Tetrahedron Letters,Vol.23,No.13,pp 1409-1412,1982 0040-4039/82/131409-04$03.00/0
Printed in Great Britain

STEREOSPECIFIC CYCLOPROPENIC SYNTHESIS OF CIS-CHRYSANTHEMIC METHYL ESTER.2. THE BY-PASSING DIAZOALKANE WAY (1).

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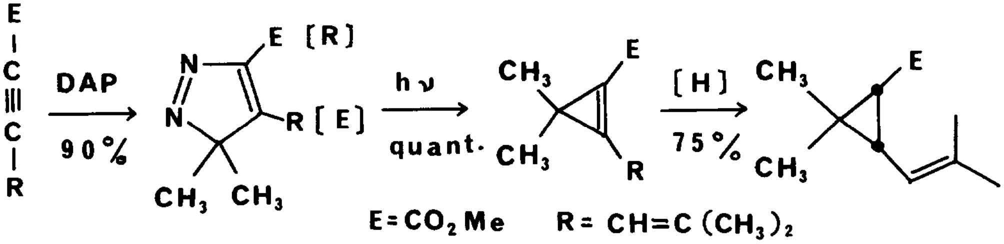
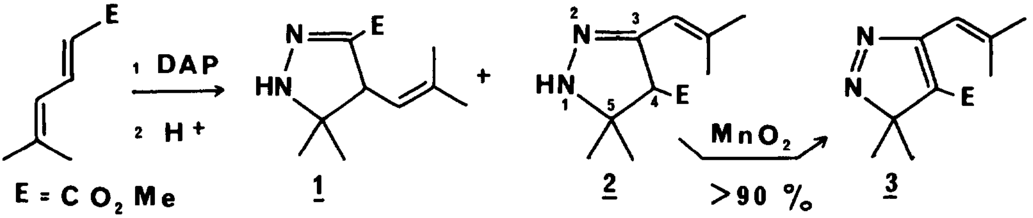
A stereospecific synthesis of cis-chrysanthemate by catalytic hydrogenation of a cyclopropene is described The required precursor, a 3H-pyrazole, is obtained here via a novel dianion reaction and MnO_2 dehydrogenation of a Δ^2-pyrazoline, instead of the more cumbersome diazoaddition method.

The powerful natural insecticides from pyrethrum are all esters of trans-chrysanthemic or pyrethric acids. It was however seen that unnatural cis-chrysanthemic esters can show higher activities (2). We reported recently on one of the very few total stereospecific syntheses of cis-chrysanthemic methyl ester in which the key step involved the selective hydrogenation of the corresponding cyclopropenic ester (3) :

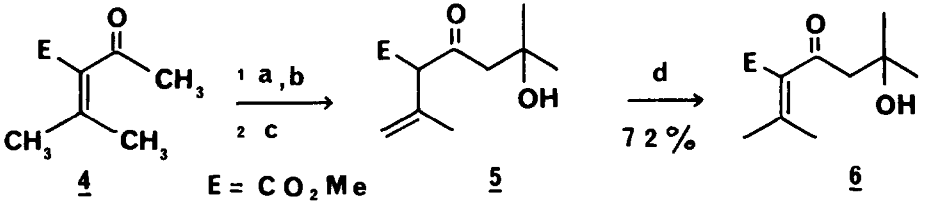


This synthesis, although very simple and fortunately devoid of complications, suffers nevertheless from some drawbacks, the main of which being the use of the highly unstable 2-diazopropane (DAP). This paper describes now a new cyclopropenic synthesis of cis-chrysanthemic ester which does not necessitate an acetylenic starting ester nor an unstable diazoalkane. Furthermore, no sophisticated selective hydrogenation step is required.

The easiest way to reach to a cyclopropenic ester being still the photolysis of a 3H-pyrazole, the problem was to obtain the latter otherwise than by a 1,3-dipolar cycloaddition reaction. With this goal in mind, we found that a number of 5,5-dimethyl Δ^2-pyrazolines can rapidly be dehydrogenated in high yields to 3H-pyrazoles with manganese dioxide (4,5). The ease of this conversion is however strongly dependent from the substitution pattern and we had,at first, to check the feasibility of the reaction in this particular case. The cycloaddition of 2-diazopropane to methyl δ-methylsorbate leads, after acidic treatment, to a mixture of the Δ^2-pyrazolines 1 and 2 (4,6). The reversed regioisomer 2, is cleanly oxidized by MnO_2 into the known 3H-pyrazole 3 (3), whereas the isomeric structure 1 is transformed into a mixture of several unidentified compounds.



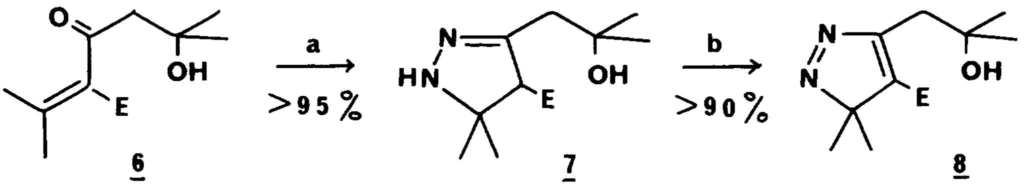
The required Δ^2-pyrazoline, bearing the ester group in position 4, has now to be obtained without a diazoalkane. This is generally achieved most simply by condensation of hydrazine and an α,β-unsaturated ketone (7). As the isobutenylic double bond can be formed in the last step, and in order to escape side reactions during the condensation step with hydrazine, we started from the tertiary alcoholic enone ester 6 conveniently prepared from the known compound 4 (8) by a novel dianion reaction (4,9) :



a: 1,1 equiv. NaH , THF , 65°C b 1,1 equiv Buli , 0°C , 15 min
c 3 equiv. CH_3COCH_3 , r.t. , 15 min d 10g Al_2O_3 basic form for 1g crude 5 , MeOH ; 12 h

6: pale yellow liquid, isolated in 72 % yield from 4, by SiO_2 column chromatography (Hexane-Ether 1 1) , IR ν(OH) 3500 cm^{-1} (broad), ν(C=O) 1720 cm^{-1} and 1685 cm^{-1} , ν(C=C) 1630 cm^{-1}, NMR δ = 1,30 (6H,s) 1,96 (3H,s) 2,12 (3H,s) 2,74 (2H,s) 3,74 (3H,s) and 3,90 (1H, broad s)

The condensation with hydrazine hydrate has to be performed rather drastically, by heating in acetic acid as solvent, distilling finaly the acid under normal pressure, until the temperature of the mixture reaches 180°C. In these conditions the almost pure Δ^2-pyrazoline 7 is obtained in nearly quantitative yield after simple dilution with water and extraction with chloroform. The following oxidation with MnO_2 (10) in methylene chloride is a rapid reaction, giving the sole 3H-pyrazole 8 (11) :

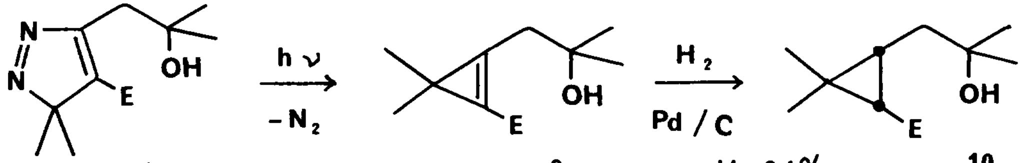


a. 1,1 equiv. N_2H_4,H_2O , AcOH, 180°C
b. 8g MnO_2 for 1g 7 , CH_2Cl_2 under Argon , r t. , 1 h

7 pale yellow liquid , IR broad absorption between 3300 and 3500 cm^{-1}

8. pale yellow liquid, isolated pure in 86 % yield from 6, by filtration on SiO_2 , IR ν(OH) 3500 cm^{-1}, ν(C=O) 1710 cm^{-1}, C=C-C=N 1635 cm^{-1} , UV λmax = 262 nm (7600) and 368 nm (280) , NMR δ = 1,30 (6H,s) 1,53 (6H,s) 3,32 (2H,s) 3,48 (1H,s) and 3,85 (3H,s).

The photolysis of the 3H-pyrazole 8 (12) leads then to the unique cyclopropene 9, which has not to be isolated and is directly hydrogenated catalytically over 5% Palladium on chaircoal. Rapid adsorption of the stoechiometric amount of hydrogen occurs giving the cis-cyclopropanic derivative 10.



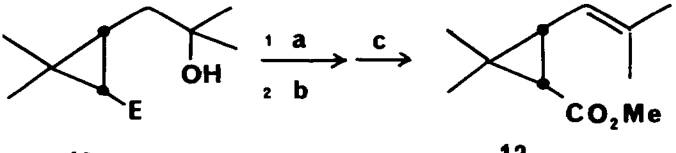
8 9 overall 94% 10

9 can be obtained in 95% yield by evaporation of the irradiation solvent, but not further purified ; liquid, IR ν(OH) 3450 cm^{-1} (broad), caracteristic cyclopropenic absorption at 1825 cm^{-1}, ν(C=O) 1680 cm^{-1}, NMR δ = 1,25 (6H,s) 1,30 (6H,s) 2,76 (2H,s) 3,82 (3H,s) and 4,02 (1H,s)

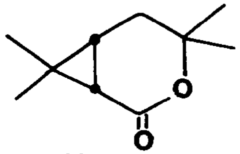
10 colourless liquid, isolated pure in 94% yield by filtration on SiO_2 (Hexane-Ether 2 1) , IR ν(OH) 3400 cm^{-1} (broad), ν(C=O) 1705 cm^{-1} , NMR δ = 1,20 (6H,s) 1,24 (6H,s) 3,62 (3H,s) other H as multiplets between 1,30 and 1,92 (5H).

The clean conversion of the pyrazole 8 into a cyclopropene is remarkable here in view of the fact that the reaction proceeds in this case through an alkylvinylcarbene with an alcoholic function in the same molecule (13).

The last step, i.e. the introduction of the double bond was best achieved with mesyle chloride in presence of an excess of triethylamine. In these conditions no lactonization is observed, in spite of the favourable cis configuration (14), and a 1:2 mixture of cis-chrysanthemic and cis-isochrysanthemic methyl esters is obtained (85%). Isomerization with sulfuric acid, a known procedure (15), gives then the sole cis-chrysanthemate 12 isolated after SiO_2 filtration (2% Ether in hexane) in 76% yield based on the 3H-pyrazole 8 (Overall yield from compound 4 : 47%). A second possibility, in fact the first we tried, is to transform, in contrary, the alcohol 10 into the lactone 11 (t. BuOK , bz, 80°C ; 1 h) which can in turn lead to cis-chrysanthemic acid (60% from the pyrazole) by the known procedure of J. Martel et al. ($MgBr_2$, pyridine ; 125°C ; 14 h) (16).



10 12



11

a. 3,5 equiv. Et_3N , CH_2Cl_2 b 1,5 equiv MsCl ; CH_2Cl_2 -5°C, 20 min , r t , 12 h
c. H_2SO_4 cat , diox. 80°C, 4 h

This work was supported by the CNRS (ATP "Agrochimie", Décision n° 3513). We are also grateful for financial support from Roussel-Uclaf.

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The indicated yields are corresponding to products which gave satisfactory microanalyses, IR ($CHCl_3$), UV (CH_3CN) and H^1-NMR ($CDCl_3$/TMS) spectra

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A general study of dianions obtained from isopropylydene acetoacetates will be published later.

10.) The best reproducible results were obtained with the MnO_2 from Merck Mangan (IV) oxid gefallt aktiv zur Synthese Art. 805958.

11) By successive treatment of this compound with phosphorus tribromide and 1,5-Diazabicyclo [5.4 0]undecene-5, the isobutenylic pyrazole of our previous synthesis is obtained (3).

12.) Medium pressure lamps Philips HPK 125 ; Pyrex glass filter , 0,5% solution in ethyl acetate , 15°C.

13) For instance, in a similar case the intramolecular carbene insertion into an alcoholic O-H bond gave up to 40% epoxide as an unseparable by-product A.C. DAY, M C WHITING J Chem. Soc. (C) 1966, 1719.

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(Received in UK 25 January 1982)