Synthesis of Fused Ring Heterocycles from Aromatic Amines with Hydroximoyl Chlorides [1]

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Dedicated to Professor Norman H. Cromwell

Substituted 2-arylbenzimidazoles, 2-arylbenzoxazoles and 2-arylbenzothiazoles were obtained in good yield by the reaction of hydroximoyl chlorides with *ortho*-substituted aromatic amines. The benzo moiety of the benzimidazoles was shown by nmr to be symmetrical, indicating that the N-H group proton of the imidazole ring is exchanging with the water protons in the DMSO-d_6 solvent.

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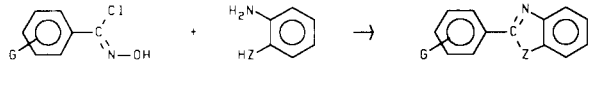
Hydroximoyl chlorides **1** have been extensively studied since they were discovered by Nef [4] in 1894. They are versatile intermediates for the synthesis of nitrile oxides which undergo various dipolar 1,3-cycloaddition and 1,3-addition reactions leading to cyclic and open chain products, respectively [5-10]. Recently, we have reported a convenient synthesis of fused heterocycles from α-ketohydroximoyl chlorides and heterocyclic amines [11]. In the present work we have extended the method of Sasaki *et al.* [12] who first used the reactions of the hydroximoyl chlorides **1a-c** with aromatic amines that have an *ortho*-substituent (-OH or -SH) that can participate in a cyclization reaction. The method reported here offers milder conditions and better yields than either of the usual methods of preparing compounds of this type, the oxidation reactions of the corresponding anils [13] or the condensation reactions of *o*-substituted aromatic amines with acid chlorides [14]. While the compounds used in this study were chosen to illustrate the utility of the hydroximoyl chlorides as synthons and not because ot their biological activity, it is likely that the route can afford compounds of biological interest.

Scheme



1a G = H
1b G = p-Cl
1c G = m-NO_2

2 Z = NH
4 Z = O
6 Z = S

3a G = H, Z = NH
3b G = p-Cl, Z = NH
3c G = m-NO_2, Z = NH
5a G = H, Z = O
5b G = p-Cl, Z = O
5c G = m-NO_2, Z = O
7a G = H, Z = S
7b G = p-Cl, Z = S
7c G = m-NO_2, Z = S

Treatment of the hydroximoyl chloride **1a** with two equivalents of *o*-phenylenediamine **2** in ethanol at room temperature gave a single product **3a** in quantitative yield (according to tlc). Elemental analysis indicates that the product has the molecular formula $C_{13}H_{10}N_2$ and the mass spectrum shows the expected m/e 194. The 200 MHz ^{1}H-nmr spectrum in deuterated dimethyl sulfoxide contains three multiplets at δ 7.2 ppm (2H), δ 7.5 ppm (5H), and δ 8.2 ppm (2H). A COSY experiment makes it clear that this spectrum is composed of two overlapping sets of peaks. The first set, from the benzo group, is composed of an AA'BB' pattern that contributes the δ 7.2 ppm multiplet coupled to two of the 5 protons at δ 7.5 ppm. The second set, from the phenyl group, has the *meta*- and *para*-protons overlapping the δ 7.5 ppm multiplet with coupling to the *ortho*-protons at 8.2 ppm. Despite the overlapping of the phenyl protons with a part of the AA'BB' pattern, the major peaks were not obscured and it was possible to assign the chemical shifts and coupling constants of the benzo group using "PANIC," a microcomputer version of "LAOCOON III" supplied by Bruker Instruments (Table 3).

Because the ^{1}H-nmr spectra were obtained in dimethyl sulfoxide-d_6 and the N-H proton cannot be seen, it is presumed to be exchanging with the water singlet at δ 3.4 ppm [15]. This is confirmed by the observation that C_{2v} symmetry is indicated by the AA'BB' pattern observed for the four protons of the benzo group of compound **3a** as well as by the observation of eight peaks in the ^{13}C-nmr spectrum instead of the eleven that would be expected if symmetry were absent (Table 4). Although the δ 7.2 peak overlaps the solvent peak in deuteriochloroform, the visible portions of the spectrum indicate that the benzo group lacks symmetry in this solvent.

The ^{1}H-nmr spectrum of compound **3b** has the doublets expected for a *para*-substituted phenyl group but they overlap the AA'BB' pattern of the protons of the benzo group which precludes an exact analysis of the spectrum.

Table 1

Synthesized Heterocycles

Compound No.	Mp, °C (mp, lit)	Yield %	Molecular formula	Analysis Calcd./(Found) C, %	H, %	N, %
3a	292 (293) [a]	80	$C_{13}H_{10}N_2$	80.39 (80.14)	5.19 (5.26)	14.42 (14.42)
3b	294 (295) [a]	90	$C_{13}H_9ClN_2$	68.28 (67.75)	3.97 (3.94)	12.25 (12.00)
3c	308 (208) [b]	60	$C_{13}H_9N_3O_2.H_2O$	60.49 (60.74)	4.68 (4.19)	16.27 (16.20)
5a	103 (102) [a]	85	$C_{13}H_9NO$	79.92 (79.82)	4.65 (4.74)	7.18 (7.12)
5b	147 (148) [a]	90	$C_{13}H_8ClNO$	67.97 (67.15)	3.51 (3.48)	6.10 (6.21)
5c	218 (221-223) [c]	85	$C_{13}H_8N_2O_3$	64.99 (64.59)	3.36 (3.34)	11.66 (11.73)
7a	115 (114) [a]	95	$C_{13}H_9NS.H_2O$	68.08 (68.80)	4.83 (4.30)	– –
7b	116 (116) [a]	95	$C_{13}H_8ClNS.H_2O$	59.20 (60.10)	3.82 (3.40)	– –
7c	209 (188-189) [c]	85	$C_{13}H_8N_2O_2S.H_2O$	56.92 (57.44)	3.67 (3.30)	– –

[a] Ref [19]. [b] Probably a typographical error in ref [20]. The *o*-nitro isomer has a mp of 170°, the *p*-nitro isomer 329° [20,21]. [c] Ref [12].

Table 2

Electronic Absorption Spectra of the Compounds under Study

Compound No.	λ max (Ethanol), nm (log ε)
3a	236 (4.11), 298 (4.38), 312 (4.19)
3b	242 (4.29), 296 (4.48), 303 (4.51), 317 (4.28)
3c	244 (4.00), 353 (3.99), 298 (4.41)
5a	232 (3.84), 287 (4.45), 298 (4.41)
5b	222 (4.08), 237 (4.11), 290 (4.51), 300 (4.52)
5c	216 (4.31), 260 (4.42), 290 (4.44)
7a	224 (3.95), 252 (3.44), 294 (3.97)
7b	244 (4.00), 253 (3.99), 298 (4.41)
7c	219 (4.75), 249 (4.20), 270 (4.23), 294 (4.25)

Although the carbon analysis is somewhat low, the other analytical data show that the structure is correct. The ^{13}C-nmr spectrum has seven of the expected eight peaks.

The ^1H-nmr spectrum of compound **3c** is composed of the two portions of an AA'BB' pattern at δ 7.2 and δ 7.6 ppm plus the four regions and pattern expected for a *m*-nitrophenyl group. The data for the benzimidazole derivatives **3a-c** are listed in Tables 1 to 4.

The reaction of **1a-c** with *o*-aminophenol **4** in ethanol afforded the corresponding 2-arylbenzoxazoles **5a-c**. The ^1H-nmr spectrum of **5a** shows two of the benzo protons at δ 7.4 and the other two at δ 7.8 ppm. An analysis of the benzo group pattern indicates that it is of the ABCD type and that symmetry is absent. The *meta*- and *para*-protons of

Table 3

^1H-NMR Spectra of the Products in DMSO-d_6

Compound No.	Benzo Protons [a] A	B	C	D	Phenyl Protons
3a	7.30 (J_{AB} = 8.26)	7.00 ($J_{BB'}$ = 7.30)	7.00	7.30	7.3 (m, 3H), 8.0 (m, 2H)
3b	7.6	7.2	7.2	7.6	7.6 (m, 2H), 8.2 (d, 2H)
3c	7.61 (J_{AB} = 7.40)	7.21 ($J_{BB'}$ = 6.03)	7.21	7.61	7.8 (t, 1H), 8.2 (d, 1H), 8.6 (d, 1H), 9.0 (s, 1H)
5a	7.76 (J_{AB} = 8.23)	7.41 (J_{BC} = 7.47)	7.39 (J_{CD} = 8.73)	7.79	7.65 (m, 3H), 8.2 (m, 2H)
5b	7.82 (J_{AB} = 8.57)	7.44 (J_{BC} = 7.86)	7.47 (J_{CD} = 8.62)	7.84	7.7 (m, 2H), 8.2 (m, 2H)
5c	7.88 (J_{AB} = 7.99)	7.48 (J_{BC} = 7.17)	7.52 (J_{CD} = 7.76)	7.89	7.9 (t, 1H), 8.45 (d, 1H), 8.6 (d, 1H), 8.9 (s, 1H)
7a	8.1	7.5	7.5	8.1	7.5 (m, 3H), 8.1 (m, 2H)
7b	8.1	7.5	7.5	8.1	7.5 (m, 2H), 8.1 (m, 2H)
7c	8.15 (J_{AB} = 8.21)	7.61 (J_{BC} = 7.43)	7.53 (J_{CD} = 7.98)	8.22	7.9 (t, 1H), 8.4 (d, 1H), 8.5 (d, 1H), 8.8 (s, 1H)

[a] Where coupling constants are shown the chemical shifts (ppm) and coupling constants (Hz) were assigned using "PANIC", a microcomputer version of "LAOCOON III", supplied by Bruker Instruments.

Table 4

^{13}C-NMR Spectra of the Products in DMSO-d_6

Compound No.	^{13}C-NMR Chemical Shifts (ppm)
3a	111.5, 119.2, 122.4, 126.5, 129.0, 129.9, 130.2, 151.2
3b	112.1, 128.5, 122.3, 128.1, 129.0, 134.4, 134.4, 150.1
3c	115.4, 120.8, 122.7, 124.1, 130.5, 131.6, 132.4, 148.2, 149.0
5a	110.7, 119.6, 124.6, 125.3, 126.2, 127.0, 129.1, 131.7, 141.3, 150.0, 162.0
5b	110.9, 112.0, 125.0, 125.2, 125.7, 128.9, 129.9, 136.7, 141.3, 150.2
5c	111.3, 120.3, 121.7, 125.3, 126.3, 126.3, 128.0, 131.3, 133.2, 141.2, 148.4, 150.4, 160.4
7a	110.9, 119.9, 124.9, 125.5, 126.4, 127.2, 129.3, 131.9, 141.5, 150.2, 162.2
7b	122.2, 122.7, 125.5, 126.5, 128.6, 129.2, 131.4, 134.3, 135.8, 153.2, 165.7
7c	121.1, 122.6, 123.3, 124.6, 125.6, 126.2, 127.1, 131.2, 133.6, 134.2, 134.2, 148.4, 153.2, 164.8

the phenyl group are at δ 7.65 and the *ortho*-protons are at δ 8.2 ppm. The ^{13}C-nmr spectrum shows the expected eleven resonances. The ^{1}H-nmr spectra of compounds **5b** and **5c** make it clear that the benzo pattern is also of the ABCD type in both cases. The analyses and electronic spectral data of **5a-c** are presented in Tables 1 and 2, respectively, and the ^{1}H-nmr and ^{13}C-nmr spectra are in Tables 3 and 4.

The reaction of **1a-c** with 2-aminothiophenol **6** in ethanol at room temperature gave the corresponding 2-arylbenzothiazoles **7a-c** in quantitative yield (by tlc). The proposed structures of **7a-c** are in accord with their elemental analyses and spectral data (Tables 1 to 4). The ^{1}H-nmr spectra of compounds **7a** and **7b** show only two broad multiplets at δ 7.4-7.7 ppm and 8.0-8.2 ppm. The ^{1}H-nmr spectrum of compound **7c** was analyzed with the aid of "PANIC" and was of the ABCD type showing that symmetry was absent. The *m*-nitrophenyl group contributes a singlet at δ 8.8 ppm, two doublets at δ 8.4 and 8.5 ppm and a triplet at δ 7.9 ppm. The ^{13}C-nmr spectra have the expected number of resonances. The analyses and electronic spectral data are listed in Tables 1 and 2 and the ^{1}H-nmr and ^{13}C-nmr data are given in Tables 3 and 4, respectively.

EXPERIMENTAL

All melting points are corrected and were determined on a Thomas-Hoover capillary melting apparatus. The ^{1}H-nmr and ^{13}C-nmr spectra were obtained at 30°C in saturated dimethyl sulfoxide-d_6 solution on an IBM NR 200 AF spectrometer, with tetramethylsilane as the internal reference. The 200.13 MHz ^{1}H shift correlated 2D nmr COSY(45) spectra were collected into a 256 x 256 data matrix. The spectral width was 500 Hz and each transient taken was sampled 64 times with a 3 s pulse delay. The mass spectra were taken on a DuPont 491 mass spectrometer. The ir spectra were determined in Nujol using a Perkin-Elmer 580B infrared spectrophotometer with a Perkin-Elmer 3500 data station. The electronic spectra were measured in ethanol on a Varian Cary 118 spectrophotometer. Elemental analyses were carried out by Desert Analytics, Tucson, AZ, and by the Microanalytical Centre of the University of Cairo, Giza, Egypt. The hydroximoyl chlorides **1a-c** were prepared as previously described [6,16-18]. The aromatic amines used in this work were obtained from Aldrich Chemical Co., Milwaukee, WI.

2-Arylbenzimidazoles **3a-c**, 2-Arylbenzoxazoles **5a-c**, and 2-Arylbenzothiazoles **7a-c**.

To a solution (0.01 mole) of *o*-phenylenediamine **2**, *o*-aminophenol **4**, or *o*-aminothiophenol **6** in ethanol (15 ml), the appropriate arylhydroximoyl chloride **1a-c** (0.005 mole) was added and the resulting mixture was stirred for 0.5-3 hours at room temperature. The solid formed was collected, washed with water, and crystallized from ethanol or ethanol-water. The analyses of the compounds prepared, **3a-c**, **5a-c** and **7a-c**, are listed in Table 1 and the respective spectra are in Tables 2, 3 and 4.

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