The Sequential Sonogashira–Click Reaction: A Versatile Route to 4-Aryl-1,2,3-triazoles

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This paper is dedicated to Professor Béla Csákvári on the occasion of his 85th birthday.

Abstract: Aryl halides can be easily transformed in a one-pot procedure into 4-aryl-1,2,3-triazoles with palladium/copper-catalyzed Sonogashira–click reaction sequence, using trimethylsilylacetylene as acetylene surrogate.

Key words: alkynes, azides, cycloadditions, copper, cross-coupling

The development of new, economic organic processes is one of the major challenges in modern organic synthesis. The application of transition-metal-catalyzed sequential reactions in a ‘one-pot’ manner offers a straightforward method for the synthesis and transformation of molecules containing triple bond without the isolation of the intermediates. The two most frequently used synthetic methodologies in acetylene chemistry are the palladium-catalyzed and copper-assisted Sonogashira coupling of terminal acetylenes and aryl halides,1 and the copper-catalyzed regioselective Huisgen cycloaddition of alkynes and azides (the so-called ‘click’ reaction).2 Both reactions involve the formation of copper acetylides during the catalytic cycle, therefore, the possibility is given for driving these two reactions in a sequential manner under one-pot conditions. Introduction of the triple bond into an aromatic system can be achieved with the aid of protected acetylenes such as trimethylsilylacetylene (TMSA),3 2-methylbut-3-yn-2-ol4 or 1-ethynylcyclohexan-1-ol5 in terms of a Sonogashira coupling reaction. After removal of the protecting group, the terminal acetylene is ready for further transformations. The newly formed terminal acetylene moiety on the aromatic ring can easily be converted into triazoles in a copper-catalyzed dipolar cycloaddition. Herein, we report a one-pot procedure for the construction of 4-aryl-1,2,3-triazoles in a Sonogashira coupling–deprotection–click reaction sequence from aryl halides, trimethylsilylacetylenes, and organic azides (Scheme 1).

The methodology was optimized using iodobenzene (1a) as the coupling partner of the protected acetylene and benzyl azide. In the presence of 1 mol% Pd(PPh3)2Cl2, 5 mol% CuI, and 2 equivalents of diisopropylamine (DIPA), the Sonogashira reaction takes place in EtOH at 25 °C within two hours. Other solvents such as toluene, dichloromethane, or pure DIPA are also applicable for the sequential reaction, however, large amount of bis(trimethylsilyl)butadiyne was formed as side product (9% vs. 3–4% in the case of EtOH). After the completion of the palladium-catalyzed coupling, 1.05 equivalents of benzyl azide (2a) was added, followed by a dichloromethane solution of 1.05 equivalents of TBAF, which was slowly added dropwise into the reaction mixture to minimize the formation of diphenylbutadiyne as side product.6 After 12 hours of reaction time, the formation of the triazole 3a was complete on the basis of the GC-MS analysis, and the product was isolated in 70% yield (Table 1, entry 1).

In order to prove the applicability of the conditions for the preparation of different triazoles bearing substituted aryl groups at position 4, we tested the methodology on a set of aryl iodides 1a–n. The Sonogashira coupling of TMSA and aryl iodides containing alkyl groups on the phenyl ring such as 3,5-dimethyliodobenzene (1b), 4-methyliodobenzene (1c), and 3-methyliodobenzene (1d) took place with the same efficiency like in the case of iodobenzene under the applied conditions within two hours. In the case of bulky 2-isopropylidobenzene (1e), the Sonogashira coupling took place in 26 hours at 25 °C. Subsequent
addition of benzyl azide followed by tetrabutylammonium fluoride (TBAF) gave rise to the formation of the appropriate triazole system 3b–e in good overall yields after chromatographic purification (Table 1, entries 2–5). Condensed aromatic compound such as iodonaphthalene (1f) also afforded the triazole product 3f in 55% yield as a result of the three-step sequential process (entry 6).

In the presence of electron-donating functional groups such as amino (1g) and methoxy (1h) group on the aromatic ring, the Sonogashira reaction provided also the TMS-protected acetylene, and subsequent deprotection and cycloaddition with benzyl azide afforded the substituted aryl triazoles 3g, h in good yields (entries 7, 8). Although the presence of strongly electron-withdrawing nitro group (1i) has significantly lowered the overall yield of the triazolic product 3i (32% yield; entry 9), the reaction worked well with other aryl iodides bearing electron-withdrawing substituent such as cyano group (1j) (entry 10). Aromatic compound with two different halides offers the possibility of regioselective coupling and transformation. Sonogashira reaction of 4-bromiodobenzene (1k) took place selectively on the iodine part with trimethylsilylethylene. Further transformation of the acetylene moiety provided the appropriate triazole in good yield (60%, entry 11), containing bromo functional group on the aromatic ring at position 4, providing possibilities for further functionalization.

Next we studied the possibility to introduce heteroaromatic rings into the triazole framework. Heteroaryl halides such as 2-iodothiophene (1l), 3-iodopyridine (1m) and 2-bromopyridine (1n) were used as starting halides in the Sonogashira coupling with the protected terminal acetylene. Fluoride-promoted removal of the trimethylsilyl group by means of TBAF took place rapidly. Subsequent click reaction with benzyl azide provided the heteroaryl triazoles straightforwardly (entries 12–14). Next, we focused on the variability of the substituents that originates from the azide. After accessing the acetylene intermediate by reacting iodobenzene (1a) with TMSA in the presence of 1 mol% Pd(PPh3)2Cl2 and 5 mol% CuI at 25 °C for two hours, azides 2b–g were tested.

Addition of the appropriate azide 2b–g to the intermediate was followed by a dropwise addition of TBAF solution to the reaction mixture at 25 °C. As expected, click reaction of the in situ generated phenylacetylene took place smoothly with aliphatic azides such as azidomethyl phenyl sulfide (2b), 5-azidovaleric acid ethyl ester (2c) or 1-azido-3-chloro-2-methylpropane (2d) affording the appropriate products 3o, p, q, respectively, in good yields (Table 2, entries 1–3). Sterically demanding azidoadamantane (2e), however, gave triazole 3r in relatively low yield, possibly due to the presence of the bulky alkyl group (entry 4). In this case, longer reaction time (40 h) was necessary, and increased amount of the by-product diphenylbutadiyne was observed indicating the more profound presence of the competing copper-catalyzed homocoupling reaction of the terminal acetylene. This finding can explain the lower yield of the adamantyltriazole 3r. Click reaction of azidocarboxyhydrate 2f and azidoamino acid 2g were also attempted in the sequential transformation routine. Under the developed conditions triazoles 3s and 3t were isolated in 54% and 61% yield, respectively.

Table 1 Sequential Transformation of Different Aryl Halides and Benzyl Azide into 1,2,3-Triazoles

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>76</td>
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<tr>
<td>4</td>
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<tr>
<td>5</td>
<td>3e</td>
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<tr>
<td>6</td>
<td>3f</td>
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<tr>
<td>7</td>
<td>3g</td>
<td>70</td>
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<td>8</td>
<td>3h</td>
<td>57</td>
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<tr>
<td>9</td>
<td>3i</td>
<td>32</td>
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<td>10</td>
<td>3j</td>
<td>62</td>
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<td>11</td>
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<td>60</td>
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<tr>
<td>12</td>
<td>3l</td>
<td>54</td>
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<tr>
<td>13</td>
<td>3m</td>
<td>63</td>
</tr>
<tr>
<td>14</td>
<td>3n</td>
<td>53</td>
</tr>
</tbody>
</table>

*Isolated yield after chromatographic purification.

In the presence of strongly electron-withdrawing nitro group (1i) has significantly lowered the overall yield of the triazolic product 3i (32% yield; entry 9), the reaction worked well with other aryl iodides bearing electron-withdrawing substituent such as cyano group (1j) (entry 10). Aromatic compound with two different halides offers the possibility of regioselective coupling and transformation. Sonogashira reaction of 4-bromiodobenzene (1k) took place selectively on the iodine part with trimethylsilylethylene. Further transformation of the acetylene moiety provided the appropriate triazole in good yield (60%, entry 11), containing bromo functional group on the aromatic ring at position 4, providing possibilities for further functionalization.

Next we studied the possibility to introduce heteroaromatic rings into the triazole framework. Heteroaryl halides such as 2-iodothiophene (1l), 3-iodopyridine (1m) and 2-bromopyridine (1n) were used as starting halides in the Sonogashira coupling with the protected terminal acetylene. Fluoride-promoted removal of the trimethylsilyl group by means of TBAF took place rapidly. Subsequent click reaction with benzyl azide provided the heteroaryl triazoles straightforwardly (entries 12–14). Next, we focused on the variability of the substituents that originates from the azide. After accessing the acetylene intermediate by reacting iodobenzene (1a) with TMSA in the presence of 1 mol% Pd(PPh3)2Cl2 and 5 mol% CuI at 25 °C for two hours, azides 2b–g were tested.

Addition of the appropriate azide 2b–g to the intermediate was followed by a dropwise addition of TBAF solution to the reaction mixture at 25 °C. As expected, click reaction of the in situ generated phenylacetylene took place smoothly with aliphatic azides such as azidomethyl phenyl sulfide (2b), 5-azidovaleric acid ethyl ester (2c) or 1-azido-3-chloro-2-methylpropane (2d) affording the appropriate products 3o, p, q, respectively, in good yields (Table 2, entries 1–3). Sterically demanding azidoadamantane (2e), however, gave triazole 3r in relatively low yield, possibly due to the presence of the bulky alkyl group (entry 4). In this case, longer reaction time (40 h) was necessary, and increased amount of the by-product diphenylbutadiyne was observed indicating the more profound presence of the competing copper-catalyzed homocoupling reaction of the terminal acetylene. This finding can explain the lower yield of the adamantyltriazole 3r. Click reaction of azidocarboxyhydrate 2f and azidoamino acid 2g were also attempted in the sequential transformation routine. Under the developed conditions triazoles 3s and 3t were isolated in 54% and 61% yield, respectively.
In summary, we have aimed at developing a new sequential procedure for accessing 4-aryltriazoles in a one-pot manner starting from aromatic halides. The methodology, based on a palladium/copper bimetallic catalytic system, involves a Sonogashira coupling–deprotection–click reaction sequence, where the aryl module of the product can be easily varied without the isolation of the terminal acetylene intermediate. The large variety of commercially available aryl halides as starting materials and easily accessible azides provide a wide range of possible triazole products in a short and good overall yielding synthetic route.

Analytical TLC was performed on Merck DC precoated TLC plates with 0.25 mm Kieselgel 60 F254. TLC spots were visualized under UV light at 254 nm. Column chromatography was carried out using silica gel 60 (0.040–0.063 mm) from Merck using hexanes–EtOAc eluent mixtures. 1H and 13C NMR spectra (exception: compound 3t) were recorded on a Bruker DRX-250 spectrometer in CDCl3. Spectra for compound 3t were acquired on a Varian VNMRS 600 MHz spectrometer equipped with a HCN triple resonance probehead. Chemical shifts (δ) are expressed in parts per million units, relative to the residual solvent peak (δ = 7.26 for 1H, δ = 77.0 for 13C) where possible or alternatively to TMS (δ = 0.00) as internal standard. Coupling constants (J) are given in Hz. Combined gas chromatography and low-resolution mass spectrometry was obtained on an Agilent 6890N gas Chromatograph (30 m × 0.25 mm column with 0.25 μm HP-5MS coating. He carrier gas) and Agilent 5973 mass spectrometer (ion source: EI, 70 eV, 230 °C, interface: 300 °C). High-resolution mass spectra were recorded on an Agilent Technologies 6210 Time of Flight mass spectrometer. IR spectra were obtained on a Bruker IFS55 spectrometer on a single-reflection diamond ATR unit. Samples for melting point determination were recrystallized from hexanes. Melting points were determined in capillary tubes with a Büchi apparatus and are uncorrected.

Starting aryl halides 1a–n and azides 2a,b,e were obtained from commercial sources (Aldrich, Fluka) and used without further purification. Compounds 2c,d, 2f, and 2g were prepared using literature procedures.

1,2,3-Triazoles 3: General Procedure
Pd[PPh3]4Cl2 (3.5 mg, 5.0 μmol, 1 mol%) and Cul (4.8 mg, 25 μmol, 5 mol%) were mixed with EtOH (1 mL) in a glass vial equipped with a screw cap. DIPA (140.2 μL, 1.0 mmol, 2 equiv) was added and the vial was flushed with argon. The appropriate aryl halide (0.5 mmol) and finally trimethylsilylacetylene (76.2 μL, 0.55 mmol, 1.1 equiv) were added and the mixture was stirred for 2–3 h. The reaction was followed by GC analysis. After completion of the Sonogashira step, the corresponding azide (0.525 mmol, 1.05 equiv) was added dropwise and the reaction mixture was stirred for additional 5 min. A solution of TBAF·3H2O (165 mg, 0.525 mmol, 1.05 equiv) in CH3Cl 0.5 mL) was added in small portions over 1 h. No precaution was taken to exclude air after the Sonogashira step had been completed. The mixture was stirred at r.t. for 12 h. All volatiles were removed under reduced pressure and the residue was subjected to column chromatography using hexane–EtOAc mixture as eluent to afford the respective 1,2,3-triazoles 3.

### Table 2 Sequential Transformation of Different Azides and Iodo-benzene into 1,2,3-Triazoles

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>Yield (%) a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3o</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td>3p</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>3q</td>
<td>69</td>
</tr>
<tr>
<td>4</td>
<td>3r</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>3s</td>
<td>54</td>
</tr>
<tr>
<td>6</td>
<td>3t</td>
<td>61</td>
</tr>
</tbody>
</table>

a Isolated yield after chromatographic purification.

Starting aryl halides 1a–n and azides 2a,b,e were obtained from commercial sources (Aldrich, Fluka) and used without further purification. Compounds 2c,d, 2f, and 2g were prepared using literature procedures.

1-Benzyl-4-phenyl-1H-1,2,3-triazole (3a)
Yield: 82 mg (70%, 0.35 mmol); white solid; mp 128–129 °C; Rf = 0.25 (hexanes–EtOAc, 3:1).

1H NMR (250 MHz, CDCl3): δ = 7.70–7.68 (m, 2 H), 7.57 (s, 1 H), 7.37–7.16 (m, 8 H), 5.42 (s, 2 H).

13C NMR (62.5 MHz, CDCl3): δ = 148.0, 134.6, 130.4, 129.0, 128.7, 128.6, 127.9, 127.6, 119.1, 54.0, 21.2.

IR (ATR): 2922, 2854, 1604, 1495, 1445, 1356, 1226, 1049 cm–1.

MS (EI, 70 eV): m/z (%) = 264 (11, [M+]), 235 (9, [M+]), 220 (14), 193 (9), 116 (100), 104 (18), 91 (98), 89 (43), 77 (11), 65 (28), 63 (20).

1-Benzyl-4-(3,5-dimethylphenyl)-1H-1,2,3-triazole (3b)
Yield: 97 mg (74%, 0.37 mmol); white solid; mp 125–126 °C; Rf = 0.42 (hexanes–EtOAc, 3:1).

1H NMR (250 MHz, CDCl3): δ = 7.62–7.55 (m, 2 H), 7.53 (s, 1 H), 7.57 (s, 1 H), 7.57–7.47 (m, 5 H), 6.83 (s, 1 H), 5.39 (s, 2 H), 2.21 (s, 6 H).

13C NMR (62.5 MHz, CDCl3): δ = 148.2, 138.1, 134.6, 130.1, 129.6, 128.9, 128.5, 127.8, 123.3, 119.4, 53.9, 21.1.

MS (EI, 70 eV): m/z (%) = 263 (11, [M+]), 235 (9, [M+]), 206 (52), 180 (11), 130 (9), 116 (100), 104 (18), 91 (98), 89 (43), 77 (11), 65 (28), 63 (20).

1-Benzyl-4-(3,5-dimethylphenyl)-1H-1,2,3-triazole (3c)
Yield: 94 mg (76%, 0.38 mmol); white solid; mp 155–157 °C; Rf = 0.42 (hexanes–EtOAc, 3:1).

1H NMR (250 MHz, CDCl3): δ = 7.70–7.68 (m, 2 H), 7.57 (s, 1 H), 7.32 (br s, 2 H), 7.25–7.14 (m, 5 H), 6.83 (s, 1 H), 5.39 (s, 2 H), 2.21 (s, 6 H).

IR (ATR): 2922, 2854, 1604, 1495, 1445, 1356, 1226, 1049 cm–1.

MS (EI, 70 eV): m/z (%) = 264 (11, [M+]), 235 (9, [M+]), 206 (52), 180 (11), 130 (9), 116 (100), 104 (18), 91 (98), 89 (43), 77 (11), 65 (28), 63 (20).


1-Benzyl-4-p-tolyl-1H-1,2,3-triazole (3d)
Yield: 94 mg (76%, 0.38 mmol); white solid; mp 155–157 °C; Rf = 0.42 (hexanes–EtOAc, 3:1).

1H NMR (250 MHz, CDCl3): δ = 7.62–7.55 (m, 2 H), 7.53 (s, 1 H), 7.27–7.17 (m, 5 H), 7.13–7.06 (m, 2 H), 5.43 (s, 2 H), 2.25 (s, 3 H).

13C NMR (62.5 MHz, CDCl3): δ = 148.1, 137.8, 134.7, 129.4, 129.0, 128.6, 127.9, 127.6, 125.5, 119.1, 54.0, 21.2.

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Yield: 94 mg (76%, 0.32 mmol); white solid; mp 74–75 °C; 

\[
\text{Rf} = 0.26 \text{ (hexanes–EtOAc, 3:1).}
\]

1-Benzyl-4-tolyl-1H-1,2,3-triazole (3d)

Yield: 90 mg (65%, 0.32 mmol); white solid; mp 120–122 °C; 

\[
\text{Rf} = 0.37 \text{ (hexanes–EtOAc, 3:1).}
\]

1-Benzyl-4-(2-isopropylphenyl)-1H-1,2,3-triazole (3e)

Yield: 75 mg (63%, 0.32 mmol); white solid; mp 109–110 °C; 

\[
\text{Rf} = 0.23 \text{ (hexanes–EtOAc, 3:1).}
\]

1-Benzyl-4-(thiophen-2-yl)-1H-1,2,3-triazole (3f)

Yield: 81 mg (62%, 0.31 mmol); white solid; mp 119–121 °C; 

\[
\text{Rf} = 0.26 \text{ (hexanes–EtOAc, 3:1).}
\]

1-Benzyl-4-(naphthalen-1-yl)-1H-1,2,3-triazole (3g)

Yield: 93 mg (70%, 0.32 mmol); white solid; mp 167–169 °C; 

\[
\text{Rf} = 0.42 \text{ (hexanes–EtOAc, 3:1).}
\]

1-Benzyl-4-(4-nitrophenyl)-1H-1,2,3-triazole (3i)

Yield: 65 mg (54%, 0.27 mmol); yellow solid; mp 102–104 °C; 

\[
\text{Rf} = 0.37 \text{ (hexanes–EtOAc, 3:1).}
\]

1-Benzyl-4-(4-nitrophenyl)-1H-1,2,3-triazole (3j)

Yield: 75 mg (63%, 0.32 mmol); white solid; mp 119–121 °C; 

\[
\text{Rf} = 0.26 \text{ (hexanes–EtOAc, 3:1).}
\]

1-Benzyl-4-(4-thiophenyl)-1H-1,2,3-triazole (3k)

Yield: 75 mg (63%, 0.32 mmol); white solid; mp 167–169 °C; 

\[
\text{Rf} = 0.42 \text{ (hexanes–EtOAc, 3:1).}
\]

1-Benzyl-4-(4-bromophenyl)-1H-1,2,3-triazole (3l)

Yield: 45 mg (32%, 0.16 mmol); yellow solid; mp 167–169 °C; 

\[
\text{Rf} = 0.23 \text{ (hexanes–EtOAc, 3:1).}
\]

1-Benzyl-4-(2-trifluoromethyl)phenyl-1H-1,2,3-triazole (3m)

Yield: 75 mg (63%, 0.32 mmol); white solid; mp 167–169 °C; 

\[
\text{Rf} = 0.42 \text{ (hexanes–EtOAc, 3:1).}
\]

1-Benzyl-4-(4-nitrophenyl)-1H-1,2,3-triazole (3n)

Yield: 75 mg (63%, 0.32 mmol); white solid; mp 167–169 °C; 

\[
\text{Rf} = 0.42 \text{ (hexanes–EtOAc, 3:1).}
\]
MS (El, 70 eV); m/z (%): 236 (9, [M+]¹), 207 (35), 180 (15), 166 (8), 130 (14), 117 (67), 104 (15), 91 (100), 77 (8), 65 (25), 63 (25).

2-(1-Benzyl-1H-1,2,3-triazol-4-yl)pyridine (3n)
Yield: 63 mg (53%, 0.27 mmol); white solid; mp 112–113 °C; Rf = 0.34 (hexanes–EtOAc, 1:1).

1H NMR (250 MHz, CDCl₃); δ: 7.75–7.70 (m, 3 H), 7.36–7.20 (m, 1 H), 5.94 (d, J = 9.0 Hz, 2 H), 5.27 (d, J = 9.1 Hz, 2 H), 4.33 (dd, J = 5.1, 12.6 Hz, 1 H), 4.15 (dd, J = 2.1, 12.6 Hz, 1 H), 4.07–4.00 (m, 1 H), 2.073, 2.067 (overlapping singlets, 6 H), 2.03 (s, 3 H), 1.87 (s, 3 H).

1-(3-Chloro-2-methylpropyl)-4-phenyl-1H-1,2,3-triazole (3o)
Yield: 113 mg (56%, 0.27 mmol); white solid; mp 128–129 °C; Rf = 0.61 (hexanes–EtOAc, 1:1).

1H NMR (250 MHz, CDCl₃); δ: 8.01 (s, 1 H), 7.85–7.81 (m, 2 H), 7.47–7.30 (m, 3 H), 5.94 (d, J = 9.0 Hz, 1 H), 5.48 (ddd, J = 9.3, 21.8 Hz, 2 H), 5.27 (t, J = 9.5 Hz, 1 H), 4.33 (dd, J = 5.1, 12.6 Hz, 1 H), 4.15 (dd, J = 2.1, 12.6 Hz, 1 H), 4.07–4.00 (m, 1 H), 2.073, 2.067 (overlapping singlets, 6 H), 2.03 (s, 3 H), 1.87 (s, 3 H).

1-(1-Adamantyl)-4-phenyl-1H-1,2,3-triazole (3r)
Yield: 33 mg (24%, 0.12 mmol); white solid; mp 203–204 °C (dec.); Rf = 0.42 (hexanes–EtOAc, 1:1).

1H NMR (250 MHz, CDCl₃); δ: 7.75–7.79 (m, 3 H), 7.19–7.36 (m, 3 H), 2.21 (br s, 9 H), 1.73 (br s, 6 H).

13C NMR (62.5 MHz, CDCl₃); δ: 146.7, 131.1, 128.7, 127.8, 125.6, 116.0, 59.5, 43.0, 35.9, 29.4.

MS (El, 70 eV); m/z (%): 279 (9, [M+]¹), 223 (12), 181 (8), 135 (100), 116 (20), 102 (15), 93 (31), 79 (36), 67 (12).

PRACTICAL SYNTHETIC PROCEDURES

Sequential Sonogashira–Click Reaction

References


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When TBAF was added before the azide, 9% diphenylbutadiyne was formed as by-product in the reaction mixture. With the addition of azide before the TBAF, we were able to suppress the homocoupling of the in situ formed terminal acetylene in every tested solvent. In EtOH–CH₂Cl₂ solvent mixture the amount of the diphenylbutadiyne side product remained below 1%.
