NEW METHODS AND REAGENTS IN ORGANIC SYNTHESIS. 53.†,[1] LITHIUM TRIMETHYLSILYLDIAZOMETHANE: A NEW SYNTHON FOR THE PREPARATION OF 2-AMINO-1,3,4-THIADIAZOLES FROM ISOTHIOCYANATES[2]

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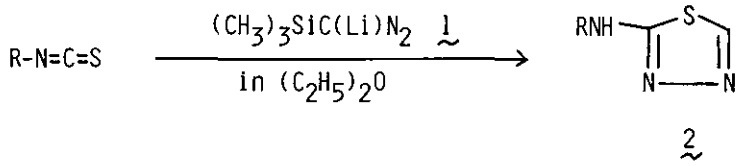
Abstract ——Lithium trimethylsilyldiazomethane reacts smoothly with isothiocyanates in diethyl ether to give 2-amino-1,3,4-thiadiazoles in good yields.

In the preceding communication,[1] we have reported that the lithium salt of trimethylsilyldiazomethane ($TMSCHN_2$, $(CH_3)_3SiCHN_2$) reacts smoothly with isocyanates to give 1-substituted 5-hydroxy-1,2,3-triazoles in good yields. Our continuous interests in the use of $TMSCHN_2$ as a [C-N-N] synthon for the preparation of azoles have led us to investigate the reaction of the lithium salt of $TMSCHN_2$ with isothoicyanates.

We have found that lithium trimethylsilyldiazomethane (1), prepared from $TMSCHN_2$ and n-butyllithium, reacts smoothly with isothiocyanates in diethyl ether to give 2-amino-1,3,4-thiadiazoles (2). It is noteworthy in this reaction that the formation of 5-mercapto-1,2,3-triazole derivatives similar to the products obtained by the reaction of 1 with isocyanates[1] can not be found.



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

A typical experimental procedure for the preparation of 2 is as follows (run 1 in Table): To a solution of $TMSCHN_2$[3] (2M hexane solution, 0.6 ml, 1.2 mmol) in diethyl ether (10 ml) was added dropwise n-butyllithium (15% hexane solution, 0.76 ml, 1.2 mmol) at 0°C under argon and the mixture was stirred for 20 min at 0°C. A solution of phenyl isothiocyanate (135 mg, 1 mmol) in diethyl ether (3 ml) was then added dropwise at 0°C. The mixture was stirred at 0°C for 2 h and treated with saturated aqueous ammonium chloride. The mixture was extracted with diethyl ether, washed with water, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by preparative layer chromatography (Merck Art. 5715, chloroform : ethanol = 20 : 1) to give 2-anilino-1,3,4-thiadiazole (147 mg, 83%), which was identified by spectroscopic comparison with an authentic sample prepared from 4-phenyl-3-thiosemicarbazide and ethyl orthoformate.[4]

The results are summarized in Table. Various isothiocyanates including aromatic and aliphatic ones react with 1 to give 2. Diethyl ether is a solvent of choice in the use of aryl isothiocyanates, but hexane is preferable in the case of aliphatic ones, though higher reaction temperature is required for the completion of the reaction.

Table[a] Preparation of 2-Amino-1,3,4-thiadiazoles (2)

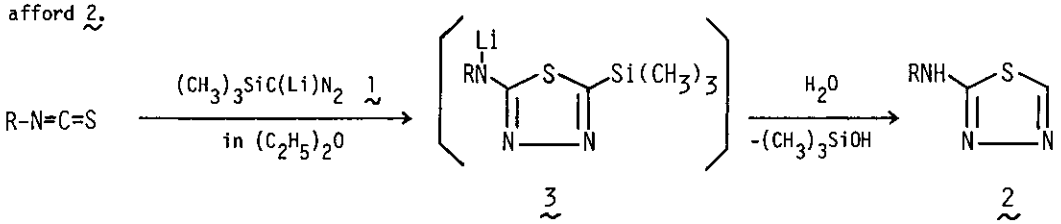
Run	R	Reaction Conditions	Yield (%)	mp (°C)	Recry. Solvent	lit. mp (°C)
1	Phenyl	0°C, 2 h	83	170–171	EtOH	173[b]
2	4-Chlorophenyl	0°C, 2 h	83	196.5–197.5	EtOH	204[c]
3	1-Naphthyl	0°C, 2.5 h	60	163.5–164.5	Benzene–Hexane	136[c,d]
4	2-Naphthyl	0°C, 1.5 h	74	182.5–183.5	$CHCl_3$	
5	Benzyl	0°C, 2 h	57	108–108.5	Benzene–Hexane	109[c]
6	Allyl	0°C, 2.5 h	40	70–72	Benzene–Hexane	73[b]
7	n-Butyl	0°C, 2 h r.t., 1.5 h	56[e]	59–60	Benzene–Hexane	
8	Cyclohexyl	0°C, 2 h r.t., 1.5 h	62[e]	163–164	Benzene–Hexane	165[b]

a) Unless otherwise stated, the reaction was carried out as a typical procedure. All products gave satisfactory elemental analysis and spectral data. b) Reference 4. c) Reference 5. d) We believe this mp will be erroneously written since a sample prepared from 4-(1-naphthyl)-3-thiosemicarbazide and ethyl orthoformate according to the literature[5] shows the same mp as that of the sample prepared by our new method. e) The reaction was carried out in hexane using a little excess of 1 (1.5 equiv).

Diazomethane is well known to react with isothiocyanates to give 5-amino-1,2,3-thiadiazoles via

1,3-dipolar cycloaddition across the thiocarbonyl bond.[6] However, Lappert and co-worker[7] have reported that with $TMSCHN_2$ nitrogen appears to be evolved and no heterocycle is isolated. In contrast with the products using diazomethane or $TMSCHN_2$, the product is 2-amino-1,3,4-thiadiazole when 1 is used.

Mechanistically, this interesting conversion of isothiocyanates to 2-amino-1,3,4-thiadiazoles may be as follows: Thiophilic attack[8] of 1 to the thiocarbonyl bond of the isothiocyanate group, followed by cyclization to give the intermediate 3, which is hydrolyzed with water during work-up to afford 2.



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The most common procedure for 2-amino-1,3,4-thiadiazoles is the condensation of 4-substituted 3-thiosemicarbazides, prepared from isothiocyanates and hydrazine, with ethyl orthoformate.[4,5,9] As compared with this procedure, the method described here provides a convenient one-step conversion of isothiocyanates to 2-amino-1,3,4-thiadiazoles.

During the course of this study, we observed a dramatic solvent effect leading to the formation of 1,2,3-triazoles in the use of tetrahydrofuran as solvent, which will be the subject of the following communication.[10]

ACKNOWLEDGEMENT

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