Unconventional Alkoxylation of Pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-Dioxides Mediated by *N*-Halosuccinimides

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One pot alkoxylation at position 7 of 6-arylpyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxides with NBS or NCS in the appropriate alcohol is described. Rationalization of the mechanism of the reaction, which does not proceed through the intermediate 7-halo derivatives, is discussed on the basis of experimental reactivity and ab initio calculations.

Introduction

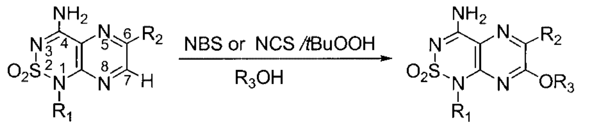
The interest in pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxides bearing a 7-alkoxy substituent, an important functional group in medicinal chemistry, is based on the pharmacological properties shown by some derivatives as platelet aggregation inhibitors.[1,2]

In general, the introduction of an alkoxy group in a heterocyclic compound can be carried out by the direct displacement of hydrogen or by the displacement of other substituents. The most often used procedures to obtain 7-alkoxy derivatives involve the nucleophilic substitution of chloro derivatives or the direct alkoxylation from appropriate *N*-oxides.

Other methods have been developed for the direct alkoxylation of nitrogen heterocycles, such as the utilization of acetyl hypofluorite (prepared by treatment of sodium acetate with fluorine) and methanol to obtain 2-methoxypyridines.[3] In the case of pteridines, there is only one report of a regioselective alkoxylation at position 6, which takes place by reaction with NBS (*N*-bromosuccinimide) and methanol by means of an electrophilic mechanism.[4]

Results and Discussion

Within this context, we would like to report a new method for the introduction of an alkoxy group directly at the 7-position of pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxides, SO_2 analogs of pteridines, by reaction with NBS or NCS (*N*-chlorosuccinimide) in an appropriate alcohol. This method is very useful for the synthesis of 7-methoxy or 7-ethoxypyrazino[2,3-*c*][1,2,6]thiadiazines and is based on a previous experimental observation of our laboratory whereby treatment of the 6-phenylpyrazino[2,3-*c*][1,2,6]thiadiazine **1** with *N*-bromosuccinimide and methanol afforded the corresponding 7-methoxy derivative **3** (Scheme 1). We want to report the application of this method to other pyrazino[2,3-*c*][1,2,6]thiadiazine derivatives and alcohols using NCS or NBS, and also a rationalization of the mechanism based on ab initio calculations.



1-2, 11-13 **3-5, 8-10**

	R1	R2
1	H	Ph
2	Me	Ph
11	H	4-NO_2Ph
12	H	4-MePh
13	H	4-ClPh

	R1	R2	R3
3	H	Ph	Me
4	H	Ph	Et
5	Me	Ph	Me
8	H	4-NO_2Ph	Me
9	H	4-MePh	Et
10	H	4-ClPh	Et

Scheme 1

The 7-ethoxy derivative **4** was obtained by reaction of **1** with ethanol. Under similar conditions, the 1-methyl-6-phenyl compound **2**[5] afforded the 7-methoxy derivative **5**. The reaction can be achieved with NCS or NBS (Table 1), although yields are higher when NCS is used.

A mechanism for the formation of these compounds is difficult to establish due to the different reactivity of NBS as a brominating agent, which involves free radical or electrophilic mechanisms, and an oxidation process.

The electrophilic substitution of pyrazino[2,3-*c*][1,2,6]thiadiazine should be an unfavourable method because of the strong π-electron deficiency of this nitrogen heterocycle. However, the electrophilic substitution of pyrazino[2,3-

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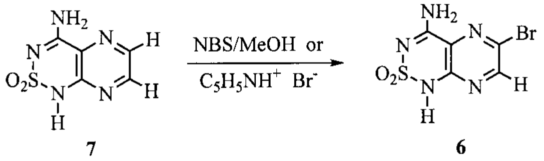
Table 1. Preparation of 7-methoxy and 7-ethoxy-6-phenyl-1*H*-pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxide

Entry	Compd.	Conditions	Reaction time (h)	Yield (%)[a]
1	3	NCS/MeOH/*t*BuOOH	12	78
2	3	NCS/MeOH	24	55
3	3	NBS/MeOH	24	40
4	4	NCS/EtOH/*t*BuOOH	72	69
5	4	NCS/EtOH	96	2
6	4	NCS/EtOH (darkness)	96	0

[a] All yields refer to pure isolated compounds.

c][1,2,6]thiadiazine is possible at position 6 and thus 6-bromopyrazino[2,3-*c*][1,2,6]thiadiazine **6** was prepared from the unsubstituted derivative **7**[6] by reaction with NBS or pyridinium bromide perbromide.(Scheme 2).



Scheme 2

In order to determine the most favourable position for a possible electrophilic attack on the pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxide, the HOMO (Highest Occupied Molecular Orbital) coefficients were calculated using a local density functional (DMol)[7] and RHF methods with the 6-31G* basis set.[8] In the case of compound **7**, the results obtained are in agreement with the formation of the 6-bromo derivative **6** by an electrophilic mechanism. Thus, the HOMO coefficients calculated for compound **7** showed larger values at C-6 (DMol 0.32; RHF/6-31G* 0.52) than at C-7 (DMol 0.15; RHF/6-31G* 0.31). In the case of the 6-phenyl derivative **1**, of the two carbons at the 6- or 7-positions C-6 has the highest HOMO coefficient (DMol 0.30; RHF/6-31G* 0.37) although the difference is smaller (C-7: DMol 0.20; RHF/6-31G* 0.28) than in compound **7**. Thus, it would be reasonable to assume that in the 6-phenyl derivative the electrophilic attack at position 7 is not favoured, and therefore the attack at this position as the initial step in the reaction does not seem probable.

In addition, the 7-methoxy derivative **3** is not formed via 7-chloro-6-phenylpyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxide when NCS is used, because the latter is not detected in the reaction mixture even though it is stable in hot methanol. This 7-chloro derivative has previously been obtained by a different procedure in our group.[9] In the alkoxylation of pyrazino[2,3-*c*][1,2,6]thiadiazines there is some evidence that the reaction may be mediated by the presence of free-radicals (Table 1). Thus, the reaction is initiated or accelerated by typical free-radical sources such as *tert*-butyl hydroperoxide when NCS is used (compare yields of entry 4 with 5) and the reaction of **1** with NCS and ethanol fails in the darkness (entry 6).

The synthesis of the alkoxy derivative substituted at the 7-position is in agreement with the fact that in free radical addition the main effect seems to be steric: when pteridines[10] or pyrazines[11] undergo homolytic radical substitution reactions with acyl radicals the substitution takes place at the unsubstituted position of the pyrazine ring.

The formation of 7-alkoxy derivatives does not therefore take place through a conventional mechanism. The formation of 7-alkoxy derivatives is not due either to the addition of alcohol to the position 7 or to substitution of the 7-bromo or 7-chloropyrazino[2,3-*c*][1,2,6]thiadiazine by alcohol, but is mediated by the presence of free radicals.

As can be seen in Scheme 1, this method is applicable also to pyrazino[2,3-*c*][1,2,6]thiadiazine bearing differently substituted phenyl groups at the 6-position. Different 7-methoxy and 7-ethoxy derivatives of 6-arylpyrazino[2,3-*c*]-[1,2,6]thiadiazines **8−10** were prepared using the corresponding derivative in methanol or ethanol with NCS and *tert*-butyl hydroperoxide (Scheme 1). The 7-methoxy-6-(4-nitrophenyl) derivative **8** was formed from the reaction of **11**[2] with NCS and methanol and the 7-ethoxy derivatives of the 6-(tolyl)- (**9**) and 6-(4-chlorophenyl)- (**10**) derivatives were obtained by reaction of compounds **12**[2] and **13**,[2] respectively, with ethanol and NCS.

In summary, we have described a novel and useful method for the preparation of 7-alkoxy derivatives of pyrazines fused to thiadiazines. The possible applications of this procedure to other heterocyclic compounds containing two or more nitrogens are under investigation.

Experimental Section

General: Melting points were determined with a Reichert-Jung Thermovar micro melting point apparatus and are uncorrected. ^{1}H (300 MHz) and ^{13}C NMR spectra (75 MHz) were recorded on a Varian XL-300 spectrometer and are reported in ppm on the δ scale. The signal of the solvent was used as reference. Elemental analyses were performed on a Heraeus CHN-O-Rapid analyzer.

4-Amino-7-methoxy-6-phenyl-1*H*-pyrazino[2,3-*c*][1,2,6]-thiadiazine 2,2-Dioxide (3): NCS (0.58 g, 4.36 mmol) and *tert*-butyl hydroperoxide (catalytic amount) were added to a suspension of **1** (1.00 g, 3.63 mmol) in methanol (60 mL). The reaction mixture was stirred at room temperature for 12 h, and then the solvent was evaporated to dryness and water was added to the residue. The precipitate was filtered and recrystallized from ethanol to give **3** (0.86 g, 78%), m.p. 290−292 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 4.06 (s, 3 H, CH_3), 7.46 (m, 3 H, Ph), 8.10 (m, 2 H, Ph), 8.26 (br. s, 1 H, NH_2), 8.33 (br. s, 1 H, NH_2), 12.45 (s, 1 H, NH) ppm. ^{13}C NMR (300 MHz, [D$_6$]DMSO): δ = 113.8 (C-4a), 135.9 (C-6), 147.4 (C-8a), 158.6 (C-4), 159.9 (C-7) ppm. $C_{12}H_{11}N_5O_3S$ (305.3): calcd. C 47.21, H 3.63, N 22.94, S 10.50; found C 47.25, H 3.66, N 22.84, S 10.19.

4-Amino-7-ethoxy-6-phenyl-1*H*-pyrazino[2,3-*c*][1,2,6]-thiadiazine 2,2-Dioxide (4): NCS (0.58 g, 4.36 mmol) and *tert*-butyl hydroperoxide (catalytic amount) were added to a suspension of **1** (1.00 g, 3.63 mmol) in ethanol (65 mL),. The reaction mixture was stirred at room temperature for 72 h, and then the solvent was evaporated to dryness and water was added to the residue. The precipitate was filtered and recrystallised from ethanol to give **4** (0.64 g, 69%). m.p. 260−262 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.39 (t, 3 H, CH_3), 4.48 (q, 2 H, CH_2), 7.46−7.37 (m, 3 H, Ph), 8.14−8.11 (m, 2 H, Ph), 8.29 (br. s, 1 H, NH_2), 8.39 (br. s, 1 H, NH_2), 12.09 (s, 1 H, NH) ppm. ^{13}C NMR (300 MHz, [D$_6$]DMSO): δ = 113.6 (C-4a), 135.6 (C-6), 147.2 (C-8a) 158.5 (C-4), 159.3 (C-7) ppm. $C_{13}H_{13}N_5O_3S$ (319.3): calcd. C 48.89, H 4.10, N 21.93, S 10.04; found C 48.59, H 4.01, N 21.74, S 9.78.

4-Amino-7-methoxy-1-methyl-6-phenylpyrazino[2,3-*c*][1,2,6]-thiadiazine 2,2-Dioxide (5): NCS (0.55 g, 4.15 mmol) and *tert*-butyl hydroperoxide (catalytic amount) were added to a suspension of **2** (1.00 g, 3.46 mmol) in methanol (70 mL). The reaction mixture was stirred at room temperature for 72 h, and then the solvent was evaporated to dryness and water was added to the residue. The precipitate was filtered and recrystallised from ethanol/water to give **5** (0.68 g, 62%). m.p. 208 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.45 (t, 3 H, CH_3), 4.11 (s, 3 H, CH_3), 7.44−8.16 (m, 5 H, Ph), 8.56 (br. s, 1 H, NH_2), 8.66 (br. s, 1 H, NH_2) ppm. ^{13}C NMR (300 MHz, [D$_6$]DMSO): δ = 114.6 (C-4a), 134.4 (C-6), 147.5 (C-8a) 158.4 (C-4), 159.5 (C-7) ppm. $C_{13}H_{13}N_5O_3S$ (319.3): calcd. C 48.89, H 4.10, N 21.93, S 10.04; found C 48.75, H 4.16 N 21.76, S 9.71.

4-Amino-6-bromo-1*H*-pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-Dioxide (6): NBS (1.08 g, 6.07 mmol) was added to a solution of **7** (1.00 g, 5.02 mmol) in methanol (10 mL). The reaction mixture was stirred at room temperature for 24 h, and then the solvent was evaporated to dryness and water was added to the residue. The precipitate was filtered and recrystallised from ethanol/water to give **6** (0.75 g, 54%), m.p. 265−267 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.59 (br. s, 1 H, NH_2), 8.71 (br. s, 1 H, NH_2), 8.78 (s, 1 H, CH) ppm. ^{13}C NMR (300 MHz, [D$_6$]DMSO): δ = 122.4 (C-4a), 129.6 (C-6), 149.3 (C-8a), 151.5 (C-7), 157.4 (C-4) ppm. $C_5H_4BrN_5O_2S$ (278.1): calcd. C 21.59, H 1.45, Br 28.73, N 25.18, S 11.53; found C 21.52, H 1.62, Br 29.00, N 24.91, S 11.24.

4-Amino-7-methoxy-6-(4-nitrophenyl)-1*H*-pyrazino[2,3-*c*]-[1,2,6]thiadiazine 2,2-Dioxide (8): This compound was prepared using the method described for **3**. Yield: 23% (EtOH/H_2O), m.p. 250−252 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 4.05 (s, 3 H, OCH_3), 8.27 (d, 2 H, Ar), 8.44 (d, 2 H, Ar), 8.45 (br. s, 1 H, NH_2), 8.46 (br. s, 1 H, NH_2) ppm. ^{13}C NMR (300 MHz, [D$_6$]DMSO): δ = 114.2 (C-4a), 132.8 (C-6), 148.0 (C-8a), 158.2 (C-4), 160.1 (C-7) ppm. $C_{12}H_{10}N_6O_3S$ (350.3): calcd. C 41.14, H 2.88, N 23.09, S 9.15; found C 41.33, H 2.64, N 24.01, S 8.99.

4-Amino-7-ethoxy-6-tolyl-1*H*-pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-Dioxide (9): This compound was prepared using the method described for **4**. Yield: 61% (EtOH), m.p. 258−259 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 1.39 (t, 3 H, OCH_2CH_3), 4.47 (q, 2 H, OCH_2CH_3), 7.50 (d, 2 H, Ar), 8.20 (d, 2 H, Ar), 8.35 (br. s, 1 H, NH_2), 8.38 (br. s, 1 H, NH_2), 12.16 (br. s, 1 H, NH) ppm. ^{13}C NMR (300 MHz, [D$_6$]DMSO): δ = 113.5 (C-4a), 135.7 (C-6), 147.0 (C-8a), 159.2 (C-7), 158.6 (C-4) ppm. $C_{14}H_{15}N_5O_3S$ (333.4): calcd. C 50.44, H 4.53, N 21.00, S 9.62; found C 50.15, H 4.29, N 21.29, S 9.65.

4-Amino-6-(4-chlorophenyl)-7-ethoxy-1*H*-pyrazino[2,3-*c*]-[1,2,6]thiadiazine 2,2-Dioxide (10): This compound was prepared using the method described for **4**. Yield: 52% (EtOH), m.p. 270−271 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.39 (t, 3 H, OCH_2CH_3), .2.35 (s, 3 H, CH_3), 4.47 (q, 2 H, OCH_2CH_3), 7.26 (d, 2 H, Ar), 8.04 (d, 2 H, Ar), 8.26 (br. s, 1 H, NH_2), 8.36 (br. s, 1 H, NH_2), 12.09 (br. s, 1 H, NH) ppm. ^{13}C NMR (300 MHz, [D$_6$]DMSO): δ = 113.7 (C-4a), 134.2 (C-6), 147.5 (C-8a), 158.5 (C-4), 159.3 (C-7) ppm. $C_{12}H_{12}ClN_5O_3S$ (353.8): calcd. C 44.14, H 3.42, N 19.72, S 10.02, Cl 11.80; found C 44.31, H 3.52, N 20.02, S 10.32, Cl 11.44.

Calculations: The HOMO coefficients were calculated with a local density functional (DMol) and RHF ab initio methods from the optimized geometries. A double zeta numerical basis set with polarisation functions in all the atoms, and the Janak−Moruzzi−Williams (JMW) exchange correlation potential were used with the DMol program. The ab inito calculations were carried out with the Gaussian-98 program at the RHF level with the 6-31G* basis set.

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