HETEROCYCLES, Vol. 75, No. 8, 2008, pp. 1997 - 2003. © The Japan Institute of Heterocyclic Chemistry
Received, 8th January, 2008, Accepted, 4th April, 2008, Published online, 8th April, 2008. COM-08-11331

EFFECTS OF AROMATIC SUBSTITUENTS OF ELECTROCHEMICALLY GENERATED HYPERVALENT IODINE OXIDANT ON OXIDATION REACTIONS

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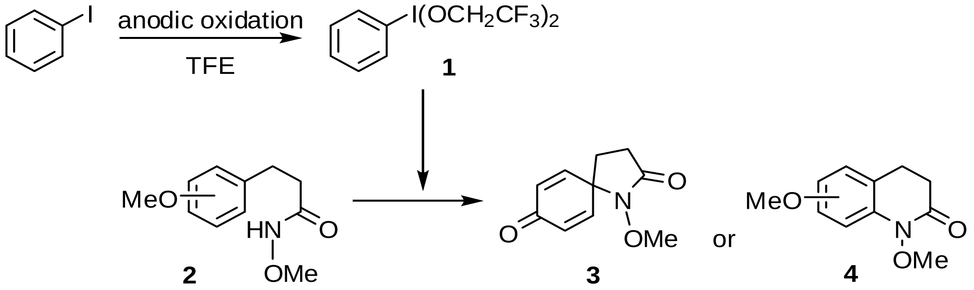
Abstract – Phenolic oxidation of 4-hydroxyphenylpropionic acid (**5**) with electrochemically generated hypervalent iodine oxidant, was performed using a variety of iodobenzene derivatives. Iodobenzene derivatives carrying electron-deficient aromatic moieties showed oxidant activity comparable to that of bis(2,2,2-trifluoroethoxy)phenyliodine(III) **1**, and better than those carrying electron-donating groups with the exception of a methyl group. In our electrochemical procedure, the oxidant from 1-iodo-4-nitrobenzene was obtained as a stable solid, while other oxidants that did not precipitate from the reaction mixture, were used *in situ*. Conversion of the methoxyamide 7 into the corresponding azaspiro derivative **3** was also performed by the oxidants carrying aromkatic substitutions.

INTRODUCTION

Hypervalent iodine oxidants, such as Dess-Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one), IBX (2-iodoxybenzoic acid), and PIFA (phenyliodine(III)bis(trifluoroacetate)), are considered as powerful tools in organic synthesis.[1] In contrast to their potent availability, the oxidants are generally expensive, and require such oxidants as H_2O_2 and percarboxylic acids for preparation. In addition, careful handling is required due to the potential explosive properties of iodo(V)benzene derivatives. During elaboration of effective construction of azaspiro and/or quinolinone-type compounds (e.g. **3** and **4**), which are synthetic intermediates of biologically active natural products (Scheme 1), we observed advantages of electrochemically generated hypervalent iodine species: (1) bis(2,2,2-trifluoroethoxy)phenyliodine(III) **1**[2] used *in situ* without purification may be a safe and environmentally benign oxidant.[3,4,5] (2) **1** provided more effective cyclization (2 eq. mol of the oxidant was used for the oxidation) of **2** leading to **3** and/or **4** than the case of direct anodic oxidation of the substrate, and yields were comparable to those of PIFA. With the expectation of advantageous properties with regard to reaction outcome, we examined the effects of aromatic substitutients of hypervalent iodine species on oxidation reaction. We describe herein the investigation process.



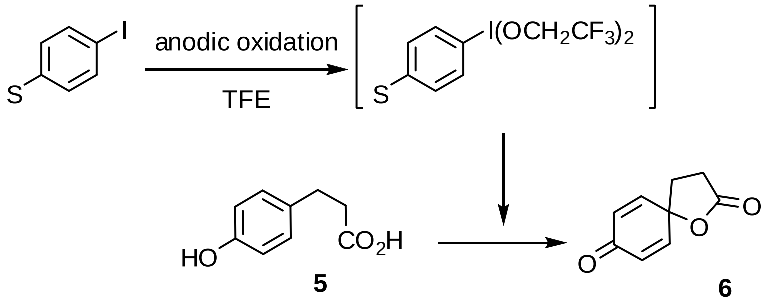
Scheme 1. The hypervalent iodine oxidant **1** and its use for oxidation of the methoxyamide derivatives **2**.

RESULTS AND DISCUSSION

Iodobenzene derivatives carrying aromatic functional groups, were subjected to anodic oxidation, and their oxidative properties were assessed by the yields of phenolic oxidation of commercially available 4-hydroxyphenylpropionic acid (**5**), yielding **6** (Table 1).[6,7,8] The *para* substitution of halogen atoms provided **6** in comparable yields (entries 2-5) to that of **1** (entry 1), with the exception of 1,4-diiodobenzene (entry 5), which provided no desired oxidation, probably due to low solubility in 2,2,2-trifluoroethanol (TFE), which interfered with the desired electron abstraction from an iodine atom.

In addition, the electron-deficient iodobenzene derivatives by electron-withdrawing substituents at the *para* position were examined: the oxidants (entries 6-10) provided the desired **6** in 79 - 89% yields, which were comparable to PIFA, and exhibited better yields than direct anodic oxidation (see Table 1). In entries 6 and 7, electricity of 3.0 F/mol was required to provide **6** in 89 and 87% yields, owing to current efficiency in oxidation reactions of the iodobenzene derivatives. When using 2.5 F/mol, entries 6 and 7 gave **6** in slightly low yields. Especially, in anodic oxidation of the 4-nitro derivative (entry 8), the desired hypervalent iodine was precipitated from the reaction mixture, and addition of **5** to the suspension provided **6** in 79% yield. On the other hand, filtration of the precipitates gave the solid oxidant in 36% yield. Although low solubility in any solvent disturbed NMR measurements, its EI mass spectrum showed a similar fragment ion $[M - CF_3CH_2O]^+$ to those of **1** produced from iodobenzene and PIFA $[M - CF_3CO_2]^+$.[3] Despite suspension in TFE, this oxidant effected oxidation of **5** to **3** in 71% yield, and the oxidant gave a similar yield even after storage at ambient temperature for several days. 4-Iodotoluene (entry 11) provided **6** in 91% yield similar to a previous study, in which this substrate was effectively utilized as a catalytic oxidant of phenolic oxidation in the presence of m-CPBA.[7] When electricity was increased up to 2.5 F/mol, the yield of **6** was reduced to 74% yield. These observation indicated that oxidation of 4-iodotoluene under our conditions proceeded preferentially at the iodine part rather than the aryl methyl group. In the case of the oxygen functional groups (entries 12 and 13), undesired side reactions evoked by non-phenolic oxidation could not be excluded for high oxidation potential of the iodo function. These results indicated that the *para* substituents did not seriously affect the reactivity of the oxidant molecules, except in the process of preparation.

Table 1. Preparation of the hypervalent iodine species carrying the 4-substituents in the aromatic rings and their use for the phenolic oxidation, compared with the cases of PIFA and anodic oxidation.

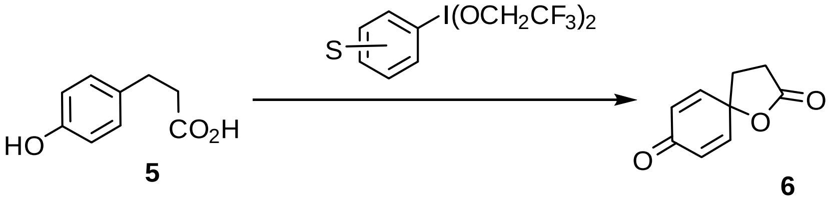


Entries	Substituents (S)	Potential *vs* SCE (V)^a	Electricity (F/mol)	Yields of **6** (%)^b
1	H	1.8 – 1.9	2.5	97
2	F	1.8	2.5	91
3	Cl	1.7 – 1.9	2.5	84
4	Br	1.3 – 1.6	2.5	84
5	I	1.8 – 3.0	-	0
6	COOMe	1.9 – 2.1	3.0	89^c
7	Ac	1.8	3.0	87^c
8	NO_2	2.1	2.5	79
9	CN	1.9 – 2.1	2.5	81
10	CF_3	1.9 – 2.1	2.5	82
11	Me	1.5 – 1.6	2.0	91^c
12	OMe	1.4 – 1.5	2.5	0
13	OAc	1.6 – 1.7	2.5	0
PIFA		-		84
Anodic oxidation		1.2 – 3.0		29

[a] Potential *vs* SCE was indicated in constant current electrolysis (CCE, at 0.3 mA/cm^2). [b] 2 Eq. mol amounts of the iodobenzene derivative were used for oxidation of **5**. [c] Yields were improved using the indicated electricity. When electricity of 2.5 F/mol was used, entries 6, 7, and 11 provided **6** in 84, 84, and 74% yields, respectively.

The effects of substitution positions in the aromatic rings were also evaluated (Table 2). In the case of the methyl group, all of the regioisomers provided **6** relatively in good yields. However, remarkable differences were observed between the 2-, 4-nitro derivatives and the 3-nitro derivative (entry 2); the latter provided **6** in 14% yield, while **6** was obtained from the former in 65 and 79% yields. Further studies to determine the reasons for these observations are currently in progress.

Table 2. Influence of the aromatic substitutions in the oxidant to the phenolic oxidation.



Entries	Substituents (S)	Substituted position / yields (%)[a]		
		2-	3-	4-
1	Me	89	81	91[b]
2	NO_2	65	14	79[b]

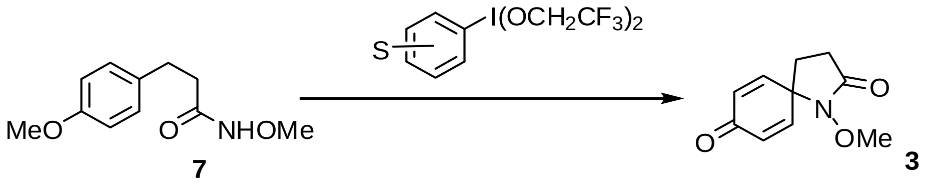
[a] The same reaction conditions and molar ratio of iodobenzene and **5** as those of Table 1.

[b] The same results as those in Table 1

In addition, the oxidants mentioned above, effected oxidation of the methoxyamide **7** to give the corresponding azaspiro derivative **3**.[3] In all entries (Table 3), the desired oxidation proceeded to provide **3** in moderate to good yields.

In conclusion, the effects of aromatic substituents on the oxidative properties of electrochemically generated hypervalent iodine oxidants, were investigated. The oxidants possessing halogen, methyl, and electron-withdrawing groups in the aromatic moieties generally provided phenolic oxidation of **5** in good yields, along with cyclization of the methoxyamide derivative **7**, with the exception of the 3-nitro derivative. 1-Iodo-4-nitrobenzene provided relatively stable hypervalent iodine species as an amorphous powder, although the other oxidants produced no precipitates, and should be utilized *in situ*. In particular, iodobenzene derivatives carrying *para* substituents, except oxygen functions, showed no remarkable differences in oxidative reactivity. These findings will be utilized for modification of the hypervalent iodine oxidants to add safer and easier handling properties involving the fluorous tag method,[9] which may enable separation of reaction products from the reaction mixture.

Table 3. Oxidation of **7** with the hypervalent iodine species carrying the 4-substituents in the aromatic rings, yielding the azaspiro compound **3**.



Entries	Substituents (S)	Potential *vs* SCE (V)[a]	Electricity (F/mol)	Yields of **3** (%)[b]
1	H	1.8 – 1.9	2.5	100
2	F	1.6 – 1.8	2.5	84
3	Cl	1.7 – 1.9	2.5	75
4	Br	1.3 – 1.6	2.5	70
5	CO_2Me	1.9 – 2.1	3.0	87
6	Ac	1.8 – 2.0	3.0	89
7	NO_2	2.0 – 2.2	2.5	53
8	CN	1.9 – 2.1	2.5	81
9	CF_3	1.9 – 2.1	2.5	80
10	Me	1.5 – 1.6	2.0	84

[a] Potential *vs* SCE was indicated the same constant current electrolysis as in the case of Table 1. [b] 2 Eq. mol amounts of the iodobenzene derivative were used for oxidation of **7**.

EXPERIMENTAL

General. IR spectra were recorded on a JASCO Model A-202 spectrophotometer. ^{1}H-NMR spectra were obtained on JNM-GX400 spectrometers in deuteriochloroform solvent using tetramethylsilane as an internal standard, otherwise stated. HRMS spectra were obtained on Hitachi M-80 B GC-Mass spectrometer. Preparative and analytical TLC were carried out on silica gel plate (Kieselgel 60 F254, E. Merck AG., Germany) using UV light and/or 5% molybdophosphoric acid in ethanol for detection.

*Oxidation of 4-hydroxyphenylpropionic acid (**5**) or N-methoxy-3-(4-methoxyphenyl)propanamide (**7**) with a electrometrically generated hypervalent iodine oxidant.*

A solution of an iodobenzene derivative (0.5 mmol, 2 eq. mol of **5** or **7**) in TFE (25 mL) containing $LiClO_4$ (133 mg, 1.3 mmol) was electrolyzed (CCE at 0.3 mA/cm^2, a glassy carbon beaker as an anode, a platinum wire as a cathode). After electrolysis indicated in Tables 1 and 3, **5** or **7** (0.25 mmol) was added to the mixture. After being stirred at ambient temperature for 30 min, the reaction mixture was

diluted with H_2O and extracted with EtOAc. The organic layer was dried ($MgSO_4$) and evaporated. The residue was chromatographed on preparative TLC ($CHCl_3$/EtOAc = 3:1) to give 1-methoxy-1-azaspiro[4.5]deca-6,9-diene-2,8-dione (**3**)[3] or 1-oxaspiro[4.5]deca-6,9-diene-2,8-dione (**6**).[7,8]
6:[7,8] δ_H 6.85 (2H, d, *J* = 10.0 Hz), 6.29 (2H, d, *J* = 10.0 Hz), 2.79 (2H, t, *J* = 8.4 Hz), 2.38 (2H, t, *J* = 8.4 Hz). HRMS: *m/z* 165.0529, calcd for $C_9H_9O_3$ (M+H) 165.0550.

*Oxidation of **5** with PIFA.*

To a solution of **5** (417 mg, 2.5 mmol) in TFE (25 mL) was added PIFA (2.17 g, 5.0 mmol) at –10 ºC. After being stirred at the same temperature for 30 min, a solution of saturated $NaHCO_3$ aq. was added. The mixture was diluted with H_2O and extracted with EtOAc. The organic layer was dried ($MgSO_4$) and evaporated. The residue was chromatographed on preparative TLC ($CHCl_3$/EtOAc = 3:1) to give **6** (345 mg, 84%).

*Anodic oxidation of **5***

A solution of **5** (82.7 mg, 0.50 mmol) in TFE (25 ml) containing $LiClO_4$ (133 mg, 1.23 mmol) was electrolyzed (CCE at 0.3 mA/cm^2, 3 F/mol, a glassy carbon beaker as an anode, a platinum wire as a cathode). After electrolysis, the reaction mixture was diluted with H_2O and extracted with EtOAc. The organic layer was dried ($MgSO_4$) and evaporated. The residue was chromatographed on preparative TLC ($CHCl_3$/EtOAc = 3:1) to give **6** (23.5 mg, 29%).

*Preparation of the oxidant from 1-iodo-4-nitrobenzene and oxidation of **5**.*

A solution of 1-iodo-4-nitrobenzene (749 mg, 3.0 mmol) in TFE (150 mL) containing $LiClO_4$ (798 mg, 7.5 mmol) was electrolyzed (CCE at 0.3 mA/cm^2, a glassy carbon beaker as an anode, a platinum wire as a cathode). After electrolysis (2.5 F/mol), H_2O (50 mL) was added to the mixture to give precipitation, which was collected by filtration, and a solid was rinsed with H_2O, then dried to give a pale yellow product (484 mg, 36%, calculated as a hypervalent iodine species).

To a solution of **5** (10 mg, 0.06 mmol) in TFE (2 mL) was added the oxidant (60 mg, 0.13 mmol, 2 eq. mol of **5**) at –10 ºC. After being stirred at the same temperature for 30 min, the reaction mixture was diluted with H_2O and extracted with EtOAc. The organic layer was dried ($MgSO_4$) and evaporated. The residue was chromatographed on preparative TLC ($CHCl_3$/EtOAc = 3:1) to give **6** (7 mg, 71%)

ACKNOWLEDGEMENTS

This work was supported by High-Tech Research Center Project for Private Universities: matching fund subsidy from MEXT, 2006-2011.

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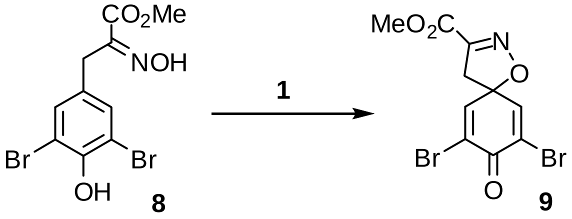

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