

**SYNTHESIS AND [3+2] CYCLOADDITION REACTION OF
3-[(TRIMETHYLSILYLMETHYLAMINO)(METHYLTHIO)]-
METHYLENE-2-COUMARANONE AND -1-METHYLOXINDOLE:
SYNTHETIC EQUIVALENT OF HETEROCYCLIC ALKYLIDENE-
AZOMETHINE YLIDE AS A NOVEL 1,3-DIPOLAR REAGENT**

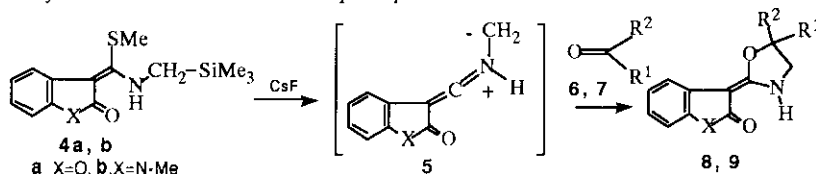
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Abstract-----3-[(Trimethylsilylmethylamino)(methylthio)]methylene-2-coumaranone (**4a**) and -1-methyloxindole (**4b**), readily prepared by reaction of the corresponding bis(methylthio)methylene-heterocyclic compounds (**2a, b**) with trimethylsilylmethylamine (**3**), were found to be synthetic equivalent of heterocyclic alkylideneazomethine ylides. Reaction of **4a, b** with reactive heterodipolarophiles such as aldehydes and ketones in the presence of cesium fluoride gave 1,3-dipolar cycloadducts, 3-(2-oxazolindinydene)-2-coumaranone and -1-methyloxindole derivatives (**8a-j, 9a-h**), via the 1,3-elimination of (methylthio)trimethylsilane.

Alkylideneazomethine ylides can be generated by the 1,3-elimination reaction of *N*-trimethylsilylmethyl-substituted ketene *N,S*-acetals promoted by fluoride ion and [3+2] cycloaddition¹ to various dipolarophiles is achieved, giving *N*-containing α -alkylideneheterocycles.² The ketene *N,S*-acetals considered as precursors of azomethine ylides are readily obtained by reactions of trimethylsilylmethylamine with the corresponding ketene dithioacetals.³ This paper reports the preparation of 3-(trimethylsilylmethylamino)(methylthio)methylene-2-coumaranone (**4a**) and -1-methyloxindole (**4b**) as synthetic equivalents of heterocyclic alkylideneazomethine ylides and reaction with hetero dipolarophiles.



Bis(methylthio)methyleneheterocyclic compounds (**2a, b**),^{4,5} readily available from reaction of 2-coumarone and oxindole, respectively, with carbon disulfide in the presence of sodium hydroxide followed by methylation with methyl iodide or dimethyl

sulfate, were treated with trimethylsilylmethylamine (3) in methanol under reflux for 30 min to afford the corresponding *N,S*-acetal derivatives(4a)⁶, (b)⁷ in high yields. The *E*-configuration of 4a, b was revealed by their ir and ¹H-nmr spectra (See Notes).

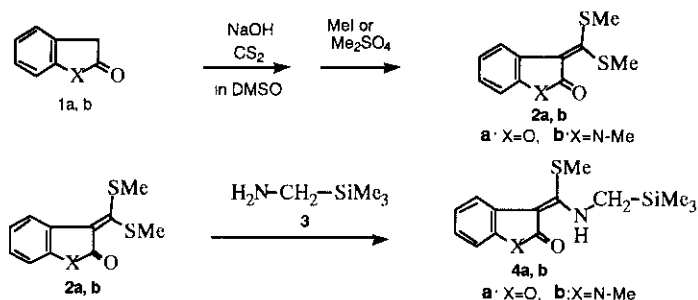
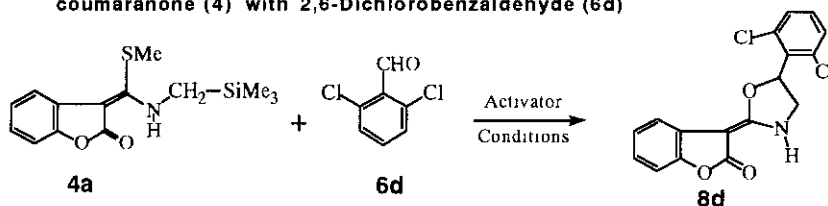


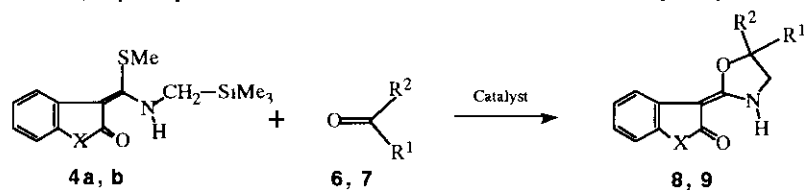
Table 1. 1,3-Dipolar Cycloaddition Reaction of 3-(Trimethylsilylmethylamino)(methylthio)-2-coumaranone (4) with 2,6-Dichlorobenzaldehyde (6d)



Entry	N,S-Acetal	Aldehyde (mmol)	Activator	Conditions	Yield(%)
1	0.5	1.0	TASF (1.0 equiv.)	THF, rt, 24 hr	72
2	0.5	1.0	TBAF (1.0 equiv.)	THF, rt, 24 hr	60
3	0.5	1.0	TBAF (0.1 equiv.)	THF, rt, 24 hr	69
4	0.5	1.5	CsF (1.2 equiv.)	CH ₃ CN, rt, 45 hr	60
5	0.5	1.0	CsF (1.2 equiv.)	CH ₃ CN, rt, 10 hr	67
6	0.5	1.0	CsF (1.2 equiv.)	CH ₃ CN, rt, 45 hr	69
7	0.5	1.0	CsF (1.2 equiv.)	CH ₃ CN, rt, 70 hr	73

TASF= Tris(dimethylamino)sulfur(trimethylsilyl) Difluoride [(CH₃)₂N]₃S((CH₃)₃SiF₂)
 TBAF= Tetrabutylammonium Fluoride {CH₃(CH₂)₃]₄NF

It was previously shown that the synthesis of 2-alkylidene-1,3-oxazolidines from alkylideneazomethine ylides and carbonyl compounds could be effectively conducted by a stoichiometric amount of cesium fluoride.^{2, 8} At the start of this study, the reaction of 4a with 2,6-dichlorobenzaldehyde (6d) was attempted in the presence of cesium fluoride in acetonitrile at room temperature for 45 h as a model reaction. The reaction proceeded smoothly to afford the corresponding 2-coumaranone (8d) in 60% yield. When 2.0 equivalents of aldehyde per one equivalent of 4a were used, the yield of cycloadduct (8d) was 73%. Tris(dimethylamino)-sulfur(trimethylsilyl) difluoride(TASF) and tetrabutylammonium fluoride (TBAF) could be served as sources of fluoride ions in this reaction (Tables 1 and 2).⁹ Acids such as trimethylsilyl trifluoromethanesulfonate, iodotrimethylsilane, and trifluoroacetic acid did

Table 2. 1,3-Dipolar Cycloaddition Reaction of N,S-acetal Derivatives with Carbonyl Compounds^{a)}

Entry	N,S-Acetal		Carbonyl compound		Catalyst	product	Yield (%)	mp (°C)
	X	R ¹	R ²					
1	O	H	C ₆ H ₅ (6a)	CsF	8a ¹²⁾	25	177	
2	O	H	4-MeC ₆ H ₄ (6b)	CsF	b	41	173	
3	O	H	4-C ₆ H ₅ C ₆ H ₄ (6c)	CsF	c	47	226	
4	O	H	2,6-Cl ₂ C ₆ H ₃ (6d)	CsF	d	73	277	
5	O	H	4-ClC ₆ H ₄ (6e)	CsF	e	60	214	
6	O	H	4-NO ₂ C ₆ H ₄ (6g)	CsF	f	17	202	
7	O	H	1-naphthyl (6h)	CsF	g	46	250	
8	O	H	Me(CH ₂) ₃ (6i)	CsF	h	22	119	
9	O	H	(E) C ₆ H ₅ CH=CH (6j)	CsF	i	24	173	
10	O	C ₆ H ₅	C ₆ H ₅ (7a)	CsF	j	11	249	
11	NMe	H	4-Me-C ₆ H ₅ (6b)	CsF	9a	75	174	
12	NMe	H	4-C ₆ H ₅ C ₆ H ₄ (6c)	CsF	b	65	284	
13	NMe	H	2,6-Cl ₂ C ₆ H ₃ (6d)	CsF	c	69	298	
14	NMe	H	2,6-Cl ₂ C ₆ H ₃ (6d)	TBAF	e	45	298	
15	NMe	H	4-ClC ₆ H ₄ (6e)	CsF	d	59	207	
16	NMe	H	4-MeOC ₆ H ₄ (6f)	CsF	e	50	213	
17	NMe	H	1-naphthyl (6g)	CsF	f	53	237	
18	NMe	H	Me(CH ₂) ₃ (6h)	CsF	g	16	163	
19	NMe	C ₆ H ₅	C ₆ H ₅ -C=O (7b)	CsF	h	11	249	

^{a)} All reactions were carried out in a system of **4** (0.5 mmol), carbonyl compound (**6** or **7**) (1.0 mmol), and CsF (0.6 mmol) in MeCN ^{b)} Yield after isolation by silica gel column chromatography

not promote the reaction. Compound (**4a**) reacted smoothly with other aldehydes (**6**) in the presence of cesium fluoride to give the corresponding 2-oxazolidinylidene substituted [3+2] cycloaddition products (**8a-i**) in 17-73% yields. The reaction of **4** with ketone (**7a**) was conducted under the same conditions. As shown in Table 2, the reaction of **4** with ketone (**7a**) proceeded smoothly to give the corresponding 5,5'-disubstituted 2-oxazolidinylidene derivative (**8j**) in 11% yield. Substituted aromatic aldehydes bearing electron-donating and electron-withdrawing groups, α,β -unsaturated aldehyde and aromatic ketone reacted with **4** to give the corresponding oxazolidinylidenes (**8**) in modest yields. Compound (**4b**) also reacted smoothly with various substituted aldehydes (**6**) and ketone (**7b**) to give the corresponding 2-oxazolidinylidene-1-methyloxindoles (**9a-h**) in yields as shown in Table 2

A typical experimental procedure is as follows: a solution of 2,6-dichlorobenzaldehyde (**6d**) (0.176 g, 1.0 mmol), *N,S*-acetal (**4a**) (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 (**8d**) which was purified by silica gel column chromatography using methanol as an eluent to give 0.100 g (0.365 mmol) of **8d** in 73% yield. This compound was recrystallized from ethanol to give colorless needles, mp 277°C.

It is evident from the present results that *N*-trialkylsilylmethyl-substituted *N,S*-acetals (**4a**, **b**) are storable and easy-to-handle synthetic equivalents of heterocyclic alkylideneazomethine ylides (**5**).¹⁰

REFERENCES AND NOTES

1. a) R.M.Kellog, *Tetrahedron*, 1976, **32**, 2165; J.W.Lown, *Rec. Chem. Prog.*, 1971, **32**, 51; C.G.Struckwisch, *Synthesis*, 1973, 469; "1,3-Dipolar Cycloaddition Chemistry" A. Padwa, ed., John Wiley & Sons, New York, 1984, Vols, 1 and 2; N.Imai, Y.Terao, and K.Achiwa, *Yuki Gousei Kagaku Kyokai-shu (J. Synth. Org. Chem. Jpn.)*, 1985, **43**, 862; E.Vedejs and F.G.West, *Chem. Rev.*, 1986, **86**, 941; A.Padwa, G.E.Fryxell, J.R.Gasdaska, M.K.Venkatramanan, and G.S.K.Wong, *J. Org. Chem.*, 1989, **54**, 644.
2. A.Hosomi, Y.Miyashiro, R.Yoshida, Y.Tominaga, T.Yanagi, and M.Hojo, *J. Org. Chem.*, 1991, **55**, 5308; Y.Tominaga, K.Ogata, S.Kohra, M.Hojo, and A.Hosomi, *Tetrahedron Lett.*, 1991, **32**, 5987.
3. Y.Tominaga and Y.Matsuda, *J. Heterocycl. Chem.*, 1985, **37**, 937; Y.Tominaga and Y.Matsuda, *Yuki Gousei Kagaku Kyokai-shu (J. Synth. Org. Chem. Jpn.)*, 1985, **43**, 669, R.K.Dieter, *Tetrahedron*, 1986, **42**, 3029; Y.Tominaga, *Yuki Gousei Kagaku Kyokai-shu (J. Synth. Org. Chem. Jpn.)*, 1989, **47**, 413; Y.Tominaga, "Synthesis of Heterocyclic Compounds Using Ketene Dithioacetals" in *Trends in Heterocyclic Chemistry*, J.Menon, ed., Council of Scientific Research Integration, Research Trends, 1991, **2**, 43.
4. **2a**: G.Kobayashi, S.Furukawa, and Y.Matsuda, *Yakugaku Zasshi*, 1966, **86**, 1152.
5. **2b**: Yield 83%, mp 59-60°C, yellow needles; ¹H-nmr(CDCl₃, 90 MHz) δ: 2.58(3H, s, SMe), 2.64(3H, s, SMe), 7.00-7.38(3H, m, aromatic-H), 8.06(1H, m, aromatic-H); ir(KBr) ν_{cm}⁻¹: 1742(CO).
6. **4a**: mp 76-78°C, yellow needles, Yield 99%. ¹H-Nmr(CDCl₃, 90MHz) δ: 0.17(9H, s, SiMe₃), 2.46(3H, s, SMe), 3.25(2H, d, J=5.9 Hz, N-CH₂-), 7.05-7.24(3H, m, aromatic-H), 7.71-7.82(1H, m, aromatic-H), 9.49(1H, bs, NH); ir(KBr) ν_{cm}⁻¹: 3190(NH), 1680(CO); mas: m/z 293(M⁺, 100).
7. **4b**: Orange oil, Yield 98%. ¹H-Nmr(CDCl₃, 90 MHz) δ: 0.18(9H, s, SiMe₃), 2.45(3H, s, SMe), 3.22(2H, d, J=5.9 Hz, N-CH₂-), 3.35(3H, s, NMe), 6.91-7.12(3H, m, aromatic-H), 7.25-8.04(1H, m, aromatic-H), 10.42(1H, bs, NH); ir(KBr) ν_{cm}⁻¹: 3190(NH), 1620(CO); mas: m/z 306(M⁺, 100).
8. Protodesilylation of **4a** in the presence of fluoride ion in acetonitrile gave the corresponding[(dimethylamino)-methylthio]methylene-2-coumarone which was alternatively prepared by the displacement reaction of **2a** with dimethylamine in methanol in good yield.
9. Satisfactory spectral (ir, ¹H-nmr, and mass) data were obtained for these compounds. The geometrical configurations of **8** and **9** were established by the ir and ¹H-nmr spectra. Absorption bands assignable to hydrogen-bonded carbonyls were present in the ir spectra. The yield is that of the material purified by column chromatography on silica gel.
10. The reactions of **4a** and **b** with activated olefins in the presence of fluoride ion gave the desired cycloadducts. Details will be published in a forthcoming paper.

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