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One-Pot Procedure for the Synthesis of Unsymmetrical Diarylalkynes

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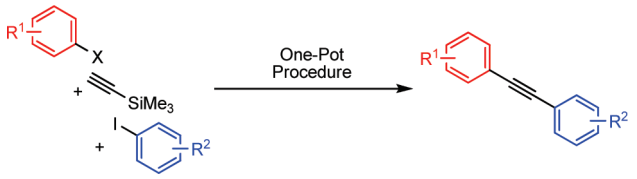
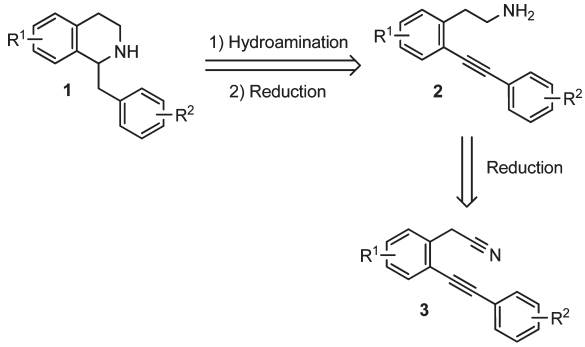


Unsymmetrical diarylalkynes are accessible by a one-pot procedure from two different aryl halides and (trimethylsilyl)acetylene. The three-component coupling is initialized by a Pd/Cu-catalyzed Sonogashira coupling of an aryl halide with (trimethylsilyl)acetylene. After subsequent desilylation of the formed aryl(trimethylsilyl)acetylene with aqueous potassium hydroxide, a second Sonogashira coupling with an aryl iodide that does not require any additional Pd/Cu-catalyst gives access to an unsymmetrical diarylalkyne.

During the past decades, the Sonogashira reaction[1,2] has become one of the most important Pd-catalyzed C−C bond-forming reactions. This cross-coupling of an aryl halide with a terminal alkyne has proven to be an experimental simple, reliable, and high-yielding reaction that can be used efficiently for the synthesis of symmetrical and unsymmetrical diarylalkynes as well as arylalkylalkynes.[2,3] Especially, the synthesis of unsymmetrically substituted diarylalkynes has attracted much attention and a typical three-step strategy for the synthesis of corresponding products starts with an initial Sonogashira coupling of an aryl halide with (trimethylsilyl)acetylene.[4] The resulting 2-aryl(trimethylsilyl)acetylene

SCHEME 1. Retrosynthesis of the 1,2,3,4-Tetrahydrobenzylisoquinoline Skeleton



3a: R^1 = H, R^2 = *p*-Cl
3b: R^1 = H, R^2 = *p*-Me
3c: R^1 = H, R^2 = *p*-CF_3

is then desilylated under basic conditions to give a terminal arylalkyne that can finally be used for a second Pd-catalyzed Sonogashira reaction with an aryl halide. In the past, we used a corresponding three-step approach toward the synthesis of (2-alkynylphenyl)acetonitriles of type **3** (Scheme 1) because these unsymmetrical diarylalkynes can be used as starting materials for the synthesis of biologically interesting 1,2,3,4-tetrahydrobenzylisoquinoline derivatives **1**.[5] For that purpose, the nitriles **3** must initially be reduced to the corresponding aminoalkynes **2**. A subsequent one-pot process that involves an intramolecular Ti-catalyzed hydroamination of **2** and a final reduction of the resulting cyclic imine then gives access to the desired 1,2,3,4-tetrahydrobenzylisoquinoline derivatives **1**. However, the synthetic flexibility of the overall process strongly depends on a short, flexible, and efficient method for the synthesis of unsymmetrical diarylalkynes of type **3**. For that reason, we decided to work toward the development of a reliable one-pot process for the synthesis of corresponding diarylalkynes. While corresponding one-pot Sonogashira processes for the synthesis of symmetrical[1,6−11] and unsymmetrical[9−11] diarylalkynes with one or two aryl halides and an acetylene equivalent [(trimethylsilyl)acetylene,[6,11] acetylene gas,[1,7,9] calcium carbide,[8] or 2-methyl-3-butyn-2-ol[10]] as the starting materials have been described before, an application of these methods for the synthesis of (2-alkynylphenyl)acetonitriles of type **3** has not been reported yet. Furthermore, most of the mentioned processes were either applied only to the synthesis of symmetrical diarylalkynes[1,6−8] or they use a large amount

(1) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.
(2) For recent reviews on Sonogashira reaction, see: (a) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874. (b) Doucet, H.; Hierso, J.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 834. (c) Plenio, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6954. (d) McGlacken, G. P.; Fairlamb, I. J. S. *Eur. J. Org. Chem.* **2009**, 4011. (e) Pal, M. *Synlett* **2009**, 2896.
(3) For a recent example of a Sonogashira reaction that is part of a one-pot procedure for the synthesis of 4-aryl-1,2,3-triazoles, see: Lorincz, K.; Kele, P.; Novak, Z. *Synthesis* **2009**, 3527.
(4) Takahashi, S.; Kuroyama, Y.; Sonogashira, N.; Hagihara, N. *Synthesis* **1980**, 627.
(5) (a) Mujahidin, D.; Doye, S. *Eur. J. Org. Chem.* **2005**, 2689. (b) Severin, R.; Mujahidin, D.; Reimer, J.; Doye, S. *Heterocycles* **2007**, *74*, 683. (c) Severin, R.; Reimer, J.; Doye, S. *Eur. J. Org. Chem.* **2010**, 51.
(6) D'Auria, M. *Synth. Commun.* **1992**, *22*, 2393.
(7) Li, C.-J.; Chen, D.-L.; Costello, C. W. *Org. Process Res. Dev.* **1997**, *1*, 325.
(8) Zhang, W.; Wu, H.; Liu, Z.; Zhong, P.; Zhang, L.; Huang, X.; Cheng, J. *Chem. Commun.* **2006**, 4826.
(9) Pal, M.; Kundu, N. G. *J. Chem. Soc., Perkin Trans. 1* **1996**, 449.
(10) Yi, C.; Hua, R.; Zeng, H.; Huang, Q. *Adv. Synth. Catal.* **2007**, *349*, 1738.
(11) Mio, M. J.; Kopel, L. C.; Braun, J. B.; Gadzikwa, T. L.; Hull, K. L.; Brisbois, R. G.; Markworth, C. J.; Grieco, P. A. *Org. Lett.* **2002**, *4*, 3199.

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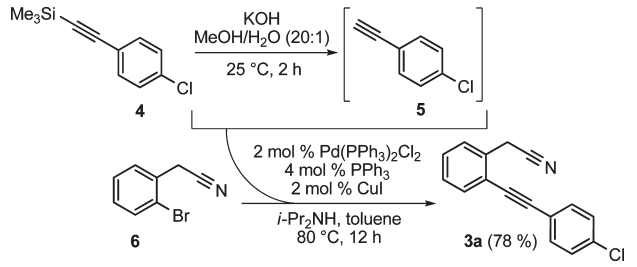
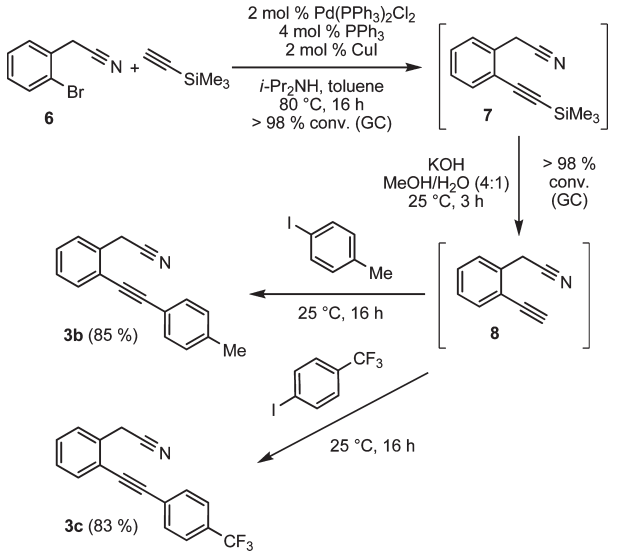
SCHEME 2. Sequential Desilylation and Sonogashira Coupling of TMS-Protected Alkyne 4



SCHEME 3. One-Pot Synthesis of (2-Alkynylphenyl)-acetonitriles



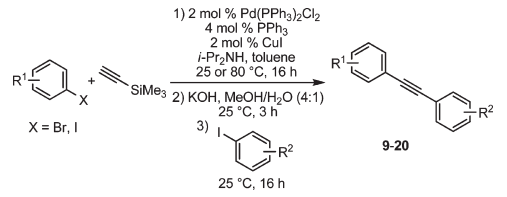
(6.0 equiv) of the expensive amidine base 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) together with a substoichiometric amount of water for the in situ desilylation of initially formed 2-aryl(trimethylsilyl)acetylenes.[11]

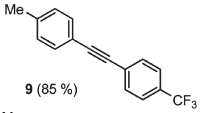
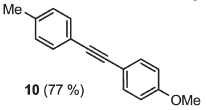
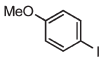
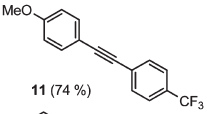
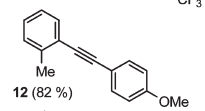
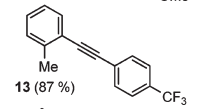
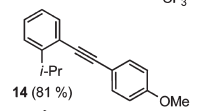
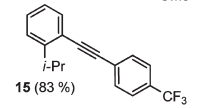
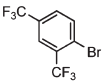
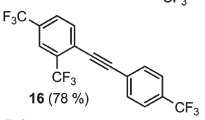
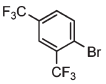
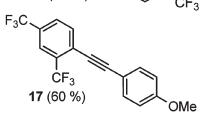
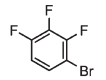
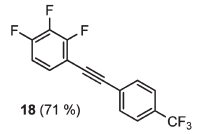
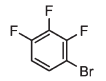
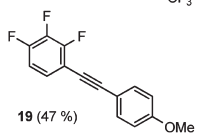
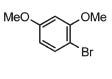
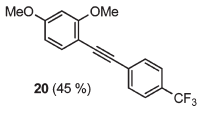
On the basis of the idea that the desilylation of 2-aryl-(trimethylsilyl)acetylenes can easily be achieved with less expensive potassium hydroxide in a mixture of methanol and water, we used these conditions for an initial one-pot reaction between 2-(4-chlorophenyl)(trimethylsilyl)acetylene (**4**) and the commercially available aryl bromide **6** (Scheme 2). For that purpose, **4** was first stirred at room temperature for 2 h with 2 equiv of KOH in a 20:1 mixture of MeOH and water. The resulting reaction mixture that contained the in situ generated terminal alkyne **5** was then added to a mixture of aryl bromide **6**, 2 mol % $Pd(PPh_3)_2Cl_2$, 4 mol % PPh_3, 2 mol % CuI, *i*-Pr_2NH, and toluene. After this mixture had been stirred for 12 h at 80 °C, the desired diarylalkyne **3a** could be isolated in 78% yield after column chromatography. This result clearly indicates that the desilylation conditions which rely on the inexpensive base KOH are compatible with the catalyst system used for the subsequent Sonogashira coupling.

In a further set of experiments (Scheme 3), we performed initial Sonogashira reactions of aryl bromide **6** with (trimethylsilyl)acetylene at 80 °C in the presence of 2 mol % $Pd(PPh_3)_2Cl_2$, 4 mol % PPh_3, 2 mol % CuI, *i*-Pr_2NH, and toluene. It must be noted that under these conditions, complete conversion to the (trimethylsilyl)alkyne **7** was observed by GC after a reaction time of 16 h while a corresponding reaction performed with NEt_3 proceeded with significantly decreased rate. The resulting crude reaction mixtures were then directly treated with a solution of 2 equiv of KOH in MeOH/H_2O (4:1) to remove the TMS group from the initially formed alkyne **7**. After the resulting mixtures had been stirred for 3 h at room temperature (>98% conversion), either 4-iodotoluene or 4-iodotrifluoromethylbenzene were added and the mixtures were stirred for an additional 16 h at room temperature to achieve a second Sonogashira coupling. Fortunately, after that time, it was indeed possible to isolate the desired, unsymmetrical diarylalkynes **3b** and **3c** in 85% and 83% yield, respectively. Most impressively, it turned out that the second Sonogashira coupling did not require the addition of any additional amounts of the Pd/Cu catalyst.

With these results in hand, we turned our attention toward the one-pot synthesis of a variety of more simple but still unsymmetrical diarylalkynes (Table 1). Corresponding three-component coupling experiments were initially performed with two different aryl iodides and (trimethylsilyl)-acetylene as the starting materials (Table 1, entries 1−7). Due to the fact that aryl iodides usually show a higher reactivity than aryl bromides in Pd-catalyzed reactions, the initial Sonogashira couplings could easily be achieved at room temperature in the presence of 2 mol % $Pd(PPh_3)_2Cl_2$, 4 mol % PPh_3, 2 mol % CuI, and *i*-Pr_2NH in toluene. Subsequent addition of a solution of 2 equiv of KOH in MeOH/H_2O (4:1) and stirring at room temperature (3 h) followed by the addition of a second aryl iodide and additional stirring at room temperature (16 h) led to the clean formation of the expected diarylalkynes **9**−**15** in very good yields (74−87%). As can be seen from Table 1 (entries 1−7), the one-pot reaction sequence tolerates electron-donating (Me, *i*-Pr, MeO) and -withdrawing (CF_3) substituents on the benzene ring of the substrates as well as ortho-substitution. Particularly impressive are the very good results obtained for the products **14** and **15** (81% and 83%) which possess a sterically demanding *i*-Pr group in the ortho-position. Additional three-component couplings could also be performed successfully with one aryl bromide, (trimethylsilyl)acetylene, and one aryl iodide (Table 1, entries 8−12). However, in these cases the initial Sonogashira coupling of the aryl bromide needs to be performed at 80 °C. Using a corresponding experimental procedure we were able to obtain the desired diarylalkynes **16**−**20** in modest to very good yields (45−78%). Again, the one-pot process makes it possible to synthesize products which bear electron-donating (MeO) and -withdrawing (F, CF_3) as well as ortho-substituents on the benzene rings. However, it must also be noted that reaction sequences which use an aryl bromide and an aryl iodide give slightly decreased yields when the Sonogashira couplings are performed in reverse order. An explanation for this observation is the more harsh reaction conditions (80 °C) which are then necessary for the second Sonogashira reaction of the aryl bromide. Under these conditions, the presence of the strong base KOH caused decomposition reactions which led to the formation of side products and consequently to decreased overall yields. On the other hand, comparable decomposition reactions were not observed when the second Sonogashira reaction was performed with

TABLE 1. One-Pot Synthesis of Unsymmetrical Diarylalkynes

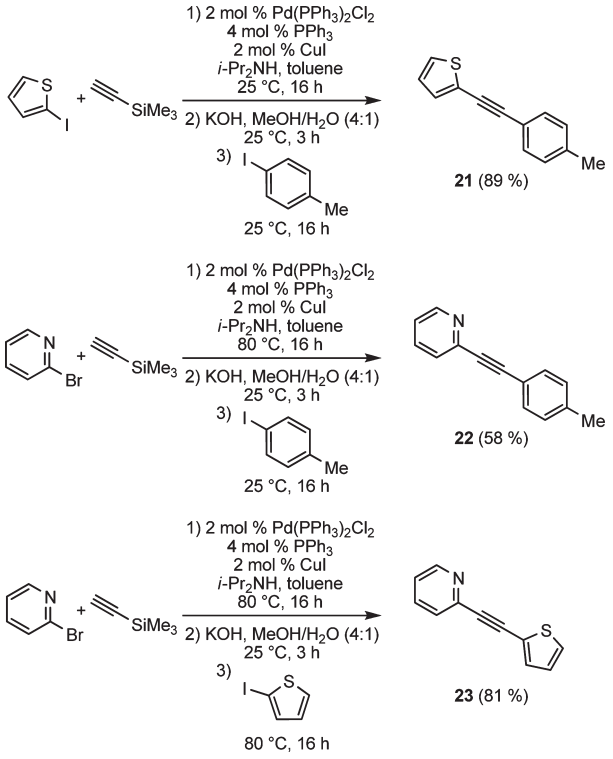


entry	aryl halide	aryl iodide	product (yield)[a]
1[b]			 **9** (85 %)
2[b]			 **10** (77 %)
3[b]			 **11** (74 %)
4[b]			 **12** (82 %)
5[b]			 **13** (87 %)
6[b]			 **14** (81 %)
7[b]			 **15** (83 %)
8[c]			 **16** (78 %)
9[c]			 **17** (60 %)
10[c]			 **18** (71 %)
11[c]			 **19** (47 %)
12[c]			 **20** (45 %)

[a]Reaction conditions: (1) aryl halide (3 mmol), (trimethylsilyl)-acetylene (3.6 mmol), $Pd(PPh_3)_2Cl_2$ (2 mol %), PPh_3 (4 mol %), CuI (2 mol %), *i*-Pr_2NH (1 mL), toluene (5 mL), 25 or 80 °C, 16 h; (2) KOH (6 mmol), MeOH (2 mL), H_2O (0.5 mL), 25 °C, 3 h; (3) aryl iodide (3 mmol), 25 °C, 16 h. [b]Initial reaction at 25 °C. [c]Initial reaction at 80 °C.

an aryl iodide at room temperature. For that reason, it is strongly recommended to perform the initial Sonogashira reaction with the less reactive aryl halide especially when the corresponding reaction needs more forcing conditions.

SCHEME 4. One-Pot Synthesis of Heteroaromatic Unsymmetrical Diarylalkynes



With these results in hand, we finally investigated the use of the two heteroaryl halides 2-iodothiophene and 2-bromopyridine as substrates for the new one-pot process (Scheme 4). Interestingly, it was initially found that the two heteroaromatic substrates could successfully be reacted under standard conditions with (trimethylsilyl)acetylene and 4-iodotoluene to give the unsymmetrical diarylalkynes **21** and **22** in 89% and 58% yield, respectively. However, when 2-bromopyridine was used together with (trimethylsilyl)acetylene and 2-iodothiophene the second Sonogashira coupling had to be performed at 80 °C to give the desired product **23** in acceptable yield (81%). Otherwise, the diarylalkyne **23** was not formed at all.

In summary, we have presented a one-pot synthesis of unsymmetrically substituted diarylalkynes. The process relies on an initial Pd/Cu-catalyzed Sonogashira coupling of (trimethylsilyl)acetylene with an aryl halide, a subsequent desilylation of the generated aryl(trimethylsilyl)acetylene performed with aqueous potassium hydroxide, and a second Sonogashira coupling with an aryl iodide that does not require the addition of any additional amounts of a Pd/Cu catalyst.

Experimental Section

Typical Reaction Procedure for the One-Pot Synthesis of Diarylalkynes Exemplified by the Synthesis of 1-Methyl-4-((4-(trifluoromethyl)phenyl)ethynyl)benzene (9, Table 1, entry 1). 1-Iodo-4-methylbenzene (654 mg, 3.00 mmol), $Pd(PPh_3)_2Cl_2$ (42 mg, 0.06 mmol, 2 mol %), CuI (11 mg, 0.06 mmol, 2 mol %), and PPh_3 (31 mg, 0.12 mmol, 4 mol %) were placed in an oven-dried and argon-filled Schlenk tube. After addition of

i-Pr_2NH (1.0 mL) and toluene (5.0 mL), the mixture was stirred at 25 °C for 5 min and (trimethylsilyl)acetylene (354 mg, 3.60 mmol) was added. After this mixture had been stirred at 25 °C for 16 h, a solution of KOH (337 mg, 6.00 mmol) in water (0.5 mL) and methanol (2.0 mL) was added in one portion and the mixture was stirred for an additional 3 h at 25 °C. Then 1-iodo-4-(trifluoromethyl)benzene (816 mg, 3.00 mmol) was added and stirring was continued for 16 h at 25 °C. The reaction mixture was quenched with saturated NH_4Cl solution (60 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with HCl (2 N, 50 mL), water (50 mL), and saturated NaCl solution (50 mL) and dried with $MgSO_4$. After concentration under vacuum, the residue was purified by flash chromatography (SiO_2, 115 g, light petroleum ether, R_f 0.30) to give **9** (662 mg, 2.54 mmol, 85%) as a light yellow solid (mp 133.4 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.37 (s, 3 H), 7.17 (d, J = 8.0 Hz, 2 H), 7.43 (d, J = 8.0 Hz, 2 H), 7.58 (d, J = 8.7 Hz, 2 H), 7.60 (d, J = 8.6 Hz, 2 H) ppm; ^{13}C NMR (126 MHz, DEPT, $CDCl_3$) δ 21.5 (CH_3), 87.4 (C), 92.0 (C), 119.5 (C), 124.0 (q, J = 272 Hz, CF_3), 125.2 (q, J = 4 Hz, CH), 127.3 (C), 129.2 (CH), 129.7 (q, J = 33 Hz, C), 131.6 (CH), 131.7 (CH), 139.1 (C) ppm; IR (neat) $1/\lambda$ 2923, 2218, 1315, 1164, 1122, 1104, 1063, 1013, 842, 819 cm^{-1}; MS (EI) m/z (%) 260 (100) $[M]^+$, 259 (32), 191 (12), 189 (16), 115 (4); HRMS calcd ($C_{16}H_{11}F_3$) 260.0813, found 260.0811.

Acknowledgment. We thank the Deutsche Forschungsgemeinschaft (DFG) for financial support of our research.

Supporting Information Available: Experimental details, analytical data, and NMR spectra for compounds **3a**−**c** and **9**−**23**. This material is available free of charge via the Internet at http://pubs.acs.org.