Synthesis of 4,5-Dimethoxy-*o*-benzoquinone by Formal [4+2] Cyclization of 2,3-Dimethoxy-1,3-butadiene with Oxalyl Chloride

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Received June 10, 2008: Revised January 16, 2009: Accepted January 16, 2009

Abstract: The cyclization of 2,3-dimethoxy-1,3-butadiene with oxalyl chloride provides a new method for the synthesis of 4,5-dimethoxy-*o*-benzoquinone.

Keywords: Arenes, cyclizations, oxalyl derivatives, enol ethers, quinines.

Ortho-quinones represent versatile synthetic building blocks [1]. For example, Waldmann and coworkers recently reported the application of 4,5-dimethoxy-*o*-benzoquinone during the synthesis of nakijiquinone natural products [2]. The reaction of 4,5-dimethoxy-*o*-benzoquinone with KOH/H_2O has been reported to result in the formation of 2,5-dihydroxy-*p*-benzoquinone in high yield. The reaction of 4,5-dimethoxy-*o*-benzoquinone with MeOH, in the presence of catalytic amounts of acid, afforded 2,5-dimethoxy-*p*-benzoquinone in quantitative yield [3]. The reaction of 4,5-dimethoxy-*o*-benzoquinone with 1,2-diaminobenzene afforded fluorindin [3]. 4,5-Dimethoxy-*o*-benzoquinone and related compounds have been applied to the synthesis of the natural product xylerithin and its analogues [4]. Several other applications have been reported.

4,5-Dimethoxy-*o*-benzoquinone has been prepared by several methods and is commercially available (1.0 g, $79.20) [5]. Recently, 4,5-dimethoxy-*o*-benzoquinone has been isolated as a natural product [6]. Its first synthesis was reported by El'tshov based on a Teuber oxidation of 4-hydroxy-veratrol [7]. Wanzlick and Jahnke were the first to report the synthesis of 4,5-dimethoxy-*o*-benzoquinone by PbO_2-mediated dehydrogenation of 1,2-dihydroxybenzene in the presence of MeOH/NaOMe [3, 8]. Although this reaction is nowadays frequently used, a drawback is the employment of stoichiometric amounts of toxic PbO_2. An alternative method for the synthesis of 4,5-dimethoxy-*o*-benzoquinone relies on the oxidation of different substituted phenols by employment of stoichiometric amounts of Frémy's salt [9]. However, its high costs prevent this reagent to be used on large scale. 4,5-Dimethoxy-*o*-quinone has also been prepared by copper-mediated oxidation of phenol with oxygen in the presence of pyridine [10]. Nematollahi and Golabi reported an efficient electro-organic synthesis of 4,5-dimethoxy-*o*-benzoquinone from catechol (95% yield) [11]. In this transformation, methanol was used as the solvent and sodium acetate as the supporting electrolyte.

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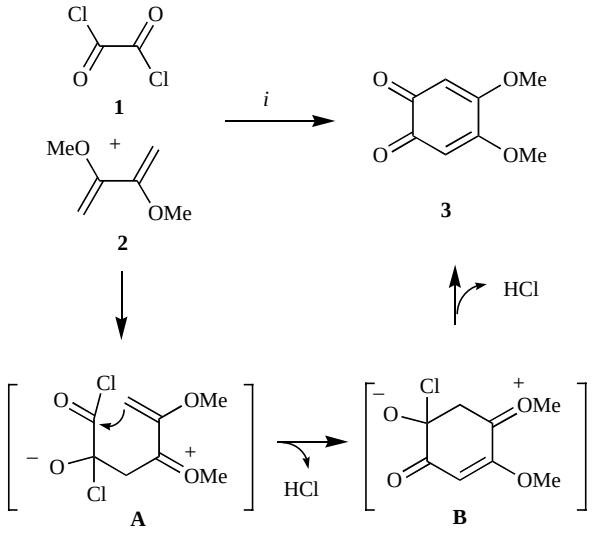
Oxalyl chloride, a bulk chemical, represents an important synthetic building block in one-pot cyclizations with silyl enol ethers [12]. We have recently reported the synthesis of γ-alkylidenebutenolides by cyclization of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with oxalyl chloride [13]. Recently, we have studied the synthesis of 4-alkoxycarbonyl-butenolides by uncatalyzed one-pot cyclization of oxalyl chloride with 1,3-bis(silyloxy)alk-1-enes [14]. We have also developed a one-pot synthesis of 3-hydroxymaleic anhydrides by cyclization of 1,1-bis(trimethylsilyloxy)ketene acetals with oxalyl chloride [15].

Herein, we report what is, to the best of our knowledge, a new synthesis of 4,5-dimethoxy-*o*-benzoquinone by cyclization of 2,3-dimethoxy-1,3-butadiene with oxalyl chloride [16].



Scheme 1. Synthesis of **3**: *i*, neat, 0 °C, 6 h.

The reaction of a CH_2Cl_2 solution (10 mL) of oxalyl chloride (**1**) (1.0 mmol) with commercially available 2,3-dimethoxy-1,3-butadiene (**2**) (1.0 mmol) at 20 °C afforded 4,5-dimethoxy-*o*-benzoquinone (**3**), albeit, in only in 7% yield. Product **3** was isolated in 18% yield when the reaction was carried out at -78 °C. After some experimentation we

1570-1786/09 $55.00+.00

have found that the reaction of **1** (1.0 mmol) with **2** (2.5 mmol) at 0 °C (neat) resulted in the formation of **3** in up to 51% yield (Scheme **1**) [17] It is worth to be noted that the reaction can be successfully carried out on a 20 mmol scale. The presence of tertiary amine bases resulted in a decrease of the yield, due to the difficult separation of the ammonium salts.

The formation of **3** can be explained by attack of enol ether **2** onto **1** to give intermediate **A**, extrusion of HCl and subsequent cyclization (intermediate **B**) and extrusion of a second molecule of HCl.

In conclusion, we have reported a new and convenient synthesis of 4,5-dimethoxy-*o*-benzoquinone by formal [4+2] cyclization of 2,3-dimethoxy-1,3-butadiene with oxalyl chloride. This strategy complements known methods for the synthesis of the synthetically important title compound.

ACKNOWLEDGEMENTS

Financial support by the State of Mecklenburg-Vorpommern is gratefully acknowledged.

REFERENCES AND NOTES

[1] Reviews: (a) Wanzlick, H. W.; Lehmann-Horchler, M.; Mohrmann, S.; Gritzky, R.; Heidepriem, H.; Pankow, B. *Angew. Chem. Int. Ed. Engl.*, **1964**, *3*, 401. (b) Nair, V.; Radhakrishnan, K. V. *Product class 2: benzo-1,2-quinones* in *Sci. Synth.*, **2006**, *28*, 181-215.

[2] Stahl, P.; Kissau, L.; Mazitschek, R.; Huwe, A.; Furet, P.; Giannis, A.; Waldmann, H. *J. Am. Chem. Soc.*, **2001**, *123*, 11586.

[3] Wanzlick, H.-W.; Jahnke, U. *Chem. Ber.*, **1968**, *101*, 3744.

[4] Wanzlick, H.-W.; Jahnke, U. *Chem. Ber.*, **1968**, *101*, 3753.

[5] Pfaltz & Bauer, Inc., 172 E. Aurora Street, Waterbury, CT, 06708, USA. Aug 13th 2008.

[6] Yang, J.; Lou, F.; Niu, Y. *Zhongguo Zhongyao Zazhi*, **2007**, *32*(14), 1416.

[7] El'tshov, A. V. *J. Gen. Chem. USSR*, **1963**, *33*, 1952; *Chem. Abstr*. **1963**, *59*, 11463.

[8] For applications of this method, see for example: Cole, E. R.; Crank, G.; Minh, H. T. H. *Aust. J. Chem.*, **1980**, *33*, 527; see also ref. 2.

[9] (a) Deya, P. M.; Dopico, M.; Raso, A. G.; Morey, J.; Saa, J. M. *Tetrahedron*, **1987**, *43*, 3523. (b) Saa, J. M.; Capo, M.; Marti, C.; Garcia-Raso, A. *J. Org. Chem.*, **1990**, *55*, 288.

[10] Prati, L.; Rossi, M. *Gazz. Chim. Ital.*, **1995**, *125*, 83.

[11] Nematollahi, D.; Golabi, S. M. *J. Electroanal. Chem.*, **1996**, *405*(1-2), 133.

[12] For a review, see: Langer, P. *Synlett*, **2006**, 3369-3381.

[13] Langer, P.; Stoll, M.; Schneider, T. *Chem. Eur. J.*, **2000**, *6*, 3204.

[14] Dede, R.; Michaelis, L.; Fuentes, D.; Yawer, M. A.; Hussain, I.; Fischer, C.; Langer, P. *Tetrahedron*, **2007**, *63*, 12547.

[15] Rotzoll, S.; Ullah, E.; Görls, H. Langer, P. *Tetrahedron*, **2007**, *63*, 2647.

[16] Effenberger, F.; Maier, R.; Schoenwaelder, K.-H.; Ziegler, T. *Chem. Ber.*, **1982**, *115*, 2766.

[17] *Procedure for the synthesis of* **3**: A mixture of 2,3- dimethoxy-1,3-butadiene (1.0 mmol) and of oxalyl chloride (2.5 mmol) was stirred at 0 °C for 6 h. The mixture was dissolved in CH_2Cl_2 (1 mL). The solution was poured into water (10 mL). The mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. A saturated CH_2Cl_2 solution of the residue was poured into *n*-heptane (150 mL) to give a precipitate. The latter was filtered off to give **3** as a colourless solid (137 mg, 51%). The reactions can be successfully carried out on larger scale following the procedure given above. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.90 (s, 6H, OCH_3), 5.77 (s, 2H, CH). ^{13}C-NMR (300 MHz, $CDCl_3$): δ = 57.0 (OCH_3), 102.9 (C), 163.6 (CH), 178.8 (C=O). IR (KBr, cm^{-1}): 3436 (br, w), 1650 (s), 1580 (s), 1250 (s), 980 (m), 824 (m). MS (EI, 70 eV): *m/z* (%) = 168 [M^+] (3), 153 (10), 140 (100), 125 (26), 82 (10), 86 (95). Anal.: calcd. for $C_8H_8O_4$: C 57.14, H 4.80. Found: C 57.07, H 4.83.