ORGANIC LETTERS

2010
Vol. 12, No. 16
3614−3617

A Direct Synthesis of Oxazoles from Aldehydes

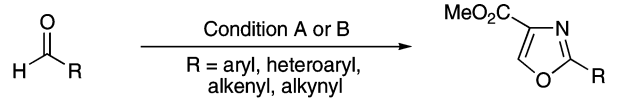
Thomas H. Graham

Merck Research Laboratories, Merck & Co., Inc., P.O. Box 2000, Rahway, New Jersey 07065-0900

thomas.graham@merck.com

Received June 11, 2010

ABSTRACT



Condition A: (i) Ser-OMe•HCl, Et_3N, $MgSO_4$, THF; (ii) $BrCCl_3$, DBU, CH_2Cl_2
Condition B: Ser-OMe•HCl, K_2CO_3, DMA then $BrCCl_3$, DBU

An expedient method for the direct conversion of aldehydes to 2,4-disubstituted oxazoles is presented. The method relies on the oxidation of an oxazolidine formed from the condensation of serine with an aldehyde and proceeds through a 2,5-dihydrooxazole intermediate. In contrast to standard methods that start from carboxylic acids, the use of aldehydes as starting materials does not require intermediate purification and affords the oxazoles under relatively mild conditions.

Efficiency is a perennial topic in organic synthesis, and the concept is described by numerous terms including atom economy,[1] step economy,[2] the Taxol problem,[3] and the arithmetic demon.[4] The concept of efficiency impacts modern pharmaceutical research when aggressive research timelines require rapid access to privileged pharmacophores.[5] With the goal of developing more efficient and expedient routes to important heterocycles, the synthesis of 2,4-disubstituted oxazoles was re-examined.

Oxazoles are a common structural motif found in numerous molecules that display antiviral, antifungal, antibacterial, and antiproliferative activities.[6] The potent biological activity and the prevalence of oxazoles in both natural products and pharmaceuticals has inspired significant interest in the synthesis of these heterocycles.[7]

2,4-Disubstituted oxazoles are incorporated into natural products by the nonribosomal peptide synthase mediated cyclization of serine-containing peptides.[8] Similarly, a common route for the synthesis of 2,4-disubstituted oxazoles relies on carboxylic acids and amino-alcohols as starting materials (Figure 1). Specifically, the coupling of a carboxylic acid with a suitable amino-alcohol followed by a dehydrative cyclization affords 2-oxazolines,[9] which are then oxidized[10] to afford the oxazole (**1**) (Figure 1, Path I). Alternatively, the oxidation step can precede the cyclization step, affording an oxo-amide intermediate, which upon dehydrative cyclization affords **1** (Figure 1, Path II).[11] Although these methods

(1) Trost, B. M. *Science* **1991**, *254*, 1471.
(2) Wender, P. A.; Croatt, M. P.; Witulski, B. *Tetrahedron* **2006**, *62*, 7505.
(3) Walji, A. M.; MacMillan, D. W. C. *Synlett* **2007**, 1477.
(4) (a) Crispino, G. A.; Ho, P. T.; Sharpless, K. B. *Science* **1993**, *259*, 64. (b) Ireland, R. E. *Organic Synthesis*; Prentice-Hall: Englewood Cliffs, NJ, 1969.
(5) (a) Nikitenko, A. *Curr. Opin. Drug Discovery* **2006**, *9*, 729. (b) Potoski, J. *Drug Discovery Today* **2005**, *10*, 115.
(6) (a) *Oxazoles: Synthesis, Reactions and Spectroscopy, Part A*; Palmer, D. C., Ed.; John Wiley & Sons: Hoboken, NJ, 2003. (b) *Oxazoles: Synthesis, Reactions and Spectroscopy, Part B*; Palmer, D. C., Ed.; John Wiley & Sons: Hoboken, NJ, 2004.
(7) (a) Jin, Z. *Nat. Prod. Rep.* **2006**, *23*, 464. (b) Yeh, V. S. C. *Tetrahedron* **2004**, *60*, 11995. (c) Wipf, P. *Chem. Rev.* **1995**, *95*, 2115.
(8) (a) Walsh, C. T. *Science* **2004**, *303*, 1805. (b) Li, Y.-M.; Milne, J. C.; Madison, L. L.; Kolter, R.; Walsh, C. T. *Science* **1996**, *274*, 1188.
(9) (a) Li, Z.; Xu, Q. *Tetrahedron Lett.* **2009**, *50*, 6838. (b) Sakakura, A.; Kondo, R.; Ishihara, K. *Org. Lett.* **2005**, *7*, 1971. (c) Wuts, P. G. M.; Northuis, J. M.; Kwan, T. A. *J. Org. Chem.* **2000**, *65*, 9223. (d) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165. (e) Yokokawa, F.; Shioiri, T. *Tetrahedron Lett.* **2002**, *43*, 8679. (f) Lafargue, P.; Guenot, P.; Lellouche, J.-P. *Heterocycles* **1995**, *41*, 947. (g) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 6267. (h) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 907. (i) Galéotti, N.; Montagne, C.; Poncet, J.; Jouin, P. *Tetrahedron Lett.* **1992**, *33*, 2807. (j) Burrell, G.; Evans, J. M.; Jones, G. E.; Stemp, G. *Tetrahedron Lett.* **1990**, *31*, 3649. (k) Vorbrüggen, H.; Krolikiewicz, K. *Tetrahedron Lett.* **1981**, *22*, 4471.

10.1021/ol101346w
Published on Web 07/19/2010

are common in modern organic synthesis, they often require intermediate purifications and moisture-sensitive reagents, which can limit the overall efficiency and utility of the process.

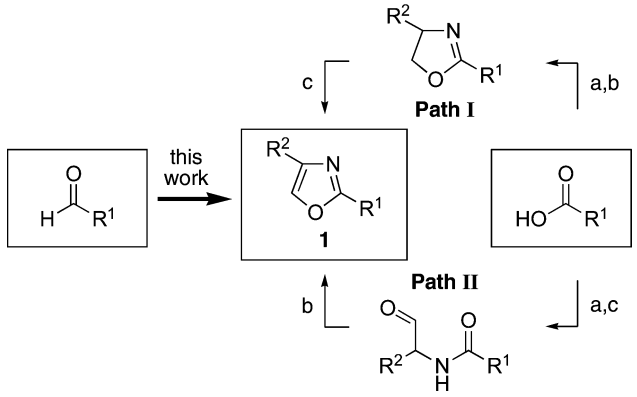


Figure 1. Common synthetic routes for accessing oxazoles from carboxylic acids: (a) amide coupling, (b) dehydrative cyclization, and (c) oxidation.

An alternative method for the preparation of oxazoles begins with aldehydes rather than carboxylic acids. Several methods for the conversion of aldehydes to oxazoles have been reported. Badr and co-workers demonstrated the transformation via an oxazolidine intermediate, formed by the condensation of an aromatic aldehyde with serine.[12] The two-step method uses *N*-bromosuccinimide in refluxing CCl_4 to oxidize the oxazolidines to 2-aryl oxazoles. In another method, the condensation of aldehydes and α-keto-oximes in HCl and acetic acid affords oxazole-*N*-oxides, which are subsequently reduced to afford the desired oxazoles.[13] A third method involves the condensation of an aldehyde with an α-amino-ketone, followed by a subsequent oxidation to give the oxazole.[14] These methods require multiple steps, harsh reaction conditions, or noncommercial starting materials, and these factors can limit the scope and utility of the transformations. Considering the potential efficiency of the process, a more mild method for the direct conversion of aldehydes to oxazoles was envisioned.

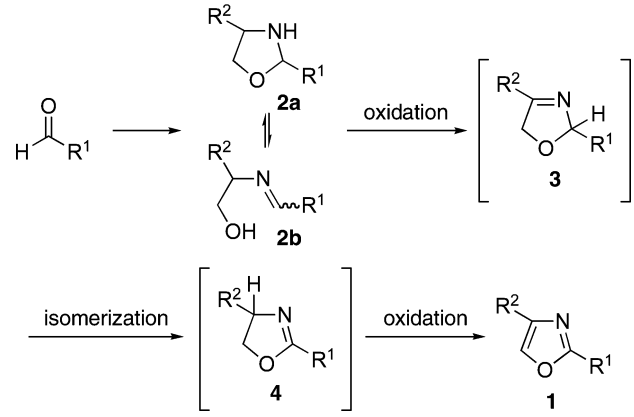


Figure 2. Proposed reaction pathway for the conversion of aldehydes to oxazoles.

The conversion of aldehydes to oxazoles discussed in this communication is based on the mechanistic hypothesis shown in Figure 2. The condensation of an aldehyde with an amino-alcohol yields the oxazolidine, which is reported to exist as a solvent-dependent equilibrium mixture of ring−chain tautomers **2a** and **2b**.[15] Oxidation of the oxazolidine affords the intermediate 2,5-dihydrooxazole **3**,[16,17] which isomerizes under the reaction conditions to give oxazoline **4**.[18] A second oxidation affords oxazole **1**. The $BrCCl_3$/ DBU system, originally developed by Williams and co-workers,[10c] was employed to oxidize the oxazolidine to the oxazole while also providing conditions to effect the required 1,3-isomerization.[19,20]

Initial studies focused on a two-step protocol to better understand the requirements for the transformation (Table

(10) (a) Yamamoto, K.; Chen, Y. G.; Buono, F. G. *Org. Lett.* **2005**, *7*, 4673. (b) Aoyama, T.; Sonoda, N.; Yamauchi, M.; Toriyama, K.; Anzai, M.; Ando, A.; Shioiri, T. *Synlett* **1998**, 35. (c) Williams, D. R.; Lowder, P. D.; Gu, Y.-G.; Brooks, D. A. *Tetrahedron Lett.* **1997**, *38*, 331. (d) Tavares, F.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 6803. (e) Barrish, J. C.; Singh, J.; Spergel, S. H.; Han, W.-C.; Kissick, T. P.; Kronenthal, D. R.; Mueller, R. H. *J. Org. Chem.* **1993**, *58*, 4494. (f) McGarvey, G. J.; Wilson, K. J.; Shanholtz, C. E. *Tetrahedron Lett.* **1992**, *33*, 2641. (g) Evans, D. L.; Minster, D. K.; Jordis, U.; Hecht, S. M.; Mazzu, A. L., Jr.; Meyers, A. I. *J. Org. Chem.* **1979**, *44*, 497.

(11) (a) Wipf, P.; Graham, T. H. *J. Org. Chem.* **2001**, *66*, 3242. (b) Wipf, P.; Lim, S. *Chimia* **1996**, *50*, 157. (c) Wipf, P.; Lim, S. *J. Am. Chem. Soc.* **1995**, *117*, 558. (d) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604.

(12) Badr, M. Z. A.; Aly, M. M.; Fahmy, A. M.; Mansour, M. E. Y. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1844.

(13) (a) Cai, X.-H.; Yang, H.-J.; Zhang, G.-L. *Synthesis* **2005**, 1569. (b) Weintraub, P. M. *J. Med. Chem.* **1972**, *15*, 419. (c) Goto, Y.; Yamazaki, M.; Hamana, M. *Chem. Pharm. Bull.* **1971**, *19*, 2050. (d) Allan, A. W.; Walter, B. H. *J. Chem Soc. C.* **1968**, 1397. (e) Bodendorf, K.; Towliati, H. *Arch. Pharm.* **1965**, *298*, 293. (f) Selwitz, C. M.; Kosak, A. I. *J. Am. Chem. Soc.* **1955**, *77*, 5370. (g) Cornforth, J. W.; Cornforth, R. H. *J. Chem Soc.* **1947**, 96. (h) von Dilthey, W.; Friedrichsen, J. *J. Prakt. Chem.* **1930**, *127*, 292. (i) Diels, O.; Riley, D. *Ber.* **1915**, *48*, 897.

(14) (a) Colotta, V.; Catarzi, D.; Varano, F.; Cecchi, L.; Filacchioni, G.; Martini, C.; Giusti, L.; Lucacchini, A. *Il Farmaco* **1998**, *53*, 375. (b) Merchant, J. R.; Desai, H. K. *Indian J. Chem.* **1973**, *11*, 433.

(15) (a) Lázár, L.; Fülöp, F. *Eur. J. Org. Chem.* **2003**, 3025. (b) Fülöp, F.; Pihlaja, K. *Tetrahedron* **1993**, *49*, 6701.

(16) (a) Johannes, K.; Jakob, J.; Hatam, M.; Martens, J. *Synthesis* **2009**, 3279. (b) Chakraborty, R.; Franz, V.; Bez, G.; Vasadia, D.; Popuri, C.; Zhao, C.-G. *Org. Lett.* **2005**, *7*, 4145. (c) Favreau, S.; Lizzani-Cuvelier, L.; Loiseau, M.; Duñach, E.; Fellous, R. *Tetrahedron Lett.* **2000**, *41*, 9787. (d) Sá, M. C. M.; Kascheres, A. *J. Org. Chem.* **1996**, *61*, 3749. (e) Dömling, A.; Bayler, A.; Ugi, I. *Tetrahedron* **1995**, *51*, 755. (f) Hua, D. H.; Khiar, N.; Zhang, F.; Lambs, L. *Tetrahedron Lett.* **1992**, *33*, 7751.

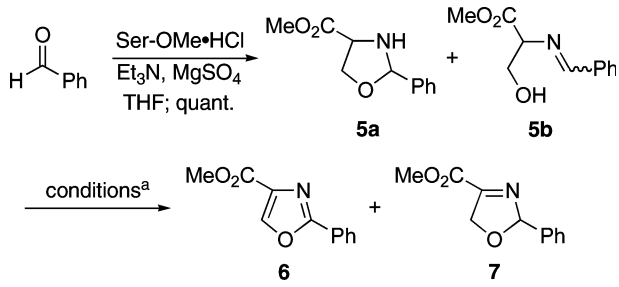
(17) Alternatively, bromination of the open-chain form followed by SN_2' cyclization would also afford the 2,5-dihydrooxazole intermediate, although both cyclizations contradict Baldwin's suggestions: Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

(18) For additional examples of oxidation-state transfer by isomerization in oxazoline systems, refer to: (a) Williams, D. R.; Berliner, M. A.; Stroup, B. W.; Nag, P. P.; Clark, M. P. *Org. Lett.* **2005**, *7*, 4099. (b) Hermitage, S. A.; Cardwell, K. S.; Chapman, T.; Cooke, J. W. B.; Newton, R. *Org. Process Res. Dev.* **2001**, *5*, 37. (c) Cardwell, K. S.; Hermitage, S. A.; Sjolin, A. *Tetrahedron Lett.* **2000**, *41*, 4239.

(19) For the conversion of oxazolidines to 2-oxazolines, refer to: (a) Takahashi, S.; Togo, H. *Synthesis* **2009**, 2329. (b) Schwekendiek, K.; Glorius, F. *Synthesis* **2006**, 2996. (c) Sayama, S. *Synlett* **2006**, 1479.

(20) For the preparation of thiazoles from aldehydes, refer to: Fernandez, X.; Fellous, R.; Lizzani-Cuvelier, L.; Loiseau, M.; Duñach, E. *Tetrahedron Lett.* **2001**, *42*, 1519.

Table 1. Optimizing the Conversion of **5a/b** to Oxazole **6**



entry	solvent	$BrCCl_3$ equiv	DBU equiv	ratio **6**:**7**	yield (%)[b]
1	CH_2Cl_2	1	1	1:2	48[c]
2	CH_2Cl_2	2	2	4:1	69
3	CH_2Cl_2	2.5	2.5	20:1	70
4	CH_2Cl_2	3	3	1:0	73
5	DMA	3	3	1:0	79

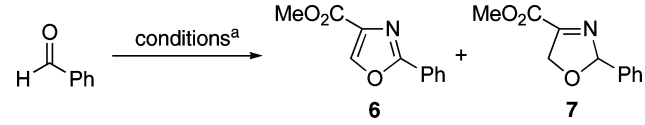
[a] Reaction conditions: $BrCCl_3$, DBU, 0 °C to rt, 12 h. [b] Yields were determined after purification by column chromatography on silica gel. [c] 2-Phenyloxazoline-4-carboxylic acid methyl ester was isolated in 10% yield.

1). The model oxazolidine was prepared from benzaldehyde and serine methyl ester hydrochloride using literature methods.[15] The oxazolidine was isolated in quantitative yield and high purity after a simple filtration to remove the Et_3N•HCl and $MgSO_4$. The oxidation of the oxazolidine was initially studied with variable amounts of $BrCCl_3$ and DBU in methylene chloride. With 1 equiv each of $BrCCl_3$ and DBU, an inseparable mixture of oxazole **6**[9d] and 2,5-dihydrooxazole **7** was isolated in a 1:2 ratio and 48% combined yield (Table 1, entry 1). The known 2-phenyloxazoline-4-carboxylic acid methyl ester,[21] corresponding to intermediate **4** in Figure 2, was also isolated in 10% yield. The presence of **7** and the 2-oxazoline, suggests the mechanism outlined in Figure 2 is operating. The use of 3 equiv each of $BrCCl_3$ and DBU was required to completely convert **5a/b** to **6** in 73% yield (Table 1, entry 4).

A solvent evaluation indicated that the use of a polar aprotic solvent such as *N*,*N*-dimethylacetamide (DMA) afforded **6** in 79% yield (Table 1, entry 5). The efficiency of the reaction in DMA is an interesting result considering that, in polar aprotic solvents, the ring−chain tautomer equilibrium of **5a** and **5b** is shifted almost exclusively toward the open form (**5b**).[15]

With the feasability of the transformation established, the one-pot conversion of an aldehyde to an oxazole was attempted (Table 2). Stirring serine methyl ester hydrochloride and benzaldehyde with triethylamine and magnesium sulfate in either methylene chloride or DMA for 12 h at ambient temperature followed by the addition of $BrCCl_3$ and DBU at 0 °C afforded inseparable mixtures of the desired oxazole **6** and the intermediate 2,5-dihydrooxazole **7** (Table 2, entries 1 and 2). The use of potassium carbonate in methylene chloride resulted in a 12% yield of **6** (Table 2, entry 3). The use of DMA as a solvent and potassium carbonate or potassium phosphate as a base provided complete conversion to **6** in 79% yield (Table 2, entries 4 and 5).

Table 2. Optimizing the One-Pot Synthesis of Oxazole **6**



entry	additive	solvent	ratio **6**:**7**	yield (%)[c]
1	Et_3N (1 equiv)[b]	CH_2Cl_2	4:1	71
2	Et_3N (1 equiv)[b]	DMA	7:1	81
3	K_2CO_3 (2 equiv)	CH_2Cl_2	1:0	12
4	K_2CO_3 (2 equiv)	DMA	1:0	79
5	K_3PO_4 (1 equiv)	DMA	1:0	79

[a] Reaction conditions: Ser-OMe•HCl (1 equiv), additive, rt, 12 h, then $BrCCl_3$ (3 equiv), DBU (3 equiv), 0 °C to rt, 12 h. [b] With $MgSO_4$ (1 equiv). [c] Yields were determined after purification by column chromatography on silica gel.

With the two efficient methods for the direct conversion of aldehydes to oxazoles, the scope of the transformation was studied (Table 3). Halogen-substituted benzaldehydes performed similarly to the parent benzaldehyde, affording the corresponding oxazoles in good yields for both the two-step (condition A) and the one-pot (condition B) procedures (Table 3, entries 1−3). In addition, both electron-poor (Table 3, entries 4 and 5) and electron-rich benzaldehydes (Table 3, entry 6) afforded the corresponding oxazoles. The method was also extended to heteroaromatic systems. Pyridines, quinolines, furans, and thiophenes (Table 3, entries 7−12) were tolerated by the reaction conditions.

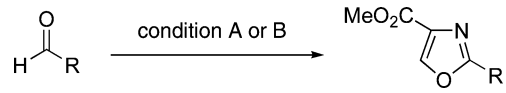
A further extension of the method affords 2-alkenyl and 2-alkynyl oxazoles. Cinnamaldehyde and α-methyl cinnamaldehyde afforded the corresponding oxazole in 72% and 70% yield, respectively, using the two-step procedure (Table 4, entries 1 and 2). 2,4-Hexadienal afforded the corresponding 2-pentadienyl oxazole in 60% yield (Table 4, entry 3). In contrast, 2-hexenal afforded the 2-pentenyl oxazole in 28% yield (Table 4, entry 4). 2-Alkynyl aldehydes also afforded the corresponding 2-alkynyl oxazoles (Table 4, entries 5 and 6). Attempts to use the one-pot method (i.e., Table 3, condition B) for any of the substrates in Table 4 resulted in a progressive darkening of the reaction mixtures from which only traces of the intended products were obtained.[22]

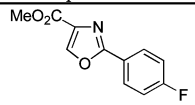
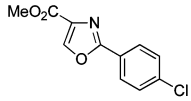
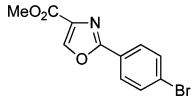
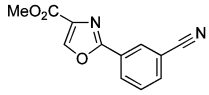
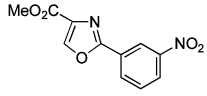
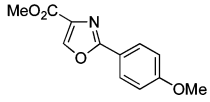
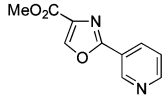
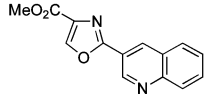
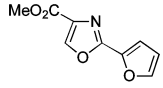
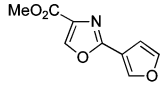
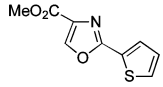
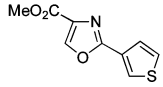
In conclusion, an efficient method for the expedient synthesis of 2,4-disubstituted oxazoles from aldehydes is described. The method relies on the oxidation of an oxazolidine formed from the condensation of serine with an aldehyde and proceeds through a 2,5-dihydrooxazole inter-

(21) Glorius, F.; Pfaltz, A. *Org. Lett.* **1999**, *1*, 141.

(22) Attempts to prepare a representative 2-alkyloxazole using hydrocinnamaldehyde under conditions A or B afforded a complex mixture of the intended 2-phenethyloxazole, the intermediate 2-phenethyl-2,5-dihydrooxazole, and other unidentified byproducts.

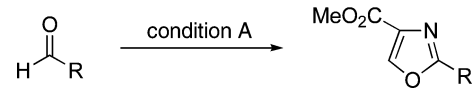
Table 3. Preparation of 2-Aryl and 2-Heteroaryl Oxazoles from Aldehydes

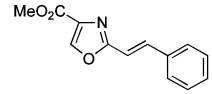
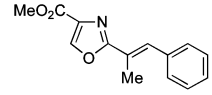
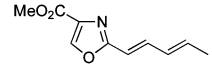
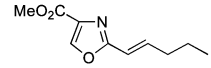
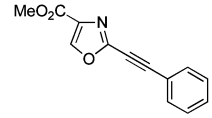
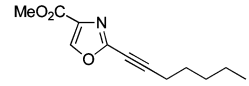


entry	product	yield (%),[a] (conditions)[b]
1		74 (A) 78 (B)
2		76 (A) 73 (B)
3		74 (A) 75 (B)
4		63 (A) 80 (B)
5		63 (A) 53 (B)
6		61 (A) 60 (B)
7		71 (A) 57 (B)
8		68 (A) 76 (B)
9		64 (A) 67 (B)
10		67 (A) 59 (B)
11		68 (A) 66 (B)
12		69 (A) 66 (B)

[a] Yields were determined after purification by column chromatography on silica gel. [b] Condition A: (i) Ser-OMe·HCl (1 equiv), Et_3N (2 equiv), $MgSO_4$ (1 equiv), THF, rt, 12 h, then filter; (ii) $BrCCl_3$ (3 equiv), DBU (3 equiv), CH_2Cl_2, 0 °C to rt, 12 h. Condition B: Ser-OMe·HCl (1 equiv), K_2CO_3 (2 equiv), DMA, rt, 12 h, then $BrCCl_3$ (3 equiv), DBU (3 equiv), 0 °C to rt, 12 h.

Table 4. Preparation of 2-Alkenyl and 2-Alkynyl Oxazoles from Aldehydes



entry[a]	product	yield (%)[b]
1		72
2		70
3		60
4		28
5		61
6		76

[a] Condition A: (i) Ser-OMe·HCl (1 equiv), Et_3N (2 equiv), $MgSO_4$ (1 equiv), THF, rt, 12 h, then filter; (ii) $BrCCl_3$ (3 equiv), DBU (3 equiv), CH_2Cl_2, 0 °C to rt, 12 h. [b] Yields were determined after purification by column chromatography on silica gel.

mediate. In contrast to other procedures, the method utilizes readily available aldehydes, does not require intermediate purification, and affords the oxazoles under relatively mild conditions. Furthermore, the results demonstrate how the careful consideration of potential reactivities can lead to a more efficient and expedient synthesis of an important heterocyclic system.

Acknowledgment. The author acknowledges Merck Research Laboratories for supporting this research. Charles Ross (MRL West Point) is acknowledged for the acquisition of high resolution mass spectrometry data.

Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL101346W