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Short Report

Palladium- and Copper-Catalyzed Highly Selective Mono-Coupling Between 2,6-Diiodoanisoles and Terminal Alkynes in the Production of Alkynylated Anisoles as Potential Precursors of Benzo[*b*]furans

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A reação de acoplamento entre 2,6-diiodoanisóis e alcinos terminais usando $Pd(PPh_3)_2Cl_2$ e CuI como catalisadores e diisopropilamina como base em tolueno a temperatura ambiente por 12 h produziu seletivamente 2-iodoanisóis aquinilados, em rendimentos de bons a excelentes (52-95%), os quais são blocos de construção úteis com potencial aplicação na síntese de benzo[*b*] furanos funcionalizados.

The coupling reaction between 2,6-diiodoanisoles and terminal alkynes using $Pd(PPh_3)_2Cl_2$ and CuI as catalysts and diisopropylamine as base in toluene at room temperature for 12 h produced selectively alkynylated 2-iodoanisoles, in good to excellent yields (52-95%), which are useful building blocks with potential application in the synthesis of functionalized benzo[*b*]furans.

Keywords: Sonogashira reaction, selective mono-coupling, alkynylated anisoles, diiodinated benzo[*b*]furans, palladium and copper catalysis

Introduction

Palladium-catalyzed cross-coupling reactions can be considered powerful transformations for the construction of carbon-carbon and carbon-heteroatom bonds,[1-4] including, for example, Sonogashira,[1] Stille,[2] Suzuki[3] and Buchwald-Hartwig[4] reactions. The mentioned transformations have been often employed in total syntheses of complex molecules,[5] in the preparation of functional materials[6] and for the production of polymers of importance in materials science.[7] Furthermore, palladium-catalyzed reactions are in agreement with some principles of green chemistry.[8] In this sense, a significant number of high-quality articles involving palladium-catalyzed cross-coupling reactions have been reported in the literature.[1-7] However, a critical evaluation of this active area of the organic chemistry indicates that methodologies for site-selective couplings,[9] involving selective mono-couplings,[10] are still required in organic synthesis, constituting a vast field for investigation. Nevertheless, significant advances for palladium-catalyzed selective couplings between organic halides and organometallic reagents have been reported in the literature.[9-11] Among them, we can mention advances achieved for selective Sonogashira mono-couplings.[11] Despite the advances mentioned, to the best of our knowledge, there is no methodology employing palladium as a catalyst for the selective mono-coupling between 2,6-diiodoanisoles and terminal alkynes, in order to produce alkynylated 2-iodoanisoles, which are useful intermediates in organic synthesis. Accordingly, aiming to enrich the literature, we wish to present in this manuscript results which conducted to the development of a selective mono-coupling between 2,6-diiodoanisoles (**1**) and terminal alkynes (**2**) using palladium and copper as catalysts in the presence of a nitrogen-containing base, in order to produce exclusively alkynylated 2-iodoanisoles (**3**) in good to excellent yields, which are useful building blocks with potential application in the synthesis of functionalized benzo[*b*]furans, that compose a class of aromatic heterocyclic compounds with an extensive number of pronounced biological activities, comprising, for

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example, anticancer,[12] antiviral[13] and anti-inflammatory[14] activities.

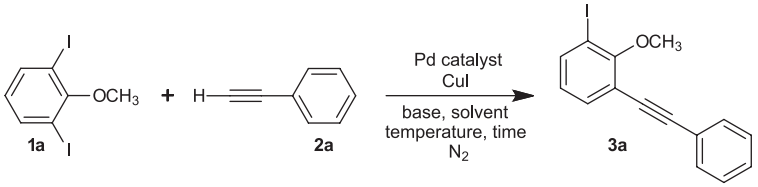
Results and Discussion

Initially, the reaction between 2,6-diiodoanisole (**1a**) and 2 equiv. of phenylacetylene (**2a**) using 10 mol% of $Pd(PPh_3)_2Cl_2$ and 10 mol% of CuI in the presence of 2 equiv. of triethylamine (Et_3N) as base and MeCN as solvent at 50 °C for 24 h gave 1-iodo-2-methoxy-3-(phenylethynyl) benzene (**3a**) in a 41% yield (Table 1, entry 1).[15] In an attempt to produce compound **3a** in a higher yield, we allowed 2,6-diiodoanisole (**1a**) to react with 1.5 equiv. of phenylacetylene (**2a**) using 5 mol% of $Pd(OAc)_2$, 10 mol% of triphenylphosphine (PPh_3) and 5 mol% of CuI in the presence of 2 equiv. of Et_3N as base and MeCN as solvent at 50 °C for 24 h and obtained the alkynylated 2-iodoanisole **3a** in a moderate yield of 43% (entry 2).[16] Thereafter, we carried out the reaction employing 2,6-diiodoanisole (**1a**), 1.5 equiv. of compound **2a**, 10 mol% of $Pd(PPh_3)_4$, 10 mol% of CuI and 2 equiv. of Et_3N in tetrahydrofuran (THF) at 60 °C. After 24 h, compound **3a** was obtained in only 37% yield (entry 3).[17] Ultimately, by the reaction between 2,6-diiodoanisole (**1a**) and 2 equiv. of phenylacetylene (**2a**) using 5 mol% of $Pd(PPh_3)_2Cl_2$ and 15 mol% of CuI in the presence of 1 equiv. of diisopropylamine (DIPA) as base and toluene as solvent at room temperature for 12 h, we produced 1-iodo-2-methoxy-3-(phenylethynyl)benzene (**3a**) in a 68% yield (entry 4).[18] We did not observe the formation of the di-alkynylated product in the transformations outlined in Table 1, although for most cases (entries 1-3) the desired product **3a** was obtained in low yields (≤ 43%). Besides, in all entries in Table 1 we observed by gas chromatography/mass spectrometry (GC/MS) the formation of the alkyne-alkyne homo-coupling as a byproduct.

Afterwards, we focused on the optimization of the conditions for the reaction shown in entry 4 of Table 1, performing variations in the stoichiometry of reagents, temperature and time of reaction, envisioning the production of 1-iodo-2-methoxy-3-(phenylethynyl)benzene (**3a**) in a higher yield. Thus, as can be seen in Table 2, the best result was achieved when we carried out the reaction between 2,6-diiodoanisole (**1a**) and 2 equiv. of phenylacetylene (**2a**) in the presence of 5 mol% of $Pd(PPh_3)_2Cl_2$ and 15 mol% of CuI using 2 equiv. of DIPA as base and toluene as solvent at room temperature for 12 h, producing the alkynylated 2-iodoanisole **3a** in a very good yield of 82% (Table 2, entry 4). In this case, we did not observe the formation of the di-alkynylated product. However, we observed by GC/MS the formation of the alkyne-alkyne homo-coupling as a byproduct.

Employing the optimal conditions shown in Table 2, entry 4, we examined the scope of the selective mono-coupling reaction using for some entries 2,6-diiodoanisoles containing electron-withdrawing and electron-donating groups (**1b**-**c**) and functionalized terminal alkynes (**2c**-**f**) (Table 3). The coupling between 2,6-diiodoanisole (**1a**) and 2 equiv. of 1-hexyne (**2b**) in the presence of 5 mol% of $Pd(PPh_3)_2Cl_2$ and 15 mol% of CuI using 2 equiv. of DIPA as base and toluene as solvent at room temperature for 12 h gave exclusively the compound **3b** in an 82% yield (entry 2). By using 4-choro-2,6-diiodoanisole (**1b**), which contains an electron-withdrawing group, reactions with the alkynes **2a** and **2b** led to the alkynylated 2-iodoanisoles **3c** and **3d**, respectively, in excellent yields (≥ 93%) (entries 3 and 4). For entries 3 and 4 we observed by GC/MS the formation of di-alkynylated products in trace amounts. On the other hand, employing 4-methyl-2,6-diiodoanisole (**1c**), which contains an electron-donating group, reactions with the alkynes **2a** and **2b** were relatively

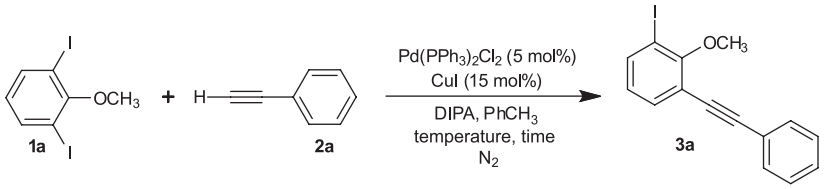
Table 1. Preparation of compound **3a**[a]



entry	Palladium catalyst (mol%)	CuI / mol%	Terminal alkyne **2a** / equiv.	Base (equiv.)	Solvent	Temperature / °C	time / h	Isolated yield / %
1	$Pd(PPh_3)_2Cl_2$ (10)	10	2	Et_3N (2)	MeCN	50	24	41
2	$Pd(OAc)_2$ (5) plus PPh_3 (10)	5	1.5	Et_3N (2)	MeCN	50	24	43
3	$Pd(PPh_3)_4$ (10)	10	1.5	Et_3N (2)	THF	60	24	37
4	$Pd(PPh_3)_2Cl_2$ (5)	15	2	DIPA (1)	$PhCH_3$	r.t.	12	68

[a]Reaction conditions: 1 mmol of compound **1a**, the indicated amount of palladium catalyst, the indicated amount of CuI, the presented amount of **2a**, the presented amount of base and 5 mL of solvent were stirred at the shown temperature for the time presented under nitrogen atmosphere. r.t.: room temperature.

Table 2. Optimization of conditions for the preparation of compound **3a**[a]



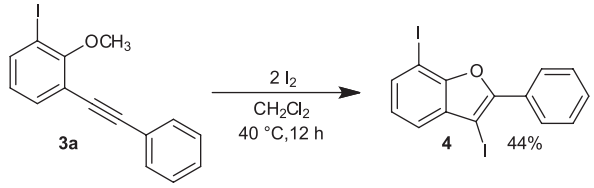
entry	**2a** / equiv.	DIPA / equiv.	Temperature / °C	time / h	Isolated yield / %
1	1	1	r.t.	12	42
2	1.5	1	r.t.	12	57
3	2	1	r.t.	12	68
4	2	2	r.t.	12	82
5	2	2	50	12	71
6	2	2	r.t.	24	81

[a]Reaction conditions: 1 mmol of compound **1a**, 5 mol% of $Pd(PPh_3)_2Cl_2$, 15 mol% of CuI, the indicated amount of **2a**, the indicated amount of DIPA and 5 mL of toluene were stirred at the shown temperature for the presented time under nitrogen atmosphere. r.t.: room temperature.

sluggish leading to the alkynylated 2-iodoanisoles **3e** and **3f**, respectively, in yields around 70% (entries 5 and 6). For entries 5 and 6 we did not observe the formation of di-alkynylated products. In addition, transformations carried out with functionalized terminal alkynes **2c**-**f** produced the mono-coupling products **3g**-**k** in good yields (52-85%) (entries 7-11). Allowing the reaction between 1-iodo-2-methoxy-3-(phenylethynyl)benzene (**3a**) and 2 equiv. of 1-hexyne (**2b**) in the presence of 5 mol% of $Pd(PPh_3)_2Cl_2$ and 15 mol% of CuI using 2 equiv. of DIPA as base and toluene as solvent at room temperature for 12 h, we obtained the unsymmetrical dialkyne **3l** in a good yield of 78% (entry 12). It is noteworthy that when we carried out the coupling reaction between 1,4-diiodobenzene and phenylacetylene (**2a**), employing the optimal conditions shown in Table 2, entry 4, by the addition of DIPA all at once, we observed the prompt formation of a viscous mixture and the exclusive production of the di-coupled product after 12 h, according to GC/MS analysis. Performing the same transformation, however, by the addition of DIPA in portions, we did not notice the formation of a viscous mixture and we observed the production of the mono-coupled product along with the di-coupled product in a ratio of 1 to 1.25 after 12 h, according to GC/MS analysis.

The highly selective formation of alkynylated 2-iodoanisoles (**3a**-**k**) was not completely rationalized until this moment, however, having in mind that iodinated aromatic compounds were employed, the transmetalation reaction can be considered the rate-determining step for the Sonogashira coupling.[1] In this sense, the transition states for the transmetalation step when we consider the catalytic cycle with alkynylated 2-iodoanisoles (**3a**-**k**) are substantially more sterically crowded and presumably present higher energies than the transition states for the transmetalation step when we consider the catalytic cycle involving 2,6-diiodoanisoles (**1a**-**c**). All these assumptions can be supported by the almost exclusive formation of alkynylated 2-iodoanisoles (**3a**-**k**) in good to excellent yields (52-95%).

The alkynylated anisoles **3a**-**l** are versatile building blocks in organic synthesis, which can find application in electrophilic cyclization reactions. Accordingly, we subjected 1-iodo-2-methoxy-3-(phenylethynyl)benzene (**3a**) to the reaction with iodine and obtained the diiodinated benzo[*b*]furan **4** in an isolated yield of 44%[19] (Scheme 1).



Scheme 1. Preparation of benzo[*b*]furan **4**.

The structures of the compounds **3a**-**l** and **4** have been assigned on the basis of a variety of spectroscopic techniques, namely, according to their mass spectra (MS), infrared (IR), ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra. All compounds (**3a**-**l** and **4**) provided high-resolution mass spectra (HRMS) that are in agreement with the proposed structures.

Conclusions

In summary, we developed a highly selective reaction for the mono-coupling between 2,6-diodoanisoles (**1**) and terminal alkynes (**2**) using $Pd(PPh_3)_2Cl_2$ and CuI as catalysts and DIPA as base, in order to produce alkynylated 2-iodoanisoles (**3**) in good to excellent yields (52-95%). Employing the same reaction conditions, the coupling

Table 3. Coupling between iodoanisoles (**1** or **3a**) and terminal alkynes (**2**) in the preparation of alkynylated anisoles (**3**) using $Pd(PPh_3)_2Cl_2$ and CuI as catalysts and diisopropylamine as base in toluene at room temperature[a]

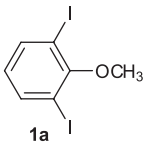
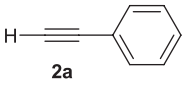
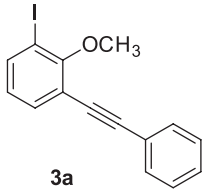
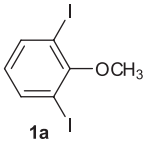
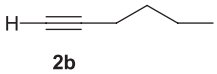
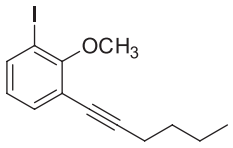
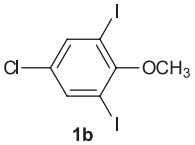
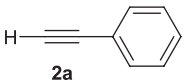
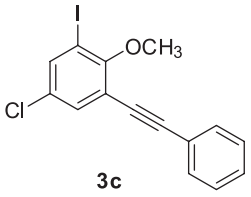
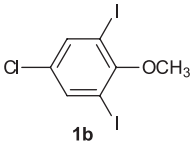
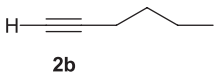
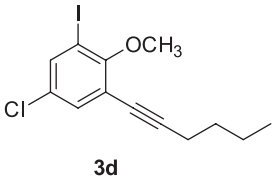
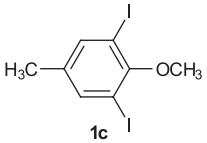
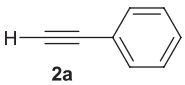
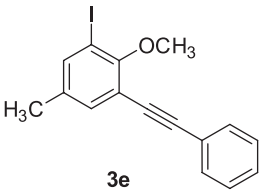
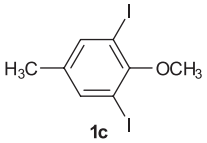
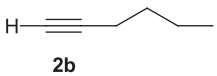
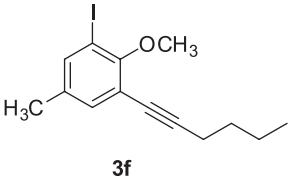
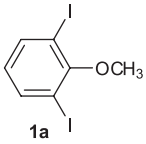
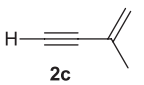
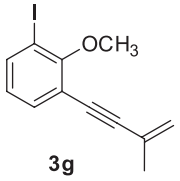
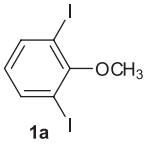
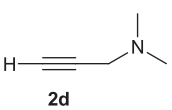
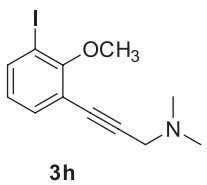
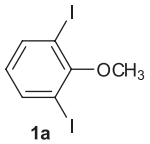
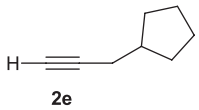
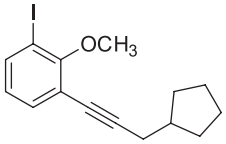
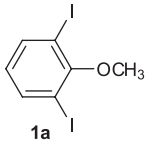
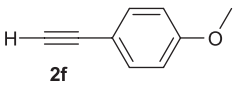
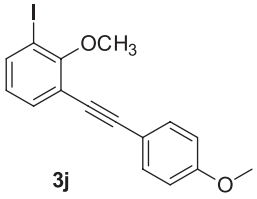
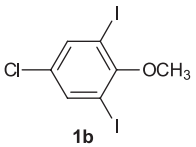
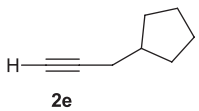
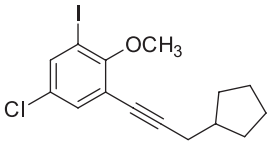
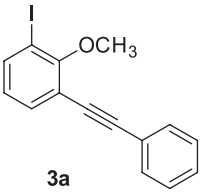
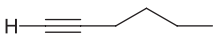
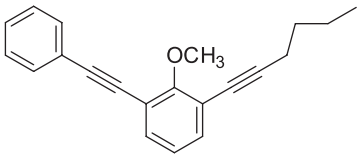
entry	Iodoanisole (**1** or **3a**)	Terminal alkyne (**2**)	Alkynylated anisole (**3**)	Isolated yield / %
1	 **1a**	 **2a**	 **3a**	82
2	 **1a**	 **2b**	 **3b**	82
3	 **1b**	 **2a**	 **3c**	95
4	 **1b**	 **2b**	 **3d**	93
5	 **1c**	 **2a**	 **3e**	70
6	 **1c**	 **2b**	 **3f**	68
7	 **1a**	 **2c**	 **3g**	65
8	 **1a**	 **2d**	 **3h**	62

Table 3. continuation

entry	Iodoanisole (**1** or **3a**)	Terminal alkyne (**2**)	Alkynylated anisole (**3**)	Isolated yield / %
9	 **1a**	 **2e**	 **3i**	78
10	 **1a**	 **2f**	 **3j**	52
11	 **1b**	 **2e**	 **3k**	85
12	 **3a**	 **2b**	 **3l**	78

[a]Reaction conditions: 1 mmol of 2,6-diiodoanisole (**1**) or compound **3a**, 5 mol% of $Pd(PPh_3)_2Cl_2$, 15 mol% of CuI, 2 mmol of terminal alkyne (**2**), 2 mmol of DIPA and 5 mL of toluene were stirred at room temperature for 12 h under nitrogen atmosphere.

between alkynylated 2-iodoanisole **3a** and 1-hexyne (**2b**) led to the formation of the unsymmetrical dialkyne **3l** in a good yield of 78%. Besides, 1-iodo-2-methoxy-3-(phenylethynyl)benzene (**3a**) has found application in the preparation of the diiodinated benzo[*b*]furan **4** in a moderate yield of 44%.

Experimental

General methods

^1H and ^{13}C NMR spectra were recorded on spectrometers operating at 300 or 200 MHz and 75 or 50 MHz, respectively. ^1H NMR spectra were taken in $CDCl_3$ and the chemical shifts of the signals are 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 of the signals are given in ppm with respect to the central peak of the deuterated solvent adjusted to 77.00 ppm and used as a reference. Infrared spectra were obtained using attenuated total reflectance (ATR) or KBr pellets in the 4000-400 cm^{-1} region. Mass spectra were registered on a mass spectrometer connected to a gas chromatograph using electron impact ionization at 70 eV. High-resolution mass spectra were performed on a time-of-flight mass spectrometer. All melting point values are uncorrected. Column chromatography separations were carried out using 70-230 mesh silica gel. Catalysts, reagents and solvents were used as obtained commercially. 2,6-Diiodoanisoles (**1a**-**c**) were prepared according to literature procedures.[20]

General procedure for preparation of mono-coupling products (**3a**-**k**) and unsymmetrical dialkyne **3l**

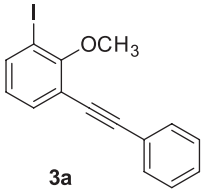
To a solution of the appropriate 2,6-diiodoanisole (**1a**-**c**) or compound **3a** (1 mmol), $Pd(PPh_3)_2Cl_2$ (0.0351 g, 0.05 mmol) and CuI (0.0285, 0.15 mmol) in toluene (5 mL) under nitrogen atmosphere were added the appropriate terminal alkyne (**2a**-**f**) (2 mmol) and diisopropylamine (0.2020 g, 2 mmol). After that, the mixture was stirred at room temperature for 12 h. Then, brine (20 mL) was added to the reaction, which was extracted with ethyl acetate (3 × 20 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, unless

otherwise indicated, affording mono-coupling products (**3a**-**k**) and the unsymmetrical dialkyne **3l**.

Procedure for preparation of benzo[*b*]furan **4**

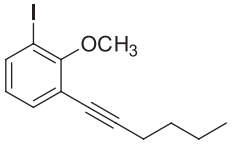
To a vial (20 mL) were added 2-iodo-2-methoxy-3-(phenylethynyl)benzene (**3a**) (0.0835 g, 0.25 mmol) and a solution of iodine (0.1270 g, 0.5 mmol) in CH_2Cl_2 (5 mL). The vial was sealed using a cap, and the mixture was stirred at 40 °C for 12 h. Afterwards, a saturated solution of sodium thiosulfate (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 3,7-diiodo-2-phenylbenzo[*b*]furan (**4**).

Characterization data for compounds **3a-l** and **4**



3a

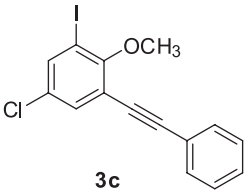
1-Iodo-2-methoxy-3-(phenylethynyl) benzene (**3a**): Rf = 0.33 (obtained after three runs in hexane); yield 0.2739 g (82%); yellowish oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.75 (dd, 1H, *J* 7.9, 1.6 Hz), 7.57-7.52 (m, 2H), 7.74 (dd, 1H, *J* 7.7, 1.6 Hz), 7.39-7.34 (m, 3H), 6.82 (t, 1H, *J* 7.8 Hz), 4.03 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 160.3, 139.4, 133.7, 131.5, 128.6, 128.4, 125.4, 122.9, 117.6, 94.5, 91.8, 85.0, 61.0; IR (ATR) ν_{max}/cm^{-1} 1653, 1238, 1026, 522; LRMS *m/z* (%) 334 (100.0), 257 (5.1), 178 (6.4), 164 (2.8); HRMS [M + Na]$^+$ found: 356.9746, calcd.: 356.9752.



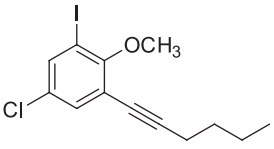
3b

1-(Hex-1-ynyl)-3-iodo-2-methoxy-benzene (**3b**): Rf = 0.63 (obtained after three runs in hexane); yield 0.2575 g (82%); yellowish oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.68 (dd, 1H, *J* 7.9, 1.6 Hz), 7.34 (dd, 1H, *J* 7.7, 1.6 Hz), 6.75 (t, 1H, *J* 7.8 Hz), 3.93 (s, 3H), 2.45 (t, 2H, *J* 6.8 Hz), 1.61-1.45 (m, 4H), 0.93 (t, 3H, *J* 7.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 160.3, 138.6, 133.8, 125.3, 118.4, 96.0, 91.7, 76.1, 60.7, 30.6, 22.0, 19.3, 13.6; IR (ATR) ν_{max}/cm^{-1} 1647, 1239, 1071, 716, 500; LRMS *m/z* (%) 314 (100.0), 299 (37.7), 257 (33.4), 144 (35.9); HRMS [M + Na]$^+$ found: 337.0050, calcd.: 337.0065.

5-Chloro-1-iodo-2-methoxy-3-(phenylethynyl)benzene (**3c**): Rf = 0.67 (obtained after three runs in hexane); yield 0.3495 g (95%); off-white solid; m.p. 68-69 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.71 (d, 1H, *J* 2.5 Hz), 7.56-7.50 (m, 2H), 7.46 (d, 1H, *J* 2.5 Hz), 7.41-7.33 (m, 3H), 4.00 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.1, 138.4, 133.1, 131.6, 129.5, 129.0, 128.5, 122.4, 118.2, 95.5, 92.0, 83.8, 61.1; IR (KBr) ν_{max}/cm^{-1} 1653, 1240, 1025, 754, 511; LRMS *m/z* (%) 368 (100.0), 206 (3.2), 291 (4.3), 178 (5.6); HRMS [M + Na]$^+$ found: 390.9352, calcd.: 390.9363.

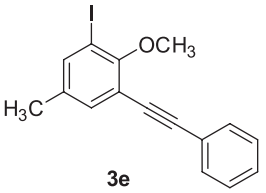


3c



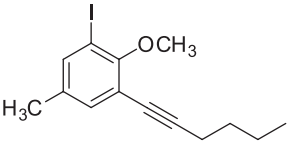
3d

5-Chloro-1-(hex-1-ynyl)-3-iodo-2-methoxybenzene (**3d**): Rf = 0.51 (obtained after three runs in hexane); yield 0.3236 g (93%); yellowish oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.65 (d, 1H, *J* 2.5 Hz), 7.32 (d, 1H, *J* 2.5 Hz), 3.91 (s, 3H), 2.44 (t, 2H, *J* 6.8 Hz), 1.61-1.46 (m, 4H), 0.95 (t, 3H, *J* 7.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.2, 137.7, 133.3, 129.3, 119.1, 97.3, 91.8, 75.1, 60.8, 30.5, 22.0, 19.3, 13.6; IR (ATR) ν_{max}/cm^{-1} 2228, 1232, 1099, 723, 509; LRMS *m/z* (%) 349 (100.0), 291 (10.9), 178 (6.6); HRMS [M + Na]$^+$ found: 370.9673, calcd.: 370.9676.



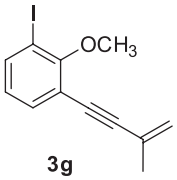
3e

1-Iodo-2-methoxy-5-methyl-3-(phenylethynyl)benzene (**3e**): Rf = 0.47 (obtained after three runs in hexane); yield 0.2436 g (70%); orange oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.56-7.48 (m, 3H), 7.36-7.31 (m, 3H), 7.26 (d, 1H, *J* 2.1 Hz), 3.97 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.1, 139.8, 135.1, 134.0, 131.4, 128.4, 128.3, 122.9, 116.8, 94.0, 91.5, 85.1, 60.9, 20.0; IR (ATR) ν_{max}/cm^{-1} 1003, 1242, 756; LRMS *m/z* (%) 348 (100.0), 347 (26.2), 178 (7.5); HRMS [M + H]$^+$ found: 349.0072, calcd.: 349.0089.



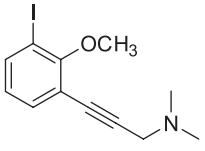
3f

1-(Hex-1-ynyl)-3-iodo-2-methoxy-5-methylbenzene (**3f**): Rf = 0.31 (obtained after three runs in hexane); yield 0.2231 g (68%); yellowish oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.49 (dd, 1H, *J* 2.2, 0.6 Hz), 7.14 (dd, 1H, *J* 2.0, 0.6 Hz), 3.89 (s, 3H), 2.45 (t, 2H, *J* 6.8 Hz), 2.21 (s, 3H), 1.61-1.46 (m, 4H), 0.95 (t, 3H, *J* 7.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.1, 139.0, 135.0, 134.2, 117.7, 95.4, 91.3, 60.6, 30.6, 29.6, 21.9, 19.9, 19.2, 13.6; IR (ATR) ν_{max}/cm^{-1} 2230, 1240, 1005, 725, 581; LRMS *m/z* (%) 328 (100.0), 313 (13.5), 271 (16.8), 171 (9.5); HRMS [M + Na]$^+$ found: 351.0210; calcd.: 351.0222.



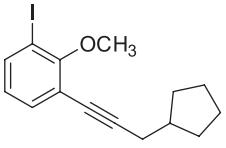
3g

1-Iodo-2-methoxy-3-(3-methylbut-3-en-1-ynyl)benzene (**3g**): Rf = 0.58 (obtained after three runs in hexane); yield 0.1937 g (65%); colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.72 (dd, 1H, *J* 7.9, 1.6 Hz), 7.38 (dd, 1H, *J* 7.7, 1.6 Hz), 6.78 (t, 1H, *J* 7.8 Hz), 5.43-5.41 (m, 1H), 5.35-5.32 (m, 1H), 3.97 (s, 3H), 2.00 (dd, 3H, *J* 1.5, 1.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 160.2, 139.3, 133.6, 126.6, 125.3, 122.4, 117.5, 95.7, 91.7, 83.9, 60.8, 23.2; IR (ATR) ν_{max}/cm^{-1} 2936, 1238, 1032, 1003, 779; LRMS *m/z* (%) 298 (100.0), 283 (22.0), 271 (0.5), 257 (4.6), 244 (0.7), 141 (13.2), 128 (57.3); HRMS [M + Na]$^+$ found: 320.9723, calcd.: 320.9752.



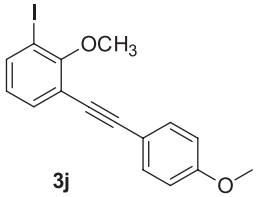
3h

3-(3-Iodo-2-methoxyphenyl)-*N,N*-dimethylprop-2-yn-1-amine (**3h**): The eluents used were ethyl acetate and then methanol. Rf = 0.62 (ethyl acetate and then methanol); yield 0.1953 g (62%); brownish solid; m.p. 49-50 ºC; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.73 (dd, 1H, *J* 7.9, 1.6 Hz), 7.40 (dd, 1H, *J* 7.7, 1.6 Hz), 6.78 (t, 1H, *J* 7.8 Hz), 3.95 (s, 3H), 3.56 (s, 2H), 2.40 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 160.3, 139.2, 133.9, 125.3, 117.5, 91.7, 89.6, 81.0, 60.9, 48.5, 44.0; IR (KBr) ν_{max}/cm^{-1} 2934, 2207, 1238, 777; LRMS *m/z* (%) 341 (25.1), 300 (10.1), 284 (15.7), 270 (100.0), 157 (8.4); HRMS [M + H]$^+$ found: 316.0196, calcd.: 316.0198.



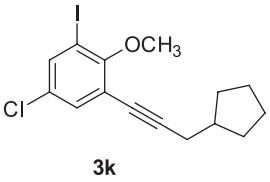
3i

1-(3-Cyclopentylprop-1-ynyl)-3-iodo-2-methoxybenzene (**3i**): Rf = 0.41 (obtained after three runs in hexane); yield 0.2652 g (78%); yellowish oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.68 (dd, 1H, *J* 7.9, 1.6 Hz), 7.34 (dd, 1H, *J* 7.7, 1.6 Hz), 6.75 (t, 1H, *J* 7.8 Hz), 3.94 (s, 3H), 2.47 (d, 2H, *J* 6.7 Hz), 2.16 (septet, 1H, *J* 7.3 Hz), 1.88-1.79 (m, 2H), 1.68-1.57 (m, 4H), 1.41-1.30 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 160.3, 138.6, 133.9, 125.3, 118.5, 95.5, 91.7, 60.7, 39.0, 32.0, 29.7, 25.4, 25.3; IR (ATR) ν_{max}/cm^{-1} 2949, 2227, 1238, 1003, 776; LRMS *m/z* (%) 340 (24.8), 325 (43.3), 297 (19.4), 257 (100.0), 146 (98.6); HRMS [M + Na]$^+$ found: 363.0217, calcd.: 363.0222.



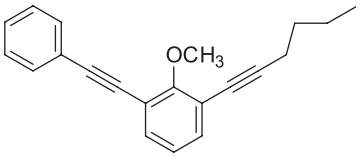
3j

1-Iodo-2-methoxy-3-((4-methoxyphenyl)ethynyl) benzene (**3j**): Rf = 0.48 (obtained after three runs in hexane); yield 0.1893 g (52%); yellowish oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.73 (dd, 1H, *J* 7.9, 1.5 Hz), 7.9-7.43 (m, 3H), 6.92-6.87 (m, 2H), 6.81 (t, 1H, *J* 7.8 Hz), 4.02 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 160.1, 159.9, 139.1, 133.6, 133.0, 125.4, 118.0, 115.1, 114.1, 94.7, 91.8, 83.7, 60.9, 55.3; IR (ATR) ν_{max}/cm^{-1} 2915, 2210, 1241, 1000, 751; LRMS *m/z* (%) 364 (98.1), 363 (100.0), 349 (9.3), 333 (11.1), 257 (2.6), 165 (6.4); HRMS [M + Na]$^+$ found: 386.9854, calcd.: 386.9858.



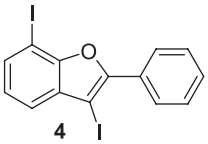
3k

5-Chloro-1-(3-cyclopentylprop-1-ynyl)-3-iodo-2-methoxybenzene (**3k**): Rf = 0.62 (obtained after three runs in hexane); yield 0.3179 g (85%); yellowish oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.65 (d, 1H, *J* 2.5 Hz), 7.32 (d, 1H, *J* 2.5 Hz), 3.91 (s, 3H), 2.46 (d, 2H, *J* 6.7 Hz), 2.15 (septet, 1H, *J* 7.3 Hz), 1.92-1.79 (m, 2H), 1.67-1.55 (m, 4H), 1.39-1.27 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.2, 137.6, 133.3, 129.3, 119.1, 96.8, 91.8, 75.2, 60.8, 38.9, 32.0, 25.4, 25.2; IR (ATR) ν_{max}/cm^{-1} 2948, 1572, 1537, 1233, 999, 577; LRMS *m/z* (%) 374 (100.0), 345 (9.3), 339 (20.8), 291 (45.9), 212 (12.2); HRMS [M + Na]$^+$ found: 396.9830, calcd.: 396.9832.



3l

1-(Hex-1-ynyl)-2-methoxy-3-(phenylethynyl) benzene (**3l**): Rf = 0.29 (obtained after three runs in hexane); yield 0.2246 g (78%); yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.49-7.44 (m, 2H), 7.33 (dd, 1H, *J* 7.7, 1.7 Hz), 7.30-7.24 (m, 4H), 6.91 (t, 1H, *J* 7.7 Hz), 3.99 (s, 3H), 2.39 (t, 2H, *J* 6.9 Hz), 1.58-1.39 (m, 4H), 0.88 (t, 3H, *J* 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8, 133.6, 132.7, 131.5, 128.3, 123.4, 123.3, 118.3, 117.4, 95.2, 93.5, 76.2, 61.1, 30.7, 21.9, 19.3, 13.6; IR (ATR) ν_{max}/cm^{-1} 3057, 2955, 2932, 1597, 1412, 1236, 1005, 754; LRMS *m/z* (%) 288 (100.0), 273 (14.1), 245 (30.2), 231 (27.3), 207 (20.3), 152 (9.1), 77 (7.4); HRMS [M + NH_4]$^+$ found: 306.1849, calcd.: 306.1858.



4

3,7-Diiodo-2-phenylbenzo[*b*]furan (**4**): Rf = 0.54 (hexane); yield 0.0490 g (44%); off-white solid; m.p. 110-112 ºC; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.23-8.17 (m, 2H), 7.70 (dd, 1H, *J* 7.7, 1.1 Hz), 7.55-7.43 (m, 3H), 7.39 (dd, 1H, *J* 7.8, 1.1 Hz), 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, 75.6, 62.4; IR (KBr) ν_{max}/cm^{-1} 3055, 1905, 1485, 1482, 1060; LRMS *m/z* (%) 446 (100.0), 319 (8.7), 192 (10.0); HRMS [M + Na]$^+$ found: 468.8548, calcd.: 468.8562.

Supplementary Information

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

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