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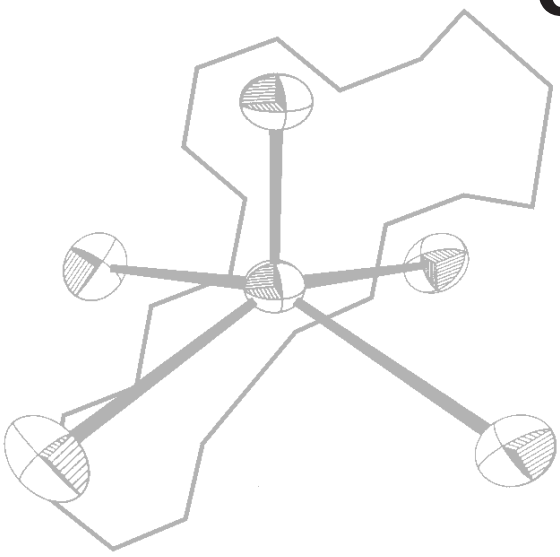

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Sulfonamide Analogues of Creatinine. The Synthesis of 3-Amino-4,5-dihydro-1,2,4-thiadiazole 1,1-Dioxides from Base-Induced Cyclization Reactions

Fares A. Fares, Damon D. Ridley and Ping Yin

School of Chemistry, University of Sydney, N.S.W. 2006.

We report the preparation of 3-amino-4,5-dihydro-1,2,4-thiadiazole 1,1-dioxide and of its 4-methyl derivative which are of interest as potential analogues of creatinine. The thiadiazoles are obtained from chloromethylsulfonylation of *S*-benzylisothiourea, followed by cyclization of the chloromethanesulfonamide under basic conditions in the presence of 2-(t-butoxycarbonyloxyimino)-2-phenylacetonitrile or of methyl iodide.

Creatinine amidohydrolyase catalyses the hydrolysis of the amide bond in creatinine (1) to give creatine.[1] In order to investigate potential inhibitors of this enzyme, we sought 3-amino-4-methyl-4,5-dihydro-1,2,4-thiadiazole 1,1-dioxide (2) because of its structural similarity to the possible transition state in the enzymic hydrolysis of creatinine.

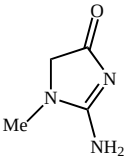
Lawson and Tinkler[2] first reported the synthesis of some 4-substituted 3-phenyl-4,5-dihydro-1,2,4-thiadiazole 1,1-dioxide derivatives (3a–d) from the alkali-induced cyclization reaction of the iodomethanesulfonamide (4a) in the presence of an acyl chloride. In a later paper, Lawson and Tinkler[3] reported the synthesis of related 4-substituted 3-phenyl-1,2,4-thiadiazole 1,1-dioxide derivatives by base-induced cyclization of iodomethanesulfonamide derivatives (4b), which were prepared from reaction of the imino chloride (5) with the corresponding amine.

In 1974, Etienne *et al.*[4] reported the synthesis of 3-thio- and 3-oxy-1,2,4-thiadiazole 1,1-dioxides (6) from the base-induced reaction of the amidines (7a,b) in the presence of carbamoyl chlorides as acylating agents. These 3-thio and 3-oxy derivatives were easily converted into 3-amino or 3-chloro derivatives, and the 3-chloro derivative could be further functionalized. However, they reported that the hydrolysis of the carbamate group under various acidic or basic conditions failed.

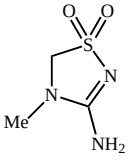
In order to prepare the sulfonamide (2), we investigated two routes both starting from the chloro sulfonamide (7b). We found that the choice of cyclization conditions was crucial, but under appropriate conditions both the parent substance and the *N*-methyl derivative (2) could be obtained in satisfactory yields.

Results and Discussion

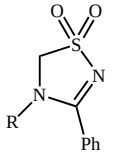
In a modification of the method of El-Hewehi,[5] 1,3,5-trithian was converted into chloromethanesulfonyl chloride which on treatment with *S*-benzylisothiourea afforded the chloromethanesulfonamide (7b). Attempted direct cyclizations of (7b) with sodium hydroxide, or sodium hydrogen carbonate in aqueous solution, or with sodium hydride in tetrahydrofuran were unsuccessful since complex mixtures of products resulted. However, when the cyclization of the chloro sulfonamide (7b) with 2 mol. equiv. of sodium hydroxide in the presence of 2-(t-butoxycarbonyloxyimino)-2-phenylacetonitrile was closely monitored by thin-layer chromatography, and when the reaction was stopped when most of the starting material had been consumed,



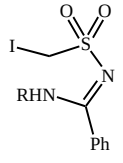
(1)



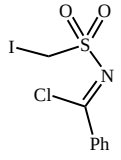
(2)



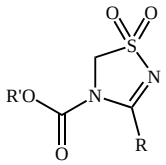
(3a) R = R'OCO
(3b) R = PhCO
(3c) R = $PhSO_2$
(3d) R = $MeSO_2$



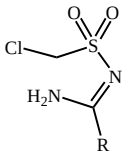
(4a) R = H
(4b) R = alkyl, aryl



(5)



(6)
R = MeS, $PhCH_2S$, PhO, EtO or MeO
R' = Me, Et, $PhCH_2$ or Ph



(7a) R = MeS, MeO, EtO, PhO
(7b) R = $PhCH_2S$

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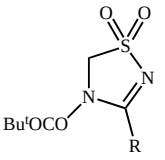
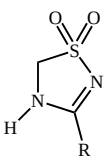
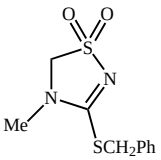
the butoxycarbonyl derivative (8a) was obtained in 61% yield. Attempts to improve the yield of (8a) by using longer reaction times, or using sodium hydrogen carbonate, or using more than 2 mol. equiv. of sodium hydroxide were unsuccessful since substantial amounts of decomposition products resulted. Further, attempted cyclization of the chloro sulfonamide (7b) with sodium hydride in tetrahydrofuran in the presence of 2-(t-butoxycarbonyloxyimino)-2-phenylacetonitrile was similarly unsuccessful.



(8a) R = SCH_2Ph
(8b) R = NH_2



(9a) R = SCH_2Ph
(9b) R = NH_2



(10)

Removal of the t-butoxycarbonyl group occurred readily when the derivative (8a) was treated with trifluoroacetic acid, and gave the deprotected thiadiazole (9a). However, this product was very insoluble in nearly all organic solvents and because of this further transformations of (9a) proved impossible. On the other hand, the t-butoxycarbonyl derivative (8a) was easily converted into the 3-amino derivative (8b) by reaction with ammonia in chloroform, and this product, on treatment with trifluoroacetic acid gave one of the required creatinine analogues (9b).

When methyl iodide was used instead of 2-(t-butoxycarbonyloxyimino)-2-phenylacetonitrile in the carefully controlled cyclization of the chloromethanesulfonamide (7b), the *N*-methyl derivative (10) was obtained in satisfactory yield, and subsequent reaction of the product with liquid ammonia gave the desired *N*-methyl analogue (2).

Attempts to cyclize the chloro sulfonamide (7b) without added 2-(t-butoxycarbonyloxyimino)-2-phenylacetonitrile or methyl iodide in the presence of 2 mol. equiv. of sodium hydroxide were unsuccessful. Complex mixtures only were obtained. It is possible that the initial cyclization occurred, but, in separate experiments, we noted that derivatives of the type (9a) which did not have substituents at the 4-position were very rapidly decomposed under basic conditions, so the failure to effect cyclization without added acylating or alkylating reagents may simply be due to instability of the initial product. It is possible that under the reaction conditions the 4-unsubstituted derivatives are ionized and that their instability is due to decomposition of the anion.

Experimental

Chloromethanesulfonyl Chloride

To a stirred suspension of 1,3,5-trithian (13·8 g, 0·1 mol) in 10 M hydrochloric acid (500 ml) at 10–15° was added, in portions, potassium chlorate (40·9 g, 0·3 mol). After addition was complete, the mixture was stirred for 5 h at room temperature during which time a yellow oil separated. The reaction mixture was poured into iced water, and was extracted with ether. The ether layer was washed with a 5% solution of sodium hydrogen carbonate, then with water, and finally was dried over magnesium sulfate. Removal of the solvent under reduced pressure gave a yellow oil which upon distillation afforded chloromethanesulfonyl chloride (18·5 g, 62%) as a colourless oil, b.p. 70°/15 mm (lit.[5] 70°/15 mm). ^{1}H n.m.r. ($CDCl_3$) δ 5·00, s, CH_2.

S-*Benzyl*-N-*chloromethylsulfonylisothiourea (7b)*

A mixture of chloromethanesulfonyl chloride (7·9 g, 53 mmol), *S*-benzylisothiouronium hydrochloride (10·7 g, 53 mmol) and anhydrous sodium carbonate (28·0 g) in anhydrous ethyl acetate (200 ml) was stirred under nitrogen for 2 days at room temperature. The reaction mixture was filtered and the solvent was removed under reduced pressure. The yellow oil was purified by flash chromatography (eluent: hexane/ethyl acetate (1:2)) and gave the chloromethanesulfonamide (7b) (10·2 g, 69%) as a colourless oil which slowly crystallized, m.p. 47–48° (lit.[4] 48°). ^{1}H n.m.r. (200 MHz, $(CD_3)_2SO$) δ 4·23, s, 2H, CH_2Cl; 4·73, s, 2H, CH_2S; 7·30–7·35, m, 5H, ArH; 8·3–8·7, br s, 2H, NH_2.

3-Benzylthio-4-t-butoxycarbonyl-4,5-dihydro-1,2,4-thiadiazole 1,1-Dioxide (8a)

To a stirred solution of the chloro sulfonamide (7b) (7·3 g, 26 mmol) and 2-(t-butoxycarbonyloxyimino)-2-phenylacetonitrile (7·03 g, 28 mmol) in acetone (250 ml) under nitrogen at room temperature was added dropwise a solution of 10 M sodium hydroxide (5·2 ml, 52 mmol) over a period of 1 h, and the mixture was stirred for another 1 h. After removal of the sodium chloride precipitate by filtration, the solvent was evaporated and the solid residue was dissolved in ethyl acetate. The solution was washed with 1 M sodium hydroxide, then with brine, and finally was dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the solid residue was recrystallized from methanol to give the *title 1,1-dioxide* (8a) (5·5 g, 61%) as colourless crystalline needles, m.p. 127–128° (Found: C, 48·9; H, 5·4; N, 8·3. $C_{14}H_{18}N_2O_4S_2$ requires C, 49·1; H, 5·3; N, 8·2%). ^{1}H n.m.r. (400 MHz, $CDCl_3$) δ 1·53, s, 9H, Bu^t; 4·32, s, 2H, CH_2S; 4·66, s, 2H, CH_2SO_2; 7·29–7·39, m, 5H, ArH. ^{13}C n.m.r. (400 MHz, $CDCl_3$) δ 28·5, Me; 39·1, CH_2S; 62·6, CH_2SO_2; 87·7, $(CH_3)_3\mathbf{C}$; 128·6, 129·4, 130·1, 134·9, Ar; 148·5, C=O; 168·8, C=N. Mass spectrum *m/z* 342 (M, 13%), 286 (24), 57 (100), 91 (81).

3-Benzylthio-4,5-dihydro-1,2,4-thiadiazole 1,1-Dioxide (9a)

A solution of the t-butoxycarbonyl derivative (8a) (150 mg, 0·438 mmol) in trifluoroacetic acid (10 ml) was stirred at room temperature for 30 min. The trifluoroacetic acid was removed under reduced pressure and the white solid was dissolved in ethyl acetate. The ethyl acetate solution was washed with saturated sodium hydrogen carbonate solution, then with brine and finally was dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure afforded a white powder that was purified by recrystallization from methanol to give the *4-unsubstituted 1,1-dioxide* (9a) (88 mg, 83%) as colourless needles, m.p. 112–113° (Found: C, 44·6; H, 4·6; N, 11·4. $C_9H_{10}N_2O_2S_2$ requires C, 44·6; H, 4·2; N, 11·6%). ^{1}H n.m.r. (400 MHz, $(CD_3)_2SO$) δ 4·36, s, 2H, CH_2S: 4·52, s, 2H, CH_2SO_2; 7·28–7·43, m, 5H, ArH; 10·05, br s, 1H, NH. ^{13}C n.m.r. (400 MHz, $(CD_3)_2SO$) 34·9, CH_2S; 60·6, CH_2SO_2, 127·6, 128·6, 129·0, 136·5, Ar; 169·2, C=N.

3-Amino-4-t-butoxycarbonyl-4,5-dihydro-1,2,4-thiadiazole 1,1-Dioxide (8b)

Ammonia gas was bubbled into a vigorously stirred solution of the benzylthio derivative (8a) (300 mg, 0·87 mmol) in chloroform (15 ml) for 2 h at room temperature. The solvent was evaporated and the white solid residue was recrystallized from methanol to yield the *title 1,1-dioxide* (8b) (120 mg, 58%) as a colourless crystalline solid, m.p. 120° (dec.) (Found: C, 35·4; H, 5·8; N, 18·2. $C_7H_{13}N_3O_4S$ requires C, 35·7; H, 5·6; N, 17·9%). ^{1}H n.m.r. (400 MHz, $CDCl_3$) δ 1·55, s, 9H, Bu^t; 4·65, s, 2H, CH_2; 6·59, br s, 1H, NH; 8·07, br s, 1H, NH. ^{13}C n.m.r. (400 MHz, $CDCl_3$) δ 28·5, Me; 62·1, CH_2SO_2; 87·6, $(CH_3)_3\mathbf{C}$; 150·7, C=O; 155·8, C=N. Mass spectrum *m/z* 235 (M, 42%), 220 (17), 57 (100).

3-Amino-4,5-dihydro-1,2,4-thiadiazole 1,1-Dioxide (9b)

The t-butoxycarbonyl derivative (8b) (100 mg, 0·425 mmol) was dissolved in trifluoroacetic acid (5 ml), and the solution was stirred at room temperature for 30 min. The solvent was removed under reduced pressure and the white solid was recrystallized from methanol to give the *4-unsubstituted 1,1-dioxide* (9b) (35 mg, 61%) as colourless crystals, m.p. 114–117° (Found: C, 17·4; H, 4·1; N, 31·0. $C_2H_5N_3O_2S$ requires C, 17·8; H, 3·7; N, 31·1%). ^{1}H n.m.r. (400 MHz, $(CD_3)_2SO$) δ 4·17, s, 2H, CH_2; 7·02, br s, 2H, NH_2; 7·70, br s, 1H, NH. ^{13}C n.m.r. (400 MHz, $(CD_3)_2SO$) δ 60·8, CH_2; 160·0, C=N.

3-Benzylthio-4-methyl-4,5-dihydro-1,2,4-thiadiazole 1,1-Dioxide (10)

Methyl iodide (279 mg, 1·97 mmol) was added dropwise to a stirred solution of the chloromethanesulfonamide (7b) (363 mg, 1·31 mmol) in acetone (15 ml). The mixture was stirred for 15 min; then a solution of 10 M sodium hydroxide (0·28 ml) was added dropwise over a period of 30 min under nitrogen at room temperature and the solution was stirred for another 2 h. The solvent was removed and the solid residue was dissolved in ethyl acetate. The solution was washed with brine, and then was dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the solid residue was recrystallized from methanol to give the *title 1,1-dioxide* (10) (224 mg, 67%) as colourless crystals, m.p. 128–129° (Found: C, 47·1; H, 5·0; N, 11·1. $C_{10}H_{12}N_2O_2S_2$ requires C, 46·9; H, 4·7; N, 10·9%). ^{1}H n.m.r. (400 MHz, $CDCl_3$) δ 3·11, s, 3H, CH_3; 4·36, s, 2H, CH_2S; 4·41, s, 2H, CH_2SO_2; 7·35–7·37, m, 5H, ArH. ^{13}C n.m.r. (400 MHz, $CDCl_3$) δ 33·8, CH_2S; 37·8, Me; 66·0, CH_2SO_2, 128·2, 128·8, 129·2, 134·7, Ar; 170·6, C=N. Mass spectrum *m/z* 256 (M, 47·5%), 192 (9), 122 (12), 91 (100).

3-Amino-4-methyl-4,5-dihydro-1,2,4-thiadiazole 1,1-Dioxide (2)

The benzylthio derivative (10) (65 mg, 0·25 mmol) was stirred in liquid ammonia for 8 h. The ammonia was evaporated, and chloroform (10 ml) was added to the solid residue. The *3-amino 1,1-dioxide* (2) (20 mg, 53%) was collected by filtration, m.p. 182–184° (Found: C, 24·0; H, 5·0; N, 27·6. $C_3H_7N_3O_2S$ requires C, 24·2; H 4·7; N, 28·2%). ^{1}H n.m.r. (200 MHz, $(CD_3)_2SO$) δ 2·93, s, 3H, Me; 4·29, s, 2H, CH_2; 7·27, br s, 2H, NH_2. ^{13}C n.m.r. (200 MHz, $(CD_3)_2SO$) δ 31·9, Me; 66·0, CH_2; 159·6, C=N. Mass spectrum *m/z* 149 (M, 19%), 85 (19), 43 (100), 42 (90).

Acknowledgment

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