Synthesis of Ubiquinones Utilizing Pd(0)-Catalyzed Stille Coupling

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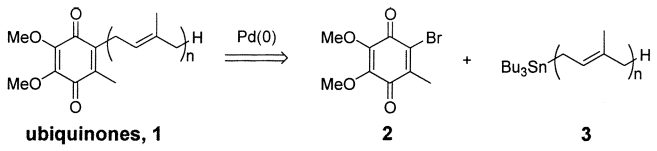
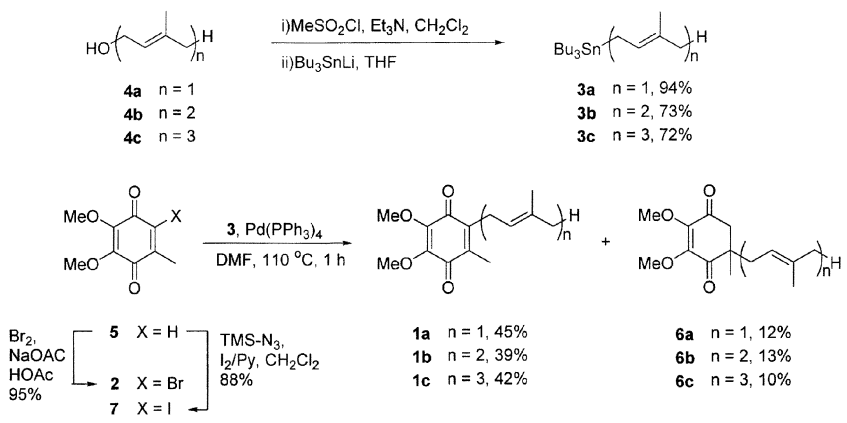
Ubiquinones, also called Coenzyme Q_n, are benzoquinones with isoprenyl units as side chain. Ubiquinones are found in mitochondria of the almost ubiquitous nature ranging from bacteria to plants and mammals, and play important roles in the respiratory chain as a redox carrier.[1] Various synthetic approaches to ubiquinones have been developed and the introduction of an isoprenyl side-chain to 2,3-dimethoxy-5-methylbenzoquinone has been attempted in most cases.[2] Among these reports, isoprenylstannanes addition to the quinone in the presence of Lewis acid provided ubiquinones and related isoprenylquinones in high yields.[3] However, general problems associated with ubiquinones synthesis are known as the maintenance of the double bond geometry, the regioselective addition of isoprenyl chains, and the avoidance of isoprenly side chain cyclization. In this regards, recent Ni(0)-induced couplings between benzyl chlorides or chloromethylquinones and vinylalanes are a novel method to ubiquinones as well as other quinone systems such as vitamines K_1 and K_2.[4] In this report, we wish to describe that Pd(0)-catalyzed Stille coupling[5] of bromoquinone or arylbromide with isoprenylstannanes proceeds to ubiquinones efficiently.



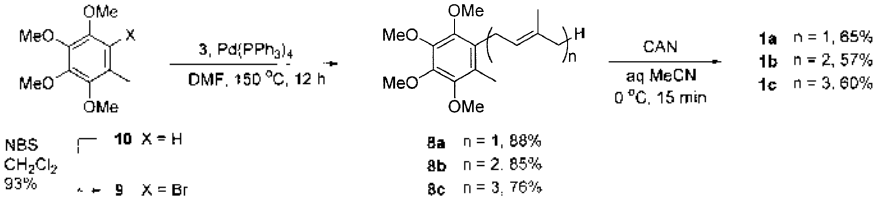
Approach I

Initially, it was anticipated that Pd(0)-catalyzed coupling of an isoprenylstannane **3** with bromoquinone **2** would provide ubiquinone **1** with the regioselective addition of isoprenyl chains as well as the avoidance of side-chain cyclization (Approach I). Therefore, we prepared bromoquinone **2** from 2,3-dimethoxy-5-methylbenzoquinone **5** with bromine and sodium acetate in acetic acid in 95% (Scheme 1).[6] The isoprenylstannane **3** was prepared from the mesylation of the corresponding alcohol **4** with mesyl chloride and BuLi in THF at -78 °C followed by stannylation with Bu_3SnLi *in situ* as previously reported.[7] The $Pd(PPh_3)_4$-catalyzed Stille coupling of **2** with **3a** was carried out at 110 °C in DMF and the desired ubiquinone **1a** was isolated in 45% yield. Unfortunately, a regioisomer **6a** was isolated (12%) and **6a** was also observed in the isoprenylation to **5**.[2a] Various solvents (toluene, dioxane, HMPA), catalysts ($Pd(Ph_3P)_2Cl_2$, $Pd(CH_3CN)_2Cl_2$) and additives (CuI, LiCl) were examined, but the yield of **1a** was not improved. Ubiquinone **1b** and **1c** were also obtained under the same conditions in 39% and 42% yields respectively from **2** with geranyltributylstannane **3b** and farnesyltributylstannane **3c**. Another attempt to improve the yield of **1a** was the Stille coupling between iodoquinone **7** and **3a**. Iodination of **5** to **7** was accomplished with treatment of **5** with trimethylsilyl azide and a mixture of iodine and pyridine in CH_2Cl_2 as the reported method (88%).[8] Although the Pd(0)-catalyzed coupling of **7** with **3a** provided **1a** in 52%, which is higher yield than the reaction of **2** with **3a**, the regioisomer **6a** was also obtained as a side product. Thus ubiquinone **1** could be simply prepared by Pd(0)-catalyzed coupling of an isoprenylstannane **3** with halobenzoquinone **2** or **7**, however the yields of **1** were not satisfactory and the formation of the regioisomer **6** is one of reasons for the low yields of **1**.

Palladium-catalyzed Stille coupling of aryl halides with organostannane reagents is one of the most useful methods for introduction of side-chains to aromatic rings. Although

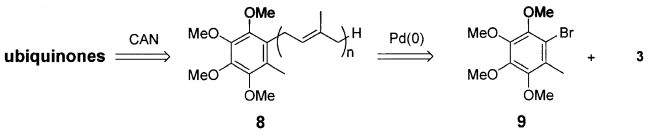


Scheme 1



Scheme 2

palladium-catalyzed allylations to hindered and electron rich aryl systems are reported quite rarely,[9] the Stille coupling between arylbromide **9** and **3** would result in the desired C-C bond. Following ceric ammonium nitrate (CAN) oxidation of **8** should proceed to ubiquinone **1** (Approach II). Bromination of **10** with NBS in CH_2Cl_2 at *r.t.* for 0.5 h afforded **9** in 93% yield (Scheme 2). Heating a solution of **9**, **3a** (1.2 eq), and $Pd(PPh_3)_4$ (3-5 mole%) in anhydrous DMF (*ca.* 0.2 M) at 150 °C for 12 h afforded **8a** in 88% isolated yield as colorless oil. Moreover, the Stille coupling using the hindered arylbromide **9** proceeded smoothly without formation of an isomeric side product, which was appeared in other system.[10] Next oxidation of **8a** using CAN was attempted in aqueous MeCN at 0 °C to give **1a** in 65% isolated yield. Synthesis of ubiquinones **1b** and **1c** were also accomplished under the same conditions.



Approach II

In conclusion, we have developed synthetic methods of ubiquinones utilizing Pd(0)-catalyzed Stille coupling, and Stille coupling between 2-bromo-3,4,5,6-tetramethoxytoluene **9** and the isoprenylstannane **3** followed by CAN mediated oxidation should be an efficient method for ubiquinones synthesis without regioisomers formation.

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References and Notes

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10. In the Stille coupling of 5-bromo-1,2,4-trimethylbenzene with the stannane **3a**, an isomeric side product **12** as well as **11** were obtained (unpublished data).