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Chlorosulfonation of 2-acylthiophenes: an examination on the reaction regiochemistry

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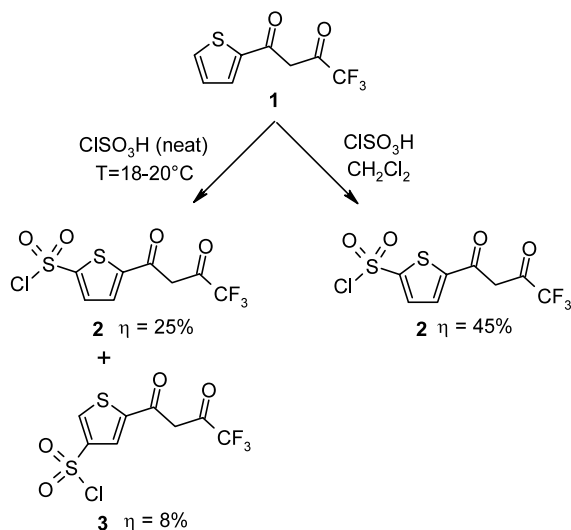
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Abstract—Chlorosulfonation of thenoyltrifluoroacetone with neat chlorosulfuric acid was found to give a 25:75 mixture of 3- and 2-chlorosulfonated thenoyltrifluoroacetone isomers in 33% overall yield. The use of dichloromethane as solvent for the chlorosulfonation reaction gave only the 2-chlorosulfonated isomer in 45% yield. On the contrary, the reaction of 2-acetylthiophene with neat chlorosulfuric acid gave only the 3-chlorosulfonated-5-acetylthiophene in 35% yield. The identity of these chlorosulfonated compounds was unambiguously established by NMR techniques and confirmed by the crystal structure determination of the 2-chlorosulfonated isomer.

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A challenging aspect of partitioning techniques is the problem associated with the separation and the decontamination of nuclear waste streams. A strategy that is gaining considerable attention is the use of synthetic receptors specifically designed for the extraction and separation of actinides from lanthanides.¹ In this context a promising binding site to be exploited for the construction of such receptors is the thenoyltrifluoroacetone (1), which has been extensively used as a reagent for the determination of lanthanide and actinide metal ions.² Therefore, a mandatory requirement for its utilization as binding site is the availability of efficient procedures for its selective functionalization, in view of its insertion, through suitable anchoring groups, onto a synthetic macrocycle. Owing to our current interest in the development of synthetic receptors for the recognition of metal ions,³ we planned to employ the chlorosulfonyl group to anchor 1 to a synthetic macrocycle through the thiophene ring. Recently, thenoyltrifluoroacetone was employed as bidentate binding site for the construction of a biotin-linked Eu(III) luminescent complex. The chlorosulfonyl group was chosen for the linkage of the thiophene ring to the biotine-bearing sidearm and the authors reported the synthesis of 3-chlorosulfonated thenoyltrifluoroacetone.⁴

However, as observed also by other authors in the case of the sulfonation of pyrrole,⁵ the regiochemistry of electrophilic aromatic substitution reaction carried out on pentaatomic substituted heterocycles still merit fundamental studies.⁶ In this paper we report a study aimed to disclosing the regiochemistry of the chlorosulfonation reaction carried out on thenoyltrifluoroacetone (1) and acetylthiophene (4).



Scheme 1. Regioselective synthesis of 2-chlorosulfonyl thenoyltrifluoroacetone.

Keywords: thiophenes; chlorosulfonation; heterocyclic compounds.

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According to literature procedure,⁴ we initially carried out the chlorosulfonation reaction of **1** with neat chlorosulfuric acid, obtaining the chlorosulfonated derivative in 33% yield. However, the ¹H NMR spectrum of this compound revealed the presence of a 25/75 mixture of two chlorosulfonated isomers. In fact, in CDCl₃, while the two enolizable protons of the β-diketone sidearm resonate as unique singlet at δ=6.50 ppm, the protons belonging to the thiophene ring of the two compounds resonate as two distinct AB systems. In particular, the two doublets at δ=7.76 and 7.89 ppm, coupled with a *J*=4.4 Hz were assigned to the 2-chlorosulfonyl-thenoyltrifluoroacetone isomer (**2**), whereas the two doublets at δ=8.13 and 8.52 ppm coupled with a *J*=1.3 Hz were assigned to the 3-chlorosulfonyl-thenoyltrifluoroacetone (**3**).⁷

All attempts to enhance the regiochemistry of this reaction, by changing the reaction conditions and ratio between reagents, failed and, although with a variable overall yield, an almost identical isomer distribution was observed. However, by using 5 equivalents of chlorosulfuric acid and using dichloromethane as solvent, we found that only the 2-chlorosulfonated isomer (**2**) had formed in 45% yield and its NMR spectrum coincides with that observed in the solvent free reaction (see Scheme 1).⁸

Further confirmation of the structure of **2** was obtained by single crystal X-ray diffraction⁹ (see Fig. 1). The analysis of the geometrical parameters shows that a delocalized double bond is spread over the O3–C5–C6–C7–O4 moiety. However the C5–O3 bond is slightly longer than the C7–O4 bond suggesting that the electron withdrawing character of the thiophene SO₂Cl group is greater than that of the CF₃ group (the C4–C5 bond distance is intermediate between a single and a double bond).¹²

In addition, the comparison between the solid state structure of **1**¹³ and **2** shows that the presence of the

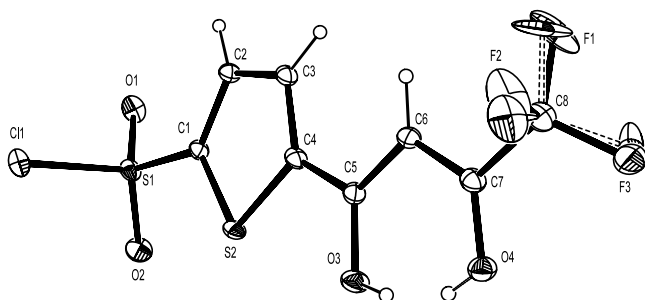
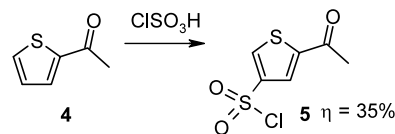


Figure 1. Perspective view of **2**. [Selected bond distances and angles: S1–C1 1.740(4) Å, S1–O1 1.416(4) Å, S1–Cl1 2.026(2) Å, S1–O2 1.425(3) Å, C4–C5 1.459(6) Å, C5–C6 1.394(5) Å, C6–C7 1.405(6) Å, C7–C8 1.530(6) Å, C5–O3 1.307(5) Å, C7–O4 1.250(5) Å, C4–C5–C6 122.8(3)°, C4–C5–O3 114.8(3)°, C5–C6–C7 118.4(4)°, C6–C7–O4 125.0(4)°, C6–C7–C8 119.8(4)°. Hydrogen bonds parameters: O3–H=0.8(2) Å, H···O4 1.8(2) Å, O3–H···O4 151(22)°, O4–H 0.7(2) Å, H···O3 2.08(2) Å, O4–H···O3 142(21)°].



Scheme 2. Chlorosulphonation reaction of 2-acetylthiophene.

electron withdrawing sulfonyl group in the latter changes the bond distance between C5–O3 and C7–O4 that is almost exactly reversed in the two compounds. This subtle change in the electron density distribution between the two carbonyl oxygen atoms strongly affect the properties of the beta-diketone of **2** in molecular recognition processes.^{14,15}

The O3–C5–C6–C7–O4 moiety is almost planar (the maximum 'out of plane' is 0.011(3) Å at C5) and does form a dihedral angle of 6.6(1)° with the least-squares plane through thiophene. As expected, the two hydrogen atoms represented in Figure 1 attached at O3 and O4 are really the result of the superposition of the two different structures corresponding to one single hydrogen atom statistically distributed (with 50% of probability) over the two oxygen atoms O3 and O4 indicating that two enol structures are present.

In order to evaluate whether this regiochemistry was restricted to the thenoyltrifluoroacetone, the chlorosulfonation reaction of 2-acetylthiophene (**4**) was studied (see Scheme 2). Quite unexpectedly, the reaction of 2-acetylthiophene with neat chlorosulfuric acid gave only the 3-chlorosulfonyl-5-acetylthiophene **5** in 35% yield and the same isomer was obtained also by using dichloromethane as solvent.^{16,17}

Although from these data it is not possible to draw general conclusions, it is nevertheless important to point out as apparently, simple electrophilic substitutions carried out on pentaatomic heterocycles like monosubstituted thiophenes, still merit fundamental studies that are undergoing in our laboratories.

Acknowledgements

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7. Thenoyltrifluoroacetone **1** (2.22 g, 0.01 mol) was added to chlorosulfuric acid (14 g, 0.12 mol) at -5°C with vigorous stirring. The reaction mixture was then allowed to warm up to rt. After 3 h, the deep red homogeneous solution was poured into a slush of 200 g of ice and extracted with dichloromethane. The organic phase was separated, washed with water (2×100 mL), dried with Na_2SO_4 and evaporated to dryness. The residue was taken up with hexane from which an orange solid crystallizes. A portion of this solid was dissolved in dichloromethane and submitted to GC/MS that revealed the presence of a 75/25 mixture of the two chlorosulfonated products. ^1H NMR (CDCl_3), **2**: δ 6.50 (s, 1H), 7.76 and 7.89 (2d, 2H, $J=4.4$ Hz); **3**: δ 6.50 (s, 1H), 8.13 and 8.52 (2d, 2H, $J=1.3$ Hz); MS(EI) $m/z=322$ (M^++2 , 10); 320 (M^+ , 30).
8. Thenoyltrifluoroacetone **1** (2.22 g, 0.01 mol) was dissolved in dry CH_2Cl_2 (100 mL) and the solution cooled at -5°C . Chlorosulfuric acid (5.8 g, 0.05 mol) was added and the reaction mixture stirred at rt for 24 h and then poured into a slush of 200 g of ice. The organic phase was separated, washed with water (2×100 mL), dried with Na_2SO_4 and evaporated to dryness. The residue was dissolved in CH_2Cl_2 (1 mL) and hexane was added (150 mL). Upon standing, **2** crystallizes as a pale yellow solid (1.45 g, 45%); mp: 98–101 $^{\circ}\text{C}$; ^{13}C NMR (CDCl_3): δ 93.8, 130.3, 134.3, 134.5, 146.8, 149.8, 174.2, 179.5.
9. X-ray studies: data were measured at 173 K on an Enraf Nonius CAD4 diffractometer using Cu-K α radiation ($\lambda=1.54178$ Å). Crystal data: $\text{C}_8\text{H}_4\text{ClF}_3\text{O}_4\text{S}_2$, $M=320.69$, monoclinic, $a=9.336(5)$, $b=15.479(5)$, $c=8.453(5)$ Å, $\beta=112.21(2)^{\circ}$, $U=1131(1)$ Å 3 , space group $P2_1/n$, $D_{\text{calcd}}=1.883$ gcm $^{-3}$, $\mu(\text{Cu-K}\alpha)=6.9$ mm $^{-1}$, 2171 symmetry independent reflections, $R1=0.088$, $wR2=0.233$ for 1758 observed reflections ($F_o>4\sigma(F_o)$), GOF=1.007, highest peak and deepest hole in the final Fourier ΔF map 1.26 and -0.89 eÅ $^{-3}$, respectively. The structure was solved by SIR92¹⁰ and refined with anisotropic atomic displacements for all non-hydrogen atoms using SHELXL-97.¹¹ The three terminal fluorine atoms are statistically distributed over the two different orientations rotated by 11.3 $^{\circ}$ along the C–CF $_3$ bond. All the hydrogen atoms were located on the Fourier ΔF map and refined with isotropic atomic displacement. Two residual peaks, located near the two O3 and O4 oxygens, were refined as hydrogen atoms with variable site occupancy factors leading to conclude that one hydrogen atom is equally distributed over the two oxygens. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-204298. Copies of the data can be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (1223) 336-033; e-mail: deposit@chemcrs.cam.ac.uk).
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16. Acetylthiophene **4** (2.52 g, 0.02 mol) was added to chlorosulfuric acid (18.0 g, 0.16 mol) with vigorous stirring. After 24 h at rt, the reaction mixture was poured into a slush of 200 g of ice and CH_2Cl_2 (100 mL). The organic phase was separated, washed with water (2×100 mL), dried with Na_2SO_4 and evaporated to dryness. The solid residue was purified by column chromatography (hexane/ $\text{CH}_2\text{Cl}_2=3/7$) to afford 1.57 g (35%) of pure **5**. mp: 91–92 $^{\circ}\text{C}$; ^1H NMR (CDCl_3): δ 2.63 (s, 3H), 8.01 and 8.44 (2d, 2H, $J=1.5$ Hz); ^{13}C NMR (CDCl_3): δ 26.5, 128.2, 138.4, 143.1, 147.2, 189.3; MS(EI) m/z : 226 (M^++2 , 10), 224 (M^+ , 35).
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