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Article

Synthesis of Unsymmetrical Aryl-Ethynylated Benzenes via Regiocontrolled Sonogashira Reaction of 1,3,5-Tribromobenzene

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O acoplamento de Sonogashira do trimetilsililacetileno com 4-alcóxi-1-iodobenzenos resultou em 2-(4-(alquilóxi)fenil)etiniltrimetilsilanos, que sofrem desproteção pela retirada do grupo TMS usando fluoreto de tetrabutilamônio (TBAF) em THF à temperatura ambiente, resultando nos 2-(4-(alquilóxi)fenil)acetilenos terminais correspondentes. O acoplamento cruzado de Sonogashira do 1,3,5-tribromobenzeno com os arilacetilenos terminais em meio aquoso resultou na formação de derivados de benzeno mono-, di- e tri-alquinilados com rendimentos de moderados a bons. Os fatores que afetam a regiosseletividade da alquinilação também foram examinados.

Sonogashira coupling of trimethylsilylacetylene with 4-alkyloxy-1-iodobenzenes gave 2-(4-(alkyloxy)phenyl)ethynyltrimethylsilanes which undergo deprotection via removal of TMS-group using tetrabutylammonium fluoride (TBAF) in THF at room temperature to afford the corresponding terminal 2-(4-(alkyloxy)phenyl)acetylenes. Regiocontrolled Sonogashira cross-coupling of 1,3,5-tribromobenzene with the terminal arylacetylenes in aqueous medium resulted in the formation of mono-, di- and tri-alkynylated benzene derivatives in moderate to good yields. Factors affecting the regioselective alkynylation were also examined.

Keywords: arylacetylenes, cross-coupling, catalysis, palladium, aqueous media

Introduction

Sonogashira cross-coupling, reaction of terminal alkynes with aryl halides in the presence of palladium(0)/copper(I) catalyst under basic conditions, has been established as one of the most convenient routes to symmetrical and unsymmetrical diarylethynes of potential biological and non-biological applications.[1-8] Synthesis of terminal arylacetylenes can be achieved through palladium-catalyzed Sonogashira coupling of aryl halides with mono-protected acetylenes followed by removal of the protecting group.[9,10] Furthermore, terminal arylacetylenes are involved in the construction of conjugated oligo- and polyarylacetylenes of wide range of industrial applications.[11-14] Polyhalogenated arenes were employed in Sonogashira coupling reactions with terminal alkynes.[15-24] In addition, aqueous organic solvents have been used for promotion of Sonogashira cross-coupling reactions in the presence of $PdCl_2(PPh_3)_2$.[25-29] In continuation of our research work on Sonogashira coupling reaction[27,30] we report in this work a regiocontrolled Sonogashira cross-coupling on 1,3,5-tribromobenzene as attractive strategy for synthesis of unsymmetrical ethynylated benzene derivatives. The effect of solvent/base ratios on the optimization of the regiocontrolled cross-coupling is evaluated.

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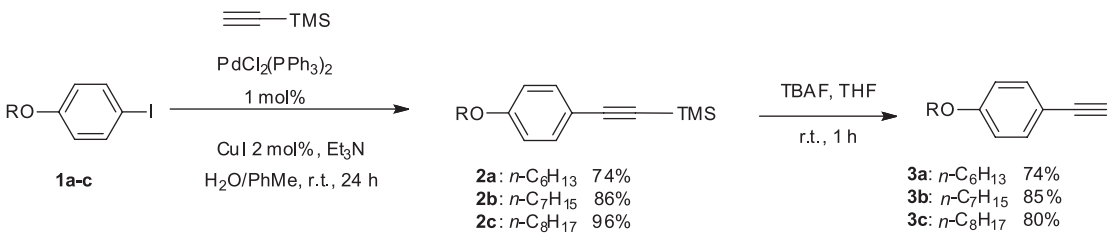
Results and Discussion

At first, three different 4-alkyloxy-1-iodobenzene derivatives **1a-c** were easily synthesized by reaction of 4-iodophenol with the appropriate alkyl bromides in dimethylsulfoxide (DMSO) in the presence of KOH at room temperature according to the reported Williamson method.[31] Then, Sonogashira coupling of trimethylsilylacetylene with 4-alkyloxy-1-iodobenzene derivatives **1a-c** using $PdCl_2(PPh_3)_2$ (1 mol%) and CuI (2 mol%) in water/toluene (2 mL, 1:1) in the presence of 2 equivalents of triethylamine (Et_3N) at room temperature for 24 h afforded 2-(4-(alkyloxy)phenyl)ethynyl-trimethylsilane **2a-c** in 74, 86 and 96% yields, respectively (Scheme 1).

Next, removal of the trimethylsilyl (TMS) group from 2-(4-(alkyloxy)phenyl)-ethynyltrimethylsilanes **2a-c** is



Scheme 1. Synthesis of 4-(alkyloxy)phenylacetylenes **2a**-**c**.

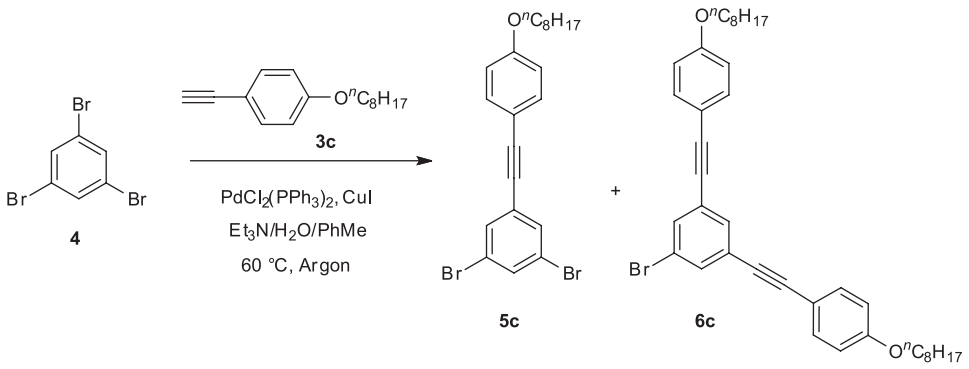
achieved under mild conditions using tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) following a related literature methodology.[32] The deprotection process is completed within one hour at room temperature to afford the corresponding terminal arylacetylene products **3a**-**c** in 74-85% yields. Further deprotection methods were reported using strong bases (such as NaH, NaOH, KOH, K_2CO_3 or *t*-BuOK) at high temperature.[33-38]

Regio-controlled Sonogashira cross-coupling of 1,3,5-tribromobenzene **4** with 1-ethynyl-4-(alkyloxy) benzenes **3a-c**

In the next part, the scope and limitations of the palladium-catalyzed regio-controlled Sonogashira cross-coupling reactions of 1,3,5-tribromobenzene **4** were investigated. Optimization of the reaction conditions for the regio-selective synthesis of mono-ethynylated dibromobenzene **5c** from 1,3,5-tribromobenzene **4** was performed and the results are outlined in Table 1. Thus, firstly the cross-coupling reaction of 1,3,5-tribromobenzene **4** with 1-ethynyl-4-(octyloxy)benzene **3c** in 1:1 molar ratio using $PdCl_2(PPh_3)_2$ (1 mol%) in the presence of CuI (2 mol%) using triethylamine (4 equiv.) was carried out in water/toluene (1:1, v/v) under argon atmosphere at 60 °C for 24 h till full conversion of **4** as examined by thin layer chromatography (TLC). After column chromatography, two products were isolated. The major product was obtained in 74% yield (Table 1, entry 1) and its structure was established as 1,3-dibromo-5-(2-(4-(octyloxy)phenyl)-ethynyl)-benzene **5c** on the basis of its spectral analyses. The mass spectrum of **5c** exhibited a peak at *m/z* 464 corresponding to its molecular ion and its ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were in accordance with the assigned structure. The minor product was isolated in 20% and was confirmed as 1-bromo-3,5-di-(2-(4-(octyloxy)phenyl)-ethynyl)benzene **6c** on the basis of its spectral analyses. Repeating the same reaction under similar conditions using three equiv. of Et_3N led to the formation of mono- and di-ethynylated bromobenzenes **5c** and **6c** in 80 and 12% isolated yields, respectively (Table 1, entry 2). Using two equiv. of Et_3N gave the desired products **5c** and **6c** in 90 and 8% isolated yields, respectively (Table 1, entry 3). The use of neat toluene as solvent under the optimized coupling conditions above employing 2 equiv. of Et_3N gave the products **5c** and **6c** in lower yields, 62 and 3% isolated yields, respectively (Table 1, entry 4). Similarly, performing the coupling reaction in degassed neat water under argon in the presence of 2 equiv. of Et_3N gave the products **5c** and **6c** in 70 and 5% isolated yields, respectively (Table 1, entry 5). Furthermore, the use of one equivalent of Et_3N in water/toluene (1:1, v/v) resulted in the formation **5c** and **6c** in 78 and 18%, respectively (Table 1, entry 6). Under the latter condition, coupling of **4** with **3c** in toluene only afforded **5c** and **6c** in 45 and 9%, respectively (Table 1, entry 7). These results of entries 1-3 and 6, Table 1, are consistent with the reported ones declaring that aqueous organic solvents enhance Sonogashira cross-coupling reactions in the presence of $PdCl_2(PPh_3)_2$.[25-29] Accordingly, the selectivity towards mono-ethynylated dibromobenzene **5c** reached its maximum when 2 equiv. of Et_3N and 1 equiv. of alkyne **3c** were employed using a mixed reaction solvent; water/toluene (1:1, v/v).

Under the optimized conditions, regio-controlled Sonogashira cross-coupling reactions of further arylacetylenes **3a**-**b** with 1,3,5-tribromobenzene **4** was achieved as depicted in Table 2. Thus, cross-coupling of 1,3,5-tribromobenzene **4** with 1-ethynyl-4-(hexyloxy) benzene **3a** and with 1-ethynyl-4-(heptyloxy)benzene **3b** were carried out in 1:1 molar ratio using $PdCl_2(PPh_3)_2$ in the presence of CuI in toluene/water mixed solvent and triethylamine as a base under argon atmosphere at 60 °C for 24 h resulted, in both cases, in full conversion into two products (major and minor) as depicted in Table 2. The reaction molar ratios were typically: 1 mmol arylacetylenes **3a**-**b**, 1 mmol 1,3,5-tribromobenzene **4**, 2 mmol Et_3N, 1 mol% $PdCl_2(PPh_3)_2$ and 2 mol% CuI in water/toluene (2 mL, 1:1 v/v). The major products were obtained in 94 and 93% yields, respectively (Table 2, entries 1 and 2) and their structures were established as 1-(3,5-dibromophenyl)-2-(4-hexyloxyphenyl)acetylene **5a** and 1-(3,5-dibromophenyl)-2-(4-heptyloxyphenyl) acetylene **5b** on the basis of their elemental and spectral analyses. The minor products were isolated in 2 and 4%, respectively (Table 2, entries 1 and 2), and were confirmed

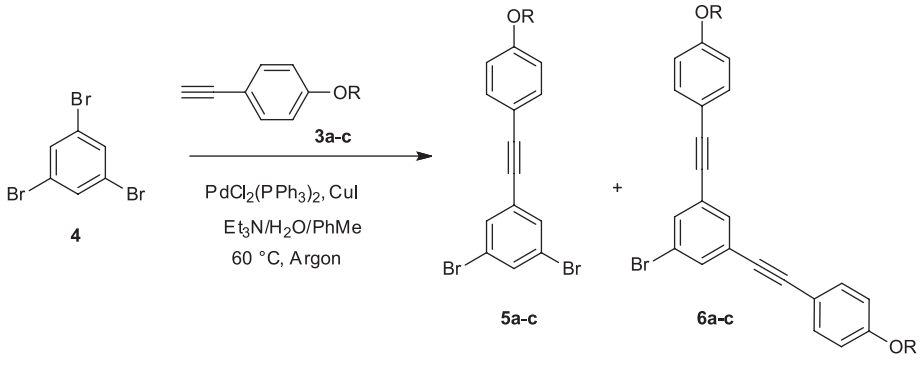
Table 1. Regio-controlled Sonogashira cross-coupling of 1,3,5-tribromobenzene **4** with 1-ethynyl-4-(octyloxy)benzene **3c**



entry	Solvent	Et_3N / equiv.	Yield[a] / %	
			5c	**6c**
1	Toluene/water (1:1)	4	74	20
2	Toluene/water (1:1)	3	80	12
3	Toluene/water (1:1)	2	90	8
4	Toluene	2	62	3
5	Water	2	70	5
6	Toluene/water (1:1)	1	78	18
7	Toluene	1	45	9

[a]Reaction condition: bromide **4**/alkyne **3c**/$PdCl_2(PPh_3)_2$ (mol%)/CuI (mol%)/solvent (mL): 1:1:1:2:2, thermal heating under argon atmosphere at 60 °C.

Table 2. Regio-controlled Sonogashira coupling of 1,3,5-tribromobenzene **4** with 1-ethynyl-4-(alkyloxy)benzenes **3a-c**



entry	R	Yield / %	
		5a-c	**6a-c**
1	n-C_6H_{13}	(**5a**) 94	(**6a**) 2
2	n-C_7H_{15}	(**5b**) 93	(**6b**) 4
3	n-C_8H_{17}	(**5c**) 90	(**6c**) 8

[a]Conditions: bromide **4**/alkynes **3a-c**/$PdCl_2(PPh_3)_2$ (mol%)/CuI (mol%)/Et_3N (equiv.)/water (mL)/toluene (mL): 1:1:1:2:2:1:1, thermal heating under argon atmosphere at 60 °C.

as 1-bromo-3,5-di-(2-(4-hexyloxyphenyl)-ethynyl) benzene **6a** and 1-bromo-3,5-di-(2-(4-heptyloxyphenyl) ethynyl)benzene **6b** on the basis of their spectral analyses (^{1}H, ^{13}C NMR and mass spectra) as mentioned in the experimental section.

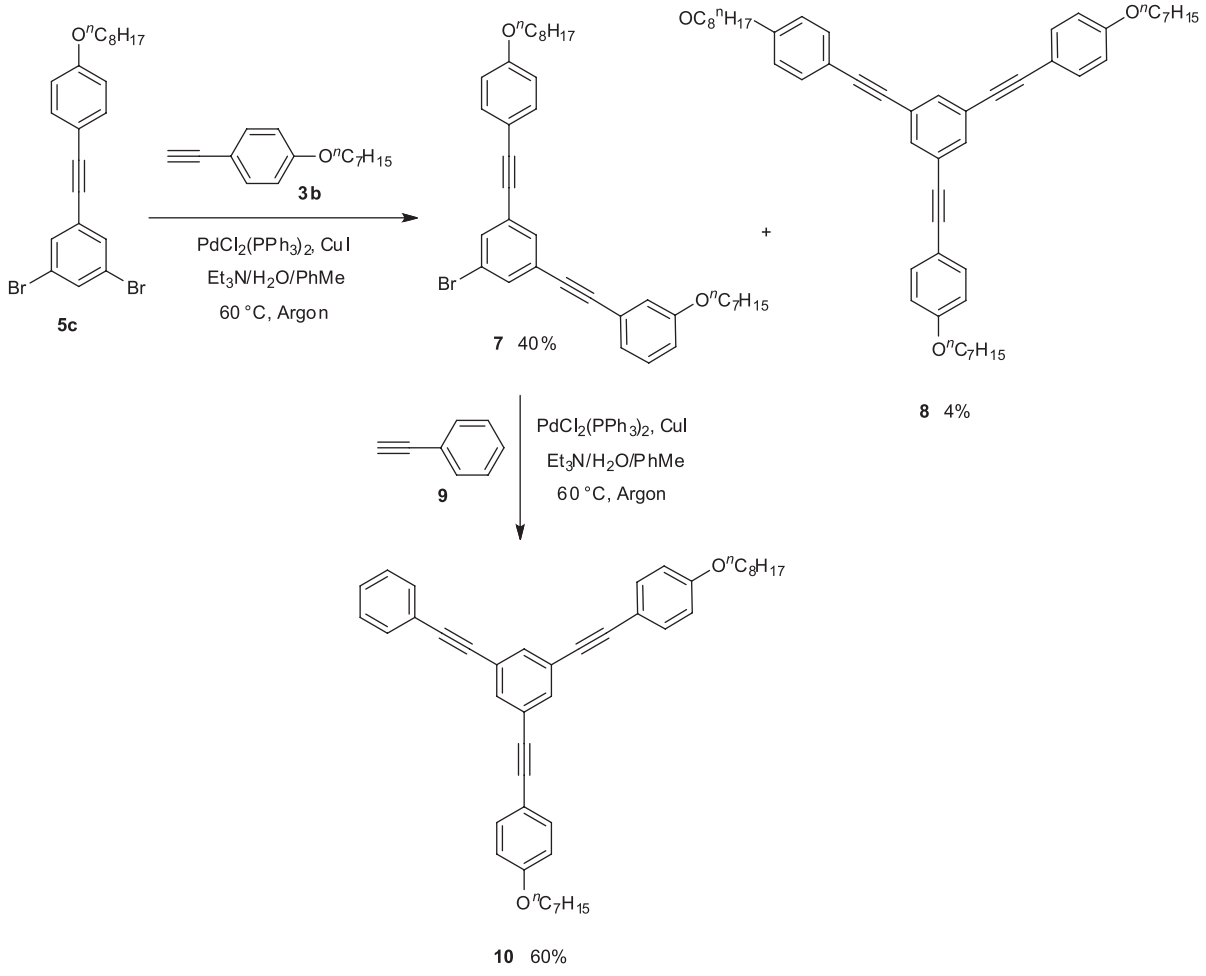
Synthesis of unsymmetrical di- and tri-ethynylated benzenes

Next, cross-coupling of the mono-ethynylated dibromobenzene **5c** with other terminal alkynes aiming to prepare unsymmetrical di- and tri-ethynylated benzenes

via two successive Sonogashira reactions is evaluated as shown in Scheme 2. Thus, Sonogashira cross-coupling reaction of 1,3-dibromo-5-(2-(4-(octyloxy)phenyl) ethynyl)-benzene **5c** with 1-ethynyl-4-(heptyloxy)benzene **3b** was performed applying the following reaction condition: **5c** (1 mmol), **3b** (1 mmol), $PdCl_2(PPh_3)_2$ (1 mol%), CuI (2 mol%) in toluene/water (2 mL, 1:1) using triethylamine (2 mmol) under argon atmosphere at 60 °C for 24 h to furnish two isolable products. After column chromatography, the obtained products were identified as 1-bromo-3-(2-(4-heptyloxyphenyl) ethynyl)-5-(2-(4-octyloxyphenyl)ethynyl)benzene (**7**) (40% yield) in addition to 1,3-di-(2-(4-heptyloxyphenyl) ethynyl)-5-(2-(4-octyloxyphenyl)ethynyl)-benzene (**8**) (4% yield), as shown in Scheme 2. Afterwards, the third regiocontrolled cross-coupling process for 1-bromo-3-(2-(4-heptyloxyphenyl)ethynyl)-5-(2-(4-octyloxyphenyl) ethynyl)benzene **7** was conducted via its reaction with 1-ethynylbenzene **9** in 1:1 molar ratio in the presence of $PdCl_2(PPh_3)_2$ (1 mol%), CuI (2 mol%) in toluene/water (2 mL, 1:1) using triethylamine (2 mmol) under argon at 60 °C for 24 h. This sequenced cross-coupling furnished the desired unsymmetrical tri-ethynylated benzene derivative; 1-(2-(4-(heptyloxy)phenyl)ethynyl)-3-(2-(4-(octyloxy)-phenyl)ethynyl)-5-(2-phenyl-ethynyl)-benzene (**10**) in 60% yield as outlined in Scheme 2. The tri-ethynylated benzene product **10** was confirmed on the basis of its nuclear magnetic resonance (^1H and ^{13}C NMR) and mass spectra (MS) (see experimental section).

Conclusions

Three different 1-ethynyl-4-(alkyloxy)benzene candidates were prepared in three steps from 4-iodophenol. Then, these terminal acetylene candidates were employed in an efficient regiocontrolled Sonogashira cross-coupling with 1,3,5-tribromobenzene **4** for the preparation of unsymmetrical mono-, di- and tri-alkynylated benzene derivatives in moderate to good yields. Water/toluene mixed solvent was found to greatly enhance the cross-coupling reaction of 4-alkyloxyphenylacetylene with 1,3,5-tribromobenzene. These results encouraged us to



Scheme 2. Regiocontrolled Sonogashira cross-coupling of compound **5c**.

conduct sequential Sonogashira followed by Susuki cross-coupling reactions on analogous candidates and the results are under progress.

Experimental

Melting points were determined in open glass capillaries with a Gallenkamp apparatus. The infrared (IR) spectra were recorded in potassium bromide disks on a Pye Unicam SP 3-300 and Shimaduz FTIR 8101 PC infrared spectrophotometer. NMR spectra were recorded with a Varian Mercury VXR-300 NMR spectrometer at 300 MHz (^{1}H NMR) and at 75 MHz (^{13}C NMR) using $CDCl_3$ as solvent and internal standard (δ 7.27 and 77.36 ppm, for ^{1}H NMR and ^{13}C NMR, respectively). Chemical shifts (δ) and *J* values are reported in ppm and Hz, respectively. Multiplicities are shown as the abbreviations: s (singlet), d (doublet), t (triplet), m (multiplet). Electrospray ionization mass spectrometry (EI-MS) analyses were obtained at 70 eV with a Shimadzu GCMQP 1000 EX spectrometer. Analytical thin-layer chromatography (TLC) was performed using pre-coated silica gel 60778 plates (Fluka), and the spots were visualized with UV light at 254 nm. Fluka silica gel 60741 (70-230 mesh) was used for flash column chromatography. For the exclusion of atmospheric oxygen from the reaction medium, the aqueous solvent was firstly deoxygenated with a stream of argon for 30 min before use. 1-Hexyloxy-4-iodobenzene (**1a**),[39,40] 1-heptyloxy-4-iodobenzene (**1b**),[39] and 1-octyloxy-4-iodobenzene (**1c**)[41] were prepared following literature procedures.

Synthesis of 4-(alkyloxy)phenylethynyltrimethylsilanes **2a-c**

To a mixture of $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol), CuI (7.6 mg, 0.04 mmol), and 1-alkyloxy-4-iodobenzenes **1a-c** (2 mmol) in toluene (2 mL) was added trimethylsilylacetylene (0.34 mL, 2.4 mmol) at room temperature under an argon atmosphere. Triethylamine (0.28 mL, 4 mmol) in water (2 mL) was then added drop-wise and stirring was continued for 24 h at room temperature. The resulting two-phase mixture was separated and the aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic layer was concentrated under reduced pressure to leave a crude solid, which was purified by chromatography on silica gel (hexane-ethyl acetate) to furnish the corresponding cross-coupled products **2a-c**.

4-(Hexyloxy)phenylethynyltrimethylsilane (**2a**):[42] this compound was purified by ethyl acetate-hexane (1:30) to yield 0.406 g of **2a** (74%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.24 (s, 9H) 0.91 (t, 3H, *J* 6.6 Hz), 1.26-1.45 (m, 6H), 1.74-1.80 (m, 2H), 3.95 (t, 2H, *J* 6.6 Hz), 6.81 (d, 2H, *J* 9.0 Hz), 7.39 (d, 2H, *J* 9.0 Hz).

4-(Heptyloxy)phenylethynyltrimethylsilane (**2b**):[43] this compound was purified by ethyl acetate-hexane (1:50) to yield 0.496 g of **2b** (86%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.24 (s, 9H), 0.91 (m, 3H), 1.28-1.46 (m, 8H), 1.76-1.81 (m, 2H), 3.95 (t, 2H, *J* 6.6 Hz), 6.81 (d, *J* 8.1 Hz, 2H), 7.39 (d, *J* 7.8 Hz, 2H).

4-(Octyloxy)phenylethynyltrimethylsilane (**2c**):[44,45] this compound was purified by ethyl acetate-hexane (1:70) to yield 0.58 g of **2c** (96%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.25 (s, 9H) 0.90 (m, 3H), 1.27-1.44 (m, 10H), 1.75-1.80 (m, 2H), 3.94 (t, 2H, *J* 6.6 Hz), 6.80 (d, 2H, *J* 8.7 Hz), 7.39 (d, 2H, *J* 9.0 Hz).

Synthesis of 1-ethynyl-4-(alkyloxy)benzenes **3a-c**

To 2-(4-(alkyloxy)phenyl)ethynyltrimethylsilane **2a-c** (0.5 mmol) in THF (3 mL), was added tetrabutylammonium fluoride (TBAF) (0.66 mL, 1 mmol) at room temperature. The resulting mixture was stirred for one hour at room temperature. The mixture was then filtered and the solvent was evaporated under reduced pressure to leave a crude oily product, which was purified by flash column chromatography using ethyl acetate-hexane (1:80) to furnish the corresponding desilylated products **3a-c** in very good yields.

1-Ethynyl-4-(hexyloxy)benzene (**3a**):[46] this compound was purified by ethyl acetate-hexane (1:80) to yield 155.5 mg (77%) as yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, 3H, *J* 7.2 Hz), 1.23-1.49 (m, 6H), 1.71-1.81 (m, 2H), 2.97 (s, 1H), 3.93 (t, 2H, *J* 6.6 Hz), 6.82 (d, 2H, *J* 9.0 Hz), 7.39 (d, 2H, *J* 9.0 Hz).

1-Ethynyl-4-(heptyloxy)benzene (**3b**):[47] this compound was purified by ethyl acetate-hexane (1:80) to furnish (162 mg, 75% yield), as yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, 3H, *J* 7.2 Hz), 1.26-1.45 (m, 8H), 1.73-1.80 (m, 2H), 2.94 (s, 1H), 3.91 (t, 2H, *J* 6.6 Hz), 6.83 (d, 2H, *J* 9.0 Hz), 7.38 (d, 2H, *J* 9.0 Hz).

1-Ethynyl-4-(octyloxy)benzene (**3c**):[41,45,48] this compound was purified by ethyl acetate-hexane (1:80) to give 184 mg (80% yield) as orange oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3H, *J* 7.2 Hz), 1.26-1.45 (m, 10H), 1.71-1.80 (m, 2H), 2.96 (s, 1H), 3.91 (t, 2H, *J* 6.6 Hz), 6.81 (d, 2H, *J* 9.0 Hz), 7.38 (d, 2H, *J* 9.0 Hz).

Synthesis of mono- and dialkynylated benzene derivatives

To $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol), CuI (3.8 mg, 0.02 mmol) in toluene (1 mL) and Et_3N (140 µL, 2 mmol) in water (1 mL) were added 1,3,5-tribromobenzene **4** (315 mg, 1 mmol) and 4-alkoxyphenylethyne **3a**-**c** (1 mmol) under an argon atmosphere. Stirring was continued for 24 h at 60 °C. Two phases of the resulting mixture were separated and the aqueous layer was extracted three times with diethyl ether (3 × 30 mL). The combined organic layer was concentrated under reduced pressure to leave a crude solid, which was purified by flash column chromatography using hexane/ethyl acetate (20:1) to give the corresponding mono and dialkynylated products **5a**-**c** and **6a**-**c**.

1,3-Dibromo-5-(2-(4-(hexyloxy)phenyl)ethynyl)benzene (**5a**): yield: 409.5 mg (94%) as white powder; m.p. 54-55 ºC; IR (KBr) υ_{max}/cm^{-1} 3065, 2926, 2210, 1550, 1464, 1243; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, 3H, *J* 5.6 Hz), 1.28-1.85 (m, 8H), 3.99 (t, 2H, *J* 6.6 Hz), 6.89-7.03 (m, 2H), 7.43-7.49 (m, 2H), 7.58 (s, 2H), 7.61 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.8, 26.1, 29.0, 31.8, 68.2, 85.3, 92.5, 114.1, 114.5, 122.7, 127.4, 132.9, 133.5, 133.8, 160.1; MS (EI, 70 eV) *m/z* 436 (M^+, 37.6%), 352 (100%), 271 (3.44%), 192 (20.8%), 163 (32.7%), 87 (7.9%), 55 (15.5%); anal. calcd. for $C_{20}H_{20}Br_2O$: C, 55.07; H, 4.62%; found: C, 55.35; H, 4.79%.

1-Bromo-3,5-bis(2-(4-(hexyloxy)phenyl)ethynyl)benzene (**6a**): yield: 11 mg (2%) as white crystals; m.p. 108 ºC; IR (KBr) υ_{max}/cm^{-1} 3068, 2929, 2206, 1592, 1463, 1245; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, 6H, *J* 6.7 Hz), 1.28-1.83 (m, 16H), 3.99 (t, 4H, *J* 6.4 Hz), 6.87-6.95 (m, 4H), 7.44 (d, 4H, *J* 7.7 Hz), 7.47-7.58 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 23.1, 26.5, 28.5, 31.8, 68.4, 86.3, 91.7, 114.3, 114.8, 122.1, 132.4, 133.1, 133.6, 134.7, 159.7; MS (EI, 70 eV) *m/z* 557 (M^+, 35.0%), 258 (4.0%), 250 (27.6%), 235 (59.4%), 205 (53.7%), 189 (95.1%), 179 (55.6%), 124 (59.1%), 93 (31.0%), 75 (27.7%), 53 (100%); anal. calcd. for $C_{34}H_{37}BrO_2$: C, 73.24; H, 6.69%; found: C, 73.13; H, 6.71%.

1,3-Dibromo-5-(2-(4-(heptyloxy)phenyl)ethynyl)benzene (**5b**): yield: 418.5 mg (93%) as white crystals; m.p. 96 ºC; IR (KBr) υ_{max}/cm^{-1} 3046, 2927, 2131, 1596, 1464, 1243; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, 3H, *J* 5.5 Hz), 1.28-1.84 (m, 10H), 3.97 (t, 2H, *J* 8.52 Hz), 6.90-7.15 (m, 2H), 7.43-7.47 (m, 2H), 7.58 (s, 2H), 7.61 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.5, 26.2, 28.7, 29.1, 31.9, 68.1, 85.2, 92.3, 114.0, 114.5, 122.5, 127.2, 132.8, 133.2, 133.6, 159.8; MS (EI, 70 eV) *m/z* 450 (M^+, 3.8%), 433 (74.8%), 332 (29.6%), 234 (97.9%), 121 (100%), 93 (25.0%), 64 (47.2%), 56 (26.8%); anal. calcd. for $C_{21}H_{22}Br_2O$: C, 56.02; H, 4.93%; found: C, 56.29; H, 4.78%.

1-Bromo-3,5-bis(2-(4-(heptyloxy)phenyl)ethynyl) benzene (**6b**): yield: 23.4 mg (4%) as white powder; m.p. 55-56 ºC; IR (KBr) υ_{max}/cm^{-1} 3042, 2923, 2219, 1550, 1463, 1249; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, 6H, *J* 6.8 Hz), 1.28-1.83 (m, 20H), 3.99 (t, 4H, *J* 6.9 Hz), 6.88-6.97 (m, 4H), 7.44 (d, 4H, *J* 7.7 Hz), 7.47-7.54 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 22.8, 26.2, 29.1, 29.6, 31.8, 68.1, 86.1, 91.2, 114.1, 114.4, 121.8, 132.4, 133.0, 133.3, 134.2, 159.4; MS (EI, 70 eV) *m/z* 585 (M^+, 6.6%), 519 (6.9%), 457 (7.8%), 254 (9.0%), 80 (52.9%), 64 (73.7%), 57 (100%), 50 (18.8%); anal. calcd. for $C_{36}H_{14}BrO_2$: C, 73.83; H, 7.06%; found: C, 73.59; H, 7.15%.

1,3-Dibromo-5-(2-(4-(octyloxy)phenyl)ethynyl)benzene (**5c**): Yield: 417.5 mg (90%) as white powder; m.p. 58-59 ºC; IR (KBr) υ_{max}/cm^{-1} 3040, 2922, 2213, 1577, 1463, 1250; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, 3H, *J* 5.4 Hz), 1.28-1.85 (m, 12H), 3.98 (t, 2H, *J* 6.5 Hz), 6.85-6.91 (m, 2H), 7.42-7.47 (m, 2H), 7.58 (s, 2H), 7.61 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 26.0, 29.1, 29.2, 29.3, 31.8, 68.1, 85.2, 92.3, 113.9, 114.6, 122.6, 127.2, 132.7, 133.2, 133.4,159.8; MS (EI, 70 eV) *m/z* 464 (M^+, 29.4%), 352 (100%), 350 (54.7%), 192 (23.3%), 163 (37.4%), 71 (13.9%), 57 (44.4%), 55 (28.9%); anal. calcd. for $C_{22}H_{24}Br_2O$: C, 56.92; H, 5.21%; found: C, 56.85; H, 5.09%.

1-Bromo-3,5-bis(2-(4-(octyloxy)phenyl)ethynyl)benzene (**6c**): yield: 49 mg (8%) as white crystals; m.p. 63 ºC; IR (KBr) υ_{max}/cm^{-1} 3042, 2923, 2205, 1589, 1464, 1247; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, 6H, *J* 6.6 Hz), 1.28-1.83 (m, 24H), 3.99 (t, 4H, *J* 6.5 Hz), 6.83-6.89 (m, 4H), 7.44 (d, 4H, *J* 7.8 Hz), 7.47-7.58 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 26.0, 29.1, 29.2, 29.3, 31.8, 68.1, 86.0, 91.4, 114.3, 114.6, 121.8, 132.7, 133.1, 133.3, 133.9, 159.7; MS (EI, 70 eV) *m/z* 614 (M^+, 39.2%), 502 (12.5%), 390 (67.7%), 250 (10.9%), 71 (56.7%), 57 (100%), 55 (57.1%); anal. calcd. for $C_{38}H_{45}BrO_2$: C, 74.37; H, 7.39%; found: C, 74.05; H, 7.19%.

Synthesis of 1-(2-(3-bromo-5-(2-(4-(octyloxy)phenyl) ethynyl)phenyl)ethynyl)-4-(heptyloxy)-benzene (**7**)

To $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol), CuI (3.8 mg, 0.02 mmol) in toluene (1 mL) and Et_3N (140 µL, 2 mmol) in water (1 mL) were added 1-(2-(3,5-dibromophenyl) ethynyl)-4-(octyloxy)benzene **5c** (464.2 mg, 1 mmol) and 1-ethynyl-4-(heptyloxy)benzene **3b** (216 mg, 1 mmol)

under argon atmosphere. The reaction mixture was stirred for 24 h at 60 °C. Two phases of the resulting mixture were separated and the aqueous layer was extracted three times with diethyl ether (3 × 30 mL). The combined extracts were evaporated under reduced pressure to leave a crude solid, which was purified by flash column chromatography on silica gel using hexane/ethyl acetate (10:1) to furnish **7** (40% yield) and **8** (4% yield).

1-Bromo-3-(2-(4-(heptyloxy)phenyl)ethynyl)-5-(2-(4-(octyloxy)phenyl)ethynyl)benzene (**7**): yield: 239.5 mg (40%) as white powder; m.p. 56-57 ºC; IR (KBr) υ_{max}/cm^{-1} 3096, 2926, 2205, 1595, 1464, 1246; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, 6H, *J* 4.3 Hz), 1.28-1.82 (m, 22H), 3.95-4.00 (m, 4H), 6.83-6.89 (m, 4H), 7.42-7.44 (m, 4H), 7.45-7.46 (m, 2H), 7.58 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 22.7, 25.9, 29.0, 29.15, 29.18, 29.2, 29.3, 29.7, 31.7, 68.1, 68.2, 81.9, 85.9, 87.9, 91.4, 114.5, 114.6, 121.8, 125.7, 125.8, 125.9, 132.7, 132.8, 133.9, 158.9, 159.7; MS (EI, 70 eV) *m/z* 599 (M^+, 17.0%), 598 (40.9%), 586 (24.7%), 390 (100%), 250 (18.9%), 96 (11.9%), 71 (20.9%); anal. calcd. for $C_{37}H_{43}BrO_2$: C, 74.11; H, 7.23%; found: C, 73.85; H, 7.09%.

1,3-Bis(2-(4-(heptyloxy)phenyl)ethynyl)-5-(2-(4-(octyloxy)phenyl)ethynyl)benzene (**8**): yield: 29 mg (4%) as yellow oil; IR (KBr) υ_{max}/cm^{-1} 3048, 2925, 2208, 1602, 1465, 1247; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (m, 9H), 1.28-1.80 (m, 32H), 3.96-4.01 (m, 6H), 6.87-6.90 (m, 6H), 7.44-7.47 (m, 6H), 7.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.6, 25.9, 29.0, 29.2, 29.7, 31.7, 68.2, 86.7, 90.5, 114.7, 124.3, 133.1, 133.4, 159.5; MS (EI, 70 eV) *m/z* 735 (M^+, 17.0%), 718 (15.9%), 575 (19.5%), 486 (24.5%), 462 (36.7%), 410 (24.5%), 351 (23.6%), 220 (43.7%), 107 (74.5%), 82 (100%), 65 (34.7%), 50 (13.5%); anal. calcd. for $C_{52}H_{62}O_3$: C, 84.97; H, 8.50%; found: C, 84.85; H, 8.48%.

Synthesis of 1-(2-(4-(heptyloxy)phenyl)ethynyl)-3-(2-(4-(octyloxy)-phenyl)ethynyl)-5-(2-phenylethynyl)benzene (**10**)

To a mixture of 1-(2-(3-bromo-5-(2-(4-(octyloxy) phenyl)-ethynyl)phenyl)ethynyl)-4-(heptyloxy)benzene (**7**) (599 mg, 1 mmol) and phenylethyne (**9**) (90 µL, 1 mmol), in toluene (1 mL) and water (1 mL), was added Et_3N (140 µL, 2 mmol) followed by adding $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol) then CuI (3.8 mg, 0.02 mmol) under argon atmosphere. The reaction mixture was stirred for 24 h at 60 °C. Two phases of the resulting mixture were separated and the aqueous layer was extracted three times with diethyl ether (3 × 30 mL). The combined extracts were evaporated under reduced pressure to leave a crude solid, which was purified by flash column chromatography on silica gel using hexane/ethyl acetate (10:1) to give compound **10** in 372.5 mg (60% yield) as yellow oil. IR (KBr) υ_{max}/cm^{-1} 3046, 2922, 2205, 1573, 1464, 1246; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91-0.94 (m, 6H), 1.30-1.84 (m, 22H), 3.99 (t, 4H, *J* 6.4 Hz), 6.90 (d, 4H, *J* 6.7 Hz), 7.37-7.39 (m, 3H), 7.49 (d, 4H, *J* 5.7 Hz), 7.56 (d, 2H, *J* 3.9 Hz), 7.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 22.6, 25.9, 26.0, 29.0, 29.1, 29.2, 29.3, 29.6, 29.7, 31.7, 31.8, 68.1, 86.6, 88.0, 90.3, 90.7, 114.5, 114.6, 122.9, 123.9, 124.4, 128.3, 128.5, 131.7, 132.8, 133.1, 133.5, 133.7, 159.5; MS (EI, 70 eV) *m/z* 621 (M^+, 22.5%), 598 (0.4%), 430 (29.9%), 406 (36.3%), 234 (51.2%), 210 (100%), 181 (18.2%), 57 (70.3%), 55 (20.6%); anal. calcd. for $C_{45}H_{48}O_2$: C, 87.05; H, 7.79%; found: C, 86.87; H, 7.68%.

Supplementary Information

Supplementary data are available free of charge at http://jbcs.sbq.org.br as PDF file.

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