Tetrahedron 65 (2009) 2916–2920

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

β-Nitroacrylates and silyl enol ethers as key starting materials for the synthesis of polyfunctionalized β-nitro esters and 1,2-oxazine-2-oxides

Roberto Ballini *, Giovanna Bosica, Serena Gabrielli, Alessandro Palmieri

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

ARTICLE INFO

Article history:
Received 7 November 2008
Received in revised form 21 January 2009
Accepted 5 February 2009
Available online 11 February 2009

ABSTRACT

The reaction of silyl enol ethers with β-nitroacrylates, in the presence of tetrabutyl ammonium fluoride as catalyst, allows the formation of polyfunctionalized β-nitro esters, or hexahydro-4*H*-benzoxazine-2-oxides, depending on the nature of the starting silyl enol ethers.

1. Introduction

The conjugate addition of a nucleophilic carbon to an electron-poor system is one of the most important reactions in organic synthesis for the formation of new C–C bonds.[1] In this context, nitroolefins are widely used as Michael acceptors due to the highly electron-withdrawing effect of the nitro group.[2]

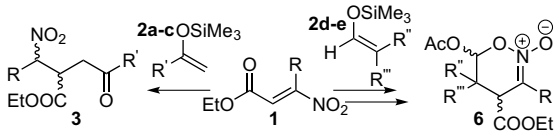
In the last few years, β-nitroacrylates **1** have been shown to be a highly versatile class of nitroalkenes prone to give easy access to a variety of polyfunctionalizsed molecules as a consequence of the presence of both nitro and ester groups.[3]

1,2-Oxazine-2-oxides are important class of key building blocks for the synthesis of a large number of useful products, such as pyrrolizidine, pyrrolidines, β-lactam-*N*-oxides, oxazine, γ-nitro-ketones, etc.[4] 1,2-Oxazine-2-oxides are generally obtained by [4+2] cycloaddition of nitroolefins with electron-rich alkenes.[4,5] In the last few years, new approaches via addition of silyl enol ethers to nitroalkenes have been reported and most of these require the presence of a Lewis acid.[6] In addition, very recently Pizzo et al. reported[7] a new solvent- and metal-free synthesis of 1,2-oxazine-2-oxides, starting from cyclic silyl enol ethers and a specific class of nitroalkenes in which the double bond must be conjugated, at the same time, with the nitro, cyano, and phenyl groups.

β-Nitro esters are another valuable class of compounds, which are used as intermediates for the synthesis of natural products.[8] These compounds can be prepared by direct nitration of the corresponding unsaturated ester,[9] by nitration of the corresponding β-halo carbonyl derivatives,[8a,10] or through the conjugate addition of the appropriate nitroalkane to 2-ene-1,4-dicarbonyl systems.[11] However, the syntheses of β-nitro esters require very mild reaction conditions since the concomitant presence of an acidic hydrogen in the α-position to the carbonyl and the nitro group in the vicinal carbon can promote the elimination of nitrous acid.[11,12]

2. Results and discussion

As a continuation of our studies in the use of β-nitroacrylates as strategic starting materials for the synthesis of a variety of fine chemicals, we wish to report a new method for the preparation of both the targets **3** and **6**, arising from silyl enol ethers. In fact, the reaction of silyl enol ethers **2** with **1** allows, selectively, the formation of the γ′-keto-β-nitro esters **3**, or the 1,2-oxazine-2-oxides **6**, depending on the nature of **2** (Scheme 1). The regioselectivity of the conjugate addition can be explained in terms of stronger electron-withdrawing power of the nitro group with respect to the ester functionality.



Scheme 1.

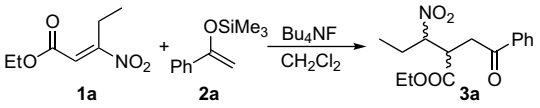
We first examined the preparation of **3** starting from silyl enol ethers derived from ketones and, as a sample reaction, we tested the conjugate addition of **2a** to β-nitroacrylate **1a**. As shown in Table 1, we found the best results were obtained at −45 °C, using 1.3 equiv of silyl enol ethers and 1.95 equiv of tetrabutylammonium fluoride,[13] respectively, and in dichloromethane as solvent.

In order to test the generality of our method we extended the procedure to a series of starting materials and in all cases we obtained the product in good to excellent yield (72–94%) in short reaction times (Table 2).

* Corresponding author. Tel.: +39 0737 402270; fax: +39 0737 402297.
E-mail address: roberto.ballini@unicam.it (R. Ballini).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.02.009

Table 1
Optimization of the reaction

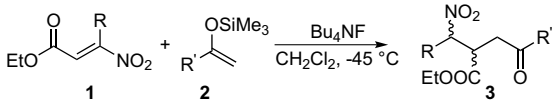


1a 2a 3a

equiv of **2a**	equiv of Bu_4NF	Temperature (°C)	Yield[a] (%) of **3a**	Reaction time (h)
1.05	1.5	0	60	1.5
1.3	1.95	0	67	1
1.3	1.95	−45	94	1

[a] Yield of pure isolated product.

Table 2



1 2 3

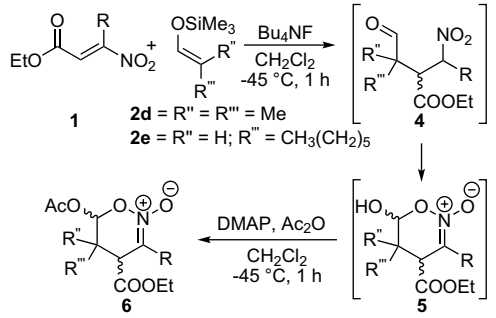
R	R′		Yield[a] (%) of **3**	Reaction time (h)	Diastereomeric ratio[b]
Et	Ph	**3a**	94	1	50:50
$PhCH_2CH_2$	Ph	**3b**	87	1	50:50
$MeOCO(CH_2)_4$	Ph	**3c**	91	1	50:50
$CH_3(CH_2)_3$	Ph	**3d**	94	1	50:50
Me	Me	**3e**	75	1.5	50:50
$PhCH_2CH_2$	Me	**3f**	93	1	50:50
$MeOCO(CH_2)_4$	Me	**3g**	87	1.5	60:40
Me	*t*-Bu	**3h**	72	1	50:50
Et	*t*-Bu	**3i**	88	1	50:50
$PhCH_2CH_2$	*t*-Bu	**3j**	89	1	50:50

[a] Yield of pure isolated product.
[b] Diastereomeric ratio was evaluated by ^1H NMR spectroscopy.

The reactions work well with a variety of silyl enol ethers and β-nitroacrylates, including hindered precursors (R^1=*t*-Bu). Moreover, under our reaction conditions, the method shows high chemoselectivity since products arising from the elimination of nitrous acid were not observed.

Finally, we tested the preparation of the 1,2-oxazine-2-oxides **6**, starting from a silyl enol ether arising from an aldehyde. As reported in Table 3, the Michael addition of **2d** to **1**, followed by the in situ acetylation of the formed hydroxyl group (**5** to **6**), directly afforded the target compounds **6**. Although compounds **5** can be isolated by chromatography, they were unstable and we circumvented this problem, by the in situ acetylation of the hydroxyl group in the presence of DMAP and acetic anhydride. All the products were obtained in good yields and in good diastereoselectivity, in particular, compound **6c** was isolated as single diastereoisomer. A different behavior was observed using the silyl enol ether **2e**. In fact, although the reaction seems to work, the acetylated product **6f** resulted unstable in the purification step, affording 40% yield of a diastereomeric mixture (63:37).

Table 3



1 **2d** = R″ = R‴ = Me; **2e** = R″ = H; R‴ = $CH_3(CH_2)_5$

R	R″	R‴		Yield[a] (%) of **6**	Diastereomeric ratio
Et	Me	Me	**6a**	80	78:22
Bu	Me	Me	**6b**	83	79:21
Ph	Me	Me	**6c**	47[b]	100:0
$PhCH_2CH_2$	Me	Me	**6d**	79	73:27
$MeOCO(CH_2)_4$	Me	Me	**6e**	76	80:20
Bu	$CH_3(CH_2)_5$	H	**6f**	40	63:37

[a] Yield of pure isolated product.
[b] The addition of Bu_4NF was performed at −45 °C, and then the temperature was left to increase to 0 °C over 5 h and, finally, DMAP and Ac_2O were added.

3. Conclusion

In conclusion, we have found new procedures for the preparation of both hexahydro-4*H*-benzoxazine-2-oxides and a new class of polyfunctionalized β-nitro esters, from common starting materials, simply by changing the nature of the silyl enol ethers. The procedure shows good yields and good chemoselectivity and, in addition, represents an extension of the chemical versatility of an emerging class of key building blocks such as β-nitroacrylates.

4. Experimental

4.1. General

^1H NMR spectra were recorded at 400 MHz on a Varian Mercury Plus 400 in $CDCl_3$ as solvent. ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$ as solvent. Microanalyses were performed with a CHNS-O analyzer Model EA 1108 from Fisons Instruments. IR spectra were recorded with a Perkin–Elmer Paragon 500 FT-IR. 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). β-Nitroacrylates were prepared by the standard procedure.[3a]

4.2. Typical procedure for the synthesis of compounds 3a–j

β-Nitroacrylate **1** (1.0 mmol) was dissolved in 10 mL of dry CH_2Cl_2 and the solution was cooled, under a nitrogen atmosphere, to −45 °C. Then, silyl enol ether **2a**–**c** (1.3 mmol) was added to the reaction mixture, followed by a solution of 1 M Bu_4NF (THF, 1.95 mmol) that was slowly dropped (over 15 min). The reaction was stirred for the appropriate time (TLC), and then treated with 2 M aq HCl (10 mL), followed by the separation of the two layers. The aqueous phase was extracted with CH_2Cl_2 (2×10 mL) and the collected organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure and the crude product **3** was purified by flash column chromatography (cyclohexane–ethyl acetate).

4.2.1. Ethyl 3-nitro-2-(2-oxo-2-phenylethyl)pentanoate, ***3a***

Yield: 94%. Yellow oil. IR (cm^{-1}, neat): 1736, 1711, 1556, 1362, 1024. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.97–1.05 (m, 3H), 1.20–1.29 (m, 3H), 1.76–1.98 (m, 1H), 2.04–2.21 (m, 1H), 3.02–3.11 (m, 0.5H), 3.30 (dd, 0.5H, *J*=4.2, 18.2 Hz), 3.51–3.75 (m, 2H), 4.11–4.27 (m, 2H), 4.78–4.89 (m, 1H), 7.42–7.51 (m, 2H), 7.54–7.63 (m, 1H), 7.91–7.98 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.6, 10.7, 14.2, 14.3, 24.6, 25.2, 36.6, 36.7, 43.2, 43.9, 62.0, 62.1, 89.6, 90.0, 128.3, 128.4, 128.9, 129.0, 133.8, 133.9, 136.2, 136.3, 170.8, 171.2, 196.8, 196.9. GC–MS (70 eV) *m*/*z*: 246 (8), 217 (5), 201 (16), 173 (10), 105 (100), 77 (66), 51 (10), 29 (9). Anal. Calcd for $C_{15}H_{19}NO_5$ (293.32): C, 61.42; H, 6.53; N, 4.78. Found: C, 61.98; H, 6.82; N, 4.56.

4.2.2. Ethyl 3-nitro-2-(2-oxo-2-phenylethyl)-5-phenylpentanoate, ***3b***

Yield: 87%. Yellow oil. IR (cm^{-1}, neat): 1735, 1707, 1557, 1364, 1018. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.16–1.26 (m, 3H), 2.00–2.17 (m, 1H), 2.41–2.57 (m, 1H), 2.57–2.70 (m, 1H), 2.71–2.82 (m, 1H), 3.06 (d, 0.5H, *J*=14.9 Hz), 3.21 (dd, 0.5H, *J*=4.3, 18.0 Hz), 3.53–3.66 (m, 1.5H), 3.71–3.78 (m, 0.5H), 4.11–4.21 (m, 2H), 4.83–4.96 (m, 1H), 7.13–7.35 (m, 5H), 7.47 (t, 2H, *J*=7.7 Hz), 7.56–7.62 (m, 1H), 7.94 (d, 2H, *J*=7.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 14.2, 32.2, 32.3, 32.6, 32.7, 36.4, 36.5, 43.5, 43.6, 62.0, 62.1, 87.2, 87.5, 126.8, 126.9, 128.3, 128.4, 128.6, 128.7, 128.9, 129.0, 133.8, 133.9, 136.1, 136.2, 139.6, 139.7, 170.4, 170.5, 196.7, 196.8. GC–MS (70 eV) *m*/*z*: 275 (10), 187 (16), 105 (100), 91 (44), 77 (48), 51 (7). Anal. Calcd for $C_{21}H_{23}NO_5$ (369.16): C, 68.28; H, 6.28; N, 3.79. Found: C, 68.57; H, 6.54; N, 3.45.

4.2.3. 1-Ethyl 8-methyl 3-nitro-2-(2-oxo-2-phenylethyl)-octanedioate, ***3c***

Yield: 91%. Yellow oil. IR (cm^{-1}, neat): 1736, 1709, 1555, 1367, 1023. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.19–1.28 (m, 3H), 1.33–1.47 (m, 2H), 1.56–1.88 (m, 3H), 2.06–2.20 (m, 1H), 2.31 (t, 2H, *J*=7.3 Hz), 3.05 (d, 0.5H, *J*=14.5 Hz), 3.28 (dd, 0.5H, *J*=4.7, 18.0 Hz), 3.51–3.74 (m, 2H), 3.65 (s, 1.5H), 3.66 (s, 1.5H), 4.12–4.24 (m, 2H), 4.84–4.95 (m, 1H), 7.43–7.51 (m, 2H), 7.55–7.62 (m, 1H), 7.91–7.98 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.2, 14.3, 24.4, 25.6, 30.8, 31.3, 33.7, 36.6, 36.7, 43.4, 44.0, 51.9, 54.0, 62.1, 87.9, 88.3, 128.4, 129.0, 133.9, 136.1, 136.2, 170.6, 171.0, 173.8, 196.8. GC–MS (70 eV) *m*/*z*: 379 (1), 333 (3), 287 (15), 255 (17), 105 (100), 91 (6), 77 (70). Anal. Calcd for $C_{19}H_{25}NO_7$ (379.40): C, 60.15; H, 6.64; N, 3.69. Found: C, 60.47; H, 6.91; N, 3.47.

4.2.4. Ethyl 3-nitro-2-(2-oxo-2-phenylethyl)heptanoate, ***3d***

Yield: 94%. Yellow oil. IR (cm^{-1}, neat): 1738, 1708, 1558, 1365, 1021. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.85–0.96 (m, 3H), 1.21–1.28 (m, 3H), 1.29–1.42 (m, 4H), 1.70–1.86 (m, 1H), 2.04–2.19 (m, 1H), 3.06 (d, 0.5H, *J*=14.5 Hz), 3.28 (dd, 0.5H, *J*=4.3, 18.2 Hz), 3.51–3.76 (m, 2H), 4.10–4.27 (m, 2H), 4.86–4.94 (m, 1H), 7.43–7.51 (m, 2H), 7.55–7.62 (m, 1H), 7.92–7.99 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 14.2, 14.3, 22.2, 22.3, 28.1, 28.2, 30.7, 31.3, 36.5, 36.6, 43.5, 44.1, 62.0, 88.2, 88.5, 128.3, 128.4, 128.9, 129.0, 133.8, 133.9, 136.2, 136.3, 170.8, 171.1, 196.9. GC–MS (70 eV) *m*/*z*: 275 (6), 229 (15), 201 (14), 105 (100), 77 (40). Anal. Calcd for $C_{17}H_{23}NO_5$ (321.37): C, 63.54; H, 7.21; N, 4.36. Found: C, 63.21; H, 7.01; N, 4.61.

4.2.5. Ethyl 2-(1-nitroethyl)-4-oxopentanoate, ***3e***

Yield: 75%. Yellow oil. IR (cm^{-1}, neat): 1739, 1709, 1555, 1366, 1025. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.21–1.29 (m, 3H), 1.52 (d, 1.5H, *J*=7.3 Hz), 1.55 (d, 1.5H, *J*=6.9 Hz), 2.19 (s, 1.5H), 2.20 (s, 1.5H), 2.51 (dd, 0.5H, *J*=3.4, 18.0 Hz), 2.66 (dd, 0.5H, *J*=4.7, 18.0 Hz), 2.93–3.08 (m, 1H), 3.36–3.47 (m, 0.5H), 3.56–3.63 (m, 0.5H), 4.07–4.27 (m, 2H), 4.86–4.98 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.2, 16.4, 16.9, 30.1, 30.2, 40.5, 43.7, 44.3, 61.9, 62.0, 82.2, 82.6, 170.7, 170.8, 205.2, 205.3. GC–MS (70 eV) *m*/*z*: 172 (5), 141 (9), 125 (48), 97 (40), 81 (13), 73 (17), 55 (35), 43 (100), 29 (31). Anal. Calcd for $C_9H_{15}NO_5$ (217.22): C, 49.76; H, 6.96; N, 6.45. Found: C, 50.12; H, 7.21; N, 6.19.

4.2.6. Ethyl 3-nitro-2-(2-oxopropyl)-5-phenylpentanoate, ***3f***

Yield: 93%. Yellow oil. IR (cm^{-1}, neat): 1737, 1712, 1558, 1366, 1022. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.17–1.27 (m, 3H), 1.19–2.05 (m, 1H), 2.18 (s, 3H), 2.32–2.78 (m, 4H), 2.95–3.07 (m, 1H), 3.36–3.44 (m, 0.5H), 3.50–3.57 (m, 0.5H), 4.08–4.21 (m, 2H), 4.71–4.86 (m, 1H), 7.10–7.42 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 14.2, 30.2, 30.3, 32.2, 32.3, 32.4, 33.1, 40.8, 40.9, 43.3, 43.6, 62.1, 86.9, 87.2, 126.8, 126.9, 128.6, 128.7, 129.0, 139.5, 139.6, 170.4, 170.8, 205.2, 205.3. GC–MS (70 eV) *m*/*z*: 213 (23), 171 (30), 143 (25), 129 (46), 117 (27), 91 (100), 79 (11), 65 (25), 43 (96), 29 (18). Anal. Calcd for $C_{16}H_{21}NO_5$ (307.34): C, 62.53; H, 6.89; N, 4.56. Found: C, 62.83; H, 7.05; N, 4.32.

4.2.7. 1-Ethyl 8-methyl 3-nitro-2-(2-oxopropyl)octanedioate, ***3g***

Yield: 87%. Yellow oil. IR (cm^{-1}, neat): 1735, 1560, 1364, 1020. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.20–1.28 (m, 3H), 1.29–1.42 (m, 2H), 1.54–1.77 (m, 3H), 1.98–2.12 (m, 1H), 2.17 (s, 1.2H), 2.18 (s, 1.8H), 2.29 (t, 2H, *J*=7.3 Hz), 2.52 (dd, 0.4H, *J*=3.0, 18.0 Hz), 2.69 (dd, 0.6H, *J*=4.3, 18.0 Hz), 2.91–3.06 (m, 1H), 3.29–3.37 (m, 0.4H), 3.44–3.54 (m, 0.6H), 3.64 (s, 3H), 4.10–4.22 (m, 2H), 4.72–4.83 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 14.2, 24.3, 25.5, 25.6, 30.1, 30.2, 30.4, 31.1, 33.6, 40.8, 40.9, 43.1, 43.6, 51.8, 62.0, 87.6, 87.8, 170.4, 170.8, 173.6, 173.7, 205.1, 205.2. GC–MS (70 eV) *m*/*z*: 225 (21), 193 (46), 165 (33), 149 (43), 123 (36), 95 (29), 81 (26), 67 (18), 55 (28), 43 (100), 29 (22). Anal. Calcd for $C_{14}H_{23}NO_7$ (317.33): C, 52.99; H, 7.31; N, 4.41. Found: C, 53.24; H, 7.11; N, 4.18.

4.2.8. Ethyl 5,5-dimethyl-2-(1-nitroethyl)-4-oxohexanoate, ***3h***

Yield: 72%. Yellow oil. IR (cm^{-1}, neat): 1738, 1709, 1556, 1367, 1023. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.12 (s, 4.5H), 1.13 (s, 4.5H), 1.19–1.25 (m, 3H), 1.51 (d, 1.5H, *J*=6.8 Hz), 1.53 (d, 1.5H, *J*=7.3 Hz), 2.51 (dd, 0.5H, *J*=3.8, 18.0 Hz), 2.71 (dd, 0.5H, *J*=4.3, 18.3 Hz), 3.00–3.15 (m, 1H), 3.38–3.45 (m, 0.5H), 3.53–3.60 (m, 0.5H), 4.06–4.23 (m, 2H), 4.86–4.96 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.2, 14.3, 16.6, 17.0, 26.6, 26.7, 34.5, 34.6, 43.8, 44.3, 44.4, 61.8, 82.4, 82.9, 170.8, 170.9, 212.8. GC–MS (70 eV) *m*/*z*: 214 (5), 202 (50), 167 (17), 155 (25), 127 (46), 99 (27), 57 (100), 41 (32), 29 (25). Anal. Calcd for $C_{12}H_{21}NO_5$ (259.30): C, 55.58; H, 8.16; N, 5.40. Found: C, 55.83; H, 8.42; N, 5.19.

4.2.9. Ethyl 5,5-dimethyl-2-(1-nitropropyl)-4-oxohexanoate, ***3i***

Yield: 88%. Yellow oil. IR (cm^{-1}, neat): 1738, 1708, 1555, 1368, 1021. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.95–1.02 (m, 3H), 1.14 (s, 4.5H), 1.16 (s, 4.5H), 1.22–1.29 (m, 3H), 1.70–1.87 (m, 1H), 1.98–2.15 (m, 1H), 2.55 (dd, 0.5H, *J*=3.4, 18.0 Hz), 2.79 (dd, 0.5H, *J*=4.7, 18.3 Hz), 3.02–3.17 (m, 1H), 3.34–3.42 (m, 0.5H), 3.47–3.55 (m, 0.5H), 4.09–4.25 (m, 2H), 4.68–4.78 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.6, 10.7, 14.2, 14.3, 24.5, 25.1, 26.6, 26.7, 34.9, 35.0, 43.0, 43.7, 44.3, 61.9, 89.6, 90.0, 170.8, 171.2, 212.9, 213.0. GC–MS (70 eV) *m*/*z*: 216 (46), 181 (12), 169 (22), 141 (31), 113 (27), 57 (100), 41 (26), 29 (13). Anal. Calcd for $C_{13}H_{23}NO_5$ (273.33): C, 57.13; H, 8.48; N, 5.12. Found: C, 57.44; H, 8.75; N, 4.97.

4.2.10. Ethyl 5,5-dimethyl-2-(1-nitro-3-phenylpropyl)-4-oxohexanoate, ***3j***

Yield: 89%. Yellow oil. IR (cm^{-1}, neat): 1738, 1709, 1556, 1368, 1022. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.10–1.27 (m, 12H), 1.92–2.07 (m, 1H), 2.28–2.48 (m, 1H), 2.50–2.79 (m, 3H), 3.02–3.17 (m, 1H), 3.38–3.45 (m, 0.5H), 3.49–3.57 (m, 0.5H), 4.07–4.22 (m, 2H), 4.71–4.87 (m, 1H), 7.11–7.36 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 14.2, 26.6, 26.7, 32.2, 32.3, 32.6, 33.3, 34.8, 34.9, 43.3, 43.8, 44.3, 61.9, 87.2, 87.5, 126.8, 126.9, 128.6, 128.7, 128.9, 139.5, 139.7, 170.5, 170.9, 212.8. GC–MS (70 eV) *m*/*z*: 301 (3), 255 (17), 199 (9), 171 (21), 143 (23), 129 (21), 117 (28), 91 (100), 57 (94), 41 (18), 29 (11). Anal. Calcd for $C_{19}H_{27}NO_5$ (349.42): C, 65.31; H, 7.79; N, 4.01. Found: C, 65.61; H, 7.96; N, 3.88.

4.3. Typical procedure for the synthesis of compounds 6a–f

β-Nitroacrylate **1** (1.0 mmol) was dissolved in dry CH_2Cl_2 (10 mL) and the solution was cooled, under a nitrogen atmosphere, to −45 °C. Then, silyl enol ether **2d** or **2e** (1.3 mmol) was added to the reaction mixture, followed by a solution of 1 M Bu_4NF (THF, 1.95 mmol) that was slowly dropped (over 15 min). The solution was stirred for 1 h at the same temperature, and then DMAP (3 mmol) and dry Ac_2O (3 mmol) were added in sequence. The

reaction was stirred for 1 h, and then was treated with 2 M aq HCl (10 mL), followed by the separation of the two layers. The aqueous phase was extracted with CH_2Cl_2 (2×10 mL) and the collected organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated under vacuum and the crude product **6** was purified by flash column chromatography (cyclohexane–ethyl acetate).

4.3.1. 6-Acetoxy-4-(ethoxycarbonyl)-3-ethyl-5,5-dimethyl-5,6-dihydro-4H-1,2-oxazine 2-oxide, **6a** (dr=78:22)

Major diastereomer. Yield: 62%. Yellow solid, mp=42–44 °C. IR (cm^{-1}, Nujol): 1759, 1725, 1616, 1455, 1217. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.10–1.17 (m, 9H), 1.30 (t, 3H, J=7.3 Hz), 2.13 (s, 3H), 2.18–2.30 (m, 1H), 2.48–2.62 (m, 1H), 3.47 (s, 1H), 4.19–4.29 (m, 2H), 6.17 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.4, 14.4, 20.9, 22.0, 23.4, 26.1, 33.4, 50.3, 62.0, 98.3, 120.5, 168.6, 168.7. API-ES (m/z): 310 (M^++Na), 326 (M^++K), 333 (M^++2Na), 597 (2 M^++Na). Anal. Calcd for $C_{13}H_{21}NO_6$ (287.31): C, 54.35; H, 7.37; N, 4.88. Found: C, 54.68; H, 7.56; N, 4.95.

Minor diastereomer. Yield: 18%. Yellow solid, mp=105–107 °C. IR (cm^{-1}, Nujol): 1756, 1720, 1622, 1451, 1219. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.10–1.16 (m, 6H), 1.25 (s, 3H), 1.31 (t, 3H, J=7.3 Hz), 2.08 (s, 3H), 2.11–2.24 (m, 1H), 2.61–2.73 (m, 1H), 3.14 (s, 1H), 4.08–4.18 (m, 1H), 4.23–4.33 (m, 1H), 6.10 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.4, 14.4, 20.9, 21.4, 26.6, 26.7, 33.4, 50.8, 61.9, 98.0, 120.1, 168.2, 168.9. API-ES (m/z): 310 (M^++Na), 326 (M^++K), 333 (M^++2Na), 597 ($2M^+$+Na). Anal. Calcd for $C_{13}H_{21}NO_6$ (287.31): C, 54.35; H, 7.37; N, 4.88. Found: C, 54.53; H, 7.54; N, 4.59.

4.3.2. 6-Acetoxy-3-butyl-4-(ethoxycarbonyl)-5,5-dimethyl-5,6-dihydro-4H-1,2-oxazine 2-oxide, **6b** (dr=79:21)

*Major diastereom*er. Yield: 65%. Yellow waxy solid. IR (cm^{-1}, neat): 1757, 1723, 1620, 1453, 1218. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.91 (t, 3H, J=7.3 Hz), 1.13 (s, 3H), 1.14 (s, 3H), 1.26–1.42 (m, 5H), 1.44–1.69 (m, 2H), 2.05–2.17 (m, 1H), 2.12 (s, 3H), 2.60–2.70 (m, 1H), 3.45 (s, 1H), 4.17–4.31 (m, 2H), 6.17 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 14.5, 21.0, 22.1, 22.6, 23.5, 26.0, 32.1, 33.5, 50.8, 62.1, 98.3, 119.8, 168.6, 168.7. API-ES (m/z): 338 (M^++Na), 354 (M^++K), 361 (M^++2Na), 653 ($2M^+$+Na). Anal. Calcd for $C_{15}H_{25}NO_6$ (315.36): C, 57.13; H, 7.99; N, 4.44. Found: C, 56.89; H, 8.21; N, 4.19.

Minor diastereomer. Yield 18%. Yellow solid, mp=110–113 °C. IR (cm^{-1}, Nujol): 1750, 1723, 1619, 1453, 1223. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.92 (t, 3H, J=7.3 Hz), 1.14 (s, 3H), 1.26 (s, 3H), 1.27–1.41 (m, 5H), 1.42–1.65 (m, 2H), 1.99–2.07 (m, 1H), 2.08 (s, 3H), 2.65–2.75 (m, 1H), 3.13 (s, 1H), 4.08–4.18 (m, 1H), 4.22–4.34 (m, 1H), 6.10 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.8, 14.2, 20.7, 21.2, 22.6, 25.9, 26.6, 32.7, 33.2, 51.0, 61.7, 97.8, 119.2, 168.0, 168.6. API-ES (m/z): 338 (M^++Na), 354 (M^++K), 361 (M^++2Na), 653 ($2M^+$+Na). Anal. Calcd for $C_{15}H_{25}NO_6$ (315.36): C, 57.13; H, 7.99; N, 4.44. Found: C, 57.44; H, 8.12; N, 4.21.

4.3.3. 6-Acetoxy-4-(ethoxycarbonyl)-5,5-dimethyl-3-phenyl-5,6-dihydro-4H-1,2-oxazine 2-oxide, **6c** (dr=100:0)

Yield: 47%. White solid, mp=147–150 °C. IR (cm^{-1}, Nujol): 1732, 1593, 1456, 1225. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.94 (t, 3H, J=7.3 Hz), 1.24 (s, 3H), 1.25 (s, 3H), 2.15 (s, 3H), 3.88–4.04 (m, 2H), 4.06 (s, 1H), 6.29 (s, 1H), 7.30–7.43 (m, 3H), 7.72–7.79 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 21.0, 22.4, 23.6, 33.6, 50.6, 61.7, 98.4, 117.0, 127.7, 128.5, 129.6, 132.1, 168.6, 168.8. API-ES (m/z): 358 (M^++Na), 374 (M^++K), 381 (M^++2Na), 693 ($2M^+$+Na). Anal. Calcd for $C_{17}H_{21}NO_6$ (335.35): C, 60.89; H, 6.31; N, 4.18. Found: C, 60.69; H, 6.38; N, 4.12.

4.3.4. 6-Acetoxy-4-(ethoxycarbonyl)-5,5-dimethyl-3-phenethyl-5,6-dihydro-4H-1,2-oxazine 2-oxide, **6d** (dr=73:27)

Major diastereomer. Yield: 58%. White solid, mp=93–95 °C. IR (cm^{-1}, Nujol): 1755, 1723, 1623, 1457, 1222. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.04 (s, 3H), 1.13 (s, 3H), 1.31 (t, 3H, J=7.3 Hz), 2.07 (s, 3H), 2.39–2.49 (m, 1H), 2.83–3.08 (m, 3H), 3.22 (s, 1H), 4.24 (q, 2H, J=7.3 Hz), 6.16 (s, 1H), 7.18–7.32 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.4, 20.9, 22.0, 23.3, 29.6, 33.3, 34.1, 50.9, 62.0, 98.2, 118.9, 126.6, 128.5, 128.8, 140.5, 168.6, 168.7. API-ES (m/z): 749 ($2M^+$+Na). Anal. Calcd for $C_{19}H_{25}NO_6$ (363.40): C, 62.80; H, 6.93; N, 3.85. Found: C, 63.02; H, 7.06; N, 3.61.

Minor diastereomer. Yield: 21%. Yellow solid, mp=137–139 °C. IR (cm^{-1}, Nujol): 1750, 1718, 1621, 1449, 1216. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.96 (s, 3H), 1.03 (s, 3H), 1.29 (t, 3H, J=7.3 Hz), 2.08 (s, 3H), 2.21–2.33 (m, 1H), 2.71 (s, 1H), 2.83–2.97 (m, 1H), 3.00–3.11 (m, 2H), 4.07–4.17 (m, 1H), 4.21–4.31 (m, 1H), 6.01 (s, 1H), 7.16–7.35 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.4, 20.8, 21.2, 26.4, 29.4, 33.5, 35.0, 52.2, 61.9, 98.0, 118.9, 126.8, 128.8, 128.9, 140.2, 168.2, 168.8. API-ES (m/z): 749 ($2M^+$+Na). Anal. Calcd for $C_{19}H_{25}NO_6$ (363.40): C, 62.80; H, 6.93; N, 3.85. Found: C, 63.04; H, 7.09; N, 3.63.

4.3.5. 6-Acetoxy-4-(ethoxycarbonyl)-3-(5-methoxy-5-oxopentyl)-5,5-dimethyl-5,6-dihydro-4H-1,2-oxazine 2-oxide, **6e** (dr=80:20)

Major diastereomer. Yield: 61%. Yellow oil. IR (cm^{-1}, neat): 1749, 1718, 1622, 1455, 1224. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.12 (s, 6H), 1.29 (t, 3H, J=7.3 Hz), 1.50–1.76 (m, 4H), 2.08–2.19 (m, 1H), 2.12 (s, 3H), 2.31 (dt, 2H, J=1.7, 7.3 Hz), 2.58–2.68 (m, 1H), 3.45 (s, 1H), 3.63 (s, 3H), 4.16–4.29 (m, 2H), 6.15 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.4, 20.9, 22.0, 23.3, 23.4, 24.5, 31.9, 33.4, 33.7, 50.6, 51.7, 62.0, 98.3, 119.2, 168.5, 168.7, 173.8. API-ES (m/z): 396 (M^++Na), 412 (M^++K), 419 (M^++2Na), 769 ($2M^+$+Na). Anal. Calcd for $C_{17}H_{27}NO_8$ (373.40): C, 54.68; H, 7.29; N, 3.75. Found: C, 54.87; H, 7.51; N, 3.56.

Minor diastereomer. Yield: 19%. Yellow waxy solid. IR (cm^{-1}, neat): 1750, 1718, 1621, 1449, 1216. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.11 (s, 3H), 1.24 (s, 3H), 1.28 (t, 3H, J=7.3 Hz), 1.49–1.69 (m, 4H), 2.00–2.10 (m, 1H), 2.06 (s, 3H), 2.32 (t, 2H, J=7.3 Hz), 2.60–2.72 (m, 1H), 3.13 (s, 1H), 3.64, (s, 3H), 4.06–4.17 (m, 1H), 4.20–4.31 (m, 1H), 6.07 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.3, 20.8, 21.4, 23.4, 24.7, 26.7, 32.8, 33.4, 33.7, 51.2, 51.7, 61.9, 98.0, 118.9, 168.1, 168.8, 173.8. API-ES (m/z): 396 (M^++Na), 412 (M^++K), 419 (M^++2Na), 769 ($2M^+$+Na). $C_{17}H_{27}NO_8$ (373.40): C, 54.68; H, 7.29; N, 3.75. Found: C, 54.45; H, 7.08; N, 3.89.

4.3.6. 6-Acetoxy-3-butyl-4-(ethoxycarbonyl)-5-hexyl-5,6-dihydro-4H-1,2-oxazine 2-oxide, **6f** (dr=63:37)

Major diastereomer. Yield: 25%. Yellow oil. IR (cm^{-1}, neat): 1735, 1622, 1551, 1213. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.81–0.95 (m, 6H), 1.15–1.51 (m, 16H), 1.59–1.76 (m, 1H), 2.11 (s, 3H), 2.12–2.22 (m, 1H), 2.47–2.62 (m, 2H), 3.25 (d, 1H, J=10.7 Hz), 4.13–4.30 (m, 2H), 6.55 (d, 1H, J=2.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 14.2, 14.3, 20.9, 22.5, 22.6, 26.1, 26.2, 29.2, 29.5, 31.0, 31.6, 36.4, 46.8, 62.4, 93.1, 119.2, 168.7, 169.9. API-ES (m/z): 765 ($2M^+$+Na). Anal. Calcd for $C_{19}H_{33}NO_6$ (371.47): C, 61.43; H, 8.95; N, 3.77. Found: C, 61.65; H, 9.08; N, 3.58.

Minor diastereomer. Yield: 15%. Yellow oil. IR (cm^{-1}, neat): 1738, 1618, 1556, 1217. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.79–0.99 (m, 6H), 1.15–1.68 (m, 17H), 2.00 (s, 3H), 2.19–2.36 (m, 1H), 2.48–2.58 (m, 1H), 2.70–2.81 (m, 1H), 3.16 (br s, 1H), 4.06–4.19 (m, 1H), 4.21–4.33 (m, 1H), 6.38 (d, 1H, J=2.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 14.2, 14.3, 20.9, 22.7, 22.8, 26.1, 26.6, 29.1, 30.5, 31.7, 33.3, 35.2, 44.0, 62.1, 95.7, 119.2, 168.3, 169.6. API-ES (m/z): 765 ($2M^+$+Na). Anal. Calcd for $C_{19}H_{33}NO_6$ (371.47): C, 61.43; H, 8.95; N, 3.77. Found: C, 61.71; H, 9.14; N, 3.60.

Acknowledgements

Financial support from the University of Camerino and MUR-Italy (National Project 'Sintesi organiche ecosostenibili mediate da nuovi sistemi catalitici').

References and notes

1. Perlmutter, P. *Conjugated Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992.
2. Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: NewYork, NY, 2001; pp 70–103.
3. (a) Ballini, R.; Fiorini, D.; Palmieri, A. *Tetrahedron Lett.* **2004**, *45*, 7027; (b) Ballini, R.; Fiorini, D.; Palmieri, A. *Tetrahedron Lett.* **2005**, *46*, 1245; (c) Ballini, R.; Araújo-Bazán, N.; Bosica, G.; Palmieri, A. *Tetrahedron Lett.* **2008**, *49*, 3865; (d) Ballini, R.; Gabrielli, S.; Palmieri, A.; Petrini, M. *Tetrahedron* **2008**, *64*, 5435.
4. (a) Nielsen, A. T.; Archibald, T. G. *Tetrahedron* **1970**, *26*, 3475; (b) Miyashita, M.; Yanami, T.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1976**, *98*, 4679; (c) Daneo, S.; Pitacco, G.; Risaliti, A.; Valentin, E. *Tetrahedron* **1982**, *38*, 1499; (d) Miyashita, M.; Yanami, T.; Kumazawa, T.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1984**, *106*, 2149; (e) Yoshikoshi, A.; Miyashita, M. *Acc. Chem. Res.* **1985**, *18*, 284; (f) Varma, R. S.; Kabalka, G. W. *Heterocycles* **1986**, *24*, 2645; (g) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1993**, *58*, 3857; (h) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1995**, *60*, 3221; (i) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137; (j) Uittenbogaard, R. M.; Seerden, J.-P. G.; Sheeren, H. W. *Tetrahedron* **1997**, *53*, 11929; (k) Denmark, S. E.; Dixon, J. A. *J. Org. Chem.* **1998**, *63*, 6178; (l) Denmark, S. E.; Hurd, A. R. *J. Org. Chem.* **1998**, *63*, 3045; (m) Kuster, G. J.; Kalmoua, F.; De Gelder, R. H.; Scheeren, W. *Chem. Commun.* **1999**, 855; (n) Denmark, S. E.; Seierstad, M. *J. Org. Chem.* **1999**, *64*, 1610; (o) Avalos, M.; Babiano, R.; Cintas, P.; Higes, F. J.; Jiménez, J. L.; Palacios, J. C.; Silva, M. A. *J. Org. Chem.* **1999**, *64*, 1494; (p) Benedetti, F.; Drioli, S.; Nitti, P.; Pitacco, G.; Valentin, E. *Arkivoc* **2001**, 140; (q) Denmark, S. E.; Cottell, J. J. In *The Chemistry of Heterocyclic Compounds: Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley-Interscience: New York, NY, 2002; pp 83–167; (r) Tsoungas, P. G. *Heterocycles* **2002**, *57*, 1149.
5. (a) Seebach, D.; Brook, M. A. *Helv. Chim. Acta* **1985**, *68*, 319; (b) Brook, M. A.; Seebach, D. *Can. J. Chem.* **1987**, *65*, 850; (c) Seebach, D.; Lyapkalo, I. M.; Dahinden, R. *Helv. Chim. Acta* **1999**, *82*, 1829.
6. Denmark, S. E.; Xie, M. *J. Org. Chem.* **2007**, *72*, 7050.
7. Bellachioma, G.; Castrica, L.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Green Chem.* **2008**, *10*, 327.
8. (a) Bakuzis, P.; Bakuzis, M. L. F.; Weingartner, T. F. *Tetrahedron Lett.* **1978**, *19*, 2371; (b) Seebach, D.; Colvin, E. W.; Lehr, F. *Chimia* **1979**, *1*, 33.
9. Miyakoshi, T.; Saito, S.; Kumanotani, J. *Chem. Lett.* **1981**, 1677.
10. (a) Fuso, R.; Rossi, S. *Chem. Ind. (London)* **1957**, 1650; (b) Gelbart, G. *Synthesis* **1977**, 113.
11. Ballini, R.; Palmieri, A. *Adv. Synth. Catal.* **2006**, *348*, 1154.
12. Ballini, R.; Bosica, G.; Palmieri, A.; Petrini, M.; Pierantozzi, C. *Tetrahedron* **2003**, *59*, 7283.
13. We tried to use, as source of fluoride, CsF or KF on basic alumina without any success.