2-Metallo-2-nitropropanes as Isopropylidene Transfer Reagents for the Cyclopropanation of Electrophilic Alkenes. Application to the Synthesis of *trans*-Chrysanthemic Acid[1]

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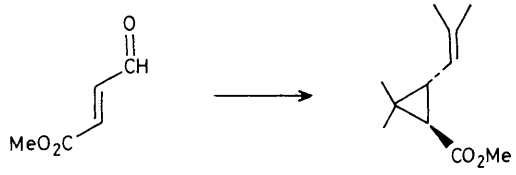
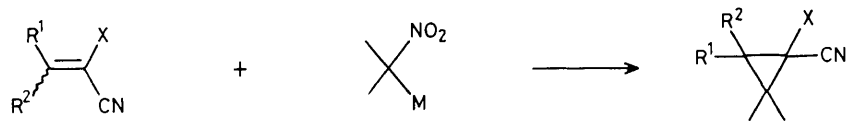
2-Metallo-2-nitropropanes have been successfully used for the cyclopropanation of electrophilic alkenes and act as isopropylidene transfer reagents.

Cyclopropanecarboxylic esters play an important role in organic synthesis.[2] The *gem*-dimethylcyclopropanecarboxylic acid unit is also found in pyrethroids, an important class of insecticide.[3,4] We have already described several syntheses of such derivatives,[5,6] most involving as the key step the construction of the cyclopropane ring possessing the required functionalities from α,β-unsaturated esters and isopropylidenetriphenylphosphorane.[5,6] Here, the phosphorus ylide acts as a carbene, formally delivering an isopropylidene moiety (Scheme 1), and has the advantages of being readily available, highly reactive, and thermally stable; also, the triphenylphosphine formed can be recycled. However, a strongly basic system (Bu^nLi, THF) is required for formation of the ylide from the corresponding phosphonium bromide, and also a three-carbon unit only is produced from quite a large starting material ($C_{21}H_{22}PBr$).

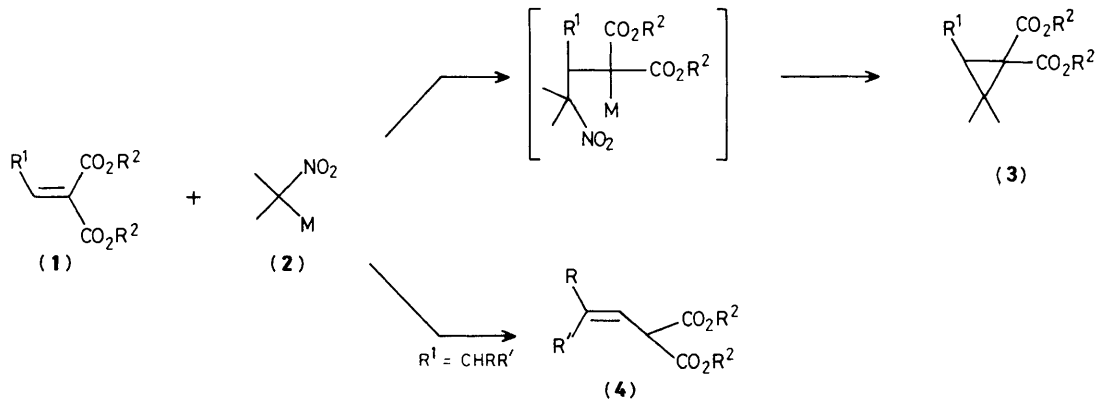


Scheme 1. *Reagents and conditions:* $Ph_3P{=}CMe_2$ (2 equiv.), tetrahydrofuran (THF), −20 to 0 °C, 0.5 h, 75% yield.



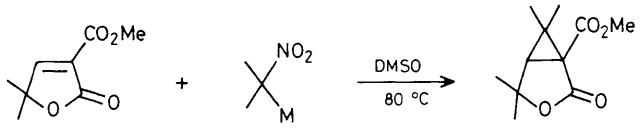
Entry	X	R^1	R^2	M	Conditions: solvent,[a] θ/°C, *t*/h	Method	% Yield
a	CO_2Me	H	Me	Li	DMF, 20, 24	A	61
b	CO_2Me	H	Pr^i	Li	DMF, 20, 24	A	51
c	CO_2Me	H	Pr^i	K	DMSO, 20, 20	A	65
d	CO_2Me	H	Pr^i	K	DMSO, 80, 1	A	75
e	CO_2Me	H	Pr^i	K	MeOH, 65, 1	A	63
f	CO_2Me	H	Pr^i	K	K_2CO_3–MeOH, 65, 1	B	70
g	CO_2Me	H	Pr^i	K	K_2CO_3–DMSO, 80, 1	B	70
h	CO_2Me	Me	Et	K	DMSO, 80, 1	A	50[b]
i	CO_2Me	Me	Et	K	K_2CO_3–DMSO, 80, 1	B	55
j	CN	H	Pr^i	Li	DMF, 20, 24	A	75

Scheme 2. [a] DMF = dimethylformamide; DMSO = dimethyl sulphoxide. [b] No reaction in MeOH at 65 °C for 1 h.



Entry	R^1	R^2	M	Conditions: solvent, θ/°C, *t*/h	% Yield in of (**3**)
a	H	Et	K	THF, 20, 3, then DMSO, 60, 20	56
b	Et	Me	Li	DMSO, 80, 2	57
c	Et	Me	K	DMSO, 80, 1	65
d	Pr^i	Me	Li	DMSO, 80, 16	21[a]
e	Pr^i	Me	K	DMSO, 80, 4	51[b]
f	Pr^i	Me	K	DMF, 25, 1, then 80, 2	56
g	Pr^i	Me	K	DMSO, 80, 6	61

Scheme 3. All the reactions were performed with the preformed 2-metallo-2-nitropropane. [a] Together with 35% of (**4**) and 4% of recovered (**1**). [b] Together with 34% of (**4**).



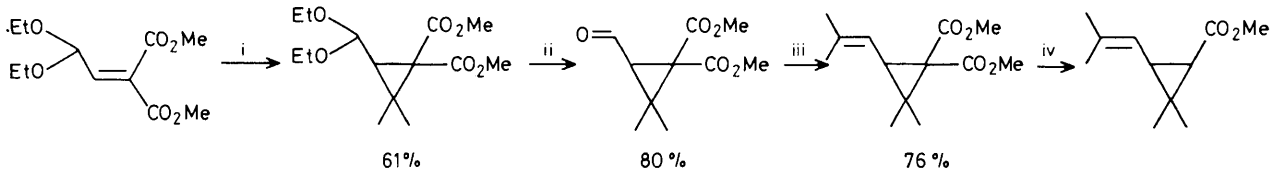
M	Time/h	% Yield
Li	2	47
K	0.5	82

Scheme 4

We have therefore searched for other reagents, with the above advantages, but not the inconveniences. We found that 2-metallo-2-sulphonylpropanes[1,7] and, especially, 2-metallo-2-nitropropanes[1] fulfil our requirements, and now report our results with the nitro derivatives.

2-Metallo-2-nitropropanes[8,9] are readily available by metallation of 2-nitropropane[8] with lithium, sodium, or potassium methoxides in methanol or with caesium hydroxide in water. The crystalline salts can be recovered after removal of the solvent and can be stored without decomposition. Nitroalkanes have been reported to react with α,β-unsaturated esters to produce γ-nitroesters in moderate to low yields[10,11] but cyclisation of the intermediate α-metallo-γ-nitro esters to the corresponding cyclopropanecarboxylates was never observed. We have confirmed the previous results, but have found that such a cyclopropanation is possible when another group, such as a nitrile or an ester which can stabilize the carbanionic centre (softer carbanion) is present in the starting material. The reactions have been performed with the preformed salts (method A) or with the salts formed *in situ* (method B). Those involving alkylidenemalononitriles proceed well under both conditions in different solvents, regardless of the counter ion (Scheme 2, entries **a**—**i**).

In most cases the reaction works equally well with the potassium salt in methanol or in DMSO at 60—80 °C but the DMSO was preferable, especially with the Knoevenagel adduct derived from butan-2-one. In DMSO the cyclopropane was formed in >60% yield whereas it was not obtained in methanol. Method B is simpler, since it involves merely mixing 2-nitropropane, the alkylidenemalononitrile, and *e.g.*, K_2CO_3 in methanol or DMSO.



Scheme 5. *Reagents and conditions:* i, $Me_2C(NO_2)K$, DMSO, 80 °C, 6 h; ii, $HClO_4$, THF–H_2O, 20 °C, 5 h; iii, $Ph_3P{=}CMe_2$, THF, 20 °C, 4 h; iv, see ref. 14.

The reaction is highly stereoselective and exclusively produces, within the accuracy of the analytical methods used (g.c., ^1H and ^{13}C n.m.r.), one of the two stereoisomers with methyl 4-methyl-2-cyanopent-2-enoate. It has been extended to alkylidenemalonodinitriles, the reaction then taking place even more efficiently (Scheme 2, entry **j**).

Our reactions have little precedent in the literature;[12]† Wiechert has, for example, described[12] the successful cyclopropanation of alkylidenemalonodinitriles derived from steroids with the potassium salt of nitromethane but the reaction occurs under quite drastic conditions (Bu^{t}OH, 100 °C) and leads to poor yields of the cyclopropane in the case of the alkylidenemalonodinitrile derived from isobutyraldehyde (20%).

Although 2-metallo-2-nitropropanes are able efficiently to effect the cyclopropanation of α,β-unsaturated nitriles bearing a β-ester or -nitrile group, the resulting *gem*-dimethylcyclopropanes cannot be easily transformed to the *gem*-dimethylcyclopropanemonocarboxylic acid units present in pyrethroids.[3,4] We therefore expected that alkylidenemalonates would be the preferred starting materials for such synthesis. The precedents however were not encouraging. For example whereas cyclopropanes are formed on reaction of potassionitromethane in ethanol with alkylidenemalonodinitriles or with α-cyano-α,β-unsaturated esters,[12] under the same conditions this reagent cleaves malonic diesters and produces dialkyl malonates.[12]

We nevertheless decided to try to adapt this reaction to the synthesis of chrysanthemic acid and its dihalogeno vinyl analogues, mostly using 2-metallo-2-nitropropanes and isopropylidenemalonate as model in place of the more complex potential precursor of chrysanthemic acid and analogues, methyl 4,4-diethoxy-2-methoxycarbonylbutenoate.

In general this reaction is more difficult to carry out than that in Scheme 2. Best conditions for the cyclopropanation of several alkylidenemalonates (Scheme 3) and of 2-methoxycarbonyl-4,4-dimethylbutenolide (Scheme 4) involve the use of 2-potassio-2-nitropropane in DMSO, yields being lower with the lithium derivative or with DMF as solvent.‡ Surprisingly the reaction does not occur in methanol under conditions which were suitable for the cyclopropanation of malononitriles, and it requires at least one hydrogen atom on the double bond system. We were unable to find conditions which allow the cyclopropanation of dialkyl substituted alkylidenemalonates.

Isopropylidenemalonate provided the only example among those studied where a product resulting from the isomerisation of the carbon–carbon double bond was formed besides the desired cyclopropane[15] (Scheme 3, entries **f**,**g**).

We have used this reaction for the synthesis[16] of chrysanthemic acid from a functionalized alkylidenemalonate[17] and 2-potassio-2-nitropropane (Scheme 5), by a strategy reminiscent of one of our earlier approaches[5] using isopropylidenetriphenylphosphorane as the carbenoid. The results in Scheme 5 show the advantages of this novel reaction: easy synthesis of the reagent and good yield of the *gem*-dimethylcyclopropanecarboxylic acid. 2-Nitropropane is therefore able to transfer the isopropylidene moiety with the concomitant loss of the easily removable nitrite ion. This compares favourably with our previous approach.[5]

The cyclisation reported in this paper can proceed through a nucleophilic substitution pathway[18] or *via* a single-electron transfer[19] but we have no experimental evidence at present in favour of either mechanism;[15] we are now studying the mechanism.

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1 For the first example of such a cyclopropanation, see A. Krief, *Tetrahedron*, 1980, **36**, 2531, report 94; see equation 21b, p. 2538. The present results were taken in part from: P. Mathy, mémoire de fin d'étude d'Ingénieur (Ecole d'Ingénieur Industriel de Mons), June 1982, work performed in our laboratory, and G. Chaboteaux, Mémoire de Licence (Namur), June 1984, and presented by A. Krief at the symposium Advances in Methods of Organic Synthesis, Jadwinsin, Poland, July 1984, and the Fifth International Conference on Organic Synthesis (I.U.P.A.C.), Freiburg, August, 1984, proceedings in the press.
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† After the submission of this work, two papers describing the cyclopropanation of α,β-unsaturated esters bearing a nitrile in the α-position appeared.[13,14] These reports are closely related to our present and previous[1] work. The advantages of the use of DMSO as solvent for the cyclopropanation of β,β-dialkyl substituted alkylidenemalononitriles are apparent from a comparison of the present results reported here with those in ref. 13.

‡ Other counter-ions (*e.g.* Na or Cs), and other solvents (*e.g.* hexamethylphosphoramide) have been used, but with less satisfactory results.