Pummerer-type Rearrangement on Aromatic Rings: an Unprecedented *ipso*-Substitution of the Sulfinyl Group of *p*-Sulfinylphenyl Ethers into Oxygen Functional Groups leading to Protected Dihydroquinone Derivatives

Shuji Akai, Kiyosei Iio, Yoshifumi Takeda, Hiroshi Ueno, Kayoko Yokogawa and Yasuyuki Kita*

Faculty of Pharmaceutical Sciences, Osaka University, 1-6, Yamada-oka, Suita, Osaka 565, Japan

The treatment of *p*-(phenylsulfinyl)phenyl ethers **1** with trifluoroacetic anhydride in the presence of styrene selectively caused the direct *ipso*-substitution of the sulfinyl groups by trifluoroacetoxy groups, giving the protected dihydroquinone derivatives **3** in high to quantitative yields.

ipso-Substitution of suitably *para*-functionalized phenols by oxygen nucleophiles has been developed to give protected *p*-dihydroquinone derivatives,[1–3] which are often used in the preparation of biologically active natural products.[4] These methods, however, need relatively high temperatures and/or strong basic conditions, and they are, in some cases, inconsistent with the presence of carbonyl groups.[2] Here, we present a novel and mild preparation of protected *p*-dihydroquinone derivatives **3** through the unprecedented direct *ipso*-substitution of the sulfinyl group of *p*-sulfinylphenyl ethers **1** to give oxygen functional groups.[5,6]

It was expected that the reaction of *p*-sulfinylphenyl ethers **1** with trifluoroacetic anhydride (TFAA) would cause a Pummerer-type rearrangement on the sulfinyl group to give the electrophilic oxonium intermediate **A**, which would be predominantly attacked by the nucleophile at the sulfur atom to give the desired dihydroquinones **3**.†,[7] For success of this reaction, the OR^1 group must be efficiently electron-donating and the O–R^1 bond must be stable in the intermediate **A**.

Although the reaction of the acetate **1a** with TFAA did not proceed even after 2 d at room temperature (run 1 in Table 1), similar treatment of methyl ether **1b** with TFAA was completed at 0 °C within 30 min to give the desired trifluoroacetoxy derivative **3b** (51% yield) accompanied by the reduced product **4b** (48% yield) (run 2). The reaction of the *tert*-butyldimethylsilyl ether **1c** produced **3c** in better yield (58%) (run 3). Although the use of the electron-donating (*p*-methoxyphenyl)sulfinyl derivative **1d** instead of **1c** increased the yield of **3c** to 73% yield (run 4), we could not depress the formation of **4** by changing the silyl groups (for example, R^1 = $SiPr^i_3$, $SiBu^tPh_2$) and the R^2 groups (for example, runs 5 and 6).

Since it is thought that the attack of the trifluoroacetoxy anion on the sulfur atom of the intermediate **A** gives **3** and the sulfenyl trifluoroacetate **2** [indeed, the addition of 3 equiv. of tri-

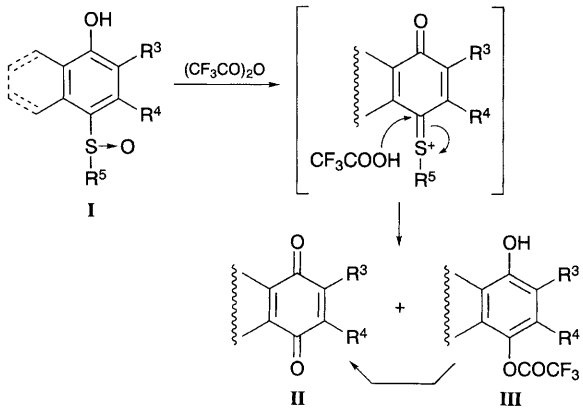
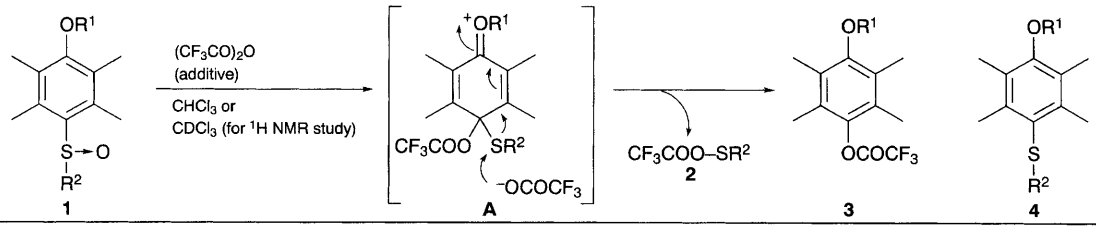
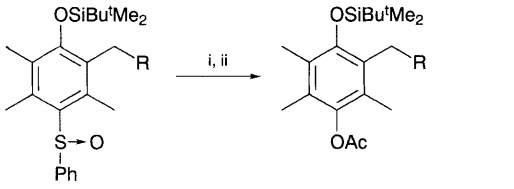


Table 1 Pummerer-type rearrangement of the *p*-sulfinylphenol derivatives **1a–f**



Run[a]		Substrate **1** R^1	R^2	Additive (equiv.)	Reaction conditions	Product/% yield[b] **3**	**4**
1	**a**	Ac	Ph	—	room temp., 2 d	**a** —	**a** *ca.* 10
2	**b**	Me	Ph	—	0 °C, 30 min	**b** 51 (50[c])	**b** 48 (42[c])
3	**c**	$SiBu^tMe_2$	Ph	—	0 °C, 30 min	**c** 58	**c** 39
4	**d**	$SiBu^tMe_2$	C_6H_4-*p*-OMe	—	0 °C, 2 h	**c** 73 (66[c])	**d** 27 (25[c])
5	**e**	$SiBu^tMe_2$	Bu^t	—	0 °C, 10 min	**c** 60	**e** *ca.* 10
6	**f**	$SiBu^tMe_2$	Me	—	0 °C, 10 min	**c** trace[d]	**f** trace
7	**c**	$SiBu^tMe_2$	Ph	CF_3CO_2H (3)	0 °C, 1 h	**c** 68	**c** 28
8	**c**	$SiBu^tMe_2$	Ph	PhSH (2)	0 °C, 30 min	**c** 15	**c** 84
9	**c**	$SiBu^tMe_2$	Ph	*o*-$HSC_6H_4CO_2H$ (1)	0 °C, 2 h	**c** 54	**c** 44
10	**c**	$SiBu^tMe_2$	Ph	$P(OMe)_3$ (1)	0 °C, 2 h	**c** 51	**c** 40
11	**c**	$SiBu^tMe_2$	Ph	Styrene (3)	0 °C → room temp., 1 h	**c** 98 (79[c], 96[e])	**c** —
12	**c**	$SiBu^tMe_2$	Ph	$Bu^tCH{=}CH_2$ (3)	0 °C → room temp., 1 h	**c** 98 (90[e])	**c** —
13	**c**	$SiBu^tMe_2$	Ph	$PhI(OCOCF_3)_2$ (1)	0 °C, 15 min	**c** 97	**c** —
14	**b**	Me	Ph	Styrene (3)	0 °C → room temp., 15 h	**b** 98 (84[c])	**b** —

[a] 10 equiv. of $(CF_3CO)_2O$ was used for runs 1, 7–14 and 5 equiv. of $(CF_3CO)_2O$ was used for runs 2–6. [b] Yield was estimated by ^1H NMR analysis run in $CDCl_3$ with an internal standard ($Cl_2CHCHCl_2$). [c] The same reaction was run in $CHCl_3$ and isolated yield by flash column chromatography on SiO_2 is shown. [d] The corresponding *p*-[(trifluoroacetoxy)methylsulfanyl]phenyl silyl ether was obtained in 94% yield. [e] Isolated yield of the corresponding acetate is shown (see footnote §).



1g R = $CH{=}CH_2$	**3d** R = $CH{=}CH_2$	95%
h R = $(CH_2)_2OSiBu^tMe_2$	**e** R = $(CH_2)_2OSiBu^tMe_2$	86%
i R = $(CH_2)_2OAc$	**f** R = $(CH_2)_2OAc$	98%
j R = CH_2CHO	**g** R = CH_2CHO	62%
k R = $(CH_2)_2OH$	**f** R = $(CH_2)_2OAc$	98%

Scheme 1 *Reagents and conditions*: i, $(CF_3CO)_2O$ (10 equiv.), styrene (3 equiv.), $CHCl_3$, 0 °C → room temp., 0.5–2 h; ii, aq. $NaHCO_3$, MeOH then Ac_2O, pyridine, CH_2Cl_2

fluoroacetic acid slightly improved the yield of **3c** (run 7)],[8] formation of **4** may be due to reaction of **2** with unreacted **1**. Therefore, we examined the *in situ* trapping and/or decomposition of **2**. Although the addition of thiophilic compounds such as thiols and $P(OMe)_3$ did not work for this purpose (runs 8–10), alkenes such as styrene or 3,3-dimethylbut-1-ene efficiently trapped **2** to give a 98% yield of **3c** (runs 11 and 12).‡,[9] The use of $PhI(OCOCF_3)_2$, to oxidatively decompose **2**, also increased the yield of **3c** to 97% yield (run 13), but it was not useful for **1** having other functional groups. Similarly the methyl ether **1b** was converted to the corresponding **3b** in high yield, though it took a long time (run 14).§

Next, we examined this method using an olefinic compound as additive with the silyl ethers **1g–j** having allyl, (*tert*-butyldimethylsilyl)oxy, ester, and formyl groups and found that the corresponding dihydroquinones **3d–g** were obtained in good to excellent yields without decomposition of the functional groups (Scheme 1). The hydroxy group of **1k** also did not disturb the reaction and the product **3f** was obtained almost quantitatively.

In conclusion, we have succeeded in the unprecedented direct *ipso*-substitution of the sulfinyl group of *p*-sulfinylphenyl ethers to give oxygen functional groups on aromatic rings. Since this method offers very mild reaction conditions, simple operation, and formation of high to excellent yields of the dihydroquinones whose two hydroxy groups are protected by different protective groups, it should greatly expand the synthetic utility of aromatic sulfur compounds.[5,6] Extension of the present method to other substrates and natural product synthesis is in progress.

This study was performed using Special Coordination Funds of the Science and Technology Agency of the Japanese Government.

Received, 24th July 1995; Com. 5/04844C

Footnotes

† Recently we reported that treatment of *p*-sulfinylphenols **I**, not the ethers **1**, with trifluoroacetic anhydride caused a Pummerer-type rearrangement to give mixtures of *p*-quinones **II** and dihydroquinone derivatives **III**,[7] which is useful for the preparation of the *p*-quinones **II**, but is not suitable for the dihydroquinone derivatives **III**.

‡ We isolated the adduct, 1-phenyl-2-(phenylsulfanyl)ethyl acetate, in 87% yield after acyl exchange treatment§ (run 11).

§ Although about 10–20% of the trifluoroacetates **3** decomposed during purification by flash column chromatography on SiO_2 (see Table 1), we could obtain excellent yields of the corresponding acetates as follows: under a nitrogen atmosphere, to an ice-cooled solution of the *p*-sulfinylphenyl ether **1b** (97 mg, 0.25 mmol) and styrene (0.086 cm^3, 0.75 mmol) in $CHCl_3$ (7 cm^3) was added trifluoroacetic anhydride (0.35 cm^3, 2.5 mmol). The reaction mixture was stirred at 0 °C for 30 min and then at room temp. for 2 h. The reaction mixture was diluted with AcOEt (20 cm^3). The whole mixture was poured onto a mixture of ice (20 g) and saturated $NaHCO_3$ (20 cm^3). The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with water, dried with Na_2SO_4, and concentrated *in vacuo*. This crude product was stirred with saturated $NaHCO_3$ (4 drops) in MeOH (8 cm^3) at room temperature for 1 h, and AcOEt (16 cm^3) and saturated NH_4Cl (4 drops) were added. The mixture was dried with Na_2SO_4 and concentrated *in vacuo*. The residue was acetylated using acetic anhydride (0.24 cm^3, 2.5 mmol) and pyridine (0.24 cm^3, 3.0 mmol) in dry CH_2Cl_2 (4 cm^3) at room temp. overnight and purified by column chromatography on SiO_2 (hexane–AcOEt 20 : 1) to give 4-(*tert*-butyldimethylsilyl)oxy-2,3,5,6-tetramethylphenyl acetate (90 mg, 96%).

References

1 A recent example of *ipso*-substitution reaction of *p*-hydroxyphenyldiazonium salts: N. Yoneda, T. Fukuhara, T. Mizokami and A. Suzuki, *Chem. Lett.*, 1991, 459.
2 R. G. R. Bacon and S. C. Rennison, *J. Chem. Soc. (C)*, 1969, 312.
3 Baeyer–Villiger rearrangement of *p*-acylphenols has a similar effect on this transformation: recent example: L. Syper, *Synthesis*, 1989, 167.
4 Examples: K. Shishido, K. Goto, S. Miyoshi, Y. Takaishi and M. Shibuya, *J. Org. Chem.*, 1994, **59**, 406; A. V. Rama Rao, A. R. Mehendale and K. Bal Reddy, *Tetrahedron Lett.*, 1983, **24**, 1093.
5 Although the *ipso*-substitution of sulfinyl groups of the aromatic compounds into heterofunctional groups was reported, yields are high only for substrates having strongly electron-withdrawing nitro and sulfonyl groups on the aromatic ring: S. Oae and N. Furukawa, *Adv. Heterocycl. Chem.*, 1990, **48**, 1; R. R. King, *J. Org. Chem.*, 1978, **43**, 3784.
6 Recently, the two-step *ipso*-substitution of aromatic sulfinyl groups into phenoxy groups was reported: M. E. Jung, D. Jachiet, S. I. Khan and C. Kim, *Tetrahedron Lett.*, 1995, **36**, 361.
7 S. Akai, Y. Takeda, K. Iio, Y. Yoshida and Y. Kita, *J. Chem. Soc., Chem. Commun.*, 1995, 1013.
8 P. Hamel, Y. Girard and J. G. Atkinson, *J. Org. Chem.*, 1992, **57**, 2694.
9 T. Morishita, N. Furukawa and S. Oae, *Tetrahedron*, 1981, **37**, 3115.