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The Vilsmeier Reaction on Dithioketals: A Facile Method for the Stereoselective Synthesis of β-Alkylthioethylenic Aldehydes

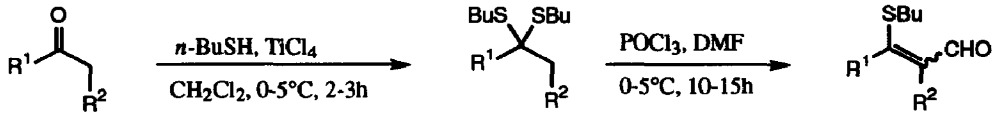
C.V. Asokan* and Annie Mathews

School of Chemical Sciences, Mahatma Gandhi University
Priyadarsini Hills, Kottayam, Kerala 686 560, India

Abstract: *An expedient and general method for the synthesis of β-alkylthioethylenic aldehydes from dithioketals under Vilsmeier-Haack reaction conditions is described.*

β-Alkylthioethylenic aldehydes are of interest as potential multifunctional synthons useful in carbocyclic and heterocyclic synthesis.[1-3] However, the reactivity pattern of this class of compounds has not yet been examined in detail, apparently due to the non-availability of expedient methods for their synthesis. As part of our continuing interest in studies on Vilsmeier reactions on sulfur compounds,[4] we examined the reactivity of dithioketals **2** under Vilsmeier conditions.[5] Work-up of the reaction with cold saturated potassium carbonate leads to the stereoselective formation of *n*-butyl thioethylenic aldehydes **3** in good yields (Scheme 1).[6] The reaction has been found to be very general and dithioketals derived from aromatic, aliphatic and cyclic ketones could be effectively converted to the corresponding *n*-butylthioethylenic aldehydes.

Scheme 1

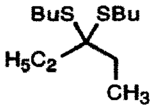
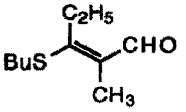
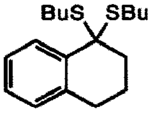
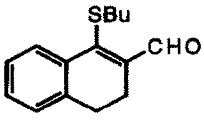
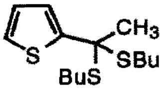
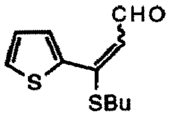
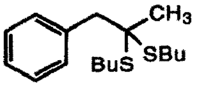
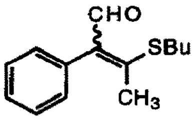
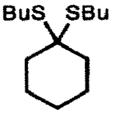
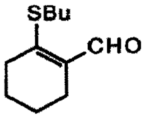
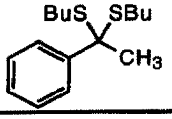
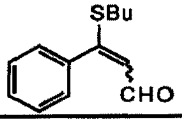


1 **2** **3**

The dithioketals **2** were routinely prepared from the respective ketones and *n*-butyl thiol in the presence of titanium tetrachloride.[7] A solution of dithioketal in dry methylene chloride was treated with Vilsmeier reagent at 0° C for 2h and then at room temperature for 12-15h.[6] The reaction of 3,3-bis(*n*-butylthio)pentane under these conditions gave exclusively *E*-3-butylthio-2-methyl-2-pentenal in 67% yield (entry 1, table 1). The *E*-configuration is assigned on the basis of the chemical shift of the aldehyde protons in the ^{1}H nmr spectrum. The proximity of sulfur to the aldehyde proton in the *E*-isomer causes a deshielding of this proton, thus making it fairly easy to distinguish between geometrical isomers with the help of proton nmr spectra. Other examples of ene aldehydes prepared are shown in table 1. In acyclic systems formation of the *E*-isomer is largely favoured. Only the dithioketal derived from benzyl methyl ketone (entry 4) leads to a preferential formation of the Z-isomer of the ene aldehyde.

The reaction apparently involves a vinyl sulfide intermediate which undergoes further formylation. The success of the present procedure is mainly due to the stability of the vinyl sulfide functionality under aqueous alkaline work-up conditions of the Vilsmeier reaction.[8]

Table 1. Transformation of dithioketals to β-alkylthioethylenic aldehydes

Entry	Dithioketal	Ethylenic aldehyde[a]	Yield(%)[b]	*E*:*Z* ratio[c]
1			67	
2			65	
3			72	80:20
4			70	30:70
5			65	
6			69	95:5

[a] All the products gave appropriate ^{1}H NMR, IR and mass spectra. [b] Isolated yield based on dithioacetal. [c] Determined by ^{1}H NMR.

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6. General Procedure: To dimethyl formamide (0.20 mol) under argon atmosphere at 0°C, phosphorous oxychloride (0.20 mol) was added over 15 minutes. To the Vilsmeier reagent thus prepared, the dithioketal 2 (0.01 mol) was introduced slowly at 0°C. The reaction mixture was gradually brought to room temperature. After stirring for 12-15h, the mixture was poured over 100 ml of cold saturated aqueous potassium carbonate solution. Extracted with diethyl ether (4 x 50 ml), dried (Na_2SO_4), and evaporated. The crude product thus obtained was purified by flash column chromatography over silica gel using hexane:ethyl acetate (95:5) as eluent.

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8. For instance, enol ethers under Vilsmeier-Haack reaction conditions lead to the formation of β-keto aldehydes. Lester, M. G.; Petrov, V.; Stephenson, O. *Tetrahedron* **1964**, *20*, 1407.

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