One-Step Conversion of Aldehydes to Oxazolines and 5,6-Dihydro-4*H*-1,3-oxazines Using 1,2- and 1,3-Azido Alcohols

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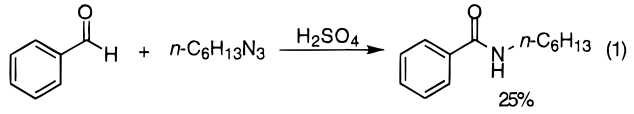
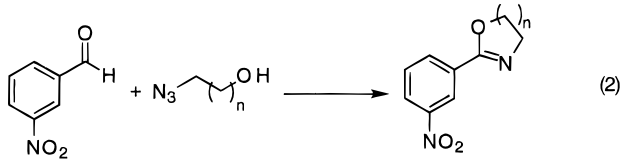
The reactions of 1,2- and 1,3-hydroxy azides with aldehydes under acidic conditions were examined. A variety of Lewis acids were examined, of which $BF_3{\cdot}OEt_2$ was found the most convenient. Trimethylsilyl ether derivatives of the alcohols could also be reacted using trimethylsilyl triflate as the promoter. Twenty-five examples that proceed in moderate to quantitative yields are reported.

In 1955, Boyer and co-workers found that the reaction of alkyl azides with aromatic aldehydes could be carried out using H_2SO_4 in benzene to afford amides in 10−25% yields (eq 1).[1] In contrast, using 2-azidoethanol (**1**) or 3-azido-1-propanol (**2a**) under similar conditions afforded oxazolines or dihydrooxazines, respectively, with much greater efficiency (eq 2).



(1)



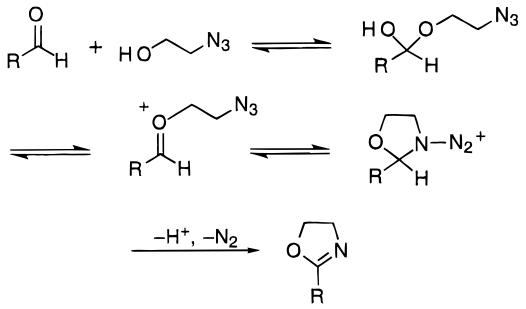
(2)

1, n = 1
2a, n = 2

n = 1, 73%
n = 2, 82%

These authors proposed that both reactions proceeded via mechanisms involving initial nitrogen attack, and attributed better yields of the latter process to increased acid stability of the hydroxy azides.[1b,c] With the benefit of hindsight and mindful of recent developments in reactions of alkyl azides with carbonyl and carbocation electrophiles,[2] we recently proposed the mechanism shown in Scheme 1.[2g] In this scenario, initial hemiketal formation is followed by dehydration to set up an intramolecular attack of the azide on the resulting oxonium ion. Elimination of H^+ and N_2 directly affords the heterocyclic products. An alternative mechanism involving a 1,2-hydride shift coupled with N_2 loss followed by proton loss is also possible, but seems less likely in light of the poor migratory ability of H in similar processes.[2e,3]

Scheme 1



As originally disclosed, the Boyer reaction was reported to be limited severely in scope, resulting in good yields only when electron-poor aldehydes were used as reactants. Recently, we reported a similar reaction using ketones.[3] In the present paper, we disclose that modification of Boyer's original reaction conditions allows for a substantial extension of the scope of the process. Thus, reactions of a range of aldehydes with azido alcohols **1** and **2a** and (±)-1-azido-2-phenylethanol (**3**) result in efficient routes to a variety of oxazolines and dihydrooxazines. Oxazolines are subunits in a number of natural products and have found use as asymmetric catalysts and as peptidomimetics.[4]

Results and Discussion

Our first goal was to see whether Lewis acid promotion would overcome the reported limitations of the reaction to electron-poor aromatics. In particular, we hoped to extend the reach of this process to include 2-alkyl heterocycles. Using benzaldehyde and hexanal as test cases, we found that 1,3-azidopropanol **2a** underwent smooth addition using a variety of Lewis acids (Table 1). To our slight surprise, the list of effective reagents for the reaction of hexanal included H_2SO_4, in spite of the previous report to the contrary.[1a] We also established, following the precedent of Markó,[5] that 1-azido-3-[(tri-

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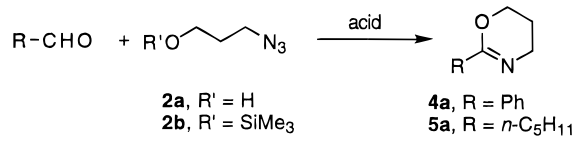
0022-3263/96/1961-2484$12.00/0

Table 1. Effect of Lewis Acid on the Synthesis of 5,6-Dihydro-4*H*- 1,3-oxazines



2a, R' = H
2b, R' = $SiMe_3$

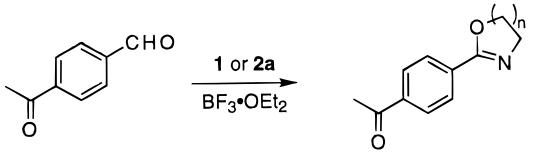
4a, R = Ph
5a, R = *n*-C_5H_{11}

entry	aldehyde	azide	acid	product	yield(%)
1	benzaldehyde	**2a**	BF_3•OEt_2	**4a**	86
2		**2a**	H_2SO_4		88
3		**2a**	$TiCl_4$		30
4		**2a**	$SnCl_4$		90
5		**2a**	TMSOTf		70
6		**2b**	TMSOTf (cat.)		78
7	hexanal	**2a**	BF_3•OEt_2	**5a**	100
8		**2a**	H_2SO_4		49
9		**2a**	$TiCl_4$		72
10		**2a**	$SnCl_4$		79
11		**2a**	TMSOTf		46
12		**2b**	TMSOTf (cat.)		61

methylsilyl)oxypropane (**2b**) could be directly reacted with aldehydes using TMSOTf catalysis. Of the various Lewis acids, BF_3•OEt_2 was judged most convenient in terms of availability, effectiveness, and ease of workup.

Accordingly, a range of aldehydes were subjected to reactions with **1**, **2a**, and **3** in the presence of BF_3•OEt_2 (Table 2). Overall, good yields could be obtained for the entire range of aromatic—including electron-rich—and aliphatic aldehydes examined. ^1H and ^{13}C NMR spectra show that the products were obtained in good purity. However, many of these compounds were hydrolyzed to corresponding amides upon exposure to atmospheric moisture.

Two additional examples merit particular mention. First, *p*-acetylbenzaldehyde was prepared and subjected to the reaction conditions to determine the chemoselectivity of the reaction. Clean reaction of the aldehyde in the presence of the ketone was observed in this case (eq 3).

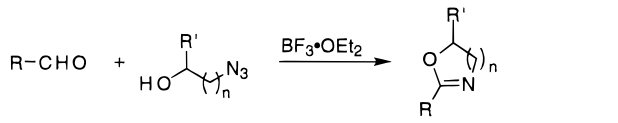


(3)

12a (from **2a**), 70%
12b (from **1**), 54%

Finally, we note that the reaction was problematic when reactions with α,β-unsaturated aldehydes were attempted. We presume that the availability of additional electrophilic sites in the aldehyde results in formation of competing products. Still, moderate yields could be obtained using favorable substrates (e.g., eq 4).

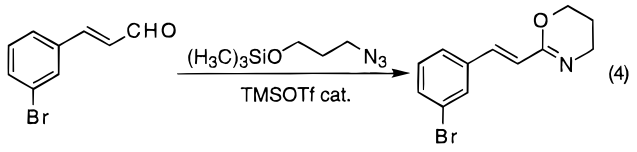
Table 2. Reactions of Azidohydrins with Aldehydes in the Presence of BF_3•OEt_2



1, R' = H, n = 1
2a, R' = H, n = 2
3, R' = Ph, n = 1

a, R' = H, n = 2
b, R' = H, n = 1
c, R' = Ph, n = 1

entry	aldehyde, R =	azide	time (h)	product	yield (%)
1	C_6H_5	**1**	1	**4b**	78
2		**3**	4.5	**4c**	96
3	C_5H_{11}	**1**	2.5	**5b**	67
4		**3**	3	**5c**	79
5	2-(1,3-Benzodiox-5'-yl)-	**2a**	12	**6a**	73
6		**1**	2.5	**6b**	56
7		**3**	5	**6c**	37
8	$(CH_3)_3C$-	**2a**	2	**7a**	70
9		**1**	2	**7b**	76
10		**3**	3	**7c**	69
11	$C_6H_5CH_2$-	**2a**	11	**8a**	70
12		**1**	12	**8b**	75
13		**3**	1.5	**8c**	80
14	*p*-$O_2NC_6H_4$-	**2a**	12	**9a**	76
15		**1**	14	**9b**	18
16		**3**	12	**9c**	60
17	*p*-$MeO_2CC_6H_4$-	**2a**	1	**10a**	75
18		**1**	1	**10b**	55
19		**3**	14	**10c**	82
20	*p*-$CH_3OC_6H_4$-	**2a**	24	**11a**	75
21		**1**	14	**11b**	55



(4)

13, 40%

Despite this limitation, the reactions of azido alcohols with aldehydes show promise for the preparation of a variety of useful heterocycles.

Experimental Section

General methods have been published.[2g] *CAUTION*. Although we have not experienced any problems, alkyl azides should be treated as potential explosion hazards. Except where noted, all reagents were obtained commercially.

3-Azido-1-propanol (2a). To 70 mL of DMF was added 3-bromo-1-propanol (10 g, 72 mmol). Sodium azide (19 g, 290 mmol) was added slowly. The mixture was stirred vigorously at room temperature for 10.5 h at which time 200 mL of Et_2O was added. The organic layer was washed with H_2O (50 mL) and brine (50 mL). The aqueous layer was extracted with Et_2O (5 × 50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated at 1 atm. The crude product was purified by column chromatography (1:1 → 3:1 Et_2O/pentane)

to afford 7.0 g of **2** (96%):[6] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78 (pentet, J = 6.0 Hz, 2H), 2.37 (br s, 1H), 3.39 (t, J = 6.0 Hz, 2H), 3.68 (t, J = 6.0 Hz, 2H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 31.8, 48.8, 60.0; IR (NaCl, CCl_4) 3400, 2940, 2085, 1250 cm^{-1}.

General Procedure for the Preparation of 2-Substituted-5,6-dihydro-4*H*-1,3-oxazines and 2-Substituted Oxazolines. A solution of aldehyde (1.0 equiv) and azide (1.1 equiv) in CH_2Cl_2 (0.2−0.5 M) was cooled to 0 °C followed by dropwise addition of BF_3·OEt_2 (2.0 equiv); the addition of acid was accompanied by gas evolution. The reaction mixture was allowed to warm to room temperature and the solution stirred for the specified time in Table 2. Saturated $NaHCO_3$ (ca. 25−35 mL) was added slowly, and the solution was stirred until bubbling ceased. The reaction mixture was extracted with Et_2O, EtOAc, or CH_2Cl_2 (3 × 30 mL), and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated to afford the crude product, which was purified by silica gel chromatography.

2-*n*-Pentyl-5-phenyloxazoline (5c): 259 mg, 79% yield; R_f 0.4 (3:1 hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84−0.94 (m, 3H), 1.33−1.40 (m, 4H), 1.68−1.73 (m, 2H), 2.37 (t, J = 7.7 Hz, 2H), 3.76 (dd, J = 6.3, 7.9 Hz, 1H), 4.24 (dd, J = 3.9, 10.2 Hz, 1H), 5.45 (dd, J = 2.1, 8.1 Hz, 1H), 7.27−7.41 (m, 5H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 14.4, 22.7, 26.1, 28.6, 31.8, 63.0, 81.0, 126.0, 128.6, 129.1, 141.6, 168.5; IR (NaCl, $CHCl_3$) 1660, 1485, 1445, 1425, 1220, 1160 cm^{-1}; MS (FAB), m/z 218 (M^+ + H), 120; HRMS calcd for $C_{14}H_{20}NO$ 218.1545 (M^+ + H), found 218.1551.

2-(1,3-Benzodioxan-5-yl)-5,6-dihydro-4*H*-1,3-oxazine (6a): 150 mg, 73% yield; R_f 0.3 (1:1 hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.96 (pentet, J = 5.7 Hz, 2H), 3.58 (t, J = 5.8 Hz, 2H), 4.33 (t, J = 5.6 Hz, 2H), 5.97(s, 2H), 6.78 (d, J = 8.1 Hz, 1H), 7.37 (d, J = 1.8 Hz, 1H), 7.44 (dd, J = 8.1, 1.8 Hz, 1H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 22.0, 42.6, 65.2, 101.3, 107.4, 107.6, 121.4, 147.5, 155.0; IR (NaCl, $CHCl_3$) 3400, 1640, 1500, 1485, 1440, 1250 cm^{-1}; MS (FAB), m/z 206 (M^+ + H), 149; HRMS calcd for $C_{11}H_{12}NO_3$ 206.0817(M^+ + H), found 206.0804.

2-(1,3-Benzodioxan-5-yl)-oxazoline (6b): 107 mg, 56% yield; R_f 0.4 (1:1 hexane/EtOAc); mp 114−117 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.03 (t, J = 9.3 Hz, 2H), 4.40 (t, J = 9.3 Hz, 2H), 6.02 (s, 2H), 6.83 (d, J = 8.1 Hz, 1H), 7.41 (d, J = 1.2 Hz, 1H), 7.50 (dd, J = 6.9, 1.2 Hz, 1H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 55.3, 68.0, 101.9, 108.4, 108.7, 122.2, 123.5, 148.0, 150.6, 164.6; IR (NaCl, $CHCl_3$) 1640, 1500, 1490, 1450, 1255 cm^{-1}; MS (FAB), m/z 192 (M^+ + H), 149; HRMS calcd for $C_{10}H_{10}NO_3$ 192.0661 (M^+ + H), found 192.0663.

2-(1,3-Benzodioxan-5-yl)-5-phenyloxazoline (6c): 50 mg, 37% yield; R_f 0.5 (1:1 pentane/Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.96 (dd, J = 6.6, 7.8 Hz, 2H), 4.45 (dd, J = 4.5, 10.2 Hz, 1H), 5.64 (dd, J = 1.8, 8.0 Hz, 1H), 6.03 (s, 2H), 6.85 (d, J = 8.1 Hz, 1H), 7.33−7.41 (m, 5H), 7.49 (s, 1H), 7.58 (d, J = 8.4 Hz, 1H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 63.6, 81.5, 102.0, 108.5, 108.9, 122.1, 123.7, 126.1, 128.7, 129.2, 141.5, 148.1, 150.7, 164.0; IR (NaCl, $CHCl_3$) 1640, 1495, 1480, 1440, 1250 cm^{-1}; MS (FAB), m/z 268 (M^+ + H), 149, 91; HRMS calcd for $C_{16}H_{14}NO_3$ 268.0974 (M^+ + H), found 268.0984.

2-*tert*-Butyl-5-phenyloxazoline (7c): 123 mg, 69% yield; R_f 0.4 (1:1 hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 9H), 3.75 (dd, J = 6.3, 7.8 Hz, 1H), 4.26 (dd, J = 4.2, 10.2 Hz, 1H), 5.45 (dd, J = 2.4, 7.8 Hz, 1H), 7.26−7.41 (m, 5H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 28.2, 33.7, 63.3, 81.0, 125.9, 128.5, 129.2, 142.1, 174.5; IR (NaCl) 3400, 1650, 1490, 1470, 1450, 1255 cm^{-1}; MS (FAB), m/z 204 (M^+ + H), 146, 120; HRMS calcd for $C_{13}H_{18}NO$ 204.1388 (M^+ + H), found 204.1404.

2-Benzyl-5,6-dihydro-4*H*-1,3-oxazine (8a): 148 mg, 70% yield; R_f 0.4 (5% MeOH/$CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84 (pentet, J = 5.7 Hz, 2H), 3.39 (t, J = 5.9 Hz, 2H), 3.45 (s, 2H), 4.13 (t, J = 5.6 Hz, 2H), 7.22−7.36 (m, 5H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 22.0, 42.7, 43.0, 65.5, 127.0, 128.8, 129.3, 137.1, 159.5; IR (NaCl, $CHCl_3$) 3400, 1660, 1490, 1350, 1240, 1080 cm^{-1}; MS (FAB), m/z 176 (M^+ + H), 91; HRMS calcd for $C_{11}H_{14}NO$ 176.1075 (M^+ + H), found 176.1071.

2-Benzyl-5-phenyloxazoline (8c): 158 mg, 80% yield; R_f 0.4 (1:1 hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.71 (s, 2H), 3.74−3.82 (m, 1H), 4.13 (dd, J = 6.9, 7.2 Hz, 1H), 4.27 (dd, J = 3.9, 10.2 Hz, 1H), 5.47 (dd, J = 2.4, 7.8 Hz, 1H), 7.17−7.39 (m, 10H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 35.4, 63.1, 73.2, 81.5, 126.0, 127.5, 128.6, 129.2, 129.6, 135.3, 141.4, 167.0; IR (NaCl) 3400, 1660, 1485, 1445, 1230, 1150 cm^{-1}; MS (FAB), m/z 238 (M^+ + H), 120, 91; HRMS calcd for $C_{16}H_{16}NO$ 238.1232 (M^+ + H), found 238.1231.

2-(*p*-Nitrophenyl)-5-phenyloxazoline (9c): 80 mg, 80% yield; R_f 0.3 (3:1 pentane/Et_2O); mp 143−145 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20 (dd, J = 7.2, 8.1 Hz, 1H), 4.54 (dd, J = 5.1, 10.2 Hz, 1H), 5.73 (dd, J = 2.1, 8.1 Hz, 1H), 7.34−7.55 (m, 5H), 8.24 (AB q, $\Delta\nu$ = 30.4 Hz, J = 9.0 Hz, 4H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 63.7, 82.2, 124.0, 126.2, 129.0, 129.3, 129.7, 133.8, 140.7, 150.0, 162.6; IR (NaCl, $CHCl_3$) 3400, 1640, 1590, 1520, 1330 cm^{-1}; MS (FAB), m/z 269 (M^+ + H), 253, 150, 135, 120, 104, 91; HRMS calcd for $C_{15}H_{13}N_2O_3$ 269.0926 (M^+ + H), found 269.0934.

2-(*p*-Carbomethoxyphenyl)-5,6-dihydro-4*H*-1,3-oxazine (10a): 160 mg, 75% yield; R_f 0.4 (1:1 hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00 (pentet, J = 5.7 Hz, 2H), 3.63 (t, J = 5.9 Hz, 2H), 3.92 (s, 3H), 4.38 (t, J = 5.4 Hz, 2H), 7.99 (AB q, $\Delta\nu$ = 22.4 Hz, J = 8.7 Hz, 4H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 22.4, 43.1, 52.6, 65.8, 127.4, 129.7, 132.1, 138.1, 155.3, 167.2; IR (NaCl, $CHCl_3$) 1710, 1640, 1425, 1400, 1340, 1270, 1125, 1090 cm^{-1}; MS (FAB), m/z, 220 (M^+ + H), 163; HRMS calcd for $C_{12}H_{14}NO_3$ 220.0974 (M^+ + H), found 220.0960.

2-(*p*-Carbomethoxyphenyl)oxazoline (10b): 102 mg, 55% yield; R_f 0.4 (1:1 hexane/EtOAc); mp 130−132 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.93 (s, 3H), 4.09 (t, J = 9.5 Hz, 2H), 4.46 (t, J = 9.5 Hz, 2H), 8.04 (AB q, $\Delta\nu$ = 20.0 Hz, J = 8.4 Hz, 4H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 52.7, 55.5, 68.2, 128.5, 129.9, 132.1,132.8 164.2, 166.8; IR (NaCl, $CHCl_3$) 1710, 1635, 1430, 1400, 1270 cm^{-1}; MS (FAB), m/z 206 (M^+ + H), 163; HRMS calcd for $C_{11}H_{13}NO_3$ 206.0817 (M^+ + H), found 206.0835.

2-(*p*-Carbomethoxyphenyl)-5-phenyloxazoline (10c): 131 mg, 82% yield; R_f 0.6 (2:1 hexane/EtOAc); mp 94−95 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95 (s, 3H), 4.03 (dd, J = 6.9, 8.1 Hz, 1H), 4.52 (dd, J = 4.8, 10.2 Hz, 1H), 5.70 (dd, J = 1.8, 8.1 Hz, 1H), 7.34−7.43 (m, 5H), 8.07−8.13 (m, 4H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 52.7, 63.7, 81.8, 126.2, 128.7, 128.8, 129.3, 130.0, 132.1, 133.0, 141.1, 163.6; IR (NaCl, $CHCl_3$) 3400, 1710, 1635, 1270 cm^{-1}; MS (FAB), m/z 282 (M^+ + H), 163; HRMS calcd for $C_{17}H_{16}NO_3$ 282.1130 (M^+ + H), found 282.1139.

2-(*p*-Methoxyphenyl)-5,6-dihydro-4*H*-1,3-oxazine (11a): 200 mg, 70% yield; R_f 0.2 (1:1 hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.92 (pentet, J = 5.7 Hz, 2H), 3.54 (t, J = 6.0 Hz, 2H), 3.78 (s, 3H), 4.30 (t, J = 5.4 Hz, 2H), 6.82 (d, J = 9.0 Hz, 2H), 7.79 (d, J = 8.7 Hz, 2H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 22.1, 42.6, 55.3, 65.1, 113.3, 126.8, 128.4, 155.3, 161.4; IR (NaCl, $CHCl_3$) 2950, 1640, 1605, 1510, 1350, 1305, 1280, 1270, 1250 cm^{-1}; MS (FAB), m/z 192 (M^+ + H), 135; HRMS calcd for $C_{11}H_{14}NO_2$ 192.1025 (M^+ + H), found 192.1033.

2-(*p*-Acetylphenyl)-5,6-dihydro-4*H*-1,3-oxazine (12a): 146 mg, 73% yield; R_f 0.4 (3:1 EtOAc/hexane); mp 95−97 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.33 (t, J = 5.4 Hz, 2H), 3.58 (t, J = 5.9 Hz, 2H), 2.57 (s, 3H), 1.95 (pentet, J = 5.7 Hz, 2H), 7.91 (AB q, $\Delta\nu$ = 10.7 Hz, J = 9.0 Hz, 4H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 22.2, 27.1, 43.1, 65.6, 127.4, 128.3, 138.5, 138.6, 155.5, 198.0; IR (NaCl, $CHCl_3$) 1645, 1675, 1605, 1300, 1260, 1130, 1100 cm^{-1}; MS (FAB), m/z 204 (M^+ + H), 147; HRMS calcd for $C_{12}H_{14}NO_2$ 204.1025 (M^+ + H), found 204.1039.

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2-(*p*-Acetylphenyl)oxazoline (12b): 80 mg, 42% yield; R_f 0.3 (3:1 EtOAc/hexane); mp 102−105 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.55 (s, 3H), 4.01 (t, J = 9.3 Hz, 2H), 4.38 (t, J = 9.6 Hz, 2H), 7.96 (AB q, $\Delta\nu$ = 12.0 Hz, J = 9.0 Hz, 4H); ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 27.2, 55.5, 68.2, 128.6, 132.2, 139.4, 164.2, 197.9; IR (NaCl, $CHCl_3$) 1680, 1640, 1610, 1355, 1260 cm^{-1}; MS (FAB), m/z 190 (M^+ + H), 147; HRMS calcd for $C_{11}H_{12}NO_2$ 190.0868 (M^+ + H), found 190.0855.

Synthesis of Known Dihydrooxazines and Oxazolines. The following known compounds were prepared as described as above: **4a**,[7] **4b**,[8] **4c**,[9] **5a**,[10] **5b**,[7] **7a**,[8,11] **7b**,[7] **8b**,[12] **9a**,[13] **9b**,[13,14] and **11b**.[14,15]

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Supporting Information Available: Synthetic procedures and characterization data for *p*-acetaldehyde, **1**, **2b**, and **3** and copies of ^{1}H and ^{13}C NMR spectra for compounds **2b**, **5c**, **6a**, **6b**, **6c**, **7c**, **8a**, **8c**, **9c**, **10a**, **10b**, **10c**, **11a**, **12a**, **12b**, and **13a** (35 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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