Electrochemical Oxidation of 2-Substituted 3-(*N*-Arylamino)-4,4,4-trifluoro-2-butenoate. An Access to 3-Substituted 2-(Trifluoromethyl)-3*H*-indoles

Masafumi Kobayashi, Keiji Sadamune, Hiromichi Mizukami, and Kenji Uneyama*

Department of Applied Chemistry, Faculty of Engineering, Okayama University, Okayama 700, Japan

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Much attention has been focused on the synthesis of fluorinated indoles in view of their bioactivity.[1] Perfluoroalkylated indoles are prepared in general by direct perfluoroalkylation of the corresponding indoles with perfluoroalkanoyl peroxides[2] or perfluoroalkyl halides.[3] The direct perfluoroalkylation, however, results in low regioselectivity and poor yields of the desired perfluoroalkylindoles. In particular, it is not easy to introduce a trifluoromethyl group to an indole skeleton. Utilization of trifluoromethylated building blocks is another approach to synthesizing (trifluoromethyl)indoles.[4] Some 2-(trifluoromethyl)-3*H*-indoles can be synthesized from 2-(trifluoromethyl)quinoline.[5]

We have reported a novel synthetic method of 2-(trifluoromethyl)benzimidazoles (**6**) by electrochemical cyclization[6] of *N,N'*-disubstituted 2,2,2-trifluoroethanimidamides (**4**) and Lewis acid-catalyzed cyclization[7] of the electrochemically prepared *p*-benzoquinone imines **5** (Scheme 1). Therefore, the corresponding carbon analogues **2** are also expected to be cyclized to 2-(trifluoromethyl)indole derivatives. Methyl 2-substituted-3-*N*-aryl-4,4,4-trifluorobutenoate and its derivatives **1** would be promising precursors of the corresponding *p*-benzoquinone imine **2**. Here, we describe an electrochemical oxidation of **1** to **2**, and the conversion of **2** to 2-(trifluoromethyl)-indoles (**3**) via intramolecular cyclization.

The starting compounds **1**[8] are easily prepared in good yields by the nucleophilic reaction of active methylene compounds with *N*-(2-substituted 4-methoxyphenyl)-2,2,2-trifluoroacetimidoyl chlorides (**7**).[9] Table 1 shows the results. The spectral data suggest that all compounds of type **1** favor the enamine form **1** and not the imine form **1'** as shown in Scheme 2. The ^{1}H NMR spectrum of **1a** shows NH signal at 13.5 ppm in $CDCl_3$ and the IR spectrum reveals an absorption of N–H bond in the range of 3240–3170 cm^{-1}.

Electrolysis of **1** (0.5 mmol) was conducted in an MeCN (6 mL)–saturated $NaHCO_3$ aqueous (2 mL) system using a glassy carbon (2.0 × 1.5 cm^2) anode and a platinum foil (2.0 × 1.5 cm^2) cathode in a constant current of 5 mA/cm^2 for 2.5 F/mol at −10 °C. The electrooxidation of **1a** using an undivided cell resulted in the formation of the desired *p*-benzoquinone imine[10] **2a** (91%) (Table 2). Lower current density was favorable for the preparation of **2a** (83, 73, and 16% yields at 5, 20, and 50 mA/cm^2, respectively). The reaction temperature also affected the yield and a lower temperature was better suited for

Scheme 1

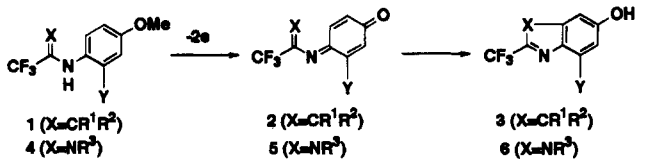

Table 1. Syntheses of Compounds 1 from Imidoyl Chlorides 7 and Active Methylene Compounds ($R^1CH_2R^2$)

entry	Y	R^1	R^2	yield (%)
1	H	CO_2Me	CO_2Me	1a (91)
2	H	COMe	CO_2Et	1b (65)
3	H	CN	CO_2Et	1c (71)
4	H	Ph	CO_2Et	1d (85)
5	H	CN	CN	1e (94)
6	OMe	CO_2Me	CO_2Me	1f (90)
7	Me	CO_2Me	CO_2Me	1g (90)
8	NO_2	CO_2Me	CO_2Me	1h (92)

Scheme 2

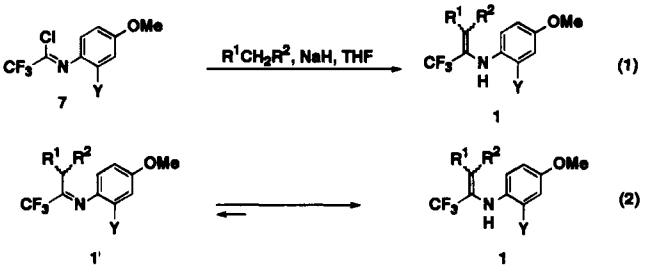

Table 2. Electrochemical Preparation of *p*-Benzoquinone Imines 2

entry	1	conditions[a]	cell	yield (%)
1	1a	A	undivided	2a (91)
2	1b	A	undivided	2b (26) 9b (54)
3	1b	B	divided[b]	2b (83)
4	1c	B	divided[b]	2c (81)
5	1d	C	divided[b]	2d (52)
6	1e	D	divided[b]	2e (94)[c]
7	1f	A	undivided	2f (64)
8	1g	B	divided[b]	2g (94)
9	1h	E	undivided	2h (48)

[a] Electrolysis conditions: A, MeCN (6 mL), saturated $NaHCO_3$ (2 mL); B, MeCN (5 mL), H_2O (3 mL), saturated $NaHCO_3$ (3 mL); C, MeCN (5 mL), saturated $NaHCO_3$ (3 mL), NaOMe (0.4 mmol); D, MeCN (8 mL), $NaClO_4$ (1.2 mmol); E, MeCN (6 mL), H_2O (2 mL), NaOEt (0.5 mmol). [b] A glass filter was used for the H-type divided cell. [c] ^{19}F NMR yield.

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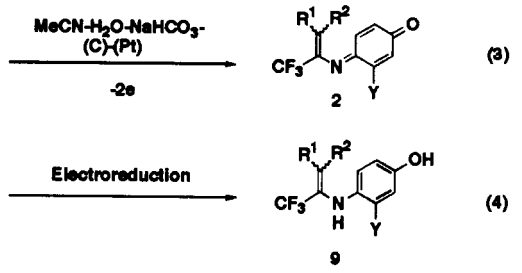
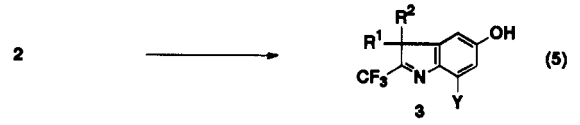
Scheme 3



(3)

(4)

Scheme 4



(5)

Table 3. Cyclization of 2 to 2-(Trifluoromethyl)indoles 3

entry	2	conditions[a]	yield (%)
1	2a	A	3a (66)
2	2b	A	3b (8)
3	2c	A	3c (0)
4	2d	C	3d (42)
5	2f	B	3f (63)
6	2g	A	3g (67)

[a] Reaction conditions: A, neat, 150 °C; B, 0.1 equiv of CAN in MeOH, rt; C, 1.0 equiv of BF_3·Et_2O in benzene, 80 °C.

obtaining higher yields (91, 82, and 52% at −10, 0, and 40 °C, respectively). The yield of **2a** is proportional to the amount of water in low concentrations of water in MeCN. However, a concentration of water of more than 25 vol % decreased the yield of **2a** and increased the yield of the *p*-aminophenol derivative **9a**. The electrooxidation of **1b** (R^1 = Ac, R^2 = CO_2Et) in an undivided cell lowered the yield of **2b** (26%) and preferentially formed the *p*-aminophenol derivative **9b**, which may be produced by cathodic reduction of **2b**. In fact, product **2b** was obtained in a reasonable yield (83%) in a divided cell. Likewise, the 2-cyano (**1c**) and 2-phenyl (**1d**) compounds provided the *p*-benzoquinone imines **2c** and **2d** in 81 and 52% yields, respectively. Electrolysis of **1e** (R^1 = R^2 = CN) in dry MeCN gave the desired *p*-benzoquinone imine **2e** in 94% yield in contrast to the poor yield in aqueous MeCN. It is notable that no base is required for the transformation of the highly acidic compound **2e** (R^1 = R^2 = CN), while a rather stronger base (NaOMe) is required for that of the less acidic compound **1d**. The *N*-(2-substituted 4-methoxyphenyl) compounds **1f–h** also gave the similar results. In the case of 2,4-dimethoxyphenyl compound **1f** the product was the *p*-benzoquinone imine **2f** and not the corresponding *o*-benzoquinone imine derivative. The reaction would proceed via an ECEC mechanism.[11] A sequential reaction of one-electron oxidation, deprotonation from an amino group, a further one-electron oxidation, addition of water, and subsequent demethoxylation would lead to the *p*-benzoquinone imines **2**.

These *p*-benzoquinone imines **2** were readily transformed to 3*H*-indole derivatives **3** (Scheme 4). The results are listed in Table 3. The thermal cyclization of **2a** (Y = H, R^1 = R^2 = CO_2Me) and **2g** (Y = Me, R^1 = R^2 = CO_2Me) gave the desired indoles **3a** (66%) and **3g** (67%), respectively. The ^1H NMR spectrum of **3a** shows only three aromatic protons and the IR spectrum reveals an absorption of O–H bond in the range of 3256–3288 cm^{-1}. However, **2f** (Y = OMe, R^1 = R^2 = CO_2Me) provided a poor yield (20%) of **3f** and many inseparable byproducts were formed under the same thermal conditions. In the presence of ceric ammonium nitrate (CAN), however, **2f** was transformed to **3f** in 63% yield. Neither thermal nor CAN-catalyzed reaction of 2-phenyl compound **2d** gave **3d**. But, BF_3·Et_2O catalyzed the cyclization, affording the desired **3d** in 42% yield. In contrast to the case of the diesters (**2a**, **2f**, and **2g**), cyclization of the acetyl (**2b**) and the cyano (**2c**) compounds failed.

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Experimental Section

The ^1H and ^{19}F NMR were recorded in $CDCl_3$ on a Varian VXR-200 or 500 using TMS for ^1H and C_6F_6 for ^{19}F as internal standards. Melting points were uncorrected.

Preparations of Compounds 1. *N*-(4-Methoxyphenyl)-2,2,2-trifluoroacetimidoyl chloride (**7a**) (5 mmol) in THF (5 mL, distilled by the treatment of sodium–benzophenone) was added into a mixture of dimethyl malonate (7 mmol) and sodium hydride (7 mmol) in THF (10 mL) and the solution was stirred at rt for 4 h. The reaction mixture was extracted with ethyl acetate (5 mL × 3) and the extracts were washed with brine. The organic layer was dried over anhydrous magnesium sulfate, condensed in vacuo, and then recrystallized from benzene–hexane solution.

Methyl 4,4,4-Trifluoro-3-[*N*-(4-methoxyphenyl)amino]-2-(methoxycarbonyl)-2-butenoate (1a): colorless crystals (91%); mp 70–71 °C; IR (CH_2Cl_2) 3240, 1764, 1725, 1255 cm^{-1}. Anal. Calcd for $C_{14}H_{14}F_3NO_5$: C, 50.46; H, 4.23; N, 4.20. Found: C, 50.56; H, 4.27; N, 4.18.

Ethyl 2-Acetyl-4,4,4-trifluoro-3-[*N*-(4-methoxyphenyl)-amino]-2-butenoate (1b): colorless crystals (65%); mp 68–69 °C; IR (CH_2Cl_2) 1652, 1256 cm^{-1}. Anal. Calcd for $C_{15}H_{16}F_3NO_4$: C, 54.38; H, 4.86; N, 4.23. Found: C, 54.50; H, 4.82; N, 4.17.

Ethyl 2-Cyano-4,4,4-trifluoro-3-[*N*-(4-methoxyphenyl)-amino]-2-butenoate (1c): colorless crystals (71%); mp 98–100 °C; IR (CH_2Cl_2) 3240, 2220, 1664, 1238 cm^{-1}. Anal. Calcd for $C_{14}H_{13}F_3N_2O_3$: C, 53.51; H, 4.17; N, 8.91. Found: C, 53.36, H, 4.03, N, 8.95.

Ethyl 4,4,4-Trifluoro-3-[*N*-(4-methoxyphenyl)amino]-2-phenyl-2-butenoate (1d): yellow oil (85%); IR (CH_2Cl_2) 3232, 1752, 1258 cm^{-1}. Anal. Calcd for $C_{19}H_{18}F_3NO_3$: C, 62.46; H, 4.97; N, 3.83. Found: C, 62.57; H, 5.20; N, 3.46.

2-Cyano-4,4,4-trifluoro-3-[*N*-(4-methoxyphenyl)amino]-2-butenonitrile (1e): yellow crystals (94%): mp 142–143 °C; IR (CH_2Cl_2) 3236, 2228, 1706, 1182 cm^{-1}. Anal. Calcd for $C_{12}H_8F_3N_3O$: C, 53.94; H, 3.02; N, 15.72. Found: C, 54.17; H, 2.92; N, 15.48.

Methyl 4,4,4-Trifluoro-3-[*N*-(2,4-dimethoxyphenyl)amino]-2-(methoxycarbonyl)-2-butenoate (1f): colorless crystals (90%); mp 98–99 °C; IR (CH_2Cl_2) 1678, 1278 cm^{-1}. Anal. Calcd for $C_{15}H_{16}F_3NO_6$: C, 49.59; H, 4.44; N, 3.85. Found: C, 49.68; H, 4.43; N, 3.83.

Methyl 4,4,4-Trifluoro-3-[*N*-(4-methoxy-2-methylphenyl)amino]-2-(methoxycarbonyl)-2-butenoate (1g): colorless crystals (90%); mp 63–65 °C; IR (CH_2Cl_2) 3156, 1734, 1278 cm^{-1}. Anal. Calcd for $C_{15}H_{16}F_3NO_5$: C, 51.88; H, 4.64; N, 4.03. Found: C, 51.86; H, 4.60; N, 3.97.

Methyl 4,4,4-Trifluoro-3-[*N*-(4-methoxy-2-nitrophenyl)-amino]-2-(methoxycarbonyl)-2-butenoate (1h): orange crystals (92%); mp 79–81 °C; IR (CH_2Cl_2) 3384, 2960, 1690, 1250 cm^{-1}. Anal. Calcd for $C_{14}H_{13}F_3N_2O_7$: C, 44.45; H, 3.46; N, 7.40. Found: C, 44.44; H, 3.43; N, 7.26.

Typical Procedure of Electrolysis. Electrochemical Preparation of *p*-Benzoquinone Imine 2a. The amine **1a** (0.5 mmol) dissolved in a mixture of acetonitrile (6 mL) and saturated aqueous sodium hydrogen carbonate (2 mL) containing sodium perchlorate (0.4 mmol) was electrooxidized at −10 °C in an undivided cell using a glassy carbon for anode and a platinum foil for cathode in the constant current of 5 mA/cm^2 for 2.5 F/mol of electricity. After evaporation of most of acetonitrile in vacuo, the organic phase was extracted with ethyl acetate. The extracts

were washed with brine and concentrated in vacuo. The residue was chromatographed over SiO_2 to give **2a**.

Methyl 4,4,4-Trifluoro-3-[*N*-(4-oxo-2,5-cyclohexadien-1-ylidene)amino]-2-(methoxycarbonyl)-2-butenoate (2a): red oil (91%); IR (neat) 1742, 1660, 1234 cm^{-1}. Anal. Calcd for $C_{13}H_{10}F_3NO_5$: C, 49.22; H, 3.18; N, 4.42. Found: C, 49.19; H, 3.23; N, 4.42.

Ethyl 2-Acetyl-4,4,4-trifluoro-3-[*N*-(4-oxo-2,5-cyclohexadien-1-ylidene)amino]-2-butenoate (2b): red oil (83%); IR (neat) 1728, 1234 cm^{-1}. Anal. Calcd for $C_{14}H_{12}F_3NO_4$: C, 53.34; H, 3.84; N, 4.44. Found: C, 53.13; H, 3.97; N, 4.53.

Ethyl 2-Cyano-4,4,4-trifluoro-3-[*N*-(4-oxo-2,5-cyclohexadien-1-ylidene)amino]-2-butenoate (2c): red oil (81%); IR (neat) 2228, 1728, 1660, 1234 cm^{-1}. Anal. Calcd for $C_{13}H_9F_3N_2O_3$: C, 52.36; H, 3.04, N, 9.39. Found: C, 52.13; H, 3.12; N, 9.54.

Ethyl 4,4,4-Trifluoro-3-[*N*-(4-oxo-2,5-cyclohexadien-1-ylidene)amino]-2-phenyl-2-butenoate (2d): red oil (52%); IR (neat) 1732, 1660, 1222 cm^{-1}. Anal. Calcd for $C_{18}H_{14}F_3NO_3$: C, 61.89; H, 4.04; N, 4.01. Found: C, 62.22; H, 4.43; N, 3.84.

2-Cyano-4,4,4-trifluoro-3-[*N*-(4-oxo-2,5-cyclohexadien-1-ylidene)amino]-2-butenonitrile (2e): red oil (94%); IR (neat) 2240, 1662, 1262 cm^{-1}. Anal. Calcd for $C_{11}H_4F_3N_3O$: C, 52.61; H, 1.61; N, 16.72. Found: C, 52.82; H, 1.58; N, 16.66.

Methyl 4,4,4-Trifluoro-3-[*N*-(2-methoxy-4-oxo-2,5-cyclohexadien-1-ylidene)amino]-2-(methoxycarbonyl)-2-butenoate (2f): red oil (64%); IR (neat) 1734, 1652, 1248 cm^{-1}. Anal. Calcd for $C_{14}H_{12}F_3NO_6$: C, 48.42; H, 3.48; N, 4.03. Found: C, 48.53; H, 3.87; N, 4.02.

Methyl 4,4,4-Trifluoro-3-[*N*-(2-methyl-4-oxo-2,5-cyclohexadien-1-ylidene)amino]-2-(methoxycarbonyl)-2-butenoate (2g): red oil (94%); IR (neat) 1740, 1658, 1244 cm^{-1}. Anal. Cacld for $C_{14}H_{12}F_3NO_5$: C, 50.76; H, 3.65; N, 4.23. Found: C, 50.53; H, 3.87; N, 4.02.

Methyl 4,4,4-Trifluoro-3-[*N*-(2-nitro-4-oxo-2,5-cyclohexadien-1-ylidene)amino]-2-(methoxycarbonyl)-2-butenoate (2h): red oil (48%); IR (neat) 1740, 1658, 1244 cm^{-1}. Anal. Calcd for $C_{13}H_9F_3N_2O_7$: C, 43.11; H, 2.50; N, 7.73. Found: C, 42.98; H, 2.36; N, 7.77.

2-(Trifluoromethyl)-5-hydroxy-3,3-bis(methoxycarbonyl)-3*H*-indole (3a). Neat **2a** (0.5 mmol) was heated at 150 °C for 3 h. The crude product was purified by flash column chromatography on silica gel with hexane–AcOEt as an eluent to afford **3a**: colorless crystals (66%); mp 133–135 °C; IR (CH_2Cl_2) 3256, 1748, 1250 cm^{-1}. Anal. Calcd for $C_{13}H_{10}F_3NO_5$: C, 49.07; H, 3.18; N, 4.42. Found: C, 49.12; H, 3.12; N, 4.38.

3-Acetyl-3-(ethoxycarbonyl)-2-(trifluoromethyl)-5-hydroxy-3*H*-indole (3b): colorless crystals (8%); mp 175–176 °C; IR (CH_2Cl_2) 3288, 2992, 1650, 1252 cm^{-1}. Anal. Calcd for $C_{14}H_{12}F_3NO_4$: C, 53.34; H, 3.84; N, 4.44. Found: C, 53.13; H, 3.97; N, 4.53.

3-(Ethoxycarbonyl)-2-(trifluoromethyl)-5-hydroxy-3-phenyl-3*H*-indole (3d). A mixture of **2d** (0.5 mmol) and boron trifluoride etherate (0.5 mmol) in benzene (3 mL) was stirred in the refluxing temperature under N_2 for 2 days: viscous oil (42%); IR (neat) 3388, 1740, 1252 cm^{-1}. Anal. Calcd for $C_{18}H_{14}F_3NO_3$: C, 61.89; H, 4.04; N, 4.01. Found: C, 62.22; H, 4.43; N, 3.84.

2-(Trifluoromethyl)-5-hydroxy-7-methoxy-3,3-bis(methoxycarbonyl)-3*H*-indole (3f). A mixture of **2f** (0.5 mmol) and CAN (0.05 mmol) in MeOH (3 mL) was stirred at rt under N_2 for 7 h. The reaction mixture was extracted with ethyl acetate (5 mL × 3): colorless crystals (63%); mp 133–135 °C; IR (CH_2Cl_2) 3628, 1744, 1284 cm^{-1}. Anal. Calcd for $C_{14}H_{12}F_3NO_6$: C, 48.42; H, 3.48; N, 4.03. Found: C, 48.53; H, 3.87; N, 4.02.

2-(Trifluoromethyl)-5-hydroxy-7-methyl-3,3-bis(methoxycarbonyl)-3*H*-indole (3g): colorless crystals (63%); mp 106–107 °C; IR (CH_2Cl_2) 3272, 1746, 1268 cm^{-1}. Anal. Calcd for $C_{14}H_{12}F_3NO_5$: C, 50.76; H, 3.65; N, 4.23. Found: C, 50.44; H, 3.92; N, 4.0.

Methyl 4,4,4-Trifluoro-3-[*N*-(4-hydroxyphenyl)amino]-2-(methoxycarbonyl)-2-butenoate (9a): viscous oil; IR (neat) 3400, 1684, 1248 cm^{-1}. Anal. Calcd for $C_{13}H_{12}F_3NO_5$: C, 48.91; H, 3.79; N, 4.39. Found: C, 48.67; H, 4.13; N, 4.09.

Ethyl 2-Acetyl-4,4,4-trifluoro-3-[*N*-(4-hydroxyphenyl)-amino]-2-butenoate (9b): viscous oil; IR (neat) 3388, 1719, 1266 cm^{-1}. Anal. Calcd for $C_{14}H_{14}F_3NO_4$: C, 53.06; H, 4.45; N, 4.41. Found: C, 52.64; H, 4.48; N, 4.44.

2-Cyano-4,4,4-trifluoro-3-[*N*-(4-hydroxyphenyl)amino]-2-butenonitrile (9e): green crystals; mp 230–233 °C; IR (CH_2Cl_2) 3404, 2228, 1704, 1148 cm^{-1}. Anal. Calcd for $C_{11}H_6F_3N_3O$: C, 52.19; H, 2.39; N, 16.59. Found: C, 51.96; H, 2.51; N, 16.55.

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