STERIC AND ELECTRONIC EFFECTS CONTROLLING THE SYNTHESIS OF BRIDGEHEAD NITROGEN HETEROCYCLES

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This paper is dedicated to Professor Edward C. Taylor on the occasion of his 70th birthday.

Abstract - The synthesis of imidazo[2,1-b][-1,3,4-] thiadiazoles via the condensation of an α-haloketone with 2-amino-1,3,4-thiadiazoles is controlled by the nature of the substituent at the 5-position of the thiadiazole.

The synthesis of bridgehead nitrogen heterocycles has been extensively reviewed.[1,2] Our interest in these fused heterocycles was influenced by several reports of their diverse biological activities. Kaminski[3] and co-workers have reported on the gastric antisecretary and cytoprotective properties of imidazo[1,2-*a*]pyridines. On the other hand, Black[4] *et al.* have shown that 2-arylimidazo-[1,2-*a*]pyrimidines exhibit significant inotropic effects in experimental animals. Imidazo[1,2-a]pyrazines[5] have also been shown to elicit inotropic effects. The activity of levamisole[6] as an immunomodulatory and antiinflammatory agent has led

to the synthesis of a variety of imidazo[2,1-*b*]thiazoles[7] and imidazo[2,1-*b*]benzothiazoles[8] which have been found to have similar biological properties.

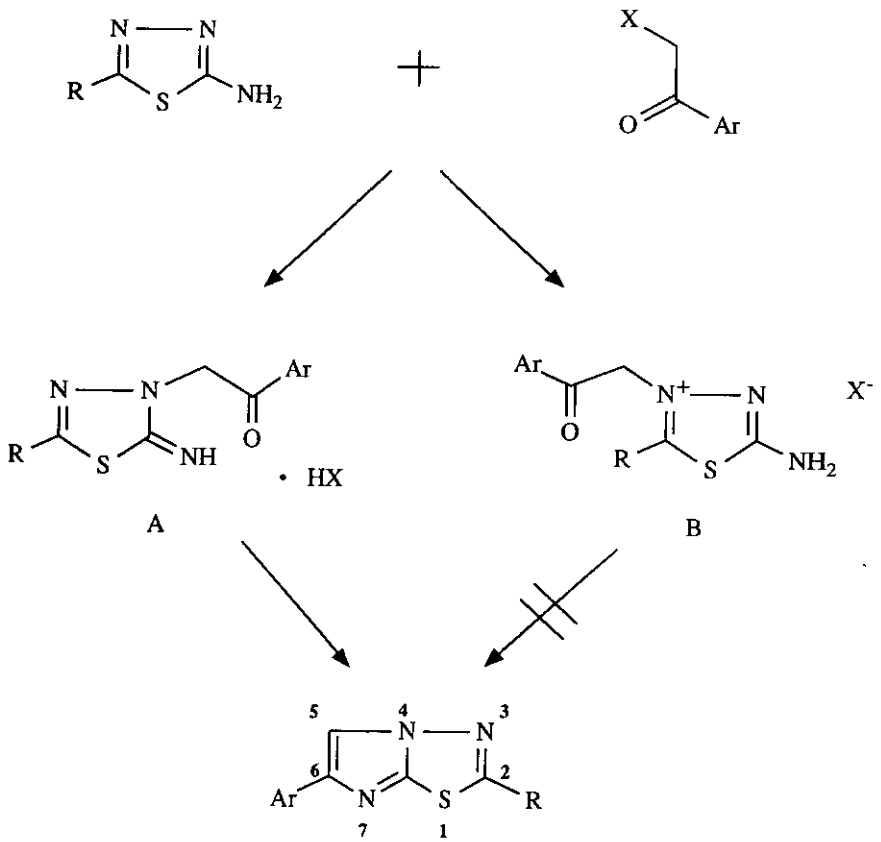
In the 1950s Ban and Matsukawa[9-11] prepared an extensive number of imidazo[2,1-*b*][1,3,4]thiadiazoles which were evaluated for their cardiovascular effects. Later Barnish[12] *et al*. synthesized several imidazo[2,1-*b*][1,3,4]thiadiazole sulfonamides related to acetazolamide and these substances were found to increase cerebral blood low in animals without producing metabolic acidosis.

This finding of the increase in cerebral blood flow let us to consider this class of fused heterocycle as potential candidates for the treatment of Alzheimer's disease. The synthesis of the imidazo[2,1-*b*][1,3,4]thiadiazoles is usually carried out by the condensation of a 2-amino-1,3,4-thiadiazole with an α-haloketone under reflux in ethanol. It is well established that this reaction proceeds via the intermediate iminothiadiazole (A) (See Scheme) which under reflux temperature spontaneously undergoes ring closure to form the desired fused heterocycle.[12]

In all cases under discussion substituted α-haloacetophenones were used as condensing agents with the 5-substituted-2-amino-1,3,4-thiadiazoles. Early in our study it was determined that reaction between the α-haloketone and the 2-amino-1,3,4-thiadiazole substituted at the 5 position with either H, CH_3 or C_2H_5 gave rise in high yield to a singular product which resisted cyclization in boiling water,[13] acetic acid, dimethyl formamide or polyphosphoric acid.[14] Thus, it appeared that the intermediate iminothiadiazole had not been formed.

To elucidate the structure of the intermediate, recourse was had to the spectral data of the prototype compound, 2-amino-1,3,4-thiadiazole, and to the corresponding intermediate, A or B, in which R=H.

Scheme



The infrared spectrum of the intermediate structure shows a strong absorption in the area of 1700 cm^{-1} indicating the presence of the carbonyl group. The infrared, however, does not offer any assistance as to which nitrogen is alkylated.

A similar situation arises in the mass spectrum. The fragmentation pattern is consistent with alkylation occurring on either nitrogen. There does not appear to be any rearrangement apparent that would conclusively prove one structure or the other.

Proof of structure lies in the proton nmr. The H-nmr spectrum of 2-amino-1,3,4-thiadiazole shows that the chemical shift of the hydrogen at the 5-position is 8.22 ppm. If intermediate A is formed, then the chemical shift of hydrogen at position 5 should remain relatively the same. The magnetic environment of that hydrogen is not significantly changed such that it becomes more or less shielded.

However, if B is formed, the hydrogen at position 5 is now in an environment that is markedly altered. The hydrogen is now adjacent to a quaternary nitrogen while other environmental factors remain relatively constant. This causes the hydrogen to be more deshielded and should significantly increase the chemical shift. Indeed it was found that for compound (1) (see Table I) the chemical shift for the proton at C-5 is now increased to 9.05 ppm. These data confirm the assignment of the quaternary salt structure B as the product of the condensation of α-halocetophenones with 2-amino-1,3,4-thiadiazoles containing at position 5, hydrogen, methyl or ethyl. In other words, the nucleophilic character of the nitrogen at position 4 is much greater than the nitrogen at 3 resulting in the formation of intermediate B.[15]

This effect is dramatically exhibited by the condensation of a 2-bromo-4'-chloroacetephenone with 2-amino-5-methyl-1,3,4-thiadiazole giving rise to the

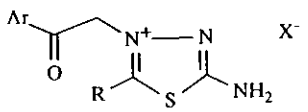
quaternary compound (4) (Table I). On the other hand, the above condensation reaction using 2-amino-5-trifluoromethyl-1,3,4-thiadiazole gave an excellent yield of the corresponding imidazo[2,1-*b*][1,3,4]thiadiazole (7), Table II. The trifluoromethyl group is strongly electronegative and consequently by its inductive effect imparts less nucleophilic character to the nitrogen at position 4 of the 1,3,4-thiadiazole. Thus, the alkylation of this thiadiazole occurs at the 3-nitrogen with subsequent ring closure to form the corresponding bridgehead nitrogen heterocycle.

Similarly the condensation of substituted α-halacetophenones with 2-amino-5-ethylmercapto-1,3,4-thiadiazole also gave rise to the imidazo[2,1-*b*][1,3,4]-thiadiazoles (Compounds (10 and 11)). Again the inductive effect of the 3d orbital of the sulfur of the ethylmercapto group at C-5 of the heterocycle reduces the nuclophilic character of the nitrogen at position 4.

A further extension of this research led us to explore the influence of steric factors in the synthesis of imidazo[2,1-*b*][1,3,4]thiadiazoles. The condensation of substituted α-haloacetophenones with 2-amino-5-*t*-butyl-1,3,4thiadiazole gave excellent yields of the corresponding imidazo[2,1-*b*][1,3,4]-thiadiazole (Compounds (12 and 13)). The strong singlet at 8.8 ppm for the C-5 hydrogen is typical for all the ring closed compounds. Thus, the bulky character of the *t*-butyl group prevents the α-haloacetophenone from attacking the more nucleophilic 4-nitrogen and as a consequence allowing reaction to occur at N-3 followed by ring closure to the desired fused heterocycle.

However, condensation of 2-bromo-4'-chloroacetophenone with 2-amino-5-cyclopropyl-1,3,4-thiadiazole led to the isolation of two products. Compound (6) (Table I) gave a strong band at 1695 cm^{-1} in the infrared and was shown to be the "open" compound. The other product (14) of the reaction was devoid of the carbonyl band in the infrared, but gave a strong signal at 8.7 ppm for the vinyl

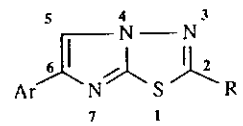
Table I



Compd	Ar	R	X	mp(°C)	Yield(%)	Formula	Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
1	4-Cl-C_6H_4	H	Br	233-234	69	$C_{10}H_9N_3OBrClS$	35.89	2.71	12.56	36.21	2.69	12.42
2	C_6H_5	CH_3	Cl	235-238	62	$C_{11}H_{12}N_3OClS$	48.97	4.48	15.58	49.06	4.29	15.32
3	4-Cl-C_6H_4	CH_3	Br	271-273	54	$C_{11}H_{11}N_3OBrClS$	37.89	3.18	12.05	37.86	3.07	11.95
4	4-CH_3O-C_6H_4	CH_3	Br	229-230	71	$C_{12}H_{14}N_3OBrS$	41.87	4.10	12.21	41.83	4.16	12.18
5	C_6H_5	C_2H_5	Cl	167-169	36	$C_{12}H_{14}N_3OClS$ H_2O	47.76	5.34	13.92	47.85	5.33	13.77
6	4-ClC_6H_4	CH_2 | CH / CH_2	Br	212-213	27	$C_{13}H_{10}N_3OBrClS$	41.67	3.50	11.22	41.65	3.37	11.07

Each of these compounds gave a strong band at 1690-1700 cm^{-1} in the infrared.

Table II



Compd	Ar	R	mp(°C)	Yield(%)	Formula	Calcd C	Calcd H	Calcd N	Found C	Found H	Found N	Chemical shift, ppm H_5
7	4-Cl-C_6H_4-	CF_3	156-157	60	$C_{11}H_6N_3SClF_3$	43.50	1.66	13.83	43.40	1.56	13.59	8.15
8	3-CH_3O-C_6H_4	CF_3	238-240	41	$C_{12}H_8N_3OF_3S$•HBr	37.90	2.38	11.05	38.07	2.28	11.14	8.20
9	C_6H_5	CH_3CH_2-S-	100-102	42	$C_{12}H_{11}N_3S_2$	55.14	4.24	16.08	55.13	4.31	16.07	8.65
10	4-CH_3O-C_6H_4	CH_3CH_2S	104-105	65	$C_{13}H_{13}N_3OS_2$	53.58	4.50	14.42	53.56	4.48	14.23	8.75
11	3,5-Cl_2-C_6H_3	CH_3CH_2S	107-108	43	$C_{12}H_9N_3Cl_2S_2$	43.64	2.75	12.72	43.56	2.54	12.60	8.41
12	4-CH_3-C_6H_4	t-C_4H_9	92	53	$C_{15}H_{17}N_3S$	66.36	6.29	15.39	66.36	6.29	15.39	8.71
13	3-CH_3O-C_6H_4	t-C_4H_9	231-232	59	$C_{15}H_{17}N_3S$•HBr	48.91	4.92	11.41	49.06	4.87	11.27	8.75
14	4-Cl-C_6H_4	CH_2 | CH / CH_2	245-246	15	$C_{13}H_{10}N_3ClS$•HBr	43.77	3.11	11.78	43.75	3.17	11.67	8.40

hydrogen at C-5 of the imidazo[2,1-*b*][1,3,4]thiadiazole.

Therefore, the cyclopropyl group being larger than the ethyl group but smaller than the *t*-butyl group, does not completely prohibit the approach of the alkylating agent to N-4 and so allows both reactions to occur.

These results illustrate the significance of electronic and steric factors at position 5 of 2-amino-1,3,4-thiadiazole in determining the course of its reaction with substituted α-haloacetophenones. These conclusions are also applicable to other amino heterocycles containing two nitrogens in the ring.[5,15]

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Hoover apparatus and are uncorrected. The ^1H-nmr spectra were recorded on a Varian Gemini-200 instrument at 200 MHZ in deuteriochloroform or DMSO-d_6 solutions using TMS as internal standard and chemical shifts are expressed in ppm. Mass spectra were scanned on a Finnigan 4500 direct probe MS. Infrared spectra were obtained using a Perkin-Elmer 1420 ratio recording instrument.

All chemicals herein outlined and used as reactants were purchased from Aldrich Chemical Company, Milwaukee, Wisconsin. α-haloacetophenones: 2-Chloroacetophenone, 2-bromo-4'-chloroacetophenone, 2-bromo-4'-methoxyacetophenone, 2-bromo-3'-methoxyacetophenone, 2-bromo-4'-methylacetophenone, 2-bromo-3', 5'-dichloroacetophenone.

2-amino-1,3,4-thiadiazoles: 2-amino-1,3,4-thiadiazoles, 2-amino-5-methyl-1,3,4-thiadiazole, 2-amino-5-ethyl-1,3,4-thiadiazole, 2-amino-5-cyclopropyl-1,3,4-thiadiazole, 2-amino-5-*t*-butyl-1,3,4-thiadiazole, 2-amino-5-trifluoromethyl-1,3,4-thiadiazole and 2-amino-5-ethylthio-1,3,4-thiadiazole.

Preparation of 2-amino-4-(4'-chlorobenzoylmethyl)-1,3,4-thiadiazolium bromide. (General procedure for compounds 1-5 shown in Table I).

A mixture of 2.02 g (0.02 mol) of 2-amino-1,3,4-thiadiazole and 4.67 g. (0.02 mol) of 2-bromo-4'-chloroacetophenone was dissolved in 50 ml of ethyl alcohol and heated under reflux for 8 h. A copious white precipitate was formed within the first hour of the reaction. The mixture was chilled overnight and the precipitate then collected, the crude yield was 5.40 g. After recrystallization for analysis from 300 ml of ethyl alcohol, 4.61 g. (69% yield) of product was obtained. Ir 1700cm^{-1}; ^{1}H-nmr, δ 6.20 (s,2H,CH_2), δ 7.75-8.15 (m-4aromatic H), δ 9.05 (s,1H); ms [m/z, I] (254,100).

Preparation of 2-trifluoromethyl-6-(4'-chlorophenyl)imidazo[2,1-*b*][1,3,4]thiadiazole. (General procedure for the preparation of compounds 7-13 in . Table II)

2-Amino-5-trifluoromethyl-1,3,4-thiadiazole (3.38 g, 0.02 mol) was dissolved in 30 ml of ethyl alcohol and to this solution was added 4.67g (0.02 mol) of 2-bromo-4'-chloroacetophenone. The solution was heated under reflux for 8 h. After standing in the refrigerator overnight, the crystals were collected on a Buchner funnel and then recrystallized from 25ml of ethyl alcohol to yield fine, white-needle-like crystals (3.64 g, 60%).

Preparation of compounds 6 and 14

To 2.82 g (0.02 mol) of 2-amino-5-cyclopropyl-1,3,4-thiadiazole dissolved in 30 ml of ethyl alcohol was added 4.67 g (0.02 mol) of 2-bromo-4'-chloroacetophenone. The solution was heated under reflux for 8 h. After chilling overnight at 0°, a tan colored solid was isolated (5.37 g) which was recrystallized from 100 ml of ethyl alcohol. The recrystallized material was collected on a Buchner funnel

and was found to consist of two crystal forms: (a) 3.08 g of fine white needles, mp 214-218°C; and (b) light tan cubes (1.64 g, mp 245-246°C.) These were separated manually.

(a) was recrystallized from 75 ml of ethyl alcohol to yield white crystalline needles (2.02 g) mp 212-213°C. This substance exhibited a strong absorption band at 1695cm^{-1} in the infrared. Ms: M^+, m/z=294. This compound was identified as 2-amino-4-(4'-chlorobenzoylmethyl)-5-cyclopropyl-1,3,4-thiadiazolum bromide (compound (6), Table I).

(b) was recrystallized from 10 ml of ethyl alcohol to yield 1.20 g of tan crystals, mp 245-246°C. This substance was devoid of the 1695 cm^{-1} absorption band in the infrared. The ^{1}H-nmr revealed the signal of the H-5 vinyl proton at 8.40; ppm ms: [m/z, I] = 275 (100). This substance was identified as 2-cyclopropyl-6-(4'-chlorophenyl)imidazo[2,1-*b*][1,3,4]thiadiazole hydrobromide (compound (14), Table II).

Preparation of 2-amino-4-(4'-bromobenzoylmethyl)pyrazinium bromide

2-Aminopyrazine (2.85 g, 0.03 mol) dissolved in 50 ml of ethyl alcohol was allowed to react with 7.26 g (0.03 mol) of 2, 4'-dibromoacetophenone with stirring under reflux for 1 h. On cooling the precipitate was collected on a Buchner funnel and air dried. Yield, 8.67 g, (85.75%) mp 215°C. One recrystallization from 300 ml of ethyl alcohol gave 5.07 g (50%) of pure product, mp 218°C. Ir 1700 cm^{-1}; ^{1}H-nmr, δ 6.35 (s, 2H, CH_2), δ 7.9-8.2 (m, aromatic H), δ 8.80 (s,1H on C-3); ms: [m/z, I] (291, 293, S) (183, 100).

Anal. calcd for $C_{12}H_{11}N_3OBr_2$: C, 38.64; H, 2.97; N, 11.26. Found: C, 39.10; H, 2.92; N, 10.98.

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15. These results confirm and extend the findings of Spitzer *et al.*,[5] who noted that in 2-aminopyrazine, 2-aminopyrimidine and 2-aminopyridazine, the ring nitrogen that is not adjacent to the amino function is the most nucleophilic. In this regard, we found the chemical shift for proton at C-3 for 2-aminopyrazine to be 7.75 p.p.m. The C-3 proton signal for 2-amino-4-

(4'-bromobenzoyl) methylpyrazinium bromide is 8.80 ppm, showing a significant deshielding effect due to the quaternary nitrogen. The reaction of α-haloketones with 2,5-diamino-1,3,4-thiadiazole to yield 6-amino-[2,1-*b*]-1,3,4-thiadiazole as reported by H. Paul, A. Sitte, and R. Wessel (Monatsh Chem., 1977 108, 665) is not relevant to this study since the reactant heterocycle is symmetrical.

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