Lewis Acid Promoted Hetero Diels-Alder Cycloaddition of α -Acetoxynitroso Dienophiles

Géraldine Calvet, Marion Dussaussois, Nicolas Blanchard and Cyrille Kouklovsky*

Laboratoire de Synthèse des Substances Naturelles, Bâtiment 410
Université d'Orsay, 91400 Orsay-FRANCE

email: cykoulko@icmo.u-psud.fr

SUPPORTING INFORMATION

Experimental procedures for synthesis of and tabulated spectroscopic data for **3**, **5**, **6**, **12**, **14**, **16**, **18**, and **20** (9 pages). This material is available free of charge via the Internet at <http://pubs.acs.org>

Entry	Lewis acid	ratio 5/6	GC Yield ^a
1	TiCl ₄	12/88	9
2	Sn(OTf) ₂	30/70	9
3	SnCl ₄	60/40	11
4	PdCl ₂	3/97	15
5	PdCl ₂ (PPh ₃)	8/92	16
6	ZnBr ₂	2/98	17
7	ZnF ₂	2/98	19
8	MgCl ₂	3/97	19
9	ZrCl ₄	3/97	19
10	Sc(OTf) ₃	40/60	23
11	BF ₃ •OEt ₂	20/80	24
12	Ti(O- <i>i</i> Pr) ₄	2/98	25
13	LiBr	4/96	25
14	AgBF ₄	93/7	26
15	AgOAc	3/97	26
16	CeCl ₃	5/95	28
17	Yb(OTf) ₃	2/98	32 ^b
18	FeCl ₃	2/98	34
19	Zn(OTf) ₂	5/95	36

Table 1

^a GC yields calibrated toward an internal standard (dibutyl phthalate). See “General” for retention times of **5**, **6** and the internal standard ^b Isolated yield.

General. All reactions were conducted in flame-dried or oven dried glassware under an atmosphere of dry nitrogen. All solvents were purified before use unless otherwise indicated. Tetrahydrofuran, diethyl ether and toluene were distilled over sodium/benzophenone ketyl anion under argon. Dichloromethane was distilled over CaH_2 under argon. All other reagents were purchased and used without further purification. Molecular sieves (powdered, 4Å) was heated at 560 °C for 14 hours, cooled *in vacuo* and stored in a Schlenk under dry nitrogen. Solvent removal was performed using a rotary evaporator at reduced pressure via water aspiration. Analytical thin layer chromatography (TLC) was performed on Kieselgel 60 F₂₅₄ glass precoated with a 0.25 mm thickness of silica gel. The TLC plates were visualized by shortwave UV light, potassium permanganate, *p*-anisaldehyde or ceric ammonium molybdate stain. Flash chromatography was performed according to the method of Still¹ on Kieselgel 60 (230–400 mesh) silica gel. Infrared spectra were recorded as thin films on NaCl plates using a Perkin-Elmer Spectrum One FT-IR spectrophotometer. ¹H NMR spectra were measured at 360 MHz on a Bruker AC360, at 250 MHz on a Bruker AC250 or AM250 and at 200 MHz on a Bruker AC200 using CDCl_3 as solvent. Chemical shifts are reported in δ units to 0.01 ppm precision with coupling constants reported to 0.1 Hz precision using residual chloroform (δ 7.27 ppm) as an internal reference. Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, bs = broad singlet. ¹³C NMR spectra were measured at 50 or 62.5 MHz using CDCl_3 (δ 77.0 ppm) as an internal reference. The GC device (9000 series, Fisons instruments, capillary column CP Sil 19 CB, 25 m length, 0.25 mm inside diameter, 0.20 μm film thickness, helium as carrier gas) is fitted with a hardware (NCI 9000 series interface) and software (Turbochrom) system developed by Perkin Elmer. GC conditions are: 140 to 280 °C, 10 °C / min, p_{He} = 50 kPa. Retention times (r.t.) are: **5**, r.t. = 5.41 min.; **6**, r.t. = 6.32 min.; internal standard (dibutylphthalate), r.t. = 9.65 min. Mass spectra were measured on a MAT 95S Finnigan-Thermo spectrometer at the Institut de Chimie Moléculaire d'Orsay (ICMMO) Mass Spectrometry Laboratory. Elemental analyses were performed at the ICSN 91198 Gif sur Yvette Cedex, France.

¹ Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

2,2-Dimethyl-5-nitroso-[1,3]dioxanyl acetate **3**

To a solution of oxime **13**² (2.05 g, 14.14 mmol) in CH₂Cl₂ (70 mL) at 0 °C under argon was added (diacetoxyiodo)benzene (5.47 g, 17 mmol). After 2 h at 0 °C, the reaction mixture was poured into a saturated aqueous solution of NaHCO₃ (25 mL). The aqueous layer was extracted with CH₂Cl₂, washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude blue oil was purified by flash chromatography on silica gel (pentane/diethyl ether = 95:5 to 80:20) to give 1.91 g (67% from **4**) of **3** as a bright blue oil; **3** could be stored as a frozen benzene solution (50 mg/mL) for several months without decomposition. *R_f* (heptane/ethyl acetate = 80:20) = 0.46; ¹H NMR (200 MHz, CDCl₃) δ 4.29 (d, *J* = 12.7 Hz, 2H), 3.78 (d, *J* = 12.7 Hz, 2H), 2.23 (s, 3H), 1.54 (s, 3H), 1.47 (s, 3H); ¹³C NMR (62.5 MHz, CDCl₃) 166.8, 121.0, 100.3, 59.8, 23.6, 23.0, 20.5; IR (thin film) 1756, 1570, 1375, 1294, 1221, 1100 cm⁻¹; LRMS (ES) 775.3 [4(M-Me)+Na]⁺, 399.1 [2(M-Me)+Na]⁺ *m/z*, Anal. Calcd. for C₈H₁₃NO₅ C 47.29, H 6.45, N 6.89; found: C: 47.26, H 6.51, N 6.81.

General procedure for the Lewis acid promoted nitroso Diels-Alder cycloaddition of dienophile **3**:

To a dry Schlenk, equipped with a septa and a magnetic stirring bar was added 50 mg of dry molecular sieves (powdered, 4Å) and 20 mol. % of the required Lewis acid. The solids were dried under high vacuum at 125 °C overnight, with magnetic stirring. The Schlenk was cooled under vacuum and flushed with dried nitrogen. A solution of α-acetoxynitroso dienophile **3** (50 mg, 0.24 mmol) in dry toluene (0.6 mL) was added dropwise and the suspension was cooled to 0 °C. After 1 min, the required 1,3-diene (5 equivalents) was added dropwise. The resulting suspension was stirred at 0 °C until complete disappearance of the characteristic blue color of **3**. The reaction mixture was hydrolyzed with an aqueous HCl solution (1N, 1 mL) and the biphasic solution was stirred for 45 min. at room temperature. An aqueous NaOH solution (20 mol. %) was added dropwise at 0 °C to reach pH ~ 10. A solution of Boc₂O (107 mg, 0.49 mmol) in acetone (2 mL) was added and the resulting mixture was stirred at room temperature overnight. The aqueous layer was extracted with CH₂Cl₂, washed with

² Majewski, M.; Gleave, D. M.; Nowak, P. *Can. J. Chem.* **1995**, 73, 1616-1626.

brine, dried over MgSO_4 , filtered and concentrated under reduced pressure. The crude oil was purified by flash chromatography on silica gel (pentane/diethyl ether = 80:20 to 60:40) to yield **5** and **6** as colorless oils.

***t*-Butyl (1*R**,4*S**)-2-oxa-3-aza-bicyclo[2.2.2]oct-5-ene-3-carboxylate (**5**)³**

R_f (heptane/ethyl acetate = 80:20) = 0.26; ^1H NMR (360 MHz, CDCl_3) δ 6.54 (dddd, J = 1.8, 8.5, 8.5 and 12.8 Hz, 2H), 4.73 (br. m, 2H), 2.23-2.06 (2H), 1.46 (s, 9H), 1.38-1.25 (2H); ^{13}C NMR (62.5 MHz, CDCl_3) 157.7, 131.7, 131.5, 81.5, 70.6, 50.1, 28.1, 23.5, 20.5; IR (thin film) 1739, 1698, 1368, 1163, 1074 cm^{-1} .

***t*-Butyl (1*S**,4*R**)-(4-hydroxy-cyclohex-2-enyl)-carbamate (**6**)⁴**

Slowly crystallises at room temperature, white crystals, mp = 58 °C; R_f (heptane/ethyl acetate = 1:1) = 0.25; ^1H NMR (250 MHz, CDCl_3) δ 5.82 (ddd, J = 1.8, 3.1 and 11.6 Hz, 1H), 5.68 (dd, J = 3.1 and 10.4 Hz, 1H), 4.84 (br. d, J = 8.3 Hz, 1H), 4.10 (br. s, 1H), 4.04 (br. s, 1H), 2.99 (br. s (OH), 1H), 1.82-1.63 (4H), 1.41 (s, 9H); ^{13}C NMR (62.5 MHz, CDCl_3) 155.2, 132.3, 131.0, 79.5, 66.5, 45.8, 28.9, 28.4, 25.6; IR (thin film) 3334 (br., OH), 1683, 1516, 1367, 1249, 1170, 1066 cm^{-1} .

³ Zhang, D.; Süling, C.; Miller, M. J. *J. Org. Chem.* **1998**, 63, 885-888.

⁴ Hall, A.; Bailey, P. D.; Rees, D. C.; Rosair, G. M.; Whightman, R. H. *J. Chem. Soc., Perkin Trans. I* **2000**, 329-343.

***t*-Butyl (1*S**,4*R**)-2-oxa-3-aza-bicyclo[2.2.1]hept-5-ene-3-carboxylate**

R_f (heptane/ethyl acetate = 80:20) = 0.20; ^1H NMR (200 MHz, CDCl_3) δ 6.40 (2H), 5.20 (m, 1H), 4.97 (m, 1H), 1.98 (dt, J = 2.0 and 8.8 Hz, 1H), 1.71 (d, J = 8.2 Hz, 1H), 1.47 (s, 9H); ^{13}C NMR (50 MHz, CDCl_3) 158.5, 134.1, 132.9, 83.5, 82.0, 64.9, 48.1, 28.1; IR (thin film) 1738, 1702, 1369, 1331, 1163, 1089, 847, 833 cm^{-1} .

***t*-Butyl (1*S**,4*R**)-(4-hydroxy-cyclopent-2-enyl)-carbamate (14)³**

R_f (heptane/ethyl acetate = 50:50) = 0.29; ^1H NMR (360 MHz, CDCl_3) δ 5.98 (d, J = 5.8 Hz, 1H), 5.84 (d, J = 5.8 Hz, 1H), 4.83 (br. s, 1H), 4.69 (br. s, 1H), 4.42 (m, 1H), 2.81 (br. s, 1H), 2.73 (dt, J = 7.7 and 14.3 Hz, 1H), 1.53 (br. d, J = 14.3 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (62.5 MHz, CDCl_3) 155.3, 136.0, 134.1, 79.5, 75.0, 54.7, 41.3, 28.4; IR (thin film) 3335, 1689, 1525, 1367, 1250, 1171, 1059 cm^{-1} .

***t*-Butyl (1*S**,4*R**)-(4-hydroxy-cyclohept-2-enyl)-carbamate⁴ (16)**

White crystals, mp = 118 °C (litt:⁴ mp = 144-146 °C); R_f (heptane/ethyl acetate = 1:1) = 0.36; ^1H NMR (360 MHz, CDCl_3) δ 5.75 (br. d, J = 11.6 Hz, 1H), 5.54 (ddd, J = 3.0, 3.0 and 11.6 Hz, 1H), 4.74 (br. s, 1H), 4.40 (br. dd, J = 2.4 and 7.3 Hz, 1H), 4.18 (br. s, 1H), 1.98 (m, 1H), 1.87-1.75 (2H), 1.72-1.67 (2H), 1.61-1.50 (2H), 1.45 (s, 9H); ^{13}C NMR (62.5 MHz, CDCl_3) 155.1, 137.2, 133.3, 79.4, 71.5, 51.6, 36.0, 34.0, 28.4, 24.5; IR (thin film) 3342 (br. OH), 1683, 1529, 1366, 1251, 1170,

1018, 739 cm^{-1} ; Anal. Calcd. for $\text{C}_{12}\text{H}_{21}\text{NO}_3$ C 63.41, H 9.31, N 6.16; found: C: 63.49, H 9.41, N 5.96.

***t*-Butyl (1*R**,4*S**)-(4-hydroxy-1-methyl-pent-2-enyl)-carbamate (18-*cis*).**

White crystals, mp = 75 °C; R_f (heptane/ethyl acetate = 70:30) = 0.31; ^1H NMR (360 MHz, CDCl_3) δ 5.43 (br. t, J = 9.9 Hz, 1H), 5.10 (br. t, J = 10.4 Hz, 1H), 4.81 (br. s, 1H), 4.67 (m, 1H), 4.45 (m, 1H), 4.22 (br. s, 1H), 1.36 (s, 9H), 1.18 (d, J = 6.1 Hz, 3H), 1.13 (d, J = 6.5 Hz, 3H); ^{13}C NMR (90 MHz, CDCl_3) 155.5, 134.9, 132.4, 79.8, 61.8, 43.6, 28.2, 22.2, 20.5; IR (thin film) 3415, 3294, 1687, 1525, 1366, 1176, 1067 cm^{-1} . Anal. Calcd. for $\text{C}_{11}\text{H}_{21}\text{NO}_3$ C 61.37, H 9.83, N 6.51; found: C 61.11, H 9.71, N 6.38.

***t*-Butyl (1*S**,4*S**)-(4-hydroxy-1-methyl-pent-2-enyl)-carbamate (18-*trans*).**

R_f (heptane/ethyl acetate = 60:40) = 0.32; ^1H NMR (400 MHz, CDCl_3) δ 5.45 (dd, J = 11.1 and 7.5 Hz, 1H), 5.20 (dd apparent t, J = 10.2 Hz, 1H), 4.68 (m, 1H), 4.56 (br. s, 1H), 3.16 (br. s, 1H), 1.42 (s, 9H), 1.27 (d, J = 6.4 Hz, 3H), 1.19 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) 155.1, 134.5, 131.8, 79.5, 65.0, 43.7, 28.3, 23.8, 21.8; IR (thin film) 3334, 1688, 1525, 1367, 1251, 1174, 1103, 1050 cm^{-1} .

***t*-Butyl (4-hydroxy-1,3-dimethyl-but-2-enyl)-carbamate (20)**

R_f (heptane/ethyl acetate = 70:30) = 0.20; ^1H NMR (360 MHz, CDCl_3) δ 4.87 (br. s, 1H), 4.12 (d, J = 6.1 Hz, 2H), 3.74 (d, J = 6.1 Hz, 2H), 3.28 (br. s, 1H), 1.79 (s, 3H), 1.68 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (90 MHz, CDCl_3) 156.4, 132.4, 128.8, 79.4, 62.6, 42.6, 28.3, 17.7, 16.9; IR (thin film) 3342 (br.), 1689, 1531, 1367, 1274, 1252, 1172, 1004 cm^{-1} . Anal. Calcd. for $\text{C}_{11}\text{H}_{21}\text{NO}_3$ C 61.37, H 9.83, N 6.51; found: C 61.01, H 9.85, N 6.39.

***tert*-Butyl ((*Z*)-1-formyl-2-hydroxyvinyl)((1*S**,4*R**)-4-hydroxycyclohex-2-enyl)carbamate**

R_f (toluene/ethyl acetate = 60:40) = 0.50; ^1H NMR (200 MHz, CDCl_3) δ 9.32 (s, 1H, H8), 7.81 (s, 1H, H9), 5.83 (s, 2H, H2+3), 4.41 (s, 1H, H1), 4.06 (s, 1H, H4), 2.04-1.79 (4H, H5+6), 1.56 (s, apparent 8H, first rotamer, H12), 1.37 (s, apparent 6H, second rotamer, H12); ^{13}C NMR (125 MHz, CDCl_3) 187.9 (C8), 153.3 (C9), 151.9 and 148.7 (C10, rotamers), 131.7 (C2 or C3), 130.6 (C3 or C2), 127.0 (C7), 86.4 (C11), 63.0 (C4), 54.8 (C1), 29.8 (C5), 28.0 and 27.5 (C12, rotamers), 22.0 (C6); IR (thin film) 3440 (br. OH), 1776, 1705, 1662, 1256, 1139, 845 cm^{-1} ; LRMS (ESI, Na^+) 210.2 ($[\text{M}-t\text{-BuO}]^+$), 306.1 ($[\text{M}+\text{Na}]^+$) m/z .

Selected multinuclear 2D experiments for compound X (Figure 1)

$^1\text{H}-^{13}\text{C}$ HMBC	H4-H5	H8-H7	H1-H3
	H4-H6	H8-H9	
	H4-H2	H8-H1	
$^1\text{H}-^{15}\text{N}$ HMBC	H8-N1		
	H9-N1		
Significant nOe enhancement	H8-H9		

Figure 1