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β-Nitroacrylates: Synthesis and applications as Electrophiles

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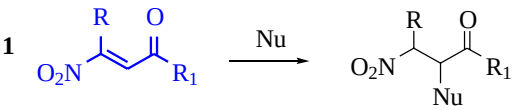
Introduction

As reported above, nitro compounds can be distingue between nucleophiles and electrophiles. Particular behavior have been demonstrated β-nitroacrylates **3** as electrophiles, in fact, they are a very useful source for the synthesis of a large variety of fine chemicals. β-Nitroacrylates[1] are a class of electron-poor alkenes having two electron-withdrawing groups in α- and β-positions. This peculiarity makes their chemical behavior more interesting with respect to the classical conjugated nitroalkenes and, in the last few years, there has been a growing interest in the chemistry of these molecules because they have been used as key building blocks for the synthesis of useful structures, including fragments of natural substances and biologically active compounds. The molecular structure presents an olefin conjugated with the nitro group, so, the carbon in the α position becomes more electropositive and it is subjected to a regioselective nucleophilic attack (**Scheme 1**).



R_1 = Alkyl or OR

Scheme 1. β-Nitroacrylates

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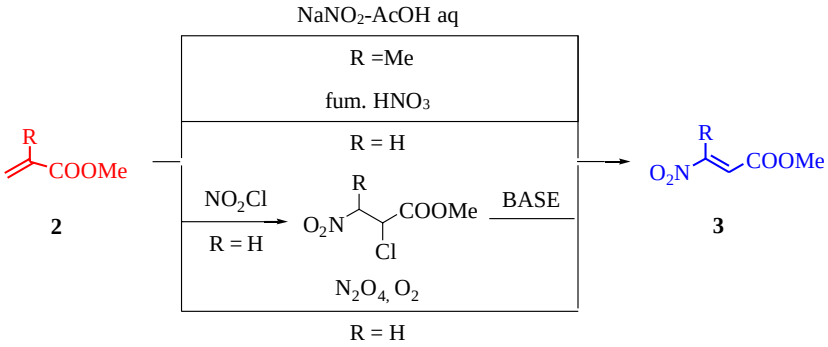
Synthesis of β-nitroacrylates

The synthesis of β-nitroacrylates has not been very large investigated during the last decade, in fact, although some preparations of them were reported, only recently their useful and very efficient synthesis was developed. However, we can distingue two different ways to make them:

- By nitration of acrylates;
- Via nitroaldol (Henry) reaction.

Nitration of acrylates

Initially, β-nitroacrylates were synthetized starting from acrylate systems and nitryl chloride.[2] After that other alternative processes were developed using different nitrating agents, such as, dinitrogen teroxide,[3] nitrous acid,[4] and fuming nitric acid,[5](**Scheme 2**).



Scheme 2. β-Nitroacrylates starting from acrylate systems

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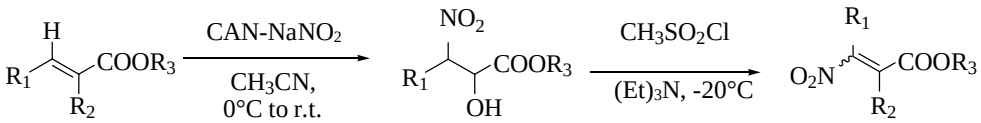
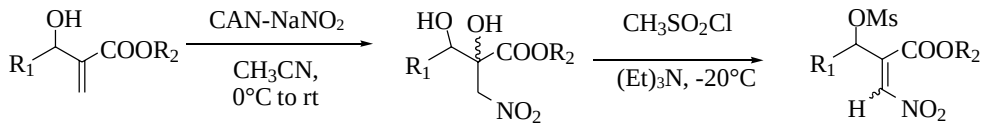
Recently, Vankar *et al.*[6] following their studies onto nitro compounds found that the system CAN ($NaNO_2$-ceric ammonium nitrate) could be a very efficient nitrating agent for a large variety of acrylic esters, in fact, as reported in (**Scheme 3**) several nitro derivatives can be obtained through out this way, being the starting material alkylic or cynnamic esters.



4 **5** **6**

Scheme 3. Nitration of acrylic esters using CAN

Furthermore, with the goal to extend their work, also acrylic esters derived from the Baylis-Hilman reaction were tested (**Scheme 4**). So, the corresponding diols were obtained, and then dehydrated into the corresponding β-nitroacrylates.



7 **8** **9**

Scheme 4. Nitration of acrylic esters derived from the Baylis-Hilman reaction

Nitroaldol reaction (Henry reaction)

Taking into account that all these procedures were demonstrated to be a valuable source for the synthesis of β-nitroacrylates, it should be note that in our laboratory we developed a new method to synthesize these compounds in a very easier way. In fact, we exploited a well-known reaction between carbonyl compounds and nitro compounds, in order to perform a new efficient two-step synthesis of β-nitroacrylates. The first step, is the reaction between nitroalkanes **10** and ethyl glyoxalate **11**, under heterogeneous conditions by using Amberlyst A-21 as a solid base,[7] followed by a

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dehydration step to nitroalkenes **13** (mainly as *E* isomer) by mesylation of

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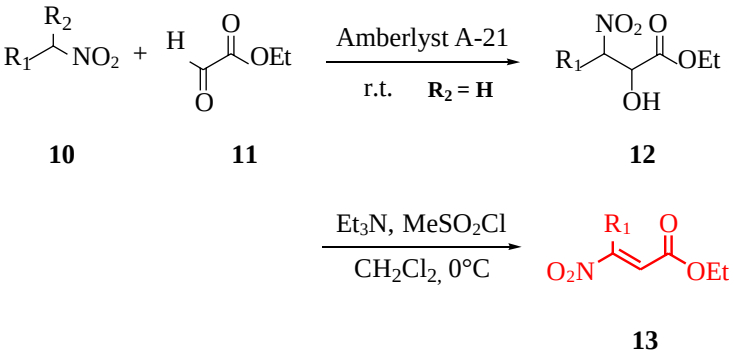
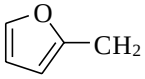
the hydroxyl group, and subsequent basic elimination of methane sulfonic acid (**Scheme 5**).[8]



Scheme 5. Synthesis of β-nitracrylates through the Henry-elimination two-step sequence

We tested different nitroalkanes as reported in **Table 1**, the yields are good (65-94%) even in the presence of other functional groups such as ketone, ketal, ester and heteroaromatic systems.

Table 1. Synthesis of β-nitroacrylates

R_1	Yield (%) of **12** (reaction time)	Yield (%) of **13**
Et	75(18)	85
n-Pr	70(16)	87
n-Bu	76(16)	86
$PhCH_2$	82(17)	71
	73(19)	87
$CH_3C(OCH_2)_2(CH_2)_2$	78(20)	73
	80(18)	94
Ph	87(21)	71

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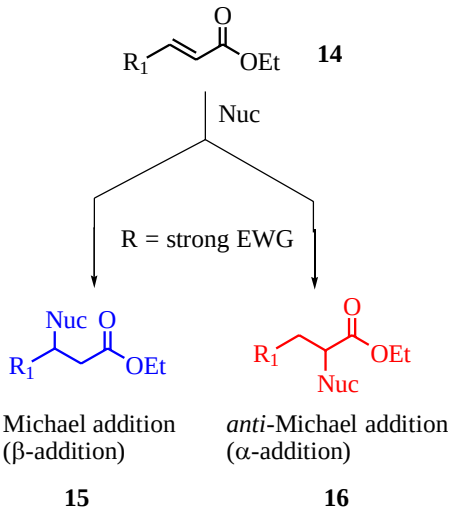
Reactivity of β-nitroacrylates

As reported in the last chapter, the conjugate addition of nucleophilic species to α,β-unsaturated compounds is a fundamental concept in organic chemistry. Among the large variety of C-C bond forming reactions, the Michael addition, also called 1,4-addition, is especially valuable for selectively creating a new bond at the β position of activated olefins **14**. When we take into account β-nitroacrylates, we will have the completely reverse of the medal, or else, in the presence of both the nitro group at the β position and the ester at the α position onto the alkene species, the regioselectivity of the nucleophilic attack is inverted, so the α position results activated. In this case we will get the product **16** (**Scheme 6**). This is known as *anti*-Michael reaction, *contra*-Michael addition, abnormal Michael reaction or simply, attack at α carbon.



Scheme 6. Regiospecific C-C (or C-heteroatom) bond formation of an activated olefin

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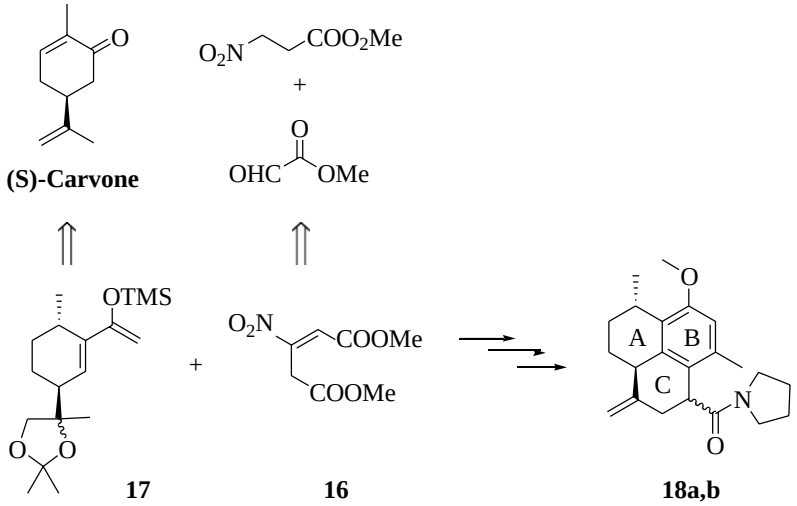
Dield-Alder reaction of β-nitroacrylates

One of the most important reactions of β-nitroacrylates is the cycloaddition with conjugated dienes, so, they are of special interest due to the presence of the ester functionality. In this context, Koz Kozikowski and Wu[9] developed an enantioselective approach to get analogues structures (**18a,b**) of the pseudopterosins family, that possess both potent *anti*-inflammatory and analgesic properties,[10-11] *via* the Diels-Alder reaction of β-nitroacrylate **16** with the diene **17** (**Scheme 7**).



Scheme 7. Syntheis of analogues structures (**18a,b**) of the pseudopterosins

Furans have also been used as dienes, in the reaction with nitroacrylates, yielding a mixture of cycloadducts, favoring the *endo* nitro isomer **19** (**Scheme 8**), then this compound can be transformed into (i) α-methylenebutyrolactone **20** which constitutes the main fragment of a number of sesquiterpenes,[12] (ii) compactin **21** which is an important metabolite participating to the biosynthesis of cholesterol,[13] and (iii) oryzoxymycin **22** which exhibits antibacterial effects with respect to *Xanthomonas oryzae*.[14]

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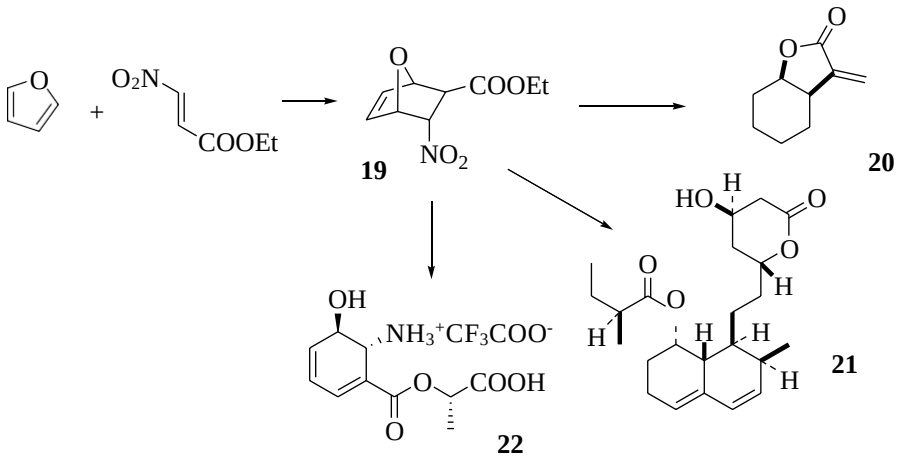
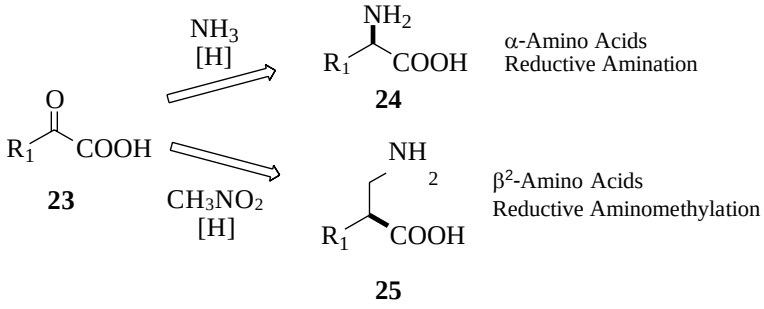


Scheme 8. Synthesis of cycloadducts **20, 21, 22**

Synthesis of β²-amino acids and β-substituited α-amino acids

β²-Amino acids are a growing synthetic targets because peptides containing these residues can assume different structures than those of α-amino acids and their peptide bonds resist to protease degradation.[15] In contrast to α-amino acids, for which a variety of reliable, high-yielding methods have been devised, β²-amino acids remain challenging synthetic targets. In analogy to an enzymatic reductive amination of α-cheto acids **23** with ammonia, a hypothetic reductive amino-methylation with nitromethane should lead to β²-amino acids **25** (**Scheme 9**).



Scheme 9. Synthesis of α-amino acids and β²-amino acids

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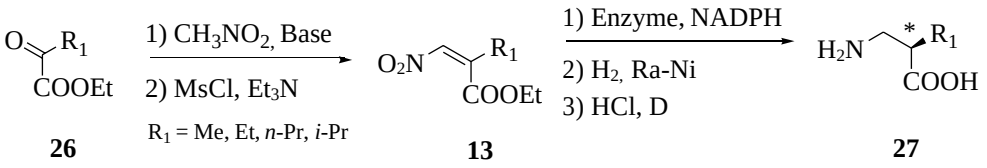
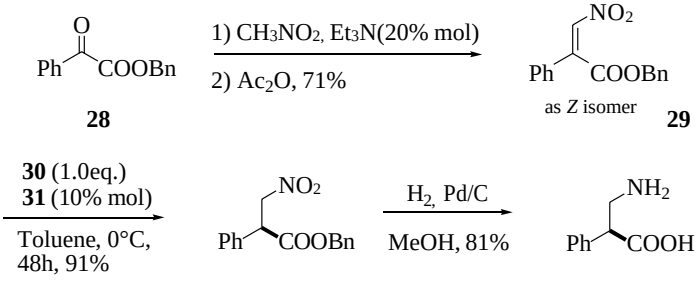
The reduction of β-nitroacrylates is one of the most important reaction, concerning these derivatives, because following this way we can prepare a collection of other functionalities in which the nitro group could be kept or coulde be transformed into an amino group. Stewart *at al*.[16] developed a reduction of β-nitroacrylates by *Saccharomyces carlsbergensis*-old yellow enzyme as reported in (**Scheme 10**).



Scheme 10. Reduction of β-nitroacrylates by *Saccharomyces carlsbergensis*

Further, a highly enantioselective conjugate reduction of β-nitroacrylates, has been performed, using Jacobsen-type thiourea **31** as a suitable catalyst.[17] The α-ketoester **28**, reacts first with nitromethane in the presence of Et_3N (20% mol) in order to get the nitroacrylates **29**, then treating **29** with Hantzsch ester **30** and thiourea **31**, and by subsequent reduction, we will have the desired product **32** (**Scheme 11**).



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Scheme 11. Highly enantioselective conjugate reduction of β-nitroacrylates

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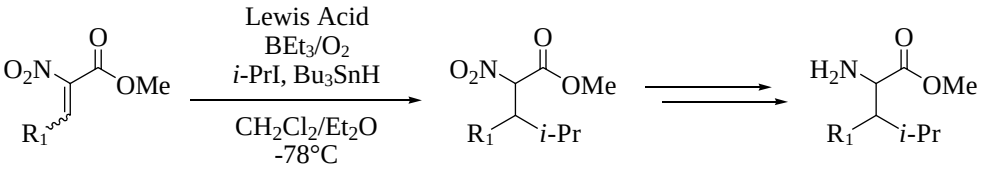
β-Substituited α-amino acids are also very important, because they are present in several peptidic natural products,[18] Several methods have recently been devised for their preparation,[19] including some that employ conjugate additions to α,β-unsaturated amino acid precursors.[20-22]

Castle *et al.*[23] reported that α-substituted α,β-unsaturated α-nitro esters and amides are viable substrates in, Lewis acid promoted, radical conjugate additions,[24] as shown in (**Scheme 12**).



33 **34** **35**

Scheme 12. Radical conjugate addition, Lewis acid promoted, onto nitroacrylates

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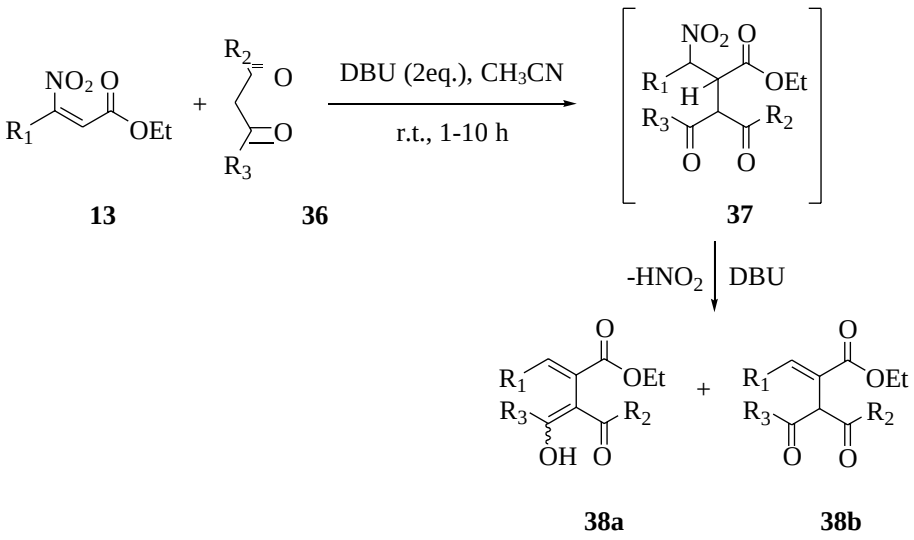
Carbanions as nucleophiles with β-nitroacrylates

With the aim to generate new C-C bonds and consequently, a wide variety of fine chemicals, consideration has been focused toward the reaction of β-nitroacrylates, as *anti*-Michael acceptors, with carbanions. The first example is relative to the synthesis of highly polyfuctionalized α,β-unsaturated esters, that are of a great importance in organic synthesis[25] since they can be further functionalized by the Michael or Diels-Alder reactions giving access to valuable molecules of considerable interest, especially in the synthesis of natural products.[26-27] The procedure[28] is based on a domino 'Michael addition-elimination' process and the key point is the simultaneous behavior of the nitro group as both an electron-withdrawing group and a good leaving group. The presence of (i) an acidic hydrogen in the α-position to the ester functionality, (ii) a nitro group in the vicinal position with respect to the acidic hydrogen and (iii) a base, induces the *in situ* elimination of nitrous acid, with the one-pot formation of polyfunctionalized α,β-unsaturated ester **38a,b** (**Scheme 13**)



13 **36** **37** **38a** **38b**

Scheme 13. Synthesis of polyfunctionalized α,β-unsaturated esters

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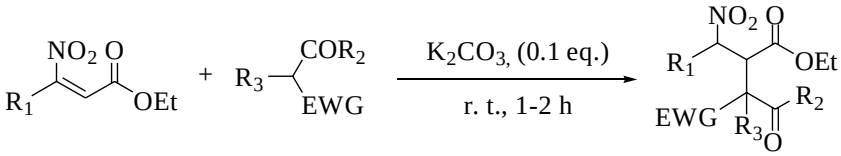
Another application of the 3-nitroalkenoates is also the synthesis of polyfunctionalized nitroalkanes. Nitroalkanes, as reported in the last chapter, are an important class of starting materials for the generation of both other functionalities and new C-C bonds.[29-31]

Thus, as reported in literature, in many processes happen that, the reaction conditions help the *in situ* elimination of the nitro group, and this behavior represent a loss of both, atom efficiency and also a loss due to the easy conversion of this group into important and useful other functionalities. Recently, in our laboratory, has been optimized a new method that permits the reaction between β-nitroacrylates **13** and active methylene compounds **39**, in the presence of catalytic amount of K_2CO_3 (**Scheme 14**).



13 **39** **40a-e**

Scheme 14. Synthesis of polyfunctionalized nitroalkanes **40a-e**

Under these mild, solvent-free conditions various polyfunctionalized nitro derivatives **40a-e** are obtained in high yields (75-95%, **Table 2**), *via* an *anti* Michael reaction and with complete chemoselectivity since no elimination of nitrous acid from the adducts is observed.

Table 2. Synthesis of various polyfunctinalized nitro derivatives

	R_1	R_2	R_3	EWG	Yield (%) of **40**
a	Et	Me	H	COMe	75
b	Me	EtO	H	COOEt	85
c	*n*-C_5H_{11}	EtO	H	CN	87
d	Ph	EtO	H	CN	84

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e	$Ph(CH_2)_2$	EtO	H	CN	94

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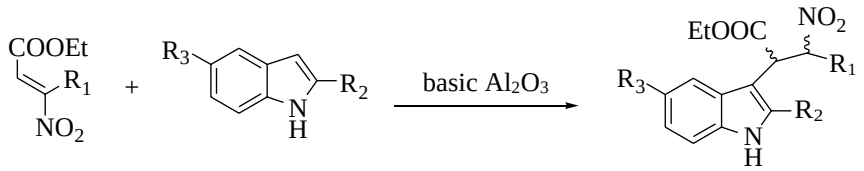
Also the reaction with indoles exploited by Bartoli *et al.*[32] is important because permits to incorporate functionalized substituents at the 3th position of this heterocycle. For this reason, due to the great importance of the target **43**, the study of this reaction allowed to perform a new method, under heterogeneous conditions, using basic alumina (basic Al_2O_3) as reported in (**Scheme 15**) and **Table 3**.



13 **45a-e** **46a-e**

Scheme 15. A new method, under heterogeneous conditions, to synthesize **46 a-e**

Table 3. Generality of the method

	R_1	R_2	R_3	Yield (%) of **46**
a	Me	H	H	90
b	*n*-Pr	H	OMe	88
c	*n*-Bu	H	H	94
d	*n*-Bu	Me	H	92
e	$AcO(CH_2)_3$	H	OMe	91

We reported further studies about the optimized overall procedure relative to the addition of β-nitroacrylates to indoles,[36] starting from the nitroaldol condensation of nitroalkanes **47** with ethylglyoxalate **11**, carried out under totally heterogeneous conditions with Amberlyst A-21 as basic promoter, the second step is carried out in acidic conditions with Amberlyst 15 (a macroreticular resin endowed with acid character, which is able to promoter the acetylation process) in the presence of Ac_2O, which is able to promote the acetylation process of **12** to **48**. The latter is then converted into the target **49**, under basic Al_2O_3. Finally, is important to take into account also

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the *anti*-Michael addition of silyl enol ethers to β-nitroacrylates, in fact, these compounds are an important class of stabilized carbanions very useful for the introduction of carbonyl functionalities. The useful reaction between them, permits to obtain both, polyfuctionalized β-nitro esters **53**, used as intermediates for the preparation of natural products[37-38] or 1,2-oxazine-2-oxide **55**, useful for the subsequent synthesis of pyrrolizidine, pyrrolidines, β-lactames-*N*- oxide, etc., the whole processes depending on the nature of the starting silyl enol ethers.

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