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One-pot syntheses of 2,6-diiododiaryl ethers from *para*-EWG-substituted phenols by diacetoxyiodobenzene

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Abstract 2,6-Diiododiaryl ethers are not only useful blocks to construct substituted diaryl ethers but are also characteristic drug precursors. In this research, a one-pot tandem oxidation of phenols substituted with electron-withdrawing group at the *para* position by excess diacetoxyiodobenzene is proven as a novel and efficient method for preparing 2,6-diiododiaryl ethers. Using this method, three new 2,6-diiododiaryl ethers, namely, methyl 3,5-diiodo-2-methoxy-4-phenoxybenzoate (**2**), methyl 3,5-diiodo-4-phenoxybenzoate (**6**), and 1-(2,6-diiodo-4-nitrophenoxy)benzene (**7**) were readily obtained from the corresponding phenols, and the yields were good.

Keywords Diacetoxyiodobenzene · Drug precursors · Electron-withdrawing group (EWG) · 2,6-Diiododiaryl ethers · Tandem oxidation

Introduction

Diaryl ethers are common structures in many natural products and are biologically active compounds, with some of these compounds being recognized as potential drugs [1–4]. In particular, 2,6-diiododiaryl ethers have received considerable attention as promising skeletons for anticancer drug molecules (Fig. 1) [5, 6]. Furthermore, construction of diaryl ether structures is a very important step in the

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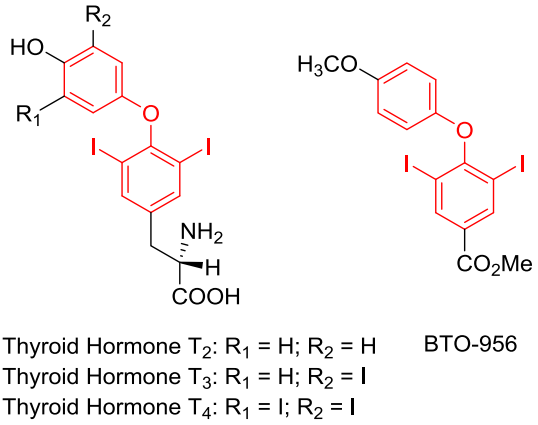


Fig. 1 Sampling of potential drugs containing the 2,6-diiododiaryl ether core

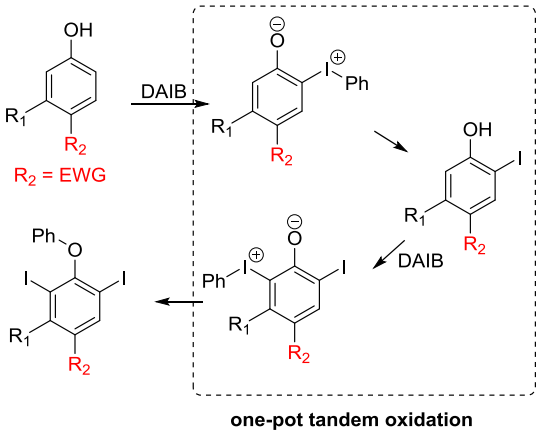
syntheses of natural products, vancomycin, and other glycopeptide antibiotics [7–11]. In spite of more than a century of attempting to determine efficient synthetic routes to these compounds, production of substituted diaryl ethers for applications in the pharmaceutical industry and life sciences still remains difficult [12, 13].

The classical metal catalytic cross-couplings of phenols and aryl halides have become very useful and popular in recent years. However, all of them need expensive reagents and harsh reaction conditions [14–17]. Although arylation of phenols to construct substituted diaryl ethers using diaryl iodonium salts has been reported recently, only one substrate substituted with electron withdrawing groups (EWGs) at the *para* position was investigated [18].

The use of hypervalent iodine reagents has recently gained considerable attention in organic syntheses [19–21]. Diacetoxyiodobenzene (DAIB) has been used for synthesizing *ortho*-iodo-diaryl ethers in the presence of EWGs at the *para* position from corresponding phenols [22–24]. Furthermore, iodobenzenes play an important role in organic chemistry because of their broad application; iodobenzenes can be transformed into different aromatic compounds via Suzuki, Negishi and Heck reactions [25–27]. Although construction of 2,6-diiododiaryl ethers from diamine diaryl ethers was reported in 2002, the route comprised three steps, and the total yield was under 30 % [28]. In this context, we have developed an efficient one-pot route to construct 2,6-diiododiaryl ethers from corresponding phenols substituted with EWGs at the *para* position (Scheme 1).

Experimental

All chemical reagents were obtained from commercial suppliers (Aldrich, Kanto Chemical, Tokyo Chemical Industry, Aladdin, Wako Pure Chemical Industries) and used without further purification. Anhydrous solvents were obtained from commercial protocols. All nonaqueous reactions were carried out under Ar atmosphere. Thin layer chromatography (TLC) was performed on silica gel 60



Scheme 1 Our strategy for the construction of 2,6-diiododiaryl ethers from phenols in one-pot tandem oxidation

F_{254} glass plates precoated with a 0.25 mm thickness of silica gel (Merck). Column chromatography was carried out on Cica Silica Gel 60*N* (spherical, neutral, 40–50 or 63–210 μm). ^{1}H and ^{13}C NMR spectra were obtained on a Varian UNITY plus 300 (300 MHz for ^{1}H and 75 MHz for ^{13}C) instrument, with $CDCl_3$, CD_3OD or DMSO-d_6 as an internal reference. IR spectra were measured on a JNM FT/IR-460Plus spectrometer. Mass spectra were recorded on a JEOL D-200, JEOL JMS-GCmate II, SHIMAZU GC–MS–QP 500, or JEOL AX 505 spectrometer. Melting points were taken with a Yanagimoto micro-melting point apparatus and are uncorrected.

General procedure for the preparation of 2,6-diiododiaryl ethers *from the corresponding phenols*

A mixture of phenols (**1**, **4**, **5**) (10 mg) and $PhI(OAc)_2$ (5 equivalent) in MeOH (5 mL) was stirred at room temperature for about 20 min until the substrates (**1**, **4**, **5**) disappeared completely, then NaOMe (five equivalent) was added and run at 40 °C for 1 h, then heated to reflux. After refluxing for 4–8 h, the reaction mixture was quenched with saturated NaCl (10 mL), extracted with ethyl acetate (10 mL × 3), combined the organic layers, dried over $MgSO_4$ and concentrated in vacuum. The residue was purified by column chromatography on silica gel to afford the desired products (**2**, **6**, **7**).

*Methyl 2,4-diiodo-6-methoxy-3-phenoxybenzoate (**2**)* The resultant residue was purified by flash silica gel column chromatography (5 g, hexane:ethyl acetate = 100:1–30:1) to afford the product (**2**) (23 mg, 82 %) as a white solid, mp 108–110 °C.

IR (KBr, cm^{-1}) 2922, 2361, 1715, 1561, 1491, 1415, 1371, 1246, 1188; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.93$ (3 H, s), 3.95 (3 H, s), 6.78 (2 H, d, $J = 7.80$ Hz), 7.07 (1 H, t, $J = 7.80$ Hz), 7.31 (2 H, t, $J = 7.80$ Hz), 8.36 (1 H, s); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 52.76$ (q), 62.60 (q), 84.62 (s), 93.15 (s), 115.48 (d), 122.61

(d), 123.63 (s), 129.65 (d), 142.19 (d), 155.47 (s), 158.22 (s), 161.78 (s), 163.56 (s); MS: 510 (M^+); HRMS calcd for $C_{15}H_{12}I_2O_4$ 509.8825, found 509.8802.

*Methyl 3,5-diiodo-4-phenoxybenzoate (**6**)* The resultant residue was purified by flash silica gel column chromatography (5 g, hexane:ethyl acetate = 30:1–10:1) to afford the product (**6**) (16 mg, 51 %) as a white solid, mp 133–134 °C.
IR (KBr, cm^{-1}) 3071, 2947, 1723, 1489, 1457, 1272, 1195; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.94$ (3 H, s), 6.78 (2 H, d, $J = 7.79$ Hz), 7.08 (1 H, t, $J = 7.79$ Hz), 7.32 (2 H, t, $J = 7.79$ Hz), 8.52 (2 H, s); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 52.75$ (q), 90.83 (s), 115.48 (d), 122.66 8d), 129.66 (d), 130.00 (s), 141.41 (d), 155.54 (s), 157.49 (s), 163.61 (s); MS: 480 (M^+); HRMS calcd for $C_{14}H_{10}I_2O_3$ 479.8719, found 479.8733.

*1,3-Diiodo-5-nitro-2-phenoxybenzene (**7**)* The resultant residue was purified by flash silica gel column chromatography (5 g, hexane:ethyl acetate = 50:1–30:1) to afford the product (**7**) (15.8 mg, 47 %) as a white solid, mp 128–130 °C.
IR (KBr, cm^{-1}) 2924, 1523, 1346, 1243, 900, 755; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.79$ (2 H, d, $J = 7.69$ Hz), 7.11 (1 H, t, $J = 7.69$ Hz), 7.34 (2 H, t, $J = 7.69$ Hz), 8.73 (2 H, s); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 90.58$ (s), 115.49 (d), 123.14 (d), 129.84 (d), 135.25 (d), 145.20 (s), 155.16 (s), 159.35 (s); MS: 467 (M^+); HRMS calcd for $C_{12}H_7I_2NO_3$ 466.8516, found 466.8525.

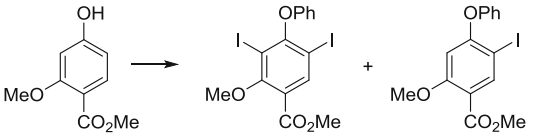
Results and discussion

The desired reaction was investigated using methyl 4-hydroxy-2-methoxybenzoate (**1**) as the model substrate, and the results are shown in Table 1. Methanol was used as reaction solvent in the initial experiments, and the reactions were refluxed directly with DAIB (Table 1, entries 1–4). The desired product (**2**) did not appear, but compound (**3**) was formed at 93 % yield when two equivalents of DAIB were used (Table 1, entry 1). With increasing amounts of DAIB, the desired product yield increased (Table 1, entries 1–3). However, continuing to increase the amounts of DAIB did not afford better yield of products (Table 1, entry 4). Based on the results, five equivalents of oxidant DAIB may be sufficient, and the desired product can be obtained at 62 % yield. When the reaction was stirred at ambient temperature for 20 min and at 40 °C for 1 h, then subsequently heated to reflux, the desired product (**2**) was obtained at 66 % yield (Table 1, entry 5). After testing other solvents (DMF, MeCN, and AcOH), AcOH was considered as the best, and the desired product was obtained at 75 % yield without any additives (Table 1, entries 6–8). Furthermore, the use of nucleophilic additives revealed that both NaOAc (in AcOH) and NaOMe (in MeOH) greatly benefited the reaction (Table 1, entries 9 and 10).

Using the optimal reaction conditions, substrates methyl 4-hydroxybenzoate (**4**) and 4-nitrophenol (**5**) were treated with DAIB in NaOMe. The desired compounds (**6**) and (**7**) were obtained at 51 and 47 % yields, respectively (Scheme 2).

Next, the mechanism underlying this reaction was studied, and the following reactions were carried out. The phenols (**1**, **4** and **5**) were treated with two

Table 1 Study the conditions for synthesis of methyl 3,5-diiodo-methoxy-4-phenoxybenzoate (**2**) from methyl 4-hydroxy-2-methoxybezoate (**1**) with DAIB



1 **2** **3**

Entry	DAIB/equiv.	Solv.	Time (h)	Yield/% of **2**, **3**
1[a]	2	MeOH	24	2, 93
2[a]	3	MeOH	24	43, 50
3[a]	5	MeOH	24	62, 36
4[a]	10	MeOH	24	61, 35
5[b]	5	MeOH	24	66, 21
6[b]	5	DMF	5	1, 90
7[b]	5	MeCN	24	1, 88
8[b]	5	AcOH	15	75, 14
9[b,c]	5	AcOH	4	79, 3
10[b,d]	5	MeOH	6	82, 9

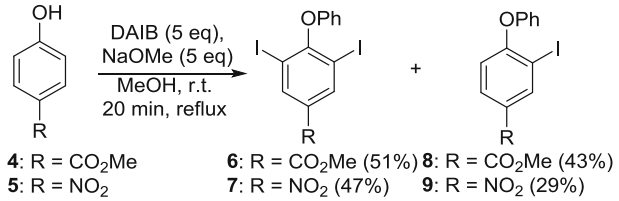
All the reactions were performed with 10 mg of (**1**) in 5 ml of solvent under argon

[a] Refluxed directly

[b] Before refluxing, the reactions were run at ambient temperature for 20 min and 40 °C over 1 h

[c] After stirring 20 min at ambient temperature, five equivalent of NaOAc was added then heated to 40 °C

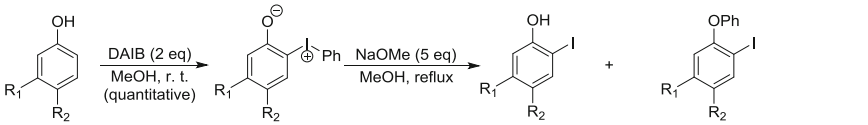
[d] After stirring 20 min at ambient temperature, five equivalent of NaOMe was added then heated to 40 °C



Scheme 2 Syntheses of methyl 3,5-diiodo-4-phenoxy-benzoate (**6**) and 1,3-diiodo-5-nitro-2-phenoxy-benzene (**7**) from the corresponding phenols

equivalents of DAIB to give phenyliodoniophenolates (**10**, **11** and **12**) at nearly quantitative yields. Compounds (**10**, **11** and **12**) could be transformed to iodophenols (**13**, **14** and **15**) at reasonable yields. Simultaneously, *ortho*-iodo-diaryl ethers (**3**, **8** and **9**) were afforded as the by-products (Scheme 3).

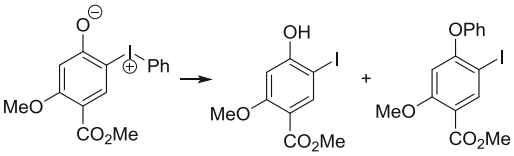
As outlined in Table 2, the reaction mixture was run in methanol at room temperature for 4 days. Phenyl iodoniophenolate (**10**) can be transformed into the desired iodophenol (**13**) and the undesired iodo-diaryl ether (**3**) at 59 and 35 %



1: R_1 = OMe, R_2 = CO_2Me **10**: R_1 = OMe, R_2 = CO_2Me **13**: R_1 = OMe, R_2 = CO_2Me (70%) **3**: R_1 = OMe, R_2 = CO_2Me (23%)
4: R_1 = H, R_2 = CO_2Me **11**: R_1 = H, R_2 = CO_2Me **14**: R_1 = H, R_2 = CO_2Me (61%) **8**: R_1 = H, R_2 = CO_2Me (31%)
5: R_1 = H, R_2 = NO_2 **12**: R_1 = H, R_2 = NO_2 **15**: R_1 = H, R_2 = NO_2 (58%) **9**: R_1 = H, R_2 = NO_2 (33%)

Scheme 3 Preparation of iodophenols (**13**, **14**, **15**) from corresponding phenols

Table 2 The reaction conditions for preparation of the compound (**13**) from the compound (**10**)



10 **13** **3**

Entry	Additive	Temp. (°C)	Time	Yield/% of **13**, **3**
1	–	25	4 days	59, 35
2	–	40	35 h	57, 40
3	–	Reflux	6 h	1, 81
4	NaOMe	25	24	73, 19
5[a]	NaOMe	40	1 h	70, 23
6[a,b]	NaOMe	40	1 h	70, 23

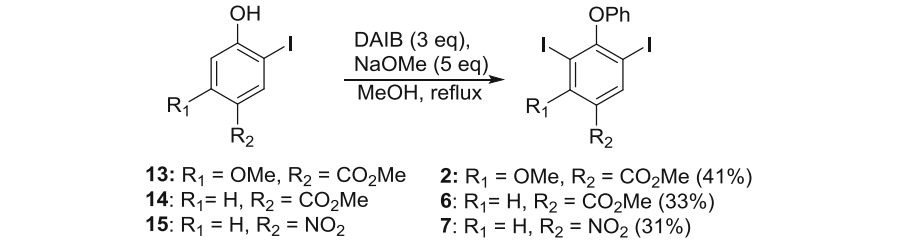
Unless otherwise noted, all the reactions were performed with 10 mg of (10), 5 equivalent of NaOMe in 5 ml of MeOH under argon

[a] The reactions were run at 40 °C for 1 h

[b] The reaction was performed with 5 mg of (10), 5 equivalent of NaOMe in 2 ml of CD_3OD

yields, respectively (Table 2, entry 1). The substrate disappeared rapidly under heating conditions, but unfortunately the yield of the desired product (**13**) decreased with increasing reaction temperature (Table 2, entries 2 and 3). In the presence of sodium methoxide, the reaction was performed at room temperature for 24 h, and the product (**13**) was obtained at 73 % yield (Table 2, entry 4). If the reaction was run at 40 °C for 1 h, the desired product (**13**) was afforded at 70 % yield (Table 2, entry 5). To check whether the anisole appeared as a by-product in this reaction, deuterated methanol was used as a reaction solvent, and the reaction was analyzed by NMR and MS spectroscopy without workup. As predicted, (methoxy-d_3)benzene was found in both spectra (Table 2, entry 6).

The amounts of iodophenols (**13**, **14** and **15**) were sufficient, and we investigated whether iodophenols could be converted into the desired 2,6-diiododiaryl ethers by the oxidant DAIB. As shown in Scheme 1, the synthesized compounds (**13**, **14** and **15**) were oxidized by DAIB, and compounds (**2**, **6** and **7**) were obtained at normal



Scheme 4 Syntheses of 3,5-diiodo-2-methoxy-4-phenoxy-benzoate (**2**) methyl 3,5-diiodo-4-phenoxybenzenoate (**6**) and 1,3-diiodo-5-nitro- 2-phenoxybenzene (**7**) from the corresponding iodophenols

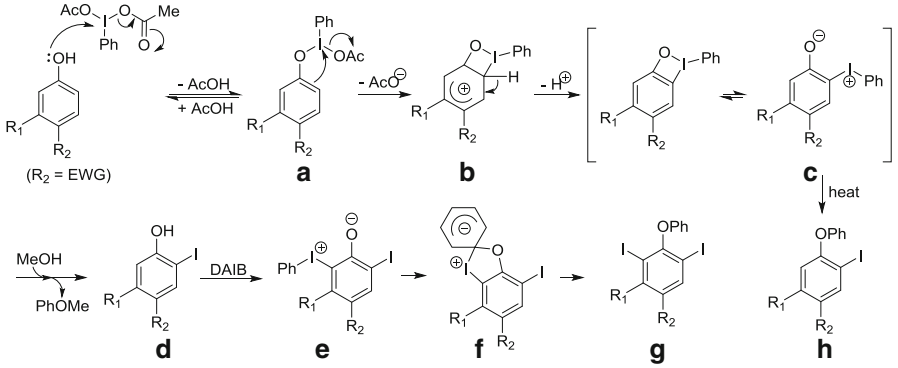


Fig. 2 The possible mechanism of the tandem oxidation reaction

yields (Scheme 4). However, when *ortho*-iodo-diaryl ethers (**3**, **8** and **9**) were treated with DAIB, the corresponding 2,6-diiododiaryl ethers did not appear.

Based on experiment results and those of previous reports [25–27], the possible mechanism of the tandem oxidation reaction is shown in Fig. 2. Initially, the lone pair of phenol attacks the iodine of DAIB, losing an acetic acid to form intermediate **a**. Intramolecular electrophilic aromatic substitution reaction with the loss of an acetate anion gives cation **b**. Deprotonation yields intermediate **c**, which reacts with a nucleophilic solvent (methanol or acetic acid) to afford iodophenol **d**. Iodophenol is then oxidized by the excess DAIB to obtain intermediate **e**. The phenyl group shifts from iodine to oxygen through intermediate **f**, thereby producing the desired product *ortho*-diiodo-diaryl ether **g**. However, intermediate **c** tends to form the undesired iodo-diaryl ether **h** at high temperatures.

Conclusion

In this work, we developed an effective one-pot synthesis of 2,6-diiododiaryl ethers from corresponding phenols, which were substituted with EWG at the *para* position by tandem oxidation reaction with DAIB. Using this method, three 2,6-diiododiaryl

ethers with extensive usability were synthesized in good yields. Furthermore, based on our results and those of previous reports, a possible mechanism is proposed. The phenols were oxidized to 2,6-diiododiaryl ethers through two important intermediates, namely, phenyliodoniophenolates and iodophenols.

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