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SYNTHESIS OF ISO-ARTEMISIA AND ARTEMISIA KETONES FROM ETHYLENIC DITHIOESTERS.

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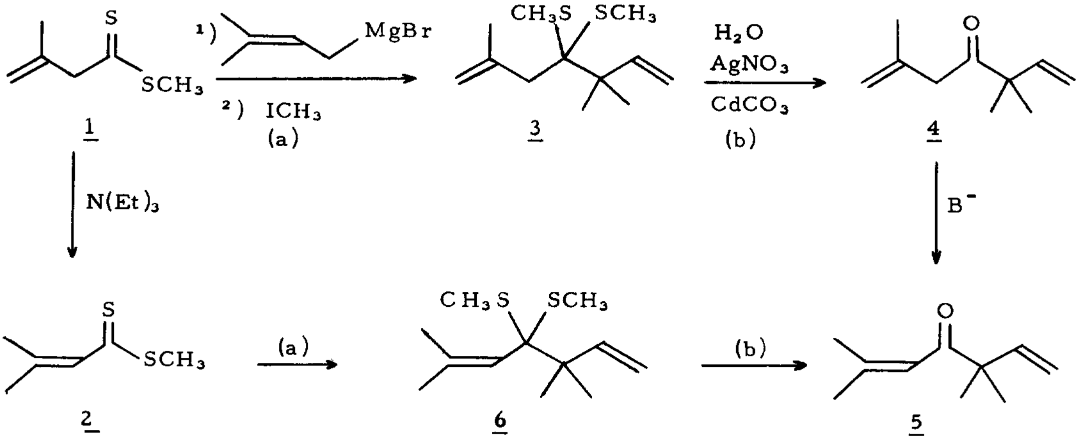
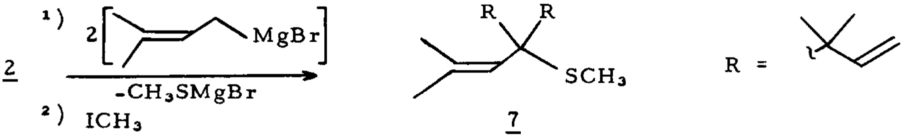
We have recently shown that both carbophilic and thiophilic additions of Grignard reagents to dithioesters could be conveniently used for the synthesis of β-unsaturated ketones (1). The scope of this synthetic path could be broadened by using olefinic dithioesters. We have now developped in our laboratory a new general method for the synthesis of dithioesters which enables us to prepare some α-and β -unsaturated dithioesters with good yields (2). We report here the synthesis of iso-artemisia ketone 4 (2,5,5-trimethylhepta-1,6-dien-4-one) and artemisia ketone 5 (3,3,6-trimethylhepta-1,5 dien-4 one) (3) via their dithioacetals obtained by the carbophilic addition of prenyl magnesium bromide (with the expected "inversion" of the allylic chain (1)) to respectively methyl 3-methyl-3-butenedithioate 1 and methyl 3-methyl-2-butenedithioate 2 , followed by alkylation (scheme). However, the first path gave the better yield and ketone 5 was obtained in 63 % yield after quantitative isomerisation of ketone 4 by a trace of base.



Experimental : Under nitrogen and with stirring, 0.125 mole of dithioester 1 mixed with 0.4 mole of methyliodide were added in 2 hrs, to a solution cooled at -78°C of prenylmagnesium bromide (prepared with 0.5 mole of prenylbromide in 300 ml of tetrahydrofuran according to known procedure (4)). After addition and complete disappearance of the yellow color of dithioester, the temperature was allowed to rise slowly to -15°C in order to achieve the methylation. The mixture was then hydrolysed and the dithioacetal 3 was extracted with petroleum ether and dried over sodium sulfate.

After evaporation of the solvent, crude 3 [25.8 g ; Yield : 90 % ; NMR (CCl$_4$, δ_{TMS}= 0): 1.2 (s, 6H) ; 1.97 (broad s, 3H) ; 2.03 (s, 6H) ; 2.42 (~s, 2H) ; 4.67-5.13 (m, 4H) 5.9-6.43 (m, 1H)] was treated, in 800 ml of methanol and in the presence of 75 g of cadmium carbonate, by a solution of 38,23 g of silver nitrate in 42 ml of water according to a procedure already described (5,1). 16.05 g of crude iso-artemisia ketone 4 were isolated. [NMR ^{1}H (CCl$_4$) : 1.18 (s, 6H) ; 1.68 (broad s, 3H) ; 3.05 (~s, 2H) ; 4.6 (broad s, 1H) ; 4.77 (broad s, 1H) ; 4.87-5.28 (m, 2H) ; 5,6-6.15 (m, 1H). NMR ^{13}C (CDCl$_3$, TMS) : 22.64 (CH$_3$ on C$_2$) ; 23.56 (2CH$_3$ on C$_5$) ; 46.20 (C$_3$) ; 51.30 (C$_5$) ; 114.56 and 114.68 (C$_1$, C$_7$) ; 139.76 (C$_2$) ; 143.46 (C$_6$) ; 210.30 (C$_4$). IR : $\nu_{C=O}$ = 1695 cm^{-1}]. 4 was refluxed 36 hrs in 75 ml of ether containing 0.6 g of piperidine and after washings with dilute chlorhydric acid, drying over sodium sulfate, evaporation of ether and distillation through a vigreux column, 11,19 g of artemisia ketone 5 was collected. [b.p.$_{13\ mm}$: 67° ; Yield : 63 %; NMR ^{1}H (previously reported (6)) ; NMR ^{13}C (CDCl$_3$, TMS) : 20.82 (CH$_3$ on C$_6$) ; 23.68 (2CH$_3$ on C$_3$) ; 27.81 (CH$_3$ on C$_6$) ; 50.33 (C$_3$) ; 113.71 (C$_1$) ; 120.69 (C$_5$) ; 143.40 (C$_2$) ; 155.60 (C$_6$) 220.71 (C$_4$) ; IR : $\nu_{C=O}$= 1660 cm^{-1}] . Isomerisation 4 → 5 can also be obtained in methanol by a trace of sodium hydroxyde.

From dithioester 2 and with the same experimental procedure dithioacetal 6 was obtained [NMR (CCl$_4$) : 1.17 (s, 6H) ; 1.79 (d,~1 Hz, 3H) ; 2.00 (s and d, 6H + 3H) ; 4.73-6.45 (m, 4H)] . The NMR spectra showed that crude 6 was not pure. After hydrolysis of crude 6, artemisia ketone was obtained in only 15 % yield. The secondary product 7 was identified (NMR, mass spectra) as the double addition (7) product of the Grignard reagent to 2 .



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7. Double addition occured extensively when we attempted to prepare the dithioacetal of ketone 4 by using methyl 2,2-dimethyl-3-butenedithioate (2) and methallylmagnesium chloride.