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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 409–412

Oxidation of 4-arylphenol trimethylsilyl ethers to *p*-arylquinols using hypervalent iodine(III) reagents

François-Xavier Felpin*

Université Bordeaux-I, Laboratoire de Chimie Organique et Organométallique, 351 Cours de la Libération, 33405 Talence Cedex, France

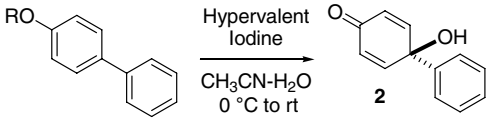
Received 19 October 2006; revised 8 November 2006; accepted 10 November 2006
Available online 30 November 2006

Abstract—An efficient synthesis of *p*-arylquinols by the oxidation of 4-arylphenol trimethylsilyl ethers with phenyliodine(III) diacetate (PIDA) is reported. This protocol greatly improved the yield of *p*-quinol by minimizing oligomer side products compared to the oxidation of free phenol with hypervalent iodine(III) reagents. The innocuity of phenyliodine(III) diacetate associated with the mild conditions make the method highly competitive over metal-mediated oxidation reactions. The proposed reaction mechanism is discussed and compared to the generally accepted mechanism of 4-substituted phenols to explain the yield improvement.

p-Quinols are important skeletons found in many biologically active natural products[1] as well as being important intermediate skeletons in multi-steps synthesis.[2] On the other hand, Westwell et al. reported *p*-quinols based antitumor agents, which represent structurally new and original skeletons.[3] Westwell et al. prepared *p*-quinols by dearomatization of phenols using Phenyliodine(III) bis-trifluoroacetate (PIFA) as the oxidating agent. However, yields of the required *p*-quinols were low due to the generation of radical species that might lead to unwanted by-products. Consequently, although attractive due to the non toxic nature of hypervalent iodine(III) reagents and the simplicity of the method,[4] this approach is often hampered by limited yields as a result of competitive *ortho* oxidation and/or oligomerization processes. As part of a program directed at the discovery of new anticancer agents, we were interested in the incorporation of *p*-quinol skeletons in our own structures.[5] For this purpose, we have re-examined the hypervalent iodine(III) mediated oxidation of phenol derivatives.

We first selected 4-phenyl phenol **1** as a model substrate in the presence of water as nucleophile (Table 1). Despite numerous attempts, we were unable to isolate the corresponding *p*-arylquinol **2** in higher yield than 43% (entry 1). We observed extensive oligomerization dramatically decreasing the yields of isolated *p*-arylquinol **2**. Phenyliodine(III) bis-trifluoroacetate (PIFA) has a deleterious effect on the yield causing much more oligomerization than phenyliodine(III) diacetate (PIDA) (entry 1 vs 2). We believe that the side products are formed as a result of the formation of a highly reactive phenoxonium ion (vide infra). With the intention to minimize this intermediate, we envisaged the oxidation of the corresponding protected phenol. Although oxidative dealkylation has been reported for the formation of quinones,[6] phenol methyl ether **3** was found to be mostly

Table 1. Study of phenol protecting group



Entry	*R*	Substrate	Hypervalent iodine	Yield (%)
1	H	**1**	$PhI(OAc)_2$	43
2	H	**1**	$PhI(OCOCF_3)_2$	17
3	CH_3	**3**	$PhI(OAc)_2$	Trace
4	CH_3	**3**	$PhI(OCOCF_3)_2$	Trace
5	CH_3SO_2	**4**	$PhI(OAc)_2$	0
6	CH_3SO_2	**4**	$PhI(OCOCF_3)_2$	0
7	$\mathbf{Si(CH_3)_3}$	**5**	$\mathbf{PhI(OAc)_2}$	**82**
8	$Si(CH_3)_3$	**5**	$PhI(OCOCF_3)_2$	35

Keywords: *p*-Arylquinols; Hypervalent iodine(III) reagents; Oxidation; Dearomatization.
* Tel.: +33 5 40 00 62 87; fax: +33 5 40 00 62 86; e-mail: fx.felpin@lcoo.u-bordeaux1.fr

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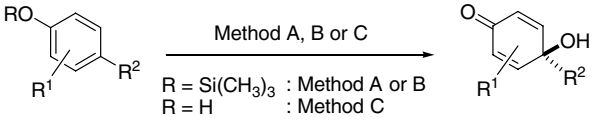
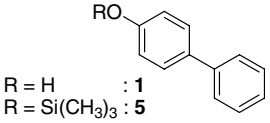
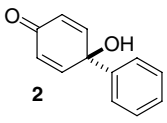
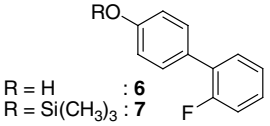
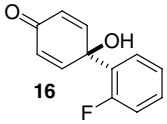
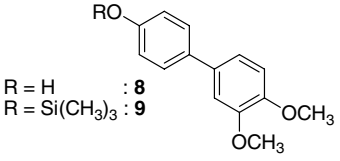
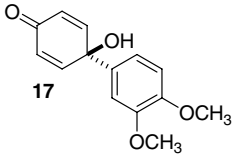
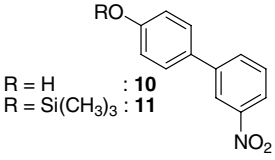
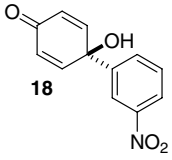
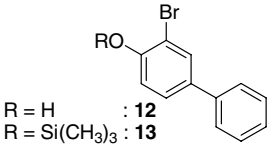
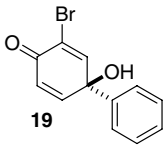
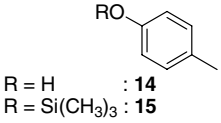
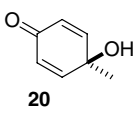
doi:10.1016/j.tetlet.2006.11.073

unreactive in our studies (entries 3 and 4). Mesyl protecting group also inhibited the oxidative dearomatization (entries 5 and 6). Then, we studied the reactivity of trimethylsilyl ether **5**.[7] Although the oxidation of **5** with PIFA gave disappointing low yields causing extensive oligomerization (entry 8), we found that the use of PIDA led to the desired *p*-arylquinol **2** in an excellent yield and purity (entry 7). These results are of importance since trimethylsilyl ethers are easily accessible by a simple heating of the free phenols with HMDS in the presence of pyridine.[8]

We then examined the impact of the structure of the 4-arylphenol derivatives on the reaction outcome (Table 2). With a variety of phenols or their trimethylsilyl ether derivatives in hand, we studied the hypervalent iodine(III)-mediated dearomatization, in the presence of water as nucleophile, with three different methods: (A) oxidation of 4-arylphenol trimethylsilyl ethers with PIDA, (B) oxidation of 4-arylphenol trimethylsilyl ethers with PIFA and (C) oxidation of 4-arylphenols with PIDA. As expected, method A (e.g., oxidation of 4-arylphenol trimethylsilyl ethers with PIDA) proved to be the most efficient way to obtain *p*-arylquinols as the only identifiable product by TLC. In most cases, we found a spectacular positive effect for the yield when the oxidation was carried out on protected phenols as illustrated by the most impressive one in entry 5. While

Table 2. Screening of 4-arylphenol derivatives oxidation



Entry	Substrate	Product	Yield (%) Method[a]		
			A	B	C
1	 R = H : **1** R = Si(CH3)3 : **5**	 **2**	**82**	35	43
2	 R = H : **6** R = Si(CH3)3 : **7**	 **16**	**76**	56	38
3	 R = H : **8** R = Si(CH3)3 : **9**	 **17**	**0**	0	0
4	 R = H : **10** R = Si(CH3)3 : **11**	 **18**	**78**	70	49
5	 R = H : **12** R = Si(CH3)3 : **13**	 **19**	**70**	59	0
6	 R = H : **14** R = Si(CH3)3 : **15**	 **20**	**66**	62	44

[a] Method A: oxidation of 4-arylphenol trimethylsilyl ethers with PIDA; Method B: oxidation of 4-arylphenol trimethylsilyl ethers with PIFA; Method C: oxidation of 4-arylphenol with PIDA.

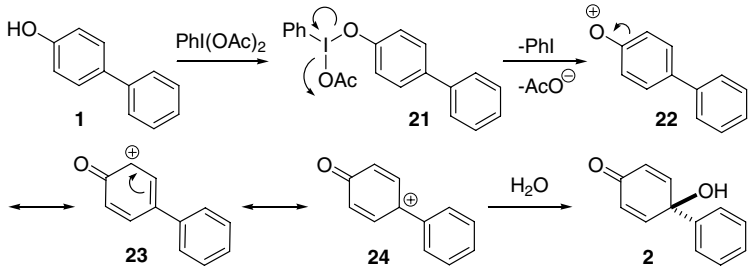
the oxidation of free phenol **12** only led to oligomerization by-products, a complete reversal of reactivity was observed when the oxidation was performed on 4-arylphenol trimethylsilyl ether **13**, allowing the isolation of *p*-arylquinol **19** in a good yield (70%). We also demonstrated unambiguously that PIDA is much more efficient than PIFA. We noted a higher reactivity of PIFA, leading to the consumption of starting material after few minutes at 0 °C probably due to partial instability of TMS ether under these conditions.[9] On the other hand, PIDA-mediated oxidation required approximately 1 h at 0 °C and 2 h at room temperature to go to completion. For some reason, oxidation of the electron rich substituted substrates **8** and **9** gave only degradation products, irrespective of the method used (entry 3). In the case of the less reactive 4-alkylphenol trimethylsilyl ether **15**, a significant enhancement of the yield was reached (entry 6). However, the reaction required longer reaction times (5 h) to fully consume the starting material and TLC analysis of the crude reaction mixture showed along with the expected *p*-arylquinol **20** unidentified by-products, which were not observed with 4-arylphenols.

It has been postulated that intermediate **21** dissociates to give a very reactive phenoxonium ion **22**, which could react either at C2 and/or C4 positions depending on the stability of the resulting carbocations **23**–**24** (Scheme 1).[10] In the case of 4-arylphenols, the carbocation at C4 is highly favored leading to the formation of the expected *p*-arylquinols. On the other hand, it has been recently reported that free radical species could also be involved in the oxidation of 2,6-dimethylphenol by PIDA.[11] In order to address this issue, the potent radical scavenger TEMPO was added to the reaction mixture during the oxidation of 4-phenylphenol by PIDA. Interestingly, we did not observe any change in the outcome of the reaction, indicating that the free radical species are not likely involved in this oxidation process.

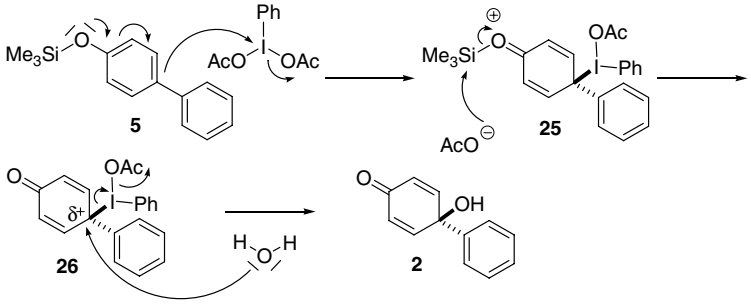
In contrast, the oxidation of 4-arylphenol trimethylsilyl ethers to *p*-arylquinols could not be explained by the formation of the highly reactive phenoxonium ion. Although a detailed understanding of the reaction mechanism awaits further study, we postulated the formation of a more stable C-iodonylated cyclohexadienone **26** at C4 (Scheme 2). The resulting phenyliodono group, which has a leaving ability 8×10^5 times greater than a triflate group,[12] could then act as a powerful nucleofuge when substituted by water to give the corresponding *p*-phenylquinol **2**. Stabilization of the partial positive charge at C4 by aryl group could explain the origin of the high regioselectivity observed.

To support our hypothesis, it would be interesting to take into consideration the results of entry 4 (Table 2). While the yields of methods B and C are significantly higher compared to other substrates, we did not observe any improvement with method A. These results could be explained by the ability of the 3-nitrophenyl substituent in stabilizing the carbocation at C4. In the case of method A, we suggest that the carbocation at C4 is not formed, annihilating the influence of the 3-nitrophenyl group. Clearly, these observations support our mechanistic explanations.

In summary, we have reported a highly efficient synthesis of *p*-arylquinols by dearomatization of 4-arylphenol trimethylsilyl ethers with PIDA. We demonstrated that the protection of phenols as their trimethylsilyl derivatives greatly improve the yields by minimizing undesired oligomerization processes. We believe that such an



Scheme 1. Accepted mechanism of phenol oxidation to *p*-quinol using PIDA.



Scheme 2. Proposed mechanism of 4-arylphenol trimethylsilyl ethers oxidation using PIDA.

improvement can be explained by the formation of a more stable C-iodonylated cyclohexadienone at C4 instead of a highly reactive phenoxonium ion as potential intermediates. We are currently incorporating this chemistry to conceptually novel structures in the aim to find new antitumor agents.

Acknowledgements

The author thanks Mr. Soumya Mitra (The Ohio State University), Mr. Edouard Godineau (University Bordeaux 1), and Mrs. Géraldine Rousseau (University Bordeaux 1) for helpful discussions. The University of Bordeaux 1 and the Centre National de la Recherche Scientifique (CNRS) are gratefully acknowledged for financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.11.073.

References and notes

1. For recent examples, see: (a) Soriente, A.; Rocca, A. D.; Sodano, G.; Trincone, A. *Tetrahedron* **1997**, *53*, 4693–4702; (b) Patil, A. D.; Freyer, A. J.; Killmer, L.; Offen, P.; Carte, B.; Jurewicz, A. J.; Johnson, R. K. *Tetrahedron* **1997**, *53*, 4693–4702; (c) Ata, A.; Kerr, R. G.; Moya, C. E.; Jacobs, R. S. *Tetrahedron* **2003**, *59*, 4215–4222; (d) Acaraz, L.; Macdonald, G.; Ragot, J. P.; Lewis, N.; Taylor, R. J. K. *J. Org. Chem.* **1998**, *63*, 3526–3527.
2. (a) Milić, D. R.; Gašić, M. J.; Muster, W.; Csanádi, J. J.; Šolaja, B. A. *Tetrahedron* **1997**, *53*, 14073–14084; (b) Milić, D. R.; Kapor, A.; Markov, B.; Ribar, B.; Strümpel, M.; Juranić, S.; Gašić, M. J.; Šolaja, B. *Molecules* **1999**, *4*, 338–352.
3. (a) Wells, G.; Berry, J. M.; Bradshaw, T. D.; Burger, A. M.; Seaton, A.; Wang, B.; Westwell, A. D.; Stevens, M. F. G. *J. Med. Chem.* **2003**, *46*, 532–541; (b) Berry, J. M.; Bradshaw, T. D.; Fichtner, I.; Ren, R.; Schwalbe, C. H.; Wells, G.; Chew, E.-H.; Stevens, M. F. G.; Westwell, A. D. *J. Med. Chem.* **2006**, *48*, 639–644; (c) Lion, C. J.; Matthews, C. S.; Wells, G.; Bradshaw, T. D.; Stevens, M. F. G.; Westwell, A. D. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5005–5008.
4. For an excellent review, see: Magdziak, D.; Meek, S. G.; Pettus, T. R. R. *Chem. Rev.* **2004**, *104*, 1383–1429.
5. Taylor, R.; Felpin, F.-X., unpublished results.
6. Tohma, H.; Morioka, H.; Hashizume, M.; Kita, Y. *Tetrahedron Lett.* **2001**, *42*, 6899–6902.
7. McKillop, A.; McLaren, L.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2047–2048.
8. Friedman, S.; Kaufman, M. L.; Wender, I. *J. Org. Chem.* **1962**, *27*, 664–666.
9. A control experiment in the absence of water showed that **5** degrades completely in 1 h with PIFA, while in the presence of PIDA, **5** is unaffected after 2 h of stirring.
10. Pelter, A.; Ward, R. S. *Tetrahedron* **2001**, *57*, 273–282.
11. Boldron, C.; Aromi, G.; Challa, G.; Gamez, P.; Reedijk, J. *Chem. Commun.* **2005**, 5808–5810.
12. Okuyama, T.; Takino, T.; Sueda, T.; Ochiai, M. *J. Am. Chem. Soc.* **1995**, *117*, 3360–3367.