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Investigations on the synthesis of monoarylated diynes by monoprotection/cross-coupling/deprotection approach

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ABSTRACT

The presented experimental work investigates the usefulness of temporary monoprotection of symmetrical terminal diynes in the coupling with aryl iodides. The monoprotection/cross-coupling/deprotection approach proved to be efficient for the coupling of diynes with aryl substrates avoiding the formation of diarylated byproducts. The high importance of the ratio of solvents in the Sonogashira coupling is demonstrated.

The efficient and selective synthesis of compounds with different functionalities starting from substrates containing several potential reaction sites with comparable reactivity has engaged the chemists since long. The preparation or coupling of increasingly complex, differently functionalized molecules has evolved into an extensive field of work for synthetic chemists, especially those using transition metal complexes.[1] Recently one of the most reviewed methodologies is the transition metal-catalyzed cross-coupling reaction because of the importance of the C–C-bond formation.[2] Selectivity in these processes can be provided by, for example the occurrence of different leaving groups, which can selectively be addressed using different catalyst systems.

While the fundamentals of cross-coupling chemistry are quite well investigated, the refinements of reaction conditions for certain substrates are an ongoing process. We are regularly applying the Sonogashira reaction for the synthesis of substrates for [2+2+2] cycloaddition reactions.[3] For synthetic as well as mechanistic investigations we are interested in the synthesis of monoarylated diynes with different linker groups between the diyne moieties, providing access to annellated rings of varying size in the backbone of the newly formed heterobiaryl ring systems during the cycloaddition process. The Sonogashira reaction has become an established and extremely useful synthetic tool over the last two decades due to its wide and general applicability.[4] However, the preparation of mono-functionalized diynes starting from symmetrical terminal diynes with aryl halides brings out a special challenge because of the similar reactivity of the terminal alkyne units of the starting material and the monosubstitution product. As a result in general mono- as well as undesired diarylated product is obtained together and might result in problems during the separation and purification processes. In addition, significant amounts of aryl iodide are consumed for the undesired product, which is especially aggravating in the case of complex or expensive aryl substrates. Even with large excessive amounts of diyne being applied or slow addition of aryl halides over time to the reaction mixture containing the diynes using a syringe pump, no significant improvements were achievable. A general solution to this problem by applying selective catalyst systems to unfunctionalized terminal diynes has not been provided yet. However, the problem has been approached in few cases by detours, like demonstrated by synthetic work by Pale and co-workers, providing access to differently substituted diynes and triynes from silylated acetylenes using Pd-/Ag-mediated reactions.[5]

For the Sonogashira reaction, the observed yields of the desired monoarylated products usually drop to less then 50%, while the formation of a significant amount of byproduct occurs. Slightly better results were reported in a work by Crisp et al., who used zinc halides instead of classical copper co-catalyzed Sonogashira reaction conditions (Scheme 1).[6]

We thought that using a temporary monoprotection for one alkyne moiety of the diyne and deprotection after the coupling procedure under optimized Sonogashira conditions can be useful for avoiding the separation problems of mono- and diarylated diynes and allowing the best return for the applied aryl substrate. In work published by Cheng and co-workers, they described a

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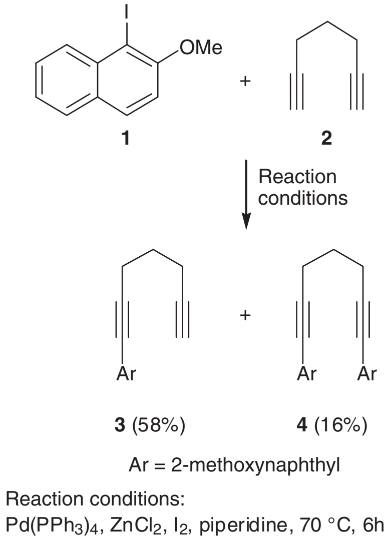
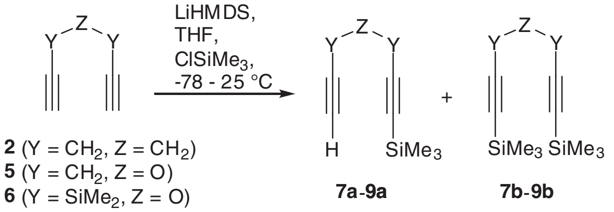


Scheme 1. Two different products from the cross-coupling of 1-iodo-2-methoxynaphthalene (**1**) with 1,6-heptadiyne (**2**).

Table 1
Results for the silylation reaction of different diynes



Entry	Compound	Yield[a]/ratio mono:di[b]
1	Y = CH_2, Z = CH_2 (**2**)	80%/4.3 (**7a**):1 (**7b**)
2	Y = CH_2, Z = O (**5**)	74%/2.8 (**8a**):1 (**8b**)
3	Y = $SiMe_2$, Z = O (**6**)	45%/1.4 (**9a**):1 (**9b**)

[a] Isolated yield of the monosilylation product.

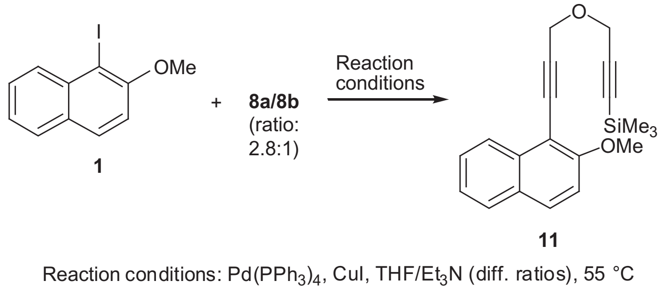
[b] Ratio of the mono- to disilylated diyne, determined by NMR analysis.

convenient method for the monoprotection of alkynes by deprotonation with lithium hexamethyldisilazide (LiHMDS) and subsequent silylation.[7] We adapted the procedure for our purposes and applied the monoprotection to three different alkynes (Table 1).

In all reactions mono- (**7a**–**9a**) as well as disilylated products (**7b**–**9b**) were formed. Interestingly the results of the experiments provided different ratios for the mono- and disilylated diynes. The ratios varied in favor of the desired excessive monoprotected diyne with ratios of 4.3:1 (**7a**:**7b**) for **2** and 2.8:1 (**8a**:**8b**) in the case of **5** to nearly equal amounts of mono- and disilylated diynes for **6** (ratio 1.4:1 for **9a**:**9b**). The best result for the monoprotection was therefore found in the silylation of 1,6-heptadiyne (**2**), yielding the monosilylated diyne **7a** with 80%. The lowest yield was observed for the monosilylated disiloxane diyne **9a** from **6** with 45%.

Unfortunately, we could not separate the mono- and the diprotected products (**7a**–**9a** vs **7b**–**9b**) by either column chromatography or Kugelrohr distillation.[8] However, since the product mixture was easily isolated by Kugelrohr distillation, we decided to investigate the Sonogashira cross-coupling reaction of naphthyl iodide **1** with mixtures of mono- and disilylated diynes. The disilylated compounds **7b**–**9b** should not interfere with the coupling reaction of the monosilylated diynes **7a**–**9a**. In the first step, we wanted to optimize the coupling conditions for the Sonogashira reaction, utilizing the mixture of **8a**/**8b** for this purpose with a slight excess of the monosilylated diyne (1.2 equiv). In general, Sonogashira coupling reactions are performed in pure amines or in mixtures with differing amounts of amine and another solvent, often THF. The use of solvent mixtures can be required, when solubility issues play a role in the reaction. We therefore investigated different solvent mixtures consisting of THF and triethylamine (NEt_3) in varying ratios (Table 2). The total volume of the solvent mixture was kept fairly in the same range except for entry 6, where a larger volume was used.

Table 2
Surveying the role of the solvent ratio THF/NEt_3 in the cross-coupling of **1** with a mixture of the protected dipropargylether (**8a**/**8b**, ratio 2.8:1)



Entry	Reaction solvent ratio THF/NEt_3	Yield (**11**)[a] (%)
1	4:1	14
2	1:1	21
3	1:2	22
4	1:6	80
5	1:9	82
6	1:20	76

[a] Isolated yield, based on the aryl iodide compound. For the Sonogashira coupling 1.2 equiv of the monosilylated diyne were applied.

However, the optimized yields are going through an optimum with an excess of NEt_3 (entry 5, THF/NEt_3 1:9), providing 82% yield of **11** as the best result. With an even larger excess of NEt_3 (entry 6) the yield decreases slightly to 76% yield, which might be due to solubility reasons. It can therefore be assumed that a certain concentration of the amine is necessary for the efficient proceeding of the reaction and to furnish high yields. The addition of co-solvents like THF, although necessary sometimes, can have drastically effects on the yield, highly depending on the amount added.

With the optimized reaction conditions for the Sonogashira reaction in our hands, we applied these for the coupling of the protected diynes. The results of the coupling with **7**(**a**/**b**)–**9**(**a**/**b**) are displayed in Table 3. The isolated yields for the coupling products from the Sonogashira reaction were very high to excellent. Subsequent desilylation using KF in methanol of the compounds **10**–**12** was realized with practically quantitative yields to obtain the target molecules **13**, **14,** and **15**. It is very remarkable to note that in diyne **12**, containing three potentially cleavable alkynyl-Si bonds, under the chosen conditions (3 equiv KF in MeOH) only the terminal $SiMe_3$ group was selectively cleaved off. The resulting diyne **15** containing an intact disiloxane unit was stable enough to be isolated with good yields.

When we combine all the obtained results and calculate the total yield of the discussed reaction routes including the monoprotection/deprotection step it is interesting to compare the total yield to the direct coupling of the diynes with **1** (Table 4). One can recognize that in two cases (entries 1 and 2) the yield with the protection step is superior to the direct coupling procedure. Only in the last example (entry 3) the yield is lower compared to the direct coupling, which can be traced back to the unfavorable ratio obtained from the silylation reaction (see Table 1, entry 3).