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Uncatalyzed, *anti*-Michael addition of amines to β-nitroacrylates: practical, eco-friendly synthesis of β-nitro-α-amino esters

Roberto Ballini *, Noelia Araújo Bazán, Giovanna Bosica, Alessandro Palmieri *

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

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Abstract

A variety of primary and secondary amines give the conjugate reaction with β-nitroacrylates, via an *anti*-Michael addition, without any catalyst and/or solvent, allowing good yields of β-nitro-α-amino esters.

Keywords: Solvent free; Anti-Michael addition; Uncatalyzed reaction; Amines; β-Nitro-α-amino esters

β-Nitro amino esters are an important class of building blocks for the synthesis of a variety of important targets such as (i) α,β-dehydro-α-amino acids,[1] which are common components of naturally occurring peptides[2] and (ii) β-nitro-α-amino acids that have been studied as enzyme inhibitor[3] and as precursors in the synthesis of a variety of α-amino acids and diamino acids.[4,5] In addition, the nitro group, which is often entitled a 'chemical chameleon', can be easily transformed into other useful functional groups including amines, aldehydes, or acid moieties via nucleophilic addition reaction, reduction reaction, Meyer reaction, and other conversions,[6] thus giving the opportunity for further elaborations into a variety of other chemical structures.

Inspite of the great importance of the β-nitro amino esters, only few methods have been reported for their synthesis. In fact, they can be obtained starting from nitroalkanes by their nucleophilic reaction with bromoglycine derivative,[1] or with imines.[7] In addition, athree-component synthesis of β-nitro-α-amino acids, starting from nitroalkanes, amines and glyoxalate, was reported,[8] but the limited number of substrates reported and the modest yields obtained seem to indicate that the procedure is not of general application.

The *aza*-Michael reaction is widely recognized as one of the most important C–N bond-forming reactions in organic synthesis.[9] The most common procedures require basic or acidic activators;[10] however, to avoid the side reactions that are normally encountered in the presence of strong acid or base, a number of alternative methods have been developed and, in this context, various Lewis-acid-induced reactions and microwave-accelerated reactions have been reported.[11] However, many of these procedures involve the use of expensive catalysts, stoichiometric amounts of the reagents, poor regioselectivity, and extended reaction times.

β-Nitroacrylates are an emerging class of electron-poor alkenes, having two electron-withdrawing groups in α- and β-positions,[12] employed as versatile electrophilic acceptors[13] under different catalytic systems.

During our studies on the conjugate additions of nucleophiles to β-nitroacrylates,[12b,13g] we found that the reaction of 1 equiv of amines **1** with 1 equiv of β-nitroacrylates **2**, performed at room temperature and under solvent-free and catalyst-free conditions, allows good yields of β-nitro-α-amino esters **3**, via an *anti*-Michael fashion[14,15] (see Scheme 1).

* Corresponding authors. Tel.: +39 0737 402270; fax: +39 0737 402297 (R.B.); tel.: +39 0737 402341; fax: +39 0737 402297 (A.P.).
E-mail addresses: roberto.ballini@unicam.it (R. Ballini), alessandro.palmieri@unicam.it (A. Palmieri).

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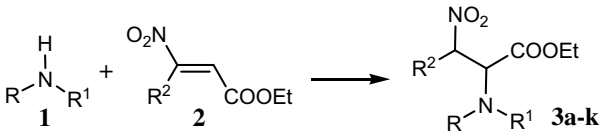
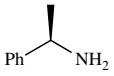


Scheme 1.

Table 1
The prepared β-nitro-α-amino esters

Entry	Amine **1**	R^2	Yield[a] (%) of **3**	Time (h)	dr[b]
1	$PhNH_2$	Et	**3a** (92)	2	1:1
2		Et	**3b** (88)	1.5	75:25
3		Et	**3c** (90)	1.5	1:1:1:1
4	*p*-$MeOC_6H_4NH_2$	*n*-Pr	**3d** (88)	2.5	1:1
5	*p*-$MeOC_6H_4NH_2$	*n*-Bu	**3e** (95)	2	1:1
6	$BnNH_2$	*n*-Bu	**3f** (91)	1.5	1:1
7	$BnNH_2$	$Ph(CH_2)_2$	**3g** (89)	1.5	1:1
8	*n*-$C_5H_{11}NH_2$	$Ph(CH_2)_2$	**3h** (92)	1.5	1:1
9		Ph	**3i** (80)	1.5	95:5
10	*i*-$PrNH_2$	$MeOCO(CH_2)_4$	**3j** (78)	1.5	1:1
11	Et_2NH	$MeOCO(CH_2)_4$	**3k** (79)	1.5	95:5

[a] Yield of pure, isolated product.
[b] Diastereomeric ratio was determinated by ^1H NMR studies.

We tried the reaction with different, selected amines and β-nitroacrylates in order to verify the synthetic potentiality of our method. A variety of both primary and secondary amines and β-nitroacrylates produce very good yields (78–95%) of the *anti*-Michael adducts **3** (Table 1), under very short reaction times (1.5–2.5 h). Moreover, the Michael addition of secondary amines shows good diastereoselectivity: **3b** = 75:25, **3i** and **3k** = 95:5. This difference is probably due to the higher steric hindrance of the substituents R^2 bonded to C-3 of β-nitroacrylate, which respect to the volume of ethyl group present in compound **3b**.

The procedure seems to be independent from the aromatic or aliphatic nature of the amines as well as from their cyclic or acyclic structures. Because the preparation of **3** was performed using a solvent-free procedure, at the end of the reaction (checked by TLC) the crude mixture was directly charged on a chromatographic column to give the pure adducts, avoiding any tedious and dangerous workup. Thus, this *anti-aza*-Michael reaction constitutes a general, practical manner to obtain an important class of molecules such as β-nitro-α-amino esters under high convenient reaction conditions. In fact, the latter compounds can be prepared at room temperature, without the need of any solvent or any catalyst, using stoichiometric amount of both starting materials and without the need of any workup.

In conclusion, the method shows the following advantages from the economical and ecological points of view: very mild conditions, short reaction times, good yields, atom economy (100%), minimal production of waste, limited energy consumption, and environmentally benign.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.04.076.

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14. A previous example of *anti*-Michael addition of a large amount of ammonia to β-nitroacrylates has been reported under high pressure condition: see Ref. 5.
15. *General procedure: Amine* **1** (2 mmol) was added to β-nitroacrylate **2** (2 mmol), then the mixture was stirred at room temperature for the appropriate time (see Table 1), after this the crude product was directly charged on the head of the flash chromatography column and eluted by a mixture of hexane and ethyl acetate.