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ARTICLE

Synthesis and properties of fluorous benzoquinones and their application in deprotection of silyl ethers

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1,4-Benzoquinone derivatives bearing trifluoromethyl, perfluorobutyl and perfluorohexyl groups were prepared and employed in the deprotection of silyl ethers. The fluorous character of these compounds was examined by measuring the partition coefficient between the fluorous and organic solvents. The benzoquinone derivatives showed significant fluorous character, indicating that they can be recovered from the reaction mixtures using a fluorous/organic biphasic system. The oxidising ability of the fluorous benzoquinones was estimated by cyclic voltammetry and these compounds were found to be strong oxidisers. The fluorous benzoquinones were utilised in the oxidative desilylation of silyl ethers to afford the deprotected alcohols in high yield. In addition, the reduced fluorous benzoquinones were recovered from the reaction mixtures in good yields using a fluorous/organic biphasic system.

Introduction

The fluorous biphasic system (FBS)[1] has been developed in organic chemistry as an environmentally benign recycling process. This concept is based on the physical phenomena that highly fluorinated compounds (fluorous materials) are immiscible in organic solvents and form another phase (fluorous phase). They are then easily separable from organic compounds by extraction using perfluorinated solvents such as FC-72 (perfluorohexanes) or by liquid/solid extraction using fluorous silica gel.[2] Work in our laboratories[3] in this field has been directed towards the design, synthesis and application of novel environmentally benign fluorous reaction media,[4] as well as effective fluorous reagents and catalysts. To this end, we previously reported fluorinated versions of diethyl ether[3a-3c] and DMF[3d] that function as easily recyclable reaction media. In addition, we prepared chiral and achiral lithium diisopropylamide[3e] derivatives bearing a perfluoroalkyl chain, which produced lithium enolates in excellent chemical and optical yields comparable with the parent non-fluorous lithium amides. After the reaction, the fluorous lithium amides were recovered as fluorous amines by liquid-liquid extraction or chromatography. Perfluoroalkyl groups reveal strong electron-withdrawing effects in nature and many studies[5] in fluorous chemistry utilise this property.

It is well known that 1,4-benzoquinone is easily reduced to hydroquinone, and 1,4-benzoquinones bearing electron-withdrawing groups, for example 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 1) and 2,3,5,6-tetrachloro-1,4-benzoquinone (chloranil, 2) have been used in many organic reactions[6,7] as oxidising or dehydrogenating agents. However, DDQ is toxic,[8] while the oxidising ability of chloranil is generally modest. In addition, a stoichiometric amount of the oxidiser is usually required for the reactions. These drawbacks of benzoquinone derivatives do not fit with the principles of green chemistry and prompted us to develop reusable benzoquinone derivatives. Herein, we report the preparation of 1,4-benzoquinones bearing perfluoroalkyl chains 3. The fluorous character and electronic properties of benzoquinones 3a-c were examined and it was found that the benzoquinones would work as strongly oxidising fluorous reagents; benzoquinones 3 were then applied to catalytic desilylation reaction of silyl ethers.[9]


1   2   3a: Rf = CF$_3$, X = H
                  3b: Rf = C$_4$F$_9$, X = H
                  3c: Rf = C$_6$F$_{13}$, X = Cl
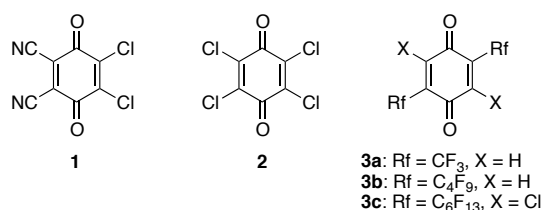
## Results and discussion

Preparation of fluorous benzoquinone

Fluorous benzoquinones 3a-c were synthesised according to the procedure outlined in Scheme 1.[10] Thus, 2,5-diiodo-1,4-dimethoxybenzene (5) was prepared from 1,4-dimethoxybenzene (4), iodine and iodic acid[11,12] in 76% yield.

The diiodide was then converted to perfluoroalkyl compounds using copper catalysis. Treatment of diiodide **5** with sodium trifluoroacetate and copper iodide afforded 1,4-dimethoxy-2,5-bis(trifluoromethyl)benzene (**6a**)[10] in 51% yield, while reacting **5** with perfluorobutyl iodide in the presence of copper and 2,2′-bipyridine[13] afforded 1,4-dimethoxy-2,5-bis(perfluorobutyl)benzene (**6b**) in 82% yield. Deprotection of the dimethoxy groups using sodium ethanethiolate[14] and boron tribromide[10] afforded hydroquinone derivative **7**.[15] Hydroquinone **7** was oxidised to benzoquinone **3** using chromium oxide[10] (Rf = CF$_3$) or silver oxide[16] (Rf = C$_4$F$_9$) in 77% and 73% yield, respectively. Fluorous benzoquinones **3a** and **3b** were yellow columns and brown needles with melting point of 110 °C (sublimation) and 107-109 °C, respectively.
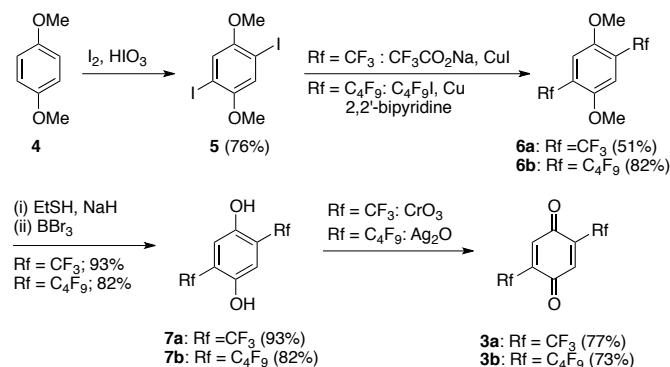
Scheme 1 Synthetic pathway of fluorous benzoquinone **3a** and **3b**.

Chlorine-substituted fluorous benzoquinone **3c** was also synthesised as shown in Scheme 2. Perfluorohexyl iodide was treated with diiodobenzene **5** in the presence of copper and 2,2′-bipyridine to afford 2,5-bis(perfluorohexyl)-1,4-dimethoxybenzene (**8**) in 95% yield. Compound **8** was chlorinated using sulphuryl chloride and disulphur dichloride in the presence of aluminium chloride.[17] Demethylation and oxidation proceeded simultaneously during the chlorination, affording fluorous benzoquinone **3c** in 86% yield. Compound **3c** was orange columns with melting point of 78.5-80.0 °C.
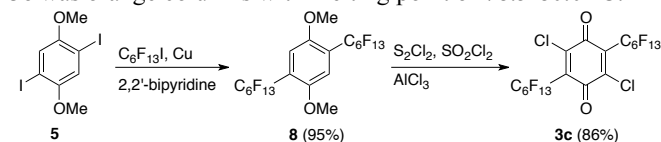
Scheme 2 Synthetic pathway of fluorous benzoquinone **3c**.

Partition coefficient of fluorous benzoquinone

The approximate partition coefficients of fluorous benzoquinones **3a-c** were measured at 25 °C according to the procedure reported by Curran group.[18] The results are summarised in Fig. 1. Most of trifluoromethyl analogue **3a** is distributed in the organic solvents, whereas perfluorobutyl and perfluorohexyl analogues **3b** and **3c** are preferentially distributed in the FC-72 (perfluorohexanes) phase. Chloroform was found to be the best solvent to recover **3b** from the reaction mixture using the biphasic system, while all solvents (except THF) can be used to recover **3c** efficiently (Fig. 1).
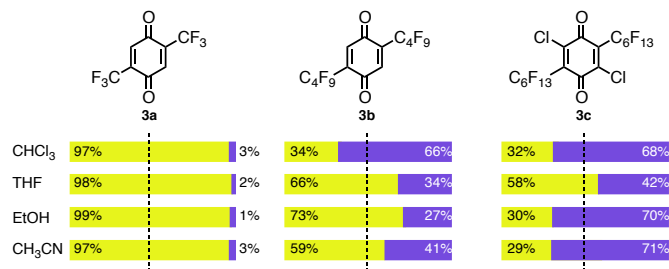
Fig. 1 Partition coefficient of fluorous benzoquinones (yellow: organic phase; purple: fluorous phase).

Cyclic voltammogram of fluorous benzoquinone

To assess the oxidising ability of the prepared fluorous benzoquinones, their cyclic voltammometry were measured in acetonitrile solution. The voltammogram of fluorous benzoquinone **3b** is illustrated in Fig. 2, voltammograms of compound **3a** and **3c** are displayed in ESI.
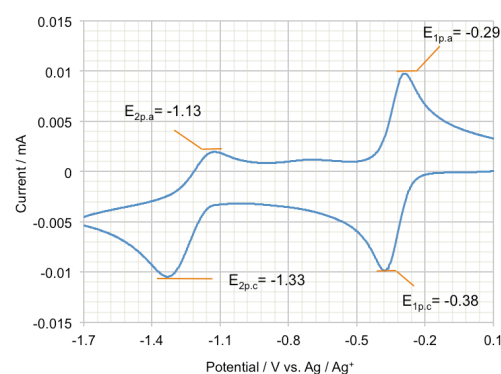
Fig. 2 Cyclic voltammogram of fluorous benzoquinone **3b**.

Inspection of the voltammogram of fluorous benzoquinones revealed two reversible redox steps (Fig. 2). The first and second reduction peaks were found at -0.38 V and -1.33 V (vs. Ag/Ag$^+$), respectively, while first and second oxidation peaks were observed at -0.29 V and -1.13 V, respectively. The first reduction peaks ($E_{1p.c}$) of the fluorous benzoquinones were chosen to estimate their oxidising ability (Fig. 3). $E_{1p.c}$ of xyloquinone, chloranil and DDQ were also measured and included for comparison.
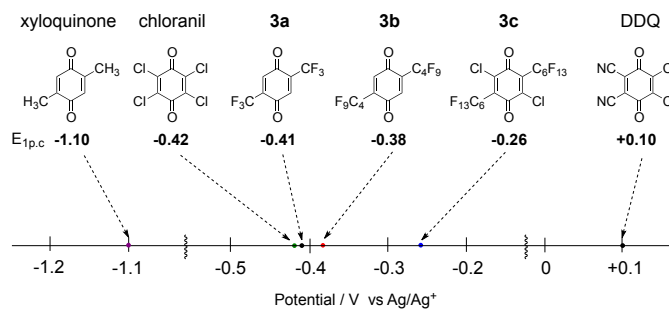
Fig. 3 First reduction peak of benzoquinone derivatives.

As shown in Fig. 3, fluorous benzoquinone **3a** and **3b** showed similar oxidising ability to chloranil and much larger to that of xyloquinone. In addition, **3c** was a stronger oxidizing agent than **3a**, **3b** and chloranil. The order of oxidising ability of the benzoquinones is: xyloquinone << chloranil ~ **3a** < **3b** < **3c** <<

DDQ, indicating that fluorous benzoquinones **3a-c** would work as strong oxidising agents. To test fluorous benzoquinones **3a-c** as alternative oxidising agents to DDQ, the fluorous compounds were tested in oxidation reactions.
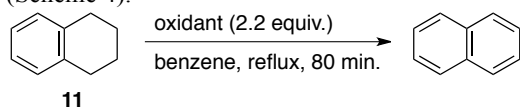
Application of fluorous benzoquinone in organic synthesis

Cinnamyl alcohol (**9**) was successfully converted to cinnamaldehyde (**10**)[19] using 1.5 equivalent of fluorous benzoquinone **3b** (Scheme 3). This result shows that the product yield and the reaction time using **3b** are comparable to those conducted using chloranil and DDQ. After fluorous/organic biphasic workup using FC-72 and chloroform, **3b** was recovered in 98% yield from the fluorous phase as the corresponding hydroquinone derivative.
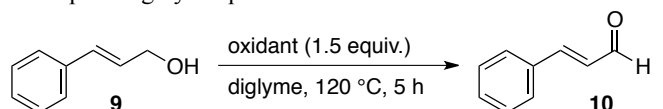
oxidant	Yield (%)
3b	80%
DDQ	77%
chloranil	86%

**Scheme 3** Oxidation of cinnamyl alcohol.

DDQ is known to work as a dehydrogenating reagent.[6a] Thus, aromatisation of tetralin (**11**)[20] was attempted using fluorous benzoquinone **3b**. However, the reaction did not proceed as expected and the starting material was recovered quantitatively (Scheme 4).

oxidant	Yield (%)
3b	0%
DDQ	62%
chloranil	0%

Scheme 4 Aromatisation of tetralin.

Next, desilylation of silyl ethers using catalytic amounts of fluorous benzoquinone **3b** was investigated. In the presence of **3b**, the desilylation[9] of *tert*-butyldimethylsilyl ether of dodecanol (**12**) proceeded smoothly to afford the corresponding alcohol **13** in 96% yield, which was vastly superior to the yield achieved when DDQ was used (Scheme 5). In addition, **3b** was recovered in 92% yield as the corresponding hydroquinone **7b** by fluorous/organic biphasic workup using FC-72 and chloroform.
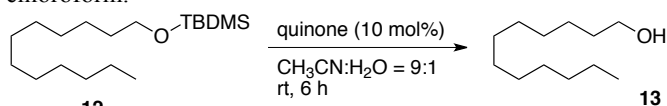
quinone	Yield (%)
3b	96%
DDQ	65%
chloranil	0%

Scheme 5 Deprotection of TBDMS ether of dodecanol.

The scope and limitation of this desilylation reaction were then investigated. Deprotection of various silyl ethers using catalytic amounts of fluorous benzoquinones **3b** and **3c** in acetonitrile/water (9:1) were carried out; the results shown in Tables 1 and 2, respectively. For reference, results for chloranil and DDQ are summarized in Tables S1 and S2 in ESI, respectively.
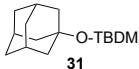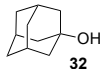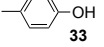
Table 1 Deprotection of silyl ethers using fluorous benzoquinone **3b**[a]

Entry	Substrate[b]	Product	Temp.	Yield[c](recovery of **3b**)[d]
1	**12**	**13**	rt	96%(88%)
2	**14**	**15**	rt	90%(83%)
3	**16**	—	rt / 50 °C	nr / nr
4	**17**	**18**	rt	92%(90%)
5	**19**	**20**	rt	78%(86%)
6	**21**	—	rt / 50 °C	nr / nr
7	**22**	**13**	rt / 50 °C	nr / 97%(61%)
8	**23**	—	rt / 50 °C	nr / nr
9	**24**	—	rt / 50 °C	nr / nr
10	**25**	**26**	rt	76%
11	**27**	**28**	rt	73%(79%)
12	**29**	**30**	rt	71%(88%)

[a] Reaction conditions: **3b** (10 mol%), $CH_3CN:H_2O$ = 9:1, 6 h. [b] TBDMS: *tert*-butyldimethylsilyl; TIPS: triisopropylsilyl; TBDPS: *tert*-butyldiphenylsilyl; PMB: *p*-methoxybenzyl. [c] Isolated yield. [d] **3b** was recovered as hydroquinone **7b**.

As shown in Table 1, *tert*-butyldimethylsilyl (TBDMS)-protected primary and secondary alcohols were cleaved using fluorous benzoquinone **3b** in high yield at room temperature, while TBDMS-protected tertiary alcohol and phenol were stable under these conditions (entries 1-6). The triisopropylsilyl (TIPS) group could not be deprotected at room temperature; however, it was deprotected it was at 50 °C (entry 7). In comparison, *tert*-butyldiphenylsilyl (TBDPS) and *p*-methoxybenzyl (PMB) groups were stable at ambient and elevated temperatures (entries 8, 9). It is worth noting that selective deprotection of TBDMS group in the presence of TIPS and PMB groups was achieved using **3b** (entries 10-12). After the reactions, **3b** was recovered as hydroquinone **7b** in high yields using the fluorous/organic biphasic workup. Hydroquinone **7b** was converted to **3b** using Ag_2O (75% yield) and reused in the second reaction.

Table 2 Deprotection of silyl ethers with fluorous benzoquinone **3c**

Entry	Substrate	Product	Temp.	Yield (recovery of **3c**)[a]
1	O-TBDMS **31**	OH **32**	r.t. 50 °C	nr 96%
2	**21**	OH **33**	r.t	90%
3	**22**	**13**	r.t	86%(73%)
4	**23**	**13**	r.t. 50 °C	nr 84%
5	**24**	——	r.t. 50 °C	nr nr

[a] Catalyst **3c** was recovered as hydroquinone.

Results revealed that **3c** was more efficient in cleaving the silyl protecting groups compared to **3b** (Table 2). For example, the TIPS group was cleaved using **3c** at room temperature (entry 3). The TBDMS group of phenol was also deprotected under the same conditions (entry 2). TBDMS-protected tertiary alcohol and TBDPS-protected primary alcohol were not cleaved using **3c** at room temperature, but were cleaved at 50 °C (entries 1 and 4) while PMB was still stable under elevated temperatures (entry 5). In addition, compound **3c** could be recovered using the fluorous/organic biphasic workup as the corresponding hydroquinone and was successfully converted to **3c** using the same procedure as for hydroquinone **7b**.

As can be seen in Tables S1 and S2 in ESI, chloranil did not cleave the TBDMS group at room temperature, while DDQ deprotected TIPS, PMB and TBDMS even at room temperature. This suggests that fluorous benzoquinones **3b** and **3c** are superior to chloranil and DDQ in achieving selective deprotection of silyl groups. It should be noted that using fluorous benzoquinone **3a** under the same reaction conditions as those for **3b**, deprotection of TBDMS group of dodecyl TBDMS ether (**12**) proceeded smoothly to afford decanol (**13**) in 79% yield. However, recovery of **3a** using fluorous/organic biphasic workup was unsuccessful because of the less fluorous character of **3a**.

Conclusions

The results obtained suggest that fluorous benzoquinones **3b** and **3c** are strong oxidising agents, which can be used in organic synthesis. The oxidising ability of **3b** and **3c** lies between that of chloranil and DDQ, and selective deprotection of silyl groups was achieved using the synthesised fluorous benzoquinones. The fluorous benzoquinones **3b** and **3c** were subsequently recovered as their corresponding hydroquinones using a fluorous/organic biphasic workup. In addition, the hydroquinones were converted to fluorous benzoquinones **3b** and **3c** with Ag$_2$O and reused successfully.

Experimental

1,4-Bis(perfluorobutyl)-2,5-dimethoxybenzene (6b)

A mixture of **5** (1.01 g, 2.59 mmol), perfluorobutyl iodide (3.50 g, 7.70 mmol), copper powder (976 mg, 15.4 mmol), 2,2′-bipyridine (80 mg, 0.51 mmol) and DMSO (5 mL) was heated at 120 °C under N$_2$ for 2 days. After cooling to room temperature, water was added. The mixture was filtered through a pad of Celite and the pad was washed with diethyl ether. The aqueous layer was separated and extracted with diethyl ether. The combined organic layer was washed with brine, dried over sodium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: chloroform) to yield **6b** (1.37 g, 92%) as lemon-yellow crystals. Mp 63.0-64.0 °C; ν_{max}/cm^{-1} (KBr) 2976, 2952, 2868, 2843, 1520, 1406, 1352, 1248, 1131, 836, 741; ^{1}H NMR (500 MHz, CDCl$_3$) δ_H 3.86 (6H, s, OCH$_3$), 7.14 (2H, s, ArH); ^{13}C NMR (126 MHz, CDCl$_3$) δ_C 56.8, 113.8, 110.0-118.0, 121.5, 152.0; LRMS (EI) 574(M$^+$, 100%), 405(64), 188(93). HRMS (EI) (Found: [M]$^+$ 574.0232. C$_{16}$H$_8$F$_{18}$O$_2$$^+$ requires 574.0237).

2,5-bis(perfluorobutyl)-1,4-hydroquinone (7b)

A mixture of ethanethiol (2.61 g, 42.1 mmol), sodium hydride, 60% oil dispersion (1.69 g, 42.1 mmol) and DMF (25 mL) was stirred at room temperature under N$_2$ for 1 h. Then, **6b** (4.03 g, 7.02 mmol) dissolved in DMF (70 mL) was added to the reaction mixture and heated to 70 °C for one day. After cooling to room temperature, 2 M HCl was added until the pH was neutral. The aqueous layer was then separated and extracted with diethyl ether. The combined organic layer was washed with brine, dried over sodium sulphate and concentrated under reduced pressure to afford crude solid (4.55 g). A mixture of the crude product (4.55 g) and dichloromethane (120 mL) was stirred under N$_2$ and cooled to -15 °C using an ice-salt bath. Boron tribromide (7.0 mL, 74 mmol) was added dropwise and the mixture was then warmed slowly to room temperature. After stirring for 2 days, the mixture was quenched by adding water dropwise at 0 °C. The aqueous layer was separated and extracted with diethyl ether. The combined organic layer was washed with brine, dried over sodium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/diethyl ether=3/1) to yield **7b** (3.21 g, 84%) as light brown crystals. Mp 129-131 °C; ν_{max}/cm^{-1} (KBr) 3467, 1427, 1353, 1236, 1204, 1131, 796, 741; ^{1}H NMR (500 MHz, CDCl$_3$) δ_H 7.23 (2H, s, ArH), 9.19 (2H, s, OH); ^{13}C NMR (126 MHz, CDCl$_3$) δ_C 107.9-119.8, 118.6, 120.3, 150.0; LRMS (EI) 546(M$^+$, 61%), 377(100), 208(76); HRMS (EI) (Found: [M]$^+$ 545.9927. C$_{14}$H$_4$F$_{18}$O$_2$$^+$ requires 545.9924).

2,5-Bis(perfluorobutyl)-1,4-benzoquinone (3b)

A mixture of **7b** (3.21 g, 5.88 mmol), silver oxide (5.45 g, 23.5 mmol) and sodium sulphate (426 mg, 3.00 mmol) in diethyl ether (50 mL) was heated under reflux for 24 h. After cooling to room temperature, insoluble salt precipitate was filtered off. The filtrate was then concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (eluent: hexane/toluene =3/1) to yield **3b** (3.17 g, 73%) as brown crystals. Mp 107-109 °C; ν_{max}/cm^{-1} (KBr) 1674, 1363, 1261, 1236, 1205, 1138, 1082, 940, 747, 498; ^{1}H NMR (500 MHz, CDCl$_3$) δ_H 7.22 (s); ^{13}C NMR (100 MHz, CDCl$_3$) δ_C 110.0-118.7, 135.2, 139.2, 179.3; LRMS (EI) 544(M$^+$, 28%), 525(36), 375(68), 347(100). HRMS (EI) (Found: [M]$^+$ 543.9761. C$_{14}$H$_2$F$_{18}$O$_2$$^+$ requires 543.9767).

1,4-Bis(perfluorohexyl)-2,5-dimethoxybenzene (8)

A mixture of **5** (1.95 g, 5.00 mmol), perfluorohexyl iodide (6.69 g, 15.0 mmol), copper powder (1.91 g, 30.0 mmol) and 2,2′-bipyridine (156 mg, 1.00 mmol) in DMSO (25 mL) was heated to 110 °C under N$_2$ for 2 days. After cooling to room temperature, water was added. The mixture was then filtered

through a pad of Celite and the pad was washed with diethyl ether. The aqueous layer was separated and extracted with diethyl ether. The combined organic layer was washed with brine, dried over sodium sulphate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: chloroform) to yield **8** (3.55 g, 91%) as white crystals. Mp 66.0-67.5 °C; ν_{max}/cm^{-1} (KBr) 2948, 2869, 1514, 1469, 1398, 1273, 1202, 1174, 1122, 1047, 744, 719; ^1H NMR (500 MHz, CDCl$_3$) δ_H 3.86 (6H, s, OCH$_3$), 7.14 (2H, s, ArH); ^{13}C NMR (126 MHz, CDCl$_3$) δ_C 56.8, 114.0, 108.4-118.4, 121.5-121.9, 152.1; LRMS (EI) 774(M$^+$,100%), 755(17), 505(39), 188(59); HRMS (EI) (Found: [M$^+$] 774.0113. C$_{20}$H$_8$F$_{26}$O$_2^+$ requires 774.0109).

2,5-Bis(perfluorohexyl)-3,6-dichloro-1,4-benzoquinone (3c)

A mixture of aluminium trichloride (255 mg, 2.00 mmol) and sulphuryl chloride (60 mL) was heated under reflux. Then, **8** (3.10 g, 4.00 mmol) dissolved in sulphuryl chloride (20 mL) and disulphur dichloride (1.2 mL, 15.0 mmol) was added dropwise. After stirring for 24 h, the mixture was quenched with water. The aqueous layer was separated and extracted with diethyl ether. The combined organic layers were washed with brine, dried over sodium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: chloroform) to yield **3c** (2.65 g, 86%) as orange crystals. Mp 78.5-80.0 °C; ν_{max}/cm^{-1} (KBr) 1694, 1586, 1235, 1219, 1174, 1145, 1126, 1095, 743, 725; ^{13}C NMR (126 MHz, CDCl$_3$) δ_C 108.0-119.0, 131.5, 149.8, 171.2; LRMS (EI) 814 (1.4%), 812(M$^+$, 1.7), 795(6), 793(9), 774(11), 565(16), 517(82), 515(100), 286(22), 261(45), 259(46), 246(33), 233(37), 231(38); HRMS (EI); (Found: [M]$^+$ 811.8865. C$_{18}^{35}$Cl$_2$F$_{26}$O$_2^+$ requires 811.8860).

Deprotection of silyl ether using benzoquinone 3b; Typical procedure

A mixture of silyl ether (1.00 mmol), **3b** (54 mg, 0.10 mmol) and acetonitrile (4.5 mL) in water (0.5 mL) was stirred for 6 h at room temperature. Diethyl ether was added to the reaction mixture and the aqueous layer was separated off. The organic layer was dried over sodium sulphate and evaporated under reduced pressure. The residue was diluted with chloroform, and perfluorohexane (FC-72) was then added to the solution. The FC-72 layer was separated, and the chloroform layer was extracted with FC-72 three times. The combined FC-72 layer was evaporated under reduced pressure to yield 2,5-bis(perfluorobutyl)-1,4-hydroquinone (**7b**), while the chloroform layer was evaporated under reduced pressure to afford the unprotected alcohol.

Acknowledgements

Notes and references

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