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Oxidation of 2-(4-chlorobenzoyl)-thiophene into 1-oxide Diels-Alder dimers, sesquioxide and a sulfone-water adduct.

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Abstract

Oxidation of 4-chlorophenyl, thien-2-yl-methanone **1** with 0.2 eq H_2O_2 in TFA gave the 1-oxide Diels-Alder dimer **3a** . Use of an 1-5 eq H_2O_2 afforded the sesquioxide **4** (4,7 di [4-chlorobenzoyl]-3,10-dithiatricyclo [5.2.1.$0^{2,6}$] deca-4,8- diene 3,3,10-trioxide). Oxidation of **1** with mCPBA in CH_2Cl_2-excess BF_3-etherate gave **3a** (4,7-di [4-chlorobenzoyl] -3,10-dithiatricyclo [5.2.1.$0^{2,6}$] deca-4,8- diene 3,10-dioxide) in acceptable yield and the minor isomer **3b** in low yield. Oxidation of **1** with 6 eq dimethyldioxirane in acetone gave 3-hydroxy 2,3-dihydrothiophene 1,1-dioxide **6**, a 1,1-dioxide-water adduct.

Keywords : thiophene; oxidation, peracid, dioxirane;

Introduction

Oxidation of thiophenes to thiophene 1-oxides as possible biologically reactive intermediates has been postulated in the formation of the metabolites isolated from thiophene [1-3] and tienilic acid isomer [4, 5] and in the immunoallergic hepatitis induced by tienilic acid [6, 7]. It has been known for long that thiophenes can be oxidized by peracids to 1,1-dioxides with thiophene 1-oxides as intermediates [8]. However thiophene 1-oxides are generally highly reactive and only a few stabilized by sterically hindering electro-donating substituents have been isolated and characterized [9-14]. Most of the time, these intermediate 1-oxides undergo [4 + 2] cycloaddition and dimerize to 1-oxide dimers [2, 13-15] which overoxidize to sesquioxides (formally the adduct of a 1-oxide and a 1,1-dioxide) [2, 8, 16-18], or react in presence of dienophiles to [4 + 2] adducts [8, 19]. Howeover, thiophenes 2-substituted with electron withdrawing groups have been said to be very difficult to oxidize [16]. The aim of the present paper is to demonstrate that the oxidation of 2-aroyl-thiophenes is possible. We describe the oxidation of [4-chlorophenyl] [thien-2-yl] methanone **1** [20] [1] to thiophene 1-oxide dimers **3**, sesquioxide **4** and the sulfone adduct **6**.

[1] **1** : NMR ($CDCl_3$, ∂) ^1H : 7.92 (dd, 4.8Hz, 1Hz, 1H, H5); 7.86 (d, 8.6Hz, 2H, H3', H5'); 7.69 (dd, 3.8Hz, 1Hz, 1H, H3); 7.58 (d, 8.6Hz, 2H, H2', H6'); 7.25 (dd, 3.8Hz, 4.8Hz, 1H, H4); ^{13}C : 186.9 (CO); 143.2 (s); 138.7 (s); 136.4 (s); 134.7 (2C, d); 130.6 (2C, d); 128.7 (2C, d); 128 (d).

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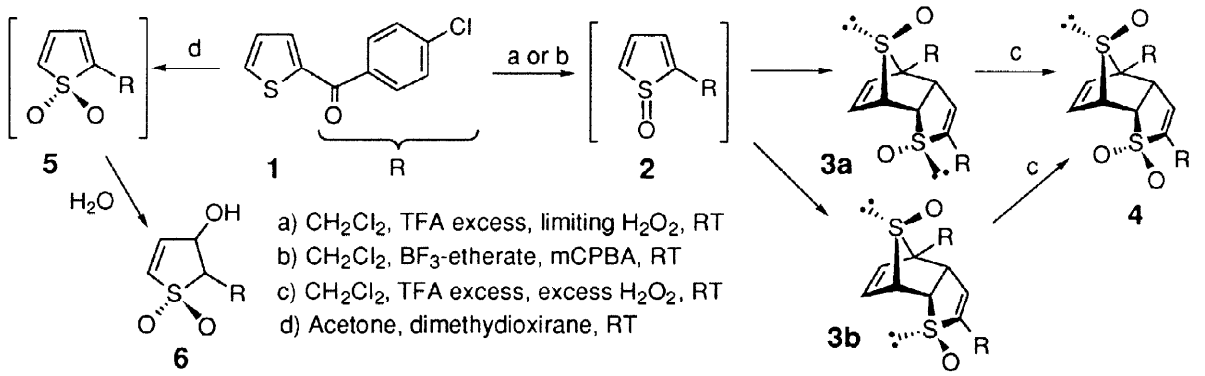
Scheme 1



Results and discussion

As shown in table 1 attempts to oxidize **1** in CH_2Cl_2 or $CHCl_3$ with mCPBA failed both at 20°C and 80°C. However oxidation in TFA with 0.2 eq of H_2O_2 at 20°C gave the 1-oxide dimer **3** in low yield and traces of **4** (1-2 days). Use of 1 to 5 equivalents H_2O_2 increased the yield of **4** but **3** was no more detectable. When lowering the temperature to 0°C the reaction did not proceed to an appreciable rate.

Compounds **3** and **4** could be isolated by silicagel chromatography (CH_2Cl_2-MeOH 95:5) and are cristalline compounds [2] . Comparison of their NMR spectra with those of thiophene-1-oxide dimers and thiophene sesquioxide [2, 18] established their structures as shown on scheme 1. The bridged sulfoxide had the endo stereochemistry as usual for Diels-Alder adducts of thiophene-1-oxides [18, 19]. Using an excess H_2O_2 did not improve the yield of **4**, 4-chlorobenzoic acid (**CBA**) being formed possibly by acid catalyzed Baeyer-Villiger oxidation. Attempts to trap the transient thiophene 1-oxide **2** with dienophile like benzoquinone or N-phenylmaleimide [17, 19] were not successfull. Oxidation of **3** with mCPBA in CH_2Cl_2 afforded **4** [2]. Thus **4** is most probably formed through oxidation of **3**; however Diels Alder cycloaddition of the 1-oxide and the 1,1-dioxide is also a possibility. This is in agreement with the reaction of thiophene with TFA-H_2O_2 where two 1-oxide dimers were found, corresponding to the endo-syn and endo-anti configurations [2]. In the case of **3**, a very small amount of a minor isomer could be detected by NMR, but examination of the NMR spectra established the major one as **3a** the endo-syn isomer.

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[2] In a typical experiment, 272 mg of **1** were disolved in 7 ml CH_2Cl_2, 1.1 ml TFA was added and 0.11 ml H_2O_2 (30%, 1eq) was added at 0°C. After 72 h no oxidant remained (KI paper), and the solvant was evaporated. TLC (silicagel, CH_2Cl_2-MeOH 99:1) showed formation of **4** and 4-chlorobenzoic acid and the mixture was quantified by proton NMR ($CDCl_3$). Purification by cristallisation fron CH_3CN. **4** : 4,7 di [4-chlorobenzoyl]-3,10-dithiatricyclo [5.2.1.$0^{2,6}$] deca-4,8- diene 3,3,10-trioxide; mp 129°C; analysis: $C_{22}H_{14}Cl_2O_5S_2$; NMR ($CDCl_3$, ∂) ^1H : 7.99 (d, 8.8Hz, 2H, H3', H5'); 7.70 (d, 8.8Hz, 2H, H3", H5"); 7.45-7.41 (m, 4H, H2', H2", H6', H6"); 7.11 (, 2.8Hz, 1H, H3); 6.8 (dd, 6.8Hz, 3.2Hz, 1H, H6); 6.33 (d, 6.8Hz, 1H, H5); 5.1 (dd, 8Hz, 2.8Hz, 1H, H3a); 4.71 (dd, 8Hz, 3.8Hz, 1H, H7a); 4.51 (t, 4Hz, 1H, H7); ^{13}C: 190.3 (CO); 184.1 (CO); 146.1 (s); 144.3 (d); 141.6 (s); 140.8 (s); 134.4 (s); 132.2 (s); 131.2 (d); 130.6 (d); 129.4 (d); 129.3 (d); 127.9 (d); 84.1 (s); 63.5 (d); 63.1 (d); 47.1 (d). IR (KBr) : 1365 (w); 1140 (m) (SO_2); 1080 (w) (SO). MS : (CI, NH_3) 510 (M+ NH_4^+).

Table 1

Oxidation of 1 with various oxidants:

Oxidant	**1**[b]	**3**[b]	**4**[b]	**CBA**[b]	**6**[b]
mCPBA[a], 20° or 80°C	100	0	0	0	0
TFA[a], 0.2 eq H_2O_2, 20°C	80	6 (60%)	4 (40%)	0	0
TFA[a], 1 eq H_2O_2, 20°C	58	0	19 (90%)	4 (10%)	0
TFA[a], 5 eq H_2O_2, 20°C	27	0	28 (79%)	15 (21%)	0
BF_3-etherate[a], 0.25 eq mCPBA	83	8 (90%)	traces	0	0
BF_3-etherate[a], 0.5 eq mCPBA	60	15 (75%)	2 (10%)	6 (15%)	0
Dimethyldioxirane[c], 20°C	55	0	traces	0	35 (77%)

[a] : The solvent was CH_2Cl_2; [b]: proportions estimated by proton NMR in CD_2Cl_2 or $CDCl_3$ after work-up but before chromatography, percentage yield on transformed **1**, (**3** and **4** consume 2 eq of **1**). [c] : The solvent was acetone.

The newly described Lewis acid-catalyzed oxidation method of Furukawa [12] using BF_3-etherate and mCPBA was also tested on **1**. With 0.5 eq of mCPBA the reaction proceeded neither at -20°C nor at 0°C, but at 20°C the reaction was slow (2days) and afforded **3** in acceptable yield [3] . This method can be preparative since the starting material is recovered easily after flash chromatography. Excess of mCPBA did not increase the yield of dimers **3.** Only some sesquioxide **4** and degradation products were formed.

In presence of TFA or BF_3-etherate, the sulfur is oxidized with acid catalysis to the mono oxide which probably forms a complex with the acid or the Lewis acid, slowing down further oxidation, and allowing accumulation of the 1-oxide. This trick has been used for the oxidation to the 1-oxide of benzo[b]thiophene [4, 21], 2,5-diphenylthiophene [10], bis-trimethylsilyl-thiophene [12] and bis-*tert*-butylthiophenes [14]. However thiophenes 2-substituted with electron withdrawing groups have been said to be "impossible" to oxidize [16]. In fact, the electronegativity of the aroyl substituant of **1** decreases the reactivity of the sulfur such that it does not react at -20°C nor 0°C, and the reaction proceeds at 20°C only in presence of acid catalyst (TFA or BF_3 etherate). Compared with thiophene or dimethyl-thiophene, the oxidation was at least 100-1000 time slower. Examination of the BF_3-etherate catalyzed reaction by NMR showed slow consumption of mCPBA but no signal corresponding

[3] In a typical experiment, 272 mg of **1** were disolved in 10 ml CH_2Cl_2, at 0°C 1.1 ml BF_3 etherate was added and then 10 ml of a dried ($MgSO_4$) solution of mCPBA (0.25eq) in CH_2Cl_2. After 32 h at 20°C no oxidant remained (KI paper), the solution was neutralised with saturated $NaHCO_3$ and the organic phase concentrated under vacuum. TLC (silicagel, CH_2Cl_2-MeOH 95:5) showed formation of **3** (Rf 0.3) and the mixture was quantified by proton NMR ($CDCl_3$). Purification by flash chromatography (silicagel, CH_2Cl_2-THF 95:5) afforded pure **3a** and **3b** (still containing some **3a**). **3a** : 4,7-di [4-chlorobenzoyl] -3,10-dithiatricyclo [5.2.1.$0^{2,6}$] deca-4,8- diene 3,10-dioxide. Mp : 135°C (dec); analysis $C_{11}H_7ClO_2S$; NMR ($CDCl_3$, ∂) ^1H : 8.09 (d, 8.8Hz, H3', H5'); 7.66 (d, 8.8Hz, 2H, H3", H5"); 7.48 (d, 8.8Hz, 2H, H2', H6'); 7.43 (d, 8.8Hz, 2H, H2", H6"); 6.97 (d, 2.6Hz, 1H, H3); 6.85 (dd, 6.8Hz, 4.4Hz, 1H, H6); 6.24 (dd, 6.8Hz, 0.5Hz 1H, H5); 5.13 (dd, 8Hz, 2.4Hz, 1H, H3a); 5.01 (dd, 8Hz, 3.9Hz, 1H, H7a); 4.38 (dd, 4.4Hz, 3.9Hz, 1H, H7); ^{13}C : 191 (CO); 186.8 (CO); 150.3 (s);144.6 (d); 141.4 (s); 140.3 (s); 134.7 (s); 132.5 (s); 131.3 (2C, d) 130.5 (2C, d); 129.9 (d); 129.3 (d);129.2 (2C, d); 126.0 (d); 87.3 (s); 65.1 (d); 55.7 (d). MS : (CI, NH_3) : 494 (M+ NH_4^+, 1%), 428 (M-SO, 100%). **3b** : not fully characterized. ^1H NMR ($CDCl_3$, ∂) : 6.90 (d, 2.6Hz, 1H, H3); 6.74 (dd, 6.6Hz, 4.4Hz, 1H, H6); 6.35 (d, 6.8Hz, 1H, H5); 5.15 (dd, 8.2Hz, 2.8Hz, 1H, H3a); 4.77 (dd, 8.2Hz, 4.1Hz, 1H, H7a); 4.38 (dd, 4.4Hz, 4.1Hz, 1H, H7).

to dimer **3**. However soon after neutralisation of the Lewis acid with Na_2CO_3 (less than 3 min), those signals were present. This would imply that when removing the complexing Lewis acid the 1-oxide is not any more hindered and can dimerize by cycloaddition. The 4-chlorobenzoyl group is not bulky enough to prevent it. Dienophiles like benzoquinone and N-phenylmaleimide are not reactive enough to compete with the dimerization. This also implies that the 1-oxide **2** is much more reactive than the above mentioned dienophiles [14].

As an alternative to the former methods, dimethyldioxirane oxidation of **1** was also studied [22]. The reaction did not proceed at -20°C and was slow at 20°C. It unexpectively afforded a cristalline compound **6** in 50% yield [4] , the adduct of water on the transient 1,1-dioxide **5**. Using molecular sieves dried dioxirane, a transient product was observed by TLC, but **6** was isolated again after workup. Its formation can be explained by the reaction of the transient sulfone with moisture.

The reactions above allow the preparation of thiophene 1-oxide dimers and sesquioxide of reputably difficult to oxidize 2-aroyl-thiophenes. Attempts to prepare other thiophene 1-oxides in order to study their reactivity are under way.

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[4] Reaction of 102 mg **1** with an acetonic solution of dimethyldioxirane (25 ml, 0.09M) at 20°C until no oxidant remained (48h) afforded after chromatoraphy 50 mg **1** and 37 mg **6** : 2-[4-chlorobenzoyl] 2,3-dihydro-3-hydroxy-thiophene 1,1-dioxide; NMR ($CDCl_3$, ∂) ^1H: 8.13 (d, 8.6Hz, 2H, H3',H5'; 7.59 (d, 8.6Hz, 2H, H2', H6'); 6.96 (dd, 6.6Hz, 2.8Hz, 1H, H4); 6.79 (dd, 6.6Hz, 1.6Hz, 1H, H5); 5.64 (m, 1H, H3); 5.13 (d, 4Hz, IH, H2). ^{13}C: 188.5 (CO); 143.1(d); 141.5 (s); 135.8 (s); 131.6 (d); 130.2 (d); 72.8 (d); 71.4 (d). IR (KBr): 3470 (s, OH); 1300 (b, SO_2); 1150 (s,SO_2); MS (CI, NH_3) 290 (100, $M+NH_4^+$); 273 (20, $M+H^+$).