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Novel generation of azomethine imines from α-silylnitrosamines by 1,4-silatropic shift and their cycloaddition

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Abstract

Novel and facile generation of azomethine imines from α-silylnitrosamines and subsequent cycloaddition with dipolarophiles leading to a variety of pyrazole derivatives have been developed. The key to the reaction is a 1,4-silatropic shift caused by strong affinity of the nitroso oxygen atom toward the silicon atom. Thus, α-silylnitrosamines are treated with 1 equiv. of dipolarophiles in refluxing toluene for 1 h to give pyrazole derivatives in good to excellent yields.

1,3-Dipolar cycloaddition represents one of the most fundamental reactions in organic chemistry and several types of 1,3-dipoles have been utilized for the synthesis of five-membered rings.[1] Among these, azomethine ylides[2] and azomethine imines[3] are useful intermediates for the synthesis of various five-membered nitrogen heterocycles. In earlier papers, we have reported that azomethine ylides can be generated from *N*-(silylmethyl)imines[4] or *N*-(silylmethyl)amides[5] via an intramolecular silatropic shift. These reactions are based on the strong affinity between silicon and oxygen or nitrogen. On the other hand, *N*-nitrosamines are close analogues of tertiary amides and a lone pair of electrons on the amino nitrogen are delocalized into the π-electron system of the N=O bond to a greater extent than those of amides.[6] Thus, dipole moments of *N*-nitrosamines are significantly larger than those of tertiary amides, and, as a result, this would cause a larger affinity of the nitroso oxygen atom toward the silicon atom.[6] With these facts in mind, it might be expected that α-silylnitrosamines are excellent precursors of azomethine imines.

For example, *N*-methyl-*N*-nitroso-α-(trimethylsilyl)benzylamine (**1a**)[7] was treated with 1 equiv. of dimethyl acetylenedicarboxylate (DMAD) in refluxing toluene for 1 h to give 3,4-dimethoxycarbonyl-1-methyl-5-phenylpyrazole (**2**) in 83% yield (Eq. 1). The product was isolated by silica gel chromatography and the structure was determined by spectral analysis. The role of the silyl group is very important, as evidenced by the fact that *N*-methyl-*N*-nitrosobenzylamine (**3**), which lacks a silyl group, did not give any cycloadduct with DMAD in refluxing toluene for 10 h (Eq. 2).

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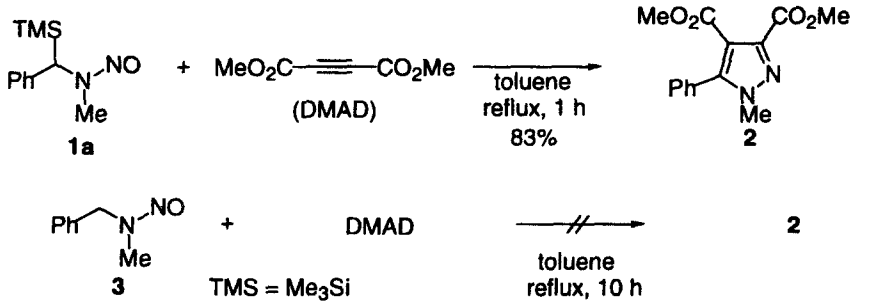
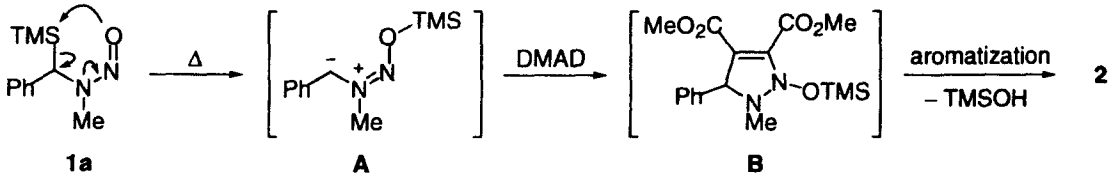


Scheme 1 shows a plausible mechanism which accounts for the formation of the azomethine imine A and the subsequent cycloaddition. A thermal 1,4-shift of the silyl group onto the oxygen of nitroso group gives the azomethine imine intermediate (**A**) which undergoes 1,3-dipolar cycloaddition with DMAD to give the five-membered ring adduct (**B**). Elimination of a silanol from **B** affords the aromatized product, pyrazole **2**.



Scheme 1.

To assess the reaction efficiency, we examined the effect of temperature on the reaction of **1a** with DMAD (Table 1). The reaction was rather sluggish at room temperature and **2** was obtained in 30% yield after 7 d, with ca. 50% of the starting **1a** remaining (entry 1). The reaction was accelerated by heating and was essentially complete after 12 h at 50°C or 1 h at 80°C (entries 2, 3). Furthermore, it is noteworthy that at 110°C, the reaction was complete within 5 min, giving a quantitative yield of **2** (entry 4). To gain additional insights into the reaction mechanism, the rates of formation of **2** at 80°C under several concentrations of substrates were compared.[8] For all concentrations, the reaction rates were nearly the same, indicating that the formation of the azomethine imine involves an intramolecular silatropic shift and is the rate-limiting step.

Table 1
Effect of temperature on the reaction of **1a** with DMAD[a]

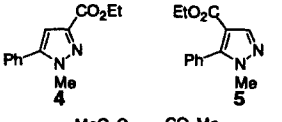
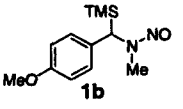
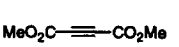
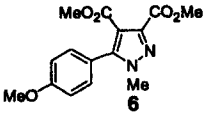
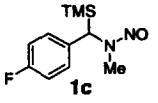
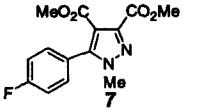
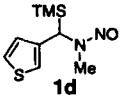
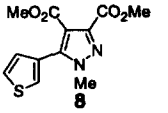
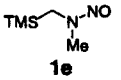
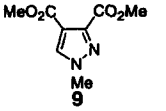
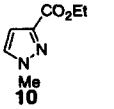
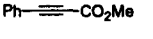
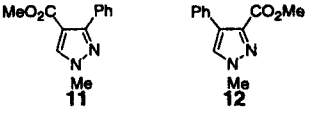
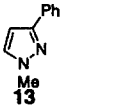
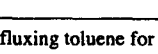
run	T (°C)	time (h)	yield of **2** (%)[b]
1	25	168	30
2	50	12	82
3	80	1	98
4	110	0.05	100

[a] The reactions were carried out under N_2 with **1a** (0.05 mmol), DMAD (0.05 mmol) in C_6D_6 in a sealed NMR tube. [b] Determined by ^1H NMR analysis.

In Table 2 are listed the results of the cycloadditions of α-silylnitrosamines (**1a–e**)[9] with several dipolarophiles. When **1a** was reacted with a monosubstituted dipolarophile such as ethyl propiolate, a mixture of 3- and 4-substituted pyrazoles was obtained in good yield (entry 1). These pyrazoles were readily separable by silica gel chromatography and the ratio of 3- and 4-substituted pyrazoles was found to be 85:15. Both substrates bearing electron-donating (4-methoxy, **1b**) and electron-withdrawing (4-

fluoro, **1c**) substituents at the phenyl group reacted smoothly with DMAD to afford the desired pyrazoles in excellent yields (entries 2, 3). Thus, it appears likely that the substituents at the 4-position of the phenyl group had no effect on the high reactivity of the α-silylnitrosamines. 3-Thienyl substituted substrate **1d** also reacted with DMAD under the same conditions to give a quantitative yield of pyrazole **8** (entry 4). We next examined whether or not the less-stabilized azomethine imines, which possess no ylide-stabilizing substituents on the carbon, can be generated. Thus **1e** was treated with 1 equiv. of DMAD in refluxing toluene for 1 h to give pyrazole **9** in 84% yield, suggesting that this reaction proceeds via a less-stabilized azomethine imine intermediate (entry 5). The results of extensive experiments with other dipolarophiles are also summarized (entries 6–9). The reaction with ethyl propiolate gave regioselectively one product, the 3-substituted pyrazole **10** (entry 6). However, with an unsymmetrically disubstituted dipolarophile such as methyl phenylpropiolate, a mixture of **11** and **12** was obtained with no selectivity (entry 7).

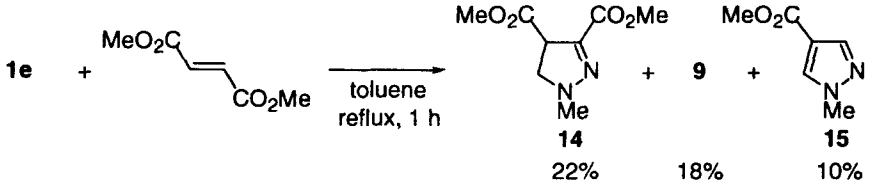
Table 2
Cycloaddition reactions of α-silylnitrosamines with dipolarophiles[a]

entry	substrate	dipolarophile	product	yield[b]
1	**1a**		 **4** **5**	72% (85 : 15)
2	 **1b**	 (DMAD)	 **6**	96%
3	 **1c**	DMAD	 **7**	88%
4	 **1d**	DMAD	 **8**	98%
5	 **1e**	DMAD	 **9**	84%
6	**1e**		 **10**	83%
7	**1e**		 **11** **12**	70% (57 : 43)
8	**1e**		 **13**	11%
9	**1e**		No reaction	0%

[a] All reactions were carried out in refluxing toluene for 1 h with 1 equiv. of the dipolarophile. [b] Isolated yield.

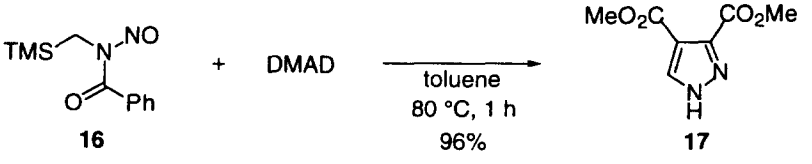
The reaction with phenylacetylene also proceeded to give only the 3-substituted pyrazole **13** albeit in a low yield (entry 8). Diphenylacetylene showed no reactivity toward **1e** (entry 9). The observed order of reactivity of these acetylenes is in good agreement with those of the cycloadditions of well-known 1,3-dipoles with dipolarophiles.[10]

Reactions with olefinic dipolarophiles were also examined, but the yields of the anticipated pyrazoline derivatives were rather low. This was mainly due to the formation of the unexpected pyrazole derivatives. For example, **1e**, when reacted with 1 equiv. of dimethyl fumarate in refluxing toluene for 1 h, gave pyrazoline **14** (22%), accompanied by pyrazoles **9** (18%) and **15** (10%) (Eq. 3). Pyrazole **9** could have been produced by the aromatization of **14** under reaction conditions used, although no detailed studies on the mechanism of formation of the monosubstituted pyrazole **15** have been reported to date, to the best of our knowledge.



(3)

All the reactions described above gave *N*-substituted pyrazole derivatives, since the readily available substrates **1** are secondary nitrosamines.[11] For the synthesis of *N*-unsubstituted pyrazole derivatives, α-silylnitrosoamide was chosen as a precursor of the 1,3-dipole. A similar 1,4-silatropic shift would generate *N*-acylazomethine imines which react with dipolarophiles to afford *N*-acylpyrazole derivatives, whose acyl group is expected to be a potent leaving group as, for example, acyl pyrazoles are readily hydrolyzed to *N*-unsubstituted pyrazoles.[12] Indeed, this strategy was so successful that *N*-unsubstituted pyrazole derivatives were obtained without any treatment after cycloaddition. For example, α-silylnitrosoamide **16** was reacted with 1 equiv. of DMAD in toluene at 80°C for 1 h to give *N*-unsubstituted pyrazole **17** in 96% yield (Eq. 4). Two reaction paths are possible; one involving the cycloaddition of an azomethine imine generated by a silicon shift onto the nitroso group, and the other involving the generation of a diazomethane derivative, via the rearrangement of the acyl group onto the nitroso group.[13] We are currently investigating the mechanism in more detail, as well as applications to the synthesis of other *N*-unsubstituted pyrazoles.



(4)

Acknowledgements

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5. Ohno, M.; Komatsu, M.; Miyata, H.; Ohshiro, Y. *Tetrahedron Lett.* **1991**, *32*, 5813.
6. Challis, B. C.; Challis, J. A. In *Supplement F: The chemistry of amino, nitroso and nitro compounds and their derivatives*; Patai, S., Ed.; John Wiley & Sons: New York, 1982; Chapter 26.
7. Nitrosamine **1a** was prepared as follows. Benzyltrimethylsilane (a commercially available inexpensive compound) was reacted with *N*-bromosuccinimide (NBS) in CCl_4 to give α-(trimethylsilyl)benzyl bromide. Thus obtained bromide was substituted with methylamine in methanol to afford *N*-methyl-α-(trimethylsilyl)benzylamine. Nitrosation of the α-silylamine with sodium nitrite under weakly acidic condition gave **1a**. In general, nitrosamines may be mutagenic and carcinogenic. All operations with those compounds should be performed in a well-ventilated hood, and the operator should wear disposable gloves.
8. Reactions were carried out with **1a** and an equimolar amount of DMAD in C_6D_6 in a sealed NMR tube under several concentrations of **1a** (2.0×10^{-2} M, 1.0×10^{-2} M, 2.0×10^{-3} M) and yields were determined by ^1H NMR spectroscopy.
9. Nitrosamines **1b–d** were prepared in the same manner for the preparation of **1a** (see Ref. 7). Nitrosamine **1e** was prepared from commercially available *N*-nitrosodimethylamine by α-lithiation using lithium diisopropylamide followed by electrophilic substitution with trimethylsilyl chloride.
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11. In general, primary nitrosamines are unstable and only a few examples are known (see Ref. 6).
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