THE SYNTHESIS OF 2-SUBSTITUTED 3-KETOTETRAHYDROTHIOPHENES USING A HIGHLY ACTIVE DIECKMANN CATALYST. 11-DESOXY-9-THIAPROSTAGLANDIN

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A highly active form of sodium methoxide permits the Dieckmann cyclisation of diesters of general structure 1 at r.t., without concomitant β-elimination of the sulfide moiety. The conversion of 2-(6'-methoxycarbonylhexyl)-3-ketotetrahydrothiophene (4) to 11-desoxy-9-thiaprostaglandin (8) is described.

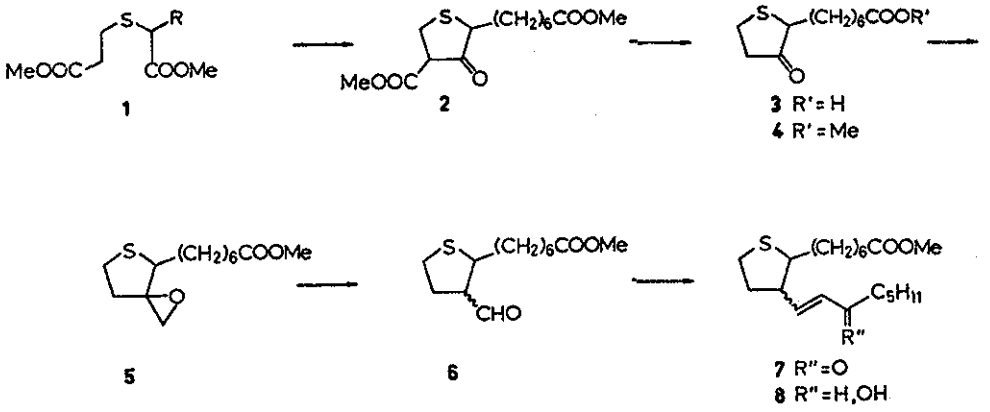
In connection with a program directed to prostaglandin analogs we needed 2-substituted 3-ketotetrahydrothiophenes, since we anticipated their ready conversion to 11-desoxy-9-thiaprostaglandins.

Two suitable general routes to tetrahydrothiophenes are (i) the reaction of 1,4-dihalides with sodium sulfide and (ii) the Dieckmann cyclisation of substituted sulfides.[1] The former method, however, is less useful with functionalised systems, because of the strong nucleophilic nature of sodium sulfide. A good Dieckmann synthesis of 3-ketotetrahydrothiophene is available in the literature,[2] but we were unable to introduce the side chain by alkylation at the 2-position.[3]

The Dieckmann cyclisation of diesters of general structure 1, with built-in side chain, is always accompanied by appreciable β-elimination of the sulfide moiety[1] followed by polymerisation of the formed acrylic ester. In order to suppress this side reaction it is essential to use a low reaction temperature. However, none of the bases published thusfar in the literature can catalyse the Dieckmann cyclisation of 1 below the temperature where elimination is prevented.

We now wish to report an extremely active form of sodium methoxide which can cyclise 1 at r.t. in practically quantitative yield. The procedure, which has been successfully applied by us to esters 1 with various groups R, is exemplified by the ring-closure of 2-methoxycarbonylethyl (dimethyl 2'-azelayl) sulfide (1, $R=(CH_2)_6COOMe$).[4]

The procedure cannot be applied to the sulfone diesters, corresponding to 1 since the better leaving group character of the sulfinate anion causes complete elimination, followed by the formation of SO_2 and dimethyl azelate upon acidification.[5]



General Dieckmann cyclisation procedure

Sodium (4.6 g, 0.2 mol) was dissolved in the minimal quantity of methanol. Toluene (150 ml) was added to the refluxing solut-

ion. The solvent was slowly distilled while a gentle stream of nitrogen was passed through the apparatus. The volume of the liquid was kept constant by the gradual addition of toluene. When the distillate reached the temperature of 106°C the suspension of sodium methoxide was chilled in ice and the ester 1 (R=$(CH_2)_6$-COOMe, 33.4 g, 0.1 mol) was introduced dropwise. After stirring at r.t. (20 hr) the mixture was again chilled and acetic acid (12.6 g, 0.21 mol, in 150 ml ether) was dropped in. The mixture was stirred at r.t. (15 min), the precipitated sodium acetate filtered off and flushed with ether. Evaporation of the organic solvents afforded the β-ketoester 2 as an almost colourless oil (29.5 g, 97%) which crystallised upon cooling (mp 11-14°C).

Decarboxylation of 2 and conversion to 8

The decarboxylation of 2 was performed by stirring a mixture of 2 (29.5 g, 97 mmol), acetic acid (75 ml) and sulfuric acid (300 ml, 12.5%) under nitrogen for 4 hr at 85-90°C. After cooling solid bicarbonate was slowly added until the mixture was acid to litmus paper and neutral to universal indicator paper. Icy water was added to dissolve the inorganic salts. The precipitated acid 3 was collected, washed with icy water and dried (18.3 g, 82%, mp 43-47°C, contaminated with less than 3% of the corresponding methyl ester).

Esterification of 3 with azeotropically dried acidic ion resin at r.t.[6] gave 4 which was converted without purification to a mixture of the stereoisomeric epoxides 5 (in a 4:1 ratio) by the use of dimethyloxosulfonium methylide[7] at r.t.

Part of the mixture 5 was oxidised to the corresponding sulfones and separated into the diastereomeric racemates by chromatography. To the isomer formed in excess we tentatively assigned

the structure with the epoxide oxygen cis with respect to the side chain, based upon Johnson's theory[8] and the nmr data.

The remainder of the mixture 5 was isomerised to the formyl derivative 6 and subsequently condensed with diethyl 2-oxoheptylphosphonate to give 7. Reduction of the enone gave 11-desoxy-9-thiaprostaglandin 8 as a mixture of C_{15}-epimers.

References and notes

1. (a) D.E. Wolf and K. Folkers, "Organic Reactions", ed. by R. Adams, J. Wiley & Sons Inc., New York, Vol. VI, 1951, p. 410; (b) J.P. Schaefer and J.J. Bloomfield, Ibid., Vol. 15, 1967, p. 1.
2. R.B. Woodward and R.H. Eastman, J.Amer.Chem.Soc. 1946, 68, 2229.
3. The low yield in the preparation of 2-acetyl-3-ketotetrahydrothiophene, reported by G. Büchi, P. Degen, F. Gautschi and B. Willhalm, J.Org.Chem., 1971, 36, 199, is an indication of the generality of this problem.
4. Prepared by the reaction of methyl 3-mercaptopropionate and dimethyl α-bromoazelate.
5. A comparable decomposition has been described by J.A. Reuterskiöld, J.Prakt.Chem., 1930, 127, 269 and has also been observed by us when dimethyl α-mercaptoazelate was oxidised to the corresponding sulfinic acid following W.G. Filby, K. Günther and R.D. Penzhorn, J.Org.Chem., 1973, 38, 4070.
6. G.F. Vesley and V.I. Stenberg , Ibid., 1971, 36, 2548.
7. When the temperature is raised to complete the reaction, almost all epoxide decomposes. A comparable observation has been made by P.L. Stotter and R.E. Hornish , J.Amer.Chem.Soc., 1973, 95, 4444.
8. C.R. Johnson, C.W. Schroeck and J.R. Shanklin, Ibid., 1973, 95, 7424.

Received, 27th December, 1976