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Tandem Sonogashira Coupling: An Efficient Tool for the Synthesis of Diarylalkynes

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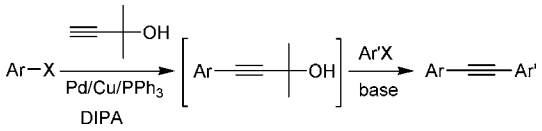
ABSTRACT



The tandem Sonogashira coupling reaction of aryl halides provides an efficient method for the synthesis of diarylalkynes. Several aryl halides were coupled with 2-methyl-3-butyn-2-ol as acetylene source in the presence of $PdCl_2(PPh_3)_2$ and CuI. Following the deprotection of the acetylene moiety in the same pot using a strong base, the Sonogashira coupling of a second aryl halide led to the formation of the appropriate diarylakyne. The established protocoll was successfully extended to the preparation of compound libraries.

The palladium-catalyzed (Sonogashira) coupling of terminal acetylenes with aryl and vinyl halides is an important and widely used carbon−carbon bond-forming reaction in organic synthesis.[1] In addition to serving as synthetic intermediates en route to complex systems including natural products,[2] the formed products often have interesting physical properties that are utilized in materials science. The Sonogashira coupling also offers a very powerful tool for the preparation of oligomers and polymers.[3] These conjugated systems have received much attention recently as a result of their optical[4] and electronic applications.[5]

A challenging objective in this chemistry is the construction of terminal arylacetylenes. If the use of acetylene is considered tedious, coupling is usually carried out using a protected acetylene that is simpler to handle, followed by the release of the protecting group. Probably the most frequently used monoprotected acetylene derivative in lab-scale experiments is trimethylsilyl-acetylene.[6] Removal of the protecting group usually requires the presence of fluoride ion or a base at ambient temperature, enabling the preparation of terminal acetylene derivatives under mild conditions.

Another route is offered for the preparation of the same compound classes by 2-methyl-3-butyn-2-ol as acetylene source.[7] Its low cost, however, is offset by the relative harshness of the conditions required for the release of the protecting group. The applied hard bases and high temper-

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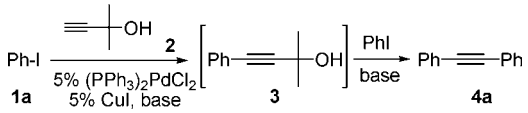
ature in the presence of less tolerant functional groups lead frequently to undesired side reactions.

In principle the release of the terminal acetylene might be combined with another Sonogashira coupling and lead formally to a tandem Sonogashira coupling on acetylene. An elegant procedure developed by Chow follows this strategy, realizing the simultaneous removal of acetone and the Sonogashira coupling of the released terminal acetylene with a second aryl halide under phase transfer conditions.[8] Brisbois and co-workers[9] described an efficient method for the preparation of symmetrical and nonsymmetrical diarylalkynes from aryl halides and trimethylsilyl-acetylene, where both the Sonogashira couplings and the removal of the silyl protection by DBU are carried out in the same pot. The aim of our research was to establish an efficient one-pot tandem Sonogashira coupling protocol, where the more economic 2-methyl-3-butyn-2-ol could be used instead of trimethylsilylacetylene.[10]

The first set of experiments was directed toward the establishment of the optimal conditions for the removal of the protecting acetone group and the subsequent Sonogashira coupling. Iodobenzene (**1a**) was coupled as model compound with 2-methyl-3-butyn-2-ol (**2**) in the presence of 5 mol % bis(triphenylphosphino)palladium dichloride, 5 mol % copper(I) iodide, and an added base in various solvents. In most cases the first coupling leading to **3** was complete and the deprotection−coupling sequence led to the appearance of diphenylacetylene (**4a**) in the reaction mixture.

Although the deprotection is usually run in a heterogeneous system in apolar solvents, such as toluene or benzene, it was reported[11] that the use of polar solvents, which usually have a beneficial effect on the following Sonogashira coupling, is also acceptable. *n*-Butanol as a high boiling solvent was tested first, and using potassium hydroxide the reaction went to near completion (Table 1, entry 1). Interestingly, change of the base to potassium carbonate initiated a different transformation and only the selective addition of benzene onto **3** was observed (entry 2). By changing the solvent to the lower boiling 2-propanol (entry 3) the second coupling was less efficient in the presence of potassium hydroxide. DMSO and KOH (entry 4) gave results similar to those with entry 1, whereas the change of base to potassium carbonate or diisopropylamine (entries 5 and 6) inhibited the second coupling. The use of aqueous DMA (entries 7 and 8) not only stopped the deprotection and the second coupling, but using NaOH the first coupling did not take place either. Change of the solvent to diisopropylamine (entry 9) increased the efficiency of the tandem coupling dramatically, and using KOH the reaction reached full conversion in a couple of hours. The use of toluene (entry 10) as a less polar, high boiling solvent also led to tandem coupling. In this case only sodium hydride was effective as base, and the reaction was over in less than 1 h. The efficiency of the diisopropylamine/KOH and the toluene/NaH systems prompted us to select both for further testing.

Table 1. Testing of the Tandem Sonogashira Coupling of Iodobenzene (**1a**) and 2-Methyl-3-butyn-2-ol (**2**) under Various Conditions



entry	solvent	base	yield of **4a**[a](%)
1	*n*-butanol	KOH	78
2	*n*-butanol	K_2CO_3	0[b]
3	isopropanol	KOH	49
4	DMSO	KOH	85
5	DMSO	K_2CO_3	0
6	DMSO	DIPA	0
7	aq DMA[c]	NaOH	0[d]
8	aq DMA[c]	K_2CO_3	0
9	DIPA	KOH	100
10	toluene	NaH[e]	100

[a] The reactions were run for 24 h in a 110 °C oil bath or at the boiling point of the solvent if below 110 °C. Yields were determined by the GC analysis of the reaction mixture. [b] 4,4-Diphenyl-2-methyl-3-buten-2-ol was formed in 74% yield.[12] [c] A 20:1 mixture of DMA and distilled water. [d] Already the first coupling fails. [e] 1.2 equiv of DIPA was added to facilitate the first coupling.

The next experiments were directed at establishing the scope and limitations of the tandem Sonogashira protocol. In these reactions first an aryl halide (**1a**−**e**) was coupled with 2-methyl-3-butyn-2-ol (**2**), and the intermediates then were deprotected and coupled in situ to give the diarylacetylenes **4a**−**n** (Table 2.). We carried out the reactions using two different sets of conditions. In DIPA (Method A) the reactions were run at 70 °C in the presence of 5 mol % of both $PdCl_2(PPh_3)_2$ and CuI as catalyst,[13] and after the completion of the first step and addition of 8 equiv of KOH another 5 mol % of catalyst had to be added to the system to achieve high conversion in the second coupling.[14]

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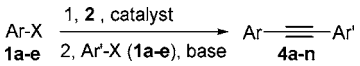
(13) A number of tests were conducted to establish the optimal catalyst system, but the use of more active palladium complexes did not have a major influence on the outcome of the process, while the omitting of copper stopped the process. The lowering of the catalyst loading did also lead to decreased yields as a result of incomplete conversion.

(14) **Method A. General Procedure.** Aryl halide (10 mmol), 351 mg of $PdCl_2(PPh_3)_2$ (0.5 mmol, 5%), and 95 mg of CuI (0.5 mmol, 5%) were placed into a flame-dried Schlenk flask. Next, 20 mL of diisopropylamine was added to the flask, followed by 1260 μL of 2-methyl-3-butyn-2-ol (13 mmol, 1091 mg). The reaction mixture was stirred under argon for 1 h at 50 °C. Then 4.48 g of KOH (80 mmol), 351 mg of $PdCl_2(PPh_3)_2$ (0.5 mmol, 5%), 95 mg of CuI (0.5 mmol, 5%), and 10 mmol of aryl halide were added, and the rection mixture was heated for 5 h in a 110 °C oil bath. After cooling to room temperature, the KOH was neutralized with 1 M HCl, and then the mixture was extracted with DCM. The combined organic phases were dried over $MgSO_4$ and then evaporated. The crude product was purified by column chromatography.

Table 2. Synthesis of Diarylacetylenes in the Tandem Sonogashira Coupling of Various Aryl Halides (**1a**−**e**) and 2-Methyl-3-butyn-2-ol (**2**)



entry	ArX	Ar′X	product	yield (%)
1	iodobenzene (**1a**)	**1a**	**4a**	84,[a,c] 56[b]
2	**1a**	**1b**	**4b**	29,[a] 57[b]
3	**1a**	**1c**	**4c**	69[b]
4	**1a**	**1d**	**4d**	38,[a] 47[b]
5	**1a**	**1e**	**4e**	56[a]
6	4-iodoanisole (**1b**)	**1a**	**4b**	64,[a] 68[b]
7	**1b**	**1b**	**4f**	17,[a] 66[b]
8	**1b**	**1c**	**4g**	79[b]
9	**1b**	**1d**	**4h**	68,[a] 41[b]
10	**1b**	**1e**	**4i**	65[a]
11	3-iodotoluene (**1c**)	**1a**	**4c**	84[b]
12	**1c**	**1b**	**4g**	66[b]
13	**1c**	**1c**	**4j**	78[b]
14	**1c**	**1d**	**4k**	40[b]
15	2-bromochlorobenzene (**1d**)	**1a**	**4d**	71[b]
16	**1d**	**1b**	**4h**	75[b]
17	**1d**	**1c**	**4k**	59[b]
18	**1d**	**1d**	**4l**	67,[a] 32[b]
19	3-bromo-pyridine(**1e**)	**1d**	**4m**	62[a]
20	**1e**	**1e**	**4n**	84[a]

[a] Method A, isolated yield of **4**. [b] Method B, isolated yield of **4**. [c] The reaction worked equally well on the mole scale.

Running the reactions in toluene (Method B) we used only 2.8 mol % of both $PdCl_2(PPh_3)_2$ and CuI as catalyst and 1.2 equiv DIPA as base to facilitate the first coupling, which was complete in 1 h (except for **1d**, which required 48 h) at 80 °C. Heating for 5 h at 110 °C after the addition of 2 equiv of NaH and the other aryl halide led in most cases to complete conversion (N.B. no extra catalyst was needed).[15] The products were isolated using column chromatography.

On the basis of the data presented in Table 2, we can establish that both tandem coupling protocols are quite efficient, and practically all products could be prepared in good yield. There are some significant differences in the behavior of the two methods, however, that should be mentioned.

Using Method A the process is sensitive to the order in which electron-rich reagents are added. Starting from iodobenzene (**1a**) the coupling with 4-iodoanisole (**1b**) gave **4b** in 29% (entry 2) yield, whereas running the process in reverse order (entry 6) gave 64% yield. In the same reactions Method B turned out to be less sensitive and gave 57% and 68% yields, respectively. The increased sensitivity of Method A is even more pronounced in entry 7, where its poor yield of **4f** (17%) is facing a 66% yield by Method B.

In the coupling of less electron-rich substrates (**1d,e**) on the other hand, Method A has a clear advantage over Method B, and in the preparation of the symmetrical systems **4l,n** (entries 18 and 20), it gave superior yields.

Using Method B on electron-deficient substrates, we face a situation similar to that of Method A for electron-rich compounds. The coupling of **1a** or **1b** with **1d** (entries 4 and 9), for example, gave only mediocre yields (47% and 41%), whereas reversing the order and carrying out the first coupling on the less electron-rich aryl halide **1d** (entries 15 and 16) resulted in a significant improvement, yielding 71% and 75%. In general, the two protocols seem to complement one another, as one is usually effective where the other fails to achieve good yields.

The scope of the presented tandem Sonogashira reaction does not have to be limited to the preparation of diarylethynes. Because the products of the Sonogashira coupling frequently have interesting physical (e.g., fluorescence) properties, we decided to test the effectivity of the protocol in the preparation of compound libraries. Such compositions, which would arise from the addition of a mixture of aryl halides in the second coupling step, might be separated using simple thin-layer chromatography, and some of their more important photophysical characteristics might be determined "from the plate".

In our first test 3-bromopyridine (**1e**) was coupled with **2** following literature procedures,[2b] and the pyridylbutynol (**3e**) was isloated. The deprotection of **3e** and the sequential Sonogashira coupling were carried out using the KOH/DIPA system, and a 1:1:1 mixture (0.33 equiv each) of iodobenzene (**1a**), 4-iodoanisole (**1b**), and 3-iodotoluene (**1c**) was used as coupling partner (Figure 1.). The progress of the reaction was monitored by GC, GC−MS, and TLC (Figure 2).

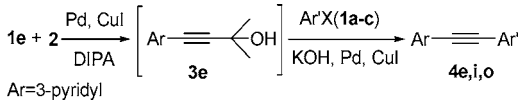


Figure 1. Arylethynyl-pyridine library synthesis using the tandem Sonogashira protocol.

The deprotection−coupling sequence worked well for all three aryl iodides, iodoanisole (**1b**) reacting somewhat more slowly than the others, and the library synthesis was complete in 2 h.

In the next experiment we carried out the whole library synthesis in one pot. Following the conversion of **1e** to **3e** under the conditions outlined for Method A, the mixture of the aryl iodides (**1a**−**c**), KOH, and 5 mol % catalyst were

(15) **Method B. General Procedure.** Aryl halide (5 mmol), 100 mg of $PdCl_2(PPh_3)_2$ (0.14 mmol, 2.8%), and 28 mg of CuI (0.14 mmol, 2.8%) were placed into a flame-dried Schlenk flask. Next, 12 mL of toluene and 1200 μL of diisopropylamine were added to the flask, followed by 630 μL of 2-methyl-3-butyn-2-ol (6.5 mmol, 546 mg). The reaction mixture was stirred at 80 °C under argon until the first coupling was complete. Then the temperature of the oil bath was increased to 110 °C, and 400 mg of NaH (55% dispersion, 9.16 mmol) was addedd slowly to the mixture. After 5 min of stirring, 5 mmol of the appropriate aryl halide was added to the reaction mixture, and the stirring was continued. After 25 min another 100-mg portion of NaH (1.83 mmol) was added carefully, and the solution was stirred further at 110 °C until the reaction was complete (ca. 1 h). After cooling to room temperature, the suspension was filtered, and the separated amine-hydrochloride was washed with toluene. Evaporation of the combined toluene solutions gave a crude product, which was purified by column chromatography.

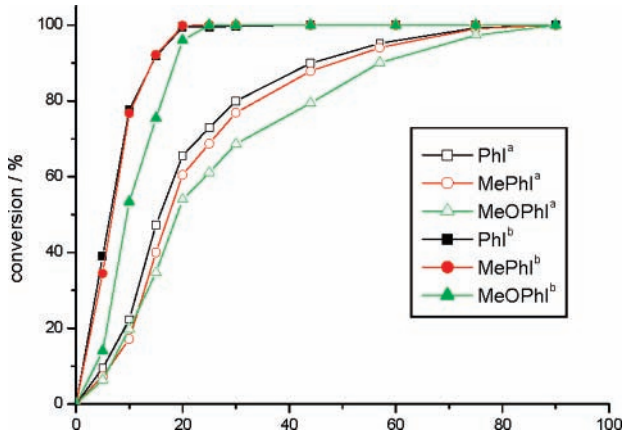


Figure 2. Product formation in the two-step (a) and tandem (b) 3-arylethynyl-pyridine library synthesis (GC).

added to the reaction, and the second coupling was complete in less than 0.5 h.[16] The fact that in the one-pot reaction we observe faster product formation and also the absence of an induction period might be attributed to the fact that some of the catalyst used in the first coupling is still in its active form. Unfortunately, neglect of the addition of the second catalyst portion leads to incomplete conversion in the second coupling. These results prove that the tandem Sonogashira−coupling protocol is effective in the synthesis of product mixtures, and its application for the preparation and screening of new fluorescent materials is in progress in our laboratories.

In summary, an efficient method is reported for the one-pot synthesis of different diarylalkynes starting from easily available aryl halides and 2-methyl-3-butyn-2-ol. By variation of the conditions a complementary set of conditions was established, which allows for the efficient coupling of both electron-rich and electron-deficient substrates. The protocol was also successfully extended to the preparation of diarylethyne libraries.

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Supporting Information Available: Experimental procedures and characterization data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) **One-Pot Library Synthesis.** $PdCl_2(PPh_3)_2$ (180 mg, 0.25 mmol, 5%) and 47 mg of CuI (0.25 mmol, 5%) were placed into a flame-dried Schlenk flask, followed by 12 mL of diisopropylamine. Then 790 mg (5 mmol) of 3-bromopyridine and 532 μL of 2-methyl-3-butyn-2-ol (5.5 mmol, 462 mg) were added to the solution. The reaction mixture was stirred at 70 °C under argon until the first coupling was complete (1 h). Then 180 mg of $PdCl_2(PPh_3)_2$ (0.25 mmol, 5%), 47 mg of CuI (0.25 mmol, 5%), 186 μL of iodobenzene (1.66 mmol, 339 mg), 213 μL of 3-iodotoluene (1.66 mmol, 362 mg), and 388 mg of 4-iodoanosole (1.66 mmol) were added to the mixture, followed by 2.24 g KOH. The Schlenk flask was purged with argon, sealed, and heated in an oil bath at 110 °C until completion of the second coupling.