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Short Report

Synthesis of Diiodo-Functionalized Benzo[*b*]furans via Electrophilic Iodocyclization

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An electrophilic iodocyclization reaction involving alkynylated 2-iodoanisoles and molecular iodine in the presence of sodium bicarbonate was developed and diiodo-functionalized benzo[*b*]furans were obtained in yields from 45 to 99%.

Keywords: electrophilic iodocyclization, molecular iodine, diiodo-functionalized benzo[*b*]furans, functionalized heteroaromatics, diiodinated compounds

Introduction

Heterocyclic aromatic compounds constitute a class of substances with a considerable diversity of pharmacological properties.[1] Accordingly, natural and synthetic heteroaromatic compounds have been employed as drugs.[2] Focusing on benzo[*b*]furans (**1**), we came across an important subclass of heterocyclic aromatic compounds, which comprises various biological activities, such as anticancer,[3-6] antiviral,[7-9] anti-inflammatory,[10-12] and immunosuppressive.[13,14] In this sense, we present the structures of the benzo[*b*]furans obovaten (**2**), a natural product with pronounced antitumor activity,[15,16] and amiodarone (**3**), a commercial antiarrhythmic drug[17] (Figure 1).

A number of approaches have been developed towards the efficient construction of benzo[*b*]furan scaffolds.[18-26] Among them we highlight the metal-catalyzed cross-coupling/cyclization reactions[18-22] and the electrophilic cyclization reactions employing alkynylanisoles.[23-26] The latter approach can be illustrated by the iodocyclization reaction developed by Larock and co-workers.[26] Nevertheless, in the course of our research activities aiming to the synthesis of diiodo-functionalized compounds,[27-29] for application in selective cross-coupling reactions,[30,31] we observed that diiodo-functionalized benzo[*b*]furans could not be achieved through the reaction between alkynylated 2-iodoanysoles and molecular iodine, using the Larock's conditions for the preparation of iodinated benzo[*b*]furans.[26] In this context, we focused on development of a novel methodology to obtain diiodo-functionalized benzo[*b*]furans via electrophilic iodocyclization reaction, employing alkynylated 2-iodoanysoles and molecular iodine.

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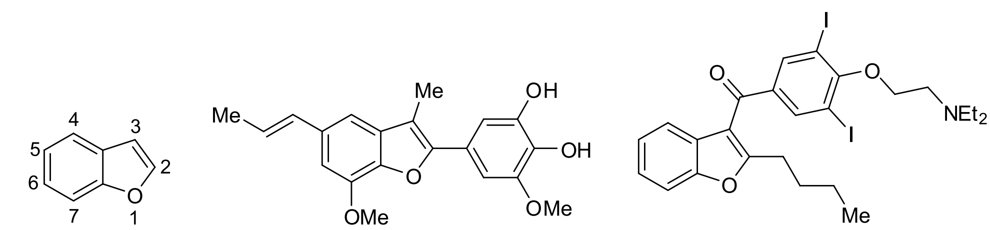
Results and Discussion

Initially, the reaction between the alkynylated 2-iodoanysole **4a** and 2 equiv. of iodine in dichloromethane at room temperature for 3 h provided the diiodo-functionalized benzo[*b*]furan **5a** in a yield lower than 5% (Table 1, entry 1). In an attempt to improve the yield, we performed the reaction between compound **4a** and 2 equiv. of iodine in dichloromethane at room temperature for 12 h and obtained the desired product **5a** in 34% yield (entry 2). When the same transformation was carried out at 40 °C, the diiodo-functionalized benzo[*b*]furan **5a** was isolated in 44% yield (entry 3).

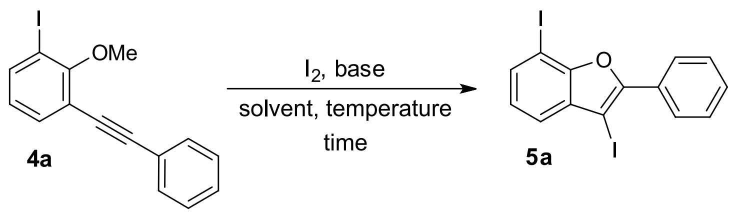
Allowing the reaction between the alkynylated 2-iodoanysole **4a**, 2 equiv. of iodine, and 2 equiv. of $NaHCO_3$ in dichloromethane at 40 °C for 12 h, we obtained the diiodo-functionalized benzo[*b*]furan **5a** in 65% yield (Table 1, entry 4). By employing other bases, namely 2 equiv. of K_2CO_3 and 2 equiv. of *n*-Bu_4NI, the heteroaromatic compound **5a** was obtained in yields of



benzo[*b*]furan (**1**) obovaten (**2**) amiodarone (**3**)

Figure 1. Structures of benzo[*b*]furan compounds.

Table 1. Preparation of diiodo-functionalized benzo[*b*]furan (**5a**)[a]



entry	I_2 (equiv.)	Base (equiv.)	Solvent	Temperature / °C	time / h	Isolated yield / %
1	2	–	CH_2Cl_2	r.t.	3	< 5
2	2	–	CH_2Cl_2	r.t.	12	34
3	2	–	CH_2Cl_2	40	12	44
4	2	$NaHCO_3$ (2)	CH_2Cl_2	40	12	65
5	2	K_2CO_3 (2)	CH_2Cl_2	40	12	51
6	2	*n*-Bu_4NI (2)	CH_2Cl_2	40	12	63
7	2	$NaHCO_3$ (2)	$ClCH_2CH_2Cl$	70	12	82
8	2	$NaHCO_3$ (3)	$ClCH_2CH_2Cl$	70	12	85
9	2	$NaHCO_3$ (3)	$ClCH_2CH_2Cl$	70	24	89
10	3	$NaHCO_3$ (3)	$ClCH_2CH_2Cl$	70	12	87
11	3	$NaHCO_3$ (3)	$ClCH_2CH_2Cl$	70	24	97

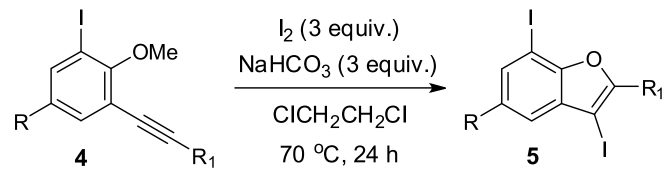
[a]Reaction conditions: 0.25 mmol of compound **4a**, the indicated amount of I_2, the indicated amount of base, and 5 mL of solvent were maintained under stirring at the temperature shown for the indicated time.

51 and 63%, respectively (entries 5 and 6). In order to increase the reaction temperature, we decided to evaluate another solvent. Thus, we carried out the reaction between the alkynylated 2-iodoanysole **4a**, 2 equiv. of iodine, and 2 equiv. of $NaHCO_3$ in 1,2-dichloroethane at 70 °C for 12 h and obtained the diiodo-functionalized benzo[*b*]furan **5a** in 82% yield (entry 7). By using 3 equiv. of $NaHCO_3$, compound **5a** was isolated in 85% yield (entry 8). When the alkynylated 2-iodoanysole **4a** was allowed to react with 2 equiv. of iodine and 3 equiv. of $NaHCO_3$ in 1,2-dichloroethane at 70 °C for 24 h, the diiodo-functionalized benzo[*b*]furan **5a** was obtained in 89% yield (entry 9). By using 3 equiv. of iodine for 12 h, compound **5a** was isolated in 87% (entry 10). Ultimately, the reaction between the alkynylated 2-iodoanysole **4a**, 3 equiv. of iodine, and 3 equiv. of $NaHCO_3$ in 1,2-dichloroethane at 70 °C for 24 h provided the heteroaromatic compound **5a** in 97% isolated yield (entry 11).

Employing the optimal conditions (Table 1, entry 11), we examined the scope of the transformation using alkynylated 2-iodoanysoles **4** with electron-donating and -withdrawing groups attached to the aromatic ring as well as alkyl and aryl groups bonded to the triple bond (Table 2).

Allowing compounds **4a** and **4b** to react with 3 equiv. of iodine and 3 equiv. of $NaHCO_3$ in 1,2-dichloroethane at 70 °C for 24 h, we obtained the desired products **5a** and **5b** in 97 and 71% yields, respectively (Table 2, entries 1 and 2). The reactions between chloro-containing compounds **4c** and **4d** were more sluggish than the transformations presented in entries 1 and 2 and the chloro-containing heteroaromatic compounds **5c** and **5d** were isolated in 57 and 46% yields, respectively (entries 3 and 4). When compounds **4c** and **4d** were allowed to react for 48 h, the desired products **5c** and **5d** were obtained in 92 and 52% yields, respectively (Table 2,

Table 2. Diiodo-functionalized benzo[*b*]furans (**5a**-**i**) prepared by the electrophilic iodocyclization reaction[a]



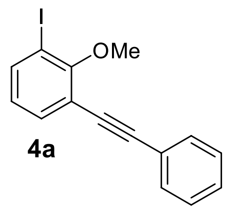
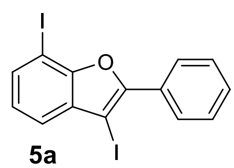
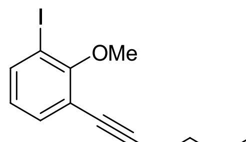
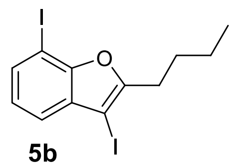
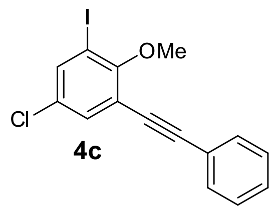
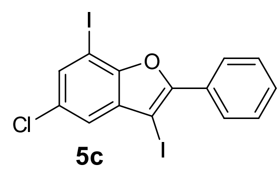
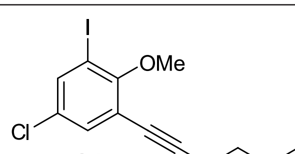
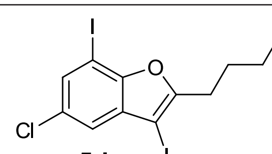
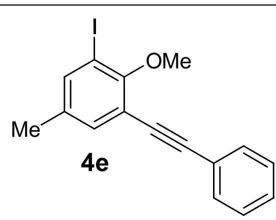
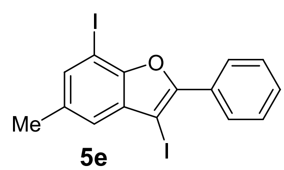
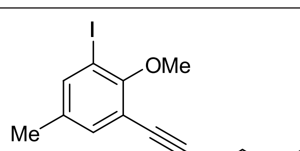
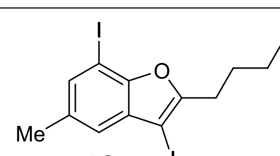
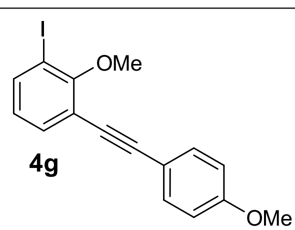
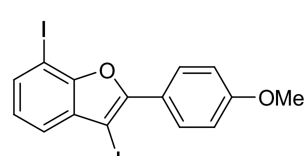
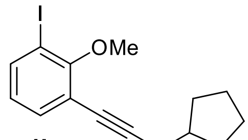
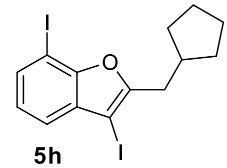
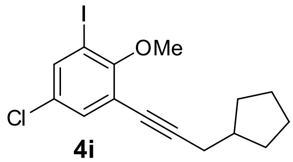
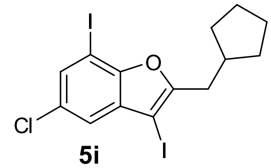
entry	Alkynylated 2-iodoanisole (**4**)	Functionalized benzo[*b*]furan (**5**)	Isolated yield / %
1	 **4a**	 **5a**	97
2	 **4b**	 **5b**	71
3	 **4c**	 **5c**	57 (92)[b]
4	 **4d**	 **5d**	46 (52)[b]
5	 **4e**	 **5e**	99
6	 **4f**	 **5f**	75
7	 **4g**	 **5g**	99

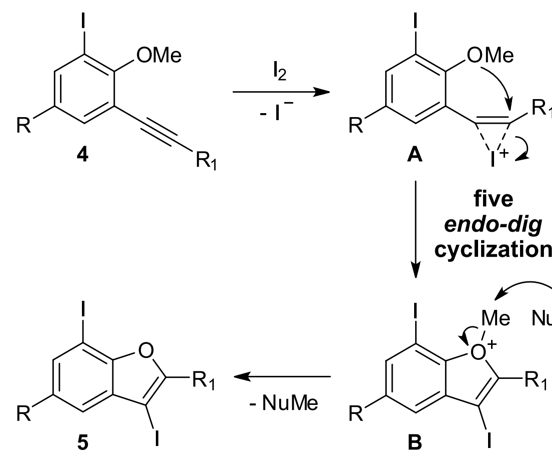
Table 2. Diiodo-functionalized benzo[*b*]furans (**5a**-**i**) prepared by the electrophilic iodocyclization reaction[a] (cont.)

entry	Alkynylated 2-iodoanisole (**4**)	Functionalized benzo[*b*]furan (**5**)	Isolated yield / %
8	 **4h**	 **5h**	69
9	 **4i**	 **5i**	45

[a]Reaction conditions: 0.25 mmol of compound **4a**-**i**, 0.75 mmol of I_2, 0.75 mmol of $NaHCO_3$, and 5 mL of $ClCH_2CH_2Cl$ were maintained under stirring at 70 °C for 24 h; [b]this yield was obtained after 48 h of reaction.

entries 3 and 4). Reactions with methyl-containing compounds **4e** and **4f** in the presence of 3 equiv. of iodine and 3 equiv. of $NaHCO_3$ in 1,2-dichloroethane at 70 °C for 24 h gave the methyl-containing heteroaromatic compounds **5e** and **5f** in isolated yields of 99 and 75%, respectively (entries 5 and 6). When the alkynylated 2-iodoanysole **4g** bearing an electron-rich aromatic ring bonded to the triple bond was subjected to the reaction, the heteroaromatic compound **5g** was obtained in 99% yield (entry 7). We did not try to perform the iodocyclization of an alkynylated 2-iodoanysole bearing an electron-poor aromatic ring bonded to the triple bond. In addition, when the alkynylated 2-iodoanysole **4h** bearing an alkyl group attached to the triple bond was allowed to react, the heteroaromatic compound **5h** was isolated in 69% yield (entry 8). Treatment of the chloro-containing alkynylated 2-iodoanysole **4i** having an alkyl group bonded to the triple bond with 3 equiv. of iodine and 3 equiv. of $NaHCO_3$ in 1,2-dichloroethane at 70 °C for 24 h afforded the desired product **5i** in a moderate yield of 45% (entry 9). Alkynylated anisoles bearing an alkyl group attached to the triple bond fail to undergo electrophilic cyclizations employing the protocol published by Larock and co-workers.[26] However, using our protocol the alkynylated 2-iodoanysoles bearing an alkyl group (**4b**, **4d**, **4f**, **4h**, and **4i**) provided diiodo-functionalized benzo[*b*]furan (**5b**, **5d**, **5f**, **5h**, and **5i**) in reasonable yields (Table 2, entries 2, 4, 6, 8, and 9).

Presumably, the iodocyclization reported proceed through the formation of the iodonium ion **A**, followed by a five *endo-dig* cyclization leading to the oxonium ion **B**, which undergoes methyl group removal via SN_2 displacement by a nucleophile present in the reaction mixture[23-26] (Scheme 1).



Scheme 1. Proposed mechanism for the electrophilic iodocyclization developed.

The structures of compounds **5a-i** were assigned according to their ^1H nuclear magnetic resonance (NMR), ^{13}C NMR, infrared (IR), and mass spectra. All new compounds (**5b-i**) provided high-resolution mass spectra (HRMS) that are in agreement with the proposed structures.

Conclusions

In summary, an electrophilic iodocyclization reaction involving alkynylated 2-iodoanisoles and molecular iodine in the presence of sodium bicarbonate was developed and diiodo-functionalized benzo[*b*]furans were obtained in yields from 45 to 99%. Our transformation provided benzo[*b*]furans even when alkynylated 2-iodoanisoles bearing alkyl groups attached to the triple bond were employed. The iodocyclization reported can be considered a convenient approach to prepare diiodo-functionalized benzo[*b*]furans and should find use in the construction of molecules with interesting biological properties and applications in materials science.

Experimental

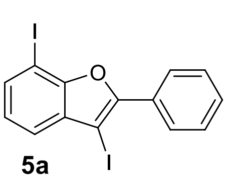
General methods

^{1}H and ^{13}C NMR spectra were recorded on spectrometer operating at 200 and 50 MHz, respectively. ^{1}H NMR spectra were taken in $CDCl_3$, and the chemical shifts were given in ppm with respect to tetramethylsilane (TMS) used as an internal standard. ^{13}C NMR spectra were taken in $CDCl_3$, and the chemical shifts were given in ppm with respect to the deuterated solvent used as a reference. Infrared spectra were obtained using attenuated total reflectance (ATR) technique or KBr pellets in the 4000-400 cm^{-1} region. Mass spectra were carried out employing a gas chromatograph connected to a mass spectrometer using electron impact ionization (EI) at 70 eV. High resolution mass spectra were obtained using a time-of-flight (TOF) mass spectrometer. Melting point values are uncorrected. Column chromatography separations were carried out using 70-230 mesh silica gel. Commercially obtained reagents and solvents were employed without purification. Alkynylated 2-iodoanysoles (**4a-i**) were prepared according to the literature.[31]

General procedure for the preparation of diiodo-functionalized benzo[*b*]furans (**5a**-**i**)

To a vial (20 mL) were added the alkynylated 2-iodoanysole **4** (0.25 mmol), $NaHCO_3$ (63 mg, 0.75 mmol), and a solution of iodine (190 mg, 0.75 mmol) in 1,2-dichloroethane (5 mL). The vial was sealed using a cap, and the mixture was stirred at 70 °C for 24 hours. Afterwards, a saturated solution of sodium thiosulfate (10 mL) was added to the reaction, which was extracted with ethyl acetate (3 × 10 mL). The organic phase was dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using hexane as eluent, affording the diiodo-functionalized benzo[*b*]furan **5**.

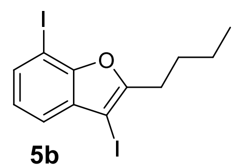
3,7-Diiodo-2-phenylbenzofuran (**5a**)



5a

Yield: 108 mg (97%); off-white solid; m.p. 110-112 °C (lit.[31] m.p. 110-112 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.23-8.18 (m, 2H), 7.70 (dd, 1H, *J* 7.7, 1.1 Hz), 7.55-7.37 (m, 4H), 7.06 (t, 1H, *J* 7.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.9, 153.4, 134.4, 132.4, 129.5, 129.4, 128.5, 127.5, 125.0, 121.9, 74.5, 61.4; IR (KBr) ν_{max} / cm^{-1} 3055, 1905, 1485, 1482, 1060; LRMS *m/z* (%) 446 (100.0), 319 (8.7), 192 (10.0).

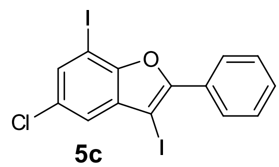
2-Butyl-3,7-diiodobenzofuran (**5b**)



5b

Yield: 75 mg (71%); orange oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.63 (dd, 1H, *J* 7.7, 1.1 Hz), 7.27 (dd, 1H, *J* 7.8, 1.1 Hz), 7.01 (t, 1H, *J* 7.7 Hz), 2.89 (t, 2H, *J* 7.5 Hz), 1.83-1.68 (m, 2H), 1.47-1.25 (m, 2H), 0.96 (t, 3H, *J* 7.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.8, 154.3, 133.4, 131.0, 124.7, 120.9, 74.4, 63.0, 29.9, 27.7, 22.2, 13.8; IR (ATR) ν_{max} / cm^{-1} 2891, 2893, 2916, 2918, 2920, 3045, 1164; LRMS *m/z* (%) 426 (100.0), 383 (31.1), 257 (17.4); HRMS (EI-TOF MS) calculated for $[C_{12}H_{12}I_2O]^+$: 425.8978; found: 425.8986.

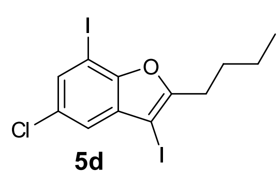
5-Chloro-3,7-diiodo-2-phenylbenzofuran (**5c**)



5c

Yield: 68 mg (57%); off-white solid; m.p. 125-126 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.20-8.15 (m, 2H), 7.67 (d, 1H, *J* 2.0 Hz), 7.56-7.45 (m, 3H), 7.38 (d, 1H, *J* 2.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.9, 152.8, 133.7, 133.1, 129.9, 129.0, 128.6, 127.6, 121.6, 74.6, 60.3; IR (KBr) ν_{max} / cm^{-1} 3064, 1483, 1225, 1058; LRMS *m/z* (%) 480 (100.0), 353 (16.0), 226 (10.6); HRMS (EI-TOF MS) calculated for $[C_{14}H_7ClI_2O]^+$: 479.8275; found: 479.8280.

2-Butyl-5-chloro-3,7-diiodobenzofuran (**5d**)

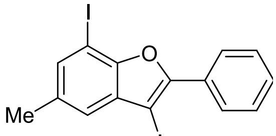


5d

Yield: 53 mg (46%); off-white solid; m.p. 95-96 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.59 (d, 1H, *J* 2.0 Hz), 7.25 (d, 1H, *J* 2.0 Hz), 2.87 (t, 2H, *J* 7.5 Hz), 1.78-1.70 (m, 2H), 1.50-1.32 (m, 2H), 0.96 (t, 3H, *J* 7.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 161.4, 153.1, 132.6, 131.7, 129.4, 120.6, 74.5, 62.2, 29.7, 27.7, 22.2, 13.7; IR (KBr) ν_{max} / cm^{-1} 3100, 2958, 2945, 1436, 1157; LRMS *m/z* (%) 460 (100.0), 417 (62.3), 291 (25.8); HRMS (EI-TOF MS) calculated for $[C_{12}H_{11}ClI_2O]^+$: 459.8588; found: 459.8599.

3,7-Diiodo-5-methyl-2-phenylbenzofuran (**5e**)

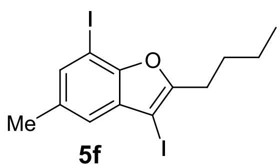
Yield: 114 mg (99%); off-white solid; m.p. 120-121 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.22 (dd, 2H, *J* 8.1, 1.6 Hz),



5e

7.54-7.45 (m, 4H), 7.17 (d, 1H, *J* 0.6 Hz), 2.45 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.5, 152.5, 135.4, 135.1, 132.2, 129.6, 129.4, 128.5, 127.5, 121.9, 74.0, 61.1, 20.9; IR (KBr) ν_{max} / cm^{-1} 3014, 3018, 2910, 2842, 1236, 1064; LRMS *m/z* (%) 460 (100.0), 333 (11.2), 207 (5.8); HRMS (EI-TOF MS) calculated for $[C_{15}H_{10}I_2O]^+$: 459.8821; found: 459.8825.

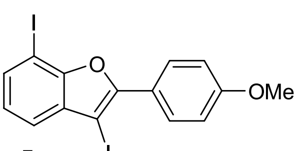
2-Butyl-3,7-diiodo-5-methylbenzofuran (**5f**)



5f

Yield: 82.5 mg (75%); orange oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.47 (d, 1H, *J* 0.9 Hz), 7.05 (d, 1H, *J* 0.6 Hz), 2.87 (t, 2H, *J* 7.5 Hz), 2.41 (s, 3H), 1.81-1.66 (m, 2H), 1.47-1.35 (m, 2H), 0.96 (t, 3H, *J* 7.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.9, 152.8, 134.7, 134.3, 130.9, 120.9, 73.9, 62.7, 29.9, 27.7, 22.2, 20.8, 13.7; IR (ATR) ν_{max} / cm^{-1} 3002, 2925, 2921, 1518, 1135; LRMS *m/z* (%) 440 (100.0), 397 (26.6), 271 (11.1); HRMS (EI-TOF MS) calculated for $[C_{13}H_{14}I_2O]^+$: 439.9134; found: 439.9140.

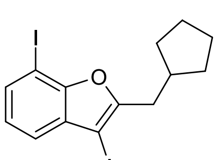
3,7-Diiodo-2-(4-methoxyphenyl)benzofuran (**5g**)



5g

Yield: 118 mg (99%); off-white solid; m.p. 135-137 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.18-8.13 (m, 2H), 7.68 (dd, 1H, *J* 7.7, 1.1 Hz), 7.37 (dd, 1H, *J* 7.8, 1.1 Hz), 7.1-7.0 (m, 3H), 3.89 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 160.6, 153.8, 153.7, 133.9, 132.5, 129.2, 125.0, 122.0, 121.6, 114.0, 74.40, 59.6, 55.4; IR (KBr) ν_{max} / cm^{-1} 3025, 3010, 2980, 2850, 1250, 1120; LRMS *m/z* (%) 476 (100.0), 397 (26.6), 271 (11.1); HRMS (EI-TOF MS) calculated for $[C_{15}H_{10}I_2O_2]^+$: 475.8770; found: 475.8775.

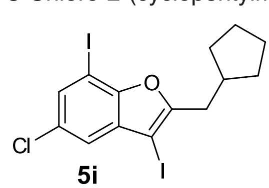
2-(Cyclopentylmethyl)-3,7-diiodobenzofuran (**5h**)



5h

Yield: 78 mg (69%); orange oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.63 (dd, 1H, *J* 7.7 0.9 Hz), 7.27 (d, 1H, *J* 7.7 Hz), 7.01 (t, 1H, *J* 7.7 Hz) 2.88 (d, 2H, *J* 7.4 Hz), 2.41-2.33 (m, 1H), 1.82-1.76 (m, 2H), 1.71-1.66 (m, 2H), 1.59-1.53 (m, 2H), 1.35-1.30 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.7, 154.4, 133.4, 131.0, 124.7, 120.9, 74.4, 63.4, 39.1, 33.6, 32.4, 24.9; IR (ATR) ν_{max} / cm^{-1} 2993, 2920, 2922, 3020, 1591, 1435, 1220; LRMS *m/z* (%) 452 (100.0), 384 (74.1), 257 (58.7); HRMS (EI-TOF MS) calculated for $[C_{14}H_{14}I_2O]^+$: 451.9134; found: 451.9145.

5-Chloro-2-(cyclopentylmethyl)-3,7-diiodobenzofuran (**5i**)



5i

Yield: 54.7 mg (45%); orange oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.60 (d, 1H, *J* 2.0 Hz), 7.26 (d, 1H, *J* 2.0 Hz), 2.87 (d, 2H, *J* 7.4 Hz), 2.39-2.32 (m, 1H), 1.83-1.78 (m, 2H), 1.71-1.67 (m, 2H), 1.60-1.55 (m, 2H), 1.34-1.29 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 161.4, 153.3, 132.7, 131.8, 129.5, 120.8, 74.5, 62.6, 39.1, 33.7, 32.4, 24.9. IR (ATR) ν_{max} / cm^{-1} 3090, 2963, 2951, 1495, 1101; LRMS *m/z* (%) 486 (100.0), 360 (74.1), 233 (38.7); HRMS (EI-TOF MS) calculated for $[C_{14}H_{13}ClI_2O]^+$: 485.8744; found: 485.8755.

Supplementary Information

Supplementary data (^{1}H and ^{13}C NMR spectra) are available free of charge at http://jbcs.sbq.org.br as a PDF file.

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