A Convenient and Easy Synthesis of γ-Nitro-α-Acetamido Esters

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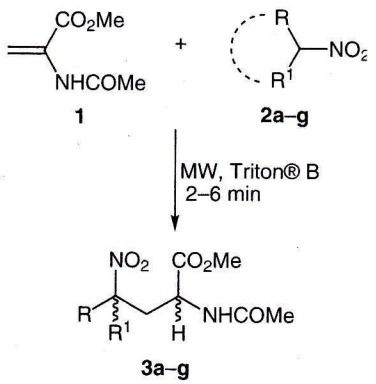
Abstract: A microwave-assisted synthesis of γ-nitro acetamido esters, under mild conditions and without solvent, is described. The desired products were obtained via Michael additions from the commercial methyl acetamidoacrylate and nitroalkanes.

Key words: microwave-assisted synthesis, α-amino acids, acetamidoacrylate, nitroalkane, Michael addition

Derivatives of unnatural γ-nitro-α-amino acids, as **3** or differently protected ones, are acknowledged as effective intermediates in the synthesis of natural and synthetic bioactive substances.[1–3] They are also versatile starting materials for the preparations of unusual α-amino acids, thanks to the many interconversions of functionality allowed by the chemistry of nitro group.[4–10]

In an effort to make some previously reported procedures (Wieland,[11] Crossley[12]) general and faster, we recently experimented successfully[13] with a microwave-assisted synthesis of γ-nitro-α-amino acids by means of conjugate additions of nitroalkanes to methyl *N*-(diphenylmethylene) protected 2,3-didehydro-α-aminopropanoate, an electrophilic acceptor that must be prepared from serine methyl ester.[14] Then, in order to improve the above procedure[13] and to extend its generality, we tried to extend our protocol to an easier available starting Michael acceptor such as the commercial acetamidoacrylate **1**.



Scheme 1 The 0.5–2 mmol scale of **1**, catalyst–substrate–nitroalkane 0.125:1:1.5

Although the compound **1** is known to be reluctant to the addition of nitro anions [in fact the literature refers[12] that **1** does not react on heating for several days in nitromethane with KF as catalyst, while by reaction with 2-nitropropane gave rise to the adduct **3b** (Table 2) in 76% yield, only after 66 hours in refluxing toluene], we looked for new conditions in order to find an efficient procedure to add nitroalkanes to the acceptor **1**. In connection with our interest in the application of the adduct **3a** as the key building block for the synthesis of natural products, we first investigated the reaction of nitromethane (**2a**) with **1**, in order to find the best reaction conditions. As detailed in the Table 1, it is evident that the best results in terms of yields (40%) were obtained in the presence of Triton® B (benzyltrimethyl ammonium hydroxide, 40% in MeOH), with a molar ratio of catalyst–substrate–nitroalkane = 0.125:1:1.5, in the absence of any solvents, and with the help of microwave (MW) irradiation (120 W).

In order to verify the generality of our procedure, we tested our method (that could be performed on a 0.5–2 mM scale of **1**) in an open reaction vessel, with several nitroalkanes (Scheme 1). As reported in Table 2, we obtained good yields (66–98%), in few minutes (2–6 min) with both linear and cyclic nitroalkanes, in a power range of 120–280 W.

It is important to note that, under our conditions, both nitromethane (**2a**) and 2-nitropropane (**2b**) afforded, in few minutes, **3a** and **3b** in 40% and 98% yields, respectively.

Thus, the MW-assisted reactions give good and reproducible results despite the use of a domestic microwave oven, are inexpensive in terms of catalyst and solvent, are practically solvent-free, and employ a favorable, very low, nitroalkane/Michael acceptor ratio. All these features underpin substantial advantages offered by the method here reported. This MW technique boosts the synthesis of 4-nitroamino acids precursors, as it is general, time-saving and, above all, it is a basic approach to obtain **3a**.

The methyl acetamidoacrylate, nitroalkanes and Triton B® were acquired from Aldrich and used directly. The methyl 4-nitropropanoate was prepared according to literature.[15] Reactions were carried out in a domestic microwave oven in an open vessel. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 200 spectrometer. Chemical shifts (δ scale) are reported in ppm regarding the central peak of the solvent. Coupling constants (*J* values) are given in Hz. EI–MS spectra (70 eV) were taken on a Fisons Trio 1000 instrument. Only molecular ions [M$^+$] and base peaks are given. IR spectra were obtained on a Bruker FT-48 spectrometer; ab-

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Table 1 Addition of Nitromethane to Methyl Acetamido Acrylate

Solvent	Temperature or Power (W)	Ratio **1**/CH_3NO_2	Ratio **1**/Triton B	Time	Yield (%) of **3a**
none	120 W	1:10	1:0.125	6 min	40
THF	r.t.	1:10	1:0.125	Overnight	0
THF	Reflux	1:10	1:0.125	8 h	0
CH_3NO_2	r.t.	1:50	1:1	Overnight	3–4
CH_3NO_2	Reflux		KF	66 h	0[12]

Table 2 Synthesis of γ-Nitro α-Acetamido Esters **3**

3	R	R^1	Power (W)	Time (min)	Yield (%)[a] of **3**
a	H	H	120[b]	6	40
b	CH_3	CH_3	280	2	98
c	CH_3CH_2	H	280	2	68
d	$CH_3(CH_2)_2$	H	280	2	66
e	$-(CH_2)_4-$		170[c]	2	70
f	$-(CH_2)_5-$		170[c]	3	76
g	$MeOCO(CH_2)_2$	H	280	2	70

[a] Yields of pure, isolated compounds.
[b] High power induces degradation.
[c] High power induces partial elimination of HNO_2.

sorbances are reported in ν (cm^{-1}). Melting points were determined on a Büchi SMP-510 capillary melting point apparatus and are uncorrected. Column chromatography purifications were performed under flash conditions using Merck 230–400 Mesh silica gel. TLC analysis was carried out on silica gel plates. A satisfactory elemental analysis (C, H, N ± 0.4% from the theoretical value) was obtained for the new compounds (Carlo Erba analyzer).

Microwave/Triton® B Induced Reaction of 1 with Nitro Compounds; General Procedure

The nitro derivative (1.5 equiv) and Triton® B (40% MeOH, 0.125 equiv) were introduced in a round-bottomed flask and were let to react for 2 min. Then, the methyl acetamidoacrylate (**1**; 1 equiv, 0.5–2.0 mmol) was added, and the flask was gently heated at 40 °C for 3 min, in order to obtain a homogeneous mixture. The open reaction vessel was placed inside a domestic microwave oven (halfway on the radius of the rotating plate) and irradiated at 120–280 W for 2–6 min. After cooling, the vitreous pale yellow or yellow-brown solids obtained were dissolved in EtOAc (20–80 mL) and quickly washed with 0.1 N HCl (2–8 mL) and water (3 × 2–8 mL). The organic phases, after drying over anhyd Na_2SO_4, were evaporated under reduced pressure. The residues were purified using flash chromatography for **3a,e–g**. Compounds **3b–d** were homogeneous enough to obtain satisfactory analysis.

Methyl 2-Acetylamino-4-nitrobutanoate (3a)

White solid; mp 57–59 °C.

IR (KBr): 3271, 1732, 1643, 1554 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.05 (s, 3 H), 2.3–2.4 (m, 1 H), 2.6–2.7 (m, 1 H), 3.79 (s, 3 H), 4.4–4.5 (m, 2 H), 4.6–4.7 (m, 1 H), 6.52 (br, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.04, 29.86, 49.86, 53.01, 71.65, 170.40, 171.36.

MS (EI): *m/z* = 158 [M^+ – 46], 127, 115, 98.

Anal. Calcd for $C_7H_{12}N_2O_5$ (204.18): C, 41.18; H, 5.92; N, 13.72. Found: C, 41.30; H, 5.95; N, 13.80.

Methyl 2-Acetylamino-4-methyl-4-nitropentanoate (3b)

Physical and spectroscopic data are identical to those reported in the literature.[12]

Methyl 2-Acetylamino-4-nitrohexanoate (3c)

Pale yellow oil; diastereomeric mixture (1:1 from ^1H NMR).

IR (film): 3287, 1746, 1660, 1552 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.3 Hz, 6 H), 1.6–1.9 (m, 4 H), 2.00 (s, 3 H), 2.01 (s, 3 H), 2.0–2.7 (m, 4 H), 3.73 (s, 3 H), 3.74 (s, 3 H), 4.4–4.6 (m, 2 H), 4.6–4.7 (m, 2 H), 6.5 (br, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.86, 9.88, 22.86, 27.35, 27.73, 34.96, 35.08, 49.71, 50.02, 52.78, 52.84, 86.12, 86.40, 170.55, 170.72, 171.44, 171.54.

MS (EI): *m/z* = 186 [M^+ – 46], 173, 143, 126, 84.

Anal. Calcd for $C_9H_{16}N_2O_5$ (232.23): C, 46.55; H, 6.94; N, 12.06. Found: C, 46.90; H, 7.00; N, 12.20.

Methyl 2-Acetylamino-4-nitroheptanoate (3d)
Pale yellow oil; diastereomeric mixture (1:1 from ^{1}H NMR).

IR (KBr): 3294, 1743, 1654, 1551 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.2 Hz, 6 H), 1.2–1.4 (m, 4 H), 1.6–1.9 (m, 4 H), 2.02 (s, 3 H), 2.04 (s, 3 H), 2.3–2.7 (m, 4 H), 3.76 (s, 3 H), 3.77 (s, 3 H), 4.5–4.6 (m, 2 H), 4.7–4.8 (m, 2 H), 6.19 (br, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.30, 13.33, 18.79, 22.93, 35.41, 35.50, 36.00, 36.34, 49.78, 50.16, 52.85, 52.92, 84.68, 84.83, 170.37, 170.59, 171.36, 171.44.

MS (EI): *m/z* = 200 [M$^+$ – 46], 187, 157, 140, 98.

Anal. Calcd for $C_{10}H_{18}N_2O_5$ (246.26): C, 48.77; H, 7.37; N, 11.38. Found: C, 48.90; H, 7.55; N, 11.66.

Methyl 2-Acetylamino-3-(1-nitrocyclopentyl)propanoate (3e)
Pale yellow viscous oil.

IR (KBr): 3306, 1747, 1659, 1539 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.78–1.80 (m, 6 H), 1.97 (s, 3 H), 2.44–2.71 (m, 4 H), 3.72 (s, 3 H), 4.71–4.83 (m, 1 H), 5.87 (d, *J* = 7.9 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.90, 24.08, 24.10, 36.63, 39.06, 40.33, 49.32, 52.57, 97.16, 170.02, 171.74.

MS (EI): *m/z* = 212 [M$^+$ – 46], 152, 110, 88.

Anal. Calcd for $C_{11}H_{18}N_2O_5$ (258.27): C, 51.15; H, 7.02; N, 10.85. Found: C, 51.30; H, 7.15; N, 11.01.

Methyl 2-Acetylamino-3-(1-nitrocyclohexyl)propanoate (3f)
Pale yellow viscous oil.

IR (KBr): 3290, 1747, 1655, 1539 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.37–1.82 (m, 8 H), 1.94 (s, 3 H), 2.24–2.35 (m, 2 H), 2.39–2.43 (m, 2 H), 3.70 (s, 3 H), 4.78 (ddd, *J* = 6.24 Hz, *J* = 7.93 Hz, *J* = 8.93 Hz, 1 H), 5.9 (d, *J* = 8.93 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.03, 22.13, 22.78, 24.61, 32.50, 35.77, 40.12, 47.87, 52.60, 89.29, 170.11, 170.91.

MS (EI): *m/z* = 272 [M$^+$ – 46], 166, 124, 88.

Anal. Calcd for $C_{12}H_{20}N_2O_5$ (272.30): C, 52.93; H, 7.40; N, 10.29. Found: C, 53.00; H, 7.45; N, 10.36.

2-Acetylamino-4-nitro-1,7-heptanedioic Acid Dimethyl Ester (3g)
Pale yellow oil; diastereomeric mixture (1:1 from ^{1}H NMR).

IR (film): 3349, 1737, 1643, 1519 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.03 (s, 3 H), 2.05 (s, 3 H), 2.1–2.7 (m, 12 H), 3.70 (s, 6 H), 3.71 (s, 3 H), 3.76 (s, 3 H), 4.4–4.5 (m, 2 H), 4.6–4.7 (m, 2 H), 6.21 (br s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.35, 28.80, 29.05, 29.77, 29.85, 35.54, 35.57, 49.63, 49.89, 51.96, 52.41, 52.95, 83.77, 83.95, 170.31, 170.52, 171.19, 171.34, 172.34.

MS (EI): *m/z* = 244 [M$^+$ – 46], 201, 184, 170, 142.

Anal. Calcd for $C_{11}H_{18}N_2O_7$ (290.27): C, 45.52; H, 6.25; N, 9.65. Found: C, 45.80; H, 6.55; N, 9.75.

References

(1) Adamczyk, M.; Johnson, D. D.; Reddy, R. E. *Tetrahedron: Asymmetry* **2000**, *11*, 3063.
(2) Büchi, G.; Botkin, J. H.; Lee, G. C. M.; Yakushijin, K. *J. Am. Chem. Soc.* **1985**, *107*, 5555.
(3) Rowley, M.; Leeson, P. D.; Williams, B. J.; Moore, K. W.; Baker, R. *Tetrahedron* **1992**, *48*, 3557.
(4) Rosini, G.; Ballini, R. *Synthesis* **1988**, 833.
(5) Rosini, G.; Ballini, R.; Petrini, M.; Marotta, E.; Righi, P. *Org. Prep. Proced. Int.* **1990**, *22*, 707.
(6) Ballini, R. *Studies in Natural Products Chemistry*, Vol. 19; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, **1997**, 117–184.
(7) Ballini, R. *Synlett* **1999**, 1009.
(8) Ono, N. *The Nitro Group in Organic Synthesis*; John Wiley: New York, **2001**.
(9) Calderari, G.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1592.
(10) Crossley, M. J.; Fung, Y. M.; Kyriakopoulos, E.; Potter, J. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1123.
(11) Wieland, T.; Ohnacker, G.; Ziegler, W. *Chem. Ber.* **1957**, *90*, 194.
(12) Crossley, M. J.; Fung, Y. M.; Potter, J. J.; Stamford, A. W. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1113.
(13) Ballini, R.; Balsamini, C.; Bartoccini, F.; Gianotti, M.; Martinelli, C.; Savoretti, N. *Synthesis* **2005**, 296.
(14) (a) Balsamini, C.; Duranti, E.; Mariani, L.; Salvatori, A.; Spadoni, G. *Synthesis* **1990**, 779. (b) Jayakanthan, K.; Madhusudanan, K. P.; Vankar, Y. D. *Tetrahedron* **2004**, *60*, 397.
(15) Ballini, R.; Bosica, G. *J. Chem. Res., Synop.* **1993**, 435.