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Thiophene Ring Hydroxylation: A Novel Application of *trans*-(±)-2-(Phenylsulfonyl)-3-Phenyloxaziridine.

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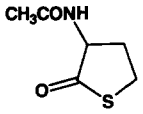
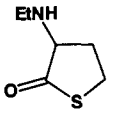
Abstract: A synthesis of the thiolactone moiety by thiophene ring hydroxylation was achieved. Isolation and characterization of by-product **8** suggests the direct attack of anion **5a** at the carbon center of the oxidizing reagent.

Introduction

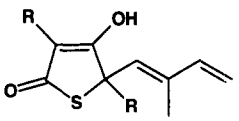
In recent years a number of natural products containing a thiolactone moiety have been isolated. Some of them, like compounds **1-3**, have shown antibiotic activity.[1,2,3]



(**1**)



(**2**)

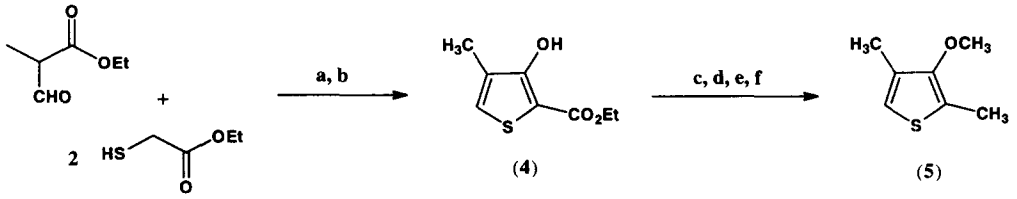


(**3a**) R=Me
(**3b**) R=Et

A thiolactone ring, like the one in compounds **1** or **2**, may exhibit keto-enol tautomerism, the enol form being a 2-hydroxythiophene if the ring already contains a double bond.[4] Since the keto form strongly predominates in this equilibrium, the preparation of a thiolactone can be achieved by methods of synthesis of 2-hydroxythiophenes. Our interest in the synthesis of analogs of the thiomycins **3** led us to investigate if we could take advantage of this fact to obtain thiolactone **7**. Accordingly we prepared a suitable precursor **5**, and studied its conversion to **7** by thiophene hydroxylation methods. We wish to report here the results of our study.

Results and Discussion

Compound **5** was obtained as outlined in Scheme 1. Its precursor **4** was prepared by modifying slightly



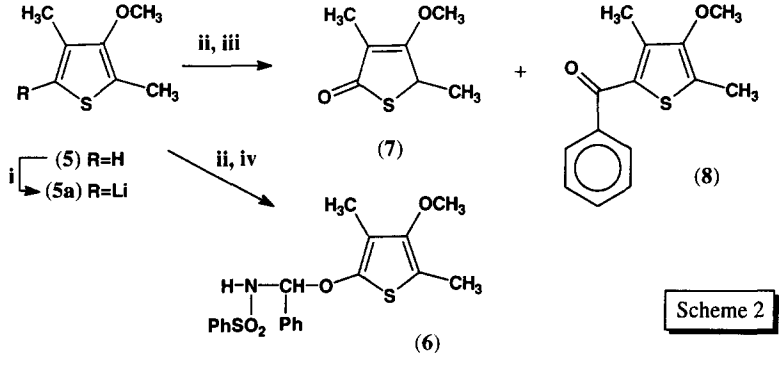
(**4**)

(**5**)

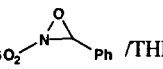
Scheme 1

a: HCl (g); **b:** KOH/EtOH; **c:** CH_2N_2/Et_2O; **d:** $LiAlH_4$/THF; **e:** PDC/CH_2Cl_2; **f:** 1. $H_2NNH_2\,H_2O$; 2. KOH

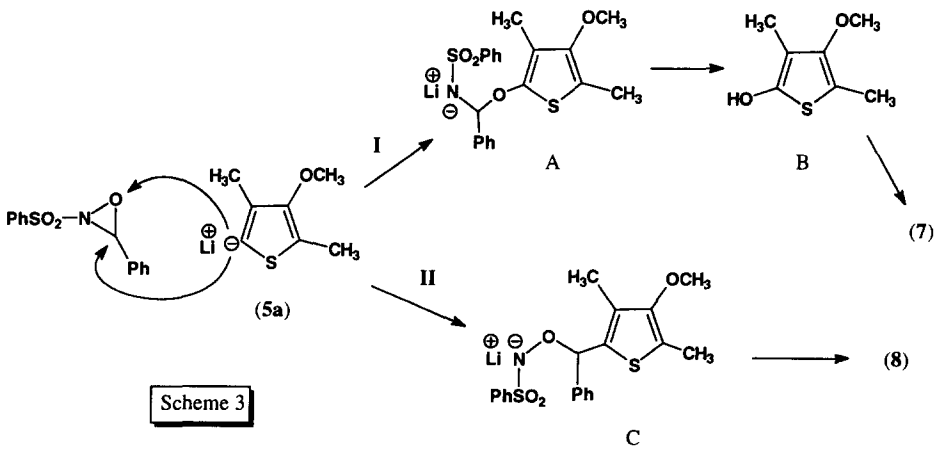
Fiesselman's thiophene synthesis.[5] Reduction of the carbethoxy moiety in **4** to the methyl in **5** could be achieved in satisfactory yield (60% overall) in a stepwise fashion, as indicated in Scheme 1. With **5** at hand, current methods for hydroxylation of mono- and disubstituted thiophenes were tried but found to be unsuccessful.[6] Vilsmeier formylation of **5** was successfully carried out, but Baeyer-Villiger oxidation of the formylated product did not work. While looking for other methods to carry out the desired transformation, we decided to try Davis' protocol. This procedure was initially used for the oxidation of organometallic compounds to phenols or alcohols.[7] It has found application for the oxidation of various other compounds.[8,9,10] Indeed, adding 2-(phenylsulfonyl)-3-phenyloxaziridine to a THF solution of **5a** produced an intense red solution which after hydrolysis with aqueous NH_4Cl and chromatographic separation afforded **7** in 59% yield, together with a 24% yield of **8** (see Scheme 2).[11,12]



Scheme 2

i: n-BuLi/THF,-15°C; **ii:**  /THF,-20°C; **iii:** NH_4Cl/H_2O; **iv:** H_2O

Initial experiments were worked up without adding NH_4Cl, only by evaporating the extract and subjecting the residue to chromatography. In this way we could isolate hemiaminal **6**[11,12] in 46% yield, providing yet another example where such an intermediate has been isolated and thus supporting the proposed mechanism.[13]

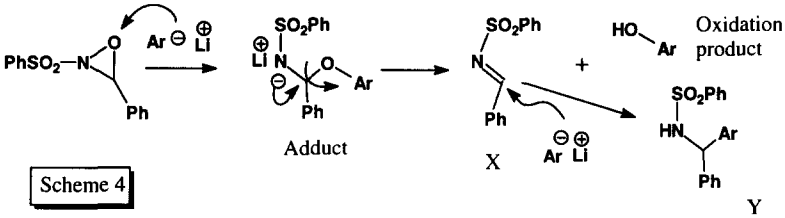


Scheme 3

In Scheme 3 we illustrate the two pathways by which we believe **5a** reacts with 2-(phenylsulfonyl)-3-phenyloxaziridine. Pathway **I** leads to the expected hydroxylation product **7** as a consequence of attack at the

oxygen atom, while in pathway **II**, the anion attacks at the carbon atom to form intermediate **C**, which after treatment with NH_4Cl affords ketone **8**.

In a previous study,[13b] the isolation of sulfonamides **Y** (Scheme 4) was explained as a consequence of the organometallic anion's attack on the carbon atom originally present in the oxaziridine ring. That is, if the initial adduct is short-lived, it splits into the sulfonylimine **X** and the normal oxidation product. The organometallic anion still present in the reaction medium adds to the imine to give **Y**. No such sulfonamide was detected in our work, hence the formation of **8** can only be explained by a direct attack of **5a** on the oxaziridine.



Scheme 4

Both, the hydroxylation of a heterocycle using Davis' oxaziridine reagent as well as the direct attack at the ring carbon of this reagent are to the best of our knowledge, unprecedented.

Conclusions

The hydroxylation of a trisubstituted thiophene was successfully carried out using 2-(phenylsulfonyl)-3-phenyloxaziridine to give a thiolactone moiety. The isolation of hemiaminal **6** gives support to the generally accepted hydroxylation mechanism, while ketone **8** provides evidence for an unusual mode of attack by **5a** at the ring carbon atom of the oxaziridine.[14]

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6. See Ref. 4, pp. 22-38; for example, **5a** was treated without success with butyl borate exactly as described in: a) Hörnfeldt, A. B.; *Ark. Kemi*, **1969**, *29*, 427. b) Hörnfeldt, A. B.; Gronowitz, S. *Acta Chem. Scand.* **1962**, *16*, 789. Transmetalation of **5a** with $MgBr_2$ followed by treatment with MCPBA or bromination of **5**, followed by halogen/metal exchange and oxidation with t-butyl perbenzoate did not work either.
7. Davis, F. A.; Lamendola, Jr., J.; Nadir, U.; Kluger, E. W.; Sedergran, T. C.; Panunto, T. W.; Billmers, R.; Jenkins, Jr., R.; Turchi, I. J.; Watson, W. H.; Shyong Chen, J.; Kimura, M. *J. Am. Chem. Soc.* **1980**, *102*, 2000.
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11. **Experimental Procedure:** A solution of 0.26g (2 mmol) of thiophene **5** in 10mL freshly distilled anhydrous THF under inert atmosphere in a dry 100mL round bottom flask fitted with a septum was cooled to -20°C. Next, 0.1mL of anhydrous HMPA, followed by 5mL (2.4 mmol) of 1.6M n-BuLi was added via syringe and the mixture was stirred for 15 minutes. To the resulting intense yellow transparent solution of **5a** at -20°C, 0.5g (2 mmol) of 2-phenylsulfonyl-3-phenyloxaziridine dissolved in 5mL anhydrous THF was added. The cooling bath was removed and the mixture was stirred for 12h whereby its color changed to deep red. The mixture was worked up by the addition of 15mL of saturated aqueous NH_4Cl, extraction with Et_2O (3 × 15mL), drying the separated organic phase with Na_2SO_4 and evaporating under vacuum the organic solvent. The residue was chromatographed on a 20 × 10cm silica gel plate using as eluent hexane/ethyl acetate 7:3 to afford 0.17g (59%) of product **7** and 0.07g (24%) of product **8**. For the isolation of **6**, the red solution was evaporated at reduced pressure, distilled water was added to the residue and the mixture extracted with ethyl acetate. Drying and evaporating the solvent and purifying the residue on a silica gel plate as above, employing this time as eluent hexane/ethyl acetate 8:2 provided the hemiaminal in 46% yield.
12. Spectral data for compounds **6**, **7** and **8** follow:

Compound 6:

IR (film, cm^{-1}): ν_{max} 3377, 3069, 3042, 2955, 2980, 1602, 1161. **^{1}H-NMR** ($CDCl_3$, δ, ppm): 7.4 (m, 10H), 5.8 (d, 1H, J=8Hz), 5.15 (d, 1H, J=8Hz), 2.2 (s,3H), 1.9 (s, 3H). **MS** m/z (%): 418 (M^+, 7).

Compound 7:

IR (film, cm^{-1}): ν_{max} 1678; 1627. **^{1}H-NMR** ($CDCl_3$, δ, ppm): 4.17 (qt, 1H, J=7Hz, J=1Hz), 4.06 (s, 3H), 1.88 (d, 3H, J=1Hz), 1.61 (d, 3H, J=7Hz). **MS** m/z (%): 158 (M^+, 13).

Compound 8:

IR (film, cm^{-1}): ν_{max} 1632. **^{1}H-NMR** ($CDCl_3$, δ, ppm): 7.83 (m, 2H), 7.5 (m, 3H), 3.7 (s, 3H), 2.39 (s, 3H), 2.37 (s, 3H). **^{13}C-NMR** ($CDCl_3$, δ, ppm): 189.1 (s), 154.6 (s), 139.9 (s), 139.7 (s), 131.9 (s), 131.7 (s),129.5 (d), 128.8 (d, 2C), 128.1 (d, 2C), 61.1 (c), 13.6 (c), 11.7 (c). **MS** m/z (%): 246 (M^+, 9).

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14. This is contribution N° from the Instituto de Química UNAM.

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