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ON THE MECHANISM OF THE CHRYSANTHEMIC ESTER SYNTHESIS

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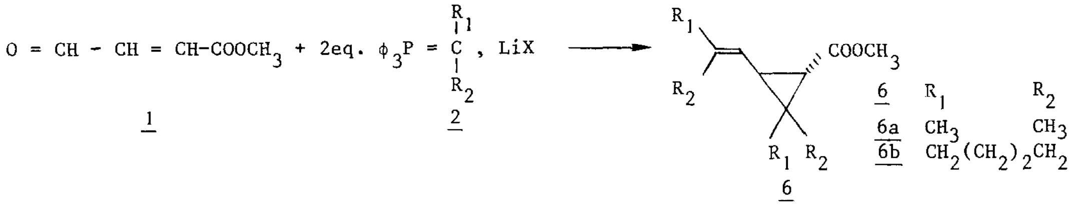
Summary : The intimate mechanism of the one pot synthesis of chrysanthemic esters from methyl 4-oxo-butenoate and phosphorus ylide is disclosed. The first equivalent of ylide reacts selectively on the aldehyde function and the cyclopropanation occurs on the preformed betaine prior to its decomposition.

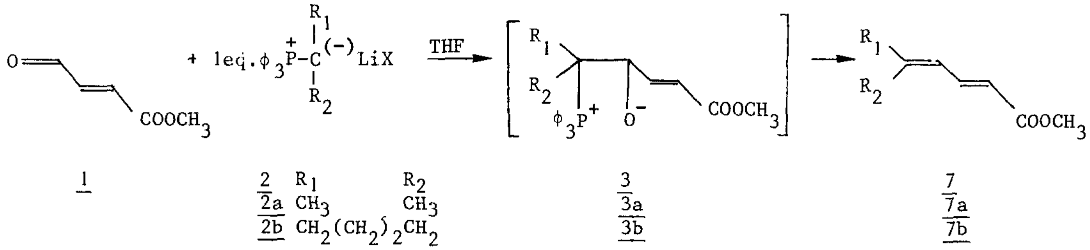
We recently proposed [1] new synthetic routes to chrysanthemic esters 6 identically substituted on the carbon-carbon double bond and on the cyclopropane ring, from methyl 4-oxobutenoate 1 and isopropylidene or cyclopentylidene triphenyl phosphoranes 2 (Scheme I).

SCHEME I



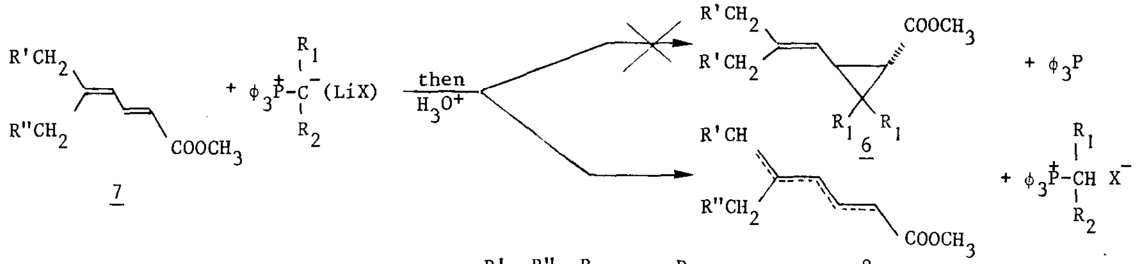
During the course of this work [1], we found that dienoic esters 7 are exclusively formed when only one equivalent of ylide 2 is reacted on methyl 4-oxobutenoate 1 (Scheme II).

SCHEME II



Surprisingly, these dienoic esters 7 do not produce even trace of expected chrysanthemic derivatives 6 when reacted with one further equivalent of ylide 2. Instead quantitative metalation occurs (in THF at -78°C or -20°C) leading on hydrolysis to the starting phosphonium salt (100%) and a mixture of starting and isomerized dienoic esters 8 (Scheme III).

SCHEME III



R'	R"	R_1	R_2	
H	H	CH_3	CH_3	8a
CH_2-CH_2		$CH_2(CH_2)_2CH_2$		8b

These results suggest that in the reaction outlined in Scheme I, the first equivalent of ylide 2 reacts on the aldehydic function of methyl 4-oxobutenoate 1 and that the cyclopropanation occurs on betaïne 3.

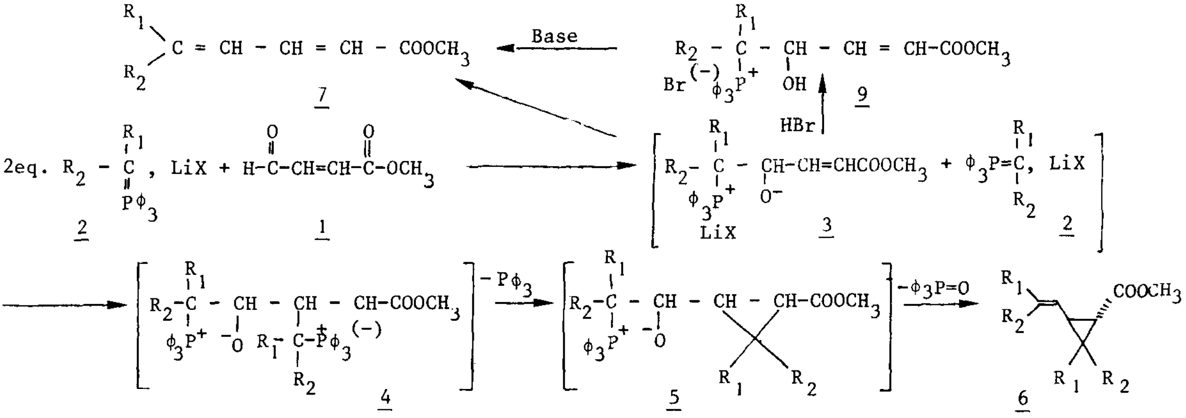
We therefore propose that the real sequence of elementary steps is the one depicted in Scheme IV betaïnes 3 being the key intermediates. These can be the site of two competitive reactions. The cyclopropanation reaction which leads finally to chrysanthemicesters 6 and the phosphinoxide elimination which leads to dienoïc esters 7 which cannot be further transformed to 6.

So the success of the transformation (1 → 6) should strictly depend on the relative rate of reactions 3 → 6 and 3 → 7. In addition, the rate of the reaction 3 → 6 has to be much faster than the one of 3 → 7.

Accordingly we found that the yield in chrysanthemic ester 6a (Scheme I) is substantially lowered (13% instead of 60%[1]) in favour of dienoic esters 8a when tbuOK (2 eq. in THF), known[3] for its propensity to decompose betaïnes[4] to olefins, is present from the beginning, in the reaction medium.

Comparable results are observed (6a, 6% instead of 60%) when the reaction (Scheme I) is performed in ether, a solvent in which the cyclopropanation of α,β-unsaturated esters is very slow[5].

SCHEME IV



In order to support such scheme and to maximally take advantage of the versatility of our reaction (see accompanying paper), we decided to determine both the thermal stability of the key intermediate 3 and the lowest temperature at which its cyclopropanation occurs.

The first objective was thus to determine the thermal stability of betaïnes 3.

We found that these intermediates instantaneously and quantitatively formed at -78°C [from 1 and one equivalent of 2 prepared from the corresponding phosphonium salt with nBuLi in THF at -78°C], did not decompose at this temperature even when stirred for 3 hrs. Quenching with HBr 10% in water, allows trapping of the corresponding water soluble phosphonium salt 9 in 100% yield . However, increasing percentage of decomposition to dienoic esters 7 are observed by raising the temperature prior quenching and, lower yields in salt 9 are isolated after 1 hour of stirring (3a:-40°C, 90%; -25°C, 64%; -10°C, 20%; 20°C, 10% — 3b : -40°C, 90%; -25°C, 63%; -10°C, 8%).

The second objective was to learn more about the reaction of two equivalents of the same ylide 2 (prepared as described above) on methyl 4-oxobutenoate 1.

We observed that the cyclopropanation reaction does not occur at -78°C and in spite of the presence of the second equivalent of ylide 2, β-hydroxyphosphonium salts 9 are quantitatively recovered (quenching with HBr/H_2O, 10%).

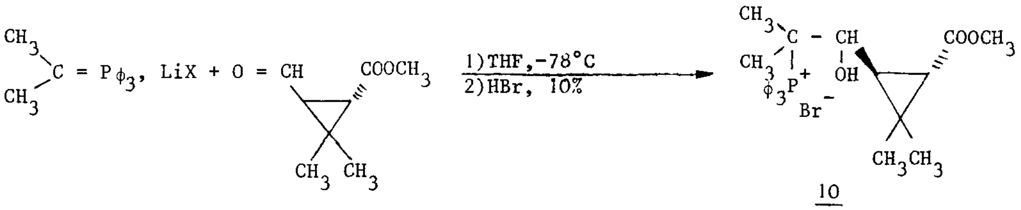
We further performed a series of experiments in order to determine the lowest temperature which allows the synthesis of the desired chrysanthemic ester. We found that its formation is still very slow at -40°C (20% yield after stirring 3 hrs at -40°C) and occurs at reasonable rate (so that 3a is not decomposed to dienoic ester 7) between -25°C and 0°C.

We took advantage of this study to have definite proof on the validity of Scheme IV by trapping the betaine 5 as the corresponding β-hydroxy phosphonium bromide 10.
Methyl 4-oxobutenoate 1 was reacted at -78°C with two equivalents of isopropylidene triphenyl phosphorane and the mixture rapidly heated up to (-25°C, 0.3 hr; -10°C, 0.3 hr) prior to quenching at this temperature by HBr (10% in H_2O) and extracted with ether. Removal of the water from the aqueous solution leads to a mixture of phosphonium bromides derived from 2a, 3a and 5a in the ratio : ~ 2 : 2 : 8.

The presence of the phosphonium 10 in this mixture is confirmed by the recovery of triphenyl phosphine (56% yield)[6] in the ethereal phase and also by comparison of the crude NMR spectra (^{1}H , ^{13}C) that one of an authentic sample prepared from isopropylidene triphenyl phosphorane and hemicaronic aldehyde [1] (THF, -78°C, 0.1 hr, HBr, 10%) (Scheme V).

Furthermore, when the previous mixture of salts is reacted with KOH (2M in water), a mixture of chrysanthemic ester 6a (45% yield based on starting 1) and dienoic ester 7a (14% yield based on starting 1) are isolated [7].

SCHEME V



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References and notes

1. M.J. Devos, L. Hevesi, P. Bayet and A. Krief, Tet. Lett., 3911 (1976)
2. a) For successful cyclopropanation of this ester with sulfur ylides, E.J. Corey and M. Jautelat, J. Amer. Chem. Soc., 89, 3912 (1967)

   b) Surprisingly, Dauben has described the cyclopropanation of methyl sorbate with isopropylidene triphenyl phosphorane : W.G.Dauben and A.P.Kozikowski,Tet.Lett.3711, (1973)
3. M. Schlosser and K.F. Christman, Justus Liebigs Ann. Chem., 708, 1 (1967)
4. We also found that chrysanthemic esters are not formed when salt free [3] conditions are used
5. M.J. Devos and A. Krief, results to be published
6. Dienoic esters 8a and methyl chrysanthemate were also found, in ∿10% yield
7. Triphenyl phosphine 3% is also recovered
8. The authors acknowledge I.R.S.I.A. (Belgium) for the support of this research (Fellowship to M.J.D.)

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