Synthesis of 1,3,4-Thiadiazol-2-ylacetic Acid Derivatives

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1,3,4-Thiadiazol-2-ylacetic acids **4** were prepared by lithiation of 2-methyl-1,3,4-thiadiazoles **1**, followed by treatment with carbon dioxide. Diethyl 1,3,4-thiadiazol-2-ylmalonates **6** were prepared by nucleophilic displacement reaction of the corresponding bromides **5** with diethyl malonate. Introduction of the amino group at the α-position of **4** or **6** was carried out *via* oximation or bromination to give the amino ester **9** or **4**. Attempts to prepare DL-α-amino-1,3,4-thiadiazol-2-ylacetic acids from **9** or **4** were unsuccessful because the amino acids were decarboxylated too rapidly to be isolated in the free form.

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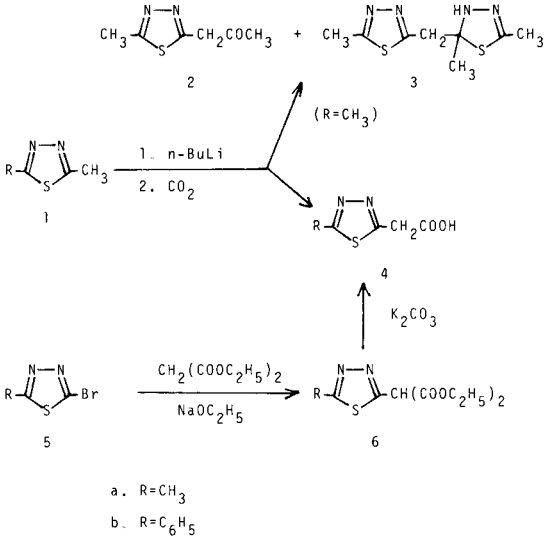
Our previous publication has described that 6-(DL-α-amino-4-thiazolylacetamido)penicillanic acids were a new class of highly active antibiotics (1). The finding prompted us to examine the synthesis of the closely related 1,3,4-thiadiazole derivatives. There are a few reports on the synthesis of 1,3,4-thiadiazol-2-ylacetic acids (2,3). In this paper, we wish to report the synthesis of 1,3,4-thiadiazol-2-ylacetic acids and the malonic acid derivatives. Moreover, an attempted synthesis and the remarkably easy decarboxylation of DL-α-amino-1,3,4-thiadiazol-2-ylacetic acids are also described.

It has been reported that 2-methyl-1,3,4-thiadiazol-5-ylacetic acid (**4a**) was obtained in 80% yield by lithiation of 2,5-dimethyl-1,3,4-thiadiazole (**1a**), followed by treatment with carbon dioxide (2). When this reaction was repeated according to the published procedure, no formation of **4a** was observed and the dimerization products, **2** and **3**, were isolated in 9% and 13% yields, respectively, from the complex reaction mixture (Scheme 1). Therefore, this reaction was carried out under the diluted conditions to produce the desired **4a** in 31% yield. Similarly, 2-phenyl-5-methyl-1,3,4-thiadiazole (**1b**) gave **4b** in 72% yield.

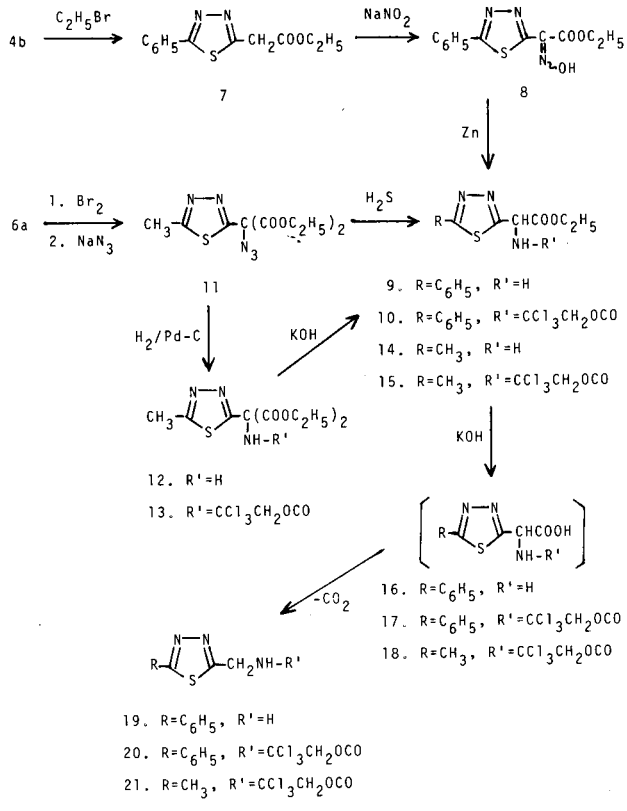
Scheme 1



Alternative synthesis of **4** involves the nucleophilic displacement of the bromide **5** with ethyl malonate. The bromides **5a** and **5b** were prepared by Sandmeyer reaction of the corresponding 2-amino-1,3,4-thiadiazoles. Reaction of **5a** and **5b** with ethyl malonate in the presence of sodium ethoxide in ethanol gave **6a** and **6b** in 50% and 44% yields, respectively. Hydrolysis of **6b** with potassium carbonate in boiling aqueous ethanol afforded the acid **4b** in 89% yield. However, similar treatment of **6a** produced the decarboxylated product **1a**.

Next, the synthesis of DL-α-amino-1,3,4-thiadiazol-2-ylacetic acids was examined (Scheme 2). The acid **4b** was converted into the ethyl ester **7** by treatment with ethyl

Scheme 2



bromide and sodum carbonate in DMF. Oximation of **7** proceeded smoothly with sodium nitrite in acetic acid to give **8** in 78% yield. Reduction of the oxime **8** with activated zinc produced the amino ester **9**, which was converted into the *N*-2,2,2-trichloroethoxycarbonyl derivative **10** (94% overall yield).

An alternative route from **6** was also developed. Bromination of **6a**, following treatment with sodium azide, gave the azide **11**. Catalytic reduction of **11** with palladium on carbon afforded the amine **12**, which was very unstable and immediately converted into the *N*-2,2,2-trichloroethoxycarbonyl derivative **13** (56% overall yield). Hydrolysis of **13** with an equimolecular amount of potassium hydroxide in aqueous acetone gave **15**. On the other hand, reduction of **11** with hydrogen sulfide was attended by the elimination of one of the ethoxycarbonyl groups to afford directly the amino ester **14**, which was converted into **15** (30% overall yield).

Hydrolysis of **10** or **15** with aqueous potassium hydroxide was however accompanied by decarboxylation to give **20** or **21**. In an effort to isolate the free amino acid **16**, the amino ester **9** was hydrolyzed with potassium hydroxide in methanol to yield the potassium salt. Careful neutralization of the potassium salt with hydrochloric acid at 0° also effected simultaneous evolution of gaseous carbon dioxide to yield the amine **19**.

We have previously observed the remarkably easy decarboxylation of DL-α-amino-2-thiazolylacetic acids (4). The present case also indicates that the substitution of the amino group at the α-postion of 1,3,4-thiadiazol-2-ylacetic acids makes the decarboxylation much easier.

EXPERIMENTAL

Melting points (capillary) were uncorrected. The ir spectra were recorded on a JASCO IRA-1 spectrometer. The ^{1}H nmr spectra were determined with TMS as an internal standard on a Hitachi R-24 or Hitachi R-20 spectrometer, chemical shifts being given in ppm downfield from TMS. The uv spectra were measured with a Hitachi 124 spectrometer. Elemental analyses were performed in the material analysis center of this institute. Columns of chromatography were packed with Wakogel C-200.

2-Methyl-1,3,4-thiadiazol-5-ylacetic Acid (**4a**).

Preparation of this compound was tried according to the procedure reported (2): a solution of **1a** (3.42 g, 30 mmoles) in anhydrous tetrahydrofuran (50 ml) was cooled at -70° and a solution of *n*-butyllithium in hexane (30 mmoles) was added with stirring at such a rate that the temperature was maintained below -60°. After 30 minutes at -70°, the mixture was poured through a glass tube onto fine powder of Dry-Ice and the mixture was brought gradually to room temperature. The solvent was removed *in vacuo* and the residue was dissolved in water. The solution was washed with ether, acidified with hydrochloric acid, and extracted with ethyl acetate (30 ml × 3). The extracts were dried (magnesium sulfate) and evaporated *in vacuo*. The residue was chromatographed on silica gel to give **2** (200 mg, 9%) and **3** (450 mg, 13%). The physical properties of **2** are: mp 76-80°; ir (nujol): 1720 cm^{-1}; nmr (deuteriochloroform): δ 2.31 (s, 3H), 2.76 (s, 3H), and 4.27 (s, 2H).

Anal. Calcd. for $C_6H_8N_2OS$: C, 46.13; H, 5.17; N, 17.93; S, 20.52. Found: C, 45.96; H, 5.06; N, 18.25; S, 20.28.

The physical properties of **3** are: mp 108-109°; ir (nujol): 3170 cm^{-1}; nmr (deuteriochloroform): δ 1.74 (s, 3H), 2.13 (s, 3H), 2.75 (s, 3H), 3.58 (ABq, J_{AB} = 14 Hz, δ_{AB} = 17 Hz, 2H), and 5.62 (m, 1H); uv (ethanol): nm 252 sh (3.22); ms: m/e 228 (M$^+$).

Anal. Calcd. for $C_8H_{12}N_4S_2$: C, 42.07; H, 5.31; N, 24.54; S, 28.08. Found: C, 42.02; H, 5.21; N, 24.24; S, 28.27.

This reaction was repeated under diluted conditions. The compound **1a** (2.28 g, 20 mmoles) was dissolved in anhydrous tetrahydrofuran (200 ml) and treated with *n*-butyllithium (23.5 mmoles) and then gaseous carbon gas at -70°. Usual work-up gave **4a** (1.0 g, 31%) as crystals, mp 109-110° dec [lit (2) mp 106-107° dec].

2-Phenyl-1,3,4-thiadiazol-5-ylacetic Acid (**4b**).

By the use of the procedure described above for **4a**, this compound was prepared from **1b** (5) (3.52 g, 20 mmoles). The crystalline product precipitated from the acidified aqueous solution to yield **4b** (3.2 g, 72%), mp 107-108° (from acetone); ir (nujol): 1731 cm^{-1}.

Anal. Calcd. for $C_{10}H_8N_2O_2S$: C, 54.53; H, 3.67; N, 12.72. Found: C, 54.56; H, 3.47; N, 12.86.

2-Bromo-5-phenyl-1,3,4-thiadiazole (**5b**).

2-Amino-5-phenyl-1,3,4-thiadiazole (6) (23.6 g, 133 mmoles) was stirred into 48% hydrobromic acid (66 ml) and the mixture was cooled in an ice-salt bath. To the mixture, bromine (60 ml, 1 mole) was added dropwise over 30 minutes, and then a solution of sodium nitrite (23.3 g, 341 mmoles) in water (33 ml) was added slowly at 0-10° over 2 hours. After being stirred for 30 minutes at 0°, the mixture was neutralized at 20-25° by addition of an aqueous solution saturated with sodium hydroxide (50 g) and extracted with chloroform (4 × 100 ml). The extracts were dried (magnesium sulfate) and evaporated *in vacuo* to give yellow crystals. Recrystallization from water afforded pure **5b** (17.5 g, 55%), mp 88-90°.

Anal. Calcd. for $C_8H_5BrN_2S$: C, 39.85; H, 2.09; N, 11.62. Found: C, 39.74; H, 2.18; N, 11.89.

Diethyl 2-Phenyl-1,3,4-thiadiazol-5-ylmalonate (**6b**).

Diethyl malonate (1.6 g, 10 mmoles) and successively a solution of **5b** (2.41 g, 10 mmoles) in anhydrous sodium ethoxide prepared from sodium (0.23 g, 10 mmoles) and absolute ethanol (20 ml), and the mixture was poured into ice-water (50 ml), acidified with hydrochloric acid, and extracted with chloroform. The extracts were dried (magnesium sulfate) and evaporated *in vacuo*. The crystalline residue was recrystallized from ethanol to yield **6b** as colorless needles (1.20 g, 44%), mp 145-146°; ir (chloroform): 1615 cm^{-1}.

Anal. Calcd. for $C_{15}H_{16}N_2O_4S$: C, 56.23; H, 5.03; N, 8.75; S, 10.01. Found: C, 56.40; H, 5.09; N, 8.70; S, 10.20.

This compound could be converted into 2-phenyl-1,2,4-thiadiazol-5-ylacetic acid (**4b**) as follows. A mixture of **6b** (0.8 g, 2.5 mmoles) and potassium carbonate (0.35 g, 5 mmoles) in 70% aqueous ethanol was refluxed for 8 hours. The solution was ice-cooled and acidified with hydrochloric acid. The pale-yellow solid was collected by filtration, dried, and recrystallized from acetone to give **4b** as needles (0.49 g, 89%), which was identical with that prepared by lithiation of **1b**.

Diethyl 2-Methyl-1,3,4-thiadiazol-5-ylmalonate (**6a**).

By the use of the procedure described above for **6b**, **5a** (7) was reacted with ethyl malonate to give **6a** in 50% yield, mp 146-147° (from ethanol); ir (chloroform): 1620 cm^{-1}.

Anal. Calcd. for $C_{10}H_{14}N_2O_4S$: C, 46.50; H, 5.46; N, 10.85; S, 12.41. Found: C, 46.55; H, 5.54; N, 10.83; S, 12.57.

Ethyl 2-Phenyl-1,3,4-thiadiazol-5-ylacetate (**7**).

A mixture of **4b** (1.5 g, 68 mmoles), ethyl bromide (0.85 g, 79 mmoles) and potassium carbonate (0.36 g, 68 mmoles) in DMF (15 ml) was stirred overnight at room temperature. The mixture was poured into ice-water, and the solid was collected by filtration, washed with water, dried, and then crystallized from hexane to give **7** as white needles (1.44 g, 85%), mp 88-89°; ir (chloroform): 1733 cm^{-1}.

Anal. Calcd. for $C_{12}H_{12}N_2O_2S$: C, 58.04; H, 4.87; N, 11.28. Found: C, 57.90; H, 4.62; N, 11.34.

Ethyl α-Oximino-2-phenyl-1,3,4-thiadiazol-5-ylacetate (**8**).

A solution of sodium nitrite (0.8 g, 11.6 mmoles) in water (3 ml) was added at 0° over 30 minutes to a suspension of **7** (2.48 g, 10 mmoles) in ethanol (10 ml) and acetic acid (7 ml), and the mixture was stirred for 30 minutes. The clear solution was diluted with water and then left for 2 hours at 0°. The solid was collected by filtration, washed with cold water, dried, and crystallized from ethanol to give **8** (2.13 g, 78%) as pale yellow prisms, mp 143-144°; ir (chloroform): 1708 cm^{-1}.

Anal. Calcd. for $C_{12}H_{11}N_3O_3S$: C, 51.97; H, 4.00; N, 15.16; S, 11.56. Found: C, 52.00; H, 3.73; N, 15.17; S, 11.25.

Ethyl α-Amino-2-phenyl-1,3,4-thiadiazol-5-ylacetate (**9**).

Zinc powder (1.0 g, 15.3 mmoles) was slowly added at -5° to a solution of **8** (1.5 g, 5.4 mmoles) in tetrahydrofuran (20 ml), formic acid (12 ml) and water (8 ml), and the mixture was stirred at -5 ~ 0° for an hour. The mixture was filtered, and the filtrate was treated with 20% hydrochloric acid (1 ml) and concentrated *in vacuo*. The residue was diluted with water, neutralized with sodium bicarbonate and extracted with dichloromethane. The extracts were dried and evaporated *in vacuo* to give **9** as pale-yellow solid (1.2 g), which was unstable and on standing turned dark red-brown. The product was dissolved in tetrahydrofuran (30 ml) and treated at -40° with pyridine (0.53 ml, 6.55 mmoles) followed by 2,2,2-trichloroethoxycabonyl chloride (1.37 g, 6.46 mmoles). After being stirred for 3 hours at -20°, the mixture was poured into water and extracted with ethyl acetate. The extracts were dried and evaporated *in vacuo*. The residue was chromatographed on silica gel to give **10** as an oil (2.23 g, 94%); ir (dichloromethane): 3400 and 1745 cm^{-1}; nmr (deuteriochloroform): 1.32 (t, J = 7 Hz, 3H), 4.33 (q, J = 7 Hz, 2H), 4.78 (s, 2H), 5.90 (d, J = 8.4 Hz, 1H), 6.55 (m, 1H), and 7.45-8.04 (m, 5H); ms: m/e 438 (M^+).

Anal. Calcd. for $C_{15}H_{14}Cl_3N_3O_4$: C, 41.07; H, 3.22; N, 9.58. Found: C, 40.86; H, 3.20; N, 9.43.

Diethyl α-Amino-2-methyl-1,3,4-thiadiazol-5-ylmalonate (**12**).

A solution of bromine (0.8 g, 5 mmoles) in chloroform (5 ml) was added dropwise at 0° to a suspension of **6a** (1.29 g, 5 mmoles) and sodium bicarbonate (0.54 g, 5 mmoles) in chloroform (30 ml), and the mixture was stirred for an hour at room temperature. After the solvent was replaced with DMF (20 ml), sodium azide (0.36 g, 5.5 mmoles) was added and the mixture was stirred ovrnight. The mixture was poured into ice-water, and extracted with benzene. The extracts were dried (magnesium sulfate), and evaporated *in vacuo* to give **11** as an oil (1.05 g); ir (dichloromethane): 2120 and 1753 cm^{-1}; nmr (deuteriochloroform): 1.35 (t, J = 7 Hz, 6H), 2.82 (s, 3H), and 4.42 (q, J = 7 Hz, 4H).

A mixture of the crude **11** and 10% palladium on carbon(100 mg) in ethanol containing concentrated hydrochloric acid (0.4 ml) was placed under a hydrogen atmosphere at atmospheric pressure, and stirred for 3 hours. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was diluted with water, neutralized with sodium carbonate, and extracted with dichloromethane. The extracts were dried (magnesium sulfate) and evaporated *in vacuo* to give **12** as an oil, which is very unstable and immediately converted into **13** by the use of the procedure described above for **10**. Overall yield 1.259 g (56%), mp 125.5-126.5° (from ether-hexane); ir (dichloromethane): 3400 and 1750 cm^{-1}.

Anal. Calcd. for $C_{13}H_{16}Cl_3N_3O_6$: C, 34.80; H, 3.59; N, 9.36. Found: C, 34.78; H, 3.51; N, 9.22.

Ethyl α-(2,2,2-Trichloroethoxycarbonylamino)-2-methyl-1,3,4-thiadiazol-5-ylacetate (**15**).

The crude azide **11**, prepared from **6a** (1.29 g, 5 mmoles) according to the procedure described above for **12**, was dissolved in dry dichloromethane (20 ml) and cooled in an ice bath. Triethylamine (0.466 ml, 3.34 mmoles) was added and then a stream of hydrogen sulfide gas bubbled in for 5 minutes. The solution was allowed to stand for an hour until evolution of gas ceased, and evaporated *in vacuo* to give **14** as a yellow oil.

The crude amino ester **14** was acylated with 2,2,2-trichloroethoxycarbonyl chloride according to the procedure described above for **10** to give **15** as an oil (0.564 g, 30% overall yield from **6a**); ir (dichloromethane): 3400 and 1750 cm^{-1}; nmr (deuteriochloroform): 1.28 (t, J = 7 Hz, 3H), 2.77 (s, 3H), 4.30 (q, J = 7 Hz, 2H), 4.76 (s, 2H), 5.83 (d, J = 8 Hz, 1H), and 6.75 (m, 1H); ms: m/e 376 (M^+).

Anal. Calcd. for $C_{10}H_{12}Cl_3N_3O_4$: C, 31.89; H, 3.21; N, 11.16. Found: C, 32.39; H, 3.28; N, 11.12.

The compound **15** was also obtained by hydrolysis of **13** as follows. To a solution of **13** (0.35 g, 0.78 mmoles) in acetone (5 ml), 1*M* aqueous potassium hydroxide solution (0.82 ml) was added dropwise at 0° and the mixture was stirred overnight at room temperature. The solution was acidified and extracted with ethyl acetate. The extracts were dried and evaporated *in vacuo*. The residue was purified by preparative thin layer chromatography on silica gel (60 F254, E Merk) to give **15** (0.126 g, 43%), which was identical with that obtained above.

Hydrolysis of Ethyl α-(2,2,2-Trichloroethoxycarbonylamino)-2-methyl-1,3,4-thiadiazol-5-ylacetate (**15**).

By the use of the procedure described above for hydrolysis of **13**, **15** (0.39 g, 1.03 mmoles) was treated with aqueous potassium hydroxide to give **21** (0.124 g, 39%), mp 85-87° (from ether-hexane); ir (dichloromethane): 3450 and 1745 cm^{-1}; nmr (deuteriochloroform): 2.76 (s, 3H), 4.78 (s, 2H), 4.80 (d, J = 6 Hz, 2H), and 6.20 (m, 1H).

Anal. Calcd. for $C_7H_8Cl_3N_3O_2S$: C, 27.60; H, 2.65; N, 13.80. Found: C, 27.54; H, 2.53; N, 13.78.

Hydrolysis of Ethyl α-Amino-2-phenyl-1,3,4-thiadiazol-5-ylacetate (**9**).

To a solution of **9** (1.0 g, 3.8 mmoles) in methanol (10 ml), 1*M* solution of potassium hydroxide in methanol (3.5 ml) was added at 0° and the mixture was stirred overnight at room temperature. The solid was filtered off and dried to yield the potassium salt (0.64 g, 59%). The potassium salt (0.64 g) was dissolved in water and the solution was slowly neutralized at 0° with hydrochloric acid, while evolution of gaseous carbon dioxide was observed. The oil was extracted with chloroform and the extracts were dried (magnesium sulfate) and evaporated *in vacuo* to yield the amine **19** as a brown oil. The oil was converted to the 2,2,2-trichloroethoxycarbonyl derivative **20** according to the procedure described for **10**, mp 117-118° (from ethanol); ir (nujol): 1738 cm^{-1}.

Anal. Calcd. for $C_{12}H_{10}Cl_3N_3O_2$: C, 39.30; H, 2.72; N, 11.46. Found: C, 39.35; H, 2.48; N, 11.32.

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