Tetrahedron Letters No. 9, pp 817 - 820.
©Pergamon Press Ltd. 1979. Printed in Great Britain.

0040-4039/79/0222-0817$02.00/0

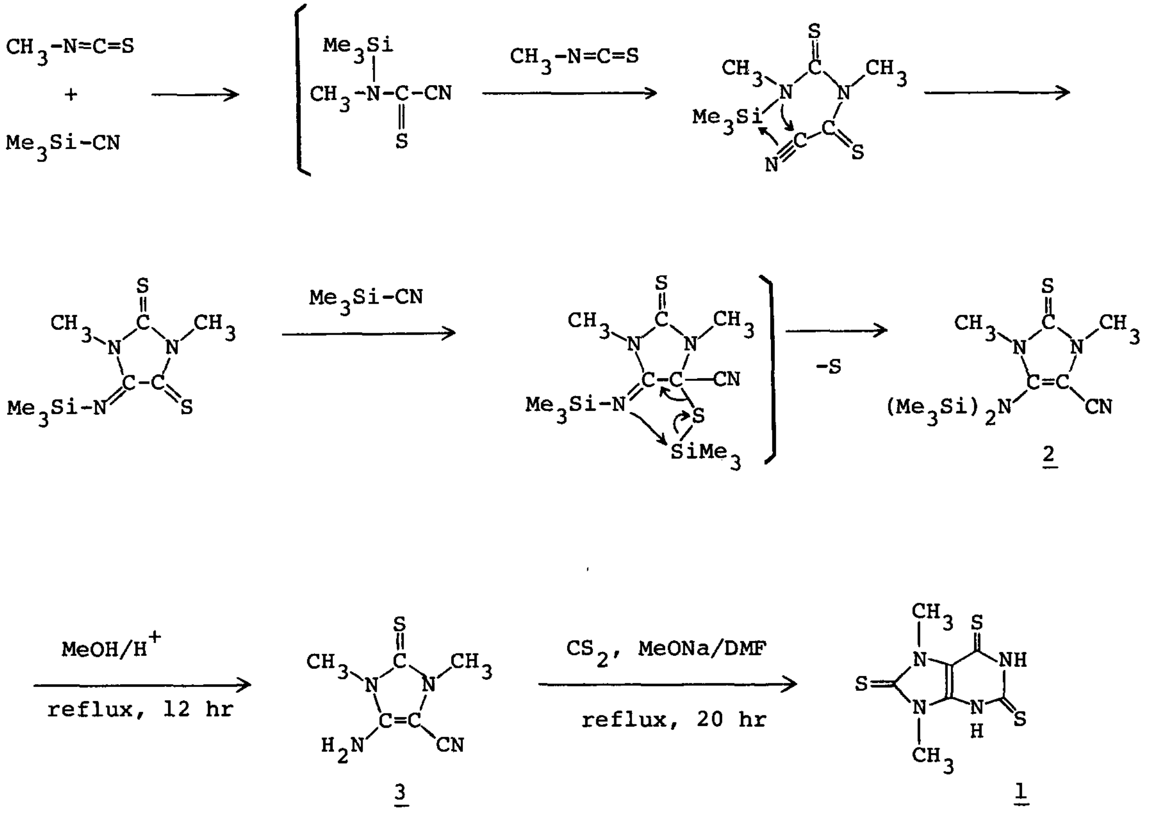
A CONVENIENT SYNTHESIS OF 1,3-DIMETHYL(5H,7H)IMIDAZO(4,5-d)PYRIMIDINE-2,4,6-TRITHIONE AND ITS UNUSUAL CHARACTER

Iwao Ojima* and Shin-ichi Inaba
Sagami Chemical Research Center, Nishi-Ohnuma 4-4-1, Sagamihara,
Kanagawa 229 (Japan)

Summary: 1,3-Diemthyl(5H,7H)imidazo(4,5-d)pyrimidine-2,4,6-trithione (1) was synthesized by the reaction of carbon disulfide with 1,3-dimethyl-4-cyano-5-aminoimidazolidine-2-thione (3) which was produced by reacting trimethylsilyl cyanide with methyl isothiocyanate followed by methanolysis. An unusual reversible formation of the dimethylamine salt of 1 is also described.

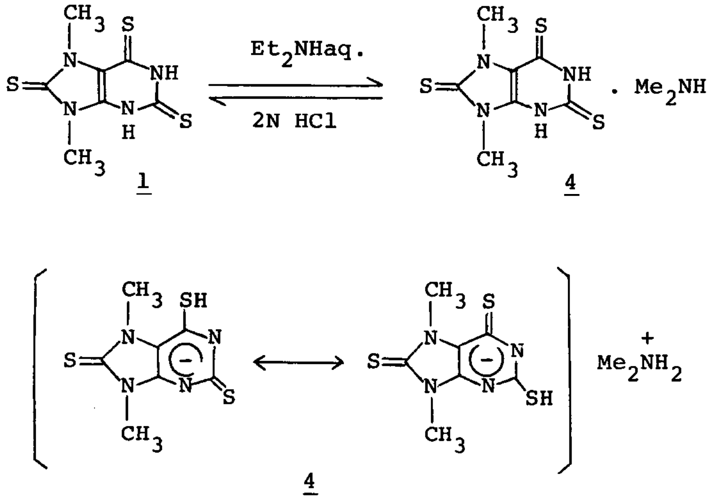
Of late years, trimethylsilyl cyanide has been shown to be a good reagent for the preparation of O-trimethylsilylcyanohydrin derivatives, which are employed as a selective carbonyl protective group or a masked carbanion precursor in organic synthesis.[1] The cyanosilylation of Schiff bases has provided a novel route to α-aminonitriles and α-amino acids.[2] It was also found that 5-iminoimidazolidine-2,4-diones and 2,4,5-triiminoimidazolidines were easily synthesized in excellent yields by the reactions of trimethylsilyl cyanide with isocyanates and carbodiimides followed by methanolysis, respectively.[3] We wish to describe here a convenient synthesis of a purin derivative via the reaction of trimethylsilyl cyanide with a isothiocyanate, and its unusual amine salt formation.

We found that the reaction of trimethylsilyl cyanide with methyl isothiocyanate gave 1,3-dimethyl-4-cyano-5-bis(trimethylsilyl)aminoimidazolidine-2-thione (2), which was desilylated by methanol - p-touluenesulfonic acid to give 1,3-dimethyl-4-cyano-5-aminoimidazolidine-2-thione (3). The ortho-aminonitrile 3, thus obtained, was allowed to react with carbon disulfide in the presence of sodium methoxide in N,N-dimethylformamide (DMF) following Taylor's method[4] to give 1,3-dimethyl(5H,7H)imidazo(4,5-_d_)pyrimidine-2,4,6-trithione (_1_) after acidic work-up using hydrochloric acid. A possible reaction pathway is depicted in Scheme 1.



Scheme 1

A typical procedure is as follows. A mixture of trimethylsilyl cyanide (2.0 g, 20 mmol) and methyl isothiocyanate (1.46 g, 20 mmol) was heated under reflux for 26 hr. After the reaction mixture had been cooled to ambient temperature, _n_-hexane (3 ml) was added. The resulting precipitates were recrystallized from ether to give 1.68 g (54%) of _2_.[5] A mixture of _2_ (1.56 g, 5.0 mmol) and p-toluenesulfonic aicd (60 mg) in methanol was heated under reflux for 12 hr, and the resulting precipitates were recrystallized from acetone to give 0.84 g (100%) of _3_.[6] A mixture of _3_ (0.84 g, 5.0 mmol), carbon disulfide (9 ml) and sodium methoxide (0.48 g) in DMF (20 ml) was heated under reflux for 20 hr. The solvent was removed by distillation under reduced pressure and the residue was dissolved in 1N NaOH, and filtered. The filtrate was acidified (pH 1) with hydrochloric acid to afford the precipitates, which were recrystallized from ethanol to give 0.68 g (56%) of 1.[7]



Scheme 2

When acetic acid was employed instead of hydrochloric acid for acidification, the obtained product (4) was an amine salt of 1. The amine salt structure of 4 was elucidated by i) a reversible salt formation of 1, and ii) a molecular weight determination using a vapor-pressure osmometer. Namely, 4 was produced in quantitative yield by simple mixing of 1 with dimethylamine in water,[8] and 1 was reproduced also in quantitative yield by treating 4 with hydrochloric acid as shown in Scheme 2; the apparent molecular weight of 4 was determined to be 164 in DMF, i.e., the fact clearly demonstrates that 4 is virtually separated to two ions since the true value for 4 is 289.44. Consequently, our results confirm that 4 is not an amine adduct, but the amine salt of 1, and also indicate that 1 is a considerably strong acid.[9] The reason why 1 is such a strong acid is unclear, but the observed unusual character is worth to be accounted in the investigations of hetero-cyclic systems similar to 4.

Acknowledgment

The authors are grateful to Dr. Renji Okazaki of The University of Tokyo for his helpful discussions.

References and Notes

1. e.g., W. Lidy and W. Sundermeyer, Chem. Ber., 106, 587 (1973); H. Neef, J. prakt. Chem., 316, 817 (1974); D. A. Evans, J. M. Hoffman and L. K. Truesdale, J. Amer. Chem. Soc., 95, 5822 (1973); D. J. Hart, P. A. Cain and D. A. Evans, ibid., 100, 1548 (1978); S. Hünig and G. Wenner, Synthesis, 180, 391 (1975), and references therein.

2. I. Ojima, S. Inaba, K. Nakatsugawa and Y. Nagai, Chem. Lett., 331 (1975); I. Ojima, S. Inaba and Y. Nagai, ibid, 737 (1975); Y. Nakajima, T. Makino, J. Oda and Y. Inouye, Agr. Biol. Chem., 39, 571 (1975).

3. I. Ojima, S. Inaba and Y. Nagai, JCS Chem. Comm., 826 (1974); Idem, J. Organometal. Chem., 99, C5 (1975).

4. E. C. Taylor, A. McKillop and R. N. Warrender, Tetrahedron, 23, 891 (1967).

5. 2: Colorless needles; mp. 132-135°C; IR (KBr disk) 2220 ($\nu_{C\equiv N}$), 1600 ($\nu_{C=C}$) and 1250 cm^{-1} (δ_{SiMe}); NMR ($CDCl_3$) δ 0.23 (s, 18H, SiMe), 3.40 (s, 3H, CH_3), and 3.67 (s, 3H, CH_3); elemental analysis gave sufficient results.

6. 3: Pale yellow needles; mp. 252-254°C; IR (KBr disk) 3340-3160 (ν_{NH}), 2220 ($\nu_{C\equiv N}$), 1670 ($\nu_{C=C}$) and 1600 cm^{-1} (δ_{NH}); NMR (d_6-acetone) δ 3.47 (s, 3H, CH_3), 3.50 (s, 3H, CH_3) and 6.13 (broad s, 2H, NH_2); elemental analysis gave sufficient results.

7. 1: Yellow needles; mp. >300°C; IR (KBr disk) 3200-2500 (ν_{NH} and ν_{SH}) and 1530 cm^{-1} (δ_{NH}); NMR (d_6-DMSO) δ 3.53 (s, 3H, CH_3), 3.97 (s, 3H, CH_3) and 5.80 (broad s, 2H, NH and SH); elemental analysis gave sufficient results.

8. 4: Yellow prisms; mp. >300°C; IR (KBr disk) 3100, 3030s, 2675, 2410 (ν_{NH} and ν_{SH}) and 1570 cm^{-1} (δ_{NH}); NMR (d_6-DMSO) δ 2.63 (s, Me_2N, 6H), 3.49 (s, CH_3, 3H) and 9.00 (broad s, NH and SH, 3H); elemental analysis gave sufficient results.

9. The pKa value of 1 was determined to be 3.81 by using a pH meter.

(Received in Japan 4 December 1978)