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A Simple Synthetic Strategy For The Synthesis Of Benzoxepinopyrrolidines Under Microwave Condition

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ABSTRACT

Simplemethod synthesis of 2-benzoxepines starting material from (E)-2-nitro-3-arylprop-2-en-1-ols with paraformaldehyde. Furthermore, the 1,3-dipolar cycloaddition of 2-benzoxepines with azomethineylides using paraformaldehyde led to the formation of tricyclic benzoxepinopyrrolidine architectures for the first timeunder microwave condition process.

KEYWORDS: Baylis-Hillman reaction, Benzoxepine, allyl alcohol, cyclization, nitroolefin, [3+2] azomethine,

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INTRODUCTION

The Baylis-Hillman adducts and their derivatives are useful intermediates for the synthesis of many natural products and biologically active molecules.[1-3,] Benzoxepine is an important benzo-fused medium-sized heterocycle, because there are numerous biologically active natural products[4] and synthetic molecules,[5] which contain this structural framework. Thus synthesis of benzoxepine derivatives constitutes an important objective in morden organic synthesis.[6-8]Though Baylis-Hillman adduct derived from methyl acrylate have been used for the synthesis of benzoxepine derivative, there is no report for the construction of benzoxepine skeleton using Baylis-Hillman adducts derived from nitroolefins. Moreover the Baylis-Hillman adducts derived from β-substituted nitroolefin is a trisubstituted allyl alcohol and was not utilized so far for the construction of benzoxepine derivatives. As mentioned in the previous chapter, 1,3-dipolar cycloaddition reaction is one of the important reaction which allows to construct useful five membered heterocycles. In azomethine ylide based on [3+2] cycloaddition reaction, variety of dipoles have been used, however nitroolefin have not been used much as dipolarophile in the [3+2] azomethine ylide dipolar cycloaddition reaction

The benzoxepine ring system occurs in number of biologically active natural products isolated mainly from plant sources. Some of the examples which contain benzoxepine moiety are (**Fig 1**)[9] radulanin A (**1**), heliannuol D (**2**), pterulone (**3**), eranthin (**4**) and ptaeroxylin (**5**).

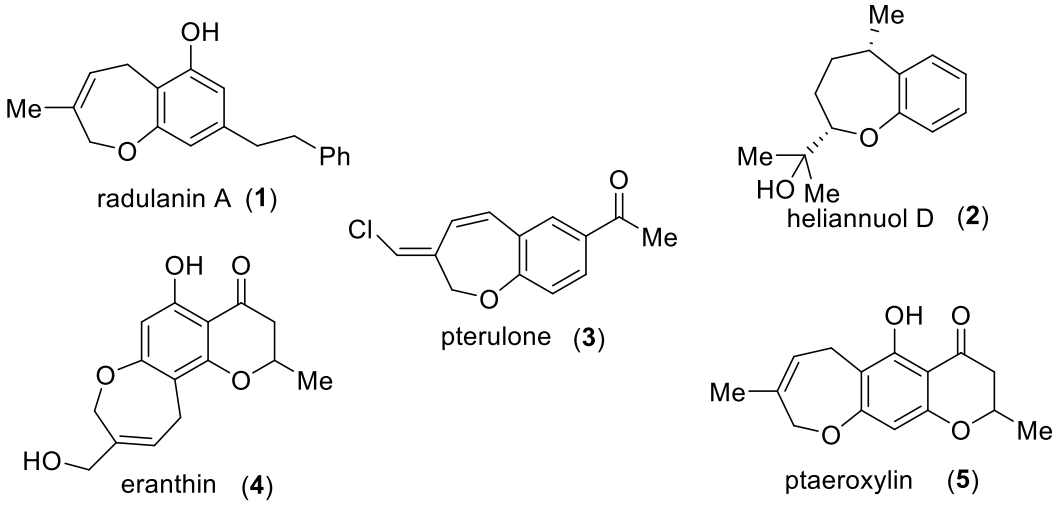


Figure 1. Natural products containing benzoxepine skeleton

The 2-benzoxepine moiety is an important structural unit present in many biologically important molecules such as doxaminol (vasodilator and β-sympathomimetic agent),[10] isoxepac (antiinflammatory agent),[11] oxepinac (antiinflammatory, analgesic, antipyretic agent),[12] and pinoxepin (neuroleptic agent, tranquilliser used for treatment of schizophrenia).[13,14] Natural products such as cassialactone,[15] psorolactone,[16] secofuranoeremophilane[17] have also possessing benzoxepinecore structure. Also synthetic 2-benzoxepine derivatives are found to possess oral hypotensive and antiulcer activities.[18]

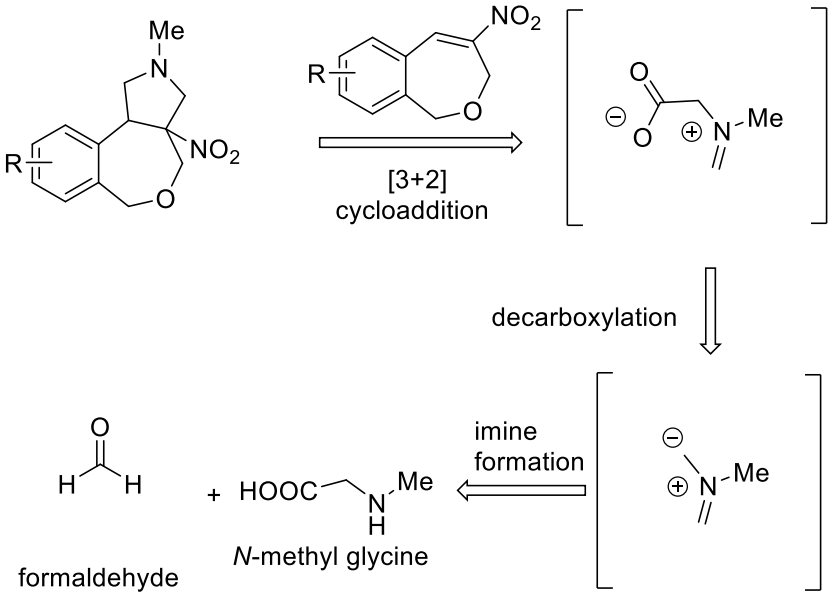
Since the benzoxepine skeleton present in many natural products and bioactive molecules, the development of new synthetic methodologies for the construction of benzoxepine scaffold is an important and interesting endeavor in the area of synthetic organic chemistry and medicinal chemistry. There are varieties of methods known for the synthesis of benzoxepine skeleton in the literature.[19] However synthesis of benzoxepine scaffold from Baylis-Hillman adduct not known except a single report. Due to their interesting and important biological properties, development of simple and convenient methodologies for the synthesis of 2-benzoxepine containing derivatives represents an attractive and interesting endeavor in synthetic organic chemistry and medicinal chemistry[20].

RESULT AND DISCUSSION

To the best of our knowledge we could not find any report on the synthesis of benzoxepine fused pyrrolidines and spiropyrrolidines compounds from microwave condition in the literature. Based on this, we envisaged that the reaction of benzoxepines possessing nitrofunctionality with various diploes will lead to the interesting novel class of benzoxepine fused pyrrolidines and spiropyrrolidines. Intrigued by this idea we have decided to make an attempt for the utilization of our newly synthesized benzoxepines in the cycloaddition domain with the various dipoles to construct the novel class of potentially biologically active benzoxepine fused pyrrolidine and spiropyrrolidine derivatives for the first time.

To our knowledge, benzoxepine have been never used as 2π components in cycloaddition reaction using azomethine ylide. We herein report a simple and convenient route for the regio-and stereoselective synthesis of six, seven and five membered benzoxepine fused pyrrolidine frameworks using the benzoxepine derivative with *N*-methyl glycine based dipole generated *viain situ* imine formation, decarboxylation and intermolecular [3+2] cycloaddition as shown below in the retrosynthetic strategy (Scheme 1).

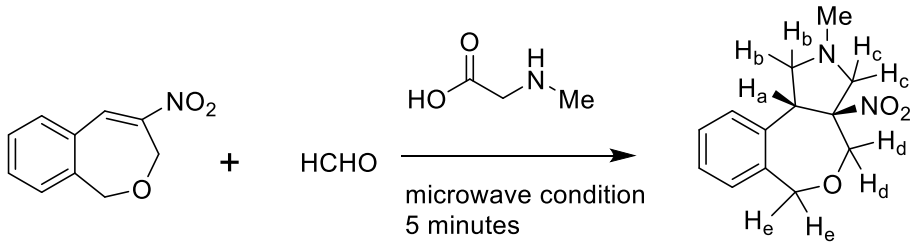
Scheme 1



Retrosynthetic Strategy for the Synthesis of benzoxepine fused pyrrolidine/spiropyrrolidine frameworks with Angular Substitution

To execute our idea, we first selected benzoxepine**(6)** as a starting material for [3+2] cycloaddition reaction with dipoles generated from *N*-methyl glycine with paraformaldehyde. Best results were obtained when **6a** was treated with paraformaldehyde and *N*-methyl glycine without any catalyst in microwave condition for 5 minutes successfully provided the desired tricyclic benzoxepine fused pyrrolidine compound **9a** in excellent yield (94%) (Scheme 2).

Scheme 2



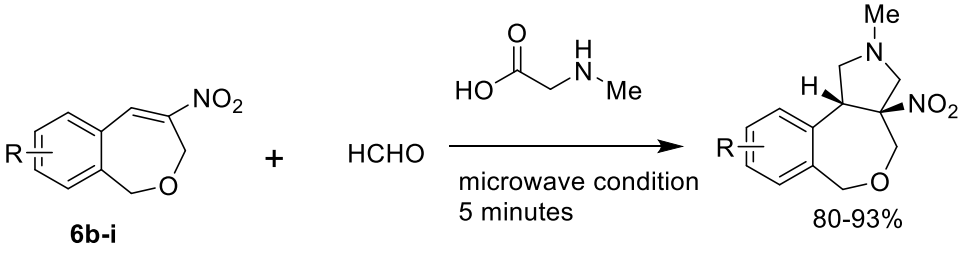
6a 94%

9a

Structure of the compound **9a** was elucidated by IR, ^{1}H &^{13}C NMR, mass spectral data and elemental analysis. Interestingly high stereoselectivity was observed, which was clearly evidenced by ^{1}H NMR data. The ^{1}H NMR spectrum of compound **9a** showed a singlet for N-CH_3 proton at δ 2.41 and triplet for benzylic proton (H_a) at δ 4.62. The two H_b protons of pyrrolidine ring appeared as two triplets at δ 2.86 and δ 3.29. The two H_c protons of pyrrolidine ring appeared as two doublets at δ 2.78 and δ 3.59. The two H_e protons of seven membered ring appeared as two doublets at δ 3.78 and δ 4.14. The two H_d protons of seven membered ring appeared as AB doublet at δ 4.89. The aromatic protons appeared in the region of δ 7.17-7.34.

Encouraged by this result, we utilized a variety of 2-benzoxepines **(9b-j)** with *N*-methyl glycine and paraformaldehyde for cycloaddition reaction without any catalyst in microwave condition for 5 minutes successfully led to the desired six, seven and five membered benzoxepinopyrrolidine compounds**(9b-j)** in 80-93% yields (Scheme 3). The results are summarized in Table 1.

Scheme 3



6b-i 80-93%

9b-i

R = 2-Me, 4-Me, 4-Et, 4-*i*-pr, 3,4-OCH_2O-, 2-Cl, 3-Cl, 2,3-CH=CH-CH=CH-

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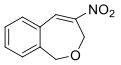
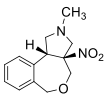
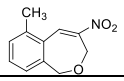
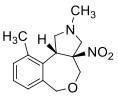
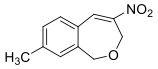
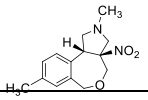
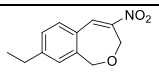
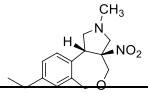
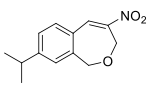
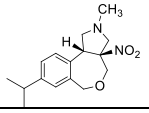
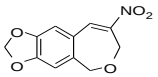
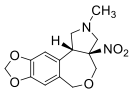
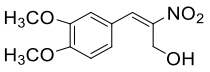
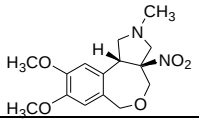
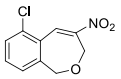
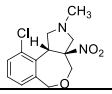
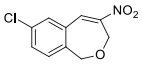
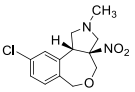
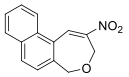
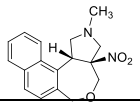
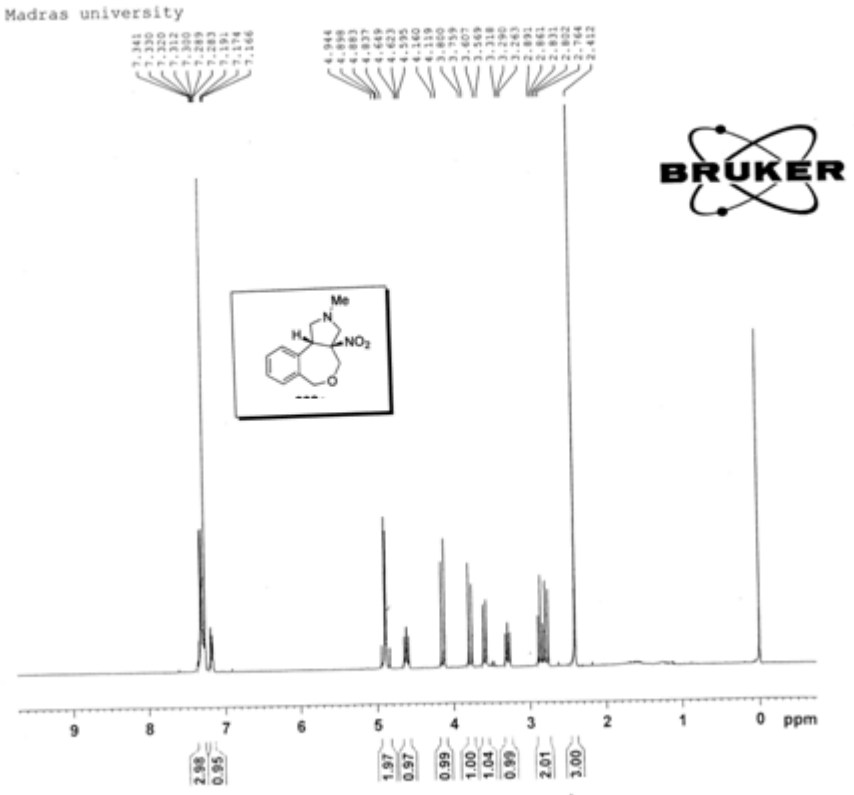
For easy understanding and continuity, the benzoxepine fused pyrrolidines were numbered as **9b-i** which was synthesized from the corresponding benzoxepines **6a-i** respectively.

Table 5.Synthesis of benzoxepinopyrrolidine compounds from benzoxepine derivatives

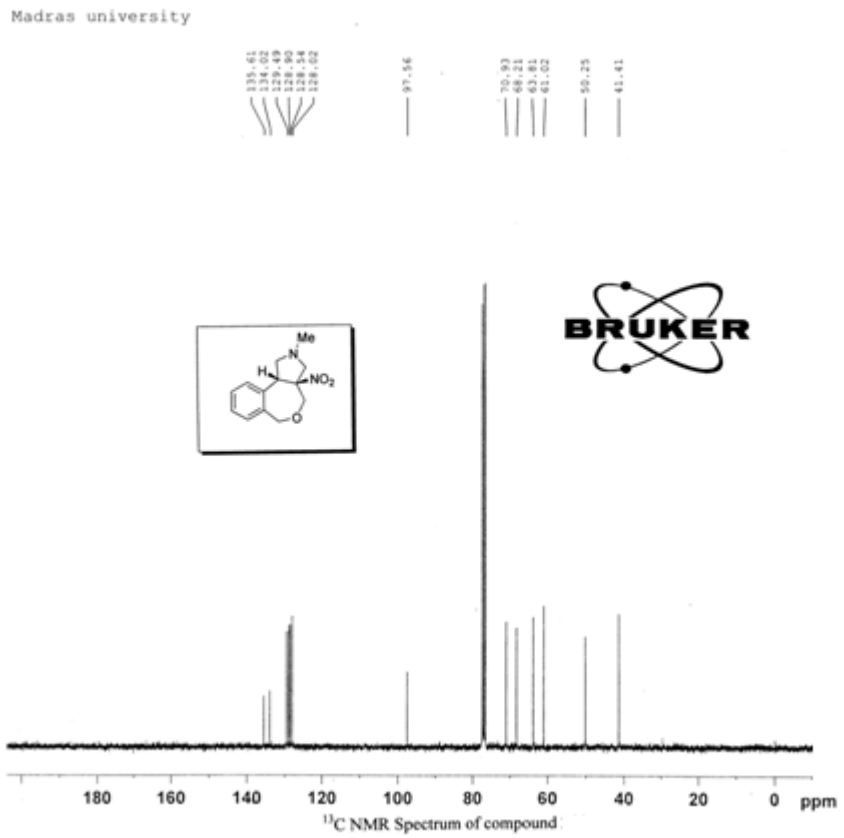
Entry	Benzoxepine	Benzoxepinopyrrolidine[a, b]	Yield (%)[C]
1	**6a** 	**9a**[d] 	94
2	**6b** 	**9b** 	80
3	**6c** 	**9c** 	84
4	**6d** 	**9d** 	83
5	**6e** 	**9e** 	81

6	**6f** 	**9f** 	87
7	**6g** 	**9g** 	92
8	**6h** 	**9h** 	93
9	**6i** 	**9i** 	92
10	**6j** 	**9j** 	81

[a]All reactions were carried out with 2 mmol scale of benzoxepine **(6b-j)** with *N*-methyl glycine and paraformaldehyde in microwave for 10 minutes temperature. [b]All products gave satisfactory IR, ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz), mass spectral data and elemental analyses. [c]Yields of the pure products (**9a-j**) obtained by recrystalization method in diethyl ether.[d]Structure of these molecule was further confirmed by single-crystal X-ray analysis.



^{1}H NMR Spectrum of compound



^{13}C NMR Spectrum of compound

CONCLUSION

In conclusion, the simple an efficient protocol using acyclic reaction for the novel synthesis of benzoxepine derivatives connecting a tandem building of C–O and C–C bonds using Baylis–Hillman adducts with paraformaldehyde under the catalist of H_2SO_4 was successfully realised. We also established that these 2-benzoxepine results are useful for constructing wide variety of tricyclic benzoxepinopyrrolidines in very good yields. Since benzoxepines and its derivatives are well known for their biological properties, the newly synthesized benzoxepines and its derivatives also may exhibit significant bioactivities.

General procedure for the synthesis of benzoxepino pyrrolidines (**6a**):
A mixture of (E)-1,3-dihydro-4-nitrobenzo[c] oxepine (2) (1 mmol), paraformaldehyde (6 mmol) and sarcosine (2.5 mmol) in toluene (10 mL) was kept under microwave condition. After the completion of the reaction as indicated by TLC, the reaction mixture was dissolved with ethyl acetate. Then the resulting crude mass was diluted with water (20 mL) and extracted with ethyl acetate (3 x10 mL). The combined organic layer thus obtained was washed with brine (3 x 10 mL) and dried over anhydrous Na_2SO_4. The organic layer was concentrated and recrystallized using diethyl ether to provide benzoxepino pyrrolidines 3 in excellent yieldslayer thus obtained was washed with brine (3 x 10 mL) and dried over anhydrous Na_2SO_4. The organic layer was concentrated and recrystallized using solvent to provide benzoxepino pyrrolidines **6a** in very good yields.

Benzoxepino pyrrolidine
Colourless solid
Yield : 94%
M. P : 114-116 ^{0}C
IR (KBr) : 1534, 1340 cm^{-1}
^{1}H NMR ($CDCl_3$, 300 MHz) : δ 2.41 (s, 3H), 2.78 (d, *J* = 11.4Hz, 1H), 2.86 (t, *J* = 9.0Hz, 1H), 3.29 (t, *J* = 8.4Hz, 1H), 3.59 (d, *J* = 11.4Hz, 1H), 3.78 (d, *J* = 12.3Hz, 1H), 4.14 (d, *J* = 12.3Hz, 1H), 4.62 (t, *J* = 7.8Hz, 1H), 4.89 (AB(d), *J* = 13.8, 18.3Hz, 2H), 7.17-7.34 (m, 4H).
^{13}CNMR ($CDCl_3$, 75 MHz) : δ 41.41, 50.25, 61.02, 63.81, 68.21, 70.93, 97.56, 128.02, 128.54, 128.90, 129.49, 134.02, 135.61.
MS (m/z) : 249 (M^++1).
Elemental Analysis for $C_{13}H_{16}N_2O_3$
Calculated : C, 62.89; H, 6.50; N, 11.28.
Found : C, 62.93; H, 6.46; N, 11.31.

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REFERENCES:

1. Macias, F. A.; Varela, R. M.; Torres, A.; Molinillon, J. M. G. Tetrahedron Lett. 1999, 40, 4725.
2. Wijnberg, J. B. P. A.; van Veldhuizen, A.; Swarts, H. J.; Frankland, J. C.; Field, J. A. Tetrahedron Lett. 1999, 40, 5767.
3. Huckle, D.; Lockhart, I. M.; Webb, N. E. J. Chem. Soc (C) 1971, 2252.
4. Mericüli, F.; Mericüli, A. H.; Becker, H.; Ulubelen, A. Phytochemistry 1996, 42, 1257.
5. Kahnberg, P.; Sterner, O. Tetrahedron 2001, 57, 7181. 8. Tandon, V. K.; Khanna, J. M.; Chandra, A.; Anand, N. Tetrahedron 1990, 46, 2871.
6. Rosini, M.; Budriesi, R.; Bixel, M. G.; Bolognesi, M. L.; Chiarini, A.; Hucho, F.; Krogsgaard-Larsen, P.; Mellor, A.; Minarini, A.; Tumiatti, V.; Usherwood, P. N. R.; Melchiorre, C. J. Med. Chem. 1999, 42, 5212.
7. Winter , W.; Thiel, M.; Stach, K.; Roesh, E.; Sponer, G. Ger. Offen. 23335943, 1975
8. Dictionary of Drugs; Elks, J., Ganellin, C. R., Eds.; 1sted.; Chapman and Hall:
9. Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765.
10. Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484.
11. Petrovskaia, O.; Taylar, B. M.; Hauze, D. B.; Carroll, P. J.; Joullie, M. M. J. Org.Chem. 2001, 66, 7666.
12. FoKas, D.; Ryan, W.J.; Casebier, D. S.; Coffen D. L. *Tetrahedron Lett*. **1998**, *39*, 2235.
13. Ghandi, M.; Rezaei, S. J. T.; Yari, A.; Taheri, A. *Tetrahedron Lett*. **2008**, *49*, 5899
14. Panja, S. K.; Karmakar, P.; Chakraborty, J.; Ghosh, T.; Bandyopadhyay, C. *Tetrahedron Lett*. **2008**, *49*, 4397.
15. a) Shanmugam, P.; Viswambharan, B.; Madhavan, S. *Org. Lett*. **2007**, *9*, 4095; b) Shanmugam, P.; Viswambharan, B.; Selvakumar, K.; Madhavan, S. *Tetrahedron Lett.* **2008**, *49*, 2611
16. Nyerges, M.; Bitter, I.; Kadas, I.; Toth, G.; Toke, L. *Tetrahedron.* **1995**, *51*, 11489.
17. Alimohammadi, K.; Sarrafi, Y.; Tajbakhsh, M.; Yeganegi, S.; Hamzehloueian, M. *Tetrahedron.* **2011**, *67*, 1589.
18. Rastogi, N.; Namboothiri, I. N. N.; Cojocaru, M. *Tetrahedron Lett*. **2004**, *45*, 4745.
19. Basavaiah, D.; Sekhara reddy, B.; Badsara, B. S. *Chem. Rev.* **2010**, *110*, 5447.
20. Padwa, A. *Pure Appl. Chem*., Vol. 75, No. 1, pp. 47-62, 2003. © 2003 IUPAC.
21. Toczko, M. A.; Heathcock, C. H. *J. Org. Chem*. **2000**, *65*, 2642.
22. Paquette, L. A.; Hu, Y.; Luxenburger, A.; Bishop, R. L. *J. Org. Chem*. **2000**, *72*, 209.