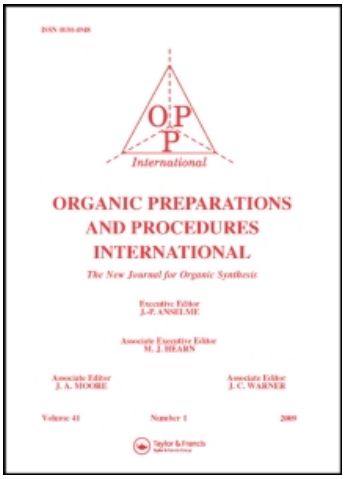

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A SIMPLE AND CONVENIENT SYNTHESIS OF 5-SUBSTITUTED BENZOXAZOLES

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A SIMPLE AND CONVENIENT SYNTHESIS OF 5-SUBSTITUTED BENZOXAZOLES

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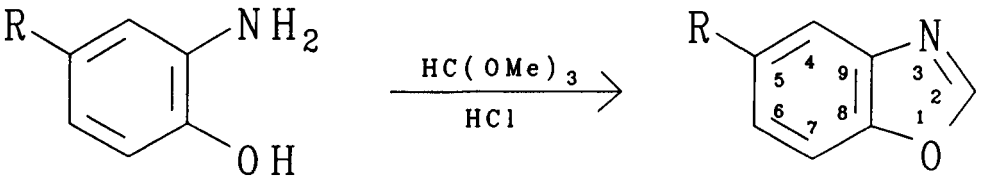
We desired a general method of preparing a series of 5-substituted benzoxazoles, unsubstituted at the 2-position, for the determination of substituent effects by factor analysis and multiple linear regression on the ^{13}C NMR chemical shifts. Of the numerous methods that have been reported for the synthesis of 2-substituted benzoxazoles,[1] many are not



applicable to the synthesis of a benzoxazole unsubstituted in the 2-position. The oldest method, used in the synthesis of the parent compound,[2] the 5- and 6-carbomethoxybenzoxazoles,[3] 5-carboxybenzoxazole,[4] 5-chlorobenzoxazole,[5] and the 5-[5,6] and 6-nitrobenzoxazoles,[5] involves heating or

distilling 2-formamidophenols (with or without isolation) at elevated temperatures. Benzoxazole has also been synthesized by the dry distillation of formamide and 2-aminophenol.[7] The 5- and 7-methylbenzoxazoles were synthesized[8] by distilling the appropriate aminocresol hydrochlorides with sodium formate. More recent procedures involve cyclization of a 2-aminophenol with s-triazine,[9] triethyl orthoformate[10,11] or isonitriles,[12,13] and 2-hydroxybenzonitrile photochemically;[14] only reference 11 describes the synthesis of benzoxazoles (6-nitro-, 5-methyl-, 5-chloro-6-methyl-, 5-chloro-7-methyl- and 5-methyl-7-chloro-) other than the parent compound. Our attempts to use the reaction of triethyl orthoformate and 2-aminophenols, with or without sulfuric acid,[10,11] as a general procedure for the preparation of 5-substituted benzoxazoles either resulted in charring and poor yields or failed, respectively. This report describes the conversion of 4-substituted 2-aminophenols to 5-substituted benzoxazoles by treatment with trimethyl orthoformate and concentrated aqueous HCl (Table 1).

The structures of the benzoxazoles were confirmed by ^{13}C NMR spectroscopy. Chemical shift assignments were made on the basis of benzene substituent-induced chemical shift values[15] and proton-coupled spectra. No peaks due to impurities were observed. Fig. 1 illustrates the ^{13}NMR coupled and decoupled spectra of 5-iodobenzoxazole. Indication of cyclization is given by the C-2 resonance. Both its chemical shift and splitting, in the coupled spectrum, are characteristic of these compounds. The C-2 resonances occur at 154-158 ppm which is downfield from the chemical shifts found for the benzene carbons of the benzoxazoles (Table 2) and 4-substituted 2-aminophenols studied. The ^{1}J(C-2,H-2) values of 233-237 Hz are much larger than ^{1}J(C,H) values of benzene rings, which are 160-170 Hz whether in benzoxazoles or substituted benzene compounds.

TABLE 1. 5-Substituted Benzoxazoles

C-5-Substituent	mp. (°C)	Yield (%)	Elemental Analysis C	H	Calcd(Found) N
Acetamido	178-180	88	61.36(61.60)	4.58(4.68)	15.90(16.02)
Benzoyl	129-130	61	75.33(75.17)	4.06(3.93)	6.27(6.26)
Bromo	33-34	77	42.46(42.14)	2.04(2.12) Br: 40.35(40.11)	7.07(7.11)
Chloro	36-37	83	lit.[5] mp. 36-37°		
Cyano	87-88	25	66.67(66.68)	2.80(2.84)	19.44(19.60)
Iodo	55-56	77	34.31(34.09)	1.65(1.69) I: 51.79(51.64)	5.72(5.73)
Methoxy	46-47	65	64.42(64.19)	4.73(4.88)	9.39(9.30)
Methyl	43-44	95	lit.[8] mp. 45°		
Nitro	124-125	75	lit.[6] mp. 127°		
Propionyl	93-94	84	68.56(68.69)	5.18(5.34)	8.00(8.06)

TABLE 2. ^{13}C NMR Data for the 5-Substituted Benzoxazoles

Substituent	Chemical Shift in ppm from Internal TMS						
	C-2	C-4	C-5	C-6	C-7	C-8	C-9
$NHCOCH_3$	154.8	110.3	136.5	117.8	110.9	145.5	139.9
COC_6H_5	155.8	122.1	134.1	127.7	111.5	152.0	139.7
Br	155.5	122.8	116.6	128.4	112.9	148.5	141.5
Cl	155.7	119.9	129.0	125.7	112.5	148.2	141.0
CN	156.3	125.1	107.6	129.9	112.9	151.3	140.0
I	154.9	128.6	88.3	134.0	113.3	149.1	141.8
OCH_3	154.9	103.2	157.1	114.1	111.3	144.0	140.7
CH_3	154.2	119.9	134.0	126.6	110.4	147.7	140.0
NO_2	157.3	116.2	144.9	121.5	112.0	153.0	140.0
COC_2H_5	155.5	120.4	133.8	125.7	111.2	152.1	139.9

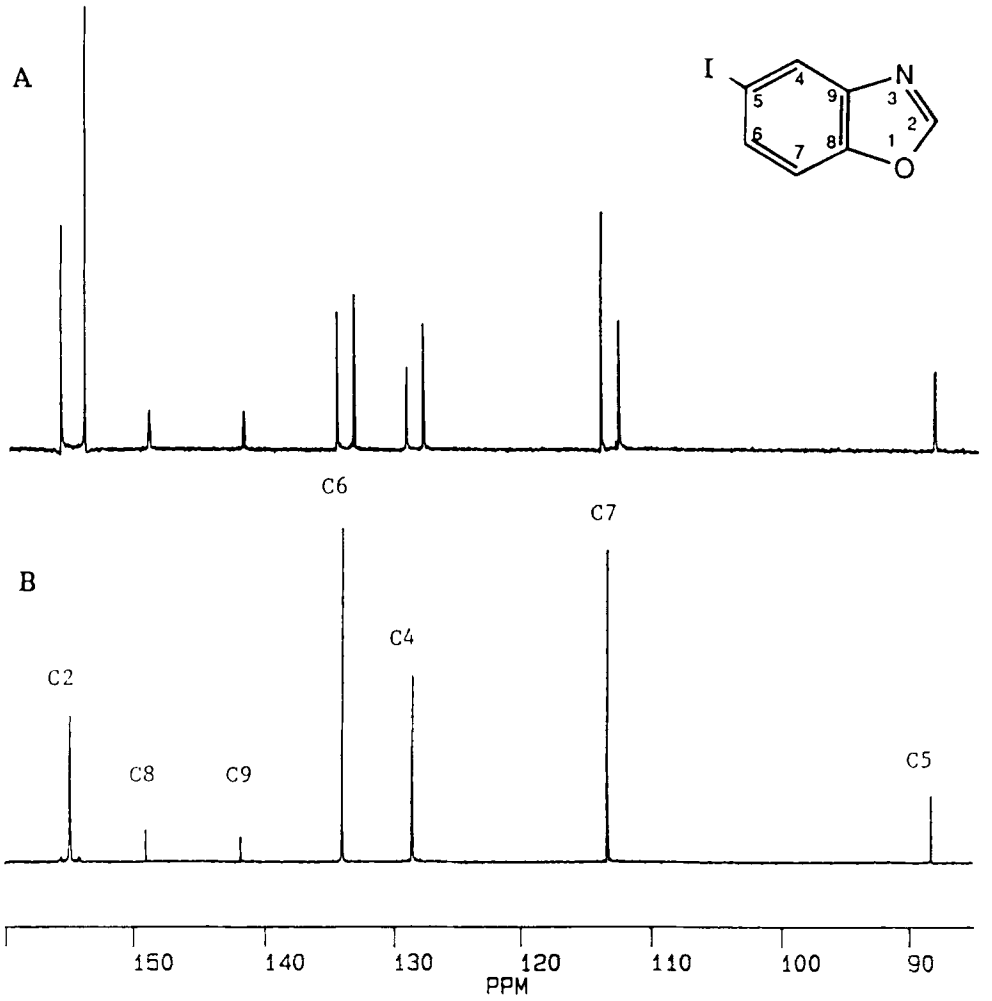


FIG. 1

Coupled (**A**) and Decoupled (**B**) ^{13}C NMR Spectra of 5-Iodobenzoxazole in DMSO

EXPERIMENTAL SECTION

Trimethyl orthoformate and some of the 4-substituted 2-aminophenols, namely the chloro, methyl, and nitro derivatives, were obtained commercially and used without further purification. The following 2-aminophenols were synthesized: 4-acetamido-,[16] 4-benzoyl-,[17] 4-bromo-,[18] 4-cyano-,[19] 4-iodo-,[18] 4-methoxy-,[18] and 4-propionyl-2-aminophenol.[20] The ^{13}C NMR spectra were run on 1.0 M solutions (except for the benzoyl and propionyl analogs, where nearly saturated solutions of 0.47 and 0.65 M, respectively, were used) in dimethylsulfoxide (DMSO) at 30° using a Varian CFT-20 spectrometer. A coaxial tube containing D_2O provided an external lock. Chemical shifts were referenced to TMS by setting the DMSO resonance at 40.5 ppm.

General Procedure.- In a typical benzoxazole synthesis, concentrated HCl (42 μL) was added to a stirred solution of the 4-substituted 2-aminophenol (17 mmol) and trimethyl orthoformate (25 mmol) in methanol (5 mL) at room temperature. The mixture was slowly heated to 90-95° in a simple distillation apparatus and maintained there until methanol stopped distilling. The residue was extracted with ether (2 x 50 mL) and the extracts filtered and washed with 5% NaOH followed by water. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to yield the corresponding 5-substituted benzoxazole. The new compounds were sublimed in vacuum (15 mm Hg) for elemental analyses and melting points.

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