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The Friedel−Crafts Allylation of a Prenyl Group Stabilized by a Sulfone Moiety: Expeditious Syntheses of Ubiquinones and Menaquinones

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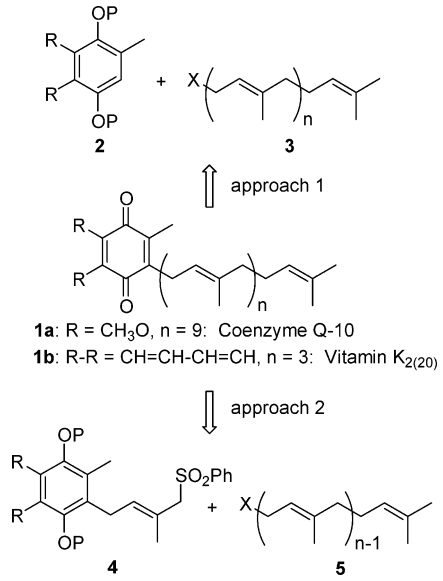
Abstract: An efficient synthetic method for the protected *p*-hydroquinone compounds **4** containing the C_5 trans allylic sulfone moiety has been developed by the direct Friedel−Crafts allylation of the protected dihydroquinone **2** with 4-chloro-2-methyl-1-phenylsulfonyl-2-butene (**7a**) or 4-hydroxy-2-methyl-1-phenylsulfonyl-2-butene (**7b**). Expeditious total syntheses of coenzyme Q-10 and vitamin $K_{2(20)}$ have been demonstrated from these valuable key compounds **4a** and **4b**.

Isoprenoid natural products containing a *p*-quinone head group play important roles in biological processes of higher plants and animals. Ubiquinones ubiquitously exist in mitochondria of every cell to participate in the electron transport process for respiration, thus producing energy for living organisms.[1] Coenzyme Q-10 (**1a**), the ubiquinone of humans, also has a treatment effect on heart-related disease.[2] Menaquinones, known as vitamin K_2 (**1b**), promote normal clotting of the blood.

There have been extensive synthetic efforts for these indispensable natural products,[3] where the key issue was the coupling method of the quinone core and the polyprenyl side chain. Coupling of the *p*-hydroquinone **2** (P = H) and the polyprenyl chain **3** (X = OH or halogen) by the Friedel−Crafts reaction (approach 1, Scheme 1) was a straightforward method,[4] which, however, suffered from low yields especially due to cyclization within the polyprenyl side chain and cyclization of the coupling product to form chromanol. Some modifications of this method have appeared,[5] but the stereoselectivity at $^2\Delta$ and the intrinsic instability problems of polypreniol or the corresponding halide under acidic condition has not been overcome. Coupling of the protected *p*-hydroquinone **4** containing the C_5 allylic sulfone moiety and the polyprenyl chain **5** (X = halogen) by the Julia sulfone protocol[6] (approach 2, Scheme 1), originally delineated by Terao for coenzyme Q-10 synthesis,[7] was an excellent method in that not only a high yield of the coupling product was obtained, but also the *E*-configuration at $^2\Delta$ as well as at the other double bonds was retained, which would provide better biological activities. The more attractive point of the above method is that solanesol, C_{45} *all-E*-polyprenyl alcohol, that is readily obtained by extraction from the leaves of tobacco or potato can be directly utilized in the synthesis of coenzyme Q-10. The potential of this approach then relied on the efficient preparation of compound **4**.

SCHEME 1. Disconnection Approaches to Isoprenoid Natural Products Containing a *p*-Quinone Head Group



The first preparation of **4** (P = benzyl, R = OCH_3) by Terao[7] from 2,3-dimethoxy-5-methyl-1,4-benzoquinone (coenzyme Q-0) was lengthy and thus industrially inapplicable. A better procedure has been proposed by Fujita[8] that made use of 4-chloro-2-methyl-1-phenylsulfonyl-2-butene (**7a**) (Scheme 2). 2,3-Dimethoxy-5-methyl-1,4-hydroquinone **2** (P = H, R = OCH_3), which was obtained by reduction of coenzyme Q-0, was brominated at the unsubstituted ring carbon. Protection of the hydroquinone as 2-methoxyethoxymethyl (MEM) ether to give **6** (P = MEM, R = OCH_3) was followed by the Grignard

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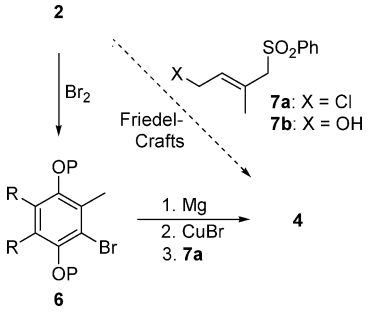
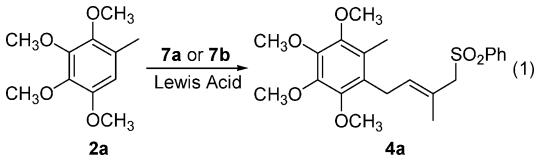
SCHEME 2. Preparation of the Protected *p*-Hydroquinone 4 Containing the Prenyl Unit with a Phenylsulfonyl Group



reagent generation. Copper-mediated coupling of the Grignard reagent and **7a** then produced **4** (P = MEM, R = OCH_3). This multistep sequence from rather expensive coenzyme Q-0, however, still needs improvement for industrial application. It was envisioned based on the stability of the white-crystalline C_5 chloroallylic sulfone **7a** that **7a** might be used in the Friedel−Crafts reaction with the protected *p*-hydroquinone **2** to directly produce compound **4**. Furthermore, tetramethoxytoluene (**2a**), which can be economically prepared from a readily available precursor without going through the coenzyme Q-0,[9] might be an ideal electron-rich substrate for the Friedel−Crafts reaction.

(*E*)-4-Chloro-2-methyl-1-phenylsulfonyl-2-butene (**7a**) has been reported to be prepared from the copper-catalyzed addition of benzenesulfonyl chloride to isoprene at the reflux temperature of acetonitrile for 2 h in 42% yield.[10] We were able to improve the yield of this reaction up to 90% by lowering the temperature to 60 °C and extending the time to 15 h. (*E*)-4-Hydroxy-2-methyl-1-phenylsulfonyl-2-butene (**7b**) was then prepared from **7a** by trivial transformations: substitution of chloride by acetate followed by hydrolysis of the acetate.[11] The Friedel−Crafts allylation of tetramethoxytoluene (**2a**) with **7a** or **7b** (eq 1) has been thoroughly studied under various Lewis acidic conditions, and the results are summarized in Table 1.

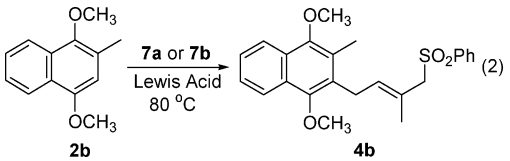


The standard condition of the Friedel−Crafts allylation with 1.2 equiv of Lewis acid in 1,2-dichloroethane at 80 °C for 8 h (condition A in Table 1) was established according to our preliminary study, where a little conversion to **4a** was observed at 40 °C in CH_2Cl_2 with use of a stoichiometric amount of Lewis acid (condition C in Table 1). The reaction also proceeded at 80 °C with a less than stoichiometric amount (0.1∼0.3 equiv) of Lewis acids (condition B in Table 1); however, it required longer reaction times to produce lower yields of **4a**. $MgBr_2$ and $AlEt_3$ were no good in activating **7a** for the coupling reaction; on the other hand, extensive decomposition of the starting materials was observed in the cases with $TiCl_4$ and $FeCl_3$. A similar trend of each Lewis acid for **7a** and **7b** in providing the yield and *E*/*Z* ratio of the coupling product **4a** was noticed. Overall, better yields were obtained with allylic alcohol **7b** than allylic chloride **7a** as an electrophile, and zinc(II) halide consistently produced high yields of **4a**, where the *E*/*Z* ratio of 10:1 was maintained. It is also noteworthy that an appreciable amount of the *Z*-isomer of the coupling product **4a** was obtained for the $SnCl_4$ case, even though a good yield was obtained. The *E*/*Z* ratio of the coupling product **4a** was kinetically determined, and the ratio at 20% conversion was mostly maintained throughout the entire reaction. The pure *E*-isomer of the coupling product **4a** was fully recovered without isomerization to the *Z*-isomer under the above standard reaction condition with $ZnCl_2$. The best condition (89%, *E*/*Z* = 10:1) was observed when **2a** and **7b** were coupled under the above standard condition with $ZnBr_2$. The Friedel−Crafts allylation of 1,4-dimethoxy-2-methylnaphthalene (**2b**)[12] with **7a** or **7b** (eq 2) under various Lewis acids also has been studied for vitamin K synthesis. The above standard reaction condition (1.2 equiv of Lewis acid in 1,2-dichloroethane at 80 °C for 8 h) has been used, and the results are summarized in Table 2.

TABLE 1. The Friedel−Crafts Allylation of Tetramethoxytoluene (2a) with 7a or 7b

entry	C_5 sulfone	Lewis acid (equiv)	condition	% of **4a** (*E*/*Z*)
1	**7a**	$MgBr_2$ (1.2)	A[a]	0 (−)
2	**7a**	$AlEt_3$ (1.2)	A[a]	0 (−)
3	**7a**	$TiCl_4$ (1.2)	A[a]	−[b] (−)
4	**7a**	$FeCl_3$ (1.2)	A[a]	−[b] (−)
5	**7a**	$AlCl_3$ (1.2)	A[a]	20 (*E*)
6	**7a**	BF_3·OEt_2 (1.2)	A[a]	20 (*E*)
7	**7a**	$ZnBr_2$ (1.2)	A[a]	30 (5:1)
8	**7a**	$ZnCl_2$ (0.1)	B[c]	44 (10:1)
9	**7a**	$ZnCl_2$ (0.3)	B[c]	62 (10:1)
10	**7a**	$ZnCl_2$ (1.2)	C[d]	56 (10:1)
11	**7a**	$ZnCl_2$ (1.2)	A[a]	69 (10:1)
12	**7a**	$SnCl_4$ (0.3)	B[c]	68 (3:1)
13	**7a**	$SnCl_4$ (1.2)	A[a]	92 (3:1)
14	**7b**	$AlCl_3$ (1.2)	A[a]	42 (*E*)
15	**7b**	BF_3·OEt_2 (1.2)	A[a]	58 (10:1)
16	**7b**	$ZnCl_2$ (1.2)	C[d]	30 (10:1)
17	**7b**	$ZnCl_2$ (1.2)	A[a]	68 (10:1)
18	**7b**	$SnCl_4$ (1.2)	A[a]	84 (3:1)
19	**7b**	$ZnBr_2$ (1.2)	A[a]	89 (10:1)

[a] Condition A: 1,2-dichloroethane at 80 °C for 8 h. [b] Decomposition of the starting materials was observed. [c] Condition B: 1,2-dichloroethane at 80 °C for 12 h. [d] Condition C: CH_2Cl_2 at 40 °C for 24 h.



A much different result was obtained for the Friedel−Crafts allylation of the less electron-rich naphthalene

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TABLE 2. The Friedel−Crafts Allylation of 1,4-Dimethoxy-2-methylnaphthalene (2b) with 7a or 7b

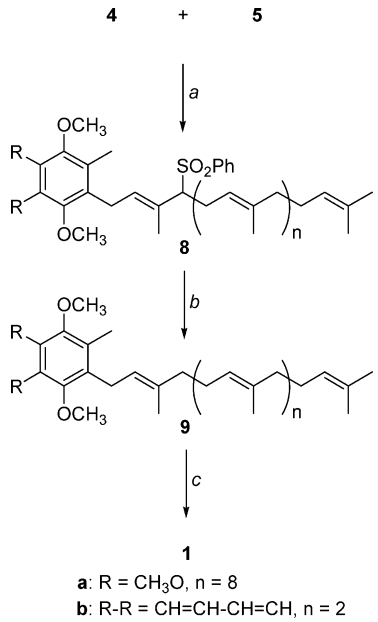
entry	C_5 sulfone	Lewis acid [a]	% of **4b** (*E*/*Z*)
1	**7a**	$BF_3{\cdot}OEt_2$	0 (−)
2	**7a**	$MgBr_2$	0 (−)
3	**7a**	$TiCl_4$	−[b] (−)
4	**7a**	$FeCl_3$	55 (4:1)
5	**7a**	Et_2AlCl	56 (7:1)
6	**7a**	$SnCl_4$	56 (*E*)
7	**7a**	$ZnBr_2$	60 (7:1)
8	**7a**	$ZnCl_2$	67 (7:1)
9	**7a**	$AlCl_3$	72 (*E*)
10	**7b**	$AlCl_3$	0 (−)
11	**7b**	$ZnCl_2$	0 (−)
12	**7b**	Et_2AlCl	0 (−)
13	**7b**	$SnCl_4$	−[b] (−)
14	**7b**	$FeCl_3$	22 (*E*)
15	**7b**	$ZnBr_2$	40 (7:1)
16	**7b**	$BF_3{\cdot}OEt_2$	41 (5:1)

[a] 1.2 equiv of Lewis acid was used. [b] Decomposition of the starting materials was observed.

derivative **2b**, where the yields of the coupling product **4b** were generally better for the allylic chloride **7a** than those for the allylic alcohol **7b**. Furthermore, different trends of each Lewis acid for **7a** and **7b** in providing the yield and *E*/*Z* ratio of the coupling product **4b** were noticed. $MgBr_2$ and $TiCl_4$ were no good as an activator for the coupling reaction. Zinc(II) halide generally produced decent yields of the coupling product **4b**, where the *E*/*Z* ratio of 7:1 was maintained. The best condition (72%, *E* only) was observed when **2b** and **7a** were coupled under the above standard condition with $AlCl_3$. The success of the above Friedel−Crafts allylations is presumably due to the presence of the rigid sulfone moiety in the prenyl compounds **7a** and **7b**, which prevents a further cyclization to form chromanol even in the reaction with trimethylhydroquinone. It has been reported that the chromanol product was exclusively obtained for the Friedel−Crafts reaction of trimethylhydroquinone with the tertiary allylic alcohol containing a flexible sulfide group.[13]

With the key compounds **4a** and **4b** in our hands, we then attempted the total syntheses of coenzyme Q-10 (**1a**) and vitamin $K_{2(20)}$ (**1b**) (Scheme 3). The Julia-type coupling reaction of **4a** and solanesyl bromide **5** (X = Br, *n* = 9), prepared from solanesol by reaction with PBr_3, produced compound **8a** containing all the required carbon atoms for coenzyme Q-10. Several conditions can be used in the coupling reaction such as *t*-BuOK/THF-DMF/−20 °C or *n*-BuLi/THF/−78 °C. Two consecutive functional group transformations from **8a** would provide coenzyme Q-10. Among the various hydrodesulfonation conditions reported, the $Pd(dppe)Cl_2$-catalyzed substitution reaction by $LiEt_3BH$ was the best.[14] Any other conditions with Li or Na(Hg) invariably produced an appreciable amount of the side products derived from the C=C bond migration at $^2\Delta$ or indiscriminating demethylations of the methoxy groups at the aromatic ring. The final oxidation with CAN (ammonium cerium(IV) nitrate)[15] gave rise to

SCHEME 3. Total Syntheses of Coenzyme Q-10 (1a) and Vitamin $K_{2(20)}$ (1b) from 4a and 4b[a]



[a] Reagents: (a) **4a**, *n*-BuLi in THF at −78 °C then **5** (X = Br, *n* = 9), 90% for **8a**, or **4b** and **5** (X = Br, *n* = 3), *t*-BuOK in THF at −20 °C, 95% for **8b**; (b) $Pd(dppe)Cl_2$ (0.05 equiv), $LiEt_3BH$ in THF, 77% for **9a**, 91% for **9b**; (c) CAN in $MeCN/CH_2Cl_2/H_2O$, 61% for **1a**, 72% for **1b**.

coenzyme Q-10 (**1a**) in 42% overall yield from **4a**. Likewise, vitamin $K_{2(20)}$ (**1b**) was synthesized from **4b** by the Julia-type coupling reaction with farnesyl bromide **5** (X = Br, *n* = 3), hydrodesulfonation ($LiEt_3BH$ catalyzed by $Pd(dppe)Cl_2$), followed by CAN oxidation in 62% overall yield.

In conclusion, we have developed an efficient synthetic method for the key compound **4** by direct Friedel−Crafts allylation of the protected *p*-hydroquinone **2** with 4-chloro-2-methyl-1-phenylsulfonyl-2-butene (**7a**) or 4-hydroxy-2-methyl-1-phenylsulfonyl-2-butene (**7b**). The success of this approach is presumably due to the stabilization provided by a phenylsulfonyl group in **7a** or **7b** under the conditions with Lewis acids. Furthermore, the *E*-configuration of the C=C bond was mostly retained in **4** after the Friedel−Crafts reaction. Expeditious total syntheses of coenzyme Q-10 (**1a**) and vitamin $K_{2(20)}$ (**1b**) were demonstrated from **4a** and **4b**, respectively. This approach can be generally applied to the syntheses of various isoprenoid natural products containing a *p*-quinone head group.

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Supporting Information Available: Experimental procedures, characterization data, and ^1H NMR spectra of **8a** and **8b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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