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Stereoselective Lewis acid promoted Kharasch-type addition of 3-bromoacetyl-2-oxazolidinones to norbornadiene

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Abstract—Ytterbium trifluoromethanesulfonate promoted radical atom-transfer addition of 3-bromoacetyl-2-oxazolidinones to norbornadiene afforded stereoselectively the corresponding 5-*exo*-3-bromo-5-nortricycleneacetic acid derivatives in good yields. Following clean tri(trimethylsilyl)silane reduction of the bromides, 3-*exo*-nortricycleneacetic acid derivatives were obtained with excellent diastereoselectivities (90–96% de) when using the chiral 4-isopropyl- and 4-benzyl-substituted 2-oxazolidinone auxiliaries. The stereochemistry of the studied compounds was investigated by 1D and 2D NMR spectroscopy.

1. Introduction

Radical atom-transfer Kharasch reactions[1], have been intensively investigated in recent years for their synthetic utility.[2] Porter et al.[3] have proposed a new useful variation, by using a Lewis acid to promote atom-transfer additions of 3-bromoacetyl-2-oxazolidinones to terminal and internal alkenes. It was shown that Lewis acid complexation increased both the rate of addition of the α-carbonyl radical to the alkene and the halogen abstraction by the resulting nucleophilic carbon radical.[3] This allows the reactions to proceed in good yields at lower temperatures, with the potential of achieving good diastereoselectivities for the halogen transfer. We report herein the application of this approach for the highly diastereoselective addition of chiral 3-bromoacetyl-2-oxazolidinones to norbornadiene (Scheme 1).

2. Results and discussion

Classical Kharasch-type atom-transfer additions to norbornadiene have been performed by Davies et al.,[4] who showed that the reaction of norbornadiene with methylene bromide, ethyl bromoacetate and methyl bromoacetate required high temperatures and long reaction times to give ca. 1:1 mixtures of the corresponding *exo*-*cis*- and *trans*-3,5-disubstituted nortricyclane isomers. In contrast we found that in the presence of $Yb(OTf)_3$ as the Lewis acid, the radical addition of bromoacetyloxazolidinone **1a** to norbornadiene proceeded cleanly at room temperature in 1,2-dichloroethane and at −78 °C in a dichloromethane/tetrahydrofuran (9:1) co-solvent system, producing exclusively the corresponding 5-*exo*-3-bromo-5-nortricycleneacetic acid derivatives **2a** in good yield as a *cis*/*trans*-mixture of epimers, with the *trans*-isomer strongly prevailing (Scheme 1). The *cis*- and *trans*-epimers of **2a** could be separated by chromatography. However, the reduction of the crude *cis*/*trans*-mixture of **2a** with tri(trimethylsilyl)silane at 75 °C in benzene with AIBN initiation produced the corresponding stable 3-*exo*-nortricycleneacetic acid derivative **3a** as a single product. The initial attack occurs exclusively from the less hindered *exo*-face of the norbornadiene molecule, as confirmed by the 2D NOESY NMR spectra of *cis*-**2a** and *trans*-**2a** (Fig. 1). The norbornenyl radical thus formed then underwent rearrangement to a nortricyclyl radical before chain transfer.

The precise assignment of the ^{1}H NMR spectra of *cis*-**2a** and *trans*-**2a** was accomplished by 2D homonuclear correlation (COSY) and then additionally confirmed by 2D inverse detected heteronuclear (C–H) correlation (HMQC). The chemical shifts are consistent with the expected *exo*-stereochemistry of both compounds (Table 1).

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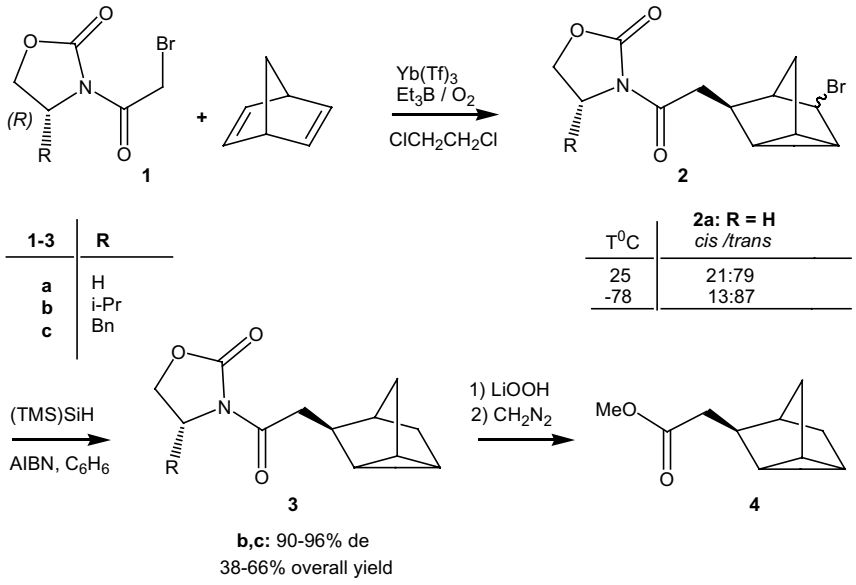

Scheme 1.

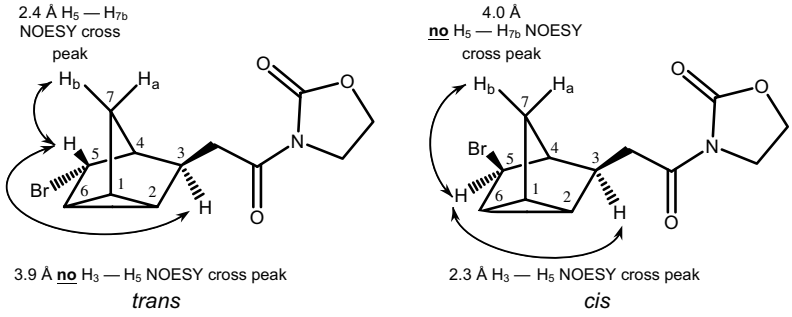

Figure 1. H_5–H_{7b} and H_3–H_5 internuclear distances in *exo-cis*-**2a** and *trans*-**2a** isomers calculated with PCMODEL. The cross peaks observed in the NOESY spectra are also indicated.

Table 1. ^{1}H chemical shifts and NOESY cross peaks for *exo-cis* and *trans*-isomers of **2a**

Atom number	*trans*		*cis*	
	Chemical shifts *J* constants (Hz)	NOESY cross peaks	Chemical shift *J* constants (Hz)	NOESY cross peaks
H_1	1.26–1.29, m, 1H	H_6, H_2	1.38–1.43, m, 1H	H_6, H_2, CH_2, H_{7b}
H_6	**1.51–1.56, m, 1H	H_2, H_1, H_5	*1.50–1.58, m, 1H	H_2, H_1, H_5
$\underline{H_5}$	3.99, t, 1H $J_{3,4} \approx J_{3,2} = 1.53$	H_4, H_6, **$\underline{H_{7b}}$**	**4.00, br t, 1H	H_4, H_6, **$\underline{H_3}$**
H_4	2.06, br s, 1H	H_{7a}, H_{7b}, H_5, CH_2, H_3	2.10, br s, 1H	H_{7a}, H_{7b}, H_5, CH_2, H_3
$\underline{H_3}$	*2.83–2.93, m, 1H	H_4, H_2	2.16, tdd, 1H $J_{5,8} = 7.20$	H_4, H_2, CH_2, **$\underline{H_5}$**
H_2	***1.39–1.44, m, 1H	H_3, H_1, H_6, CH_2	1.24–1.28, m, 1H	H_3, H_1, H_6, CH_2
H_{7a}	**1.51–1.62, ddd, 1H $J_{7a,7b} = 11.5$ $J_{7a,2} \approx J_{7a,4} = 1.55$	H_{7b}, H_4, CH_2	*1.58, br d, 1H $J_{7a,7b} = 11.7$	H_{7b}, H_4, CH_2
$\underline{H_{7b}}$	***1.39, dt, 1H $J_{7a,7b} = 11.5$ $J_{7b,2} \approx J_{7b,4} = 1.27$	H_{7a}, H_4, **$\underline{H_5}$**	1.99, dt, 1H $J_{7a,7b} = 11.7$ $J_{7b,2} \approx J_{7b,4} = 1.25$	H_{7a}, H_4
CH_2	*2.83–2.93, m, 2H	H_4, H_{7a}, H_2, NCH_2	2.85–2.92, m, 2H	H_4, H_{7a}, H_2, H_1, H_3, NCH_2
OCH_2	4.38–4.46, m, 2H	no	4.38–4.45, m, 2H	no
NCH_2	4.01–4.07, m, 2H	CH_2	**3.98–4.07, m, 2H	CH_2

Note: Signals marked with an equal number of asterisks are partially overlapped. Key protons used for assignment of stereochemistry are given in bold and underlined.

In the ^{1}H NMR spectrum of the *exo-cis*-isomer, H_{7b} and H_1 appear further downfield than the respective protons of the *trans*-isomer. In the *exo-cis*-isomer, the Br atom is above the plane determined by C2–C3–C5–C6. This position leads to steric repulsion between the Br and H_{7b} (van der Waals effect), which causes deshielding of H_{7b} (1.99 ppm) in comparison with the *trans*-isomer (1.39 ppm).[5] The deshielding of H_1 (1.38–1.43 ppm) in

the *cis*-isomer in comparison with the *trans*-isomer (1.26–1.29 ppm) is associated with the same effect. In the ^{1}H NMR spectrum of the *trans*-isomer, H_3 and H_2 appear further downfield than the respective protons of the *cis*-isomer. In this case, the Br atom is below the plane determined by C2–C3–C5–C6 and on the same side as H_3 and H_2. The steric interactions between the Br atom and these protons result in a shift downfield of the signals for H_3 and H_2 in comparison to the *cis*-isomer. For more details see Table 1.

The configuration of *cis*-**2a** and *trans*-**2a** was confirmed by the 2D NOESY spectra. The signals observed in NOESY spectra correspond to through-space interproton interactions. The key cross peaks are those between H_5–H_{7b} and H_3–H_5 protons (Fig. 1). The molecular geometry was optimized and the relative internuclear distances determined with the PCMODEL program using MMX force field. Figure 1 shows the calculated internuclear distances between the key protons and the respective cross peaks observed in the NOESY spectra of the *cis*-**2a** and *trans*-**2a** isomers. The calculated internuclear distances are consistent with the NOE interactions observed in the NOESY spectra of both compounds.

The NOESY spectrum of the *cis*-isomer shows a cross peak between H_3 and H_5, but no correlation signal is observed between H_5 and H_{7b}. These results confirm the *exo*-position of the Br atom in the *cis*-isomer, since H_3 is in close proximity to H_5 with a calculated internuclear distance of 2.3 Å between the two protons. The lack of an NOE cross peak between H_5 and H_{7b} also supports the *exo*-*cis* configuration, since the calculated distance of 4.0 Å between H_5 and H_{7b} is too large to cause any observable cross relaxation effect (see Fig. 1). The NOESY spectrum of the *trans*-**2a** isomer shows a well defined correlation peak between H_5 and H_{7b}, which are very close (2.4 Å). No cross signal is observed between H_3 and H_5, in agreement with the *endo* configuration of the Br-substituent.

The stereoselective reaction of norbornadiene with a chiral radical precursor was subsequently demonstrated. Highly diastereoselective atom-transfer addition was achieved using the chiral (4*R*)-isopropyl and (4*R*)-benzyl 2-oxazolidinone auxiliaries **1b** and **c**, respectively. The crude bromides **2b** and **c** were reduced with tri(trimethylsilyl)silane at 75 °C in benzene with AIBN initiation (Scheme 1), producing the corresponding 3-nortricycleneacetic acid derivatives **3b** and **c** with excellent diastereoselectivities (Table 2). The stereocontrol achieved

Table 2. Diastereoselectivity and yields of **3a–c**

Entry	**1** (*R*)	*T* (°C)	**3a–c**	
			dr 3*S*/3*R*	Yield (%) from **1**
1	**1a** (H)	25	—	66
2	**1a** (H)	−78	—	43
3	**1b** (*i*-Pr)	25	97:3	61
4	**1b** (*i*-Pr)	−78	97:3	44
5	**1c** (Bn)	25	95:5	53
6	**1c** (Bn)	−78	98:2	38

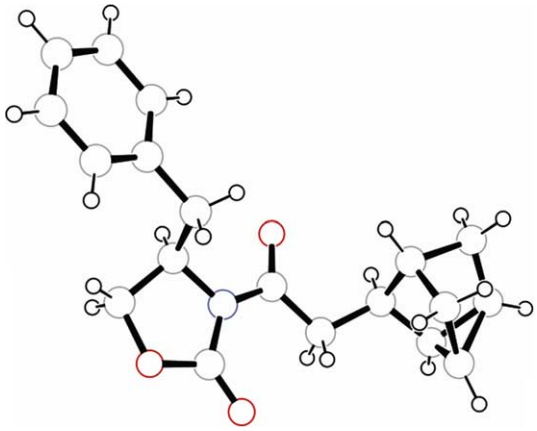

Figure 2. X-ray crystal structure of **3c**.

with the isopropyl group in **1b** was equally effective at 25 °C and −78 °C, while the diastereoselectivity induced by the benzyl-substituted **1c** was enhanced by lowering the temperature. Standard hydrolysis of the chiral auxiliaries[3a] provided 3-nortricycleneacetic acid and its methyl ester **4** (Scheme 1).[6] The enantiomeric purity of the acid was confirmed by its conversion back to the oxazolidinone imide derivative.

The (3*S*)-configuration of the new stereogenic centre as generated from the *exo*-addition was established by X-ray crystallographic analysis of **3c**[7] (Fig. 2).

The observed stereoselection is consistent with the Lewis acid chelation model in which the radical bearing the chiral auxiliary is in the fixed *syn* conformation. Addition from the less hindered face of the chiral radical then leads to stereoselection between the enantiotopic sp^2 carbon atoms of the two double bonds.

3. Conclusion

In summary, high diastereoselectivity has been induced for the first time in a Lewis acid promoted Kharasch-type addition to cycloalkenes by stereoselection between the enantiotopic terminals of the alkene. Highly enantiomerically pure nortricycleneacetic acid, the santalene sesquiterpene nortricycloekasantalic acid[8] analogue, has been obtained in good yield.

4. Experimental

3-Bromoacetyl (2-oxazolidinone) imides were prepared according to reported methods.[9,10] All other reagents were purchased from commercial suppliers and used without further purification. Isomeric ratios were determined by GC column HP-5–30 m × 0.25 mm × 0.25 μm; injector temp. 280 °C; detector temp 280 °C; oven-temp 100–250 and 15 °C/min, 250–280 at 5 °C/min; NMR spectra were recorded on a Bruker DRX–250 spectrometer, operating at 250.13 MHz for ^{1}H, using dual ^{1}H/^{13}C probe head. The studied compounds were dissolved in $CDCl_3$ with TMS as an internal standard.

4.1. A. Atom transfer reaction—general procedure

3-Bromoacetyl-2-oxazolidinones **1a**–**c** (0.5 mmol) were dissolved in 1,2-dichloroethane (10 mL), $Yb(OTf)_3$ (310 mg, 1 equiv) added and the mixture stirred for 15 min, purged with dry air for 5 min and norbornadiene (2.5 mmol, 5 equiv) and Et_3B (1 M in hexanes, 250 μL, 0.5 equiv) added sequentially. Et_3B (1 M in hexanes, 250 μL, 0.5 equiv) was then added every 30 min while being stirred. After 2 h the mixture was diluted with ether (150 mL), washed with saturated ammonium chloride solution (100 mL), dried over anhydrous magnesium sulfate, filtered and the volatiles removed by rotary evaporation. Crude products **2a**–**c** were reduced with tri(trimethylsilyl)silane for elemental analysis. *cis*-**2a** and *trans*-**2a** were separated by flash chromatography on silica gel, using 20% ethyl acetate in hexanes. For the low temperature experiments 10% solution of tetrahydrofuran in methylenechloride was used as the solvent and the reaction mixture cooled to −78 °C before norbornadiene addition and initiation with Et_3B.

4.2. B. Tri(trimethylsilyl)silane reduction of bromide products

Under argon, the crude bromides **2a**–**c** (0.5 mmol) were dissolved in degassed benzene (10 mL), tri(trimethylsilyl)silane (0.20 mL, 1.3 equiv) added and the mixture was warmed to 75 °C. AIBN (30 mg) dissolved in benzene (0.5 mL) was added and the mixture heated for 2 h. The reaction was quenched with saturated ammonium chloride solution (100 mL) and extracted with ether (100 mL), dried over anhydrous magnesium sulfate and concentrated. Products **3a**–**c** were isolated by column chromatography on silica gel, using 20% ethyl acetate in hexanes.

4.3. 3-(2-Tricyclo[3.2.1.0^{3,6}]oct-2-yl-acetyl)-oxazolidin-2-one

Compound **3a** was obtained as an oil from **2a** and **b** following procedure **B**. ^{1}H NMR: δ 0.99 (m, 3 H, H_1, H_2, H_6), 1.13 (d, 1H, 10.9 Hz, H_{7b}), 1.23 (d, 1H, 10.1 Hz, H_{5a}), 1.32 (d, 1H, 10.1 Hz, H_{5b}), 1.45 (d, 1H, 10.9 Hz, H_{7a}), 1.79 (br s, 1H, H_4), 1.97 (t, 1H, 7.3 Hz, H_3), 2.71–2.88 (m, 2H, CH_2), 3.40 (t, 2H, 8.3 Hz, N–CH_2), 4.38 (t, 2H, 8.3 Hz, O–CH_2). ^{13}C NMR: δ 9.6 (C_1), 11.3 (C_2), 14.7 (C_6), 29.3 (C_7), 33.1 (C_4), 33.9 (C_5), 35.4 (*C*H_2–C=O), 40.4 (C_3), 42.5 (N–CH_2), 61.9 (*C*H_2–O–C=O), 153.5 (CH_2–*C*=*O*), 173.1 (N–*COO*). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.17; H, 7.08; N, 6.21.

4.4. (*R*)-4-Isopropyl-3-((*S*)-2-tricyclo[3.2.1.0^{3,6}]-oct-2-yl-acetyl)-oxazolidin-2-one 3b

Mp 97–100 °C, $[\alpha]_D$ = −46.3 (*c* 2.55, CH_2Cl_2); ^{1}H NMR: δ: 0.86 (d, 3H, 7.1 Hz, CH_3), 0.91 (d, 3H, 7.1 Hz, CH_3), 0.95–1.10 (m, 3H, H_1, H_2, H_6), 1.12–1.16 (m, 1H, H_{7b}), 1.26–1.21, (m, 1H, H_{5a}), 1.29–1.34 (m, 1H, H_{5b}), 1.44–1.47 (m, 1H, H_{7a}), 1.78 (br s, 1H, H_4), 1.97 (m, 1H, H_3), 2.30–2.43 (m, 1H, C*H*–*i*-Pr), 2.59–2.95 (m, 2H, CH_2), 3.9–4.1 (m, 2H, OCH_2), 4.40–4.46 (m, 1H, N–CH); ^{13}C NMR: δ 9.6 (C_1), 11.3 (C_2), 14.6 (C_6, CH_3–*i*-Pr—overlapped signals), 17.9 (CH_3–*i*-Pr), 28.3 (CH–*i*-Pr), 29.3 (C_7), 33.2 (C_4), 33.8 (C_5), 35.7 (*C*H_2–C=O), 40.6 (C_3), 58.3 (CH–N), 63.2 (*C*H_2–O–C=O), 154.0 (N–COO), 172.8 (N–C=O). Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.21; H, 8.33; N, 5.02.

4.5. (*R*)-4-Benzyl-3-((*S*)-2-tricyclo[3.2.1.0^{3,6}]oct-2-yl-acetyl)-oxazolidin-2-one 3c

Mp 91–94 °C, $[\alpha]_D$ = −37.2 (*c* 2.4, CH_2Cl_2); ^{1}H NMR: δ 0.85–1.13 (m, 3H, H_1, H_2, H_6), 1.18 (br d, 1H, 10.7 Hz, H_{7b}), 1.27 (br d, 1H, 9.9 Hz, H_{5a}), 1.37 (br d, 1H, 9.9 Hz, H_{5b}), 1.53 (br d, 1H, 10.7 Hz, H_{7a}), 1.84 (br s, 1H, H_4), 2.02 (m, 1H, H_3), 2.59–2.95 (m, 3H, CH_2, C*H*$_2$–Ph), 3.26–3.30 (m, 1H, C*H*$_2$–Ph), 3.15–4.20 (m, 2H, OCH_2), 4.64–4.70 (m, 1H, N–CH), 7.20–7.37 (m, 5H, Ph); ^{13}C NMR: δ 9.7 (C_1), 11.4 (C_2), 14.7 (C_6), 29.3 (C_7), 33.1 (C_4), 33.2 (C_5), 33.9 (*C*H_2–C=O), 35.8 (CH_2–Ph), 37.9 (C_3), 55.1 (CH–N), 66.1 (*C*H_2–O–C=O), 127.3 (Ph, *p*) 128.9 (Ph, *o*), 129.4 (Ph, *m*), 135.3 (Ph), 153.4 (N–COO), 172.9 (N–C=O). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 72.93; H, 6.86; N, 4.47.

4.6. Tricyclo[2.2.2.0^{2,6}]hept-3-(*S*)-yl-acetic acid—$[\alpha]_D$ = +0.3 (*c* 2.15, C_5H_5N); tricyclo[2.2.2.0^{2,6}]-hept-3-(*S*)-yl-acetic acid methyl ester 4

^{1}H NMR: δ 0.88–1.04 (m, 3H, H_1, H_2, H_6), 1.07 (d, 1H, 10.8 Hz, H_{7b}), 1.17 (d, 1H, 10.2 Hz, H_{5a}), 1.25 (d, 1H, 10.2 Hz, H_{5b}), 1.34 (d, 1H, 10.8 Hz, H_{7a}), 1.56 (br s, 1H, H_4), 1.84 (m, 1H, H_3), 2.11 (d, 2H, 7.89 Hz, CH_2), 3.60 (s, 3H, $COOCH_3$); ^{13}C NMR: δ 9.5 (C_1), 11.4 (C_2), 14.8 (C_6), 29.1 (C_7), 33.2 (C_4), 33.9 (C_5), 34.7 (*C*H_2–C=O), 41.2 (C_3), 51.4 (COO*C*H_3), 173.9 (*COO*CH_3). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.90; H 8.48.

Acknowledgements

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