

NEW METHODS AND REAGENTS IN ORGANIC SYNTHESIS. 54.†,1

LITHIUM TRIMETHYLSILYLDIAZOMETHANE: A NEW SYNTHON FOR THE PREPARATION OF 1-SUBSTITUTED 5-ALKYLTHIO-1,2,3-TRIAZOLES FROM ISOTHIOCYANATES

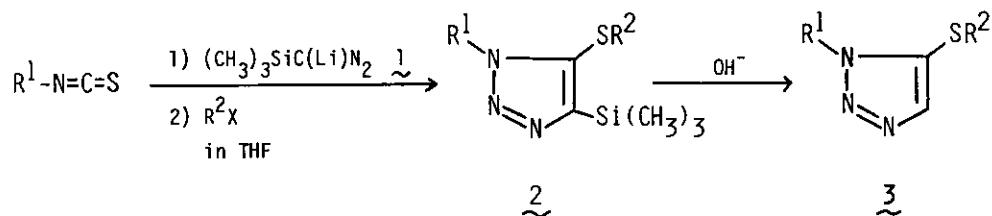
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Abstract — Lithium trimethylsilyldiazomethane (1) reacts smoothly with isothiocyanates in tetrahydrofuran to give 1-substituted 4-trimethylsilyl-5-alkylthio-1,2,3-triazoles (2) after quenching with alkyl halides. Desilylation of 2 is easily achieved with 10% aqueous potassium hydroxide in methanol to afford 1-substituted 5-alkylthio-1,2,3-triazoles (3).

In the preceding communication,¹ we have reported that the lithium salt of trimethylsilyldiazomethane (TMSCHN₂, (CH₃)₃SiCHN₂) reacts with isothiocyanates in diethyl ether to give 2-amino-1,3,4-thiadiazoles in good yields. During the course of our studies on this reaction, a dramatic solvent effect leading to the formation of 1,2,3-triazoles was observed in the use of tetrahydrofuran in place of diethyl ether as solvent.

We have found that treatment of isothiocyanates with lithium trimethylsilyldiazomethane (1), prepared from TMSCHN₂ and *n*-butyllithium, followed by quenching with alkyl halides in tetrahydrofuran gives 1-substituted 4-trimethylsilyl-5-alkylthio-1,2,3-triazoles (2) in excellent yields. In




† Dedicated to Professor Shun-ichi Yamada on the occasion of his 70th birthday.

this reaction, 2-amino-1,3,4-thiadiazoles obtained in the use of diethyl ether as solvent could not be detected at all. Removal of the trimethylsilyl group of 2 has been easily carried out with 10% aqueous potassium hydroxide in boiling methanol to give 1-substituted 5-alkylthio-1,2,3-triazoles (3) in almost quantitative yields.

The results are summarized in Table. Various isothiocyanates including aromatic and aliphatic ones react with 1 to give 2. Tetrahydrofuran is essential as solvent to conduct the reaction. Desilylation of 2 is easily achieved with 10% aqueous potassium hydroxide in methanol. Tetra-n-butylammonium chloride and potassium fluoride dihydrate in acetonitrile² may be also effectively used for desilylation (see run 8 in Table).

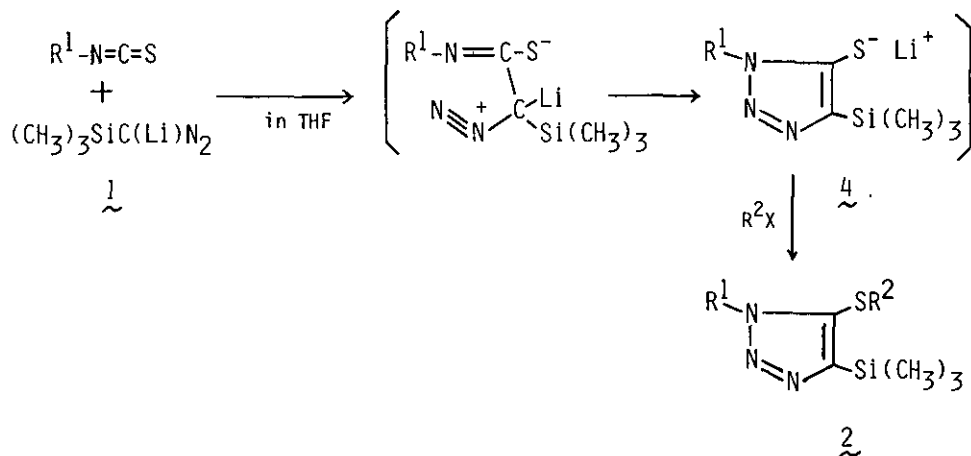
Table^a Preparation of 1-Substituted 4-Trimethylsilyl-5-alkylthio-1,2,3-triazoles (2) and 1-Substituted 5-alkylthio-1,2,3-triazoles (3)

Run	R ¹	R ² X	Yield(%) <u>2</u>	mp(°C) or bp(°C) (mmHg)	Yield(%) <u>3</u>	mp(°C) or bp(°C) (mmHg)
1	Ph-	CH ₃ I	98	100-115 (0.005)	94	120-130 ^b (0.01)
2	Ph-	PhCH ₂ Br	99	58-59 ^c	97	135-145 (0.005)
3	CH ₃ -	CH ₃ I	96	70-80 (0.01)	100	55-60 ^d (0.005)
4	CH ₃ -	PhCH ₂ Br	90	48-49 ^c	98	120-130 (0.005)
5	CH ₃ (CH ₂) ₃ -	PhCH ₂ Br	97	125-135 (0.05)	95	125-140 (0.005)
6		PhCH ₂ Br	98	62-63 ^c	96	76-78 ^c
7	PhCH ₂ -	PhCH ₂ Br	91	90-91 ^e	99	82-83 ^{c, f}
8	CH ₂ =CHCH ₂ -	PhCH ₂ Br	91	51-53 ^c	83 (99) ^g	120-125 (0.005)

a) Unless otherwise stated, the reaction was carried out as a typical procedure. All compounds gave satisfactory elemental analysis and spectral data. b) Lit.,³ bp 112-114°C/0.005mmHg. c) Recrystallized from diethyl ether-hexane. d) Lit.,³ bp 68-69°C/0.03mmHg. e) Recrystallized from benzene-hexane. f) Lit.,⁴ mp 82°C. g) Desilylation was carried out using tetra-n-butylammonium chloride and potassium fluoride dihydrate at 60-70°C for 3 h in acetonitrile.

Although the great differences in the reactivity of 1 to isothiocyanates caused by the use of diethyl ether and tetrahydrofuran can not be explained at the present time, a probable mechanism of

the formation of 2 may be as follows: Nucleophilic attack of 1 on the carbon atom of the isothiocyanate group, followed by cyclization will give a 1,2,3-triazole intermediate 4 which is trapped with an alkyl halide to afford 2.



1-Substituted 5-alkylthio-1,2,3-triazoles are generally prepared by the rearrangement of 5-amino-1,2,3-thiadiazoles under basic conditions⁵ or the reaction of isothiocyanates with an excess of diazomethane.³ As compared with these procedures, the method described here provides a novel, simple one-pot and high-yield conversion of isothiocyanates to 5-alkylthio-1,2,3-triazoles. Furthermore, combined with preceding observation,¹ the lithium salt of $TMSCHN_2$ can be efficiently used for the chemoselective preparation of 2-amino-1,3,4-thiadiazoles and 5-alkylthio-1,2,3-triazoles from isothiocyanates.

Typical experimental procedures for each reaction are as follows:

Preparation of 1-Substituted 4-Trimethylsilyl-5-alkylthio-1,2,3-triazoles (2) To a solution of $TMSCHN_2$ ⁶ (2M hexane solution, 0.6 ml, 1.2 mmol) in tetrahydrofuran (10 ml) was added dropwise *n*-butyllithium (15% hexane solution, 0.76 ml, 1.2 mmol) at $-78^\circ C$ under argon and the mixture was stirred for 20 min at $-78^\circ C$. A solution of isothiocyanate (1 mmol) in tetrahydrofuran (3 ml) was then added dropwise at $-78^\circ C$. After 1 h at $-78^\circ C$, alkyl halide (1.2 mmol) was added at $-78^\circ C$, and the mixture was stirred at $-78^\circ C$ for 1 h, then at $0^\circ C$ for 2 h. The mixture was treated with ice-water and extracted with benzene. The organic layer was washed with water, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography (Merck Art. 7734, hexane : diethyl ether : ethyl acetate = 9 : 2 : 1) to give 2.

Desilylation of 2 A mixture of 2 (1 mmol), 10% aqueous potassium hydroxide (5 ml), and methanol (10 ml) was heated at reflux for 2 h. After concentration in vacuo, water was added to the residue and the mixture was extracted with benzene. The benzene layer was washed with water, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by

silica gel column chromatography (Merck Art. 7734, hexane : diethyl ether : ethyl acetate = 6 : 3 : 1) to give 1-substituted 5-alkylthio-1,2,3-triazole (3).

REFERENCES AND NOTES

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