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ONE POT SYNTHESIS OF CHRYSANTHEMIC ESTERS ANALOGS [1]

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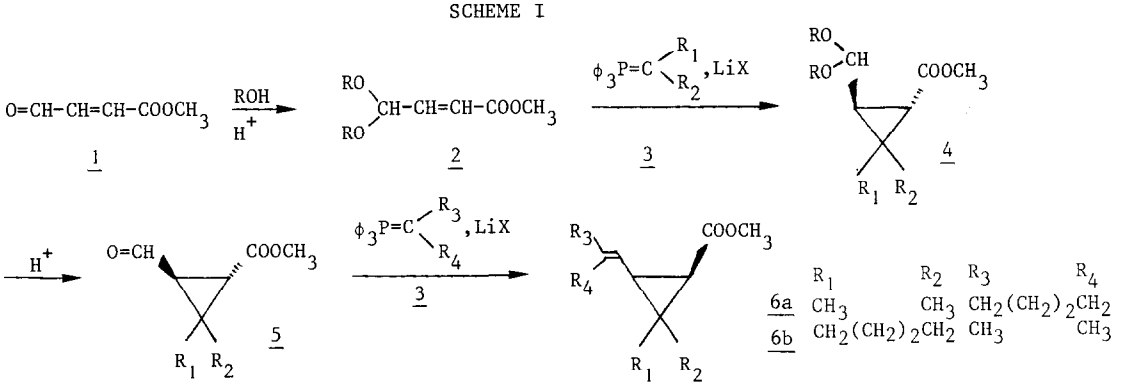
Summary : Chrysanthemic esters analogues diversely substituted on the cyclopropane ring and on the carbon-carbon double bond can be conveniently prepared in one pot from methyl 4-oxobutenoate by delayed addition of two differently substituted phosphorus ylides.

We recently proposed [2] a synthetic route to chrysanthemic esters 6 diversely substituted on the carbon-carbon double bond and on the cyclopropane ring from methyl-4 oxobutenoate 1 (Scheme I).

SCHEME I



1 2 3 4 5 3

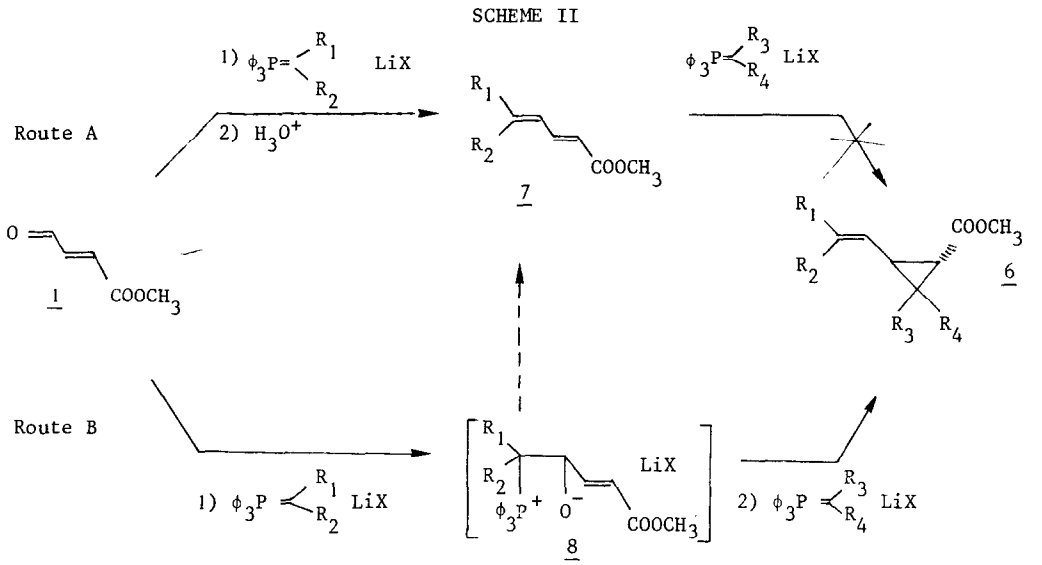
	R_1	R_2	R_3	R_4
6a	CH_3	CH_3	$CH_2(CH_2)_2CH_2$	
6b	$CH_2(CH_2)_2CH_2$	CH_3		CH_3

The protection of the aldehyde function was strictly required since we found that the first equivalent of ylide reacts exclusively [2] on the aldehydic function of 1 and that the resulting dienoic ester 7 does not produce the desired chrysanthemic analogs 6 when reacted with an equivalent of another ylide 3 (Scheme II, route A).

We had, in a recent [3] study, the opportunity to know more about the mechanism of the reaction of two equivalents of phosphorous ylides with 1 and to find that the betaines 8 are the key intermediates on which the second equivalent of ylide reacts. We also found that -25°C is the lowest temperature at which the cyclopropanation occurs at appreciable rate.

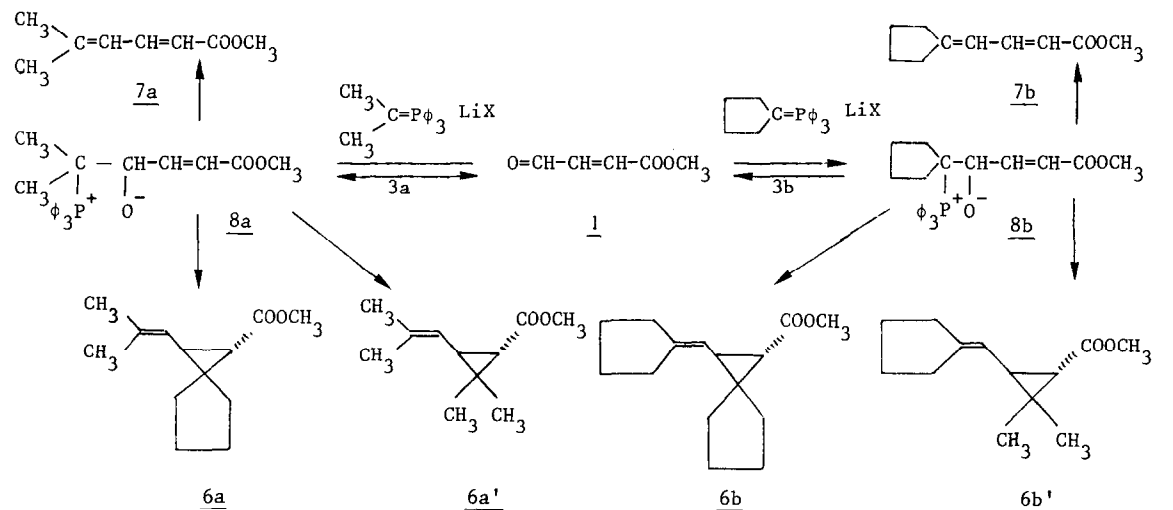
We decided therefore to take advantage of this study to devise a one pot synthesis of the chrysanthemic analogs 6 by reacting one after the other two equivalents of different ylides on oxobutenoate 1 (Scheme II, route B).

SCHEME II



This simple synthetic scheme requires, to be successful, the strict requirement of the stability of betaine 8 which must not decompose before the cyclopropanation occurs not only irreversibly to the dienoic ester 7 (as shown on Scheme III)[4], but also reversibly to the starting components (Scheme III). This last reaction which has been in several instances noticed [5] during the Wittig reaction would be disastrous for us since it would give rise to an inextricable mixture of all four possible esters 6a, 6a', 6b, 6b' (Scheme III).

SCHEME III



In fact, this equilibrium between the two betaïnes 8a and 8b (Scheme III) was once encountered when the reaction was performed in ether : [addition of 1 to a cooled (-78°C) etheral solution of 3b (1 eq.), followed, after *complete reaction*, by addition of 3a in ether at -78°C and rapid heating to -25°C, 1.5 hr then 20°C, 1 hr].Under these conditions, chrysanthemic esters 6 are not formed, but we instead isolated a mixture[6] of dienoic esters 7a (60%) and 7b (40%) in 70% overall yield.

However, when THF is used as solvent[7], the only desired chrysanthemic ester analogs 6 (Scheme II, B) is obtained.

Thus methyl 4-oxobutenoate 1 is added at -78°C to one equivalent of isopropylidene triphenyl phosphorane 3a in THF. Instantaneous decolorization occurs. Further addition of one equivalent of cyclopentilydene triphenyl phosphorane 3b at this temperature followed by rapid heating of the medium (-23°C, 1.5 hr; + 20°C, 0.5 hr) lead to the chrysanthemic ester analog 6a in 54% yield, free of any other isomers 6a', 6b' and 6b. A small amount of dienoic ester 7a (10% yield) free from 7b is also isolated.

If the order of addition of the two ylides is reversed — i.e. cyclopentylidene triphenyl phosphorane first added to methyl 4-oxobutenoate followed by addition of isopropylidene triphenyl phosphorane — the chrysanthemic analog 6b is formed in 45% yield, again free of other isomers, along with the corresponding dienoic ester 7b (16% yield).

Both synthetic schemes I and IIB allow the selective synthesis of chrysanthemic analogs 6a and 6b from the same starting materials. The order of the steps is however reversed. The *first ylide added* will be part of the cyclopropane ring in the first version but part of the carbon-carbon double bond in the version just disclosed, whereas the second ylide added gives rise respectively to the carbon-carbon double bond (Scheme I) and to the cyclopropane ring (Scheme II, B).

The reactions just disclosed (Scheme II,B) present a great improvement in simplicity and yield over the route, we previously described (SchemeI). They allow *a two steps one pot synthesis* of the chrysanthemic analogs (6a, 54% yield, 6b, 45% yield) instead of the four distinct steps required for the former synthesis which lead to the products 6 in a 25% overall yield.

We are generalizing these reactions.[8]

References and notes

1) Procédé de préparation d'esters d'acides cyclopropane carboxyliques racémiques de structure trans, A. Krief, Brevet d'invention Français n° 78.168.59 (June 6, 1978) (Roussel Uclaf - France)

2) a) M.J. Devos, L. Hevesi, P. Bayet and A. Krief, Tet. Lett., 3911 (1976)
b) M. Sevrin, L. Hevesi and A. Krief, Tet. Lett., 3918 (1976)

3) M.J. Devos and A. Krief, accompanying paper
4) Dienoic esters 7 are metallated under these conditions and lead to a mixture of isomeric dienoic esters 8 on hydrolysis : for similar results, see our reference 3
5) See for example, A.W. Johnson, "Ylide Chemistry", Organic Chemistry, a series of monographs, Academic Press (1966)
6) The ratio 7a/7b found in different experiments varies from 60/40 to 40/60
7) Dimethoxyethane (DME) and methylal have also been used under similar reaction conditions but lead to enhanced formation of dienoic esters 8a[3] (DME 6:29%, 7:26%) (methylal 6:37%, 8:28%)
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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