide. Cathodic reduction of 1a was carried out at a Pt cathode in DMF and MeCN containing Et4NBF4 in the presence of methyl acrylate as a Michael acceptor in a divided cell. The results are summarized in Table 5.

As shown in Table 5, the expected Michael adduct 4a was formed in 12% yield (run 1). Use of MeCN instead of DMF resulted in a two-fold increase of the yield (run 2). Then, cathodic reduction 1a was performed with various cathode materials other than Pt. Glassy carbon (GC) and copper (Cu) cathodes were found to be more efficient than a Pt cathode (runs 3 and 4), while a lead (Pb) cathode was not effective (run 5). In the latter case, a small amount of defluorination by-product 5 was formed. Notably, a titanium (Ti) cathode was found to be the best choice to give 4a in 64% yield (run 6). When the amount of activated olefin i.e. Michael acceptor, acrylate was reduced, the yield also decreased (runs 7 and 8).

Next, we investigated cathodic Michael addition of 1a to other acceptors such as acrylonitrile and acrylamide using a Ti cathode similarly. Cathodic Michael addition to acrylonitrile took place to give the corresponding adduct 4b in moderate yield (45%) (Table 5, run 9) while the use of acrylamide resulted in no formation of the expected adduct (run 10). In this case, the corresponding trifluoroethyamine derived from 1a was detected in the crude product by \(^{19}\text{F} \text{NMR} \text{ and MS spectra.}\)
Table 5. Cathodic Michael addition of 1a to activated olefins.

| Run | Cathode | Solvent | Activated olefin | EWG Equiv. | Charge passed (F/mol) | Yield of 4 (%)a |
|-----|---------|---------|------------------|------------|-----------------------|-----------------|
| 1   | Pt      | DMF     | COOMe            | 5          | 0.9                   | 12              |
| 2   | Pt      | MeCN    | COOMe            | 5          | 0.8                   | 25              |
| 3   | GC      | MeCN    | COOMe            | 5          | 1.0                   | 31              |
| 4   | Cu      | MeCN    | COOMe            | 5          | 1.3                   | 30              |
| 5   | Pb      | MeCN    | COOMe            | 5          | 1.0                   | 3b              |
| 6   | Ti      | MeCN    | COOMe            | 5          | 0.9                   | 64 (48)c        |
| 7   | Ti      | MeCN    | COOMe            | 3          | 0.8                   | 35              |
| 8   | Ti      | MeCN    | COOMe            | 1          | 0.9                   | 12              |
| 9   | Ti      | MeCN    | CN               | 5          | 1.7                   | 45 (28)c        |
| 10  | Ti      | MeCN    | CONH2            | 5          | 2.2                   | 0d              |

a) Determined by 19F NMR. b) By-product 5 (3%) was detected by 19F NMR. c) Isolated yield is shown in parentheses. d) CF3CH2NHCHPh2 was detected by 19F NMR (5.85 ppm (t, J = 9 Hz)) and MS spectra (m/e = 265 [M+]).

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| 4   | Cu      | MeCN    | COOMe            | 5          | 1.3                   | 30              |
| 5   | Pb      | MeCN    | COOMe            | 5          | 1.0                   | 3b              |
| 6   | Ti      | MeCN    | COOMe            | 5          | 0.9                   | 64 (48)c        |
| 7   | Ti      | MeCN    | COOMe            | 3          | 0.8                   | 35              |
| 8   | Ti      | MeCN    | COOMe            | 1          | 0.9                   | 12              |
| 9   | Ti      | MeCN    | CN               | 5          | 1.7                   | 45 (28)c        |
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a) Determined by 19F NMR. b) By-product 5 (3%) was detected by 19F NMR. c) Isolated yield is shown in parentheses. d) CF3CH2NHCHPh2 was detected by 19F NMR (5.85 ppm (t, J = 9 Hz)) and MS spectra (m/e = 265 [M+]).

Scheme 11. Plausible mechanism of cathodic Michael addition.

Cathodic Michael addition of imine 1a seems to proceed as shown in Scheme 11. The calculated LUMO of 1a is mainly located on the C=N bond. Therefore, one-electron transfer takes place at the C=N bond to generate radical anion followed by elimination of an H atom to generate anion intermediate C, which should be stabilized by a counter quaternary ammonium ion similarly to the reported case (Path A).28 The resulting anion intermediate C reacts with acrylate and acrylonitrile to form anionic intermediate D, followed by protonation to give the corresponding Michael adduct 4a and 4b, respectively.

Since a large excess amount of acrylate and acrylonitrile as a Michael acceptor was necessary to form 4a and 4b, these activated olefins would be also reduced simultaneously in spite of their more negative reduction potentials compared to 1a. The resultant radical anion intermediate E abstracts a proton from 1a to generate C (Path B). Michael addition of anion C to the activated olefin gives anion D, which would abstract a proton from acrylamide itself prior to from 1a as shown in Scheme 12. Thus, no formation of the Michael adduct with acrylamide is explained reasonably. Even if anionic intermediate C is generated, C abstracts a proton from acrylamide prior to addition of C to acrylamide (Scheme 13).
The desired anion $C$ can be generated by the reaction of $1a$ with a strong base. However, treatment with $n$-BuLi followed by addition of acrylate did not form $4a$ at all. In this case, the elimination of HF proceeded predominantly to form $5$ solely in high yield as shown in Scheme 14. Since Li counter cation has a strong affinity for the fluorine atom, the defluorination seems to be accelerated.26–28

Scheme 14. Reaction of $1a$ with $n$-BuLi in the presence of acrylate.

4. Conclusions

We have disclosed electrochemical properties of Schiff base derivatives of 2,2,2-trifluoroethylamine and glycine ester by cyclic voltammetric studies, and we have achieved their anodic derivatives of 2,2,2-trifluoroethylamine Schiff base to activated olefin using a Ti cathode. Thus, we have illustrated the first successful examples of electrochemical fluorination of open-chain amino acid and cathodic Michael addition.

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