# Reactions of 1-Arylbenziodoxolones with Azide Anion: Experimental and Computational Study of Substituent Effects

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**Abstract:** New substituted 1-arylbenziodoxolones were prepared and their reactivity with azide anion nucleophile was investigated. It was found that independent on the presence of substituents, all reactions of 1-arylbenziodoxolones proceed as nucleophilic substitution of the iodonium leaving group in the electron-deficient benziodoxolone benzene ring. The presence of bulky substituents in the *ortho*-position of the aryl ring slowers the reaction, while the presence of a moderately electron-withdrawing bromine substituent in the *para*-position to iodine in the benziodoxolone ring moderately increases the rate of substitution. The presence of a strongly electron-withdrawing nitro group in the *para*-position to iodine in the benziodoxolone ring dramatically increases the rate of substitution. These observations are in agreement with the electronic requirements for internal nucleophilic substitution in the benziodoxole ring. A quantum-chemical computational study of the possible reaction paths is in agreement with the observed effects of substituents on the reactivity of arylbenziodoxolones in this reaction.

## Introduction

In recent years, organohypervalent iodine compounds have emerged as versatile and environmentally benign reagents for organic synthesis.[1] Aryliodonium salts, $Ar_2I^+X^-$, belong to an important class of organohypervalent iodine(III) derivatives with broad applications in organic synthesis,[2] polymer chemistry,[1a] biological studies,[1a] and positron emission tomography.[3] The chemistry of diaryliodonium salts is a hot area of current research. Diaryliodonium salts are especially useful reagents for transition metal-catalyzed[4] or metal-free[2] arylations of carbon and heteroatom nucleophiles.

1-Arylbenziodoxolones can be formally classified as internal iodonium salts bearing the anionic carboxylate moiety in *ortho*-position to the iodonium group. The zwitterionic structure of 1-arylbenziodoxolones has been confirmed by X-ray structural analysis.[5] In particular, the observed bond distance between the carboxylic oxygen atom and the iodonium cation is about 2.5 Å, which is indicative of a significant ionic character of this bond as shown by resonance contributors in Figure 1.[5] The presence of the internal I•••O interaction causes a lower electrophilic character of the iodonium moiety and a reduced reactivity of arylbenziodoxoles toward nucleophiles in comparison with the noncyclic iodonium salts, $Ar_2I^+X^-$. The zwitterionic structure of 1-phenylbenziodoxolone is emphasized by the common name of this compound known as diphenyliodonium-2-carboxylate. Diphenyliodonium-2-carboxylate is a classical reagent that is commonly used for the generation of benzyne under heating or UV-irradiation.[6]

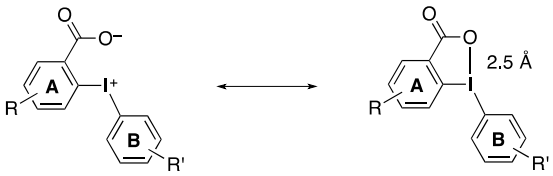


**Figure 1.** Resonance presentation of the structure of 1-arylbenziodoxolones.

Despite a significant current interest in 1-substituted benziodoxoles as atom-transfer reagents for trifluoromethylations, azidations and halogenations,[7] the reactivity of 1-arylbenziodoxoles as electrophilic arylating reagents remains essentially unexplored. Previously, we have demonstrated that the unsubstituted 1-phenylbenziodoxolone **1** has a very low reactivity towards nucleophiles.[5b] In particular, compound **1** is completely unreactive toward sodium azide in aqueous acetonitrile under reflux conditions. However, the introduction of a substituent in the benziodoxole ring **A** ortho to the iodine atom, leads to a significant increase in reactivity. The reaction of 7-methyl-1-phenylbenziodoxolone **2** with sodium azide under similar conditions is complete in 30 min with complete conversion to 2-azido-3 methylbenzoic acid **3** (Scheme 1).[5b]

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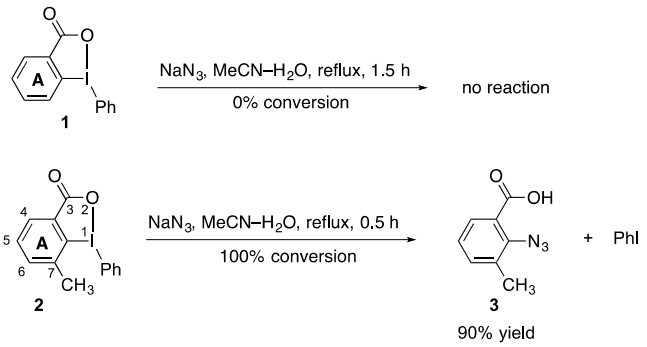
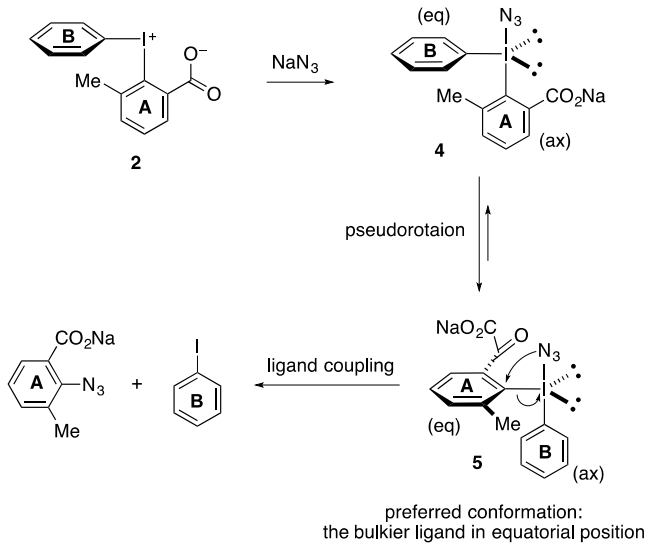



**Scheme 1.** Reactivity of 1-phenylbenziodoxolone **1** and 7-methyl-1-phenylbenziodoxolone **2** toward azide anion.

Such a dramatic effect was explained by the increased bulkiness of the aromatic ring **A**, forcing it to stay predominantly in the equatorial position of the trigonal bipyramidal intermediate **5** (Scheme 3).[5b,8] In the intermediate **4** formed by the initial addition of nucleophile $N_3^-$ to the iodonium center, the most electron-deficient ligands, the azide and the benzoate ring **A**, occupy the axial positions. Ligand coupling, which proceeds as the $S_NAr$ substitution reaction between the axial ligand $N_3$ and the aryl group in equatorial position,[8] is unlikely to occur in the intermediate **4** due to the electron–rich character of the equatorial phenyl ring **B**. However, since the equatorial positions are roomier than the axial positions, the bulkier *ortho*-substituted group would be forced to occupy the equatorial position, switching the equilibrium toward the intermediate **5**. Ligand coupling in the intermediate **5** leads to a reductive elimination of PhI and transfer of the nucleophile $N_3^-$ to the *ortho*–substituted electron–deficient aryl group **A** situated in the equatorial position (Scheme 2).



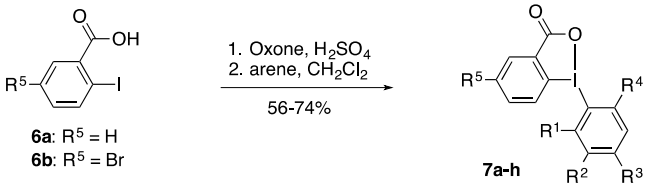

**Scheme 2.** Explanation of enhanced reactivity of ortho-substituted benziodoxolone **2** toward azide anion.

The present paper is aimed at further investigation of the role of substituents in aromatic rings **A** and **B** on the reactivity of 1-arylbenziodoxolones with nucleophiles. In particular, we attempted to clarify the role of substituents in ring **B** *in the absence of the activating ortho substituent in ring* ***A***. Because of the very low reactivity of the *ortho* unsubstituted benziodoxoles (Scheme 1), we have also investigated activation of ring **A** by introduction of the electron-withdrawing substituents (Br or $NO_2$) in the *para* position to iodine. Experimental observations have been verified by computational studies of the possible reaction paths.

## Results and Discussion

### Synthesis of substituted 1-arylbenziodoxolones and reactivity studies

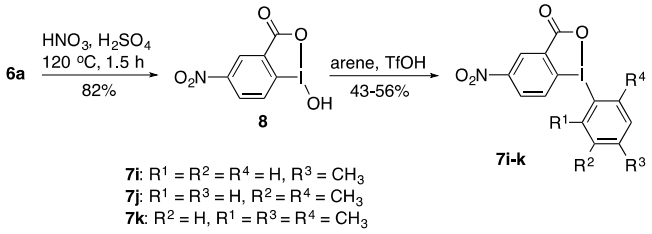
We have synthesized a series of unsubstituted and 5-bromo-substituted 1-arylbenziodoxolones **7a-h** starting from 2-iodobenzoic acids **6a** or **6b** by a one-pot two-step procedure outlined in Scheme 3. In the initial step, iodobenzoic acid **6** is oxidized by Oxone in $H_2SO_4$ to the corresponding iodine(III) species, which are converted in situ to the final products **7** by treatment with the appropriate arene. The starting 5-bromo-2-iodobenzoic acid **6b** can be readily prepared from the commercially available 2-iodobenzoic acid **6a** by bromination with NBS in $H_2SO_4$ at 60 °C.




**7a**: $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = CH_3$
**7b**: $R^1 = R^3 = R^5 = H$, $R^2 = R^4 = CH_3$
**7c**: $R^2 = R^5 = H$, $R^1 = R^3 = R^4 = CH_3$
**7d**: $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = Cl$
**7e**: $R^5 = Br$, $R^1 = R^2 = R^4 = H$, $R^3 = CH_3$
**7f**: $R^5 = Br$, $R^1 = R^3 = H$, $R^2 = R^4 = CH_3$
**7g**: $R^5 = Br$, $R^2 = H$, $R^1 = R^3 = R^4 = CH_3$
**7h**: $R^5 = Br$, $R^1 = R^2 = R^4 = H$, $R^3 = Cl$

**Scheme 3.** Synthesis of 1-arylbenziodoxolones **7a-h**.

5-Nitro-substituted 1-arylbenziodoxolones **7i-k** were prepared in two steps starting from 2-iodobenzoic acid **6a** (Scheme 4). A high temperature nitration/oxidation of 2-iodobenzoic acid with $HNO_3/H_2SO_4$ produced 1-hydroxy-5-nitrobenziodoxolone **8**,[9] which was converted to products **7i-k** by treatment with the appropriate arene in the presence of triflic acid.




**Scheme 4.** Synthesis of 1-aryl-5-nitrobenziodoxolones **7i-k**.

Reactivity studies were performed by heating 1-arylbenziodoxolones **7** with a $NaN_3$ solution in DMSO-$d_6$ to 80 °C in an NMR tube. According to NMR, each reaction mixture contained only products of nucleophilic substitution of iodine in the electron-deficient aromatic ring **A** (Scheme 5) along with aryliodides **10** and unreacted compounds **7**. The reaction of unsubstituted 1-phenylbenziodoxolone **1** (see Scheme 1) under these conditions ($NaN_3$, DMSO, 80 °C, 4 h) gave 16% conversion to 2-azidobenzoic acid. Conversions of substituted arylbenziodoxolones **7** to products **9** after 4 h heating are listed in Table 1. Representative isolated yields of the azidation products **9b** and **9c** are very close to the conversion values for the corresponding substrates **7h** and **7i** (Table 1). Examples of actual NMR spectra of reaction mixtures are provided in the supporting information.


**Scheme 5.** Reactions of 1-arylbenziodoxolones **7** with azide anion.

Analysis of conversion data in Table 1 allows us to make the following qualitative conclusions about reactivity of 1-arylbenziodoxolones with a nucleophile:

1) Independent on the presence of substituents, all reactions of 1-arylbenziodoxolones occur as nucleophilic substitution of the iodonium leaving group in the electron-deficient aromatic ring **A**.

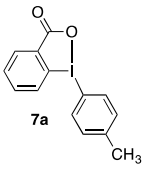
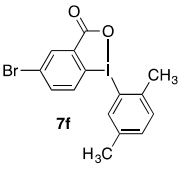
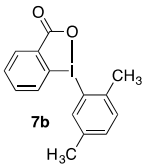
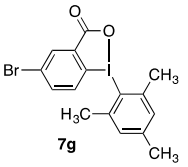
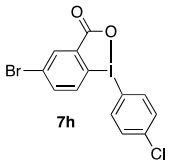
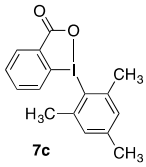
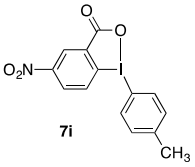
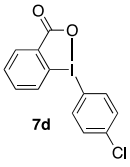
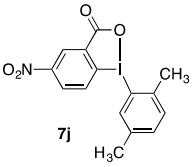
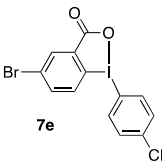
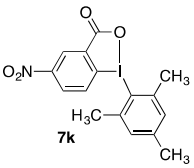
2) The presence of bulky substituents in the *ortho*-position of ring **B** (compounds **7b**, **7c**, **7f**, and **7g**) slows the reaction down. This observation is in agreement with the general mechanism shown in Scheme 2: a bulkier ring **B** favors intermediate **4**, in which internal nucleophilic substitution is unlikely.

3) The presence of the electronegative chlorine substituent in the *para*-position of ring **B** (compounds **7d** and **7h**) moderately increases the rate of substitution.

4) The presence of a moderately electron-withdrawing bromine substituent in the *para*-position to iodine in ring **A** (compounds **7e-7h**) moderately increases the rate of substitution.

5) The presence of a strongly electron-withdrawing nitro group in the *para*-position to iodine in ring **A** (compounds **7i-7k**) dramatically increases the rate of substitution. This observation is in agreement with the electronic requirements for internal nucleophilic substitution in ring **A**. Such a dramatic increase in reactivity can also be explained by change of the mechanism to a classical $S_NAr$ substitution via of a Meisenheimer intermediate.

**Table 1.** Reactions of compounds **7** with $NaN_3$ in DMSO-$d_6$ at 80 °C.[a]

| Compound **7** | Conversion [%][b,c] | Compound **7** | Conversion [%][b,c] |
|---|---|---|---|
|  **7a** | 26 |  **7f** | 61 |
|  **7b** | 18 |  **7g** | 34 |
| | |  **7h** | 68 (70)[d] |
|  **7c** | 12 | | |
| | |  **7i** | 99 (95)[e] |
|  **7d** | 41 |  **7j** | 99 |
|  **7e** | 70 |  **7k** | 99 |

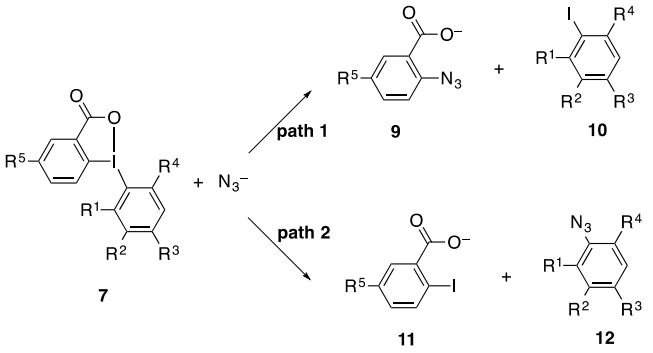
[a] Reactions were performed by heating 1-arylbenziodoxolones **7** with $NaN_3$ solution in DMSO-$d_6$ to 80 °C for 4 h. [b] Conversion was measured by NMR. [c] Only products **9**, **10** and unreacted starting material **7** were present in each reaction mixture. [d] Isolated yield of azide **9b** after 5 h heating. [e] Isolated yield of azide **9c**.

In order to further clarify these experimental results we performed computational studies of the possible reaction paths of this reaction.

## Computational evaluation

We calculated the reaction pathways of arylbenziodoxolones and azide anions in DMSO at 80 °C. Due to inadequate results of COSMO[10] and PCM[11] solvation models with ionic compounds, all calculation were carried out in the gas phase at 353 K. It should be noted that semiempirical AM1 method demonstrated good qualitative results[12,13] and even often comparable with the density functional results[14,15], too. Therefore the geometry optimization and energy calculations were carried out using AM1 method in Gaussian 09 software confirmed by the comparison of geometric parameters of salts **7** with X-ray crystal data[5b] (supporting information).

We calculated the energies for the two possible reaction pathways (Scheme 6). In the initial step, the ion-dipole complex (IDC) is formed (Figure 2). It should be noted that IDCs for all compounds have a lower energy than starting materials, associated, probably, with the formation of two close contacts of the azide anion with carbon and iodine atoms. The geometry of calculated complex is similar for all salts (SI); the negligible discrepancies have been observed only for salt **7g** (Figure 2). The IDC transforms to the appropriate azides through the transition states TS1 and TS2. According to calculation results, the geometry of transition states for both reaction paths is different (Figure 2). In the case of the first reaction path, we observed an essential formation of a bond between azide-anion and iodine and carbon of ring **A** (TS1). In contrast, the transition state of reaction path 2 (TS2) assumed the formation of a bond between azide and carbon of ring **B** (Figure 2).




**Scheme 6.** Possible reaction paths.

The energetic profiles of reaction paths 1 and 2 for the salts **7h** and **7g** are presented on Figure 3. Despite the slight differences between geometries of IDC and TS of salts **7h** and **7g** the energetic profiles are similar (Figure 3). The observed regularities have been preserved for all salts **7a**-**k** (Table 2). It should be noted, that the provided energies were calculated relative to IDC energies.

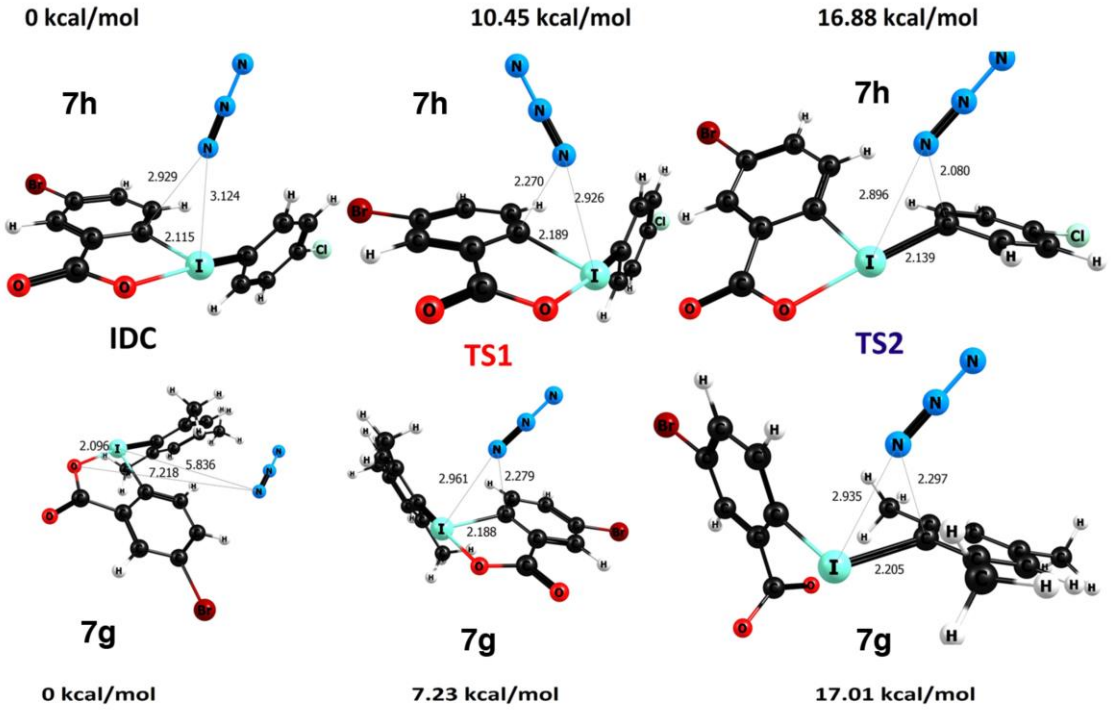



**Figure 2.** The calculated structures of ion-dipole complex (IDC) and transitions states (TS1 and TS2) for **7h** and **7g**

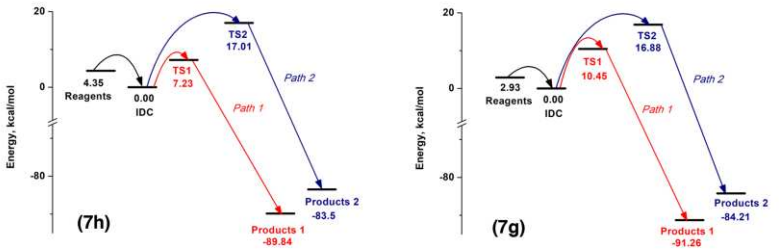



**Figure 3.** The energy profiles of reaction of **7h** and **7g**

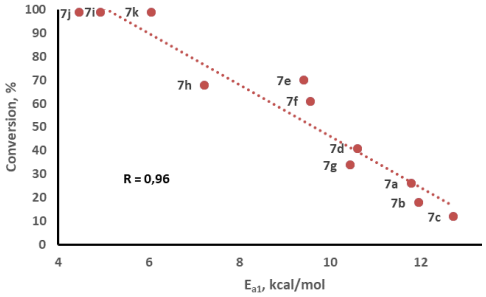



**Figure 4.** The correlation between conversion and calculated barriers of reaction (**path 1**)

The calculated energies and barriers explained the observed selectivity of process: the differences of energies between IDC and TS for the reaction path 1 are obviously smaller than the barriers for reaction path 2. Moreover, the conversion of starting materials has a good correlation with energy barriers with R = 0.96 (Figure 4). The quantum-chemical calculations confirmed the observed effects of substituents in ring **A** and **B**. Thus, the smallest barrier of substitution has been observed for the $NO_2$-substituted salts **7i**-**7k** and the largest for **7a**-**d** (Table 2), which is in agreement with electron-withdrawing effects of substituents. In contrast, the electron-donating substituents decrease the conversion and increase the energy barriers. The effect is most noticeable for the mesitylene derivatives **7c**, **7g**. In case of salt **7k** the negative effect of mesitylene ring is negligible and we achieved full conversion of starting materials during 240 minutes, but the energy barrier was slightly larger (1 – 1.5 kcal/mol), than salts **7i**-**j** (Table 2).

An intriguing effect of the chlorine substituent in ring **B** has been observed. The presence of electronegative substituent decreases the energy barriers down to 2 kcal/mol and, consequently, increases the reaction rate and conversion with high selectivity (**7d**, **7f**).

Thus, the quantum-chemical evaluation confirmed the observed effects of substituents on the reactivity of arylbenziodoxolones. The computed low-energy structures of IDC and TS are not in exact agreement with the intermediates **4** and **5** shown in Scheme 2. It should be noted that the widely adopted ligand coupling mechanism (Scheme 2) has been developed exclusively for the noncyclic iodonium salts, $Ar_2IX$.[8] The observed distortion is probably explained by the presence of a significant I•••O interaction in the benziodoxole ring forcing it to stay in a planar configuration.

**Table 2.** Relative energies (kcal/mol) of starting materials, IDC (complexes), products **9**+**11** and **11**+**12**, activation energies $E_a$ (AM1 level of theory, 353 K).

| Substrates | Starting materials | IDC | Product (**9**+**10**) | Product (**11**+**12**) | $E_{a1}$ (TS1-IDC) | $E_{a2}$ (TS2-IDC) | Substrates | Starting materials |
|---|---|---|---|---|---|---|---|---|
| **7a** | 2.85 | 0 | -86.09 | -80.2 | 11.8 | 21.42 | **7a** | 2.85 |
| **7b** | 2.58 | 0 | -86.52 | -80.8 | 11.96 | 23.85 | **7b** | 2.58 |
| **7c** | 1.61 | 0 | -87.48 | -80.96 | 12.74 | 18.59 | **7c** | 1.61 |
| **7d** | 4.33 | 0 | -84.73 | -78.91 | 10.61 | 19.52 | **7d** | 4.33 |
| **7e** | 3.97 | 0 | -89.96 | -83.54 | 9.43 | 19.92 | **7e** | 3.97 |
| **7f** | 3.73 | 0 | -90.37 | -84.12 | 9.57 | 22.26 | **7f** | 3.73 |
| **7g** | 2.81 | 0 | -91.26 | -84.21 | 10.45 | 16.88 | **7g** | 2.81 |
| **7h** | 4.35 | 0 | -89.84 | -83.5 | 7.23 | 17.01 | **7h** | 4.35 |
| **7i** | 7.04 | 0 | -96.3 | -88.51 | 4.93 | 17.7 | **7i** | 7.04 |
| **7j** | 6.26 | 0 | -97.27 | -89.66 | 4.46 | 19.36 | **7j** | 6.26 |
| **7k** | 5.14 | 0 | -97.79 | -88.38 | 6.06 | 14.13 | **7k** | 5.14 |

## Conclusions

We have demonstrated that independent on the presence of substituents, reactions of 1-arylbenziodoxolones with azide anion occur as nucleophilic substitution of the iodonium leaving group in the electron-deficient benziodoxole ring. The presence of bulky substituents in the *ortho* position of the aryl ring slowers the reaction, while the presence of a moderately electron-withdrawing bromine substituent in the *para*-position to iodine in in the benziodoxole ring moderately increases the rate of substitution. The presence of a strongly electron-withdrawing nitro group in the para position to iodine in the benziodoxole ring dramatically increases the rate of substitution. This observation is in agreement with the electronic requirements for internal nucleophilic substitution in the benziodoxole ring. A quantum-chemical computational study of the possible reaction paths confirmed the observed effects of substituents on the reactivity of arylbenziodoxolones in this reaction.

## Experimental Section

**General:** 2-Iodobenzoic acid, all aromatic precursors, and other reagents and solvents were from commercial sources and used without further purification from freshly opened containers. NMR spectra were recorded at 300, 400 and 500 MHz ($^1$H NMR) and 75, 100 and 125 MHz ($^{13}$C NMR). Chemical shifts (δ) are reported in parts per million. Mass spectrometric measurements were performed by the EPSRC Mass Spectrometry Service Centre, Swansea University or by R. Jenkins/R. Hick/S. Waller at Cardiff University. Ions were generated by the atmospheric pressure chemical ionisation (APCI), Electrospray (ES) or Electron Ionisation (EI).

**5-Bromo-2-iodobenzoic acid (6b).** A mixture of 1.0 g (4.03 mmol) of 2-iodobenzoic acid **6a**, 900 mg (5.05 mmol) of *N*-bromosuccinimide and 8.0 mL $H_2SO_4$ was heated at 60 °C and stirred for 2 h. After completion of reaction, the mixture was cooled to room temperature and poured into ice-cold water with stirring. The light yellow solid was crystallized from mixture ethanol - water 1:1, filtered and dried to afford the desired product **6b** as white crystals (1.14 g, 86.5% yield), mp 162-163 °C (lit.[16] mp 161-163 °C). $^1$H NMR ($CDCl_3$, 300 MHz): δ 8.15 (d, *J* = 2.4 Hz, 1 H), 7.91 (d, *J* = 8.7 Hz, 1 H), 7.34 (dd, *J* = 2.4, 8.4 Hz, 1 H).

**General procedure for preparation of 1-arylbenziodoxolones (1 and 7a-h).** Following reported procedure[5b] the finely crushed, solid 2-iodobenzoic acid **6a** or **6b** (1.0 mmol) was mixed with powdered Oxone (400-430 mg, 0.65-0.7 mmol) in a 50 mL round-bottom flask and stirred without solvent for 5 min using a magnetic stirrer until a homogeneous reaction mass was formed. Then the reaction mixture was cooled with ice to 5 °C and, under magnetic stirring, pre-cooled to 5 °C $H_2SO_4$ (total 0.8-1.0 mL) was added by 0.2 mL portions to the center of the reaction mixture. After addition of each portion of $H_2SO_4$ the reaction mass was mechanically shaken to achieve better mixing; the color of the resulting mass can vary from pale yellow to brown depending on the intensity of mixing. After adding all $H_2SO_4$, the magnetic stirring was continued for 30 min at room temperature, then the mixture was cooled to 5 °C and $CH_2Cl_2$ (4 mL) and ArH (1.5-3.0 mmol) were added. The magnetic stirring of the resulting mixture was continued at room temperature for 3-5 h. The reaction mixture was recooled to 5 °C and $CH_2Cl_2$ (3-5 mL) and then a saturated aqueous solution of $NaHCO_3$ were added by small portions until pH 8.0. The organic layer was separated, and the aqueous layer was additionally extracted with $CH_2Cl_2$ (5 mL). The organic extracts were combined, dried with $Na_2SO_4$, the solvent was evaporated and the crystalline product was dried in vacuum. Additional purification of products **7a-h** can be performed by crystallization from water.

**1-Phenyl-1,2-benziodoxol-3-(1*H*)-one (1).** The reaction of 2-iodobenzoic acid **6a** (248 mg, 1.0 mmol), Oxone (400 mg, 0.65 mmol), $H_2SO_4$ (total 0.8 mL) and benzene (0.2 mL) according to the general procedure afforded 288 mg (88%) of product **7a** monohydrate, isolated as off-white crystals; mp 221-222 °C (from water) (lit.[5b] mp 221-222 °C). $^1$H NMR (500 MHz, $CDCl_3$) δ 8.38 (dd, *J* = 7.5, 1.5 Hz, 1H), 8.01 (dd, *J* = 8.0, 1.0 Hz, 2H), 7.75 (t, *J* = 7.5 Hz, 1H), 7.59 (t, *J* = 7.5 Hz, 2H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.37 (td, *J* = 7.5, 1.5 Hz, 2H), 6.74 (d, *J* = 8.0 Hz, 1H).$^{13}$C NMR (125 MHz, $CDCl_3$) δ 166.84, 137.26, 133.54, 133.43, 132.49, 132.44, 131.75, 130.45, 126.45, 115.73, 115.40.

**1-(4-Methylphenyl)-1,2-benziodoxol-3-(1*H*)-one (7a).** The reaction of 2-iodobenzoic acid **6a** (248 mg, 1.0 mmol), Oxone (400 mg, 0.65 mmol), $H_2SO_4$ (total 0.8 mL) and toluene (0.2 mL) according to the general procedure afforded 288 mg (81%) of product **7a** monohydrate, isolated as off-white crystals; mp 217-219 °C (from water); $^1$H NMR ($CDCl_3$, 500 MHz): δ 8.36 (dd, *J* = 1.5, 7.5 Hz, 1 H), 7.88 (d, *J* = 8.0 Hz, 2 H), 7.53 (m, 1 H), 7.38 (m, 3 H), 6.76 (d, *J* = 8.5 Hz, 1 H), 2.50 (s, 3 H); $^{13}$C NMR ($CDCl_3$, 125 MHz): δ 166.7, 143.6, 137.2, 133.5, 133.4, 132.7, 132.6, 130.6, 126.1, 115.6, 111.1, 21.8; Anal. Calcd for $C_{14}H_{13}IO_3$: C, 47.21; H, 3.68; I, 35.63. Found: C, 47.23; H, 3.59; I, 35.66.

**1-(2,5-Dimethylphenyl)-1,2-benziodoxol-3-(1*H*)-one (7b).** The reaction of 2-iodobenzoic acid **6a** (248 mg, 1.0 mmol), Oxone (400 mg, 0.65 mmol), $H_2SO_4$ (total 0.8 mL) and p-xylene (0.2 mL) according to the general procedure afforded 293 mg (83%) of product **7b**, isolated as white crystals; mp 214-214.5 °C (from ethanol-water 1:1); $^1$H NMR ($D_2O$, 500 MHz): δ 8.78 (dd, *J* = 1.5, 7.5 Hz, 1 H), 8.45 (s, 1H), 8.20 (t, *J* = 7.5 Hz, 1 H), 8.06 (s, 2 H), 7.60 (m, 1 H), 8.01 (dt, *J* = 1.5, 7.5 Hz, 1 H), 7.33 (d, *J* = 7.5 Hz, 1 H), 2.98 (s, 3 H), 2.88 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 166.7, 139.8, 139.6, 139.0, 138.9, 134.4, 133.7, 133.1, 131.3, 131.0, 124.4, 118.3, 114.4, 24.6, 20.8 ppm; HRMS (AP+) Calcd for $C_{15}H_{14}IO_2$ [M+H$^+$] m/z 353.0039. Found: 353.0056.

**1-(2,4,6-Trimethylphenyl)-1,2-benziodoxol-3-(1*H*)-one (7c).** The reaction of 2-iodobenzoic acid **6a** (248 mg, 1.0 mmol), Oxone (400 mg, 0.65 mmol), $H_2SO_4$ (total 0.8 mL) and 1,3,5-trimethylbenzene (0.15 mL, 1.1 mmol) according to the general procedure afforded 300 mg (78%) of product **7c** monohydrate, isolated as off-white crystals; mp 220-222 °C (from ethanol-water – 1:2) (lit.[5b], mp 223-223.5 °C); $^1$H NMR ($CD_3OD$, 500 MHz): δ 8.31 (dd, *J* =1.5, 7.5 Hz, 1 H), 7.66 (m, 1H), 7.49 (ddd, *J* = 1.5, 7.0, 9.0 Hz), 1H), 7.29 (s, 2H), 6.79 (d, *J*= 8.5 Hz, 1 H), 2.53 (s, 6H), 2.43 (s, 3 H); $^{13}$CNMR ($CD_3OD$, 125 MHz): δ 170.2, 145.7, 145.0, 135.7, 135.4, 133.9, 132.2, 131.0, 127.5, 120.4, 114.3, 26.6, 21.4.

**1-(4-Chlorophenyl)-1,2-benziodoxol-3-(1*H*)-one (7d)**. The reaction of 2-iodobenzoic acid **6a** (248 mg, 1.0 mmol), Oxone (400 mg, 0.65 mmol), $H_2SO_4$ (total 0.8 mL) and chlorobenzene (0.20 mL, 1.97 mmol) according to the general procedure afforded 215 mg (57%) of product **7d**

monohydrate, isolated as off-white crystals: mp 226-226.5 °C (from water); $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.21 (d, *J*=8.4 Hz, 2H), 8.14 (d, *J*=7.2 Hz, 1H), 7.70 (d, *J*=8.4 Hz, 2H), 7.62 (t, *J*=7.2 Hz, 1H), 7.54 (d, *J*=7.2 Hz, 1H), 6.75 (d, *J*=8.4 Hz, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 165.7, 139.0, 137.3, 134.2, 133.6, 131.5, 131.4, 130.2, 127.4, 116.0, 115.4. Anal. Calcd for $C_{13}H_{10}ClIO_3$: C, 41.46; H, 2.68; I, 33.70. Found: C, 41.56; H, 2.54; I, 33.82.

**5-Bromo-1-(4-methylphenyl)-1,2-benziodoxol-3-(1*H*)-one (7e).** The reaction of 5-bromo-2-iodobenzoic acid **6b** (327 mg, 1.0 mmol), Oxone (400 mg, 0.65 mmol), $H_2SO_4$ (total 0.8 mL) and toluene (0.3 mL) according to the general procedure afforded 371 mg (89%) of product **7e**, isolated as white crystals; mp 215-216 °C (from ethanol-water 1:1) $^1$H NMR (300 MHz, $CDCl_3$-$CD_3OD$ 10:1) δ 8.32 (d, *J*=2.4, 1H), 7.74 (d, *J*=8.1 Hz, 2H), 7.40 (dd, *J*=2.4,8.7 Hz, 2H), 7.30 (d, *J*=8.4 Hz, 2H), 6.49 (d, *J*=8.7 Hz, 1H), 2.40 (s, 3H).$^{13}$C NMR (75 MHz, $CDCl_3$) δ 166.4, 144.2, 137.0, 136.6, 135.4, 134. 8, 132.9, 128.1, 125.8, 113.2, 109.7, 21.6. HRMS (TOF, ES+) m/z: $[M+H]^+$ Calcd. for $C_{14}H_{11}O_2BrI$: 416.8987; Found: 416.8975.

**5-Bromo-1-(2,5-dimethylphenyl)-1,2-benziodoxol-3-(1*H*)-one (7f).** The reaction of 5-bromo-2-iodobenzoic acid **6b** (327 mg, 1.0 mmol), Oxone (400 mg, 0.65 mmol), $H_2SO_4$ (total 0.8 mL) and p-xylene (0.3 mL) according to the general procedure afforded 228 mg (53%) of product **7f**, isolated as white crystals; mp 213-214 °C (from ethanol-water 1:1). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J*=2.4, 1H), 7.83 (s, 1H), 7.47-7.43 (m, 3H), 7.50 (d, *J*=8.8 Hz, 1H), 2.49 (s, 3H), 2.39 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 165.9, 139.7, 139.0, 136.6, 136.4, 135.9, 135.7, 134.5, 131.3, 127.5, 126.0, 118.4, 113.0, 24.7, 20.8. HRMS (TOF, AP+) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{13}O_2BrI$: 430.9144; Found: 430.9150.

**5-Bromo-1-(2,4,6-trimethylphenyl)-1,2-benziodoxol-3-(1*H*)-one (7g).** The reaction of 5-bromo-2-iodobenzoic acid **6b** (327 mg, 1.0 mmol), Oxone (400 mg, 0.65 mmol), $H_2SO_4$ (total 0.8 mL) and mesitylene (0.3 mL) according to the general procedure afforded 275 mg (62%) of product **7g**, isolated as white crystals; mp 221-223 °C (from ethanol-water 1:1) $^1$H NMR (500 MHz, $CDCl_3$ – $(CD_3)_2CO$ 1:5) δ 8.35 (d, *J*=2.5, 1H), 7.34 (dd, *J*=2.5, 8.0 Hz, 1H), 7.07 (s, 2H), 6.42 (d, *J*=8.5 Hz, 1H), 2.45 (s, 6H), 2.34 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 166.1, 144.0, 143.6, 136.4, 136.0, 130.0, 126.6, 125.9, 119.4, 112.6, 26.6, 21.5. HRMS (TOF, ES+) m/z: $[M+H]^+$ Calcd. for $C_{16}H_{15}O_2BrI$: 444.9300; Found: 444.9303.

**5-Bromo-1-(4-chlorophenyl)-1,2-benziodoxol-3-(1*H*)-one (7h).** The reaction of 5-bromo-2-iodobenzoic acid **6b** (327 mg, 1.0 mmol), Oxone (400 mg, 0.65 mmol), $H_2SO_4$ (total 0.8 mL) and chlorobenzene (0.3 mL) according to the general procedure afforded 175 mg (40%) of product **7h**, isolated as white crystals; mp 237-238 °C (from methanol-water 1:1). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.22(d, *J*=8.4 Hz, 2H), 8.17 (s, 1H), 7.73-7.70 (m, 3H), 6.66 (d, *J*=8.4 Hz, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 164.2, 138.9, 137.5, 136.4, 136.0, 133.6, 131.5, 129.5, 124.1, 114.9, 114.8. HRMS (TOF, ES+) m/z: $[M+H]^+$ Calcd. for $C_{13}H_8O_2ClBrI$: 436.8441, found: 436.8448.

**5-Nitro-2-iodosobenzoic acid (8).** Following a reported procedure[9], nitric acid (1.5 mL) was added to 2-iodobenzoic acid **6a** (1.0 g, 4.03 mmol, 1 equiv) in concentrated $H_2SO_4$ (4.5 mL). The reaction flask was equipped with a condenser and was heated at 100 °C for 2 h. The reaction mixture was then poured in ice-water and filtered. The resulting solid was refluxed in water (50 mL) for 1.5 h and then filtered and washed with acetone (10 mL) to afford product **8** (1.11 g, 3.58 mmol, 89 %). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.83 (d, J=2.7 Hz, 1H), 8.30 (d, J= 8.7 Hz, 1H), 8.04 (dd, J=2.7, 8.7 Hz, 1H).

## General procedure for the syntesis of 5-nitro-1-aryl-1,2-benziodoxol-3-(1*H*)-ones (7 i-k)

Suspension of 5-nitro-2-iodosobenzoic acid **8** (309 mg, 1 mmol) in DCM (8 mL) was added to trifluoromethanesulfonic acid (2 equiv, 0.18 mL) at -30°C. Reaction mixture was stirred for 10 min, then arene (0.3 mL) was added. The magnetic stirring of the resulting mixture was continued overnight at room temperature. Then reaction mixture was washed with water (3x5 mL). The organic layer was separated, the organic extracts were combined, dried with $Na_2SO_4$, the solvent was evaporated and the crystalline product was dried in vacuum. Additional purification of products **7i-k** can be performed by crystallization from water.

**5-Nitro-1-(4-methylphenyl)-1,2-benziodoxol-3-(1*H*)-one (7i).** The reaction of 5-nitro-2-iodosobenzoic acid **8** (309 mg, 1.0 mmol), triflic acid (0.18 mL), and toluene (0.3 mL) according to the general procedure afforded **7j** 214 mg (56%) of product **7i**, isolated as white crystals; mp 213-215 °C $^1$H NMR (300 MHz, $CDCl_3$) δ 8.99 (d, *J*=2.7 Hz, 1H), 8.13 (dd, *J*=2.7, 9.0 Hz, 1H), 7.93 (d, *J*=8.1 Hz, 2H), 7.43 (d, *J*=7.8 Hz, 2H), 6.95 (d, *J*=9.0 Hz, 1H), 2.54 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$-$CD_3OD$ 2:1) δ 165.8, 150.0, 144.4, 136.8, 135.4, 133.0, 128.4, 127.4, 126.4, 121.0, 110.3, 21.4. HRMS (TOF, ES+) m/z: $[M+H]^+$ Calcd. for $C_{14}H_{11}NO_4I$: 383.9733; Found: 383.9727.

**5-Nitro-1-(2,5-dimethylphenyl)-1,2-benziodoxol-3-(1*H*)-one (7j).** The reaction of 5-nitro-2-iodosobenzoic acid **8** (309 mg, 1.0 mmol), triflic acid (0.18ml), p-xylene (0.3 mL) according to the general procedure afforded 246 mg (62%) of product **7j**, isolated as white crystals; mp 208-209 °C. $^1$H NMR (300 MHz, $CDCl_3$-$CD_3OD$ 5:1) δ 8.90 (d, *J*=2.7 Hz, 1H), 8.06 (dd, *J*=2.7, 9.0 Hz, 1H), 7.69 (s, 1H), 7.38-7.32 (m, 2H), 6.77 (d, *J*=8.7 Hz, 1H), 2.33 (s, 3H), 2.24 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$-$CD_3OD$ 10:1) δ 165.9, 150.1, 139.9, 139.2, 138.5, 135.8, 134.7, 131.3, 127.9, 127.6, 126.7, 119.8, 117.9, 24.1, 20.3. HRMS (TOF, ES+) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{13}NO_4I$: 397.9889; Found: 397.9880.

**5-Nitro-1-(2,4,6-trimethylphenyl)-1,2-benziodoxol-3-(1*H*)-one (7k).** The reaction of 5-nitro-2-iodosobenzoic acid **8** (309 mg, 1.0 mmol), triflic acid (0.18 mL), p-xylene (0.3 mL) according to the general procedure afforded 312 mg (76%) of product **7k**, isolated as white crystals; mp 227-228 °C. $^1$H NMR (300 MHz, $CDCl_3$-$CD_3OD$ 2:1) δ 9.02 (d, *J*=2.7 Hz, 1H), 8.25 (dd, *J*=2.7, 8.7Hz, 1H) , 7.27 (s, 2H), 6.97 (d, *J*=8.7 Hz, 1H), 2.54 (s, 6H), 2.44 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$-$CD_3OD$ 2:1) δ 167.2, 151.0, 145.4, 144.1, 137.2, 130.9, 130.7, 128.6, 127.4, 120.03, 119.98, 26.6, 21.5. HRMS (TOF, AP+) m/z: $[M+H]^+$ Calcd. for $C_{16}H_{15}NO_4I$: 412.0046; Found: 412.0031.

## General procedure for the synthesis of 2-azidobenzoic acid (9)

1-Arylbenziodoxolones **7** (0.2 mmol) and $NaN_3$ (68 mg, 1 mmol) were mixed with DMSO (1 mL) and the resulting mixture was heated at 80 °C. Then the reaction mixture was diluted with water (5 mL) and washed with $CH_2Cl_2$ (3x5 mL). Hydrochloric acid was added to the reaction mixture until acidic pH. Obtained azide was isolated by extraction with $CH_2Cl_2$ (3x5 mL). The organic extracts were dried with $Na_2SO_4$, the solvent was evaporated and the crystalline product **9** (as an acid) was dried in vacuum.

**5-Bromo-2-azidobenzoic acid (9b).** The reaction mixture of 1-arylbenziodoxolone **7h** (87 mg, 0.2 mmol), $NaN_3$ (68 mg, 1 mmol) and dry DMSO (1 mL) was heated for 5 h according to the general procedure affording 34 mg (70%) of product **9b**, isolated as white crystals; mp 148-150 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.70 (d, *J*=8.4 Hz, 1H), 7.16 (d, *J*=8.8 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 167.48, 139.63, 137.33, 135.98, 122.31, 121.41, 117.86.

**5-Nitro-2-azidobenzoic acid (9c)**. The reaction mixture of 1-arylbenziodoxolone **7i** (76.6 mg, 0.2 mmol), $NaN_3$ (68 mg, 1 mmol) and dry DMSO (1 mL) was heated for 10 min according to the general procedure affording 39.5 mg (95%) of product **9c**, isolated as white crystals; mp 149-150 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, J=2.4 Hz, 1H), 8.37 (dd, J=2.8, 8.8 Hz, 1H), 7.36 (d, J=8.8 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$-DMSO-$d_6$ – 10:1) δ 165.6, 146.6, 144.1, 128.4, 128.1, 123.2, 120.7.

### NMR experiment

DMSO-$d_6$ (0.5 mL) was added to the mixture of 1-arylbenziodoxolones **7a-k** (0.05 mmol) and sodium azide (0.25 mmol, 16.2 mg) in NMR tube. The mixture was heated at 80 °C for 240 min and then NMR spectra were recorded.

### Computational Details

All calculations were carried out using Gaussian 09 revision C. 01.[17] We used AM1 method for the optimization of equilibriums and transitions of ground electronic state for the all considered compounds. The cartesian coordinates of all structures are provided as supplementary material. The geometry of transition state (TS) for all considered structures and reaction pathways were obtained using the synchronous transit-fuided quasi-newton (STQN) method.[18] In this method IDC was used as the initial structure of reagents.

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**Keywords:** iodine • hypervalent iodine • iodonium • benziodoxole • computational chemistry

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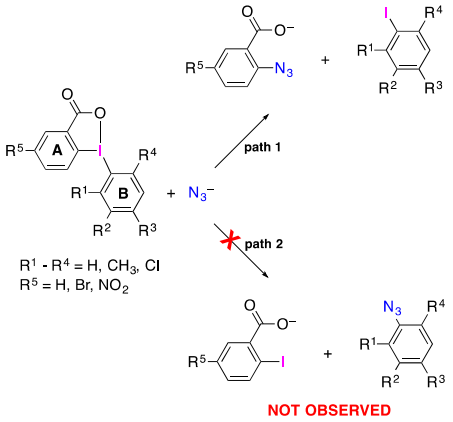
## Entry for the Table of Contents

# FULL PAPER

Several new substituted 1-arylbenziodoxolones were prepared and their reactivity with azide anion as a nucleophile was investigated by experimental and computational studies.




*reactivity of 1-arylbenziodoxolones

**Key Topic***

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**Reactions of 1-Arylbenziodoxolones with Azide Anion: Experimental and Computational Study of Substituent Effects**