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A Novel Solvent Effect in the Practical Synthesis of Ubiquinone-10

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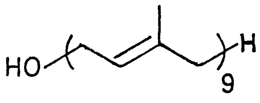
The mixed solvent of nitromethane and hexane exhibited high stereoselectivity with good yields in the synthesis of ubiquinone-10 by the coupling of 2,3-dimethoxy-5-methylhydroquinone and isodecaprenol in the presence of a catalytic amount of $BF_3 \cdot OEt_2$.

Ubiquinone-10 (4) is a coenzyme participating in the electron transport system during oxidative phosphorylation in mitochondria of mammalia[1-3] and has been clinically used for the treatment of heart diseases.[4] In order to clarify the biological role of ubiquinones and supply 4 for therapeutic purposes, establishment of a fully controlled process has been desired. Various methods were developed to introduce the prenyl moiety into protected[5] or nonprotected[6] hydroquinone or quinone.[7] Some of these techniques were applied to the synthesis of 4. Although direct coupling of isodecaprenol (2), which is efficiently derived from solanesol (1) contained in tobacco leaf, with 2,3-dimethoxy-5-methylhydroquinone (3) followed by oxidation seems to be the most straightforward and practical reaction sequence, the yield was reportedly low (18%)[6c] and the stereoselectivity (E to Z) was at the most 5 to 1 by our reexamination. Derivatization of 2 to organometalic intermediates, such as π-decaprenylnickel halide[5a,5b] or decaprenylstannane,[7f,7g] gave successful yields in the coupling of the decaprenyl chain with (hydro)quinone derivatives with good stereoselection at the Δ^2-position of the decaprenyl side chain. Starting decaprenyl bromide, however, was obtained as a mixture of the E



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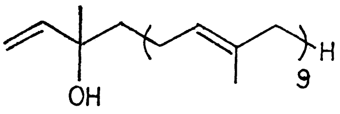

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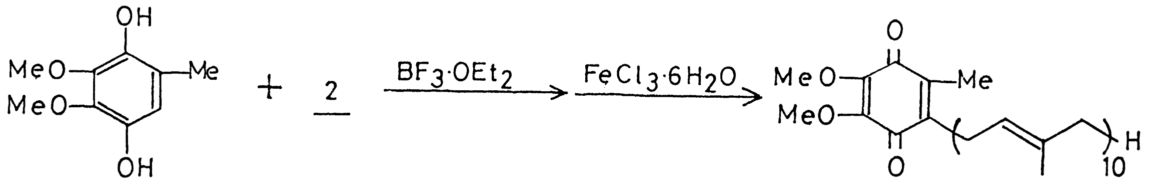

3 4

Table 1. Solvent Effect in the Synthesis of 4

Run	Solvent[a] (ml)	BF$_3$·OEt$_2$ (equiv. to 2)[b]	3(mmol)	Yield/%[c,d]	Isomer ratio[c] (E:Z)
1	NM(20)-hexane(10)	0.20	20	52(46)	11.0:1
2	NM(20)-hexane(10)	0.45	20	34	11.8:1
3	NM(30)-hexane(10)	0.24	20	43	17.7:1
4	NM(30)-hexane(10)	0.24	40	50	8.3:1
5	NM(20)-i-Pr$_2$O (10)	0.63	20	31	7.0:1
6	NM(20)-toluene(10)	0.16	20	35	7.1:1
7	NM(20)-octane(10)	0.20	20	48	12.2:1
8	NE(20)-hexane(10)	0.24	20	51(40)	6.1:1
9	1-NP(20)-hexane(10)	0.16	20	28	4.3:1
10	2-NP(20)-hexane(10)	0.16	20	40	5.5:1

a) Abbreviations used; NM:nitromethane, NE:nitroethane, 1-NP:1-nitropropane, 2-NP: 2-nitropropane. b) 2 mmol of 2 was used. c) Quantitative analysis and configurational assignment were performed by HPLC and ^{1}H-NMR, respectively.[8] d) Figures in parentheses are isolated yields.

and Z forms in the ratio of 82:18 from 2. Therefore, the formation of a substantial amount of the stereoisomer was not avoided in the process of converting 2 to 4 and caused purification problems.

During the extensive research to establish the practically applicable synthetic method and to improve the yield and stereoselectivity by optimizing reaction conditions, we found quite unprecedented solvent effects and, herein, report a coupling reaction in the heterogeneous system in the presence of a catalytic amount of BE$_3$·OEt$_2$.

Our preliminary observation that 2 and the dihydro form of 4 decomposed by themselves when in contact with a Lewis acid prompted us to separate those substrates and Lewis acid into two layers. In order to dissolve 2 and the dihydro form of 4 in a nonpolar solvent and $BF_3 \cdot OEt_2$ in a polar solvent, the combination of nitroalkane and hydrocarbon was examined (Table 1). In the mixed solvent system of nitromethane and hexane or octane, the reaction proceeded smoothly with a good yield in a short period without a phase transfer catalyst in spite of the formation of two layers. Additionally, use of excess 3 was not a disadvantage because unreacted 3 was easily recovered quantitatively from the nitromethane layer by simple separation. Moreover, less than one equivalent of $BF_3 \cdot OEt_2$ was surprisingly sufficient to complete the reaction and the yield was much improved beyond ones under other reaction conditions. Regarding the stereochemistry of the Δ^2-position of the decaprenyl side chain, this solvent system showed a remarkable E/Z ratio more than 90 to 10 which had never been attained by the conventional reaction of 2 and 3. Since 3 was distributed more in the nitromethane layer than in the hexane layer, higher stereoselectivity turned out to be attributed to the lower concentration of 3 in the nitromethane layer (Runs 1, 3, 4). This excellent stereoselectivity enabled simpler purification and raised the yield after gravity column chromatography and crystallization.

Another nitroalkane (nitroethane, 1-nitropropane, 2-nitropropane) and hexane system was shown to be less effective than nitromethane and hexane from the viewpoint of either yield or stereoselectivity. In case of using nitromethane and diisopropyl ether (or toluene), the reaction was homogeneous and the result was unsatisfactory. When nitromethane was replaced by another hydrophilic solvent, such as DMF, AcOH, DMSO, sulfolane, these solvent systems formed two phases but did not provide any product (Data not shown).

In summary, 4 was synthesized from easily available starting materials with high stereoselectivity and good yields. Although the details of this solvent effect are unclear, this method enables production of 4 in a practical sense.

The following procedure is representative.

To a warm solution of 2 (72% purity, 38.8 g, 40 mmol) and 3 (98% purity, 75.1 g 400 mmol) in hexane (200 ml) and nitromethane (400 ml) at 43 °C was quickly added $BF_3 \cdot OEt_2$ (1.0 ml, 8 mmol) in nitromethane (20 ml). The mixture was stirred for 10 min at 43 °C and was quenched by adding 2.5% aq. sodium hydrosulfite solution (200 ml) and then diluted with hexane (100 ml). Each of the hexane, nitromethane, and aqueous phases were separated and 3 (64.1 g) was recovered from the nitromethane layer (97% yield).

The hexane layer was oxidized with $FeCl_3 \cdot 6H_2O$ (21.6 g, 80 mmol) in 2-propanol (200 ml) at room temperature for 1 h. Extractive work up and HPLC analysis showed that the yield was 51% and the stereoselectivity (E/Z) was 92/8. Purification using silica-gel column chromatography and crystallization from EtOH gave 15.8 g of 4 (Yield was 46%, E/Z ratio was more than 99 to 1).

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