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Synthesis of novel β-aryl-β-(methylthio)acroleins via Vilsmeier–Haack protocol as potential 1,3-dielectrophilic three-carbon building blocks

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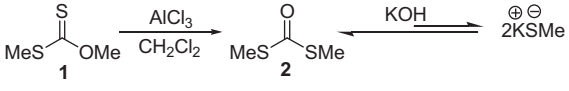
ABSTRACT

A new general route for the synthesis of novel β-aryl-β-(methylthio)acroleins, a class of stable potential 1,3-dielectrophilic synthons, has been reported. The overall protocol involves treatment of either β-chloroacroleins or their precursor iminium salts (generated in situ from the corresponding active methylene ketones under Vilsmeier–Haack reaction conditions) with S,S-dimethyldithiocarbonates (DDC)/aqueous KOH in either a one-pot or two-step process. The dimethyldithiocarbonate (DDC)/30% aqueous KOH has been shown to be an excellent source of methylthiolate anion.

The versatile formylation reaction of electron rich aromatics and heteroaromatics developed by Vilsmeier and Haack in 1927[1] was successfully extended by Arnold and Zamlicka[2] to active methylene carbonyl compounds yielding the corresponding β-chloroacroleins[3a–h] in good to excellent yields. The β-chloroacrolein chemistry has since been extensively explored as potential 1,3-dielectrophilic building blocks for the synthesis of a variety of five and six membered heterocycles.[4a–c] Additionally, it is known that the β-chloro group can be replaced by nucleophiles such as alkoxides and aryloxides to yield the corresponding β-alkoxy/aryloxyacroleins in excellent yields.[5] However, these chloroacroleins are unstable as they rapidly undergo polymerization[6] even at room temperature, though addition of anhydrous sodium acetate (1 g/100 mL) may extend their stability for some time. Thus, most of these chloroacroleins are generally prepared and used immediately. Our experience in organosulfur chemistry prompted us to develop a methodology for the corresponding β-(methylthio)acroleins **6a–r** (Scheme 3), which we conceived, would be more stable and thus assume a positive advantage over the unstable β-chloroacroleins. To transform these β-chloroacroleins to the corresponding β-(methylthio)acroleins, methylthiolate (CH_3SNa) anion is required, which is generated by treatment of methylmercaptan with a base. Since methylmercaptan is a gas, alternatively its sodium salt is generated by basic hydrolysis of precursors such as thiolesters or *S*-methylthiouronium salt etc. Interestingly, Degani and co-workers[7a,b] have used a symmetrical *S,S*-dimethyldithiocarbonate **2** as a new useful source of methylthiolate anion to prepare the corresponding methylsulfides. The required *S,S*-dimethyldithiocarbonate **2** has been reported to be prepared by rearrangement of easily available dimethyl xanthate **1** in the presence of tetrabutylammonium salt.[8a] However in our hands, it resulted in an uncontrollable spontaneous exothermic reaction. Alternatively in the present studies, we found that the xanthate **1** undergoes a facile rearrangement in the presence of anhydrous aluminium chloride in boiling dichloromethane to yield the corresponding dimethyldithiocarbonate **2** in more than 80% yield[8b] (Scheme 1). We therefore preferred to follow the aluminium



Scheme 1. Preparation of dimethyldithiocarbonate (DDC).

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† crystal structure of **6f** and **6o**.

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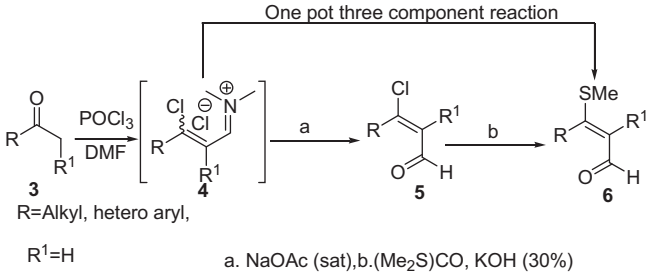
chloride method for the preparation of **2** in the present studies. Interestingly, the dimethyldithiocarbonate **2** alone cannot be hydrolysed by 30% potassium hydroxide solution either in the presence or in the absence of quaternary ammonium salts. The reaction occurs only when the electrophilic reagent is present in the reaction mixture. It is therefore concluded that the hydrolysis of **2** is a reversible reaction involving methylthiolate anion and **2** which are at equilibrium with very low concentration of the potassium methylthiolate (Scheme 1).

In the present work we have examined the transformation of β-chloroacroleins **5** or their precursors **4** (generated from corresponding active methylene ketones **3**) to β-(methylthio)acroleins **6** through manipulating the Vilsmeier–Haack protocol either in one pot reaction or in two-step conversion by utilizing *S*,*S*-dimethyldithiocarbonate (DDC) **2** as an excellent source of methylthiolate anion. We herein report the results of these studies.

With cyclic ketones **3a–d** (Table 1) the reaction could be conducted in a one pot manner by heating intermediate β-chloroiminium salts directly with dimethyldithiocarbonate (DDC) **2** in the presence of 30% potassium hydroxide at 90 °C affording the corresponding cyclic β-(methylthio)acroleins **6a–d** in 57–81% overall yields (Table 1, Scheme 2). Our literature survey at this stage revealed that β-(methylthio)acroleins **6b**[9a] and **6c**[9b] (Table 1) have been reported in the literature involving a two step protocol by treating the corresponding β-chloroacroleins with sodium methylthiolate in comparable yields.

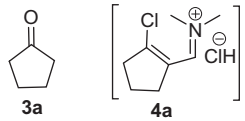
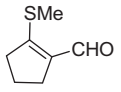
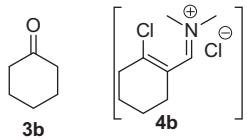
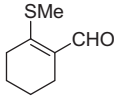
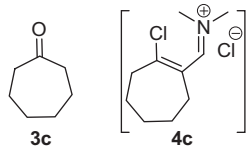
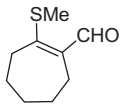
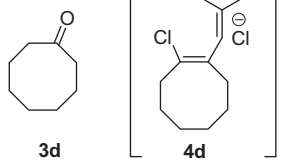
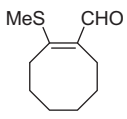
We next examined the methylthiolation of the corresponding open-chain chloroacrolein precursors. The above single step procedure did not yield the satisfactory results, when applied to iminium salts **4e–r** generated in situ from the corresponding active methylene ketones. Therefore we examined the methylthiolation of the corresponding open-chain β-chloroacrolein precursors **5**, which were isolated in pure form by treatment of the corresponding iminium salts **4** with aqueous sodium acetate.[7a] Thus treatment of β-chloroacrolein **5e** with dimethyldithiocarbonate(DDC) **2**/30% aqueous KOH, as described above, afforded the corresponding



Scheme 2. Synthesis of β-(methylthio)acroleins from ketones.

β-phenyl-β-(methylthio)acrolein **6e** in 82% yield (Table 2, entry 1). The reaction was equally facile with other β-aryl-β-chloroacroleins bearing either electron donating (**5f–h**, entries 2–4) or electron withdrawing groups (**5i–j**, entries 5 and 6) in the *para* position of the aryl ring. On the other hand decreased yield of product **6k** was obtained from chloroacrolein **5k** bearing a *o*-chlorophenyl group (entry 7). The corresponding β-(*m*-nitrophenyl)chloroacrolein **5l** also afforded the corresponding β-aryl-(methylthio)acrolein **6l** in 67% yield (Table 2, entry 8), however the reaction was not successful with β-(*p*-nitrophenyl)chloroacrolein **5m**, with no trace of **6m**, yielding only an intractable mixture of products. The corresponding β-(2-naphthyl)- and β-(2-thienyl)-β-(methylthio)acroleins **6n–o** were also obtained in good yields from the respective β-chloroacroleins **5n–o** (entries 10 and 11). On the other hand, the α-methyl-β-phenylchloroacrolein **5p** furnished the respective tetrasubstituted β-(methylthio)acrolein **6p** only in 47% yield (entry 12), which may be due to release of electron to the chlorocarbon through hyperconjugation by the methyl group. The reaction could also be extended to the cyclic and heterocyclic chloroaldehydes **5q–r** affording the corresponding (methylthio)aldehydes **6q–r** in moderate to good yields (entries 13 and 14) under the identical conditions. Degani and co-workers[7a,b] have invariably used tetrabutylammonium bromide as phase transfer catalyst in transforming

Table 1
Synthesis of β-(methylthio)acroleins from cyclic ketones-one pot protocol

Entry	Ketones	Product	Time (h)	Yield (%)
1	 **3a** **4a**	 **6a**	3.5	57
2	 **3b** **4b**	 **6b**	3.5	68
3	 **3c** **4c**	 **6c**	3.5	81
4	 **3d** **4d**	 **6d**	3.5	57

Reaction conditions: $POCl_3$ (15 mmol) was added dropwise to a mixture of DMF (15 mmol) and Toluene (15 mL) at rt. After 30 min ketone (10 mmol) was added dropwise. The reaction mixture was stirred for 2.55–3.5 h at rt (monitored by TLC). The reaction mixture was cooled to 0 °C and DDC (10 mmol) was added followed by 30% aq KOH until the reaction mixture is basic and heated to 90 °C for 45 min.