Improved Procedures for the Palladium-Catalyzed Coupling of Terminal Alkynes with Aryl Bromides (Sonogashira Coupling)†

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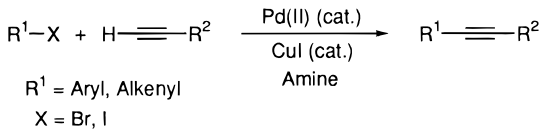
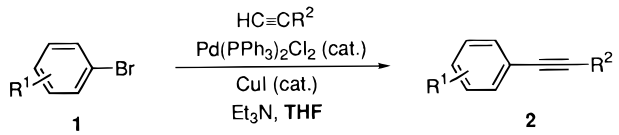
One of the most straightforward methods for the preparation of arylalkynes and conjugated enynes is the palladium-catalyzed coupling of terminal alkynes with aryl or alkenyl halides which was described for the first time by Sonogashira et al. in 1975.[1] Usually, the Sonogashira coupling is carried out in the presence of catalytic amounts of a palladium(II) complex as well as copper(I) iodide in an amine as solvent.[2] Numerous applications in natural product synthesis have been reported,[2] for example in the construction of the complex unsaturated framework of the enediyne antibiotics (Scheme 1).[3]

Scheme 1



In the course of a current research program directed toward the synthesis of functionalized arylalkynes, we required a reliable and operationally simple procedure for the Sonogashira coupling of aryl bromides with terminal alkynes. Typically, the aryl bromide is mixed with the alkyne in an amine (normally di- or triethylamine), and the mixture is either stirred at room temperature or heated under reflux for varying amounts of time.[3−5] However, the experimental conditions for the preparation of some compounds vary considerably, especially with respect to reaction time and temperature, and in our hands, it turned out to be difficult to reproduce some of the excellent yields reported in the literature. Careful examination of the published procedures reveals several difficulties which can affect the efficiency and practicability of the Sonogashira coupling: (i) The reactivity of the coupling of aryl bromides is often rather low, so that harsh conditions have to be used; alternatively, more reactive aryl iodides are employed which, however, are more expensive and difficult to prepare. (ii) In some cases, acceptable yields are only obtained after cumbersome purification of the reactants and with strict exclusion of oxygen,[5] diminishing the practical value of the method. (iii) Under the conditions of the Sonogashira coupling, the oxidative homocoupling (Glaser coupling) of the alkyne to the corresponding symmetrical diyne is also catalyzed if oxygen is not excluded completely.[6] Therefore, a large excess of the (sometimes expensive) alkyne is usually employed, and the separation of the diyne from the desired product may be difficult.

Scheme 2



To solve these problems, we varied the reaction conditions and found that the desired products **2** are formed with good-to-excellent yields when the coupling is carried out with THF as solvent (Scheme 2). For example, 4-bromobenzaldehyde (**1a**) and 4-bromoacetophenone (**1b**) gave the products **2a** and **2b** with yields of 99% and 92%, respectively (Table 1), when trimethylsilylacetylene (1.05 equiv) was added to a mixture of the aryl bromide, 2 mol % of $Pd(PPh_3)_2Cl_2$, 4 mol % of CuI, and 1.5 equiv of triethylamine in THF (method A). These yields are equal to or higher than those reported in the literature[4,5] (see Table 1) and were obtained after only 1 h of reaction time at room temperature with ordinary, nondegassed reagent-grade reactants.

The use of solvents such as THF[7] or DMF[8] in Sonogashira couplings has been reported occasionally but without emphasizing a possible solvent effect on the rate of the transformation.[9] Our results suggest a remarkable increase of reactivity when the coupling is performed in THF instead of an amine as solvent. Analysis of the crude products by GC−MS showed that only traces (<5%) of the diyne are formed by homocoupling of the alkyne under our conditions; thus, this side reaction is prevented almost completely by slow addition of the alkyne, which keeps its concentration in the reaction mixture low (it seems that this dilution technique has not yet been used in Sonogashira couplings). Additionally, workup of the reaction mixture is simple, and the crude product is often analytically pure.

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(9) In some cases, the choice of the amine also affects the yield of Sonogashira coupling products. For example, see: McGaffin, G.; De Meijere, A. *Synthesis* **1994**, 583−591 and references therein.

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Table 1. Yields of Arylalkynes 2 Obtained by Sonogashira Coupling of Aryl Bromides 1 with Terminal Alkynes

			this work (solvent: THF)			literature (solvent: Et_3N)	
arylalkyne	R^1	R^2	method	conditions	yield (%)	conditions	yield (%)
2a	4-CHO	Me_3Si	A	25 °C, 1 h	99	refl, 2 h	99[a]
2b	4-COMe	Me_3Si	A	25 °C, 1 h	92	25 °C, 4 h	80[4]
2c	2-CO_2Me	Me_3Si	B	25 °C, 16 h	88	80 °C, 3 h	81[b]
2d	3-CO_2Me	Me_3Si	B	25 °C, 16 h	87	100 °C, 16 h	70[5]
2e	4-CO_2Me	Me_3Si	B	25 °C, 16 h	88	100 °C, 4 h	69[5]
2f	4-COMe	*n*-Bu	B	25 °C, 16 h	91	140 °C, 2 h	73[c]
2g	4-COMe	Ph	B	25 °C, 16 h	87	refl., 3 h	83[12]
2h	4-CHO	Ph	B	25 °C, 16 h	82	100 °C, 1 h	66[13]
						refl, 3 h	64[14]

[a] Reference 5; the authors used triethylamine that had been distilled over phenylisocyanate and degassed. We obtained similar yields under these conditions; however with triethylamine which was distilled from CaH_2 under argon, our yield was only 44%. [b] Reference 10; an autoclave was employed with acetontrile as solvent. [c] Reference 11; 1:1 mixture of **2f** and other products, using an autoclave and microwave irradiation.

Compared with substrates **1a**,**b** methyl bromobenzoates are known to be less reactive in Sonogashira couplings; for example, the reaction of methyl 2-bromobenzoate (**1c**) with trimethylsilylacetylene was only achieved until now with 81% yield under high pressure in an autoclave.[10] Accordingly, this reaction proceeded only sluggishly at room temperature when method A was applied; at elevated temperatures, the catalyst decomposed rapidly with formation of a black precipitation. However, careful optimization of the reaction conditions enabled us to convert even the very unreactive aryl bromide **1c** into the corresponding arylalkyne **2c**. Here, larger amounts of trimethylsilylacetylene (1.5 equiv) and the palladium catalyst (5 mol %) were used, and the presence of triphenylphosphine improved the stability of the catalyst. In particular, it turned out to be favorable to employ a very small amount (ca. 1 mol %) of copper iodide and to add this as the last component to the reaction mixture (method B).[2e] Under these conditions, **2c** was isolated with 88% yield after stirring for 16 h at room temperature. The analogous reactions of methyl 3- and 4-bromobenzoate (**1d**,**e**) with trimethylsilylacetylene gave the arylalkynes **2d**,**e** with 87% and 88% yield, respectively. Previously, harsh conditions (heating to 100 °C for 4−16 h) had to be employed with triethylamine as solvent (boiling point: 89 °C) in order to obtain inferior yields of these products (see Table 1).[5]

To demonstrate the scope of our new procedures, we also examined Sonogashira couplings of aryl bromides **1a**,**b** with less reactive alkyl- and aryl-substituted alkynes. Application of method B, i.e., treatment of 4-bromoacetophenone (**1b**) with 1-hexyne or phenylacetylene in THF in the presence of $Pd(PPh_3)_2Cl_2$, PPh_3, Et_3N, and CuI for 16 h at room temperature, gave coupling products **2f**,**g** with high yields (91% and 87%, respectively). Again, the conditions are much milder than those employed previously,[11,12] and our yields are higher (see Table 1). Likewise, coupling of 4-bromobenzaldehyde (**1a**) with phenylacetylene in THF as solvent gave arylalkyne **2h** with 82% yield, compared to 64−66% obtained after heating in triethylamine for 1−3 h.[13,14] Additionally, our improved procedures can also be utilized for the synthesis of conjugated enynes by coupling alkenyl bromides with terminal alkynes. For example, the coupling of methyl (*Z*)-3-bromo-2-propenoate with 3,3-dimethylbutyne according to method A gave methyl (*Z*)-6,6-dimethyl-2-hexen-4-ynoate with 67% yield.[15]

In summary, reliable and practical procedures for the synthesis of arylacetylenes by Sonogashira coupling of aryl bromides with terminal alkynes were developed which involve the use of THF as solvent. By careful choice of the composition of the reaction mixture and the mode of addition of the reactants, even very unreactive substrates were converted into the products with good-to-excellent yields at room temperature with ordinary, reagent-grade starting materials. Currently, we are further exploring the scope of our procedures in order to extend them to other substrate types.

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Experimental Section

General Information. THF was distilled from potassium/benzophenone prior to use. All other chemicals were of reagent grade and were used without further purification.

4-(Trimethylsilylethinyl)benzaldehyde (2a)[5] (Method A). To a stirred mixture of 9.25 g (50.0 mmol) of 4-bromobenzaldehyde (**1a**), 380 mg (2.0 mmol) of CuI, and 700 mg (1.0 mmol) of $Pd(PPh_3)_2Cl_2$ in 50 mL of THF was added 10.1 g (75.0 mmol) of triethylamine. A solution of 5.15 g (52.5 mmol) of trimethylsilylacetylene in 10 mL of THF was then added over 1 h. The solvent was evaporated, and the residue was treated with pentane. Filtration through Celite and evaporation of the solvent yielded 10.02 g (99%) of analytically pure **2a** [mp: 66 °C (lit.[5] 66−67 °C)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.99 (s, 1H), 7.81 (dm, J = 8.4 Hz, 2H), 7.59 (dm, J = 8.4 Hz, 2H), 0.26 (s, 9H).

4-(Trimethylsilylethinyl)acetophenone (2b)[4] was prepared according to the preparation of **2a** from 39.8 g (0.20 mol) of 4-bromoacetophenone (**1b**). Yield: 39.65 g (92%) of **2b** after distillation of the crude product (bp$^{0.7}$: 97 °C) as an oil which solidified upon standing [mp: 36 °C (lit.[4] 36−37 °C)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (dm, J = 8.4 Hz, 2H), 7.52 (dm, J = 8.4 Hz, 2H), 2.57 (s, 3H), 0.25 (s, 9H).

Methyl 2-(Trimethylsilylethinyl)benzoate (2c)[10] (Method B). A mixture of 1.08 g (5.0 mmol) of methyl 2-bromobenzoate (**1c**), 175 mg (0.25 mmol) of $Pd(PPh_3)_2Cl_2$, 33 mg (0.125 mmol) of PPh_3, 736 mg (7.5 mmol) of trimethylsilylacetylene, and 1.01 g (7.5 mmol) of triethylamine in 20 mL of THF was stirred for

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20 min at room temperature, and 12 mg (0.06 mmol) of CuI was then added. After being stirred for 16 h, the mixture was worked up as in method A. Column chromatography of the crude product (SiO_2; cyclohexane/ethyl acetate, 15:1) yielded 1.02 g (88%) of **2c** as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (ddd, J = 7.9/1.5/0.5 Hz, 1H), 7.57 (ddd, J = 7.6/1.5/0.5 Hz, 1H), 7.43 (td, J = 7.5/1.5 Hz, 1H), 7.35 (td, J = 7.6/1.4 Hz, 1H), 3.91 (s, 3H), 0.25 (s, 9H).

Methyl 3-(trimethylsilylethinyl)benzoate (2d)[5] was prepared according to the preparation of **2c** from 1.08 g (5.0 mmol) of methyl 3-bromobenzoate (**1d**). Yield: 1.01 g (87%) of **2d** (mp: 49−50 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (t, J = 1.4 Hz, 1H), 7.96 (dt, J = 7.9/1.6 Hz, 1H), 7.62 (dt, J = 7.7/1.5 Hz, 1H), 7.36 (td, J = 7.8/0.5 Hz, 1H), 3.90 (s, 3H), 0.25 (s, 9H).

Methyl 4-(trimethylsilylethinyl)benzoate (2e)[5] was prepared according to the preparation of **2c** from 1.08 g (5.0 mmol) of methyl 4-bromobenzoate (**1e**). Yield: 1.02 g (88%) of **2d** [mp: 56−57 °C (lit.[4] 57−59 °C, lit.[5] 55 °C)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (dm, J = 8.6 Hz, 2H), 7.51 (dm, J = 8.6 Hz, 2H), 3.90 (s, 3H), 0.25 (s, 9H).

4-(1-Hexyn-1-yl)acetophenone (2f)[11] was prepared according to the preparation of **2c** from 995 mg (5.0 mmol) of 4-bromoacetophenone (**1b**) and 616 mg (7.5 mmol) of 1-hexyne. Yield: 909 mg (91%) of **2f**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (dm, J = 8.6 Hz, 2H), 7.37 (dm, J = 8.6 Hz, 2H), 2.20 (t, J = 7.0 Hz, 2H), 2.02 (s, 3H), 1.46−1.26 (m, 4H), 0.80 (t, J = 7.1 Hz, 3H).

4-(Phenylethinyl)acetophenone (2g)[12] was prepared according to the preparation of **2c** from 995 mg (5.0 mmol) of 4-bromoacetophenone (**1b**) and 766 mg (7.5 mmol) of phenylacetylene. Yield: 957 mg (87%) of **2g** [mp: 98−99 °C (lit.[12] 99−100 °C)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (dm, J = 8.6 Hz, 2H), 7.54−7.49 (m, 2H), 7.41 (dm, J = 8.6 Hz, 2H), 7.04−6.97 (m, 3H), 2.02 (s, 3H).

4-(Phenylethinyl)benzaldehyde (2h)[13,14] was prepared according to the preparation of **2c** from 925 mg (5.0 mmol) of 4-bromobenzaldehyde (**1a**) and 562 mg (5.5 mmol) of phenylacetylene. Yield: 840 mg (82%) of **2h** [mp: 96−97 °C (lit.[13] 98−98.5 °C, lit.[14] 98−99 °C)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.55 (s, 1H), 7.52−7.43 (m, 2H), 7.37 (dm, J = 8.6 Hz, 2H), 7.37 (dm, J = 8.4 Hz, 2H), 7.04−6.97 (m, 3H).

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