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A novel and facile synthesis of dienals and substituted 2*H*-pyrans *via* the Vilsmeier reaction of α-oxo-ketenedithioacetals

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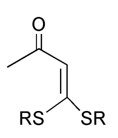
A novel and facile synthesis of dienals (3a, 3b) and substituted 2*H*-pyrans (4c, 4d) from a series of α-oxo ketenedithioacetals containing a methyl group adjacent to the carbonyl group (1a–d) *via* the Vilsmeier reaction has been developed and a mechanism for the reactions has been proposed.

Over the last decades, the Vilsmeier reaction, associated with its mild reaction conditions, commercial viability of the reagents and improved understanding of the reaction mechanism, has proven to be a versatile pathway to the synthesis of various heterocyclic compounds, such as quinolines, indoles, quinazolines, pyridines, and naphthyridines.[1–5] On the other hand, α-oxo ketenedithioacetals as the organic synthetic intermediates have been widely used in the formation of heterocycles, aromatic compounds and various valuable reactive intermediates.[6–10] The α-oxo ketenedithioacetals owe their potential synthetic applications to their varied intrinsic chemical properties. The presence of the carbonyl functionality and its position in conjugation with the double bond carrying the bis(alkylthio) groups at the β-position places α-oxo ketenedithioacetals among the versatile 1, 3-electrophilic 3-carbon equivalents.[6] Meanwhile, we note that the bis(alkylthio) groups as electron-donating groups, may activate at least to a certain extent, the carbonyl group of the α-oxo ketenedithioacetals. Such activation might drive the α-oxo ketenedithioacetals to react with the Vilsmeier reagent, and hence develop new strategies towards the synthesis of heterocycles *via* the cyclization potential of the resulting halomethyleniminium salts. To the best of our knowledge, the novelty of the process lying in the Vilsmeier reaction of α-oxo ketenedithioacetals is unprecedented, although there are a few reports on the Vilsmeier reactions of α-hydroxy ketenedithioacetals[12] and α-oxoketene-*N,S*-acetals.[13] As a continuation of our interest in the chemistry of α-oxo ketenedithioacetals,[9,10] we herein wish to report a novel synthetic strategy of dienals and 2*H*-pyrans directly from α-oxo-ketenedithioacetals *via* the Vilsmeier reaction.

In this communication, a series of α-oxo ketenedithioacetals **1a**–**1d** (Scheme 1) containing a methyl group adjacent to the carbonyl group was prepared in very high yields (up to 99%) according to our earlier reported procedure.[11] The Vilsmeier reactions of **1a**–**1d** were investigated using varied conditions (Schemes 2 and 3), some results are listed in Tables 1 and 2.



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Entry	R	R
1a	$-(CH_2)_2-$	
1b	$-(CH_2)_3-$	
1c	CH_3	CH_3
1d	$PhCH_2$	$PhCH_2$

Scheme 1

The initial studies were performed on the reactions of acyclic α-oxo ketenedithioacetals, **1a** and **1b**, with Vilsmeier reagent (1 equiv.) at 0 °C, respectively. Halogenation products **2a** and **2b**

Table 1 Vilsmeier reaction of **1a** and **1b**

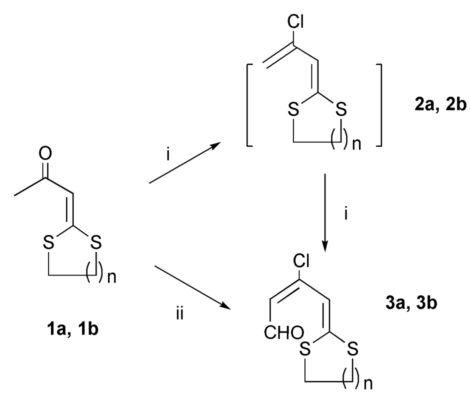
Entry	*n*	Yields (%) [a]	Mp/°C [a]	*Trans* : *cis* [b]
2a, 3a	1	92.5	82–84	90 : 10
2b, 3b	2	84.8	43–45	85 : 15

[a] Isolated yields and melting points for **3a** and **3b**, respectively. [b] Isomer ratio for **3a** and **3b** according to ^{1}H NMR spectra.

Table 2 Vilsmeier reaction of **1c** and **1d**

Entry	R	R	Mp/°C [a]	Yields (%) [a]
2c, 3c, 4c	CH_3	CH_3	39–41	70.3
2d, 3d, 4d	$PhCH_2$	$PhCH_2$	82–84	61.5

[a] Isolated yields and melting points for **4c** and **4d**, respectively.



Scheme 2 *Reagents and conditions*: (i) $POCl_3$–DMF (1 equiv.), r.t., 6 h; (ii) $POCl_3$–DMF (2 equiv.), r.t., 12 h.

were detected, however, they were not stable. The addition of another one equivalent of Vilsmeier reagent to the halogenated reaction mixture subsequently resulted in the formation of haloformylation product, dienal (**3a** or **3b**), in very high yield. According to the ^{1}H NMR spectra, the haloformylation product is a mixture of isomers with the *trans*-isomer as the predominant one (Table 1†). One-pot conversion to dienal **3a** or **3b** was successfully achieved when 2 equivalents of the Vilsmeier reagent was employed. The above results indicate that the bis(alkylthio) group of the α-oxo ketenedithioacetals can activate the carbonyl group and lead to the commencement of the Vilsmeier reaction (*i.e.* the halogenation reaction and the haloformylation reaction). Moreover, the haloformylation reaction exhibits stereoselectivity.

In an extension of this reaction, we next turned our attention to the Vilsmeier reaction of cyclic α-oxo ketenedithioacetals, **1c** and **1d**. The reactions of **1c** and **1d** with the Vilsmeier reagent (1 equiv.) were carried out at 0 °C, respectively. Just like compounds **2a**, and **2b**, halogenation products **2c** and **2d**

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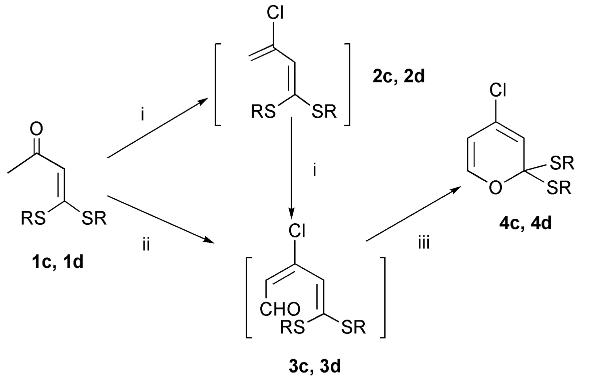
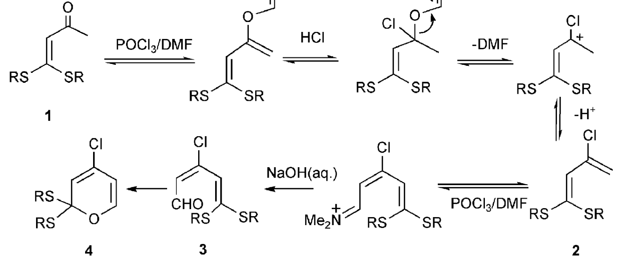


Scheme 3 *Reagents and conditions*: (i) $POCl_3$–DMF (1 equiv.), r.t., 6 h.; (ii) $POCl_3$–DMF (2 equiv.), r.t., 12 h; (iii) diethyl ether, r.t., 48 h.

were detected and unstable. With the addition of another one equivalent of the Vilsmeier reagent to the halogenated mixture, haloformylation products **3c** and **3d** were formed and detected, but it was found they were not stable, either. Kept in diethyl ether at room temperature for about 48 h, **3c** and **3d** were further converted to the corresponding 2*H*-pyrans **4c** and **4d**. One-step conversion to **4c** and **4d** was successfully achieved by the treatment of **1c** and **1d** with 2 equivalents Vilsmeier reagents, respectively.‡ It was noted that the conversion could be speeded up with increasing the reaction temperature. Obviously, the cyclization gives the evidence that the haloformylation is a stereo-selective reaction and the cyclization might follow a 6π-electrocyclic ring-closure mechanism.[1d] It is worthy of note that **3c** and **3d** could not undergo the reaction to afford 2*H*-pyrans under similar conditions.

In general, the carbonyl and the β-carbon atoms in α-oxo ketenedithioacetals can be regarded as hard and soft electrophilic centers. Therefore, many regioselective reagents can be selected either from hard nucleophiles undergoing 1,2-addition or from soft nucleophiles adding preferentially in a 1,4-fashion.[6b] However, in our previous work on the addition of Grignard reagents to α-oxo ketenedithioacetals with cyclic alkyldithio groups (*e.g.* $S(CH_2)_2S$ and $S(CH_2)_3S$) rather than acyclic groups (*e.g.* SCH_3), only 1,2-addition products were formed.[9] We attributed this to the steric hindrance effect of the rigid cyclic dithioacetal moiety. The present work further demonstrates that there is great difference between the α-oxo ketenedithioacetals with cyclic alkyldithio groups and those with acyclic alkyldithio groups from the synthetic intermediate point of view. The reason for this difference is complicated and worthy of further investigation.

A possible mechanism for the Vilsmeier reactions to yield dienals and 2*H*-pyrans from α-oxo ketenedithioacetals is depicted in Scheme 4.



Scheme 4

In summary, the reactions between Vilsmeier reagents and a series of α-oxo ketenedithioacetals containing a methyl group adjacent to the carbonyl group (**1a**–**d**) were investigated. A novel and convenient route to dienals and substituted 2*H*-pyrans directly from α-oxo ketenedithioacetal *via* the Vilsmeier reaction has been developed. The potential applications and extension of the scope of the methodology are currently under investigation in our laboratory.

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Notes and references

† Typical procedure for **3**: The Vilsmeier reagent was prepared by adding $POCl_3$ (10 mmol) dropwise to ice cold dry *N,N*-dimethylformamide (DMF, 10 mL) under stirring. The mixture was then stirred for 10–15 min at 0 °C. To the above Vilsmeier reagent was added **1a** (5 mmol) as a solution in DMF (5 mL). Then the mixture was allowed to warm to room temperature and was stirred for 12–15 h. After the starting material was consumed (monitored by TLC), the reaction mixture was poured onto crushed ice (10 g) with stirring, followed by basification with cold aqueous NaOH (0.5 M) to adjust the pH value of the solution to 9. The mixture was extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with brine (3 × 20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to yield the crude product which was purified by chromatography over silica gel using diethyl ether–hexane (1 : 80) as eluent.

Analytical data for **3a**: ^1H NMR (400 MHz, $CDCl_3$, 25 °C): (1) *trans*-isomer: 3.40 (2H, m, $-SCH_2$), 3.60 (2H, m, $-SCH_2$), 6.18 (1H, d, J = 8 Hz, –H), 6.37 (1H, s, –H), 10.03 (1H, d, J = 8 Hz, –CHO); (2) *cis*-isomer: 3.54 (2H, m, $-SCH_2$), 3.55 (2H, m, $-SCH_2$), 6.03 (1H, d, J = 8 Hz, –H), 7.28 (1H, s, = –H), 9.73 (1H, d, J = 8 Hz, –CHO); IR: 2933, 2864, 1640, 1557, 1177cm^{-1}; MS *m*/*z* [(M − 1)$^+$]: 206.

Analytical data for **3b**: ^1H NMR (400 MHz, $CDCl_3$, 25 °C): (1) *trans*-isomer: 2.22 (2H, m, $-CH_2$), 3.03 (4H, t, $-SCH_2$), 6.17 (1H, d, J = 8 Hz, –H), 6.37 (1H, s, –H), 10.04 (1H, d, J = 8 Hz, –CHO); (2) *cis*-isomer: 2.22 (2H, m, $-CH_2$), 3.03 (4H, t, $-SCH_2$), 6.22 (1H, s, –H), 6.70 (1H, d, J = 8 Hz, –H), 9.59 (1H, d, J = 8 Hz, –CHO); IR: 2980, 2833, 1744, 1651, 1550, 1131cm^{-1}; MS *m*/*z* [(M − 1)$^+$]: 220.

‡ Typical procedure for **4**: following the same procedure described above, the Vilsmeier reaction of **1c** was carried out. The resulting reaction mixture containing **3c** was worked up. The dried organic extracts were stirred at room temperature for 48 h, then concentrated under reduced pressure. The crude product was purified by chromatography over silica gel using diethyl ether–hexane (1 : 80) as eluent to yield **4c** as a yellow solid.

Analytical data for **4c**: ^1H NMR(400 Hz, $CDCl_3$, 25 °C): 2.36 (3H, s, $-SCH_3$), 2.42 (3H, s, $-SCH_3$), 6.15 (1H, s, –H), 7.43 (1H, d, J = 14 Hz, = –H), 7.50 (1H, d, J = 14 Hz, –H); IR: 3068, 2921, 1656, 1572, 1541, 1428, 1043 cm^{-1}; MS *m*/*z* [(M − 1)$^+$]: 208.

Analytical data for **4d**: ^1H NMR (400 Hz, $CDCl_3$, 25 °C): 4.10 (2H, s, $-SCH_2$), 4.18 (2H, s, $-SCH_2$), 6.11(1H, s, –H), 7.36 (11H, m, –H, –PhH), 7.68 (1H, d, J = 16 Hz, –H); IR: 3060, 1647, 1563, 1534, 1032, 698 cm^{-1}; MS *m*/*z* [(M − 1)$^+$]: 360.

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