A Facile Synthesis of Methyl 2-Substituted-4-benzoxazolecarboxylates

Steven W. Goldstein* and Paul J. Dambek

Pfizer Central Research,
Groton, CT 06340

Received June 27, 1989

Methyl 2-substituted-4-benzoxazolecarboxylates were synthesized from methyl 2-amino-3-hydroxybenzoate and the corresponding acid chloride or ortho acetal with pyridinium *p*-toluenesulfonate as an acid catalyst. Decomposition due to hydration at the 2-position was seen for some compounds during purification.

J. Heterocyclic Chem., **27**, 335 (1990).

The 4-carboxybenzoxazole ring system is found in nature in a number of polycyclic antibiotics such as X-14885A [1], Calcimycin [2] and Cezomycin [3]. The majority of these compounds have electron donating substituents at the 5 position of the benzoxazole ring. We desired a facile route to the chemically simpler but potentionally less stable 5-unsubstituted-4-carboxybenzoxazole system, of which there are only a few examples [4] in the literature. In contrast the analogous **5**, **6** and **7** carboxy compounds [5,6] are well characterized species. We reasoned that the 2-position in the 5-unsubstituted ring system would be significantly more electrophilic than the corresponding analogs substituted at the 5- position with electron donating groups. Thus we anticipated instability of these compounds due to nucleophilic attack at this center a likely problem.

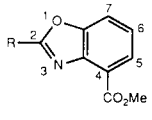
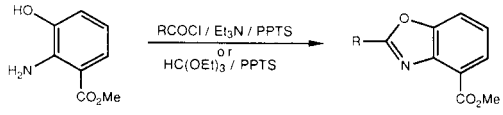


Figure 1.

The readily available 2-amino-3-hydroxybenzoic acid (**1**) [7] was easily converted to the corresponding methyl ester **2** [8] with methanol and gaseous hydrochloric acid. Treatment of **2** with 1.1 equivalents of benzoyl chloride and 1.1 equivalents of triethylamine in refluxing xylenes effected nitrogen acylation without concomitant dehydration to the benzoxazole. Prolonged heating caused only a small amount of material to be converted into a compound which was later identified as **3d**. This last step was more readily accomplished by the addition of 3 mole % of pyridinium *p*-toluenesulfonate and continued heating until the conversion was completed. Once the need for a soluble acid catalyst was recognized, the transformation from methyl 2-amino-3-hydroxybenzoate to the methyl 2-substituted-4-benzoxazolecarboxylates could be accomplished in a single step by the simultaneous addition of 2-25 mole % pyridinium *p*-toluenesulfonate with the acylating reagent and trialkylamine base. Following an aqueous workup, the yield of isolated and purified compound ranged from 54-86% (Scheme 1).

Scheme 1



2 **3a-h**

3	R
a	H
b	Me
c	t-Bu
d	Ph
e	p-(OMe)-C_6H_4
f	2-furoyl
g	p-(NO_2)-C_6H_4
h	3-pyridyl

Our anticipation regarding the instability of the compounds was soon confirmed. Attempted recrystallization of **3a** from ethyl acetate-hexanes afforded a compound whose spectroscopic data and elemental analysis were consistent with hydrolysis to the corresponding *N*-formylamide. The same decomposition pathway was seen to occur for **3g** when it was heated in a chloroform solution. In both cases hydrolysis was presumably effected by adventitious water. Clearly the electron withdrawing carbomethoxy group at C-4 increases the electrophilic nature of C-2. This does not seem to be a problem with the 5 substituted cases.

EXPERIMENTAL

The ^{1}H-nmr spectra were recorded on a Bruker WM-250 instrument with deuteriochloroform utilized as internal standard and deuterium lock. Chemical shifts are reported in ppm. Infrared spectra were recorded on a Perkin-Elmer 283 spectrophotometer. Low resolution and high resolution mass spectra were obtained respectively on Finnigan 4510 and AEI MS-30 instruments. Melting points are uncorrected and determined in open capillaries. Combustion analyses were performed by the Analytical Department of Pfizer, Inc. Solvents and reagents were used as obtained from commercial sources.

Methyl 2-Amino-3-hydroxybenzoate (**2**).

2-Amino-3-hydroxybenzoic acid (**1**) (22.7 g, 0.150 mole) was

suspended in dry methanol (800 ml) and gaseous hydrochloric acid was bubbled through until the solution was saturated. The reaction mixture was then heated to reflux for 12 hours, cooled to room temperature and then concentrated to a solid. This was then dissolved in water (200 ml), neutralized to *p*H 7 with sodium bicarbonate, saturated with sodium chloride and extracted with ethyl acetate (4 x 100 ml). The organic layer was dried (magnesium sulfate) and concentrated to afford a solid (21.5 g, 87%), mp 94-97° (lit 97-98° [8]).

Benzoxazoles **3**. General Procedure.

Method A for Benzoxazoles **3b-h**.

A solution of methyl 2-amino-3-hydroxybenzoate (**2**) (0.50 g, 3.0 mmoles), the acid chloride (3.3 mmoles), triethylamine (0.33 g, 3.3 mmoles) and pyridinium *p*-toluenesulfonate (0.20 g, 0.80 mmole) in xylene (50 ml) was heated to reflux for 16 hours. The reaction was cooled to ambient temperature, diluted with ethyl acetate (200 ml) and washed with water (100 ml). The organic layer was then dried (magnesium sulfate) and concentrated to afford the impure product **3** as an oil. This was then purified by radial chromatography on silica gel with a gradient elution ranging from hexanes to 30% ethyl acetate in hexanes to afford **3b-h**.

Methyl 2-Methyl-4-benzoxazolecarboxylate (**3b**).

This compound was obtained in 78% yield as colorless needles (hexanes), mp 77-79°; ir: 1726, 1606, 1572, 1428, 1287 cm^{-1}; pmr: δ 2.71 (s, 3H), 4.02 (s, 3H), 7.35 (t, 1H, J = 8.0 Hz), 7.66 (dd, 1H, J = 1.0, 8.1 Hz), 7.97 (dd, 1H, J = 1.0, 7.8 Hz); ms: (m/e) 191 (M+, 64), 160 (100), 132 (53).

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.35. Found: C, 62.78; H, 4.72; N, 7.31.

Methyl 2-*t*-Butyl-4-benzoxazolecarboxylate (**3c**).

This compound was obtained in 86% yield as a colorless solid without purification, mp 67-69°; ir: 1708, 1598, 1559, 1432, 1309 cm^{-1}; pmr: δ 1.50 (s, 9H), 3.99 (s, 3H), 7.32 (t, 1H, J = 8.1 Hz), 7.65 (dd, 1H, J = 1.6, 8.0 Hz), 7.94 (dd, 1H, J = 1.6, 8.0 Hz); ms: (m/e) 233 (M+, 90), 218 (61), 186 (100).

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.00. Found: C, 66.48; H, 6.68; N, 5.92.

Methyl 2-Phenyl-4-benzoxazolecarboxylate (**3d**).

This compound was obtained in 71% yield as a colorless solid after chromatography, mp 78-81°; ir: 1704, 1607, 1548, 1307, 1296 cm^{-1}; pmr: δ 4.04 (s, 3H), 7.38 (t, 1H, J = 7.8 Hz), 7.52 (m, 3H), 7.75 (dd, 1H, J = 1.8, 8.0 Hz), 8.00 (d, 1H, J = 8.0 Hz), 8.32 (dd, 2H, J = 1.8, 7.8 Hz); ms: (m/e) 253 (M+, 83), 222 (99), 195 (100).

Anal. Calcd. for $C_{15}H_{11}NO_3$: C, 71.13; H, 4.38; N, 5.53. Found: C, 71.07; H, 4.28; N, 5.55.

Methyl 2-(4-Methoxyphenyl)-4-benzoxazolecarboxylate (**3e**).

This compound was obtained in 79% yield as colorless solid after chromatography, mp 96-98°; ir: 1720, 1613, 1502, 1300, 1257 cm^{-1}; pmr: δ 3.90 (s, 3H), 4.05 (s, 3H), 7.03 (d, 2H, J = 9.0 Hz), 7.37 (t, 1H, J = 8.0 Hz), 7.74 (dd, 1H, J = 1.1, 8.1 Hz), 8.00 (dd, 1H, J = 1.1, 7.9 Hz), 8.28 (d, 2H, J = 9.0 Hz); ms: (m/e) 283 (M+, 69), 252 (56), 225 (100).

Anal. Calcd. for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.95. Found: C, 67.56; H, 4.54; N, 4.80.

Methyl 2-(2-Furyl)-4-benzoxazolecarboxylate (**3f**).

This compound was obtained in 64% yield as colorless solid after chromatography, mp 137-139°; ir: 1713, 1634, 1613, 1534, 1301 cm^{-1}; pmr: δ 4.05 (s, 3H), 6.63 (dd, 1H, J = 1.7, 3.5 Hz), 7.40 (d, 1H, J = 3.5 Hz), 7.41 (t, 1H, J = 8.0 Hz), 7.70 (app s, 1H), 7.76 (d, 1H, J = 8.1 Hz), 8.03 (d, 1H, J = 7.8 Hz); ms: (m/e) 243 (M+, 92), 212 (100), 185 (84).

Anal. Calcd. for $C_{13}H_9NO_4$: C, 64.20; H, 3.73; N, 5.76. Found: C, 63.98; H, 3.55; N, 5.56.

Methyl 2-(4-Nitrophenyl)-4-benzoxazolecarboxylate (**3g**).

This compound was obtained in 98% yield as yellow solid without purification, mp 186-189°; ir: 1729, 1556, 1521, 1340, 1273 cm^{-1}; pmr: δ 4.05 (s, 3H), 7.51 (t, 1H, J = 7.7 Hz), 7.82 (dd, 1H, J = 1.6, 8.2 Hz), 8.07 (dd, 1H, J = 1.6, 8.0 Hz), 8.37 (d, 1H, J = 9.2 Hz), 8.51 (d, 1H, J = 9.2 Hz); ms: (m/e) 298 (M+, 81), 267 (100), 240 (93).

HRMS Calcd. for $C_{15}H_{10}N_2O_5$: 298.0590. Found: 298.0580.

Methyl 2-(3-Pyridyl)-4-benzoxazolecarboxylate (**3h**).

This compound was obtained in 54% yield as colorless solid after chromatography, mp 124-126°; ir: 1724, 1610, 1546, 1433, 1269 cm^{-1}; pmr: δ 4.06 (s, 3H), 7.46 (t, 1H, J = 7.9 Hz), 7.49 (d, 1H, J = 8.1 Hz), 7.82 (dd, 1H, J = 1.0, 8.2 Hz), 8.06 (dd, 1H, J = 1.0, 7.8 Hz), 8.62 (dt, 1H, J = 2.0, 8.0 Hz), 8.79 (dd, 1H, J = 1.6, 4.8 Hz), 9.54 (s, 1H); ms: (m/e) 254 (M+, 78) 223 (100), 196 (62).

Anal. Calcd. for $C_{14}H_{10}N_2O_3$: C, 66.14; H, 3.96; N, 11.02. Found: C, 65.96; H, 4.12; N, 10.89.

Methyl 4-Benzoxazolecarboxylate (**3a**).

A solution of methyl 2-amino-3-hydroxybenzoate (**2**) (1.50 g, 3.0 mmoles), triethyl orthoformate (1.46 g, 9.87 mmoles) and pyridinium *p*-toluenesulfonate (0.10 g, 0.40 mmole) in xylene (100 ml) was heated to reflux for 16 hours. The reaction was cooled to ambient temperature, diluted with ethyl acetate (200 ml) and washed with water (100 ml). The organic layer was then dried (magnesium sulfate) and concentrated to afford the impure product as an oil. This was then purified by radial chromatography on silica gel with 25% ethyl acetate in hexanes to afford **3a** in 67% yield as a colorless solid, mp 107-109°; ir: 3088, 1719, 1511, 1274 cm^{-1}; pmr: δ 4.02 (s, 3H), 7.44 (t, 1H, J = 8.2 Hz) 7.76 (d, 1H, J = 8.3 Hz), 8.04 (d, 1H, J = 8.1 Hz), 8.22 (s, 1H); ms: (m/e) 177 (M+, 70), 146 (100), 118 (59).

Anal. Calcd. for $C_9H_7NO_3$: C, 61.01; H, 3.98; N, 7.91. Found: C, 60.93; H, 3.95; N, 7.91.

REFERENCES AND NOTES

[1] J. W. Westly, J. W. Liu, J. F. Blount, L. H. Sello, N. Troupe and P. A. Miller, *J. Antibiotic.*, **36**, 1275 (1983).

[2] M. O. Chaney, P. V. Demarco, N. D. Jones and J. L. Occolowitz, *J. Am. Chem. Soc.*, **96**, 1932 (1974).

[3] L. David and A. Dergomard, *J. Antibiotic.*, **35**, 1409 (1982).

[4] Methyl 2-(2-dimethylaminophenyl)-4-benoxazolecarboxylate is known: D. Uemura and Y. Hirata, *Bull. Chem. Soc. Japan*, **50**, 2005 (1977).

[5] H. Frischkorn, U. Pintschovius and E. Schinzel, *Ann. Chem.*, 931 (1983).

[6] W. Aumueller, R. Weyer, V. Hitzel and M. Huebner, German Offen. 2,225,544; *Chem. Abstr.*, **80**, 70799t (1974).

[7] J. L. Warnell, *Biochem. Prep.*, **6**, 20 (1958).

[8] J. Gripenberg, *Acta Chem. Scand.*, **13**, 1305 (1959).