Difluoro- and Trifluoromethylation of Electron-Deficient Alkenes in an Electrochemical Microreactor

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Introduction

Difluoromethyl (CHF₂) and trifluoromethyl (CF₃) groups are important structural motifs in many pharmaceutically relevant molecules because they are known to enhance chemical and metabolic stability, lipophilicity and binding selectivity.[1] As a result, much effort has been directed toward the development of facile and efficient synthetic methods for the introduction of CHF₂ and CF₃ groups into aromatics and heteroaromatics as well as alkenes. Increased effort has been focused on the development of new reagents, which can be effective sources of reactive radicals or nucleophilic species of CHF₂ and CF₃, such as Togni’s,[2] Umemoto’s,[3] and Baran’s reagent[4] and application of those reagents to copper-catalyzed trifluoromethylation of unactivated alkenes to enable the formation of a sp³-C–CF₃ bond.[5]

Uneyama and co-workers previously reported the electrooxidation of trifluoroacetic acid (TFA) in the presence of various alkenes for the preparation of trifluoromethylated aliphatic compounds.[6] TFA is of low cost and the generated CF₃ radicals based on Kolbe electrolysis can efficiently react with various electron-deficient alkenes in a batch system.[6] Very recently, Buchwald and Chen reported a rapid and efficient protocol for trifluoromethylation of aryl and heteroaryl iodides using potassium trifluoroacetate as a source of CF₃ radicals in a continuous flow system, which enabled a rapid rate of reaction.[7]

On the basis of these results it is proposed that an electrochemical trifluoromethylation might be improved by using a flow system.

We recently reported a practical procedure for electrochemical syntheses including dimerization of diphenylacetic acid coupled with Kolbe electrolysis by using an electrochemical microreactor, combining the advantages of flow and electrochemistry.[8] The electrochemical microreactor has a flow channel sandwiched between two platinum electrodes as shown in Figure 1, where very short diffusion distances lead to high space-time yields (see Supporting Information for more details on the electrochemical microreactor).

Figure 1. A) Flow setup for electrochemical di- and trifluoromethylation. B) FEP micro flow channel.

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Figure 1. A) Flow setup for electrochemical di- and trifluoromethylation. B) FEP micro flow channel.
In short, it enables a rapid and effective progress of oxidative and reductive reactions without redox reagent because the anode and cathode act as oxidant and reductant, respectively, during the passage of reactants through the flow channel. Different microreactor systems have already been developed for chemistry and have been successfully used for electrochemical reactions without added electrolyte. In verity, some synthetic protocols and other examples for practical use of such reactors have been reported.

Results and Discussion

Kolbe electrolysis

In this paper, we report the rapid and efficient electrochemical addition of CHF₂ and CF₃ radicals to various electron-deficient alkenes. The radicals are produced by Kolbe electrolysis of di- and trifluoroacetic acid, respectively, at the platinum anode (see Scheme 1). The Kolbe electrolysis of trifluoroacetic acid in the presence of electron-deficient alkenes such as acrylates and acrylamides in batch conditions has been reported in the literature. Herein we describe the usefulness of the flow protocols for di- and trifluoromethylation on the basis of these earlier results.

![Scheme 1. Anodic Kolbe electrolysis of di- and trifluoroacetic acid.](image)

A typical electrochemical di- and trifluoromethylation of alkenes 2 in acetonitrile/water as a solvent mixture is shown in Scheme 2. The addition of radical 1a or 1b to alkenes 2 is followed by dimerization of the radical intermediates A to yield products 3.

![Scheme 2. Di- and trifluoromethylation of olefins.](image)

Optimization

To demonstrate the usability of the electrochemical microreactor for radical trifluoromethylation, we initially examined the dimerization by using methyl acrylate 2a (R₁ = CO₂Me, R₂ = H) as the substrate, which is a well-established reaction in batch chemistry. The electrolysis was performed by continuous introduction of a water/acetonitrile solution containing 2a, trifluoroacetic acid and triethylamine into the electrochemical microreactor with a flow channel (23 μL volume; Figure 1B, left) at constant current and room temperature (Figure 1). The reaction conditions were optimized by preliminary experiments. Hydrogen is formed at the cathode through proton reduction and is visible at the exit of the reactor; however, the amounts generated do not disturb the reaction. After purification, dimer 3a was obtained in 52% yield as a 5:3 mixture of dl and meso isomers as determined by 13C NMR spectroscopy. This yield is comparable to previous reports, although the reaction time with 66 s was much shorter than in the batch reaction (16 h). Similarly, the electrolysis of trifluoroacetic acid in the presence of ethyl acrylate 2b (R₁ = CO₂Et, R₂ = H), tert-butyl acrylate 2c (R₁ = CO₂Bu, R₂ = H), or methyl methacrylate 2d (R₁ = CO₂Me, R₂ = Me) afforded dimers 3c, 3e and 3g as a mixture of dl and meso isomers in the ratio of 1:1, 1:1 and 10:1, in 45, 45 and 11% yield, respectively. It has been previously reported by Renaud et al. that dimer 3g can be obtained in about 10% isolated yield by electrolysis under batch conditions. Under batch conditions, the dimers are typically formed in a 1:1 dl:meso ratio.

In order to expand the feasibility of the Kolbe electrolysis using other acids (1) as a source of fluoromethyl radicals, the reaction conditions optimized for the trifluoromethylation of 2a were applied to the electrolysis using difluoroacetic acid 1b in the presence of acrylates 2. As a result, similar difluoromethylated dimers 3b, 3d, 3f and 3h were obtained as summarized in Table 1.

**Table 1. Di- and trifluoromethylation of acrylates.**

| Entry | Acid 1 | Alkene 2 | Product | dl:meso | Yield [%] |
|-------|--------|----------|---------|---------|-----------|
| 1     | 1a     | 2a       | 3a      | 5:3     | 52[a]     |
| 2     | 1b     | 2a       | 3b      | 1:1     | 38[a]     |
| 3     | 1a     | 2b       | 3c      | 1:1     | 45        |
| 4     | 1b     | 2b       | 3d      | 1:1     | 40        |
| 5     | 1a     | 2c       | 3e      | 1:1     | 45        |
| 6     | 1b     | 2c       | 3f      | 1:1     | 40        |
| 7     | 1a     | 2d       | 3g      | 10:1[b] | 11[b]     |
| 8     | 1b     | 2d       | 3h      | 6.5[c]  | 16        |

[a] Batch yield: 50% (1:1 dl:meso), ref. [6]. [b] Batch yield: 45% (1:1 dl:meso), ref. [11e]. [c] or 1:10. [d] Batch yield: 10% (1:1 dl:meso), ref. [11a]. [e] or 5:6.

Di- and trifluoromethyl acetalidation

Changing the substituents on the C–C double bond of alkenes should affect not only the yield but also the selectivity in the product due to the modification of the thermodynamic and kinetic stability of the radical intermediates A and their affinity to the electrodes. When the electrolysis of trifluoroacetic
acid 1a in the presence of 2d was carried out under the above-described conditions for the dimerization, not only 3g, but also small amounts of 4a and 5a, obtained through a 1,2-addition of trifluoromethyl and acetamido groups, were observed by 1H NMR analysis as shown in Scheme 3. It has been reported that this type of reaction can occur from nucleophilic attack of acetoni trile to the carbocation B during the electrolysis of trifluoroacetic acid in the presence of 2d under low current densities (1 mA cm⁻²) at 0 °C.¹¹(b)

To investigate the trifluoromethyl acetylation in flow chemistry we examined other reaction conditions. Initially, similar reaction conditions as described in the literature were applied in the flow reaction at a flow rate of 0.05 mL min⁻¹ (residence time: 28 s). However, no conversion of 2d to 4a at this low current density (1 mA cm⁻²) was observed. When the current was raised to 50 mA cm⁻², the two amide-proton signals corresponding to 4a and 5a at 6.45 ppm and 6.68 ppm, respectively, were clearly observed by 1H NMR. This is consistent with the previous report by Uneyama et al.¹¹(b) The products were observed in the crude reaction mixture in a ratio of 2:3 and 3:1 (4a:5a) at residence times of 22 s and 13 s, respectively. From these experiments, it can be concluded that the initially generated mono-trifluoromethyl-substituted product 4a can undergo conversion to 5a through a different radical intermediate. However, from the crude NMR spectra of the reactions, it is obvious that these products are only a minority within the crude reaction mixture.

To establish a suitable protocol for the trifluoromethyl acetylation, which is a useful reaction for the synthesis of α-methyl amino acids as building blocks for peptide and protein synthesis,¹³ we further investigated the trifluoromethylation of 2d using other reaction conditions. The electrolysis in the electrochemical microreactor using a larger flow channel (53 µL; Figure 1B, right) at the flow rate of 5 µL min⁻¹ (residence time: 10.5 min) and a low current density (2.4 mA cm⁻²) led without dimerization to the preferential generation of 4a and 4b in 25% and 27% isolated yields, respectively. The trifluorocacetamidation of 2d giving 20% isolated yield of 4a under batch conditions was previously achieved in 8 h reaction time at 0–5 °C.¹¹(c) In our experiments, the isolated yield was improved using much shorter reaction times at room temperature. Thus, the results of electrolysis by using 2d as a substrate clearly showed that the electrochemical microreactor is suitable not only for radical dimerization of acrylates, but also for nucleophilic addition of acetonitrile accompanied with di- and trifluoromethylation. It should be noticed that a 1,2-addition of di- and trifluoromethyl and acetamido groups to acrylates 2a-c was not observed even when applying the conditions for the synthesis of 4a and 4b.

**Bis(difluoromethylation) and bis(trifluoromethylation)**

In order to further demonstrate the usefulness of the electrochemical microreactor for di- and trifluoromethylation, the electrolysis of 1a and 1b in the presence of acrylamide 2e was investigated. According to the literature,¹¹(c) the 1,2-addition of trifluoromethyl radicals as shown in Scheme 4 can be selectively progressed. The nitrogen atom of the radical intermediate A of acrylamide can strongly absorb on the platinum electrode surface, so that A diffuses slowly to the bulk solution and consequently reacts with another Rf radical on the electrode surface without dimerization, preferentially promoting bis(trifluoromethylation) when the current density is kept high.

![Scheme 4. Di- and trifluoromethylation of acrylamide 2e and 2f.](Image)

It was previously demonstrated that bis(trifluoromethylation) to 6 can be achieved in 35% yield without dimerization and trifluorocacetamidation by electrolysis of 2e in an undivided cell for 3.5 h at 200 mA cm⁻² at 0 °C.¹¹(c) In addition, Uneyama et al. reported that this reaction is successfully progressed in flow systems that employed a large flow cell with platinum electrodes to give 48% yield of 6a (Rf=CF₃, R=H); 6b (R=CF₂=CF₂, R=H); 6c (R=CF₂=CF₂, R=Me, R=H) without dimerization.¹¹(c, 13) Thus, the examination of electrochemical bis(trifluoromethylation) in a micro flow channel and comparison of the result with the previous report is important in evaluating the usability of our method. The best conditions for this reaction (see Experimental Section for details) were found to be the electrolysis of 2e with 1a and triethylamine in 7:1 acetonitrile/water at constant current (110 mA cm⁻²) at a flow rate of 0.05 mL min⁻¹ (residence time = 28 s) at room temperature. Compounds 6a and 6b (R=CHF₂, R=H) were selectively obtained in 67% and 47% yield, respectively, dramatically improving the reported yields.¹¹(c, 13) Thus, these results further and strongly support that the electrochemical microreactor is a useful device to achieve rapid and effective di- and trifluoromethylation for electro-deficient alkenes based on Kolbe electrolysis.

The reaction conditions were also applied to the electrolysis of 1a and 1b in the presence of N,N-dimethylacrylamide 2f. In contrast to the high selectivity and yields of 6a and 6b, some other side products, which could not be identified by NMR analysis, were observed in this reaction. Only in the case of...
electrolysis of 1\textit{b}, was the bis(difluoromethyl)acetylene (2:1 hexene/ETOAc), 3\textit{b} was obtained as a colorless liquid (collection of 5 mL; yield: 0.262 g, 38\%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}); \deltav = 5.86 (tm, \textit{J} = 5.6 Hz, CH\textsubscript{3}, CH\textsubscript{2} and CH\textsubscript{2}O, 3.67 (s, CH\textsubscript{3}O, 3.66 (s, CH\textsubscript{3}O or CH=O), 3.02–2.93 (m, 2H, CH\textsubscript{2} and CH\textsubscript{2}O), 2.39–2.15 (m, 2H, CH\textsubscript{2} and CH\textsubscript{2}O), 1.97–1.73 (m, 2H, CH\textsubscript{2} and CH\textsubscript{2}O) ppm; 13C NMR (100 MHz, CDCl\textsubscript{3}); \deltav = 33.42 (t, \textit{J} = 22.2 Hz, CH\textsubscript{3} or CH=O), 33.76 (t, \textit{J} = 22.2 Hz, CH\textsubscript{3} or CH=O), 40.96 (dd, \textit{J} = 6.8, 10.9 Hz, CH\textsubscript{3} or CH=O), 41.23 (dd, \textit{J} = 6.6, 10.7 Hz, CH\textsubscript{3} or CH=O), 52.85 (s, CH\textsubscript{3}O or CH=O), 52.92 (s, CH\textsubscript{3}O or CH=O), 116.01 (t, \textit{J} = 237.9 Hz, CH\textsubscript{2} or CH=O), 116.11 (t, \textit{J} = 237.8 Hz, CH\textsubscript{2} or CH=O), 172.60 (s, C=O, CH\textsubscript{2} or CH=O) ppm; MS (APCI): \textit{m/z}: 275.09 (100) [M+H]\textsuperscript{+}

**Diethyl 2,3-bis(2,2-trifluoroethyl)succinate (3c):** Following purification of the crude product using column chromatography (3:1 hexene/ETOAc), 3\textit{c} was obtained as a colorless liquid (collection of 5 mL; yield: 0.378 g, 45\%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}); \deltav = 4.18–4.10 (m, 4H, CH\textsubscript{2} and CH\textsubscript{2}O), 3.04–2.91 (m, 5H, CH\textsubscript{2} and CH\textsubscript{2}O), 2.81–2.61 (m, 2H, CH\textsubscript{2} or CH=O), 2.18–2.06 (m, 5H, CH\textsubscript{2} or CH=O), 2.17–2.05 (m, 2H, CH\textsubscript{2} or CH=O) ppm; 13C NMR (100 MHz, CDCl\textsubscript{3}); \deltav = 13.28 ppm; HRMS (EI): \textit{m/z}: [M+H]\textsuperscript{+}

**Diethyl 2,3-bis(2,2-difluoroethyl)succinate (3d):** Following purification of the crude product using column chromatography (3:1 hexene/ETOAc), 3\textit{d} was obtained as a colorless liquid (collection of 5 mL; yield: 0.300 g, 40\%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}); \deltav = 5.06 (tm, \textit{J} = 55.4 Hz, 2H, CH\textsubscript{2} or CH=O), 4.27–4.14 (m, 4H, CH\textsubscript{2} and CH\textsubscript{2}O), 3.09–2.98 (m, 2H, CH\textsubscript{2} or CH=O), 2.74–2.27 (m, 2H, CH\textsubscript{2} or CH=O), 2.02–1.85 (m, 2H, CH\textsubscript{2} or CH=O), 1.32–1.24 (m, 6H, CH\textsubscript{2} or CH=O) ppm; 13C NMR (100 MHz, CDCl\textsubscript{3}); \deltav = 14.25 ppm; HRMS (EI): \textit{m/z}: [M+H]\textsuperscript{+}

**Diethyl 2,3-bis(2,2-Trifluoroethyl)succinate (3e):** Following purification of the crude product using column chromatography (3:1 hexene/ETOAc), 3\textit{e} was obtained as a colorless liquid (collection of 5 mL; yield: 0.440 g, 45\%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}); \deltav = 2.87–2.72 (m, 2H, CH\textsubscript{2} and CH\textsubscript{2}O), 2.70–2.57 (m, 2H, CH\textsubscript{2} and CH\textsubscript{2}O), 2.30–2.18 (m, 2H, CH\textsubscript{2} or CH=O), 2.13–2.01 (m, 2H, CH\textsubscript{2} or CH=O) ppm; 13C NMR (100 MHz, CDCl\textsubscript{3}); \deltav = 26.80 ppm; MS (APCI): \textit{m/z}: 393.1624, found: 393.1621.

**Diethyl 2,3-bis(2,2-Difluoroethyl)succinate (3f):** Following purification of the crude product using column chromatography (3:1 hexene/ETOAc), 3\textit{f} was obtained as a colorless liquid (collection of 5 mL; yield: 0.400 g, 40\%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}); \deltav = 1.88.
Following purification of the crude product using column chromatography (3:1 hexane/EtOAc), 4b was obtained as a white solid (collection of 10 mL; yield: 0.113 g, 27%): mp: 56.2–57.2 °C; 1H NMR (CDCl3): δ = 6.74 (1H, 7.5Hz, J = 5.8 Hz, 1H), 3.71 (3H, 3H), 2.86–2.72 (m, 1H, 1H), 2.54–2.42 (m, 1H, 1H), 1.52 (3H, 3H) ppm; 13C NMR (100 MHz, CDCl3): δ = 22.7 (CH3), 22.8 (CH3), 36.6 (q, J = 27.0 Hz, CH2), 52.4 (s, OCH3), 55.3 (3J, J = 2.3 Hz, CNH), 124.6 (q, J = 276.0 Hz, CF2), 169.1 (s, C=O), 172.3 (2C=O) ppm; HRMS (EI): m/z: [M+H]+ calcd for C16H14F4NO2: 228.0842, found: 228.0841.

**Methyl 2-(acetylamo)-2-methyl-4,4,4-difluorobutyrate (4a)**

Following purification of the crude product using column chromatography (1:1 hexane/EtOAc), 4a was obtained as a colorless solid (collection of 10 mL; yield: 0.114 g, 27%): mp: 79.6–80.3 °C; 1H NMR (CDCl3): δ = 7.03 (1H, 7.5Hz, J = 5.8 Hz, 1H), 3.86 (3H, 3H), 2.81–2.72 (1H, 1H), 2.63–2.49 (1H, 1H), 2.37 (3H, 3H) ppm; 13C NMR (100 MHz, CDCl3): δ = 22.7 (CH3), 22.8 (CH3), 36.6 (q, J = 27.0 Hz, CH2), 52.4 (s, OCH3), 70.3 (s, C=O), 17.0 (3C=O) ppm; HRMS (ESI): m/z: [M+H]+ calcd for C16H14F4NO2: 228.0842, found: 228.0841.

**Electrochemical bis(trifluoromethylation):** A mixture of 1a or 1b (16 mmol), 2 (1 mmol), and Et3N (0.06 mmol) dissolved in CH3CN/H2O (7:1 v/v, 10 mL) was introduced into the electrochemical microreactor equipped with a large FEP channel (Figure 1B, left) through a syringe pump (5 µL min⁻¹; residence time: 28 s) with an applied current of 200 mA (current density: 111 mA cm⁻²) and collected in a glass vial at the outlet. The reaction solution was neutralized with saturated aq NaHCO3 (6 mL), the organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO4, and concentrated in vacuo. The residual yellow oil was purified by column chromatography (silica gel) equilibrated with a mixture of hexane and EtOAc as eluent. The yields of 6 were determined on the basis of the used alkenes.

**4,4-Trifluoro-2-(trifluoromethyl)butanamide (6a)**

Following purification of the crude product using column chromatography (3:1 hexane/EtOAc), 6a was obtained as a colorless solid (collection of 10 mL; yield: 0.141 g, 67%): mp: 86.9–93.0 °C; 1H NMR (400 MHz, CDCl3): δ = 8.18 (1H, 7.5 Hz, J = 1.8 Hz, 1H), 3.63–3.54 (m, 1H, 1H), 3.08–2.93 (m, 1H, 1H), 2.68–2.56 (m, 1H, 1H) ppm; 13C NMR (100 MHz, CDCl3): δ = 30.04 (q, J = 30.7 Hz, CH2), 144.16 (q, J = 27.3 Hz, CH3), 124.57 (q, J = 277.5 Hz, CF, 125.86 (q, J = 273.8 Hz, CF2), 167.44 (s, C=O) ppm; MS (APCI): m/z (%): 210.03 (100) [M+H]+.

**2-(Difluoromethylene)-4,4-difluorobutanamide (6b)**

Following purification of the crude product using column chromatography (4:1 EtO/EtOAc), 6b was obtained as a colorless solid (collection of 10 mL; yield: 78 mg, 45%): mp: 73.1–74.2 °C; 1H NMR (400 MHz, CDCl3): δ = 7.61 (1H, 1H), 6.86 (1H, 1H), 5.62 (tm, J = 55.8 Hz, 2.74–2.63 (m, 1H, 1H), 2.10–1.94 (m, 1H, 1H), 1.83–1.69 (1H, 1H) ppm; 13C NMR (100 MHz, CDCl3): δ = 31.92 (q, J = 227.2 Hz, CH3), 31.95 (tm, J = 227.2 Hz, CH2), 24.16 (tm, J = 21.7, CH), 117.37 (t, J = 236.6 Hz, CHF), 117.81 (t, J = 241.5 Hz, CHF2), 164.94 (s, C=O) ppm; HRMS (APCI): m/z: [M+H]+ calcd for C13H10F3NO: 214.0537, found: 214.0534.

**2-(Difluoromethylene)-4,4-difluoro-N-methylbutanamide (6c)**

Following purification of the crude product using column chromatography (3:1hexane/EtOAc), 6b was obtained as a colorless oil (collection of 10 mL; yield: 61 mg, 32%): 1H NMR (400 MHz, CDCl3): δ = 9.21 (1H, 1H), 5.92 (tm, J = 55.6 Hz, 2H, 3.70 (br, 1H, CH), 3.13 (s, 3H), 2.62–2.46 (m, 1H, 1H), 2.29–2.14 (1H, 1H) ppm; 13C NMR (100 MHz, CDCl3): δ = 27.98 (CH3), 31.88 (t, J = 21.1 Hz, CH2), 42.75 (t, J = 22.4 Hz, CH), 114.82 (t, J = 159.0 Hz, CHF3), 115.90 (t, J = 162.63 Hz, CHF2), 162.06 (s, C=O) ppm; HRMS (ESI): m/z: [M+H]+ calcd for C12H14F4NO: 188.0693, found: 188.0692.
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