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Vilsmeier cyclization of α-acetyl-α-aroyl ketene-*N*,*S*-acetals: direct and efficient synthesis of halogenated pyridin-2(1*H*)-ones†

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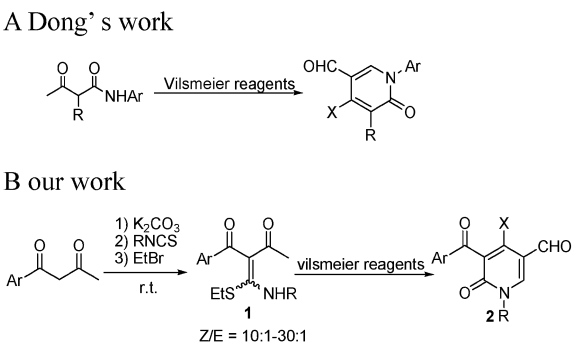
An efficient synthetic route to 3-aroyl-5-formyl-4-halo pyridin-2(1*H*)-ones has been developed *via* Vilsmeier cyclization of 2-(ethylthio(arylamino)methylene)-1-alkylbutane-1,3-dione. The synthetic protocol has demonstrated the first example of Vilsmeier cyclization of α-acetyl-α-aroylketene-*N*,*S*-acetals, providing a novel route to 4-bromo/chloro pyridin-2(1*H*)-ones.

Pyridin-2(1*H*)-ones are very important heterocycles in medicinal chemistry and pharmacology due to their diverse pharmacological and biological activities.[1,2] Halogenated pyridin-2(1*H*)-ones are an important subset of pyridin-2(1*H*)-ones and have been utilized as versatile synthetic intermediates for further elaboration of the pyridine-2(1*H*)-one core[3] and a wide variety of potent bioactive heterocycles.[4] Although the halogenation of pyridin-2(1*H*)-ones occurs very easily, a mixture of mono- and dihalogenated products is often obtained.[5] Consequently, the direct preparation of halogenated pyridine-2(1*H*)-ones from acyclic substrates is a worthy research challenge. Marcoux and co-workers investigated the annulation reaction of esters bearing active methane with vinamidinium hexafluorophosphate salts, and 5-chloro pyridine-2(1*H*)-ones were successfully obtained.[6] Dechoux *et al.* efficiently prepared 3-bromo pyridine-2(1*H*)-ones by bromo-cyclization of the ensuing δ-dienaminoester.[7] Zhu and co-workers reported the synthesis of 3-fluoro-4-aryl-pyridine-2(1*H*)-ones from Michael-adduct of fluoronitroacetate and α,β-unsaturated ketones.[8] Recently, Dong, *et al.* researched in detail Vilsmeier cyclization of 3-oxo-*N*-phenylbutanamide derivatives[9,10] such as 1-acetyl-*N*-arylcycl-opropanecarboxamides,[10a] α-acetyl-α-carbamoylketene dithioacetals,[10b] 2-arylamino-3-acetyl-5,6-dihydro-4*H*-pyrans,[10c] β-oxo amides[10d] and 2-((dimethylamino)methylene)-3-oxo-*N*-arylbutanamides,[10e] and a variety of halogenated pyridine-2(1*H*)-ones were efficiently synthesized in good yields (Scheme 1A). Compared with other work,[6–8] this Vilsmeier cyclization efficiently afforded halogenated pyridine-2(1*H*)-ones bearing formyl groups, which may render them extremely versatile as synthons in further synthetic transformations, and was characterized by good generality, simple execution, readily available substrates, and mild conditions. As a result, these advantages make the Vilsmeier cyclization of acyclic substrates to yield halogenated pyridine-2(1*H*)-ones very attractive.

Readily available ketene-*N*,*S*-acetals have emerged as versatile intermediates in the synthesis of heterocyclic compounds.[11] Over the past decades, great attention was focused on the investigation of α-aroyl/cyano ketene-*N*,*S*-acetals, because their α-position can act as nucleophile and react with electrophilic species resulting in their further functionalization and subsequent transformations to a variety of heterocycles.[12] To date, the investigation on the synthesis and application of α-acetyl-α-aroyl ketene-*N*,*S*-acetals are not reported. As part of our contributions to the chemistry of ketene-*S*,*S*-acetals,[13–15] we recently investigated the synthesis of α-acetyl-α-aroyl ketene-*N*,*S*-acetals and examined



Scheme 1 Vilsmeier cyclization of acyclic substrates.

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their reactions with Vilsmeier reagents. We found that 2-(ethylthio(arylamino)methylene)-1-alkylbutane-1,3-dione **1** could stereoselectively be synthesized in excellent yields, followed by its efficient Vilsmeier cyclization to afford 3-aroyl-5-formyl-4-halo pyridin-2(1*H*)-ones **2** in good yields (Scheme 1B). Herein, we would like to report our findings.

Kirsch and co-workers reported the synthesis of symmetric α,α-dioxoketene-*N*,*S*-acetals such as (methylthio(phenylamino) methylene)pentane-2,4-dione and diethyl 2-(methylthio(phenylamino)methylene)malonate.[16] Therefore, according to the procedure described by Kirsch, we initially examined the preparation of 2-(ethylthio(phenylamino)methylene)-1-*p*-tolylbutane-1,3-dione **1a** from one-pot reaction of 1-*p*-tolylbutane-1,3-dione, isorhodanides and bromoethane in the presence of K_2CO_3 at room temperature and found that **1a** was obtained in 85% yield. The reaction showed high stereoselectivity and favored the formation of (*Z*)-**1a** which is confirmed by X-ray crystallographic analysis (Fig. 1).[17] In a similar fashion, compounds **1b–k** were prepared in excellent yields and with high stereoselectivity. Results of our findings are listed in Table 1. It is noteworthy that compounds **1** are stable at room temperature and could be stored indefinitely without decomposition.

With α-acetyl-α-aroyl ketene-*N*,*S*-acetals **1** in hand, we started our investigation on Vilsmeier cyclization of compound **1** resulting in the formation of halogenated pyridin-2(1*H*)-ones. The reaction of **1a** with Vilsmeier reagent $POCl_3$/DMF was selected as model reaction to screen the experimental conditions. It was found that **1a** reacted with Vilsmeier reagent $POCl_3$/DMF (4 equiv.) below 70 °C to afford an unstable major product at room temperature (Table 2, entry 1–3). To our delight, when the reaction was carried out at 80 °C for 12 h, a stable white solid product was obtained in 35% yield. From the spectral and analytical data, the product was characterized as desirable product 4-chloro-5-(4-benzoyl)-6-oxo-1-phenyl-1,6-dihydropyridine-3-methylcarbaldehyde **2a** (Table 2, entry 4). Additionally, the yield of **2a** was not markedly improved by either prolonging reaction time or further elevating reaction temperature (Table 2, entry 5 and 6). However, the reaction showed dependence on the amount of Vilsmeier reagent $POCl_3$/DMF (Table 2, entry 7–9), becoming more efficient with an increased load of this reagent. Consequently, **2a** was obtained in 85% yield when **1a** reacted with 6.0 equiv. of Vilsmeier reagent at 80 °C for 4 h (Table 2, entry 8). Accordingly, the optimal reaction conditions are 6.0 equiv. of Vilsmeier reagent and a temperature of 80 °C.

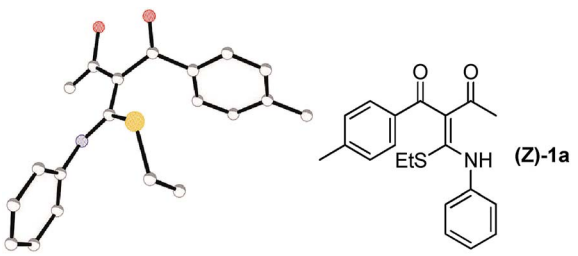
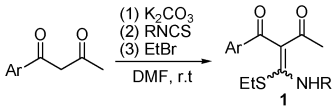


Fig. 1 Molecular structure of (*Z*)-**1a**.

Table 1 Synthesis of α-acetyl-α-aroyl ketene-*N*,*S*-acetals **1a–k**[a]

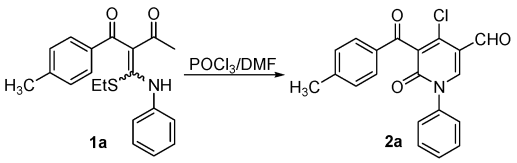


Entry	Ar	R	**1**	Yield[b] (%)	*Z*/*E*[c]
1	4-MeC_6H_4	Ph	**1a**	85	13 : 1
2	3-MeC_6H_4	Ph	**1b**	86	10 : 1
3	4-$MeOC_6H_4$	Ph	**1c**	84	14 : 1
4	Ph	Ph	**1d**	88	10 : 1
5	4-BrC_6H_4	Ph	**1e**	90	13 : 1
6	2-Thiophenyl	Ph	**1f**	86	15 : 1
7	Ph	4-MeC_6H_4	**1g**	83	11 : 1
8	Ph	3-MeC_6H_4	**1h**	85	11 : 1
9	Ph	4-FC_6H_4	**1i**	75	10 : 1
10	Ph	4-BnC_6H_4	**1j**	87	27 : 1
11	Ph	2-MeC_6H_4	**1k**	81	11 : 1

[a] Reaction conditions: 1-arylbutane-1,3-dione (5 mmol), isorhodanides (5 mmol), EtBr (5 mmol) and K_2CO_3 (10 mmol). [b] Isolated yields. [c] Molar ratio of *Z*/*E*-**1** isomers determined by ^1H NMR.

Next, we used the optimized reaction conditions to define the scope of this Vilsmeier cyclization for the synthesis of halogenated pyridin-2(1*H*)-ones, and the results are summarized in Table 3. The Vilsmeier cyclization of **1a–j** and $POCl_3$/DMF proceeded smoothly under the optimized conditions to efficiently afford corresponding 3-aroyl-4-chloro-5-formylpyridin-2(1*H*)-ones in high yields (Table 3, entry 1–10). It is noteworthy that the electronic effects of aromatic substituents on both aroyl and aryl amino groups are insignificant to the cyclization reaction. In the case of 2-((ethylthio)-(*o*-tolylamino)-

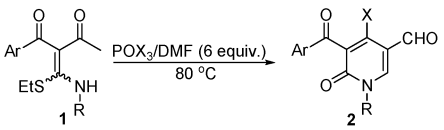
Table 2 Screening of conditions for Vilsmeier cyclization of α-acetyl-α-aroyl ketene-*N*,*S*-acetals[a]

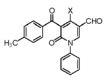
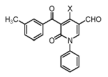
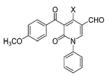
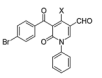
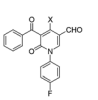
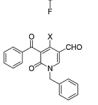
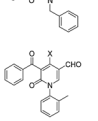


Entry	$POCl_3$/DMF (equiv.)	*T* [°C]	Time [h]	Yield [%] of **2a**[b]
1	4	25	12	—[c]
2	4	60	12	—[c]
3	4	70	12	—[c]
4	4	80	12	35
5	4	80	24	34
6	4	90	12	37
7	5	80	7	63
8	6	80	4	85
9	7	80	4	83

[a] Reaction conditions: **1a** (0.25 mmol), solvent (1 mL). [b] Isolated yields. [c] An unstable product was yielded at room temperature.

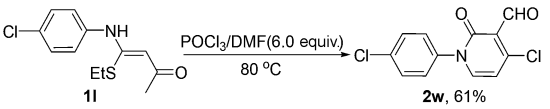
Table 3 Synthesis of various halogenated pyridin-2(1*H*)-ones **2**[a]



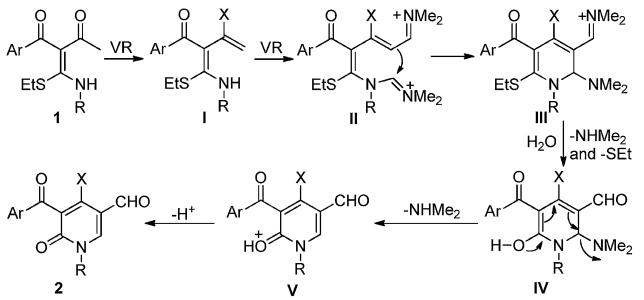
Entry	1	Product 2		Yield[b] (%)
1	**1a**		**2a** X = Cl	85
			2b X = Br	21[c]
				81
2	**1b**		**2c** X = Cl	82
			2d X = Br	80
3	**1c**		**2e** X = Cl	85
			2f X = Br	83
4	**1d**		**2g** X = Cl	84
			2h X = Br	84
5	**1e**		**2i** X = Cl	79
			2j X = Br	77
6	**1f**		**2k** X = Cl	80
			2l X = Br	79
7	**1g**		**2m** X = Cl	85
			2n X = Br	81
8	**1h**		**2o** X = Cl	82
			2p X = Br	83
9	**1i**		**2q** X = Cl	79
			2r X = Br	78
10	**1j**		**2s** X = Cl	85
			2t X = Br	85
11	**1k**		**2u** X = Cl	32
				77[d]
			2v X = Br	74[d]

[a] Reaction conditions: **1** (0.25 mmol), $POCl_3$/DMF or $POBr_3$/DMF (1.5 mmol), 80 °C, 4–5 h. [b] Isolated yields. [c] The reaction of **1a** and PBr_3/DMF under the optimized conditions. [d] Reaction conditions: **1k** (0.25 mmol), $POCl_3$/DMF or $POBr_3$/DMF (2.5 mmol), 120 °C, 12 h.

methylene)-1-phenylbutane-1,3-dione **1k**, **2k** was isolated in 32% yield, which might stem from the steric hindered effect of the *ortho*-substituted methyl group on the benzene ring of aryl amine (Table 3, entry 11). However, when **1k** reacted with $POCl_3$/DMF (10 equiv.) at 120 °C for 12 h, the yield of **2k** was enhanced up to 77% (Table 3, entry 11). The reaction was also successfully extended to the synthesis of 4-bromo pyridin-2(1*H*)-ones. According to Dong's work, the reaction of **1a** and PBr_3/DMF initially carried out under the optimized conditions afforded 4-bromo-5-(4-methylbenzoyl)-6-oxo-1-phenyl-1,6-dihydropyridine-3-carbaldehyde **2b** in 21% yield (Table 3, entry 1). To our delight,



Scheme 2 Reaction of **1l** and $POCl_3$/DMF.



Scheme 3 Plausible Mechanism of Vilsmeier cyclization of α-acetyl-α-aroyl ketene-*N*,*S*-acetals **1**.

when **1a** reacted with Vilsmeier reagent $POBr_3$/DMF under the same conditions, **2b** was efficiently produced in 81% yield (Table 3, entry 1). Similarly, **1b–k** underwent the Vilsmeier cyclization to efficiently afford the corresponding 3-aroyl-4-bromo-5-formyl pyridin-2(1*H*)-ones in high yields (Table 3, entry 2–11).

Junjappa and co-workers investigated Vilsmeier reaction of α-acetyl ketene-*N*,*S*-acetals with $POCl_3$/DMF (1.5 equiv.) at 80 °C and found that the diketonealdehyde enamine was obtained in moderate yield.[18] In our research, we also checked the Vilsmeier reaction of α-acetyl ketene-*N*,*S*-acetals **1l** under the above optimized conditions. Unlike Junjappa's work, the reaction furnished 4-chloro-1-(4-chlorophenyl)-2-oxo-1,2-dihydropyridine-3-carbaldehyde **2w** in 61% yield (Scheme 2).

On the basis of the results obtained together with the relevant reports,[9,10] a possible reaction mechanism is proposed in Scheme 3. It is clear that the reaction commenced from the halogenation of **1** in the presence of Vilsmeier reagent to generate vinyl chloride **I**. Sequential Vilsmeier reactions of **I** lead to the formation of intermediate **II**, which occurs intramolecular aza-cyclization reaction to give the intermediate **III**. Upon treatment with water, **III** is converted into the intermediate **IV**, which sheds dimethylamine to give the intermediate **V**. Finally, halogenated pyridine-2(1*H*)-ones **2** are obtained after the removal of H proton.

Conclusion

In conclusion, we firstly prepared (*Z*)-α-acetyl-α-aroyl ketene-*N*,*S*-acetals **1** and confirmed their configuration by X-ray crystallographic analysis. Subsequently, a facile and efficient one-pot synthesis of 3-aroyl-5-formyl-4-halopyridin-2(1*H*)-ones **2** was successfully developed from Vilsmeier cyclizations of readily available substrate **1**. Further application of synthesized halogenated pyridin-2(1*H*)-ones **2** is ongoing in our group.

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