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Highly efficient one- or two-step sequences for the synthesis of fine chemicals from versatile nitroalkanes

Roberto Ballini,[a,*] Alessandro Palmieri[a] and Paolo Righi[b]

[a]*Green Chemistry Group, Dipartimento di Scienze Chimiche, dell'Università and Consorzio Interuniversitario 'La Chimica per l'Ambiente' (INCA), UdR di Camerino1, Via S. Agostino n. 1, 63032 Camerino (MC), Italy*
[b]*Dipartimento di Chimica Organica 'A. Mangini', Alma Mater Studiorum—Università di Bologna, Viale del Risorgimento n. 4, 40136 Bologna, Italy*

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This Review is dedicated to our mentor Professor Goffredo Rosini

Contents

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* Corresponding author. Tel.: +39 0737402270; fax: +39 0737402297; e-mail: roberto.ballini@unicam.it

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1. Introduction

Despite the great success and the importance of chemistry to the quality of life, its public image has deteriorated. This can be explained by the increasing importance of environmental issues to our society and the fear that chemistry could negatively influence the ecological balance. The preparation of fine chemicals and pharmaceuticals is frequently accompanied by the production of large amounts of waste reaching values of 25- to 100-fold higher than those of the target compounds.[1] Today, it is not only a question of what we can synthesize, but also how we do it. Major problems in chemical production are the handling of waste and the search for environmental tolerable procedures.

The synthesis of complex molecules is traditionally performed by a chain of separate steps, each of which requires its own conditions, reagents, solvent, and catalyst. After each reaction is complete, the solvent and the waste products are removed and discarded, and the intermediate product is separated and purified. Environmental and economic pressures are now forcing the chemical community to search for more efficient ways of performing chemical transformations.[2] However, it would be much more efficient if two or more bonds could be formed or two or more transformations realized in one or few synthetic sequences without isolating the intermediates. It is obvious that this type of reaction would allow the minimization of waste, making its management much easier since, compared to stepwise reactions, the amount of solvents, reagents, adsorbents, and energy would be dramatically decreased as well as the amount of work. Moreover, the one-pot process can drive the equilibria to the desired direction. Thus, these reactions would allow an ecologically and economically favorable production.

A one-pot process can be planned by the right choice of different parameters such as (i) reaction conditions, (ii) catalyst, (iii) addition sequence of reactants, or (iv) use of starting materials with a high chemical versatility, e.g., nitroalkanes.

Nitroalkanes are a valuable source of stabilized carbanions since the high electron-withdrawing power of the nitro group provides an outstanding enhancement of the hydrogen acidity at the α-position.[3–7] The nitronate anions that can be generated from nitroalkanes under basic conditions act as carbon nucleophiles with common electrophiles, leading to single[8] or double carbon–carbon bond formation. Moreover, the nitro group can be easily turned into a respectable array of functional groups by (i) reduction to a primary amine, (ii) replacement with hydrogen,[5,9] (iii) conversion into a carbonyl (Nef reaction),[2,5,10] and (iv) transformation into other important functionalities such as nitriles, nitrile oxides, oximes, hydroxylamines, thiols, etc.[11]

In recent years, nitroalkanes have proved to be very useful building blocks for the one-pot synthesis of a variety of important targets and, therefore, the aim of this report is to focus on the main representative examples of one- or two-step synthetic sequences for the preparation of fine chemicals starting from nitroalkanes.

2. Synthesis of 1,3-difunctionalized derivatives

1,3-Difunctionalized molecules are of interest because they are the main structures in several important compounds with biological activity or they serve as key building blocks for the synthesis of important structures. In this context, 1,3-diols and 1,3-dinitro derivatives are of particular interest.

2.1. One-pot synthesis of polyfunctionalized 1,3-diols

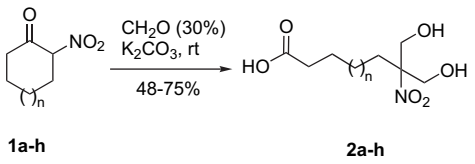
The chemistry of 1,3-diols has been extensively investigated and their potential utility for organic synthesis has been well established.[12] Moreover, polyfunctionalized 1,3-diols are of considerable interest, especially those functionalized in the 2-position,[13] and their preparation usually requires long sequences of steps.

A few years ago, we reported[14] that α-nitrocycloalkanones **1** can be conveniently used as precursors of 2-nitro-1,3-diol-ω-alkanoic acids **2**, a new interesting class of polyfunctionalized diols, through a one-pot double nitroaldol reaction–ring cleavage (Scheme 1).

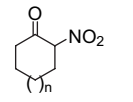
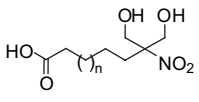
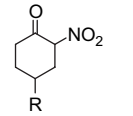
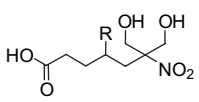
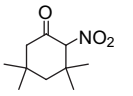
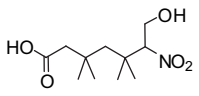
The reaction of **1** with an excess of 30% aqueous solution of formaldehyde proceeds at room temperature, in the presence of potassium carbonate. Product **2** was obtained in respectable yields regardless of the ring size of the cycloalkanones **1**. However, when 3,3,5,5-tetramethyl-2-nitrocyclohexanone **1h** was employed as the starting material, β-nitroalcohol **2h** was obtained as the sole product. This result seems to be strongly dependent on the steric effect of the substituents in the 3-position.

A surprising result was achieved with 2-nitrocyclododecanone **1d**, which afforded macrolactone **5** in one-pot and with 50% overall yield, while if the reaction was performed at 50 °C the expected nitrodiol **2d** was obtained in 55% yield (Scheme 2).

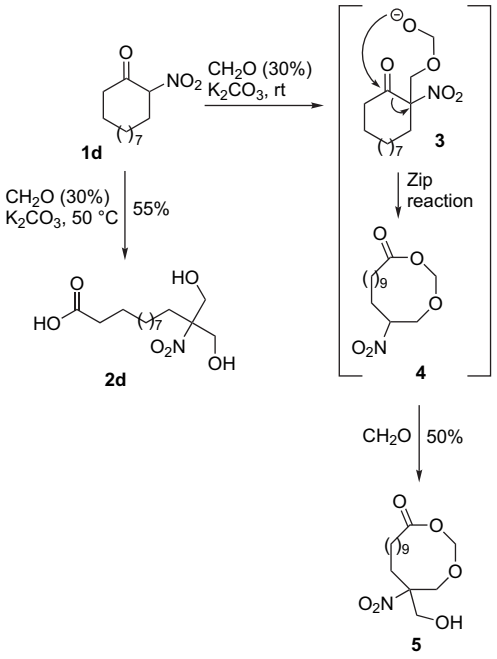
A possible explanation concerning the formation of **5** could be the formation of the intermediate **3**, which, via 'Zip



1a-h 2a-h

	1	2	Yield (%)
a: n=0			60
b: n=1			75
c: n=2			60
d: n=7			55
e: n=10			48
f: R=Me			65
g: R=*t*-Bu			63
h			54

Scheme 1.



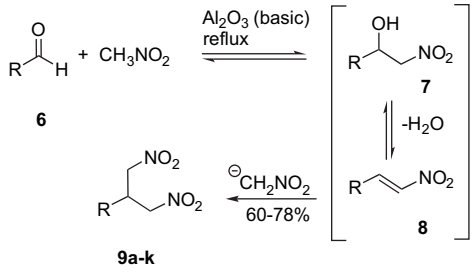
Scheme 2.

reaction',[15] would afford lactone **4** that, after further nitroaldol reaction with formaldehyde, is converted into **5**. Thus, this new class of 1,3-diols **2**, which possess two other important functionalities with valuable opportunities for further elaborations, due to the high versatility of both carboxylic[16] and nitro groups, can be easily prepared in a one-pot manner using simple reaction conditions.

2.2. One-pot synthesis of 1,3-dinitropropane derivatives

1,3-Dinitro compounds are of great interest in organic synthesis, because they could be used as precursors for a variety of (i) 1,3-difunctionalized molecules, (ii) heterocycles,[17] (iii) carbohydrate derivatives,[18] and (iv) potentially active energetic materials.[19]

The standard procedures for the preparation of 1,3-dinitro compounds proceed through the conjugate addition (Michael reaction) of nitroalkanes to pre-prepared nitroalkenes.[17,18,20] However, it is well-known that the syntheses of nitroolefins are often intricate and proceed in poor yields, due to their high reactivity and easy conversion into dimeric or polymeric derivatives. Moreover, their synthesis requires two more steps [(i) nitroaldol reaction and (ii) dehydration] starting from aldehydes and aliphatic nitro compounds.[21] Based on our previous experience of the use of basic alumina for the generation of new C–C bonds starting from nitroalkanes,[22] it was planned to carry out a one-pot synthesis of 1,3-dinitropropane derivatives by using basic alumina as a solid catalyst, generating the nitroolefin in situ. In fact, the reaction of aldehydes **6** with an excess of nitromethane (Scheme 3),[23] in the presence of basic alumina and under reflux, provides the direct formation of the 1,3-dinitroalkanes **9**.



	R	Yield (%) of **9**
a	$Ph(CH_2)_2$	78
b	*i*-Pr	62
c	$Me(CH_2)_4$	65
d	$Me(CH_2)_2$	68
e	$Me(CH_2)_9$	69
f	*p*-$NO_2C_6H_4$	60
g	Ph	71
h	*p*-$CF_3C_6H_4$	72
i	*p*-$MeOC_6H_4$	74
j	3-Pyr	60
k	2-Furanyl	70

Scheme 3.

The reaction originates from the nitroaldol reaction of nitromethane, which acts both as a nucleophile and as a solvent, with the aldehydes **6**, with the formation of β-nitroalkanol **7** as an intermediate that converts into nitroalkene **8**. The conjugate attack of a second molecule of nitromethane, to the electron-poor alkene **8** completes the one-pot synthesis of **9**. It is important to point out that the equilibrium conversion (**6** into **7**) and the successive generation of nitroalkene **8** are both strongly assisted by the in situ trapping of **8** with nitromethane, avoiding any possible decomposition of the formed conjugate nitroolefin.

The target compounds **9** were obtained in good yields from a variety of aliphatic, aromatic, and heteroaromatic aldehydes.

It is important to stress that the use of a heterogeneous catalyst (basic Al_2O_3) prevents any aqueous work up, since the catalyst can be simply removed by filtration, washed with EtOAc, and the filtrate concentrated under vacuum to afford the crude product **9** that was directly subjected to flash

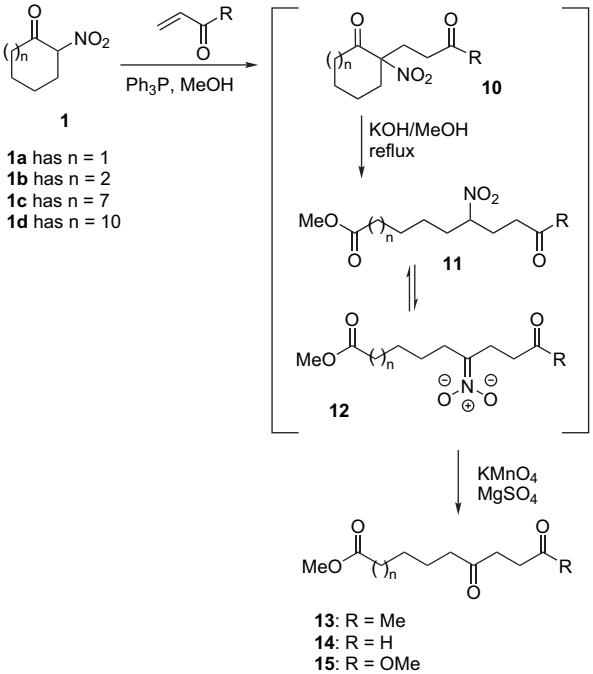
chromatography. Moreover, under these reaction conditions, other functionalities such as ethers, trifluoromethyl groups, and heterocycles can be preserved.

3. Synthesis of 1,4-difunctionalized derivatives

1,4-Difunctionalized derivatives are valuable intermediates in organic synthesis, since they can be transformed into a plethora of valuable compounds such as cyclopentenones and several heterocyclic systems. In particular, 1,4-dicarbonyl and 1,4-diol derivatives are the key building blocks in the preparation of several important targets.

3.1. One-pot synthesis of 1,4-diketones, γ-oxoaldehydes, and γ-keto esters from α-nitrocycloalkanones

Functionalized 1,4-diketones and γ-oxoaldehydes are both valuable classes of compounds, because of their importance in the synthesis of cyclopentenones and heterocyclic systems such as furans, pyrroles, thiophenes, and pyridazines,[24] while γ-oxoesters are highly useful intermediates for the preparation of lactones, lactam antibiotics, isoquinolines, and lactonic sex pheromones.[25] Numerous methods have been reported for the synthesis of these compounds, but most of these suffer from drawbacks such as the use of harsh conditions, employment of expensive chemicals, tedious procedures, and several reaction steps. A few years ago, one-pot procedure was reported for the preparation of compounds **13–15**, starting from α-nitrocycloalkanones as common precursors (Scheme 4).[26]



	Yield (%) of **13**	Yield (%) of **14**	Yield (%) of **15**
a	87	92	70
b	75	75	67
c	93	73	50
d	80	70	50

Scheme 4.

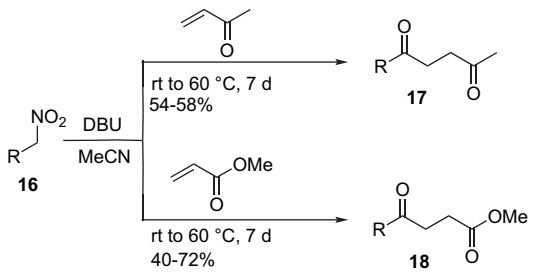
The syntheses are achieved by the conjugate addition of the cyclic nitro ketones **1** with the appropriate enone [acrolein (R=H), methyl vinyl ketone (R=Me), or methyl acrylate (R=OMe)] in methanol and in the presence of a catalytic amount of triphenylphosphine for 2–12 h. Then, the ring cleavage of the intermediate **10** takes place after the addition of methanolic KOH and refluxing for 8 h (strongly assisted by the electron-withdrawing effect of the nitro group and the nucleophilic effect of methanol). The formed polyfunctionalized nitronate **12** can be directly treated with $KMnO_4/MgSO_4$ and the 1,4-dicarbonyl derivatives **13–15** are accordingly synthesized in one-pot, in moderate-to-high overall yields (50–92%).

The one-pot conversion of **1** into **13–15** is favored by (i) the presence of the nitro group, which promotes a variety of reactions such as formation of the C–C bond (**1** to **10**), cleavage of the C–C bond (**10** to **11**), and generation of a new carbonyl moiety (**12** to **13–15**), (ii) the appropriate choice of the addition sequence of the reactants, and (iii) the selection of methanol as solvent, since it acts, firstly, as a good solvent in Michael addition, and then as a reagent in the ring cleavage and, finally, as the appropriate solvent in Nef transformation.

It is important to point out that the methodology is independent of the ring size and affords the polyfunctionalized targets **13–15** with simple and economical chemicals.

3.2. One-pot synthesis of γ-diketones and γ-keto esters from nitroalkanes and DBU

Recently, an unprecedented, selective Nef conversion of secondary nitroalkanes, promoted under basic conditions, by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), a tertiary amidine base, has been reported.[27] This discovery, combined with the peculiarity of the aliphatic nitro compounds in the formation of C–C single bonds under basic conditions,[3–5] suggested a new approach for a one-pot synthesis of γ-diketones and γ-keto esters.[28] In fact, the reaction of primary nitroalkanes **16** with methyl vinyl ketone (MVK) or methyl acrylate (MA) (Scheme 5), in the presence of 2 equiv of DBU in MeCN, allows, after 7 days (room temperature to



R	Acceptor	Yield (%) of **17**	Yield (%) of **18**
$Me(CH_2)_2$	MVK	58	-
$Me(CH_2)_4$	MVK	54	-
$Me(CH_2)_2$	MA	-	60
$Me(CH_2)_4$	MA	-	72
$MeC(OCH_2)_2(CH_2)_2$	MA	-	71
$HO(CH_2)_4$	MA	-	40
$PhCH_2$	MA	-	47

Scheme 5.

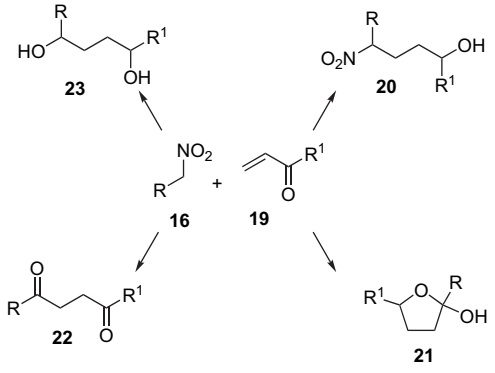
60 °C), the one-pot formation of γ-diketones **17** or γ-keto esters **18**, respectively.

The overall yields are satisfactory-to-good (40–72%), even when functionalized nitroalkanes are employed as the starting materials.

Thus, DBU serves both as a base for the generation of the nitro-carbanion and as a reagent for Nef conversion of the nitro group.

3.3. One-pot synthesis of 1,4-diketones, 1,4-diols, δ-nitroalkanols, and hydroxytetrahydrofurans from nitroalkanes in aqueous media

The synergy between nitroalkanes and aqueous media has been the principle idea for the one-pot synthesis of (i) δ-nitroalkanols **20**, which have proved to be the key building blocks for the synthesis of tetrahydrofurans and spiroacetals,[29] (ii) hydroxytetrahydrofurans (lactols) **21**, intermediates in the synthesis of cyclic ethers,[30] dihydrofurans, zoapatanol derivatives (the menses and labor-inducing principle of the Mexican plant *Montanoa tomentosa*),[31] and nonactic acid,[32] a component of the macrolide antibiotic, nonactin; the hydroxytetrahydrofuran unit is also present in natural products such as seco-furoeremophilane derivatives, which are characteristic constituents of the plants of genus *Euryops*,[33] (iii) 1,4-diketones **22**, and (iv) diols **23**, widely used molecules for the preparation of important heterocycles such as γ-lactones, pyrroles, and tetrahydrofurans (Scheme 6).[30,34]

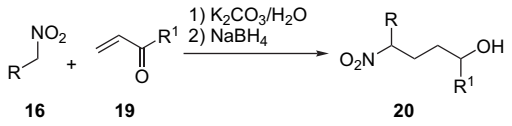


Scheme 6.

All compounds **20**–**23** were obtained from the same starting materials using an aqueous medium.[35]

The preparation of δ-nitroalkanols **20** was carried out in good yields (78–94%) by the conjugate addition of nitroalkanes **16** to unsaturated ketones **19**, under aqueous K_2CO_3, followed by in situ reduction with $NaBH_4$ (Scheme 7). The latter reducing agent was chosen, both because it can be used in water and because it does not reduce the nitro group.

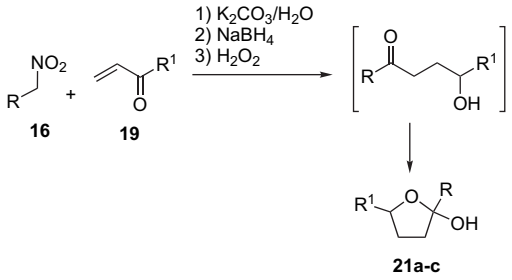
Nitroalkanols **20** were obtained as a 1:1 diastereoisomeric mixture. If, however, conjugated cyclohexenone was employed as an acceptor in the reaction with nitroethane, two of the four possible diastereomers were isolated (86% overall yield).



	R	R^1	Yield (%) of **20**
20a	Me	Me	82
20b	Et	Me	86
20c	*n*-Pr	Me	83
20d	Me	Et	94
20e	Et	Et	82
20f	*n*-Pr	Et	78
20g	Ph	Et	79

Scheme 7.

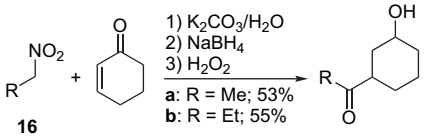
This one-pot synthesis of δ-nitroalkanols **20** can be extended to their in situ Nef reaction, using a 30% aqueous solution of H_2O_2 to afford lactols **21** (Scheme 8).



	R	R^1	Yield (%) of **21**
21a	Me	Me	55
21b	Et	Me	58
21c	*n*-Pr	Et	48

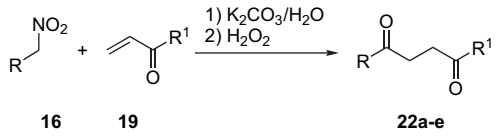
Scheme 8.

The conversion of the nitro group into a carbonyl function can be accomplished by several alternative methods,[10] although the use of H_2O_2/K_2CO_3 appeared to be the most compatible to develop environmentally friendly processes. As reported in Scheme 8, γ-hydroxyketones could not be isolated, since they spontaneously cyclized to the corresponding lactols **21**. When cyclohexenone was used as Michael acceptor, the cyclization could not take place and the hydroxyketones were obtained in satisfactory yields (Scheme 9).



Scheme 9.

In view of the good results for the synthesis of lactols **21**, the use of H_2O_2 for the one-pot preparation of 1,4-diketones **22** has been further investigated. Thus, after the addition of nitroalkanes **16** to unsaturated ketones **19** (Scheme 10), the mixture was treated with a 30% aqueous solution of H_2O_2, giving the corresponding diketones **22** in good yields.

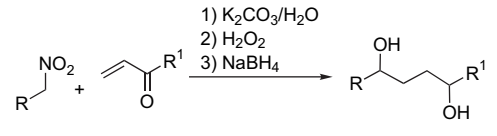


16 **19** **22a-e**

	R	R^1	Yield (%) of **22**
22a	Me	Me	73
22b	Me	Et	68
22c	Et	Et	72
22d	*n*-Pr	Et	70
22e	Ph	Me	69

Scheme 10.

1,4-Diols **23** were prepared by in situ reduction of the 1,4-diketones **22** obtained as reported above, using an excess of $NaBH_4$ as the reducing agent (Scheme 11).



16 **19** **23a-e**

	R	R^1	Yield (%) of **23**
23a	Me	Me	60
23b	Et	Et	64
23c	*n*-Pr	Et	61
23d	Ph	Me	72
23e	*n*-Bu	Me	60

Scheme 11.

The reported yields refer to the 1:1 diastereomeric inseparable mixture of diols.

Moreover, it is important to point out the crucial role of three different factors for the one-pot synthesis of **20**–**23** from the common intermediates **16** and **19**: (i) the chemical versatility of nitroalkanes, (ii) the use of water as solvent, and (iii) the appropriate sequence of addition of the reagents.

4. Synthesis of α,ω-dicarbonyl derivatives

α,ω-Dicarbonyl derivatives are valuable intermediates in organic synthesis, due to the many synthetic transformations originating from this class of compounds.[12a–c]

4.1. One-pot synthesis of α,ω-dicarboxylic acid dimethyl esters

Long-chain dicarboxylic acid dimethyl esters have been found as components of important natural products,[36] in acid-resistant raw forest humus,[37] to show antifungal properties,[38] or to be the key building blocks for the synthesis of a variety of other important targets.[39]

Several methods have been proposed for their preparation, but many of these require multi-step sequences with low yields, strong oxidizing conditions, or the extension of skeletons following tedious procedures.

Following the pioneering study of Feuer and Pivawer,[40] in which some α-nitrocycloalkanones were converted into α,ω-dicarboxylic acid dialkyl esters in moderate yields and using strongly acidic conditions, a new one-pot synthesis of α,ω-dicarboxylic acid dimethyl esters **25a**–**n** has been reported by ring cleavage of α-nitrocycloalkanones **24a**–**n**, employing potassium persulfate as a mild oxidant, in the presence of methanol (Scheme 12).[41]

24 **25a-n**

	24	**25**	Yield (%) of **25**
a: n=0			92
b: n=1			93
c: n=2			90
d: n=3			86
e: n=4			80
f: n=5			81
g: n=6			85
h: n=7			88
i: n=10			78
j: R=Me **k**: R=Ph **l**: R=*t*-Bu			79 88 85
m			58
n			90

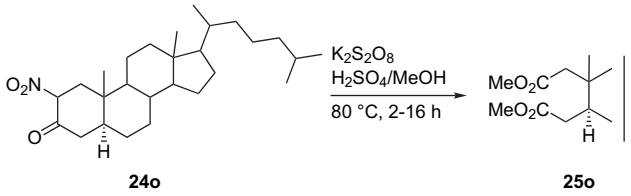
Scheme 12.

The success of the process is due to the key role of the nitro group that firstly assists the cleavage of the C–C bond between the carbonyl group and the nitro-substituted atom, under the nucleophilic attack of methanol, then undergoes the in situ transformation affording an additional carboxylic functionality.

A variety of 2-nitrocycloalkanones are cleaved in good yields, regardless of the ring size; alkylated nitro ketones **24** are also easily converted into **25**, producing the substituted dimethyl esters in a one-pot process.

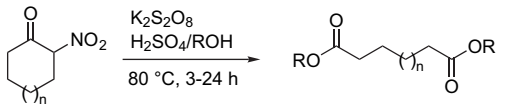
A further valuable application of this process is the direct ring cleavage of steroidal systems, such as 2α-nitro-5α-cholestan-3-one **24o**, which affords the corresponding diester **25o** in 68% overall yield (Scheme 13).

Although the dimethyl esters **25** are the most valuable derivatives of dicarboxylic acids, diethyl and diisopropyl esters can be also obtained in a one-pot way using the corresponding alcohols (Scheme 14).



24o 25o

Scheme 13.



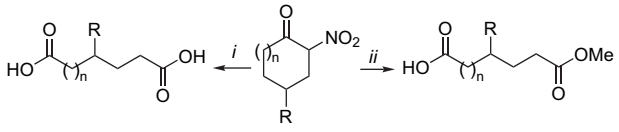
24 26a-f

	n	R	Yield (%) of **26**
a	1	Et	90
b	1	*i*-Pr	71
c	2	Et	83
d	2	*i*-Pr	73
e	10	Et	83
f	10	*i*-Pr	72

Scheme 14.

4.2. Modulated one-pot synthesis of α,ω-dicarboxylic acids and α,ω-dicarboxylic acid monomethyl esters

α,ω-Dicarboxylic acids, or their corresponding monomethyl esters, can be selectively prepared by a modulated oxidative ring cleavage of α-nitrocycloalkanones, using Oxone® as oxidant.[42] Thus, the reaction of **24** (Scheme 15), in an aqueous solution of 0.5 M Na_2HPO_4 and 1 M NaOH, with 2.5 mol of Oxone® affords high yields (78–99%) of the α,ω-dicarboxylic acids **27a–j**, while compounds **28a–j** have been prepared by heating **24** in a methanolic solution of KOH, and then Oxone®, 3 mol in an aqueous solution of 0.5 M Na_2HPO_4 and 1 M NaOH, is added to the cold solution. Compounds **28a–j** were obtained in 84–94% yields.



27a-j 24 28a-j

i. a) MeOH, 0.5 *M* Na_2HPO_4, 1 *M* NaOH, 70 °C;
b) Oxone®, H_2O, rt
ii. a) MeOH, KOH, 65 °C;
b) 0.5 *M* Na_2HPO_4, 1 *M* NaOH, Oxone®, H_2O, rt

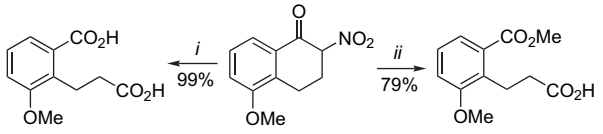
	R	n	Yield (%) of **27**
27a	H	1	93
27b	*t*-Bu	1	99
27c	Me	1	88
27d	H	7	87
27e	Ph	1	78
27f	H	2	94
27g	H	6	99
27h	H	5	98
27i	H	10	98
27j	H	3	99

	R	n	Yield (%) of **28**
28a	H	1	89
28b	*t*-Bu	1	99
28c	Me	1	90
28d	H	7	82
28e	Ph	1	92
28f	H	2	91
28g	H	6	93
28h	H	5	84
28i	H	10	84
28j	H	3	86

Scheme 15.

The conversion of **24** into **27** proceeds via the oxidative ring cleavage of the nitrocycloalkanones, followed by in situ Nef conversion of the formed primary nitro group, while the transformation of **24** into **28** originates from the ring cleavage of **24** promoted by methanol (that acts as a nucleophile with the consequent conversion of the carbonyl into an ester) followed by in situ oxidative transformation of the formed primary nitro group into a carboxylic functionality.

This process is also effective for the ring opening of α-nitrocycloalkanones derived from unsymmetrical ketones, such as 5-methoxy-2-nitrotetranal-1-one **29**, which affords (Scheme 16) the corresponding dicarboxylic acid **30** in 99% yield, while the monomethyl ester **31** is obtained in 79% yield.



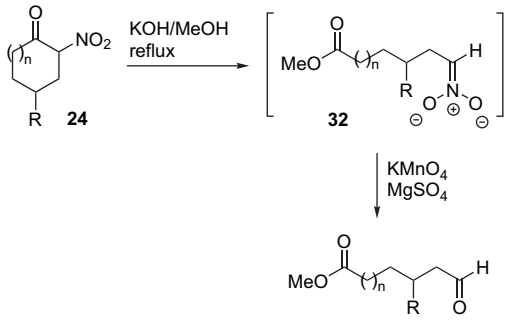
30 29 31

Scheme 16. For i and ii see Scheme 15.

By this oxidative fission a variety of cyclic nitro ketones are efficiently cleaved in a one-pot procedure, regardless of the ring size and/or the presence of an alkyl group as substituent.

4.3. One-pot synthesis of ω-oxoalkanoates

ω-Functionalized aldehydes, well-known powerful building blocks, especially for the synthesis of natural products,[43] can be easily obtained in a one-pot process from α-nitrocycloalkanones. The procedure consists (Scheme 17) of the ring cleavage of **24** with methanol, as nucleophile, under basic conditions (KOH) and, in situ, Nef conversion of the obtained nitronate **32** with an aqueous solution of $KMnO_4$/$MgSO_4$. Compounds **33a–h** are obtained in satisfactory-to-good yields (60–84%).[26]



24 32 33a-h

	n	R	Yield (%) of **33**
33a	0	H	60
33b	1	H	77
33c	1	Me	66
33d	1	*t*-Bu	60
33e	2	H	75
33f	6	H	63
33g	7	H	61
33h	10	H	84

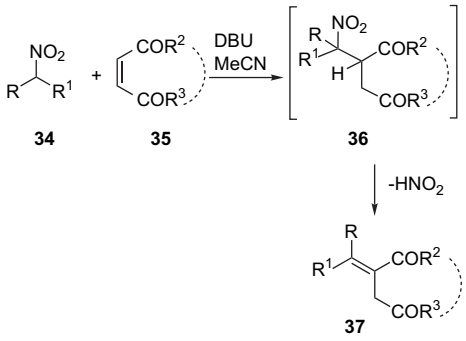
Scheme 17.

5. Stereoselective synthesis of electron-poor alkenes

The many synthetic transformations originating from electron-poor alkenes have made their preparation an important synthetic problem of long-standing interest and, therefore, methods allowing the direct formation of polyfunctionalized unsaturated carbonyl derivatives are considered to be very important. The resultant compounds can be further functionalized by Michael or Diels–Alder reactions in order to furnish polyfunctionalized molecules of considerable use, especially in the synthesis of natural products.[44,45]

5.1. One-pot synthesis of polyfunctionalized unsaturated carbonyl derivatives

Nucleophilic addition of carbanions to electrophilic alkenes activated by one or two electron-withdrawing groups (Michael reaction) is one of the most important tools[46] in organic synthesis for the formation of a new carbon–carbon bond. However, if nitroalkanes react with electron-poor alkenes having two carbonyl groups in the α- and β-position, a tandem Michael addition–elimination process takes place, giving the unsaturated 1,4-dicarbonyl derivatives with enhanced *E* stereoselectivity (Scheme 18).[47]



R	R^1	R^2	R^3	Yield (%) of **37**
Me	H	OMe	OMe	93
Me	Me	OMe	OMe	95
$THPOCH_2$	H	OMe	OMe	80
$MeCO(CH_2)_2$	H	OMe	OMe	90
Me_2CHCH_2	H	Me	Me	96
$HO(CH_2)_4$	H	Me	Me	85
$-(CH_2)_5-$		Me	Me	85
$MeOCO(CH_2)_3$	H	-N(Ph)-		80
Me	Me	-N(Ph)-		70
$MeOCO(CH_2)_3$	H	-N(Et)-		90
$-(CH_2)_5-$		-N(Et)-		80
$Me(CH_2)_4$	H	-N(Et)-		88

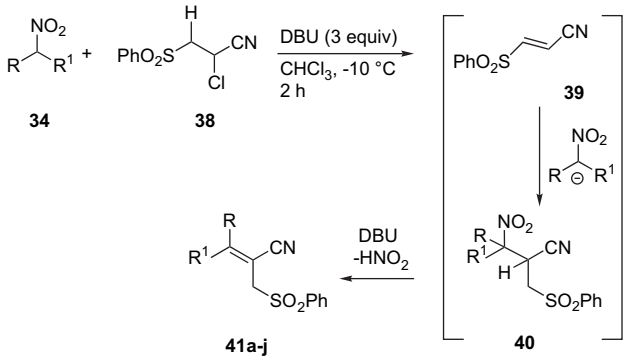
Scheme 18.

The success of the one-pot process is due to the simultaneous behavior of the nitro group both as an electron-withdrawing group and as a good leaving group. The reaction proceeds through Michael addition of primary or secondary nitroalkanes **34** to a variety of alkenes **35**, in acetonitrile and with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base; the α,β-unsaturated enone derivatives **37** are produced in high yields and in very short reaction times (usually 0.25–3 h) via the adduct **36** in which the in situ elimination of nitrous acid takes place, which is induced by the presence of an electron-withdrawing group at the β-position to the nitro group. The very mild conditions allow high selectivity as supported by the absence of the typical side reactions (bis-addition, polymerization, β-fission, etc.), and, more interestingly, several functionalities such as hydroxyl, ketone, ester, ketal, and tetrahydropyranyl are preserved.

5.2. One-pot synthesis of polyfunctionalized α,β-unsaturated nitriles

The synthesis of α,β-unsaturated nitriles is of great interest in synthesis, since the nitrile group represents one of the classical functional groups of organic chemistry and conjugated examples are versatile reagents, which have been extensively used as electrophilic acceptors and as key precursors in the synthesis of different heterocycles.[48]

A new synthetic approach to the one-pot stereoselective preparation of polyfunctionalized (*E*)-α,β-unsaturated nitriles has been developed, starting from primary or secondary nitroalkanes **34** and 2-chloro-3-phenylsulfonylpropanenitrile **38** as Michael acceptor precursor, in $CHCl_3$ in the presence of DBU (3 equiv), at −10 °C (Scheme 19).[49]



	R	R^1	Yield (%) of **41**
a	$-(CH_2)_5-$		63
b	$-(CH_2)_4-$		64
c	Me	Me	68
d	Et	H	61
e	*n*-Pr	H	74
f	*n*-Bu	H	70
g	$n\text{-}C_5H_{11}$	H	71
h	$THPOCH_2$	H	51
i	$MeC(OCH_2CH_2O)CH_2$	H	50
j	$MeOCO(CH_2)_4$	H	66

Scheme 19.

The reaction firstly proceeds through the base-induced elimination of HCl from **38** to **39**, followed by generation of the nitro-carbanion that, by a conjugate addition, allows the formation of Michael adducts **40**, which are prone to immediate nitrous acid elimination under the basic reaction conditions used. Thus, the one-pot formation of functionalized α,β-unsaturated nitriles **41a–j** with complete *E* selectivity has been realized.

The yields are satisfactory (50–74%), but it should be pointed out that these are the overall yields of three different steps [(i) HCl elimination, (ii) conjugate addition, and (iii) nitrous acid elimination].

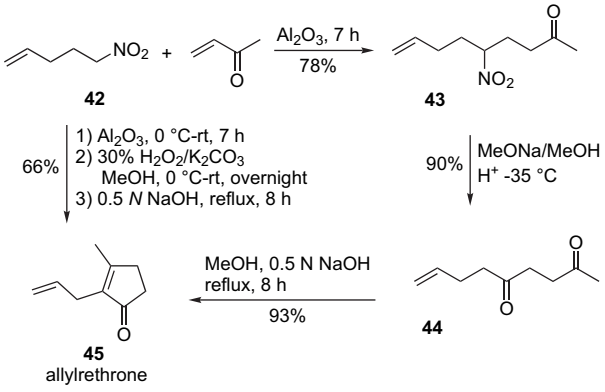
The method works well with both primary and secondary nitro compounds and with a variety of nitroalkanes (**34a–j**), so that the final products include several interesting functionalities that could allow further manipulation.

6. Synthesis of homocyclic compounds

Cyclic structures are one of the most recurring structural units in targets of relevant practical interest,[12] and their preparation from acyclic compounds is one of the main goals in organic synthesis.

6.1. One-pot synthesis of cyclopentenones

Cyclopentenones are important moieties present in many natural products such as allylrethrone **45**, which is an important component of insecticidal pyrethroids and an important intermediate for the synthesis of allethrolone and pyrethrins.[50] Commercial 5-nitro-1-pentene **42** has been chosen for an improved synthesis of allylrethrone, following two different approaches: (i) using a three-step sequence and (ii) using a one-pot process (Scheme 20).[51]

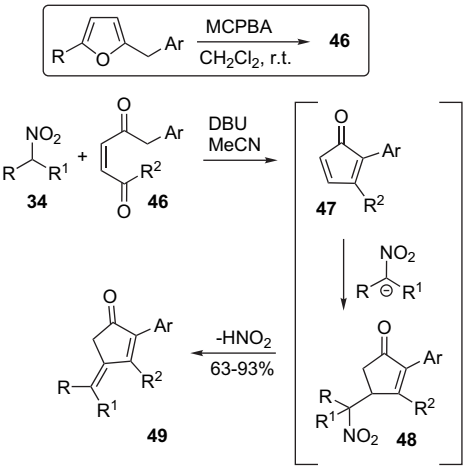


Scheme 20.

The starting point of the first approach is Michael addition of **42** to methyl vinyl ketone (MVK) with basic alumina as a solid catalyst, giving the γ-nitro ketone **43**, in 78% yield, which can be converted into the 1,4-diketone **44**, in 90% yield, by Nef reaction. The reaction is performed by addition of the corresponding nitronate to a mixture of methanol and concentrated sulfuric acid at −35 °C. Subsequent basic intramolecular aldolization–dehydration affords **45** in 65% overall yield. Alternatively (second approach), allylrethrone can be obtained in a one-pot reaction by the conjugate addition of 5-nitro-1-pentene to MVK on alumina, followed by in situ oxidation with hydrogen peroxide in methanol, and then in situ basic cyclization with 0.5 N sodium hydroxide, giving **45** in 66% overall yield.

The one-pot process is strongly favored both by the choice of alumina as catalyst for the first step and by the versatility of the nitro group that serves to generate a carbanion in Michael reaction and as a precursor of the carbonyl.

Nitroalkanes are also the key precursors for the one-pot synthesis of conjugated cyclopentadienones, very precious materials that are difficult to prepare.[52] A solution to the preparation of cyclopentadienones has been realized in a one-pot process from nitroalkanes and unsymmetrical 2-ene-1,4-diketones (easily obtained by oxidative cleavage of the corresponding furan precursors), as reported in Scheme 21.[53]



R	R^1	R^2	Ar	Yield (%) of **49**
Me	Me	Me	Ph	77
n-C_9H_{19}	H	Me	Ph	76
n-C_5H_{11}	H	Me	Ph	81
CH_2=CH$(CH_2)_3$	H	Me	Ph	68
HO$(CH_2)_5$	H	Me	Ph	78
MeCO$(CH_2)_2$	H	Me	Ph	84
MeOCO$(CH_2)_2$	H	Me	Ph	80
MeOCO$(CH_2)_2$	H	Et	Ph	79
n-C_5H_{11}	H	Me	3-MeOC_6H_4	87
MeOCO$(CH_2)_4$	H	Et	4-FC_6H_4	73
n-C_5H_{11}	H	Me	3-ClC_6H_4	93

Scheme 21.

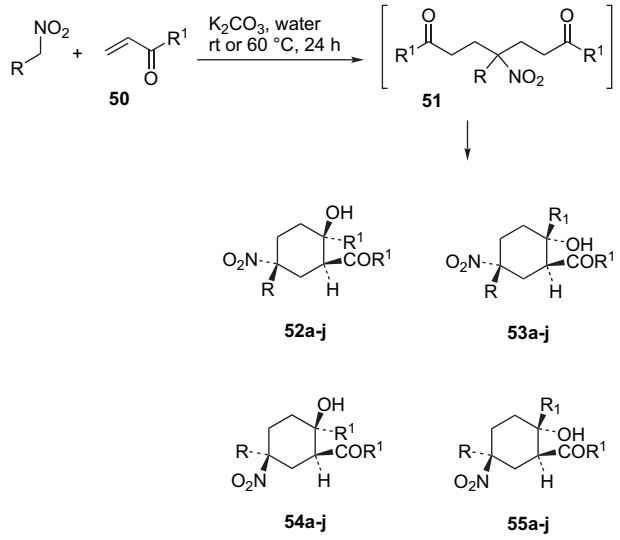
Nitroalkanes react with diketones **46** in the presence of DBU in acetonitrile, affording directly 4-alkylidene-2-en-1-ones **49** in good yields and high *E* diastereoselectivity. The nature of product **49** is consistent with the mechanism depicted in Scheme 21. A chemoselective intramolecular aldol condensation of enedione **46**, promoted by the presence of the aromatic ring, gives cyclopentadienone **47** as a reactive intermediate that, under the same conditions, reacts with the nitroalkane carbanion, affording Michael adduct **48**. Nitroenone **48** undergoes a base-assisted elimination of nitrous acid giving cyclopentenones **49**. Thus, functionalized 4-alkylidenecyclopent-2-en-1-ones are readily available compounds by a simple procedure involving three different reactions carried out in a tandem process.

6.2. One-pot synthesis of cyclohexane derivatives

Cyclohexane derivatives are useful building blocks of relevant practical interest that provide an efficient entry into important frameworks.

2-Acyl-4-nitrocyclohexanols are a valuable class of polyfunctionalized molecules bearing three stereogenic centers. These compounds can be prepared by a one-pot diastereoselective synthesis from primary nitroalkanes and conjugated enones in an aqueous medium.[54] In fact, the reaction

in water (Scheme 22) of a primary nitroalkane with 2 equiv of α,β-unsaturated ketones **50**, in the presence of potassium carbonate as base, provides, after 24 h at the appropriate temperature (room temperature or 60 °C), the one-pot formation of nitrocyclohexanol derivatives **52–55** in excellent chemical and stereochemical yields.



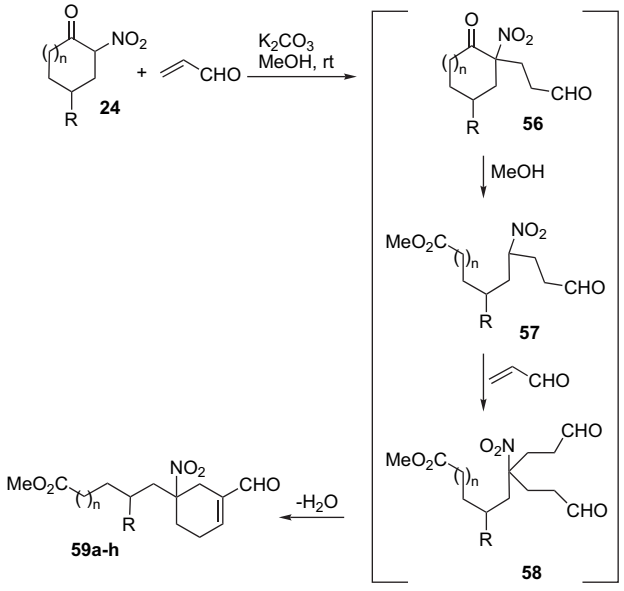
	R	R^1	Yield (%) of **52-55**	Diastereomeric ratio
a	Me	Me	90	5.4:1:1
b	Et	Me	85	12.8:3:1
c	*n*-Pr	Me	93	9 :2.2:1
d	*n*-Bu	Me	95	12 :5.2 :1
e	*n*-C_5H_{11}	Me	95	9:2:1
f	*i*-Pr	Me	75	17:1
g	Ph	Me	70	16.5:1:1
h	Me	Et	77	18.5:4:2 :1
i	Et	Et	75	27:5:2:1
j	Me	*n*-Pr	80	17:3.5:1.5:1

Scheme 22.

The first step of the reaction is the double Michael addition of the nitroalkane to the enone, followed by an in situ intramolecular aldol reaction of the adduct **51**. Cyclohexanols are obtained in 70–95% yield with predominance of the diastereomer **52**.

Another important class of six-membered homocyclic structures are the cyclohexene derivatives, especially the functionalized derivatives such as those (**59**) reported in Scheme 23. These compounds can be synthesized, in one-pot, from α-nitrocycloalkanones **24** by their reaction with acrolein via an anionic domino process. The reaction of **24** with 2 equiv of acrolein proceeds, at room temperature, in a methanolic solution of potassium carbonate, affording the adduct **56**, which is subjected to ring cleavage by the nucleophilic behavior of methanol. The formed nitro derivative **57** undergoes a further Michael addition to acrolein, allowing the nitro-1,7-dialdehyde that is prone to give intramolecular aldolic condensation, with the formation of **59a–h**.

Nitro group favors the two Michael reactions (**24** to **56** and **57** to **58**) and the ring cleavage in the transformation of **56** to **57**.



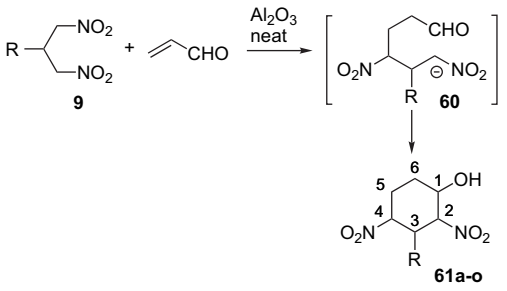
	n	R	Yield (%) of **59**
59a	0	H	64
59b	1	H	53
59c	1	Me	51
59d	1	*t*-Bu	55
59e	2	H	50
59f	5	H	38
59g	6	H	49
59h	10	H	53

Scheme 23.

The process works well, regardless of the ring size of **24**, and the overall yields are respectable considering that it is composed of four different steps.

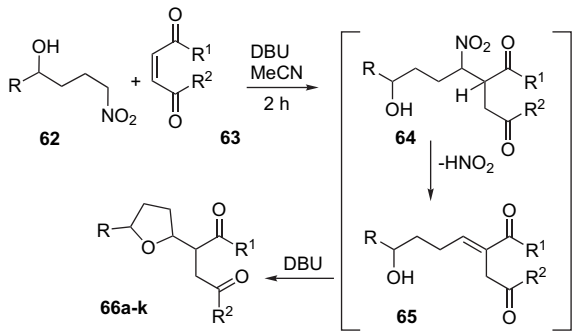
Dinitrocyclohexanols are a new class of cyclohexane derivatives in which the presence of two nitro functionalities offers a variety of synthetic opportunities, due to the great versatility of the nitro groups. Thus, the synthesis of these compounds has been reported from 1,3-dinitroalkanes in a one-pot procedure and under solvent-free conditions (Scheme 24).[55]

Thus, treating a mixture of 1,3-dinitroalkanes **9a–o** and acrolein with basic alumina (activity I), at 0 °C, without any solvent, and then stirring at 0 °C for 15 min at room temperature for 4–48 h, affords the target 3-alkylated-2,4-dinitrocyclohexanol derivatives **61** with satisfactory-to-good yields (65–84%). The synthesis results in a tandem process in which the first step is the conjugate addition of **9** to acrolein, yielding the intermediate **60** that is prone to give **61** through an intramolecular nitroaldol (Henry) reaction. By following these mild conditions, several dinitrocyclohexanol derivatives can be obtained and other important functionalities, such as furanyl, phenyl, ether, C–C double bond, cyano, heteroaromatic, and phenol, can be introduced and preserved. Although four stereogenic centers are present in compounds **61**, the stereoisomers **61′** (±)-(1*R**,2*S**,3*R**,4*R**) and **61″** (±)-(1*S**,2*S**,3*R**,4*R**) are predominant (>95%).



	R	Yield (%) of **61**	**61'**:**61"**
a	Furyl	72	51:49
b	Ph	71	61:39
c	*n*-Pr	83	15:85
d	*i*-Pr	65	20:80
e	*n*-C_8H_{17}	87	53:47
f	*o*-$NO_2C_6H_4$	70	51:49
g	*p*-$MeOC_6H_4$	76	54:46
h	*p*-$CF_3C_6H_4$	71	56:44
i	*cis*-$Me(CH_2)_4CH{=}CH(CH_2)_2$	71	30:70
j	*c*-C_6H_{11}	84	22:78
k	*m*-$NO_2C_6H_4$	68	53:47
l	*m*-CNC_6H_4	70	50:50
m	$Ph(CH_2)_2$	74	35:65
n	*o*-Py	71	63:37
o	*m*-(OH)-*p*-$MeOC_6H_3$	72	48:52

Scheme 24.



	R	R^1	R^2	Yield (%) of **66**
a	H	Me	Me	79
b	H	-N(Ph)-		75
c	Me	Me	Me	77
d	Me	OMe	OMe	70
e	Me	-N(Me)-		77
f	Me	-N(Et)-		79
g	Me	-N(*t*Bu)-		77
h	Me	-N(Ph)-		81
i	Et	Me	Me	85
j	Et	-N(Me)-		82
k	Et	-N(Et)-		86

Scheme 25.

7. Synthesis of oxygenated heterocyclic compounds

Of the 12.5 million chemical compounds currently registered, about one half contains heterocyclic systems. Heterocycles are important not only because of their abundance but, above all, also because of their chemical, biological, and technical significances.[56]

7.1. One-pot synthesis of tetrahydrofuran derivatives

Cyclic ethers, such as tetrahydrofurans, are often present in naturally occurring compounds and, furthermore, are useful synthetic intermediates.[57] Tetrahydrofuran derivatives can be easily obtained in a one-pot procedure from δ-nitroalkanols **62**. The key idea is the use of the hydroxy-functionalized nitroalkanes **62** as nucleophiles and the enones **63** as electrophiles. In fact (Scheme 25), by bringing together, at room temperature, 1 mol of **62** and **63** (1 mol) and in the presence of DBU as base, results in the direct formation of the tetrahydrofuran derivatives **66a–k** in good yields (70–86%).[58]

The nature of **66** is consistent with the formation of Michael adduct **64**, followed by base-promoted elimination of nitrous acid with consequent generation of the conjugate enone **65** in which the basic conditions favor the intramolecular conjugate addition of the hydroxyl to the formed electrophilic alkene. The ring closure is poorly stereoselective; indeed tetrahydrofurans **66** are obtained as a mixture of diastereomers that are hardly separable using conventional chromatographic techniques.

It should be noted that the reaction works well with a variety of electrophilic acceptors **63**, so that polyfunctionalized mono- (**66a**,**b**) and disubstituted (**66c–k**) tetrahydrofurans can be easily obtained in a one-pot process. Moreover, compounds **66** include other important frameworks such as heterocyclic systems (**66b**,**e–h**,**j**,**k**) or 1,4-dicarbonyl structures that could allow selective manipulation to give other important functionalities.

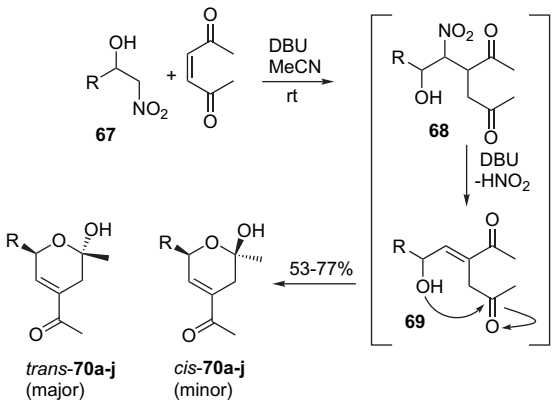
7.2. One-pot diastereoselective synthesis of dihydropyranols

The widespread occurrence of substituted dihydropyranol derivatives as substructures in an unusually large range of natural products, and their relevant practical interest as useful building blocks that provide an efficient entry to important frameworks,[59] has promoted considerable interest in the development of synthetic routes to these compounds.

Recently, an anionic domino process for the one-pot diastereoselective synthesis of dihydropyranols, from β-nitroalkanols, has been discovered.[60]

The basis of the procedure (Scheme 26) is the use of β-nitroalcohols **67** as nucleophilic starting materials.

Thus, by adding together, at room temperature, the nitro derivative **67** and *cis*-3-hexen-2,5-dione, in the presence of DBU as the base in acetonitrile, the one-pot diastereoselective synthesis of **70** has been achieved. The synthesis proceeds with the formation of the adduct **68**, followed by base-promoted elimination of nitrous acid, with the formation of the structure **69**. Then, the formed allylic hydroxyl group of **69** assists the diastereoselective cyclization through the formation of a hemiketal functionality, with the consequent generation of dihydropyrans **70a–j**. Compounds **70a–j** are obtained in satisfactory-to-good overall yields (53–77%) as a *cis/trans* diastereomeric mixture in which the *trans* form is strongly prevalent.



	R	Yield (%) of **70**	*cis*/*trans*
a	H	77	18:82
b	Me	60	16:84
c	Et	61	20:80
d	*n*-Pr	54	15:85
e	*n*-C_6H_{13}	55	19:81
f	*n*-$C_{13}H_{27}$	58	19:81
g	Me_2CH	56	16:84
h	$MeCH_2CH{=}CH(CH_2)_5$	60	15:85
i	$Ph(CH_2)_2$	68	17:83
j	$MeOCO(CH_2)_3$	53	18:82

Scheme 26.

7.3. Two-step sequence synthesis of spiroketals

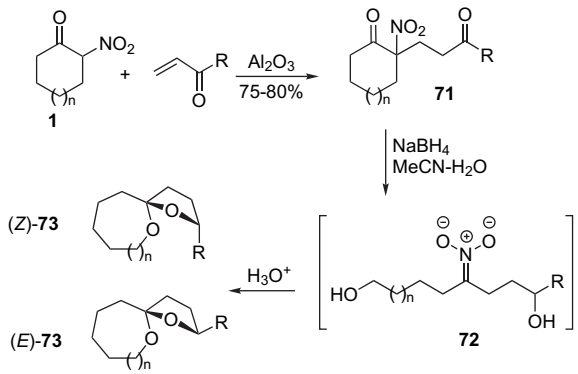
Spiroketals enjoy widespread occurrence as substructures of naturally occurring substances from many sources, including insects, microbes, plants, fungi, and marine organisms.[61] The increasing pharmacological importance of compounds containing spiroketal assemblies has triggered intense interest in both their chemical reactivity and their synthesis.

Nitroalkanes have been demonstrated to be very useful starting materials for the preparations of a variety of spiroketals and some of these syntheses can be realized in a sequence of only two steps.

A few years ago, it was found that cyclic α-nitro ketones can be employed as starting compounds for the synthesis of 2-alkyl-1,6-dioxaspiro[4.5]decanes and 2-alkyl-1,6-dioxaspiro[4.6]decanes.[62]

Thus, as reported in Scheme 27, the procedure starts with Michael addition of **1** to conjugated enones, under basic alumina catalysis, with the formation of the adducts **71** in good yields. The latter compounds were directly converted into the spiroketals **73** by regiospecific reductive cleavage with sodium borohydride in acetonitrile/water (3:2). The tandem reductive ring cleavage and spiroketalization proceed, very likely, via the dihydroxynitronates **72** that, by acidification, convert into the carbonyl derivatives, which spontaneously cyclize to the spiroketals **73** with prevalence of the *E*-isomer. 1,6-Dioxaspiro[4.5]decane (**73**: *n*=0, R=Me) is an important pheromonic component of *Paravespula vulgaris*.[63]

It is important to point out the importance of the nitro group in this process, since it firstly assists the generation of a new C–C bond (**1** to **71**), then the cleavage of a C–C bond (**71** to **72**) and, finally, the spiroketalization through the generation of a carbonyl moiety (**72** to **73**).

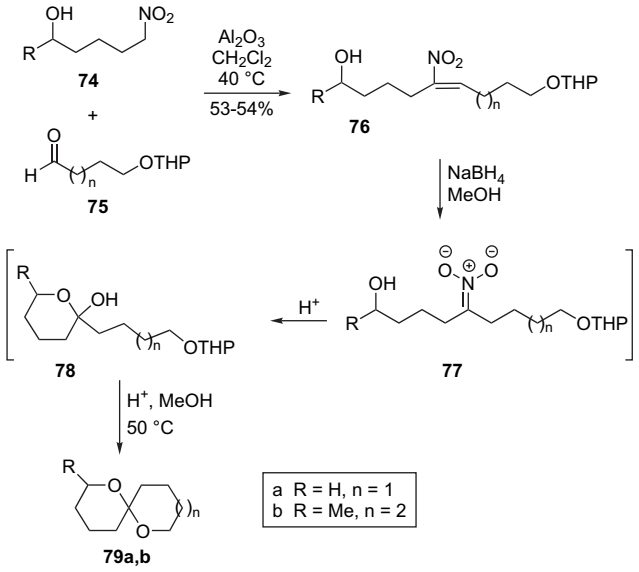


n	R	Yield (%) of **73**	*E*/*Z*
0	Me	65	1.5
0	Et	70	1.5
1	Me	75	1.5
1	H	60	

Scheme 27.

Later, two important spiroketals, such as 1,7-dioxaspiro[5.6]undecane **79a**, the major component of the olive fruit fly (*Dacus oleae*) sex pheromone,[64] and (*E*)-2-methyl-1,7-dioxaspiro[5.6]dodecane **79b**, a component of the pheromone of *Andrena haemorrhoa*,[65] have been chosen as target molecules for their total two-step syntheses from nitroalkanes.[66]

As reported in Scheme 28, the nitroaldol condensation between 5-nitroalcohols **74** and hydroxyl aldehydes **75** provides a one-pot formation of nitroalkenes **76**, which are converted directly into the spiroketals **79** by reduction with sodium borohydride in methanol.



Scheme 28.

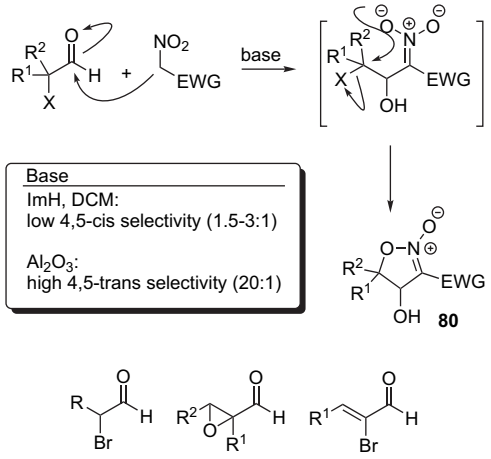
The tandem reduction–spiroketalization of the nitroalkenes **76** probably proceeds via the nitronates **77** that, by acidification, are converted into the carbonyl derivatives, which spontaneously cyclize to hemiketals **78**. Removal of the tetrahydropyranyl group, by heating the acidic mixture during

the work up, affords, in a one-pot reaction from **76**, the desired spiroketals in 64–66% yields. The spiroketalization of **76** to **79a** and **79b** proceeds in high stereoselectivity.

7.4. One-pot synthesis of 4-hydroxy-4,5-dihydroisoxazoles and their derivatives from activated primary nitroalkanes

4-Hydroxy-4,5-dihydroisoxazoles (**80**) represent a very interesting subclass of the dihydroisoxazole family[67] that can lead to expeditious preparations of biologically interesting compounds.[68,69] Unfortunately, the usual method for the preparation of 4,5-dihydroisoxazoles, nitrile oxide cycloaddition to alkenes, cannot be applied to the synthesis of 4-hydroxy derivatives.[70] An even more difficult problem is represented by the preparation of enantiomerically pure products. Some approaches to this problem have been devised,[68,71,72] but each of these methodologies suffers from disadvantages. One-pot methodologies were successfully employed to overcome these synthetic problems, allowing an easy and general access to enantiomerically pure 4-hydroxy-4,5-dihydroisoxazoles.

Some years ago, it was reported that the reaction of aldehydes bearing a leaving group on the α-carbon with activated primary nitroalkanes, in the presence of a base (Scheme 29), results in the stereoselective formation of a heterocycle, a 4-hydroxy-4,5-dihydroisoxazole 2-oxide (**80**). The overall reaction can be depicted as a two-step tandem process. The first step is a nucleophilic attack of the nitro compound or the carbonyl group of the aldehyde (Henry reaction),[73] forming a new C–C bond, followed by an intramolecular ring closure with displacement of the leaving group.

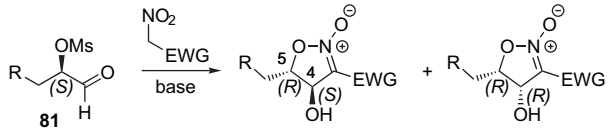


Scheme 29.

This turned out to be a general process that works with different leaving groups and with different electrophiles. With α,β-epoxy aldehydes, the leaving group is the epoxide oxygen. In this case, the second step of the reaction, the intramolecular ring closure, results in a regio- and stereospecific ring opening of the oxirane.[74] The process is also successful with 2-bromo aldehydes[75] and with 2-bromo enones: in the latter case, the first step is a conjugate attack of the nitroalkane or the 3-position of the enone.[76]

The 4,5-*cis/trans* selectivity can be controlled, to a certain extent, by changing the reaction conditions. Under homogeneous conditions, with a base in a polar solvent, there is a slight predominance of the cis-isomer, while under heterogeneous conditions, with chromatographic alumina as the base and without any solvent, *trans*-4,5-dihydroisoxazole largely predominates.

7.4.1. Use of labile reactants. The preparation of products in a non-racemic form required the use of optically active and labile aldehydes bearing a leaving group on the chiral α-carbon. In this case, the outcome of such a reaction would be a pair of enantiomerically pure diastereoisomers (Scheme 30).



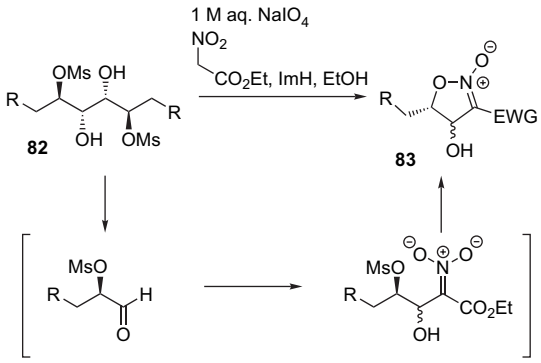
Scheme 30.

α-Hydroxyaldehyde derivatives such as **81** (Scheme 30) would be the perfect starting material for such processes, since they are easily available from D-mannitol by multigram methods that afford both enantiomerically pure forms. In addition, the hydroxy group can be activated for its nucleophilic displacement. However, subjecting them to the tandem one-pot procedure depicted in Scheme 30 invariably led to racemic products.[77] This is due to the exceptionally chemically and stereochemically labile starting aldehydes that are not able to survive even in these mild reaction conditions.

The stereodivergent conversion of D-mannitol into either enantiomer of **81** can be achieved by a simple sequence of well-known reactions.[78] The last step of this sequence is the oxidative cleavage of diols such as **82**, leading to 2 equiv of identical enantiopure aldehyde **81**.

One-pot methodologies turned out to be useful and allowed the aldehyde lability problem to be overcome. In fact, in order to avoid the need to isolate, or even manipulate, the stereochemically labile aldehyde, a new domino process was set up (Scheme 31),[77] where the real starting material is the diol **82**, which is the precursor of the aldehyde. In this process, all the reagents, the diol, the 1 M aqueous solution of periodate, the nitroacetate, and the base, are added together at the beginning of the reaction (Scheme 31). These components added one after the other in the right order in a three-step multi-bond-forming domino process. Pairs of 4,5-*cis*- and 4,5-*trans*-4,5-dihydroisoxazoles **83** were obtained, the enantiopurity and absolute configuration of which were determined by combined HPLC and NMR analyses of the corresponding Mosher's esters.[77]

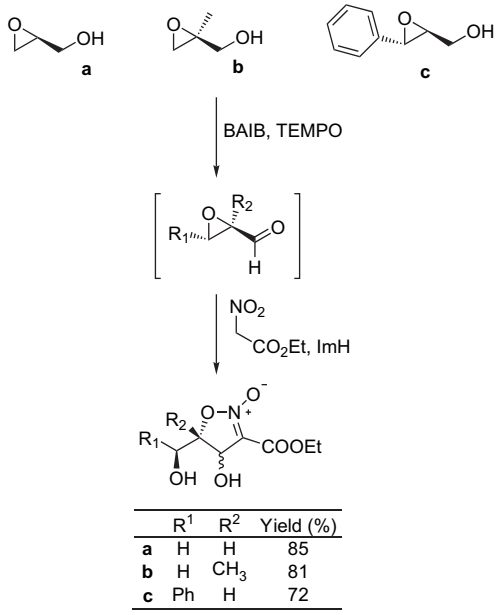
The same approach was then applied to other labile enantiopure substrates, such as the easily accessible α,β-epoxy aldehydes. The goal was to devise a new multi-step one-pot procedure that could transform enantiomerically pure epoxy alcohols into a pair of enantiomerically pure diastereoisomeric



	R	Yield (%)
a	*n*-Pr	93
b	*n*-Bu	86
c	3-Butenyl	90
d	Cyclohexyl	quant.
e	(2*S*)-2-Methylbutyl	95

Scheme 31.

2-isoxazoline derivatives, without the need for the isolation of 2,3-epoxy aldehydes (Scheme 32). Epoxy alcohols, easily available in both enantiomerically pure forms through Sharpless asymmetric epoxidation, are much more stable than the corresponding aldehydes, and what was needed was an oxidation procedure compatible with the rest of the process to be included in the new one-pot procedure.

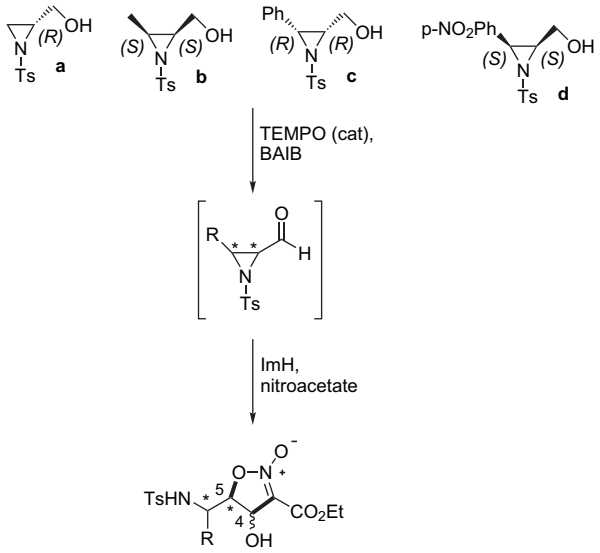


	R^1	R^2	Yield (%)
a	H	H	85
b	H	CH_3	81
c	Ph	H	72

Scheme 32.

The oxidation procedure developed by the group of Piancatelli in Rome[79] that makes use of bis(acetoxy)iodobenzene (BAIB) as the oxidant and the tetramethylpiperidinyloxy (TEMPO) radical as the catalyst proved to be the method of choice. Under these conditions, it was possible to set up a new three-step one-pot process that directly converts enantiomerically pure 2,3-epoxy alcohols into the enantiomerically pure 4-hydroxy-4,5-dihydroisoxazole 2-oxides in good yields (Scheme 32).[80] This process turned out to be very useful in general, but especially in the case of epoxy alcohols **a** and **b** (see table in Scheme 32), since the corresponding epoxy aldehydes are very volatile and extremely water soluble and tend to rapidly give oligomeric materials that are very difficult to treat. Actually, this was the first time that the corresponding heterocycles could be obtained.

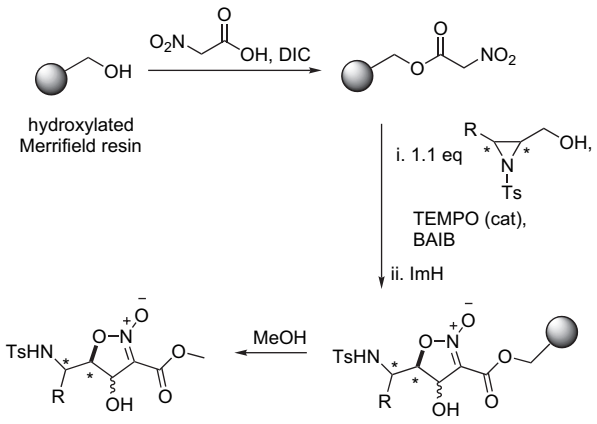
Aziridine alcohols could be subjected to same protocol as for the three-step one-pot procedure devised for the epoxy alcohols, in the presence of BAIB, TEMPO, and, subsequently, imidazole and ethyl nitroacetate at room temperature (Scheme 33). The corresponding products were obtained in very good yields,[81] except for the last entry (see table in Scheme 33), where the product turned out to be extremely water soluble, making its isolation very difficult. In the case of aziridine alcohols, the products are obtained with much larger trans selectivities than those obtained in the case of the epoxy alcohols and actually, in the last two entries, the trans-isomer was the only isomer observed.



	R	Yield (%)	*cis*:*trans*
a	H	90	42:58
b	Me	94	88:12
c	Ph	92	100:0
d	*p*-NO_2Ph	55	100:0

Scheme 33.

A solid-phase application of this new multi-step one-pot procedure could be developed[81] by using solid-supported nitroacetate. Hydroxylated Merrifield resin-supported nitroacetate (Scheme 34) was added to the reaction mixture of the aziridine alcohol, BAIB, and TEMPO. The course of the reaction is easily monitored by IR, checking for the disappearance of the strong band corresponding to the nitro group. This one-pot solid-phase reaction requires no large excess of reagent, and usually only a 10% excess of the aziridine alcohol is enough to drive the reaction to completion. A simple transesterification reaction with methanol cleaves the products from the resin. The isolated yields of the products are quite good (see table in Scheme 34), and the selectivities are even more shifted to the trans-isomer compared to the reaction in solution.



	R	Yield (%)	*cis*:*trans*
a	H	72	75:25
b	Me	85	95:5
c	Ph	82	100:0

Scheme 34.

7.4.2. Building up molecular complexity. Another feature is that the one-pot multi-step methodologies can achieve the rapid building up of molecular complexity. As an example, the 4,5-dihydroisoxazole 2-oxides described above can be envisaged as cyclic nitronates, which include a nitrone moiety. Nitrones are known to be potent dipoles and an olefinic residue could be linked to the hydroxyl to achieve an intramolecular 1,3-dipolar cycloaddition (Fig. 1).

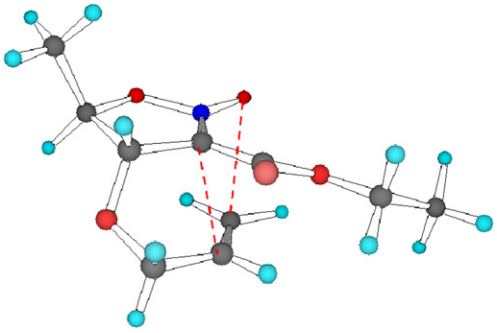
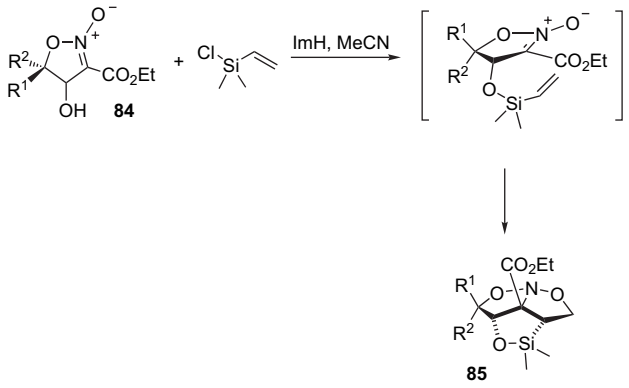


Figure 1.

On treating 4,5-dihydroisoxazole 2-oxides **84** with 1 equiv of chlorodimethylvinylsilane in the presence of imidazole at room temperature, a new one-pot domino process takes place. First, the silyl group binds to the free hydroxyl of the heterocycle and then an intramolecular 1,3-dipolar cycloaddition occurs spontaneously under the very mild conditions required for hydroxyl derivatization (Scheme 35).[82]

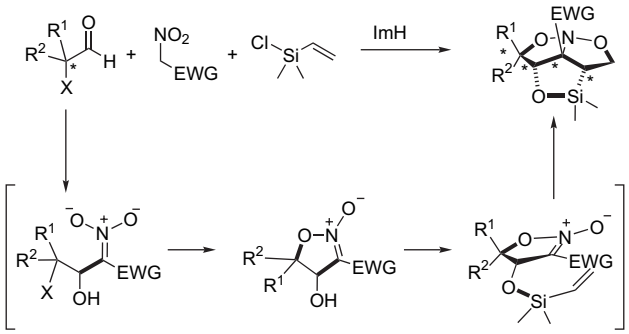
The process gives rise to a previously unknown type of heterotricycles (**85**) featuring three functionalities: an uncommon nitroso acetal functionality at the rear, the silyl ether, and the ester group. This was the first silicon-tethered[83] 1,3-dipolar cycloaddition ever reported in the literature. Isolated yields of the products are very high, usually averaging above 95% and, in the large majority of cases, the product is obtained in a rather pure form and needed no further purification.



	R^1	R^2	Yield (%)
a	H	PhCH(OH)	95
b	Ph	Me	98
c	*n*-$C_{12}H_{25}$	H	79
d	–$(CH_2)_5$–		97
e	Me	Me	91
f	PhCH(OH)	H	98
g	Et	Et	98
h	Bu	H	97

Scheme 35.

A further step forward was achieved by condensing both the 4,5-dihydroisoxazole generation and the heterotricycle formation in a single three-component, four-step, one-pot domino process (Scheme 36).[84] This process forms five new bonds and four new chiral centers in one step and, according to the complexity index defined by Bertz and Sommer, on going from reactants to products it has an increase in molecular complexity of about 170.[85]



	R^1	R^2	X	EWG	Yield (%)
a	H	*n*-$C_{12}H_{25}$	Br	COOEt	61
b	H	*n*-$C_{12}H_{25}$	Br	SO_2Ph	57
c	H	Me	OTs	COOEt	60
d	H	Me	OTs	SO_2Ph	76
e	Ph	Me	Br	COOEt	72
f	H	$PhCH_2CH_2$	OTs	COOEt	89
g	H	$PhCH_2CH_2$	OTs	SO_2Ph	87

Scheme 36.

The reaction (Scheme 36) works with aldehydes bearing different leaving groups, and with nitroalkanes with different electron-withdrawing groups. The substantial increase in structural complexity on going from the reactants to the products illustrates very nicely the great synthetic efficiency of such reaction sequences: starting from acyclic substrates

with only one chiral center, easily available as enantiomerically pure, they involve the formation of five contiguous chiral centers, four carbons, and one nitrogen, and the regio- and stereoselective building of three condensed five-membered rings assembled through the formation of five new bonds (two C–C, two C–O, and one O–Si), all occurring with good yields (see table in Scheme 36) with a minimum of problems in work up, separation, and purification. In each case, the reaction gives rise to the formation of a roughly 1:1 mixture of only two out of the 16 possible diastereoisomers.

7.4.3. Domino processes as a tool to recover substandard reactions. In the sections above, a variety of electrophiles were used as starting materials for these processes, while little variation was ever tried for the nitroacetic acid derivatives.

Nitroacetic acid derivatives are simple, yet elusive, intermediates, useful in the preparation of biologically interesting compounds such as nitrogen-containing heterocycles[86] and unusual α-amino acids.[87] In spite of this, very few general and convenient methods for their preparation are available.[88] The reaction between α-haloesters and nitrite anion is a general method to prepare α-nitroesters **86**,[89] although varying amounts of the corresponding nitrite esters **87** are obtained.

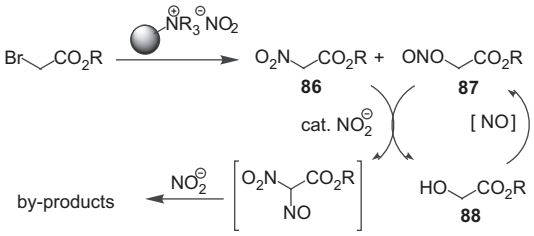
Although iodoacetates and silver nitrite can sometimes be used,[90] the readily available bromoacetates and sodium nitrite would represent a more convenient alternative.[91] Unfortunately, nitroacetates cannot be prepared by this method.[92] Gelbard and Colonna[93] reported that branched α-bromoesters, when treated with polymer-supported nitrite anion (Amberlite® IRA 900, NO_2^- form), in anhydrous benzene, at room temperature, form the corresponding α-nitroesters.[94] Again, no preparation of nitroacetic acid esters was reported.

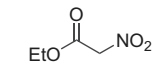
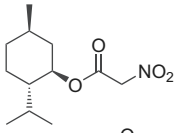
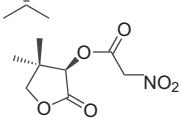
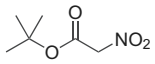
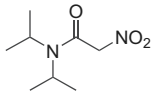
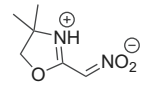
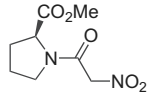
When these reaction conditions were applied to ethyl bromoacetate, an almost instantaneous reaction took place, leaving ethyl hydroxyacetate **88** (R=Et) as the only detectable product, instead of the expected nitro/nitrite mixture of products (Scheme 37).

Careful investigation of the reaction conditions allowed the achievement of the first reported synthesis[95] of nitroacetic acid derivatives via substitution of the corresponding bromoacetic acid derivatives.

Although this new preparation of nitroacetic acid esters and amides by a halogen exchange reaction of the corresponding bromoacetic acid derivatives can be regarded as a very good achievement in relative terms—in the literature this reaction is considered as not viable—[96] this is a substandard process in absolute terms.

However, by-products **88** (Scheme 37) are inert under the reaction conditions required for the preparation of diversely substituted 4,5-dihydroisoxazoles. The adoption of a new one-pot domino procedure, generating the nitroacetic acid derivatives in the presence of the aldehyde, overcame the problem. In fact, nitroacetates are rapidly engaged in the nitroaldol equilibrium, being subjected to the decomposition process depicted in Scheme 37.



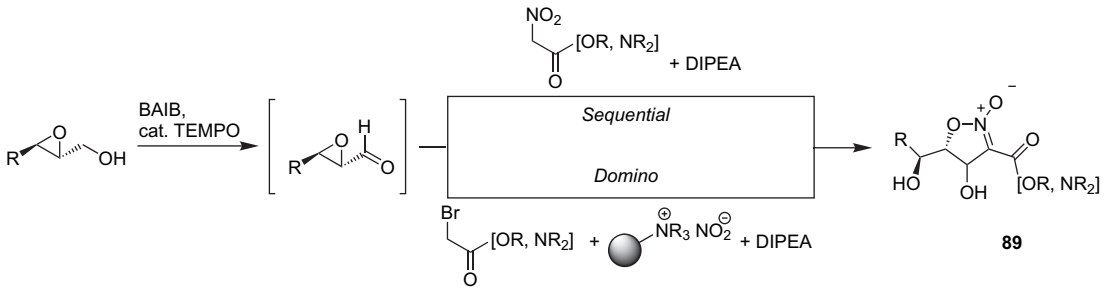
	Product	Yield (%) of **86**	Yield (%) of **87**
a		65	28
b		57	19
c		31	48
d		74	10
e		68	18
f		53	27
g		60	17

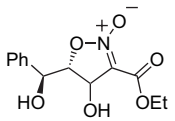
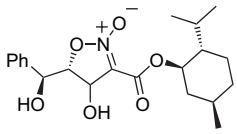
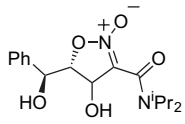
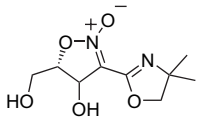
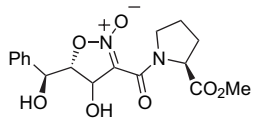
Scheme 37.

According to the procedure, glycidaldehyde was generated in situ by oxidation of the corresponding alcohol (1 equiv) at room temperature. The mixture was cooled to 0 °C and the domino reaction (Scheme 38) was started by adding to the aldehyde, the bromoacetic acid derivative (1 equiv), the polymer-supported nitrite (2 equiv), and diisopropylethylamine (3.3 equiv). After stirring for 24 h at 0 °C, the corresponding 4,5-dihydroisoxazoles (see table of Scheme 38) were isolated as a ca. 6:4 mixture of 4,5-*cis*- and 4,5-*trans*-isomer.

This one-pot multi-bond-forming process employs a glycidol, polymer-supported nitrite anion, and a bromoacetic acid or amide as the starting materials. After the initial in situ oxidation, three steps occur in a domino fashion: a halogen exchange, a nitroaldol C–C bond formation, and an intramolecular ring closure, allowing a substantial increase in structural complexity on going from the reactants to products.

As a control, the same reactions were also performed in the usual two-step sequential manner (Scheme 38): first, the halogen exchange reaction was performed according to Scheme 37, and then the crude product obtained was used as the nitroacetic component in the following 4,5-dihydroisoxazole preparation. The overall yields of the two processes are reported in table of Scheme 38.



entry	Product	Domino (%)	Two-step (%)
a		84	45
b		81	48
e		74	20
f		89	33
g		80	45

Scheme 38.

These results clearly show that this new domino process[97] benefits not only from the reduction of waste, solvents, reagents, adsorbents, energy, and labor that is characteristic of every efficient domino process, when compared to stepwise processes, but then it also allows the products to be obtained in significant higher yields than those that could be expected from the combination of the yields of each single step.

Therefore, this process demonstrates a concept that can find wider applicability: the domino methodology can be a powerful tool to exploit reactions that are to be considered substandard if run in a stepwise manner.

8. Synthesis of aromatic derivatives

Aromatic compounds are important substrates. Aromatization of acyclic precursors is undoubtedly a useful reaction in their synthesis and, although several methods to obtain aromatic compounds are known,[98] the use of nitroalkanes in the synthesis of substituted benzenes has only been introduced in the last few years.

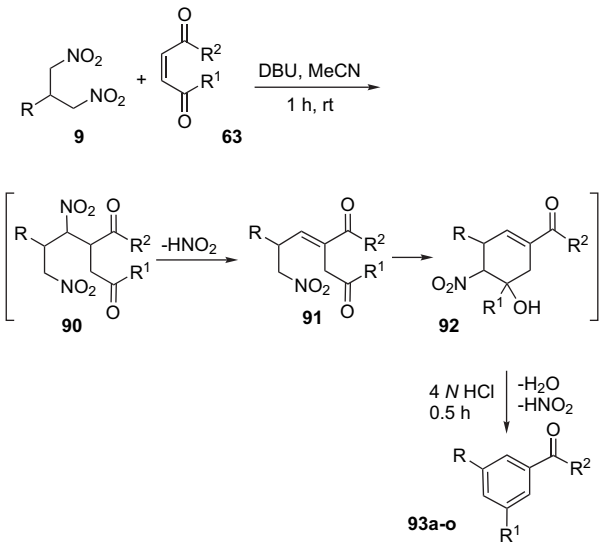
8.1. One-pot synthesis of 3,5-alkylated acetophenone and methyl benzoate derivatives

3,5-Alkylated acetophenones and methyl benzoates are key building blocks in the synthesis of retinoic acids and a variety of other important targets.[99]

1,3-Dinitropropanes **9** have been demonstrated to be very powerful building blocks for the one-pot synthesis of both 3,5-alkylated acetophenones and methyl benzoate derivatives by their reaction with conjugated enediones **63**.[100] In fact, the reaction of **9** with **63** in acetonitrile (Scheme 39), using DBU as base, proceeds as a tandem process in which a regioselective Michael addition (yielding **90**) is presumably followed by the elimination of nitrous acid to give the corresponding nitroenone derivatives **91**.

The latter compounds are prone to an intramolecular nitroaldol (Henry) reaction, yielding nitrocyclohexenols **92** in less than 1 h.

The formation of **92** can be easily observed in situ by TLC. Treatment of **92** with 4 N hydrochloric acid favors the



	R	R^1	R^2	Yield (%) of **93**
a	*n*-C_5H_{11}	Me	Me	55
b	*n*-C_5H_{11}	Ph	Me	62
c	*n*-C_8H_{17}	Me	Me	58
d	$Ph(CH_2)_2$	Me	Me	57
e	*n*-C_8H_{17}	Ph	Me	61
f	*n*-C_5H_{11}	Me	MeO	60
g	$Ph(CH_2)_2$	Me	MeO	59
h	*m*-$CF_3C_6H_4$	Me	Me	58
i	*p*-$MeOC_6H_4$	Ph	Me	61
j	*m*-$CF_3C_6H_4$	Me	MeO	60
k	*p*-$MeOC_6H_4$	Me	MeO	77
l	*p*-$MeOC_6H_4$	Me	Me	66
m	*m*-$NO_2C_6H_4$	Me	MeO	42
n	Ph	Me	MeO	76
o	2-Py	Me	MeO	43

Scheme 39.

elimination of water and a second molecule of nitrous acid, thus allowing the one-pot synthesis of molecules **93** in 42–77% overall yields.

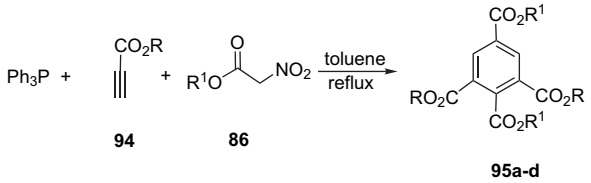
It is important to note the key role of the dinitro compounds **9**, in which their nitro functionalities act both as good electron-withdrawing groups and as good electron-leaving groups. This makes possible the formation of two carbon–carbon double bonds, paving the way to aromatization of the ring system.

Several advantages can be seen in this approach, such as the avoidance of *ortho–meta–para* mixtures, common in conventional aromatic synthesis. In fact, this regiodefined preparation method for acetophenone and benzoate derivatives is very difficult to undertake by electrophilic substitution of aromatics. In this context, a significant example is the synthesis of compound **93n**, a key building block in the preparation of farnesyl-protein transferase inhibitors. In fact, **93n** has been previously prepared in eight steps from orcinol in only 3% overall yield,[101] while the same product was prepared in 76% yield via the above one-pot procedure.

8.2. One-pot synthesis of benzene-1,2,3,5-tetracarboxylates

The chemistry of aromatic polycarboxylates has recently received considerable attention, owing to the variety of bridging abilities of these compounds in the formation of inorganic–organic frameworks. In particular, multiple benzenecarboxylate ligands were shown to be good building blocks in the design of organometallic materials with the desired topologies, owing to their rich coordination modes.[102]

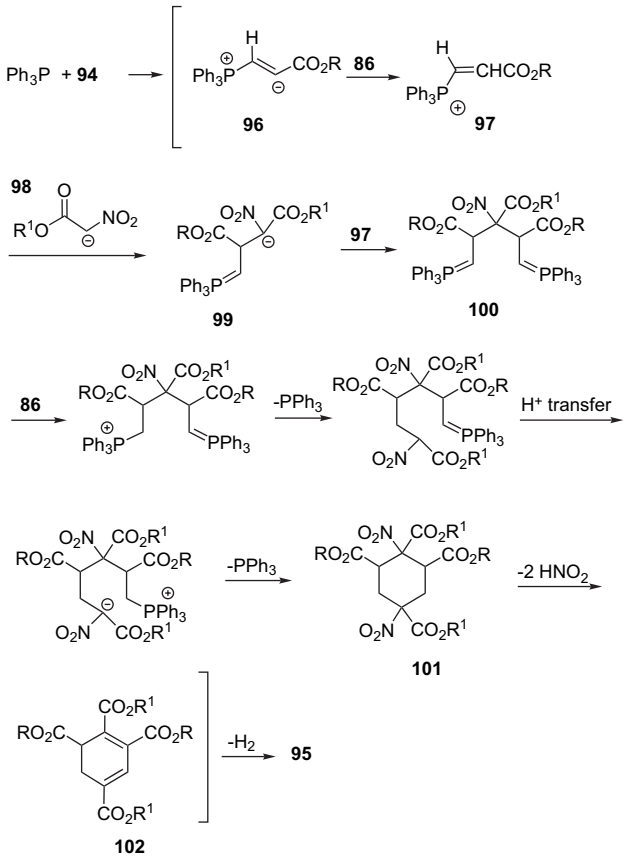
Benzene-1,2,3,5-tetracarboxylates **95a–d** can be easily obtained in a one-pot sequence by the reaction of alkyl propiolates **94** with alkyl 2-nitroethanoates **86** in the presence of triphenylphosphine (Ph_3P) under refluxing toluene (Scheme 40).[103]



	R	R^1	Yield (%) of **95**
a	Me	Me	42
b	Me	Et	36
c	Et	Me	38
d	Et	Et	39

Scheme 40.

Although the mechanistic details of the reaction are not known, a plausible mechanism may be proposed to rationalize the product formation (Scheme 41). Presumably,

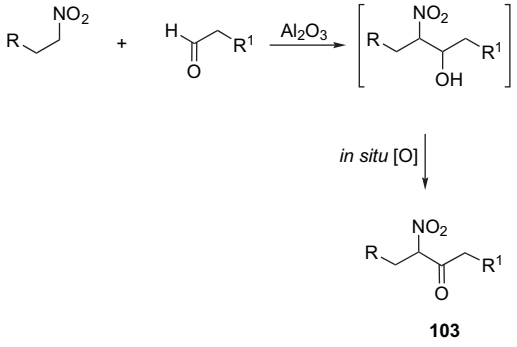


Scheme 41.

a zwitterionic intermediate of the type **96**, formed from Ph_3P and alkyl propiolate, is protonated by **86** to furnish the intermediate **97**, which is attacked by the carbanion **98** to produce ylide **99**. Further reaction of the latter ylide with **97** leads to bis-ylide **100**, which could undergo stepwise cyclization with **86** to produce the cyclohexane derivative **101** by elimination of Ph_3P. Cyclohexadiene **102**, obtained by elimination of HNO_2, is finally converted into **95** by aromatization.

9. Two-step sequences for the preparation of alkanes from nitroalkanes

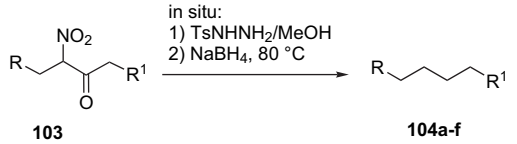
It is well-known that nitroalkanes are good building blocks in the nitroaldol (Henry) reaction,[73] with the formation of β-nitroalkanols. These nitroalkanols can be directly converted into the corresponding α-nitro ketones **103** by different one-pot procedures (Scheme 42).[104]



Scheme 42.

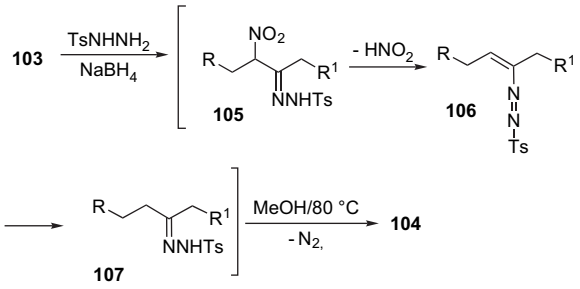
Compounds **103** could be useful precursors of the corresponding alkanes by a simultaneous denitration–deoxygenation. In fact, it has been found[105] that on adding tosylhydrazine to a methanolic solution of **103**, followed by in situ addition of $NaBH_4$ at 80 °C, a tandem denitration–deoxygenation of α-nitro ketones occurs (Scheme 43) in satisfactory-to-good yields, allowing the formation of the alkanes **104**. Thus, starting from nitroalkanes, it is possible to obtain alkanes, with higher molecular weights, in a two-step sequence.

A plausible mechanism for the transformation of **103** into **104** is reported in Scheme 44. α-Nitro ketone converts into the corresponding tosylhydrazone **105**, which, under basic



	R	R^1	Yield (%) of **104**
a	H	$PhCH_2$	71
b	Et	$PhCH_2$	68
c	MeO_2CCH_2	*n*-C_7H_{15}	54
d	*n*-Bu	*n*-$C_{10}H_{21}$	54
e	*n*-Pr	*c*-C_6H_{11}	60
f	Me	*p*-$NO_2C_6H_4CH_2$	47

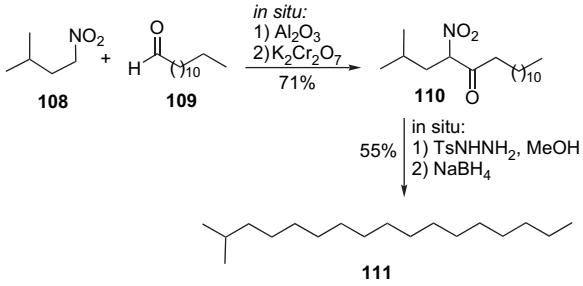
Scheme 43.



Scheme 44.

conditions (sodium borohydride), undergoes 1,4-elimination of nitrous acid allowing the formation of the tosyldiazoalkene **106**. Reduction of the latter alkene furnishes hydrazone **107** that is susceptible to the 'protected-carbonyl to methylene conversion' under the reported reaction conditions.[106]

An application of this method is a two-step synthesis of 2-methylheptadecane **110** from 1-nitro-3-methylbutane **108** (Scheme 45). 2-Methylheptadecane has been isolated and identified as an important component of the sex attractant pheromone of at least nine species of the Arctidae family (tiger moth).[107] It has also been characterized as flavor component in four mango varieties[108] and in black soya beans (a variety of *Glycine max*),[109] as an odorous constituent of blue-green algae,[110] and as a chemical component of essential oils[111] from *Clematis hexapetala* Pall and *Inula nervosa* Wall.



Scheme 45.

Thus, a nitroaldol reaction of 1-nitro-3-methylbutane **108** with tridecanal **109**, followed by in situ oxidation of the formed nitroalkanol, gives the nitro ketone **110** in 71% yield. Tandem denitration–deoxygenation of the latter ketone allows the formation of the target alkane **111** in 55% yield and in 39% overall yield.[112]

10. Conclusions

Nitroalkanes have been demonstrated to be promoters, in the same synthetic process, of (i) the generation of new carbon–carbon single or double bonds, (ii) a variety of different chemical transformations, and (iii) the elimination of the nitro group as good leaving group. Thus, the availability of a variety of nitroalkanes, and their chemical versatility and reactivity make these compounds extremely powerful precursors and intermediates for cascade processes.

The aim of this review has been to report the most representative synthetic accesses to several fine chemicals, in one- or two-step synthetic sequences, from nitroalkane derivatives. We believe that this account will provide an incentive for further studies in this field.

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Biographical sketch

Roberto Ballini obtained the Laurea degree of Chemist at the University of Camerino (Italy), and then he moved to ENI-ANIC petrochemical industry in Ravenna. After 2 years, R.B. began his academic career at the University of Camerino, firstly as Research Fellowship, then as Assistant Professor, Associate Professor, and, finally, as Full Professor of Organic Chemistry. His research interests include a large area of the chemistry of aliphatic nitro compounds, with particular interest to the generation of new carbon–carbon single and double bonds, and the cleavage of carbon–carbon bond. Other special fields of extensive interest concern the study and the application of solid catalysis in organic synthesis, the exploitation of solvent-free reactions, the application of aqueous medium in organic transformations, and the development of new eco-friendly processes such as the one-pot syntheses of fine chemicals.

Alessandro Palmieri was born in Jesi, Italy, on 1978. He began his studies in Chemistry in 1997 at the University of Camerino (Italy), where he received his Laurea degree *cum laude* in 2002, under the guidance of Professor Enrico Marcantoni. Then, after a scholarship in the laboratory of Professor Roberto Ballini, where he studied the synthesis of natural products with important biological activities, in March 2004 he started the Ph.D. studies and in February 2007 he got the Ph.D degree in Chemical Sciences. His research interests include natural products' synthesis, the application of aliphatic nitro compounds in the formation of new single and double carbon–carbon bonds, and the development of new eco-friendly processes.

Paolo Righi was born in Modena (Italy) on 1963. He graduated *cum laude* in 1987 under the tutorship of Professor Antonino Fava, and got the Ph.D degree in Chemical Sciences from the University of Bologna in 1991 under the guidance of Professor Goffredo Rosini. In 1992 he joined as a Research Assistant in the group of Professor Goffredo Rosini at the University of Bologna, working on novel tandem, domino, and multi-component processes employing nitroalkanes, and the preparation and utilization of bicyclo[3.2.0]heptenones for the synthesis of natural products and new versatile building blocks. In 2002 he was appointed as an Associate Professor at the Faculty of Industrial Chemistry of the University of Bologna.