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# Vilsmeier–Haack reactions of α-hydroxyketenedithioacetals: a facile synthesis of substituted pyridines

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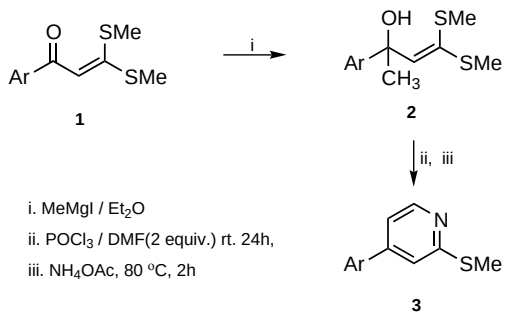
**Abstract**—The reaction of α-hydroxyketenedithioacetals, generated by the 1,2-addition of methyl Grignard reagent to α-oxoketenedithioacetals, with the Vilsmeier reagent was investigated. The reaction proceeds with acid-catalysed dehydration to afford sulphur substituted 1,3-butadienes, which undergo subsequent iminoalkylations. The intermediate iminium salts formed were successfully transformed into 2-methylsulfanyl substituted 4-aryl pyridines, in the presence of ammonium acetate 

The Vilsmeier–Haack reaction is one of the useful general methods employed for the formylation of various electron rich aromatic, aliphatic and heteroaromatic substrates[1] and the halomethyleneiminium salt intermediates are highly versatile for the synthesis of heterocycles.[2] For instance, by the condensation of enamines with iminium salts, Risch and co-workers developed a simple method for the synthesis of substituted pyridines.[3] Boruah and co-workers have reported the reactions of conjugated steroidal oximes with the Vilsmeier reagent resulting in a pyrido-steroidal product.[4] Jutz et al. have demonstrated that the cyclisation of the intermediate iminium salts formed by the multiple iminoalkylations of certain alkenes, in the presence of ammonium acetate leads to the formation of substituted pyridines and naphthyridines.[5] We have recently generalised this protocol, starting from appropriate tertiary alcohols, rather than alkenes.[6] We envisaged that a similar ammonium acetate induced cyclisation of the intermediates formed by the treatment of α-hydroxyketenedithioacetals would afford a useful method for the synthesis of substituted pyridines.

The chemistry of α-oxoketenedithioacetals leading to the formation of heterocycles, aromatic compounds, and various valuable reactive intermediates has been studied extensively.[7] Potts et al.[8–10] and Junjappa et al.[11] have used α-oxoketene dithioacetals extensively for the synthesis of substituted pyridines. Potts and co-workers have studied the conjugate addition of active methylene ketones to α-oxoketenedithioacetals in the presence of potassium *t*-butoxide in THF. The 1,5-enediones formed in these reactions have been subsequently exploited for the synthesis of substituted pyridines and annulated pyridines in moderate yields.[8,9] The same protocol was applied for the synthesis of oligopyridines and quinquepyridines as well.[10] 1,2-Addition of lithioacetonitrile or lithiopropionitrile to α-oxoketenedithioacetals afforded enol acetals which underwent intramolecular Ritter reactions accompanied by a 1,3-methylthio shift in the presence of $H_3PO_4$ to give a variety of substituted and annulated 2,6-bis-(methylthio)pyridines in good yields.[11] Transformations of α-hydroxyketenedithioacetals, readily available by the chemoselective reduction or 1,2-nucleophilic addition reactions of α-oxoketenedithioacetals, have also been well studied. Their reaction with the chloromethylene iminium salt proceeds with dehydration followed by iminoalkylation to afford conjugated




**Scheme 1.**

*Keywords*: pyridines; ketenedithioacetals; Vilsmeier reagent; iminoalkylations; sulphur compounds.

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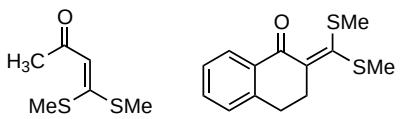
pentadiene–aldehydes, on aqueous alkaline workup. This protocol has been established as a useful procedure for the synthesis of conjugated polyene aldehydes and polyene esters by *1,n*-carbonyl group transpositions.[12]

In the present work we studied the reactions of α-hydroxy-ketenedithioacetal[13] **2a**, generated by the 1,2-addition of the methyl Grignard reagent to α-oxo-ketenedithioacetal **1a**, with the Vilsmeier reagent. The intermediate iminium salt formed was successfully transformed into 2-methylsulfanyl-4-phenylpyridine[14,15] **3a** in 51% yield, in the presence of ammonium acetate (Scheme 1).

The reactions of other aryl substituted α-hydroxy-ketenedithioacetals **2b–f** with chloromethylene–iminium salt also proceeded in a similar fashion, to afford the 4-aryl-2-(methylsulfanyl)pyridines[14] **3b–f** in 41–56% overall yields (Table 1). Our attempts to synthesise pyridines from acyl ketene dithioacetal **4** and other systems such as ketenedithioacetals of α-tetralone **5**, propiophenone **6** etc. afforded complex reaction mixtures. All the substituted pyridines prepared were fully characterised with the help of spectral and analytical data.

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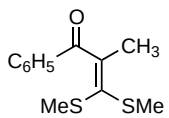


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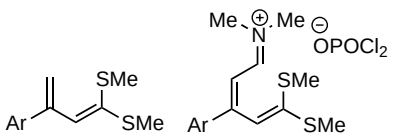


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A probable mechanistic pathway leading to the formation of 4-aryl-2-(methylsulfanyl)pyridines **3** involves the dehydration of α-hydroxy ketenedithioacetals induced by the presence of Vilsmeier reagent to afford 1,1-bis-(methylthio)-3-aryl-1,3-butadienes **7**. Further reaction of the diene with chloromethylene iminium salt leads to the iminoalkylated intermediate **8**, which on cyclisation in the presence of ammonium acetate affords 4-aryl-2-(methylsulfanyl)pyridines **3**. It is interesting to note that products derived from further iminoalkylations have not been isolated from these reactions. This could be attributed to the relatively lower electron rich character of bis(methylthio)substituted 1,3-butadienes compared to the *N,N*-dimethylamino substituted 1,3-butadienes which are intermediates in the multiple iminoalkylation reactions of aliphatic tertiary alcohols.

**Table 1.** 4-Aryl-2-(methylsulfanyl)pyridines **3** prepared

| Entry | Substrate | Product | Yield (%) |
|---|---|---|---|
| 1 | (**1a**), Ar = $C_6H_5$ | **3a** | 51 |
| 2 | (**1b**), Ar = 4-$ClC_6H_4$ | **3b** | 55 |
| 3 | (**1c**), Ar = 4-$MeOC_6H_4$ | **3c** | 53 |
| 4 | (**1d**), Ar = 4-$MeC_6H_4$ | **3d** | 51 |
| 5 | (**1e**), Ar = 4-$BrC_6H_4$ | **3e** | 56 |
| 6 | (**1f**), Ar = 2-Naphthyl | **3f** | 41 |

Alkyl and arylthio substituents α or γ to a ring nitrogen are reactive leaving groups in nucleophilic substitution reactions[16] and their oxidised forms, the sulfoxides and sulfones are even more readily displaced. Thus, the alkylthiopyridines **3** could serve as precursors for further synthetic transformations. In short our studies, directed towards the exploitation of the synthetic utility of functionalised ketenedithioacetals has led to the development of an expedient method for the synthesis of 2-methylsulfanyl substituted 4-arylpyridines.

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13. *General procedure for the preparation of α-hydroxyketenedithioacetals from α-oxoketenedithioacetals:* The methyl Grignard reagent was prepared from 1.06 g (7.5 mmol) methyl iodide, 0.21 g (8.75 mmol) magnesium and a pinch of iodine crystals (0.10 g) in ether. The methyl magnesium iodide was cooled to 0–5°C and the ketenedithioacetal (5 mmol) in ether was added slowly over 15 min. The mixture was stirred at this temperature for half an hour and was poured over cold saturated ammonium chloride solution. It was then extracted with ether (3×50 mL). The combined organic layer was washed with water and dried over anhydrous sodium sulphate. Ether was removed and the α-hydroxyketenedithioacetal formed was used for the next step without further purification.
14. *General procedure for the synthesis of 4-aryl-2-(methylsulfanyl)pyridines from α-hydroxyketenedithioacetals:* The Vilsmeier reagent was prepared by mixing ice cold dry DMF (50 mL) and $POCl_3$ (1.24 mL, 10 mmol). The mixture was then stirred for 15 min at room temperature. The α-hydroxyketenedithioacetals **2a**–**f** (5 mmol) obtained from the Grignard reaction were dissolved in dry DMF and added in about 15 min at 0–5°C. The reaction mixture was stirred for 24 h at room temperature. Solid ammonium acetate was added to the reaction mixture in excess (15 equiv., 5.8 g) and the mixture was again stirred for a further 2 h. The mixture was then added to cold saturated $K_2CO_3$ solution (300 mL) and extracted with diethyl ether (3×50 mL). The organic layer was washed with water, dried over anhydrous $Na_2SO_4$ and evaporated to give the crude product which was chromatographed over silica gel using hexane: ethyl acetate, (98:2) as eluent to give the 4-aryl-2-(methylsulfanyl) pyridines **3a**–**f**.
15. All compounds gave satisfactory spectroscopic data and elemental analyses. Spectral data of representative compound 2-(methylsulfanyl)-4-phenylpyridine **3a** was obtained from the reaction of 4,4-bis(methylsulfanyl)-2-phenyl-3-buten-2-ol **2a** (1.35 g, 5 mmol) as a brown oil, yield: 0.51 g (51%); IR (neat, $\nu_{max}$) 1580, 1530, 1445, 1360, 1120 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.59 (s, 3H, $SCH_3$); 7.16 (d, $J=6$ Hz, 1H, Py 5-H); 7.37 (s, 1H, Py 3-H); 7.40–7.60 (m, 5H, aromatic); 8.46 (d, $J=6$ Hz, 1H, Py 6-H) ppm. $^{13}C$ NMR (50.33 MHz, $CDCl_3$): $\delta$ 13.78 ($SCH_3$), 118.01, 119.63, 127.39, 128.44, 128.76, 129.07, 129.47, 138.41, 148.76, 150.12, 160.94 ppm (aromatic); EIMS $m/z$ (%): 201 (100, $M^+$), 200 (88.7), 128 (39.4). Anal. calcd for $C_{12}H_{11}NS$: C, 71.61; H, 5.51; N, 6.96; S, 15.93. Found: C, 71.57; H, 5.48; N, 6.82; S, 15.86%
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