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Sequential and domino Sonogashira coupling: Efficient tools for the synthesis of diarylalkynes ☆

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Abstract

The Sonogashira coupling reaction of aryl halides with a masked acetylene, leading to the formation of diarylethynes is reviewed. The process is either run in a sequential coupling–deprotection–coupling manner, or sometimes it is carried out in one-pot, a reaction we coined domino coupling. The procedures were also extended to the synthesis of compound libraries.

Keywords: Sonogashira reaction; Cross-coupling; Diarylalkynes; Palladium

1. Introduction

The palladium-catalyzed coupling of terminal acetylenes with aryl and vinyl halides is an important and widely used carbon–carbon bond forming reaction in organic synthesis. The Sonogashira coupling is a very useful method for the introduction of the acetylene function into aromatic ring systems and olefins [1]. The reaction has been extended to alternate solvent systems (fluorous solvents [2], ionic liquids [3]) and its applications in the fields of fine chemicals synthesis [4] and pharmaceutical chemistry [5] have been highlighted recently. The Sonogashira reaction also offers a very powerful tool for the preparation of conjugated oligomers and polymers [6]. The conformational rigidity of the acetylene bond makes these conjugated systems one of the key building blocks of optical [7] and molecular electronic applications [8].

The key step in the construction of the **3** diarylacetylenes (Scheme 1) is the Sonogashira coupling of an aryl halide (**1**) and a terminal arylacetylene (**2**) [9]. The way the acetylene (**2**) is employed might serve as the basis for the (arbitrary) division of these reactions. In cases, where the arylacetylene (**2**) is available, we coin the coupling conventional (Eq. a). When the synthesis starts from the protected form of the arylacetylene (**4**) and carries out its deprotection and the following coupling parallel, then we term the process sequential coupling (Eq. b). A third possibility is the coupling of the aryl halide (**1**) with a protected acetylene (**5**), followed by the parallel removal of the protecting group and subsequent Sonogashira coupling with an aryl halide in the same pot, a process we call domino coupling (Eq. c). While other sources discuss the conventional coupling in detail, the present article is aimed at reviewing the recent progress in sequential and domino Sonogashira coupling reactions.

Key to the success of sequential and domino Sonogashira couplings is the proper choice of the protected acetylene (**5**). Probably the most frequently used mono protected acetylene derivative in lab-scale experiments is trimethylsilyl-acetylene (**5a**) [10]. 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

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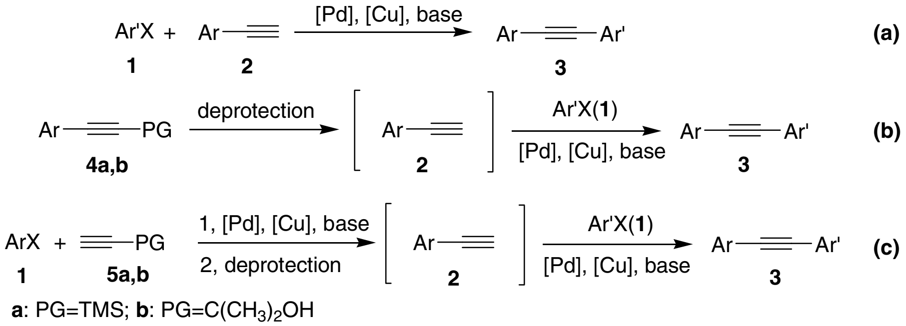


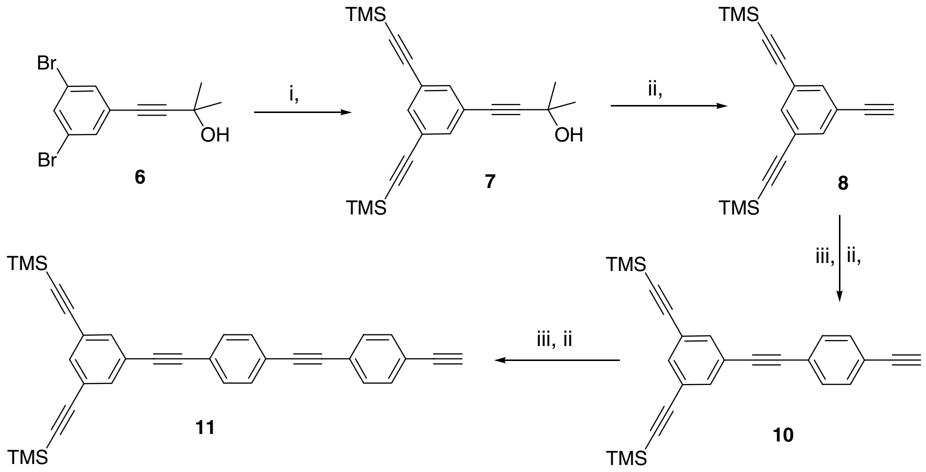
Scheme 1. Synthesis of diarylalkynes in (a) conventional, (b) sequential and (c) domino Sonogashira coupling.

conditions, a possibility that has been exploited by several research groups. An alternative route is offered for the preparation of the same compound class by the use of 2-methyl-3-butyn-2-ol (**5b**) as acetylene source. Its relatively low cost makes this "acetone protected" acetylene molecule an attractive reagent for the preparation of acetylene derivatives. The major drawback of the existing methods based on the application of **5b** is the harshness of the reaction conditions required for the release of the protecting group. The applied hard bases and high temperature in the presence of less tolerant functional groups lead frequently to undesired side reactions. In spite of these limitations 2-methyl-3-butyn-2-ol (**5b**), like trimethylsilyl-acetylene (**5a**) has been used successfully by several groups to introduce the acetylene moiety onto aromatic compounds in a step-by-step manner [11].

The complimentary nature of **5a** and **5b** might even be utilized to build in a series of acetylene groups into polyfunctional molecules in a selective manner. A fine example of this principle was presented by Rodriguez, who introduced three acetylene functions onto the same benzene ring to extend the molecule in the following reactions in only one direction [12]. In the process shown in Scheme 2, the acetone protection was removed selectively in the presence of TMS groups and in a series of coupling and deprotection reactions the dendrimeric **11** was prepared from **7** in good yield. The protected phenylethyne subunits were incorporated in the form of 4-(3′-hydroxy-3′-methyl-1′-butynyl)-iodobenzene (**9**), and the deprotection was achieved using sodium hydroxide in boiling toluene.

2. Sequential coupling reactions

In the sequential Sonogashira coupling the release of the terminal acetylene function and the cross-coupling are carried out in the same vessel, usually by the concurrent addition of all reagents. This approach is frequently utilized in the preparation of "high added value" compounds, which allows for the use of the more expensive trimethylsilyl protecting group. Removal of the silyl protection is easily achieved by the addition of fluorides or bases, the former being compatible with most



(i) TMS-ethyne, $(PPh_3)_2PdCl_2$, CuI, Et_3N. (ii) NaOH, toluene at reflux
(iii) $(PPh_3)_2PdCl_2$, CuI, Et_3N, 4-(3'-hydroxy-3'-methyl-1'-butynyl)-iodobenzene (**9**)

Scheme 2. Selective deprotection of the methylbutynol moiety in the presence of trimethylsilyl-ethyne functions and consecutive Sonogashira coupling of the formed acetylene.