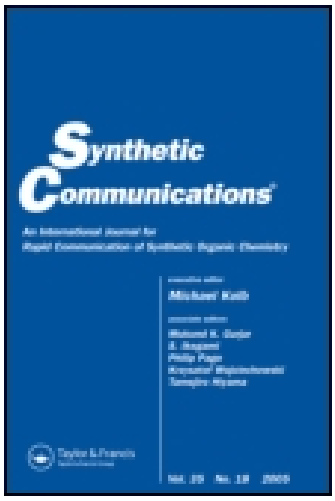


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Samarium Diiodide Mediated Barbier-Type Reaction of 2-Chloromethylbenzoxazole and 2-Chloromethylbenzothiazole with Carbonyl Compounds: A Convenient Synthesis of 1-(β-Hydroxyalkyl)benzoxazoles and 1-(β-Hydroxyalkyl)benzothiazoles

Professor Xiaoliang Xu [a] & Yongmin Zhang [a b]

[a] Department of Chemistry , Zhejiang University (Campus Xixi) , Hangzhou, P.R. China

[b] State Key Laboratory of Organometallic Chemistry , Shanghai Institute of Organic Chemistry , Chinese Academy of Sciences , Shanghai, P.R. China

Published online: 15 Aug 2006.

To cite this article: Professor Xiaoliang Xu & Yongmin Zhang (2003) Samarium Diiodide Mediated Barbier-Type Reaction of 2-Chloromethylbenzoxazole and 2-Chloromethylbenzothiazole with Carbonyl Compounds: A Convenient Synthesis of 1-(β-Hydroxyalkyl)benzoxazoles and 1-(β-Hydroxyalkyl)benzothiazoles, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 33:20, 3551-3559, DOI: 10.1081/SCC-120024742

To link to this article: http://dx.doi.org/10.1081/SCC-120024742

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

SYNTHETIC COMMUNICATIONS®
Vol. 33, No. 20, pp. 3551–3559, 2003

Samarium Diiodide Mediated Barbier-Type Reaction of 2-Chloromethylbenzoxazole and 2-Chloromethylbenzothiazole with Carbonyl Compounds: A Convenient Synthesis of 1-(β-Hydroxyalkyl)benzoxazoles and 1-(β-Hydroxyalkyl)benzothiazoles

Xiaoliang Xu[1] and Yongmin Zhang[1,2,*]

[1]Department of Chemistry,
Zhejiang University (Campus Xixi),
Hangzhou, P.R. China
[2]State Key Laboratory of Organometallic Chemistry,
Shanghai Institute of Organic Chemistry,
Chinese Academy of Sciences, Shanghai, P.R. China

*Correspondence: Yongmin Zhang, Professor, Department of Chemistry, Zhejiang University (Campus Xixi), Tianmu-Shan Road, Hangzhou, 310028, P.R. China; State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai, 200032, P.R. China; Fax: 86-571-88807077; E-mail: yminzhang@mail.hz.zj.cn.

DOI: 10.1081/SCC-120024742 0039-7911 (Print); 1532-2432 (Online)

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

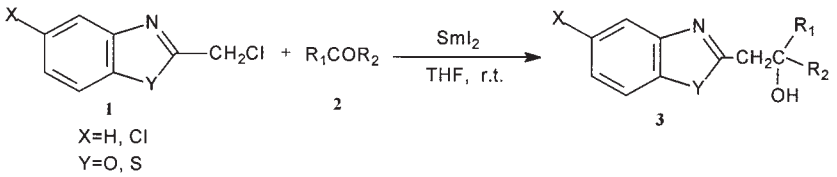
ABSTRACT

1-(β-Hydroxyalkyl)benzoxazoles and 1-(β-hydroxyalkyl)benzothiazoles were prepared via reductive addition reactions of 2-chloromethylbenzoxazole and 2-chloromethylbenzothiazole with carbonyl compounds under mild conditions mediated by SmI_2.

Key Words: 2-Chloromethylbenzoxazole; 2-Chloromethylbenzothiazole; Carbonyl compounds; 1-(β-Hydroxyalkyl)benzoxazole; 1-(β-Hydroxyalkyl)benzothiazole; Samarium diiodide.

The metal mediated carbon–carbon bond formation between alkyl halides and carbonyl compounds, the Barbier-type reaction, is a fundamental reaction in organic chemistry.[1] Such a reaction has played the key role in synthesizing numerous important biological and abiological compounds. Samarium diiodide, the Kagan's reagent, has found the widespread application to promote the inter- and intramolecular Barbier-type reactions.[2] A large variety of organic halides such as, primary and secondary alkyl halides, allylic and benzylic halides, 1-iodoalkynes, a-heterosubstituted alkyl halides can be used as substrates in this transformation.[2e] In contrast, the α-heterocyclic substituted alkyl halides have remained unexplored. To the best of our knowledge, no literature reported the synthesis of 1-(β-hydroxyalkyl)benzoxazole and 1-(β-hydroxyalkyl)benzothiazole by using SmI_2 as a reagent. Herein, we wish to describe a novel Barbier-type reaction of 2-chloromethylbenzoxazole and 2-chloromethylbenzothiazole[3] with carbonyl compounds mediated by SmI_2 (Sch. 1).

When substrates **1** and carbonyl compounds **2** were added to a solution of 2.2 equiv. of SmI_2 in THF at room temperature under a nitrogen atmosphere, the deep blue color of SmI_2 changed to a yellow color immediately. TLC showed that the reductive coupling reaction was complete within a few minutes and afforded 1-(β-hydroxyalkyl)benzoxazole and 1-(β-hydroxyalkyl)benzothiazole smoothly in good to excellent yields upon subsequent protonation.



Scheme 1.

Benzoxazole and benzothiazole derivatives constitute an important class of heterocyclic compounds for their antibacterial and antifungal activities.[4] Several methods have already been reported for the preparation of 1-(β-hydroxyalkyl)benzoxazole and 1-(β-hydroxyalkyl)-benzothiazole. The aldol-type method for the preparation of 1-(β-hydroxyalkyl)benzoxazole and 1-(β-hydroxyalkyl)benzothiazole requires the use of *n*-BuLi at the temperature $-70^{\circ}C \sim -100^{\circ}C$[5] or the unavailable 9-BBN triflate.[6] In addition, these derivatives can also be obtained from reductive coupling of 2-(bromodifluoromethyl)benzoxazole and aldehydes with the aid of *tetrakis*(dimethylamino)ethylene.[7] Although the existing methodology can afford the desired products, they often involve in the expensive reagents, low temperature conditions, and unsatisfactory yields.

To investigate the ability of SmI_2 to promote these Barbier-type reactions, different experiments were performed. Table 1 summarizes our results. All the reactions were completed at room temperature within 5 min. The reactions proceeded in good to excellent yields for the aliphatic aldehydes and ketones. However, when acetophenone or benzaldehyde

Table 1. Barbier-type reaction of 2-chloromethylbenzoxazole and 2-chloromethylbenzothiazole with carbonyl compounds promoted by SmI_2.

Entry	*X*, *Y*	R_1, R_2	Product	Yield (%)[a,b]
1	H, O	CH_3, CH_3	3a	92, 85[c], 70[d]
2	H, O	CH_3, CH_3CH_2	3b	87
3	H, O	CH_3, $CH_3(CH_2)_3$	3c	95
4	H, O	H, $(CH_3)_2CH$	3d	82
5	H, O	H, $(CH_3)_2CHCH_2$	3e	85
6	H, O	Cyclopenxanone	3f	97
7	H, O	Cyclopentanone	3g	81
8	H, O	C_6H_5, C_6H_5	3h	77
9	Cl, O	CH_3, CH_3	3i	87
10	Cl, O	H, $(CH_3)_2CH$	3j	76
11	Cl, O	Cyclohexanone	3k	95
12	H, S	CH_3, CH_3	3l	90
13	H, S	H, $(CH_3)_2CH$	3m	87
14	H, S	Cyclohexanone	3n	96
15	H, S	Cyclopentanone	3o	83

[a]All compounds were fully characterized by ^1H NMR, MS, EA, and IR.
[b]Yields refer to % of isolated products based on substrate **1**.
[c]0.5 mL HMPA was added.
[d]2 mmol MeOH was added.

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

used as substrates, which are more easily reduced to pinacol by samarium diiodide than aliphatic aldehydes and ketones, they only gave complex mixtures. As for the benzophenone, 77% yield of the product is obtained. When 0.5 mL HMPA or 2 mmol MeOH were added to the reaction system, the yields of the products were relatively lower.

Although the mechanism of the above reaction has not been studied, the requirement of at least 2 M equiv. of samarium diiodide would suggest for the initial formation of a radical species and its further reduction to an organosamarium species by the second equivalent of samarium diiodide.

In conclusion, the method outlined for the synthesis of 1-(β-hydroxyalkyl)benzoxazoles and 1-(β-hydroxyalkyl)benzothiazoles represents a convenient approach with some advantages to known procedures: good to excellent yields, mild and neutral conditions, easy work-up of the reaction and recovery of the products. Thus, this procedure may provide a practical method to synthesize the above compounds.

EXPERIMENTAL

Tetrahydrofuran was distilled from sodium-benzophenone immediately prior to use. All reactions were conducted under a nitrogen atomsphere. Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Bruker 400 MHz instrument as $CDCl_3$ solutions using TMS as internal standard. Infrared spectra were recorded using KBr disks or thin films with a Bruker Vector-22 infrared spectrometer. Elemental analyses were performed on a EA-1110 instrument. Metallic samarium and all solvents were purchased from commercial sources, and used without further purification.

General procedure for the synthesis of 1-(β-hydroxyalkyl)benzoxazole and 1-(β-hydroxyalkyl)benzothiazole. A solution of 2-chloromethylbenzoxazole and 2-chloromethylbenzothiazole (1 mmol) with aldehydes or ketones (1.2 mmol) in dry THF (3 mL) was added to the solution of SmI_2 (2.2 mmol) in THF (20 mL) at room temperature under a nitrogen atmosphere. The deep blue color of the solution immediately changed to yellow. After being stirred for 5 min (Table 1, the reaction was monitored by TLC), the reaction mixture was quenched with 0.1 M hydrochloric acid (5 mL) and extracted with ether (3×15 mL). The organic phase was successively washed with brine (15 mL), water (15 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude products, which were purified by preparative TLC using ethyl acetate and cyclohexane (1:5) as eluant.

Compound 3a. M.p.: 74–75°C. ν_{max}: 3316, 3054, 2973, 2932, 1614, 1570, 1462, 1247, 1227, 767, 748 cm^{-1}. δ_H ($CHCl_3$): 7.68–7.73 (1H, m), 7.56–7.62 (1H, m), 7.32–7.52 (2H, m), 3.68 (1H, brs), 3.13 (2H, s), 1.40 (6H, s). *m*/*z* (%): 192 ($M^+ + 1$, 4.90), 176 (6.70), 134 (21.49), 133 (1.00), 104 (12.52), 59 (68.57). Anal. calcd. $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.12; H, 6.71; N, 7.23%.

Compound 3b. Viscous oil. ν_{max}: 3379, 2973, 2937, 1613, 1567, 1456, 909, 733 cm^{-1}. δ_H ($CDCl_3$): 7.66–7.71 (1H, m), 7.47–7.49 (lH, m), 7.28–7.30 (2H, m), 3.68 (1H, brs), 3.02–3.12 (2H, q), 1.62–1.64 (2H, m), 1.29 (3H, s), 0.96–1.03 (3H, t). *m*/*z* (%): 206 ($M^+ + 1$, 100), 188 (14.59), 133 (100), 73 (48.96), 43 (57.26). Anal. calcd. $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.13; H, 7.36; N, 6.89%.

Compound 3c. Viscous oil. ν_{max}: 3342, 2935, 2912, 1614, 1567, 1456, 1381, 902 cm^{-1}. δ_H ($CDCl_3$): 7.70–7.50 (2H, m), 7.31–7.33 (2H, m), 3.62 (IH, brs), 3.03–3.13 (2H, q), 1.30–1.62 (9H, m), 0.89–0.93 (3H, t). *m*/*z* (%): 234 ($M^+ + 1$, 4.26), 216 (4.21), 176 (10.07), 133 (100), 101 (18.00), 43 (39.98). Anal. calcd. $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.15; H, 8.33; N, 5.87%.

Compound 3d. M.p.: 52–54°C. ν_{max}: 3365, 2964, 2865, 1614, 1569, 1456, 745 cm^{-1}. δ_H ($CDCl_3$): 7.43–7.63 (2H, m), 7.25–7.27 (2H, m), 3.99–4.05 (1H, m), 3.78 (1H, brs), 2.95–3.08 (2H, m), 1.80–1.83 (1H, m), 0.99–1.02 (6H, d). *m*/*z* (%): 206 ($M^+ + 1$, 100), 188 (13.80), 162 (8.08), 133 (29.71), 119 (0.79), 105 (7.95), 43 (25.49). Anal. calcd. $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.09; H, 7.33; N, 6.75%.

Compound 3e. Viscous oil. ν_{max}: 3386, 2958, 2870, 1614, 1579, 1244, 734 cm^{-1}. δ_H ($CDCl_3$): 7.45–7.65 (2H, m), 7.27–7.29 (2H, m), 4.25–4.32 (1H, m), 3.81 (1H, brs), 2.96–3.09 (2H, m), 1.85–1.91 (1H, m), 1.57–1.61 (1H, m), 1.32–1.39 (1H, m), 0.95–0.97 (6H, d). *m*/*z* (%): 220 ($M^+ + 1$, 1.22), 201 (3.35), 186 (1.24), 162 (10.77), 133 (100), 77 (7.06), 43 (22.19). Anal. calcd. $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.34; H, 7.75; N, 6.42%.

Compound 3f. M.p.: 80–81°C. ν_{max}: 3333, 2937, 2860, 1610, 1567, 1218, 1142, 870 cm^{-1}. δ_H ($CHCl_3$): 7.51–7.70 (2H, m), 7.27–7.35 (2H, m), 3.44 (1H, brs), 3.11 (2H, s), 1.52–1.73 (10H, m). *m*/*z* (%): 232 ($M^+ + 1$, 3.55), 214 (2.85), 188 (1.90), 133 (100), 77 (9.70), 41 (24.93). Anal. calcd. $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.59; H, 7.37; N, 6.12%.

Compound 3g. M.p.: 70–72°C. ν_{max}: 3372, 2952, 2867, 1610, 1568, 1457, 1241, 748 cm^{-1}. δ_H ($CHCl_3$): 7.52–7.70 (2H, m), 7.32–7.35 (2H, m), 3.67 (1H, brs), 3.21 (2H, s), 1.67–1.90 (8H, m). *m*/*z* (%): 218 ($M^+ + 1$, 62.61), 200 (32.15), 188 (1.72), 175 (6.21), 133 (100), 104 (19.13), 41

(48.13). Anal. calcd. $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.95; H, 6.97; N, 6.32%.

Compound 3h. M.p.: 164–165°C. ν_{max}: 3420, 3027, 1608, 1564, 1454, 697 cm^{-1}. δ_H ($CHCl_3$): 7.53–7.62 (6H, m), 7.21–7.33 (8H, m), 5.78 (1H, brs), 3.89 (2H, s). *m/z* (%): 316 ($M^+ + 1$, 1.04), 315 (M^+, 4.10), 238 (0.92), 183 (38.85), 133 (91.40), 105 (100), 77 (74.94). Anal. calcd. $C_{21}H_{17}NO_2$: C, 79.98; H, 5.43; N, 4.44. Found: C, 79.86; H, 5.51; N, 4.45%.

Compound 3i. M.p.: 103–104°C. ν_{max}: 3363, 2989, 2971, 2934, 1600, 1451, 752 cm^{-1}. δ_H ($CHCl_3$): 7.68 (1H, s), 7.30–7.45 (2H, m), 3.53 (1H, brs), 3.11 (2H, s), 1.39 (6H, s). *m/z* (%): 226 ($M^+ + 1$, 17.04), 228 ($M^+ + 3$, 5.54), 208 (11.00), 167 (57.33), 132 (2.71), 59 (100), 43 (55.86). Anal. calcd. $C_{11}H_{I2}ClNO_2$: C, 58.54; H, 5.36; N, 6.21. Found: C, 58.57; H, 5.31; N, 6.32%.

Compound 3j. M.p.: 99–101°C. ν_{max}: 3299, 2961, 2876, 1615, 1559, 1464, 1447, 821 cm^{-1}. δ_H ($CDCl_3$): 7.66 (1H, s), 7.28–7.44 (2H, m), 3.99–4.03 (1H, m), 3.21 (1H, brs), 2.98–3.13 (2H, m), 1.83–1.88 (1H, m), 1.02–1.06 (6H, m). *m/z* (%): 240 ($M^+ + 1$, 7.69), 242 ($M^+ + 3$, 2.55), 222 (2.28), 196 (27.57), 167 (100), 132 (4.23). Anal. calcd. $C_{12}H_{14}ClNO_2$: C, 60.13; H, 5.89; N, 5.84. Found: C, 60.11; H, 5.97; N, 5.76%.

Compound 3k. M.p.: 107–109°C. ν_{max}: 3328, 2932, 2858, 1616, 1565, 1257, 802 cm^{-1}. δ_H ($CHCl_3$): 7.67 (1H, s), 7.28–7.44 (2H, m), 3.26 (1H, brs), 3.08 (2H, s), 1.50–1.73 (10H, m). *m/z* (%): 266 ($M^+ + 1$, 100), 268 ($M^+ + 3$, 32.19), 248 (16.44), 222 (0.61), 167 (8.86), 41 (14.13). Anal. calcd. $C_{14}H_{16}ClNO_2$: C, 63.28; H, 6.07; N, 5.27. Found: C, 63.22; H, 6.11; N, 5.39%.

Compound 3l. M.p.: 55–57°C. ν_{max}: 3278, 2966, 2927, 1619, 1557, 1502, 762 cm^{-1}. δ_H ($CHCl_3$): 7.82–7.99 (2H, m), 7.31–7.48 (2H, m), 4.12 (IH, brs), 3.23 (2H, s), 1.34 (6H, s). *m/z* (%): 208 ($M^+ + 1$, 100), 190 (19.40), 149 (29.04), 108 (9.03), 43 (28.89). Anal. calcd. $C_{11}H_{13}NOS$: C, 63.73; H, 6.32; N, 6.76. Found: C, 63.82; H, 6.41; N, 6.87%.

Compound 3m. Viscous oil. ν_{max}: 3367, 2975, 2898, 1611, 1557, 732 cm^{-1}. δ_H ($CDCl_3$): 7.83–7.96 (2H, m), 7.28–7.47 (2H, m), 3.97–4.02 (1H, m), 3.85 (1H, brs), 3.16–3.26 (2H, m), 1.88–1.93 (1H, m), 1.02–1.06 (6H, m). *m/z* (%): 222 ($M^+ + 1$, 0.82), 206 (0.58), 178 (26.58), 149 (100), 108 (10.43), 43 (15.92). Anal. calcd. $C_{12}H_{15}NOS$: C, 65.12; H, 6.83; N, 6.33. Found: C, 65.23; H, 6.92; N, 6.34%.

Compound 3n. M.p.: 103–104°C. ν_{max}: 3384, 3053, 2985, 2950, 1570, 1456, 1436, 1254, 757 cm^{-1}. δ_H ($CHCl_3$): 7.99–8.01 (1H, d), 7.86–7.87 (1H, d), 7.28–7.48 (2H, m), 3.86 (1H, brs), 3.25 (2H, s), 1.51–1.68 (10H, m). *m/z* (%): 248 ($M^+ + 1$, 4.90), 230 (1.57), 204 (2.05), 149 (100), 108 (8.66), 81 (22.53). Anal. calcd. $C_{14}H_{17}NOS$: C, 67.98; H, 6.93; N, 5.66. Found: C, 67.87; H, 7.05; N, 5.61%.

Compound 3o. M.p.: 58–60°C. ν_{max}: 3372, 2945, 2853, 1615, 1447, 1227, 738 cm^{-1}. δ_H ($CHCl_3$): 7.84–7.99 (2H, m), 7.35–7.49 (2H, m), 4.12 (1H, brs), 3.34 (2H, s), 1.65–1.88 (8H, m). *m/z* (%): 233 (M^+, 3.52), 216 (0.62), 204 (2.04), 149 (100), 108 (9.30). Anal. calcd. $C_{13}H_{15}NOS$: C, 66.92; H, 6.48; N, 6.00. Found: C, 66.93; H, 6.48; N, 6.12%.

ACKNOWLEDGMENT

We are grateful to the National Natural Science Foundation of China (Project No. 20072033) and the Specialized Research Fund for the Doctoral Program of Higher Education of China for financial support.

REFERENCES

1. (a) Barbier, P. Compt. Rend. **1898**, *128*, 110; (b) Blomberg, C. *The Barbier Reaction and Related One-Step Processes*; Springer-Verlag: New York, 1993; 183 pp; (c) Zn-promoted coupling: Hong, F.; Tang, X.Q.; Hu, C.M. Zinc-promoted Barbier-type reaction of 2-bromo-3,3,3-trifluoropropene with aldehydes. Chem. Commun. **1994**, 289; (d) Sm-mediated coupling: Kunishima, M.; Hioki, K.; Kono, K.; Sakuma, T.; Tani, S. Barbier-type reactions of aryl halides with ketones mediated by samarium diiodide. Chem. Pharm. Bull. **1994**, *42*, 2190; (d) Comparison with Ni(0) insertion chemistry for intramolecular cyclization: Kihara, M.; Kashimoto, M.; Kabayashi, Y. A convenient synthesis of 4-substituted 1,2,3,4-tetrahydroisoquinolin-4-ols by a novel intramolecular barbier reaction and by an insertion reaction; reaction scope and limitations. Tetrahedron **1992**, *48*, 67.
2. For reviews see: (a) Steel, P.G. J. Chem. Soc. Perkin Trans. 1 **2001**, 2727; (b) Girard. P., Namy, J.L.; Kagan, H.B. Divalent lanthanide derivatives in organic synthesis 1. Mile preparation of SmI_2 and YbI_2 and their use as reducing or coupling agents. J. Am. Chem. Soc. **1980**, *102*, 2693; (c) Krief, A.; Laval, A.M.; Coupling of organic halides with carbonyl compounds promoted by SmI_2, the kagan reagent. Chem. Rev. **1999**, *99*, 745; (d) Molander, G.A. Acc. Chem. Res., Diverse methods for medium ring synthesis. **1998**, *31*, 603; (e) Molander, G.A.; Harris, C.R.; Sequenced reactions with samarium(II) iodide. Tetrahedron **1998**, *54*, 3321; (f) Molander, G.A.; Harris, Sequenced reactions with samarium(II) iodide. C.R.

Chem. Rev. **1996**, *96*, 307; (g) Imamoto, T. *Lanthanides in Organic Synthesis*; Academic Press: London, 1994; Chapter 4; (h) Molander, G.A.; Application of lanthanide reagents in organic synthesis. Chem. Rev. **1992**, *92*, 29; (i) Curran, D.P.; Fevig, T.L.; Jasperse, C.P.; Totleben, M.J.; New mechanistic insights into reductions of halides and radicals with samarium(II) iodide. Synlett. **1992**, 943.

3. 2-Chloromethylbenzoxazole and 2-chloroanethylbenzothiazole were easily prepared by the literature: Kristinsson, H. Syntese von heterocyclen; IV. Neuer synthese weg zur herstellung von heterocyclischen nitrilen. Synthesis **1979**, 102.
4. (a) Hisano, T.; Ichikawa, M.; Tsumoto, K.; Tasaki, M. Synthesis of benzoaxoles, benzothiazoles and benzimidazoles and evaluation of their antifungal, insecticidal and herbicidal activities. Chem. Pharm. Bull. **1982**, *30*, 2996; (b) Prudhomme, M.; Guyot, J.; Jeminet, G. Semi-synthesis of A23187 (calcimycin) analogs. IV. Cation carrier properties in mitochondria of analogs with modified benzoxazole rings, antimicrobial activity. J. Antibiotics **1986**, *39*, 934; (c) Ersan, S.; Nacak, S.; Berkem, R.; Ozden, T. Synthesis and antimicrobial activities of 2-[(α-methylbenzylidene)hydrazino] benzoxazoles. Arzneim. Forsch. **1997**, *47*, 963; (d) Sener, E.; Yalcin, I.; Sungur, E. Synthesis and antimicrobial activities of 5-amino-2-(p-substituted-phenyl)benzoxazole derivatives. Quant. Struct. Act. Relat. **1991**, *10*, 223; (e) Gunawardana, G.P.; Kohmoto, S.; Gunasekara, S.P.; McConnel, O.J.; Koehn, F.E. Dercitine, a new biologically active acridine alkaloid from a deep water marine sponge, dercitus sp. J. Am. Chem. Soc. **1988**, *110*, 4856; (f) Gunawardana, G.P.; Kohmoto, S.; Burres, N.S. New cytotoxic acridine alkaloids from two deep water marine sponges of the family pachastrellidae. Tetrahedron Lett. **1989**, *30*, 4359; (g) Gunawardana, G.P.; Koehn, F.E.; Lee, A.Y.; Clardy, J.; He, H.Y.; Faulkner, J.D. Pyridoacridine alkaloids from deep-water marine sponges of the family pachastrellidae: structure revision of dercitin and related compounds and correlation with the kuanoniamines. J. Org. Chem. **1992**, *57*, 1523; (h) Carroll, A.R.; Scheuer, P.J. Kuanoniamines A, B, C, and D: pentacyclic alkaloids from a tunicate and its prosobranch mollusk predator chelynotus semperi. J. Org. Chem. **1990**, *55*, 4426; (i) Kim, J.S.; Sun, Q.; Gatto, B.; Yu, C.; Liu, A.; Liu, L.F.; LaVoie, E.J. Structure-activity relationships of benzimidazoles and related heterocycles as tepoisomerase I poisons. Bioorg. Med. Chem. **1996**, *4*, 621.
5. Hoffman, J.M.; Smith, A.M.; Rooney, C.S.; Fisher, T.E.; Wai, J.S.; Thomas, C.M.; Bamberger, D.L.; Barnes, J.L.; Williams, T.M.; Jones, J.H.; Olson, B.D.; O'Brien, J.A.; Goldman, M.E.; Nunberg,

J.H.; Quintero, J.C.; Schleif, W.A.; Emini, E.A.; Anderson, P.S. J. Med. Chem. **1992**, *56*, 953.
6. Hamana, H.; Sugasawa, T. An aldol-type reaction of active methyl groups of nitrogen-containing heteroaromatic compounds. Chem. Lett. **1983**, 333.
7. Burkholder, C.; Dolbier, W.R., Jr. Reaction of the 2-(bromodifluoromethyl) benzoxazole with tetrakis(dimethylamino)ethylene (TDAE) in the presense of aldehydes. A convenient synthesis of 2-(difluoromethyl) benzoxazole alcohols. Tetrahedron Lett. **1997**, *38*, 821.

Received in Japan March 1, 2003

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016