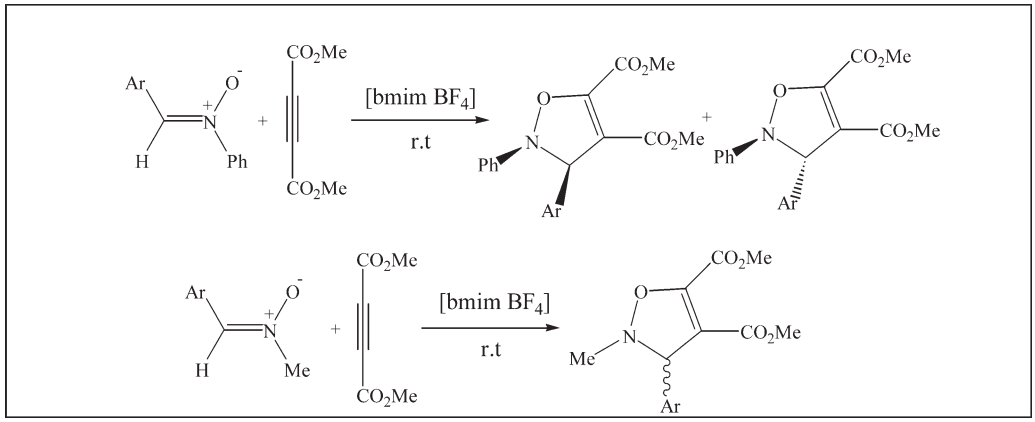
Reaction of *N*-(Phenyl and methyl)-*C*-arylnitrones with DMAD in Ionic Liquid: Efficient Synthesis of Δ^4-Isoxazolines

Hassan Valizadeh,[a,*] Esmail Vesally,[b] and Leila Dinparast[c]

[a]Department of Chemistry, Islamic Azad University, Myianeh Branch, Myianeh, Iran
[b]Payame Noor University (PNU), Zanjan, Iran
[c]Department of Chemistry, Faculty of Science, Azarbaijan University of Tarbiat Moallem, P. O. Box 53714-161, Tabriz, Iran
*E-mail: hvalizadeh2@yahoo.com

Received June 20, 2010
DOI 10.1002/jhet.682
Published online 13 October 2011 in Wiley Online Library (wileyonlinelibrary.com).



Facile synthesis of *N*-(methyl and phenyl)-Δ^4-isoxazolines via the reaction of (Z)-*N*-(methyl and phenyl)-*C*-arylnitrones with dimethyl acethylenedicarboxylate, DMAD, in ionic liquid is described. (Z)-*N*-methyl-*C*-arylnitrones afforded the high yield of *N*-methyl-Δ^4-isoxazolines **4a-4e** in ionic liquid, [bmim]BF_4, at room temperature. However, the reaction of (Z)-*N*-phenyl-*C*-arylnitrones with DMAD afforded the mixtures of cis and trans isomers of related *N*-phenyl-Δ^4-isoxazolines (**5a–j**, **6a–j**) under these conditions.

J. Heterocyclic Chem., **49**, 106 (2012).

INTRODUCTION

Nitrogen and oxygen containing heterocyclic compounds are very important organic compounds because of their wide range of pharmacological activity. Isoxazolines represent one of the active classes of compounds possessing a wide spectrum of biological activities such as antidiabetic [1], diuretic [2], analgesic [3], anthelimentic [4], hypolipaemic [5] and antimicrobial activity [6]. One of the most common procedures for the synthesis of these compounds is cycloaddition reaction of 1,3-dipoles to olefins. The 1,3-diolar cycloaddition, also known as the Huisgen cycloaddition, is a well-known reaction in organic chemistry consisting of the reaction of alkenes with a 1,3-dipolar compounds that allows the synthesis of various heterocycles such as isoxazolines [7]. A range of different substituents can be included in the dipole and the dipolarophile, resulting in a broad range of possible cycloadducts, which can serve as useful synthetic building blocks. These reactions are synthetically very useful because of their high stereospecificity and stereoselectivity [8–10].

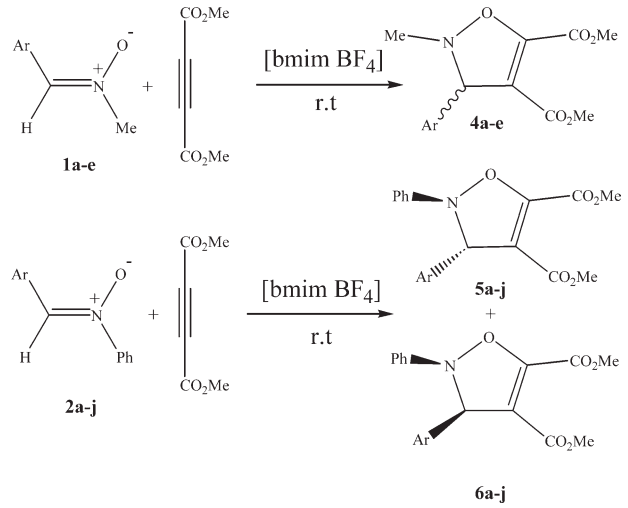
Nitrone 1,3-dipoles have been used for the synthesis of isoxazoline derivatives by 1,3-dipolar cycloaddition reactions [11–21]. Despite the other 1,3-dipoles, nitrones are stable compounds and do not require an *in situ* formation. In continuation of our interest to use ionic liquids (ILs), water or solvenless systems as green reaction medium [22–29], in this report, we wish to highlight our results on cycloaddition reactions of (Z)-nitrones, **1a–e** and **2a–j**, with DMAD to produce related Δ^4-isoxazoline derivatives in good to excellent yields (Scheme 1).

RESULTS AND DISCUSSION

In a typical experiment, *N*-methyl-*C*-phenylnitrone **1a** (15 mmol) and DMAD (15 mmol) were charged into a 10-mL flask containing [bmim]Cl (2 mL) and mixed thoroughly. Then, the mixture was stirred at room temperature. The whole reactions were monitored by TLC using (EtOAc/petroleum 1:6) as eluent and found that the reaction was completed to afford N-methyl-Δ^4-

© 2011 HeteroCorporation

Scheme 1. Reaction of *N*-(methyl and phenyl)nitrones with DMAD in [bmim] BF_4^-



isoxazoline **4a** after 22 min in 80% yield. Several butylmethylimidazolium-based ILs, [bmim]X, with varying anions such as PF_6^-, Br^-, and BF_4^-, were screened for this reaction for complete conversions as monitored by TLC to afford product (Table 1).

Evidently, [bmim] BF_4^- was found to be superior in terms of yield (92%) and reaction time (15 min) as compared with other ILs (entries 2–5). For optimizing the conditions, we used the substrates in different ratios. It was found that the best results were obtained using 1:1 reactants ratio. The reaction in [bmim] BF_4^- was conducted at higher temperatures for optimizing the conditions and no significant improvements were observed in yields or reaction times. We examined the reaction under neat conditions, without using ionic liquid, to demonstrate the catalytic ability of [bmim] BF_4^- (Table 1). This result clearly indicates that [bmim] BF_4^- has significant catalytic role in this reaction (entry 1). When optimizing the reaction conditions, we extended this procedure to *N*-phenyl-*C*-phenylnitrone **2a** to obtain the corresponding *N*-phenyl-Δ^4-isoxazoline (Scheme 1). This reaction led to formation of the diastereomeric mixture of 2,3-diphenyl-Δ^4-isoxazoline (**5a** and **6a**) in 82% yield. The structures of two diastereomers were confirmed on the basis of IR and ^{1}H NMR spectroscopic data. The IR spectrum of the mixture of two diastereomers exhibited two sharp bands at 1741 and 1719 cm^{-1}(C=O) and a series of bands in the region of 1640–1560 cm^{-1}(C=C). In the ^{1}H NMR spectrum ($CDCl_3$), two singlets at δ 3.63 and 3.65 (CO_2Me), two singlets at δ 5.14 and 5.13 (benzylic proton), and multiplet at δ 7.20–8.12 (Ar-H) were observed. The ratio of two diastereomers was evaluated from the ^{1}H NMR spectroscopic data.

To examine the versatility of the procedure, the reaction of *N*-methyl-*C*-arylnitrones **1a–e** and *N*-phenyl-*C*-arylnitrones **2a–j** containing electron-rich, electron-poor, or electron-neutral substituents with DMAD were examined and high yields (>82% yields) of related Δ^4-isoxazolines were synthesized (Table 2).

As it can see from Table 2, the reaction of *N*-methyl nitrones was occurred faster and in higher yields in comparison with *N*-phenyl nitrones. This different behavior is probably due to the resonance of double bond, C=N of nitrones **2a–j** with phenyl substituent on *N* atom. Interesting results were found by comparison of the ^{1}H NMR spectroscopic data of products from the reaction of *N*-methyl and *N*-phenyl nitrones with DMAD. These data showed that the reaction of *N*-phenyl nitrones with DMAD afforded diastereomeric mixture of Δ^4-isoxazolines. However, in the case of *N*-methyl nitrones with DMAD, only one product was isolated. These results showed that inversion energy barrier of nitrogen atom in *N*-phenyl-Δ^4-isoxazolines are higher than *N*-methyl-Δ^4-isoxazolines due to higher steric strain between larger phenyl groups during inversion was occurred in the compounds **4a–e** in comparison with products **5a–j** and **6a–j**. Hartree Fock (HF) with STO-3G basis set were used to calculate the inversion energy barrier for typical compounds **4a** and **5a**. The calculations were clarified a larger inversion energy for **5a**

Table 1

Reaction of *N*-(methyl and phenyl)-*C*-phenylnitrones (**1a** and **2a**) with DMAD under different conditions.

Entry	Nitrone	Ar	Reaction medium	Product	Time (min)	Yield[a] (%)
1	**1a**	Ph	Neat	**4a**	45	45
2	**1a**	Ph	[bmim]Cl	**4a**	22	80
3	**1a**	Ph	[bmim]Br	**4a**	25	82
4	**1a**	Ph	[bmim]PF_6	**4a**	20	83
5	**1a**	Ph	[bmim]BF_4	**4a**	16	92
6	**1b**	4-Me-Ph	[bmim]BF_4	**4b**	16	93
7	**2a**	Ph	[bmim]BF_4	**5a, 6a**	25	82
8	**2b**	2-OH-Ph	[bmim]BF_4	**5b, 6b**	27	86

[a] Isolated yield of products after flash chromatography.

Table 2

Synthesis of *N*-(methyl and phenyl)-3-aryl-Δ^4-isoxazolines in [bmim]BF_4 at room temperature.

Entry	Nitrone	Ar	L(+)-Diethyl tartrate (mol %)	Time (min)	Product(s) (ratio of isomers)	Yield[a] (%)
1	**2a**	Ph	0	25	**5a, 6a** (55/45)	83
2	**2b**	2-OH-Ph	0	27	**5b, 6b** (57/43)	86
3	**2c**	5-Br-Ph	0	22	**5c, 6c** (54/46)	85
4	**2d**	5-NO_2-Ph	0	19	**5d, 6d** (55/45)	90
5	**2e**	2-Cl-Ph	0	20	**5e, 6e** (53/47)	82
6	**2f**	2-NO_2-Ph	0	25	**5f, 6f** (57/43)	86
7	**2g**	3-OMe-Ph	0	18	**5g, 6g** (55/45)	87
8	**2h**	3-NO_2-Ph	0	25	**5h, 6h** (58/42)	91
9	**2i**	2-OMe-Ph	0	20	**5i, 6i** (53/47)	85
10	**2j**	3-Cl-Ph	0	24	**5j, 6j** (56/44)	86
11	**2a**	Ph	10	20	**5a, 6a** (82/18)	82
12	**2b**	2-OH-Ph	10	22	**5b, 6b** (85/15)	80
13	**2c**	5-Br-Ph	10	23	**5c, 6c** (88/12)	82
14	**2d**	5-NO_2-Ph	10	25	**5d, 6d** (80/20)	81
15	**1a**	Ph	–	15	**4a**	94
16	**1b**	4-Me-Ph	–	16	**4b**	91
17	**1c**	3-NO_2-Ph	–	16	**4c**	90
18	**1d**	2-OMe	–	14	**4d**	93
19	**1e**	2-Cl	–	15	**4e**	95

[a] Isolated yield of products.

(16.56 kcal mol^{-1}) respect to **4a** (16.56 kcal mol^{-1}). The diagram of energy versus torsional angle was presented (Fig. 1). Another HF calculation was done for acetyl rotation in the mentioned molecules **4a** and **5a**. However, lower rotation energies (2.24 and 2.03 kcal mol^{-1}) were obtained for molecules **4a** and **5a**, respectively (Fig. 2).

In the case of *N*-phenyl nitrones with DMAD, products **5a–j** and **6a–j** were isolated by column chromatography and the ratios of diastereoisomers were calculated (Table 2). To assign the compounds **5a–b** and **6a–b**, nuclear Overhauser effects (NOE) have been used to establish a space proximity relation between H-3 and *N*-phenyl substituent. On irradiation of proton H-3 in isomers **5a–j**, the NOE induced the enhancement of the signals of protons at the ortho position of phenyl substituent. On the other hand, no effect on the signal of *N*-phenyl protons of isomers **6a–j** was observed by irradiation of the H-3 proton. This lack of effect proves that in products **6a–j**, the H-3 proton exists on opposite side of *N*-phenyl substituent. As shown in Table 2, in all cases the

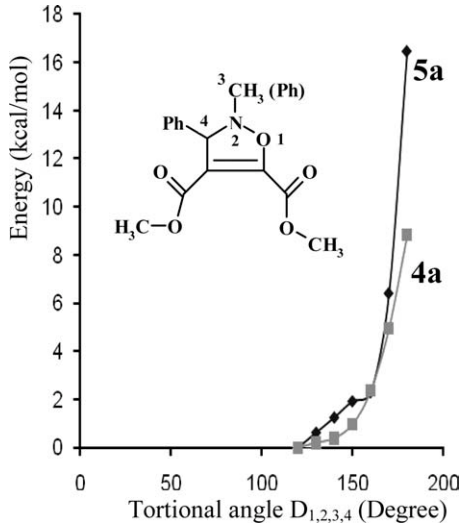


Figure 1. Inversion energy barrier diagram for typical compounds **4a** and **5a**.

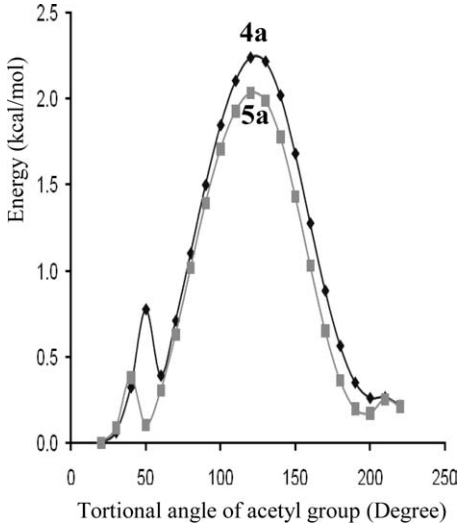


Figure 2. Acetyl group rotation diagram of typical compounds **4a** and **5a**.

yields of isomers **5a–j** are higher than yields of isomers **6a–j**.

For comparison, we also examined the reaction of nitrones **2a–d** with DMAD in chiral medium containing L(+)-diethyl tartrate and the ratio of diastereoisomers were evaluated under these conditions (entries 11–14, Table 2). As it can be seen from Table 2, the selectivity of the reaction was increased under these conditions.

CONCLUSIONS

In summary, we have developed a convenient and efficient synthetic approach to synthesize *N*-(methyl and phenyl)-Δ^4-isoxazolines via the 1,3-dipolar cycloaddition reaction of (Z)-*N*-(methyl and phenyl) nitrone derivatives with DMAD in [bmim] BF_4^- at room temperature. (Z)-*N*-phenyl nitrones afforded good to high yield of the diastereomeric mixture of related Δ^4-isoxazolines in this procedure. Moreover, fast reaction times, simple experimental procedure and good yields of the products are the advantages. We believe our procedure will find important applications in the synthetic organic chemistry.

EXPERIMENTAL

General information. All reagents were purchased from Merck (Germany) company and used without further purification. Infrared spectra were recorded in KBr and were determined on a Perkin Elmer FTIR spectrometer. ^{1}H NMR spectra were obtained in $CDCl_3$ solution from Bruker Avance AC-400 MHz and ^{13}C NMR spectra at 100 MHz on the aforementioned instruments. Elemental analyses were carried out on a Perkin-Elmer 240C elemental analyzer and are reported in percent atomic abundance. Analytical thin-layer chromatography was performed using precoated silica gel 60 F254 plates (Merck, Darmstadt), and the spots were visualized with UV light at 254 nm. Merck silica gel 60 (230–400 mesh) was used for flash chromatography.

Synthesis of 2-(methyl and phenyl)-3-aryl-Δ^4-isoxasolines, general p procedure. Nitrone (15 mmol) and DMAD (15 mmol) were added to [bmim] BF_4^- (2 mL) in a 10-mL conical flask, and the mixture was shaken for a period of time at room temperature (TLC) as listed in Table 2. After completion of the reaction, the mixture was extracted three times with 7 mL of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulphate and evaporated under reduced pressure. Then, the crud mixture was purified by flash chromatography on silica gel to afford corresponding cycloadduct (Table 2).

Selected spectroscopic data. ***2-Methyl-3-phenyl-4,5-dicarbomethoxy-Δ^4-isoxazoli-ne (4a)*** White crystals; mp 64.9–65.6°C; IR (KBr): 1753, 1716, 1654, 1116 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.25 (m, 5H, Ar-H), 5.00 (s, 1H, CH), 3.89 (s, 3H, Me), 3.61 (s, 3H, Me), 2.95 (s, 3H, Me). ^{13}C NMR ($CDCl_3$. 100 MHz) δ = 33.95, 52.40, 50.72, 87.98, 111.64, 119.72, 125.32, 127.63, 129.56, 134.33, 159.58, 162.71. Anal. Calcd. (%) for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found (%): C, 60.87; H, 5.37; N, 4.90.

2-Methyl-3-(4-methylphenyl)-4,5-dicarbomethoxy-Δ^4-isoxazoline(4b) White crystals; mp 50–51°C; IR (KBr): 1750, 1711, 1648, 1110 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.25 (m, 4H, Ar-H), 5.11 (s, 1H, CH), 3.88 (s, 3H, Me), 3.69 (s, 3H, Me), 3.05 (s, 3H, Me), 2.38 (s, 3H, Me). ^{13}C NMR ($CDCl_3$. 100 MHz) δ = 24.12, 33.95, 52.40, 50.72, 87.98, 111.64, 119.72, 124.44, 126.36, 129.96, 135.55, 159.58, 162.71. Anal. Calcd. (%) for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found (%): C, 62.02; H, 5.67; N, 4.62.

2-Methyl-3-(3-nitrophenyl)-4,5-dicarbomethoxy-Δ^4-isoxazoline(4c) White crystals; mp 78–79°C; IR (KBr): 1752, 1709, 1638,1535, 1356,1120 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.05 (m, 4H, Ar-H), 4.95 (s, 1H, CH), 3.80 (s, 3H, Me), 3.61 (s, 3H, Me), 3.05 (s, 3H, Me). ^{13}C NMR ($CDCl_3$ 100 MHz) δ = 32.95, 51.43, 50.32, 86.18, 113.64, 120.12, 121.26, 123.98, 125.65, 127.87, 128.90, 133.33, 160.18, 164.11. Anal. Calcd. (%) for $C_{14}H_{14}N_2O_7$: C, 52.18; H, 4.38; N, 8.69. Found (%): C, 52.25; H, 4.23; N, 8.50.

2,3-Diphenyl-4,5-dicarbomethoxy-Δ^4-isoxazoline (5a, 6a) Colorless liquid; IR (KBr): 1771, 1718, 1654, 1114 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–8.12 (m, 10H, Ar-H), 5.14 and 5.13 (two singlets, 1H, CH), 3.80 and 3.82 (two singlets, 3H, CO_2Me), 3.63 and 3.65 (two singlets, 3H, CO_2Me). Anal. Calcd. (%) for $C_{19}H_{17}NO_5$: C, 67.25; H, 5.05; N, 4.13. Found (%): C, 68.11; H, 5.10; N, 4.15.

2-Phenyl-3-(5-bromophenyl)-4,5-dicarbomethoxy-Δ^4-isoxazoline (5c,6c) Colorless liquid; IR (KBr): 1746, 1718, 1610, 1118 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62–7.28 (m, 9H, Ar-H), 5.18 and 5.16 (two singlets, 1H, CH), 3.81 and 3.79 (two singlets, 3H, CO_2Me), 3.70 and 3.68 (two singlets, 3H, CO_2Me). Anal. Calcd. (%) for $C_{19}H_{16}BrNO_5$: C, 54.56; H, 3.86; N, 3.35. Found (%): C, 55.12; H, 3.88; N, 3.34.

2-Phenyl-3-(2-chlorophenyl)-4,5-dicarbomethoxy-Δ^4-isoxazoline (5e, 6e) Colorless liquid; IR (KBr): 1732, 1721, 1618, 1115 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15–7.29 (m, 9H, Ar-H), 5.24 and 5.22 (two singlets, 1H, CH), 4.03 and 3.99 (two singlets, 3H, CO_2Me), 3.58 and 3.56 (two singlets, 3H, CO_2Me). Anal. Calcd. (%) for $C_{19}H_{16}ClNO_5$: C, 61.05; H, 4.31; N, 3.75. Found (%): C, 61.94; H, 4.37; N, 3.73.

2-Phenyl-3-(3-methoxyphenyl)-4,5-dicarbomethoxy-Δ^4-isoxazoline (5g, 6g) Colorless liquid; IR (KBr): 1742, 1713, 1612, 1114 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42-7.28 (m, 9H, Ar-H), 5.15 and 5.13 (two singlets, 1H, CH), 3.95 (s, 3H, OMe), 3.79 and 3.76 (two singlets, 3H, CO_2Me). Anal. Calcd. (%) for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79. Found (%): C, 66.01; H, 5.20; N, 3.81.

Acknowledgments. The offices of the Research Vice Chancellor of Myianeh Branch of Islamic Azad University and Azarbaijan University of Tarbiat-Moallem are gratefully acknowledged.

REFERENCES AND NOTES

[1] (a) Honna, R.; Ogawa, K.; Tanaka, M.; Yamada, S.; Hashumoto, S.; Suzue, T. Jpn Kokai Tokkyo Koho 7,914,968, 1979; (b) Honna, R.; Ogawa, K.; Tanaka, M.; Yamada, S.; Hashumoto, S.; Suzue, T. Chem Abstr 1980, 92, 41920.

[2] (a) Ito, N.; Saijo, S. Jpn Kokai Tokkyo Koho 7,595,272, 1975; (b) Ito, N.; Saijo, S. Chem Abstr 1976, 84, 105567.

[3] Carr, J. B.; Durhum, H. G.; Hass, D. K. J Med Chem 1977, 20, 934.

[4] (a) Nadelson, J. US Pat. 4,032,644, 1977; (b) Nadelson, J. Chem Abstr 1977, 87, 102314.

[5] Eckhard, I. F.; Lehtonen, K.; Staub T.; Summers, L. A. Aust J Chem 1973, 26, 2705.

[6] Thakar K. A.; Bhawal, B. M. J Ind Chem Soc 1977, 54, 875.

[7] Huisgen, R. Angew Chem Int Ed Engl 1963, 2, 565.

[8] Pandey, G.; Sahoo, A. K.; Gadre, S. R.; Bagul, T. D. J Org Chem 1999, 64, 4990.

[9] Werner, K. M.; de los Santos, J. M.; Weinreb, S. M.; Shang, M. J Org Chem 1999, 64, 4865.

[10] Young, D. G. J.; Gomez-Bengoa, E.; Hoveyda, A. H. J Org Chem 1999, 64, 692.

[11] Conti, P.; Dallanoce, C.; Amici, M. D.; Micheli, C. D.; Klotz, K. -N. Bioorg Med Chem 1998, 6, 401.

[12] Kanesama, S.; Oderatoshi, Y.; Tanaka, J.; Wada, E. J Am Chem Soc 1998, 120, 12355.

[13] Suga, H.; Nakajima, T.; Itoh, K.; Kakehi, A. Org Lett 2005, 7, 1431.

[14] Viton, F.; Bernardinelli, G.; Kündig, E. P. J Am Chem Soc 2002, 124, 4968.

[15] Kodama, H.; Ito, J.; Hori, K.; Ohta, T. Tetrahedron Lett 2001, 42, 6715.

[16] Kano, T.; Hashimoto, T.; Maruoka, K. J Am Chem Soc 2005, 127, 11926.

[17] Jensen, K.; Gothelf, K. V.; Hazell, R. G.; Jorgensen, K. A. J Org Chem 1997, 62, 2471.

[18] Carmona, D.; Lamata, M. P.; Viguri, F.; Rodriguez, R.; Oro, L. A.; Balana, A. I.; Lahoz, F. J.; Tejero, T.; Merino, P.; Franco, S.; Montesa, I. J Am Chem Soc 2004, 126, 2716.

[19] Kobayashi, S.; Kawamura, M. J Am Chem Soc 1998, 120, 5840.

[20] Bortolini, O.; De Nino, A.; Maiuolo, L.; Russo, B.; Sindona, G.; Tocci, A. Tetrahedron Lett 2007, 48, 7125.

[21] Padar, P.; Bokros, A.; Paragi, G.; Forgó, P.; Kele, Z.; Howarth, N. M.; Kovacs, L. J Org Chem 2006, 71, 8669.

[22] Valizadeh, H.; Dinparast, L. Heteroatom Chem 2009, 20, 177.

[23] Valizadeh, H.; Mamaghani, M.; Badrian, A. Synth Commun 2005, 35, 785.

[24] Valizadeh, H.; Heravi, M. M.; Amiri, M. Mol Divers, to appear; doi: 10.1007/s11030–009-9189-x.

[25] Valizadeh, H.; Amiri, M.; Gholipour. H. J Heterocycl Chem 2009, 46, 108.

[26] Valizadeh, H.; Shockravi, A. Synth Commun 2009, 39, 4341.

[27] Valizadeh, H.; Fakhari, A. J Heterocycl Chem 2009, 46, 1392.

[28] Valizadeh, H.; Vaghefi, S. Synth Commun 2009, 39, 1666.

[29] Valizadeh, H.; Shockravi, A. Heteroatom Chem 2009, 20, 5, 284.