A Practical Large-Scale Synthesis of 3-Carbomethoxy-3-sulfolene

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Received 26 August 1999; revised 11 October 1999

Abstract: A simple, efficient one-flask procedure for the large-scale preparation of 3-carbomethoxy-3-sulfolene from trimethylphosphonoacetate is described. The procedure incorporates a cheap and simple sulfide to sulfone oxidation using Oxone®. No chromatography or intermediate purification steps are involved and the product is isolated by crystallisation.

Key words: 3-carbomethoxy-3-sulfolene, 2,5-dihydroxy-1,4-dithiane, Oxone

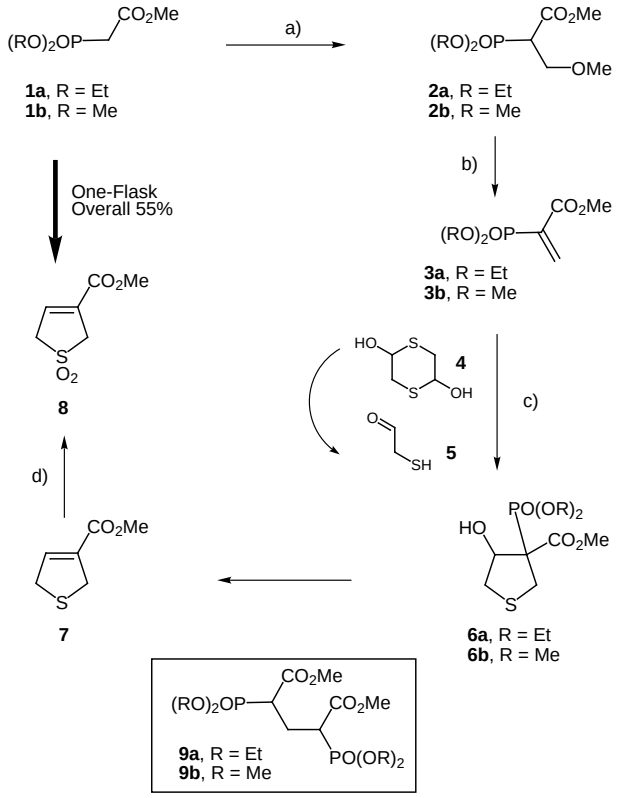
3-Carbomethoxy-3-sulfolene (**8**) is a very useful template for the construction of functionalised masked dienes. In our synthetic studies towards various alkaloids we have exploited the highly selective prenylation of its dianion, to provide flexible 2,3-substituted diene precursors for use in inverse demand intramolecular Diels–Alder reactions.[1-6] Although 3-carbomethoxy-3-sulfolene is commercially available it is prohibitively expensive. A neat synthetic route was published by McIntosh and Sieler some time ago and initially we used this to prepare small quantities of the compound.[7] We found that each step of the route was effective, but overall it was very labour intensive and expensive to carry out the preparative sequence on a large scale. We identified the main problems as being: the mixed ester starting material **1a** was expensive; isolation and distillation of intermediates **3a** and **7** were very time consuming and there were significant material losses during these operations; the final oxidation procedure used *m*-CPBA which is expensive for large-scale work and requires a cumbersome workup.

We required a procedure that would enable us to prepare >100g batches of material routinely without the commitment of time consuming and technically demanding experimental work. Our aim at the outset was to convert the literature synthesis into a one-flask procedure, avoiding isolation of any intermediates. Since 3-carbomethoxy-3-sulfolene is highly crystalline, we hoped that we would also be able to avoid any purification procedures, apart from crystallisation of the final product.

Our study began by carefully monitoring (^{1}H NMR and GC-mass spectrometry) the progress of each step of the synthetic process reported by McIntosh and Sieler. Reaction of **1a** with excess paraformaldehyde in methanol at reflux progressed slowly, but the phosphonate was eventually converted completely (~20 h) to a mixture containing mainly **2a** together with a smaller amount of vinyl phosphonate **3a**. We found that the cheaper reagent, trimethyl phosphonoacetate **1b**, reacted faster than **1a**, but if it was added too quickly compound **9b** was formed in significant amounts. The formation of this by-product was avoided by slow addition of **1b** to a solution of paraformaldehyde (2 equivalents) over a period of 3 hours. The reaction was found to be complete after 5 hours, but we normally found it convenient to leave this step of the process overnight.

To convert methyl ether **2a** into vinyl phosphonate **3a** the methanol solvent was replaced by toluene and the mixture heated at reflux with a catalytic quantity of *p*-toluene sulfonic acid. We found that after 4 hours at reflux, the mixtures formed from either **1a** or **1b** had been converted cleanly into either **3a** or **3b** respectively, and GC/ GC-mass spectrometry indicated that the material formed would be clean enough to use directly in the next step of the procedure. We thought that it would be useful to avoid the change of solvent from methanol to toluene during this first step, so we carried out a range of experiments using toluene, toluene/methanol and toluene/acetic acid mixtures. These trial reactions were also studied at different temperatures. However, in all cases, even using 50% methanol/toluene, the rate of formation of **2a** was reduced and significant quantities of by-products were formed. The most prominent of these was **9a**, formed by reaction of **2a** or **3a** with **1a**. Thus, after much experimentation it was apparent that the slight practical inconvenience of changing solvents from methanol to toluene during the preparation of **3a** was worth accepting in order to maximise the efficiency of its formation.

In the next step of the McIntosh and Sieler sequence 2,5-dihydroxy-1,4-dithiane was cracked, at reflux in dichloromethane, then a solution of distilled **3a** in dichloromethane was added to the α-mercaptoacetaldehyde produced. Instead, we simply allowed the toluene solution from the formation of **3b** (or **3a**) to cool to about 50 °C, then added 2,5-dihydroxy-1,4-dithiane directly and allowed it to react for 3 hours. After this time the vinyl phosphonate had completely disappeared (by GC) and a TLC spot corresponding to dihydrothiophene **7** was the only significant product detected. We particularly wanted to avoid isolation of this intermediate, because of the stench associated with the work-up procedure. An initial attempt to oxidise the thiophene in situ did not provide a very high yield of the sulfolene. However, simply washing the toluene solution with dilute HCl prior to the oxidation step caused a dramatic improvement. We were able to detect some of the intermediate **6a** in the reaction mixture prior



Reagents and conditions: a) paraformaldehyde/piperidine (cat.)/ MeOH/reflux, 24 h; b) Toluene/TsOH/reflux, 4 h; c) i. Toluene/Et_3N/ reflux, ii. HCl wash; d) Toluene/aqueous Oxone/vigorous stirring

Scheme

to the acid wash and this may have been responsible for the low yield.

The use of *m*-CPBA is prohibitively expensive on a large scale and removal of the *m*-chlorobenzoic acid by-product can be problematic. We therefore sought an alternative cheap oxidising agent, which could be used to oxidise the dihydrothiophene before isolation from the toluene solution. A variety of oxidising agents are commonly employed to convert sulfides to sulfoxides. Oxone® (potassium peroxymonosulfate ($2KHSO_5.KHSO_4.[K_2SO_4]$) is a cheap reagent and convenient to use. Trost and Curran reported sulfide to sulfone oxidations using Oxone in methanol and this methodology should probably be more widely exploited. [8a-c] In some cases catalysts have been required to activate the reagent.[9a,b] We wanted to oxidise dihydrothiophene **7** in situ in toluene and we found that simply stirring a two phase mixture of the toluene solution with aqueous Oxone brought about a clean transformation to the sulfolene **8**. Furthermore, following subsequent extraction and evaporation of the toluene solution, 3-carbomethoxy-3-sulfolene was isolated by simple crystallisation from ethanol in 55% overall yield. The procedure works just as well with the cheaper trimethyl phosphonoacetate starting material **1b** and has been carried out on various scales up to 200 g.

Thus, we have developed a very simple and cheap one-flask method for the preparation of 3-carbomethoxy-3-sulfolene, which can be carried out on any scale. No chromatography or intermediate purification steps are involved, the procedure does not require a high level of technical skill and can indeed be carried out with very little attention in less than two days.

3-Carbomethoxy-3-sulfolene

A stirred suspension of paraformaldehyde (6 g, 0.20 mol) and piperidine (1.3 mL, 1.5 g, 0.018 mol) in MeOH (100 mL) was heated at reflux for 1 h. A solution of trimethylphosphonoacetate (18.6 g, 0.1 mol) in MeOH (100 mL) was then added over 3 h. After a further 2 h at reflux, GC analysis indicated that all the starting material had reacted and the solution contained a mixture of vinyl phosphonate **3b** and methanol adduct **2b**. Most of the MeOH was then removed by rotary evaporation and the residue was dissolved in toluene (200 mL). *p*-Toluene sulfonic acid monohydrate (0.3g, 0.0016 mol) was added to the mixture and it was heated under reflux in a Dean–Stark apparatus for 5 h. During this time solvent (~2 mL aliquots) was removed from the collecting leg of the Dean–Stark apparatus at intervals, until a total of 50 mL had been removed over about 3 h. After 4 h GC analysis indicated complete conversion of the original mixture to the vinyl phosphonate **3b**. The mixture was then allowed to cool to about 50 °C prior to the addition 2,5-dihydroxy-1,4-dithiane (8.0 g, 0.053 mol) and Et_3N (18 mL, 0.25 mol). After 4 h, all the vinyl phosphonate **3b** had disappeared (by GC). The mixture was then allowed to cool to r.t., and washed with 2M HCl (3 x 100 mL). The acid solution was back-washed with CH_2Cl_2 (2 x 30 mL) and the combined organic extracts were then cooled in an ice bath and stirred vigorously. A solution of Oxone (92.2 g, 0.15 mol) in H_2O (400 mL) was then added over about 30 min and stirring was continued for a further 30 min. The toluene was then separated from the aqueous layer and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated. 3-Carbomethoxy-3-sulfolene (**8**) (8.43 g, 48% yield) crystallised from EtOH, and a further 1.30 g was obtained upon concentration of the mother liquor (total, 9.73 g, 55% yield).

Mp: 64 °C (Lit.,[7b] 57–58 °C).

IR(thin film): ν_{max} = 1721, 1313, 1268, 1214, 1133, 1073 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.81 (s, 3H, CO_2Me), 3.96–4.04 (m, 4H, 2-H_2, 5-H_2), 6.98–7.04 (m, 1H, 4-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.2, 54.7, 57.4, 129.3, 133.5, 162.2.

MS (NH_3, Cl): *m/z* = 194 $[M+NH_4]^+$ (100%).

HRMS: *m/z* calc for $C_6H_8O_4S+NH_4$ $(M+NH4)^+$: 194.0487. Found: 194.0488.

Anal. Calc for $C_6H_8O_4S$ (176): C, 40.87; H, 4.58. Found: C, 41.09; H, 4.56.

Acknowledgement

We would like to thank Dr. M. Stuckey at the University of Salford for NMR spectra and Mrs. R. Howarth for GC-mass spectra. We also thank Glaxo–Wellcome Research and Development for a studentship (ABH).

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Article Identifier:
1437-210X,E;1999,0,04,0507,0509,ftx,en;P05599SS.pdf