

NEW METHODS AND REAGENTS IN ORGANIC SYNTHESIS. 41.¹
LITHIUM TRIMETHYLSILYLDIAZOMETHANE. A NEW SYNTHON
FOR THE PREPARATION OF PYRAZOLES FROM α,β -UNSATURATED NITRILES

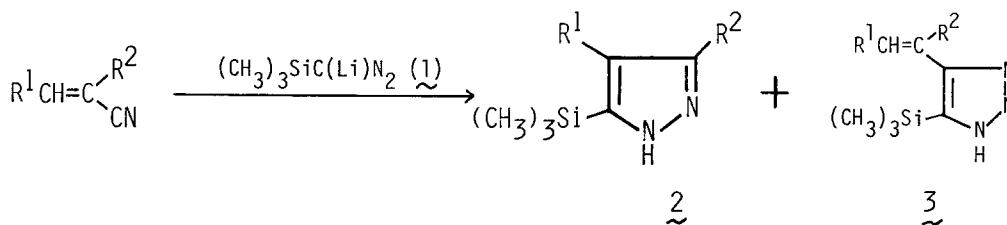
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Lithium trimethylsilyldiazomethane reacts smoothly with various α,β -unsaturated nitriles to give 3(or 5)-trimethylsilylpyrazoles in good yields.

We have already reported that the lithium salt of trimethylsilyldiazomethane (TMSCHN_2 , $(\text{CH}_3)_3\text{SiCHN}_2$) reacts smoothly with methyl esters of carboxylic acids and various nitriles to give tetrazoles² and 1,2,3-triazoles³, respectively. Our continuous interest on the utilization 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 α,β -unsaturated nitriles.

We have found that lithium trimethylsilyldiazomethane (1), easily prepared from TMSCHN_2 and n-butyllithium, reacts smoothly with α,β -unsaturated nitriles to give 3(or 5)-trimethylsilylpyrazoles (2) in good yields. In some cases, small amounts of 5-trimethylsilyl-1,2,3-triazoles (3) are formed as by-products.

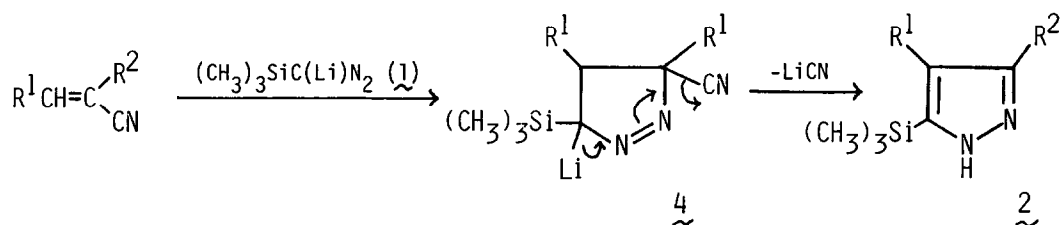


A typical experimental procedure for the preparation of 2 is as follows (run 9 in Table): To a solution of TMSCHN_2 ⁴ (2.2 M hexane solution, 0.68 ml, 1.5 mmol) in tetrahydrofuran (10 ml) was added dropwise n-butyllithium (15% hexane solution, 0.95 ml, 1.5 mmol) at -78°C under argon and the mixture was stirred for 20 min at -78°C . A solution of cinnamitrile (129 mg, 1 mmol) in tetrahydrofuran (3 ml) was then added dropwise at -78°C . The mixture was stirred at -78°C for 0.5 h, allowed to warm to -45°C during 1.5 h, then stirred at 0°C .

for 4 h. The mixture was treated with saturated aqueous ammonium chloride and extracted with benzene. The organic layer was 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, chloroform : diethyl ether = 20 : 1) to give 4-phenyl-3-trimethylsilylpyrazole (190 mg, 88%), mp 117-118.5°C (Lit.,⁵ mp 121.5-122.5°C).

The results are summarized in Table. Various α,β -unsaturated nitriles including aliphatic and aromatic ones reacted with 1 to give 2. Although α,β -unsaturated nitriles bearing bulky substituents at α and/or β positions of the nitrile group underwent the reaction with 1 to give 2 in diethyl ether at 0°C, considerable amounts of 1,2,3-triazoles (3), resulting from the reaction of 1 and the nitrile group,³ were formed.⁶ In these cases, the reaction temperature did not significantly affect the ratio of 2 and 3. However, changing the reaction solvent from diethyl ether to tetrahydrofuran had a remarkable effect on the ratio of 2 and 3, and the former was mainly formed. No difference of the reactivity of (E)- and (Z)-isomers to 1 was observed (runs 4 and 5). Benzylidenemalononitriles and benzylidenecyanoacetate also reacted with 1 to give the corresponding 3-cyano and 3-methoxycarbonylpyrazoles, respectively. Removal of the trimethylsilyl group of 2 has been easily carried out with 10% aqueous potassium hydroxide or hydrochloric acid-potassium fluoride in ethanol to give 4-substituted or 3,4-disubstituted pyrazoles in good yields.⁷



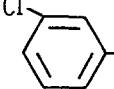

Mechanism of the conversion of α,β -unsaturated nitriles to pyrazoles may be as follows: Nucleophilic attack of 1 on the β -carbon of the nitrile group, followed by cyclization gives pyrazoline intermediates (4).⁸ Subsequent elimination of lithium cyanide from 4 occurs to give pyrazoles 2.



Pyrazoles are generally prepared by the condensation of 1,3-diketones with hydrazines or the cycloaddition of acetylenes to diazoalkanes.⁹ The principal drawback of these methods is that unsymmetrical 1,3-diketones or acetylenes generally produce two regioisomeric pyrazoles. By contrast, the method described herein has no such regiochemical problem. Moreover, it should be noted that the reaction of α,β -unsaturated nitriles with diazoalkanes¹⁰ including TMSCHN₂¹¹ generally affords pyrazolines in place of pyrazoles.¹² Thus, the present method provides a new and convenient preparation of pyrazoles from α,β -unsaturated nitriles.

Acknowledgement This work was supported in part by a Grant-in-Aid for Scientific Research (No. 58570882) from the Ministry of Education, Science and Culture, Japan and by Takeda Science Foundation, to which our thanks are due. We thank Mr. Kimio Sudo for his able preliminary experiments.

Table.^a Reaction of Lithium Trimethylsilyldiazomethane (1)
with α,β -Unsaturated Nitriles

| Run | R ¹ | R ² | Reaction Solvent | Reaction Conditions | Yield.% | |
|-----|--|---|-------------------|--|-----------------|----------|
| | | | | | <u>2</u> | <u>3</u> |
| 1 | H | H | Et ₂ O | 0°C, 1.5h | 65 | - |
| 2 | CH ₃ - (E/Z = 36/64) | H | Et ₂ O | 0°C, 1.5h | 82 | - |
| 3 | H | CH ₃ - | Et ₂ O | 0°C, 1.5h | 76 | - |
| 4 | CH ₃ (CH ₂) ₂ - (E) | H | Et ₂ O | 0°C, 1.5h | 66 | 7 |
| 5 | CH ₃ (CH ₂) ₂ - (Z) | H ^b | Et ₂ O | 0°C, 1.5h | 68 | 5 |
| 6 | (CH ₃) ₃ C- (E/Z = 55/45) | H | THF | -78°C, 2h 4h → -8°C | 71 | 6 |
| 7 | CH ₃ CH ₂ - (E/Z = 24/76) | CH ₃ (CH ₂) ₂ - | THF | -78°C, 2.5h 3.5h → -8°C | 59 | 3 |
| 8 | -CH ₂ CH(t-Bu)(CH ₂) ₂ - | | THF | -78°C, 2.5h 2.5h → -52°C | 49 | 20 |
| 9 |  (E) | H | THF | -78°C, 0.5h 1.5h → -45°C 0°C, 4h | 88 | - |
| 10 |  | CN | Et ₂ O | -78°C, 1h 0°C, 1h | 82 ^c | - |
| 11 |  | CN | Et ₂ O | -78°C, 1h 0°C, 1h | 80 ^c | - |
| 12 |  | CO ₂ CH ₃ | Et ₂ O | -78°C, 1h 0°C, 1h | 39 ^c | - |

- a) Unless otherwise stated, the reaction was carried out as a typical procedure. Satisfactory elemental analysis and spectral data were obtained for all products.
- b) The starting (Z)-hex-2-enenitrile was prepared according to the reported method, see Y. Sato and Y. Niinomi, *J. Chem. Soc. Chem. Commun.*, 1982, 56.
- c) A little excess of 1 (1.2 equiv) was used.

References and Notes

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- 4 S. Mori, I. Sakai, T. Aoyama, and T. Shioiri, Chem. Pharm. Bull., 30, 3380 (1982).
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- 6 For example, β -t-butylacrylonitrile was treated with 1 at 0°C in diethyl ether for 1.5 h, 2 (39%) and 3 (51%) were obtained.
- 7 a) Desilylation with 10% potassium hydroxide: 3-Cyano-4-phenyl-5-trimethylsilylpyrazole (48 mg, 0.2 mmol) was refluxed with 10% aqueous potassium hydroxide (1 ml) in ethanol (1 ml) for 1 h to give 3-cyano-4-phenylpyrazole in 97% yield. Analogously, 4-methylpyrazole was obtained from its 3-trimethylsilyl derivative in 68% yield.
 b) Desilylation with hydrochloric acid—potassium fluoride: 4-Phenyl-3-trimethylsilylpyrazole (216 mg, 1 mmol) was refluxed with concentrated hydrochloric acid (0.2 ml) and potassium fluoride (58 mg, 1 mmol) in ethanol (10 ml) for 10 h to give 4-phenylpyrazole in 75% yield.
- 8 In fact, when cinnamionitrile was treated with 1 at -78°C in diethyl ether for 1.5 h and quenched at -78°C, the corresponding pyrazoline ((E)-5-cyano-4-phenyl-3-trimethylsilyl-2-pyrazoline) was obtained in 39% yield, accompanied with 4-phenyl-3-trimethylsilylpyrazole (15%) and 4-trans-styryl-5-trimethylsilyl-1,2,3-triazole (7%).
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- 12 However, cinnamionitrile was reported to react with diazomethane, giving 4-phenylpyrazole. K. v. Auwers and O. Ungemach, Ber., 66, 1198 (1933).

(Received in Japan 18 October 1983)