Preparation of Apoptotic Inducers, 2,2-Diphenyl-1,3,2-oxazaborolidin-5-ones, Under Alkaline Conditions

Benjamín Velasco-Bejarano,*[a,b] José Trujillo-Ferrara,[a] René Miranda[b]

[a] Departamento de Bioquímica Médica, Escuela Superior de Medicina-IPN, México D.F., 11340, México

[b] Departamento de Ciencias Químicas, Facultad de Estudios Superiores Cuautitlán-UNAM, Estado de México, 54740, México
Fax +52(55)56232056; E-mail: qfbbevebe@gmail.com

Received 13 July 2006

Abstract: An efficient and high-yielding procedure has been developed for the synthesis of a set of fifteen 2,2-diphenyl-1,3,2-oxazaborolidin-5-ones, through the reaction of the corresponding α-amino acid with diphenyl borinic acid under alkaline conditions (pH 7.5–8). It is of note that these compounds showed potent cytotoxic activity on K-562 and HCT-15 cell lines.

Key words: α-amino acids, diphenyloxazaborolidinones, boron complexes, apoptosis, diphenylborinic acid

Much interest is currently focused on the synthesis of boron-containing compounds due to their biological importance. In particular, certain molecules containing boron–nitrogen bonds have shown interesting biological activity, including insecticidal, fungicidal, herbicidal,[1] antibacterial,[2,3] inhibitor thrombin-induced Ca^{2+},[4] and apoptotic activity.[5] Belonging to this class of nitrogen–boron-coordinated compounds is a group that deserves particular attention, 2,2-dialkyl or 2,2-diphenyl-1,3,2-oxazaborolidin-5-ones (Figure 1), which are generally obtained by the reaction of α-amino acids with alkyl boranes, aryl boranes or alkylborinates under acidic conditions. For example, Lang et al.[6] prepared several of these compounds, using glycine and L-methionine with tri-*n*-propylborane or triarylboranes in refluxing *o*-xylene under nitrogen. Another protocol was described by Skoog,[7] employing a diaryl alkyl borinate with glycine, alanine, leucine or aminoethanol, thus obtaining the corresponding borinates. In addition, Shih-Hua et al.[8] reported the synthesis of various diarylborinates by treating several amino acids with *n*-butyldiarylborane. Nefkens et al.[9] produced a series of diethyl or diphenyl oxazaborolidinones from glycine, phenylalanine, tryptophan, aspartic acid, glutamic acid, cysteine, lysine and methionine, employing a slight excess of triethylborane or triphenylborane in tetrahydrofuran.

Flückiger et al.[10] reported the use of the ethanolamine complex of diphenylboronic acid in acidic conditions to give a set of twenty 2,2-diphenyl-1,3,2-oxazaborolidin-5-ones generated from the corresponding α-amino acids. Strang et al.[11] obtained various oxazaborolidinones using the ethanolamine complex of diphenyl borinic acid in a mixture of water, 2-propanol and acetic acid. Another method using an acidic medium was reported by Farfán et al.[12] and Trujillo et al.[13]Chremos et al.[14] described a facile method of both preparing and liberating the ethanolamine ester of diphenylborinic acid. As a continuation of our efforts in this area,[13] we addressed our attention to the effect of alkaline conditions in the production of a set of fifteen 2,2-diphenyl-1,3,2-oxazaborolidin-5-ones (**3a**–**o**). Thus, the aim of this work is to report a new and convenient protocol under mild alkaline conditions[16] for the production of target molecules (Scheme 1). In addition, the cytotoxic activity of **3a**–**o** was evaluated against two tumor cell lines, HCT-15 (human colon cancer) and K-562 (human leukemia) using the sulforhodamine B assay.[17]

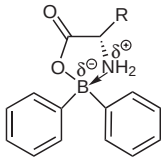
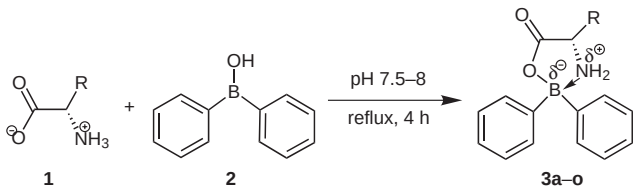


Figure 1

To explore the scope of our reaction, fifteen α-amino acids were converted to oxazaborolidinones (Table 1). In addition, compounds **3a**, **3b**, **3e**, **3f**, **3g**, **3i**, **3m**, **3n** and **3o**, were obtained in better yields when compared to previously reported procedures.[7,8,12]



Scheme 1

The corresponding spectroscopic data were used for the structural attribution of **3a**–**o**.[18] In general, the signal between +3.0 and 6.7 ppm in the ^{11}B NMR spectrum was assigned to a tetra-coordinated boron. In regard to the carbon signals of the aromatic ring, the *i*-carbon atoms appeared in the range 148–149 ppm, the *o*-carbons atoms at 131–132 ppm, the *m*-carbons atoms at 127–128 ppm and the *p*-carbons atoms at 125–126 ppm. In general, a single signal assigned to the carbon of the fourth position in the

SYNLETT 2007, No. 6, pp 0921–0924
Advanced online publication: 26.03.2007
DOI: 10.1055/s-2007-973886; Art ID: S14606ST
© Georg Thieme Verlag Stuttgart · New York

oxazaborolidinonic moiety was present in the range 42–62 ppm and in the ^{1}H NMR spectra, the proton at the fourth position displayed common signals around 3.3–3.7 ppm. Finally, in the corresponding MS (EI), the target compounds showed the expected molecular ions as well as common ions; $[M - 1]^+$, $[M - 44]^+$, and $[M - 77]^+$.

Table 1 Production of 2,2-diphenyl-1,3,2-oxazaborolidin-5-ones **3a**–**3o**[a]

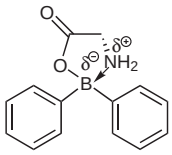
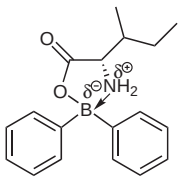
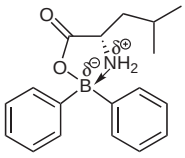
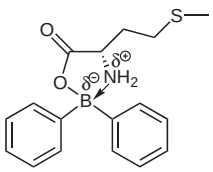
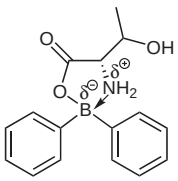
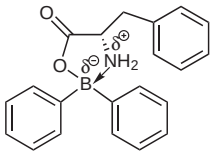
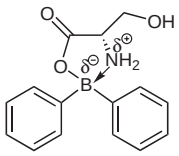
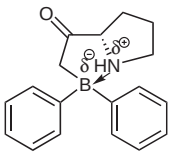
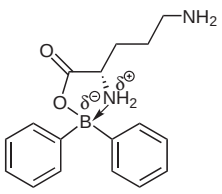
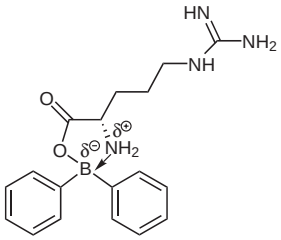
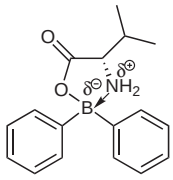
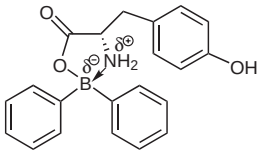
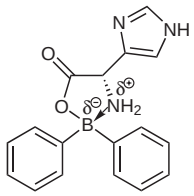
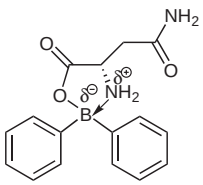
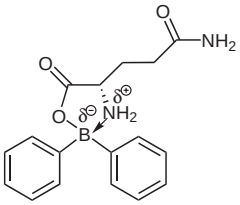
Product	α-aa	Structure	pH	Yield[b] (%)	Yield[c] (%)	Mp (°C)
3a	Gly (G)		8.0	51[7] 48.7[8] 26[12] 45[4]	94	241–243
3b	L-Ile (I)		7.5	88[12]	93	221–223
3c	L-Leu (L)		7.5	88[7] 68.5[8] 100[12]	90	171–174
3d	L-Met (M)		8.0	78[12]	78	222–224
3e	L-Thr (T)		8.5	12.6[8] 58[12]	88	202–203
3f	L-Tyr (Y)		7.5	21[12]	91	149–150
3g	L-Ser (S)		7.5	43.4[8] 36[12]	93	259-260
3h	L-Pro (P)		8.0	100[12] 87[15]	98	268–269
3i	L-Orn		8.5	60[13]	90	213–215

Table 1 Production of 2,2-diphenyl-1,3,2-oxazaborolidin-5-ones **3a**–**3o**[a] (continued)

Product	α-aa	Structure	pH	Yield[b] (%)	Yield[c] (%)	Mp (°C)
3j	L-Arg (R)		8.5	–	89	244–246
3k	L-Val (V)		7.5	79.78[8]	80	243–245
3l	L-Phe (F)		8.0	70[9]	65	222–224
3m	L-His (H)		8.0	45.99[8]	92	275–277
3n	L-Asn (N)		8.5	–	76	150–151
3o	L-Gln (Q)		8.5	–	83	240–242

[a] All the products were characterized by their spectroscopic data [^{1}H NMR, ^{13}C NMR, ^{11}B NMR, MS (EI) and IR].
[b] Published procedure.
[c] Our procedure.

In addition, the cytotoxic effect of these compounds was studied using the Sulforhodamin assay on HCT-15 and K-565 cell lines. The results show that compounds **3a**–**o** exhibit a cytotoxic effect on both the HCT-15 and K-562 cell lines. Meanwhile, **3a** and **3j** showed the best growth inhibition in the HCT-15 cell line, while compounds **3a**, **3b**, **3c**, **3g**, **3j**, **3l** and **3n** showed good inhibition in the K-562 cell line (>70% growth inhibition).

In summary, this paper describes an efficient and convenient procedure for the preparation of 2,2-diphenyl-1,3,2-oxazaborolidin-5-ones in good yields, under alkaline conditions. These compounds have shown themselves to be attractive molecules for further studies into their antineoplastic activity.

Acknowledgment

B.V.B. thanks CONACyT, México, for a scholarship, and Cátedra IN1-71 FESC-UNAM for financial support. The authors acknowledge financial support from COFAA-IPN and EDI-IPN, México.

References and Notes

(1) Dembitsky, V. M.; Srebnik, M. *Tetrahedon* **2003**, *59*, 579.
(2) Jabbour, A.; Steinberg, D.; Dembitsky, V. M.; Moussaieff, A.; Zaks, B.; Srebnik, M. *J. Med. Chem.* **2004**, *47*, 2409.
(3) Bailey, P. J.; Cousin, G.; Snow, G. A.; White, A. *Antimicrob. Agents Chemother.* **1980**, *17*, 549.
(4) Dobrydneva, Y.; Abelt, C. J.; Dovel, B.; Thadigiri, C. M.; Williams, R. L.; Blackmore, P. F. *Mol. Pharmacol.* **2006**, *69*, 247.
(5) Velasco, B.; Trujillo-Ferrara, J. G.; Fabila, L. H.; Miranda, R.; Sánchez-Torres, L. E. *Life Sci.* **2007**, *80*, 1007.
(6) Lang, K.; Nuetzel, K.; Schubert, F. German Patent 1130445, **1962**; *Chem. Abstr*. **1963**, *58*, 1488a.
(7) Skoog, I. H. *J. Org. Chem.* **1964**, *29*, 492.
(8) Shih-Hua, T.; Kuo-Min, C.; Shih-Lu, T.; Chia-Chun, L.; Shih-Lin, C. *Chem. Abstr.* **1967**, *66*, 37990m.
(9) Nefkens, G. H. L.; Zwanenburg, B. *Tetrahedron* **1983**, *39*, 2995.
(10) Flückinger, R.; Henson, E.; Hess, G. M.; Gallop, P. M. *Biomed. Mass Spectrom.* **1984**, *11*, 611.
(11) Strang, C. J.; Henson, E.; Okamoto, Y.; Paz, M. A.; Gallop, P. M. *Anal. Biochem.* **1989**, *178*, 276.
(12) Farfán, N.; Silva, D.; Santillan, R. *Heteroat. Chem.* **1993**, *4*, 533.
(13) Trujillo, J.; Höpfl, H.; Castillo, D.; Santillan, R.; Farfán, N. *J. Organomet. Chem.* **1998**, *571*, 21.
(14) Chremos, G. N.; Weidmann, H.; Zimmerman, H. K. *J. Org. Chem.* **1961**, *26*, 1683.
(15) Rettig, S. J.; Trotter, J. *Can. J. Chem.* **1977**, *55*, 958.
(16) **Typical procedure (Table 1, entry 1, 3a)**: Glycine (0.5g, 6.6 mmol) was dissolved in H_2O (3 mL) and the pH was adjusted to 8 with NaOH (5%, 2 mL). A solution of diphenylborinic acid was prepared from 2-aminoethyl-diphenylborinate (1.59 g, 6.6 mmol) as described in the literature.[14] The solutions were mixed together and heated at reflux for 4 h. The solvent was evaporated slowly and the product was filtered and washed with cold H_2O and *n*-hexane, yielding 1.49 g of **3a** (6.26 mmol, 94%).
(17) **Cytotoxicity in K-562 and HCT-15 cell lines, using the sulforhodamine B assay**: Skehan P., Storeng R., Scudiero D., Monks A., McMahon J., Vistica D., Warren J. T., Bokesh H., Kenney S., Boyd M.R.; *J. Natl. Cancer Inst.*; **1990**, *82*: 1107; 24 h after treatment, the treated and control cell cultures were fixed with ice-cold 10% CCl_3COOH for 30 min. The 96-well plates were washed in H_2O and then sulforhodamine (SRB, 100 μL, 0.4%) dissolved in AcOH (1%) was added to each well and left for 15 min. The SRB was removed, washed in AcOH (1%) and allowed to air-dry. Then aqueous Tris base [tris(hydroxymethyl)aminoethane] (100 μL, 10 mM) was added to each well to solubilize the cell-bound dye and the absorbance at 550 nm was measured. The results are expressed as a percentage of control cell growth.
(18) **2,2-Diphenyl-1,3,2-oxazaborolidin-5-one (3a)**: White solid; mp 241–243 °C (Lit. 242–245 °C); IR (KBr): 3428, 3243, 3074, 1720, 1604, 1434, 1302, 1217, 963, 702 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 7.35 (d, *J* = 7 Hz, 4 H), 7.22 (t, *J* = 7 Hz, 4 H), 7.16 (t, *J* = 7 Hz, 4 H), 7.07 (br t, 2 H, NH), 3.43 (t, *J* = 6 Hz, 2 H); ^{13}C NMR (DMSO-d_6): δ = 42.9, 126.1, 127.1, 131.0, 147.8, 172.5; ^{11}B NMR (DMSO-d_6): δ = +5.03; MS (EI): *m*/*z* = 239, 238, 162 (base peak), 161, 132, 104, 77.

Copyright of Synlett is the property of Georg Thieme Verlag Stuttgart and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.