Preparation of 1,2,5-Thiadiazole-3-carboxaldehydes

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1,2,5-Thiadiazole-3-carboxaldehydes **1a-c** were prepared by the acid-catalyzed decomposition of 3-azidomethyl-1,2,5-thiadiazoles **2a-c** in 68-83% yields, respectively. Pyrolysis of **2a** and **2b** afforded the imidazoles **4a** and **4b** in low yields. NBS-bromination of **1a** and **1b** gave the corresponding carboxylic acids **10a** and **10b** *via* acid bromides **9**. Azides **2a** and **2b** gave the *s*-triazines **8a** and **8b** on treatment with NBS.

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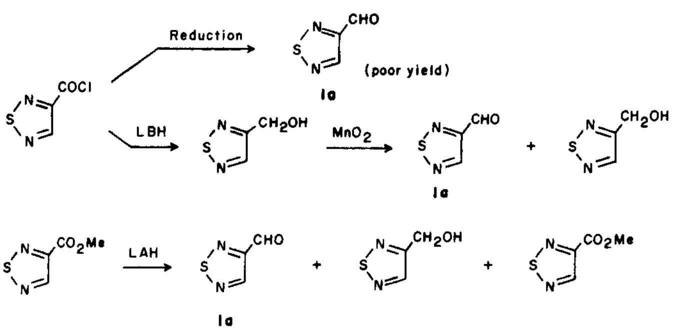
Heterocycles bearing functional group(s) are important synthons in organic syntheses. Recently, we have investigated [1] the bromination of easily accessible methyl-1,2,5-thiadiazoles by *N*-bromosuccinimide (NBS) as a key step for the preparation of functionalized 1,2,5-thiadiazoles. As a continuation of the above, we now report the preparation of 1,2,5-thiadiazole-3-carboxaldehydes **1** by the decomposition of 3-azidomethyl-1,2,5-thiadiazoles **2**.

Results and Discussion.

Earlier, Carmack and co-workers [2] tried the synthesis of 1,2,5-thiadiazole-3-carboxaldehyde **1a** by several standard methods with unsatisfactory results as shown in Scheme 1.

Scheme I



As an azidomethyl group is known to give an aldehyde on decomposition under various conditions, we prepared azidomethyl-1,2,5-thiadiazoles **2** from 3-bromomethyl derivatives **3** in high yields. Compounds **2** are stable, volatile liquids and purified by distillation under reduced pressure without any appreciable decomposition.

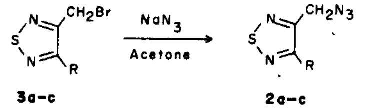


Table 1

Preparation of **2**

2	R	Yield (%)	Bp (°C)
a	H	83	99°/21 mm Hg
b	CH_3	92	69-71°/7 mm Hg
c	Ph	79	140°/3 mm Hg

First pyrolysis of **2** was investigated and the results are summarized in Table 2. In refluxing xylene or decalin, it took a long time to decompose **2** and tris(1,2,5-thiadiazol-3-yl)imidazoles **4** were obtained in low yields, accompanied by a large amount of resinous materials, but not the expected **1**. Thermolysis in diphenyl ether at reflux also gave **4** in the shorter reaction time, but the yields are low.

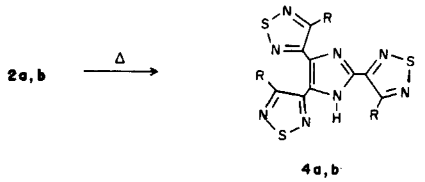


Table 2

Pyrolysis of **2**

2	R	solvent	time (hours)	Yield of **4** (%)
a	H	PhOPh	0.25	13
b	CH_3	PhOPh	0.25	6
b	CH_3	*m*-xylene	65	9
b	CH_3	decalin	70	8

Interestingly in the pmr spectrum of **4b**, three methyl signals were observed at $\delta = 2.20, 2.96$ and 3.05 ppm with equal intensities, thus suggesting that three methyl groups of **4b** are in different environment, each other. On the other hand, only one single peak was observed in the spectrum of **4a**.

Next, we tried the acid-catalyzed decomposition of **2** according to the usual manner, but **2** was fairly stable in refluxing chloroform containing concentrated sulfuric acid. So, the decomposition of **2** was carried out by dropping **2** in cold concentrated sulfuric acid at 0-5° and by stirring the mixture at room temperature until the evolution of nitrogen gas ceased. The desired aldehydes **1** were obtained in high yields, as shown in Table 3, by continuously extracting the reaction mixture with methylene chloride overnight. The aldehydes **1a** [3] and **1b** easily form oximes **5a** and **5b**, and tosylhydrazones **6a** and **6b**. From their pmr spectra (Table 4), it is suggested that **6** exists as a mixture of *syn-* and *anti*-form.

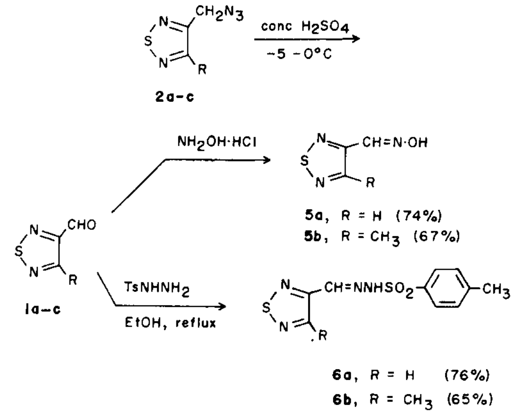


Table 3

Preparation of **1**

1	R	Yield (%)	Bp (°C)
a	H	68	165°
b	CH_3	80	163-170°
c	Ph	83	100°/2 mm Hg

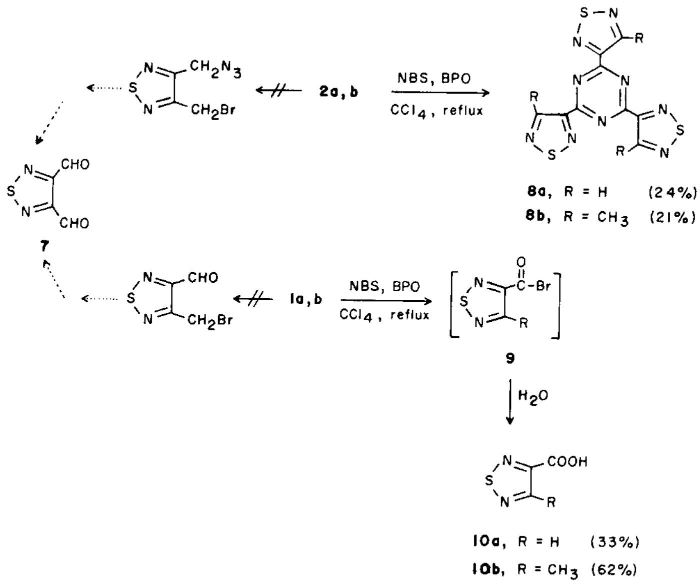
Table 4

PMR Data of **6**

6	ppm [a]	ppm [b]
a (R = H)	8.64 (s, 1/2H)	9.04 (s, 1H)
	8.92 (s, 1/2H)	
b (R = CH_3)	2.68 (s, 9/4H)	2.60 (s, 8/4H)
	2.76 (s, 3/4H)	2.76 (s, 4/4H)

[a] In deuteriochloroform. [b] In hexadeuteriodimethyl sulfoxide.

Finally, as a possible route for the preparation of the bis-aldehyde **7**, bromination of **2b** and **1b** was investigated. Bromination of **2b** with NBS gave *s*-triazine (**8b**) but not the expected bromide. Compound **1b** afforded moisture-sensitive acid bromide **9** which, on addition of water, gave the carboxylic acid **10b**. Bromination of **2a** and **1a** also afforded **8a** and **10a** [4], respectively.



EXPERIMENTAL

All melting points are uncorrected. The ir spectra were measured on a Nippon Bunko A-102 spectrophotometer as potassium bromide pellets or as liquid films on sodium chloride plates. The ^{1}H-nmr spectra were determined at 100 MHz on a Nippon Denshi JEOL FT-100 using TMS as an internal standard. Mass spectra were obtained on a Nippon Denshi JMS-01SG-2 mass spectrometer at 75 eV using a direct inlet system.

Preparation of **2a**. Typical Procedure.

A mixture of 19.5 g (0.1 mole) of **3a**, 28 g (0.4 mole) of sodium azide and a catalytic amount of sodium iodide in 200 ml of acetone was stirred at room temperature overnight. It was added to aqueous sodium thiosulfate solution and was extracted with ether. The extract was dried over sodium sulfate and evaporated *in vacuo* to give pale yellow oil which was distilled under reduced pressure to give 12.8 g (83%) of **2a**.

3-Azidomethyl-1,2,5-thiadiazole (**2a**).

This compound was obtained as colorless oil; ir: ν N_3 2080 cm^{-1}; ms: m/e (relative intensity) 141 (M$^+$, 11), 112 (12), 99 (17), 85 (73), 72 (20), 59 (100); ^{1}H-nmr (deuteriochloroform): δ 4.68 (s, 2H), 8.56 (s, 1H) ppm.

3-Azidomethyl-4-methyl-1,2,5-thiadiazole (**2b**).

This compound was obtained as colorless oil; ir: ν N_3 2080 cm^{-1}; ms: m/e (relative intensity) 155 (M$^+$, 12), 126 (20), 113 (23), 73 (100); ^{1}H-nmr (deuteriochloroform): δ 2.56 (s, 3H), 4.50 (s, 2H) ppm.

3-Azidomethyl-4-phenyl-1,2,5-thiadiazole (**2c**).

This compound was obtained as colorless oil; ir: ν N_3 2100 cm^{-1}; ms: m/e (relative intensity) 217 (M$^+$, 0.2), 188 (100), 135 (13), 104 (21), 77 (18); ^{1}H-nmr (deuteriochloroform): δ 4.56 (s, 2H), 7.38-7.70 (m, 5H) ppm.

Anal. Calcd. for $C_9H_7N_5S$: C, 49.76; H, 3.25; N, 32.24. Found: C, 49.98; H, 3.27; N, 32.03.

Pyrolysis of 3-Azidomethyl-1,2,5-thiadiazole (**2a**).

After a mixture of 2.00 g (14 mmoles) of **2a** in 20 ml of diphenyl ether was heated, solvent was evaporated *in vacuo* to give red oil which was treated with acetone to give yellow solid. Recrystallization from a mixture of hexane and benzene gave 0.20 g (13%) of **4a**.

2,4,5-Tris(1,2,5-thiadiazol-3-yl)imidazole (**4a**).

This compound was obtained as pale yellow powder; mp 275° dec; ir: ν NH 3100 cm^{-1}; ms: m/e (relative intensity) 320 (M$^+$, 17), 319 (100); ^{1}H-nmr (hexadeuteriodimethyl sulfoxide): δ 9.40 (s).

Anal. Calcd. for $C_9H_4N_8S_3$: C, 33.74; H, 1.26 N, 34.98. Found: C, 34.18; H, 1.66; N, 35.06.

Pyrolysis of 3-Azidomethyl-4-methyl-1,2,5-thiadiazole (**2b**).

After a mixture of 2.00 g (13 mmoles) of **2b** in 20 ml of diphenyl ether was heated, it was treated as described above to give 0.09 g (6%) of **4b**.

2,4,5-Tris(4-methyl-1,2,5-thiadiazol-3-yl)imidazole (**4b**).

This compound was obtained as colorless needles (hexane-benzene) mp 217-218°; ir: ν NH 3280 cm^{-1}; ms: m/e (relative intensity) 362 (M^+, 8), 361 (43), 346 (100), 319 (43); ^{1}H-nmr (deuteriochloroform): δ 2.20 (s, 3H), 2.96 (s, 3H), 3.05 (s, 3H), 10.72 (s, 1H).

Anal. Calcd. for $C_{12}H_{10}N_8S_3$: C, 39.82; H, 2.78; N, 30.95. Found: C, 39.90; H, 2.95; N, 30.57.

Acid-Catalyzed Decomposition of **2a**. Typical Procedure.

In a 200 ml flask fitted with thermometer, was placed 80 ml of concentrated sulfuric acid, and to it was slowly added, with continuous stirring, 10.0 g (71 mmoles) of **2a**, keeping the temperature between −5° and 0°. Nitrogen was evolved during 24 hours. The reaction mixture was poured into a mixture (320 ml) of water and cracked ice, and was continuously extracted with methylene chloride (200 ml) overnight. Solvent was removed to leave pale yellow oil, which was distilled to give 5.5 g (68%) of **4a**.

3-Formyl-1,2,5-thiadiazole (**1a**).

This compound was obtained as colorless oil; ir: ν CO 1700 cm^{-1}; ms: m/e (relative intensity) 114 (M^+, 42), 86 (28), 59 (100); ^{1}H-nmr (deuteriochloroform): δ 9.08 (s, 1H), 10.23 (s, 1H).

3-Formyl-4-methyl-1,2,5-thiadiazole (**1b**).

This compound was obtained as colorless oil; ir: ν CO 1700 cm^{-1}; ms: m/e (relative intensity) 128 (M^+, 24), 127 (23), 126 (100); ^{1}H-nmr (deuteriochloroform): δ 2.80 (s, 3H), 10.24 (s, 1H).

Anal. Calcd. for $C_4H_4N_2OS$: C, 37.49; H, 3.15; N, 21.86. Found: C, 37.19; H, 3.18; N, 21.74.

3-Formyl-4-phenyl-1,2,5-thiadiazole (**1c**).

This compound was obtained as colorless oil; ir: ν CO 1700 cm^{-1}; ms: m/e (relative intensity) 190 (M^+, 100), 189 (20), 136 (68), 103 (29), 58 (21), 43 (47); ^{1}H-nmr (deuteriochloroform): δ 7.40-7.54 (m, 3H), 7.68-7.83 (m, 2H), 10.24 (s, 1H).

Anal. Calcd. for $C_9H_6N_2OS$: C, 56.83; H, 3.18; N, 14.73. Found: C, 56.75; H, 3.28; N, 14.27.

Reaction of **4** with Hydroxylamine Hydrochloride. Typical Procedure.

To a mixture of 2.00 g (29 mmoles) of hydroxylamine hydrochloride in water (10 ml) was added 20 ml of aqueous 1*N* sodium hydroxide, and then 0.67 g (6 mmoles) of **4a**. After a mixture was warmed on water-bath for 15 minutes, it was cooled by ice-bath to give colorless solid which, on recrystallization from a mixture of ethanol and water, afforded 0.56 g (74%) of **5a**.

1,2,5-Thiadiazol-3-carboxaldehyde Oxime (**5a**).

This compound was obtained as colorless needles; mp 145- 146°; ms: m/e (relative intensity) 129 (M^+, 100), 112 (46), 59 (69); ^{1}H-nmr (hexadeuteriodimethyl sulfoxide): δ 8.40 (s, 1H), 9.08 (s, 1H), 12.10 (s, 1H).

Anal. Calcd. for $C_3H_3N_3OS$: C, 27.90; H, 2.34; N, 32.54. Found: C, 27.71; H, 2.36; N, 32.61.

4-Methyl-1,2,5-thiadiazole-3-carboxaldehyde Oxime (**5b**).

This compound was obtained as colorless prisms (ethanol-water); mp 129°; ms: m/e (relative intensity) 143 (M^+, 45), 126 (100); ^{1}H-nmr (hexadeuteriodimethyl sulfoxide): δ 2.68 (s, 3H), 8.40 (s, 1H), 12.05 (s, 1H).

Anal. Calcd. for $C_4H_5N_3OS$: C, 33.56; H, 3.52; N, 29.35. Found: C, 33.55; H, 3.72; N, 29.32.

Reaction of **1** with Tosylhydrazine. Typical Procedure.

After a mixture of 0.48 g (4 mmoles) of **1a** and 0.79 g (4 mmoles) of tosylhydrazine in ethanol (15 ml) was refluxed for one hour, the solvent was evaporated *in vacuo* to give colorless solid which, on recrystallization from ethanol, gave 0.91 g (76%) of **6a**.

1,2,5-Thiadiazole-3-carboxaldehyde *p*-Toluenesulfonyl Hydrazone (**6a**).

This compound was obtained as colorless needles, mp 172-173°; ms: m/e (relative intenstiy) 382 (1), 127 (100).

Anal. Calcd. for $C_{10}H_{10}N_4O_2S_2$: C, 42.54; H, 3.57; N, 19.84. Found: C, 42.76; H, 3.56; N, 20.04.

4-Methyl-1,2,5-thiadiazole-3-carboxaldehyde *p*-Toluenesulfonyl Hydrazone (**6b**).

This compound was obtained as colorless needles (ethanol), mp 154-155°; ms: m/e (relative intensity) 296 (M^+, 3), 141 (100).

Anal. Calcd. for $C_{11}H_{12}N_4O_2S_2$: C, 44.58; H, 4.08; N, 18.90. Found: C, 44.60; H, 4.05; N, 18.85.

Bromination of **2a**.

After a mixture of 2.00 g (14 mmoles) of **2a**, 2.80 g (15 mmoles) of NBS and a catalytic amount of benzoyl peroxide in 20 ml of carbon tetrachloride was refluxed for 3 hours, succinimide was filtered. The filtrate was evaporated *in vacuo* to give red oil which was treated with ether to leave yellow powder. Recrystallization from methanol gave 0.38 g (24%) of **8a**.

2,4,6-Tris(1,2,5-thiadiazol-3-yl)triazine (**8a**).

This compound was obtained as yellow needles; mp 232- 234°; ms: m/e (relative intensity) 333 (M^+, 100), 112 (33), 111 (32); ^{1}H-nmr (deuteriochloroform): δ 9.60 (s).

Anal. Calcd. for $C_9H_3N_9S_3$: C, 32.43; H, 0.91; N, 37.81. Found: C, 32.53; H, 0.95; N, 37.99.

Bromination of **2b**.

After a mixture of 2.00 g (13 mmoles) of **2c**, 2.50 g (14 mmoles) of NBS and a catalytic amount of benzoyl peroxide in 20 ml carbon tetrachloride was refluxed for 6 hours, it was treated as described above to give 0.34 g (21%) of **8b**.

2,4,6-Tris(4-methyl-1,2,5-thiadiazol-3-yl)triazine (**8b**).

This compound was obtained as colorless needles (hexane-benzene), mp 240°; ms: m/e (relative intensity) 375 (M^+, 100), 126 (46); ^{1}H-nmr (deuteriochloroform): δ 3.10 (s, 9H).

Anal. Calcd. for $C_{12}H_9N_9S_3$: C, 38.39; H, 2.42; N, 33.58. Found: C, 38.61; H, 2.55; N, 33.71.

Bromination of **1a**.

After a mixture of 1.00 g (9 mmoles) of **1a**, 1.70 g (10 mmoles) of NBS and a catalytic amount of benzoyl peroxide in 40 ml of carbon tetrachloride was refluxed for 30 minutes, succinimide was filtered and the filtrate was evaporated *in vacuo* to give pale yellow oil which was poured onto 20 ml of water, stirred at 80° and extracted with ethyl acetate to give colorless solid. Recrystallization from a mixture of benzene and ethyl acetate gave 0.37 g (33%) of **12a**.

1,2,5-Thiadiazol-3-carboxylic Acid (**9a**).

This compound was obtained as colorless needles; mp 167-169° (lit [3] mp 162-164°); ir: ν CO 1700 cm^{-1}; ms: m/e (relative intensity) 130 (M^+, 26), 113 (12), 85 (73), 59 (100); ^{1}H-nmr (deuteriochloroform): δ 9.12 (s).

Anal. Calcd. for $C_3H_2N_2O_2S$: C, 27.69; H, 1.55; N, 21.53. Found: C, 27.83; H, 2.01; N, 21.24.

Bromination of **4c**.

After a mixture of 2.00 g (16 mmoles) of **1b**, 3.10 g (17 mmoles) of NBS and a catalytic amount of benzoyl peroxide in 40 ml of carbon tetrachloride was refluxed for 5 hours, it was treated as described above to give 1.40 g (62%) of **9b**.

4-Methyl-1,2,5-thiadiazol-3-carboxylic Acid (**9b**).

This compound was obtained as colorless prisms (benzene-ethyl acetate); mp 148-150°; ir: ν CO 1710 cm^{-1}; ms: m/e (relative intensity) 144 (M$^+$, 26), 126 (100); ^{1}H-nmr (deuteriochloroform): δ 2.88 (s, 3H), 9.34 (br, 1H).

Anal. Calcd. for $C_4H_4N_2O_2S$: C, 33.33; H, 2.80; N, 19.43. Found: C, 33.44; H, 2.85; N, 19.19.

Acknowledgement.

We are grateful to Professor Emeritus M. Carmack of Indiana University for a copy of the infrared spectrum of **1a**.

REFERENCES AND NOTES

[1] S. Mataka, M. Kurisu, K. Takahashi and M. Tashiro, *J. Heterocyclic Chem.*, **21**, 1157 (1984).

[2] M. Carmack, personal communication.

[3] Because **1a**, **2a** and **2b** are volatile, their elemental analysis gave unsatisfactory results.

[4] L. M. Weinstock, P. Davis, B. Handelsman and R. Tull, *J. Org. Chem.*, **32**, 2823 (1967).