One-Pot Synthesis of Substituted Pyridines via the Vilsmeier–Haack Reaction of Acyclic Ketene-*S*,*S*-acetals

Shaoguang Sun, Yingchun Liu, Qun Liu,* Yulong Zhao, Dewen Dong*

Department of Chemistry, Northeast Normal University, Changchun, 130024, P. R. China
Fax +86(431)5268966; E-mail: dongdw663@nenu.edu.cn

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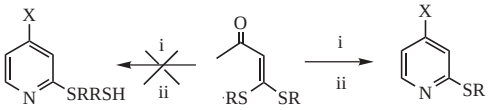
Abstract: A one-pot synthesis of substituted pyridines from acyclic ketene-*S*,*S*-acetals containing α-acetyl, α-vinyl or α-ethynyl group via the Vilsmeier–Haack reaction has been developed.

Key words: α-oxo ketene-*S*,*S*-acetal, substituted pyridine, Vilsmeier–Haack reaction, Vilsmeier reagent

Functionalized pyridines and their benzo/hetero-fused analogues represent an important class of organic molecules for their presence in numerous natural products along with useful bio-, physio- and pharmacological activities.[1,2] The synthesis of the pyridine derivatives can principally be realized either by modification of the pre-constructed pyridine nucleus or through the construction of the pyridine ring from appropriately substituted open chain precursor, which have been extensively reviewed.[1] Nevertheless, it is still of continued interest and great importance to explore novel and efficient synthetic approaches for this class of compounds, especially those with wide general applicability to achieve more flexible substitution patterns.

Over the last two decades, α-oxo ketene-*S*,*S*-acetals are emerging as versatile organic synthons in the formation of heterocycles, aromatic compounds and various valuable reactive intermediates.[3] Indeed, the attempts have been made by some research groups to synthesize pyridine derivatives from such synthons. Potts and co-workers reported earlier a one-pot two-component procedure involving the in-situ generation of unsaturated 1,5-diketones from the reaction of α-oxo ketene-*S*,*S*-acetals with methyl ketone carbonions.[4] Junjappa et al. prepared series of substituted pyridines by the cycloaromatization of α-oxo ketene-*S*,*S*-acetals with lithio acetonitrile.[5] Wang and co-workers synthesized poly-functionalized quinolines and quinolones directly from the reaction of α-oxo ketene-*S*,*S*-acetals with *o*-aminobenzoates.[6] Recent researches have revealed that pyridine derivatives can also be synthesized by the Vilsmeier–Haack reaction[7] of α-oxo ketene-*S*,*S*-acetals derived intermediates such as α-hydroxyketene-*S*,*S*-acetals[8] and α-oxo ketene-*N*,*S*-acetals.[9] Most recently, we investigated the Vilsmeier–Haack reaction of α-oxo ketene-*S*,*S*-acetals and developed a facile approach for the synthesis of 2*H*-pyrans[10] and a novel, nonthiolic, odorless thioacetalization reagent.[11] As continuation of these studies, we wish to report here a one-pot synthesis of substituted pyridines directly from the Vilsmeier–Haack reaction of α-oxo ketene-*S*,*S*-acetals.

In this communication, α-oxo ketene-*S*,*S*-acetals **1a**–**e** containing methyl group adjacent to the carbonyl group were prepared in high yields (up to 99%) according to our earlier reported procedure.[12]



2d–e **1a–e** **2a–c, 2a'–c'**

Substrate	R	R
1a	CH_3	CH_3
1b	CH_2CH_3	CH_2CH_3
1c	CH_2Ph	CH_2Ph
1d	$(CH_2)_2$	
1e	$(CH_2)_3$	

Scheme 1 *Reagents and conditions*: (i) $POCl_3$- or PBr_3-DMF (2 equiv), 0 °C, 6–24 h; (ii) NH_4OAc, 80 °C, 0.5 h.

In our previous work,[10] it was found that the Vilsmeier–Haack reaction of **1a** could proceed and the haloformylation product was detected although it was not stable. The result indicated the iminoalkylated salt could be formed at that stage. In the present work, the initial studies were performed on the reaction of α-oxo ketene-*S*,*S*-acetal **1a** with Vilsmeier reagent $POCl_3$–DMF (2 equiv) at 0 °C (Scheme 1).[13] The resulting intermediate iminium salt was further converted into 2-methylthio-4-chloro-pyridine (**2a**) in the presence of ammonium acetate in moderate yield (Table 1).

With expect to extend the scope of this reaction, the reactions of other ketene-*S*,*S*-acetals with Vilsmeier reagent $POCl_3$–DMF proceeded in a similar fashion. Subsequently, substituted pyridines **2b** and **2c** were obtained from α-oxo ketene-*S*,*S*-acetals **1b** and **1c** in moderate yields, respectively. Some of the results are summarized in Table 1. It is worth noting that other acyclic ketene-*S*,*S*-acetals with α-vinyl or α-ethynyl group, such as **1f** and **1g**, could also react with the Vilsmeier reagent to afford the corresponding substituted pyridines **2f** and **2g** in 49.5% and 54.6% yields, respectively (Scheme 2). In contrast, α-oxo cyclic ketene-*S*,*S*-acetals **1d** and **1e** could not undergo the

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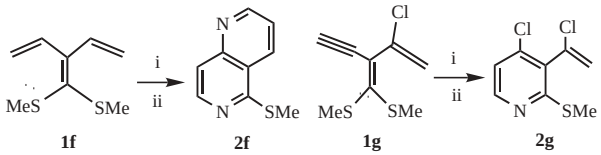
Table 1 The Vilsmeier–Haack Reaction of α-Oxo Ketene-*S*,*S*-acetals **1a–c**

Product[a]	R	X	Yield (%)[b]	State
2a	CH_3	Cl	61.2	oil
2b	CH_2CH_3	Cl	56.5	oil
2c	$PhCH_2$	Cl	58.6	oil
2a′	CH_3	Br	53.4	oil
2b′	CH_2CH_3	Br	52.3	oil
2c′	$PhCH_2$	Br	50.5	oil

[a] All products were characterized by ^{1}H NMR and IR, some products were characterized by mass spectroscopy.
[b] Yield refers to pure products after chromatography over silica gel.



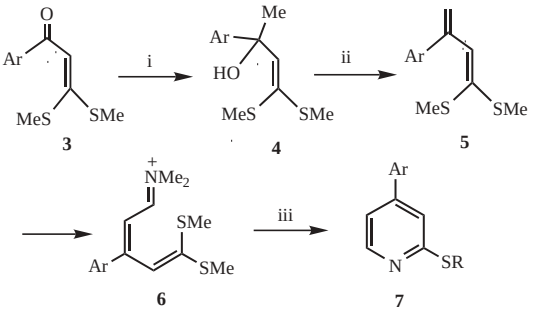
Scheme 2 *Reagents and conditions*: (i) $POCl_3$ (2 equiv), 0 °C, 6 h; (ii) NH_4OAc, 80 °C, 0.5 h.

analogous cyclization to the corresponding pyridines; the complex reaction mixtures were obtained in both cases.

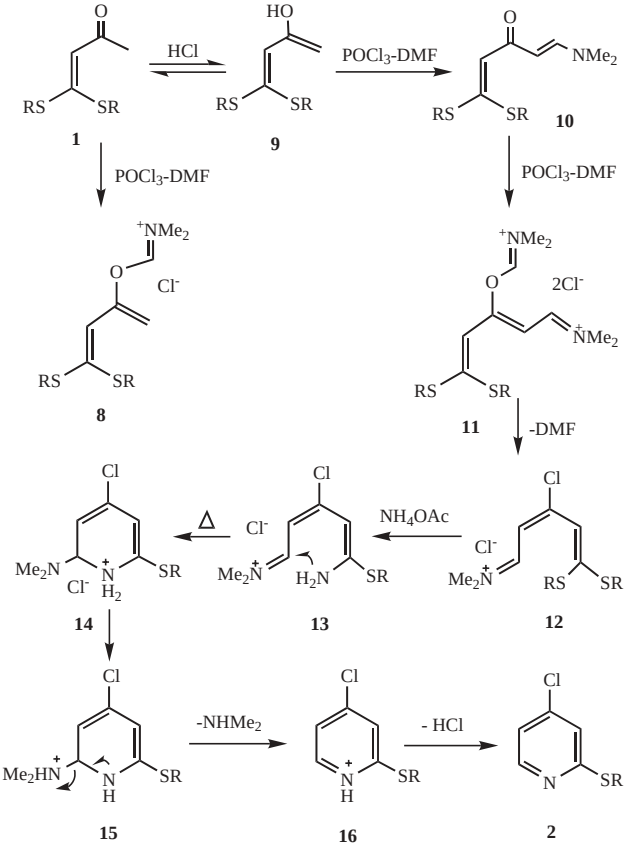
Generally, the carbonyl and the β-carbon atoms in α-oxo ketene-*S*,*S*-acetals can be regarded as hard and soft electrophilic centers, respectively.[3b] Therefore, many regioselective reagents can be selected either from hard nucleophiles that can undergo 1,2-addition or from soft nucleophiles that can add preferentially in 1,4-fashion. Our earlier work on the addition of various Grignard reagents to α-oxo ketene-*S*,*S*-acetals with cyclic alkyldithio group, e.g. $S(CH_2)_2S$ and $S(CH_2)_3S$, revealed that only 1,2-addition products were formed,[14] which was attributed to the steric hindered effect of the rigid cyclic dithioacetals moiety. The present work has further demonstrated that there is great difference between α-oxo cyclic ketene-*S*,*S*-acetals and α-oxo acyclic ketene-*S*,*S*-acetals from the view of synthetic intermediates. Actually, the reasons for the difference might be much complicated and worthy of further investigation.

In a further extension of these studies, we next investigated the Vilsmeier–Haack reaction of **1a–c** with a different type Vilsmeier reagent, PBr_3–DMF, under the similar conditions (Scheme 1). Accordingly, 4-bromo substituted pyridines **2a′–c′** were successfully obtained in moderate yields, and some of the results are also listed in Table 1.

In this section, it is worth mentioning a most recent work on the Vilsmeier–Haack reaction of α-hydroxy-ketene-*S*,*S*-acetals reported by Asokan and co-workers.[8] As shown in Scheme 3, they synthesized substituted pyridines and proposed a mechanism for the Vilsmeier–Haack reaction, however, their attempt to apply this



Scheme 3 *Reagents and conditions*: (i) MeMgI–Et_2O, (ii) $POCl_3$–DMF (2 equiv), r.t., 24 h; (iii) NH_4OAc, 80 °C, 2 h.



Scheme 4 A proposed mechanism for the Vilsmeier–Haack reaction of α-oxo ketene-*S*,*S*-acetals **1a–c**.

protocol to some other α-oxo ketene-*S*,*S*-acetals, such as α-oxo ketene-*S*,*S*-acetal **1a**, was unsuccessful.

Obviously, different results have been achieved from the Vilsmeier–Haack reaction of different precursors, i.e. α-oxo ketene-*S*,*S*-acetal **1a** and α-hydroxyketene-*S*,*S*-acetal derived from the Grignard Reaction between **1a** and methyl magnesium iodide. In our present work, the halogenated pyridines implied that the Vilsmeier–Haack reaction might follow a mechanism different from that described in Scheme 3. On the basis of our results, a plausible mechanism has been proposed for the reactions of α-oxo ketene-*S*,*S*-acetals to yield substituted pyridines, as shown in Scheme 4.[7d,15] The electrophilic attack by the

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Vilsmeier reagent on the weakly basic carbonyl oxygen atom of α-oxo ketene-*S*,*S*-acetals **1** slowly forms salt **8** and HCl. The released HCl catalyzes the equilibrium between tautomers **1** and **9**, the latter undergoes rapid substitution by the Vilsmeier reagent giving β-*N*,*N*-dimethyl aminovinyketone **10**. Additionally, salt **8** may formylate the enol **9** to give **10**, too. The further reaction of **10** with the Vilsmeier reagent gives the labile bisiminium chloride **11**, which readily collapses to the iminium salt **12**. With addition of ammonium acetate, a nucleophilic displacement (sequential amino-addition and alkylthio-elimination) on **12** by amine occurs and leads to the intermediate ketene-*N*,*S*-acetal **13**. At 80 °C, the reaction proceeds through the intramolecular nucleophilic attack of the iminium species within **13** to yield the intermediate **14**, which is followed by elimination of dimethylamine group and subsequent loss of HCl to give the corresponding pyridines **2**.

In summary, one-pot synthesis of substituted pyridines from the Vilsmeier–Haack reaction of acyclic ketene-*S*,*S*-acetals containing α-acetyl, α-vinyl or α-ethynyl group (**1a**–**c**, **1f** and **1g**) has been developed and a mechanism for the reaction was proposed. The alkylthio and halogen substituents at α- and γ-position to the ring nitrogen of pyridine are quite reactive groups, for example in nucleophilic substitution reaction and Suzuki Coupling reaction, which makes this kind of compounds good candidates to serve as precursors for further synthetic transformations. The potential applications and extension of the scope of the methodology are currently under investigation in our laboratory.

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(13) **Typical Procedure for 2a:** The Vilsmeier reagent was prepared by adding $POCl_3$ (6.0 mmol, 0.56 mL) 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** (3.0 mmol, 0.49 g) as a solution in DMF (5 mL). The starting material was quickly consumed within 30 min monitored by TLC. The mixture was allowed to warm to r.t. and stirred for about 6 h. Then NH_4OAc (3.5 g, 45 mmol) was added as a solid into the reaction system. After stirred at r.t. for 10 min., the mixture was heated to 80 °C under stirring for 30 min. Cooled down to r.t., the reaction mixture was poured into cold sat. K_2CO_3 aq (50 mL), extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (3 × 20 mL), dried over anhyd Na_2SO_4, filtered and concentrated under reduced pressure to yield the crude product **2a** which was purified by chromatography over silica gel using Et_2O/petroleum ether (1:80) as eluent. Compounds **2b** and **2c** were synthesized following the same procedure. **2a′-c′** were also synthesized via the similar procedure except that prolonging reaction time (18–24 h) was needed before the feed of NH_4OAc.
2-Methylthio-4-chloropyridine **2a** (light yellow liquid): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.56 (3 H, s, -SCH_3), 6.98 (1 H, dd, PyH-5, J_1 = 1.6 Hz, J_2 = 5.6 Hz), 7.19 (1 H, d, PyH-3, J = 1.6 Hz), 8.32 (1 H, d, PyH-6, J = 5.6 Hz). IR (KBr, neat): 3046, 2924, 1564, 1541, 1453, 1356, 1150, 793, 689 cm^{-1}. MS: *m/z* $[M - 1]^+$ = 159.
2-Ethylthio-4-chloropyridine **2b** (light yellow liquid): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): 1.37 (3 H, t, CH_3, J = 7.5 Hz), 3.16 (2 H, q, -SCH_2, J = 7.5 Hz), 6.97 (1 H, dd, PyH-5, J_1 = 1.5 Hz, J_2 = 5.5 Hz), 7.17 (1 H, d, PyH-3, J = 1.5 Hz), 8.31 (1 H, d, PyH-6, J = 5.5 Hz). IR (KBr, neat): 3049, 2968, 2926, 1566, 1540, 1452, 1355, 1150, 785, 693 cm^{-1}. MS: *m/z* $[M - 1]^+$ = 173.
2-Benzylthio-4-chloropyridine **2c** (light yellow liquid): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.43 (2 H, s, -SCH_2), 6.99 (1 H, dd, PyH-5, J_1 = 1.6 Hz, J_2 = 5.6 Hz), 7.17 (1 H, d, PyH-3, J = 1.6 Hz), 7.29 (5 H, m, PhH), 8.33 (1 H, d, PyH-6, J = 5.6 Hz). IR (KBr, neat): 3031, 1678, 1563, 1539, 1452, 1357, 791, 696 cm^{-1}.
2-Methylthio-4-bromopyridine **2a′** (light yellow liquid): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.55 (3 H, s, -SCH_3), 7.13 (1 H, dd, PyH-5, J_1 = 1.5 Hz, J_2 = 5.5 Hz), 7.35 (1 H, d, PyH-3, J = 1.5 Hz), 8.24 (1 H, d, PyH-6, J = 5.5 Hz). IR (KBr, neat): 3039, 2924, 1557, 1537, 1452, 1351, 771, 678 cm^{-1}.
2-Ethylthio-4-bromopyridine **2b′** (light yellow liquid): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.37 (3 H, t, CH_3, J = 7.5 Hz), 3.15 (2 H, q, -SCH_2, J = 7.5 Hz), 7.12 (1 H, d,

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PyH-5, *J* = 5.5 Hz), 7.33 (1 H, s, PyH-3), 8.22 (1 H, d, PyH-6, *J* = 5.5 Hz). IR (KBr, neat): 3049, 2968, 2926, 1558, 1541, 1451, 1350, 1136, 769 cm^{-1}.

2-Benzylthio-4-bromopyridine **2c′** (light yellow liquid): ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 4.43 (2 H, s, $-SCH_2$), 7.15 (1 H, d, PyH-5, *J* = 5.0 Hz), 7.30 (1 H, PyH-3), 7.38 (5 H, m, PhH), 8.26 (1 H, d, PyH-6, *J* = 5.0 Hz). IR (KBr, neat): 3060, 3029, 2947, 1591, 1545, 1509, 1447, 1355, 765, 697 cm^{-1}. MS: *m/z* $[M - 1]^+$ = 279 (281).

5-(methylthio)-1,6-naphthyridine **2f** (light yellow liquid): ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.48 (3 H, s, $-SCH_3$), 7.45 (2 H, m, NapyH-3, NapyH-8), 7.57 (1 H, m, NapyH-4), 7.97 (2 H, m, NapyH-4, NapyH-7). IR (KBr, neat): 2922, 2857, 1687, 1514, 1401, 771, 678 cm^{-1}.

2-Methylthio-3-(1-chlorovinyl)-4-chloropyridine **2g** (light yellow liquid): ^1H NMR (400 MHz, $CDCl_3$, 25 °C), 2.54 (3 H, s, $-SCH_3$), 5.55 (1 H, s, $=CH_2$), 5.89 (1 H, s, $=CH_2$), 7.08 (1 H, d, PyH-5, *J* = 3.6 Hz), 8.30 (1 H, d, PyH-6, *J* = 3.6 Hz). IR (KBr, neat): 3101, 3036, 2926, 1635, 1545, 1438, 904, 807, 693 cm^{-1}.

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