

Potassium Fluoride/Basic Alumina as Far Superior Heterogeneous Catalyst for the Chemoselective Conjugate Addition of Nitroalkanes to Electron-Poor Alkenes Having Two Electron-Withdrawing Groups in α - and β -Positions

Roberto Ballini^{a,*} and Alessandro Palmieri^a

^a Green Chemistry Group, Dipartimento di Scienze Chimiche, Università di Camerino, via S. Agostino 1, 62032 Camerino, Italy
Fax: (+39)-073-740-2297; e-mail: roberto.ballini@unicam.it

Received: March 14, 2006; Accepted: May 19, 2006



Supporting information for this article is available on the WWW under <http://asc.wiley-vch.de/home/>.

Abstract: The chemoselective, conjugate addition of nitroalkanes to electron-poor alkenes, with two electron-withdrawing groups in the α - and β -positions, can be easily performed at room temperature under solventless conditions using potassium fluoride/basic alumina as heterogeneous catalyst.

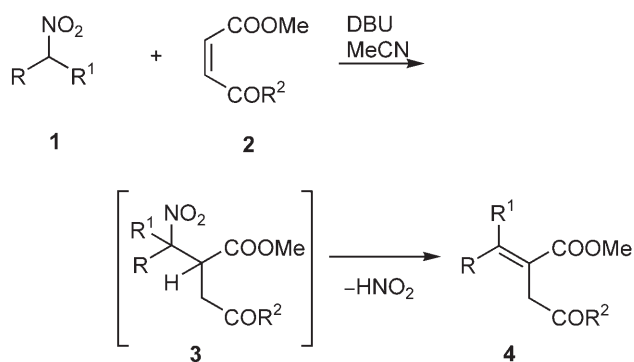
Keywords: conjugate addition; heterogeneous catalysis; nitroalkanes; potassium fluoride/basic alumina; solventless reaction

Nitroalkanes are a source of great utility for stabilized carbanions since the high electron-withdrawing power of the nitro group provides an outstanding enhancement of the hydrogen acidity at the α -position. Nitronate anions, generated from nitroalkanes under basic conditions, can be conveniently employed as carbon nucleophiles for conjugate addition (Michael reaction) to electron-poor alkenes.^[1] Usually, these reactions afford valuable nitro derivatives which can be converted into an array of other molecules thanks to the great versatility of the nitro group.^[2] However, if the nitro group is present in a suitable position on the substrate, it could act as a leaving group with subsequent elimination of nitrous acid from the Michael adduct. In fact, we have reported that the reaction of nitroalkanes **1** with electron-poor alkenes bearing two electron-withdrawing groups in the α - and β -positions, **2**, under DBU catalysis, proceeds *via* a tandem Michael addition-elimination process affording the unsaturated molecules **4** with enhanced *E* stereoselectivity (Scheme 1).^[3] The nitrous acid elimination is induced by the presence of the electron-withdrawing group at

the β -position to the nitro function in the intermediate **3**.

This discovery represents the key step for the one-pot preparation of a large variety of unsaturated systems, from nitroalkanes.^[4] However, in spite of the great utility of the obtained unsaturated systems **4**, the elimination of the nitro group from the Michael adduct **3** represents an important loss in terms of (i) atomic economy and (ii) chances for further synthetic applications, due to the easy conversion of the nitro group into a variety of other powerful functionalities. Thus, a new, chemoselective catalytic procedure for the conjugate addition of **1** to **2**, preserving the presence of the nitro group would be highly welcomed.

Solid catalysis is crucial to chemical technology, in fact, product isolation is easier, the reactions often run under milder conditions and it favours higher selectivity. In addition, the atom efficiency of the reaction is improved, the process is simplified, the precious raw materials used in the manufacture of the catalyst are given increased lifetime (through reuse),

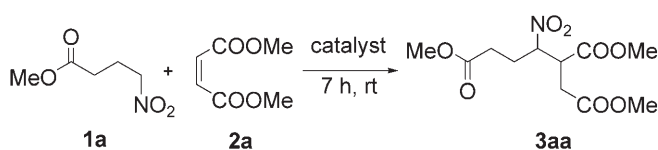


Scheme 1.

the volume of waste is significantly reduced, and product isolation is often made easier.^[5]

In this context, aliphatic nitro compounds have demonstrated a great reactivity under solid catalysis, mainly in the formation of new carbon-carbon single bonds.^[6] Thus, we investigated the possibility to perform the chemoselective conjugate addition of nitroalkanes to alkenes of type **2**, with the aim of avoiding any elimination of the nitro group from the Michael adducts **3**, under mild basic conditions with the help of solid catalysts. Our idea was first tested (Scheme 2) in the reaction of methyl 4-nitrobutanoate (**1a**) with dimethyl maleate (**2a**), under solventless conditions and at room temperature, simple by mixing the substrates on a bed of a variety of solid, basic catalysts. As detailed in Table 1, it is evident that the best results were obtained under adsorbed KF catalysis,^[7] in particular using KF/basic alumina.^[7c]

In order to verify the generality of our procedure, we examined our method with several substrates, including primary and secondary nitroalkanes, and we obtained good yields (70–92 %, Table 2) of the adducts **3** in which the nitro functionality is preserved. This procedure furnishes a diastereomeric mixture of



Scheme 2.

the nitro adduct from primary nitroalkanes (**1a–c**); nevertheless, this seems not to be a problem since the most widely used transformation of the nitro group is the Nef reaction (nitro to carbonyl)^[2d] in which one stereogenic center is lost.

Moreover, KF/basic Al₂O₃ catalysis offers one more chance since, through the appropriate selection of the temperature, the direct formation of the α,β -unsaturated esters **4** can be also performed from the starting materials.

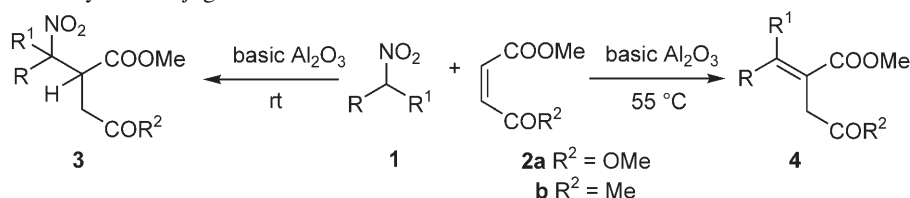
In fact, if the reaction of **1** with **2** on KF/basic Al₂O₃ was carried out under solventless conditions and at 55 °C, the product **4** is directly obtained, in profitable yields (67–81 %), from primary nitroalkanes by the *in situ* conjugate addition-nitrous acid

Table 1. Tested solid catalysts.

Catalyst	Yield [%] ^[a] of 3aa
KF/basic alumina	80
KF/neutral alumina	71
Basic alumina	4
Hydrotalcite MG 70	7
Hydrotalcite MG 30	6
Amberlyst A-21	25
Amberlyst A-27	21
Silica supported-1,5,7-triazabicyclo-[4.4.0]dec-5-ene (TBD)	36
<i>N,N</i> -Diethylpropylamine supported on amorphous silica (KG-60-NEt ₂)	19

^[a] The reaction was stopped after 7 h.

Table 2. Results obtained by the conjugate addition of **1** to **2** under KF/basic alumina.



1	R	R ¹	2	Yield of 3 [% , h] ^[a,b]	Yield of 4 [% , h] ^[a,c]
a	MeOOC(CH ₂) ₂	H	a	aa (80, 7)	aa (78, 7)
a	MeOOC(CH ₂) ₂	H	b	ab (78, 5)	ab (67, 6)
b	CH ₃ CH ₂	H	a	ba (71, 6)	ba (79, 6)
b	CH ₃ CH ₂	H	b	bb (76, 6)	bb (72, 6)
c	Ph(CH ₂) ₂	H	a	ca (73, 6)	ca (81, 16)
c	Ph(CH ₂) ₂	H	b	cb (84, 6)	cb (71, 12)
d	-(CH ₂) ₅ -		a	da (92, 6)	da (traces)
d	-(CH ₂) ₅ -		b	db (70, 3)	db (traces)
e	CH ₃	CH ₃	a	ea (75, 6)	ea (traces)
e	CH ₃	CH ₃	b	eb (70, 6)	eb (traces)

^[a] Yield of pure, isolated product.

^[b] The reaction has been performed at room temperature.

^[c] The reaction has been performed at 55 °C.

elimination, while secondary nitroalkanes convert into the adduct **3**, with traces of the elimination product **4**. It is important to point out that the formation of the unsaturated 1,4-dicarbonyl derivatives **4**, from primary nitroalkanes shows high *E* stereoselectivity since the ratio *E/Z* is, for all the products, > 95/5.

Thus, by the modular choice of the temperature, the conjugate addition of nitroalkanes **1** to electron-poor alkenes **2** having two electron-withdrawing groups in the α - and β -positions, performed under KF/basic Al_2O_3 catalysis, can be easily directed to the (i) stereoselective (*E*) formation of a C/C double bond (compounds **4**), or (ii) chemoselective generation of a C/C single bond (compounds **3**).

In conclusion, we have developed the first heterogeneous, solventless, chemoselective (or stereoselective) catalysis for the conjugate addition of both primary and secondary nitroalkanes to electron-poor alkenes possessing two electron-withdrawing groups in the α - and β -positions. In addition, the very simple and mild conditions make our procedure of great interest from the practical point of view. At the present time we are aiming to enlarge the potential of our procedure and to verify its stereoselective outcome.

Experimental Section

General Remarks

GLC analyses were performed with an SE-54 fused silica capillary column (25 m, 0.32 mm internal diameter), FID detector and nitrogen as carrier gas. GS-MS analyses were carried out by means of the EI technique (70 eV). All chemicals were purchased and used without further purification. KF/basic alumina was prepared according to the reported method.^[7c]

Typical Procedure for the Chemoselective Addition of Nitroalkanes **1** to Alkenes **2**; Preparation of **3**

To a stirred mixture of nitroalkane **1** (1 mmol) and Michael acceptor **2** (1 mmol), 0.6 g of KF/basic alumina were added and the heterogeneous mixture was stirred at room temperature for the appropriate time (Table 2). At the end of the reaction, the mixture was extracted with CH_2Cl_2 and the catalyst was filtered on a Buchner funnel, then washed with CH_2Cl_2 . The filtrate was concentrated under vacuum and the crude product **3** was purified by flash chromatography.

Typical Procedure for the “One-Pot”

Addition-Elimination of Nitroalkanes **1** to Alkenes **2**; Preparation of **4**

Following the same procedure as above, the reaction was carried out at 55 °C.

Acknowledgements

Financial support from University of Camerino and MIUR is gratefully acknowledged.

References

- [1] R. Ballini, G. Bosica, D. Fiorini, A. Palmieri, M. Petrini, *Chem. Rev.* **2005**, *105*, 933–971.
- [2] a) D. Seebach, E. W. Colvin, F. Lehr, T. Weller, *Chimia* **1979** *33*, 1–18; b) G. Rosini, R. Ballini, *Synthesis* **1988**, 833–847; c) N. Ono, *The Nitro Group in Organic Synthesis*, Wiley, New York, **2001**; d) R. Ballini, M. Petrini, *Tetrahedron* **2004**, *60*, 1017–1047.
- [3] R. Ballini, A. Rinaldi, *Tetrahedron Lett.* **1994**, *35*, 9247–9250.
- [4] See, for example: a) R. Ballini, E. Marcantoni, S. Perella, *J. Org. Chem.* **1999**, *64*, 2954–2957; b) R. Ballini, G. Bosica, M. Damiani, P. Righi, *Tetrahedron* **1999**, *55*, 13451–13456; c) R. Ballini, G. Bosica, A. Masè, M. Petrini, *Eur. J. Org. Chem.* **2000**, 2927–2931; d) R. Ballini, G. Bosica, A. Palmieri, M. Petrini, C. Pierantozzi, *Tetrahedron* **2003**, *59*, 7283–7289.
- [5] J. H. Clark, *Acc. Chem. Res.* **2002**, *35*, 791–797.
- [6] See, for example: a) R. Ballini, G. Bosica, M. Parrini, *Tetrahedron Lett.* **1998**, *39*, 7963–7964; b) R. Ballini, F. Bigi, E. Gogni, R. Maggi, G. Sartori, *J. Catal.* **2000**, *191*, 348–353; c) R. Ballini, G. Bosica, D. Fiorini, *Tetrahedron Lett.* **2001**, *42*, 8471–8473; d) R. Ballini, G. Bosica, D. Livi, A. Palmieri, R. Maggi, G. Sartori, *Tetrahedron Lett.* **2003**, *44*, 2271–2273; e) R. Ballini, D. Fiorini, M. V. Gil, A. Palmieri, *Green Chem.* **2003**, *5*, 475–476; f) R. Ballini, G. Bosica, D. Fiorini, A. Palmieri, *Synthesis* **2004**, 1938–1940.
- [7] a) J. H. Clark, D. G. Cork, M. S. Robertson, *Chem. Lett.* **1983**, 1145–1148; b) J. H. Clark, D. G. Cork, H. W. Gibbs, *J. Chem. Soc., Perkin Trans. 1* **1983**, 2253–2258; c) D. E. Bergbreiter, J. J. Lalonde, *J. Org. Chem.* **1987**, *52*, 1601–1603.