HETEROCYCLES, Vol 27, No 2, 1988

NEW METHODS AND REAGENTS IN ORGANIC SYNTHESIS. 74.[1]
LITHIUM TRIMETHYLSILYLDIAZOMETHANE. A USEFUL REAGENT FOR THE PREPARATION OF PYRAZOLES FROM α,β-UNSATURATED SULFONES

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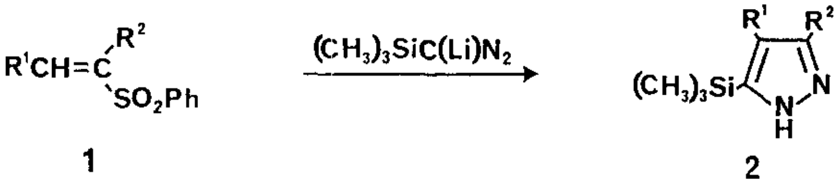
Abstract —— Lithium trimethylsilyldiazomethane smoothly reacts with various α,β-unsaturated sulfones to give 3 (or 5)-trimethylsilylpyrazoles in excellent yields.

Recent reports[2] from these laboratories have demonstrated that lithium trimethylsilyldiazomethane (TMSC(Li)N_2, $(CH_3)_3SiC(Li)N_2$), easily prepared from trimethylsilyldiazomethane (TMSCHN_2, $(CH_3)_3SiCHN_2$) and n-butyllithium, is quite useful as a [C-N-N] synthon for the preparation of azoles. For instance, pyrazole skeletons can be conveniently constructed[3] by the reaction of TMSC(Li)N_2 with α,β-unsaturated nitriles. In some cases, however, 1,2,3-triazole derivatives have been formed as by-products though in lower yields. Our continued interest in the azole synthesis using TMSC(Li)N_2 prompts us to report an exceptionally convenient procedure for the preparation of pyrazoles **2** by the reaction of TMSC(Li)N_2 with α,β-unsaturated sulfones **1** :



Replacement of the leaving function from the cyano group to the phenylsulfonyl one led to a significant improvement of the efficiency of the pyrazole synthesis. The following general procedure indicates the simplicity of the method : To TMSCHN_2 (1.8M hexane solution,[4] 0.67ml, 1.2mmol) in diethyl ether (8ml) was added dropwise n-butyllithium (15% hexane solution, 1.38ml, 2.2mmol) at -78°C under argon and the mixture was stirred for 20min at -78°C. α,β-Unsaturated sulfone (1mmol) in diethyl ether (2ml) was added at -78°C. The mixture was stirred at -78°C for

1h, then at 0°C for 2h. After the addition of cold water (5ml), the mixture was extracted with diethyl ether. The organic layer was washed with water and saturated aqueous sodium chloride, and dried over magnesium sulfate. Removal of the solvent in vacuo followed by the purification of the residue by column chromatography on silica gel (BW-820 MH, Fuji Davison) afforded 3 (or 5)-trimethylsilylpyrazole.

The results of the pyrazole synthesis are compiled in Table. Various α,β-unsaturated sulfones **1** including aliphatic and aromatic ones react with $\mathrm{TMSC(Li)N_2}$ to give the pyrazoles **2** in excellent yields. As can be seen from Table, the geometry of the double bond is not critical in the reaction. Two equivalents of n-butyllithium is usually required to conduct the reaction smoothly. Changing n-butyllithium to lithium diisopropylamide improved the yields when the use of n-butyllithium was not efficient. A strong base as n-butyllithium or lithium diisopropylamide is essential in this reaction since $\mathrm{TMSCHN_2}$ alone does not react with **1** at all and the use of 1,8-diazabicyclo[5.4.0]undec-7-ene as a base is completely ineffective. Both diethyl ether and tetrahydrofuran can be used as a reaction solvent. Addition of hexamethylphosphoramide as a co-solvent does not affect the reaction at all.

α,β-Unsaturated sulfones **1** may be replaced with the corresponding sulfoxides but not enol sulfonates. Phenyl phenylethynyl sulfone easily reacts with $\mathrm{TMSC(Li)N_2}$ (1.2 equiv.) under similar reaction conditions as above to give 3-phenylsulfonyl-4-phenyl-5-trimethylsilylpyrazole in 74% yield. Removal of the trimethylsilyl group of the pyrazoles **2** has been easily carried out with 10% aqueous potassium hydroxide in refluxing ethanol or hydrochloric acid-potassium fluoride in ethanol.[3]

The reaction mechanism we currently prefer for this pyrazole synthesis is outlined below. In analogy with related studies,[5] we suggest that the first step is a nucleophilic attack of $\mathrm{TMSC(Li)N_2}$ to the β-carbon of the vinylsulfone **1**. Subsequent cyclization would then produce the pyrazoline intermediate **3** in equilibrium with **4**. Elimination of lithium benzenesulfinate finally would produce the pyrazole **2**.

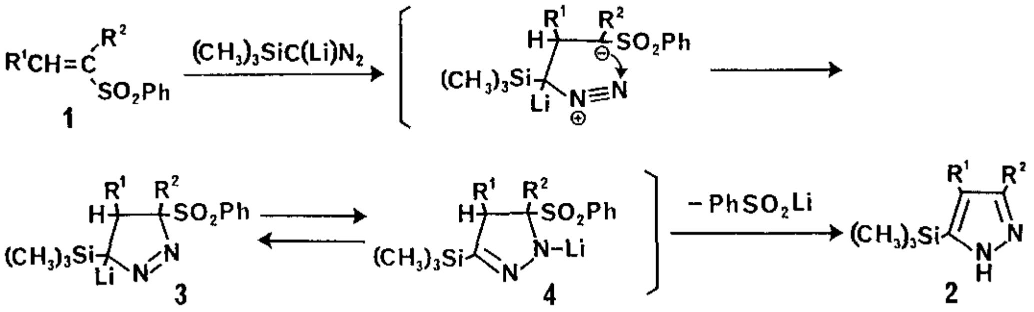
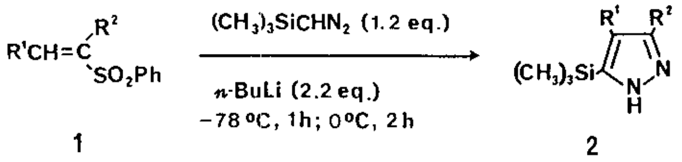


Table. A New Pyrazole Synthesis by Reaction of Lithium Trimethylsilyldiazomethane with α,β-Unsaturated Sulfones



Run	R^1	R^2	Double Bond Geometry	Reaction Solvent	Yield (%)[a]	mp (°C)	Reference of **1**
1	H	H		THF	86 (65)	72–73	6
2	H	H		Et_2O	85[b]	〃	6
3	CH_3	H	E	Et_2O	85 (82)	66–68	7
4	H	CH_3		Et_2O	74[c] (76)	132–133	8
5	H	CH_3		Et_2O	98[d]	〃	8
6	$(CH_3)_3C$	H	E	Et_2O	86	127–127.5	9
7	$CH_3(CH_2)_2$	H	E/Z = 2/1	Et_2O	83 (68)	58–60	10
8	CH_3CH_2	$CH_3(CH_2)_2$	Z	Et_2O	88[e] (59)	58–60	8
9	$-CH=CHCH_2CH_2-$		Z	THF	67[f]	183–183.5	11
10	$-CH=CHCH_2CH_2-$		Z	THF	85[d]	〃	11
11	$-CH_2CH(t\text{-}Bu)(CH_2)_2-$			Et_2O	85 (49)	143–144.5	12
12	Ph	H	E	Et_2O	84 (88)	117.5–118.5	9
13	4-Cl-Ph	H	E	THF	93	175–177	9
14	Ph	Ph	Z	THF	92	155.5–156	9
15	CH_3O	CH_3O	E	Et_2O	36	91–92	13
16	4-Cl-Ph	CN		THF	87[g]	194–197	14

a) Yields in parentheses were obtained by the reaction of $TMSC(Li)N_2$ with the α,β-unsaturated nitriles.[3]
b) Two equivalents of $TMSC(Li)N_2$ was used.
c) The yield was 49% when 1.2 eq. of n-BuLi was used.
d) Lithium diisopropylamide was used instead of n-BuLi.
e) The yield was 40% when 1.2 eq. of n-BuLi was used.
f) The yield was 53% when 1.2 eq. of n-BuLi was used.
g) n-BuLi(1.2 eq.) was used.

One equivalent of n-butyllithium is sufficient to form $TMSC(Li)N_2$ from $TMSCHN_2$. The reason for the necessity of another equivalent of n-butyllithium may be due to the proton abstraction from the α- or β-position of the sulfonyl group in the pyrazoline intermediate **3** or **4**. Interestingly, 4-tert-butylcyclohexylidenemethyl phenyl sulfone did not give any 4,4-disubstituted pyrazole, which might suggest the importance of the presence of at least one hydrogen atom at the β-position of the sulfonyl group in this pyrazole synthesis.

When 3-(4-chlorophenyl)-2-phenylsulfonyl-2-propenenitrile was used as a substrate, elimination of the phenylsulfonyl group preferentially occurred to give 4-(4-chlorophenyl)-3-cyano-5-trimethylsilylpyrazole. Furthermore, in this particular case, the use of 1.2 equivalents of *n*-butyllithium was enough to obtain the pyrazole in good yield. This fact may be explained that the nucleophilic attack of $TMSC(Li)N_2$ on the β-carbon of the sulfonyl group would take place much faster than the deprotonation in the pyrazoline intermediate owing to the activation of the double bond by two electron-withdrawing substituents.

Reaction of α,β-unsaturated sulfones with diazomethane are known[15] to produce sulfonylpyrazolines, which easily undergo the desulfonylation by treatment with potassium hydroxide to give pyrazoles. In addition to the use of hazardous diazomethane, another disadvantage of this method is that both Δ^2- and Δ^1-pyrazolines are formed when styrylsulfones are used as substrates, hence 4- and 3-substituted pyrazoles are produced, respectively.

In conclusion , the pyrazoles **2** can be very easily and safely prepared by the reaction of $TMSC(Li)N_2$ with α,β-unsaturated sulfones **1** under mild reaction conditions. The high yields obtained for the wide variety of substrates demonstrate the generality of this pyrazole synthesis.

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Received, 30th October, 1987