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TOTAL STEREOSPECIFIC SYNTHESIS OF CIS-CHRYSANTHEMIC METHYL ESTER : THE CYCLOPROPENIC WAY (1).

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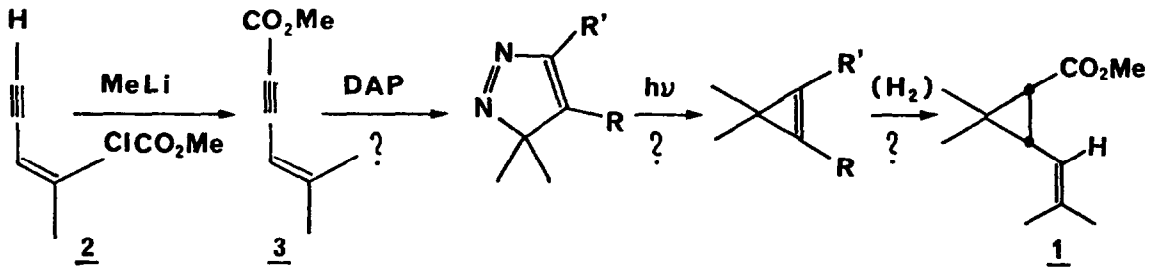
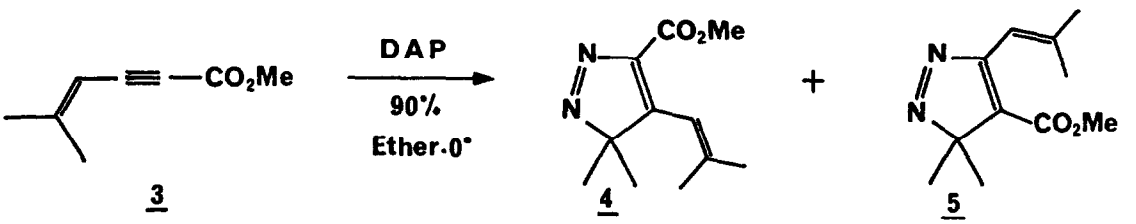
By cycloaddition of 2-diazopropane to isobutenylpropiolic methyl ester one obtains two isomeric gem-dimethyl 3H-pyrazoles. Both isomers give by photolysis the same cyclopropene which can be selectively hydrogenated to cis-chrysanthemic methyl ester.

The powerful natural insecticides pyrethrins and cinerins are all esters of trans-chrysanthemic or pyrethric acids (2). It was however suggested that the unnatural cis-chrysanthemic esters can show higher activities (3). In spite of this, only one stereospecific cis-chrysanthemic acid synthesis was reported (4) when we began our own investigations. The major difficulty in synthesizing this molecule is obviously the stereospecific creation of the cis-disubstitution pattern at the cyclopropane. We described recently a gem-dimethylcyclopropene ester synthesis (5) whose efficiency could, a priori, open up the way to a high yield synthesis of such cis-disubstituted cyclopropane derivatives by mean of simple cis-hydrogenation (6). This paper describes our attempts to apply this scheme to the synthesis of cis-chrysanthemic methyl ester 1 from the known vinylacetylene 2, which is easily converted into the starting acetylenic ester 3 (90% yield).



The 1,3-dipolar cycloaddition reaction (5a) of 2-diazopropane (DAP) to the unsaturated ester 3 at 0°C leads quantitatively to a mixture of the 3H-pyrazoles 4 and 5 ; however the reverse adduct 5 is the major component. No further reaction on any double bond could be detected. The two heterocycles 4 and 5 can thus be easily separated by column chromatography on SiO_2 with hexane-ether solvent in 26% and 63% yield, respectively.

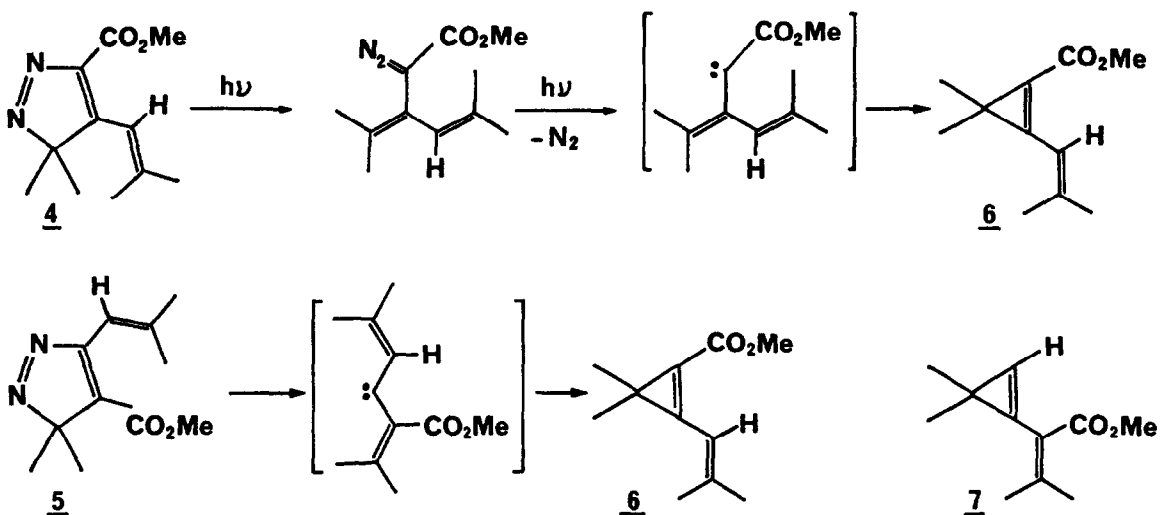


3 4 5

4 :pale yellow crystals F = 98°C ; IR ν(C=O) 1725cm^{-1} ν(C=C) 1610cm^{-1} and 1640cm^{-1} ; UV : λmax 361nm (940) and 303nm (6650) ; NMR : δ(gem CH_3) 1,37ppm (6H,s), isobutenyl signals at 1,60ppm (3H,d) 1,98ppm (3H,d) and 5,83ppm (1H,m) J = 1,0 Hz,δ(CH_3ester) 3,96ppm (3H,s)

5 :pale yellow crystals F = 29°C ; IR ν(C=O) 1700cm^{-1} ν(C=C) 1585cm^{-1}and 1645cm^{-1} ; UV · λmax 384nm (260), 316nm (8050) and 236 (12160) ; NMR : δ(gem CH_3) 1,52ppm (6H,s), isobutenyl signals at 2,05ppm (3H,d) 2,34ppm (3H,d) and 6,76ppm (1H,m) J = 1,0 Hz,δ(CH_3ester) 3,85ppm (3H,s).

UV-irradiation of the minor component 4 causes quantitative expulsion of N_2 giving the cyclopropene 6, as expected on the basis of mechanistical considerations (5b, 7). Very fortunately for our synthesis, the major isomer 5 gives the same cyclopropene 6 by photolysis, a result which could not be as easily forecast. It seems however from general considerations (8) and from our own experience in this field (9) that the cyclization of vinylcarbenes to cyclopropenes is strongly dependent of the steric compression between the vicinal substituents of the vinylic bond. The formation of the most substituted cyclopropene 6 is thus favoured in our case as compared to the cyclopropene 7 in the competing cyclization processes. What so ever, the NMR-spectra of the crude photolysis products from both 3H-pyrazoles 4 and 5 are identical, corresponding to the sole cyclopropene 6 formed almost quantitatively. If formed, the least substituted cyclopropene 7 amounts only traces not detectable by NMR.

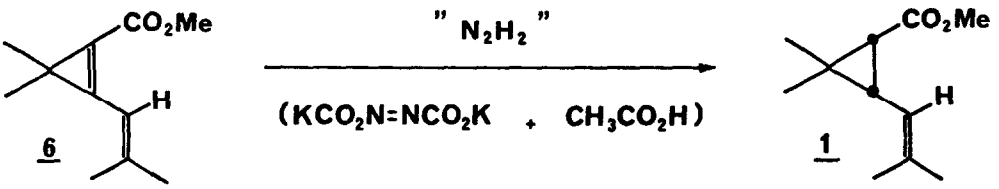


4 6

5 6 7

6 .liquid ; IR 1785cm^{-1}(cyclopropene), ν(C=O) 1695cm^{-1}, ν(C=C) 1620cm^{-1} ; NMR δ(gem CH_3) 1,26ppm (6H,s), isobutenyl signals at 1,95ppm (6H,d) and 6,28ppm (1H,m) J = 1,5 Hz,δ(CH_3ester) 3,75ppm (3H,s).

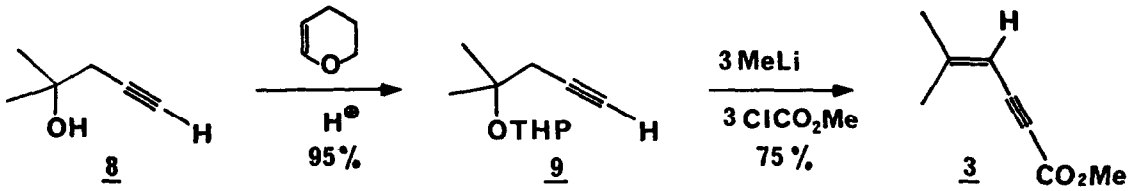
The next step which is the crucial one for the success of the employed methodology, is the selective cis-hydrogenation of the cyclopropenic double bond without reduction of the isobutenyl group. This means that we have to hydrogenate a tetrasubstituted double bond in preference to a trisubstituted one, where however the tetrasubstituted bond is highly strained. From many tested hydrogenation catalysts Nickel boride PI prepared in situ (10) performed the best, with a well defined hydrogen absorption rate difference between the two double bonds. No trans-chrysanthemic ester could be detected. However reduction by diimide (11), was finally found to be the most convenient method. Direct treatment of the crude photolysis product with the dipotassium salt of azodicarboxylic acid in the presence of acetic acid (12) gave us cis-chrysanthemic methyl ester in nearly 90% crude yield from the 3H-pyrazoles. By careful HPLC examination the obtained product was however shown to contain about 5% of an isomeric less polar constituent which was not the trans-chrysanthemate (13). Pure cis-chrysanthemate was finally obtained by SiO_2 column chromatography in 75% yield.



The preparation of pure cis-chrysanthemate from the acetylenic ester 3 could thus actually be achieved with an overall yield of 68%.

We could transform the enyne 2 into the ester 3 in a simple high-yield reaction, but unfortunately the enyne 2 itself is prepared in only 12% yield from the tertiary acetylenic alcohol 8 (14). Therefore we developed a new synthesis of the acetylenic ester 3 from this same alcohol 8,which is readily available from acetone and propargyl bromide (15). We found that the THP protected alcohol 9 is directly converted into the enyne ester 3 by use of an excess of reagents, the O-THP part acting as a good leaving group in these conditions. The transformation of the alcohol 8 into the O-THP derivative followed by this new one-pot elimination-substitution reaction leads to the ester 3 in 71% yield.

3 : colourless liquid , IR ν(C≡C) 2190cm^{-1} ; ν(C=O) 1705cm^{-1}, ν(C=C) 1625cm^{-1} ; UV : λmax 260 nm (10100) ; NMR : isobutenyl signals at 1,89ppm (3H, large s) 1,98ppm (3H, large s) and 5,35ppm (1H,m), δ(CH_3ester) 3,76ppm (3H, s).



The overall yield of our total 6 step synthesis starting from the cheap commercial materials acetone and propargyl bromide is then 40%, which compares favourably with the previous stereospecific synthesis of cis-chrysanthemic acid. Hence the speculative use of a cyclopropene proved to be effective. This was equally shown in another recent approach to the same compound where a cyclopropene is also the key intermediate (16).

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

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