REACTION OF LITHIUM TRIMETHYLSILYLDIAZOMETHANE WITH β-AMINO-α,β-UNSATURATED KETONES†

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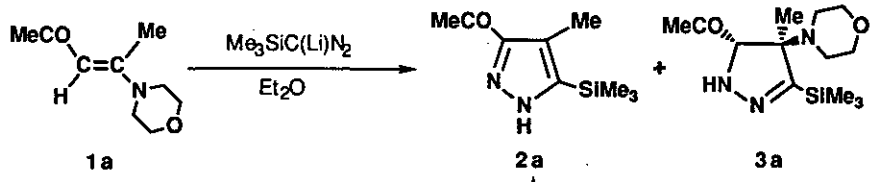
Abstract - Reaction of lithium trimethylsilyldiazomethane with various β-morpholino- (and piperidino)-α,β-unsaturated ketones gives 3- (or 5)-acyl-pyrazoles, while the reaction with β-pyrrolidino derivatives mainly affords 1,2-diazabicyclo[3.2.0]hepta-2,6-dienes.

We have already revealed that the lithium salt of trimethylsilyldiazomethane (TMSC(Li)N_2), a useful [C-N-N]azole synthon,[1] smoothly reacts with α,β-unsaturated nitriles,[2] α,β-unsaturated sulfones,[3] and ketenimines[4] to give the corresponding pyrazoles in good to high yields. As an extension of these works, we now wish to report the reaction of TMSC(Li)N_2 with β-amino-α,β-unsaturated ketones which give 3-(or 5)-acylpyrazoles (**2**), pyrazolines (**3**), or 1,2-diazabicyclo[3.2.0]hepta-2,6-dienes (**5**), depending upon substrates.

First, TMSC(Li)N_2, easily prepared from trimethylsilyldiazomethane and butyllithium, was allowed to react with 4-morpholino-3-penten-2-one (**1a**) in ether at 0°C for 3 h. The products were found to be a mixture of 3-acetyl-4-methyl-5-trimethylsilylpyrazole (**2a**) and 5-acetyl-4-methyl-4-morpholino-3-trimethylsilyl-2-pyrazoline (**3a**), as shown in Scheme 1. The latter was quantitatively transformed to the former by treatment with 2 N hydrochloric acid in methanol at room temperature for 20 min. When the reaction of TMSC(Li)N_2 with **1a** was followed by direct acidic treatment, the pyrazole (**2a**) was obtained as the sole product.

†Dedicated to Professor Edward C. Taylor on the occasion of his 70 th birthday.

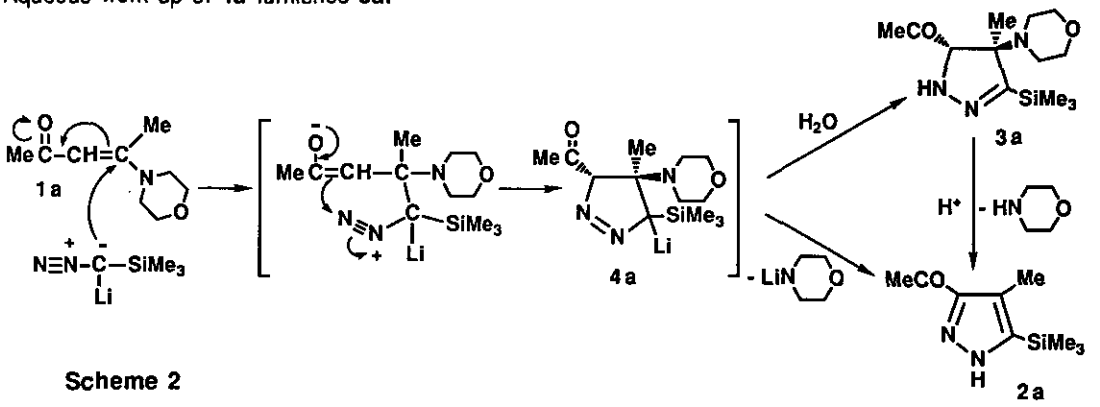


Reaction conditions	Yield(%) 2a	3a
0°C, 3 h	24	36
0°C, 3 h [a)]	56	-

a) Quenched with 2 N aq. HCl - MeOH.

Scheme 1

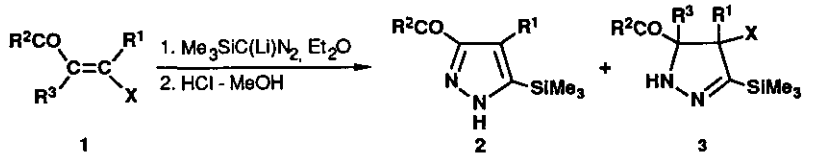
The reaction mechanism of the formation of **2a** and **3a** may be as shown in Scheme 2: In analogy with related studies,[2,3] the Michael addition of $TMSC(Li)N_2$ to **1a** followed by cyclization gives the pyrazoline intermediate (**4a**). Subsequent elimination of lithium morpholide from **4a** produces the pyrazole (**2a**). Aqueous work up of **4a** furnishes **3a**.[5]



Scheme 2

The reaction has been found to have generality as shown in Table I. Various β-morpholino-α,β-unsaturated ketones (**1**) including aliphatic and aromatic ones underwent the reaction with $TMSC(Li)N_2$ to give **2**. Replacement of the morpholino group in **1a** with the piperidino group gave rise to the pyrazole (**2a**) without acidic treatment, revealing the superiority of the piperidino group as a leaving group. Interestingly, in the case of **1e**, in addition to the desired pyrazole (**2e**), almost equimolar amounts of the abnormal product, 3,5-diphenylpyrazole,[6] was obtained. 2-(Morpholinomethylene)cyclohexanone (**1l**) also smoothly reacted with $TMSC(Li)N_2$ to give the pyrazoline (**3i**) in high yield after being quenched with water. Ether seems to be the solvent of choice. The use of the other solvent such as hexane or tetrahydrofuran showed the decrease in yield. Butyllithium is essential to conduct the reaction since $TMSCHN_2$ does not react with **1** at all without butyllithium.

Table I



1 2 3

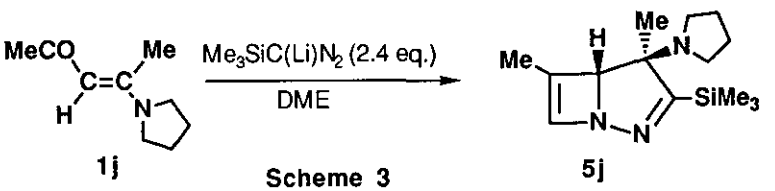
Starting material	R^1	R^2	R^3	X	Yield (%) 2	Yield (%) 3	mp (°C) (recry. solvent)
1a	Me	Me	H		56	—	88-90 (benzene / hexane)
1b	Me	Me	H		55 [a]	—	
1c	Me	Ph	H		27	—	133-135 (benzene / hexane)
1d	Et	Et	H		53	—	76-78 (pentane)
1e	Ph	Ph	H		31 [b) c)]	—	157-160 (benzene / hexane)
1f	-$(CH_2)_3$-		H		57	—	200(decomp.) (benzene / hexane)
1g	H	Me	H		33	—	94-95 (benzene / hexane)
1h	H	*t*Bu	H		64 [a) d)]	—	197-198 (EtOAc / hexane)
1i	H	-$(CH_2)_4$-			—	84 [a]	85-87 (benzene / hexane)

a) Quenched with water. b) $Me_3SiC(Li)N_2$ (2 eq.) was used.

c) 3,5-Diphenylpyrazole was also obtained in 27% yield.

d) $Me_3SiC(Li)N_2$ (2.2 eq.) was used and the reaction mixture was stirred at 0°C for 2 h, then at room temperature for 13 h.

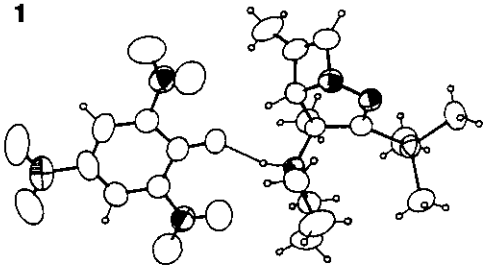
In contrast to the above results, replacement of the leaving group of **1** from morpholino or piperidino groups to pyrrolidino one took another reaction course. Thus, 1,2-diazabicyclo[3.2.0]hepta-2,6-diene (**5j**) was obtained by treatment of 4-pyrrolidino-3-penten-2-one (**1j**) with $TMSC(Li)N_2$ in dimethoxyethane (DME), as shown in Scheme 3. In this reaction, the pyrazole derivatives could not be detected at all. The structure of **5j** was determined by its spectral data (ir, ^1H and ^{13}C nmr spectra) and elemental analysis. Final and conclusive evidence for the structure of **5j** was obtained by X-ray crystallographic study of its picrate (mp 50-52°C), as shown in the ORTEP stereoview (Figure 1).[7]

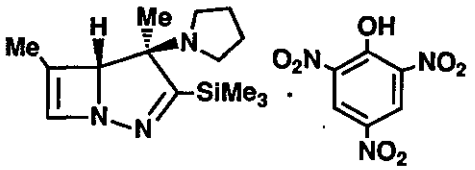


1j **5j**

Scheme 3

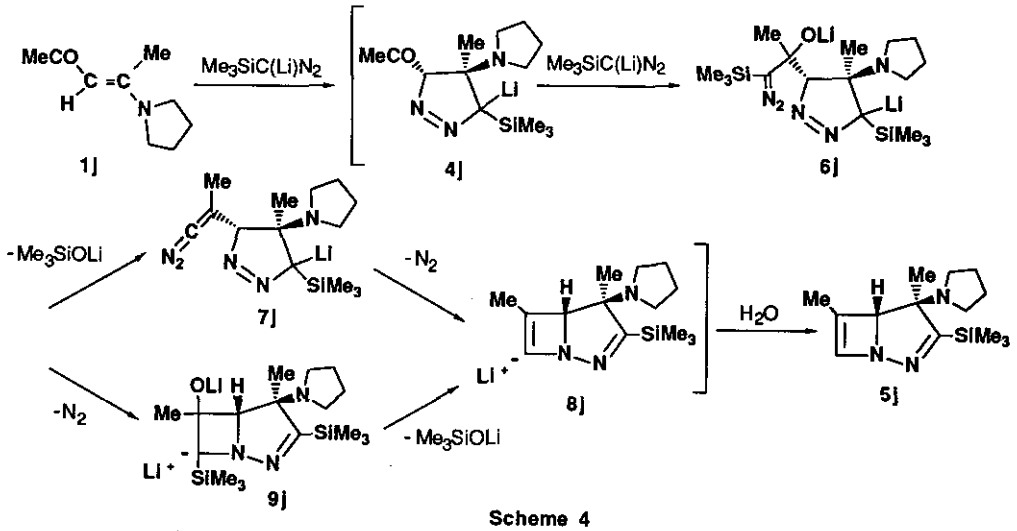
Figure 1





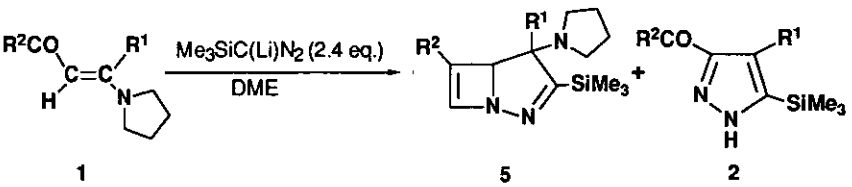
5j · picrate

Although the reason for differences in the reactivity to TMSC(Li)N_2 remains unclear at the moment, the interesting conversion of **1j** to **5j** may be explained as shown in Scheme 4: A first possible intermediate in this reaction would be the pyrazoline (**4j**) as described above. The nucleophilic attack at the carbonyl carbon atom of **4j** with a second molecule of TMSC(Li)N_2 followed by elimination of TMSOLi would give the diazoethene (**7j**).[8] Subsequent cyclization of **7j** accompanied with expulsion of nitrogen would produce the bicyclic intermediate (**8j**), which would be hydrolyzed with water to afford **5j**. Alternatively, cyclization of **6j** with expulsion of nitrogen would afford **9j**, from which TMSOLi would be eliminated to give **5j** via **8j**.



Scheme 4

The methyl phenyl analog (**1k**) also underwent the similar reaction with TMSC(Li)N_2 to afford **5k**, as shown in Table II. However, in the case of **1l**, the desired bicyclic compound (**5l**) was obtained as the minor product and the major product was the pyrazole (**2l**). Lithium diisopropylamide (LDA) as the base was more effective than butyllithium and two equivalents of TMSC(Li)N_2 are required to conduct the reaction smoothly. DME seems to be the solvent of choice, though tetrahydrofuran can also be used. Interestingly, the use of ether or hexane gave a mixture of **2** and **5**.

Table II 

1 5 2

Starting material	R^1	R^2	Yield (%) 5	2
1j	Me	Me	53	—
1k	Me	Ph	18	—
1l	Et	Et	14	27

In conclusion, $TMSC(Li)N_2$ reacts with β-morpholino- and piperidino-α,β-unsaturated ketones to give 3- (or 5)-acylpyrazoles, while the reaction with β-pyrrolidino derivatives affords 1,2-diazabicyclo-[3.2.0]hepta-2,6-dienes. A typical experimental procedure for the preparation of **2** and **5** is as follows:

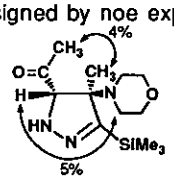
General method for the preparation of 2 --- To a solution of $TMSCHN_2$ (1.9 M hexane solution, 0.63 ml, 1.2 mmol) in ether (7 ml) was added dropwise butyllithium (1.64 M hexane solution, 0.73 ml, 1.2 mmol) at 0°C under argon and the mixture was stirred at 0°C for 20 min. A solution of β-morpholino- (or piperidino)-α,β-unsaturated ketone (**1**)[9] (1 mmol) in ether (3 ml) was then added dropwise at 0°C. The mixture was stirred at 0°C for 3 h and concentrated *in vacuo*. The residue was dissolved in a mixture of methanol (5 ml) and 2 N hydrochloric acid (2.5 ml) at 0°C, and the mixture was stirred at room temperature for 20 min. After concentration *in vacuo*, the residue was neutralized with saturated aqueous $NaHCO_3$, salted out by the addition of NaCl, and extracted with benzene. The extracts were washed with saturated brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (BW-200, Fuji Davison) using hexane - ethyl acetate (3:1-10:1) to give **2**.

General method for the preparation of 5 --- A solution of LDA, prepared from diisopropylamine (0.17 ml, 1.2 mmol) and butyllithium (1.14 M hexane solution, 0.73 ml, 1.2 mmol) in DME (0.3 ml), was added dropwise to a solution of $TMSCHN_2$ (1.9 M hexane solution, 0.63 ml, 1.2 mmol) in DME (5 ml) at -50°C, and the mixture was stirred at -50°C for 20 min. A solution of β-pyrrolidino-α,β-unsaturated ketone (**1**)[9] (0.5 mmol) in DME (2 ml) was then added dropwise at -50°C. The mixture was stirred at

-50°C for 2 h, at -30 ~ -20°C for 1 h, and then at 0°C for 2 h. After addition of cold water, the mixture was extracted with benzene - ethyl acetate (1:1). The organic extracts were washed with saturated brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (BW-200, Fuji Davison) using hexane - ethyl acetate (2:1-4:1) to give **5**.

REFERENCES AND NOTES

1. For a review, see T. Shioiri and T. Aoyama, *J. Synth. Org. Chem. Japan*, 1986, **44**, 149; T. Aoyama, *Yakugaku Zasshi*, 1991, **111**, 570.
2. T. Aoyama, S. Inoue, and T. Shioiri, *Tetrahedron Lett.*, 1984, **25**, 433.
3. T. Asaki, T. Aoyama, and T. Shioiri, *Heterocycles*, 1988, **27**, 343.
4. T. Aoyama, T. Nakano, K. Marumo, Y. Uno, and T. Shioiri, *Synthesis*, 1991, 1163.
5. The relative stereochemistry of **3a** was assigned by noe experiments:



6. The structure of 3,5-diphenylpyrazole was confirmed by comparison with the authentic sample prepared from dibenzoylmethane and hydrazine hydrate, see D.M.W. Anderson, J.L. Duncan, and F.J.C. Rossotti, *J. Chem. Soc.*, 1961, 4201.
7. Single crystal X-ray diffraction analysis of the picrate of **5j** was performed by using standard procedures. Its details will be discussed elsewhere.
8. Analogous intermediates have been proposed in the reaction of TMSC(Li)N_2 and carbonyl compounds, see E.W. Colvin and B.J. Hamill, *J. Chem. Soc., Perkin Trans. 1*, 1977, 869.
9. Starting β-amino-α,β-unsaturated ketones (**1**) were prepared according to the reported methods, see (a) P.W. Hickmott and G. Sheppard, *J. Chem. Soc., Perkin Trans. 1*, 1972, 1038, for **1a**, **1b**, **1c**, **1j**, and **1k**; (b) E.J. Cone, R.H. Garner, and A.W. Hayes, *J. Org. Chem.*, 1972, **37**, 4436, for **1f**; (c) T. Nishio and Y. Omote, *Synthesis*, 1980, 390, for **1e**; (d) C.A. Maggiulli and P.W. Tang, *Org. Prep. Proced. Int.*, 1984, **16**, 31, for **1g**; (e) R. Jacquier, C. Petrus, F. Petrus, and M. Valentin, *Bull. Soc. Chim. Fr.*, 1970, **7**, 2678, for **1i**. The ketones (**1d**, **1h**, and **1l**) were prepared analogously.

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