Synthesis of Mesoionic 1,2,3,5-Thiatriazoles

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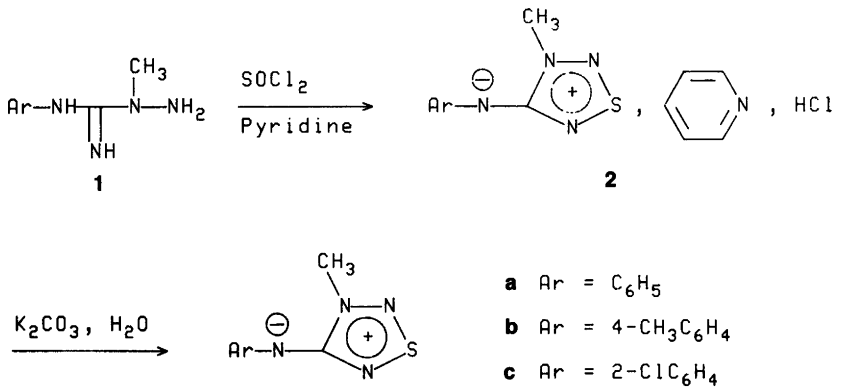
Felding, G. and Holm, A., 1988. Synthesis of Mesoionic 1,2,3,5-Thiatriazoles. – Acta Chem. Scand., Ser. B 42: 63–66.

On treatment of 1-amino-1-alkyl-3-arylguanidines with thionyl chloride in pyridine, yellow complexes between mesoionic 1,2,3,5-thiatriazoles (anhydro-3-alkyl-4-arylamino-1,2,3,5-thiatriazolium hydroxides) and pyridinium chloride are formed. The strongly coloured mesoionic compounds are liberated by treatment with base (aryl = phenyl, 4-methylphenyl, 2-chlorophenyl; alkyl = methyl). On attempted synthesis of 5-phenyl-1,2,3,5-thiatriazole by treatment of benzamidrazone with thionyl chloride in pyridine, spontaneous evolution of nitrogen and formation of benzonitrile and sulfur were observed.

Heteroaromatic 1,2,3,4-thiatriazoles, including mesoionic 1,2,3,4-thiatriazoles,[1,2] are a well-known class of compounds.[1,3,4] Heteroaromatic 1,2,3,5-thiatriazoles are as yet unknown, but certain 1,2,3,5-thiatriazolines and thiatriazolidines are described[1,5] and nonclassical 1,2,3,5-thiatriazole heteropentalenes have been reported.[1,6] In this report we describe the first preparation of mesoionic 3-substituted 5-arylimino-1,2,3,5-thiatriazoles and evidence for formation of unstable 5-phenyl-1,2,3,5-thiatriazole.

We have observed that the reaction of 1-amino-1-methyl-3-phenylguanidine (**1a**) with approximately 2 equiv. of thionyl chloride with pyridine as solvent affords a yellow complex **2a** of the stoichiometric composition shown below (Scheme 1). The dark-violet mesoionic 1,2,3,5-thiatriazole (**3a**) was liberated on treatment with aqueous potassium carbonate. The structure of **3a** was established on the basis of elemental analysis and spectral data. Its IR spectrum is devoid of NH absorptions and the ^1H



Scheme 1.

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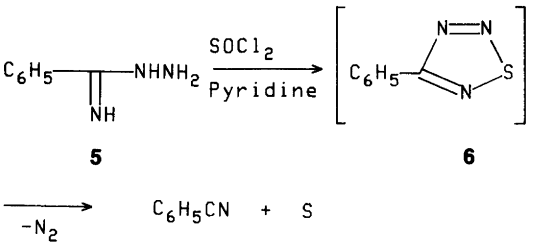
NMR spectrum exhibits an aromatic multiplet at 6.8–7.4 (5H) and a methyl group at 3.9 ppm (3H). The mesoionic thiatriazoles **3b** and **3c** were prepared similarly.

The structure of **2a** was established on the basis of its spectral as well as chemical data. The electronic absorption spectrum of **3a** exhibits a long-wavelength absorption at 463 nm in methanol. On admixture of an equivalent amount of pyridinium chloride, complex **2a** is formed and the absorption shifts accordingly to 350 nm.

The mesoionic thiatriazoles are sensitive towards aqueous mineral acid and aqueous alkali, as evidenced by a rapid disappearance of the colour. They also react with 1,3-dipolarophiles such as dimethyl acetylenedicarboxylate. Thus, when thiatriazole **3a** was mixed with the dipolarophile at room temperature, a complete transformation had taken place within 2 h. However, the primary product appears labile and gives rise to several products on attempted isolation. These were not further investigated.

The formation of **3** on reaction of 1-amino-1-alkyl-3-arylguanidines with thionyl chloride may be considered to proceed via an *S*-oxide (**4**) which rapidly undergoes elimination of water. If one equiv. of thionyl chloride was used for the cyclization of **1a**, only 18 % thiatriazole was isolated. A 40 % yield was obtained with two equiv. but no further increase could be obtained even with seven equiv. of thionyl chloride. These results indicate a complex reaction in the formation of **3**, leading to other products as well. Elimination of water from **4** may be thionyl chloride assisted. The closely related cyclization of aromatic 1,2-diamines with thionyl chloride has been considered to involve an intermediate thionitroso oxide which undergoes cyclization to an *S*-oxide, followed by loss of water to form an $N{=}S^{+}{-}N^{-}$ grouping.[6,7]

Synthesis of the hitherto unknown heteroaromatic 1,2,3,5-thiatriazoles has been attempted. Thus, benzamidrazone **5** was treated with 1.07 equiv. of thionyl chloride in the presence of pyridine (Scheme 2). At 0 °C evolution of nitrogen was observed, and after completion of the reaction benzonitrile was formed in 37 % yield based on **5**. The yield of benzonitrile could be raised to 63–65 % by using 2.14 equiv. of thionyl chloride. Under the latter conditions elemental sulfur was isolated in ca. 60 % yield. The nature of the main products formed thus suggests intermediate formation of the 1,2,3,5-thiatriazole **6**, probably via an *S*-oxide.



5 6

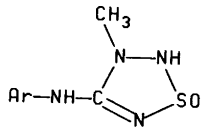
Scheme 2.

We have carried out the reaction between benzamidrazone and thionyl chloride at 0 °C in the presence of pyridine and benzonitrile (35 equiv.). As an indication of the intermediate formation of benzonitrile sulfide (**7**) from decomposing **6**, 3,5-diphenyl-1,2,4-thiadiazole was isolated, albeit in low yield (7 %). The low yield may, however, be due in part to a reported yield–temperature effect.[8,9]

Experimental

^{1}H NMR spectra were obtained with a JEOL FX 90 Q instrument (DMSO; $SiMe_4$ as internal standard), and UV spectra (methanol) with a Unicam SP 800A instrument. GLC was performed with a Hewlett Packard 5840A instrument.

Preparation of 1-amino-1-methyl-3-arylguanidine hydroiodides. The *N*-arylthiourea (0.1 mol) and methyl iodide (0.1 mol) were dissolved in ethanol (100 ml) and the solution was heated under reflux (1 h). The mixture was evaporated to dryness, and the remaining material was washed with dichloromethane or dry peroxide-free ether



4

C_6H_5CNS

7

and dried. The hydroiodide (0.1 mol) was dissolved in water (100 ml) and methylhydrazine (0.1 mol) was added, which caused formation of an oil. The mixture was left in a sealed flask with stirring until the oil had redissolved (ca. 72 h). The solution (*warning:* strong smell of methyl mercaptan) was filtered and evaporated to dryness *in vacuo*. The resulting material was dissolved in absolute ethanol and the solution was evaporated to dryness in order to remove methyl mercaptan. The crystalline product can be used directly for preparation of the respective mesoionic thiatriazole. Aryl: *Phenyl,* 80 % yield, m.p. 154–155 °C (absolute ethanol). Anal. $C_8H_{13}N_4I$: C, H, N. *4-Methylphenyl,* 41 % yield, m.p. 125–126.5 °C (absolute ethanol). Anal. $C_9H_{15}N_4I$, $1/2\,C_2H_5OH$: C, H, N. *2-Chlorophenyl,* 65 % yield, m.p. 157–157.5 °C (absolute ethanol). Anal. $C_8H_{12}N_4ClI$: C, H, N.

Preparation of anhydro 3-methyl-4-arylamino-1,2,3,5-thiatriazolium hydroxides. a. Formation of pyridinium chloride complexes. The 1-amino-1-methyl-3-arylguanidine (3.4 mmol) was dissolved in dry pyridine (4 ml) and the solution was cooled to 0 °C. Thionyl chloride (6.8 mmol) in dry ether (2 ml) was added with stirring over a period of 10 min, resulting in formation of a yellow precipitate. Excess thionyl chloride was removed by adding methanol (1 ml) and removing the solvent *in vacuo* at 25–30 °C. This process was repeated twice to give the thionyl chloride-free pyridinium chloride complex.

b. Formation of the mesoionic thiatriazole. The pyridinium chloride complex from *a* was dissolved in water (10 ml), the solution filtered and the filter washed with water (3×5 ml). Ether (10 ml) and then potassium carbonate (2 g) were added with stirring. The phases were separated and the aqueous phase extracted with ether (2×10 ml). The combined ether phases were washed with water (2 ml), dried over sodium sulfate and evaporated to dryness. The product was dissolved in a small volume of methanol (8 ml) and subjected to column chromatography (Kiesel 60, Merck, 15 g) with methanol as eluent. The strongly coloured band was collected and the solvent removed *in vacuo*. The thiatriazole was redissolved in ether; the solution was centrifuged to remove column material, and the supernatant was evaporated to dryness and the solid recrystallized from ether by cooling in acetone-dry ice. Aryl: *Phenyl,* 40 % yield, m.p. 94–94.5 °C. Violet-black, metallic luster. Anal. $C_8H_8N_4S$: C, H, N. NMR(δ): 3.9 (NCH_3), 6.8–7.4 (m, C_6H_5). UV (nm, log ε): 223, 4.03; 273, 4.26; 463, 2.87. *4-Methylphenyl,* 25 % yield, m.p. 123.5–124.5 °C. Dark purple, metallic luster. Anal. $C_9H_{10}N_4S$: C, H, N. NMR(δ): 2.2 (CH_3), 3.9 (NCH_3), 6.9–7.3 (q, C_6H_4), UV (nm, log ε): 223, 4.02; 270, 4.23; 468, 2.82. *2-Chlorophenyl,* 12 % yield, m.p. 123–123.5 °C. Dark brown, metallic luster. Anal. $C_8H_7N_4SCl$: C, H, N. NMR(δ): 4.0 (NCH_3), 6.7–7.7 (m, C_6H_4). UV (nm, log ε): 228, 4.00; 275, 4.07; 440, 2.90.

Reaction of benzamidrazone with thionyl chloride. a. Benzonitrile formation. Benzamidrazone (1.667 mmol) was dissolved in ether (5 ml) which has been dried by passing through alumina. Pyridine (1.5 ml) was added, the solution was cooled to 0 °C and thionyl chloride (1.78, 3.57 or 5.33 mmol) in ether (1 ml) was added over a period of 2–3 min. The reaction mixture was heated to room temperature and left with stirring for 30 min. Benzyl cyanide (0.2000 g) was added as internal standard for GLC determination of the amount of benzonitrile formed. Yields were determined as 37, 63–65, and 60 %, respectively.

b. Trapping of benzonitrile sulfide. Benzamidrazone (1.32 mmol) was dissolved in pyridine (0.75 ml). Benzonitrile (3.00 g, dried by passage through alumina) was added, the solution was cooled to 0 °C and thionyl chloride (2.60 mmol) in benzonitrile (1.70 g corresponding in total to a 35-fold excess) was added over a period of 2–3 min. Ether (30 ml) was added with stirring, the solution was filtered and the precipitate was washed with ether (5 ml). The filtrate was extracted with 2 M hydrochloric acid (2×10 ml) and washed with water (2×2 ml). The combined aqueous phases were extracted with ether (5 ml), and the combined ether phases were dried over sodium sulfate and evaporated to dryness. Benzonitrile was removed by distillation *in vacuo*. The resulting product was purified by preparative TLC (silica gel) with dichloromethane/petroleum ether (1:1) as eluent. The band corresponding to 3,5-diphenyl-1,2,4-thiadiazole was extracted from the solid support to give 21 mg of thiadi-

azole (7 % based on benzamidrazone), identified by comparison with an authentic sample. Besides the thiadiazole, only sulfur was present.

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Received August 24, 1987.