http://dx.doi.org/10.5012/bkcs.2013.34.4.1257

A Large Scale Formal Synthesis of CoQ_{10}: Highly Stereoselective Friedel-Crafts Allylation Reaction of Tetramethoxytoluene with (*E*)-4-Chloro-2-methyl-1-phenylsulfonyl-2-butene in the Presence of Montmorillonite K-10

Sang Who Lee, Hee Bong Lee, Bong Chan Kim, Kadivendi Sadaiah, Kyuwoong Lee, and Hyunik Shin*

*Chemical Development Division, LG Life Sciences, Ltd./R&D, Daejeon 305-380, Korea. *E-mail: shin_7@daum.net*
Received December 25, 2012, Accepted January 12, 2013

Key Words : Coenzyme Q_{10}, CoQ_{10}, Montmorillonite, Friedel-Crafts, Solvent-free

Ubiquinone, as its name represents, exists ubiquitously in human body, particularly in the heart. It mediates the electron transfer process in mitochondria and also exerts strong antioxidant effect[1] in its reduced form. In clinical trial, it showed beneficial effect on heart-related diseases such as myocardial infarction, angina, and other related symptoms to cause decreased mortality compared to the placebo group.[2]

These interesting biological effects have induced various synthetic efforts[3] towards Coenzyme Q_{10} (CoQ_{10}). Among them, two approaches seem practical for a large scale production in terms of the supply of the starting material, solanesol and their synthetic efficiency: for the construction of its complete carbon framework, Koo's synthesis[4] used the coupling of the sulfone **2** with solanesyl bromide (**3**) and Lipsultz group employed nickel catalyzed cross coupling reaction[5] of **4** with vinyl aluminum reagent **5** as the key steps, respectively (Figure 1).

Earlier in our synthetic study towards CoQ_{10}, we investigated the reproducibility of the Koo's synthetic procedure toward **2** obtained from the Friedel-Crafts reaction of (*E*)-4-chloro-2-methyl-1-phenylsulfonyl-2-butene (**7**) with tetramethoxytoluene **6**. Surprisingly, the reaction itself was pretty complicated with the formation of many side products in much lowered *E*:*Z* selectivity of *ca*. 3:1 to 7:1 than reported. Use of zinc chloride and bromide resulted in 3.3:1 and 7.4:1 *E*:*Z* ratio, respectively (Table 1, entries 1-2) with yields usually less than 20%. Best ratio of 7.6:1 was obtained by the use of boron trifluoride etherate, however with low conversion of *ca*. 20%. Aluminum chloride also showed marginal conversion of 21% with 3.4:1 *E*:*Z* selectivity. Details of the HPLC profiles of these reaction mixtures were provided in Figure 2. Other Lewis acid such as $MgBr_2$, $AlEt_3$, $TiCl_4$, $FeCl_3$ led to complete decomposition of starting materials and no sign of the formation of the desired product was observed by HPLC analysis.

To improve the yield and stereoselectivity of the reaction, we turned our attention to the use of montmollironite K-10 (MK-10),[7] in which the reaction partners might be confined in the layered space, thus rendering the stereoselectivity increased.[8] First we tested commercial MK-10 for the reaction of **6** with **7**. Happily, first attempt led to much cleaner reaction profile with significantly improved *E*:*Z* selectivity (Table 2, entry 1). However, the reaction did not complete in prolonged reaction time – the maximum conversion was accomplished in 18 h (74%). We speculated that the low conversion might be caused by residual water in clay (6.9% for commercial MK-10). In this respect, we tested a series of

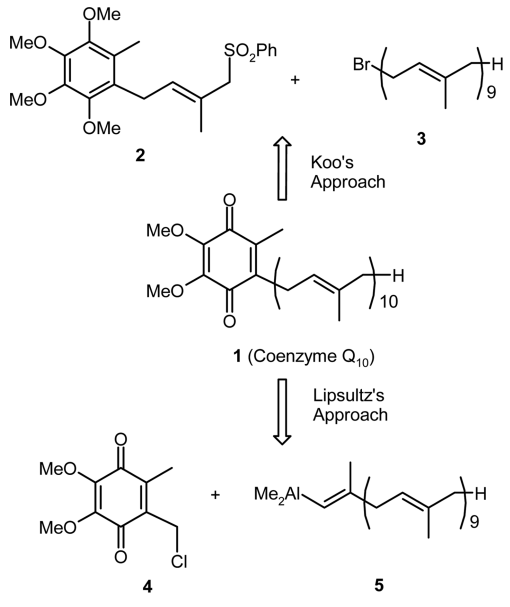
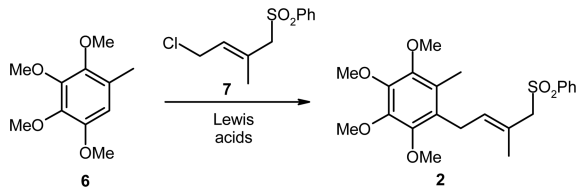


Figure 1

Table 1. Friedel-Crafts reaction of **6** and **7** using various Lewis acids[a]



Entry	Lewis acid (equiv)	Conversion (%)	Ratio (*E*/*Z*)[b]
1	$ZnCl_2$ (0.3)	> 95	3.3:1
2	$ZnBr_2$ (1.2)	> 95	7.4:1
3	$AlCl_3$ (1.2)	21	3.4:1
4	$BF_3{\cdot}OEt_2$ (1.2)	25	7.6:1

[a]To a stirred solution of **6** (1.0 mmol) and **7** (1.2 equiv) in dichloroethane (1.0 mL) was added Lewis acid, and the reaction mixture was heated at 85 °C over 18 h. [b]Determined by HPLC.

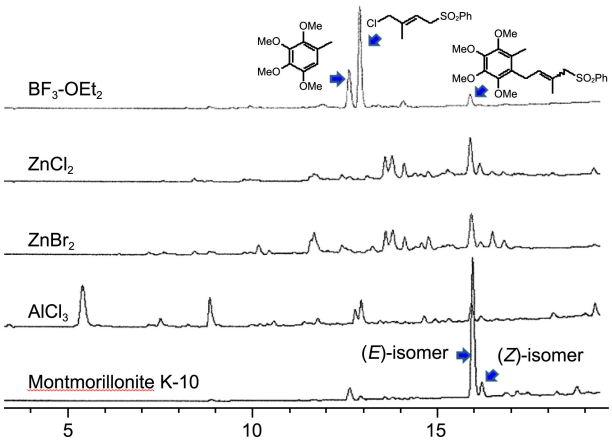


Figure 2. HPLC profiles of Friedel-Crafts reactions using various Lewis acid catalysts.[6]

Table 2. Friedel-Crafts reaction of **6** and **7** in the presence of MK-10 as a catalyst[a]

Entry	H_2O content[b]	Conversion (%)	Ratio (*E*/*Z*)[c]
1	6.9%	74.1	20.4 : 1
2	4.6%	76.2	18.7 : 1
3	2.2%	86.2	20.2 : 1
4	1.3%	90.9	14.2 : 1

[a]A mixture of 75 wt % of Montmorillonite K-10 of **6**, **6** (1.0 mmol) and **7** (1.2 equiv) in dichloroethane (1.0 mL) was heated at 85 °C over 18 h. [b]H_2O content was analyzed by Karl Fisher titrator. [c]Determined by HPLC.

reaction with MK-10 having different water contents,[9] which clearly showed the increased conversion as the water content diminished (entries 2-4) in parallel with slight deterioration of the stereoselectivity.

Although the reaction proceeded well in dichloroethane, various solvents were further investigated with MK-10 of 2.2% water content for identifying environmentally more acceptable media (Table 3). No reaction was observed in CH_3CN, *i*-PrOH, and DMF (entries 4-6), while partial 45-50% conversion was obtained in dioxane and ethyl acetate (entries 2-3).

With dichloroethane determined as an optimal solvent, we investigated the optimal amount of MK-10. As summarized in Table 4, 50-100 wt % MK-10 of **6** showed indiscriminative conversion of *ca.* 90%, while use of 25% and 200% resulted in incomplete and best conversion of 50% and 95%,

Table 3. Solvent effect on the F-C reaction of **6** and **7**[a]

Entry	Solvent	Conversion (%)	Ratio (*E*/*Z*)[b]
1	DCE	86.2	20.2:1
2	dioxane	46.2	13.3:1
3	EtOAc	50.3	15.8:1
4	CH_3CN	0.0	-
5	*i*-PrOH	0.0	-
6	DMF	0.0	-

[a]To a stirred solution of **6** (1.0 mmol) and **7** (1.2 equiv) in organic solvent (1.0 mL) was added Montmorillonite (2.2% water content, 75 wt % of **6**) and the reaction was heated at 85 °C over 18 h. [b]Determined by HPLC.

Table 4. Optimization on the amount of MK-10[a]

Entry	MK-10[b]	Conversion (isolated yield: %)	Ratio (*E*/*Z*)[b]
1	25 wt %	49.9 (–)	34.3:1
2	50 wt %	89.5 (75)	19.3:1
4	100 wt %	90.3 (–)	18.3:1
5	200 wt %	95.2 (–)	10.3:1

[a]To a stirred solution of **6** (1.0 mmol) and **7** (1.2 equiv) in dichloroethane (1.0 mL) was added Montmorillonite K-10 (2.2% H_2O content) and the reaction was heated at 85 °C over 18 h. [b]Determined by HPLC.

Table 5. Friedel-Crafts reaction of **6** and **7** with MK-10 under solvent-free conditions[a]

Entry	Reaction condition[a] (wt % of MK-10/°C/h)	Conversion (isolated yield: %)	Ratio[c] (*E*/*Z*)
1	50/100/5	87.7 (–)	21.7:1
2	50/100/5	91.5 (57)	14.2:1
3	100/100/5	87.8 (–)	19.1:1
4	200/100/5	95.3 (–)	14.7:1
5	100/80/16	88.0 (–)	24.2:1
6[b]	50/reflux/18	99 (87)	13.3:1

[a]All the reactions was carried out with MK-10 of 1.3% H_2O content. [b]The reaction was carried out in dichloroethane. [c]Determined by HPLC.

respectively. Interestingly, *E*/*Z* stereoselectivity was deteriorated gradually from 34.3:1 to 10.3:1 as the amount of MK-10 increased from 25% to 200%. Based upon the conversion and stereoselectivity, the optimal amount of MK-10 was determined to be in the range of 50-100 wt % of **6**.

The reaction could be carried out under solvent-free conditions as summarized in Table 5. At 100 °C under solvent-free conditions, the reaction showed fast conversion compared to the reaction performed in dichloroethane with similar stereoselectivity (entry 1). Lowering temperature to 80 °C slightly improve the stereoselectivity to 24.2:1 (entry 5). Increased amount of MK-10 to 100 and 200 wt % respectively did not show any significant changes in yield and stereoselectivity (entries 3-4). However, when the reaction scale was increased to 10 mmol, the result obtained with 1 mmol scale (Table 4, entry 2) could not be reproduced to result in lowered yield of 57% isolated yield (entry 2). In contrast, the same scale reaction in dichloroethane provided the product **2** in 87% isolated yield (entry 6). Moreover, this optimized condition has been reproducibly scaled up to multi-hundred kg scale (see the experimental section).

In summary, we disclosed that MK-10 is a highly effective catalyst for the Friedel-Crafts reaction of **6** and **7** in terms of yield and of stereoselectivity. Although there are numerous applications of clays in Friedel-Crafts reaction, there is very limited example which demonstrated its effect on the stereoselectivity. In that context, our result is significant and further expansion in this direction is highly envisioned.

Experimental

Large-scale Preparation of 2. A suspension of MK-10

(116.5 kg) in dichloroethane (1,756 kg) was heated at 82-84 °C to azeotropically distill-off H_2O (6.65 kg collected). The reaction mixture was cooled to *ca*. 70 °C, to which was added DCE (1756 kg), tetramethoxytoluene **6** (212.3 kg, 1.10 kmol) and sulfone **7** (276 kg, 1.1 equiv) in sequence. The mixture was heated at reflux for 7 h, at which < 3.0% starting material **6** was detected by HPLC. The reaction mixture was cooled to 50 °C, filtered through a pad of Celite (5.49 kg) and the filter cake was washed with DCE (292.7 kg). The combined filtrates were concentrated under reduced pressure. To the residue was added anhydrous EtOH (729 kg). The clear solution was slowly cooled to −10 °C and kept for 10 h. The formed solid was filtered, washed with cold EtOH (292 kg), and dried by N_2 purge to provide **2** (277.0 kg, 85% yield, *E*/*Z* ratio = 98:2) as a white solid.

Pure (*E*)- and (*Z*)-isomers were purified by column chromatography and their respective full analytical data are provided. **Spectroscopic data of (*E*)-1,2,3,4-tetramethoxy-5-methyl-6-(3-methyl-4-(phenylsulfonyl)but-2-enyl)benzene (2):** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.4 Hz, 2 H), 7.50 (m, 1 H), 7.38 (m, 2 H), 4.89 (t, *J* = 6.4 Hz, 1 H), 3.87 (s, 3 H), 3.84 (s, 3 H), 3.74 (s, 3 H), 3.68 (s, 2 H), 3.67 (s, 3 H), 3.21 (d, *J* = 6.4 Hz, 2 H), 1.95 (s, 3 H), 1.90 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.9, 147.6, 145.4, 144.7, 138.3, 134.5, 133.4, 128.9, 128.5, 127.2, 125.2, 123.3, 66.0, 61.2, 61.1, 61.0, 60.7, 26.3, 17.0, 11.8. HRMS (ESI) calcd for $C_{22}H_{29}O_6S$, 421.1685 $[M+H]^+$, found 421.1688.

Spectroscopic data of (*Z*)-1,2,3,4-tetramethoxy-5-methyl-6-(3-methyl-4-(phenylsulfonyl)but-2-enyl)benzene: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.2 Hz, 2 H), 7.66 (m, 1 H), 7.59 (m, 2 H), 5.41 (t, *J* = 6.7 Hz, 1 H), 4.04 (s, 2 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 3.75 (s, 3 H), 3.68 (s, 3 H), 2.76 (d, *J* = 6.7 Hz, 2 H), 2.00 (s, 3 H), 1.82 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 147.5, 145.5, 144.7, 139.1, 134.0, 132.9, 129.3, 128.7, 127.2, 125.0, 123.2, 61.1, 61.0, 60.9, 60.7, 59.7, 25.9, 24.2, 11.9.

Acknowledgments. We thank Man-Young Yoon for performing early exploratory experiments of this project. And the publication of this paper was supported by the Korean Chemical Society.

References

1. (a) Lenaz, G.; Coenzyme Q. *Biochemistry, Bioenergetics, and Clinical Applications of Ubiquinone*; Wiley-Interscience: New York, 1985. (b) Thomson, R. H. *Naturally Occurring Quinones*, 3rd ed.; Academic Press: New York, 1987.
2. Otani, H.; Tanaka, H.; Inoue, T.; Umemoto, M.; Omoto, K.; Tanaka, K.; Sato, T.; Osako, T.; Masuda, A. *Cir. Res.* **1984**, *55*, 168. (b) Singh, R. B.; Wander, G. S.; Rastogi, A.; Shukla, P. K.; Mittal, A.; Sharma, J. P.; Mehrotra, S. K.; Kapoor, R.; Chopra, R. K. *Cardiovasc. Drugs Ther.* **1998**, *12*, 347.
3. (a) Zheng, Y. F.; Lin, J. D.; Li, C. P.; Li, J. H. *J. Chem. Res*. **2007**, 686. (b) Yu, X. J.; Dai, H. F.; Chen, F. E. *Helv. Chim. Acta* **2007**, *90*, 967. (c) Ravada, S. R.; Emani, L. R.; Garaga, M. R.; Meka, B.; Golakoti, T. *Am. J. Infect. Dis*. **2009**, *5*, 83. (d) Negishi, E. I.; Liou, S. Y.; Xu, C.; Huo, S. *Org. Lett*. **2002**, *4*, 261. (e) Yangisawa, A.; Nomura, N.; Noritake, Y.; Yamamoto, H. *Synthesis* **1991**, 1130. (f) Keinan, E.; Eren, D. *Pure & Appl. Chem*. **1988**, *60*, 89. (g) Eren, D.; Keinan, E. *J. Am. Chem. Soc*. **1988**, *110*, 4356. (h) Mohri, M.; Kinoshita, H.; Inomata, K.; Kotake, H.; Takagaki, H.; Yamazaki, K. *Chem. Lett*. **1986**, 1177. (i) Masaki, Y.; Hashimoto, K.; Kaji, K. *Chem. Pharm. Bull*. **1984**, *32*, 3959. (j) Sato, K.; Miyamoto, O.; Inoue, S.; Yamamoto, T.; Hirasawa, Y. *J. Chem. Soc. Chem. Commun*. **1982**, 153. (k) Fujita, Y.; Ishiguro, M.; Onishi, T.; Nishida, T. *Bull. Chem. Soc. Jpn*. **1982**, *55*, 1325. (l) Terao, S.; Kato, K.; Shiraishi, M.; Morimoto, H. *J. Org. Chem*. **1979**, *44*, 868. (m) Van Liemt, W. B. S.; Steggerda, W. F.; Esmeijer, R.; Lugtenburg, J. *Recl. Trav. Chim. Pays-Bas*. **1994**, *113*, 153. (n) Eto, H.; Eguchi, C. *Chem. Lett*. **1988**, 1597. (o) Yoshizawa, T.; Toyofuku, H.; Tachibana, K.; Kuroda, T. *Chem. Lett*. **1982**, 1131. (p) Naruta, Y.; Maruyama, K. *Chem. Lett*. **1979**, 885. (q) Inoue, S.; Yamaguchi, R.; Saito, K.; Sato, K. *Bull. Chem. Soc. Jpn*. **1974**, *47*, 3098. (r) Ruegg, R.; Gloor, U.; Goel, R. N.; Ryser, G.; Wiss, O.; Isler, O. *Helv. Chim. Acta* **1959**, *42*, 2616.
4. Min, J.-H.; Lee, J.-S.; Yang, J.-D.; Koo, S. *J. Org. Chem*. **2003**, *68*, 7925.
5. (a) Lipsultz, B. H.; Lower, A.; Berl, V.; Schein, K.; Wetterich, F. *Org. Lett*. **2005**, *7*, 4095. (b) Lipshutz, B. H.; Bulow, G.; Fernandez-Lazaro, F.; Kim, S.-K.; Lowe, R.; Mollard, P. M.; Stevens, K. L. *J. Am. Chem. Soc*. **1999**, *121*, 11664. (c) Lipshutz, B. H.; Mollard, P. M.; Pfeiffer, S. S.; Chrisman, W. *J. Am. Chem. Soc*. **2002**, *124*, 14282. (d) Lipshutz, B. H.; Frieman, B.; Pfeiffer, S. S. *Synthesis* **2002**, 2110.
6. Chromatograms were obtained under the conditions: Shiseido C18 column; 4.6 × 250 mm; 256 nm; run time 22 min; injection volume 5 μL; flow rate 1 mL/min; gradient elution of 0.1% trifluoroacetic acid solution of 20% acetonitrile/80% H_2O to 0.1% trifluoroacetic acid solution of 100% acetonitrile in 20 min.
7. For reviews, see: (a) Dasgupta, S.; Török, B. *Org. Prep. Proced. Int*. **2008**, *40*, 1. (b) Clark, J. H.; Macquarrie, D. *J. Chem. Soc. Rev*. **1996**, *25*, 303. (c) Laszlo, P. *Acc. Chem. Res*. **1986**, *19*, 121. (d) Izumi, Y.; Onaka, M. *Adv. Catal*. **1992**, *38*, 245.
8. Mitsudome, T.; Nose, K.; Mizugami, T.; Jitsukawa, K.; Kaneda, K. *Tetrahedron Lett*. **2008**, *49*, 5464.
9. MK-10 was dried by a heat gun under reduced pressure.