$W(CO)_5(L)$-catalyzed Cyclization of ω-Acetylenic Silyl Enol Ethers for the Preparation of Nitrogen-containing Cyclic Compounds

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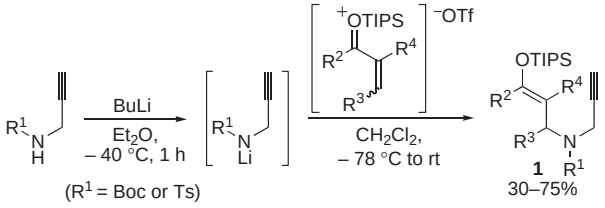
Electrophilic alkyne activation of nitrogen-containing 7-siloxy-6-en-1-ynes by $W(CO)_5(L)$ allows the preparation of synthetically useful heterocycles. Two types of cyclized products, 5-exo and 6-endo, could be obtained selectively under the appropriate conditions.

Electrophilic alkyne activation by transition-metal catalysts and subsequent functionalization has become a new and attractive method to construct synthetically useful polycyclic compounds.[1] The nucleophilic attack of enolates[2] or their equivalents[3,4] on alkynes activated by transition metals belongs to this class of reaction, and a new method of cyclization of ω-acetylenic silyl enol ethers by the use of tungsten hexacarbonyl as an effective catalyst has already been developed in our laboratory.[5] The most attractive point of this reaction is that when 7-siloxy-6-en-1-ynes are employed as substrates, both 5-exo- and 6-endo-cyclized products can be obtained in high yields and selectivity under appropriate conditions.[5a,5b] We have got interested in extending this strategy to nitrogen-containing substrates, since nitrogen-containing 5- or 6-membered cyclic compounds are highly useful synthetic intermediates for the synthesis of various kinds of alkaloids.[6]

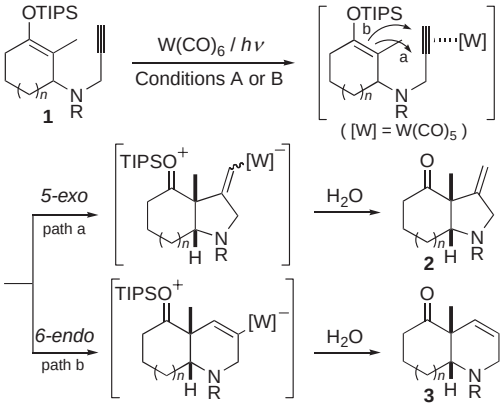
First of all, we tried to develop a concise method for the preparation of the requisite substrates, the nitrogen-containing ω-acetylenic silyl enol ethers. And it was found that they could be successfully obtained from tosyl- or *tert*-butoxycarbonyl-protected 2-propynylamine by the following procedure. Thus, deprotonation of the protected 2-propynylamine by *n*-BuLi in diethyl ether, solvent exchange with dichloromethane and addition via cannula of TIPSOTf-activated α,β-unsaturated ketones lead to the desired substrates in moderate to good yields (Scheme 1). Preactivation of the ketone with the silylating reagent is crucial to the success of this procedure, substantial amounts of directly silylated amine being formed otherwise.

The reaction conditions for the cyclization were examined employing the nitrogen-containing silyl enol ethers **1a** and **1b** prepared from 2-methyl-2-cyclohexen-1-one and Boc- and tosyl-protected 2-propynylamine, respectively (Scheme 2). According to the previously developed procedure for the exo-cyclization, **1a** was treated with 10 mol % of $W(CO)_6$ in THF under direct irradiation with a high-pressure Hg lamp at room temperature in the presence of 10 equiv. of water. And the reaction was found to proceed as expected through the electrophilic activation of the alkyne towards the nucleophilic attack of the silyl enol ether moiety,[7] and the Boc-protected derivative **1a** gave higher selectivity for the formation of the 5-exo-cyclized product **2a** than the corresponding tosyl-protected substrate **1b** (**2**:**3** = 93:7 for **1a** vs 75:25 for **1b**). The same tendency was observed for the 6-endo-cyclization. The reaction of **1a** carried out in toluene with a stoichiometric amount of $W(CO)_6$ and 2 equiv. of MeOH under direct photoirradiation gave the desired 6-endo-cyclized product **3a** with higher selectivity than that of **1b** (**2**:**3** = 11:89 for **1a** vs 29:71 for **1b**). Thus, conversion to the 5-exo- and 6-endo-cyclized products was found to proceed in good yield and selectivity even when a nitrogen-containing silyl enol ether was employed as substrate by the appropriate tuning of the reaction conditions.

We next examined the generality of this reaction. Boc-protected silyl enol ether **1c** derived from 2-methylcyclopentenone also afforded both of the products with good selectivity, simply by changing the reaction conditions (Scheme 2, Entries 5 and 6).



Scheme 1. Synthesis of nitrogen-containing ω-acetylenic silyl enol ethers.



Entry	*n*	R	Conditions[a]	Yield/%	Ratio of **2**:**3**
1	1	Boc (**1a**)	A	75	93:7
2			B[b]	74	11:89
3	1	Ts (**1b**)	A[c]	80	75:25
4			B[d]	84	29:71
5	0	Boc (**1c**)	A	69	95:5
6			B	64	15:85

[a]Conditions A: $W(CO)_6$ (10 mol %), H_2O (10 equiv.), $h\nu$/THF, rt, Conditions B: $W(CO)_6$ (1 equiv.), H_2O (2 equiv.), $h\nu$/toluene, rt. [b]MeOH (2 equiv.) was employed instead of H_2O. Acidic work-up. [c]Carried out with pre-irradiated $W(CO)_5$(thf) (10 mol %) in THF. [d]Carried out with pre-irradiated $W(CO)_5(H_2O)$ in toluene.

Scheme 2. Cyclization of the substrates **1a**–**1c**.

We next examined the generality of this reaction. Boc-protected silyl enol ether **1c** derived from 2-methylcyclopentenone also afforded both of the products with good selectivity, simply by changing the reaction conditions (Scheme 2, Entries 5 and 6).

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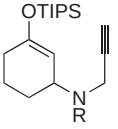
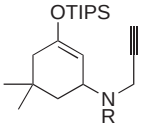
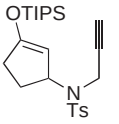
Table 1. Cyclization of the substrates **1d**–**1h**

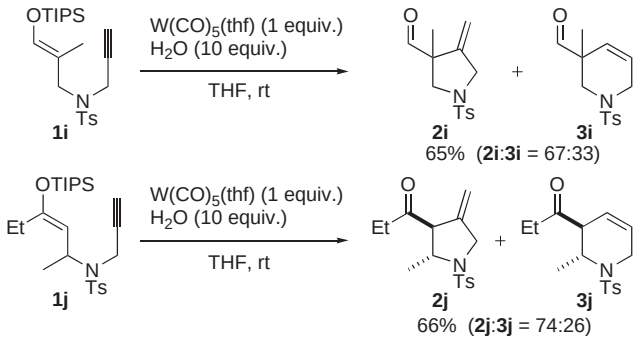
Substrate		Conditions[a]	Yield/%	5-exo:6-endo
	R = Boc (**1d**)	A	82	88:12
	R = Ts (**1e**)	B	77	29:71
	R = Boc (**1f**)	A	72	75:25
	R = Ts (**1g**)	B	86	12:88
	**1h**	A	69	84:16
		B	78	75:25

[a]Conditions A: $W(CO)_5$(thf) (10 mol %), H_2O (10 equiv.)/THF, rt, Conditions B: $W(CO)_5$(L) (1 equiv.), EtOH (2 equiv.)/ toluene, rt; acidic work-up.

For the substrates derived from α,β-unsaturated ketones that do not bear a methyl group on the α-position, the global selectivity of the process is somewhat lower, and in some cases the Boc-protected derivatives did not give the endo-cyclized products in good yield. Nevertheless, by replacing the Boc-group by a tosyl as protecting group on the nitrogen, we could optimize the reaction conditions for the endo-mode of cyclization and make it predominant in toluene (Table 1).[8] Thus, substrates **1d**–**1g** afforded the desired 5-exo- and 6-endo-cyclized products by choosing the appropriate protecting group and the solvent. However, substrate **1h** afforded the 5-exo-cyclized product as major product even in toluene.

Finally, we extended this methodology for *acyclic* substrates. The 1,4-addition of tosyl-protected 2-propynylamine proceeded not only for α,β-unsaturated ketones but also for α,β-unsaturated aldehydes. Although the selectivity of the cyclization could not be controlled as expected under several reaction conditions, the corresponding cyclized products were obtained in good yield, even for the substrate prepared from methacrolein (Scheme 3).

In conclusion, two types of nitrogen-containing cyclic compounds are prepared in good yield and selectivity from the same starting material with appropriate choice of the reaction conditions. Combined with the facile preparation of the cyclization precursors, this $W(CO)_5$(L)-promoted method would afford an attractive protocol for the preparation of synthetically useful nitrogen-containing heterocycles.



Scheme 3. Cyclization of acyclic silyl enol ethers.

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Dedicated to Prof. Teruaki Mukaiyama on the occasion of his 80th birthday.

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7 Only π-complex is shown here for simplicity, but vinylidene complex is also a possible reactive species in this reaction. See Refs. 5a and 5b.

8 For these silyl enol ethers, we used the preformed $W(CO)_5$(L) complex as catalyst (L = THF or EtOH) due to their relative unstability under photoirradiation.

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