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Development of a one-pot sequential Sonogashira coupling for the synthesis of benzofurans

Márton Csékei, Zoltán Novák, András Kotschy *

Institute of Chemistry, Eötvös Loránd University, Pázmány Péter s. 1/A, H-1117 Budapest, Hungary

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Dedicated to Professor Lajos Novák on the occasion of his 70th birthday

ABSTRACT

An efficient one-pot protocol was developed for the construction of the benzofuran system from aryl halides and protected iodophenols using carbinol-based acetylene sources. The sequence includes alternating palladium-catalyzed Sonogashira couplings and deprotection steps concluded by a ring closure. The developed one-pot procedure was compared with the stepwise approach and its efficiency was also demonstrated by the total synthesis of vignafuran, a benzofuran natural product.

1. Introduction

The design and implementation of new economic synthetic processes is one of the major challenges in modern organic synthesis. The application of cascade,[1] domino[2] or tandem[3] reactions in a 'one-pot' manner offers a straightforward method for the construction of new bonds simultaneously or in a stepwise manner without the isolation of the intermediates, making the whole procedure economically sustainable and environmentally conscientious. Among the nearly unlimited combination of organic transformations in a reaction sequence, palladium-catalyzed carbon-carbon bond forming reactions can act as an efficient synthetic step in a designed multi step reaction.[4] A member of this reaction class is the Sonogashira-Hagihara reaction[5] of aryl halides and terminal alkynes, which is a powerful tool for the construction of acetylene derivatives. The introduction of a triple bond between two aryl halide moieties can also be achieved in a 'one-pot' multi step sequence, the domino Sonogashira reaction of aryl halides and a masked acetylene, in a coupling-deprotection-coupling sequence. As acetylene source, trimethylsilylacetylene,[6] 2-metyl-3-butyn-2-ol[7] or 1-ethynyl-cyclohexanol[8] can be used with comparable efficiency.[9]

The use of the Sonogashira coupling is not confined to the synthesis of acetylene derivatives. This reaction also offers an efficient route for the preparation of condensed heterocycles,[10] for benzofurans[11] in particular, which has been demonstrated in the total synthesis of diverse natural products.[12] In spite of the development of efficient 'one-pot' procedures for the preparation of internal acetylenes, to the best of our knowledge there is no report on their extension to the synthesis of benzofurans. The present work was aimed at the establishment of an efficient 'one-pot' procedure for the preparation of benzofurans from the appropriate aryl halides and masked acetylenes. Besides comparing the developed 'one-pot' procedure to the stepwise approach, we planned to test its synthetic utility in the total synthesis of a benzofuran natural product, vignafuran.[13]

2. Results and discussion

The first approach tested was the sequential Sonogashira coupling of aryl halides and protected acetylenes to give diarylalkynes that are capable of cyclizing to benzofurans. To this purpose, a series of aryl iodides (**1a**–**e**) were coupled with 1-ethynyl-cyclohexanol (**2**) and *O*-triisopropylsilyl-2-iodophenol (**3a**) in a one-pot procedure to give the desired 2-arylethynyl-phenol derivatives (**4a**–**e**) in good yield (Table 1). The coupling conditions were selected on the basis of our previous experience on similar sequential couplings.[8] The use of the analogous acetylene source 2-methyl-3-butyn-2-ol resulted in decreased yields. The use of ethynyl-trimethylsilane instead of **2** required the change of the deprotection agent from KOH to TBAF, which did not allow for the isolation of the diarylacetylene derivatives, but gave the appropriate benzofurans directly (vide infra).

To get a feeling for the efficiency of the protocol aryl halides bearing both electron donating (entries 2 and 4) and electron withdrawing (entries 3 and 5) groups were tested and found to work equally well. The placement of the substituents on the aryl halide had no significant impact on the yield either. The ring closure of the obtained diarylacetylenes in the presence of TBAF proceeded smoothly and the expected 2-arylbenzofurans (**5a**–**e**) were obtained in excellent yield. One can envisage that the alkynes (**4a**–**e**) might

* Corresponding author. Tel.: +36 1 372 2910; fax: +36 1 372 2909.
E-mail address: kotschy@elte.hu (A. Kotschy).

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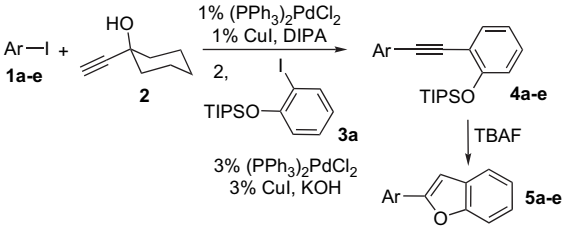
Table 1
The synthesis of TIPS-protected 2-arylethynyl-phenols (**4a–e**) and their ring closure to benzofurans **5a–e**



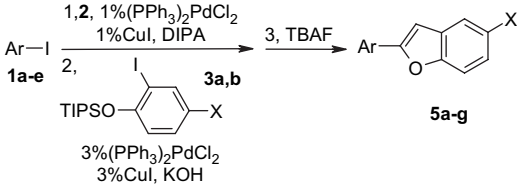
Entry	Ar	**4**[a]/%	**5**[a]/%
1	Phenyl (**1a**)	89	96
2	4-Anisyl (**1b**)	80	99
3	2-Bromophenyl (**1c**)	76	90
4	3-Tolyl (**1d**)	85	98
5	4-Nitrophenyl (**1e**)	69	92

[a] Yield after purification.

also serve as a starting material for electrophile induced ring closure[14] and lead to the appropriate 2,3-disubstituted benzofuran derivatives.

The next attempts were directed at combining the five reaction steps converting the aryl halide, the iodophenol derivative and the protected acetylene into a benzofuran derivative in a 'one-pot' protocol. In the first experiments (Table 2, entries 1–5), we tested the different acetylene surrogates in the coupling. Iodobenzene (**1a**) and *O*-triisopropylsilyl-2-iodophenol (**3a**) were coupled with 1-ethynyl-cyclohexanol (entry 1), 2-methyl-3-butyn-2-ol (entry 2) and ethynyltrimethylsilane (entry 3) to give the desired 2-phenylbenzofuran (**5a**) in good to excellent yield. The highest yield was obtained by using 1-ethynyl-cyclohexanol, while the lower yield obtained when using the TMS-protected acetylene is probably due to the fact that under the deprotection conditions **3a** is converted faster into 2-iodophenol than it undergoes the second coupling. This is also supported by the fact that on replacing **3a** with 2-iodophenol we obtained 2-phenylbenzofuran in 65% yield. These two acetylene surrogates were also compared in their coupling with 4-iodoanisole, both giving the anisylbenzofuran **5b** in good yield, with 1-ethynyl-cyclohexanol being superior in efficiency again.

Table 2
The one-pot synthesis of 2-arylbenzofuran derivatives from aryl halides (**1a–e**), *O*-protected 2-iodophenol derivatives (**3a,b**) and 1-ethynyl-cyclohexanol (**2**)



Entry	Ar	X	yield[a]/%
1	Phenyl	H (**3a**)	87 (**5a**)
2	Phenyl	H (**3a**)	76 (**5a**)[b]
3	Phenyl	H (**3a**)	65 (**5a**)[c]
4	4-Anisyl	H (**3a**)	82 (**5b**)[d]
5	2-Bromophenyl	H (**3a**)	62 (**5c**)
6	3-Tolyl	H (**3a**)	84 (**5d**)
7	4-Nitrophenyl	H (**3a**)	68 (**5e**)
8	4-Anisyl	Br (**3b**)	80 (**5f**)
9	4-Nitrophenyl	Br (**3b**)	70 (**5g**)

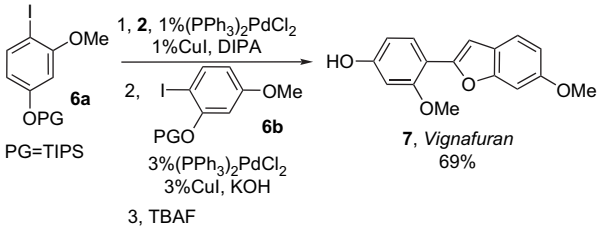
[a] Yield after purification.
[b] Yield obtained using 2-methyl-3-butyn-2-ol instead of **2**.
[c] Yield obtained using ethynyltrimethylsilane instead of **2** and 2-iodophenol instead of **3**. TBAF was added in place of KOH in the second step and step 3 was omitted.
[d] Ethynyltrimethylsilane gave **5b** in 76% yield.

Following these studies, we appended the appropriate aryl moieties of 2-bromo-iodobenzene (entry 5), 3-iodotoluene (entry 6) and 4-nitro-iodobenzene (entry 7) onto the benzofuran core with good efficiency, using 1-ethynyl-cyclohexanol (**2**) and *O*-triisopropylsilyl-2-iodophenol (**3a**). Again, the electron donating or withdrawing nature and the placement of the substituents on the phenyl ring had little effect on the efficiency of the coupling sequence.

In order to introduce a further site for functionalization, we carried out some experiments using *O*-triisopropylsilyl-4-bromo-2-iodophenol (**3b**) in the second coupling step. Starting either from 4-iodoanisole (entry 8) or from 4-nitro-iodobenzene (entry 9), we obtained the appropriate 2-aryl-5-bromobenzofurans (**5f** and **5g**) in high yield. The switch from **3a** to **3b** (cf. entries 4 and 8, and 7 and 9) had practically no effect on the efficacy of the protocol.

To demonstrate the usefulness of the devised protocol, we selected a natural product, vignafuran, as a benchmark. This compound has been synthesized by different approaches,[13b,c,h] one of them utilizing a Sonogashira coupling based route.[13f] Common to all strategies is the significant number of reaction steps and purifications encountered on the way. The 'one-pot' domino Sonogashira coupling approach could offer a convenient alternative to these routes.

The appropriate *O*-methyl-iodoresorcinols were silylated to provide the necessary aryl halides **6a**[15] and **6b**.[16] The coupling of **6a** and 1-ethynyl-cyclohexanol (**2**) was followed by TLC, and upon its completion potassium hydroxide, **6b** and additional catalyst were added to the reaction mixture to give rise to the intermediate diarylacetylene. This compound was converted to vignafuran (**7**) on treatment with tetrabutylammonium fluoride (Scheme 1) that was isolated by column chromatography in 69% yield, nicely demonstrating the efficacy of the 'one-pot' domino Sonogashira coupling based approach.



Scheme 1. The 'one-pot' synthesis of vignafuran.

In summary, we have developed a convenient protocol for the 'one-pot' preparation of benzofurans from aryl halides, *O*-silylated 2-iodophenol derivatives and 1-ethynyl-cyclohexanol. The devised procedure allows the convenient introduction of different aryl moieties into the 2-position of the benzofuran core and its ability to build substituents onto the phenyl moiety of the benzofuran ring was also demonstrated. The effectiveness of the protocol was demonstrated by the synthesis of vignafuran.

3. Experimental part

3.1. General

Unless otherwise indicated, all starting materials were obtained from commercial suppliers and were used without further purification. All coupling reactions were performed under an atmosphere of argon. Analytical thin-layer chromatography (TLC) was performed on Merck DC pre-coated TLC plates with 0.25 mm Kieselgel 60 F_{254}. Visualization was performed with a 254 nm UV lamp. Silica gel column chromatography was carried out with flash silica gel (0.040–0.063 mm). The ^{1}H and ^{13}C NMR spectra were recorded

at 250 and 62.5 MHz in $CDCl_3$. Chemical shifts are expressed in parts per million (δ). For ^1H NMR spectra the residual peak of $CHCl_3$ (7.26 ppm) was used as the internal reference, while for ^{13}C NMR spectra the central peak of $CDCl_3$ (77.0 ppm) was used as the reference. Coupling constants (J) are reported in hertz (Hz). Splitting patterns are designated as s (singlet), br s (broad singlet), d (doublet), t (triplet), m (multiplet), dd (doublet doublet), dt (doublet of triplets) and td (triplet of doublets). Combination gas chromatography and low resolution mass spectrometry were obtained on a 30 m×0.25 mm column with 0.25 μm HP-5MS coating using He carrier gas, and with the following ion source: EI^+, 70 eV, 230 °C; interface: 300 °C. The purity of the products whose elementary analysis for carbon differed by more than 0.5% from the calculated value was above 95% by HPLC in all cases.

3.1.1. *O-Triisopropylsilyl-2-iodophenol (**3a**)*

2-Iodophenol (2.20 g, 10 mmol) was dissolved in dichloromethane (30 mL). Triisopropylsilyl chloride (2.31 g, 12 mmol) was added slowly and then imidazole (1.70 g, 25 mmol) was added in one portion. The reaction was followed by TLC and GC–MS. Upon completion, the reaction mixture was washed with water (2×10 mL) and then with brine (5 mL). The organic phase was dried over magnesium sulfate, filtered and evaporated. The crude product was purified by column chromatography, using pure hexane as eluent, to give 3.54 g colourless liquid (**3a**) (9.41 mmol, 94%). ^1H NMR ($CDCl_3$, 250 MHz): δ 7.76 (dd, 1H, J=7.9, 1.6 Hz), 7.19 (td, 1H, J=8.2, 1.6 Hz), 6.85 (dd, 1H, J=8.2, 1.4 Hz), 6.66 (td, 1H, J=7.9, 1.4 Hz), 1.42–1.28 (m, 3H), 1.17–1.14 (m, 18H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 155.5, 139.5, 129.2, 122.4, 118.1, 90.3, 18.1, 13.1; MS (EI, 70 eV) m/z (% relative intensity, ion): 376 (1, [M^+]), 334 (18), 333 (100), 305 (15), 277 (13). Analysis calculated for $C_{15}H_{25}IOSi$: C, 47.87; H, 6.70. Found: C, 47.18; H, 6.62.

3.1.2. *4-Bromo-O-triisopropylsilyl-2-iodophenol (**3b**)*

4-Bromophenol (1.73 g, 10 mmol) was dissolved in 25% aqueous NH_3 (40 mL). Potassium iodide (7.97 g, 48 mmol) and iodine (2.54 g, 10 mmol) dissolved in water (20 mL) were added rapidly. The reaction was followed by TLC and GC–MS. When the iodination was complete (approximately an hour), the reaction mixture was cooled and diluted with ice and acidified with concd HCl (40 mL). It was extracted with ethyl acetate (3×200 mL). The combined organic phase was washed with saturated $NaHCO_3$ (40 mL), saturated $Na_2S_2O_3$ (40 mL) and brine (20 mL). It was dried over magnesium sulfate, filtered and evaporated. The crude product was purified by column chromatography, using hexane–chloroform as eluent, to give 4-bromo-2-iodophenol (**3b′**) as a white solid. Yield: 2.14 g (7.16 mmol, 72%). Mp: 71 °C.[17] ^1H NMR ($CDCl_3$; 250 MHz): δ 7.76 (d, 1H, J=2.2 Hz), 7.34 (dd, 1H, J=8.7, 2.4 Hz), 6.87 (d, 1H, J=8.7 Hz), 5.20 (br s, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 154.2, 139.7, 133.0, 116.2, 113.0, 86.1; MS (EI, 70 eV) m/z (% relative intensity, ion): 300 (100, [M^+]), 298 (100, [M^+]), 173 (22), 171 (22), 145 (30), 143 (31), 63 (83). Analysis calculated for C_6H_4BrIO: C, 24.11; H, 1.35. Found: C, 24.04; H, 1.33.

4-Bromo-2-iodophenol (**3b′**) (2.06 g, 6.88 mmol) was dissolved in dichloromethane (20 mL). Triisopropylsilyl chloride (1.59 g, 8.26 mmol) was added slowly and then imidazole (1.17 g, 17.2 mmol) was added in one portion. The reaction was followed by TLC and GC–MS. Upon completion, the reaction mixture was washed with water (2×5 mL) and then with brine (5 mL). The organic phase was dried over magnesium sulfate, filtered and evaporated. The crude product was purified by column chromatography, using pure hexane as eluent, to give 2.50 g colourless liquid (**3b**) (5.49 mmol, 80%). ^1H NMR ($CDCl_3$, 250 MHz): δ 7.89 (d, 1H, J=2.2 Hz), 7.31 (dd, 1H, J=8.6, 2.2 Hz), 6.73 (d, 1H, J=8.6 Hz), 1.39–1.28 (m, 3H), 1.19–1.16 (m, 18H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 154.9, 141.3, 132.0, 118.9, 113.2, 91.0, 18.0, 13.0; MS (EI, 70 eV) m/z (% relative intensity, ion): 456 (1, [M^+]), 454 (1, [M^+]), 413 (100), 411 (100), 385 (15), 383 (15), 357 (12), 355 (12). Analysis calculated for $C_{15}H_{24}BrIOSi$: C, 39.57; H, 5.31. Found: C, 39.78; H, 5.20.

3.1.3. *4-Iodo-3-methoxy-O-triisopropylsilylphenol (**6a**)*

4-Iodo-3-methoxyphenol (278 mg, 1.11 mmol) was dissolved in dichloromethane (3 mL). Triisopropylsilyl chloride (257 mg, 1.33 mmol) was added slowly and then imidazole (189 mg, 2.78 mmol) was added in one portion. The reaction was followed by TLC and GC–MS. When the protection was complete the reaction mixture was washed with water (2×1 mL) and then with brine (1 mL). The organic phase was dried over magnesium sulfate, filtered and evaporated. The crude product was filtered through a pad of silica with pure hexane to give 403 mg colourless liquid (**6a**) (0.99 mmol, 89%). ^1H NMR ($CDCl_3$, 250 MHz): δ 7.60 (d, 1H, J=8.7 Hz), 6.45 (d, 1H, J=2.7 Hz), 6.31 (dd, 1H, J=8.7, 2.7 Hz), 3.75 (s, 3H), 1.41–1.32 (m, 3H), 1.17–1.14 (m, 18H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 160.9, 156.1, 139.1, 107.9, 105.2, 79.3, 55.3, 18.1, 13.0; MS (EI, 70 eV) m/z (% relative intensity, ion): 406 (4, [M^+]), 363 (100), 335 (10), 180 (12), 166 (12), 154 (16), 151 (26). Analysis calculated for $C_{16}H_{27}IO_2Si$: C, 47.29; H, 6.70. Found: C, 46.90; H, 6.59.

3.1.4. *2-Iodo-5-methoxy-O-triisopropylsilylphenol (**6b**)*

2-Iodo-5-methoxyphenol (250 mg, 1.00 mmol) was dissolved in dichloromethane (3 mL). Triisopropylsilyl chloride (231 mg, 1.2 mmol) was added slowly and then imidazole (170 mg, 2.5 mmol) was added in one portion. The reaction was followed by TLC and GC–MS. When the protection was complete, the reaction mixture was washed with water (2×1 mL) and then with brine (1 mL). The organic phase was dried over magnesium sulfate, filtered and evaporated. The crude product was filtered through a pad of silica with pure hexane to give 321 mg colourless liquid (**6b**) (0.79 mmol, 79%). ^1H NMR ($CDCl_3$, 250 MHz): δ 7.54 (d, 1H, J=8.5 Hz), 6.42 (d, 1H, J=2.5 Hz), 6.31 (dd, 1H, J=8.5, 2.5 Hz), 3.83 (s, 3H), 1.29–1.23 (m, 3H), 1.12–1.09 (m, 18H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 158.7, 157.7, 138.9, 113.9, 104.0, 75.0, 56.1, 17.8, 12.6; MS (EI, 70 eV) m/z (% relative intensity, ion): 406 (96, [M^+]), 363 (93), 335 (52), 307 (62), 293 (18), 277 (12), 236 (20), 221 (39), 208 (16), 193 (47), 180 (62), 166 (67), 153 (100), 151 (55), 135 (29), 121 (18), 76 (19), 59 (21). Analysis calculated for $C_{16}H_{27}IO_2Si$: C, 47.29; H, 6.70. Found: C, 47.81; H, 6.95.

3.2. General procedure for the synthesis of 2-arylethynyl-*O*-triisopropylsilylphenols

Aryl halide (**1**) (1 mmol), 1-ethynyl-cyclohexanol (**2**) (136 mg, 1.1 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol, 1 mol %) and CuI (2 mg, 0.01 mmol, 1 mol %) were placed into a flame-dried Schlenk flask. Diisopropylamine (7 mL) was added and the mixture was stirred under argon at 80 °C. The reaction was followed by TLC and GC–MS. When the first coupling was complete (typically less than 30 min), 2-iodo-*O*-triisopropylsilylphenol (**3a**) (376 mg, 1 mmol), KOH (224 mg, 4 mmol), $PdCl_2(PPh_3)_2$ (21 mg, 0.03 mmol, 3 mol %) and CuI (6 mg, 0.03 mmol, 3 mol %) were added. The mixture was stirred under argon at 80 °C until the reaction was complete. After evaporating the solvent, the product (**4**) was separated by column chromatography, using hexane–ethyl acetate mixtures as eluent.

3.2.1. *2-Phenylethynyl-O-triisopropylsilylphenol (**4a**)*

Yellow oil, 313 mg (0.89 mmol, 89%). ^1H NMR ($CDCl_3$, 250 MHz): δ 7.56–7.48 (m, 3H), 7.38–7.32 (m, 3H), 7.21 (td, 1H, J=7.6, 1.8 Hz), 6.96–6.87 (m, 2H), 1.43–1.31 (m, 3H), 1.19–1.16 (m, 18H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 156.7, 133.6, 131.4, 129.4, 128.2, 127.9, 120.8, 119.1, 115.4, 111.1, 92.8, 87.0, 18.0, 13.0; MS (EI, 70 eV) m/z (% relative intensity, ion): 350 (4, [M^+]), 308 (27), 307 (100), 265 (77), 249 (21), 237 (75), 221 (23), 176 (37), 125 (51). Analysis calculated for $C_{23}H_{30}OSi$: C, 78.80; H, 8.63. Found: C, 78.26; H, 8.93.

*3.2.2. 2-(4′-Methoxyphenylethynyl)-O-triisopropylsilylphenol (**4b**)*

Yellow solid, 305 mg (0.80 mmol, 80%). Mp: 44–46 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.49–7.45 (m, 3H), 7.19 (td, 1H, J=7.9, 1.8 Hz), 6.95–6.87 (m, 4H), 3.83 (s, 3H), 1.40–1.29 (m, 3H), 1.19–1.16 (m, 18H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 159.3, 156.6, 133.4, 132.8, 129.0, 120.7, 119.0, 116.0, 115.7, 113.9, 92.7, 85.6, 55.2, 18.0, 12.9; MS (EI, 70 eV) m/z (% relative intensity, ion): 380 (18, [M$^+$]), 338 (28), 337 (100), 295 (30), 267 (36), 187 (23), 140 (43). Analysis calculated for $C_{24}H_{32}O_2Si$: C, 75.74; H, 8.47. Found: C, 75.47; H, 8.69.

*3.2.3. 2-(2′-Bromophenylethynyl)-O-triisopropylsilylphenol (**4c**)*

Yellow oil, 327 mg (0.76 mmol, 76%). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.46–7.36 (m, 3H), 7.13–7.03 (m, 2H), 6.97 (td, 1H, J=7.7, 1.7 Hz), 6.81–6.72 (m, 2H), 1.28–1.16 (m, 3H), 1.03–1.00 (m, 18H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 156.7, 133.9, 132.8, 132.3, 129.8, 128.9, 126.8, 125.9, 125.6, 120.8, 119.0, 115.1, 91.8, 91.3, 18.0, 13.0; MS (EI, 70 eV) m/z (% relative intensity, ion): 430 (3, [M$^+$]), 428 (3, [M$^+$]), 388 (26), 387 (100), 385 (95), 345 (64), 343 (63), 301 (30), 263 (48), 235 (93), 221 (53), 176 (41), 165 (31), 117 (27). Analysis calculated for $C_{23}H_{29}BrOSi$: C, 64.32; H, 6.81. Found: C, 64.86; H, 6.79.

*3.2.4. 2-(m-Tolylethynyl)-O-triisopropylsilylphenol (**4d**)*

Yellow oil, 310 mg (0.85 mmol, 85%). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.48 (dd, 1H, J=7.6, 1.4 Hz), 7.36–7.32 (m, 2H), 7.27–7.12 (m, 3H), 6.96–6.86 (m, 2H), 2.36 (s, 3H), 1.43–1.31 (m, 3H), 1.18–1.15 (m, 18H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 156.7, 137.8, 133.6, 132.1, 129.3, 128.8, 128.4, 128.1, 123.7, 120.8, 119.1, 115.5, 93.0, 86.7, 21.3, 18.0, 13.0; MS (EI, 70 eV) m/z (% relative intensity, ion): 364 (5, [M$^+$]), 322 (29), 321 (100), 279 (67), 251 (63), 189 (21), 132 (30). Analysis calculated for $C_{24}H_{32}OSi$: C, 79.06; H, 8.85; Found: C, 79.77; H, 9.11.

*3.2.5. 2-(4′-Nitrophenylethynyl)-O-triisopropylsilylphenol (**4e**)*

Orange solid, 273 mg (0.69 mmol, 69%). Mp: 93–95 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 8.21 (dt, 2H, J=9.0, 2.1 Hz), 7.63 (dt, 2H, J=9.0, 2.1 Hz), 7.48 (dd, 1H, J=7.7, 1.7 Hz), 7.25 (td, 1H, J=8.2, 1.8 Hz), 6.97–6.88 (m, 2H), 1.41–1.27 (m, 3H), 1.17–1.14 (m, 18H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 157.1, 146.7, 133.8, 131.9, 130.8, 130.5, 123.6, 120.9, 119.1, 114.2, 92.8, 91.0, 18.0, 12.9; MS (EI, 70 eV) m/z (% relative intensity, ion): 395 (3, [M$^+$]), 353 (27), 352 (100), 310 (73), 282 (82), 249 (23), 236 (25), 221 (22), 176 (26). Analysis calculated for $C_{23}H_{29}NO_3Si$: C, 69.84; H, 7.39; N, 3.54. Found: C, 69.44; H, 7.33; N, 3.28.

3.3. General procedure for the synthesis of 2-arylbenzofurans

One-pot sequential coupling: aryl halide (**1**) (1 mmol), 1-ethynylcyclohexanol (**2**) (136 mg, 1.1 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol, 1 mol %) and CuI (2 mg, 0.01 mmol, 1 mol %) were placed into a flame-dried Schlenk flask. Diisopropylamine (7 mL) was added and the mixture was stirred under argon at 80 °C. The reaction was followed by TLC and GC–MS. When the first coupling was complete (typically less than 30 min), KOH (224 mg, 4 mmol), $PdCl_2(PPh_3)_2$ (21 mg, 0.03 mmol, 3 mol %), CuI (6 mg, 0.03 mmol, 3 mol %) and 2-iodo-*O*-triisopropylsilylphenol (**3a**) (376 mg, 1 mmol) or 4-bromo-2-iodo-*O*-triisopropylsilylphenol (**3b**) (455 mg, 1 mmol) were added. The mixture was stirred under argon at 80 °C, until the second coupling was complete. Then TBAF was added in 1 M THF solution (1.1 mL, 1.1 mmol) and the reaction mixture was stirred under argon at 80 °C until the reaction was complete. After evaporating the volatiles, the product (**5**) was separated by column chromatography using hexane–ethyl acetate mixtures as eluent.

Deprotection and ring closure of 2-arylethynyl-O-triisopropylsilylphenols: 2-arylethynyl-*O*-triisopropylsilylphenol (**4**) (0.50 mmol) and TBAF·3H$_2$O (173 mg, 0.55 mmol) were dissolved in toluene (4 mL), and the reaction mixture was stirred at 80 °C. The reaction was followed by TLC and GC–MS. When the deprotection and the ring closure were complete (typically less than 10 min), the solvent was evaporated and the product (**5**) was separated by column chromatography, using hexane–ethyl acetate mixtures as eluent.

*3.3.1. 2-Phenylbenzofuran (**5a**)[18]*

White solid, 'one-pot' process yielded 169 mg (0.87 mmol, 87%), while the ring closure from **4a** yielded 93 mg (0.48 mmol, 96%). Mp: 119–120 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.89–7.84 (m, 2H), 7.60–7.19 (m, 7H), 7.02 (d, 1H, J=0.8 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 155.9, 154.9, 130.5, 129.2, 128.8, 128.5, 124.9, 124.2, 122.9, 120.9, 111.2, 101.3; MS (EI, 70 eV) m/z (% relative intensity, ion): 194 (100, [M$^+$]), 165 (66), 139 (11), 97 (12), 82 (11).

*3.3.2. 2-(4′-Methoxyphenyl)benzofuran (**5b**)[19]*

Yellow solid, 'one-pot' process yielded 184 mg (0.82 mmol, 82%), while the ring closure from **4b** yielded 111 mg (0.49 mmol, 99%). Mp: 152–154 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.70 (dt, 2H, J=9.0, 2.5 Hz), 7.47–7.38 (m, 2H), 7.20–7.09 (m, 2H), 6.88 (dt, 2H, J=8.8, 2.5 Hz), 6.78 (d, 1H, J=0.8 Hz), 3.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 159.9, 156.0, 154.6, 129.5, 126.4, 123.7, 123.3, 122.8, 120.5, 114.2, 110.9, 99.6, 55.3; MS (EI, 70 eV) m/z (% relative intensity, ion): 224 (100, [M$^+$]), 209 (77), 181 (57), 152 (37), 112 (11).

*3.3.3. 2-(2′-Bromophenyl)benzofuran (**5c**)[20]*

Pale yellow solid, 'one-pot' process yielded 169 mg (0.62 mmol, 62%), while the ring closure from **4c** yielded 123 mg (0.45 mmol, 90%). Mp: 36–37 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.96 (dd, 1H, J=7.9, 1.7 Hz), 7.71–7.61 (m, 2H), 7.53–7.50 (m, 2H), 7.40 (td, 1H, J=7.6, 1.1 Hz), 7.35–7.14 (m, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 154.3, 153.1, 134.2, 131.0, 129.8, 129.4, 128.8, 127.5, 124.8, 123.0, 121.4, 120.7, 111.1, 107.0; MS (EI, 70 eV) m/z (% relative intensity, ion): 274 (88, [M$^+$]), 272 (97, [M$^+$]), 165 (100), 137 (21), 82 (36).

*3.3.4. 2-(m-Tolyl)benzofuran (**5d**)*

White solid, 'one-pot' process yielded 175 mg (0.84 mmol, 84%), while the ring closure from **4d** yielded 102 mg (0.49 mmol, 98%). Mp: 75–76 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.68–7.63 (m, 2H), 7.57–7.49 (m, 2H), 7.34–7.13 (m, 4H), 6.97 (d, 1H, J=0.8 Hz), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 156.1, 154.8, 138.4, 130.3, 129.3, 129.2, 128.7, 125.5, 124.1, 122.8, 122.1, 120.8, 111.1, 101.1, 21.5; MS (EI, 70 eV) m/z (% relative intensity, ion): 208 (100, [M$^+$]), 178 (18), 165 (28), 89 (10). Analysis calculated for $C_{15}H_{12}O$: C, 86.51; H, 5.81; Found: C, 86.54; H, 6.10.

*3.3.5. 2-(4′-Nitrophenyl)benzofuran (**5e**)[19]*

Yellow solid, 'one-pot' process yielded 162 mg (0.68 mmol, 68%), while the ring closure from **4e** yielded 110 mg (0.46 mmol, 92%). Mp: 182–183 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 8.30 (dt, 2H, J=9.2, 2.2 Hz), 7.99 (dt, 2H, J=9.0, 2.2 Hz), 7.64 (dt, 1H, J=7.7, 0.7 Hz), 7.56 (d, 1H, J=8.2 Hz), 7.37 (td, 1H, J=7.7, 1.5 Hz), 7.28 (td, 1H, J=7.4, 1.1 Hz), 7.23 (d, 1H, J=0.9 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 155.4, 153.2, 147.2, 136.3, 128.6, 125.8, 125.2, 124.3, 123.5, 121.6, 111.5, 105.1; MS (EI, 70 eV) m/z (% relative intensity, ion): 239 (95, [M$^+$]), 209 (27), 193 (23), 181 (25), 165 (100), 163 (36), 139 (11).

*3.3.6. 5-Bromo-2-(4′-methoxyphenyl)benzofuran (**5f**)[21]*

White solid, 'one-pot' process yielded 242 mg (0.80 mmol, 80%). Mp: 167–169 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.77 (d, 2H, J=8.7 Hz), 7.66 (s, 1H), 7.48–7.35 (m, 2H), 6.97 (d, 2H, J=8.7 Hz), 6.80 (s, 1H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 160.3, 157.3, 153.4, 132.9, 126.5, 126.5, 123.1, 122.7, 115.8, 114.3, 112.4, 99.0, 55.3; MS (EI, 70 eV) m/z (% relative intensity, ion): 304 (100, [M$^+$]), 302 (100, [M$^+$]), 289 (52), 287 (49), 261 (27), 259 (26), 180 (25), 152 (64), 126 (16).

*3.3.7. 5-Bromo-2-(4′-nitrophenyl)benzofuran (**5g**)*[21]

Yellow solid, 'one-pot' process yielded 222 mg (0.70 mmol, 70%). Mp: 191–192 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 8.31 (d, 2H, J=8.8 Hz), 7.98 (d, 2H, J=8.8 Hz), 7.76 (d, 1H, J=0.8 Hz), 7.48–7.40 (m, 2H), 7.17 (s, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 154.5, 154.1, 141.1, 135.6, 130.5, 128.7, 125.4, 124.3, 124.2, 116.6, 112.9, 104.2; MS (EI, 70 eV) m/z (% relative intensity, ion): 319 (75, [M$^+$]), 317 (75, [M$^+$]), 289 (53), 287 (47), 192 (52), 180 (25), 164 (55), 163 (100), 152 (24).

*3.3.8. Vignafuran (**7**)*[13f]

4-Iodo-3-methoxy-*O*-triisopropylsilylphenol (**6a**) (203 mg, 0.50 mmol), 1-ethynyl-cyclohexanol (**2**) (68 mg, 0.55 mmol), $PdCl_2(PPh_3)_2$ (4 mg, 0.005 mmol, 1 mol %) and CuI (1 mg, 0.005 mmol, 1 mol %) were placed into a flame-dried Schlenk flask. Diisopropylamine (4 mL) was added and the mixture was stirred under argon at 80 °C. The reaction was followed by TLC and GC–MS. When the first coupling was complete 2-iodo-5-methoxy-*O*-triisopropylsilylphenol (**6b**) (203 mg, 0.50 mmol), KOH (112 mg, 2 mmol), $PdCl_2(PPh_3)_2$ (10 mg, 0.015 mmol, 3%) and CuI (3 mg, 0.015 mmol, 3%) were added. The mixture was stirred under argon at 80 °C, until the second coupling was complete. Then TBAF was added in 1 M THF solution (1.1 mL, 1.1 mmol). It was stirred under argon at 80 °C until the cleavage and the ring closure were complete. The reaction mixture was diluted with water (5 mL) and the pH was set to 5 with 2 M HCl. It was extracted with ethyl acetate (3×20 mL). The combined organic layer was washed with brine (5 mL) and dried over magnesium sulfate. After evaporating the solvent, the product was purified by column chromatography, using hexane–ethyl acetate as eluent to give 93 mg brown oil (0.34 mmol, 69%). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.86 (d, 1H, J=9.0 Hz), 7.42 (d, 1H, J=8.5 Hz), 7.12 (d, 1H, J=0.8 Hz), 7.05 (d, 1H, J=1.4 Hz), 6.85 (dd, 1H, J=8.5, 2.3 Hz), 6.54–6.50 (m, 2H), 3.95 (s, 3H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 157.6, 157.5, 156.5, 154.6, 151.6, 127.6, 123.3, 120.8, 112.9, 111.3, 107.4, 104.0, 99.2, 95.6, 55.7, 55.5; MS (EI, 70 eV) m/z (% relative intensity, ion): 270 (100, [M$^+$]), 255 (92), 227 (15), 212 (19), 135 (25), 128 (14).

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