Aromatic C–H insertion of β-phenoxyalkylidenecarbenes generated by reaction of alkynyl(*p*-phenylene)bisiodonium ditrifluoromethanesulfonates (ditriflates) with phenoxide anions

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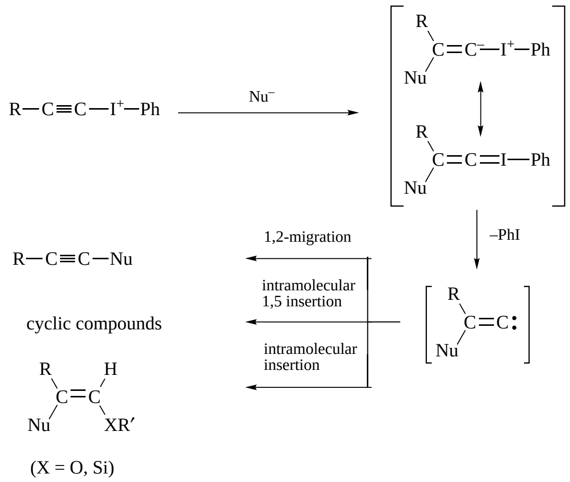
Reaction of alkynyl(*p*-phenylene)bisiodonium ditriflates with sodium phenoxide in methanol provides 2-substituted benzofurans in 49–62% yields. This result indicates that β-phenoxyalkylidenecarbenes are generated by the reaction with phenoxide anion and undergo novel intramolecular aromatic C–H insertion to afford benzofurans. 2-Phenoxy-2-phenylethenylidene generated analogously *in situ* underwent competing processes of aromatic C–H insertion and 1,2-phenyl migration. The corresponding reactions with 4-substituted phenoxide ions also afforded 5-substituted benzofurans and, as the minor products, 2-aryloxy-1-iodoalk-1-enes which were probably derived from the intermediate vinyliodonium salts. Reactions of alkynyl(*p*-phenylene)bisiodonium ditriflates with sodium [$^2H_5$]phenoxide (98% ^2H) in methanol gave deuterated 2-alkylbenzofurans in 35–40% yields and the hydrogen at the 3-position of the benzofurans was deuterated completely. This result strongly supports selective aromatic C–H insertion of the *in situ* generated β-phenoxyalkylidenecarbenes.

There has recently been considerable attention paid to hypervalent iodine compounds in organic synthesis.[1] Alkynyliodonium salts are synthetically important and mechanistically useful since they behave as synthons for 'alkynyl cations' and act as Michael acceptors generating alkylidenecarbenes.[1f,h,k,p]

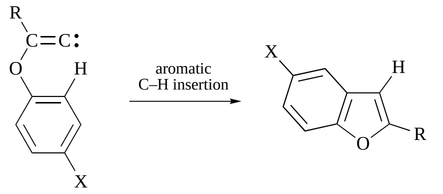
Generally accepted reaction processes for the reaction of alkynyliodonium salts with relatively soft nucleophiles are believed to involve nucleophilic β-addition generating a vinyliodonium ylide–iodoallene intermediate and the subsequent reaction of the resulting alkylidenecarbene (Scheme 1).[1f,h,k,p]



Scheme 1

The reactive alkylidenecarbene undergoes 1,2-migration of the β substituent giving an alkyne,[2,3a] intramolecular 1,5-insertion[3] or intermolecular insertion.[3c] The intramolecular 1,5-insertion of the alkylidenecarbene has been limited only to the C–H bond of the methylene groups[3] and to the O–H bond of enols and alcohols.[3a,d]

Although aromatic C–H insertions of alkylidenecarbenes in the gas phase have been observed, no examples of insertion into aromatic C–H bonds in the reaction of the alkynyliodonium salts in solution had been reported before we started this work.[4,5] When we conducted the reaction of alkynyl(*p*-phenylene)bisiodonium ditriflates with a phenolate anion, we obtained benzofuran derivatives which should be derived from the aromatic C–H insertion of the resulting alkylidenecarbene.[4] In this paper, we describe in detail the novel benzofuran formation derived from aromatic C–H insertion of the alkylidenecarbene as shown in eqn. (1). The high selectivity of aromatic C–H insertion in β-phenoxyalkylidenecarbenes and the firm evidence of the aromatic C–H insertion from deuterium incorporation are mentioned in particular.



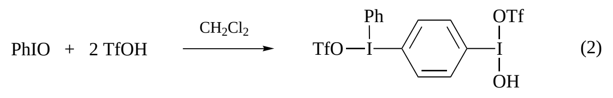
(1)

Results and discussion

Benzofuran formation

Alkynyl(*p*-phenylene)bisiodonium ditriflates (**2**) were prepared readily by interaction of our recently found bisiodine(III) reagent, 1-[(hydroxy)(trifluoromethylsulfonyloxy)iodo]-4-[(phenyl)(trifluoromethylsulfonyloxy)iodo]benzene (**1**), with 1-trimethylsilylalkynes.[6] The alkynyl(*p*-phenylene)bisiodonium ditriflates **2** react with the thiocyanate anion to yield alkynyl thiocyanates.[6] This reaction indicated that the alkynylbisiodonium ditriflates **2**, as well as the previously investigated and widely used alkynyl(phenyl)iodonium salts,[1f,k,h,p] can be used in various reactions. The advantage of the use of alkynylbisiodonium ditriflates **2** lies in the easy workup for isolation of the products.[6]

The reaction of alkynylbisiodonium ditriflates **2** with phenol-



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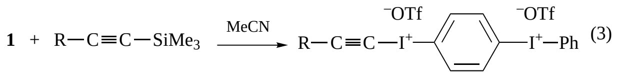
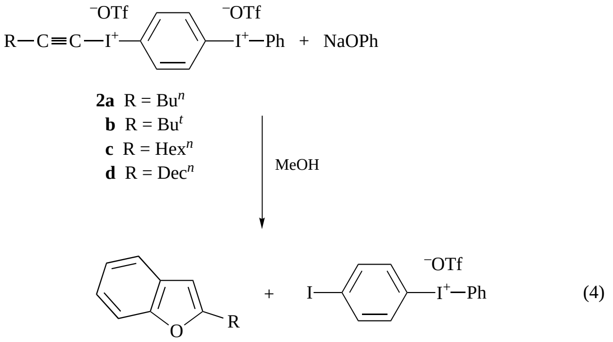


2

ate anion was conducted in methanol. Addition of sodium phenoxide to alkynylbisiodonium ditriflates **2** proceeded smoothly to give 2-substituted benzofurans **3** as the sole product, together with (*p*-iodophenyl)(phenyl)iodonium triflate (**4**)[8] which could be isolated by evaporation of the solvent and filtration after the reaction was completed.

In the cases of alkyl-substituted ethynyl(*p*-phenylene)-bisiodonium ditriflates **2a**–**d**, benzofurans **3a**–**d** were formed selectively. Noteworthy is the selective benzofuran formation even in the cases of hexyl and decyl-substituted compounds **2c** and **d**. Although such linear alkyl-substituted ethynyliodonium salts undergo selective 1,5-C–H insertion into the alkyl group leading to cyclopentene derivatives in the reactions with enolate anions and azide anion,[3] no cyclopentene derivatives (**7**) (Scheme 2) have been detected in these cases.



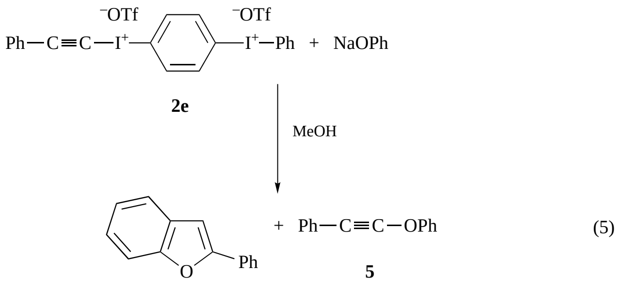
2a R = Bu^n
b R = Bu^t
c R = Hex^n
d R = Dec^n

3a R = Bu^n (62%)
b R = Bu^t (59%)
c R = Hex^n (62%)
d R = Dec^n (49%)

4

The present selective benzofuran formation can be rationalized by taking into account the nature of alkylidenecarbenes. According to the reviews[7e,d] by Stang, alkylidenecarbenes have an electrophilic character and can interact with olefinic π systems through their empty p orbitals. Although interactions of alkylidenecarbenes with aromatic substrates in solution have not been described,[7] such interaction with the aromatic component should proceed in the present case. Enhancement of the electron density on the phenyl group by the oxygen atom may assist such interaction.[9] In this situation, accordingly, it is considered that aromatic 1,5-C–H insertion becomes more favourable than aliphatic 1,5-C–H insertion, and benzofurans are formed selectively (Scheme 2).

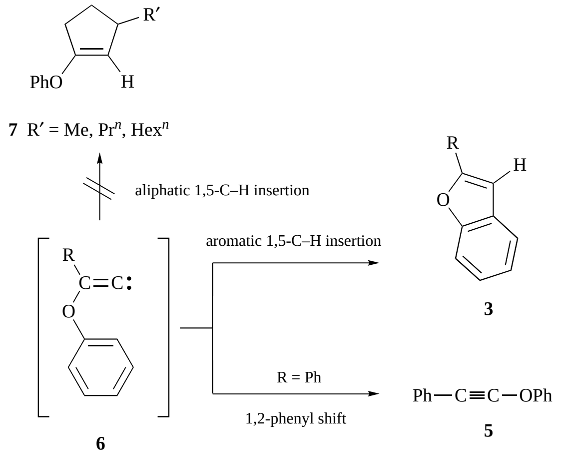
On the other hand, phenyl-substituted ethynyl(*p*-phenylene)-bisiodonium ditriflate **2e** showed a different behaviour from the alkyl-substituted examples **2a**–**d**. Interaction of **2e** with phenoxide anion gave a 59:41 mixture of 2-phenylbenzofuran **3e** and phenyl phenylethynyl ether **5** in 59% yield [eqn. (5)]. Phenyl phenylethynyl ether **5** was separated by HPLC using a silica gel column. The characteristic spectra of the carbon–carbon triple bond were observed in the ^{13}C NMR and IR spectra. The absorptions due to the triple bond at 46.23 and 92.38 ppm in the ^{13}C NMR and 2274 cm^{-1} in the IR are in good accord with those of the corresponding alkynyl carboxylates.[10] The comparable formation of benzofuran **3e** even in the β-phenylalkylidenecarbene indicates that aromatic C–H insertion occurs as easily as the 1,2-phenyl shift (Scheme 2), although aliphatic 1,5-C–H insertion cannot compete.[3a]



2e

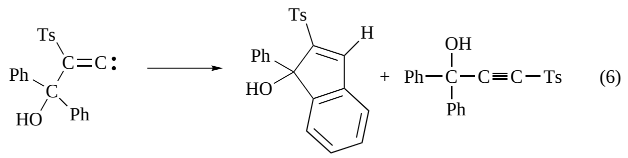
5

3e

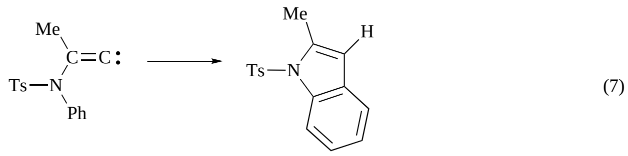


Scheme 2

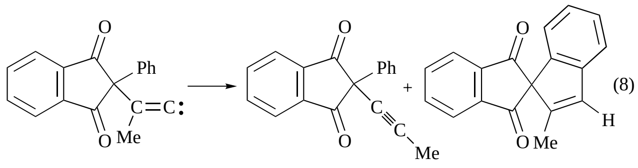
The present results are in accordance with the formation of an intramolecular aromatic C–H insertion of β-phenoxyalkylidenecarbenes (**6**) generated by the Michael addition of the phenoxide anion to **2**, followed by elimination of an iodoarene as shown in Scheme 1. Very recently, it has been reported that indenes and indoles are formed *via* other alkylidenecarbenes **8**–**10**, respectively, generated by the reaction of alkynyliodonium salts in solution [eqn. (6),[5a] (7)[5c] and (8)[5b]].



8 50% 18%



9 66%

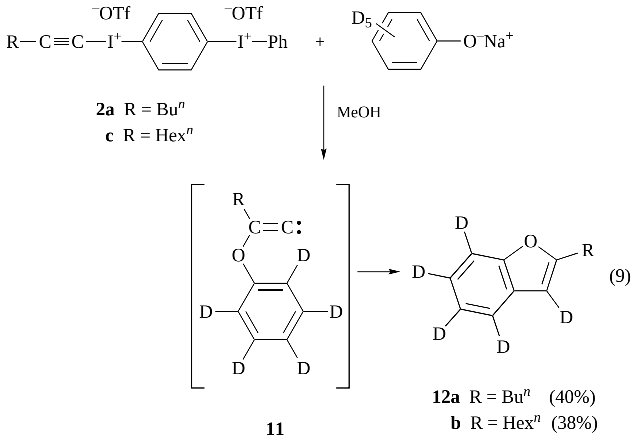


10 16% 2%

Deuterium incorporation

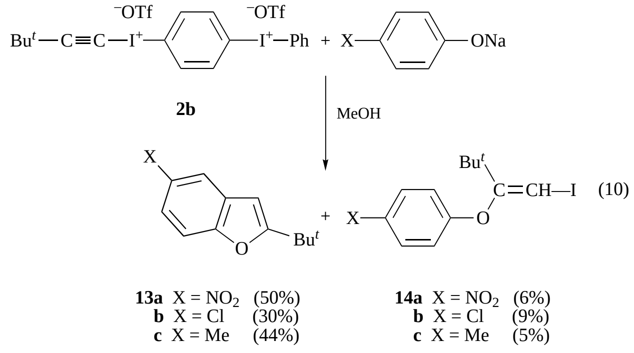
If the suggested mechanism operates in benzofuran formation, this reaction is a rare example of aromatic C−H insertion of alkylidenecarbenes in solution. Thus, we further conducted the reaction of alkynyl(*p*-phenylene)bisiodonium ditriflates **2** with a deuterated phenoxide anion in order to obtain firm evidence of the aromatic C−H insertion of alkylidenecarbenes **6**.

When hex-1-ynyl(*p*-phenylene)bisiodonium ditriflates **2a** was treated with sodium [$^2H_5$]phenoxide (98% ^{2}H) in methanol, 2-butyl[$^2H_5$]benzofuran (**12a**) was obtained in 40% yield [eqn. (9)]. The hydrogen signals at the 3-position (δ 6.35) and aromatic positions (δ 7.15–7.48) in the ^{1}H NMR were absent and calculation on the basis of the hydrogens of the butyl group revealed that only 2% of hydrogens remained. The value (2%) is the same as that of the hydrogen originally contained in the phenoxide anion (98% ^{2}H). The carbons at the 3, 4, 5, 6 and 7-positions are coupled with the respective deuterium atoms in the ^{13}C NMR. Similarly, the reactions of oct-1-ynyl(*p*-phenylene)bisiodonium ditriflate **2b** with sodium [$^2H_5$]phenoxide gave 2-hexyl[$^2H_5$]benzofuran **12b** in 38% yield. The complete incorporation of deuterium at the 3-position of benzofurans **12** supports their generation by aromatic C−D insertion of alkylidenecarbenes **11**.



Other examples

In order to assess the scope of the aromatic C−H insertion of alkylidenecarbenes, we examined the reaction with *para*-substituted phenoxide ions. When *tert*-butylethynyl(*p*-phenylene)bisiodonium ditriflate **2b** was treated with sodium *p*-nitrophenoxide in methanol, 2-*tert*-butyl-5-nitrobenzofuran (**13a**) and 1-iodo-3,3-dimethyl-2-(4-nitropentyloxy)but-1-ene (**14a**) were obtained in 54 and 6% yields, respectively. The formation of iodoalkene **14a** may be derived from the intermediate vinyl(*p*-phenylene)bisiodonium salt (**15a**) which is generated by Michael addition of *p*-nitrophenoxide ion and the successive capture of protons from the methanol solvent. The formation of this type of vinyliodonium salts in the reaction of alkynyliodonium salts has already been reported.[11] The reaction with both sodium *p*-chloro- and *p*-methyl-phenoxides gave similar results.



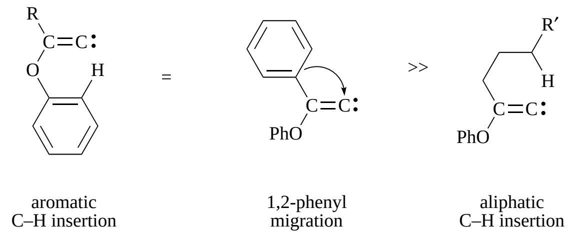
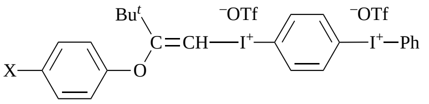


Fig. 1 Reactivity order of β-phenoxyalkylidenecarbenes



15a X = NO$_2$
b X = Cl,
c X = Me

From the above results, the selectivity for aromatic C−H insertion of β-phenoxyalkylidenecarbenes is seen to be considerable. For β-phenoxyalkylidenecarbenes **6**, the present results indicate that aliphatic C−H insertions and 1,2-migrations of alkyl and phenoxy groups do not compete with the aromatic C−H insertion. In 2-phenoxy-2-phenylethenylidene, 1,2-phenyl migration competes with the aromatic C−H insertion to give a mixture of 2-phenylbenzofuran and 1-phenoxy-2-phenylethyne in a 59 : 41 ratio. The relative ease of these processes in the β-phenoxyalkylidenecarbenes, therefore, is as shown in Fig. 1 to stress the point. The high selectivity for aromatic C−H insertion by the alkylidenecarbene may be attributable to the activation of the aromatic C−H bond by the oxygen atom since alkylidenecarbenes are electrophilic in nature.[7,9]

In conclusion, we have confirmed that β-phenoxyalkylidenecarbenes are generated by the reaction of alkynyl(*p*-phenylene)bisiodonium ditriflates with phenoxide anion and undergo the intramolecular aromatic C−H insertion to give benzofurans. Although aromatic C−H insertion of alkylidenecarbenes is rare in solution,[4,5] our results indicate that alkylidenecarbenes undergo intramolecular aromatic C−H insertion even in solution when their substitution is appropriate.

Experimental

General

Melting points were measured with a Yanaco micromelting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained with Bruker AC-250P (250 MHz) and JEOL GSX400 (400 MHz) spectrometers, and ^{13}C NMR spectra with Bruker AC-250P (62.9 MHz) and JEOL GSX (100 MHz) spectrometers. Chemical shifts are given in ppm; *J* values in Hz. IR spectra were obtained with a Horiba FT-200 spectrometer. Elemental analyses were performed by the Service Center of the Elemental Analysis of Organic Compounds, Faculty of Science, Kyushu University. HPLC was performed with a Shimadzu LC-8A. Iodosylbenzene (PhIO) was prepared from (diacetoxyiodo)benzene (Aldrich Chemical Co.) according to the reported procedure.[12] Alkynyl(*p*-phenylene)bisiodonium ditriflates **2** were prepared according to our procedure using [hydroxy(trifluoromethylsulfonyloxy)iodo]-4-[phenyl(trifluoromethylsulfonyloxy)iodo]benzene **1**.[13]

Reaction of alkynyl(*p*-phenylene)bisiodonium ditriflates 3 with phenoxide ion

To a stirred solution of alkynyl(*p*-phenylene)bisiodonium ditriflate **2** (1.0 mmol) in MeOH (10 cm^3) was added dropwise a solution of sodium phenoxide (1.1 mmol) in MeOH (5 cm^3) at 0 °C under a N_2 atmosphere. The mixture was stirred at room temp. for 12 h and quenched by addition of water (20 cm^3). The products were extracted with diethyl ether, the organic layer was washed and dried (anhydrous Na_2SO_4). Evaporation of the solvent gave oily products, which were separated by column chromatography on silica gel. Further separation of 2-phenylbenzofuran and phenyl phenylethynyl ether was conducted by HPLC (eluent: hexane). 2-Alkylbenzofurans **3a–d** were obtained exclusively in the cases of alkyl-substituted iodonium salts **2a–d**. The yields of the products are given in eqn. (4).

2-Butylbenzofuran (3a).[14] Oil; δ_H(CDCl$_3$) 0.95 (t, *J* 7.3, 3 H, Me), 1.37–1.51 (sext, *J* 7.5, 2 H, CH$_2$), 1.69–1.75 (quint, *J* 7.5, 2 H, CH$_2$), 2.75 (t, *J* 7.5, 2 H, CH$_2$), 6.35 (d, *J* 0.7, 1 H, CH), 7.15–7.48 (m, 4 H, ArH); δ_C(CDCl$_3$) 13.82, 22.29, 28.14, 29.79, 101.74, 110.67, 120.14, 122.35, 123.00, 129.02, 154.61, 159.73.

2-*tert*-Butylbenzofuran (3b).[15] Oil; δ_H(CDCl$_3$) 1.36 (s, 9 H, Me), 6.33 (s, 1 H, CH), 7.11–7.48 (m, 4 H, ArH); δ_C(CDCl$_3$) 28.83, 32.92, 98.89, 110.78, 120.32, 122.27, 123.05, 128.89, 139.29, 154.58.

2-Hexylbenzofuran (3c).[16] Oil; δ_H(CDCl$_3$) 0.88 (t, *J* 6.7, 3 H, CH$_3$), 1.26–1.44 (m, 6 H, CH$_2$CH$_2$CH$_2$), 1.72 (quint, *J* 7.4, 2 H, CH$_2$), 2.73 (t, *J* 7.5, 2 H, CH$_2$), 6.33 (d, *J* 0.8, 1 H, CH), 7.11–7.47 (m, 4 H, ArH); δ_C(CDCl$_3$) 14.10, 22.59, 27.66, 28.46, 28.90, 31.60, 101.73, 110.69, 120.14, 122.34, 123.00, 129.03, 154.63, 159.74.

2-Decylbenzofuran (3d). Oil (Found: C, 83.61; H, 10.14. Calc. for $C_{18}H_{26}O$: C, 83.67; H, 10.14%); δ_H(CDCl$_3$) 0.88 (t, *J* 6.8, 3 H, Me), 1.27–1.45 [m, 14 H, (CH$_2$)$_7$], 1.73 (quint, *J* 7.5, 2 H, CH$_2$), 2.75 (t, *J* 7.6, 2 H, CH$_2$), 6.35 (d, *J* 0.7, 1 H, CH), 7.14–7.48 (m, 4 H, ArH); δ_C(CDCl$_3$) 14.12, 22.71, 27.73, 28.49, 29.24, 29.35, 29.40, 29.57, 29.63, 31.93, 101.75, 110.70, 120.15, 122.36, 123.01, 129.09, 154.68, 159.80.

2-Phenylbenzofuran (3e). Mp 120–121 °C (EtOH) (lit., 119–120 °C,[14] 120–121 °C[16]).

Phenyl phenylethynyl ether (5).[4] Yellow oil; δ_H(CDCl$_3$) 7.12–7.48 (m, ArH); δ_C(CDCl$_3$) 46.23 (*C*≡CO), 92.38 (C≡*C*O), 114.97, 122.83, 124.39, 127.35, 128.25, 129.67, 131.69, 156.01; ν/cm^{-1} (neat) 2274 (strong, C≡C).

Reaction of alkynyl(*p*-phenylene)bisiodonium ditriflates with sodium [$^2H_5$]phenoxide

To a solution of alkynyl(*p*-phenylene)bisiodonium ditriflate **2** (1.0 mmol) in MeOH (10 cm^3) was added dropwise a solution of sodium [$^2H_5$]phenoxide (2.0 mmol) in MeOH (10 cm^3) at -50 °C under a N_2 atmosphere. The mixture was allowed to warm to room temp. and stirred for 12 h. A similar workup as above followed by column chromatography on silica gel and HPLC gave benzofuran derivatives in a pure form.

2-Butyl-[3,4,5,6,7-$^2H_5$]-benzofuran (12a). Oil; δ_H(250 MHz, CDCl$_3$) 0.94 (t, *J* 7.3, 3 H, Me), 1.40 (sext, *J* 7.4, 2 H, CH$_2$), 1.71 (quint, *J* 7.5, 2 H, CH$_2$) and 2.74 (t, *J* 7.5, 2 H, CH$_2$); δ_C(26.9 Hz, CDCl$_3$) 13.81, 22.29, 28.12, 29.78, 101.48 (t, $^1J_{C,D}$ 27), 110.32 (t, $^1J_{C,D}$ 25), 119.71 (t, $^1J_{C,D}$ 25), 121.83 (t, $^1J_{C,D}$ 24), 122.51 (t, $^1J_{C,D}$ 24), 128.87, 154.60 and 159.64.

2-Hexyl-[3,4,5,6,7-$^2H_5$]-benzofuran (12b). Oil; δ_H(250 MHz, CDCl$_3$) 0.81 (t, *J* 6.8, 3 H, Me), 1.23–1.34 (m, 6 H, CH$_2$), 1.66 (quint, *J* 7.3, 2 H, CH$_2$) and 2.68 (t, *J* 7.3, 2 H, CH$_2$). δ_C(26.9 Hz, CDCl$_3$) 14.05, 22.55, 27.64, 28.42, 28.87, 31.56, 101.45 (t, $^1J_{C,D}$ 27), 110.31 (t, $J_{C,D}$ 25), 119.69 (t, $^1J_{C,D}$ 24), 121.81 (t, $^1J_{C,D}$ 24), 122.48 (t, $^1J_{C,D}$ 25), 128.86, 154.58 and 159.69.

Reaction of *tert*-butylethynyl(*p*-phenylene)bisiodonium ditriflate 2b with substituted sodium phenoxide

To a solution of *tert*-butylethynyl(*p*-phenylene)bisiodonium ditriflate **2b** (1.0 mmol) in MeOH (10 cm^3) was added dropwise a solution of substituted sodium phenoxide (2.0 mmol) in MeOH (10 cm^3) at -50 °C under a N_2 atmosphere. The mixture was allowed to warm to room temp. and stirred for 12 h. After evaporation of the solvent, diethyl ether was added to the residue, the excess sodium phenoxide and *p*-iodophenyl(phenyl)iodonium triflate were crystallized by trituration from the residue, and filtered off. The ether-soluble oily products were passed through a column of alumina with CH_2Cl_2 eluent and then separated by column chromatography on silica gel. Further purification was conducted with HPLC (eluent: hexane). The minor oily iodoalkenes **14b** and **14c** could not be purified to satisfy the combustion analysis because of impurities.

2-*tert*-Butyl-5-nitrobenzofuran (13a). Mp 83 °C (MeOH) (Found: C, 65.62; H, 5.84; N, 6.30. Calc. for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.98; N, 6.39%); δ_H(250 MHz, CDCl$_3$) 1.40 (s, 9 H, Me), 6.48 (s, 1 H, CH), 7.43–8.37 (m, 3 H, ArH); δ_C(63 MHz, CDCl$_3$) 28.60, 33.25, 99.92, 110.96, 116.80, 119.18, 129.32, 143.87, 157.58, 171.01.

1-Iodo-2-(4-nitrophenoxy)-3,3-dimethylbut-1-ene (14a). Mp 78 °C (MeOH) (Found: C, 41.62; H, 4.18; N, 3.98. Calc. for $C_{12}H_{14}O_3NI$: C, 41.52; H, 4.07; N. 4.04%); δ_H(250 Hz, CDCl$_3$) 1.20 (s, 9 H, Me), 6.17 (s, 1 H, =CH), 7.01–8.23 (m, 4 H, ArH); δ_C(63 MHz, CDCl$_3$) 28.23, 40.00, 64.70, 115.85, 125.88, 142.51, 160.87, 166.11.

2-*tert*-Butyl-5-chlorobenzofuran (13b). Oil (Found: C, 68.77; H, 6.25. Calc. for $C_{12}H_{13}ClO$: C, 69.07; H, 6.28%); δ_H(250 MHz, CDCl$_3$) 1.35 (s, 9 H, Me), 6.27 (s, 1 H, CH), 7.11–7.42 (m, 3 H, ArH); δ_C(63 MHz, CDCl$_3$) 28.72, 33.04, 98.71, 111.68, 119.94, 123.18, 127.79, 130.30, 153.00, 168.99.

1-Iodo-2-(4-chlorophenoxy)-3,3-dimethylbut-1-ene (14b). Oil; δ_H(250 MHz, CDCl$_3$) 1.17 (s, 9 H, Me), 6.05 (s, 1 H, =CH), 6.77–7.26 (m, 4 H, ArH); δ_C(63 MHz, CDCl$_3$) 28.41, 40.00, 63.76, 116.93, 129.30, 138.80, 154.63, 166.55.

2-*tert*-Butyl-5-methylbenzofuran (13c). Oil (Found: C, 82.82; H, 8.45. Calc. for $C_{13}H_{16}O$: C, 82.94; H, 8.57%); δ_H(250 MHz, CDCl$_3$) 1.36 (s, 9 H, Me), 2.40 (s, 3 H, Me), 6.26 (s, 1 H, CH), 6.97–7.30 (m, 3 H, ArH); δ_C(63 MHz, CDCl$_3$) 21.28, 28.83, 32.93, 98.61, 110.24, 120.23, 124.18, 128.99, 131.58, 152.99, 167.48.

1-Iodo-2-(4-methylphenoxy)-3,3-dimethylbut-1-ene (14c). Oil; δ_H(250 MHz, CDCl$_3$) 1.17 (s, 9 H, Me), 2.29 (s, 3 H, Me), 6.01 (s, 1 H, =CH), 6.82–7.09 (m, 4 H, ArH); δ_C(63 MHz, CDCl$_3$) 20.56, 28.51, 40.01, 63.24, 115.38, 129.80, 138.53, 153.96, 166.78.

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Paper 7/00602K
Received 27*th January* 1997
Accepted 18*th March* 1997