Silylketenes as a Useful Building Block for Heterocycles

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1. Introduction.

Since the first report on the synthesis and characterization of diphenylketene by Staudinger in 1905 [1], ketenes have aroused interests by many organic chemists [2]. The simplest and parent ketene (CH_2=C=O) has proved to be a useful reagent in organic synthesis [2,3]. Although ketene is sometimes used on a large scale, it is a poisonous gas with a toxicity approximately eight times greater than phosgene. Further, it dimerizes quite easily to give diketene and 1,3-cyclobutanedione, the former of which is also a useful reagent in organic synthesis [4]. Hence the storage of ketene for a long period is impossible and ketene should be used in a well-ventilated fume hood immediately after its preparation.

In contrast, trimethylsilylketene (Me_3SiCH=C=O, TMS-ketene), in which one hydrogen of ketene is substituted with the trimethylsilyl group, is a fairly new chemical species [5]. It is a stable and safe liquid, and can be stored for a long time without dimerization. Thus it could be recommended, at least in laboratories, to use TMS-ketene in place of labile and dangerous ketene if TMS-ketene could exhibit various reactivities similar to ketene. Comparison of ketene with TMS-ketene is summarized in Table 1.

Table 1
Comparison of Ketene with Trimethylsilylketene

	CH_2=C=O	Me_3SiCH=C=O
State while at Room Temperature	A Colorless Gas (bp -56°)	A Colorless Liquid (bp 81-82°)
Odor	Unpleasant	Not Unpleasant
Toxicity	Very Toxic	?
Storage	Impossible (easy to dimerize)	Possible
Handling	Not Easy	Easy

Our interests on the use of stable and safe substitutes for labile and hazardous reagents [6] have led us to investigate the synthetic utility of stable and safe TMS-ketene and other silylketenes. Further, the reactivity of silylketenes as an electron rich ketene has been a matter of interest. Since an excellent bird's eye review on silylketenes has recently appeared [7], we wish to describe here the use of silylketenes as a building block for heterocycles mainly from our recent results. Figure 1 shows the representative molecular skeletons of heterocycles which have been dealt with this review. Among them, the preparation of β-lactones, β-lactams, and coumarins by use of silylketenes has been already described by precedent reviews [2,5,7], and we would like to review them briefly.

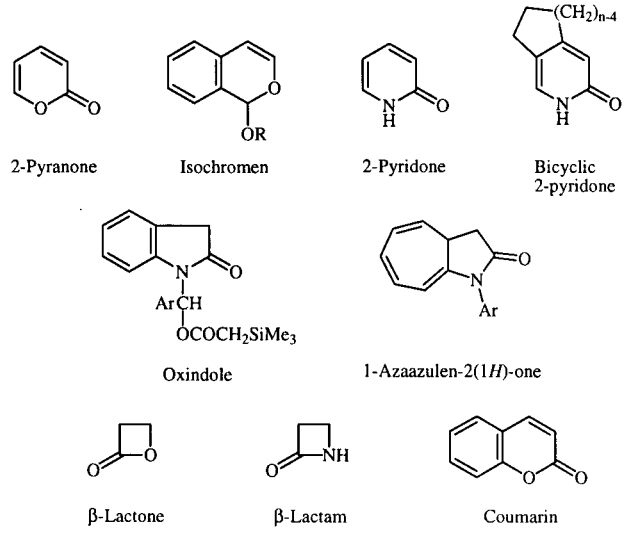
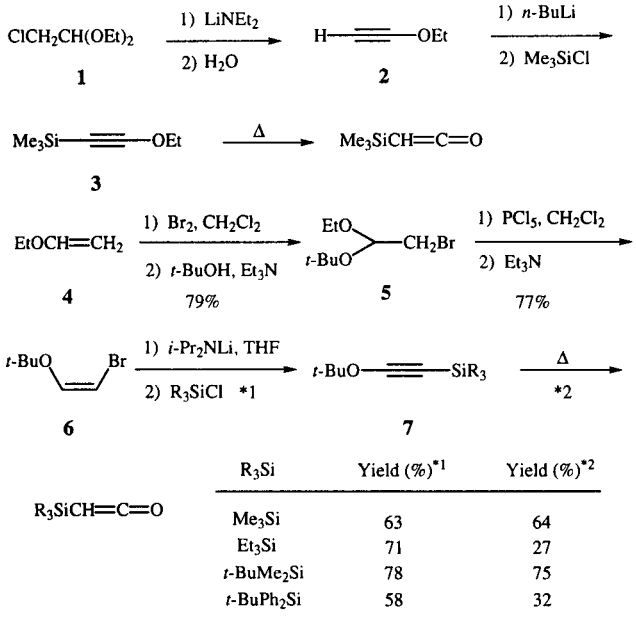


Figure 1. Heterocycles derived from TMS-ketene.

2. Preparation.

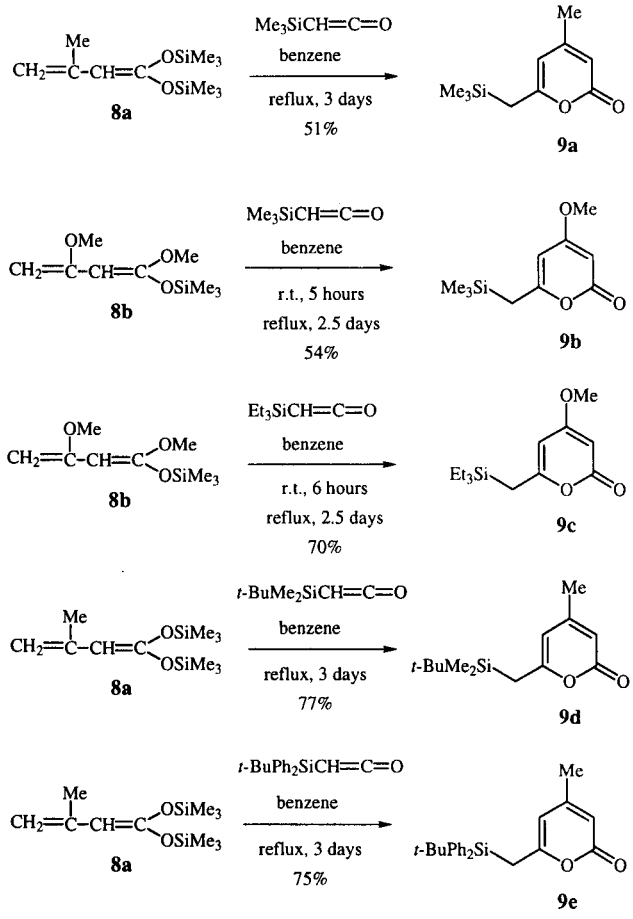
TMS-ketene is now commercially available [8], but too expensive to use as a starting material for the synthesis. Among the several reported methods for the preparation of silylketenes [5,7], the thermolysis of ethoxy- or *tert*-butoxy(trialkylsilyl)acetylenes **3** or **7** will be recommended. As shown in Scheme 1, chloroacetaldehyde diethyl acetal (**1**) is first converted to ethoxyacetylene (**2**) by treatment with lithium diethylamide and then water [9]. Lithiation of **2**, followed by treatment with chlorotrimethylsilane gives **3**, which on pyrolysis affords TMS-ketene [10]. For the preparation of *tert*-butoxy(trialkylsilyl)-acetylenes **7**, ethyl vinyl ether (**4**) is first treated with bromine followed by *tert*-butanol in the presence of triethylamine to give the bromoacetal **5**, which is converted to the (*Z*)-bromide **6** by the action of phosphorus pentachloride and then triethylamine [11]. A one-pot β-elimination and silylation of **6** produced *tert*-butoxy(trialkylsilyl)acetylenes **7**, which undergo thermolysis to give the corresponding silylketenes [12].

Scheme 1



$R_3SiCH=C=O$	R_3Si	Yield (%)*1	Yield (%)*2
	Me_3Si	63	64
	Et_3Si	71	27
	t-$BuMe_2Si$	78	75
	t-$BuPh_2Si$	58	32

Scheme 2



3. 2-Pyranones.

One of the most synthetically useful reactions of silylketenes will be [2 + 2] cycloaddition reactions with unsaturated compounds to give 4-membered ring compounds (see Sections 9 and 10). The behavior of this reaction is quite similar to that of ketene which easily undergoes [2 + 2] cycloaddition reactions, but [4 + 2] cycloadditions by use of ketene or silylketenes are quite rare [2,3,5,7]. However, we have found that silylketenes can be effectively used as heterodienophiles and undergo the [4 + 2] cycloaddition reaction with electron-rich 1,3-dienes **8** to give 2-pyranones **9** [13].

Some representative results are depicted in Scheme 2. The reaction proceeded thermally in refluxing benzene though it took a little bit longer time (1-3 days). Interestingly, Lewis acids, the usual accelerators for the [4 + 2] cycloaddition, inhibited the reaction. The reaction is completely regioselective, which will be explained by the calculated data of the atomic charge of TMS-ketene and the diene **8a**, as shown in Figure 2. Furthermore, the [4 + 2] cycloaddition proved to proceed by a stepwise process, not by a concerted cycloaddition process since the reaction of TMS-ketene with the diene **8b** at room temperature afforded a mixture of the cycloadduct **11** (R^1 = MeO) and the acyclic product **12** (R^1 = R^2 = MeO), as shown in

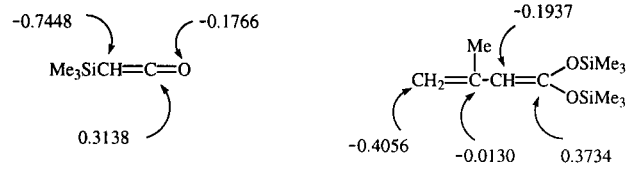
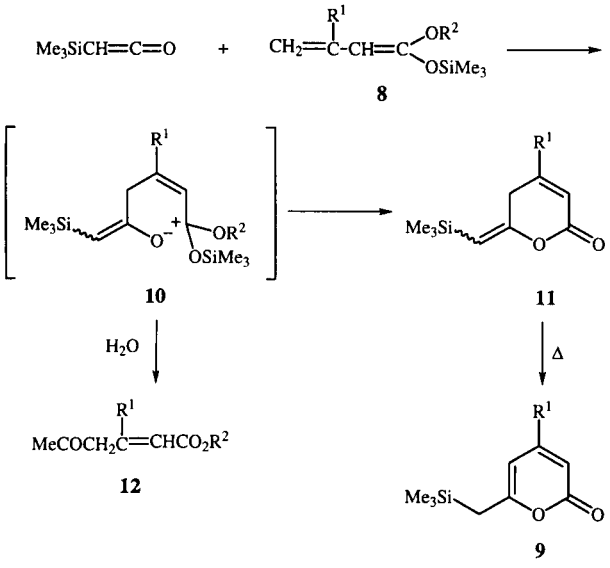


Figure 2.

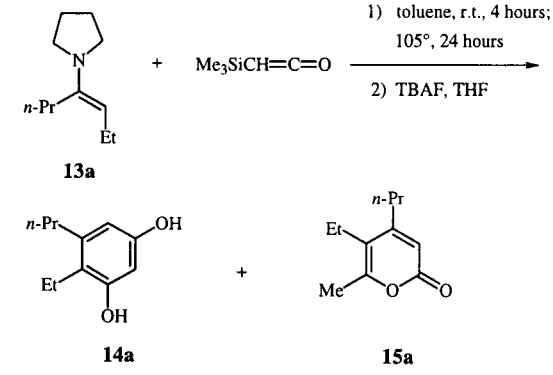
Scheme 3. Thus, the nucleophilic attack of the diene **8** on the central carbon atom of TMS-ketene first produces the betain **10** which gives a mixture of **11** and the acyclic ester **12** after aqueous workup. The adduct **11** is converted to the 2-pyranone **9** by heating and/or prolonging the reaction time through isomerization.

Scheme 3

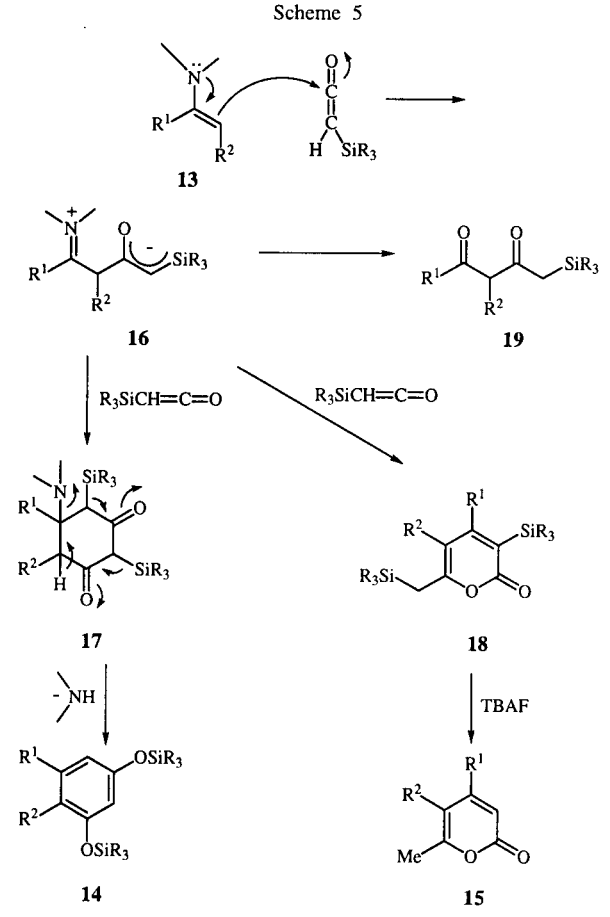


The 2-pyranone derivative **15a** was also formed, though as the minor product, by the reaction of the pyrrolidine enamine **13a** of 4-heptanone with an excess of TMS-ketene followed by treatment with tetrabutylammonium fluoride (TBAF). The major product was the resorcinol **14a**, as shown in Scheme 4 [14]. In general, enamines reacted with an excess of silylketenes to give resorcinol derivatives, of which the reaction mechanism is depicted as in Scheme 5. The silylketene reacts with the enamine **13** to give the betain **16**, which reacts with another molecule of the silylketene to furnish the cyclized product **17**. Elimination of the amine followed by the migration of the silyl group gives the resorcinol derivative **14**. The attack of the *O*-anion of **16** to the silylketene competes with the formation of **17** and the 2-pyranone **18** is formed. Compound **18** is easily desilylated with TBAF to give **15**. In some cases, β-diketones **19** were also formed by *C*-acylation of enamines [15].

Scheme 4



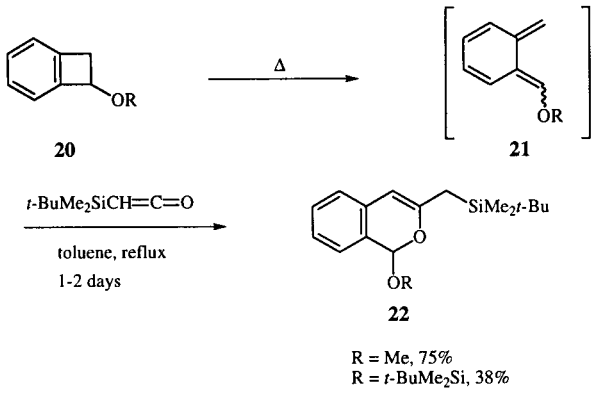
Scheme 5



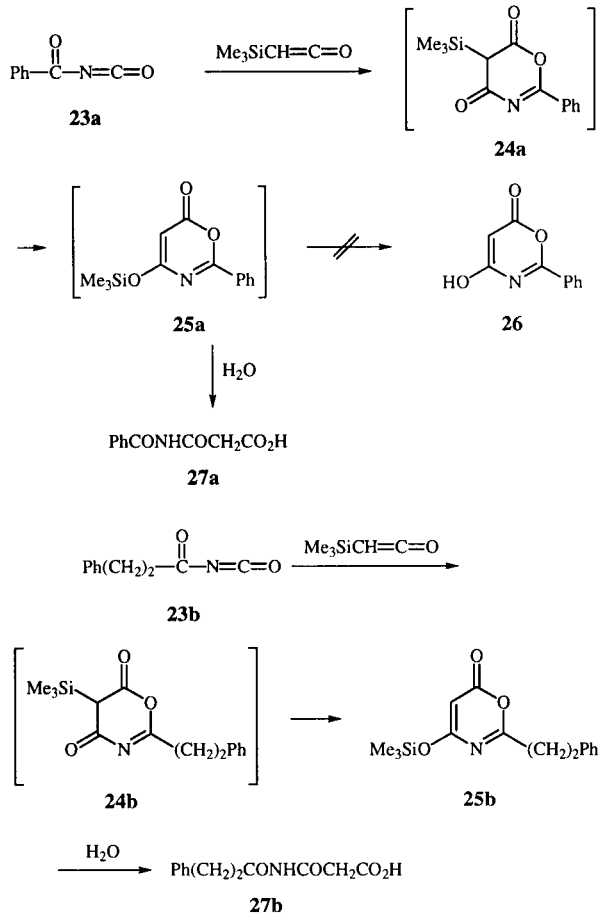
4. Isochromenes.

t-BuMe$_2$SiCH=C=O reacts with 1-methoxy- and 1-*tert*-butyldimethylsiloxybenzocyclobutenes **20** under reflux in dry toluene for 1-2 days to give the isochromene derivatives **22**, as shown in Scheme 6 [13]. The obvious intermediate is the *o*-quinodimethane **21** thermally produced from **20**, and **21** subsequently undergoes the [4 + 2] cycloaddition with the silylketene. In contrast, 1-acetoxy- and 1,1-dimethoxybenzocyclobutenes were inactive while benzocyclobutenol afforded the silylacetylation product, but not cycloadducts.

Scheme 6



Scheme 7



5. 2-Pyridones.

TMS-ketene was found to react with benzoyl isocyanate (**23a**) to give *N*-benzoylmalonamic acid (**27a**) instead of the expected oxazinone derivative **25a** after recrystallization [16]. Further, the oxazinone **26** was not detected at all. However, the ir and nmr spectra of the crude reaction mixture indicated the formation of 4-trimethylsiloxy-1,3-oxazin-6-one (**25a**), the [4 + 2] cycloadduct, which was very sensitive to moisture and immediately hydrolyzed to the acid during recrystallization [17]. On the other hand, the reaction of 3-phenylpropionyl isocyanate (**23b**) with TMS-ketene afforded 2-phenethyl-4-trimethylsiloxy-1,3-oxazin-6-one (**25b**) as a distillable oil, but it was hydrolyzed with water within a few minutes to give the malonamic acid derivative **27b**, as shown in Scheme 7. The oxazinone **25** proved to be formed from the oxazinedione **24** through the migration of the TMS group by theoretical studies [18].

Although the oxazinones **25** were labile to moisture, they were thought to act as a diene for the [4 + 2] cycloaddition. In fact, we have found that TMS-ketene smoothly reacts with various acyl isocyanates **23** to give the 1,3-oxazin-6-one intermediates **25** *via* **24**. The oxazinones **25** immediately undergo the [4 + 2] cycloaddition reaction with dimethyl acetylenedicarboxylate (DMAD) (**28**) or methyl propiolate (**29**), in *o*-dichlorobenzene or *o*-dimethoxybenzene, giving the corresponding 2-pyridones **31** or **32** after expulsion of carbon dioxide from the [4 + 2] cycloadducts **30**, as shown in Scheme 8. As shown in Table 2, various aromatic and heteroaromatic acyl isocyanates **23** smoothly react with TMS-ketene to give 2-pyridones **31** and **32** in good to modest yields while the aliphatic acyl isocyanate **23b** produced the 2-pyridone **31b** in lower yields.

Scheme 8

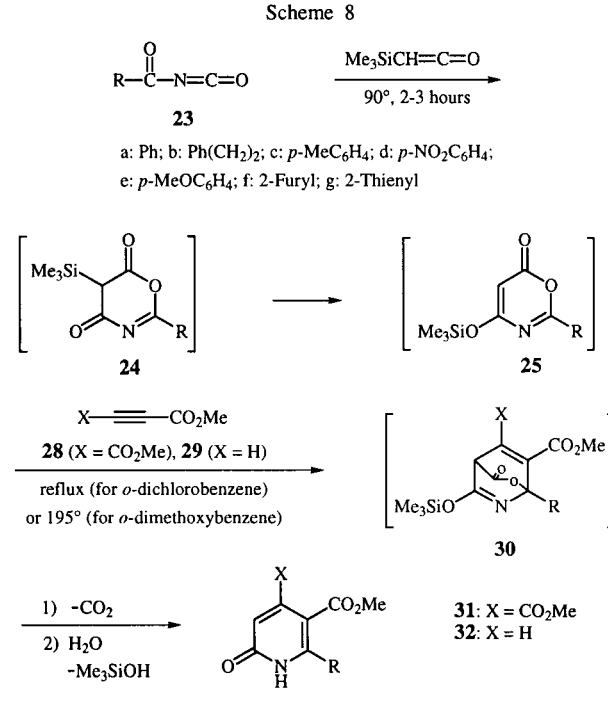


Table 2
A One-pot Preparation of 2-Pyridones **31** and **32**

Compound No.	R	X	Solvent	Reaction Time (hours)	Yield (%)
31a	Ph	CO_2Me	A	3	75
31b	$Ph(CH_2)_2$	CO_2Me	A	3	23
31c	*p*-MeC_6H_4	CO_2Me	A	3	76
31d	*p*-$NO_2C_6H_4$	CO_2Me	B	3	99
31e	*p*-$MeOC_6H_4$	CO_2Me	A	4	64
31f	2-Furyl	CO_2Me	A	3	92
31g	2-Thienyl	CO_2Me	A	3	54
32a	Ph	H	B	6	49
32d	*p*-$NO_2C_6H_4$	H	B	7	65
32e	*p*-$MeOC_6H_4$	H	B	4	22
32f	2-Furyl	H	B	5	63

Solvent A: *o*-dichlorobenzene; Solvent B: *o*-dimethoxybenzene.

The [4 + 2] cycloaddition reaction of methyl propiolate (**29**) was revealed to be completely regioselective by nmr spectral studies of the products **32**. This high selectivitiy of the addition can be explained by calculated data of atomic charges of the oxazinone **25a** and methyl propiolate (**29**), as shown in Figure 3.

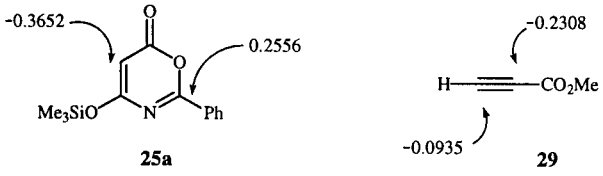


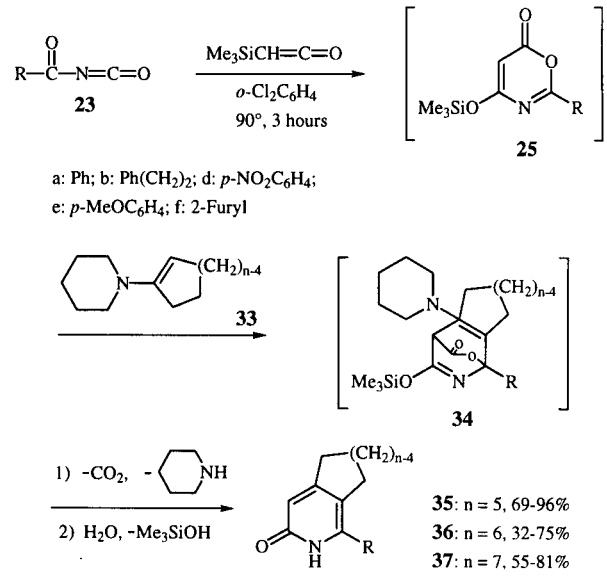
Figure 3.

Furthermore, mechanistic investigations of the above consecutive [4 + 2] cycloaddition reactions at the AM1 semiempirical level have revealed that the reaction of benzoyl isocyanate (**23a**) with TMS-ketene proceeds in a concerted manner to give **24a**, of which the TMS group is easily rearranged to give **25a** [18]. The reaction of **25a** with methyl propiolate (**29**) also proceeds by a concerted mechanism with a LUMO of **29** and a HOMO of **25a**.

6. Bicyclic 2-Pyridones.

4-Trimethylsiloxy-1,3-oxazin-6-ones **25**, generated *in situ* from TMS-ketene and acyl isocynates **23** as shown above, smoothly undergo the [4 + 2] cycloaddition reaction with the piperidine enamines **33** of cycloalkanones in *o*-dichlorobenzene to give the bicyclic 2-pyridones **35-37**, as shown in Scheme 9 [19]. The morpholino and pyrrolidino enamines could also be used though the yields slightly decreased. The obvious intermediates will be the adduct **34** which will lose both carbon dioxide and piperidine to give the pyridones **35-37** after hydrolysis of the TMS group.

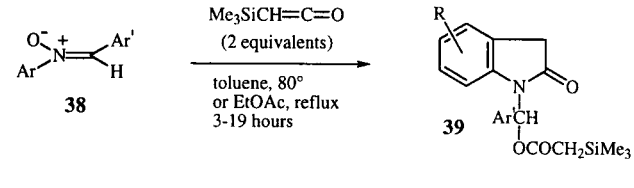
Scheme 9



7. Oxindoles.

TMS-ketene (2 equivalents) smoothly reacts with α,*N*-diarylnitrones **38** to give *N*-alkyloxindoles **39** in good yields, as shown in Scheme 10 [20]. Nitrones are well-known 1,3-dipoles, but no 1,3-dipolar cycloaddition products were obtained [21].

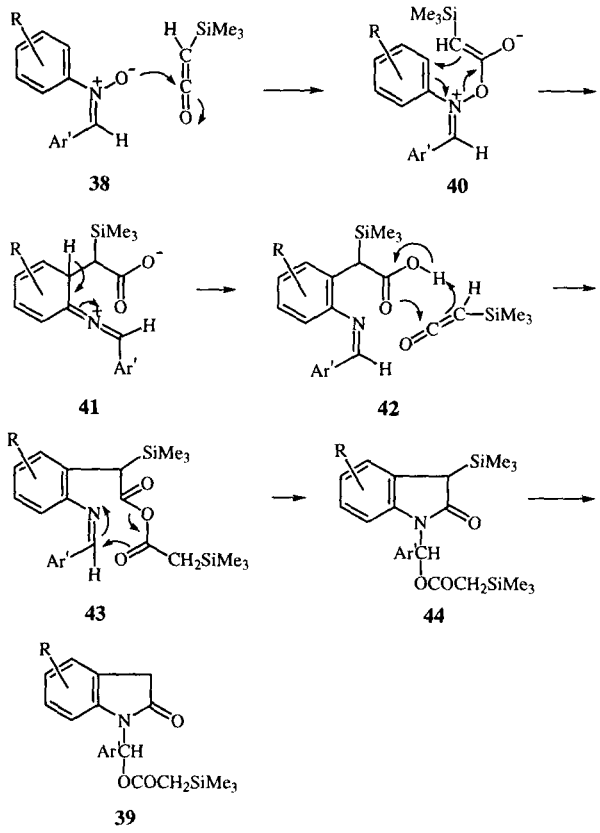
Scheme 10



Ar	Ar'	Solvent	Yield (%)
Ph	Ph	PhMe	79
o-MeC_6H_4	Ph	AcOEt	77
p-$MeOC_6H_4$	Ph	AcOEt	62
Ph	*p*-ClC_6H_4	PhMe	75

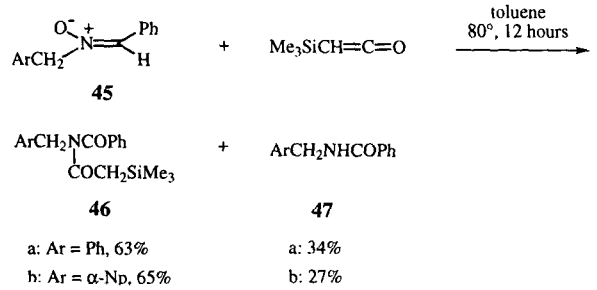
The formation of *N*-alkyloxindoles **39** is explained as shown in Scheme 11. TMS-ketene first reacts with the nitrone **38** to give the betain **40**, which undergoes a sigmatropic rearrangement to produce the *o*-imino substituted arylacetic acid **42** *via* the carboxylate intermediate **41**. Subsequently, a second molecule of TMS-ketene reacts with the carboxylic acid **42** to give the anhydride **43**, which undergoes a rearrangement to the 3-silyloxindole **44**. Hydrolytic removal of the TMS group finally furnishes the oxindole **39**.

Scheme 11



In contrast, the reaction of TMS-ketene with *N*-benzylidenebenzylamine *N*-oxide (**45a**) afforded a mixture of *N*-benzoyl-*N*-trimethysilylacetylbenzylamine (**46a**) and *N*-benzylbenzamide (**47a**). Analogously, *N*-benzylidene-α-naphthylmethylamine *N*-oxide (**45b**) gave a mixture of **46b** and **47b**, as shown in Scheme 12.

Scheme 12

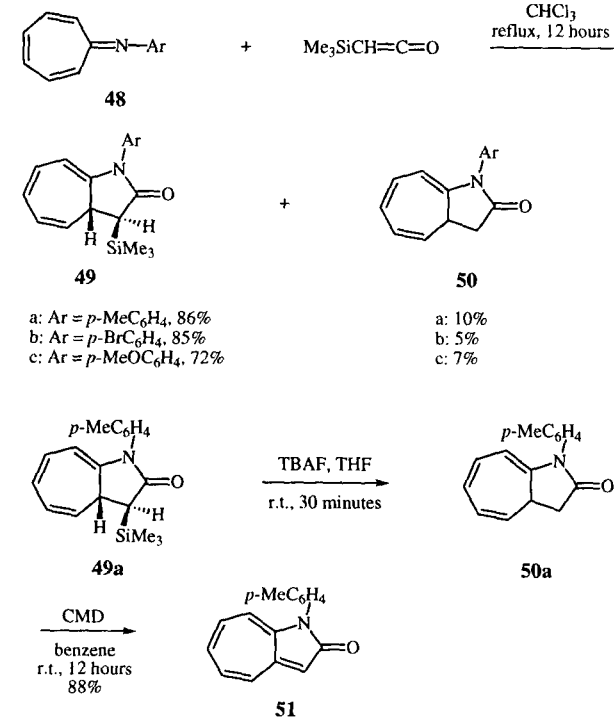


8. 3,4-Dihydro-1-azaazulen-2(1*H*)-ones.

The reaction of TMS-ketene with *N*-aryl-2,4,6-cycloheptatriene-1-imines **48** in refluxing chloroform afforded 3,3a-dihydro-3-trimethylsilyl-1-azaazulen-2(1*H*)-ones **49** together with a small amount of the desilylation products **50**, as shown in Scheme 13 [22]. The stereochemistry of C-3 and C-3a positions proved to be *trans* by nmr spectral studies. The dihydroazaazulene derivatives **49** and **50** are the [8 + 2]-type cycloadducts, which is formed by the nucleophilic attack of the nitrogen atom of **48** to the central carbon atom of TMS-ketene followed by a cyclization. Analogous [8 + 2]-type cycloaddition reactions of ketenes with **48** have been reported [23].

The TMS group of **49a** was easily removed with TBAF to give the desilylated compound **50a** which was dehydrogenated with chemical manganese dioxide (CMD) [24] to produce 1-(*p*-methylphenyl)-1-azaazulen-2(1*H*)-one (**51**).

Scheme 13

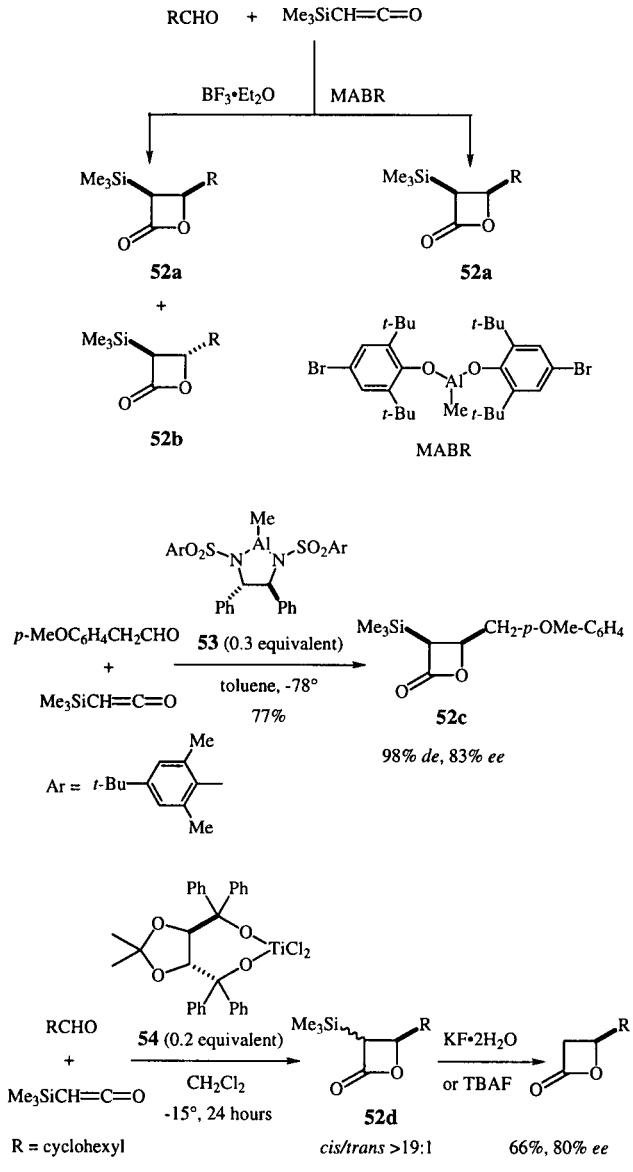


9. β-Lactones.

Formation of β-lactones by the [2 + 2] cycloaddition of silylketenes with carbonyl compounds, especially aldehydes, is a well-known useful process [5,7]. When boron trifluoride etherate is used as a Lewis acid for the reaction with aldehydes, a mixture of *cis*- and *trans*-β-lactones **52a** and **52b** are produced, as shown in Scheme 14. However, a catalytic use of methylaluminum bis(4-bromo-2,6-di-*tert*-butyl)phenoxide (MABR) mainly gives *cis*-isomers

52a [25]. Asymmetric synthesis of the β-lactones **52c** and **52d** was carried out by the reaction of TMS-ketene with aldehydes by use of the chiral bissulfonamide **53** [26] and the dichlorotitanium complex of α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL), **54**, as catalysts, respectively [27].

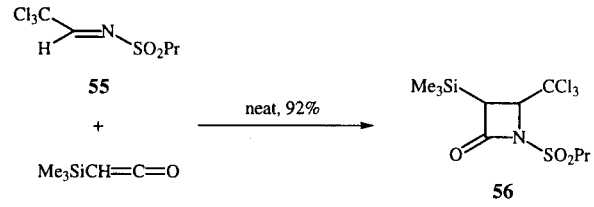
Scheme 14



10. β-Lactams.

The well-known Staudinger reaction is the formation of β-lactams by the [2 + 2] cycloaddition of ketenes with various imines, and one of the most useful routes to β-lactams [7], though silylketenes have been scarcely used for this reaction. Scheme 15 shows only one example using TMS-ketene, which reacts with the electron-deficient imine **55** to give the β-lactam **56** [28].

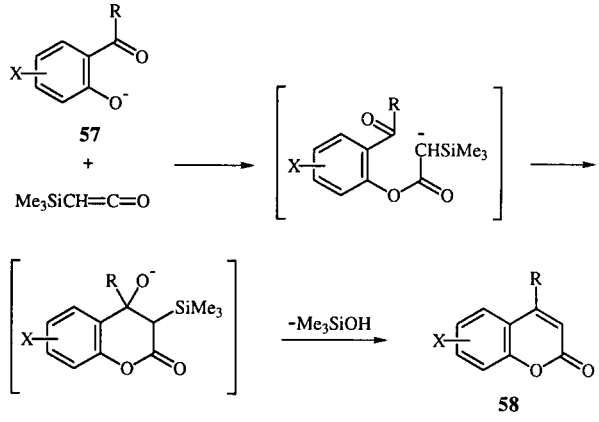
Scheme 15



11. Coumarins.

TMS-ketene reacts with *o*-acylphenols **57** under basic conditions to give coumarins **58** in high yields [29]. The first step will be the trimethylsilylacetylation of the phenol function, and the subsequent cyclization followed by the elimination of trimethylsilanol under basic conditions will afford coumarins **58**, as shown in Scheme 16.

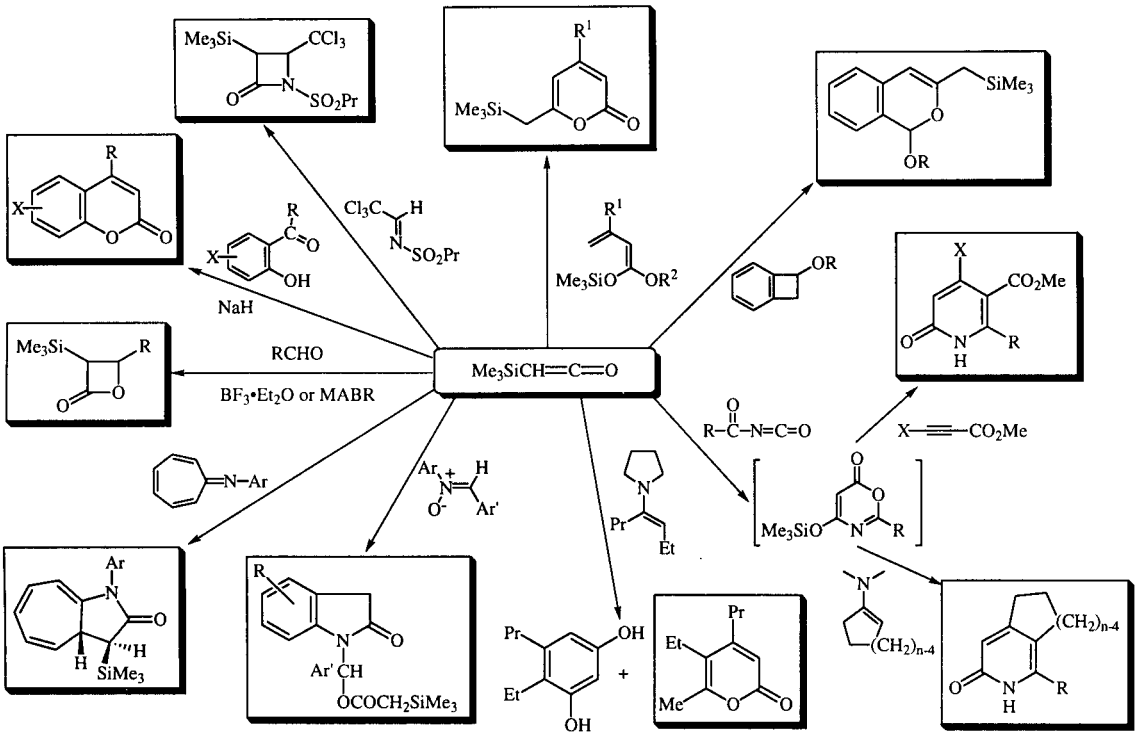
Scheme 16



12. Conclusions.

Silylketenes are stable and safe, and they can be prepared easily. Since they have interesting reactivities, they should have broader applications to organic synthesis. The construction of various heterocycles using silylketenes summarized in Scheme 17 is mainly accomplished by thermal cycloadditions without any Lewis activators, which will allow the development of environmentally benign processes. Further exploitation of reactivities and applications of silylketenes will be definitely one of the important tasks for organic chemists to carry out in the near future.

Scheme 17



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