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Facile and Highly Stereoselective One-Pot Synthesis of Either (*E*)- or (*Z*)-Nitro Alkenes

Stefania Fioravanti,* Lucio Pellacani,* Paolo A. Tardella,* and Maria Cecilia Vergari

Dipartimento di Chimica, Università degli Studi "La Sapienza", P.le Aldo Moro 2, I-00185 Roma, Italy

lucio.pellacani@uniroma1.it

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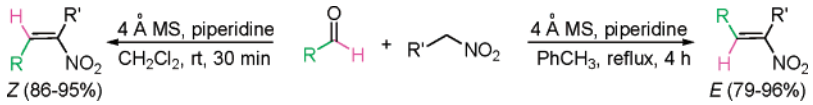
ABSTRACT

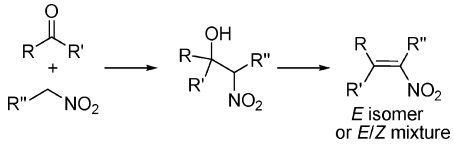


Aliphatic aldehydes were reacted with nitro alkanes in the presence of catalytic amounts of piperidine over 4 Å molecular sieves. Simply by changing reaction conditions (solvent and temperature) it is possible to control the stereochemical outcome of the reactions, obtaining pure (*E*)- and (*Z*)-nitro alkenes in high to excellent yields. The role of molecular sieves on the stereochemical control seems crucial in addition to that of piperidine, especially for the synthesis of the *Z* isomer.

Conjugated nitro alkenes have proved to be versatile compounds that have widespread use in organic chemistry. They are powerful electrophiles that readily undergo Diels−Alder reaction or Michael addition with many different nucleophiles.[1] This peculiar reactivity is due to the electron-withdrawing nature of the nitro group, which represents a very important functionality in organic synthesis due to its easy conversion into a variety of functionalities.[2] Moreover, conjugated nitro alkenes are important because of their biological use as insecticides, fungicides, and pharmacologically active substances.[3]

The most common two-step preparation of nitro alkenes is the Henry reaction[4] between a carbonyl compound and a nitro alkane,[5] followed by the dehydration of the resulting β-nitro alcohol (Scheme 1). The Henry reaction is one of the typical C−C bond-formation processes and is commonly performed under mild conditions. On the contrary, the dehydration step can require harsh conditions, which strongly influence the overall yield. The *E* isomer is obtained as the

Scheme 1. Classical Synthesis of (*E*/*Z*)-Nitro Alkene Mixtures



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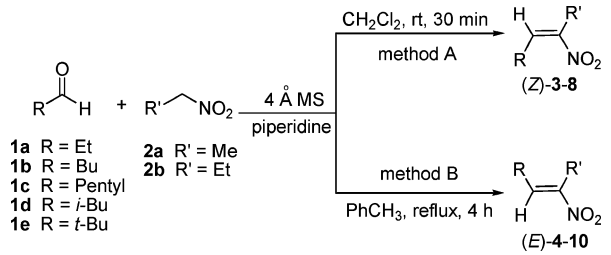
only or the major product, the *Z* isomer being always the minor product.[6]

To the best of our knowledge, only one stereoselective multistep sequence was reported to obtain (*Z*)-nitro alkenes, involving the stereospecific nitroselenylation procedure starting from unfunctionalized symmetric alkenes,[7] and there is no direct access to *Z* compounds available. Few examples of stereoselective isomerization of (*E*)-nitro alkenes have been reported to obtain the corresponding Z isomers.[8]

Being interested into the synthesis and reactivity of EWG-substituted alkenes,[9] here we report the first results of a simple and efficient one-pot method to obtain the stereoselective synthesis of (*E*)- or (*Z*)-nitro alkenes, by changing only the solvent and the reaction temperature.

Aliphatic aldehydes **1a**−**e** were reacted with nitro alkanes **2a**,**b** in the presence of catalytic amounts of piperidine[10] over 4 Å molecular sieves (MS), using toluene at reflux or methylene chloride at room temperature under anhydrous conditions and inert atmosphere (Ar). In these conditions only (*E*)-nitro alkenes **4**−**10** or (*Z*)-nitro alkenes **3**−**8** were obtained in high to excellent yields. The results are reported in Table 1.

Table 1. Stereoselective One-Pot Synthesis of (*Z*)- or (*E*)-Nitro Alkenes



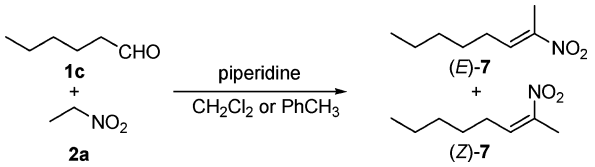
entry	nitro alkene	R	R′	yield, % *Z* (method A)[a]	yield, % *E* (method B)[a]
1	**3**	Et	Me	93	*b*
2	**4**	Et	Et	86	86
3	**5**	Bu	Me	90	92
4	**6**	Bu	Et	89	83
5	**7**	pentyl	Me	95	81
6	**8**	pentyl	Et	90	87
7	**9**	*i*-Bu	Me	*c*	96
8	**10**	*t*-Bu	Me	*c*	79

[a] After filtration of the crude mixture on celite. [b] Bp of **2a** is too low. [c] No nitro alkenes were detected.

As reported in Table 1, the synthesis of nitro alkenes is highly stereoselective, and in all cases only the *E* or *Z* isomer was obtained, as confirmed by ^{1}H NMR analysis performed on the crude mixtures. A simple filtration under argon through plugs of celite using CH_2Cl_2 as eluent gives the pure isomer in very good yields. The method seems to suffer from steric hindrance (entries 7 and 8) when the reactions were performed at room temperature;[11] on the contrary the pure *E* isomers **9** and **10**[12] were obtained when working at reflux of toluene.

To obtain information on the different stereochemical outcome observed by varying the reaction temperature and on the role played by molecular sieves, the condensation reaction between **1c** and **2a** was performed at different temperatures without the presence of molecular sieves (Table 2).

Table 2. Condensation Reactions Performed without Molecular Sieves



solvent	temp	time, h	*E*/*Z*[a]	conversion, %[b]
$PhCH_3$	rt	1	1/1	67
CH_2Cl_2	rt	1	1.1/1	70
$PhCH_3$	115 °C	4	1.3/1	73

[a] By ^{1}H NMR. [b] Calculated from the crude mixture by ^{1}H NMR with respect to aldehydic proton.

As shown in Table 2, the synthesis of nitro alkenes occurs unexpectedly in all conditions, but leading to an *E*/*Z* mixture.[13]

Consequently, molecular sieves seem to affect mainly the stereoselectivity of the reaction. To gain further data, the *β*-nitro alcohol **11**[6d] was synthesized through a typical Henry reaction and allowed to react under the same conditions used for the one-pot synthesis of *E*- and *Z*-nitro alkene **7** (Scheme 2).

While the dehydration reaction takes place at reflux in toluene in the presence of either piperidine or triethylamine, giving as expected only the *E* isomer **7**,[14] no reaction was promoted in CH_2Cl_2 and **11** was recovered as the only product even after 24 h.

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(10) Using a stoichiometric amount of piperidine, a complex mixture was obtained, in which it was not possible to detect either nitro alkenes or their precursors.

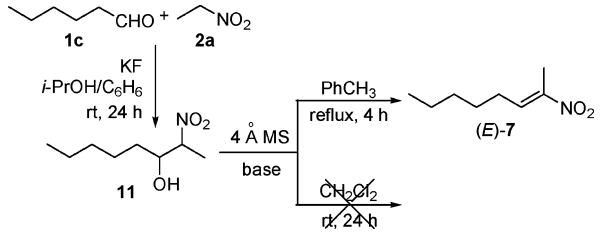
(11) Attempts to obtain nitro alkenes by using a 2-fold excess of **1d** and **1e**, a longer reaction time, and/or CH_2Cl_2 at reflux failed.

(12) Kawai, Y.; Inaba, Y.; Tokitoh, N. *Tetrahedron*: *Asymmetry* **2001**, *12*, 309−318.

(13) For a different synthesis of (*E*)- and (*Z*)-**7** see: Dumez, E.; Faure, R.; Dulcère, J.-P. *Eur. J. Org. Chem.* **2001**, 2577−2588.

(14) By using Et_3N as the base traces of *Z* isomer were also observed in ^{1}H NMR spectrum of the crude mixture.

Scheme 2. Synthesis and Dehydration of **11**



These results support the role of molecular sieves in the stereochemical control of the one-pot synthesis of nitro alkenes and moreover suggest a different reaction pathway for the synthesis of the *Z* isomer. The formation of this isomer could be explained by a nucleophilic catalysis that leads to the formation of a protonated imine as the intermediate; this latter then can undergo the nucleophilic attack by the nitronate, the same piperidine acting both as a nucleophile toward the aldehyde and as a base toward the nitro alkane. Finally an elimination gives only the *Z*-nitro alkene.

In support of our hypothesis on the role of a secondary amine, attempts to synthesize (*Z*)-**7** at room temperature using triethylamine instead of piperidine failed, and **1c** and **2a** were recovered after 24 h.

In conclusion, first results of a highly stereoselective one-pot synthesis of either (*E*)- or (*Z*)-nitro alkenes were reported. The methodology allows an easy control of the product configuration, and it seems especially appealing to obtain the *Z* isomer in high yields, avoiding multistep and expensive purification procedures. Further studies are in progress to broaden the potentiality of the procedure and to better clarify the reaction pathway.

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Supporting Information Available: Experimental procedures, analytical and spectroscopic data for (*Z*)-**3**, (*E*)- and (*Z*)-**4**−**6**, **8** and ^{1}H and ^{13}C NMR spectra of (*Z*)-**4** and (*E*)-**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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