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Efficient One-Pot Synthesis of Highly Substituted Pyridin-2(1*H*)-ones via the Vilsmeier–Haack Reaction of 1-Acetyl,1-Carbamoyl Cyclopropanes

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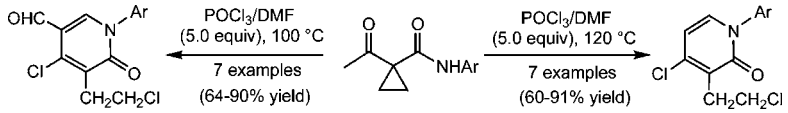
ABSTRACT



A facile and efficient one-pot synthesis of highly substituted pyridin-2(1*H*)-ones is developed via the Vilsmeier–Haack reaction of readily available 1-acetyl,1-carbamoyl cyclopropanes, and a mechanism involving sequential ring-opening, haloformylation, and intramolecular nucleophilic cyclization reactions is proposed.

Functionalized pyridin-2(1*H*)-ones and their benzo-/hetero-fused analogues represent an important class of organic heterocycles for their presence in numerous natural products and synthetic organic compounds along with diverse bio-, physio-, and pharmacological activities.[1,2] The development of efficient synthetic approaches for such nitrogen-containing heterocycles has been the focus of much research for many decades and continues to be an active and rewarding research area.[3] So far, a variety of synthetic approaches are already available, based on either the modification of the preconstructed heterocyclic ring by pyridinium salt chemistry[4] and N-alkylation[5] or the construction of the heterocyclic skeleton from appropriately substituted open chain precursors via Guareschi−Thorpe reaction,[6] intramolecular Dieckmann-type condensation,[7] hetero-Diels−Alder reaction,[8] and metal-mediated cycloaddition.[9] While each of these approaches represents an important advance toward the objective of a general method for the synthesis of pyridin-2(1*H*)-ones, each of them, however, suffers from significant limitations, such as multistep procedure, harsh conditions, low yields, or poor chemo- and regioselectivity.

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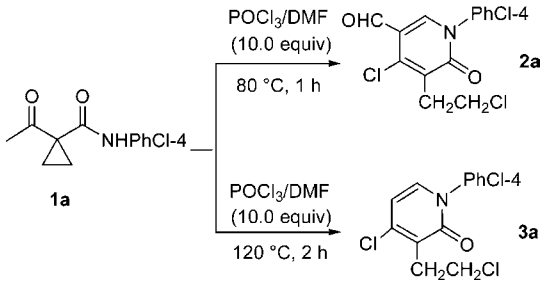
The overwhelming importance of cyclopropane derivatives in organic synthesis has been recognized for their well-known "unsaturated" character, which can lead to a variety of ring-opening reactions under the influence of a wide range of chemicals, such as electrophiles, nucleophiles, and radicals.[10] In our recent work, we developed an efficient strategy for the synthesis of furoquinoline derivatives via domino ring-opening/recyclization reactions of 1-acetyl,1-carbamoyl cyclopropanes.[11] As part of our continuing interest in the further synthetic potential of 1-acetyl,1-carbamoyl cyclopropanes and the Vilsmeier−Haack reaction for the synthesis of various heterocycles,[12] we examined their reactivity toward the Vilsmeier reagent. As a result, we achieved facile and efficient one-pot synthesis of highly substituted pyridin-2(1*H*)-ones of types **2** and **3** via the Vilsmeier−Haack reaction of readily available 1-acetyl,1-carbamoyl cyclopropanes **1**. Herein, we wish to report our preliminary results in this area.

The substrates, 1-acetyl,1-carbamoyl cyclopropanes **1**, were synthesized from commercially available *β*-oxo amides and 1,2-dibromoethane in excellent yields following the procedure described in our previous work.[11] With substrates **1** in hand, we selected 1-acetyl-*N*-(4-chlorophenyl)cyclopropanecarboxamide **1a** as the model compound to examine its behavior under different conditions.

Upon treatment of **1a** with Vilsmeier reagent ($POCl_3$/DMF, 10.0 equiv) at 0 °C for 5 h, no reaction occurred. To our delight, when the mixture was conducted at 80 °C for 1 h, it furnished a white solid after workup and purification by column chromatography. The product was characterized as 4-chloro-5-(2-chloroethyl)-1-(4-chlorophenyl)-6-oxo-1,6-dihydropyridine-3-carbaldehyde **2a** (45% yield) on the basis of its spectral and analytical data (Scheme 1). When **1a** was

Scheme 1. The Vilsmeier−Haack Reaction of **1a**



treated with Vilsmeier reagent at 120 °C for 2 h, to our surprise, the reaction exclusively afforded 4-chloro-3-(2-chloroethyl)-1-(4-chlorophenyl)pyridin-2(1*H*)-one **3a** in 69% yield (Scheme 1).

The structure of **3a** was confirmed by the X-ray single-crystal analysis (Figure 1). Comparison of NMR spectra between **2a** and **3a** let us further confirm the structure of **2a** without difficulty. In the ^{1}H NMR spectra, **3a** displayed two doublet peaks (J = 7.5 Hz) at δ 6.36 and 7.22, respectively, which were assigned to 5-H and 6-H of pyridin-2(1*H*)-one. As for **2a**, the corresponding two peaks disappeared, while two single peaks were observed, one at 8.11 for 6-H and another at 10.15 for the 5-formyl hydrogen. In the ^{13}C NMR spectra of **2a**, the 5-formyl carbon was indicated by the peak at 186.4 ppm. Additionally, in the mass spectra, the mass difference of the molecular ion peaks between **3a** (302.1 $[M]^+$) and **2a** (368.1 $[M + 39]^+$) is consistent with the NMR results.

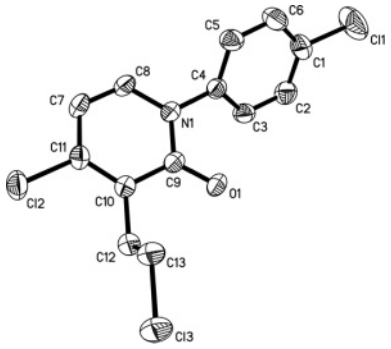


Figure 1. ORTEP drawing of **3a**.

The optimization of the reaction conditions, including reaction temperature and the feed ratio of **1a** and Vilsmeier reagent, was then investigated. The experiments revealed that 4.0 equiv of Vilsmeier reagent was effective for the reaction of **1a** to form compounds **2a** and **3a**, and the yield of **2a** reached 73% when the reaction of **1a** and Vilsmeier reagent (5.0 equiv) was performed at 100 °C, whereas the yield of **3a** could reach 78% when the reaction was performed at 120 °C.

Having established the optimal conditions for the cyclization, we aimed to determine its scope with respect to the amide motif. Thus, a series of cyclopropanes **1** were subjected to Vilsmeier reagent (5.0 equiv) at 100 and 120 °C, and some of the results are summarized in Table 1. The cyclization reaction proved to be suitable for cyclopropanes **1b**−**g**, affording the corresponding substituted pyridin-2(1*H*)-ones of types **2** and **3** in moderate to high yields (Table 1, entries 2−7).

The results shown above demonstrated the efficiency and synthetic interest of the cyclization reaction with respect to cyclopropanes **1** bearing variable amide groups. It should be noted that the richness of the functionality, for example, halogen, halogen alkyl, and formyl groups on the pyridin-2(1*H*)-ones of types **2** and **3**, may render them extremely versatile as synthons in further synthetic transformations,

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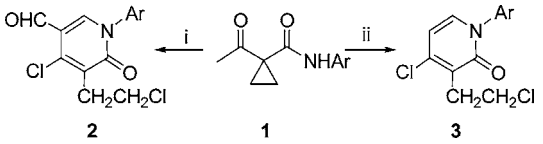
Table 1. The Vilsmeier−Haack Reaction of Cyclopropanes **1**[a]

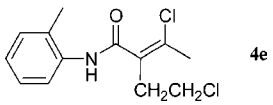


entry	1	Ar	2	yield[b] (%)	3	yield[b] (%)
1	**1a**	4-ClPh	**2a**	73	**3a**	78
2	**1b**	Ph	**2b**	88	**3b**	90
3	**1c**	4-MePh	**2c**	83	**3c**	78
4	**1d**	4-MeOPh	**2d**	67	**3d**	62
5	**1e**	2-MePh	**2e**	82	**3e**	60
6	**1f**	2-MeOPh	**2f**	90	**3f**	91
7	**1g**	2,4-Me_2Ph	**2g**	64	**3g**	61

[a] Reagents and conditions: (i) $POCl_3$/DMF (5.0 equiv), 100 °C, 0.5−1.5 h; (ii) $POCl_3$/DMF (5.0 equiv), 120 °C, 3.0−6.0 h. [b] Isolated yields.

such as metal-mediated coupling reaction,[13] Williamson reaction,[14] and Henry reaction.[15]

In contrast with our results, Amaresh and co-workers investigated the Vilsmeier−Haack reaction of β-oxo amides and obtained 2-arylimino-2*H*-pyrancarboxaldehydes.[16] The different results suggested that the cyclopropyl group of *N*-amide **1** played an important role in the present cyclization reaction. To gain insight into the mechanism of the ring-opening/recyclization reaction, some separate experiments were conducted. The reaction of **1e** with 3.0 equiv of Vilsmeier reagent ($POCl_3$/DMF) was performed at 80 °C for 10 min, then it was quenched with water. Compound **4e** was obtained in 25% yield with intact substrate (Figure 2). No



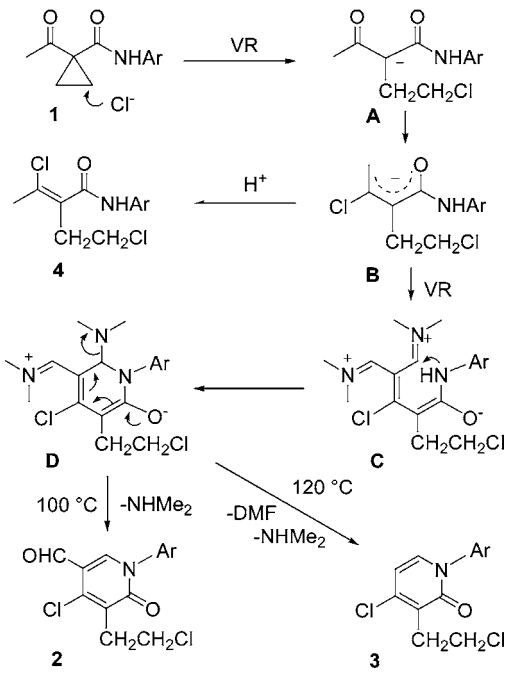
4e

Figure 2. Structure of compound **4e**.

reaction occurred when **3a** was subjected to Vilsmeier reagent ($POCl_3$/DMF, 3.0 equiv) at 120 °C for 3 h; however, **2a** could be transformed into **3a** under the same conditions.

On the basis of all of the results obtained, a plausible mechanism for the synthesis of substituted pyridin-2(1*H*)-ones of types **2** and **3** is presented in Scheme 2. The overall transformation commences from the ring opening of **1**, mediated by Vilsmeier reagent, to generate enolate **A**. Activated by the adjacent enolate, sequential Vilsmeier−Haack reactions of an acetyl group of **A** led to the formation of intermediates **B** and **C**,[17] and intramolecular aza-cyclization reaction of **C** gives the intermediate **D**, which is exclusively converted into substituted pyridin-2(1*H*)-ones of type **2** at 100 °C or **3** at 120 °C.

Scheme 2. Tentative Mechanism of the Vilsmeier−Haack Reaction of Cyclopropanes **1**



In summary, a facile and efficient one-pot synthesis of highly substituted pyridin-2(1*H*)-ones of types **2** and **3** was developed from the Vilsmeier−Haack reaction of readily available 1-acetyl,1-carbamoyl cyclopropanes **1**, which involves sequential ring-opening, haloformylation, and intramolecular nucleophilic cyclization reactions. This protocol is associated with readily available starting materials, mild conditions, high yields, wide range of synthetic potential of the product, and easy control of the reaction orientation. The potential utilization and extension of the scope of the methodology and the examination of biological activity of the novel products are currently under investigation in our laboratory.

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Supporting Information Available: General experimental procedures and spectral characterization data for **2a**−**g**, **3a**−**g**, and **4e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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