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Synthesis and Reactions of Methyl (Trimethylsilylmethyl)-acetylenecarboxylate. A General Method for the Generation of Di-*exo*-methyleneisoxazolines and Novel Access to Fused Isoxazoles[1]

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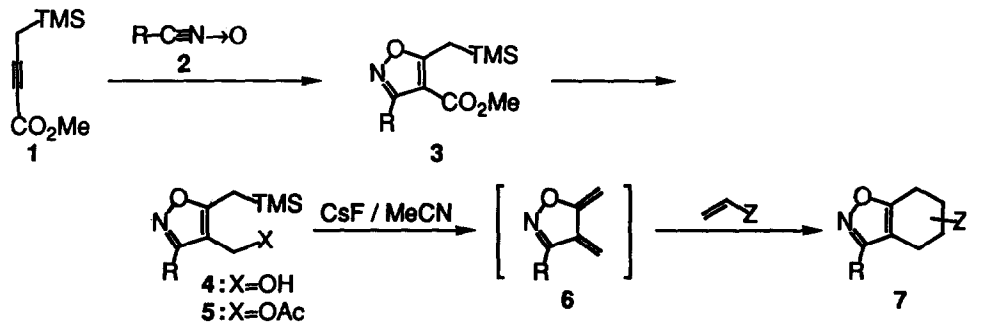
Key Words: methyl (trimethylsilylmethyl)acetylenecarboxylate, 1,3-dipolar cycloaddition; 1,4-elimination; di-*exo*-methyleneisoxazoline; Diels-Alder reaction; fused isoxazole

Abstract: Methyl (trimethylsilylmethyl)acetylenecarboxylate, which is a common key compound in preparation of precursors for di-exo-methylene derivatives of isoxazolines, reacts with nitrile oxides to yield cycloadducts, isoxazoles. Reduction and acetylation of cycloadducts leading to 4-acetoxymethyl-5-(trimethylsilylmethyl)isoxazoles followed by fluoride ion-promoted 1,4-elimination reaction in the presence of dienophiles gave fused isoxazoles.

Concomitant 1,3- and 1,4-elimination reactions of a silyl group and a proper leaving group from organosilicon compounds provide an efficient method for the generation of active species in cycloaddition reactions under mild and neutral conditions. We have already reported a novel 1,3-elimination reaction to generate 1,3-dipolar reagents, azomethine ylides and thiocarbonyl ylides, and their [3+2] cycloaddition to olefins yielding pyrrolidines[2a,c] and tetrahydrothiophenes,[2b,c] respectively. 1,4-Elimination reaction of a silyl group and an ammonium group to generate di-*exo*-methylenecyclohexane derivatives is also successfully applied to construct a decalin skeleton.[2d] Compared to carbocyclic analogue,[3] the synthetic studies on the generation of heterocyclic di-*exo*-methylene species (*o*-quinodimethane type) from heteroaromatic systems are fallen behind presumably because the structure of dienes or their precursors were limited and the synthetic route to them were not necessarily established.[4]

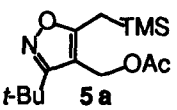
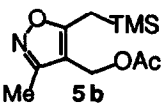
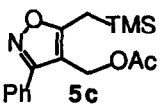


Scheme

We planed to prepare and use methyl (trimethylsilylmethyl)acetylenecarboxylate (**1**) as a dipolarophile and a common key compound leading to precursors for di-*exo*-methylene compounds which subsequently react with olefins in [4+2] cycloaddition mode to afford fused heterocyclic compounds. Here we report the new and general route toward the synthesis of the precursor **5** for di-*exo*-methyleneisoxazolines **6** and their Diels-Alder reactions leading to fused isoxazoles **7** (Scheme).

Methyl (trimethylsilylmethyl)acetylenecarboxylate (**1**) was prepared from 2-propynyltrimethylsilane and methyl chloroformate in 69% yield (deprotonation with *n*-butyllithium in Et_2O at -78 °C and methoxycarbonylation with methyl chloroformate at -78 °C-rt). Acetylenecarboxylic acid ester **1**, thus obtained, was subjected to [3+2]cycloaddition reaction with representative aliphatic (R=*t*-Bu, Me) and aromatic (R=Ph) nitrile oxides **2**. As for the generation of **2**, two methods were applied (one method is thermolysis of oxime chlorides[5] and the other is dehydration of nitro compounds[6]) and **1** as a dipolarophile was nicely converted to isoxazole derivatives **3a-c** in high yields[7] (Table 1). 4-Isoxazolecarboxylic acid esters **3a-c** were reduced with lithium aluminum hydride in Et_2O at room temperature to yield the corresponding alcohols **4a-c**. These alcohols were converted to the acetates **5a-c** by treatment with acetic anhydride and a catalytic amount of *N,N*-dimethylaminopyridine in a pyridine-THF mixed solvent at room temperature. As shown in Table 1, the precursors **5** bearing aliphatic or aromatic substituents were obtained in high yields. Except for **1**, 1-hydroxymethyl-, 1-acetoxymethyl-, 1-dimethylaminomethyl-2-(trimethylsilylmethyl)acetylenes, and trimethyl(4-trimethylsilyl-2-butynyl)ammonium iodide were not effective for the present 1,3-dipolar cycloaddition reaction.

Table 1. Conversion of **1** to the Precursors **5** for Di-*exo*-methylene Derivatives **6**.

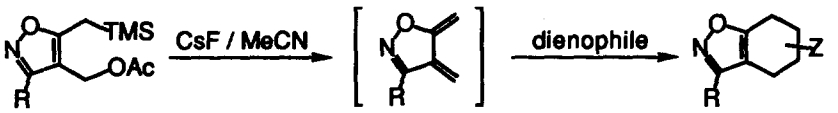
Nitrile Oxide **2**	% Yield[c]			
R	**3**	**4**	**5**	
t-Bu[a]	83 **3a**	84 **4a**	 *t*-Bu **5a**	87
Me[b]	67 **3b**	84 **4b**	 Me **5b**	82
Ph[a]	83 **3c**	86 **4c**	 Ph **5c**	78

[a] For the generation of nitrile oxide, thermolysis of the corresponding oxime chloride was used (ref. 7).

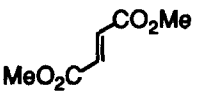
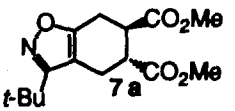
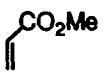
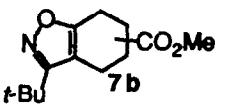
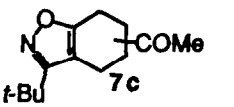
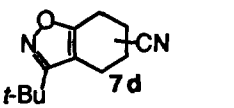
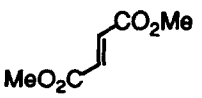
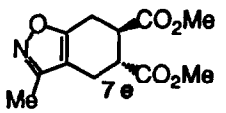
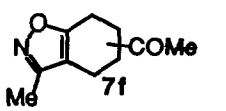
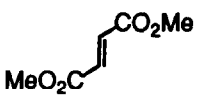
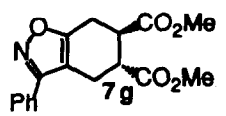
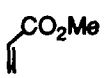
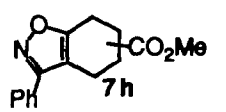
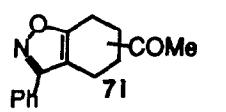
[b] For the generation of nitrile oxide, dehydration of nitro compound was used (ref.8).

[c] Isolated yield.

Table 2. Fluoride Ion-Promoted 1,4-Elimination from Diene-Precursors **5** and Diels-Alder Reaction.[a]



5 **6** **7**

Diene-precursor **5** R	Dienophile	Conditions	Product **7**	% Yield[b]
t-Bu **5a**		rt, 2.5h	 **7a**	90
		rt, 2days	 **7b**	90 (1:1.8)
		rt, 1day	 **7c**	82 (1:1.2)
		rt, 2h 55°C, 2h	 **7d**	44 62 (1:1.2)
Me **5b**		rt, 1h	 **7e**	86
		rt, 9h	 **7f**	83 (1:1.4)
Ph **5c**		rt, 3h	 **7g**	75
		rt, 1h	 **7h**	59 (1:1.6)
		rt, 1h	 **7i**	58 (1:1.3)

[a] For the procedure, see text.

[b] Isolated yield after purification by columnn chromatography on silica gel. The regioisomeric ratio was shown in parenthesis.

These precursors **5** for di-*exo*-methylene derivatives **6** were subjected to fluoride ion-promoted 1,4-elimination reaction of a silyl group and an acetoxy group in the presence of cesium fluoride. Although the formation of **6** was detected by GC-MS and a isomeric mixture of dimers of **6** was mainly obtained in the absence of the dienophile, the reaction in the presence of a dienophile proceeded smoothly to afford the corresponding fused isoxazoles **7** in excellent yields. Various kinds of fused isoxazoles **7** listed in Table 2 express efficiency of this method. The most effective conditions we examined were as follows: to a flame-dried flask containing cesium fluoride (1.0 mmol) and purged with nitrogen were successively added acetonitrile (1 ml), dimethyl fumarate (1.5 mmol) and the precursor **5a** (0.5 mmol) at room temperature. After stirring for 2.5 h at the same temperature, the reaction mixture was poured into water and extracted with Et_2O. Cycloadduct **7a** was obtained in 90% yield after purification by chromatography on silica gel. In some cases two kinds of dimers derived from **6** were also produced in a small amount in addition to **7**.

In conclusion this synthetic strategy provides a general method for the generation of di-*exo*-methylene analogue of isoxazolines and in principle this may be applicable to the other fused heterocyclic systems. Now reactions of **1** and related compounds with other 1,3-dipolar reagents and 1,3-dienes are actively examined.

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7. In all cases, a single regioisomer was obtained and the structure of **3b** was deduced as shown in Scheme **3b** was converted to methyl 3,5-dimethyl-4-isoxazolecarboxylate which showed good agreement in NMR spectrum with that prepared according to ref. 8. **3b**: ^{1}HNMR ($CDCl_3$) δ -0.06 (s, 9H), 2.25 (s, 3H), 2.53 (s, 2H), 3.68 (s, 3H); ^{13}CNMR ($CDCl_3$) δ -1.8, 11.6, 19.0, 50.8, 105.7, 159.2, 162.9, 178.5; MS m/e (% relative intensity) 227 (M^+, 3), 212 (23), 123 (17), 73 (100). Anal. Calcd for $C_{10}H_{17}NO_3Si$: C, 52.83; H, 7.54; N, 6.16. Found: C, 52.95; H, 7.33; N, 6.03.
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