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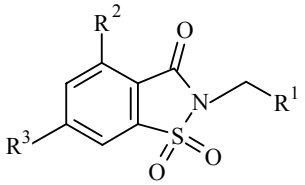
# ADDITION OF NITRILE OXIDES TO N-ALLYLSACCHARIN

**V. Dirnens, S. Belyakov, and E. Lukevics**

*The addition of nitrile oxides to N-allylsaccharin has been studied and it has been shown that the reaction occurs regiospecifically to form a 5-substituted isomer. The molecular structure of 2-{5-[(3-methyl)isoxazolin-2-yl]methyl}-3-oxo-2,3-dihydrobenz[d]isothiazole 1,1-dioxide has been determined by X-ray analysis. A feature of the crystal of this compound is the presence of a supersymmetrical crystalline structure with two independent molecules associated by a center of pseudoinversion.*

**Keywords:** N-allylsaccharin, isoxazolines, nitrile oxides.

Saccharin (3-oxo-2,3-dihydrobenz[*d*]isothiazole 1,1-dioxide) is the best known of the isothiazole 1,1-dioxide class of compound. Its synthesis, chemical properties, and reactions are gathered in several reviews [1-7]. One of the routes in the synthesis of pharmacologically interesting saccharin compounds is O- or N-modification. N-Substituted derivatives of saccharin **1** are actually inhibitors of human leukocyte elastase [8-17] and can be used as active therapeutic agents for treatment of emphysema and inflammatory lung illnesses [18].



**1**

$R^1$ = aryl(hetaryl), $R^2$ = alkyl, $R^3$ = H, alkyl

On the other hand, compounds with anti-inflammatory activity can be found amongst isoxazolines [19] and the heterocycle itself is a valuable synthon in organic chemistry for the preparation of β-hydroxy ketones [20-25], γ-amino alcohols [26-28], α,β-unsaturated oximes [29, 30], and β-hydroxy nitriles [31, 32]. Hence we have synthesized compounds which have the saccharin and isoxazoline fragments combined.

For the preparation of isoxazoline derivatives of saccharin **13-22**, in which there is a $–CH_2–$ bridge between the nitrogen atom of the saccharin and the heterocycle, we carried out a [2+3] cycloaddition reaction of the nitrile oxides **3-12** (generated from hydroxamic acid chlorides in the presence of triethylamine) to N-allylsaccharin **2**.

* Dedicated to Professor V. I. Minkin on the occasion of his anniversary

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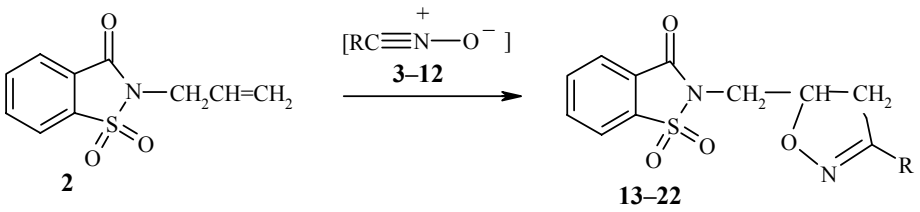



| Compound | R | Compound | R |
|---|---|---|---|
| **13** | Me | **18** | 4-$ClC_6H_4$ |
| **14** | Ph | **19** | 4-$Me_2NC_6H_4$ |
| **15** | 2-$ClC_6H_4$ | **20** | 4-$MeOC_6H_4$ |
| **16** | 2-$MeOC_6H_4$ | **21** | 3,4-$(MeO)_2C_6H_3$ |
| **17** | 4-$BrC_6H_4$ | **22** | 2,4-$Cl_2C_6H_3$ |

This "one-pot" reaction was performed successively by: 1) reaction of the aryloxime with N-chlorosuccinimide in chloroform to give the corresponding aryl(methyl)hydroxamic acid chlorides; 2) addition of the unsaturated compound; and 3) addition of triethylamine as the dehydrohalogenating agent for generation of the nitrile oxide.

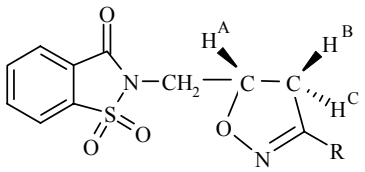
The [2+3] cycloaddition occurs regioselectively and always forms the single 5-substituted isoxazoline regioisomer.

An X-ray analysis of the crystal of compound **13** was performed in order to determine the spatial structure. Fig. 1 shows the spatial model for the **13** molecule. A feature of the structure of the crystals is the presence of a supersymmetrical crystalline structure: two crystallographically independent molecules of **13** being associated by a center of pseudoinversion. The projection of the packing of the molecule is given in

TABLE 1. Parameters for the Isoxazoline Containing Saccharins **13-22**

| Compound | Empirical formula, (molecular weight) | Found, % / Calculated, % | | | mp, °C | Yield, % |
|---|---|---|---|---|---|---|
| | | C | H | N | | |
| **13** | $C_{12}H_{12}N_2O_4S$ (280.31) | 51.45 / 51.42 | 4.34 / 4.32 | 9.95 / 9.99 | 121 | 65 |
| **14** | $C_{17}H_{14}N_2O_4S$ (342.38) | 59.52 / 59.64 | 4.11 / 4.12 | 8.21 / 8.18 | 130 | 63 |
| **15** | $C_{17}H_{13}ClN_2O_4S$ (376.82) | 54.31 / 54.19 | 3.46 / 3.48 | 7.45 / 7.43 | 131 | 61 |
| **16** | $C_{18}H_{16}N_2O_5S$ (372.40) | 58.17 / 58.06 | 4.31 / 4.33 | 7.55 / 7.52 | 145 | 73 |
| **17** | $C_{17}H_{13}BrN_2O_4S$ (421.27) | 48.63 / 48.47 | 3.13 / 3.11 | 6.62 / 6.65 | 163 | 71 |
| **18** | $C_{17}H_{13}ClN_2O_4S$ (376.82) | 54.33 / 54.19 | 3.46 / 3.48 | 7.40 / 7.43 | 129 | 67 |
| **19** | $C_{19}H_{19}N_3O_4S$ (385.45) | 59.12 / 59.21 | 4.92 / 4.97 | 10.94 / 10.90 | 156 | 59 |
| **20** | $C_{18}H_{16}N_2O_5S$ (372.40) | 58.01 / 58.06 | 4.35 / 4.33 | 7.52 / 7.52 | 152 | 64 |
| **21** | $C_{19}H_{18}N_2O_6S$ (402.43) | 56.85 / 56.71 | 4.49 / 4.51 | 7.00 / 6.96 | 199 | 69 |
| **22** | $C_{17}H_{12}Cl_2N_2O_4S$ (411.27) | 49.80 / 49.65 | 2.96 / 2.94 | 6.82 / 6.81 | 171 | 61 |

TABLE 2. $^1$H NMR Spectra of the Isoxazoline Containing Saccharins



**13–22**

| Com-pound | Chemical shifts, δ, ppm (SSCC, *J*, Hz) |
|---|---|
| **13** | 2.01 (3H, s, $CH_3$); 2.89 (1H, dd, *J* = 6.8, *J* = 16.8, $CH_C$); 3.14 (1H, dd, *J* = 9.4, *J* = 16.8, $CH_B$); 3.78 (1H, dd, *J* = 7.0, *J* = 15.4, NCH); 3.96 (1H, dd, *J* = 5.2, *J* = 15.4, NCH); 4.85-5.18 (1H, m, $CH_A$); 7.74-8.09 (4H, m, $H_{arom}$) |
| **14** | 3.27 (1H, dd, *J* = 6.8, *J* = 15.2, $CH_C$); 3.52 (1H, dd, *J* = 9.2, *J* = 15.2, $CH_B$); 3.87 (1H, dd, *J* = 6.8, *J* = 13.8, NCH); 4.07 (1H, dd, *J* = 5.4, *J* = 13.8, NCH); 5.05-5.33 (1H, m, $CH_A$); 7.32-7.43 (3H, m, $H_{arom}$); 7.58-7.72 (2H, m, $H_{arom}$); 7.76-7.94 (3H, m, $H_{arom}$); 7.95-8.09 (1H, m, $H_{arom}$) |
| **15** | 3.45 (1H, dd, *J* = 6.8, *J* = 16.1, $CH_C$); 3.69 (1H, dd, *J* = 8.3, *J* = 16.1, $CH_B$); 3.89 (1H, dd, *J* =5.9, *J* = 13.4, NCH); 4.12 (1H, dd, *J* = 4.8, *J* = 13.4, NCH); 5.09-5.45 (1H, m, $CH_A$); 7.25-7.43 (3H, m, $H_{arom}$); 7.58-7.69 (1H, m, $H_{arom}$); 7.81–8.12 (4H, m, $H_{arom}$) |
| **16** | 3.48 (1H, dd, *J* = 6.8, *J* = 17.7, $CH_C$); 3.59 (1H, dd, *J* = 9.7, *J* = 17.7, $CH_B$); 3.85 (3H, s, $OCH_3$); 3.87 (1H, dd, *J* = 7.2, *J* = 14.6, NCH); 4.03 (1H, dd, *J* = 5.9, *J* = 14.6, NCH); 5.10-5.25 (1H, m, $CH_A$); 6.95 (2H, m, $H_{arom}$); 7.38 (1H, m, *J* = 1.6, *J* = 7.3, $H_{arom}$); 7.73 (1H, dd, *J* = 1.6, *J* = 7.7, $H_{arom}$); 7.83-8.05 (3H, m, $H_{arom}$); 8.08 (1H, m, $H_{arom}$) |
| **17** | 3.29 (1H, dd, *J* = 7.7, *J* = 17.8, $CH_C$); 3.52 (1H, dd, *J* = 9.2, *J* = 17.8, $CH_B$); 3.87 (1H, dd, *J* =7.4, *J* = 16.1, NCH); 4.07 (1H, dd, *J* = 5.5, *J* = 16.1, NCH); 5.05-5.41 (1H, m, $CH_A$); 7.42 (4H, s, $H_{arom}$); 7. 82-8.12 (4H, m, $H_{arom}$) |
| **18** | 3.32 (1H, dd, *J* = 7.8, *J* = 17.8, $CH_C$); 3.49 (1H, dd, *J* = 9.2, *J* = 17.8, $CH_B$); 3.87 (1H, dd, *J* =7.4, *J* = 15.3, NCH); 4.07 (1H, dd, *J* = 5.5, *J* = 15.3, NCH); 5.07-5.43 (1H, m, $CH_A$); 7.36 (2H, d, *J* = 8.6, $H_{arom}$); 7. 61 (2H, d, *J* = 8.6, $H_{arom}$); 7. 81-8.16 (4H, m, $H_{arom}$) |
| **19** | 2.92 (6H, s, 2 × $CH_3$); 3.27 (1H, dd, *J* = 6.6, *J* = 17.8, $CH_C$); 3.47 (1H, dd, *J* = 8.6, *J* = 17.8, $CH_B$); 3.85 (1H, dd, *J* =7.4, *J* = 13.6, NCH); 4.05 (1H, dd, *J* = 5.6, *J* = 13.6, NCH); 4.98-5.32 (1H, m, $CH_A$); 6.67 (2H, d, *J* = 8.4, $H_{arom}$); 7.52 (2H, d, *J* = 8.4, $H_{arom}$); 7.76–8.09 (4H, m, $H_{arom}$) |
| **20** | 3.29 (1H, dd, *J* = 7.2, *J* = 15.4, $CH_C$); 3.49 (1H, dd, *J* = 9.1, *J* = 15.4, $CH_B$); 3.81 (3H, s, $OCH_3$); 3.85 (1H, dd, *J* =7.1, *J* = 13.6, NCH); 4.07 (1H, dd, *J* = 5.6, *J* = 13.6, NCH); 5.03-5.38 (1H, m, $CH_A$); 6.87 (2H, d, *J* = 8.4, $H_{arom}$); 7.61 (2H, d, *J* = 8.4, $H_{arom}$); 7.74-7.92 (3H, m, $H_{arom}$); 7.96-8.12 (1H, m, $H_{arom}$) |
| **21** | 3.32 (1H, dd, *J* = 7.1, *J* = 16.2, $CH_C$); 3.52 (1H, dd, *J* = 9.1, *J* = 16.2, $CH_B$); 3.85 (6H, s, 2 × $OCH_3$); 3.89 (1H, dd, *J* =7.6, *J* = 18.4, NCH); 4.25 (1H, dd, *J* = 6.1, *J* = 18.4, NCH); 5.05-5.38 (1H, m, $CH_A$); 6.83 (1H, d, *J* = 8.2, $H_{arom}$); 7. 05 (1H, dd, *J* = 1.6, *J* = 8.2, $H_{arom}$); 7.41 (1H, d, *J* = 1.6, $H_{arom}$); 7. 81-8.14 (4H, m, $H_{arom}$) |
| **22** | 3.45 (1H, dd, *J* = 6.6, *J* = 16.6, $CH_C$); 3.67 (1H, dd, *J* = 9.1, *J* = 16.6, $CH_B$); 3.89 (1H, dd, *J* =6.8, *J* = 14.4, NCH); 4.12 (1H, dd, *J* = 5.2, *J* = 14.4, NCH); 5.09-5.43 (1H, m, $CH_A$); 7. 25 (1H, dd, *J* = 1.8, *J* = 7.8, $H_{arom.}$); 7.43 (1H, d, *J* = 1.8, $H_{arom}$); 7.58 (1H, d, *J* = 7.8, $H_{arom}$); 7. 78-8.12 (4H, m, $H_{arom}$) |

Fig. 2. Basic bond lengths and valence angle values are given in Tables 4 and 5. The isoxazoline ring has an envelope conformation. The deviations of the $C_{(5)}$ atoms from the $O_{(1)}N_{(2)}C_{(3)}C_{(4)}$ plane are 0.257(4) and 0.203(5) Å for the two independent molecules. The corresponding dihedral angles between the plane of the saccharin molecule and the mean plane of the isoxazoline ring are 28.7(4) and 35.3(4)°.

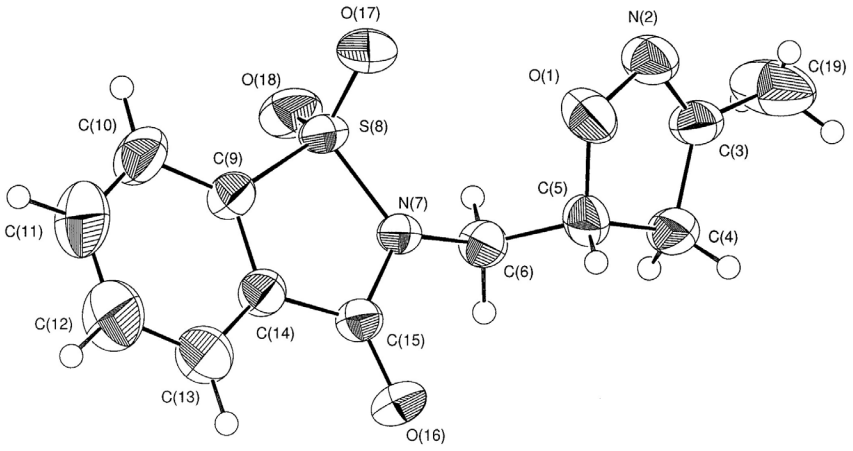



Fig. 1. Steric model for the molecule of compound **13** with atomic numbering.

## EXPERIMENTAL

The X-ray analysis was carried out on a Bruker-Nonius Kappa CCD automatic diffractometer (exposure at room temperature, molybdenum radiation with λ = 0.71073 Å, graphite monochromator, ϕ- and ω-scanning). The structure was solved by the method [33] and refined in a full matrix least squares analysis using the program [34]. The basic crystallographic parameters for compound **13** are given in Table 3.

TABLE 3. Crystallographic Data and Refinement Parameters for the Crystalline Structure of **13**

| | |
|---|---|
| Empirical formula | $C_{12}H_{12}N_2O_4S$ |
| Crystal color | Colorless |
| Monocrystal size, mm | 0.12×0.23×0.30 |
| Crystal system | Monoclinic |
| Crystalline lattice parameters, Å | |
| *a* | 10.8844(3) |
| *b* | 14.2738(4) |
| *c* | 17.2119(4) |
| β, ° | 105.304(2) |
| Volume of the unit cell, V, Å$^3$ | 2579.3(1) |
| Space group | $P\,2_1/n$ |
| *Z* | 8 |
| *F*(000) | 1168 |
| Density, $D_x$, g/cm$^3$ | 1.444 |
| μ, mm$^{-1}$ | 0.26 |
| $2\theta_{max}$, ° | 55.0 |
| Number of reflections | |
| measured | 10554 |
| independent | 6363 |
| used in the least squares analysis | 3868 ($I > 3\sigma_I$) |
| Number of refinement parameters | 373 |
| *R*-factor | 0.072 |
| $wR_2$ | 0.185 |
| $\Delta\rho_{max}$, e/Å$^3$ | 1.00 |
| $\Delta\rho_{min}$, e/Å$^3$ | -0.98 |

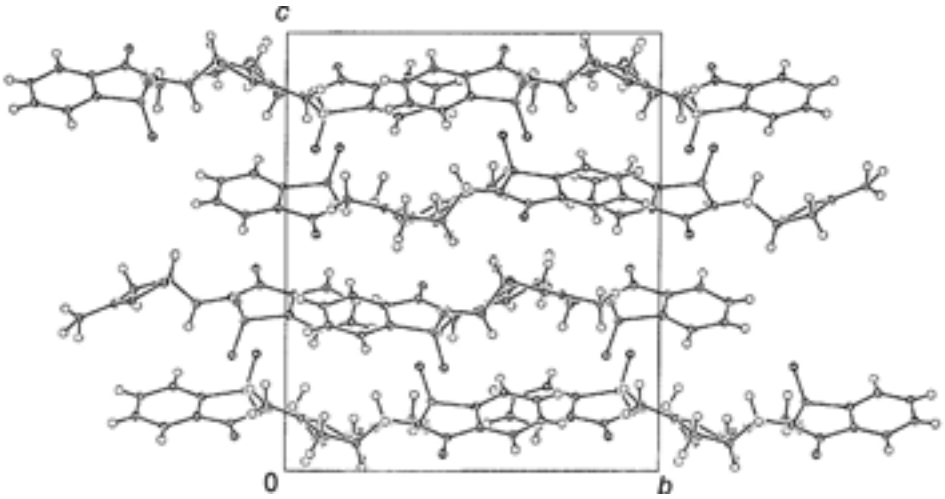



Fig. 2. Projection of the crystalline structure of compound **13** along the *x* axis.

TABLE 4. Bond Lengths (*l*) in the Structure of Compound **13**

| Bond | *l*, Å | | Bond | *l*, Å | |
|---|---|---|---|---|---|
| | molecule A | molecule B | | molecule A | molecule B |
| S(8)–O(17) | 1.423(2) | 1.419(2) | N(7)–C(15) | 1.407(4) | 1.398(4) |
| S(8)–O(18) | 1.437(2) | 1.428(2) | C(15)–C(14) | 1.480(4) | 1.479(4) |
| S(8)–N(7) | 1.655(2) | 1.677(3) | N(2)–C(3) | 1.264(4) | 1.278(4) |
| S(8)–C(9) | 1.745(3) | 1.755(3) | C(3)–C(4) | 1.486(5) | 1.477(5) |
| O(16)–C(15) | 1.206(4) | 1.201(4) | C(3)–C(19) | 1.491(6) | 1.463(6) |
| C(6)–N(7) | 1.460(4) | 1.491(4) | C(10)–C(11) | 1.390(6) | 1.383(6) |
| C(6)–C(5) | 1.520(4) | 1.466(6) | C(13)–C(12) | 1.382(6) | 1.396(6) |
| O(1)–N(2) | 1.424(4) | 1.440(4) | C(12)–C(11) | 1.367(7) | 1.364(7) |
| O(1)–C(5) | 1.433(4) | 1.450(5) | | | |

TABLE 5. Valence Angles (ω) in the Structure of Compound **13**

| Bond | ω, deg. | |
|---|---|---|
| | molecule A | molecule B |
| O(17)–S(8)–N(7) | 111.92(14) | 111.69(14) |
| O(17)–S(8)–O(18) | 117.4(2) | 117.7(2) |
| O(17)–S(8)–C(9) | 110.2(2) | 109.5(2) |
| N(7)–S(8)–O(18) | 108.48(14) | 109.04(14) |
| N(7)–S(8)–C(9) | 93.28(13) | 93.20(15) |
| O(18)–S(8)–C(9) | 112.99(14) | 113.1(2) |
| N(7')–S(8')–O(17') | 111.69(14) | 111.69(14) |
| S(8)–N(7)–C(6) | 122.5(2) | 120.8(2) |
| C(6)–N(7)–C(15) | 120.6(2) | 121.2(3) |
| N(2)–O(1)–C(5) | 108.8(2) | 108.3(3) |

$^1$H NMR spectra for compounds **13-15** and **17-22** were recorded on a Bruker WR-90 instrument (90.1 MHz) and for compound **16** on a Varian Mercury-200BB instrument (200.1 MHz) using $CDCl_3$ and TMS as internal standard.

The general method for the preparation of the isoxazolines **13-22** is given in [35] and the parameters for the obtained compounds are shown in Tables 1 and 2.

The experimental work was carried out with the help of E. Alksnis, V. Muravenko, and I. Skrastyn.

## REFERENCES


1. L. L. Bambas, in: A. Weissberger (editor), *The Chemistry of Heterocyclic Compounds*, Vol. 4, Interscience, New York (1952), p. 278.
2. H. Hettler, *Adv. Heterocycl. Chem.*, **15**, 233 (1973).
3. D. L. Pain, B. J. Peart, K. R. H. Wooldridge, in: A. R. Katritzky and C. W. Rees (editors), *Comprehensive Heterocyclic Chemistry*, Vol. 6, Pergamon Press, Oxford (1984), p. 132.
4. M. Davis, *Adv. Heterocycl. Chem.*, **38**, 105 (1985).
5. B. Schulze and K. Illgen, *J. Prakt. Chem.*, **339**, 1 (1997).
6. R. V. Kaverdin and V. I. Potkin, *Usp. Khim.*, **71**, 764 (2002).
7. Abdel-Sattar S. Hamad Elgazwy, *Tetrahedron*, **59**, 7445 (2003).
8. W. C. Groutas, M. J. Brubaker, R. Venkatamaran, J. B. Epp, N. Houser-Archield, I. S. Chong, and J. J. McClenahan, *Bioorg. Med. Chem. Lett.*, **2**, 175 (1992).
9. W. C. Groutas, M. J. Brubaker, R. Venkatamaran, J. B. Epp, N. Houser-Archield, I. S. Chong, and J. J. McClenahan, *Bioorg. Med. Chem. Lett.*, **3**, 273 (1993).
10. W. C. Groutas, N. Houser-Archield, L. S. Chong, R. Venkatamaran, J. B. Epp, He Huang, and J. J. McClenahan, *J. Med. Chem.*, **36**, 3178 (1993).
11. D. J. Hlasta, M. R. Bell, N. W. Booz, J. J. Court, R. C. Desai, C. A. Franke, A. J. Mura, S. Subramanyam, and R. P. Dunlap, *Bioorg. Med. Chem. Lett.*, **4**, 1801 (1994).
12. D. J. Hlasta and J. H. Ackerman, *J. Org. Chem.*, **59**, 6184 (1994).
13. C. Subramanyam, M. R. Bell, P. Carabateas, J. J. Court, J. A. Dority Jr., E. Ferguson, R. Gordon, D. J. Hlasta, V. Kumar, and M. Saindane, *J. Med. Chem.*, **37**, 2623 (1994).
14. C. Desai, R. P. Dunlap, R. P. Farrell, E. Ferguson, C. A. Franke, R. Gordon, D. J. Hlasta, and T. G. Talmi, *Bioorg. Med. Chem. Lett.*, **5**, 105 (1995).
15. D. J. Hlasta, M. R. Bell, J. J. Court, K. C. Cundy, R. C. Desai, E. Ferguson, R. J. Gordon, and V. Kumar, *Bioorg. Med. Chem. Lett.*, **5**, 331 (1995).
16. R. C. Desai, R. P. Farrell, J. J. Court, and J. D. Weaver, *Synth. Commun.*, **25**, 2099 (1995).
17. R. C. Desai, J. J. Court, E. Ferguson, R. Gordon, D. J. Hlasta, R. P. Dunlap, and C. A. Franke, *J. Med. Chem.*, **38**, 1571 (1995).
18. D. J. Hlasta and E. D. Pagani, *Ann. Rep. Med. Chem.*, Chapt. 21, 29 (1994).
19. D. H. Ko, M. F. Maponja, M. A. Khalil, E. T. Oriaku, Z. You, and J. Lee, *J. Med. Chem. Res.*, **313**, 8 (1998).
20. A. P. Kozikowski and P. D. Stein, *J. Amer. Chem. Soc.*, **104**, 4023 (1982).
21. D. P. Curran, *J. Amer. Chem. Soc.*, **105**, 5826 (1983).
22. B. H. Kim, Y. J. Chung, and E. J. Ryu, *Tetrahedron Lett.*, **34**, 8465 (1993).
23. S. H. Andersen, K. K. Sharma, and K. B. G. Torssell, *Tetrahedron*, **39**, 2241 (1983).
24. P. G. Baraldi, A. Barco, S. Benetti, S. Manfredini, and D. Simoni, *Synthesis*, 276 (1987).
25. J. W. Bode and E. M. Carreira, *Org. Lett.*, **3**, 1587 (2001).
26. A. P. Kozikowski and M. Adamczyk, *Tetrahedron Lett.*, **23**, 3123 (1982).
27. A. P. Kozikowski and Y. Y. Chen, *J. Org. Chem.*, **46**, 5248 (1981).
28. J. Müller and V. Jäger, *Tetrahedron Lett.*, **23**, 4777 (1982).
29. V. Jäger and H. Grund, *Angew. Chem. Int. Ed. Engl.*, **15**, 50 (1976).

30. S. Y. Lee, B. S. Lee, C. W. Lee, and D. Y. Oh, *J. Org. Chem.*, **65**, 256 (2000).
31. G. W. Moersch, E. L. Wittle, and W. A. Neuklis, *J. Org. Chem.*, **32**, 1387 (1967).
32. A. Yoshiro, Y. Nishida, K. Kobayashi, and M. Ohno, *Synth. Lett.*, 361 (2000).
33. A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori, and R. Spagna, *J. Appl. Cryst.*, **32**, 115 (1999).
34. S. McKay, C. J. Gilmone, C. Edwards, N. Stewart, and K. Shankland, *MaXus Computer Program for the Solution and Refinement of Crystal Structures*, Bruker Nonius, The Netherlands, Mac Science, Japan and the University of Glasgow (1999).
35. V. Dirnens, O. Slyadevskaya, and E. Lukevics, *Khim. Geterotsikl. Soedin.*, 499 (2002).