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Fe(II)-mediated fragmentation of 1,4-diaryl-2,3-dioxabicyclo[2.2.2]octanes through competitive single electron transfer pathway and Lewis acid pathway

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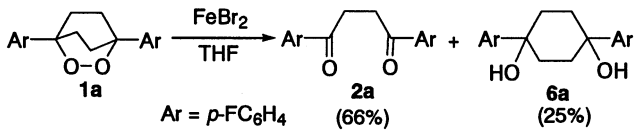
Abstract—Reactions of 1,4-diaryl-2,3-dioxabicyclo[2.2.2]octanes **1a–d** (**1a**: Ar = *p*-FC_6H_4, **1b**: Ar = Ph, **1c**: Ar = *p*-MeC_6H_4, **1d**: Ar = *p*-$MeOC_6H_4$) with $FeBr_2$ in THF afforded 1,4-diarylbutan-1,4-diones **2a–d** and 1,4-diaryl-7-oxabicyclo[2.2.1]heptanes **3a–d**. On the other hand, 4-aryl-3-cyclohexenones **4c–d** and *p*-substituted phenols **5c–d** were obtained in the reactions of **1c–d** with $FeBr_2$ in CH_2Cl_2. A new fragmentation mechanism involving an electrophilic oxyl radical 1,5-substitution and a nucleophilic *O*-1,2-aryl shift is proposed based on the product analysis. In addition, the in vitro antimalarial activities of **1a–d** were tested.

Much attention has been focused on antimalarial cyclic peroxides from both synthetic and mechanistic viewpoints.[1–16] Particularly, mechanistic studies for the fragmentation of cyclic peroxides promoted by Fe(II) ions are important to clarify potent antimalarial intermediates and to develop structurally more simple and easily prepared antimalarial cyclic peroxides.[7–16] In this regard, Posner and co-workers proposed that structurally simple and inexpensive 1,4-diaryl-2,3-dioxabicyclo[2.2.2]octanes **1a–b** are potent antimalarial compounds.[11] They also reported that the reaction of 1,4-di(*p*-fluorophenyl)-substituted cyclic peroxide **1a** with $FeBr_2$ afforded 1,4-di(*p*-fluorophenyl)butan-1,4-dione **2a** and 1,4-di(*p*-fluorophenyl)cyclohexan-1,4-diol **6a** as fragmentation products (Scheme 1).[11] These studies strongly prompted us to investigate the reactivities and the antimalarial activities of other 1,4-diarylated derivatives **1b–1d**, such as Ph, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, since we have been interested in the effects of aromatic substituents on the reactivities of an oxyl radical species generated from arylated cyclic peroxides.[17,18] We wish to report our preliminary but novel results for the Fe(II)-mediated fragmentation of **1a–d** and their antimalarial activities, which are quite different from those reported by Posner.[11,19–21]



Scheme 1.

When cyclic peroxide **1a** (0.2 mmol) was treated with 1 equiv. of $FeBr_2$ in dry THF (10 ml) under nitrogen (4 h), 1,4-diketone **2a** (43%) and 1,4-di(*p*-fluorophenyl)-7-oxabicyclo[2.2.1]heptane **3a** (15%) were obtained (Scheme 2, run 1 in Table 1).[†] Likewise, the reactions of

Keywords: 1,4-diaryl-2,3-dioxabicyclo[2.2.2]octanes; cyclic peroxides; $FeBr_2$; fragmentation; reaction mechanism; antimalarial activity; 1,2-aryl shift.

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[†] A typical experimental procedure is as follows: to a solution of **1** (0.2 mmol) in dry THF or dry CH_2Cl_2 (10 ml) was added $FeBr_2$ (0.2 mmol). The mixture was stirred at 23–25°C under nitrogen atmosphere for 4 h. The mixture was passed through a silica gel short column and eluted with CH_2Cl_2 to remove inorganic iron compounds. The eluent was concentrated and the residue was separated by TLC (*n*-hexane–CH_2Cl_2) to afford products. All products were characterized by their spectral data.

Selected data for **3d**: mp 155–157°C; IR (KBr, cm^{-1}) 3040, 2900, 2860, 1612, 1580, 1517; ^1H NMR (200 MHz, $CDCl_3$): δ 1.94–2.08 (m, 4H), 2.10–2.24 (m, 4H), 3.81 (s, 6H), 6.85–6.94 (m, 4H), 7.38–7.48 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 38.67 (t, 4C), 55.26 (q, 2C), 87.00 (s, 2C), 113.54 (d, 4C), 126.49 (d, 4C), 135.06 (s, 2C), 158.57 (s, 2C); MS (EI) 310 (M^+, 99%).

Compound **4d**: mp 68.5–69.5°C; IR (KBr, cm^{-1}) 3030, 2960, 2930, 2850, 1713 (C=O), 1607, 1570, 1505; ^1H NMR (200 MHz, $CDCl_3$): δ 2.63 (t, 2H, J = 6.7 Hz), 2.80–2.93 (m, 2H), 3.00–3.08 (m, 2H), 3.81 (s, 3H), 5.99 (m, 1H), 6.82–6.95 (m, 2H), 7.28–7.38 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.85 (t, 1C), 38.65 (t, 1C), 39.83 (t, 1C), 55.24 (q, 1C), 113.70 (d, 2C), 119.12 (d, 1C), 126.22 (d, 2C), 133.13 (s, 1C), 136.92 (s, 1C), 158.89 (s, 1C), 210.43 (s, 1C); MS (EI) 202 (M^+, 100%); UV λ_{max} (CH_3CN) 268.5 (ε 20300) nm.

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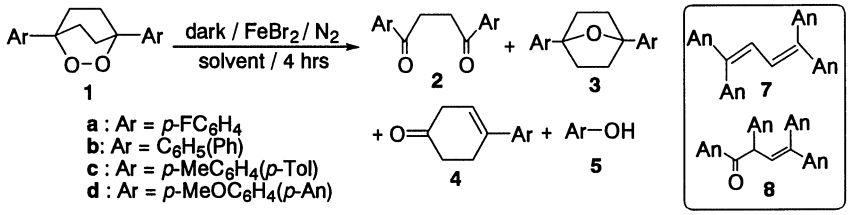


Scheme 2.

Table 1. Reactions of 1,4-diaryl-2,3-dioxabicyclo[2.2.2]octanes **1** with $FeBr_2$[a]

Run	Substrate	Solvent	Additive	Yields (%)[b]				
				2	**3**	**4**	**5**	**8**
1	**1a**	THF	None	43	15	0	0	–
2	**1b**	THF	None	55	19	0	0	–
3	**1c**	THF	None	58	23	0	0	–
4	**1d**	THF	None	56	18	0	0	–
5	**1a**	CH_2Cl_2	None	47	20	0	0	–
6	**1b**	CH_2Cl_2	None	48	37	0	0	–
7	**1c**	CH_2Cl_2	None	38	21	21	9	–
8	**1d**	CH_2Cl_2	None	0	0	74	83	–
9[c]	**1d**	CH_2Cl_2	None	0	0	83	74	–
10	**1b**	CH_2Cl_2	TABD[d]	46	36	0	0	7
11	**1d**	CH_2Cl_2	TMB[d]	0	0	57	94	–
12	**1d**	CH_2Cl_2	CHD[d]	0	0	95	97	–
13	**1d**	CH_2Cl_2	H_2O[e]	0	0	83	84	–
14	**1d**	CH_2Cl_2	TABD[d]	0	0	75	97	<1

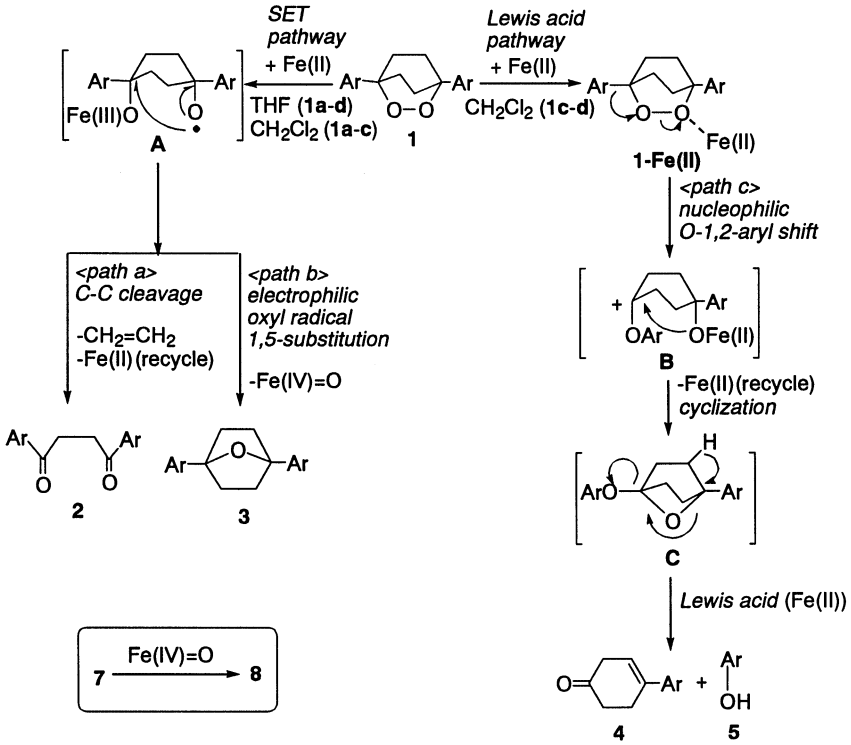
[a] **1** = 0.2 mmol, $FeBr_2$ = 0.2 mmol, solvent = 10 ml.
[b] Isolated yield by silica gel TLC.
[c] $FeBr_2$ = 0.1 mmol.
[d] Additive = 0.2 mmol.
[e] H_2O = 0.6 mmol.

1b–d with $FeBr_2$ exclusively produced **2b–d** and **3b–d** (runs 2–4). Similar product distributions were observed when **1a–b** were treated with $FeBr_2$ in dry CH_2Cl_2 (runs 5 and 6). Interestingly, when 1,4-di(*p*-methylphenyl)-substituted peroxide **1c** was treated with $FeBr_2$ in dry CH_2Cl_2, 4-(*p*-methylphenyl)cyclohex-3-en-1-one **4c** (21%) and *p*-methylphenol **5c** (9%) were newly obtained along with **2c** (38%) and **3c** (21%) (run 7). Unexpectedly, cyclohexenone **4d** (74%) and *p*-methoxyphenol **5d** (83%) were exclusively produced in the reaction of 1,4-di(*p*-methoxyphenyl)-substituted peroxide **1d** with $FeBr_2$ (run 8).

Detailed mechanistic studies further provided the following results: (i) a catalytic amount of $FeBr_2$ (0.5 equiv.) promoted the reaction of **1d** (run 9); (ii) addition of 1,2,4,5-tetramethoxybenzene (**TMB**, $E_{1/2}^{OX}$ = 0.74 V versus SCE) as an effective quencher for single electron transfer (SET) reactions[22] did not significantly affect the product distribution and the yields (run 11); (iii) addition of 1,3-cyclohexadiene (**CHD**, hydrogen donor) did not afford the expected diol **6d** at all (run 12); (iv) addition of water (nucleophile) did not produce **6d** either (run 13); (v) addition of 1,1,4,4-tetra(*p*-methoxyphenyl)-1,3-butadiene **7** (**TABD**, $E_{1/2}^{OX}$ = 0.86 V versus SCE) to capture the oxygen atom of the Fe(IV)=O species, which is proposed as a potent antimalarial intermediate,[19–21,23] afforded only a small amount of 1,2,4,4-tetra(*p*-methoxyphenyl)-3-butenone **8** (runs 10 and 14).[‡]

On the basis of the above results, we propose a plausible mechanism as shown in Scheme 3. Both in THF and CH_2Cl_2, the mono-oxyl radical intermediate **A** is generated by single electron transfer (SET) from Fe(II) to **1**.[11,24] As for the product formation from the intermediate **A**, two different pathways are possible. One is the formation of 1,4-diketone **2** accompanied with elimination of ethylene and Fe(II) through C–C bond cleavage (path a). The other is the formation of deoxygenated product **3** through an electrophilic oxyl radical 1,5-substitution accompanied with elimination of the Fe(IV)=O species (path b). In CH_2Cl_2, Fe(II) also operates as a Lewis acid that generates the complex of **1** with Fe(II) (**1-Fe(II)**). **1-Fe(II)** undergoes a nucleophilic (Baeyer–Villiger type) *O*-1,2-aryl shift to afford the intermediate **B** (path c), which is promoted by electron-donating substituents (*p*-An>*p*-Tol>Ph = *p*-FC_6H_4: runs 5–9). The intermediate **B** undergoes

[‡] Compound **8** was independently prepared by the reaction of **7** (**TABD**) with *m*-chloroperbenzoic acid.



Scheme 3.

cyclization to produce the intermediate **C** followed by Lewis acid (Fe(II))-catalyzed fragmentation to afford **4** and **5**. Thus, **2** and **3** are produced through the SET pathway while **4** and **5** are produced through the Lewis acid pathway. THF is considered to act as a Lewis base to interfere with the Lewis acid pathway. Paths a–c were probably rapid steps because the influences of **TMB**, **CHD**, water, or **TABD** on the product ratio were small.

The in vitro antimalarial activities of **1** against *P. falciparum* were evaluated to clarify the relationship between the antimalarial activities and the effects of the aromatic substituents of **1**.[14] Compounds **1a–d** showed moderate antimalarial activities, and the EC_{50} values were 5.6×10^{-7}, 1.0×10^{-6}, 5.0×10^{-7}, 1.2×10^{-6} M, respectively, for **1a–d** (Table 2). Similar antimalarial activities of **1a–d** indicate that there is no pronounced relationship between the antimalarial activities and the effects of the aromatic substituents of **1a–d**.

In conclusion, we have found that competitive SET pathway and a Lewis acid pathway are responsible for the Fe(II)-promoted O–O bond cleavage of cyclic peroxides, and that there is no pronounced relationship between the antimalarial activities and the effects of the aromatic substituents of **1a–d**. We are conducting further studies on the Fe(II)-mediated fragmentation of other cyclic peroxides to clarify the mechanism and the relationship between the reaction intermediates and the antimalarial activities.

Table 2. Antimalarial activities of **1** against *P. falciparum* (FCR-3 strain) and cytotoxicities against FM3A cell[a]

Substrate	EC_{50} (M)		Selectivity[b]
	P. falciparum	FM3A cell	
1a	5.6×10^{-7} (6.3×10^{-8})[c]	1.8×10^{-5} (61%)[d]	>32
1b	1.0×10^{-6} (2.1×10^{-7})[c]	3.2×10^{-5} (60%)[d]	>32
1c	5.0×10^{-7}	1.7×10^{-6}	3.4
1d	1.2×10^{-6}	1.8×10^{-5} (88%)[d]	>15
Artemisinin	7.8×10^{-9}	1.0×10^{-5}	1280
Chloroquine	1.8×10^{-8}	3.2×10^{-5}	1780

[a] Ref. 14.
[b] Selectivity = cytotoxicity/antimalarial activity.
[c] IC_{50} values against *P. falciparum* (NF54 strain), Ref. 11.
[d] Growth percent at the concentration indicated.

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