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Oxidative synthesis of azacyclic derivatives through the nitrenium ion: application of a hypervalent iodine species electrochemically generated from iodobenzene

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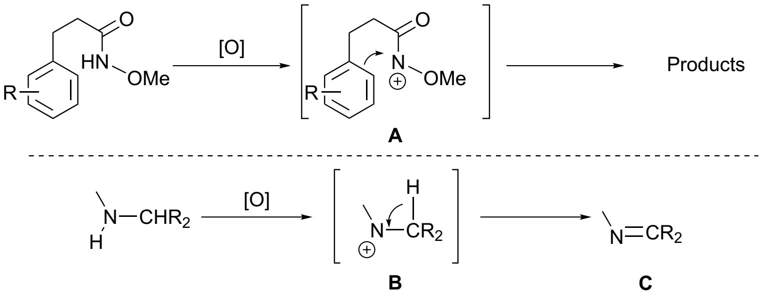
Abstract—Oxidation of the methoxyamide derivatives **1**, **4**, and **7** has been examined to elaborate efficient synthetic methodology of the azacyclic derivatives **2**, **3**, **5**, **6**, and **8**, which would be applicable as synthetic intermediates of complicated bioactive substances. In addition to direct anodic and PIFA [phenyliodine(III) bis(trifluoroacetate)] oxidations, an active species derived from iodobenzene generated under electrolytic conditions was examined as an oxidant, and its synthetic efficacy was demonstrated in comparison of the reaction outcomes with other oxidation methods. In the oxidation, the methoxy substitution of substrates modulated the cyclization mode to provide the azaspiro- (**2**, **8**) or quinolinone-type (**3**, **5**, **6**) products.

3-Aminopropylbenzene units are synthetic precursors of quinoline or 1-azaspiro[4.5]decane frameworks, which constitute families of natural products carrying diverse biological activities. Among several synthetic investigations, Kikugawa et al.[1] and Wardrop et al.[2] reported their synthesis through the nitrenium ion intermediates **A** generated mainly by oxidants such as PIFA. The nitrenium ion produced is localized and stabilized by the methoxyamide structures: upon existence of hydrogens at the neighboring positions, the nitrenium ion is converted into the corresponding imine (**B** → **C**)[3] (Scheme 1). Although the results of a number of investigations have been accumulated by using chemical oxidants,[1,2] we elaborated an electrochemical approach to this oxidation from the viewpoints of environmental benignity. Electrochemical oxidations, instead of toxic oxidants, might provide new synthetic methodology and/or generation of new active species, which would be troublesome by usual chemical reactions. With such prospect in mind, anodic oxidation of the methoxyamides was initiated. We describe herein our research process.



Scheme 1. Reaction of the nitrenium ions.

Keywords: Quinolinone; Azaspiro[4.5]decane; Hypervalent iodine; Anodic oxidation.

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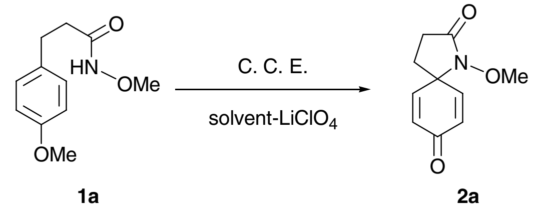
Table 1. Direct anodic oxidation of methoxyamide **1a**

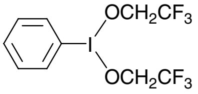


Entry	Solvent	Product (%)
1	MeOH	12
2	TFE	67
3	$MeNO_2$	32
4	MeCN	16

Anode: glassy carbon beaker, cathode: platinum wire, CCE, 2.5 F/mol.

When compound **1a** synthesized by the reported procedure[1] was submitted to anodic oxidation under the usual constant current electrolysis (CCE) conditions, the expected azaspiro derivative **2a** was produced in low to moderate yields (Table 1). Among the entries carried out, the solvent of choice was 2,2,2-trifluoroethanol (TFE) possessing a wide potential window and low nucleophilicity, which produced **2a** in 67% yield, and no notable by-products were monitored, other than polymer-like spots with high polarity on TLC.

Unfortunately, upon comparison with chemical oxidation, the reaction outcome using methoxyamide derivatives **1** showed lower yields than those by using PIFA (Table 2). To circumvent such inferiority in yields, we focused on mediator-approaches using an active species generated electrochemically, by which safety in operation and a new reaction aspect would be expected. Indeed, upon the addition of the substrates to a mixture of preoxidized iodobenzene in TFE under the CCE conditions,[4] the products were acquired in equal (entries 1 and 4) or higher yields than those by the direct oxidation and PIFA (Table 2). Although direct electrolysis of catalytic amounts of iodobenzene in the presence of the substrates might be preferable, the higher oxidation potential of iodobenzene (ca. 1.9 V vs SCE) than those of the substrates (ca. 1.3 V vs SCE) would cause undesired side reactions. At this stage, the oxidant generated was unidentified; however, the hypervalent structure [**D**] was conceivable, based on the report of similar iodobenzene derivatives generated under electrolytic conditions[5] (Fig. 1). In addition, the mixture was submitted to EI mass spectroscopy, which revealed a fragment ion at *m*/*z* 303 ($PhIOCH_2CF_3^+$). A similar ion, *m*/*z* 317 ($PhIO_2CCF_3^+$), was also observed in the EI mass of PIFA.



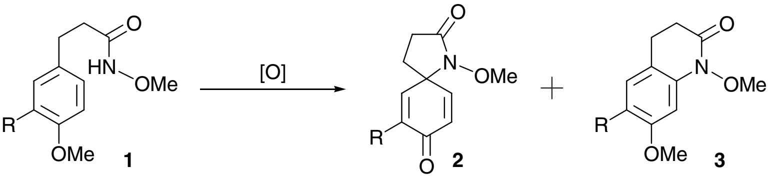
D

Figure 1. A plausible structure of the oxidant **D**.

Subsequently, oxidation of **1b–d** carrying substituents adjacent to the MeO group was examined to expand synthetic availability of the reaction products (Table 2). As a result, the oxidation of the halogenated derivatives, **1b** and **1c**, provided the desired spiro-products, **2b** and **2c**, which were obtained in better yields by the oxidant from iodobenzene than other cases (entries 2 and 3). When using the MeO group instead of a halogen atom, oxidation of **1d** produced the hydroquinolinone **3d** in 34% yield, along with the corresponding azaspiro derivative **2d** in 35% yield (entry 4 from iodobenzene). The highly electron-donating effect of the MeO group might designate the reaction point with the nitrenium ion generated, although insufficient electron-donating effect of the halogen substituent did not effectively capture the nitrenium ion at the *para*- or *ortho*-position: the spiro compounds, **2b** and **2c**, were produced by the main regulation of the MeO group (entries 2 and 3).

This property was additionally confirmed by oxidation of **4** carrying the *meta*-substitution (Table 3): ca. 7:1 mixture of **5** and **6** was produced by PIFA or the oxidant from iodobenzene (entry 1), while the direct anodic oxidation gave a complex mixture. The preferential production of **5** indicated high electron density at the *para*-position of the MeO group. A similar regulation of the regioselectivity by aromatic substituents was also reported in the oxidative cyclization of *N*,*N*′-

Table 2. Anodic oxidation of the substituted methoxyamides **1a–d**



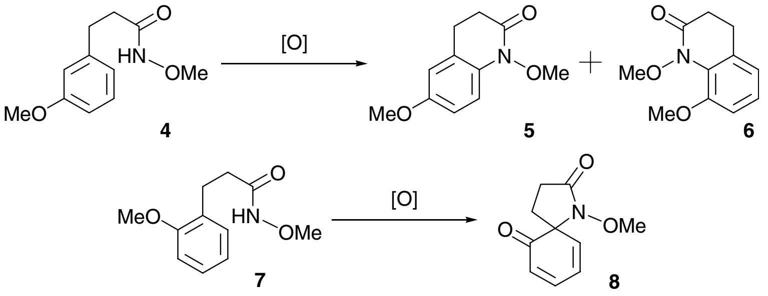
Entry	Substrate	Direct anodic oxidation[a] (%)	PIFA[b] (%)	Preoxidized iodobenzene[c] (%)
1	**1a** (R = H)	67 (**2a**)	Quant. (**2a**)	Quant. (**2a**)
2	**1b** (R = Br)	59 (**2b**)	75 (**2b**)	89 (**2b**)
3	**1c** (R = Cl)	45 (**2c**)	67 (**2c**)	94 (**2c**)
4	**1d** (R = OMe)	Multi spots	35 (**2d**), 21 (**3d**)	35 (**2d**), 34 (**3d**)

[a] Anode: glassy carbon beaker, cathode: platinum wire, CCE, 2.5 F/mol.

[b] 1.5–2 equiv mol of the oxidant was used. Entries 2 and 3 were reacted in CH_2Cl_2 to get better yields, whereas other entries were performed in TFE.

[c] See Ref. 4.

Table 3. Effects of the substitution site of the MeO group



Entry	Substrate	Direct anodic oxidation[a] (%)	PIFA[b] (%)	Preoxidized iodobenzene[c] (%)
1	**4**	Multi spots	73 (**5**), 9 (**6**)	66 (**5**), 10 (**6**)
2	**7**	44 (**8**)	52 (**8**)	82 (**8**)

[a] Anode: glassy carbon beaker, cathode: platinum wire, CCE, 2.5 F/mol.

[b] 1.5–2 equiv mol of the oxidant in TFE was used.

[c] See Ref. 4.

diacylhydrazine derivatives with PIFA.[6] As the nitrenium ion could not attack the *para*-position of the MeO group, owing to high strain, **7** exclusively provided the azaspiro compound **8** by the electrophilic attack to the *ortho*-position.

In conclusion, the nitrenium ion underwent electrophilic attack to the aromatic ring to produce the corresponding 1-azaspiro[4.5]decane (**2**, **8**) and quinolinone (**3**, **5**, **6**) derivatives. The cyclization position was modulated mainly by electron donation from the corresponding MeO substituents. While the direct electrolysis provided the corresponding oxidation products in low to moderate yields, a mixture of electrochemically preoxidized iodobenzene was a similar or superior oxidant to PIFA. This methodology is inexpensive and safer than the usual hypervalent iodine reagents prepared by such oxidants as peroxides: required amounts of the hypervalent iodine oxidant can be obtained by anodic oxidation, and used in situ to reactions without handling active oxidants. Although a catalytic cycle was at present disturbed by its high oxidation potential, detailed inspection and improvement of this oxidant are in progress.[7]

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