Lewis acid promoted Kharasch-type additions of 3-bromoacetyl-2-oxazolidinone to cycloalkenes

Ivanka K. Kavrakova*[a] and Jeremy H. Mills[b]

[a]*Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences, 1113 Sofia, Bulgaria*

[b]*Chemistry Department, Vanderbilt University, Nashville, USA*

Radical ytterbium trifluoromethanesulfonate promoted atom-transfer additions of 3–bromoacetyl-2-oxazolidinone to several cycloalkenes proceeded smoothly to give functionalised cycloalkane derivatives in good yields and stereoselectivities. All products were easily and cleanly debrominated with tri(trimethylsilyl)silane to the corresponding stable cycloalkylacetic acid derivatives.

Keywords: radical additions, stereoselection, oxazolidinones, Lewis acids, cycloalkenes

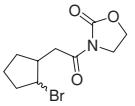
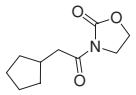
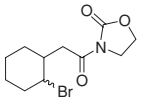
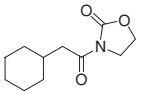
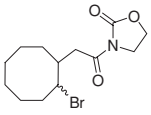
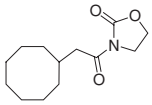
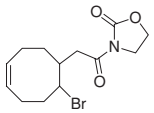
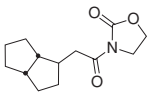
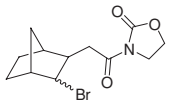
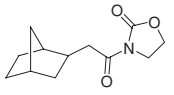
Radical atom-transfer Kharasch-type additions[1] have been extensively investigated in recent years.[2] The classical Kharasch reaction typically requires high temperatures, long reaction times and large excess of the halogenated substrate as the radical source. Only terminal alkenes are known to react in good yields preferably with halogenated precursors activated with two electron-withdrawing groups on the halide-bearing carbon. Porter and co-workers[3] have recently proposed a new useful variation of this reaction by using Lewis acids to promote additions of 3-bromo-acetyl-2-oxazolidinones to terminal and internal alkenes at room temperature or below.[3a]

We report here experiments that explore the opportunity to expand the scope of this reaction to cycloalkenes (Scheme 1, Table 1).

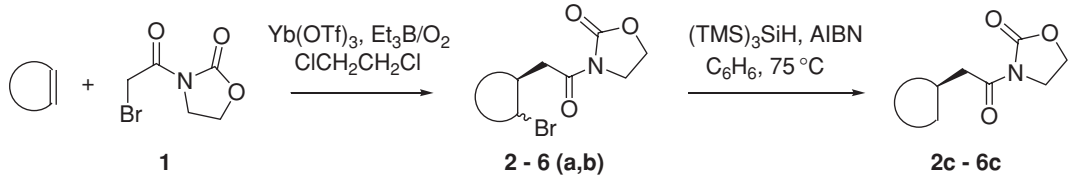
Classical Kharasch-type atom-transfer additions to cycloalkenes have been reported only with the strained cycloalkenes norbornene and norbornadiene, requiring high temperatures, long reaction times and large excesses of the halogenated substrates.[6,7] We have found that, in the presence of ytterbium trifluoromethanesulfonate, the radical addition of 3-bromoacetyl-2-oxazilidinone (**1**) to cycloalkenes (Table 1) proceeded cleanly at room temperature in dichloroethane and at –78°C in a methylenechloride/tetrahydrofuran (9:1) co-solvent system, affording in most cases only the desired addition products with small amounts of reductive debromination products. The stereoisomers were separated by flash chromatography and characterised by ^{1}H NMR, where possible. The bromide products were reduced with tri(trimethylsilyl)silane at 75°C in benzene with AIBN initiation to the corresponding stable crystalline cycloalkylacetic acid derivatives (Scheme 1).

Thus, the additions of **1** to cyclopentene and cyclohexene in the presence of $Yb(OTf)_3$ resulted in complete conversion of the reactants, producing *ca* 1:1 mixtures of *cis*/*trans*-isomers **2a,b** and **3a,b**, respectively (Table 2, entries 1 and 2). While additions to cyclohexene were generally not stereoselective, the *trans*-addition to the more rigid cyclopentene ring was strongly preferred at lower temperature. This selectivity is possibly as a result of unfavorable eclipsing interaction in the radical chain-transfer step for the formation of the *cis*-isomer **2a**. Furthermore, the isomerisation of **2a** to the more stable *trans*-isomer **2b** was observed on prolonged storage at 0°C.

Table 1 Products from atom transfer reactions with **1**

Alkene	Addition products	Reduction products
	 **2a**: *cis* **2b**: *trans*	 **2c**
	 **3a**: *cis* **3b**: *trans*	 **3c**
	 **4a**: *cis* **4b**: *trans*	 **4c**
	 **5a** and **5b**	 **5c**
	 **6a**: *cis* **6b**: *trans*	 **6c**

Gale[4] has reported the radical additions of thiols and hydrogen bromide to *cis*,*cis*-1,5-cyclooctadiene proceeding at lower temperature (ambient and –10°C) and obtained 5-substituted cyclooctene derivatives in high yields. The reduced reactivity of the double bond in *cis*-cyclooctene towards radical addition of hydrogen bromide was also confirmed



Scheme 1

* Correspondent. E-mail: ivkav@orgchm.bas.bg

Table 2 Stereoselectivity and yields of products

Entry	Addition products[a,b]			Reduction products[c]	
	Product	Ratio **a** / **b** (Yield/%)		Product	Yield/%[d]
		at 20°C	at –78°C		
1	**2a,b**	40 : 60 (54)	23 : 77	**2c**	52
2	**3a,b**	50 : 50 (66)	50 : 50	**3c**	83
3	**4a,b**	–	56 :44	**4c**	55
4	**5a,b**	33 : 66 (42)	**5a** only	**5c**	31
5	**6a,b**	81 : 19 (48)	79 : 21	**6c**	42

[a]2a, 3a, 4a, 6a – *cis*; 2b, 3b, 4b, 6b – *trans*.
[b]5a monocyclic / 5b bicyclic product.
[c]From addition reactions at -78°C.
[d]Overall yields from 1.

in competitive experiments with other cyclic olefins.[5] We observed that the Lewis acid promoted atom-transfer addition of **1** to cyclooctene proceeded at –78°C to give cleanly, but not stereoselectively, **4a,b** as a 1:1 mixture of *cis* / *trans* – isomers (Table 2). At ambient temperature the reaction gave a complex mixture of products, possibly due to the facile radical migration in the cyclooctane ring and subsequent non-selective bromine abstraction. In contrast, *cis,cis*-1,5-cyclooctadiene reacted smoothly at room temperature with **1** giving two products in a 1:2 ratio, which were separable by HPLC and were identified as the corresponding mono- and bicyclic addition products **5a** and **5b**, respectively. However, at –78°C, the reaction produced **5a** exclusively as a single isomer. Unfortunately, overlapping of the signals for the key protons H_1 and H_8 with other signals in the ^{1}H NMR spectrum of **5a** did not allow us to assign the relative configuration of this isomer.

The classical Kharasch reaction of the rigid norbornene ring systems was studied by Davies.[6] The reactions of norbornene with methylene bromide and methylbromoacetate required high temperatures and prolonged reaction times to produce the *exo* addition products, the *cis*-isomer predominating. Osborn and co-workers[7] have also reported that bulky radicals add exclusively to the less hindered *exo*-face of norbornene.

We have found that $Yb(OTf)_3$ promoted the atom-transfer addition of **1** to norbornene at ambient temperature and even at –78°C, providing the *exo* addition products *cis* **6a** and *trans* **6b** in a 81:19 ratio (Table 2). The relative configuration of **6a,b** is in agreement with the reported NMR data for analogous compounds.[6]

In summary, the stereoselective synthesis of vicinally functionalised cycloalkylacetic acid derivatives was achieved in good yields and under mild conditions via the Lewis acid promoted atom-transfer addition of 3-bromoacetyl-2-oxazolidinone to cycloalkenes. Reductive debromination of the addition products with tri(trimethylsilyl)silane provided cleanly the corresponding stable cycloalkylacetic acid derivatives **2c–6c**.

Experimental

General procedures: 3-Bromoacetyl-2-oxazolidinone was prepared according to a reported method.[8] All other reagents were purchased from commercial suppliers and used without further purification. Isomeric ratios were determined by GC (column HP-5 – 30m × 0.25mm × 0.25µm; gas, N_2, 25cm^3/s.; injector temp. 280°C; detector temp. 280°C; oven temp.100-250@15°C/min, 250-280 at 5°C/min). ^{1}H NMR spectra were recorded at 300 MHz in deuterochloroform relative to TMS as internal standard.

A. Typical atom transfer reaction: 3-Bromoacetyl -2-oxazolidinone **1** (0.5 mmols) was dissolved in 1,2-dichloroethane (10 ml). $Yb(OTf)_3$ (310 mg, 1 equiv.) were added and the mixture was stirred for 15 min., purged with dry air for 5 min. and the cycloalkene (2.5 mmols, 5 equiv.) and Et_3B (1M in hexanes, 250 µl, 0.5 equiv.) were added sequentially. Additional Et_3B (1M in hexanes, 250 µl, 0.5 equiv.) were added every 30 minutes at stirring. After 2 hours the mixture was diluted with ether (100 ml), washed with saturated ammonium chloride solution (100 ml), dried over anhydrous magnesium sulfate, filtered and volatiles removed by rotary evaporation. Products were purified and isomers were separated by flash chromatography on silica gel, using 20% ethyl acetate in hexanes. Crude products were reduced with tri (trimethylsilyl)silane for elemental analysis (see procedure B).

For the low temperature experiments 10% solution of tetrahydrofuran in methylenechloride was used as a solvent and the reaction mixture was cooled to –78°C before cycloalkene addition and initiation with Et_3B.

B. Typical tri(trimethylsilyl) silane reduction of bromide products: Under argon, the bromide product (0.5 mmols) was dissolved in degassed benzene (10 ml), tri(trimethylsilyl) silane (0.20 ml, 1.3 equiv.) were added and the mixture was heated to 75°C. AIBN (30 mg) dissolved in benzene (0.5 ml) were added and the mixture heated for 2h. 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 were isolated by column chromatography on silica gel, using 20% ethyl acetate in hexanes.

Cis and trans– 3-[2-(2-Bromocyclopentyl)acetyl]oxazolidin-2-one (**2a** and **2b**)

2a: ^{1}H NMR: δ 1.23 (m, 2H), 1.65 (m, 1H), 1.81 (m, 1H), 2.06 (m, 1H), 2.26 (m, 1H), 2.59 (m, 1H), 2.93 (m, 1H), 3.20 (dd, 1H, *J* = 5.3, 17.0 Hz), 3.96 (m, 3H), 4.39 (m, 2H).

2b: ^{1}H NMR: δ 1.53 (m, 5H), 2.24 (m, 2H), 3.17 (m, 2H), 4.0 (m, 2H), 4.40 (m, 2H), 4.74 (bs, 1H).

3-(2-Cyclopentylacetyl)oxazolidin-2-one (**2c**): m.p. 44–45°C. ^{1}H NMR: δ 1.17 (m, 2H), 1.53 (m, 4H), 1.59 (m, 2H), 1.82 (m, 1H), 2.91 (d, 2H, *J* = 7.2 Hz), 3.98 (t, 2H, *J* = 8.4 Hz), 4.37 (t, 2H, *J* = 8.4 Hz); Anal. Calcd. for $C_9H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 61.12; H, 7.70; N, 7.08.

Cis and trans – 3-[2-(2-Bromocyclohexyl)acetyl]oxazolidin-2-one (**3a** and **3b**)

3a: ^{1}H NMR: δ 1.13 (m, 1H), 1.32 (m, 2H), 1.68 (m, 2H), 1.91 (m, 2H), 2.33 (m, 2H), 2.96 (dd, 1H, J = 8.6, 17.7 Hz), 3.39 (dd, 1H, J = 3.6, 17.7 Hz), 3.94 (td, 1H, J = 4.3, 11.4 Hz), 4.00 (t, 2H, J = 9.7 Hz), 4.39 (t, 2H, J = 9.7 Hz).

3b: ^{1}H NMR: δ 1.46 (m, 1H), 1.52 (m, 3H), 1.71 (m, 2H), 1.86 (m, 1H), 2.10 (m, 2H), 2.81 (dd, 1H, J = 5.8, 17.5 Hz), 3.12 (dd, 1H, J = 7.4, 17.5 Hz, 3.99 (m, 2H), 4.39 (m, 2H), 4.70 (bs, 1H).

3-(2-Cyclohexylacetyl)oxazolidin-2-one - (**3c**): m.p. 71.5–73°C. ^{1}H NMR: δ 1.01 (m, 5H), 1.64 (m, 6H), 2.68 (d, 2H, *J* = 5.1 Hz), 3.88 (t, 2H, *J* = 6.3 Hz), 4.27 (m, 2H); Anal. Calcd. for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.56; H, 8.15; N, 6.58.

3-(2-Cyclooctylacetyl)oxazolidin-2-one (**4c**): ^{1}H NMR: δ 1.47 (m, 14H), 2.11 (m, 1H), 2.80 (d, 2H, *J* = 5.4 Hz), 3.98 (t, 2H, *J* = 6.0 Hz), 4.36 (t, 2H, *J* = 6.0 Hz); Anal. Calcd. for $C_{13}H_{21}NO_3$: C, 65.26; H, 8.93; N, 6.27. Found: C, 62.14; H, 8.83; N, 6.33.

3-[2-(8-Bromocyclooct-4-enyl)acetyl]oxazolidin-2-one (**5a**): The precise assignment of the ^{1}H NMR spectrum of **5a** was accomplished by 2D homonuclear correlation (COSY) and by 2D inverse detected heteronuclear (C-H) correlation (HMQC). ^{1}H NMR: δ 1.4–1.6 (m, 1H, H_{2a}), 1.7–2.0 (m, 1H, H_{3a}), 1.8–2.0 (m, 1H, H_{2b}), 1.99–2.1 (m, 1H, H_{6a}), 2.14–2.22 (m, 1H, H_{7a}), 2.4–2.5(m, 1H, H_{7b}), 2.3–2.7(m, 3H, H_1, H_{3b}, H_{6b}), 2.86 (dd, 1H, CH_2, *J* = 4.4, 17.8 Hz), 3.1 (dd, 1H, CH_2, *J* = 8.2, 17.8 Hz), 3.9–4.1 (m, 2H, N–CH_2), 4.4–4.5 (m, 2H, O–CH_2), 4.50–4.52 (m, 1H, H_8), 5.56–5.66 (m, 1H, H_4), 5.71–5.80 (m, 1H, H_5).

3-[2-(4-Bromooctahydro-1-pentalenyl)acetyl]oxazolidin-2-one (**5b**): ^{1}H NMR: δ 1.15 (m, 2H), 1.51 (m, 2H), 1.96 (m, 6H), 2.62 (m, 1H), 2.87 (dd, 1H), 2.97 (dd, 1H), 3.95 (m, 2H), 4.14 (m, 1H), 4.34 (m, 2H).

3-(2-(Octahydro-pentalen-2-yl-acetyl)-oxazolidin-2-one (**5c**): M.p. 64.5–66.0°C. ^{1}H NMR: δ 1.37 (m, 9H), 1.55 (m, 2H), 2.04 (m, 1H), 2.44 (m, 1H), 2.90 (dd, 1H, J = 7.9, 15.8 Hz), 3.03 (dd, 1H, J = 5.5, 15.8 Hz), 4.02(m, 2H), 4.43 (t, 2H, J = 8.1 Hz); Anal. Calcd. for $C_{13}H_{19}N_{33}$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.55; H, 8.06; N, 5.80.

Cis- and trans- 3-[2-(3-Bromobicyclo[2.2.1]hept-2-yl)acetyl] oxazolidin-2-one (**6a** and **6b**)

6a: ^{1}H NMR: δ 1.23 (m, 3H), 1.52 (m, 1H), 1.62 (m, 1H), 1.86 (m, 1H), 2.05 (d, 1H, J = 2.6 Hz), 2.45 (m, 1H), 2.55 (d, 1H, J = 4.4 Hz), 2.85 (dd, 1H, J = 5.2, 18.2 Hz), 3.37 (dd, 1H, J = 9.9, 18.2 Hz), 3.99 (t, 2H, J = 8.3 Hz), 4.32 (dd, 1H, J = 1.8, 7.1 Hz), 4.4 (t, 2H, J = 8.3 Hz).

6b: ^{1}H NMR: δ 1.40 (m, 5H), 1.96 (m, 2H), 2.15 (m, 1H), 2.42 (bs, 1H), 2.78 (dd, 1H, J = 6.9, 15.8 Hz), 3.07 (dd, 1H, J = 8.6, 15.8 Hz), 3.9 (bt, 1H, J = 4.3 Hz), 4.01 (t, 2H, J = 8.2 Hz), 4.40 (t, 2H, J = 8.2 Hz).

3-(2-Bicyclo[2.2.1]hept-2-ylacetyl)oxazolidin-2-one (**6c**): ^{1}H NMR: δ 0.97 (m, 2H), 1.12–1.24 (m, 3H), 1.43 (m, 3H), 1.86 (m, 2H), 2.09 (br.s, 1H), 2.64 (dd, 1H, J = 7.5, 16.7 Hz), 2.79 (dd. 1H, J = 7.5, 16.7 Hz), 3.89 (t, 2H, J = 8.3 Hz), 4.28 (t, 2H,,J = 8.3 Hz). Anal. Calcd. for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.44; H, 7.62; N, 6.16.

We thank Dr. Ned A. Porter, Vanderbilt University, Nashville, for his support of this work.

Received 19 October 2004; accepted 20 November 2004
Paper 04/2822

References

1 (a) M.S. Kharasch, E.V. Jensen and W.H Urry, *Science,* 1945, **102**, 128; (b) C. Walling, *Free Radicals in Solution*, Wiley and Sons: New York, 1957, p. 252.
2 (a) D.P. Curran, *Synthesis*, 1988, 489; (b) D.P. Curran, E. Bosch, J. Kaplan and M. Newcomb, *J. Org. Chem*., 1989, **54**, 1826; (d) D.P. Curran, M.H. Chen, E. Spletzer, C.M. Seong and C. Chang, *J. Am. Chem. Soc*., 1989, **111**, 8872.
3 (a) C.L. Merro and N.A. Porter, *J. Am. Chem. Soc*., 1999, **121**, 5155; (b) H. Feng, I.K. Kavrakova, D.A. Pratt, J. Tellinghuisen and N.A. Porter, *J. Org. Chem*., 2002, **67**, 6050.
4 L.H. Gale, *J. Org. Chem*., 1968, **33**, 3643.
5 L.H. Gale, *J. Org. Chem*., 1969, **34**, 81.
6 D.I. Davies, L.T. Parfitt, C.K. Alden and J.A. Claisse, *J. Chem. Soc.(C)*, 1969, 1585.
7 C.L. Osborn, T.V. Van Auken and D.J. Trecker, *J. Am. Chem. Soc*., 1968**, 90**, 5806.
8 K. Narasaka, Y. Hayashi, S. Shimada and J. Yamada, *Izr. J. Chem.,* 1991, **31**, 261.