Stereoselective Nitroolefination of Active Methine of Various Carbonyl Compounds with β-Nitroenamines

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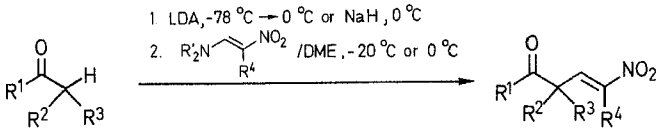
Enolates of carbonyl compounds having a methine α-carbon undergo 2-nitro-1-alkenylation (nitroolefination) to form quarternary C-atom next to the carbonyl group on reaction with β-nitroenamines *via* an addition elimination process. The geometry of the resulting nitroolefins proved to be of the *E* type.

The chemistry of β-nitroenamines has been extensively investigated and the utility of these compounds as intermediates in synthesis has been well established.[1] For instance, β-nitroenamines can be converted into synthetically useful nitroolefins by reaction with a nucleophile such as alkylmetal reagents[2] or indole[3] *via* an addition-elimination process. Also, we recently reported a new method for the asymmetric nitro-olefination of α-substituted lactones using a chiral nitroenamine.[4] Carbonyl compounds having a methyl or methylene group in the α-position react with β-nitroenamines in the presence of a base to give aci-nitroethylidene derivatives which can be converted into the corresponding α,β-unsaturated 1,4-dicarbonyl compounds.[5] Except for our previous paper, there is no report on the synthesis of nitroolefins from nitroenamines *via* a (formal) substitution reaction between enolates and the amino group in nitroenamines. Here, we discuss the reaction of various carbonyl compounds with β-nitroenamines as shown in Scheme **A** to examine the scope and limitation of this addition-elimination process.



Scheme **A**

The β-nitroenamines **1** and **2** (Scheme **B**) used in this reaction were easily prepared from nitroalkanes, triethyl orthoformate, and secondary amines.[6] We first compared the reactivity of two types of nitroenamines, **1** and **2a**, with the lithium enolate of 2-methylcyclohexanone (**3a**; 1.5 mol equiv). As shown in Table 1 (runs 1 and 2), both nitroenamines showed the same reactivity towards the enolate under the same conditions, enamine **2a** giving a somewhat higher yield than enamine **1**. This difference in yield may be attributed to the difference in nucleofugality[7] between dimethylamine and morpholine. We therefore used morpholinonitroenamines **2a, b, c** in the subsequent nitroolefination reactions.

The reaction of ketone enolates **3a, 3b, 4** with nitroenamines **2a** and **2b** produced the corresponding nitroolefins (runs 2–5). Enolates **5, 6, 7a, 7b** were also reactive in this *C*-(2-nitro-1-alkenylation) (runs 6–9). In the case of aldehyde enolate **5**, the crude product **12** was immediately reduced with Hantzsch ester[8] without previous purification to give the dihydro derivative **13**, because product **12** is unstable under the conditions of purification by silica gel column chromatography. The *C*-(2-nitro-1-alkenylation) of lactone enolates generally led to higher yields than the reactions of the other carbonyl enolates. In the case of

Table 1. *C*-(2-Nitro-1-alkenylation) of Enolates of Aldehydes or Ketones with β-Nitroenamines

Run	Enolate	Nitroenamine (mol equiv)	Temperature, Time	Product	Yield (%)	m.p. (°C)	Molecular Formula[a] or m.p. (°C) from Lit.
	Structure (mol equiv), M^+						
1	**3a** (1.5), Li	**1** (1.0)	−20° → −10°C, 1.5 h	**10a**	62	oil	$C_9H_{13}NO_3$ (183.2)
2	**3a** (1.5), Li	**2a** (1.0)	−20° → −10°C, 1.5 h	**10a**	77		
3	**3a** (3.0), Li	**2b** (1.0)	−70° → −20°C, 2 h	**10b**	48	81–81.5 (ether)	$C_{10}H_{15}NO_3$ (197.2)
4	**4** (1.5), Li	**2a** (1.0)	0° → r.t., 1.5 h	**11**	99	oil	$C_{13}H_{13}NO_3$[b] (231.2)
5	**3b** (1.0), Li	**2a** (1.5)	0°C, 2 h	**10c**	54	oil	$C_{11}H_{17}NO_3$ (211.2)
6	**5** (3.0), Na	**2a** (1.0)	0°C, 2 h	(**12** →) **13**	55[c]	oil	not determined
7	**6** (1.5), Li	**2a** (1.0)	−70°C, 20 min	**14**	71	oil	$C_{15}H_{19}NO_4$ (277.3)
8	**7a** (1.5), Li	**2a** (1.0)	−78° → 0°C, 2.5 h	**15a**	54	oil	$C_8H_{12}N_2O_3$ (184.2)

Table 1. (continued)

Run	Enolate Structure (mol equiv), M^+	Nitroenamine (mol equiv)	Temperature, Time	Product	Yield (%)	m.p. (°C)	Molecular Formula[a] or m.p. (°C) from Lit.
9	**7b** (1.5), Li	**2a** (1.0)	−78 °C, 40 min	**15b**	65	oil	$C_9H_{14}N_2O_3$ (198.2)
10	**8a** (1.5), Li	**2a** (1.0)	−10 °C, 30 min	**16a**	82	oil	$C_7H_9NO_4$ (171.2)
11	**8b** (1.3), Li	**2a** (1.0)	−78° → −20 °C, 4 h	**16b**	97	33.6–34.0 (ether/hexane)	$C_8H_{11}NO_4$ (185.2)
12	**9a** (1.5), Li	**2a** (1.0)	−78° → −40 °C, 4 h	**17a**	83	oil	$C_8H_{11}NO_4$ (185.2)
13	**9a** (1.5), Li	**2b** (1.0)	−55° → −20 °C, 1.5 h	**17b**	66	40–41 (ether)	$C_9H_{13}NO_4$ (199.2)
14	**9a** (1.5), Li	**2c** (1.0)	−50° → −25 °C, 50 min	**17c**	48	36–37 (ether)	$C_{10}H_{15}NO_4$ (213.2)
15	**9b** (1.5), Li	**2a** (1.0)	−78° → −40 °C, 3 h	**17d**	64	oil	$C_9H_{13}NO_4$ (199.2)
16	**9b** (1.5), Zn	**2a** (1.0)	−78° → −40 °C, 3 h	**17d**	95		
17	**9b** (1.5), Zn	**2b** (1.0)	−78° → −20 °C, 40 min	**17e**	72	oil	$C_{10}H_{15}NO_4$ (213.2)
				+ **17g**	4	71–72 (ether)	$C_{10}H_{15}NO_4$ (213.2)
18	**9b** (1.5), Zn	**2c** (1.0)	−78° → −20 °C, 1 h	**17f**	52	oil	$C_{11}H_{17}NO_4$ (227.3)
				+ **17h**	6	73–75 (ether)	$C_{11}H_{17}NO_4$ (227.3)

[a] Satisfactory microanalyses were obtained: C ±0.29, H ±0.24, N ±0.29.

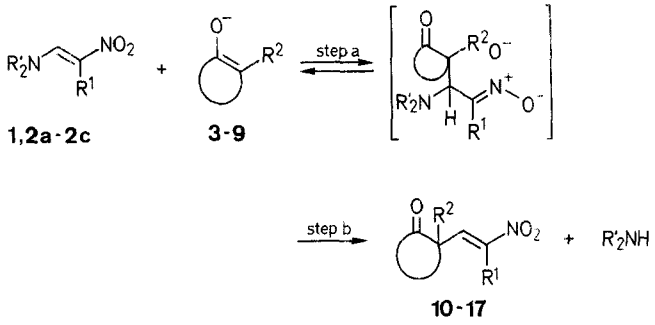
[b] C +0.41, H +0.07, N +0.39.

[c] Overall yield of **13**, based on **2a** (see separate procedure).

Table 2. Spectral Data of Compounds **10**, **11**, **14–17**

Compound	IR ($CHCl_3$) ν (cm^{-1})	UV (95% EtOH) λ_{max} (nm) (ε)	^{1}H-NMR ($CDCl_3$) δ, J (Hz)
10a	1709, 1525, 1345	229 (8500)	1.36 (s, 3H); 1.89 (m, 6H); 2.20–2.72 (m, 2H); 7.03, 7.55 (ABq, 2H, J = 13.7)
10b	1715, 1530, 1330	228 (5000), 256 (4700)	1.24 (s, 3H); 1.76 (m, 4H); 2.02 (d, 3H, J = 1.0); 2.10 (m, 2H); 2.40 (m, 2H); 7.32 (q, 1H, J = 1.0)
10c	1700, 1523, 1345	227 (4200)	1.09, 1.16, 1.33 (3s, 3H each); 1.52–2.13 (m, 6H); 6.95, 7.42 (ABq, 2H, J = 14.1)
11	1685, 1505, 1530, 1460, 1350	207 (24000), 250 (16000)	1.44 (s, 3H); 2.23 (m, 2H); 3.04 (t, 2H, J = 6.9); 6.94, 7.53 (ABq, 2H, J = 14.0); 7.08–7.60 (m, 3H); 8.04 (d, 1H, J = 7.0)
14	1722, 1523, 1345	206 (14100), 223 (9800)	1.43 (s, 9H); 1.72 (s, 3H); 7.18–7.44 (m, 5H); 6.85, 7.75 (ABq, 2H, J = 13.7)
15a	1682, 1522, 1345	206 (4500), 224 (4100)	1.39 (s, 3H); 2.15 (m, 2H); 2.90 (s, 3H); 3.40 (t, 2H, J = 6.9); 7.08, 7.31 (ABq, 2H, J = 13.7)
15b	1630, 1522, 1343	205 (9200), 225 (7500)	1.45 (s, 3H); 1.93 (m, 4H); 2.97 (s, 3H); 3.35 (br. t, 2H, J = 4.8); 7.03, 7.36 (ABq, 2H, J = 13.7)
16a	1772, 1530, 1348	229 (7400)	1.52 (s, 3H); 2.40 (m, 2H); 4.39 (t, 2H, J = 6.6 Hz); 7.11, 7.32 (ABq, 2H, J = 13.7)
16b	1770, 1532, 1345	229 (9800)	1.01 (t, 3H, J = 7.3); 1.69–2.07 (m, 2H); 2.39 (t, 2H, J = 7.0); 4.35 (t, 2H, J = 6.9); 7.11, 7.32 (ABq, 2H, J = 13.7)
17a	1723, 1525, 1346	230 (9400)	1.52 (s, 3H); 2.00 (m, 4H); 4.41 (m, 2H); 7.03, 7.32 (ABq, 2H, J = 14.0)
17b	1735, 1525, 1330	245 (5800)	1.54 (s, 3H); 2.02 (m, 4H); 2.02 (d, 3H, J = 1.0); 4.42 (m, 2H); 7.16 (q, 1H, J = 1.0)
17c	1730, 1525, 1335	246 (5400)	1.10 (t, 3H, J = 7.2); 1.54 (s, 3H); 2.02 (m, 4H); 2.66 (q, 2H, J = 7.2); 4.42 (m, 2H); 7.08 (s, 1H)
17d	1723, 1525, 1343	232 (9000)	0.97 (t, 3H, J = 7.3); 2.00 (m, 6H); 4.39 (m, 2H); 7.04, 7.30 (ABq, 2H, J = 13.7)
17e	1728, 1522, 1323	246 (3300)	1.00 (t, 3H, J = 8.0); 1.68–2.12 (m, 6H); 2.20 (d, 3H, J = 1.0); 4.41 (m, 2H); 7.13 (q, 1H, J = 1.0)
17f	1725, 1520, 1333	247 (3000)	0.99 (t, 3H, J = 8.0); 1.07 (t, 3H, J = 8.0); 1.68–2.12 (m, 6H); 2.44–2.83 (m, 2H); 4.38 (m, 2H); 7.00 (s, 1H)
17g	1720, 1521, 1346	244 (3900)	1.02 (t, 3H, J = 8.0); 1.48–2.28 (m, 6H); 2.23 (d, 3H, J = 1.3); 4.28–4.72 (m, 2H); 5.92 (q, 1H, J = 1.3)
17h	1720, 1520, 1345	242 (2900)	0.99 (t, 3H, J = 8.0); 1.11 (t, 3H, J = 8.0); 1.44–2.32 (m, 6H); 2.61 (q, 2H, J = 8.0); 4.20–4.66 (m, 2H); 5.78 (s, 1H)

enolate **9b**, zinc as a counter cation gave better results than lithium (compare run 15 and 16). Hence, in reactions with the bulkier nitroenamines **2b** and **2c** use of zinc enolate was more successful (runs 17 and 18).

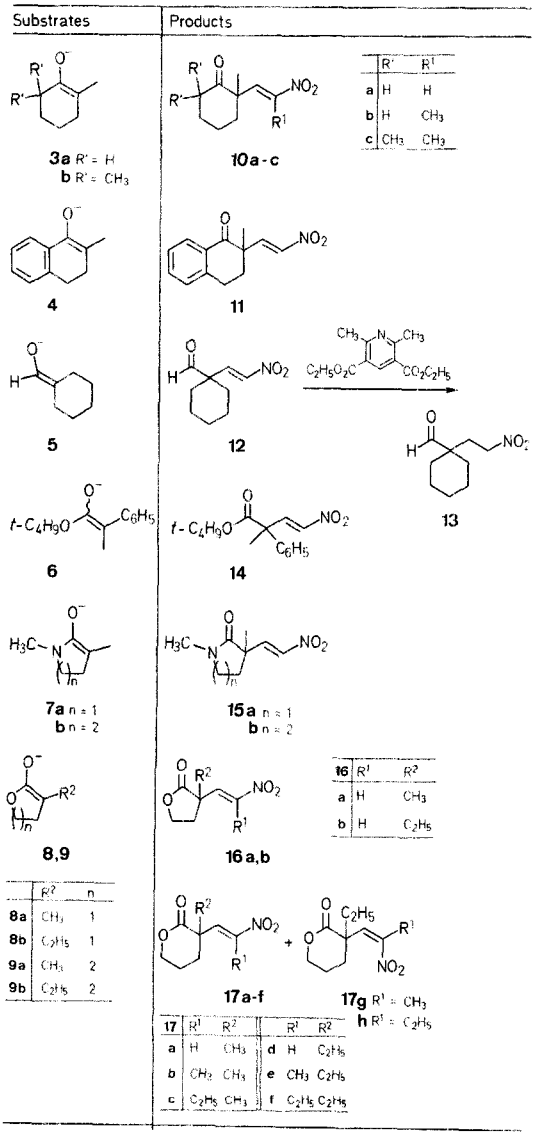


1,2a-2c 3-9 10-17

Scheme **B**

Enamines:

	R'_2N	R^1		R'_2N	R^1
1	$N(CH_3)_2$	H	2b	morpholino	CH_3
2a	morpholino	H	2c	morpholino	C_2H_5



This 2-nitro-1-alkenylation (nitroolefination) reaction is sensitive to the bulkiness of the β-nitroenamines and the yield tends to decrease as the bulkiness of the nitroenamine increases (compare runs 12–14 and 16–18). As described in our previous paper,[4] the nitroolefination of lactone enolates is a discontinuous two-step reaction (Scheme **B**). Step a is the (reversible) addition step which involves a Michael type attack of the enolate on the nitroenamine, the adduct being in equilibrium with the two substrates. Step b consists of the elimination of the amino group from the adduct under acidic conditions. The higher yield in the reaction with zinc enolate (runs 16–18) as compared with lithium enolate can be ascribed to the thermodynamic stability of the adduct by chelation of zinc ion. Whether or not an equilibrium exists in the reaction of ketone enolates and nitroenamines remains to be established.

The stereochemistry of the double bond in the nitroolefins produced was determined mainly by NMR data[9] including chemical shift, the coupling constant, and nuclear Overhauser enhancement of vinylic protons. Although this nitroolefination revealed high *E*-stereoselectivity with respect to the double bond formed, the *Z*-isomer was obtained as a minor product in the reaction with bulky substrates (runs 17 and 18).

The IR spectra were obtained on a Jasco IR-810 spectrophotometer. UV spectra were recorded on a Jasco UVIDEC-610C spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-FX 100 spectrometer. All solvents were distilled from sodium benzophenone ketyl before use.

1-Morpholino-2-nitropropene (2b):

A mixture of nitroethane (155 mL, 2.2 mol), triethyl orthoformate (128 g, 0.86 mol), morpholine (38 mL, 0.43 mol), and *p*-toluenesulfonic acid (2 g) is heated under reflux for 3 h. The volatile material is then evaporated under vacuum. The residue is diluted with CH_2Cl_2 (300 mL) and column-chromatographed on alumina (CH_2Cl_2 as eluent) to give pure **2b**; yield: 52.6 g (71%); m.p. 96.5°C (EtOH).

$C_7H_{12}N_2O_3$ (172.2) calc. C 48.83 H 7.03 N 16.27 found 48.73 7.13 16.48

IR ($CHCl_3$): ν = 1635, 1410, 1265, 1230, 1180, 1110, 1025 cm^{-1}.

UV (EtOH): λ_{max} = 373 nm (ε = 19000).

^{1}H-NMR ($CDCl_3$): δ = 2.28 (s, 3H); 3.54 (m, 4H); 3.78 (m, 4H); 8.21 (s, 1H).

1-Morpholino-2-nitro-1-butene (2c):

Prepared from 1-nitropropane (22.6 mL, 0.25 mol), triethyl orthoformate (16.5 mL, 01. mol), and morpholine (4.4 mL, 0.05 mol) as above; yield: 5.5 g (58%); m.p. 64.5°C (EtOH).

$C_8H_{14}N_2O_3$ (186.2) calc. C 51.60 H 7.58 N 15.04 found 51.36 7.71 15.17

IR ($CHCl_3$): ν = 1630, 1415, 1285, 1270, 1255, 1230, 1180, 1115, 1040 cm^{-1}.

UV (EtOH): λ_{max} = 372 nm (ε = 17100).

^{1}H-NMR ($CDCl_3$): δ = 1.12 (t, 3H, J = 8.0 Hz); 2.73 (q, 2H, J = 8.0 Hz); 3.52 (m, 4H); 3.80 (m, 4H); 8.18 (s, 1H).

2-Methyl-2-(2-nitrovinyl)-cyclohexanone (10a); Typical Procedure for Runs 1, 2, and 3:

The enol trimethylsilyl ether of 2-methylcyclohexanone (2-methyl-1-trimethylsiloxycyclohexene; 276 mg, 1.5 mmol) is added dropwise to an ethereal 1.2 molar solution of methyllithium (1.4 mL, 1.65 mmol) diluted with DME (1 mL) at room temperature, and stirring is continued for 30 min. The solution is then cooled to −20°C and added in one portion to a stirred suspension of 1-morpholino-2-nitroethylene (**2a**; 158 mg, 1.0 mmol) in DME (1 mL) at −20°C. The mixture is stirred at −20°C to −10°C for 1.5 h. It is then poured into cold 3% HCl (4 mL), and extracted with Et_2O (5 × 10 mL). The organic layer is washed with saturated NaCl solution (10 mL), dried ($MgSO_4$), and evaporated to afford a residue which is purified by column chromatography on silica gel. Elution with EtOAc/hexane (1:4) gives product **10a**; yield: 140 mg (77%); oil.

2-Methyl-2-(2-nitrovinyl)-1-tetralone (11); Typical Procedure for Runs 4, 5, 7–15:
Lithium diisopropylamide (LDA) is prepared by adding a 1.6 molar solution of buthyllithium in hexane (2.2 mL, 3.5 mmol) to a solution of diisopropylamine (0.5 mL, 3.8 mmol) in DME (5 mL) at −78 °C followed by stirring for 30 min at 0 °C. A solution of 2-methyl-1-tetralone (561 mg, 3.5 mmol) in DME (8 mL) is added dropwise to the solution of LDA at −78 °C and the mixture is stirred at −78 °C for 30 min and at 0 °C for 20 min to generate the enolate **4** which is added to a stirred suspension of 1-morpholino-2-nitroethylene (**2a**; 370 mg, 2.3 mmol) in DME (8 mL) at 0 °C. The mixture is stirred for 70 min at 0 °C, then warmed to room temperature within a 20 min period. The resulting mixture is poured into cold 0.5 normal HCl (20 mL) and extracted with Et_2O (5 × 30 mL). The extract is washed with saturated NaCl solution (30 mL), dried ($MgSO_4$), and evaporated. Chromatography of the residue on silica gel using EtOAc/hexane (1:5) as eluent gives product **11**; yield: 560 mg (99%); oil.

Zinc Enolate of 2-Ethyl-5-pentanolide (9b) (for Runs 16–18):
A 0.69 molar solution (46 mL, 32 mmol) of zinc chloride[10] in anhydrous Et_2O is added to a solution of the lithium enolate of 2-ethyl-5-pentanolide (30 mmol) in DME (60 mL) at −78 °C. Stirring for 30 min at −20 °C affords a suspension of the zinc enolate.

1-(2-Nitroethyl)cyclohexanecarboxaldehyde (13) *via* 1-(2-Nitrovinyl)-cyclohexanecarboxaldehyde (12):
To a stirred suspension of 60% sodium hydride (70 mg, washed with a small amount of DME) in DME (5 mL), a cold (0 °C) mixture of cyclohexanecarboxaldehyde (170 mg, 1.5 mmol) and 1-morpholino-2-nitroethylene (**2a**; 79 mg, 0.5 mmol) in DME (7 mL) is added dropwise at 0 °C over a period of 1.5 h. The mixture is stirred at 0 °C for 30 min, then poured into cold 0.5 normal HCl (10 mL), and extracted with Et_2O (5 × 20 mL). The extract is washed with saturated NaCl solution (20 mL), dried (Na_2SO_4), and evaporated. The residue (crude **12**; 93 mg) is dissolved in dry benzene (10 mL) and diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (Hantzsch ester; 140 mg, 0.55 mmol) and silica gel (35–70 mesh, 500 mg) are added. The mixture is stirred under reflux for 5 h in argon in the dark and filtered. The residue is washed with benzene (50 mL). The combined organic layer is washed successively with 0.5 normal HCl (2 × 10 mL) and saturated NaCl solution (10 mL), dried, and evaporated to give crude oil. Purification by silica gel column chromatography with hexane as eluent affords **13**; yield: 51 mg (55%); oil.

^{1}H-NMR ($CDCl_3$): δ = 1.27–1.98 (m, 10H); 2.22 (t, 2H, J = 8.0 Hz; 4.32 (t, 2H, J = 8.0 Hz); 9.23 (s, 1H).

Received: 24 November 1986; revised: 26 February 1987)

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