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Short Note

5-Amino-3-methyl-1,2,4-thiadiazole

R. Alan Aitken * and Alexandra M. Z. Slawin

EaStCHEM School of Chemistry, University of St Andrews, North Haugh, St Andrews, Fife KY16 9ST, UK; amzs@st-and.ac.uk

* Correspondence: raa@st-and.ac.uk; Tel.: +44-1334-463865

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Abstract: An improved procedure for isolation of 5-amino-3-methyl-1,2,4-thiadiazole in pure form on a multi-gram scale without chromatography is reported. Its ^{1}H and ^{13}C-NMR and IR data are presented and previously published erroneous data corrected. The molecular structure is confirmed by X-ray diffraction which shows layers consisting of an elaborate two-dimensional hydrogen bonded network of molecules.

Keywords: 1,2,4-thiadiazole; NMR spectra; IR spectrum; X-ray structure

1. Introduction

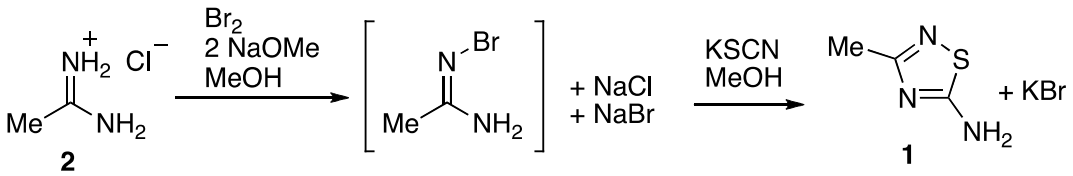
The simple heterocyclic compound 5-amino-3-methyl-1,2,4-thiadiazole **1** was first reported in 1954 [1] and has since found use as a potential pesticide [2], and as a component of medicinally important enzyme inhibitors [3], azo dyes [4], and cephalosporin antibiotics [5,6]. Its synthesis commonly involves treatment of an in situ generated *N*-haloacetamidine with a metal thiocyanate, which inevitably leads to formation of the product as a mixture with various inorganic salts. The original method relied upon recrystallisation from water to remove these, while later procedures generally used column chromatography but were conducted on a very small scale. In addition, as described in the Results section, there are several discrepancies in the reported physical and spectroscopic data for this compound. In this paper, we report a simple procedure for isolation of **1** in pure form on a 20–30 g scale, its ^{1}H and ^{13}C-NMR data in two different solvents, and detailed analysis of its molecular and crystal structure by X-ray diffraction.

2. Results

The original synthetic route to **1** (Scheme 1) starts from the readily available [7] acetamidine hydrochloride **2** and involves simultaneous addition of bromine and sodium methoxide in methanol to generate the *N*-bromoacetamidine. This is not isolated but reacts directly with added potassium thiocyanate to give the final product **1** [1]. The isolation procedure consists of filtering the reaction mixture to remove most of the inorganic salts, evaporation of the filtrate and recrystallisation of the residue from water [1]. In our hands, this procedure was not satisfactory, giving a variable low yield of a solid still containing metal halides. Extraction of the solid with isopropanol was also unsuccessful. Much better results were achieved by subjecting the solid from evaporation of the reaction filtrate to thorough Soxhlet extraction using dichloromethane. This gave a pure product free of inorganic salts in comparable yield to the original report.

Because of the early date of the first preparation, the only spectroscopic data reported there was the UV spectrum [1], and the mass spectrum was also reported in 1971 [8]. Examination of later literature reports reveals conflicting and erroneous physical and spectroscopic data. Thus, for example, while both Keillor and coworkers (CD_3OD) [3] and Inagaki and coworkers (CD_3SOCD_3) [9] give a consistent value of δ_H 2.2 for the ^{1}H-NMR signal of the methyl group, Cho and coworkers [5,6] instead report a signal at δ_H 3.27 (CD_3OD). The last reports also contain an erroneous reaction scheme

suggesting that **1** is formed by *C*- rather than *N*-chlorination of acetamidine followed by reaction with potassium thiocyanate and they do not give any melting point value, casting doubt on the nature of the product involved. While most reports give broadly consistent melting point values of 198.5–200 °C [1], 202 °C [2] and 192.5–193 °C [9], the only report of ^{13}C-NMR data for **1** is for a product with melting point 68 °C [3]. In addition, the values reported: δ_C 169.94, 133.80 and 18.48 are not at all consistent with other comparable 1,2,4-thiadiazoles which always have both ring carbons giving signals in the range δ_C 165–190 [10,11]. The ^{1}H and ^{13}C-NMR data for **1**, determined for solutions in both CD_3OD and CD_3SOCD_3, are given in the Experimental Section with the actual spectra provided as supplementary material. It is clear from these that **1** has NMR data in accordance with expectation and consistent with other 1,2,4-thiadiazoles and the values of δ_H 3.27 [5,6] and δ_C 133.80 [3] are erroneous, the latter perhaps being a misprint for 183.80. Since the only report of an infrared spectrum for this compound is also in the last mentioned paper [3], we have re-run its spectrum and find the peak at 2050 cm^{-1} reported for "N=C-S" [3] to be absent. While the other two reported signals [3] at 3250 and 1650 cm^{-1} do correspond roughly to peaks in our spectrum, there are a large number of additional peaks present and the full spectrum is listed in the Experimental section and shown in the supplementary material.



Scheme 1. Synthetic route to **1** [1].

In view of the conflicting data for **1** just discussed, we thought it wise to confirm the structure of the compound unambiguously by X-ray diffraction. The crystals obtained directly from Soxhlet extraction proved to be suitable without further purification and the resulting structure is shown in Figure 1. There are two distinct but very similar molecules in the unit cell and the bond lengths and angles within each are in good agreement with those for previously studied simple 1,2,4-thiadiazoles such as **3** [11], **4** [12], **5** and **6** [10] (Figure 2). In particular, the sulfur atom has long bonds to both C and N and an internal angle of almost 90° which is compensated for by a wide angle of 120° at the methyl-bearing carbon while the remaining internal ring angles are near to the 108° expected for a regular pentagon.

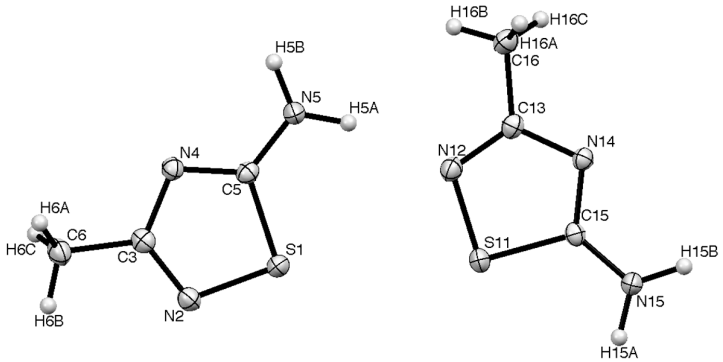


Figure 1. The two distinct molecules in the molecular structure of **1** with numbering scheme. Selected bond lengths and angles: S(1)-N(2) 1.682(1), N(2)-C(3) 1.317(2), C(3)-N(4) 1.374(2), N(4)-C(5) 1.333(2), C(5)-S(1) 1.740(1), S(11)-N(12) 1.686(1), N(12)-C(13) 1.320(2), C(13)-N(14) 1.369(2), N(14)-C(15) 1.334(2), C(15)-S(11) 1.746(2) Å; S(1)-N(2)-C(3) 107.93(9), N(2)-C(3)-N(4) 119.7(1), C(3)-N(4)-C(5) 109.0(1), N(4)-C(5)-S(1) 111.34(9), C(5)-S(1)-N(2) 92.03(6), S(11)-N(12)-C(13) 107.69(9), N(12)-C(13)-N(14) 120.1(1), C(13)-N(14)-C(15) 108.9(1), N(14)-C(15)-S(11) 111.37(9), C(15)-S(11)-N(12) 91.89(6)°.

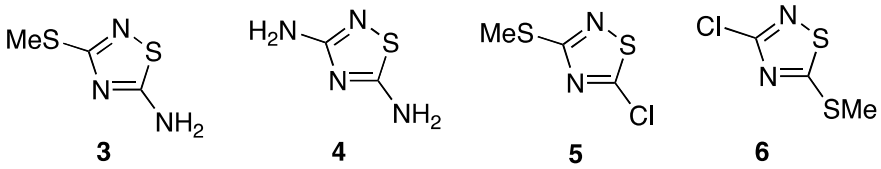


Figure 2. Comparable crystallographically characterised 1,2,4-thiadiazoles [10–12].

As might be expected, the crystal structure is dominated by hydrogen bonding with each NH_2 group forming hydrogen bonds with both N-2 and N-4 of adjacent molecules (Table 1). The result is a two-dimensional network featuring pairs of molecules bonded by head-to-tail NH to N-4 interactions, as well as 20-membered rings with four sulfur atoms pointing inward formed using only the NH to N-2 interaction, and 24-membered rings with four methyl groups pointing into the middle involving both NH to N-2 and NH to N-4 interactions (Figure 3).

Table 1. Hydrogen bonding parameters for **1** (Å, °).

D-H···A	D-H	H···A	D···A	D-H···A
N(5)-H(5A) ···N(12)	2.014(13)	0.972(15)	2.962(2)	164.5(17)
N(5)-H(5B) ···N(4)	2.013(10)	0.973(11)	2.978(2)	171.1(15)
N(15)-N(15A) ···N(2)	2.006(17)	0.973(16)	2.975(2)	173.3(16)
N(15)-N(15B) ···N(14)	2.020(20)	0.972(19)	2.992(2)	173.2(12)

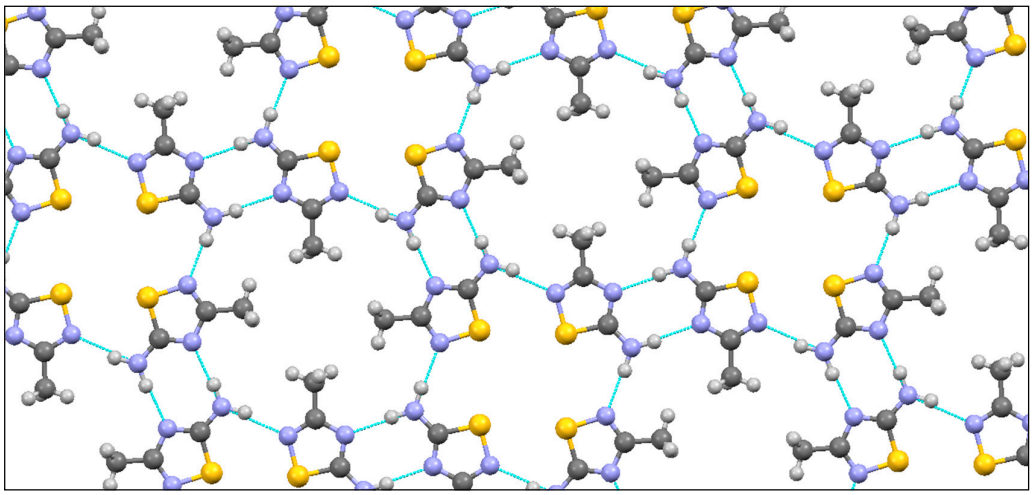


Figure 3. Two-dimensional hydrogen bonded network in the structure of **1**.

The hydrogen bonding pattern is quite different to that observed for **4** in which only one NH of each NH_2 group is involved to give infinite chains of molecules alternately bonded by two N-2 to 3-NH interactions and two N-4 to 5-NH interactions [12].

3. Experimental

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

To a stirred solution of acetamidine hydrochloride (50.0 g, 0.53 mol) in methanol (250 mL) cooled in an ice-salt bath, bromine (85 g, 0.53 mol) and a solution of sodium (24 g, 1.04 mol) in methanol (300 mL) were simultaneously added from separate dropping funnels over a period of 30 min at such a rate that the bromine was always in a slight excess. After the addition was complete, a little extra sodium methoxide solution was added to remove the slight orange colour. The mixture was stirred and cooled

in ice while a solution of potassium thiocyanate (50.5 g, 0.52 mol) in methanol (250 mL) was added over 10 min, ensuring that the temperature did not exceed 15 °C. After stirring in ice for 2 h, acetic acid (16 mL) was added followed by a sufficient quantity of aqueous sodium sulfide solution so that an aliquot of the solution did not liberate iodine from a potassium iodide test solution. The mixture was filtered and the filtrate evaporated under reduced pressure. The residual solid was subjected to Soxhlet extraction with dichloromethane for 18 h to give, after evaporation of the combined extracts under reduced pressure, the product **1** (28.0 g, 47%) as pale brown crystals, mp 202–204 °C. IR (ATR): 3265, 3073, 2766, 1645, 1537, 1489, 1379, 1331, 1123, 997, 808, 590, 577 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3SOCD_3): δ 7.82 (br s, 2H), 2.23 (s, 3H); ^{1}H-NMR (400 MHz, CD_3OD): δ 2.31 (s); ^{13}C-NMR (100 MHz, CD_3SOCD_3): δ 183.2, 169.2, 18.7; ^{13}C-NMR (100 MHz, CD_3OD): δ 185.6, 171.0, 18.5.

Crystal Data for $C_3H_5N_3S$, M = 115.15 $g{\cdot}mol^{-1}$, colourless prism, crystal dimensions 0.10 × 0.10 × 0.03 mm, triclinic, space group P-1, a = 6.9923(4), b = 7.8291(5), c = 10.8037(7) Å, α = 82.329(5), β = 89.896(5), γ = 66.020(5)°, V = 534.65(6) $Å^3$, Z = 4, D_{calc} = 1.430 $g{\cdot}cm^{-3}$, T = 93 K, $R1$ = 0.0259, $Rw2$ = 0.0712 for 2149 reflections with $I > 2\sigma(I)$ and 145 variables. Data were collected using graphite monochromated Mo Kα radiation λ = 0.71075 Å and have been deposited at the Cambridge Crystallographic Data Centre as CCDC 1590413. The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

Supplementary Materials: The following are available online, Figure S1: 400 MHz ^{1}H-NMR spectrum of **1** in CD_3OD, Figure S2: 100 MHz DEPTQ ^{13}C-NMR spectrum of **1** in CD_3OD, Figure S3: 400 MHz ^{1}H-NMR spectrum of **1** in CD_3SOCD_3, Figure S4: 100 MHz DEPTQ ^{13}C-NMR spectrum of **1** in CD_3SOCD_3, Figure S5: IR (ATR) spectrum of **1**.

Author Contributions: A.M.Z.S. collected the X-ray data and solved the structure; R.A.A. designed and performed the experiments, analysed the data and wrote the paper.

Conflicts of Interest: The authors declare no conflict of interest.

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