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DIQUAT DERIVATIVES, A PRECURSOR OF ORGANIC REDUCTANT

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Abstract – Electroreduction of diquat triflate gave a potent organic reductant, which promoted reductive dimerization of aryl bromides in the presence of palladium catalysts to give the corresponding biaryl compounds.

This manuscript is dedicated to the celebration of the 77th birthday of Prof. Isao Kuwajima, Professor emeritus of Tokyo Institute of Technology.

Bipyridinium salts, such as 1,1'-dialkyl-4,4'-bipyridinium salts (paraquats)[1] and 1,1'-dialkyl-2,2'-bipyridinium salts (diquats),[2] have been used as medicines, herbicides, and plant growth regulators. These salts are readily provided by alkylation of 4,4'-bipyridyl and 2,2'-bipyridyl, respectively. Paraquats (C_6V^{2+}) underwent two steps reversible one electron reduction to give the radical cation ($C_6V^{\cdot +}$) and neutral species (C_6V^0) (Figure 1), and the radical cation and the neutral species act as organic reductants. We already reported that the neutral species derived from paraquats promoted a palladium-catalyzed reductive coupling of aryl bromides to afford the corresponding biaryls[3] in organic solvents,[4] water,[5] and ionic liquid.[6]

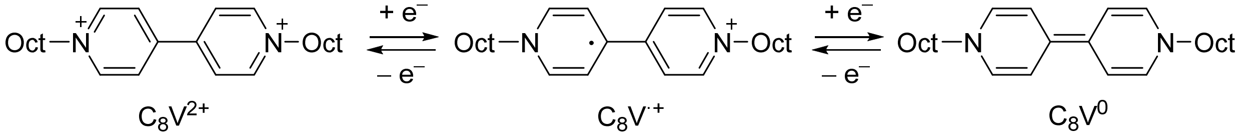


Figure 1. Reduction of Paraquat Derivatives (V^{2+})

In our continuing study on electrogeneration of organic reductants, we found that electroreduction of diquats (DQ^{2+}) similarly gave the corresponding radical cation ($DQ^{\cdot +}$) and the neutral species (DQ^0)

(Figure 2) which promoted the reductive coupling of aryl bromides (Figure 3). In this paper, we report synthesis and redox properties of diquat derivatives and the preliminary results of the reductive coupling of aryl halides with DQ^0.

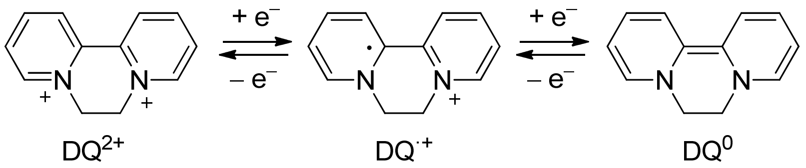


Figure 2. Electroreduction of Diquat (DQ^{2+})

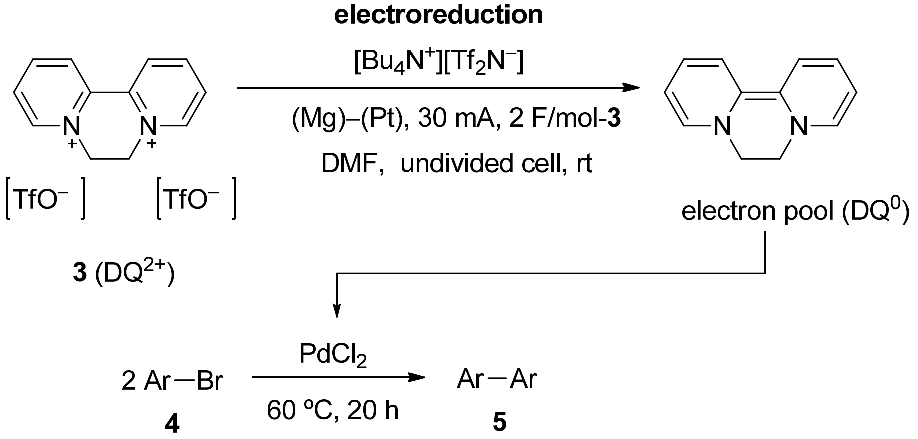
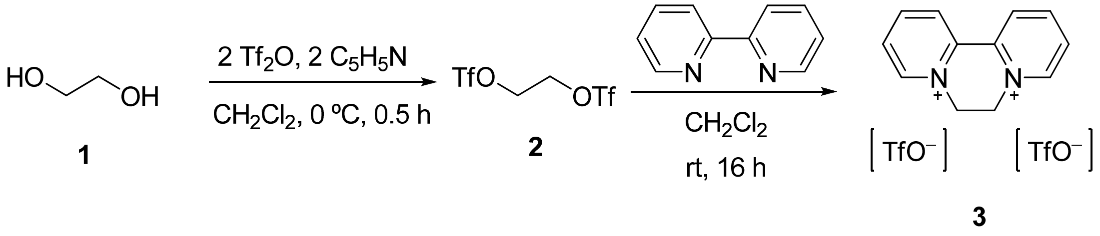


Figure 3. Electroreduction of Diquat **3** and Pd-Catalyzed Reductive Coupling of Aryl Bromides **4** to **5**

Preparation of Diquat Triflate (**3**).

Ethylene glycol was treated with triflic anhydride (2 equiv.) and pyridine (2 equiv.) in dichloromethane at 0 °C for 0.5 h to give the corresponding ditriflate **2**[7] (Scheme 1). A mixture of 2,2'-bipyridyl and **2** in dichloromethane was stirred at room temperature for 16 h to give diquat triflate (**3**) in 79% yield as colorless solids.[8]



Scheme 1. Preparation of Diquat Triflate **3**

Diquat **3** was soluble (> 10 mg/2 mL-solvent) in water and several polar organic solvents such as acetone, *N*,*N*-dimethylformamide (DMF), *N*,*N*-dimethylacetamide (DMA), 1,3-dimethylimidazolidinone (DMI), and acetonitrile, whereas **3** was scarcely soluble in less polar organic solvents such as toluene, ether, THF, and chloroform.

Electrochemical Properties of Diquat 3.

Cyclic voltammogram of diquat **3** (25 mM) was recorded in acetonitrile solution of $[Bu_4N^+][Tf_2N^-]$ (0.2 M) (Figure 4). Two sets of reversible redox peak appeared at -0.67 V ($[DQ^{2+}]/[DQ^{\cdot +}]$) and -1.17 V ($[DQ^{\cdot +}]/[DQ^0]$) vs. Ag/Ag$^+$, which were more negative than those of paraquat (-0.44 V ($[C_8V^{2+}]/[C_8V^{\cdot +}]$) and -0.89 V $[C_8V^{\cdot +}]/[C_8V^0]$),[3b] indicating that the reduced **3**, especially DQ^0, would work as more powerful organic reductant than the reduced paraquat (V^0).

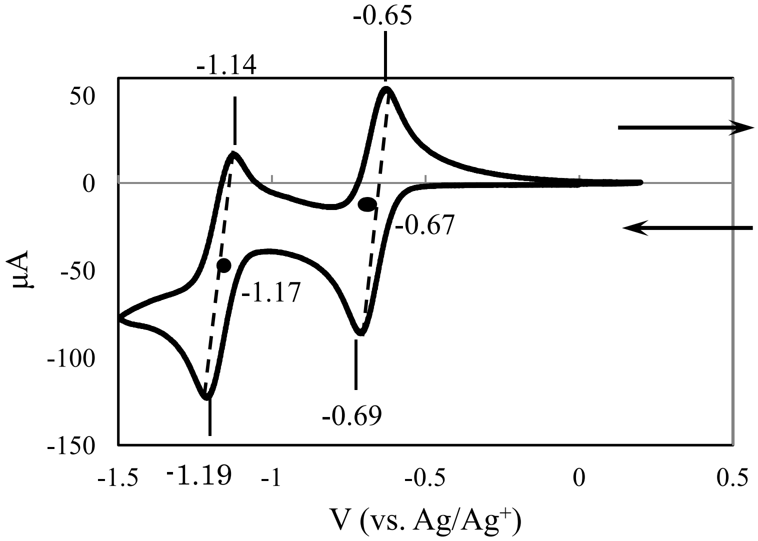
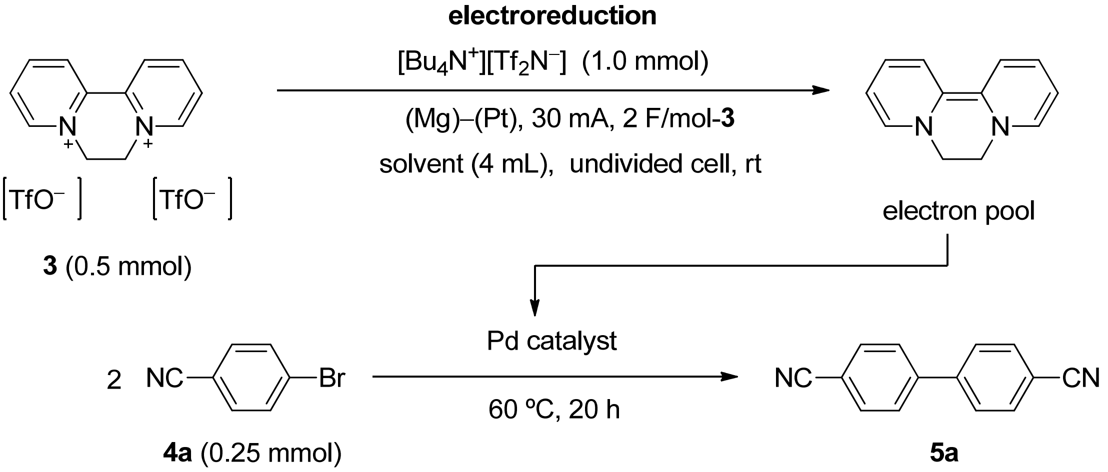


Figure 4. Cyclic Voltammogram of Diquat Ditriflate **3**
Diquat Ditriflate (**3**, 25 mM), $[Bu_4N^+][Tf_2N^-]$ (0.2 M), MeCN
working electrode: GC (ϕ = 3.0 mm), reference electrode: Ag/Ag$^+$,
counter electrode: Pt wire. Scan rate: 20 mV/s

Diquat 3-Palladium Promoted Reductive Coupling of Aryl Bromides.

Palladium-catalyzed reductive coupling of aryl bromides were examined with the organic reductant derived from **3**. A typical procedure is as follows: A mixture of **3** (0.53 mmol), $[Bu_4N^+][Tf_2N^-]$ (1 mmol), and DMF (4 mL) was reduced electrochemically (30 mA, 2 F/mol-**3**) in an undivided cell fitted with Mg anode (ϕ = 6 mm) and Pt plate cathode (1.0 × 1.5 cm^2) at room temperature to give dark-green solution of DQ^0 (electron pool). To the electron pool solution were added 4-bromobenzonitrile (**4a**, 0.27 mmol) and $PdCl_2$ (0.02 mmol), and the whole mixture was stirred at 60 ºC for 20 h to give 4,4’-dicyanobiphenyl (**5a**, 0.091 mmol, 70%) and **4a** (0.068 mmol, 26%), respectively (Table 1, Entry 1).

Table 1. Reductive Coupling of 4-Bromobenzonitrile (**4a**) by Using Electron Pool DQ^0. Optimization of Reaction Conditions.

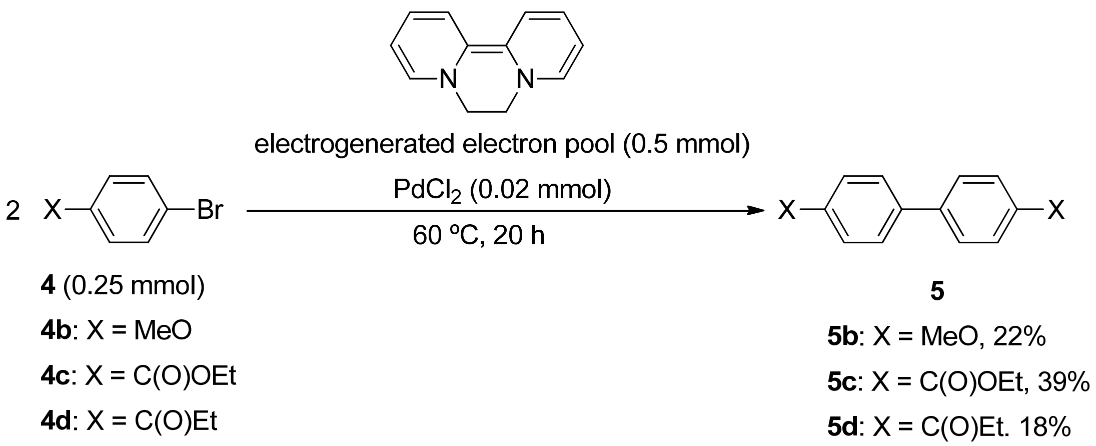


entry	solvent	catalyst	(mmol)	yield/%[a] 5a	yield/%[a] 4a
1	DMF	$PdCl_2$	0.015	70	26
2	DMF	$Pd(OAc)_2$	0.016	68	-[b]
3	DMF	$Pd_2(dba)_3$	0.008	36	63
4	DMA	$PdCl_2$	0.018	46	44
5	DMI	$PdCl_2$	0.028	66	-[b]
6	THF	$PdCl_2$	0.025	-[b]	97
7	MeCN	$PdCl_2$	0.026	-[b]	96

[a] Isolated yield. [b] Not detected by TLC.

The reaction proceeded similarly with $Pd(OAc)_2$ in DMF to give **5a** in 68% yield (Entry 2), whereas **5a** was obtained in 36% yield when $Pd_2(dba)_3$ was used as the catalyst (Entry 3). The $PdCl_2$-catalyzed coupling of **4a** also proceeded in DMA and DMI to give **5a** in 46 and 66% yields, respectively (Entries 4, 5), whereas **5a** was not obtained in THF (Entry 8)[9] and MeCN (Entry 9).

In a similar way, the reductive coupling of 4-bromoanisole (**4b**), methyl 4-bromobenzoate (**4c**), and 4-bromopropiophenone (**4d**) occurred to give the corresponding biaryl **5b**, **5c**, and **5d**, respectively (Scheme 2), whereas 2-acetyl-5-bromothiophene gave 2-acetylthiophene. On the other hand, the homo-coupling of aryl chlorides such as 4-chlorobenzonitrile, 4-chloroanisole, and methyl 4-chlorobenzoate did not occur to recover the starting chlorides.



Scheme 2. Coupling of 4-Bromoanisole (**4b**), Methyl 4-Bromobenzoate (**4c**), and 4-Bromopropiophenone (**4d**)

In conclusion, electroreduction of diquat triflate (**3**, DQ^{2+}) gave the corresponding neutral species DQ^0, which played as a potent organic reductant for $PdCl_2$ -promoted reductive coupling of aryl bromides Ar-Br leading to the corresponding biaryl Ar-Ar. Further optimization of the reaction conditions as well as expansion of the scope and limitations is now undergoing in our laboratory.

EXPERIMENTAL

Preparation of Triflate of Ethylene Glycol 2. To a mixture of CH_2Cl_2 (30 mL), triflic anhydride (5.65 g, 20.0 mmol), and pyridine (1.61 mL, 20 mmol) was added ethylene glycol (0.577 mL, 10.0 mmol) at 0 ºC, and the whole mixture was stirred at 0 ºC for 0.5 h. The resulting solution was filtered and washed with ion-exchanged water (10 mL × 3). The CH_2Cl_2 layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure, and the residue was chromatographed (silica gel, CH_2Cl_2) to afford 1,2-bis[(trifluoromethylsulfonyl)oxy]ethane (3.10 g, 9.51 mmol, 95%) as a colorless liquid. 1,2-Bis[(trifluoromethylsulfonyl)oxy]ethane : colorless liquid; R_f = 0.83 (CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.77 (s); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 118.70 (q, J = 315.45 Hz), 72.57; **IR** (KBr) 2985, 1422, 1250, 1213, 1144, 926 cm^{-1}.

Preparation of Diquat Triflate 3: A mixture of 2,2'-bipyridyl (0.057 g, 0.36 mmol) and **2** (0.120 g, 0.37 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 16 h to give colorless precipitates. The reaction mixture was concentrated under reduced pressure. The residue was suspended in $CHCl_3$. Filtration of the suspension yielded a colorless powder, which was dried *in vacuo* to afford diquat ditriflate **2** (0.139 g, 0.289 mmol, 79%) as colorless solids. Diquat ditriflate **2**: colorless solids; R_f = 0 (toluene/AcOEt = 10/1); **^{1}H NMR** (300 MHz, acetone-d_6) δ 9.50 (d, J = 6.0 Hz, 2H), 9.26 (d, J = 8.4 Hz, 2H), 9.06 (t, J = 8.0 Hz, 2H), 8.57 (t, J = 8.0 Hz, 2H), 5.69 (s, 4H); **^{13}C NMR** (75 MHz, acetone-d_6) δ

147.76, 147.35, 140.35, 130.36, 128.40; **IR** (KBr) 3090, 1503, 1267, 1153, 1030, 640 cm^{-1}.

Cyclic Voltammetry (CV) of 3: CV of **3** were measured on BAS ALS/DY2323 by use of [Et_4N^+][Tf_2N^-] (0.1 M) as a supporting electrolyte in MeCN (10 mL), 25 mM of **3**, (GC)–(Pt)–(Ag/Ag^+), 0 to -2.3 V, scan rate 20 mV/s.

Pd-Catalyzed Electroreductive Homo-coupling of Aryl Bromide Using 3 as a Precursor of Organic Reductant: In an undivided cell was placed a DMF (4.0 mL) solution of **3** (255 mg, 0.529 mmol) containing [Bu_4N^+][Tf_2N^-] (528 mg, 1.01 mmol) as a supporting electrolyte. To this solution were immersed an Mg sacrificial anode (ϕ = 6.0 mm) and a Pt cathode (1.0 × 1.5 cm^2). Under argon atmosphere, the solution was electrolyzed under a constant current (30 mA, 54 min., 2 F/mol-**3**) condition at room temperature with vigorous stirring. The resulting dark green solution of DQ^0–DMF (Electron Pool) was added to a mixture of 4-bromobenzonitrile **4a** (48.2 mg, 0.265 mmol) and a catalytic amount of $PdCl_2$ (3.6 mg, 0.02 mmol), and the whole mixture was stirred at 60 ºC for 20 h under argon atmosphere. The resultant was cooled, diluted with AcOEt, and filtered through a glass filter packed with celite. The filtrate was washed with 5% hydrochloric acid. The aq. HCl layer was extracted with AcOEt (10 mL × 3). The organic layers were combined, dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure, and the residue was chromatographed (silica gel, toluene/AcOEt = 20/1) to afford the desired product **5a** (19.0 mg, 0.0909 mmol, 70%) as colorless solids.

4,4′-Dicyanobiphenyl **5a**:[10] colorless solids; ***R**$_f$* = 0.55 (toluene/AcOEt = 10/1); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.5 Hz, 4H), 7.69 (d, *J* = 8.5 Hz, 4H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.41, 132.84, 127.89, 118.43, 112.42; **IR** (KBr) 3075, 3040, 2226, 1604, 1491, 819 cm^{-1}.

4,4’-Dimethoxybiphenyl **5b**:[10] colorless solids; ***R**$_f$* = 0.86 (hexane/AcOEt = 2/1); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.9 Hz, 4H), 6.96 (d, *J* = 8.9 Hz, 4H), 3.85 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.56, 133.36, 127.64, 114.07, 55.31; **IR** (KBr) 3015, 2957, 2839, 1606, 1500 cm^{-1}.

4,4’-Bis(ethoxycarbonyl)biphenyl **5c**:[11] colorless solids; ***R**$_f$* = 0.47 (hexane/AcOEt = 5/1); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.1 Hz, 4H), 7.69 (d, *J* = 8.1 Hz, 4H), 4.41 (q, *J* = 7.2 Hz, 4H), 1.43 (t, *J* =7.2 Hz, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.3, 144.3, 130.1, 130.0, 127.2, 61.1, 14.3; **IR** (KBr) 2981, 2906, 1716, 1607, 1278 cm^{-1}.

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