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The use of the Stille cross-coupling reaction in the prenylation of naphthoquinones

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Abstract: Prenylation reactions are important reactions in natural product chemistry. The Stille reaction was evaluated for the prenylation of naphthoquinones and applied to the synthesis of the natural product 2,3-bis-(3-methylbut-2-enyl)-1,4-naphthoquinone.

Keywords: naphthoquinones, prenylation, Stille reaction, *Tabebuia guayacan*

Introduction

Prenylation reactions are important reactions in the chemistry of quinones. Important examples of prenylquinones are vitamin K derivatives which play an important role in the vital body as hemostatic vitamins. Other prenylquinones are coenzyme Q derivatives which are useful as therapeutic agents for ischemic heart diseases.[1] The unsubstituted prenylnaphthoquinone **1**, known as desoxylapachol **1** was isolated from *Tectona grandis*, the real teak wood. The compound causes a dermatitis allergy and gives the wood resistance to termites.[2,3] Desoxylapachol **1** was also isolated from a New Zealand brown alga *Landsburgia quercifolia*. It was shown that this compound is active against P-388 leukemia cells (IC50 0.6 µg/ml) and fungi.[4] The double prenylated naphthoquinone **2** was isolated from *Tabebuia guayacan*.[5] Besides these examples the prenylquinones are the obvious precursors of important natural products, e.g. lapachol **3** and its derivatives. As a result, research was conducted to an efficient prenylation reaction.

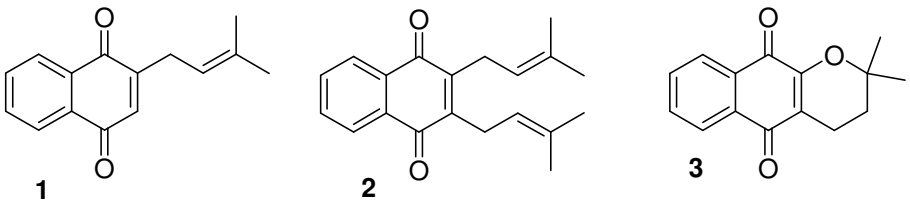
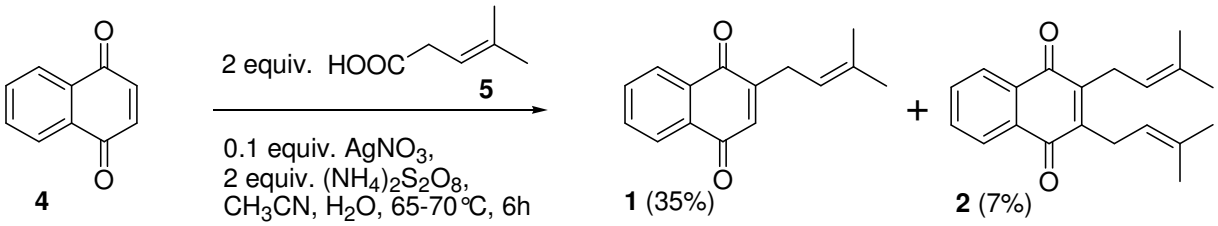


Figure 1

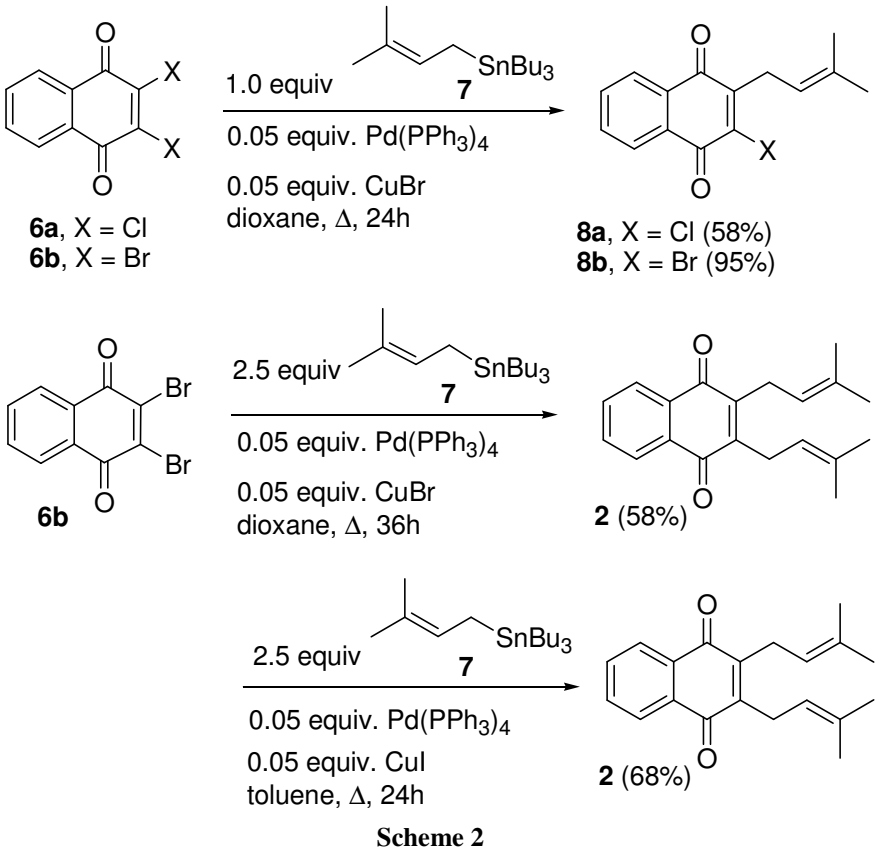
Results and discussion

The radical prenylation of 1,4-naphthoquinone **4** with 4-methyl-3-pentenoic acid **5** in the presence of silver nitrate and ammonium persulfate was reported previously to afford 2-prenyl-1,4-naphthoquinone **1** in 58% yield.[6] However, in our hands using the published procedure, mixtures of starting material together with the monoprenylated **1** and the diprenylated 1,4-naphthoquinone **2** were found in 35% and 7% yield, respectively (Scheme 1). As our interest in the double prenylated naphthoquinone arose, a series of reactions was performed in order to improve the formation of the diprenylated compound. Increasing the amount of 4-methyl-pent-3-enoic acid gave no satisfactory improvements.



Scheme 1

The Pd-catalyzed Stille cross-coupling of a prenylstannane with an arylhalide has become popular in the recent past.[7] In contrast to most other allylmetallic reagents the 3,3-



Scheme 2

disubstituted allylstannanes tend to react without allylic inversion or rearrangement in coupling reactions.[8] Performing the reaction on the dibrominated compounds (Scheme 2) **6b** with only one equivalent of the organostannane **7** resulted in a 95% yield of the monoprenylated compound **8b**, without an indication of the diprenylated compound **2**. This result made clear that the diprenylation is a difficult reaction that requires more severe reaction conditions. In a first attempt, 2.5 equivalents of the organostannane **7** were used and the reaction time was prolonged to 36 hours. This resulted in a 56% yield of the diprenylated compound **2**. When changing from dioxane to toluene and using CuI instead of CuBr, the yield increased to 68%.

In conclusion, it can be stated that the Stille cross coupling reaction is a usefull reaction for the prenylation of halogenated naphthtoquinones and the application of this reaction resulted in the synthesis of the natural product 2,3-bis-(3-methylbut-2-enyl)-1,4-naphthoquinone **2**.

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