HETEROCYCLES, Vol. 55, No.12, 2001, pp. 2283 - 2287, Received, 29th October, 2001

A FACILE SYNTHESIS OF 4(3*H*)-PYRIMIDINONES *VIA* [4 + 2] CYCLOADDITION UTILIZING TRIMETHYLSILYLKETENE

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Abstract - The [4+2]cycloaddition reaction utilizing trimethylsilylketene with 1,3-diaza-1,3-dienes smoothly proceeded to give the desired cycloadducts, 4(3*H*)-pyrimidinones, in moderate to high yields.

Trimethylsilylketene (TMS ketene, $Me_3SiCH=C=O$) has been considered as a useful building block for the introduction of the C2 unit in view of not only its higher reactivity but also easier handling, lower toxicity and chemical stability relative to the ketene itself.[1-4] The synthetic utility of TMS ketene in [2+2] cycloaddition reaction to provide β-lactones[5] and in reactions with nucleophiles[6] has been reported. Our group has been independently developing the TMS ketene chemistry for the facile and efficient synthesis of heterocycles[4] utilizing electron-rich 1,3-dienes,[7] enamines,[8] acyl isocyanates,[9] nitrones,[10] 8-azaheptafulvenes and 6-amino-1-azafulvenes.[11] In this communication, we present a new methodology for the synthesis of nitrogen heterocycles using 1,3-diaza-1,3-dienes to produce 4(3*H*)-pyrimidinone derivatives *via* the [4+2] cycloaddition.[12]

The 1,3-diaza-1,3-diene (**1a**), which is easily prepared,[13] was found to possess sufficient reactivity toward TMS ketene (**2**), and the reaction of (**1**) with two equivalents of **2** produced the desired [4+2] cycloadducts (**3a**), 4(3*H*)-pyrimidinone, under quite mild reaction conditions. Table 1 shows the results of the solvent survey, which we initially attempted. Ethyl acetate was found to be the most effective to give **3a** in 94% yield as a single product, though the other solvents such as toluene and THF also gave **3a** in moderate yield together with **4a**.

The possible mechanism of the reaction is as follows: In analogy with the related studies,[7,12] the reaction of **1** with **2** smoothly proceeds *via* a stepwise process to give the [4+2] cycloadduct. Subsequent migration of the silyl group would produce an intermediate (**A**), from which TMSNMe$_2$ (**5**) is eliminated to afford **3**. The reason why 2 equiv. of **2** is required is, we assume, dependent on the side reaction, as shown in Scheme 1. The quantitatively produced **5** would smoothly react with **2** to give the a-silylated amide (**6**) *via* the silyl enol ether. The formation of **6** was actually observed in the reaction of TMSNMe$_2$ and **2**, by GC analysis.

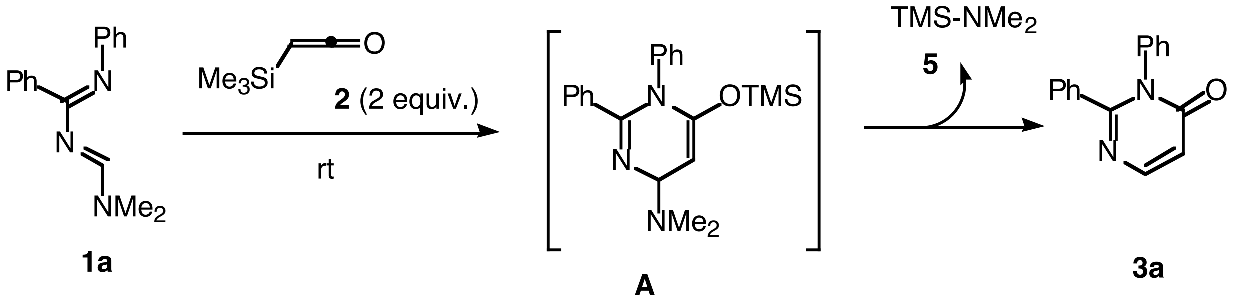
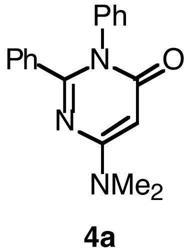
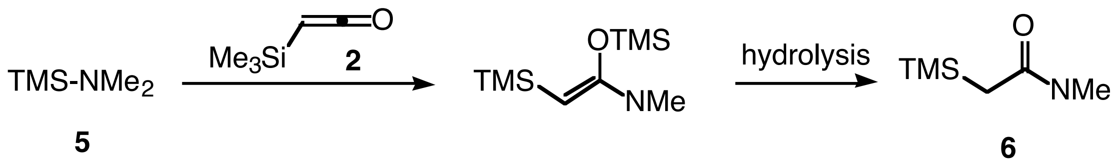


Table 1.

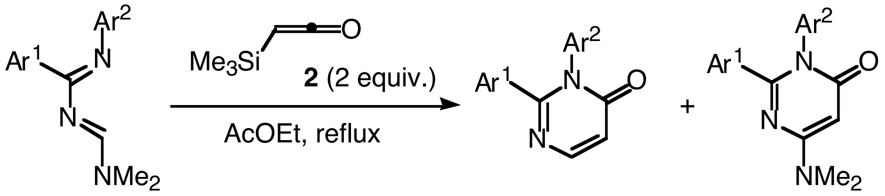
entry	solvent	time (h)	**3a** (%)	**4a** (%)
1	AcOEt	5	94	-
2	toluene	6	60	21
3	THF	6	60	15


4a

Scheme 1



Encouraged by these results, we next turned our attention to the substrate effect. As expected, this synthetic method was found to be general for 1,2-diaryldiazadienes to produce **3b-f** in high yields. For example, methylated substrates such as **1b** or **1c** were successfully transformed into the corresponding cycloadducts (**3b**) and (**3c**) in high chemical yields, respectively. The electron-withdrawing group on the benzene ring such as the chlorine atom had no affect at all, and the reaction smoothly proceeded to give **3d** in 80% yield. Although longer reaction time is required, the 2-naphthyl derivative (**1e**) was also found to be effective to give **3e** under reflux conditions. An electron-donating group such as MeO did accelerate the reaction to afford **3f** within 1 h. These results are summarized in Table 2.

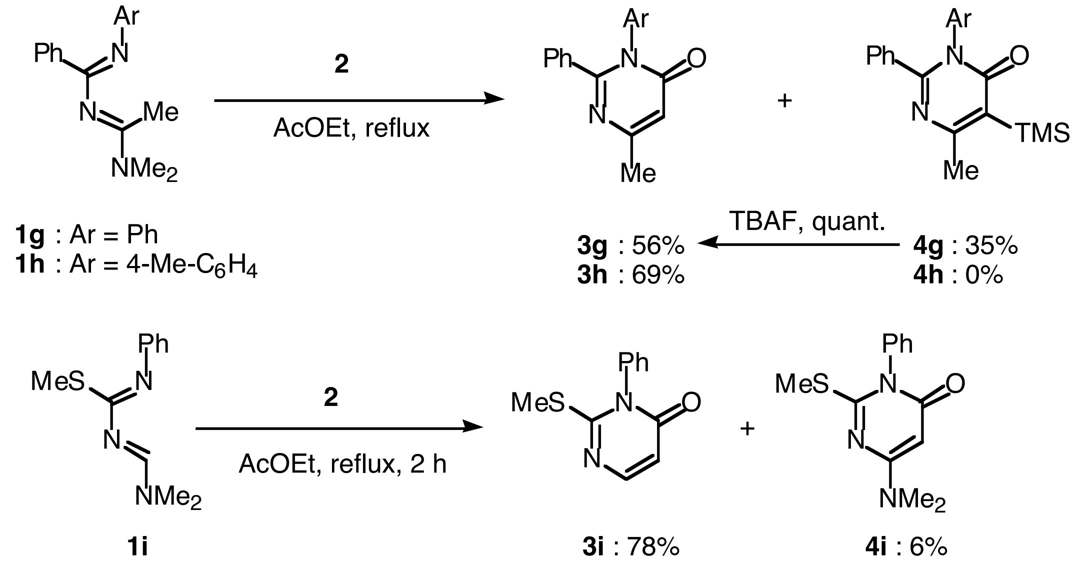


1 **3** **4**

Table 2.

entry	substrate	time (h)	**3** (%)	**4** (%)
1	**1b** : Ar^1 = Ph, Ar^2 = 4-Me-C_6H_4	3	**3b** : 87	**4b** : 3
2	**1c** : Ar^1 = 4-Me-C_6H_4, Ar^2 = Ph	5	**3c** : 84	**4c** : 5
3	**1d** : Ar^1 = Ph, Ar^2 = 4-Cl-C_6H_4	6	**3d** : 80	**4d** : 7
4	**1e** : Ar^1 = 2-naphthyl, Ar^2 = Ph	23	**3e** : 89	**4e** : 3
5	**1f** : Ar^1 = Ph, Ar^2 = 4-MeO-C_6H_4	1	**3f** : 96	**4f** : 3

Scheme 2



Other types of substituted diaza dienes such as **1g** and **1h** were also found to be effective to give the corresponding products, as shown in Scheme 2. For example, compound (**1g**) containing a methyl group at the 4 position of the diene was transformed into **3g** in moderate yield accompanied with the 5-trimethylsilyl derivatives (**4g**), though the reactivity was significantly decreased (28 h). Fortunately, the side product (**4g**)[14] was readily converted to **3g** by treatment with TBAF. Also, **1h** was successfully converted into **3h** as a single product within 3 h. Moreover, the thiomethyl group at the 2 position accelerated the reaction due to its higher electron-donating property, and **1i** was smoothly transformed into **3i** in 78% yield.[15]

In conclusion, we have demonstrated that TMS ketene acts as a useful dienophile in the [4+2] cycloaddition reactions with the 1,3-diaza-1,3-dienes. This facile method represents another aspect of the synthetic utility of TMS ketene for the preparation of nitrogen heterocycles. Further studies for its general development are now in progress.

ACKNOWLEDGEMENTS

We are grateful for the financial support from a Grant-in-Aid from the Ministry of Education, Science, Sports, Culture and Technology, Japan.

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14. We assume that the formation of **4g** depends on the elimination of $HNMe_2$ *via* the 5-silylpyrimidinone.
15. A representative experimental procedure of the cycloaddition reaction utilizing TMS ketene: synthesis of **3a**; To a solution of **1a** (126 mg, 0.5 mmol) in ethyl acetate (5.0 mL) was added the toluene solution of **2** (0.5 mL, 1.0 mmol) at rt. The reaction mixture was stirred for 5 h. Silica gel (1.5 g) was added to the reaction mixture at rt followed by column chromatography (hexane : AcOEt = 1 : 3) which gave the desired product **3a** as a white solid (117 mg, 94%). mp; 149-150℃ (hexane-AcOEt); ^{1}H NMR ($CDCl_3$, 270 MHz) δ : 6.56 (d, *J* = 6.8 Hz, 1H), 7.09-7.33 (m, 10H), 8.05 (d, *J* = 6.8 Hz, 1H); IR (KBr) n : 1693, 1504, 1219 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{12}N_2O$ 248.0950, found 248.0942; Anal. Calcd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.10; H, 5.00; N, 11.33.

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