4-Alkyl(aryl)-3-amino-1,2,5-thiadiazole 1,1-Dioxides

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Two methods have been developed for the synthesis of 3-amino-1,2,5-thiadiazole 1,1-dioxides; one leads to 4-alkyl derivatives, the other to 4-aryl analogs.

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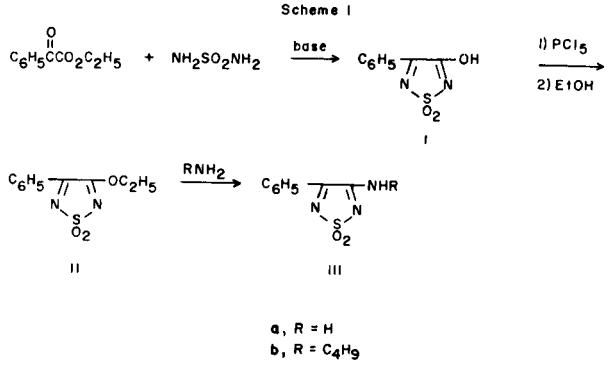
A recent report from these laboratories described the synthesis of a series of 3,4-diamino 1,2,5-thiadiazole 1-oxides with potent histamine H_2-receptor antagonist properties (1). During the course of this work, it became apparent that the corresponding monoaminothiadiazole oxides also represented a potentially interesting structural class. Although a variety of 3,4-disubstituted 1,2,5-thiadiazole 1,1-dioxides have been described, 4-alkyl-3-amino and 4-aryl-3-amino derivatives have not been reported. Since published methodologies for preparation of 1,2,5-thiadiazole 1,1-dioxides were not applicable to the syntheses of 4-alkyl or aryl-3-amino-1,2,5-thiadiazole 1,1-dioxides, two novel synthetic routes were developed for these substituted derivatives.

Synthesis of 3,4-dialkyl, 3,4-diaryl and 3-alkyl-4-aryl-1,2,5-thiadiazole 1,1-dioxides from 1,2-diketones and sulfamide have been reported (2,3). In addition, Carmack and coworkers described the synthesis of 3,4-dihydroxy-1,2,5-thiadiazole 1,1-dioxide disodio salt by the condensation of sulfamide with ethyl oxalate and the conversion of this salt into 3,4-diamino derivatives *via* either dihalo or dialkoxy intermediates (4). A combination of these syntheses in which the diketone and ethyl oxalate were replaced with an α-ketoester appeared to be a reasonable approach to 4-alkyl or aryl-3-amino derivatives. This procedure proved successful for the preparation of the aryl analogs IIIa and IIIb (Scheme I).

Scheme I

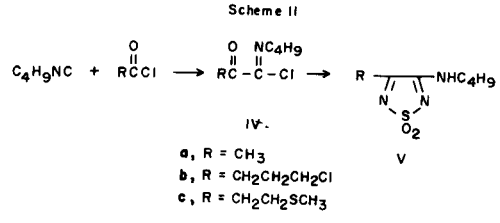


Treatment of ethyl phenylglyoxylate with sulfamide and sodium ethoxide gave a sodio salt which yielded 3-hydroxy-4-phenyl-1,2,5-thiadiazole 1,1-dioxide (I) after acidification. Refluxing I with phosphorus pentachloride in methylene chloride followed by a quench with ethanol produced 3-ethoxy-4-phenyl-1,2,5-thiadiazole 1,1-dioxide (II) in good yield. Displacement of the ethoxy group of II with ammonia or primary amines proved facile and provided the corresponding 3-amino-4-phenyl-1,2,5-thiadiazole 1,1-dioxides (III).

Attempts to utilize an alkyl α-ketoalkanoate for the preparation of 3-amino-4-alkyl analogs were not successful. Condensation of sulfamide with ethyl pyruvate in the presence of sodium ethoxide, triethylamine, or anhydrous hydrogen chloride failed to yield 3-hydroxy-4-methyl-1,2,5-thiadiazole 1,1-dioxide.

Substitution of a more reactive species, namely an α-ketoimidoyl chloride, for the α-keto ester held the promise of, in principle, leading to the direct introduction of a 3-amino substituent. *N*-Butylpyruvimidoyl chloride (IVa) (5) obtained from acetyl chloride and butylisonitrile reacted with sulfamide to yield 3-butylamino-4-methyl-1,2,5-thiadiazole 1,1-dioxide (Va). Substituted alkyl derivatives Vb and Vc were similarly prepared (Scheme II).

Scheme II



The physicochemical characteristics of these compounds were influenced by alkyl substitution of the amino function and aryl substitution of the thiadiazole 1,1-dioxide nucleus. The p*K*a's (proton lost) of IIIa, IIIb and Va in 30% ethanol were 8.75, 9.82 and 9.30, respectively. Thus substitution of the 3-amino group of IIIa with an *n*-butyl moiety lowered the NH acidity approximately tenfold while the effect of replacing the 4-phenyl group of IIIb with a 4-alkyl substituent (Va) was to increase the acidity of the 3-amino group about threefold.

In summary, two methods have been developed for the facile synthesis of 3-amino-1,2,5-thiadiazole 1,1-dioxides. One of these is applicable to 4-aryl derivatives and involves introduction of the amine functionality by displace-

ment of an ethoxy group in the final step. The other procedure leads directly to 4-alkyl-3-substituted-amino derivatives and is based on the reaction of α-ketoimidoyl chlorides with sulfamide.

EXPERIMENTAL

The ^{1}H nmr spectra were recorded on either Varian T-60 or EM-390 spectrometers. All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Yields were not optimized.

3-Hydroxy-4-phenyl-1,2,5-thiadiazole 1,1-Dioxide (I).

Sulfamide (4.8 g, 50 mmoles) in ethanol (90 ml) was added slowly with stirring under nitrogen to a solution of sodium (1.15 g, 50 mmoles) dissolved in ethanol (35 ml). The suspension was stirred for 15 minutes at room temperature and then ethyl phenylglyoxylate (8.9 g, 50 mmoles) in ethanol (15 ml) was added. After stirring 15 minutes, the mixture was refluxed overnight and concentrated under vacuum. The residue was suspended in diethyl ether, filtered and the collected solid dissolved in water (25 ml). Acidification with hydrochloric acid precipitated the product which was collected by filtration, washed with water and recrystallized from a mixture of acetonitrile (12 ml) and toluene (8 ml) to obtain 4.2 g (40%) mp 202-204°; nmr (DMSO-d_6): δ 7.29-7.89 (m, 3H), 8.19-8.49 (m, 2H).

Anal. Calcd. for $C_8H_6N_2O_3S$: C, 45.71; H, 2.88; N, 13.33. Found: C, 45.71; H, 2.75; N, 13.42.

3-Ethoxy-4-phenyl-1,2,5-thiadiazole 1,1-Dioxide (II).

Compound I (1.37 g, 6.5 mmoles) was refluxed with phosphorus pentachloride (3 g, 14.4 mmoles) in methylene chloride (50 ml) for 24 hours. The cooled reaction mixture was added with stirring over 15 minutes to ethanol (50 ml) and then refluxed 1 hour. After concentration under vacuum, the residual solid was suspended in diethyl ether, filtered and recrystallized from ethanol to obtain 1.2 g (78%) of II, mp 204-206°; nmr (DMSO-d_6): δ 1.53 (t, 3H, J = 7 Hz), 4.71 (q, 2H, J = 7 Hz), 7.34-7.83 (m, 3H), 8.07-8.32 (m, 2H).

Anal. Calcd. for $C_{10}H_{10}N_2O_3S$: C, 50.41; H, 4.23; N, 11.76. Found: C, 50.49; H, 4.34; N, 11.82.

3-Amino-4-phenyl-1,2,5-thiadiazole 1,1-Dioxide (IIIa).

Ammonia in ethanol (5 ml, 1.4*N*) was added to a suspension of II (1.19 g, 5.0 mmoles) in ethanol (25 ml). The mixture contained in a closed flask was immersed in a sonic bath until solution was effected and then concentrated under vacuum after standing ½ hour. The residue was refluxed in *n*-butyl chloride (25 ml), the supernatant decanted, and the solid washed with methylene chloride. After recrystallization from ethyl acetate, 0.72 g (73%) of IIIa was obtained, mp 213° dec; nmr (DMSO-d_6) δ 7.73 (m, 5H), 8.28 (broad s, 1H), 9.63 (broad s, 1H).

Anal. Calcd. for $C_8H_7N_3O_2S$: C, 45.92; H, 3.37; N, 20.08. Found: C, 46.00; H, 3.46; N, 20.13.

3-Butylamino-4-phenyl-1,2,5-thiadiazole 1,1-Dioxide Monohydrate (IIIb).

Compound IIIb was prepared in a manner similar to IIIa from II and butylamine, mp 100.5-102.5° after recrystallization from a mixture of 2-propanol, diethyl ether, hexane (1:4:6); nmr (DMSO-d_6): δ 0.87 (broad t, 3H, J ~ 7 Hz), 1.11-1.74 (m, 4H), 2.79 (t, 2H, J ~ 7 Hz), 7.40-7.82 (m, 3H), 8.35-8.54 (m, 2H).

Anal. Calcd. for $C_{12}H_{15}N_3O_2S \cdot H_2O$: C, 50.86; H, 6.05; N, 14.38. Found: C, 51.23; H, 6.24; N, 14.73.

3-Butylamino-4-methyl-1,2,5-thiadiazole 1,1-Dioxide (Va).

N-Butylpyruvimidoyl chloride (IVa) (5) (15.24 g, 94.3 mmoles) in dry tetrahydrofuran (10 ml) was added with stirring over 2 minutes to sulfamide (9.05 g, 94.3 mmoles) suspended in tetrahydrofuran (70 ml) cooled in an ice bath. After stirring with cooling for 20 minutes and then at room temperature overnight, the reaction mixture was concentrated under vacuum without heat. The residue was suspended in methylene chloride, reconcentrated, and then stirred in diethyl ether and filtered. The collected solid was suspended in water (20 ml), stirred for 5 minutes, filtered, washed with small portions of water and dried in vacuum to obtain 7.0 g (37%) of Va, mp 176-178° dec. Recrystallization from 2-propanol afforded pure product, mp 182-184° dec; nmr (d-THF): δ 0.94 (broad t, 3H, J ~ 7 Hz), 1.15-1.89 (m, 4H), 2.40 (s, 3H), 3.42 (broad q, 2H, J ~ 6 Hz).

Anal. Calcd. for $C_7H_{13}N_3O_2S$: C, 41.36; H, 6.45; N, 20.67. Found: C, 41.35, H, 6.70; N, 20.69.

N-Butyl-5-chloro-2-oxopentanoic Acid Iminochloride (IVb).

Butylisonitrile (4.96 g, 59.7 mmoles) was added dropwise with stirring to redistilled 4-chlorobutanoyl chloride (8.53 g, 60.5 mmoles) at 17-20° over 15 minutes. The reaction temperature was allowed to rise to 28° over ½ hour, maintained at 28° for 20 minutes and then raised to 50° for 10 minutes. The structure of the product oil was confirmed by nmr and, because of its thermal instability, used without purification for synthesis of Vb; nmr (deuteriochloroform): δ 0.97 (broad t, 3H, J ~ 6 Hz), 1.17-1.96 (m, 4H), 2.11 (quintet, 2H, J ~ 6 Hz), 3.10 (t, 2H, J ~ 7 Hz), 3.60 (t, 2H, J ~ 7 Hz), 3.70 (t, 2H, J ~ 6 Hz).

N-Butyl-4-methylthio-2-oxobutanoic Acid Iminochloride (IVc).

Compound IVc was prepared from 3-methylthiopropionyl chloride (6) in a manner similar to IVb and used without purification in the synthesis of Vc; nmr (deuteriochloroform): δ 0.96 (broad t, 3H, J ~ 6 Hz), 1.10-1.96 (m, 4H), 2.11 (s, 3H), 3.67 (t, 3H, J ~ 6.5 Hz), 2.6-2.93 (m, 2H), 3.06-3.67 (m, 2H).

3-Butylamino-4-(3-chloropropyl)-1,2,5-thiadiazole 1,1-Dioxide (Vb).

Compound Vb, mp 251-152° dec, was prepared from IVb in a manner similar to Va in 36% yield based on the butylisonitrile used in preparation of IVb and recrystallized from 2-propanol; nmr (DMSO-d_6): δ 0.90 (broad t, 3H, J ~ 6.5 Hz), 1.10-1.80 (m, 4H), 2.13 (quintet, 2H, J ~ 6.5 Hz), 3.00 (t, 2H, J ~ 7 Hz), 3.33 (broad q, 2H, J ~ 7 Hz), 3.70 (t, 2H, J ~ 6 Hz).

Anal. Calcd. for $C_9H_{16}ClN_3O_2S$: C, 40.67; H, 6.08; N, 15.81. Found: C, 40.82; H, 6.29; N, 15.97.

3-Butylamino-4-(2-methylthioethyl)-1,2,5-thiadiazole 1,1-Dioxide (Vc).

Compound Vc was prepared from IVc in a manner similar to Va and obtained in 29% yield after recrystallization from 2-propanol, mp 207-208 dec; nmr (DMSO-d_6): δ 0.90 (broad t, 3H, J ~ 5 Hz), 1.03-1.87 (m, 4H), 2.08 (s, 3H), 2.60-2.95 (m, 2H), 2.95-3.30 (m, 2H), 3.27 (sharp m, 2H).

Anal. Calcd. for $C_9H_{17}N_3O_2S_2$: C, 41.04; H, 6.51; N, 15.95. Found: C, 41.30; H, 6.63; N, 15.89.

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