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METHOXYPHENYLTHIOTRIMETHYLSILYLMETHYLLITHIUM
A CONVENIENT REAGENT FOR THE HOMOLOGATION OF CARBONYL COMPOUNDS

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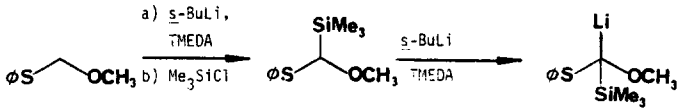
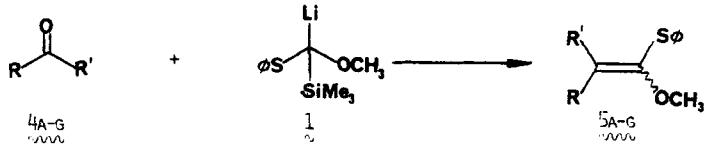
Abstract: A facile homologation procedure for the conversion of carbonyl compounds into ketene-O,S-acetals is described. These intermediates are readily converted into ketene-O-silyl,S-acetals, thioesters, and carboxamides.

The homologation of aldehydes and ketones to ester derivatives *via* the corresponding ketene dithioacetals has been widely accepted as a useful preparative method.[1] During the course of a continuing synthetic program we required a method for the homologation of carbonyl compounds which involved an exceedingly mild hydrolytic procedure and precluded the use of mercuric salts for this purpose. In this communication we wish to comment on the utility of methoxyphenylthiotrimethylsilylmethyllithium, (1), for the conversion of carbonyl compounds into thioesters and amides. The organometallic reagent, 1, is readily generated by the deprotonation of methoxyphenylthiotrimethylsilylmethane, (2) with s-butyllithium-TMEDA complex in THF at -78°C.[2] The silane 2, in turn, is conveniently prepared in multi-gram quantities *via* the sequential lithiation-silylation of methoxymethylphenylsulfide, (3).

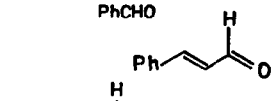
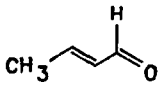
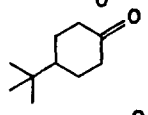
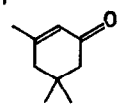
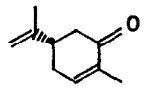


3 2 1

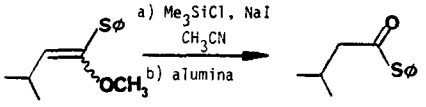
The treatment of a variety of carbonyl compounds (e.g. 4a-g) with 1 (THF, -78°C→25°C) furnished the corresponding ketene-O,S-acetals 5a-g as a mixture of Z and E isomers in fair to excellent yields.[3,4] The homologation of the ketones 4d and 4e was accompanied, to a minor extent (c.a. 7%-11%), by competing deprotonation. With l-carvone (4f), the homologation procedure was complicated both by deprotonation and competing, 1,4-addition of 1.[5] These findings are summarized in the Table.



4A-G 1 5A-G

Carbonyl Compound (4)	Equiv. of (1)	Deprotonation %	Yield %
a PhCHO	1.0	0	100
b 	1.0	0	100
c 	1.0	0	94
d 	1.0	7.2	92.6
e 	1.0	10.6	86.5
f 	1.0	21	60
g 	0.9	0	96

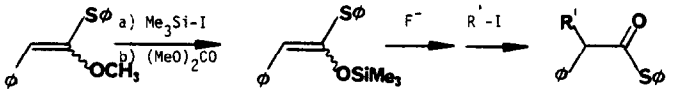
Whereas ketene-O,S-acetals have been reported to undergo acid catalyzed methanolysis in the presence of hydrogen chloride and mercuric chloride,[6] we required a cleavage procedure which could be executed under neutral or mildly basic reaction conditions. Accordingly, exposure of the ketene-O,S-acetal 5g to chlorotrimethylsilane (1.2 equiv.) and sodium iodide (1.2 equiv.) in dry acetonitrile (.05 M, 25°C, 5 min.) and subsequent filtration of the reaction mixture through alumina (act. 3)[7] afforded the phenyl thioester 6 in 90% yield.



5G 6

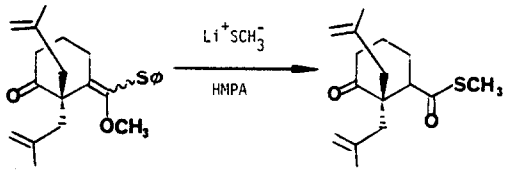
The synthetic utililty of silylenol ethers in fluoride mediated alkylation reactions[8] as well as aldol and Michael reactions[9] catalyzed by Lewis acids has been recognized extensively. In principle, the conversion of ketene-O,S-acetals to the corresponding O-trimethylsilyl derivatives would permit the execution of these, and other synthetic operations (e.g. 4a→8). Herein we report the first successful synthesis of silylenol ether derivatives from their methyl enol ether counterparts. After numerous experimental trials the following procedure was determined to be optimum. Treatment of the ketene-O,S-acetal 5a with freshly distilled (CaH_2)

iodo-trimethylsilane (2.0 equiv., CH_3CN, 80°C, 20 hr.) and subsequent quenching ($(CH_3O)_2C{=}O$, 2.0 equiv., 25°C)[10] followed by purification provided the ketene-O-silyl,S-acetals 7 in 92% yield.[11]

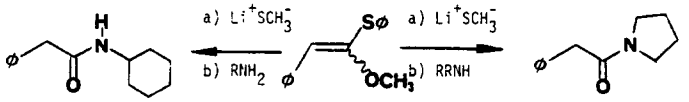


5A 7 8

An attractive alternative to the aforementioned cleavage procedure was envisaged by way of the nucleophilic demethylation of ketene-O,S-acetals. In accordance with this precept, the exposure of the ketene-O,S-acetal 9 to lithium thiomethoxide (4.0 equiv., dry HMPA, 25°C, 19 hr.) furnished the methyl thioester 10 (58% yield after purification). A variant of the above procedure has been found useful for the direct conversion of ketene-O,S-acetals to carboxamides. Thus sequential treatment of 5a with lithium thiomethoxide in HMPA followed by the addition of an appropriate amine (e.g. cyclohexylamine or pyrrolidine, 3 equiv.) provided the corresponding carboxamides 11 (94%) and 12 (95%).



9 10



11 5A 12

The yields and apparent scope of the foregoing olefination sequence in addition to the synthetic utility of the intermediate ketene and ketene-O-silyl,S-acetals, suggest that this method will strongly complement existing literature procedures for the one-carbon homologation of carbonyl compounds into carboxylic acid thioesters and amides.

Acknowledgement. Support for this research by a grant from the National Institute of Health (GM-32000) is gratefully acknowledged.

This communication is dedicated to the memory of Professor Robert V. Stevens.

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(1) (a) E.J. Corey and G. Märkl, Tetrahedron Lett., 3201 (1967) (b) P.F. Jones and M.F. Lappert, J. Chem. Soc. Chem Commun., 526 (1972) (c) D. Seebach, M. Kolb and B.T. Gröbel, Chem. Ber., 106, 2277 (1973).

(2) Alternatively, methoxyphenylthiotrimethylsilylmethane (2) can be lithiated with n-butyllithium in THF at -30°C, albeit with lower efficiency.

(3) All new compounds were fully characterized by IR and 80 MHz ^1H nmr. In addition, all possessed satisfactory elemental (C,H) analyses.

(4) The following represents a typical experimental procedure for the homologation of a carbonyl compound: A 100 mL three necked flask equipped with a magnetic stirring bar, thermometer, nitrogen inlet and rubber septum was flame-dried and charged with 1.077 gm of methoxyphenylthiotrimethylsilylmethane (4.76 mmole), and 40 mL of dry THF. To this was added 0.79 mL TMEDA (5.23 mmole) and 10 mg of 1,10-phenanthroline. The mixture was cooled to -78°C and s-butyllithium in cyclohexane was added dropwise until the deep purple color of the 1,10-phenanthroline indicator was evidenced. Then, 3.96 mL of 1.32M s-butyllithium in cyclohexane (5.23 mmole) was added dropwise at such a rate so as not to exceed -70°C. After completion of the addition, the resultant purple solution was stirred for an additional 2.5 hours at -78°C. Benzaldehyde, 0.48 mL (4.72 mmole), was then added at -78°C and the reaction mixture was allowed to warm to room temperature overnight.

The solution was poured into saturated aqueous ammonium chloride solution (100 mL), and this solution was extracted twice with pentane (100 mL). The combined pentane extracts were successively dried with brine and anhydrous sodium sulfate. The solvent was evaporated and the resultant oil was subsequently purified by bulb to bulb distillation, to afford 1.143 gm (99.9%) of a mixture of E and Z ketene-O,S-acetals 4a, as a colorless oil. NMR ($CDCl_3$,TMS) δ 3.70, 3.71 (s, 3H, CH_3), 6.19, 6.30 (s, 1H, vinyl), 7.0-7.6 (m, 10H, Ar). IR (cm^{-1}) (film) 2820-3100(C-H), 1615 (C=C).

(5) The side product resulting from 1,4-addition was fully characterized subsequent to its isolation (preparative G.C.).

(6) A. de Groot and B.J.M. Jansen, Syn. Commun., 985 (1983).

(7) T. Cohen and Z. Kosarych, Tetrahedron Lett., 3959 (1980).

(8) I. Kuwajima and E. Nakamura, J. Am. Chem. Soc., 97, 3257 (1975).

(9) (a) T. Mukaiyama, K. Banno, and K. Narasaka, J. Am. Chem. Soc., 96, 7503 (1974). (b) K. Saigo, M. Osaki, and T. Mukaiyama, Chem. Lett., 163 (1976). An investigation is currently underway to determine the utility of ketene-O,S-acetals in the $TiCl_4$ mediated aldol and Michael condensation reactions.

(10) The optimum reaction conditions entailed the use of dimethyl carbonate as an iodotrimethylsilane scavenger subsequent to the desilylation of the ketene-O,S-acetal.

(11) In addition 6% of S-methyl thio phenylacetate was formed via hydrolysis of the ketene-O-silyl,S-acetal.

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