# Regioselective Nucleophilic Addition of Methoxybenzene Derivatives to the β-Carbon of *p*-Benzoquinone Mono *O*,*S*-Acetal

Masato MATSUGI, Kenji MURATA, Gopinathan ANILKUMAR, Hisanori NAMBU, and Yasuyuki KITA*

*Graduate School of Pharmaceutical Sciences, Osaka University, 1–6, Yamada-oka, Suita, Osaka 565–0871, Japan.*
Received August 13, 2001; accepted September 21, 2001

**Regioselective nucleophilic addition of electron rich aromatics to the β-position of acetal carbon of *p*-benzoquinone mono *O*,*S*-acetal was achieved by modifying the acetal moiety.**

**Key words** quinone mono *O*,*S*-acetal; *SN*2′ reaction; C–C bond formation

We have already reported that various quinone mono *O*,*S*-acetals **1**,[1] which are intermediates in the aromatic Pummerer rearrangement,[2,3] could be isolated in high yields from 4-sulfinylphenols by the use of ethoxyvinyl esters.[4] It is very interesting to examine their reactivity, since they have many active sites in the molecule. So far, we have clarified that these compounds readily aromatize below room temperature by treatment with some nucleophiles such as allylsilanes in the presence of an acid catalyst *viz*. trimethylsilyl triflate (TMSOTf). Recently, we developed a very efficient sulfenylation method using quinone mono *O*,*S*-acetals for a variety of organic compounds such as silyl enol ethers, electron-rich aromatic compounds and heteroaromatic compounds (Chart 1, route a).[5,6] During these studies, we observed that some electron-rich methoxybenzenes caused an unexpected nucleophilic addition to the β-carbon atom of the acetal moiety in **1a** instead of sulfenylation reaction (Chart 1, route b).[6]

This conflict has now been resolved by the use of a highly active quinone mono *O*,*S*-acetal (**1b**) bearing a pentafluorophenylthio group for selective sulfenylation (Chart 2),[6,7] while the carbon–carbon bond formation products resulting from the nucleophilic addition to the β-carbon atom were avoided.

We have already clarified the steric structure of quinone mono *O*,*S*-acetals **1a**, **b** by PM3 calculation and X-ray crystallographic analysis (Fig. 1).[6]

Accordingly, the diene moiety of **1** is located between the aromatic part and the carbonyl part of the ester group. The stereo environment of the sulfur atom in **1** is generally less hindered than that of the β-carbon of the acetal part. Therefore most nucleophiles predominantly attack the sulfur atom rather than the β-carbon. We assumed that if the steric hindrance of the β-carbon could be removed, exclusive nucleophilic addition to the β-carbon would proceed smoothly. In this note, we wish to report a regioselective nucleophilic substitution of electron-rich aromatics to the β-position of acetal carbon (*SN*2′ reaction) in quinone mono *O*,*S*-acetals instead of sulfenylation reaction.

For the removal of steric hindrance at the β-carbon, the aromatic part and the carbonyl part must orient in a direction away from the dienone moiety. This was indeed achieved by synthesizing the quinone mono *O*,*S*-acetal (**4**) whose aromatic ring and ester part are directed away from the dienone moiety (Chart 3). It was obtained in quantitative yield from the corresponding sulfoxide **2** and ethoxyvinyl ester **3**.[4]

As expected, the reaction of **4** with various electron-rich aromatic compounds (**5**) gave exclusively the nucleophilic addition product **6** in good yields (Table 1). It is noteworthy that **5c** and **5d** when reacted with **1a** gave only the sulfenylation product,[5,6] while they reacted only at the β-position of acetal carbon with the cyclic *O*,S-acetal derivative **4**. The sulfenylation product was not observed (Table 1, runs 3, 4).

Thus we could achieve selective nucleophilic addition to the β-position of acetal carbon (*SN*2′ reaction) by modification of the acetal moiety. The orientation of the acetal moiety plays an important role in the regioselective nucleophilic addition. Thus by fine tuning the acetal moiety, the formation of the C–C bond or sulfenylation can be achieved at will.

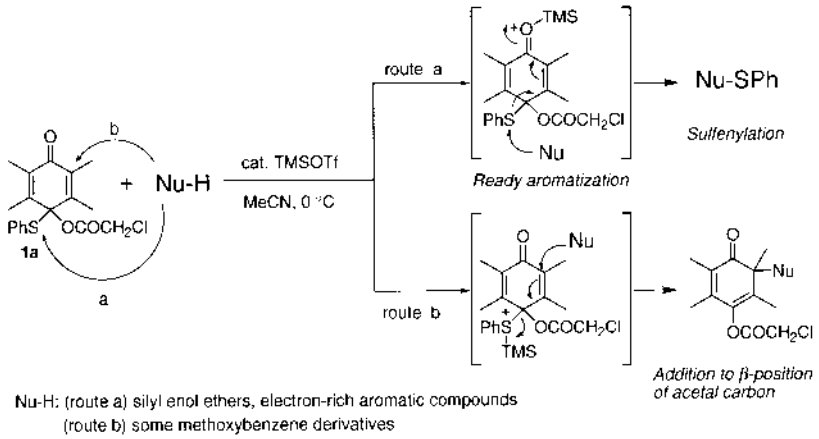



Chart 1. Sulfenylation or Nucleophilic Addition to β-Position of Acetal Carbon of **1a**

* To whom correspondence should be addressed. e-mail: kita@phs.osaka-u.ac.jp

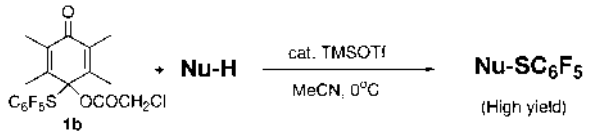



Chart 2. Selective Sulfenylation Reaction of **1b**

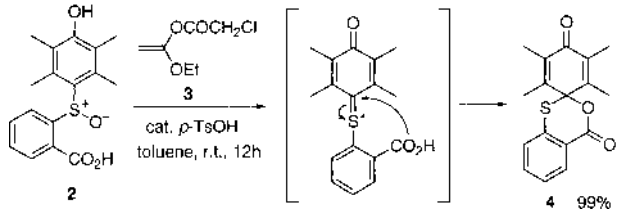



Chart 3. Preparation of Quinone Mono-*O*,*S*-acetal **4**

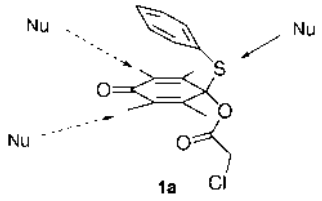
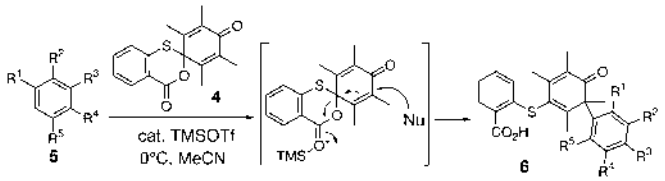



Fig. 1. Steric Structure of **1a** by PM3 Calculation

Table 1. The Nucleophilic Addition to $\beta$-Position of Acetal Carbon in **4**




| Run | Substrate (**5**) | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | **6** | Yield (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | **5a** | OMe | H | OMe | H | H | **6a** | 99 |
| 2 | **5b** | OMe | OMe | OMe | H | H | **6b** | 89 |
| 3 | **5c** | OMe | H | OMe | H | OMe | **6c** | 73 |
| 4 | **5d** | OMe | H | Me | H | OMe | **6d** | 53 |

## Experimental

Melting points are uncorrected. Infrared (IR) absorption spectra were recorded as a KBr pellet. $^1$H-NMR spectra were measured in $CDCl_3$ on 270, 300, or 500 MHz spectrometers with tetramethylsilane as the internal standard. E. Merck Silica gel 60 (70—230 mesh ASTM) and Fuji Silysia Chemical Silica gel BW-300 were used for column chromatography and flash column chromatography. The aromatic compounds **5** are commercially available and they were used without further purification.

**2,3,5,6-Tetramethyl-4′-thiaspiro[cyclohexane-4,3′-isochroman]-2,5-dien-1,1′-dione (4)** To a stirred suspension of 2-((4-hydroxy-2,3,5,6-tetramethylphenyl)sulfinyl)benzoic acid **2**[8] (420 mg, 1.3 mmol) and 1-ethoxyvinyl 2-chloroacetate **3**[6] (1.0 g, 6.6 mmol) in dry toluene (5 ml), was added *p*-toluenesulfonic acid (TsOH) (11 mg, 0.07 mmol) at room temperature (r.t.) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 12 h and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluent: hexane/AcOEt, 5 : 1) to give **4** (395 mg, 99% yield) as white crystals; mp 121—122 °C ($Et_2O$–hexane). IR cm$^{-1}$: 1732, 1646. $^1$H-NMR $\delta$: 1.93 (6H, s), 2.07 (6H, s), 7.19 (1H, d, $J$=8.0 Hz), 7.26 (1H, t, $J$=8.0 Hz), 7.50 (1H, t, $J$=8.0 Hz), 8.25 (1H, d, $J$=8.0 Hz). *Anal*. Calcd for $C_{17}H_{16}O_3S$: C, 67.98; H, 5.37. Found: C, 67.98; H, 5.43.

**General Procedure for the Reaction of 4 with 5** To a stirred solution of **4** (150 mg, 0.50 mmol) and **5a** (138 mg, 1.00 mmol) in acetonitrile (20 ml), was added TMSOTf (22 mg, 0.10 mmol) at 0 °C under nitrogen atmosphere. After 10 min, the reaction mixture was quenched with water, and extracted with AcOEt. The organic layer was washed with brine, dried with sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: hexane/AcOEt, 1 : 1) to give **6a** (219 mg, 99% yield).

2-(5-(2,4-Dimethoxyphenyl)-2,3,5,6-tetramethyl-4-oxocyclohexa-21,2-dienylthio)benzoic Acid (**6a**): 99%; white crystals; mp 213 °C (AcOEt–hexane). IR cm$^{-1}$: 2950, 1715, 1651. $^1$H-NMR $\delta$: 1.55 (3H, s), 1.80 (3H, s), 1.98 (3H, s), 2.15 (3H, s), 3.66 (3H, s), 3.78 (3H, s), 6.40 (1H, d, $J$=2.5 Hz), 6.51 (1H, dd, $J$=8.0, 2.5 Hz), 7.15—7.37 (4H, m), 8.13 (1H, d, $J$=8.0 Hz). High resolution (HR)-MS Calcd for $C_{25}H_{26}O_5S$: 438.1501. Found: 438.1500. *Anal*. Calcd for $C_{25}H_{26}O_5S$: C, 68.47; H, 5.98. Found: C, 68.16; H, 6.08.

2-(5-(2,3,4-Trimethoxyphenyl)-2,3,5,6-tetramethyl-4-oxocyclohexa-1,2-dienylthio)benzoic Acid (**6b**): 89%; colorless oil. IR cm$^{-1}$: 2946, 1713, 1646. $^1$H-NMR $\delta$: 1.54 (3H, s), 1.77 (3H, s), 1.99 (3H, s), 2.19 (3H, s), 3.67 (3H, s), 3.75 (3H, s), 3.85 (3H, s), 6.90 (1H, d, $J$=9.0 Hz), 7.16 (1H, d, $J$=9.0 Hz), 7.19 (1H, t, $J$=7.5 Hz), 7.33—7.42 (2H, m), 8.03 (1H, d, $J$=7.5 Hz). HR-MS Calcd for $C_{26}H_{28}O_6S$: 468.1606. Found: 468.1601.

2-(5-(2,4,6-Trimethoxyphenyl)-2,3,5,6-tetramethyl-4-oxocyclohexa-1,2-dienylthio)benzoic Acid (**6c**): 73%; white crystals; mp 273—274 °C (AcOEt–hexane). IR cm$^{-1}$: 2960, 1715, 1649. $^1$H-NMR $\delta$: 1.69 (3H, s), 1.97 (3H, s), 2.01 (3H, s), 2.14 (3H, s), 3.71 (3H, s), 3.79 (3H, s), 6.13 (2H, s), 7.14—7.30 (3H, m), 8.13 (1H, d, $J$=7.0 Hz). HR-MS Calcd for $C_{26}H_{28}O_6S$: 468.1606. Found: 468.1611.

2-(5-(4-Methyl-2,6-dimethoxyphenyl)-2,3,5,6-tetramethyl-4-oxocyclohexa-1,2-dienylthio)benzoic Acid (**6d**): 53%; white crystals; mp 250 °C (AcOEt–hexane). IR cm$^{-1}$: 2960, 1715, 1654. $^1$H-NMR $\delta$: 1.70 (3H, s), 1.97 (3H, s), 1.99 (3H, s), 2.16 (3H, s), 2.32 (3H, s), 3.72 (6H, s), 6.41 (2H, s), 7.14—7.33 (3H, m), 8.06 (1H, d, $J$=8.0 Hz). HR-MS Calcd for $C_{26}H_{28}O_5S$: 452.1657. Found: 452.1644. *Anal*. Calcd for $C_{26}H_{28}O_5S$: C, 69.00; H, 6.24. Found: C, 68.74; H, 6.24.

## References and Notes


1) Kita Y., Takeda Y., Matsugi M., Iio K., Gotanda K., Murata K., Akai S., *Angew. Chem. Int. Ed. Engl*., **36**, 1529—1531 (1997).
2) *a*) Akai S., Takeda Y., Iio K., Takahashi K., Fukuda N., Kita Y., *J. Org. Chem*., **62**, 5526—5536 (1997); *b*) Akai S., Takeda Y., Iio K., Yoshida Y., Kita Y., *J. Chem. Soc., Chem. Commun*., **1995**, 1013—1014; *c*) Akai S., Iio K., Takeda Y., Ueno H., Yokogawa K., Kita Y., *ibid*., **1995**, 2319—2320; *d*) Kita Y., Takeda Y., Iio K., Yokogawa K., Takahashi K., Akai S., *Tetrahedron Lett*., **37**, 7545—7548 (1996).
3) *a*) Jung M. E., Jachiet D., Khan S. I., Kim C., *Tetrahedron Lett*., **36**, 361—364 (1995); *b*) Jung M. E., Kim C., Bussche L., *J. Org. Chem*., **59**, 3248—3249 (1994); *c*) King R. R., *ibid*., **43**, 3784—3785 (1978).
4) *a*) Kita Y., Maeda H., Omori K., Okuno T., Tamura Y., *J. Chem. Soc., Perkin Trans. 1*, **1993**, 2999—3005; *b*) Kita Y., Shibata N., Kawano N., Fukui S., Fujimori C., *Tetrahedron Lett*., **38**, 3575—3576 (1994); *c*) Shibata N., Matsugi M., Kawano N., Fukui S., Fujimori C., Gotanda K., Murata K., Kita Y., *Tetrahedron Asymmetry*, **8**, 303—310 (1997).
5) Matsugi M., Gotanda K., Murata K., Kita Y., *Chem. Commun*., **1997**, 1387—1388.
6) Matsugi M., Murata K., Gotanda K., Nambu H., Anilkumar G., Matsumoto K., Kita Y., *J. Org. Chem*., **66**, 2434—2441 (2001).
7) Matsugi M., Murata K., Nambu H., Kita Y., *Tetrahedron Lett*., **42**, 1077—1080 (2001).
8) This compound was prepared by a reported procedure; Drabowicz J., Bujnicki B., Dudzinski B., *Synth. Commun*., **24**, 1207—1213 (1994).