Notes

Regioselective Electrophilic Substitutions of 4*H*-Imidazo[2,1-*c*][1,4]benzoxa(thia)zines†

K. Vara Prasad Rao‡ and V. Sundaramurthy*

Department of Chemistry, Osmania University, Hyderabad 500 007, India

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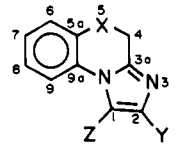
Introduction

4*H*-Imidazo[2,1-*c*][1,4]benzoxazines are known to exhibit antiallergic and broncho-dilating properties[1] and cause a 50% inhibition of passive cutaneous anaphylaxis in rats.[2,3] Rowlands et al. have reported the synthesis of 1,2-diesters and 1,2-acid esters of this heterocycle and have tested them for antiallergic activity.[4] Later, Shridhar et al. synthesized methyl 2-carbamate derivatives of imidazobenzoxa(thia)-zines, and screened them for antihelmintic activity.[5] From the literature survey, it is evident that electrophilic substitutions of this 6,6,5-tricyclic system have not been carried out, except for a solitary reference.[4] The nitration of methyl 4*H*-imidazo[2,1-*c*][1,4]benzoxazine-2-carboxylate with HNO_3/H_2SO_4 gave exclusively the 8-nitro derivative. This reaction indicated that electrophilic attack took place on benzene ring rather than on the imidazole moiety.

Recently, we have reported a facile two-step synthesis of 2-methyl- and 2-aryl-4*H*-imidazo[2,1-*c*][1,4]benzoxazines **1**[6] and their thio analogues **2**;[7] these compounds are suitable candidates for the present study of electrophilic substitutions. We have reported the ^{13}C chemical shift data for oxygen analogues **1** and predicted that electrophilic attack might take place at position 1 (imidazole ring) because C-1 resonates upfield (~109 ppm) when compared to other aromatic carbons, perhaps owing to more electron density.[6] Therefore, the objective of the present study was 2-fold: (i) to identify the preferential attack of the electrophile and (ii) to examine the relationship between electrophilic substitutions and ^{13}C chemical shifts.



1 – 8

X = O, S
Z = H, Br, I, NO_2
Y = CH_3, C_6H_5, 4'-$CH_3C_6H_4$, 4'-ClC_6H_4, 4'-BrC_6H_4

Results and Discussion

In the present investigation, we have undertaken bromination, iodination, and nitration of 2-substituted 4*H*-imidazo[2,1-*c*][1,4]benzoxa(thia)zines **1** and **2**. The reactions proceeded smoothly at position 1 and the characterization data of the products **3–8** are presented in Table I.

Bromination. Compound **1** or **2** when reacted with an equimolar quantity of Br_2 in AcOH at room temperature gave **3** or **4**, respectively (method A). These bromo derivatives were also obtained when treated with *N*-bromosuccinimide (NBS) in AcOH at room temperature (method B). Chlorination with *N*-chlorosuccinimide (NCS) of these substrates, **1** and **2**, failed to proceed under similar experimental conditions. The lower reactivity of NCS when compared to NBS may be due to the higher bond strength of N–Cl.

Iodination. Iodination of **1** or **2** was carried out using iodine monochloride (ICl) (method A) or *N*-iodosuccinimide (NIS) (method B). An equimolar quantity of ICl or NIS was added to **1** or **2** in AcOH at room temperature to give **5** or **6**, respectively.

Nitration. For nitration, $Al(NO_3)_3 \cdot 9H_2O$–Ac_2O, a selective nitrating agent, was employed; this was used earlier in our laboratories.[9,10] Nitration of **1** or **2** (Y = Ar) resulted in a yellowish brown solid that was chromatographically purified and yielded **7** or **8**, respectively, as yellow crystalline compounds. Surprisingly, nitration did not take place on **1a** or **2a** (Y = CH_3) under similar experimental conditions.

Significant Spectral Characteristics. The ^1H NMR data and ^{13}C NMR data (Table II) provide substantial evidence for the regioselective entry of electrophiles at position 1. In the ^1H NMR spectra of **1a** and **2a**, methyl protons appear as fine doublets at δ 2.30 and 2.28 ppm, respectively (J = 0.9 Hz), whereas in the corresponding bromo compounds **3a** and **4a**, methyl protons are observed as sharp singlets at δ 2.25 and 2.24 ppm. Moreover, the spectra of **3–8** (Y = Ar) do not display a characteristic singlet around 7.6 ppm due to H-1. Furthermore, the ^1H NMR spectra of **3–6** reveal that H-9 is shifted downfield when compared to H-9 of **1** and **2**. The magnitude of the downfield shift depends on the nature of the substituent at position 1. For example, in **3a** (Z = Br), the shift is 0.98 ppm and in **5a** (Z = I) the shift is 1.14 ppm. The low-field shift of H-9 has resulted from the shielding effect of Br or I at position 1. A similar situation was also noticed in structurally related systems such as 1-bromo- and 1-iodo-4-oxo-4*H*-pyrazolo[2,1-*c*][1,4]benzoxazines.[11] In the

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‡ Present address: Department of Chemistry, New Science College, Ameerpet, Hyderabad 500 016, India.

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Table I. Characterization Data for 1-Bromo-, 1-Iodo-, and 1-Nitro-2-substituted-4*H*-imidazo[2,1-*c*][1,4]benzoxa(thia)zines 3–8

compd	Y	X	Z	yield,[a] %	mp, °C	molecular formula	MS[b,c] m/e (rel int, %) M⁺, [M − Z]⁺	elem anal., % calcd/found C	H	N
3a	CH_3	O	Br	85	104–6	$C_{11}H_9BrN_2O$	264 (49.5)	50.00	3.43	10.61
				(90)			185 (100)	49.94	3.44	10.59
3b	C_6H_5	O	Br	87	130–2	$C_{16}H_{11}BrN_2O$	326 (37.3)	58.89	3.40	8.59
				(90)			243 (100)	58.69	3.49	8.50
3c	4′-$CH_3C_6H_4$	O	Br	84	124–6	$C_{17}H_{13}BrN_2O$	340 (38.0)	59.99	3.85	8.24
				(85)			261 (100)	59.90	3.98	8.13
3d	4′-ClC_6H_4	O	Br	90	158–60	$C_{16}H_{10}ClBrN_2O$	360 (21.4)	53.34	2.80	7.78
				(90)			281 (100)	53.52	2.63	7.86
4a	CH_3	S	Br	80	122–4	$C_{11}H_9BrN_2S$	280 (20.6)	47.15	3.24	10.00
				(85)			201 (100)	47.00	3.40	9.94
4b	C_6H_5	S	Br	82	127–9	$C_{16}H_{11}BrN_2S$	342 (19.8)	56.14	3.24	8.19
				(84)			263 (100)	56.25	3.37	8.23
4d	4′-ClC_6H_4	S	Br	85	157–9	$C_{16}H_{10}ClBrN_2S$	376 (17.2)	51.07	2.68	7.45
				(88)			297 (100)	51.10	2.66	7.46
4e	4′-BrC_6H_4	S	Br	80	172–4	$C_{16}H_{10}Br_2N_2S$	420 (20.0)	45.72	2.40	6.67
				(85)			341 (98.2)	45.63	2.51	6.60
5a	CH_3	O	I	86	160–2	$C_{11}H_9IN_2O$	312 (32.2)	42.31	2.90	8.97
				(80)			185 (100)	42.50	2.88	9.05
5b	C_6H_5	O	I	82	185–7	$C_{16}H_{11}IN_2O$	374 (50.8)	51.34	2.96	7.49
				(80)			247 (100)	51.28	3.00	7.19
5c	4′-$CH_3C_6H_4$	O	I	85	147–9	$C_{17}H_{13}IN_2O$	388 (48.3)	52.58	3.37	7.22
				(80)			261 (100)	52.50	3.47	7.12
5d	4′-ClC_6H_4	O	I	80	159–61	$C_{16}H_{10}ClIN_2O$	408 (25.6)	46.95	2.46	6.85
				(78)			281 (100)	47.16	2.50	6.90
6a	CH_3	S	I	78	180–2	$C_{11}H_9IN_2S$	328 (41.6)	40.25	2.76	8.54
				(75)			201 (100)	40.35	2.71	8.48
6b	C_6H_5	S	I	80	163–4	$C_{16}H_{11}IN_2S$	390 (62.7)	49.23	2.84	7.18
				(78)			263 (100)	49.01	2.89	7.02
7b[d]	C_6H_5	O	NO_2	70	154–6	$C_{16}H_{11}N_3O_3$	293 (85.8)	65.51	3.78	14.33
							247 (100)	64.93	3.66	14.41
7c[d]	4′-$CH_3C_6H_4$	O	NO_2	75	150–2	$C_{17}H_{13}N_3O_3$	307 (85.6)	66.43	4.26	13.68
							261 (100)	66.97	4.08	13.65
7d[d]	4′-ClC_6H_4	O	NO_2	72	182–4	$C_{16}H_{10}ClN_3O_3$	327 (70.9)	58.71	3.08	12.84
							281 (100)	58.23	3.00	12.78
8d[d]	4′-ClC_6H_4	S	NO_2	78	190–2	$C_{16}H_{10}ClN_3O_2S$	343 (69.8)	55.98	2.94	12.25
							297 (100)	56.29	2.99	12.19

[a] Yields in parentheses are according to method B. [b] HRMS: **2a**, calcd 265.9877, found 265.9878; **4d**, calcd 327.0411, found 327.0410. [c] Bromine and/or chlorine containing compounds show characteristic M + 2 peaks. [d] IR 1515–1523 and 1318–1325 (NO_2) cm^{-1}.

Table II. ^{13}C NMR Chemical Shifts (δ, ppm) for Selected Carbons[a] and Change in Chemical Shifts (Δδ)[b,c]

compd	carbons C-1	carbons C-2	Δδ
3a	95.25	137.97	+13.99
3b	94.94	141.89	+13.33
3c	94.86	142.40	+12.95
3d	95.09	145.98	+13.47
4a	97.26	137.89	+14.53
4b	96.52	140.09	+14.28
4d	96.80	139.00	+14.20
4e	96.79	138.98	+14.49
5a	61.28	145.13	+47.96
5b	60.00	145.21	+48.27
5c	60.05	145.35	+47.76
5d	59.68	146.10	+48.88
6a	62.35	142.09	+49.44
6b	60.50	145.19	+50.30
7b	226.58	146.96	−118.31
7c	227.86	147.60	−120.05
7d	227.32	147.05	−118.76
8d	228.06	139.10	−117.06

[a] For ^{13}C NMR of **1** see ref 8 and for **2** see supplementary material. [b] Δδ is defined as [$^{\delta}$C-1 (Z = H)] − [$^{\delta}$C-1 (Z = Br or I or NO_2)]. [c] + for upfield shift and − for downfield shift with reference to Z = H of **1** or **2**.

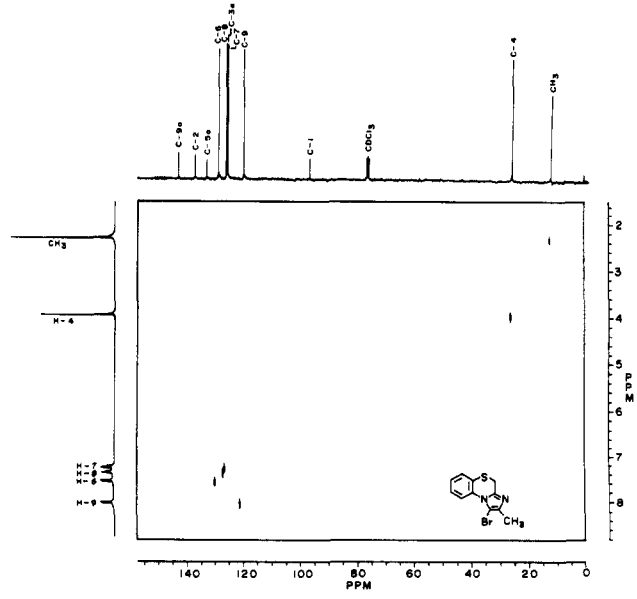
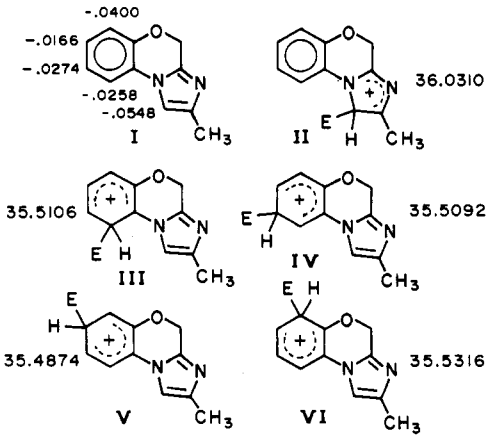


Figure 1. ^{13}C–^{1}H 2D shift correlation NMR spectrum of **4a**.

case of nitro compounds **7** and **8**, this shift is less pronounced.

The circumstantial evidence for preferential electrophilic attack at position 1 stems from ^{13}C NMR data. ^{1}H and ^{13}C chemical shift assignments are corroborated by a 2D NMR correlation experiment (e.g., **4a**, Figure 1). A doublet near 109 ppm in **1** and **2** is due to C-1. But in **3**–**8**, as a result of substituent-induced chemical shifts (SCS), C-1 appears as a low-field less intense singlet with a remarkable change in the chemical shift (Δδ) (Table II). An upfield shift of about 14 ppm in **3** and **4** is similar to the

shift observed in bromoimidazoles[12] and 1-bromoimidazo[1,2-*a*]quinoxalines.[13] These SCS indicate the predominance of the mesomeric effect over the inductive effect. The $^1J_{CH}$ coupling constants for benzene carbons of the benzoxa(thia)zines moiety and aryl group are similar to benzenoid coupling constants (~160 Hz), while $^1J_{CH}$ for CH-1 (~190 Hz) is similar to the α-carbon of pyrrole[14] and CH-1 of imidazo[1,2-*a*]quinoxaline.[13] These results demonstrate that electrophilic attack takes place regioselectively at position 1 as anticipated from the ^{13}C chemical shifts of **1** and **2**. This is further supported by the electron charge calculations (HMO) for **1a** on methine carbon atoms (I) and also resonance energies (given in units of β)



of the appropriate Wheland intermediates (II–VI).[15] Such preferential electrophilic substitutions were reported in related ring systems such as pyrrolo[2,1-*c*][1,4]benzoxazines[16] and pyrrolo[1,2-*a*]quinoxalines.[17,18]

The mass spectral fragmentation of **1a–d** mostly involves the loss of $^{\bullet}H$, $^{\bullet}CH_2CN$, and RCN.[19] In **3–8**, the principal fragmentation is due to loss of the substituent (Z) at position 1 resulting in $[M - Z]^+$ as the base peak (Table I). In addition to the accurate mass measurements (footnotes *c*, Table I), the evidence for $[M - Z]^+$ is also obtained from metastable transitions (m*) (e.g., **3a**, calcd 129.64; found 129.80).

Experimental Section

Melting points are uncorrected. The IR (KBr) spectra were recorded on a Perkin-Elmer infrared 337 spectrophotometer. The ^1H NMR spectra were measured on a Bruker WP 270 SY spectrometer or a Bruker AM 500-MHz FT-NMR spectrometer. The ^{13}C NMR spectra were scanned on JEOL JNM FX-100, Varian XL-300, or Bruker WP 270 SY spectrometers operating at 25.00, 75.30, and 67.93 MHz, respectively. Both ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS as an internal standard. ^1H chemical shifts were assigned on the basis of multiplicities, selective homonuclear decoupling technique, and also by comparison with the chemical shifts of closely related systems. Assignments for carbon resonances were made by chemical shift arguments, signal intensities, signal multiplicities as observed in SFORD, attached proton test (APT), and comparison with the chemical shifts of related systems. The mass spectra (LRMS and HRMS) were taken on a VG micromass 7070-H instrument at 70 eV. Compounds prepared by different procedures were confirmed by mixed melting points and by identity of IR spectra. NBS was recrystallized from water.

1-Bromo-2-substituted-4*H*-imidazo[2,1-*c*][1,4]benzoxa(thia)zines 3 and 4. General Procedure. Method A. Compound **1** or **2** (0.01 mol) was dissolved in glacial AcOH (20 mL). During a 5-min interval, bromine solution (0.6 mL, 0.011 mol in 5 mL AcOH) was added dropwise at room temperature while the reaction mixture was stirred; a colorless solid separated out. The stirring was continued for an additional 20 min to complete the reaction. The mixture was poured onto crushed ice and neutralized with ammonia solution. The product was collected by filtration, dried, and purified over column chromatography using neutral alumina as adsorbent and benzene as eluant to give **3** or **4**, respectively.

Method B. Compound **1** or **2** (0.01 mol) was dissolved in glacial AcOH (20 mL), and NBS (2g, 0.011 mol) was added in one portion while the reaction mixture was stirred. After 5 min, a colorless compound separated out, and stirring was continued for an additional 20 min. The reaction mixture was worked up as described in method A to yield a pure sample of **3** or **4**, respectively.

1-Iodo-2-substituted-4*H*-imidazo[2,1-*c*][1,4]benzoxa(thia)zines 5 and 6. General Procedure. Method A. Compound **1** or **2** (0.01 mol) was dissolved in glacial AcOH (20 mL), and ICl solution (0.55 mL, 0.011 mol in 5 mL of AcOH) was added dropwise while the reaction mixture was stirred at room temperature. After 5 min, a colorless solid precipitated and stirring was continued for an additional 20 min. The reaction mixture was poured onto crushed ice and neutralized with ammonia solution. The product was collected by filtration, dried, and subjected to column chromatographic purification using neutral alumina as adsorbent and benzene as eluant to yield a pure sample of **5** or **6**, respectively.

Method B. Compound **1** or **2** (0.01 mol) was dissolved in glacial AcOH (20 mL), and NIS (2.46 g, 0.011 mol) was added, in one portion, while the reaction mixture was stirred at room temperature. A colorless compound precipitated, and stirring was continued for an additional 20 min to complete the reaction. The subsequent workup was the same as described in method A to furnish **5** or **6**, respectively.

1-Nitro-2-aryl-4*H*-imidazo[2,1-*c*][1,4]benzoxa(thia)zines 7 and 8. General Procedure. Compound **1b–d** or **2d** (0.01 mol) was dissolved in glacial Ac_2O (20 mL), and $Al(NO_3)_3{\cdot}9H_2O$ (3.61 g, 0.03 mol) was added in small portions for 1 h. The reaction mixture was kept at room temperature for 12 h with occasional shaking, during which time the solution became yellow. The mixture was poured onto crushed ice, neutralized with 10% $NaHCO_3$ solution, and allowed to stand for 1 h. The resulting yellowish brown solid was collected by filtration and dried. Chromatographic purification over silica gel (200 mesh) using $CHCl_3$ as eluant gave **7** or **8**, respectively, as yellow crystalline compounds.

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Registry No. **1a**, 104971-83-7; **1b**, 104990-48-9; **1c**, 104971-78-0; **1d**, 105507-03-7; **2a**, 120622-17-5; **2b**, 120622-18-6; **2d**, 120622-20-0; **2e**, 120622-21-1; **3a**, 108144-24-7; **3b**, 137668-04-3; **3c**, 137668-05-4; **3d**, 137668-06-5; **4a**, 137668-07-6; **4b**, 137668-08-7; **4d**, 137668-09-8; **4e**, 137668-10-1; **5a**, 137668-11-2; **5b**, 137668-12-3; **5c**, 137668-13-4; **5d**, 137668-14-5; **6a**, 137668-15-6; **6b**, 137668-16-7; **7b**, 137668-17-8; **7c**, 137668-18-9; **7d**, 137668-19-0; **8d**, 137668-20-3.

Supplementary Material Available: Complete ^1H NMR data for **1–8**, ^{13}C NMR data for **2–8**, and $^1J_{CH}$ coupling constants for **1a**, **1b**, **1d**, **2a**, **3a**, and **7c** (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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