Pure Appl. Chem., Vol. 78, No. 10, pp. 1857–1866, 2006.
doi:10.1351/pac200678101857
© 2006 IUPAC

Synthesis of fine chemicals by the conjugate addition of nitroalkanes to electrophilic alkenes*

R. Ballini‡, L. Barboni, G. Bosica, D. Fiorini, and A. Palmieri

Dipartimento di Scienze Chimiche dell'Università di Camerino, Via S. Agostino 1, 62032 Camerino, Italy

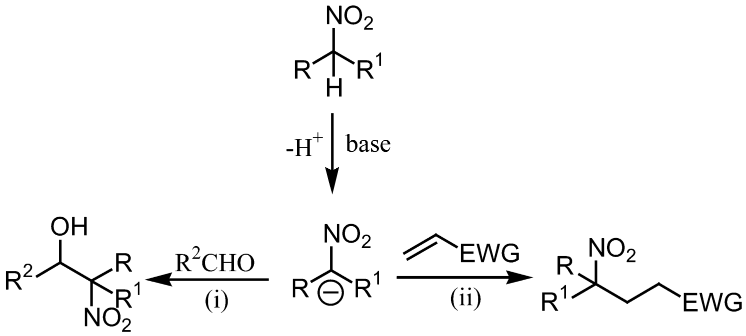
Abstract: Several aliphatic nitro compounds have been employed as stabilized carbanions in the conjugate addition to a variety of electron-poor alkenes (Michael reaction). Depending on the nature of the alkene, new carbon–carbon single or double bonds can be generated. However, all the Michael adducts can be efficiently utilized as key building blocks for the synthesis of a huge array of fine chemicals, including homo- and heterocyclic structures.

Keywords: nitroalkanes; Michael reaction; fine chemicals; carbon–carbon single bond; carbon–carbon double bond.

INTRODUCTION

The ability of primary and secondary nitroalkanes to generate carbanions, under basic conditions, strongly stabilized by the electron-withdrawing effect of the nitro group [1–4] is well known.

Thus, the main use of nitroalkanes is devoted to the generation of new carbon–carbon bonds through two main approaches (Scheme 1): (i) reaction with carbonyl derivatives (nitroaldol-Henry reaction), and (ii) Michael addition to electron-poor alkenes.



Scheme 1

---

*Paper based on a presentation at the 15th International Symposium on Fine Chemistry and Functional Polymers (FCFP-XV) and the 1st International Symposium on Novel Materials and their Synthesis (NMS-I), 17–20 October 2005, Shanghai, China. Other presentations are published in this issue, pp. 1803–1896.

‡Corresponding author: E-mail: roberto.ballini@unicam.it

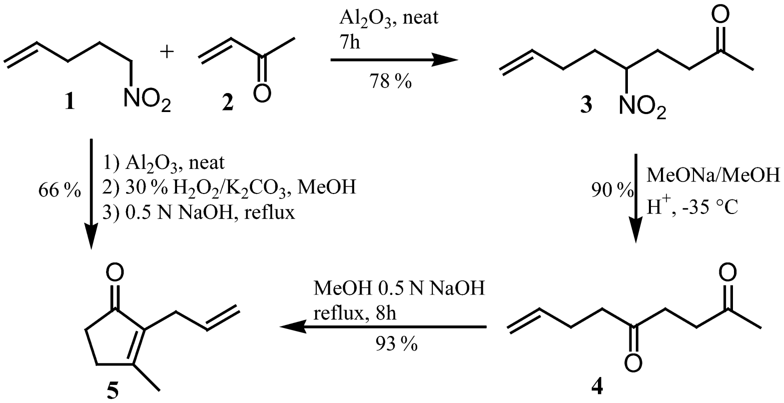
In the last years, the conjugate addition of nitroalkanes to several electron-poor alkenes has been studied under several catalytic systems, and it has been found that this reaction can be conveniently performed via [5]:

- homogeneous catalysis, using an organic base soluble in an organic solvent;
- heterogeneous catalysis, using solid catalyst, predominantly without the need of any solvent; and
- aqueous medium, using water-diluted solutions of sodium hydroxide or potassium carbonate, in the presence (or without the presence) of catalytic amounts of surfactants.

FORMATION OF CARBON–CARBON SINGLE BOND

Usually, the Michael addition of nitroalkanes to electrophilic acceptors generates a new carbon–carbon single bond, with the consequent formation of adducts (Scheme 1, pathway ii) in which the presence of a versatile functionality such as the nitro group offers a variety of synthetic opportunities.

Allylrethrone **5**, an important component of pyrethroids and a key building block for the synthesis of allethrolone and pyrethrins, has been prepared [6] using 5-nitropent-1-ene **1** as the key reagent (Scheme 2).

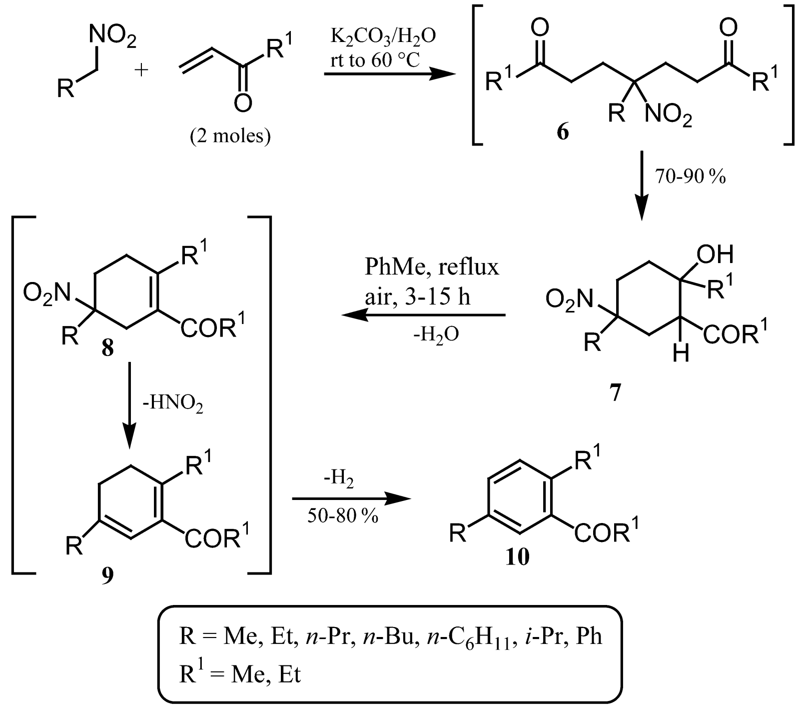


Scheme 2

The starting point is the Michael addition of **1** to butenone **2** under heterogeneous catalyst (basic alumina), giving the γ-nitro ketone **3** (78 % yield), which can be converted into the 1,4-diketone **4**, in 90 % yield, by the Nef transformation. The latter 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 **5** in 93 % yield (65 % overall yield). Alternatively, **5** can be obtained in a one-pot way by the conjugate addition of **1** to **2** on neat alumina, followed by in situ oxidation of **3** to **4** with hydrogen peroxide in methanol, and then in situ basic cyclization of **4** with 0.5 M sodium hydroxide, giving **5** in 66 % overall yield.

Aromatization of acyclic precursors is undoubtedly a useful reaction in the synthesis of highly substituted aromatic rings, and nitroalkanes have been demonstrated [7] to be very useful precursors for the production of 1-acyl-2,5-dialkylbenzene derivatives **10**.

As reported on Scheme 3, the conjugate addition of primary nitroalkanes to α,β-unsaturated enones (2 mol), catalyzed by potassium carbonate on aqueous medium, affords the double Michael adduct **6** that, after an intramolecular aldol cyclization, converts to the nitrocyclohexanols **7** (70–90 % yield). Treatment of the latter in refluxing toluene, with the simultaneous injection of air, gives three different elimination steps (water, nitrous acid, and hydrogen) in a one-pot way, allowing the direct

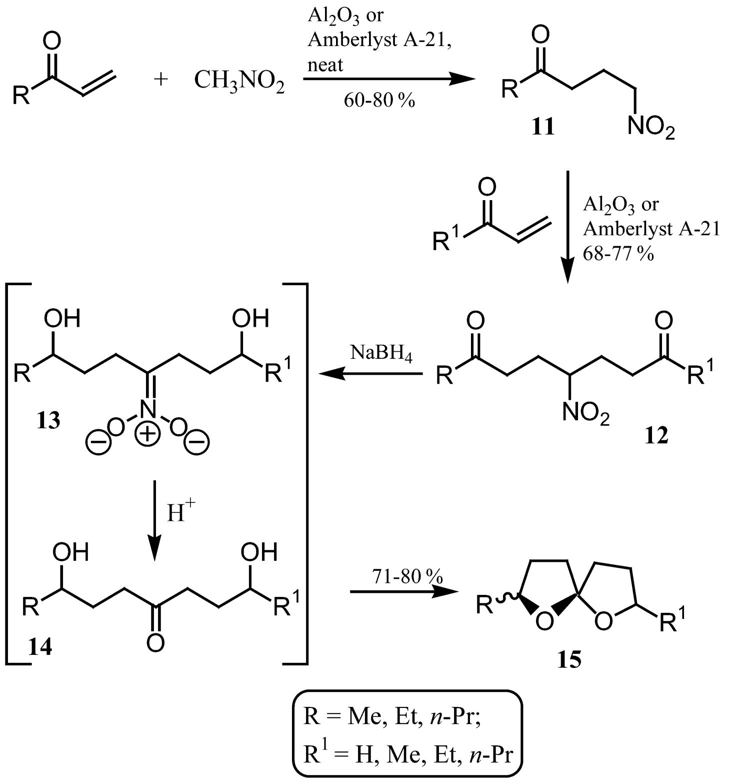


Scheme 3

preparation of **10** in good yields. This procedure provides the preparation of aromatic systems from open-chain compounds with several advantages, such as the preparation of trisubstituted compounds in only two steps and the avoidance of *o-, m-, p-*mixtures observed in conventional aromatic synthesis. In fact, the method constitutes a regiodefined synthesis of 1-acyl-2,5-dialkylbenzenes, and the appropriate choice of the starting nitroalkane and/or the alkyl vinyl ketone offers the opportunity to predict the relative positions of the substituents.

Spiroketal substructures feature widely in naturally occurring substances from many sources, including insects, microbes, plants, fungi, and marine products [8]. Many of these structures can be conveniently obtained starting from the Michael reaction of nitroalkanes with conjugated enones. In this context, 1,6-dioxaspiro[4.4]nonane derivatives **15** (Scheme 4) have been prepared [9,10] by the reaction of nitromethane with conjugated enones, under solid catalysis (Al_2O_3 or Amberlyst A-21), giving the γ-nitro ketones **11**.

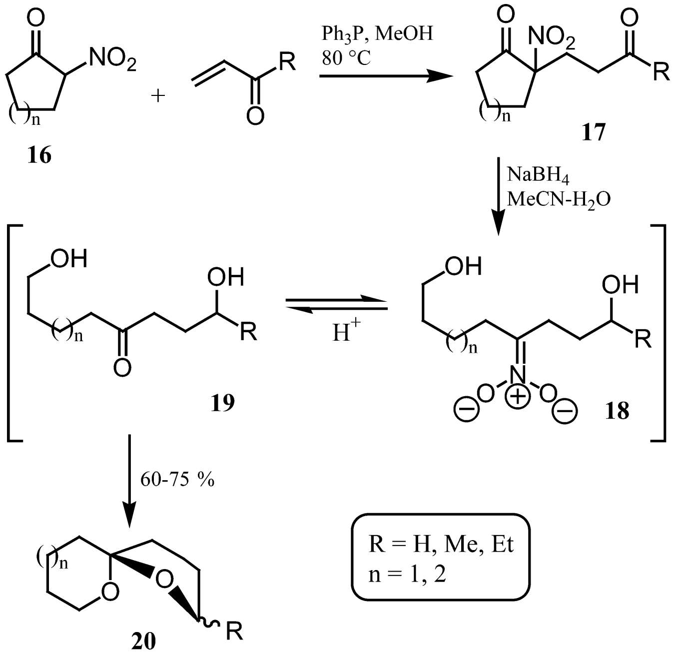
Further Michael addition of **11** with one more enone produces the nitro diketones **12** that, by treatment with $NaBH_4$, convert directly to the spiroketals **15**. In fact, since $NaBH_4$ produces both reductive and basic conditions, the carbonyls present on **12** are reduced to the corresponding hydroxyls, while the nitro group converts into its nitronate form, giving the intermediates **13** that during the acidic work-up produce the keto diols **14**, via the Nef reaction. The compounds **14** quickly convert to the target compounds **15** (mainly as *E*-isomers) by an intramolecular ketalization. Depending on the nature of the alkyl groups (R and R^1), a variety of pheromonic spiroketals have been obtained (R = Et, R^1 = H: aggregation pheromone isolated from *Pityogenes chalcografus*; R = R^1 = Me, Et: isolated from *Andrena wilkella*, *A. ocreata*, and *A. ovatula*; R = R^1 = *n*-Pr: isolated from *Andrena haemorroa*).



Scheme 4

Spiro[4.5] and spiro[4.6] ketal systems **20** can be efficiently prepared starting from α-nitrocycloalkanones **16** (commercially available or easily obtained by nitration of the corresponding ketones).

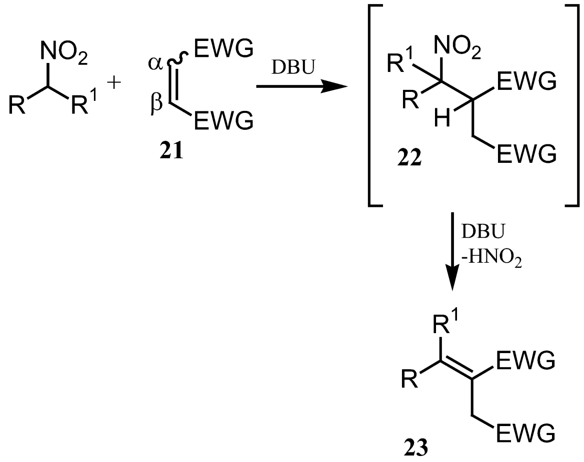
As reported in Scheme 5, the first step of the synthesis involves the conjugate addition of **16** to α,β-unsaturated ketone. The obtained Michael adducts **17** constitute the immediate precursors of the target spiroketals **20**. Thus, treatment of **17** with $NaBH_4$ in $MeCN/H_2O$ undergoes the ring cleavage of the cyclic nitro ketone moiety, followed by reductive reduction of the carbonyl functionalities and the conversion of the nitro group to the corresponding nitronate form, allowing the intermediate **18**. During the acidic work-up, the latter produces the keto diols **19**, which then convert to the target compounds **20** (*E/Z* = 1.5) in a one-pot way (from **17**) and in good yields [11]. It is important to point out that the compound **20**, with R = Me and n = 1, is an important pheromonic component isolated from *Paravespula vulgaris*.



Scheme 5

FORMATION OF CARBON–CARBON DOUBLE BOND

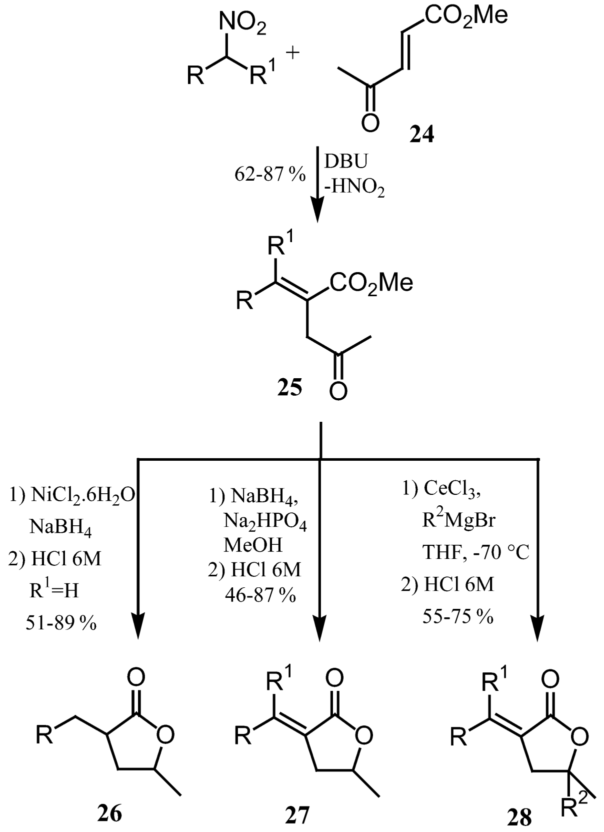
Michael addition of nitroalkanes to electron-poor alkenes is one of the main approaches for the formation of a new carbon–carbon single bond. However, by the right choice of the electrophilic acceptor and of the catalytic conditions, the formation of a new carbon–carbon double bond is also possible. A few years ago, we reported that nitroalkanes react (Scheme 6) with electrophilic alkenes **21**, having two electron-withdrawing groups in α- and β-positions, in a tandem Michael addition-elimination process giving unsaturated 1,4-difunctionalized derivatives **23** with enhanced *E* stereoselectivity [12,13].



Scheme 6

Using this strategy, a variety of important targets, such as γ-butyrolactones, furans, pyrroles, tetrahydrofurans (THFs), cyclopentadienones, and nitrocyclopropanes, have been prepared.

γ-Butyrolactones are an important class of compounds and, of particular interest, are those having an *exo*-cyclic carbon–carbon double bond. A few years ago, we reported the synthesis of three different γ-lactone systems, starting from the regiospecific Michael addition of nitroalkanes to methyl (*E*)-4-oxopentenoate **24**, catalyzed by 1,5-diazabicyclo[5.4.0]undecene-5 (DBU). The reaction, carried out at room temperature, results in full conversion and gives satisfactory yields of the Michael adduct **25** (Scheme 7), obtained after elimination of nitrous acid.



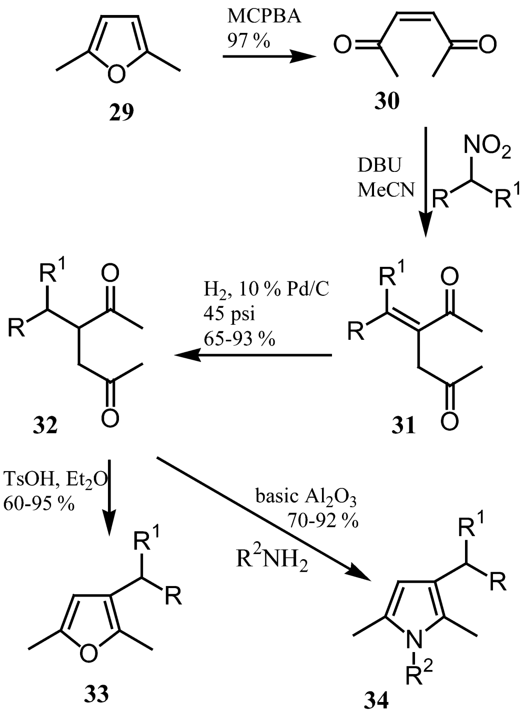
Scheme 7

The alkylated γ-keto ester **25** is prone to act as the key building block for the preparations of the γ-butyrolactones **26**–**28**. In fact, treatment of **25** with the $NaBH_4/NiCl_2$, gives the reduction of both the carbon–carbon double bond and the carbonyl. The formed alcohol, during the acidic work-up, undergoes the lactonization to the dialkylated γ-lactones **26** [14].

The reaction of **25** with sodium borohydride and in the presence of a catalytic amount of sodium hydrogenphosphate dodecahydrate ($Na_2HPO_4 \cdot 12H_2O$), followed by acidic work-up, directly affords the α-(alkylmethylene)-γ-methyl-γ-lactone **27**, in which the carbon–carbon double bond was preserved [15].

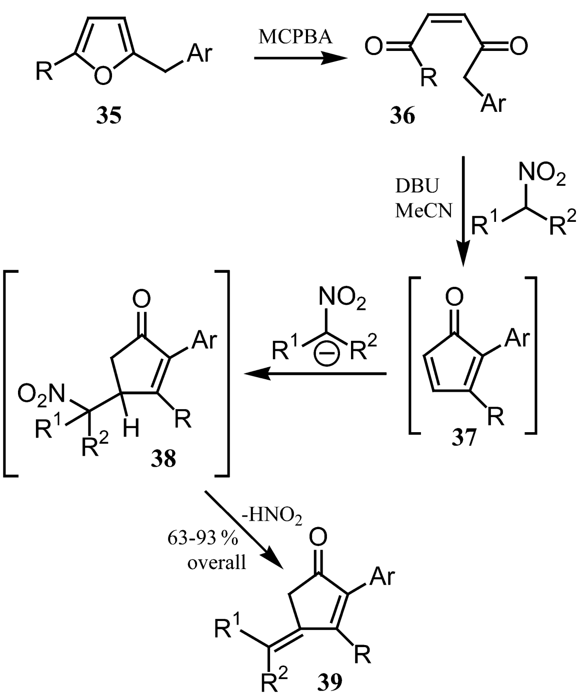
We also examined the reaction of **25** with Grignard reagents as nucleophiles [15]. In order to control the chemoselectivity, the reaction was executed at low temperature (–70 °C) and in the presence of dry cerium(III) chloride in THF. Under the above reaction conditions, the reaction results in the selective nucleophilic addition to the ketone functionality, followed, under the usual acidic quenching, by lactonization to γ,γ-dialkyl-α-(alkylmethylene)-γ-butyrolactones **28** in satisfactory yields.

Aromatic structures such as 2,5-dimethylfuran **29** can be regioselectively alkylated, to trialkylated furans and trialkylated pyrroles, by nitroalkanes. As reported in Scheme 8, the alkylation is an indirect procedure that starts by the known oxidative cleavage of **29** to (*Z*)-hexene-2,5-dione **30**. Conjugate addition of the nitro compounds to **30**, in acetonitrile and with DBU (1 equiv) as base, followed by chemoselective hydrogenation of the carbon–carbon double bond of the enone **31** (obtained by elimination of nitrous acid from the Michael adduct) completes the conversion to the alkylated γ-diketones **32**. The next step is the heterocyclization of **32** (i) into the furan derivatives **33**, using half equivalent of *p*-toluenesulfonic acid in refluxing diethyl ether [16], or (ii) into the pyrroles **34**, by reaction with primary amines in a bed of basic alumina (activity I), and in the absence of any solvent [17].



Scheme 8

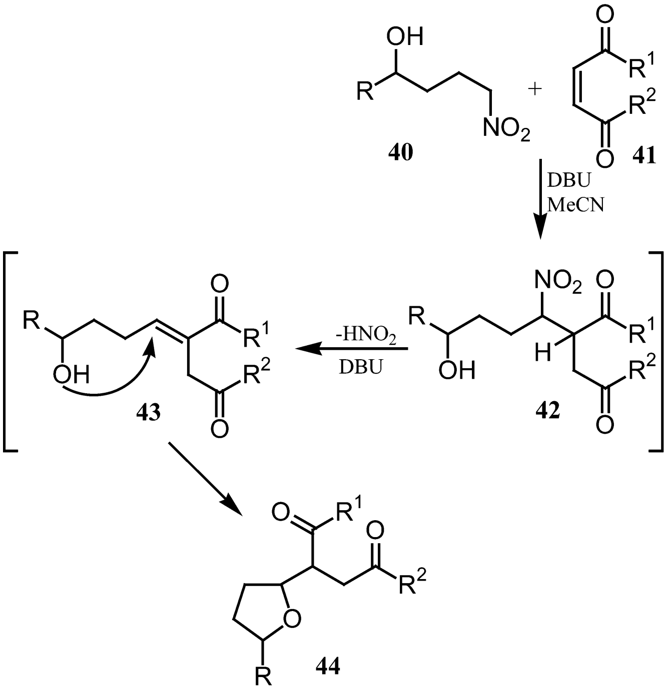
The cyclopentenone ring is one of the most recurring structural units in targets of relevant practical interest, moreover, functionalized cyclopentenones are also important building blocks that provide an efficient entry to substituted cyclopentanone frameworks. In this context, the discovery of efficient procedures for the preparation of cyclopentenones is welcomed. Recently, the reaction of nitroalkanes to unsymmetrical Δ^2-1,4-diketones has been employed for the synthesis of these structures (Scheme 9). *(Z)*-1,4-Diketones **36**, easily obtained by ring cleavage of furans **35** with *m*-CPBA, react with nitroalkanes in the presence of DBU in acetonitrile, affording 4-alkylidenecyclopent-2-enones **39** in good yields and high *E*-diastereoselectivity [18]. The nature of the obtained product **39** is consistent with the mechanism depicted in Scheme 9. A chemoselective intramolecular aldol condensation of enedione **36**, promoted by the presence of the aromatic ring, gives the cyclopentadienone **37** as reactive intermediate that, under the same conditions, reacts with the nitroalkane to afford the Michael adduct **38**. As previ-



Scheme 9

ously observed, the nitro enone undergoes a base-assisted elimination of nitrous acid giving the target compound **39** in good yields (63–93 %).

Based on the previous strategies, we have discovered a new, one-pot synthesis of an important class of compounds such as the THF derivatives. As reported in Scheme 10, the key idea is the use of δ-nitroalkanols **40** as nucleophiles. In fact, bringing together, at room temperature, 1 mol of **40** and of the enones **41**, in the presence of DBU (1 mol) in acetonitrile, the direct formation of the THF derivatives **44** is observed (70–86 % yield). The mechanism proceeds with the formation of the Michael adduct **42**, followed by elimination of nitrous acid with the consequent generation of the conjugate enone **43** 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, THFs **44** are obtained [19] 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 **41**, so that polyfunctionalized THFs can be obtained (Table 1).



Scheme 10

Table 1 Synthesis of THFs **44**.

R	R^1		R^2	Yield (%) of **44**
H	Me		Me	79
H		–N(Ph)–		75
Me	Me		Me	77
Me	OMe		OMe	70
Me		–N(Me)–		77
Me		–N(Et)–		79
Me		–N(*t*Bu)–		77
Me		–N(Ph)–		81
Et	Me		Me	85
Et		–N(Me)–		82
Et		–N(Et)–		86

The starting nitroalkanols **40** can easily prepared by $NaBH_4$ reduction of the corresponding nitro ketones [10] or by $BH_3{\cdot}S(CH_3)_2$ reduction of the corresponding nitro esters [20].

CONCLUSIONS

The Michael reactions of nitroalkanes to a variety of electron-poor alkenes provide potentially useful synthetic ways to a variety of important targets such as cyclopentenones, aromatic derivatives, spiroketals, lactones, furans, pyrroles, and THF derivatives. Moreover, by the modulate choice of the electrophilic alkenes and of the catalytic conditions, both single and double C,C bonds can be easily obtained.

REFERENCES

1. N. Ono. *The Nitro Group in Organic Synthesis*, Wiley-VCH, New York (2001).
2. G. Rosini, R. Ballini. *Synthesis* 833 (1988).
3. G. Rosini, R. Ballini, M. Petrini, E. Marotta, P. Righi. *Org. Prep. Proc. Int.* **22**, 707 (1990).
4. R. Ballini, M. Petrini. *Tetrahedron* **60**, 1017 (2004).
5. R. Ballini, G. Bosica, D. Fiorini, A. Palmieri, M. Petrini. *Chem. Rev.* **105**, 933 (2005).
6. R. Ballini. *Synthesis* 687 (1993).
7. R. Ballini, L. Barboni, G. Bosica. *J. Org. Chem.* **65**, 6261 (2000).
8. F. Perron, K. F. Albizati. *Chem. Rev.* **89**, 1617 (1989).
9. G. Rosini, R. Ballini, M. Petrini, E. Marotta. *Angew. Chem., Int. Ed. Engl.* **25**, 941 (1986).
10. R. Ballini, G. Bosica, A. Uselli. *J. Heterocycl. Chem.* **31**, 259 (1994).
11. R. Ballini, M. Petrini, G. Rosini. *Tetrahedron* **46**, 7531 (1990).
12. R. Ballini, A. Rinaldi. *Tetrahedron Lett.* **35**, 9247 (1994).
13. R. Ballini, G. Bosica. *Tetrahedron* **51**, 4213 (1995).
14. R. Ballini, G. Bosica. *Synlett* 1115 (1996).
15. R. Ballini, E. Marcantoni, S. Perella. *J. Org. Chem.* **64**, 2954 (1999).
16. R. Ballini, G. Bosica, D. Fiorini, G. Giarlo. *Synthesis* 2003 (2001).
17. R. Ballini, L. Barboni, G. Bosica, M. Petrini. *Synlett* 391 (2000).
18. R. Ballini, G. Bosica, D. Fiorini, M. V. Gil, M. Petrini. *Org. Lett.* **3**, 1265 (2001).
19. R. Ballini, D. Fiorini, M. V. Gil, A. Palmieri, E. Román, J. A. Serrano. *Tetrahedron Lett.* **44**, 2795 (2003).
20. R. Öhrlein, W. Schwab, R. Ehrler, V. Jäger. *Synthesis* 535 (1986).