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S-SILYLMETHYL-SUBSTITUTED KETENE DITHIOACETALS AS SYNTHETIC EQUIVALENT OF A NOVEL 1,3-DIPOLAR REAGENT, ALKYLIDENETHIOCARBONYL YLIDE; SYNTHESIS AND [3+2] CYCLOADDITION REACTIONS

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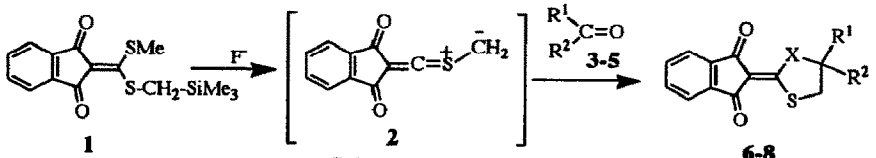
Abstract: *2-(Trimethylsilylmethylthio)(methylthio)methylene-1,3-indanedione(1), readily prepared by reaction of 2-bis(methylthio)methylene-1,3-indanedione(9) with trimethylsilylmethylmercaptane(10), was shown to be the synthetic equivalent of alkylidene-thiocarbonyl ylide. Treatment of this compound with fluoride ions in the presence of reactive hetero-dipolarophiles such as carbonyl compounds and active alkenes afforded 1,3-dipolar cycloadducts, 2-alkyliden-1,3-oxathiolanes and 2-alkylidenethiophenes, by carbonyl-substituted counterparts and concomitant desilylation.*

Thiocarbonyl ylides belong to one of the most important classes of 1,3-dipolar reagents for producing of five-membered ring sulfur-containing heterocycles such as thiophene derivatives, 1,3-oxathiolanes, and 1,3-thiazolidines.[1] Recently we reported that alkylidene-azomethine ylides can be generated by the 1,3-elimination reaction of N-(trimethylsilylmethyl) substituted ketene N,S-acetals promoted by fluoride ions and [3+2] cycloaddition to various of dipolarophiles is achieved, giving N-containing 2-alkylidene-heterocycles.[2] Ketene N,S-acetals considered as precursors of azomethine ylides, are readily obtained by addition-elimination reaction of (trimethylsilylmethyl)amine with the corresponding ketene dithioacetals.[2,3]

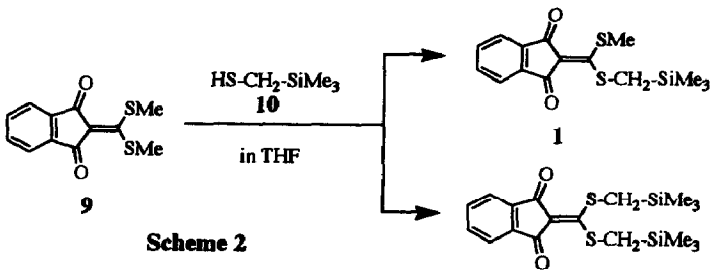


Scheme 1

In the light of earlier findings,[2] a convenient approach to the synthesis of alkylidene thiophene or 1,3-oxathiolane nucleus was cosidered to be the the pathway illustrated in Scheme 1. We report here results obtained using alkylidene-thiocarbonyl ylide, a new 1,3-dipolar reagent, derived from 2-(S-methyl-S'-trimethylsilylmethyl)methylene-1,3-indanedione(**1**) as a method for synthesizing the 1,3-oxathiolane and thiophene nucleus *via* their 1,3-dipolar [3+2] cycloaddition to various dipolarophiles such as aldehydes, ketones, and activated alkenes.

2-(Trimethylsilylmethylthio)(methylthio)methylene-1,3-indanedione(**1**) was prepared by the addition-elimination reaction of trimethylsilylmethylmercaptane (**10**) to 2-bis(methylthio)methylene-1,3-indanedione (**9**).[4] This reaction in tetrahydrofuran gave a separable mixture of **1**[5] and 2-bis(trimethylsilylmethyl-thio)methylene-1,3-indanedione (**11**)[6] in 50.7 and 20.3% yields, respectively.

α-Thiocarbanions should be readily generated by the fluoride ion-promoted desilylation of trimethylsilylmethyl sulfide under mild conditions and be conveniently applicable for obtaining of various

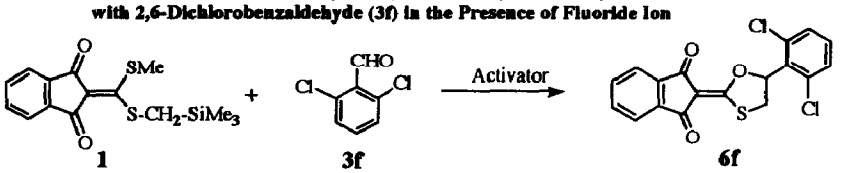


9 1 11

Scheme 2

1,3-dipolar reagents such as thiocarbonyl ylides and related species.[7] At the start of the present study, reaction of **1** with 2,6-dichlorobenzaldehyde (**3f**) in the presence of various fluoride ions were conducted to obtain 2-(1,3-oxazolidin-2-ylidene)-1,3-indanedion derivative (**6f**). The results are summarized in Table 1. Cesium fluoride as a fluoride ion source gave the best results in the reaction of **1** with **3f** at room temperature in acetonitrile. Other fluoride ion sources such as TBAF and TASF also served well as catalysts to give the corresponding **6f**, but lithium fluoride and silver fluoride were not effective for this 1,3-dipolar cycloaddition.[8] Thus cesium fluoride was used as the main fluoride ion source. As shown in Table 2, ketene dithioacetals, **1**, reacted smoothly with various aromatic, α,β-unsaturated and aliphatic aldehydes and ketones bearing electron-donating and electron-withdrawing substituents.

Table 1. Reaction of 2-(Trimethylsilylmethylthio)(methylthio)methylene-1,3-indanedione (1) with 2,6-Dichlorobenzaldehyde (3f) in the Presence of Fluoride Ion



1 3f 6f

Entry	S,S-Acetal(mmol.)	Aldehyde(mmol.)	Activator	Conditions	Yield(%) [a]
1	0.5	1.0	TASF(1.0 equiv.)	THF, rt, 2.5 h	52
2	0.5	1.0	TBAF(0.1 equiv.)	THF, rt, 20 h	50
3	0.5	1.0	TBAF(0.5 equiv.)	THF, rt, 20 h	45
4	0.5	1.0	CsF(1.2 equiv.)	MeCN, rt,20 h	66
5	0.5	1.5	CsF(1.2 equiv.)	MeCN, rt, 20 h	59
6	0.5	1.0	LiF(1.2 equiv.)	MeCN, rt, 20 h	0

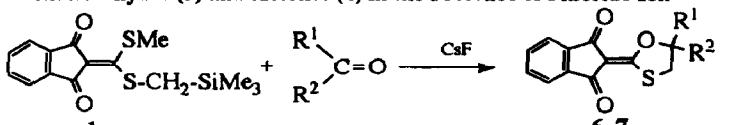
a) Isolated yyield

TASF=Tris(dimethylamino)sulfur(trimethylsily) Difluoride $(Me_3N)_3S(Me_3SiF_2)$

TBAF=Tetrabutylammonium Fluoride$[Me_3(CH_2)_3]_4NF$

To determine the stereospecificity of the reaction, the cycloaddtion of **1** with *cis* and *trans* disubstituted dioplarphiles was carried out. The thiocarbonyl ylides examined so far in the literature have been shown to undergo streospecific cycloaddition. Interestingly, treatment of **1** with dimethyl fumarate(**5a**) or dimethyl maleate(**5b**) at room temperature for 20 hr. in the presence of cesium fluoride afforded cycloadduct dimethyl 2-(1.3-dioxindan-2-ylidene)-4,5-dihydro-thiophene-*trans* 3,4-dicarboxylate(**8a**) as the exclusive product without a sterocontrolled mode. Exposure of this compound to cesium fluoride metal-assisted the rising of a carbonyl group of indanedione and concomitant desilylation to form the stabilized 1,3-dipole(**12**) as shown in Scheme 3. In these reactions, compound **13**[9] could be isolated as a stable cesium salts of **8** from the reaction mixture and was converted to the corresponding mixture of expected *cis*

Table 2. Reaction of 2-(Trimethylsilylmethylthio)(methylthio)methylene-1,3-indanedione (1) with Aldehydes (3) and Ketones (4) in the Presence of Fluoride Ion[a]

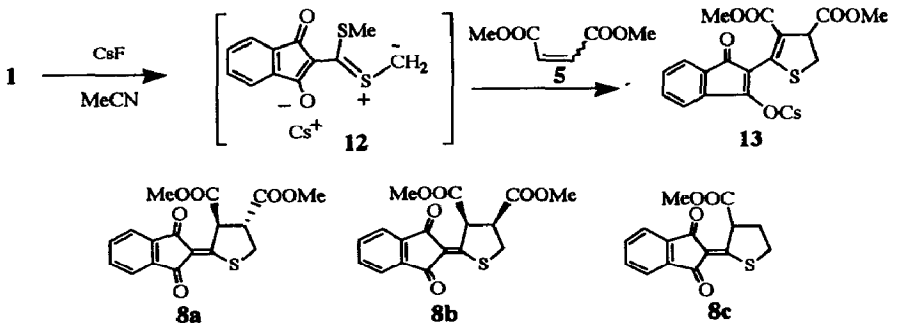


Entry	R^1	R^2	Product	Yield(%)[b]	mp(°C)
1	C_6H_5	H (3a)	6a	71	216
2	C_6H_4-Me(4)	H (3b)	6b	44	237
3	C_6H_4-OMe(4)	H (3c)	6c	21	215
4	C_6H_4-OMe(3)	H (3d)	6d	33	142
5	C_6H_4-Cl(4)	H (3e)	6e	66	226
6	C_6H_3-Cl_2(2,6)	H (3f)	6f	64	288
7	C_6H_4-C_6H_5(4)	H (3g)	6g	45	237
8	C_6H_4-CN(4)	H (3h)	6h	51	237
9	C_6H_4-NO_2(2)	H (3i)	6i	54	223
10	1-naphthyl	H (3j)	6j	78	176
11	CH=CH-C_6H_5	H (3k)	6k	11	170
12	COOEt	COOEt (4a)	7a	85	131
13	C_6H_4-NO_2(4)	Me (4b)	7b	36	231

[a]All reactions were carried out in a system of 1 (0.5 mmol), 3,4 (1.0 mmol), and CsF (0.6 mmol) in MeCN at rt. [b]Yield after isolation by silicagel column chromatography.

and *trans* alkylidene thiophene-3,4-dicarboxylates derivatives , **8a**[10] and **b**[11](Ratio of *cis* and *trans*: 10:1 by ^{1}H-NMR spectra).

The cycloaddition behavior of an unsymmetrically substituted dipolarophile was studied to determine the regioselectivity of the reaction. When methyl acrylate(**5c**) was used as a dipolarophile, cycloadduct **8c** was obtained exclusively. The structure of **8c** was rigorously established by ^{1}H-NMR, IR, and MS spectra.[12]



Scheme 3

General procedure: a solution of dimethyl fumarate (1.5 mmol), ketene dithioacetal (**1**) (0.5 mmol), and cesium fluoride (0.5 mmol) in dry acetonitrile (6 ml) was stirred at room temperature for 20 hr under a nitrogen atmosphere. After evaporating the solvent, the residue was treated with 10 ml of water and acidified with 1N-HCl solution. The mixture was extracted with ethyl acetate. The organic layer was separated and dried over sodium sulfate, and the solvent was evaporated. After purification of the crude

product by silica gel column chromatography, the thiophene **8a**, mp 167-171°C, was obtained in 81% yield.

It is evident from the present data that the new ketene dithioacetal, **1**, is the synthetic equivalent of alkylidene-thiocarbonyl ylide. The reaction shows complete regiospecificity in the cycloaddition with heterodipolarophiles and mono substituted olefins.

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5. **1**: yellow prisms, mp 71-75°C., Yield 71%. ^{1}H-NMR(90 MHz, $CDCl_3$) δ: 0.16(9H, s, $SiMe_3$), 2.45(2H, s, CH_2), 2.63(3H, s,SMe), 7.59-7.88(4H, m, aromatic-H).
6. **11**: yellow prisms, mp 94-96°C, Yield 20%. ^{1}H-NMR(90 MHz, $CDCl_3$) δ: 0.15(18H, s, $SiMe_3$), 2.44(4H, s, CH_2), 7.78-7.87(4H, m, aromatic-H).
7. *a*) A. Hosomi, K. Ogata, K. Hoashi, S. Kohra, and Y. Tominaga, *Chem. Pharm. Bull.*, **36**, 3736 (1988); *b*) A. Hosomi, K. Ogata, M. Ohkuma, and M. Hojo, *Synlett.*, **3**, 557 (1991); *c*) S. Kohra, H. Ueda, and Y. Tominaga, *Heterocycles*, **36**, 1497 (1993).
8. Satisfactory spectral (IR, ^{1}H-NMR, and MS) data were obtained for all new compounds in this work.
9. **13**: mp 266-269°C, tan crystals, IR(KBr) ν cm^{-1}: 1725, 1660(CO); ^{1}H-NMR(90MHz, DMSO-D_6)δ: 2.01(1H, dd, J=7.9, 11.2 Hz, 5a-H), 3.29(1H, dd, J=9.3,11.2 Hz, 5b-H), 3.41(3H, s, OMe), 3.59(3H, s, OMe), 4.04(1H, dd, J=7.9, 9.3 Hz, 4-H), 7.11-7.78(4H, m, aromatic-H); Fab ms: 479(M^++1): $C_{17}H_{13}O_6SCs$=478.243.
10. **8a**: mp 168-170°C, tan crystals, IR(KBr) ν cm^{-1}: 1730, 1670(CO); ^{1}H-NMR(90MHz, $CDCl_3$)δ: 3.41(1H, dd, J=6.0, 11.7 Hz, 5a-H), 3.78(1H, m, 5b-H), 3.72(3H, s, OMe), 3.74(3H, s, OMe), 3.77(1H, m, 4-H), 5.80(1H, d, J=2.0 , 3-H), 7.66-7.91(4H, m, aromatic-H).
11. This compound could not be isolated from the reaction mixture, no matter has many attempts made. However a doublet was seen at 5.75 ppm (J=6.0 Hz) due to 3-position at thiophene ring in ^{1}H-NMR spectrum.
12. **8c**: IR(KBr) ν cm^{-1}: 1670, 1660(CO); ^{1}H-NMR(90MHz, DMSO-D_6)δ: 2.36(1H, m, 4a-H), 2.80(1H, m, 4b-H), 3.28(2H, m, 5-H), 3.73(3H, s, OMe), 5.24(2H, dd, J=1.9, 7.8 Hz, 3-H), 7.34-7.94(4H, m, aromatic-H).

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