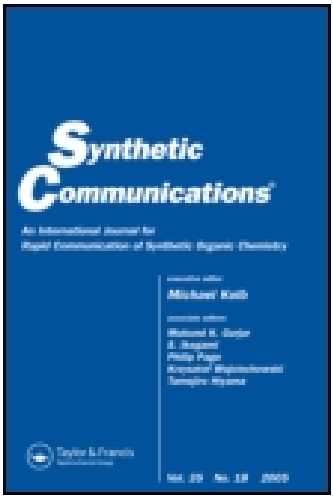


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Facile One-Pot Method for the Synthesis of Novel N-Dichloroacetyl-1,3-oxazolidines

Ying Fu [a b], Honggang Fu [a c], Fei Ye [b], Jingdong Mao [d] & Xiaotian Wen [b]

[a] Department of Applied Chemistry, Harbin Institute of Technology, Harbin, Heilongjiang, China

[b] College of Science, Northeast Agricultural University, Harbin, Heilongjiang, China

[c] School of Chemistry and Materials Science, Heilongjiang University, Harbin, Heilongjiang, China

[d] Department of Chemistry and Biochemistry, Old Dominion University, Norfolk, Virginia, USA

Published online: 16 Jun 2009.

To cite this article: Ying Fu, Honggang Fu, Fei Ye, Jingdong Mao & Xiaotian Wen (2009) Facile One-Pot Method for the Synthesis of Novel N-Dichloroacetyl-1,3-oxazolidines, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:14, 2454-2463, DOI: 10.1080/00397910802585860

To link to this article: http://dx.doi.org/10.1080/00397910802585860

Synthetic Communications®, 39: 2454–2463, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802585860

Taylor & Francis
Taylor & Francis Group

Facile One-Pot Method for the Synthesis of Novel N-Dichloroacetyl-1,3-oxazolidines

Ying Fu,[1,2] Honggang Fu,[1,3] Fei Ye,[2] Jingdong Mao,[4] and Xiaotian Wen[2]

[1]Department of Applied Chemistry, Harbin Institute of Technology, Harbin, Heilongjiang, China
[2]College of Science, Northeast Agricultural University, Harbin, Heilongjiang, China
[3]School of Chemistry and Materials Science, Heilongjiang University, Harbin, Heilongjiang, China
[4]Department of Chemistry and Biochemistry, Old Dominion University, Norfolk, Virginia, USA

Abstract: A short and efficient route to synthesis and structural characterization of a series of novel N-dichloroacetyl-5-ethyl-1,3-oxazolidine derivatives has been developed. These new compounds, characterized by the substitution at position 2 by alkyls, cycloalkanes, benzyls, or aryls, have been synthesized in good yields via a sequential procedure involving cycloaddition, condensation, and acylation. All the compounds are characterized by infrared, ^{1}H NMR, and ^{13}C NMR.

Keywords: Acylation, condensation, cycloaddition, dichloroacetyl oxazolidines, synthesis

Substituted oxazolidines are important synthetic targets because of their biological activity, pharmacological activity, and extensive use as chiral auxiliaries for synthesis of many chiral compounds.[1–6] In addition, the discovery of N-dichloroacetyl oxazolidine as an herbicide safener has drawn widespread attention in agricultural biochemistry. Some new

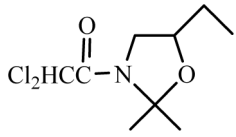
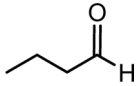
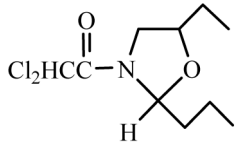
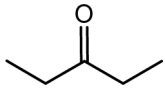
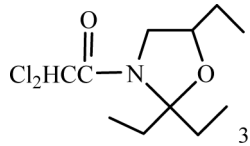
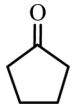
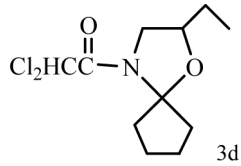
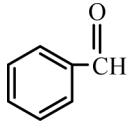
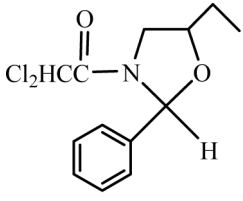
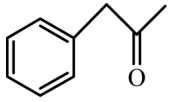
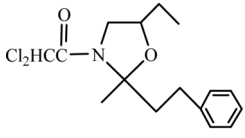
Received July 18, 2008.
Address correspondence to Honggang Fu, Department of Applied Chemistry, Harbin Institute of Technology, Harbin, 150001, China. E-mail: fuying@neau.edu.cn

methods for the synthesis of oxazolidine derivatives have been described and are generally classified into two main approaches in the literature.[7,8] The first path, more frequently used, was based on the reduction of amino acids with $NaBH_4/I_2$ or $LiAlH_4$ to yield the desired amino alcohols, followed by the condensation of β-amino alcohol with aldehydes or ketones in the presence of 4 Å molecular sieves with dichloromethane as solvent, resulting in the complete formation of the corresponding oxazolidines.[9] The second approach consists of a three-atom plus a two-atom ring closure in which the carbonyl group provided the two atoms.[10] The acylation of oxazolidines and dichloroacetyl chloride was achieved by using triethylamine as the catalyst and benzene as the reaction medium.[11,12] The literature revealed that there are few synthetic routes to 2-substituted oxazolidines characteristic of alkyls, cycloalkanes, benzyls, and aryls, with the facile one-pot conversion from epoxide with aldehydes or ketones without separating the intermediate and using any catalyst. In our study, we found that the condensation could be carried out without any catalyst and that also it was not necessary to separate the intermediate products. In the acylation, the factors influencing the yield were acid attaching agent, reaction temperature, solvent, and structures of aldehydes or ketones.

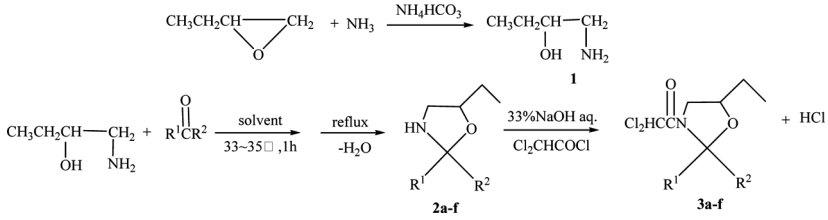
In the present study, to synthesize a novel series of N-dichloroacetyl oxazolidines with high bioactivity, we developed a new, one-pot, three-step synthetic strategy. In this approach, we prepared these compounds through cycloaddition of epoxide with ammonia to produce β-amino alcohol; then a condensation reaction with aldehydes or ketones to form 1,3-oxazolidine; and finally acylation by dichloroacetyl chloride with sodium hydroxide rather than triethylamine as the acid attaching agent. The present procedure required only simple manipulations and inexpensive reagents; thus, it should be appropriate for providing the derivatives in great demand. A series of new N-dichloroacetyl-5-ethyl-1,3-oxazolidine derivatives reported here were characterized by alkyl, cycloalkane, and phenyl at position 2 of the oxazolidine (Table 1). 1,2-Epoxybutyane, a commercially available, cheap starting material, was treated with ammonia water in alkaline solution at 33–35°C for 1.5 h. 1-Amino-2-butanol was obtained in a good yield (74.8%).[13] Oxazolidine ligands **2a–f** were prepared with 1-amino-2-butanol and aldehyde or ketone by heating at reflux for 2 h in solvent without any catalyst. Then the reaction system was cooled, and dichloroacetyl chloride was added with sodium hydroxide as the acid attaching agent to produce the N-dichloroacetyl oxazolidines in good yields (Scheme 1).

We improved the synthetic route by using a different acid attaching agent and reaction temperature. The possible process for the reaction is depicted in Scheme 2. The reaction of aldehyde or ketone with β-amino

Table 1. Formation of N-dichloroacetyl oxazolidines from aldehydes or ketones and amino alcohol

Entry	Aldehyde or Ketone	Product	Solvent	Temp (°C)	Time (h)	Yield (%)
1		 3a	CH_2Cl_2	3–8	1	69.1
2		 3b	CH_2Cl_2	3–8	1	50.2
3		 3c	CH_2Cl_2	3–8	2	54.5
4		 3d	CH_2Cl_2	−5–0	3	32.5
5		 3e	C_6H_6	−5–0	2	47.8
6		 3f	C_6H_6	3–8	3	41.2

alcohol yielded an open-chain imine, which existed in equilibrium with oxazolidine.[14] Because oxazolidine can easily become an imine under alkaline conditions,[15] we choose sodium hydroxide solution rather than

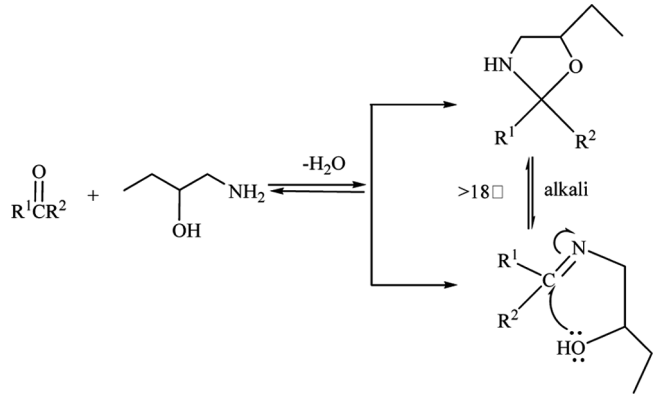


Scheme 1. Route for the synthesis of N-dichloroacetyl oxazolidines.

triethylamine as the acid attaching agent. Triethylamine is soluble in the organic layer and renders the organic phase where oxazolidine is present strongly alkaline. Under the alkaline condition, oxazolidine quickly became the imine, and the desired products cannot be attained or are hard to isolate (Table 2). In contrast, sodium hydroxide is insoluble in the organic phase, and it not only keeps the organic phase weakly alkaline but also reacts quickly with by-product HCl. The resulting NaCl can be easily removed from the organic phase.

By comparing the structures of the substituents at position 2 with the yields, we find that the more complex the structures of the substituents, the less the yields of the desired products. We suspect that the substituents at position 2 increase the steric effect and render acylation difficult (Fig. 1). Consequently, the yields of compounds **3d–f** are less than those of compounds **3a–c**. In addition, the π–π conjugation effect of benzaldehyde makes it difficult to react with amino alcohol and thus decreases the yield of **3e**.

Another factor controlling the yield is the temperature. Under the alkaline condition and as temperature greater than 18°C, oxazolidine



Scheme 2. Equilibrium between imine and oxazolidines.

Table 2. Comparison of two catalysts for the formation of **3a** and **3c**

	Yield (%)	
Compound	$(Et)_3N$	NaOH (aq.)
3a	35.2	69.1
3c	20.1	40.5

easily decomposes to the imine. Furthermore, the reaction of oxazolidine with dichloroacetyl chloride is exothermic. Logically we should employ a low reaction temperature. However, a suboptimal temperature will prolong the time required to add dichloroacetyl chloride and result in superfluous by-products. In the present study, the reaction temperature was optimized at 3–8°C, although for **3d** and **3e** the best reaction temperature is −5 to 0°C. Because benzaldehyde and cyclopentanone are unstable in atmosphere and easy to be oxidated at room temperature, their yields were increased at −5 to 0°C.

Stirring time also influences the yields. If the structure of ketone is complex, the yield can be increased by using a long stirring time (**3d** and **3f**), except for **3e** (Table 1). In the presence of sodium hydroxide

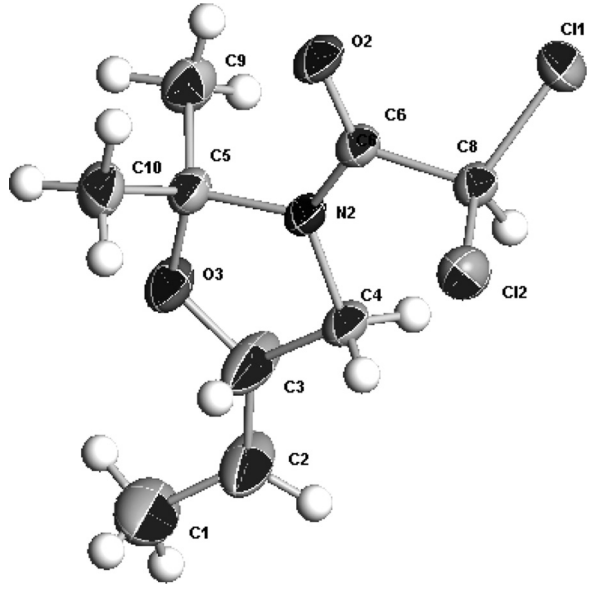


Figure 1. Molecular structure of **3a**.

solution, the Cannizzaro reaction takes place; the benzaldehyde changes to benzoic acid and benzyl alcohol, making the equilibrium (Scheme 2) back to the reactant.

Finally, in the present study, the single crystal of **3a** was obtained by dissolving it in the solvent of ethyl acetate and light petroleum, followed by slow evaporation. The colorless crystal with a dimension of 0.22 mm × 0.18 mm × 0.12 mm was selected for x-ray diffraction analysis. The bond lengths and bone angles of the oxazolidine ring were both normal, with the bond lengths of C5–N2 and C5–O3 close to the typical C–N and C–O bond lengths, respectively (Fig. 1). The C6–O2 bond length of 1.215(3) Å was indicative of a double bond C=O (1.21–1.23 Å). The p–π conjunction between N2 and C6–O2 resulted in shorter bond length of C6–N2 [1.333(4) Å] than the typical C–N bond length (1.472 Å) (Fig. 1).

In conclusion, we have developed a novel, efficient, one-pot synthesis of N-dichloroacetyl-1,3-oxazolidine derivatives via cycloaddition, condensation, and acylation. We obtained the single crystal structure for **3a** for the first time. The advantages of our approach are mild reaction conditions, short reaction time, easy workup, and good yields of products.

EXPERIMENTAL

The infrared (IR) spectra were taken on a KJ-IN-27 G IR spectrophotometer (KBr). The ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Bruker Avance 300-MHz nuclear magnetic resonance (NMR) spectrometer with $CDCl_3$ as the solvent and tetramethylsilane as the internal standard. The melting points were determined on a Beijng Taike melting-point apparatus (X-4) and are uncorrected.

Typical Procedure for the Preparation of Compounds 3a–f

1-Amino-2-butanol (0.034 mol) and 0.034 mol of the aldehyde or ketone were mixed with 20 mL of benzene. The reaction mixture was stirred at 33–35°C for 1 h. Then, the mixture was heated to reflux, water was stripped off, the mixture was cooled to 0°C, and 4.2 mL of 33% sodium hydroxide solution were added. Afterward, 4.0 mL (0.041 mol) of dichloroacetyl chloride were added dropwise with stirring and cooling in an ice bath. Stirring continued for 1 h. The organic phase was rinsed with water until pH 7. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed under vacuum. Compounds **3b** and **3d–3f** were separated on silica gel by column chromatography. The crude products **3a** and **3c** were recrystallized with ethyl acetate and light petroleum until white crystals were obtained.

Spectral and Crystal Data for New Compounds

N-Dichloroacetyl-2,2-dimethyl-5-ethyl-1,3-oxazolidine (**3a**)

White crystal, mp 97–98°C. IR(KBr, $\tilde{\nu}/cm^{-1}$): 3049–2872 (C-H), 1670 (C=O), 1414 (Cl_2HC-CO); ^1H NMR ($CDCl_3$, 300 MHz, δ ppm): 6.04 (s, 1H, Cl_2CH-), 3.91–4.10 (m, 2H, -N-CH_2-C), 3.27–3.34 (t, 1H, -C-CH-O-), 1.66 (s, 6H, CH_3-C-CH_3), 1.56–1.59 (m, 2H, C-CH_2-C), 0.97–1.02 (t, 3H, -C-CH_3); ^{13}C NMR ($CDCl_3$, 300 MHz, δ ppm): 159.634, 96.372, 75.926, 66.938, 50.526, 25.758, 25.479, 23.144, 9.730.

Crystal data of compound **3a**: $C_9H_{15}Cl_2NO_2$, monoclinic, space group P2(1)/c, a = 6.288(5) Å, b = 10.736(8) Å, c = 17.842(13) Å, α = 90°, β = 93.632(12)°, γ = 90°, V = 1202.1(16) $Å^3$, Z = 16, D_c = 1.734 g cm^{-3}, μ = 0.988 mm^{-1}, F(000) = 624. Independent reflections were obtained in the range of $2.97° < \theta < 28.29°$, 2955. The final least-square cycle gave $R_1 = 0.0593$, $\omega R_2 = 0.1609$ for 1846 reflections with $I > 2\sigma(I)$.). The maximum and minimum differences of peak and hole are 0.510 and −0.287 e/$Å^3$, respectively. Crystal data of the compound **3a** was measured on a Brukcr AXS CCD area-detector diffractometer using graphite monochromated Mo *K*a radiation (λ = 0.071073 nm) at 273(2) K. The structure was solved by direct methods using the SHELXS-97 program. All the nonhydrogen atoms were refined anisotropically by the full-matrix least square method on F2. Crystallographic data (excluding structure factors) for the structure in this article have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 686705. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)336033 or e-mail: dposit@ccdc.cam.ac.uc]. Each request should be accompanied by the complete citation of this article.

N-Dichloroacetyl-2-propyl-5-ethyl-1,3-oxazolidine (**3b**)

Oil, IR (KBr, $\tilde{\nu}/cm^{-1}$): 3151–2876 (C-H), 1670 (C=O), 1420 (Cl_2HC-CO); ^1H NMR ($CDCl_3$, 300 MHz, δ ppm): 6.05 (s, 1H, Cl_2CH-), 5.42–5.46 (m, 1H, H-C), 4.04–4.28 (m, 2H, -N-CH_2-C), 3.53–3.58 (t, 1H, -C-CH-O-), 1.61–1.81 (m, 4H, C-CH_2-CH_2-C), 1.39–1.44 (m, 2H, C-CH_2-C), 0.93–1.03 (m, 6H, -C-CH_3, -C-CH_3); ^{13}C NMR ($CDCl_3$, 300 MHz, δ ppm): 160.580, 90.603, 78.866, 66.572, 50.456, 34.625, 25.892, 17.648, 13.917, 9.762.

N-Dichloroacetyl-2,2,5-triethyl-1,3-oxazolidine (**3c**)

White crystal, mp 53–54°C. IR (KBr, $\tilde{\nu}/cm^{-1}$): 3000–2852 (C-H), 1670 (C=O), 1434 (Cl_2HC-CO); ^1H NMR ($CDCl_3$, 300 MHz, δ ppm): 6.09

(s, 1H, Cl_2CH-), 3.97–4.15 (m, 2H, -N-CH_2-C), 3.23–3.29 (m, 1H, -C-CH-O-), 2.20–2.26 (m, 2H, -C-CH_2-C), 1.95–2.04 (m, 2H, C-CH_2-C), 1.71–1.78 (m, 2H, C-CH_2-C), 0.99–1.01 (t, 3H, -C-CH_3), 0.88–0.91 (t, 3H, -C-CH_3), 0.77–0.78 (t, 3H, -C-CH_3); ^{13}C NMR ($CDCl_3$, 300 MHz, δ ppm): 159.525, 101.469, 71.994, 67.031, 51.714, 29.019, 27.951, 26.130, 9715, 8.293, 7.034.

N-Dichloroacetyl-2-ethyl-1-oxa-4-aza-spiro-4,4-noncane (**3d**)

White crystal, mp 78–79°C. IR (KBr, $\tilde{\nu}/cm^{-1}$): 3074–2869 (C-H), 1680 (C=O), 1440 (Cl_2HC-CO); ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 6.04 (s, 1H, Cl_2CH-), 3.84–3.96 (m, 2H, -N-CH_2-C), 3.23–3.29 (t, 1H, -C-CH-O-), 2.15–2.51 (m, 2H, C-CH_2-C), 1.63–1.90 [m, 8H, -$(CH_2)_4$] 0.98–1.00 (t, 3H, -C-CH_3); ^{13}C NMR ($CDCl_3$, 300 MHz, δ ppm): 159.533, 105.859, 76.345, 66.851, 50.493, 35.661, 34.921, 25.384, 25.247, 9.752.

N-Dichloroacetyl-2-phenyl-5-ethyl-1,3-oxazolidine (**3e**)

Oil, IR (KBr, $\tilde{\nu}/cm^{-1}$): 3980–2860(C-H), 1685 (C=O), 1400 (Cl_2HC-CO); ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 7.26–7.45 (m, 5H, C_6H_5-), 6.46 (s, 1H, Cl_2CH-), 6.12 (s, 1H, C-H), 3.98–4.25 (m, 2H, -N-CH_2-C), 3.71–3.74 (m, 1H, -C-CH-O-), 1.69–1.79 (m, 2H, C-CH_2-C), 0.98–1.00 (t, 3H, -C-CH_3); ^{13}C NMR ($CDCl_3$, 300 MHz, δ ppm): 150.980, 137.701, 129.284, 129.039, 128.914, 126.475, 126.237, 89.672, 78.464, 66.469, 49.472, 25.840, 9.728.

N-Dichloroacetyl-2-methyl-2-phenylethyl-5-ethyl-1,3-oxazolidine (**3f**)

White crystal, mp 72–73°C. IR (KBr, $\tilde{\nu}/cm^{-1}$): 3110–2850 (C-H), 1710 (C = O), 1415 (Cl_2HC-CO); ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 7.17–7.26 (m, 5H, C_6H_5-), 6.05 (s, 1H, Cl_2CH-), 3.96–4.16 (m, 2H, -N-CH_2-C), 3.25–3.31 (m, 1H, -C-CH-O-), 2.66–2.70 (t, 2H, C-CH_2-C), 2.08–2.43 (m, 2H, C-CH_2-C), 1.74–1.77 (m, 2H, C-CH_2-C), 1.58 (s, 3H, -C-CH_3), 1.01–1.06 (t, 3H, -C-CH_3); ^{13}C NMR ($CDCl_3$, 300 MHz, δ ppm): 159.610, 141.610, 128.517, 128.392, 128.340, 125.894, 125.810, 97.986, 75.747, 66.923, 51.346, 38.613, 29.407, 25.500, 22.691, 9.728.

ACKNOWLEDGMENTS

We are grateful for the support from the Natural Science Foundation of Heilongjiang Province (No. B200602), the Research Science Foundation

in Technology Innovation of Harbin (Nos. 2006RFXXN005 and 2007RFQXN017), the Science and Technology Research Project of Heilongjiang Education Department (No. 11521038), and the Northeast Agricultural University Doctor Foundation Project. J. D. M. thanks the Materials Research Science and Engineering Center (MRSEC) at the University of Massachusetts for NMR machine time.

REFERENCES

1. Agami, C.; Couty, F. The use of *N*-boc-1,3-oxazolidines as chiral auxiliaries in asymmetric synthesis. *Eur. J. Org. Chem.* **2004**, *4*, 677–685.
2. Iwata, A.; Tang, H.; Kunai, A.; Ohshita, J.; Yamamoto, Y.; Matui, C. Ring-opening reactions of cyclic acetals and 1,3-oxazolidines with halosilane equivalents. *J. Org. Chem.* **2002**, *67* (15), 5170–5175.
3. Agami, C.; Comesse, S.; Kadouri-Puchot, C. Asymmetric syntheses of new functionalized β-amino alcohols via diastereoselective addition of organometallic reagents onto oxazolidines. *J. Org. Chem.* **2002**, *67* (5), 1496–1500.
4. Adam, W.; Schambony, S. B. Diastereoselective epoxidation of oxazolidine-substituted alkenes by dimethyldioxirane and *m*-chloroperbenzoic acid: Facial control through hydrogen bonding by the urea functionality. *Org. Lett.* **2001**, *3* (1), 79–82.
5. Blanchet, J.; Micouin, B. L.; Husson, H.-P. Synthesis of enantiomerically pure α-substituted propargylic amines by reaction of organoaluminum reagents with oxazolidines. *J. Org. Chem.* **2000**, *65*, 6423–6426.
6. Matola, T.; Jablonkai, I. Safening efficacy of halogenated acetals, ketals, and amides and relationship between the structure and effect on glutathione and glutathione S-transferases in maize. *Crop Protection.* **2007**, *26* (3), 278–284.
7. Katarzyna, B.; Dorota, S.; Tadeusz, G. A concise synthesis of protected diethyl 1-amino-2-hydroxyalkylphosphonates. *Tetrahedron Lett.* **2003**, *44* (25), 4747–4750.
8. Guirado, A.; Andreu, R.; Galvez, J. Direct conversion of 4-amino-2-phenyl-2-oxazolines into either 2-arylimino-1,3-oxazolidine or 2-arylimino-1,3-thiazolidine hydrochlorides. *Tetrahedron Lett.* **2003**, *44* (19), 3809–3821.
9. Kirsten, S.; Frank, G. Efficient oxidative synthesis of 2-oxazolines. *Synthesis* **2006**, *18*, 2996–3002.
10. Katritzky, A. R.; Feng, D.; Qi, M. The synthesis of 3,5-di- and 3,5,5-trisubstituted-1,3-oxazolidines from primary amines and carbonyl compounds. *Tetrahedron Lett.* **1998**, *39* (38), 6835–6836.
11. Taylor, W. G.; Schreck, C. E. Synthesis and mosquito repellent properties of some 2-alkyl-*N*-acetyloxazolidines. *Pestic. Sci.* **1991**, *33* (1), 1–9.
12. Wesley, G. T.; Tse, W. H.; Carl, E. S. Synthesis and mosquito repellent properties of 2,2-dialkyl- and -2-alkyl-4,4-dimethyl-*N*-acetyloxazolidines. *Pestic. Sci.* **1996**, *46* (4), 307–314.
13. Jiying, C.; Qinfen, H.; Wensheng, C.; Fengze, L. Preparation of 2-hydroxyethylamine and 2-hydroxypropylmine. *Pharm. Ind.* **1987**, *18* (11), 14–16.

14. Nandkishor, N. K.; Girdharilal, B. T.; Sumit, V. G. Efficient oxidative conversion of aldehydes to 2-substituted oxazolines and oxazines using (diacetoxyiodo)benzene. *Synlett* **2007**, *12*, 1921–1924.
15. Manas, K. G.; Koena, G. Lewis acid mediated nucleophilic ring opening followed by cycloaddition of 2-aryl-N-tosylaziridines with carbonyl compounds: Further support towards an SN_2-type mechanism. *Tetrahedron Lett.* **2007**, *48* (18), 3191–3195.