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Effective synthesis of difluorocyclohexadienones by electrochemical oxidation of phenols

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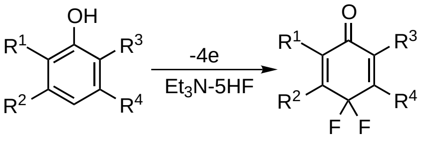
Abstract—Electrochemical oxidation of phenols was examined using Et_3N–5HF as the electrolyte and various electrodes. Carbon fiber cloth was found to be suitable as the anode and a variety of phenols could be converted to 4,4-difluorocyclohexadienone derivatives in good yields.

Anodic fluorination of phenols (**1**) using an HF-base as the electrolyte is a convenient method for synthesis of 4,4-difluorocyclohexadienone derivatives (**2**) because toxic oxidants such as PbO_2 are not required, and the resulting **2** can be used as the precursors of various substituted fluorophenols (Eq. (1)).[1] However, under the anodic oxidation conditions, side reactions such as oligomerization competitively took place,[2] and good results could be obtained only when bulky substituents were present on the benzene ring.[1b] We wish to report here an electrochemical fluorination method applicable to a wide variety of phenols.



1 **2** (1)

The electrochemical fluorination of α-naphthol was examined using Et_3N–5HF as the electrolyte and fluorine source,[3] and various electrodes to find suitable conditions (Table 1). When Pt was used as the anode, passivation took place on the anode surface and the desired product was scarcely obtained (entry 1). As graphite anodes were reported to be effective for the oxidation of phenols,[4] glassy carbon,[5] carbon felt,[6] and carbon fiber cloth[7] were applied to the reaction. When the glassy carbon was used, passivation took place again and the electrolysis was prevented (entry 2). On the other hand, the carbon felt and carbon fiber cloth gave better results and the desired difluorocyclohexadienone derivative was obtained in moderate yield (entries 3 and 4). In order to avoid the oligomerization on the anode surface, slow addition of the naphthol into the cell is effective, and without the slow addition operation, the yield decreased. Extension of the anode

Table 1. Electrochemical fluorination of α-naphthol using various anode[a]

Entry	Anode[b] (number)	Charge passed (F/mol)	Yield (%)[c]
1	Pt	0[d]	0
2	Glassy carbon	0[d]	0
3	Carbon felt	4.4	46
4	Carbon fiber cloth	4.3	64
5	Carbon fiber cloth (3 sheets)	4.0	73
6	Carbon fiber cloth (16 sheets)	3.6	83
7	Carbon fiber cloth (24 sheets)	3.6	89

[a] If otherwise not mentioned, the reaction was carried out at 1.7 V versus Ag/$AgClO_3$ in a divided cell equipped with a Nafion™ film and a platinum cathode (2×2 cm). α-Naphthol (1 mmol) in dimethyl carbonate (4 ml) was added over 6–7 h.

[b] A 2×2 cm sheet was used.

[c] Isolation yield based on the naphthol used.

[d] Passivation on the anode surface took place.

Keywords: electrochemistry; halogenation; oxidation; phenols.

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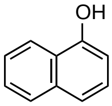
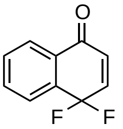
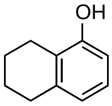
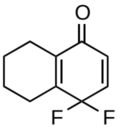
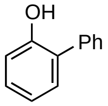
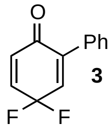
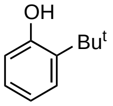
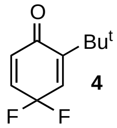
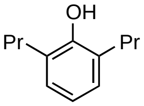
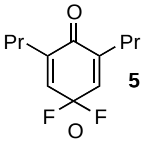
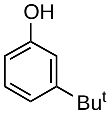
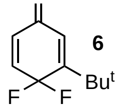
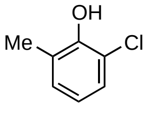
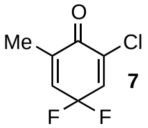
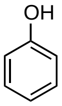
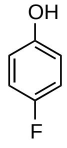
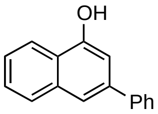
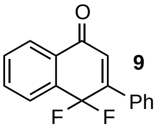
surface area was also found to be effective to improve the result. As carbon fiber cloth is flexible, it is easy to increase the number of sheets to be accommodated in a cell (entries 5–7). Finally, the best result was obtained by using 24 sheets of carbon cloth as the anode and the desired product was obtained in 89% yield (entry 7).

The present method is applicable to various phenols, and substituents at the *o*-positions are not necessary to obtain the product in good yield (Table 2). It is worth noting that even unsubstituted phenol gave the corresponding fluorinated product in 61% yield (entry 8). In the previous report,[1b] the fluorinated product was obtained only in less than 25% yield from the unsubstituted phenol. Recently, difluoromethylenephophonate moiety is of great interest as analogs of pyro- and triphosphates where the CF_2 group is an isoelectronic and isosteric replacement of ether oxygen.[8] Therefore, the compound **9** is interesting as an analog of flavonoid[9] which has an oxygen instead of the CF_2 group.

Table 2. Electrochemical fluorination of phenols[a]

Entry	Phenols	Charge passed, F/mol	Product	Yield, %[b]
1		3.6	 **1**	89
2		4.0	 **2**	76
3		5.2	 **3**	77[c]
4		4.7	 **4**	70
5		4.1	 **5**	77
6		5.8	 **6**	68
7		6.9	 **7**	62
8		4.1	 **8**	61[d,e,f]
9		5.1	 **9**	68[c,g]

a. If otherwise not mentioned, the reaction was carried out for 6 h at 1.7 V vs. $Ag/AgClO_3$. b. Isolated yield based on phenols. c. The electrolysis was carried out at 1.6 V. d. The electrolysis was carried out at 2.0 V. e. Phenol was added over 15 h. f. As product was volatile, it was reduced to fluorophenol by Zn. g. Phenol was added over 21 h.

A typical procedure is as follows: Et_3N–5HF (2×24 ml) was introduced into divided cells, made of Teflon™ PFA, equipped with a Nafion™ 117 film as the diaphragm using 24 sheets of carbon fiber cloth (20×20 mm, Nippon Carbon Co. Ltd GF-2097) for the anode and a smooth Pt plate (20×20 mm) for the cathode under a nitrogen atmosphere. (**CAUTION**: Although Et_3N–5HF is less corrosive than HF itself, it is recommended to use rubber gloves.) The electrolysis was carried out at room temperature with a constant potential (1.7 V versus $Ag/AgClO_3$) and during the electrolysis, α-naphthol (144 mg, 1 mmol) in dimethylcarbonate (4 ml) was added into the anodic cell over 6 h. The electrolysis was continued until the α-naphthol was consumed completely. The content of the anode cell was then poured into water and extracted three times with CH_2Cl_2. The combined organic layers were successfully washed with aqueous $Na_2S_2O_3$, aqueous $NaHCO_3$, and brine, and dried over $MgSO_4$. The purification by column chromatography (silica gel/hexane–ether) gave 4,4-difluoro-1-naphtoquinone in 89% yield.[10]

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10. Compound **1**: mp 60–61°C; IR (KBr) 1685, 1642, 1602 cm^{-1}; δ_H ($CDCl_3$) 6.56 (1H, d, $J=10.4$ Hz), 6.95–7.00 (1H, m), 7.64–7.75 (2H, m), 7.84 (1H, d, $J=7.8$ Hz), 8.09 (1H, d, $J=7.8$ Hz); δ_F ($CDCl_3$) −90.66 (2F, d, $J=5.5$ Hz); HRMS calcd for $C_{10}H_6F_2O$: 180.0387. Found: 180.0395. Compound **2**: IR (neat) 1686, 1658, 1634 cm^{-1}; δ_H ($CDCl_3$) 1.66–1.77 (4H, m) 2.31–2.44 (4H, m), 6.29–6.33 (1H, m), 6.76–6.81 (1H, m); δ_F ($CDCl_3$) −103.69 to −103.65 (2F, m); HRMS calcd for $C_{10}H_{10}F_2O$: 184.0700. Found: 184.0702. Compound **3**: mp 70–71°C; IR (KBr) 1652 cm^{-1}; δ_H ($CDCl_3$) 6.44 (1H, d, $J=10.3$ Hz), 6.83–6.92 (2H, m), 7.40–7.44 (5H, m); δ_F ($CDCl_3$) −97.33 (2F, t, $J=5.5$ Hz); HRMS calcd for $C_{12}H_8F_2O$: 206.0543. Found: 206.0537. Compound **4**: IR (neat) 1654 cm^{-1}; δ_H ($CDCl_3$) 1.25 (9H, s), 6.23 (1H, d, $J=10.3$ Hz), 6.55–6.59 (1H, m), 6.70–6.75 (1H, m); δ_F ($CDCl_3$) −97.97 (2F, t, $J=5.5$ Hz); HRMS calcd for $C_{10}H_{12}F_2O$: 186.0856. Found: 186.0854. Compound **5**: IR (neat) 1661 cm^{-1}; δ_H ($CDCl_3$) 0.96 (6H, t, $J=7.3$ Hz), 1.45–1.54 (4H, m), 2.28–2.33 (4H, m), 6.50 (2H, t, $J=5.3$ Hz); δ_F ($CDCl_3$) −99.30 to −98.36 (2F, m); HRMS calcd for $C_{12}H_{16}F_2O$: 214.1169. Found: 214.1175. Compound **6**: IR (neat) 1689, 1649 cm^{-1}; δ_H ($CDCl_3$) 1.32 (9H, s), 6.26–6.29 (2H, m), 6.73–6.79 (1H, m); δ_F ($CDCl_3$) −97.34 (2F, d, $J=6.7$ Hz); HRMS calcd for $C_{10}H_{12}F_2O$: 186.0856. Found: 186.0845. Compound **7**: IR (neat): 1697, 1675, 1632 cm^{-1}; δ_H ($CDCl_3$) 2.01–2.03 (3H, m), 6.62–6.66 (1H, m), 6.96–6.99 (1H, m); δ_F ($CDCl_3$) −97.97 to −97.91 (2F, m); HRMS calcd for $C_7H_5ClF_2O$: 177.9997. Found: 177.9979. Compound **8**: mp 45–46°C (lit.[3] 45–45.5°C); IR (KBr) 3229 cm^{-1}; δ_H ($CDCl_3$) 4.63 (1H, s), 6.80–6.75 (2H, m), 6.96–6.90 (2H, m); δ_F ($CDCl_3$) −124.80 to −124.87 (1F, m). Compound **9**: IR (neat) 1668 cm^{-1}; δ_H ($CDCl_3$) 6.78 (1H, s), 7.47–7.52 (3H, m), 7.64–7.68 (1H, m), 7.76–7.81 (3H, m), 7.91 (1H, d, $J=7.5$ Hz), 8.13 (1H, d, $J=7.8$ Hz); δ_F ($CDCl_3$) −88.74 (2F, s); HRMS calcd for $C_{16}H_{10}F_2O$: 256.0700. Found: 256.0706.