Reaction Between *o*-Diamino-1,2,6-thiadiazine 1,1-Dioxides and Aldehydes to Give Fused Imidazo and Pyrazino Derivatives

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Reaction between 3,4,5-triamino-1,2,6-thiadiazine 1,1-dioxides and aldehydes, in acetic acid or DMF, under anhydrous conditions, leads to a mixture of imidazo[4,5-*c*]- and pyrazino[2,3-*c*]-1,2,6-thiadiazine derivatives. The ratio of both compounds depends on the nature of the aldehydes used. The same reaction, in the absence of solvent, affords, only pyrazinothiadiazine derivatives. The uv, ^{1}H- and ^{13}C-nmr data of the new compounds are reported.

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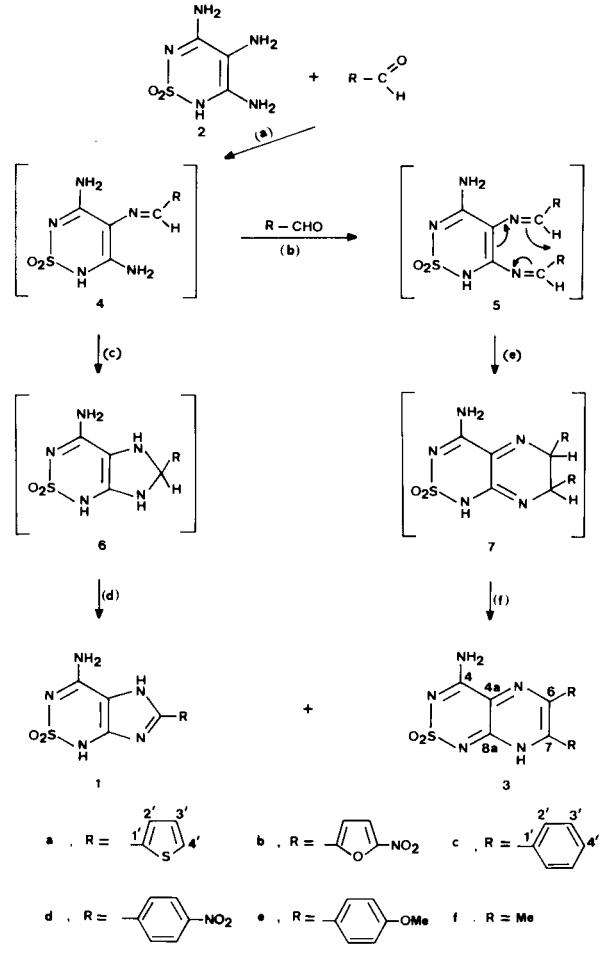
In a previous paper [1], we have described the synthesis of 6-substituted imidazo[4,5-*c*]-1,2,6-thiadiazine 2,2-dioxides **1** from 3,4,5-triaminothiadiazine 1,1-dioxide (**2**) and aldehydes, in aqueous acetic acid or aqueous dimethylformamide at room temperature. Under these conditions, only, compounds **1** were obtained. However, when the reaction was carried out in the same solvents under anhydrous conditions, at reflux temperature, another reaction product **3** together with imidazothiadiazine 2,2-dioxides **1** was isolated. Compound **3** obtained from benzaldehyde was identical to the one synthesized from **2** and benzil [2] following the Isay reaction [3]. Thus, the product was identified as the sulfur dioxide analog of pteridine **3c**.

The probable mechanism of the formation of **1** and **3** is depicted in the Scheme. The tautomeric forms drawn for **1** and **3** are the ones present in solid state [1] and in aqueous solution [2].

In a first step (a), the most reactive 4-amino group of **2** forms the Schiff's bases **4** which cyclize to the imidazothiadiazine derivatives **1** through an aromatization process [1]. On the other hand, the 5-amino group of **4**, under energetic conditions, is able to react with aldehydes (b) to give the diazahexatrienes **5**, which undergo thermal cyclization by valence isomerization [4] (e) and aromatization by an oxidation process (f) to afford 4-aminopyrazino-[2,3-*c*]-1,2,6-thiadiazine 2,2-dioxides **3**. The intermediates **4, 5, 6** and **7** could not be isolated in any case. When the reaction was carried out under a nitrogen atmosphere, compound **1** together with another derivative different from **3** could be detected by tlc. This new compound slowly converts to **3**, when the reaction mixture is allowed to stand in contact with atmospheric oxygen. It is probable that under a nitrogen atmosphere intermediate **7** exists in solution but not intermediate **6** since compound **1** is present under these conditions. The aldehyde itself can act as an oxidizing agent in the transformation from **6** to **1**, since the corresponding alcohols have been detected by tlc.



Scheme

Related diazahexatriene from *o*-phenylenediamine and benzaldehyde afforded 1,2-disubstituted benzimidazole [5], although, in our case, no 5,6-disubstituted imidazothiadiazine derivatives were obtained.

The reaction between **2** and aldehydes in the absence of solvent, under fusion conditions led to pyrazinothiadia-

Table 1

Imidazo[4,5-*c*]- and pyrazino[2,3-*c*]-1,2,6-thiadiazine 2,2-Dioxides

Run	Aldehyde	Solvent	Temperature	Time (hours)	Yield (%) **1**	Yield (%) **3**
1	2-formyltiophene [a]	AcOH	reflux	3	33	32
2	2-formyltiophene [a]	DMF	reflux	3	36	32
3	5-nitro-2-furaldehyde [a]	AcOH	reflux	1	78	-
4	benzaldehyde [a]	AcOH	reflux	8	43	37
5	benzaldehyde [b]	-	180°	2	-	51
6	*p*-nitrobenzaldehyde [a]	AcOH	reflux	8	73	-
7	*p*-nitrobenzaldehyde [b]	-	180°	2	-	44
8	*p*-methoxybenzaldehyde [a]	AcOH	reflux	8	60	10
9	*p*-methoxybenzaldehyde [b]	-	180°	2	-	46
10	Acetaldehyde [a]	AcOH	reflux	8	20	-

[a] Molar ratio **2**/aldehyde:1/2 [b] Molar ratio **2**/aldehyde:1/3.

Table 2

^{1}H-NMR [a]. Chemical shifts (ppm) and coupling constants (Hz) of **3** [b]

Compound	NH	NH-8	H-2′, H-2″	H-3′, H-3″	H-4′, H-4″	Coupling constants
3a	8.7, 8.4	12.4	7.41 (dd), 7.13 (dd)	7.18 (dd), 7.10 (dd)	7.83 (dd), 7.77 (dd)	$^3J_{H\text{-}2',H\text{-}3'}$ = 3.7 $^3J_{H\text{-}3',H\text{-}4'}$ = 5.0 $^4J_{H\text{-}2',H\text{-}4'}$ = 1.2
3c [2]	8.6, 8.4	-	7.5 (m)	7.5 (m)	7.5 (m)	-
3d	7.3	7.3	7.68 (d), 7.65 (d)	8.22 (d), 8.09 (d)	-	$^3J_{H\text{-}2',H\text{-}3'}$ = 8.8
3e	8.6, 8.4	12.4	7.46 (d), 7.40 (d)	6.93 (d), 6.89 (d)	3.77, 3.76 (s) (OMe)	$^3J_{H\text{-}2',H\text{-}3'}$ = 8.7

[a] DMSO-d_6 at 300 MHz for **3a**, 200 MHz for **3d** and **3e** and at 90 MHz for **3c**. [b] For numbering see scheme.

Table 3

^{13}C-NMR [a]. Chemical shifts (ppm) and coupling constants (Hz) of **3** [b]

Compound	C-4	C-4a	C-6	C-7	C-8a	C-1′, C-1″	C-2′, C-2″	C-3′, C-3″	C-4′, C-4″
3a	158.0	119.4 (d) J = 5.0	138.4	149.7	147.0	139.6 (dd), 138.8 (dd)	129.3, 128.7	128.1, 127.5	131.9, 130.7
3c	159.1	120.6 (d) J = 5.8	146.1	156.6	147.6	137.7 (t) $^3J_{C\text{-}1',H\text{-}3'}$ = 6.7	128.5, 128.4 (d) ^1J = 161.9	130.1 (d) ^1J = 162.0	128.9 ^1J = 161.3
3d	158.2	121.2	143.7	154.7	148.3	143.1 (t) $^3J_{C\text{-}1',H\text{-}3'}$ = 7.7	123.6, 123.4 (d) ^1J = 171.4	131.5 (dd) ^1J = 168 $^2J_{C\text{-}3',H\text{-}2'}$ = 6.4	147.6 (s)
3e	158.7	119.3	159.6	160.5	146.7	129.9, 129.6 (t) $^3J_{C\text{-}1',H\text{-}3'}$ = 7.0	131.2, 130.9 (dd) ^1J = 161.2	113.7, 113.6 (dd) ^1J = 161.5	155.4 (t) $^3J_{C\text{-}4',H\text{-}2'}$ = 3.6 55.3, 55.2 (q) (OMe) ^1J = 144.6

[a] In DMSO-d_6 + 1% TFA (60°) at 20.15 MHz for **3a**, at 50 MHz for **3c** and **3d** and at 75 MHz for **3e**. [b] For numbering see scheme.

zine derivatives **3** as the major products. Under these conditions, only traces of imidazothiadiazine derivatives **1** were detected. This procedure is a useful method to synthesize 6,7-disubstituted pyrazinothiadiazine 2,2-dioxides, when the corresponding 1,2-dicarbonyl derivatives necessary for the Isay reaction are not available.

The imidazo- and pyrazinothiadiazine derivatives prepared and the reaction conditions used are shown in Table 1.

The yield of **1** and **3** is independent of the acid or basic nature of solvents (runs 1 and 2). The use of the aldehydes with electron-withdrawing substituents makes the reaction selective in the formation of imidazothiadiazine derivatives **1**, when the reaction is carried out in the presence of

solvents (runs 3 and 6). Pyrazinothiadiazine derivative **3b** was not obtained in any case. On the other hand, the extension of the reaction to aliphatic aldehydes does not lead to compounds **3** and decreases the yield of compounds **1** (run 10).

In Table 2 the ^{1}H-nmr data of pyrazinothiadiazine derivatives **3** are shown.

The assignments were straightforward. A small difference between proton chemical shifts (δ H′, δ H″) of 6-R and 7-R substituents was found in all cases. The assignment of δ H-2′ and δ H-4′ in compound **3a** was made on the basis of the value of both ^{3}J [6].

In Table 3 the ^{13}C-nmr data of compounds **3** are reported. Owing to the prototropic tautomerism that exists in thiadiazine dioxide derivatives [7], it is necessary to add drops of TFA and record the spectra at 60° in order to see all the signals.

The ^{13}C chemical shifts assignments were made by intercomparison with the data of the reported thiadiazine derivatives [7] and related aromatic compounds [8,9]. Long-range couplings of C-1′ and C-4′, when their signals are triplets, were assigned as ^{3}J on the basis of ^{3}J > ^{2}J in aromatic compounds [10]. In compounds **3a** and **3c** the C-4a signal appears as a doublet probably due to a coupling between C-4a and one proton of the amino group. In some cases, it was not possible to measure coupling constants due to the complexity of the coupled spectra.

EXPERIMENTAL

Melting points are uncorrected. The ^{1}H-nmr spectra were recorded at 90 MHz on a Varian EM-390 at 200 MHz on a Bruker AM-200 and at 300 MHz on a Varian XL-300 spectrometer, using DMSO-d_6 as solvent and TMS as internal standard. The ^{13}C-nmr spectra were recorded at 20.15, 50 and 75 MHz on a Bruker WP-80, a Bruker AM-200 and a Varian XL-300 spectrometer respectively. The ir and uv spectra were recorded on a Perkin Elmer 257 and a Perkin Elmer 550 SE spectrophotometer respectively.

Compounds were separated by flash chromatography using as eluent chloroform/methanol mixtures of increasing polarity on silica gel 60 Merck (230-400 mesh).

General Synthetic Method (A).

A suspension of 3,4,5-triamino-2*H*-1,2,6-thiadiazine 1,1-dioxide (**2**) (2.8 mmoles) in glacial acetic acid or dry dimethylformamide (20 ml) was placed in an oil-bath at 130° and the corresponding aldehyde (5.6 mmoles) was added. The reaction mixture was refluxed for 8 hours and the solvent removed *in vacuo*. The dry residue was washed thoroughly with boiling ethanol (3 x 20 ml). The ethanolic fractions were evaporated to dryness and the two reaction products **1** and **3** were separated by flash chromatography. Compounds **3** were eluted with chloroform/methanol:10/1 and compounds **1** with chloroform/methanol:3/1.

General Synthetic Method (B).

A finely powdered mixture of 1.1 mmoles of **2** and 3.3 mmoles of aldehyde was heated for 2 hours at 180° under anhydrous conditions. The dark oil obtained was extracted with acetone. The extract was evaporated *in vacuo* and the unreacted aldehyde elimination by sublimation. The resulting solid was recrystallized in each case.

4-Amino-6,7-di(2′-thienyl)-8*H*-pyrazino[2,3-*c*]-1,2,6-thiadiazine 2,2-Dioxide (**3a**).

Following the general procedure A, the solid eluted with chloroform/-methanol:10/1 was recrystallized from water/ethanol, mp 267-269°; ir (nujol): ν 3400, 3300 (NH_2), 3240 (NH), 1650 (C=N), 1300, 1180 cm^{-1} (SO_2); uv (methanol): λ max (log ε) 256 (4.20), 259 (sh) (4.19), 293 (4.17), 315 (sh) (4.13) and 421 nm (3.90).

Anal. Calcd. for $C_{13}H_9N_5O_2S_3$ (363.4): C, 42.96; H, 2.50; N, 19.27. Found: C, 43.00; H, 2.61; N, 19.15.

4-Amino-6,7-diphenyl-8*H*-pyrazino[2,3-*c*]-1,2,6-thiadiazine 2,2-Dioxide (**3c**).

Compound **3c** was obtained following methods A and B, (Table 1). It was isolated and recrystallized from acetone/water as yellow needles, mp 277-279°, mp (lit) 277-279° [2].

4-Amino-6,7-di(4′-nitrophenyl)-8*H*-pyrazino[2,3-*c*]-1,2,6-thiadiazine 2,2-Dioxide (**3d**).

Compound **3d** obtained by method B, was recrystallized from methanol/water, mp > 350 dec; ir (nujol): ν 3450, 3330 (NH_2), 3200 (NH), 1635 (C=N), 1510, 1345 (NO_2), 1295, 1160 cm^{-1} (SO_2); uv (methanol): λ max (log ε) 271 (4.46), 367 nm (4.24).

Anal. Calcd. for $C_{17}H_{11}N_7O_6S$ (441.4): C, 46.26; H, 2.51; N, 22.21. Found: C, 46.06; H, 2.85; N, 22.00.

4-Amino-6,7-di(4′-methoxyphenyl)-8*H*-pyrazino[2,3-*c*]-1,2,6-thiadiazine 2,2-Dioxide (**3e**).

Compound **3e** was synthesized following methods A and B (Table 1), isolated and recrystallized from acetone/water, mp 276-278°; ir (nujol): ν 3410, 3300 (NH_2), 3200 (NH), 1620 (C=N), 1465 (OCH_3), 1300, 1100 cm^{-1} (SO_2); uv (methanol): λ max (log ε) 246 (sh) (4.24), 291 (4.35), 409 nm (3.98).

Anal. Calcd. for $C_{19}H_{17}N_5O_4S$ (411.4): C, 55.46; H, 4.16; N, 17.02. Found: C, 55.48; H, 4.25; N, 16.78.

6-Substituted 4-Amino-1*H*,5*H*-imidazo[4,5-*c*]-1,2,6-thiadiazine 2,2-Dioxide (**1**).

All imidazothiadiazine derivatives **1** (**1a**, **1b**, **1c**, **1d**, **1e** and **1f**) obtained following synthetic procedure A (Table 1) were identical with those previously reported [1].

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