Friedel–Crafts allylation of 2-(benzyloxy)-3,4,5-trimethoxytoluene catalysed by a metal trifluoromethanesulfonic salt: synthesis of coenzyme Q10

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In the presence of a catalytic amount of scandium triflate, 2-benzyloxy-3,4,5-trimethoxytoluene reacted with allylic derivatives **4**, giving the key intermediate **3** (R = benzyl) which was used for preparing coenzyme Q10, in moderate to high yields.

Keywords: 2-(benzyloxy)-3,4,5-trimethoxytoluene, metal triflate, Friedel–Crafts allylation, coenzyme Q10

Coenzyme Q10 (**1**, also called ubiquinone), was discovered in 1957,[1] and shown to function in mitochondria in the formation of ATP. It has been found to be beneficial for a variety of conditions,[2,3] such as heart disease and Parkinson's disease.

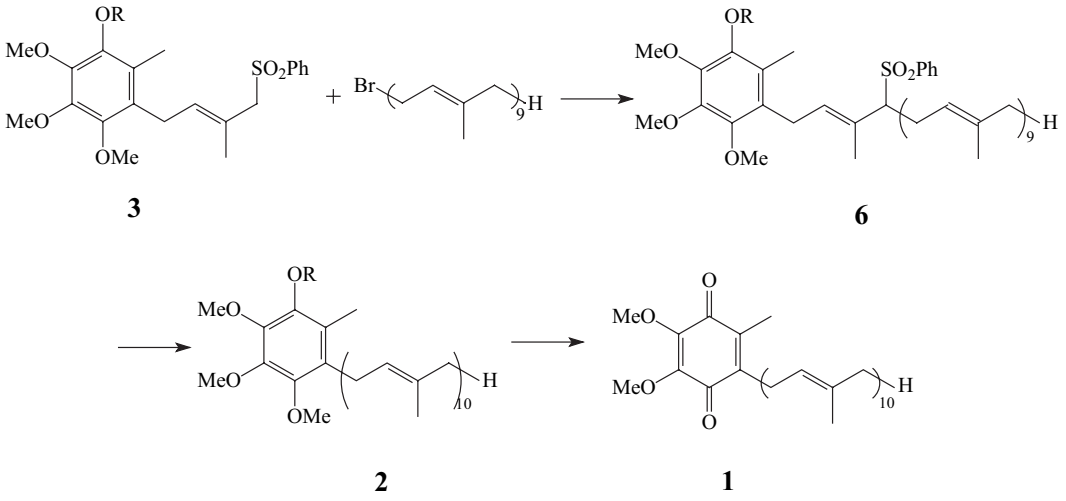
Because of those important effects, there have been extensive synthetic efforts directed at this natural product.[4-12] The key issue was the coupling of the quinone core generally derived from inexpensive trimethoxytoluene and the polyprenyl side chain derived from expensive solanesol. An ideal synthesis would seek to not only minimise the extent to which intermediates based on solanesol are manipulated *en route* to Coenzyme Q10 but also improve its overall yield. Recently, a new process for preparing Q10 (Scheme 1, R = Me) was reported.[13] Although the final step, oxidation of **2** (R = Me) with $(NH_4)_2Ce(NO_3)_6$, gave Q10 in low yield, the whole process is an improvement.

Scheme 1 shows that **3** is a key compound in the synthesis of coenzyme Q-10 (**1**). Fujita[14] reported a method for the preparation of **3** (R = Me) *via* copper-mediated coupling of (E)-4-Chloro-2-methyl-1-phenylsulfonyl-2-butene with the Grignard reagent of 2,3,4,5-tetramethoxytolyl bromide. Compared to Fujita's method, Friedel–Crafts reaction of **5** (R = alkyl) with **4** might be a simpler and more economical way to synthesise **3** (Scheme 2), because **5** (R = alkyl) is a good electron-rich substrate for the Friedel–Crafts reaction. The Friedel–Crafts reaction was achieved by Min *et al.* recently.[13] However, the low values of *E/Z* isomeric ratio of **3** (R = Me) were not desirable (*E/Z* = 10/1). Based on the potential of its industrial application, we sought the optimal process for synthesising Q10. According to Scheme 1 and the literature,[15,16] in which Q0 was prepared quantitatively by oxidation of 2-hydroxy-3,4,5-trimethoxytoluene in air, we deduced that **2** (R = H), easily obtained starting from **3** (R = Bn) *via* intermediate **2** (R = Bn), might produce Q10 in similar way to Q0 in good yield (Scheme 1). The search for a more effective method for preparation of **3** (R = Bn) is necessary.

Recently, it is found that a metal triflate, as an all-purpose Lewis acid, was generally useful as an effective catalyst in organic synthesis,[17] such as in Aldol reaction,[18,19] Mannich-type reaction,[20–24] Diels–Alder reaction[25–27] and Friedel–Crafts reaction.[28–30] To the best of our knowledge, however, metal triflate catalysed Friedel–Crafts allylation of **5** has not been reported. We now report our investigation using metal triflate as a catalyst (Scheme 2, R = Bn) with improved value of *E/Z* ratio. Compound **5** (R = Bn) and compound **5** (R = Me), both of which were derived from 2-hydroxy-3,4,5-trimethoxytoluene, are useful starting materials for synthesising Q10. The former is better compared to the latter, because at the final step in synthesising Q10, **2** (R = Bn) is more readily transformed into **2** (R = H) which leads to **1** quantitatively.

Results and discussion

As a Lewis acid, metal triflate can catalyse the Friedel–Crafts allylation of **5** (R = Bn) with **4** (X =Cl, Br) (Scheme 2). The results are summarised in Table 1.



Scheme 1 The synthetic route of Coenzyme Q10 (**1**) from the compound **3**.

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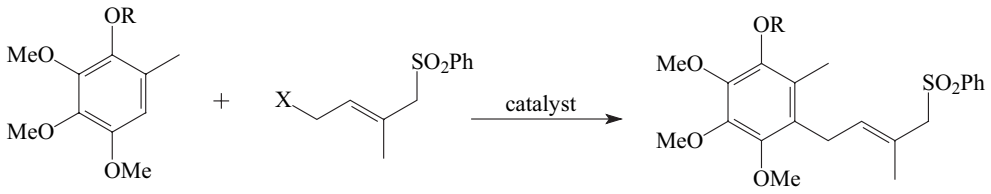


5 **4** **3**

4a, X = Cl **4b**, X = Br

Scheme 2 Preparation of the compound **3** (R = Me, Bn) catalysed by metal triflate.

Table 1 Allylation of **5** (R = Bn) in the presence of metal triflates

Entry	Allylation reagent	Catalyst (equiv)	Condition	Yield% of *E*-3 (R = Bn)
1	**4a**	AgOTf (0.5)	A[a]	ND[c]
2	**4a**	$Cu(OTf)_2$ (0.5)	A[a]	32
3	**4a**	$Y(OTf)_3$(0.5)	A[a]	51
4	**4a**	$Gd(OTf)_3$(0.5)	A[a]	54
5	**4a**	$Ce(OTf)_3$(0.5)	A[a]	62
6	**4a**	$La(OTf)_3$(0.5)	A[a]	66
7	**4a**	$Yb(OTf)_3$(0.1)	B[b]	40
8	**4a**	$Yb(OTf)_3$(0.2)	B[b]	52
9	**4a**	$Yb(OTf)_3$(0.5)	A[a]	78
10	**4a**	$Sc(OTf)_3$(0.5)	A[a]	81
11	**4b**	$Yb(OTf)_3$(0.5)	A[a]	80
12	**4b**	$Sc(OTf)_3$(0.5)	A[a]	83

[a]A: THF at reflux temperature for 12 h. [b]B: THF at reflux temperature for 18 h. [c]Not detected.

The condition of the Friedel–Crafts allylation with 0.5 equiv of metal triflate in THF at reflux temperature for 12 h (condition A in Table 1) was established according to our preliminary study. The reaction also proceeded with a less than stoichiometric amount of metal triflate (condition B in Table 1), however, it required a longer reaction time and produced a lower yield of *E*-3 (R = Bn).

From Table 1, a different effect of each metal triflate on the yield of the coupling product *E*-3 (R = Bn) was noticed. AgOTf was not a good catalyst for this coupling reaction. There was no product *E*-3 (R = Bn) detected in the case of AgOTf. $Cu(OTf)_2$, $Y(OTf)_3$, and $Gd(OTf)_3$ *etc*. generally produced low yields of the product *E*-3 (R = Bn). A good yield of the *E*-isomer of the compound **3** (R = Bn) was obtained in the case of $Yb(OTf)_3$ and $Sc(OTf)_3$. Note that $Sc(OTf)_3$ consistently produced high yields of *E*-3 (R = Bn), where the *E/Z* ratio of 15:1 was maintained. The best result (83%; *E/Z* = 15 : 1, determined by external standard method of HPLC: column VP-ODS 150 L × 4.6, flow rate 0.8 ml/min, eluent 75% methanol–water solution, λ = 254 nm) was observed when **4** (X = Br) and **5** (R = Bn) were coupled using $Sc(OTf)_3$ as catalyst under condition A, and a pure product *E*-3 (R = Bn) can be readily obtained by recrystallisation from methyl *tert*-butyl ether. It was easy to separate the *E*-isomer of **3** (R = Bn) from its *Z*-isomer, which is important and useful for industrial application.

In addition, the recovery and recycling of metal triflate were also investigated, and the results show that the reaction proceeded smoothly with recovered $Yb(OTf)_3$ With the key compound **3** (R = Bn) to hand, we attempted the total synthesis of coenzyme Q10 (**1**) (Scheme 3). Q10 (**1**) was easily prepared by similar methods to those described in the literatures:[3,15] (a) condensing **3b** with solanesyl bromide, (b) treating the resultant product **6b** with $LiHBEt_3/Pd(dppp)Cl_2$ followed by debenzylation with K/EtOH and oxidation with air.

Conclusion

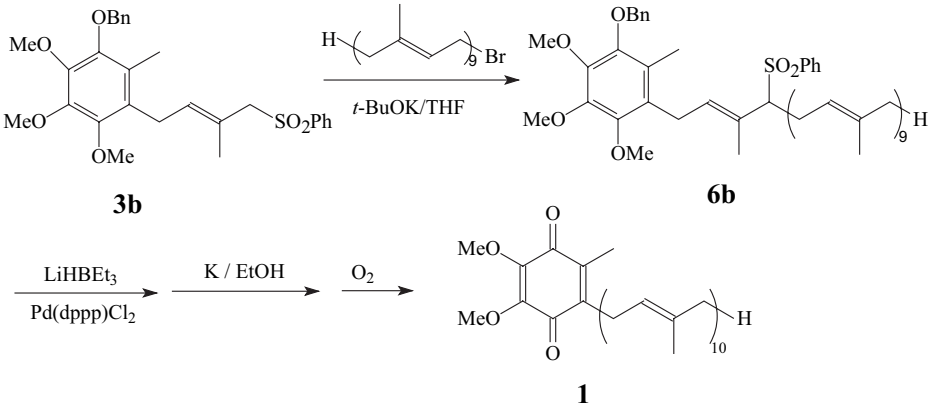
In conclusion, an efficient and convenient procedure for Friedel–Crafts allylation was carried out using a metal triflate as a catalyst under mild conditions with a simple methodology. It offered an important method for Friedel–Crafts allylation of **4** (R = Bn) in order to synthesise compound **3b**, a key intermediate for preparing coenzyme Q10 and an economical method for preparation of Q10 from **3b** was achieved (Scheme 3).

Experimental

Melting points are uncorrected. ^{1}H NMR spectra were determined on a Varian Plus 400 instrument using TMS as an internal standard and $CDCl_3$ as a solvent. IR spectra were recorded on a Perkin-Elmer 683 instrument. Mass spectra were obtained on an AEI MS-902 instrument and ESI-MS was obtained with a Finnigan TSQ 700 instrument.

Procedure for synthesis of **3b**

A solution of 2-(benzyloxy)-3,4,5-trimethoxytoluene **5** (R = Bn) (1.0 mmol) and (*E*)-4-chloro-2-methyl-1-phenylsulfonyl-2-butene **4a** (1.0 mmol) and $Sc(OTf)_3$ (0.50 mmol) in dry THF (10 ml) was refluxed for 12 h. The solution was concentrated under reduced



3b **6b**

1

Scheme 3 Preparation of the Q10 (1) from the compound **3b** (3, R = Bn); dppp: 1,3-bi(diphenylphosphino)propane

pressure and the residue was extracted twice with 1,2-dichloroethane (10 ml) and filtered. The filtrate was evaporated under reduced pressure to give a solid. The solid residue was further purified by recrystallisation from methyl *tert*-butyl ether to give **3b** (*E*) in 81% isolated yield.

3b: M.p. 76–78°C; IR (KBr, cm^{-1}): 2962, 2934, 2899, 1464, 1305, 1132, 734; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.94 (3H, s), 1.97 (3H, s), 3.24 (2H, d, *J* = 6.4 Hz), 3.75 (3H, s), 3.75 (2H, s), 3.90 (3H, s), 3.92 (3H, s), 4.91 (2H, s), 4.91 (1H, br), 7.20–7.28 (10H, m); EI-MS *m/z* (rel. intensity%): 496 (M^+, 11), 405 (100), 263 (74), 231 (48), 91 (34); Anal. calcd. for $C_{28}H_{32}O_6S$, C 67.72%, H 6.49%, Found C 67.66%, H 6.51%.

Procedure for synthesis of **6b**

To a stirred mixture of **3b** (2.0 g, 4.0 mmol), solanesyl bromide (95%, 2.9 g, 4.0 mmol) and THF (28 ml) was added *t*-BuOK (0.5 g, 4.4 mmol) at -20°C. The mixture was stirred at the same temperature for 1 h to complete the reaction, and then acidified with 5% H_3PO_4 to pH = 2-3. The whole mixture was added to water (20 ml) and methyl tert-butyl ether (20 ml) and separated into two layers. The organic layer was washed with water to pH = 7, dried over $MgSO_4$ and concentrated under reduced pressure to give an oily product. The oily residue was further purified by column chromatography on silica gel with petroleum ether/ethyl acetate (10 : 1 v/v) as an eluent to give 4.0 g of pure **6b** (yield 90%).

6b: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.58 (3H, s), 1.60 (3H, s), 1.62 (21H, s), 1.70 (3H, s), 1.85 (3H, s), 1.95 (3H, s), 2.01–2.11 (32H, s), 2.59-2.58 (1H, m), 2.63–2.88 (1H, m), 3.17 (1H, m), 3.28 (1H, m), 3.50 (1H, m), 3.70 (3H, s), 3.92 (3H, s), 3.94 (3H, s), 4.92 (2H, s), 4.90–5.16 (10H, m), 7.34–7.80 (10H, m); ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 12.0, 14.0, 15.9, 16.0, 16.3, 17.6, 24.0, 25.7, 26.0, 26.5, 26.6, 26.6, 26.7, 26.7, 39.7, 61.0, 61.0, 61.1, 61.2, 123.7, 124.1, 124.2, 124.2, 124.4, 125.5, 126.5, 127.4, 127.9, 128.1, 128.4, 128.6, 128.7, 131.2, 133.1, 134.2, 134.8, 134.9, 134.9, 134.9, 134.9, 135.0, 135.3, 137.7, 137.8, 138.5, 144.7, 145.3, 146.7, 147.6; ESI-MS *m/z* (%) 1131.7 (M + Na^+, 88), 1126.7 (M + NH_4^+, 100); Anal. calcd. for $C_{73}H_{104}O_6S$, C 79.01%, H 9.45%, Found C 78.90%, H 9.42%.

Preparation of Q10 (**1**)

To a mixture of 808 mg **6b** and $Pd(dppp)Cl_2$ (20 mg) in THF (8 ml) was added dropwise $LiHBEt_3$ in THF (1.94 ml 1 mol/l) at –30°C. After stirring for 6 h, the whole reaction mixture was quenched with 0.8 ml water and concentrated under reduced pressure to 30% of its original volume. The concentrated residue was treated with water (8 ml), extracted with petroleum ether (2 × 2.5 ml), washed with water (2 ml), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give a sticky residue (700 mg). The residue was mixed with ethanol (2 ml) and dry THF (25 ml) and K (450 mg) at –40 ~ –20°C, and stirred at the same temperature for 4 h. Then the reaction mixture was stirred with $FeCl_3$•$6H_2O$ in air for 0.5 h. The resulting mixture was partitioned with 1 mol/l HCl and isopropyl ether. The organic layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure to give an orange solid. The solid residue was further purified by column chromatography on silica gel with hexane/isopropyl ether (3:1 v/v) as an eluent, and recrystallised from acetone to give 408 mg of an orange crystalline powder **1** (yield 65%).

Q10 (**1**) m.p. 48–49°C (lit.[32] 47°C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.59 (36H, s), 1.97–2.06 (36H, m), 3.19 (2H, d, *J* = 6.0 Hz), 3.99, 6H,s 5.11 (10H, m); ESI-MS *m/z* (%) 885.6 (M + Na^+, 85), 880.6 (M + NH_4^+, 100).

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