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A STEREOSPECIFIC SYNTHESIS OF FUNCTIONALISED CYCLOPENTENE DERIVATIVES. NEW PRINCIPLE OF CARBON-CHAIN LENGTHENING.

Eric Cossement, Robert Binamé and Léon Ghosez *

Laboratoire de Chimie Organique de Synthèse

Université Catholique de Louvain, Place Louis Pasteur 1

B – 1348 Louvain-la-Neuve, Belgium

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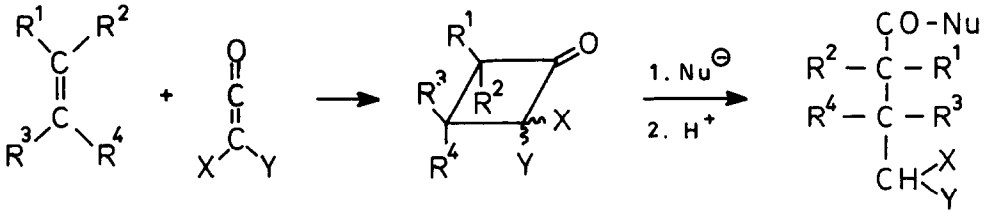
Ketenes bearing α-carbanion-stabilizing substituents are useful synthetic intermediates [1,2] offering the interesting possibility of effecting the *position- and stereospecific addition of two carbon-chains to an olefinic substrate* (scheme 1).

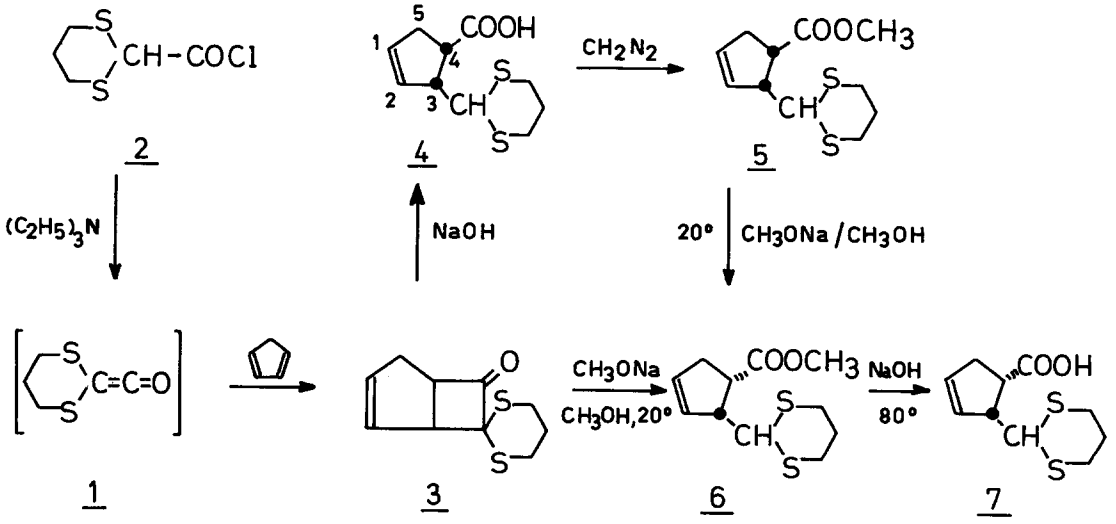


Scheme 1: General Principle

Ketenes bearing thioalkyl-substituents (X=SR, Y=alkyl, aryl, SR) should be suitable reagents for this purpose since : (a) they are expected to undergo [2+2] cycloadditions easily [1] ; (b) they should give cyclobutanones susceptible to facile cleavage by nucleophilic reagents [1,3] ; (c) they should lead to ring-opened products which still contain interesting and different functionalities.

We wish to report the successful use of 2-carbonyl-1,3-dithiane 1 for a regio- and stereospecific method of synthesis of functionalised cyclopentene derivatives.

2-Carbonyl-1,3-dithiane 1 was generated *in situ* from the reaction of 2-chlorocarbonyl-1,3-dithiane [4] 2 (18 g, 0.1 mole) with triethylamine (10.1 g, 0.1 mole) in 200 ml of ether. In the presence of a two-fold excess of cyclopentadiene (12 g, 0.2 mole), a 1:1 adduct 3, m.p. 71°9 C, was obtained in 70% yield [5] : m/e 212 (M^+ for $C_{10}H_{12}OS_2$) ; ir (KBr) 1774 ($\nu_{C=O}$), 1605 ($\nu_{C=C}$) cm^{-1}; nmr ($CDCl_3$) δ 5.95 (m, 2 olefinic H), 4.37 (d x d x d, H-C (5)) 3.3 (m, 2 CH_2), 2.75 (m, 3 allylic H), 2.02 (m, 1 CH_2). As in related adducts, obtained from various ketenes and cyclopentadiene [6] , H-C (5) couples fairly strongly (J = 8 Hz) with the exo H-C (4) but only weakly (J = 3 Hz) with the endo H-C (4). These observations established the structure of 3 and further confirmed that ketenes-cyclopentadiene cycloadditions are regiospecific. Treatment of 3 (1.06 g, 5 mmoles) with a solution of NaOH (0.29 g, 5 mmoles) in 30 ml of H_2O for 3 hrs at 70° C yielded the acid [5] 4 (1.18 g, 98%), m.p. 106.5° C, which was esterified with diazomethane to the methyl ester 5 (purified by chromatography on silica-gel, elution with ethyl acetate/benzene, 20/80). The spectroscopic properties of 4 and 5 confirmed their gross structures but did not allow establishment of the



Scheme 2

relative configurations of the side chains. However this problem was readily solved when it was observed that treatment of 5 with a catalytic amount of CH_3ONa for 16 hrs at room temperature yielded the epimeric methyl ester 6 which could be obtained independently by reacting 3 for 15 hrs at room temperature with a methanolic solution of CH_3ONa [7]. Under these conditions which cause epimerization at C(4), no isomerization to an α,β conjugated ester was observed, further confirming the position of the C=C double bond in 3. Hydrolysis of ester 6 in aqueous NaOH at 80° C gave an acid 7 m.p. 112.9° C, which showed spectral data [5] in agreement with the proposed structure but significantly different from those of 4. From these observations we assigned the *trans* configuration to the thermodynamically more stable ester 6 and acid 7 and the *cis* configuration to 4 and 5. Either *cis* or *trans* isomer can thus be specifically prepared by one of the routes chosen in scheme 2: in methanol, the strongly basic methoxide anion readily abstracts the proton α to the ester group and causes easy epimerization whereas in aqueous NaOH the initially formed *cis* configuration is preserved, since the carboxylate anion, formed by opening of the four-membered ring, does not sustain a carbanion at C(4).

In conclusion, *by the cycloaddition-ring cleavage sequence described, we have achieved the position- and stereospecific addition of two one-carbon units to a double bond of cyclopentadiene.*

This additional method of synthesis of cyclopentene derivatives offers not only the merit of being simple and inexpensive, but also results in the introduction of two structurally quite different reactive groups which should allow for specific transformations at C(3) or C(4) (e.g. further chain lengthening).

The compounds described here are potential intermediates for the synthesis of prostaglandin derivatives. Further work in this direction as well as the extension of the principle (scheme 1) to other systems will be discussed in subsequent papers.

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(4) 2 was obtained conventionally from the reaction of glyoxylic acid monohydrate with 1,3 propanedithiol in benzene containing a catalytic amount of p-toluene sulfonic acid, followed by treatment of the acid with oxalyl- or thionyl chloride (overall yield 69%).

(5) All compounds reported here gave satisfactory elemental analysis and consistent ir, nmr and mass spectra.

(6) M. Rey, S. Roberts, A. Dieffenbacher and A.S. Dreiding, Helv. 53, 417 (1970).

(7) Upon completion of this work (E. Cossement, Ph.D. Dissertation, September 1973), a similar cleavage was reported by B.M. Trost, M. Preckel, J. Amer. Chem. Soc., 95, 7862 (1973).