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NOVEL SYNTHESIS OF METHYL CARONATE

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Caronic esters have been prepared by cyclopropanation of tricarbalkoxy ethylenes by 2-metallo-2-nitropropanes or 2-metallo-2-phenylsulfonyl propanes. The best results are obtained when the two reaction steps are carried out in two different solvents.

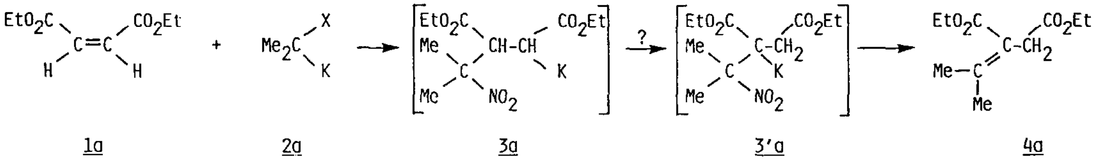
Caronic acids, which have been inter alias prepared by the cyclopropanation of maleic and fumaric esters [1,2,3] proved valuable intermediates for the synthesis of trans chrysanthemic acid and its cis gem-dihalogenovinyl analogues [4].

Isopropylidene triphenylphosphorane [1] is a particularly efficient reagent for this purpose due to its great availability and stability, the high yields of trans caronates obtained and the high asymmetric induction observed [1b] when fumarates derived from chiral alcohols are employed. However this reagent [1], as well as the corresponding sulfur ylides [2] not only require strong basic systems for their preparation but also have a high molecular weight (>218) compared to the weight of the isopropylidene moiety (42) to be transferred. We therefore wished to replace these by 2-metallo-2-nitro propanes which recently proved [5] efficient, in solvents such as DMSO of DMF, for the cyclopropanation of alkylidene malonates, and which should help to overcome the problems mentioned above.

We report here our preliminary results concerning the reaction of 2-metallo-2-nitro propanes with maleates and alkylidene malonates bearing a carbalkoxy moiety in the β position (tricarbalkoxy ethylenes 1b). At several occasions we compared the reactivity of these anions with that of 2-lithio-2-sulfonyl propane which was found to possess a closely related reactivity towards electrophilic olefins [6].

We have observed that 2-potassio-2-nitro propane in DMF and 2-lithio-2-sulfonyl propane in THF both react with diethyl maleate but do not lead to diethyl caronate. Instead they produce [7] inter alias, ethyl 2-carbethoxy-4-methyl-pent-3-enoate 4a, whose formation can be explained by : i - addition of the organometallic on the carbon-carbon double bond of the maleate leading to 3a ; ii - the transfer of the intermediate carbanion from C_2 to C_3, producing 3a' which then eliminates the nitrite or the sulfinate ion (Scheme 1).

Scheme 1



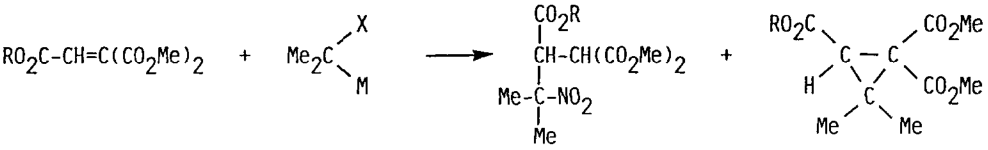
X = NO_2 DMF i) 20°, 3h - ii) 80°, 16h 46%

X = SO_2Ph THF i) -78° to +20°, 0.5h - ii) 20°, 3h 25%

This unwanted process can be suppressed if the reactions are performed in THF on tricarbalkoxy ethylenes. The Michael adducts 3b are obtained in good yields after hydrolysis but cyclopropanation does not take place in this medium (Scheme 2, entries a-c). The reactions were also performed in DMSO, under conditions which were found to be the best for the production of cyclopropane-1,1-dicarboxylates from alkylidene malonates [5,6]. Nevertheless in both cases the desired cyclopropanes are formed in very low yields (for a specific reaction see Scheme 2, entry d). The yields can however be greatly improved if the Michael adducts 3b are reacted with NaH or KH (60° for 6-7 h) in DMSO (for the nitro derivatives) or in DMF (for their phenylsulfonyl analogues) (Scheme 3, entries a-f). Interestingly, no cyclisation takes place when the reactions are carried out using potassium methoxide in methanol (Scheme 3, entries g,h) and they produce instead an olefinic triester in a manner similar to the one we observed earlier from 2-metallo-2-nitro or 2-metallo-2-sulfonyl-propane and diethyl maleate (Scheme 1).

We have taken advantage of these results to achieve the one pot cyclopropanation of tricarbalkoxy ethylenes. Thus, stepwise addition at 20° of 2-metallo-2-nitro propanes in THF on 1b (0.3 Molar) led to the enolate adducts which were directly cyclised by further addition of DMSO (to produce a 0.1 Molar solution) and heating the solution at 60° for 6 to 24 h (Scheme 2, entries d-f). When the above reaction was performed on 2-potassio-2-nitro propane and monomenthyl ester 1b (Scheme 2, entry f), the methylmonocarbomenthyloxy caronate was produced, albeit with very low asymmetric induction (~4 % determined by|GC|[2]). We have confirmed that under the conditions used in the first step (THF at 20°), the Michael adduct, which is isolated in 62 % yield (Scheme 2, entry b) consists of a ~1 to 1 mixture of the two diasteroisomers.

Scheme 2



1b 2b 3b 5b

	R	X	M	Conditions	Yield in 3b%	Yield in 5b%
a	Me	NO_2	Li	i)THF,20°,4h-ii)H_2O	92	--
b	Menthyl *	NO_2	K	i)THF,20°,2h-ii)H_2O	62	--
c	Me	SO_2Ph	Li	i)THF,20°,2h-ii)H_2O	83	--
d	Me	NO_2	Li	i)DMSO,20°,3h-ii)80°,40h-iii)H_2O	--	15
e	Me	NO_2	Na	i)THF,20°,3h-ii)DMSO,60°,24h-ii)H_2O	--	70
f	Me	NO_2	K	ibid	--	72
g	Menthyl *	NO_2	K	ibid	--	59

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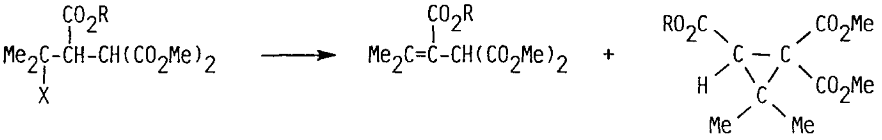
* from l-menthol

Scheme 3



3b 4b 5b

	R	X		Yield		%
				in 4b	in 5b	recovered
a	Me	NO_2	KH/DMSO,60°, 16h	--	86	--
b	Me	NO_2	NaH/DMSO,60°,24h	--	94	--
c	Menthyl *	NO_2	KH/DMSO,80°,4h	--	60	--
d	Me	SO_2Ph	KH/DMF,60°,7h	--	83	--
e	Me	SO_2Ph	NaH/DMF,60°,7h	--	86	--
f	Me	NO_2	KH/DMF,80°,6.5h	--	54	16
g	Me	NO_2	MeOK/MeOH,60°,6h	74	--	24
h	Me	SO_2Ph	MeOK/MeOH,60°,4h	83	--	--

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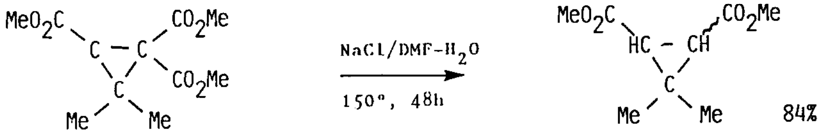
* from l-menthol

In order to obtain some insight on the intimate mechanism of the cyclisation step, we separated the two diasteroisomers by thick layer chromatography (SiO_2 Merck, ether/pentane : 1/4 Rf 0.40 and 0.35) and performed the cyclisation reaction on the fastest eluted component

(1 mol. eq. KH, DMSO, 80°, 4 h). We found that the resulting methylcarbomenthyloxy caronate, obtained in 60 % yield, consists in fact of a 62:38 mixture of the two diasteroisomers whose stereochemistry has not yet been assigned. From these results it is clear that the C_3 centre epimerizes during the process. It thus seems unlikely to us, although we lack definite proof as yet, that this is due : i - to a metallation at C_3 rather than on the more acidic C_2 site of the open chain adduct 3b, or ii - to the metallation of the carbomenthyloxy caronate. We suspect however that a micro reversible Michael reaction, leading back to the starting material, can occur in the medium. Such a process has already been observed when methyl 2-carbomethoxy-3-isopropyl-4-methyl-4-nitro pentenoate is reacted under closely related conditions.

Work is now in progress to determine how this epimerisation reaction occurs and how to avoid it. We are also searching to determine the right conditions for performing the first step of the whole process with high stereoselectivity. Finally, dimethyl carbomethoxy caronate has been successfully decarbomethoxylated on reaction with sodium chloride in DMF/H_2O and leads to methyl caronate (Scheme 4) in high yield. This can in turn be transformed via known reactions to chrysanthemates [1].

Scheme 4



References and Notes

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