HETEROCYCLES, Vol. 65, No. 12, 2005, pp. 2885 - 2892
Received, 26th July, 2005, Accepted, 22nd September, 2005, Published online, 22nd September, 2005

SYNTHESIS OF FUNCTIONALIZED 5,5-DISUBSTITUTED ISOXAZOLINES *VIA* 1,3-DIPOLAR CYCLOADDITION REACTIONS OF GEMINAL DISUBSTITUTED ALKENES

Ashton T. Hamme, II,* Jianping Xu, Jun Wang, Tiffany Cook, and Erick Ellis

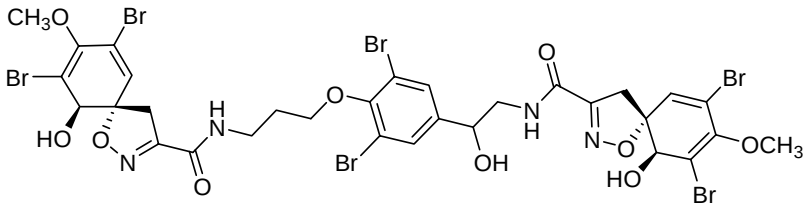
Department of Chemistry, Jackson State University, Jackson, Mississippi 39217, USA

e-mail: ashton.t.hamme@jsums.edu

Abstract – Regioselective syntheses of functionalized 5,5-disubstituted 2-isoxazolines were achieved through 1,3-dipolar cycloaddition reactions of various aromatic nitrile oxides with geminal disubstituted alkenes.

INTRODUCTION

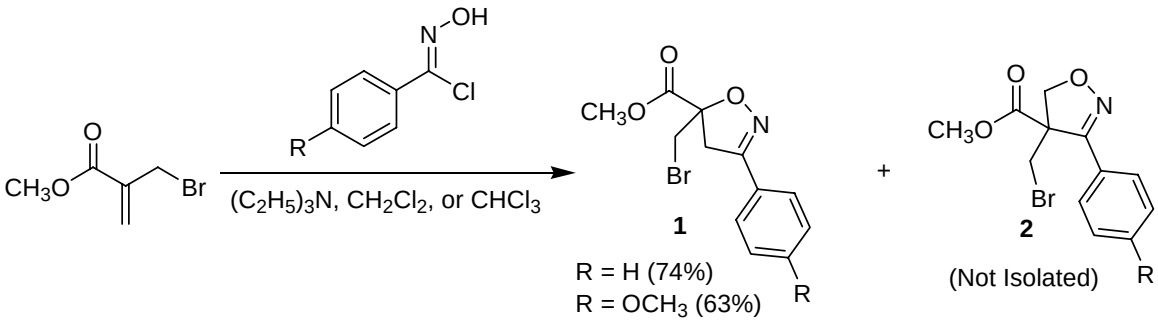
The 1,3-dipolar cycloaddition reaction of a nitrile oxide with an alkene provides an important method towards the synthesis of complex isoxazoles,[1] isoxazolines,[2] γ-amino alcohols,[3] β-hydroxy ketones,[4] and natural products.[5] A number of 1,3-dipolar cycloaddition synthetic methodologies involve 1,1-disubstituted alkenes. Synthetic and theoretical studies of the regioselectivity of the cycloaddition of nitrile oxides with 1,1-disubstituted alkenes show that the oxygen from the nitrile oxide is usually attached to the most substituted carbon of the dipolarophile thereby giving the 5,5-disubstituted 2-isoxazoline as the major product.[6,7] As part of our synthetic studies toward the synthesis of carbocyclic and heterocyclic analogues of spiroisoxazoline containing natural products, such as 11-deoxyfistularin-3,[8] the synthesis of 5,5-disubstituted isoxazolines that possess functional groups that have the potential to be further elaborated into spiroisoxazolines was investigated.[9] With this goal in mind, we decided to use 1,1-disubstituted alkenes outside of the usual Baylis-Hillman adducts or aromatic ketones or esters as the dipolarophile.[6,10] Described below are the results of our investigation of 1,3-dipolar cycloaddition reactions of electronically diverse nitrile oxides and 1,1-disubstituted alkenes that contain carbomethoxy, bromo, bromomethyl, bis-chloromethyl, bis-hydroxymethyl, and acetylamino functional groups.



11-Deoxyfistularin-3

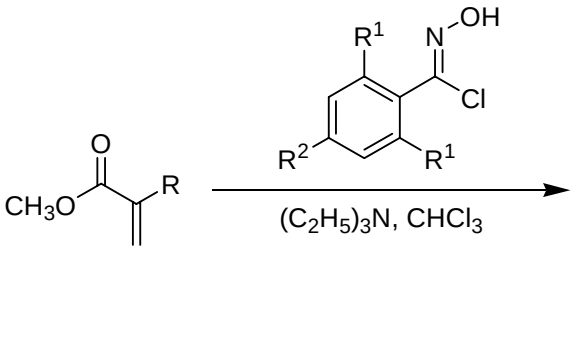
RESULTS AND DISCUSSION

The aromatic nitrile oxides were generated from the corresponding α-chlorobenzaldoximes.[11] Three electronically different α-chlorobenzaldoximes (4-methoxy, unsubstituted, and 2,6-dichloro) were prepared in order to determine if the electron density of the aromatic ring would affect the chemical yields and regioselectivity of the 1,3-dipolar cycloadditions with geminal-disubstituted alkenes. Our first examples involve the cycloaddition of either methoxy or unsubstituted aromatic nitrile oxides, which were generated *in situ* with triethylamine and the analogous chlorobenzaldoxime, with the α-bromomethyl unsaturated ester in either dichloromethane or chloroform. (Scheme 1) In these examples, only the 5,5-disubstituted 2-isoxazolines were isolated in 74% and 63% yields from the unsubstituted and 4-methoxyphenyl nitrile oxides respectively. The substitution pattern of the substituted isoxazoline was elucidated through the ^{1}H and ^{13}C NMR chemical shifts of the methylene protons (doublet, 3.6 and 4.0 ppm) and carbon (42.6 ppm) of the isoxazoline ring.[6]



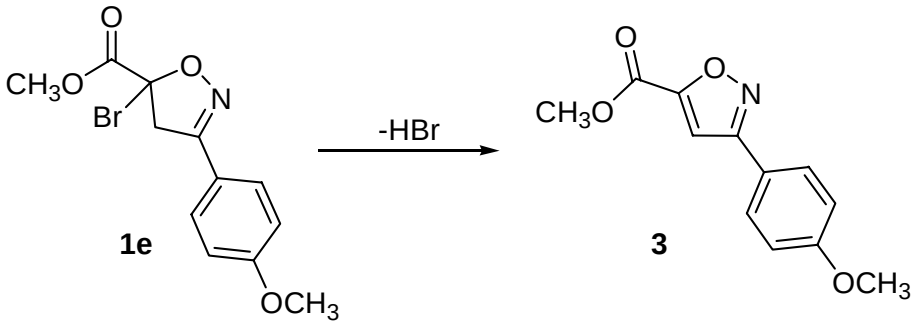
Scheme 1

A number of carbon-substituted acrylates were investigated as dipolarophiles in the 1,3-dipolar cycloaddition reaction. Scheme 2 summarizes the types of 2-substituted acrylate methyl esters that were used in this reaction as well as their chemical yields. The highest yielding (99%) reaction involved the reaction of methyl methacrylate with 4-methoxybenzonitrile oxide. The methyl methacrylate was reacted with only one nitirle oxide due to the lack of electrophilic functionality on the pendant methyl substituent of **1d**. The reaction of 4-methoxybenzonitrile oxide with methyl α-bromoacrylate afforded only 22% of the corresponding 5,5-isoxazoline (**1e**) which quickly aromatized to the corresponding isoxazole (**3**) through dehydrohalogenation[12] as shown in Scheme 3.



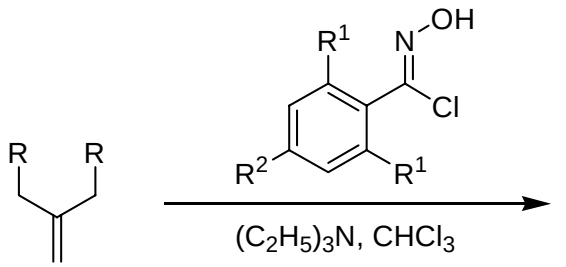
	R	R^1	R^2	% Yield
1a	CH_2Br	H	H	74
1b	CH_2Br	H	OCH_3	63
1c	CH_2Br	Cl	H	71
1d	CH_3	H	H	99
1e	Br	H	OCH_3	22

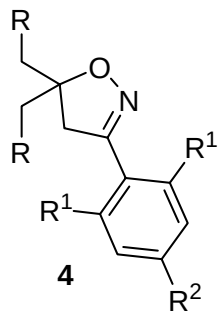
Scheme 2



Scheme 3

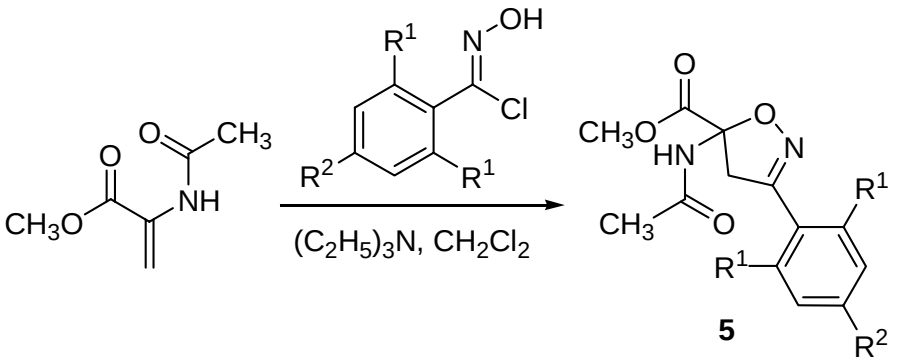
We further explored the scope and limitations of the various 1,1-disubstituted alkenes by reacting 1,1-dichloromethyl- and 1,1-dihydroxymethylalkenes with aryl nitrile oxides as shown in Scheme 4. The chemical yields of the reactions involving the dichloromethylalkenes and the aromatic 1,3-dipoles were between 48%-71%, and only the 5,5-disubstituted isoxazolines were isolated. The 1,3-dipolar cycloaddition of 2-acetylaminomethyl acrylate and the functionalized aryl nitrile oxides afforded the analogous isoxazolines in 66%-72% yield as the 5,5-disubstituted regioisomer as shown in Scheme 5.





	R	R^1	R^2	% Yield
4a	Cl	H	H	48
4b	Cl	H	OCH_3	69
4c	Cl	Cl	H	71
4d	OH	H	H	65
4e	OH	H	OCH_3	71
4f	OH	Cl	H	60

Scheme 4



	R^1	R^2	% Yield
5a	H	H	72
5b	H	OCH_3	66
5c	Cl	H	67

Scheme 5

In summary, our studies of the reaction of various aromatic nitrile oxides with a number of functionalized geminal disubstituted alkenes show that only the 5,5-disubstituted 2-isoxazoline was isolated in moderate to good yield. The potentially reactive functional groups on the dipolarophile were also compatible with the moderately basic reaction conditions.

EXPERIMENTAL

All chemical were purchased from commercial vendors and used without purification. Analytical TLC was performed on precoated aluminum plates (Merck silica gel 60, F254) and was visualized with UV light. Products of reactions were purified by flash column chromatography over Merck Silica Gel 60 (230-400 mesh). NMR spectra (^{1}H at 250 or 300 MHz, ^{13}C at 62.9 or 75 MHz) were recorded in $CDCl_3$ as the solvent, and chemical shifts are reported in parts per million relative to internal solvent signal. IR spectra were taken on a Nicolet Model Nexus 670 FTIR spectrophotometer. HRMS spectra were obtained from a Finnigan FTMS-2001 mass spectrometer.

General Procedure for the 1,3-Dipolar Cycloaddition

A solution of the alkene (3 mmol) and the hydroximinoyl chloride (3 mmol) in 18 mL of either dry chloroform or dichloromethane was treated with triethylamine (334 mg, 3.3 mmol). The reaction mixture was stirred at rt until the disappearance of the starting materials, as evidenced by TLC. After the reaction was complete, the solution was washed five times with water, the organic layer was dried with anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The crude products were purified by flash column chromatography over silical gel using hexanes-ethyl acetate (4:1) as an eluent system. The yields of the 5,5-disubstituted 2-isoxazolines are shown in Schemes 2, 4 and 5.

Methyl 5-bromomethyl-3-phenyl-4,5-dihydroisoxazole-5-carboxylate (1a)

After column chromatography (hexanes-ethyl acetate, 4:1), this compound was obtained as colorless solid, mp 67-70 ^{o}C, IR (CaF_2, CCl_4) ν 1751 cm^{-1}. ^{1}H NMR: δ 3.58 (d, J=17.4 Hz, 1H), 3.66 (d, J=10.4 Hz, 1H), 3.89 (s, 3H), 3.92 (d, J=10.4 Hz, 1H), 4.09 (d, J=17.4 Hz, 1H), 7.44-7.47 (m, 3H), 7.68-7.72 (m, 2H); ^{13}C

NMR: δ 33.4, 42.5, 53.4, 88.1, 127.0, 128.5, 128.8, 130.7, 156,3, 168.7. HR-MS *m/z* (M^+ + Na): Calcd for $C_{12}H_{12}NO_3BrNa$ (M^+ + Na): 319.9893. Found: 319.9887.

Methyl 5-bromomethyl-3-(4-methoxyphenyl)-4,5-dihydro-isoxazole-5-carboxylate (1b)

After column chromatography (hexanes-ethyl acetate, 4:1), this compound was obtained as colorless solid, mp 93-95 ^oC, IR (CaF_2, CCl_4) ν 1754 cm^{-1}. ^1H NMR: δ 3.54 (d, J=17.3 Hz, 1H), 3.64 (d, J=10.6 Hz, 1H), 3.86 (s, 3H), 3.88 (s, 3H), 3.94 (d, J=10.6, 1H), 4.05 (d, J=17.3Hz, 1H), 6.95 (d, J=8.9 Hz, 2H), 7.63 (d, J=8.9 Hz, 2H); ^{13}C NMR: δ 33.6, 42.8, 53.6, 55.5, 80.1, 114.4 (2C), 121.0, 128.7 (2C), 156.0, 161.7, 169.0. HR-MS *m/z* (M^+ + Na): Calcd for $C_{13}H_{14}NO_4BrNa$ (M^+ + Na): 349.9998. Found: 350.0009.

Methyl 5-bromomethyl-3-(2,6-dichlorophenyl)-4,5-dihydroisoxazole-5-carboxylate (1c)

After column chromatography (hexanes-ethyl acetate, 4:1), this compound was obtained as colorless solid, mp 112-114 ^oC, IR (CaF_2, CCl_4) ν 1754 cm^{-1}. ^1H NMR: δ 3.52 (d, J=17.9 Hz,1H), 3.73 (d, J=10.4 Hz, 1H), 3.93 (s, 3H), 3.95 (d, J=10.4 Hz, 1H), 4.01 (d, J=17.9 Hz, 1H), 7.30-7.42 (m, 3H); ^{13}C NMR: δ 32.8, 44.6, 53.5, 88.6, 127.5, 128.2, 131.4, 136.1, 153.9, 168.3. HR-MS *m/z* (M^+ + Na): Calcd for $C_{12}H_{10}NO_3BrCl_2Na$ (M^+ + Na): 387.9113. Found: 387.9110.

Methyl 5-methyl-3-phenyl-4,5-dihydroisoxazole-5-carboxylate (1d)

After column chromatography (hexanes-ethyl acetate, 4:1), this compound was obtained as pale yellow solid, mp 56-57 ^oC, IR (KBr) ν 1750 cm^{-1}; ^1H NMR: δ 1.72(s, 3H), 3.23(d, J=16.9 Hz, 1H), 3.81(s, 3H), 3.89(d, J=16.9 Hz, 1H), 7.38-7.42 (m, 3H), 7.64-7.68 (m, 2H); ^{13}C NMR: δ 23.7, 45.0, 53.0, 86.3, 126.9, 128.9, 129.2, 130.4, 156.4, 172.7. HR-MS *m/z* (M^+ + Na): Calcd for $C_{12}H_{13}NO_3Na$ (M^+ + Na): 242.0788. Found: 242.0781.

Methyl 3-(4-methoxyphenyl)isoxazole-5-carboxylate (3)

After column chromatography (hexanes-ethyl acetate, 4:1), this compound was obtained as pale yellow solid, mp 118-119 ^oC, IR (KBr) ν 1736 cm^{-1}; ^1H NMR: δ 3.86(s, 3H), 3.99(s, 3H), 7.00(d, J=8.9 Hz, 2H), 7.20(s, 1H), 7.76(d, J=8.9 Hz, 2H); ^{13}C NMR: δ 52.9, 55.5, 107.4, 114.7, 120.6, 128.4, 157.4, 160.6, 161.6, 162.7. HR-MS *m/z* (M^+ + Na): Calcd for $C_{12}H_{11}NO_4Na$ (M^+ + Na): 256.0586. Found: 256.0587.

5,5-Bischloromethyl-3-phenyl-4,5-dihydroisoxazole (4a)

This compound was obtained as colorless solid, mp 64-66 ^oC, IR (CaF_2, CCl_4) ν 3015 cm^{-1}. ^1H NMR: δ 3.55 (s, 2H), 3.78 (d, J=11.7 Hz, 2H), 3.89 (d, J=11.7 Hz, 2H), 7.42-7.45 (m, 3H), 7.65-7.69 (m, 2H); ^{13}C NMR: δ 41.4, 45.8, 87.8, 126.7, 128.7, 128.8, 130.6, 156.3. HR-MS *m/z* (M^+ + 1): Calcd for $C_{11}H_{12}NOCl_2$: 244.0296. Found: 244.0292

5,5-Bischloromethyl-3-(4-methoxyphenyl)-4,5-dihydroisoxazole (4b)

After column chromatography (hexanes-ethyl acetate, 4:1), this compound was obtained as colorless solid, mp 101-103 ^oC, IR (CaF_2, CCl_4) ν 2980, 2850, 1607, 1256, 1176 cm^{-1}. ^1H NMR: δ 3.46 (s, 2H), 3.79 (d, J=11.7 Hz, 2H), 3.87 (s, 3H), 3.90 (d, J=11.7 Hz, 2H), 6.94 (d, J=8.8 Hz, 2H), 7.63 (d, J=8.8 Hz, 2H); ^{13}C

NMR: δ 41.5, 45.7, 55.2, 87.2, 114.0, 121.0, 128.1, 155.7, 161.2. HR-MS *m/z* (M^+ + 1): Calcd for $C_{12}H_{14}NO_2Cl_2$ (M^+ + 1): 274.0402. Found: 274.0392.

5,5-Bischloromethyl-3-(2,6-dichlorophenyl)-4,5-dihydroisoxazole (4c)

After column chromatography (hexanes-ethyl acetate, 4:1), this compound was obtained as colorless solid, mp 88-90 °C, IR (CaF_2, CCl_4) ν 2957, 1581, 1559, 1431, 1334, 1194 cm^{-1}. ^1H NMR: δ 3.41 (s, 2H), 3.87 (d, J=11.7 Hz, 2H), 3.95 (d, J=11.7 Hz, 2H), 7.35-7.42 (m, 3H); ^{13}C NMR: δ 44.0, 45.8, 88.7, 128.1, 128.6, 131.9, 135.3, 154.5. HR-MS *m/z* (M^+ + 1): Calcd for $C_{11}H_{10}NOCl_4$ (M^+ + 1): 311.9516. Found: 311.9529.

(5-Hydroxymethyl-3-phenyl-4,5-dihydroisoxazol-5-yl)methanol (4d)

After column chromatography (hexanes-ethyl acetate, 4:1), this compound was obtained as colorless solid, mp 120-122 °C, IR (CaF_2, CCl_4) ν 3290, 2927, 1557, 1543, 1243, 1211, 1165 cm^{-1}. ^1H NMR: δ 1.84-2.20 (br s, 2H), 3.38(s, 2H), 3.77 (d, J=11.9 Hz, 2H), 3.87 (d, J=11.9 Hz, 2H), 7.41-7.45 (m, 3H), 7.67-7.71 (m, 2H); ^{13}C NMR: δ 38.5, 64.3, 89.8, 126.7, 128.7, 129.3, 130.3, 157.7. HR-MS *m/z* (M^+ + Na): Calcd for $C_{11}H_{13}NO_3Na$ (M^+ + Na): 230.0788. Found: 230.0785.

[5-Hydroxymethyl-3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]methanol (4e)

After column chromatography (hexanes-ethyl acetate, 4:1), this compound was obtained as colorless solid, mp 90-93 °C, IR (CaF_2, CCl_4) ν 3300, 2930, 1557, 1542, 1253 cm^{-1}. ^1H NMR: δ 1.97-2.32 (br s, 2H), 3.35 (s, 2H), 3.75 (d, J=12.0 Hz, 2H), 3.84 (d, J=12.0 Hz, 2H), 3.86 (s, 3H), 6.94 (d, J=8.9 Hz, 2H), 7.61 (d, J=8.9 Hz, 2H); ^{13}C NMR: δ 38.8, 55.4, 64.3, 89.4, 114.2, 121.9, 128.2, 157.1, 161.3. HR-MS *m/z* (M^+ + Na): Calcd for $C_{12}H_{15}NO_4Na$ (M^+ + Na): 260.0893. Found: 260.0900.

[3-(2,6-Dichlorophenyl)-5-hydroxymethyl-4,5-dihydroisoxazol-5-yl]methanol (4f)

After column chromatography (hexanes-ethyl acetate, 4:1), this compound was obtained as colorless solid, mp 116-119 °C, IR (CaF_2, CCl_4) ν 3316, 2938, 1557, 1429, 1191, 1153 cm^{-1}. ^1H NMR: δ 2.12-2.20 (br s, 2H), 3.29 (s, 2H), 3.83 (d, J=12.1 Hz, 2H), 3.91 (d, J=12.1 Hz, 2H), 7.29-7.41 (m, 3H); ^{13}C NMR: δ 41.3, 64.4, 90.8, 126.3, 128.6, 131.6, 135.4, 156.0. HR-MS *m/z* (M^+ + Na): Calcd for $C_{11}H_{11}NO_3Cl_2Na$ (M^+ + Na): 298.0008. Found: 297.9999.

Methyl 5-Acetylamido-3-phenyl-4,5-dihydroisoxazole-5-carboxylate (5a)

After column chromatography (hexanes-ethyl acetate, 4:1), this compound was obtained as white solid, mp 155-156 °C, IR (KBr) ν 1675,1752 cm^{-1}; ^1H NMR: δ 2.05(s, 3H), 3.88(s, 3H), 3.90(d, J=17.4 Hz, 1H), 4.05(d, J=17.4 Hz, 1H), 6.91(s, 1H), 7.41-7.43 (m, 3H), 7.66-7.69 (m, 2H); ^{13}C NMR: δ 23.3, 43.6, 53.9, 92.1, 127.0, 128.4, 128.8, 130.6, 157.0, 167.9, 170.1. HR-MS *m/z* (M^+ + Na): Calcd for $C_{13}H_{14}N_2O_4Na$ (M^+ + Na): 285.0846. Found: 285.0842.

Methyl 5-Acetylamido-3-(4-methoxyphenyl)-4,5-dihydroisoxazole-5-carboxylate (5b)

This compound was obtained as white solid, mp 155-156 ^{o}C, IR (KBr) ν 1667,1744 cm^{-1}; ^{1}H NMR: δ 2.05(s, 3H), 3.84(s, 3H), 3.88(s, 3H), 3.91(d, J=17.2 Hz, 1H), 4.05(d, J=17.2 Hz, 1H), 6.76(s, 1H), 6.92(d, J=9.0 Hz, 2H), 7.62(d, J=9.0 Hz, 2H); ^{13}C NMR: δ 23.5, 44.2, 53.9, 55.5, 92.2, 114.4, 121.1, 128.8, 156.9, 161.7, 168.0, 170.3. HR-MS *m/z* (M^+ + Na): Calcd for $C_{14}H_{16}N_2O_5Na$ (M^+ + Na): 315.0951. Found: 315.0960.

Methyl 5-Acetylamido-3-(2,6-dichlorophenyl)-4,5-dihydroisoxazole-5-carboxylate (5c)

After column chromatography (hexanes-ethyl acetate, 4:1), this compound was obtained as white solid, mp 184-185 ^{o}C, IR (KBr) ν 1685, 1741 cm^{-1}; ^{1}H NMR: δ 2.10(s, 3H), 3.82(d, J=18.0 Hz, 1H), 3.90(s, 3H), 4.05(d, J=18.0 Hz, 1H), 6.74(s, 1H), 7.29-7.41 (m, 3H); ^{13}C NMR: δ 23.4, 46.0, 54.0, 92.9, 127.5, 128.5, 131.5, 135.4, 155.3, 167.5, 170.2. HR-MS m/z (M^+ + Na): Calcd for $C_{13}H_{12}N_2O_4Cl_2Na$: 353.0066. Found: 353.0062.

ACKNOWLEDGEMENTS

We thank the National Institutes of Health (S06 GM 008047-31, G12RR13459) and the National Science Foundation (HRD-0401730) for generous financial support. T.C. thanks the National Institutes of Health RISE program (5 R25GM067112-02) for a graduate fellowship.

REFERENCES AND NOTES

1. J. W. Bode, Y. Hachisu, T. Matsuura, and K. Suzuki, *Org. Lett.,* 2003, **5**, 391; J. W. Bode, T. M. Hachisu, and K. Suzuki, *Tetrahedron Lett.,* 2003, **44**, 3555.
2. J. W. Bode, N. Fraefel, D. Muri, and E. M. Carreira, *Angew. Chem., Int. Ed.,* 2001, **40**, 2082; J. A. Stack, T. A. Heffner, S. J. Geib, and D. P. Curran, *Tetrahedron,* 1993, **49**, 995.
3. V. Jager and V. Muller, *Tetrahedron Lett.,* 1982, **23**, 4777; V. Jager, V. Muller, and E. F. Paulus, *Tetrahedron Lett.,* 1985, **26**, 2997.
4. J. W. Bode and E. M. Carreira, *Org. Lett.,* 2001, **3**, 1587.
5. J. W. Bode and E. M. Carreira, *J. Am. Chem. Soc.,* 2001, **123**, 3611; A. Brandi, C. M. Franca, A. Goti, and A. Guarna, *Tetrahedron Lett.,* 1992, **33**, 6697.
6. M. Yamauchi, *J. Heterocycl. Chem.,* 2002, **39**, 1013.
7. K. N. Houk, J. Sims, R. E. Duke, Jr., R. W. Strozier, and J. K. George, *J. Am. Chem. Soc.,* 1973, **95**, 7287; K. N. Houk, J. Sims, C. R. Watts, and L. J. Luskus, *J. Am. Chem. Soc.,* 1973, **95**, 7301.
8. R. S. Compagnone, R. Avila, A. I. Suarez, O. V. Abrams, H. R. Rangel, F. Arvelo, I. C. Pina, and E. Merentes, *J. Nat. Prod.,* 1999, **62**, 1443.
9. R. E. Sammelson, C. D. Gurusinghe, J. M. Kurth, M. M. Olmstead, and M. J. Kurth, *J. Org. Chem.,* 2002, **67**, 876.

10. W-C. Cheng, Y. Liu, M. Wong, M. M. Olmstead, K. S. Lam, and M. J. Kurth, *J. Org. Chem.,* 2002, **67**, 5673; A. A. Hagedorn, B. J. Miller, and J. O. Nagy, *Tetrahedron Lett.,* 1980, **21**, 229; R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, and L. Raimondi, *J. Org. Chem.,* 1995, **60**, 4697; B. Das, H. Holla, G. Mahender, J. Banerjee, and M. R. Reddy, *Tetrahedron Lett.,* 2004, **45**, 7347.
11. G. W. Zamponi, S. C. Stotz, R. J. Staples, T. M. Andro, J. K. Nelson, V. Hulubei, A. Blumenfeld, and N. R. Natale, *J. Med. Chem.,* 2003, **46**, 87.
12. A clean ^{1}H NMR spectrum of **1e** could not be obtained due to its rapid loss of HBr. All data were obtained from a pure sample of the resulting isoxazole (**3**).