

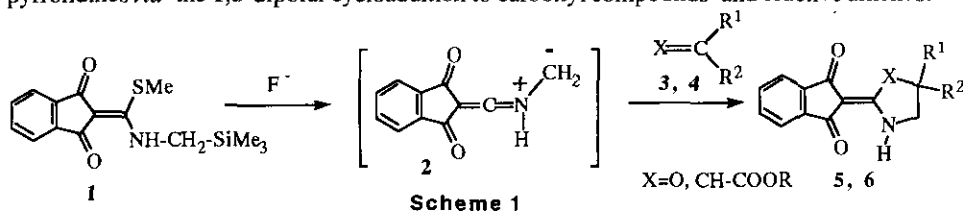
**1,3-DIPOLAR CYCLOADDITION REACTION OF
2-[(TRIMETHYLSILYLMETHYLAMINO)(METHYLTHIO)]-
METHYLENE-1,3-INDANDIONE: SYNTHETIC EQUIVALENT OF
CYCLIC DICARBONYL ALKYLIDENE-AZOMETHINE YLIDE AS
A NOVEL 1,3-DIPOLAR REAGENT**

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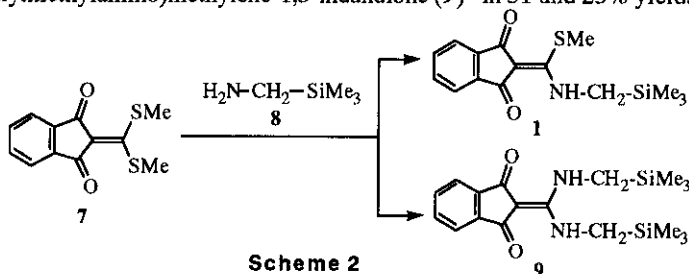
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Abstract-----2-[(Trimethylsilylmethylamino)(methylthio)]methylene-1,3-indandione (**1**), readily prepared by reaction of the corresponding 2-bis(methylthio)methylene-1,3-indandione (**7**) with trimethylsilylmethylamine (**8**), was found to be a synthetic equivalent of carbonyl alkylidene-azomethine ylide. Reaction of **1** with reactive hetero-dipolarophiles such as aldehydes and ketones and reactive alkenes in the presence of cesium fluoride gave 1,3-dipolar cycloadducts, 2-(1,3-dioxoindan-2-ylidene)-1,3-oxazolidines (**5a-i**) and 2-(1,3-dioxoindan-2-ylidene)pyrrolidines (**6a-c**).

Azomethine ylides are one of the most important classes of 1,3-dipolar reagents for the construction of nitrogen-containing five-membered heterocycles such as pyrrolidine and 1,3-oxazolidine derivatives.¹ Among them, alkylidene-azomethine ylides are also synthetically useful reagents for the preparation of *N*-containing five-membered heterocycles bearing an active methylene group at the α -position.² Alkylidene-azomethine ylides can be generated by the 1,3-elimination reaction of *N*-(trimethylsilylmethyl) substituted ketene *N,S*-acetals promoted by fluoride ion. α -Oxoketene *N,S*-acetals are also synthetically useful reagents, and numerous preparation methods and synthetic reactions have been reported.³ In an extension of the study on ketene dithioacetals for synthesis of heterocycles, we now wish to report here the preparation of α -oxoketene *N,S*-acetal, 2-[(trimethylsilylmethylamino)(methylthio)]methylene-1,3-indandione (**1**) as a new synthetic equivalent of carbonyl alkylidene-azomethine ylide and a novel synthesis of cyclic α -oxoketene *N,O*-acetals and 2-carbonyl alkylidene-pyrrolidines *via* the 1,3-dipolar cycloaddition to carbonyl compounds and reactive alkenes.



2-Bis(methylthio)methylene-1,3-indandione (**7**),⁴ readily available from reaction of 1,3-indandione with carbon disulfide in the presence of sodium hydroxide followed by methylation with methyl iodide, was treated with trimethylsilylmethylamine (**8**) in methanol under reflux for 30 min to afford a separable mixture of **1**⁵ and 2-bis(trimethylsilylmethylamino)methylene-1,3-indandione (**9**)⁶ in 51 and 23% yields, respectively.



It was previously shown that the synthesis of 2-alkylidene-1,3-oxazolidines from alkylidene-azomethine ylides and carbonyl compounds as hetero 1,3-dipolarophiles could be effectively conducted by a stoichiometric amount of cesium fluoride.² At the start of this study, the reaction of **1** with benzaldehyde (**3a**) was attempted in the presence of cesium fluoride in acetonitrile at room temperature for 45 h. The reaction proceeded smoothly to afford the corresponding 2-(1,3-dioxindan-2-ylidene)-4-phenyl-1,3-oxazolidine (**5a**) in 42% yield. Compound **1** also reacted with various aromatic aldehydes (**3b-f**) to give the corresponding 2-(1,3-dioxindan-2-ylidene)-1,3-oxazolidines (**5b-f**) in yields as shown in Table 1.^{7,8} The reaction of **1** with ketones (**3g-i**) proceeded smoothly to give the corresponding 5,5'-disubstituted 2-oxazolidine derivatives (**5g-i**) in 11-59% yields.

Table 1. Reaction of 2-(Trimethylsilylmethylamino)(methylthio)methylene-1,3-indandione (1**) with Carbonyl Compounds (**3**)^a**

Entry	R ¹ , R ² (3)	Products	mp(°C)	Yield (%) ^b
1	R ¹ =C ₆ H ₅ R ² =H (3a)	5a	245-247	42
2	R ¹ =4-MeC ₆ H ₄ R ² =H (3b)	5b	255-258	51
3	R ¹ =4-C ₆ H ₅ C ₆ H ₄ R ² =H (3c)	5c	222-225	47
4	R ¹ =2,6-Cl ₂ C ₆ H ₃ R ² =H (3d)	5d	320-322	74
5	R ¹ =4-NO ₂ C ₆ H ₄ R ² =H (3e)	5e	271-273	54
6	R ¹ =1-Naphthyl R ² =H (3f)	5f	252-256	62
7	R ¹ =C ₆ H ₅ R ² =C ₆ H ₅ (3g)	5g	213-219	11
8	R ¹ =C ₆ H ₅ R ² =C ₆ H ₅ -CO (3h)	5h	265-268	33
9	R ¹ =COOEt R ² =COOEt (3i)	5i	178-179	59

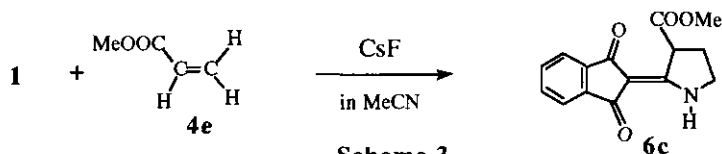
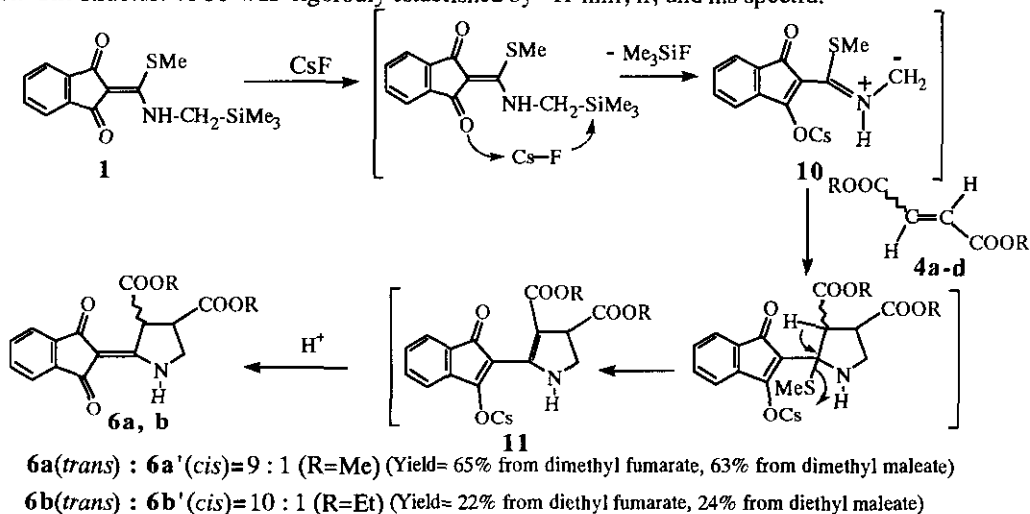
a) All reactions were carried out in a system of **1** (0.5 mmol), **3** (1.0 mmol) and CsF (0.6 mmol) in MeCN (3ml).

b) Isolated yield.

In order to ascertain the stereospecificity of the reaction, we studied the cycloaddition of **1** with *cis* and *trans* disubstituted dipolarophiles. The azomethine ylides examined so far in the literature¹ have been shown to

undergo stereospecific cycloaddition. Interestingly, treatment of **1** with either dimethyl fumarate (**4a**) or dimethyl maleate (**4b**) at room temperature for 20 h in the presence of cesium fluoride afforded a 9:1 mixture of *trans* and *cis* cycloadducts, dimethyl 2-(1,3-dioxindan-2-ylidene)pyrrolidine-3,4-dicarboxylate (**6a**, **6a'**) as the exclusive product without stereocontrolled mode. Similarly, reaction of **1** with diethyl fumarate (**4c**) and diethyl maleate (**4d**) gave the corresponding 1,3-dipolar cycloadducts (**6b**, **6b'**) in 22 and 24% yields, respectively. Initially, exposure of compound (**1**) to cesium fluoride promotes a metal-assisted ionization of the carbonyl group of indandione and a concomitant desilylation to form the stabilized 1,3-dipole (**10**). The 1,3-dipolar cycloaddition of **10** with active alkenes is readily carried out followed by the elimination of methylthio group and hydrolysis of cesium salts (**11**) to yield the corresponding final products (**6**). The reaction process without stereocontrolled mode as shown in Scheme 3 was elucidated by the formation of intermediates (**11**) and the thermodynamically resultant force.

We also examined the regioselectivity of cycloaddition reaction using an unsymmetrically substituted dipolarophile. When methyl acrylate (**4e**) was used as the dipolarophile, cycloadduct (**6c**)⁹ was the exclusive product. The structure of **6c** was rigorously established by ¹H-nmr, ir, and ms spectra.



A typical experimental procedure entailed the following steps: a solution of 2,6-dichlorobenzaldehyde (**3d**) (0.176 g, 1.0 mmol), *N,S*-acetal (**1**) (0.108 g, 0.50 mmol), and cesium fluoride (0.091 g, 0.60 mmol) in dry acetonitrile (10 ml) was stirred at room temperature for 20 h. The solvent was evaporated to give a crude product which was purified by silica gel column chromatography using a mixture of hexane and ethyl acetate (4 : 1) as an eluent to give 0.100 g (74%) of **5d**.¹⁰ This compound was recrystallized from ethanol to give colorless needles, mp 320-322°C.

It is evident from the present results that *N*-trimethylsilylmethyl-substituted *N,S*-acetal (**1**) is a storable and easy-to-handle synthetic equivalent of carbonyl alkylidene-azomethine ylide (**10**). The success of application of

oxoketene dithioacetal to a new preparation of 1,3-dipolar reagent opens new applications for use of these ketene dithioacetals.

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5. 1: Yield 51%, mp 72-73°C, yellow needles; $^1\text{H-nmr}$ (CDCl_3 , 90 MHz) δ : 0.20(9H, s, SiMe₃), 2.69(3H, s, SMe), 3.23(2H, d, J=6.1 Hz, NH-CH₂-), 7.46-7.71(4H, m, aromatic-H), 8.91(1H, br s, NH); ir(KBr) ν cm^{-1} : 3030(NH), 1675(CO); $\text{ms: } m/z$ 305(M^+ , 100).
6. 9: Yield 23%, mp 76-78°C, yellow leaflets; $^1\text{H-nmr}$ (CDCl_3 , 90 MHz) δ : 0.23(18H, s, SiMe₃), 3.02(4H, d, J=4.8 Hz, NH-CH₂-), 7.37-7.60(4H, m, aromatic-H), 8.04(1H, br s, NH), 8.90(1H, br s, NH); ir(KBr) ν cm^{-1} : 3200(NH), 1655(CO); $\text{ms: } m/z$ 360(M^+ , 91).
7. Protodesilylation of **1** in the presence of fluoride ion in acetonitrile (the proton preassembly comes from the water present) gave the corresponding 2-[(dimethylamino)(methylthio)]methylene-1,3-indandione which was alternatively prepared by the displacement reaction of **7** with dimethylamine in methanol in good yield. Tetrabutylammonium fluoride(TBAF) can be used as a source of fluoride ion in the present reaction. In the reaction of **1** with **3d**, the desired product (**5d**) was obtained in 57% yield.
8. Satisfactory spectral (ir , $^1\text{H-nmr}$, and ms) data were obtained for these compounds. The yield is that of the material purified by column chromatography on silica gel using a mixture of hexane and ethyl acetate (4 : 1) as an eluent.
9. **6c**: Yield 28%, mp 272-273°C, yellow crystals; $^1\text{H-nmr}$ (DMSO-D_6 , 90 MHz) δ : 2.25(2H, m, 4-H), 3.63(2H, m, 5-H), 3.64(3H, s, OMe), 4.47(1H, dd, J=7.6, 10.1 Hz, 3-H), 7.62(4H, m, aromatic-H), 10.00(1H, br s, NH); ir(KBr) ν cm^{-1} : 3290(NH), 1695, 1650(CO); $\text{ms: } m/z$ 271(M^+ , 100), 212(68).
10. **5d**: Yield 74%, mp 320-322°C, yellow needles; $^1\text{H-nmr}$ (DMSO-D_6 , 90 MHz) δ : 3.87(1H, dd, J=10.6, 10.7 Hz, N-CH₂-), 4.29(1H, dd, J=10.6, 10.7 Hz, N-CH₂-), 6.69(1H, dd, J=10.6, 10.7 Hz, O-CH-), 7.50-7.59(10H, m, aromatic-H), 9.80(1H, br s, NH); ir(KBr) ν cm^{-1} : 3260(NH), 1645(CO); $\text{ms: } m/z$ 361(M^+ , 53), 359(M^+ , 55), 173(42), 44(100).

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