HETEROCYCLES, Vol. 24, No. 3, 1986

NEW METHODS AND REAGENTS IN ORGANIC SYNTHESIS. 59.[1]

LITHIUM TRIMETHYLSILYLDIAZOMETHANE: A NEW SYNTHON FOR THE PREPARATION OF 5-SUBSTITUTED 1,2,3-THIADIAZOLES

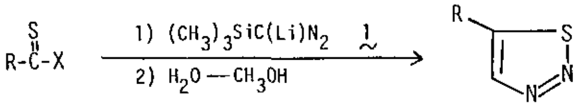
Toyohiko Aoyama,* Yuji Iwamoto, and Takayuki Shioiri*

Faculty of Pharmaceutical Sciences, Nagoya City University,
Tanabe-dori, Mizuho-ku, Nagoya 467, Japan

Abstract —— Lithium trimethylsilyldiazomethane smoothly reacts with thionoesters, dithioesters, and carbon disulfide to give 5-substituted 1,2,3-thiadiazoles.

Diazomethane is known to react with thiono and dithioesters to give 5-substituted 1,2,3-thiadiazoles.[2] However, these reactions are not general for the preparation of 1,2,3-thiadiazoles since the formation of 1,2,3-thiadiazoles depends on the substrates used and the reaction conditions. We have already demonstrated that the lithium salt of trimethylsilyldiazomethane (TMSCHN$_2$, $(CH_3)_3SiCHN_2$) is quite useful as a [C-N-N] synthon for the preparation of azoles.[3] As an extension of these works, the present communication deals with a new and convenient preparation of 5-substituted 1,2,3-thiadiazoles from thionoesters, dithioesters, and carbon disulfide.

We have found that treatment of thiono and dithioesters with lithium trimethylsilyldiazomethane (**1**), prepared from TMSCHN$_2$ with n-butyllithium, followed by direct workup with aqueous methanol gives 5-substituted 1,2,3-thiadiazoles (**2**) in good yields.

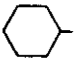
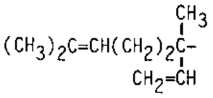
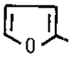
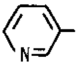


$X = OCH_3, SCH_3, SC_2H_5$

2

A typical experimental procedure for the preparation of **2** is as follows: To a solution of TMSCHN$_2$[4] (2.2 M hexane solution, 0.55 ml, 1.2 mmol) in diethyl ether (10 ml) was added dropwise n-butyllithium (15% hexane solution, 0.76 ml, 1.2 mmol) at -78°C under argon and the mixture was stirred for 20 min at -78°C. A solution of O-methyl thiobenzoate (152 mg, 1 mmol) in diethyl ether (3 ml) was then added dropwise at -78°C. The mixture was stirred at -78°C for 30 min, then

Table[a] Preparation of 5-Substituted 1,2,3-Thiadiazoles (2)

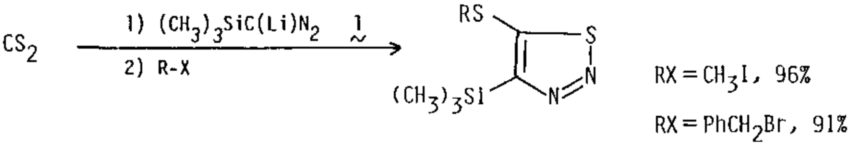
RC(S)X R	 X	Yield (%)	mp°C or bp°C(mmHg)[b]	^{1}H-NMR($CDCl_3$) δ at 4-H
Ph-	OCH_3	90	50.5-51.5[c,d]	8.93
Ph-	SCH_3	82		
$PhCH_2$-	OCH_3	83	80-85 (0.02)	8.47
$CH_3(CH_2)_8$-	OCH_3	79[e]	65-75 (0.025)	8.57
$CH_3(CH_2)_8$-	SCH_3	84[e]		
	OCH_3	70[e]	105-110 (18)	8.67
 $(CH_3)_2C{=}CH(CH_2)_2\overset{CH_3}{\underset{CH_2=CH}{C}}-$	SCH_3[f]	67[e]	125-135 (3)	8.43
PhCH=CH-	OCH_3	40	98-100[g]	8.73
	OCH_3	83	33-35[d]	9.02
	OCH_3	69[e]	91-92[g]	8.93
C_2H_5O-	SC_2H_5	67[h,i]	70-75 (4)	8.05
—$(CH_2)_3O$—		74[e]	75-80 (0.005)	8.58

a) Unless otherwise stated, the reaction was carried out as a typical procedure. All products gave satisfactory elemental analysis and spectral data. b) Distillation was carried out by a Kugelrohr apparatus. c) Lit.,[2a] mp 53-53.5°C. d) Recrystallized from benzene-hexane. e) Desilylation with aqueous methanol was carried out at reflux for 1-2 h. f) The starting dithioester was prepared in 73% yield by reaction of geranylmagnesium chloride with carbon disulfide, followed by methylation with methyl iodide. g) Recrystallized from ethyl acetate-hexane. h) The reaction with 1 was carried out at 0°C for 1 h. i) 5-Ethylthio-4-trimethylsilyl-1,2,3-thiadiazole is also obtained in 3% yield.

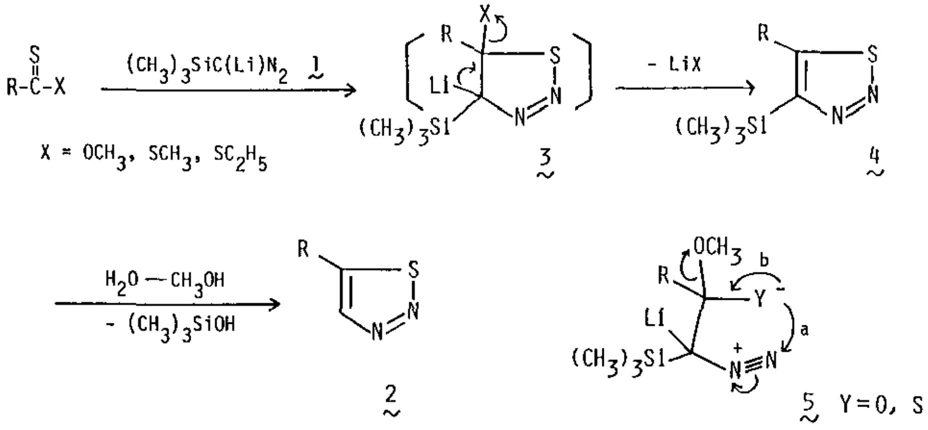
at 0°C for 30 min. After addition of water (1 ml) and methanol (5 ml), the mixture was stirred at room temperature for 1 h and concentrated in vacuo. The residue was suspended in water and extracted with benzene. The organic extracts were washed with water, saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (Merck silica gel Art. 7734, benzene : diethyl ether = 50 : 1) to give 5-phenyl-1,2,3-thiadiazole (146 mg, 90%).[5]

The results are summarized in Table. Various thionoesters including aromatic, heteroaromatic, and aliphatic ones react with **1** to give **2** in good yields. Other thiocarbonyl compounds, such as dithioesters and dihydro-2(3H)-furanthione, also undergo the reaction with **1** giving the corresponding 1,2,3-thiadiazoles. In the case of O,S-diethyl dithiocarbonate, 5-ethoxy-1,2,3-thiadiazole is formed as a major product accompanied with a small amount of 5-ethylthio-4-trimethylsilyl-1,2,3-thiadiazole.

Carbon disulfide has been reported not to give heterocyclic compounds by the reaction with diazomethane or TMSCHN$_2$.[6] In contrast to these, however, the reaction with **1** smoothly affords 5-alkylthio-4-trimethylsilyl-1,2,3-thiadiazoles after direct alkylation with alkyl halides.[7]



The reaction mechanism of the formation of 1,2,3-thiadiazoles may be considered as follows: Nucleophilic attack of **1** on the thiocarbonyl carbon of RC(S)X, followed by cyclization could give a 1,2,3-thiadiazoline intermediate **3**. Subsequent elimination of LiX from **3** occurs to give a 4-trimethylsilyl-1,2,3-thiadiazole **4**, which is hydrolyzed with alkaline aqueous methanol to afford **2**.



We have already reported that methyl esters of carboxylic acids smoothly react with two equivalents of **1** to give tetrazoles in good yields via an α-silyldiazoketone intermediate.[3a] In contrast with this reaction, the reaction of **1** with thionoesters affords 1,2,3-thiadiazoles. The differences of reactivity toward **1** between esters and thionoesters may be due to the nucleophilicity of R-S$^-$ (path a) and R-O$^-$ (path b) in the betaine intermediate **5** which seems to be initially formed.

Starting thionoesters are easily prepared by treatment of the corresponding esters with Lawesson's reagent.[8] Dithioesters are also conveniently prepared by the Grignard reaction with carbon disulfide followed by alkylation.[9] Thus, the present method in combination with the preparation of thiono and dithioesters provides a convenient, short step preparation of 5-substituted 1,2,3-thiadiazoles.

REFERENCES AND NOTES

1. For Part 58, see Y. Hamada, M. Shibata, and T. Shioiri, Tetrahedron Lett., in press.
2. a) U. Schmidt, E. Heymann, and K. Kabitzke, Chem. Ber., 1963, 96, 1478. b) J. M. Beiner, D. Lecadet, D. Paquer, A. Thuiller, and J. Vialle, Bull. Soc. Chim. Fr., 1973, 1979. c) D. S. Wulfmann, G. Linstrumelle, and C. F. Cooper, "The chemistry of diazonium and diazo groups", Part 2, ed. by S. Patai, John Wiley and Sons, 1978, Chapter 18. d) E. W. Thomas, "Comprehensive Heterocyclic Chemistry", Vol. 6, Part 4B, ed. by K. T. Potts, Pergamon Press, New York, 1984, p.447.
3. a) T. Aoyama and T. Shioiri, Chem. Pharm. Bull., 1982, 30, 3450. b) T. Aoyama, K. Sudo, and T. Shioiri, Chem. Pharm. Bull., 1982, 30, 3910. c) T. Aoyama, S. Inoue, and T. Shioiri, Tetrahedron Lett., 1984, 25, 433. d) T. Aoyama, M. Kabeya, A. Fukushima, and T. Shioiri, Heterocycles, 1985, 23, 2363. e) T. Aoyama, M. Kabeya, A. Fukushima, and T. Shioiri, Heterocycles, 1985, 23, 2367. f) T. Aoyama, M. Kabeya, and T. Shioiri, Heterocycles, 1985, 23, 2371.
4. S. Mori, I. Sakai, T. Aoyama, and T. Shioiri, Chem. Pharm. Bull., 1982, 30, 3380.
5. After the reaction with 1, aqueous treatment for 1-2 h under alkaline conditions is required to obtain 5-substituted 1,2,3-thiadiazoles cleanly. For example, a mixture of 5-phenyl-4-trimethylsilyl-1,2,3-thiadiazole (69%) and 5-phenyl-1,2,3-thiadiazole (10%) was obtained from O-methyl thiobenzoate when the reaction was carried out as a typical procedure and the reaction mixture was worked up with water immediately. The former was easily desilylated under either alkaline (KOH-H_2O-MeOH, room temp., 1 h) or acidic (conc. HCl-MeOH, reflux, 1 h) conditions, giving the latter quantitatively.
6. M. F. Lappert and J. S. Poland, J. Chem. Soc., Chem. Commun., 1969, 156; J. Chem. Soc. (C), 1971, 3910.
7. A typical experimental procedure is as follows: Carbon disulfide (152 mg, 2 mmol) in diethyl ether (3 ml) was added at -70°C to lithium trimethylsilyldiazomethane (1) prepared from $TMSCHN_2$ (2.4 mmol) and n-butyllithium in diethyl ether (10 ml). After the mixture was stirred at -70°C for 30 min, methyl iodide (341 mg, 2.4 mmol) was added. The mixture was stirred at -70°C for 30 min, then at 0°C for 2.5 h. Ice-water (1 ml) was added, and the mixture was concentrated in vacuo. The residue was worked up as in the above preparation of 5-phenyl-1,2,3-thiadiazole to give 5-methylthio-4-trimethylsilyl-1,2,3-thiadiazole.
   Desilylation of 1,2,3-thiadiazoles smoothly proceeded to give the corresponding 5-alkylthio-1,2,3-thiadiazoles by treatment with a mixture of potassium fluoride dihydrate and tetra-n-butylammonium chloride in acetonitrile at room temperature for 30 min: R= Me (95%), bp 40-50°C/0.1 mmHg; R= $PhCH_2$ (97%), mp 52-53°C (reported: mp 50-51°C, P. Demaree, M.-C. Doria, and J.M. Muchowski, J. Heterocycl. Chem., 1978, 15, 1295).
8. B. S. Pedersen, S. Scheibye, K. Clausen, and S.-O. Lawesson, Bull. Soc. Chim. Belg., 1978, 87, 293. See also, E. J. Corey and S. W. Wright, Tetrahedron Lett., 1984, 25, 2639.
9. J. Meijer, P. Vermeer, and L. Brandsma, Recl. Trav. Chim. Pays-Bas, 1973, 92, 601.

Received, 28th October, 1985