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δ-Nitroalkanols as precursors for the one-pot synthesis of substituted tetrahydrofurans

Roberto Ballini,[a,*] Dennis Fiorini,[a] Maria Victoria Gil,[a] Alessandro Palmieri,[a] Emilio Román[b] and José Antonio Serrano[b]

[a]*Dipartimento di Scienze Chimiche dell'Università, Via S. Agostino 1, 62032 Camerino, Italy*
[b]*Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Extremadura, 06071 Badajoz, Spain*

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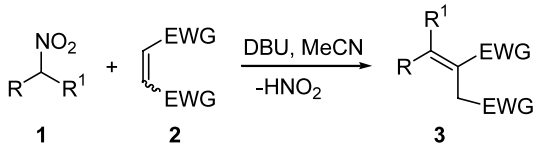
Abstract—DBU catalyses the one-pot Michael addition of nitroalkanes to 1,4-dienone derivatives, elimination of nitrous acid, then intramolecular conjugate addition-ring closure to allow the direct formation of a variety of tetrahydrofurans.

The synthesis of complex molecules is traditionally performed by a sequence of separate reaction steps, each step requiring its own conditions, reagents, solvent, and catalyst. After each reaction is completed, the solvent and the waste products are removed and discarded, and the intermediate product is separated and purified. Now environmental and economical pressures are forcing the chemical community to search for more efficient ways of performing chemical transformations.[1] These new issues can be addressed by the development of new synthetic methods that, bringing together small and simple components, generate complex structures in one pot, much the same way as nature does.[2]

These considerations are driving our efforts in developing new methodologies for the preparation of important targets[3] and now we wish to report the one-pot synthesis of heterocyclic compounds such as functionalized mono and disubstituted tetrahydrofurans.[4] Cyclic ethers are often present in naturally occurring compounds[4,8] and, furthermore, are useful synthetic intermediates. For these reasons new multistep methodologies for their preparation have been intensively studied during the last few years,[4–8] however, due to the importance of the cyclic ethers new methodologies for their preparation are still attractive.

Although, Rosini et al.[9] recently described an elegant formation of polysubstituted tetrahydrofurans by direct cyclization of 3-hydroxyalkenoic acids esters, special attention would also be paid to the accessibility of the corresponding starting materials.

Recent reports from this laboratory have disclosed that nitroalkanes **1** react with electrophilic alkenes **2** bearing two electron-withdrawing groups in the α- and β-positions, by a tandem Michael addition–elimination process, giving the unsaturated derivatives **3** with enhanced *E* stereoselectivity[10] (Scheme 1).



Scheme 1.

Depending from the electrophilic acceptors **2**, the products **3** have been demonstrated to be excellent precursors for the preparation of different heterocyclic systems,[11] such as pyrroles,[11a] lactones,[11c] pyrrolidines,[11d] furans,[11e] and succinic anhydrides.[11f]

Then, based on our previous discovery, we now wish to report a new, one-pot synthesis of an important class of compounds such as the tetrahydrofuran derivatives. As reported in Scheme 2, the key idea of our method is the use of δ-nitroalkanols **4**[12] as nucleophiles and DBU as base, in fact by bringing together, at room temperature, 1 mol of **4**, and the enones **5** (1 mol), in the presence of

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* Corresponding author. Fax: +39-0737-402297; e-mail: roberto.ballini@unicam.it

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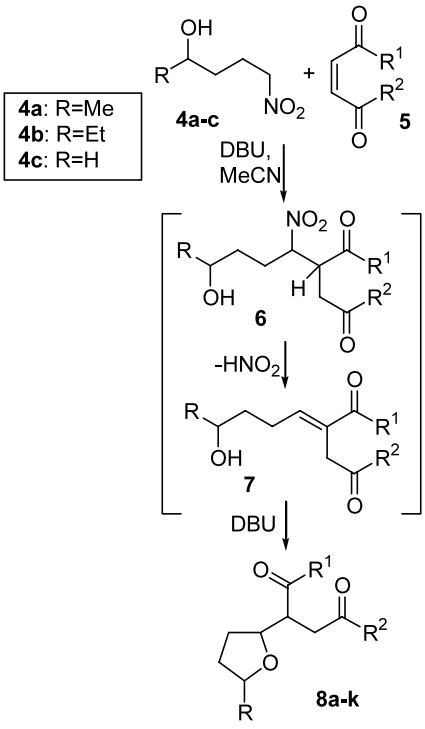

Scheme 2.

DBU (1 mol) in acetonitrile, we observe the direct formation of the tetrahydrofuran derivatives **8** in good yield (70–86%, Table 1). We tried several combinations base/solvent and we found DBU/MeCN to be the most effective.

The nature of **8** is consistent with the formation of the Michael adduct **6**, followed by base-promoted elimination of nitrous acid with consequent generation of the conjugate enone **7** in which the basic conditions favour the intramolecular conjugate addition of the hydroxyl to the formed electrophilic alkene. The ring closure is poorly stereoselective; indeed tetrahydrofurans **8** 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 **5**, so that polyfunctionalized mono (**8a**,**b**) and disubstituted (**8c**–**k**) tetrahydrofurans can be easily obtained in a one-pot way. Moreover, compounds **8** include other interesting frameworks such as heterocyclic systems (**8b**,**e**–**h**,**j**,**k**) or 1,4-dicarbonyl structures that could allow selective manipulation to give other important functionalities.[3e,11,13] The easy availability of the starting materials allows these reactions to be usually carried out on a multigram scale. In fact, nitroalkanols **4** can be easily obtained by reduction of the corresponding nitro carbonyl derivatives,[12] while enones **5** are commercially available materials.

In conclusion, mono- and disubstituted tetrahydrofurans are now readily available compounds, accessible from δ-nitroalkanols **4** and 1,4-dicarbonyl derivatives **5** by a simple procedure involving three different reactions carried out in a tandem sequence. The efficiency of the whole process is demonstrated by the good yield and by the possibility of obtaining polyfunctionalized mono and disubstituted tetrahydrofuran derivatives. Application of this synthetic methodology to important targets is currently in progress in our laboratory.

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Table 1. Preparation of substituted tetrahydrofurans **8**

Compound	R	R^1	R^2	Reaction time (h)	Yield (%)[a] of **8**
8a	H	Me	Me	1.5	79
8b	H	-N(Ph)-		2	75
8c	Me	Me	Me	2	77
8d	Me	OMe	OMe	5	70[b]
8e	Me	-N(Me)-		2	77
8f	Me	-N(Et)-		2	79
8g	Me	-N(*t*Bu)-		2	77
8h	Me	-N(Ph)-		2	81
8i	Et	Me	Me	2	85
8j	Et	-N(Me)-		1.5	82
8k	Et	-N(Et)-		2	86

[a] Yield of pure isolated product.
[b] 1.5 mol of DBU is needed.

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