Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 7, No. 19, pp. 2527-2530, 1997

0960-894X/97 $17.00 + 0.00

PII: S0960-894X(97)10010-5

EFFICIENT SYNTHESIS OF BIOLOGICALLY IMPORTANT CHIRAL 2-ALKYLAMINO BENZOXAZINONES

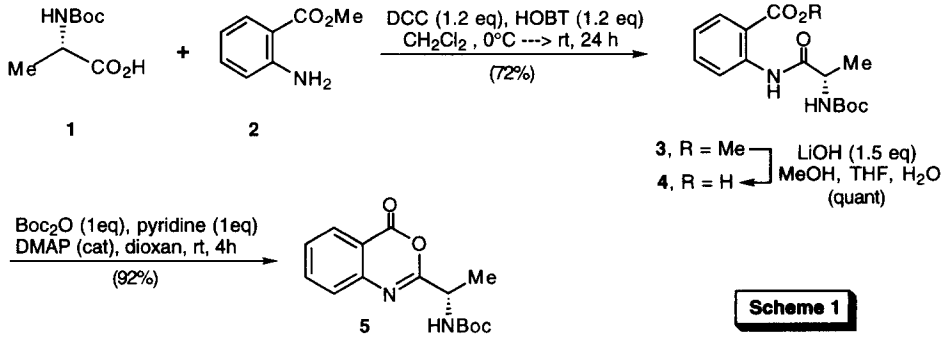
Debendra K. Mohapatra and Apurba Datta*

Organic III, Indian Institute of Chemical Technology, Hyderabad - 500 007, India

Abstract : A novel general method has been developed for the synthesis of various amino acid derived chiral 2-substituted benzoxazinones, known inhibitors of standard serine proteases of the chymotrypsin superfamily.

2-Substituted 4H-3,1-benzoxazin-4-ones have been shown to exhibit interesting pharmacological activity and are known mechanism-based inhibitors of standard serine proteases of the chymotrypsin family.[1] Interestingly, benzoxazinones containing amino acid derived functionalities at the 2-position are shown to be inhibitors of human leukocyte elastase (HLE) and the herpes simplex virus type 1 (HSV-1) protease.[2] In addition, the 2-substituted benzoxazinones have also been utilized as useful synthetic precursors for the preparation of other classes of heterocycles of biological importance.[3] Considering the above observations, development of a new general method for the construction of the benzoxazinone skeleton starting from easily available reactants and reagents, under mild reaction conditions remains a worthwhile proposition. Our recent observation that N-acyl amino acids and N-acyl anthranilic acids undergo facile intramolecular cyclodehydration in the presence of di-tert-butyl pyrocarbonate (Boc_2O), leading to the formation of oxazoles and acylanthranils respectively [4], prompted us to investigate this approach towards synthesizing the above mentioned amino acid derived benzoxazinones *via* a similar Boc_2O mediated cyclisation of N-(α-amino)acyl anthranilic acids. Results of the studies thus undertaken are reported in this communication.

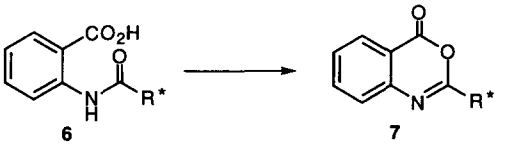
Condensation of L-N-Boc-alanine (**1**) with methyl anthranilate (**2**) under standard coupling conditions resulted in the corresponding amide **3** (Scheme 1) in 72% yield. Hydrolysis of the ester functionality then yielded the acid **4** in almost quantitative yield. Gratifyingly, the acid **4**, when treated with Boc_2O in presence of



Scheme 1

pyridine and a catalytic amount of 4-dimethylamino pyridine (DMAP) [5], smoothly afforded the expected 2-[(1*S*)-1-(tert-butoxycarbonylamino)ethyl]benzoxazinone (**5**) in high yield. The mechanism of formation of the product can be rationalized *via* Boc_2O assisted formation of mixed anhydride of the carboxylic acid followed by nucleophilic addition of the amide oxygen on the activated carboxylic acid carbon leading to the product.

Having attained the primary objective of constructing the target benzoxazinone moiety under mild and essentially non-racemizing reaction condition [6], we proceeded to extend this method for synthesizing other potentially useful 2-substituted benzoxazinones, derived from amino acids with varied substituents and different functional groups. Accordingly, the N-(α-amino)acyl anthranilic acids **6a** - **f**, prepared following a similar procedure as in scheme 1 (65 - 80% yield), were cyclized uneventfully under Boc_2O mediated cyclodehydration, affording the corresponding benzoxazinones **7a** - **f** (Table 1).[7] Besides the mild reaction condition, other note-



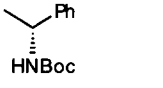
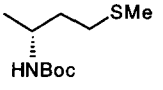
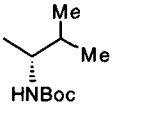
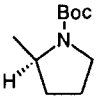
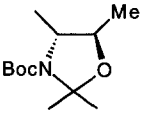
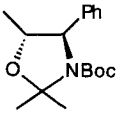
6,7	R*	% yield (7)
a		94
b		91
c		90
d		92
e		91
f		94

Table 1: Boc_2O assisted synthesis of chiral 2-[(α-amino)alkyl]bezoxazinones

worthy features of the above reaction are the relatively short reaction time (3 - 4 h) and consistently high yield of the products, allowing for easy assembling of the target benzoxazinone skeleton without effecting the other

functional groups present.

In conclusion, a novel general method has been developed for efficient synthesis of a biologically important class of 2-substituted benzoxazinones, employing Boc_2O in the crucial ring forming reaction, thereby avoiding the necessity of using carbodiimide based coupling reagents [2], which are generally more expensive and/or often causes difficulty in separation of product from the reagent derived by-products. It is hoped that the present method will prove to be an attractive alternative to the existing methodologies [2,8] for synthesizing the title compounds.

Acknowledgements : We thank Dr. M. K. Gurjar for his support and encouragement. DKM also thanks UGC, New Delhi for a research fellowship.

References and Notes

IICT Communication No. 3870

1. (a) Teshima, T.; Griffin, J.C.; Powers, J.C. *J. Biol. Chem.* **1982**, *257*, 5085. (b) Hedstrom, L.; Moorman, A.R.; Dobbs, J.; Abeles, R.H. *Biochemistry*, **1984**, *23*, 1753. (c) Spencer, R.W.; Copp, L.J.; Tam, T.F.; Liak, T.J.; Billedeau, R.J.; Krantz, A. *Biochem. Biophys. Res. Comm.* **1986**, *140*, 928. (d) Fenton, G.; Newton, C.G.; Wyman, B.M.; Bagge, P.; Dron, D.I.; Riddel, D.; Jomes, G.D. *J. Med. Chem.* **1989**, *32*, 265. (e) Krantz, A.; Spencer, R.W.; Tam, T.F.; Liak, T.J.; Copp, L.J.; Thomas, E.M.; Raffery, S.P. *J. Med. Chem.* **1990**, *33*, 464. (f) Uejima, Y.; Ishida, J.-I.; Kawabata, H.; Kokubo, M.; Kato, Y.; Fujii, K.; *Biochem. Pharmacol.* **1994**, *48*, 426.

2. (a) Stein, R.L.; Strimpler, A.M.; Visearello, B.R.; Wildonger, R.A.; Manger, R.C.; Trainor, D.A. *Biochemistry*, **1987**, *26*, 4126. (b) Jarvest, R.L.; Parratt, M.J.; Debouck, C.M.; Gorniak, J.G.; Jennings, L.J.; Serafinowska, H.T.; Strickler, J.E. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2463. (c) Jarvest, R.L.; Connor, S.C.; Gorniak, J.G.; Jennings, L.J.; Serafinowska, H.T.; West, A. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1733.

3. Smith, K.; El-Hiti, G.A.; Abdel-Megeed, M.F.; Abdo, M.A. *J. Org. Chem.* **1996**, *61*, 647.

4. Mohapatra, D.K.; Datta, A. *Synlett*, **1996**, 1129.

5. **Typical procedure :** To a solution of the acid **4** (5 mmol), pyridine (5 mmol) and catalytic amount of DMAP (25 mg) in dioxan (20 mL) at room temperature was added a solution of Boc_2O (5 mmol) in dioxan (5 mL) and the mixture stirred for 4 h. The reaction mixture was then concentrated and the residual oil purified by column chromatography (silica gel, petroleum ether/ethyl acetate) affording the product **5**.

6. Pozdnev, V.F. *Tetrahedron Lett.* **1995**, *36*, 7115, and references therein.

7. All the new compounds synthesized were fully characterized by their IR, ^1H NMR, ^{13}C NMR and Mass spectral data. Characteristic data for some of the compounds are given below :
5 : $[\alpha]_D$ = -47.5 (c 4.2, $CHCl_3$); IR (KBr) 1690 cm^{-1} : ^1H NMR (200 MHz, $CDCl_3$) δ 1.47 (s, 9 H),

1.6 (d, J = 6.7 Hz, 3 H), 4.68 (m, 1 H), 5.26 (br s, 1 H), 7.55 (m, 2 H), 7.88 (m, 1 H), 8.16 (d, J = 7.3 Hz, 1 H); MS (CI) 291 (MH+).

7d : $[\alpha]_D$ = -131.3 (c 1.3, $CHCl_3$); IR (neat) 1695 cm^{-1} : ^1H NMR (200 MHz, $CDCl_3$) δ 1.25 (s, 9 H), 1.85 - 2.5 (m, 4 H), 3.6 (m, 2 H), 4.64 (m, 1 H), 7.45 (m, 2 H), 7.76 (m, 1 H), 8.16 (m, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 161.5, 145.7, 136.5, 128.5, 126.9, 118.4, 79.8, 58.2, 31.9, 28.2, 19.3, 17.4; MS (CI) 317 (MH+).

7e : $[\alpha]_D$ = -93.5 (c 0.8, $CHCl_3$); IR (neat) 1763, 1694 cm^{-1} : ^1H NMR (200 MHz, $CDCl_3$) δ 1.17 (s, 6 H), 1.42 (s, 6 H), 1.65 and 1.66 (2s, 6 H), 4.15-4.35 (m, 2 H), 7.52 (m, 2 H), 7.78 (m, 1 H), 8.18 (m, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 160.2, 150.8, 146.2, 136.8, 136.3, 128.6, 128.5, 126.8, 116.8, 95.4, 80.3, 74.6, 66.9, 29.7, 28.3, 27.8, 26.6, 18.3; MS (FAB+) 359 (M^+ -1).

7f : $[\alpha]_D$ = -154.5 (c 1.2, $CHCl_3$); IR (neat) 1760, 1692 cm^{-1} : ^1H NMR (200 MHz, $CDCl_3$) δ 1.16 (s, 9 H), 1.7-1.85 (2s, 6H), 4.78 (d, J = 6.5 Hz, 1 H), 5.34 (br s, 1 H), 7.32 (m, 5 H), 7.66 (m, 2 H), 7.80 (m, 1 H), 8.23 (d, J = 6.2 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.6, 151.6, 145.5, 140.1, 136.6, 129.2, 128.6, 127.7, 127.6, 126.3, 117.3, 96.7, 81.7, 80.3, 63.8, 29.6, 28.0, 27.7, 26.5; MS (FAB+) 423 (MH+).

8. For general methods for the synthesis of 2-alkyl/aryl substituted benzoxazinone ring, see :
(a) Errede, L.A.; Oien, H.T.; Yarian, D.R. *J. Org. Chem.* **1977**, *42*, 12. (b) Cacchi, S.; Fabrizi, G.; Marinelli, F. *Synlett*, **1996**, 997.

(*Received in Japan* 7 *August* 1997; *accepted* 3 *September* 1997)