Pergamon

Tetrahedron Letters 42 (2001) 1077–1080

TETRAHEDRON LETTERS

An efficient sulfenylation of aromatics using highly active quinone mono *O,S*-acetal bearing a pentafluorophenylthio group

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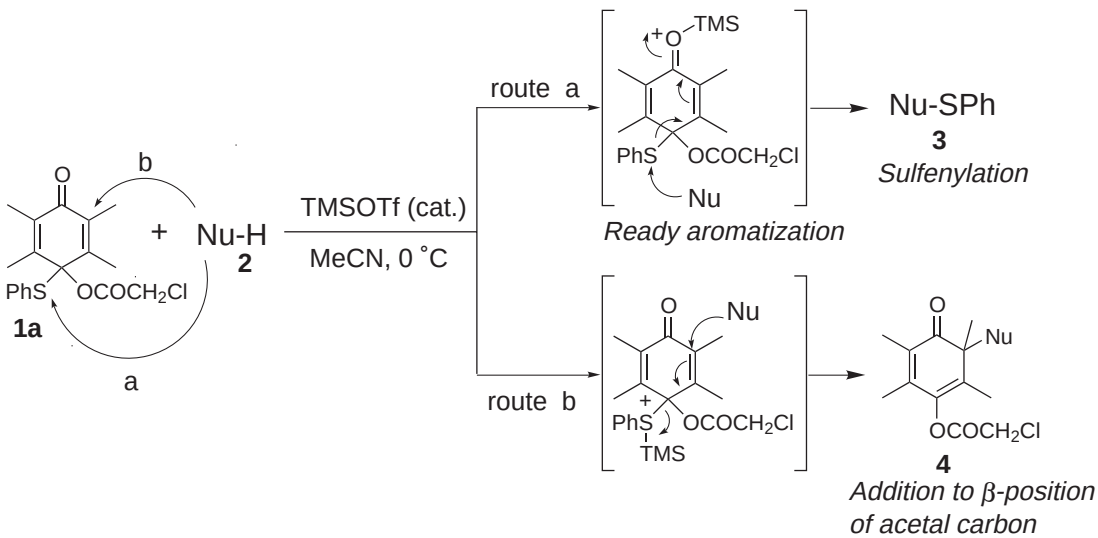
Received 10 October 2000; revised 9 November 2000; accepted 24 November 2000

Abstract—A facile sulfenylation of various aromatic nuclei was achieved by use of the novel sulfenylation reagent, the quinone mono *O,S*-acetal bearing a pentafluorophenylthio group. This reagent functions below 0°C in the presence of a catalytic amount of TMSOTf. © 2001 Elsevier Science Ltd. All rights reserved.

Sulfur functionalities have great versatility as footholds for the construction of various target molecules,[1] making the direct sulfenylation of organic compounds an important subject in synthetic organic chemistry.[2] Many methods for sulfenylation have been studied to date[3] that include (i) direct electrophilic substitution with sulfur-containing electrophiles such as sulfenyl chloride, sulfenamides, thiosulfonates, and disulfides, (ii) nucleophilic substitution of aryl halides with metal mercaptides, (iii) nucleophilic replacement via diazonium intermediates, and (iv) coupling reaction via radical cation. These approaches, however, often require basic, acidic or heating conditions during the sulfenylation process.[3g] We have recently reported a novel and efficient sulfenylation reagent (**1a**) having quinone mono *O,S*-acetal moiety under mild conditions.[4] The reagent aromatizes below room temperature during the reaction with various nucleophiles (**2**) leading to the corresponding sulfenylated products (**3**) in high yields. Although **1a** is useful for the sulfenylation of standard



Scheme 1. Sulfenylation or nucleophilic addition to β-position of acetal carbon.

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PII: S0040-4039(00)02186-9

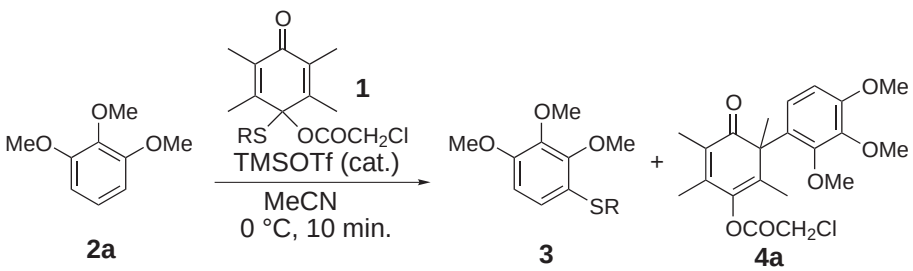
organic compounds involving silyl enol ethers and electron-rich aromatic compounds (Scheme 1, route a),[4b] unexpected desulfenylation products (**4**) were observed in some electron-rich aromatic compounds such as di- and trimethoxybenzenes (**2a–c**) in fair yields without the formation of the expected sulfenylation products. These products (**4**) may be formed by the addition of **2** to the β-position of the acetal carbon in **1a** followed by elimination of the phenylthio group (Scheme 1, route b).

We therefore looked into the development of a novel method of selective sulfenylation, because sulfur functionalities on aromatic ring as well as in aliphatic compounds are very useful for synthetic transformations. For example, a sulfur functional group on aromatics could be easily converted to an oxygen-functional group by aromatic Pummerer type rearrangement[5a,b] and also *ipso*-substitution of the sulfur functional group by carbon substituents through a ligand exchange reaction.[5c] At first, newly synthesized quinone mono *O*,*S*-acetals (**1b–g**) bearing the electron-withdrawing group on an aryl thio moiety,[6] which were obtained in 60–85% yields from the corresponding sulfoxides,[5a] were examined toward the reaction with **2a**. The results of the investigation of the reaction of this quinone with **2a** are summarized in Table 1. Similar results were observed when **1b** bearing a *para*-chlorophenyl group on the sulfur atom was used in place of **1a**. Both the thioether product **3** and compound **4a** were obtained in the reaction of **2a** with quinone mono *O*,*S*-acetals (**1c–f**) bearing a moderately strong electron-withdrawing group on the aromatic ring. The reaction of **2a** with **1g** bearing a pentafluorophenyl group on the sulfur atom exclusively afforded the sulfenylation product (**3e**) in 81% yield. Replacement of a trifluorophenyl group by a pentafluorophenyl group in **1g** makes the sulfur atom more electrophilic, allowing chemoselective sulfenylation reaction to become predominant.

From these findings, we produced the corresponding pentafluorophenylthio compounds (**3f–i**) in high yields by effective sulfenylation reaction using **1g** on various mono- or dimethoxybenzenes (**2b–e**) (Table 2, entries 1–4). When mesitylene (**2f**) was used as the substrate, sulfenylation produced the thioether product (**3j**) in 96% yield (Table 2, entry 5). The highly reactive reagent **1g** was quite effective in the sulfenylation of indole (**2g**), indole derivatives (**2h–l**), 2-methoxynaphthalene (**2m**), and various heteroaromatics (**2n–q**) (Table 2, entries 6–16). In contrast, the previously reported **1a** did not react at all with **2f** and some heteroaromatics (**2o–q**). Furthermore, **1a** did not react with *N*-tosylated indole (**2h**) while its reaction with *N*-unsubstituted indole (**2g**) afforded the corresponding thioether in 69% yield.

Finally, we could control the reactivity of quinone mono *O*,*S*-acetals by tuning the structure. The advantages of the new methodology using **1g** bearing a strong electron-withdrawing pentafluorophenyl group on the sulfur atom are as follows: (i) the sulfenylation reactions are complete within 10 minutes below 0°C under mild conditions, (ii) the dihydroquinone side product is easily removed by treatment with weak aqueous alkali, and (iii) relatively high yields are obtained even in the case of indole derivatives deactivated by electron-withdrawing groups. These reagents may prove useful in the synthesis of biologically active substances having labile functionalities which are sensitive to basic, acidic or heating conditions. Besides, we confirmed that the pentafluorophenylthio group works similarly to the phenylthio group for oxidation and the pentafluorophenyl sulfinyl group also behaves similarly to

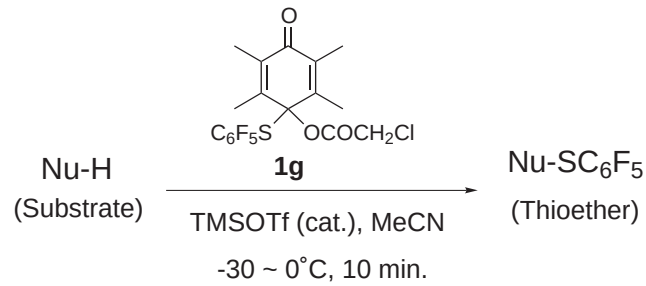
Table 1. Reaction of quinone mono *O*,*S*-acetals **1** with 1,2,3-trimethoxybenzene **2a**

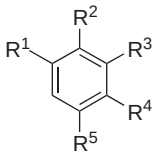
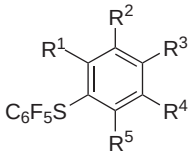
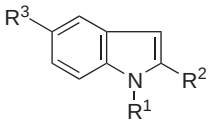
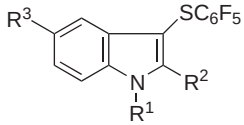
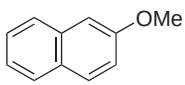
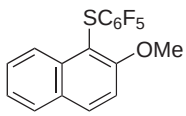
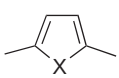
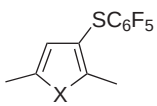
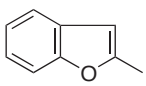
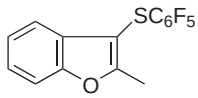


Entry		R		Yield (%)[a] 3	Yield (%)[a] 4a
1	**1a**	Ph		N.D.	45
2	**1b**	*p*-Cl-Ph		N.D.	46
3	**1c**	*p*-F-Ph	**3a**	16	25
4	**1d**	*p*-CF_3-Ph	**3b**	23	28
5	**1e**	*p*-NO_2-Ph	**3c**	76	20
6	**1f**	$C_6H_2F_3$	**3d**	79	13
7	**1g**	C_6F_5	**3e**	81	N.D.

[a] Isolated yield.

Table 2. Sulfenylation of various aromatic compounds using quinone mono *O*,*S*-acetal **1g**



Entry	Substrate (**2**)		R^1	R^2	R^3	R^4	R^5	Thioether (**3**)	Yield (%)[a]
1		**2b**	H	OMe	OMe	H	H		**3f** 94
2		**2c**	OMe	H	H	OMe	H		**3g** 60
3		**2d**	OMe	H	OMe	H	H		**3h** 83
4		**2e**	H	H	OMe	H	H		**3i** 70
5		**2f**	Me	H	Me	H	Me		**3j** 96
6		**2g**	H	H	H				**3k** 83
7		**2h**	Ts	H	H				**3l** 88
8		**2i**	Ac	H	H				**3m** 75
9		**2j**	H	CO_2Et	H				**3n** 80
10		**2k**	H	H	CN				**3o** 84
11		**2l**	H	H	NO_2				**3p** 78
12		**2m**							**3q** 99
13		**2n**	X =NH						**3r** 82
14		**2o**	X = S						**3s** 78
15		**2p**	X = O						**3t** 78
16		**2q**							**3u** 88

[a]Isolated yield.

the phenyl sulfinyl group in Pummerer type rearrangement on aromatics and *syn*-elimination in aliphatics.[7] The application of sulfenylation reagents as synthons is currently under investigation.

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S.; Morita, N.; Iio, K.; Nakamura, Y.; Kita, Y. *Org. Lett.* **2000**, *2*, 2279–2282.

6. Quinone mono *O*,*S*-acetals (**1a**–**g**) are stable for several months on storage in a refrigerator.
7. Both cyclic and acyclic α-pentafluorophenylthioalkanones are readily obtained in quantitative yield by the reaction of **1g** and the corresponding trimethylsilyl enol ethers under standard conditions.