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Vilsmeier Reaction of Enaminones: Efficient Synthesis of Halogenated Pyridin-2(1*H*)-ones

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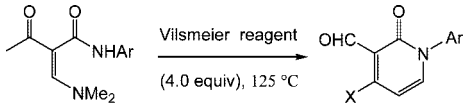

14 examples, 56-85% yield

A facile and efficient one-pot synthesis of halogenated pyridin-2(1*H*)-ones from a series of readily available enaminones under Vilsmeier conditions is described, and a mechanism involving sequential halogenation, formylation, and intramolecular nucleophilic cyclization is proposed.

Functionalized pyridin-2(1*H*)-ones and their benzo-/hetero-fused analogues represent an important class of organic aza-heterocycles for their presence in numerous natural products and synthetic organic compounds along with diverse bio-, physio-, and pharmacological activities.[1−3] In addition, functionalized pyridin-2(1*H*)-ones have been used as versatile intermediates in the synthesis of a wide range of nitrogen-containing heterocycles, such as pyridine, piperidine, quinolizidine, and indolizidine alkaloids.[3,4] Extensive work has generated many synthetic approaches for pyridin-2(1*H*)-ones including the modification of the preconstructed heterocyclic ring by pyridinium salt chemistry and *N*-alkylation[5,6] or through the construction of the heterocyclic skeleton from appropriately substituted acyclic precursors via Guareschi−Thorpe reaction, intramolecular Dieckmann-type condensation, hetero Diels−Alder reaction, and metal-mediated cycloaddition. [7−9]The development of efficient synthetic approaches for such nitrogen-containing heterocycles has been the focus of intense research for decades and continues to be an active area of research today.

Halogenated pyridin-2(1*H*)-ones are an important subset of pyridin-2(1*H*)-ones, which have been utilized as useful intermediates for the synthesis of various aza-heterocycles and evaluated as a scaffold in natural product synthesis.[10] Unfortunately, most of the available approaches for accessing pyridin-2(1*H*)-ones are not general for the preparation of halogenated pyridin-2(1*H*)-ones. Recently the direct synthesis of halogenated pyridin-2(1*H*)-ones from acyclic substrates has attracted a lot of interest in research.[11,12] During the course of our studies on Vilsmeier reactions, [13−15] we developed a facile one-pot synthesis of halogenated pyridin-2(1*H*)-ones from either cyclopropyl amides or cyclic enaminones under Vilsmeier conditions.[14] The significance of the protocol relies on the combination of construction of the pyridin-2(1*H*)-one skeleton and creation of its dense substitution patterns. As an expansion of these studies, we investigated the Vilsmeier reaction of α-monosubstituted *β*-oxo amides and successfully obtained a variety of halogenated pyridin-2(1*H*)-ones (Scheme 1).[15] It should be noted that α-unsubstituted *β*-oxo amides underwent Vilsmeier reactions to give halogenated pyridin-2(1*H*)-ones as a pair of isomers. In connection with these studies and the aim to extend the substrate scope and further clarify the mechanism involved, we prepared a series of enaminones **1** from *β*-oxo amides and

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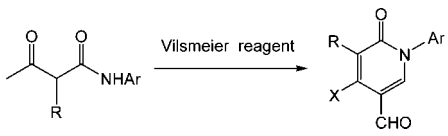
SCHEME 1



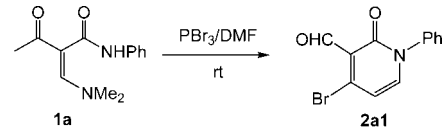
examined their reaction behaviors toward Vilsmeier conditions. By this research, we achieved an efficient synthesis of substituted pyridin-2(1*H*)-ones bearing formyl and halo substituents at the 3 and 4 positions, respectively. Herein, we wish to report our experimental results and present a proposed mechanism for the cyclization.

Enaminones and related compounds possessing the conjugated system N−C═C−C═O are versatile synthetic intermediates that combine the ambident nucleophilicity of enamines with the ambident eletrophilicity of enones.[16] So far, they have found a broad spectrum of applications in the synthesis of α- and *β*-amino acid compounds,[17] alkaloids,[18] peptides,[19] and other aza-heterocyclic compounds.[20] Recently, Elmaati and coworkers described the synthesis of 2-[(dimethylamino)methylene]-3-oxo-*N*-phenylbutanamide **1a**, an enaminone, by the reaction of 3-oxo-*N*-phenylbutanamide with *N*,*N*-dimethyl formamide dimethyl acetal (DMFDMA) in xylene under reflux.[21] In the present work, we improved the Elmaati synthesis conditions and successfully prepared a series of enaminones **1** from commercially available *β*-oxo amides and DMFDMA in the presence of K_2CO_3 in DMF at room temperature in good yields (up to 80%). With substrates **1** in hand, we selected **1a** as a model compound to examine its reaction behavior under Vilsmeier conditions.

Thus, the reaction of **1a** with Vilsmeier reagent PBr_3/DMF (5.0 equiv) was first attempted at room temperature. The resulting mixture quickly turned brown and became viscous. The reaction proceeded smoothly (monitored by TLC) and furnished a product (37% yield) after workup and purification by column chromatography of the resulting mixture. From the spectral and analytical data, the product was characterized as 4-bromo-2-oxo-1-phenyl-1,2-dihydropyridine-3-carbaldehyde **2a1** (Scheme 2). It should be mentioned that side products were obtained from the reaction system as an inseparable mixture by column chromatography over silica gel.

These results and our previous studies[14,15] encouraged us to optimize the reaction conditions, including reaction temperature and the ratio of Vilsmeier reagent PBr_3/DMF to **1a**, with the aim of improving the yield of **2a1**. A series of experiments

SCHEME 2. Reaction of 1a with Vilsmeier Reagent PBr_3/DMF



revealed that 3.0 equiv of PBr_3/DMF was effective for the pyridin-2(1*H*)-one synthesis and the yield of **2a1** depended on the reaction temperature. The optimal results were obtained when the reaction of **1a** was performed with 4.0 equiv of PBr_3/DMF at 125 °C for 1.0 h, whereby the reaction exclusively afforded **2a1** in 68% yield (Table 1, entry 1).

TABLE 1. Vilsmeier Reactions of Enaminones 2[a]

entry	1	Ar	X	2	yields (%)[b]
1	**1a**	Ph	Br	**2a1**	68
2	**1b**	2-$MeOC_6H_4$	Br	**2b1**	67
3	**1c**	4-MeC_6H_4	Br	**2c1**	70
4	**1d**	2-MeC_6H_4	Br	**2d1**	57
5	**1e**	4-ClC_6H_4	Br	**2e1**	63
6	**1f**	2,4-$Me_2C_6H_3$	Br	**2f1**	56
7	**1g**	5-Cl-2-$MeOC_6H_3$	Br	**2g1**	65
8	**1a**	Ph	Cl	**2a2**	85
9	**1b**	2-$MeOC_6H_4$	Cl	**2b2**	68
10	**1c**	4-MeC_6H_4	Cl	**2c2**	76
11	**1d**	2-MeC_6H_4	Cl	**2d2**	70
12	**1e**	4-ClC_6H_4	Cl	**2e2**	81
13	**1f**	2,4-$Me_2C_6H_3$	Cl	**2f2**	84
14	**1g**	5-Cl-2-$MeOC_6H_3$	Cl	**2g2**	79

[a] Reagents and conditions: (i) for entries 1−7, PBr_3/DMF (4.0 equiv), 125 °C, 1.0−1.5 h; (ii) for entries 8−14, $POCl_3$/DMF (4.0 equiv), 125 °C, 0.5−1.0 h. [b] Isolated yields.

Under the identical conditions as for **2a1** in Table 1, entry 1, a series of reactions of enaminones **1** was subjected to PBr_3/DMF (4.0 equiv) at 125 °C, and some of the results are summarized in Table 1. The efficiency of the cyclization proved to be suitable for enaminones **1b**−**g**, affording the corresponding substituted pyridin-2(1*H*)-ones **2b**−**g** in good yields (Table 1, entries 2−7). The versatility of this pyridin-2(1*H*)-one synthesis was further evaluated by performing the enaminones **1** with another Vilsmeier reagent $POCl_3$/DMF under the similar conditions (Table 1, entries 8−14). The results demonstrated the efficiency and synthetic interest of the cyclization reaction with respect to varied Vilsmeier reagents and substrates **1** bearing variable amide groups.

It should be noted that the richness of the functionality, e.g., halogen and formyl groups, of the pyridin-2(1*H*)-ones of type **2** obtained may render them extremely versatile as synthons in other synthetic transformations. For example, the neighboring halogen and formyl groups make it possible to establish new C−C and C−N bonds and may provide a ready access to the ring-fused heterocycles. Recently, Wittman and Ni reported a novel class of 3-(1*H*-benzo[*d*]imidazol-2-yl)-pyridin-2(1*H*)-one as potent kinase inhibitors (Chart 1).[22] In our ongoing research, we are focusing on the synthesis of substituted 3-(1*H*-benzo[*d*]imidazol-2-yl)-pyridin-2(1*H*)-ones using pyridin-2(1*H*)-ones **2** as the scaffolds, and the related results will be published in due course.

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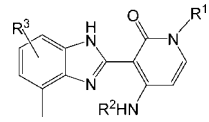
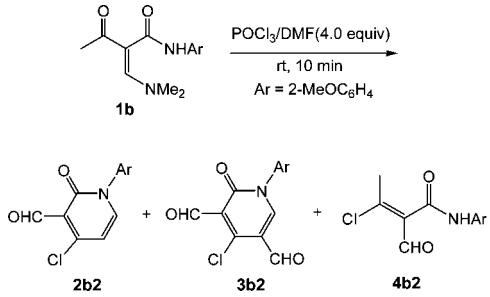
CHART 1. Structure of Substituted 3-(1*H*-Benzo[*d*]imidazol-2-yl)-pyridin-2(1*H*)-ones



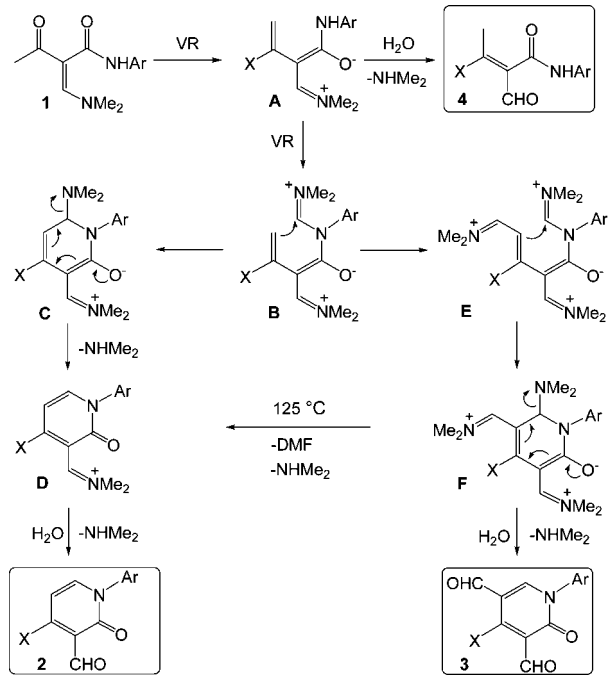
To gain insight into the mechanism of the cyclization of enaminones **1**, the reaction of **1b** with 4.0 equiv of $POCl_3$/ DMF was performed at room temperature for 10 min and then quenched with water. After workup and purification by column chromatography of the resulting mixture, 4-chloro-2-oxo-1,2-dihydropyridine-3-carbaldehyde **2b2**, 4-chloro-2-oxo-1,2-dihydropyridine-3,5-dicarbaldehyde **3b2**, and 3-chloro-2-formyl-but-2-enamide **4b2** were obtained in 26%, 12%, and 33% yields, respectively (Scheme 3).

SCHEME 3. Reaction of 1b with Vilsmeier Reagent $POCl_3$/DMF



On the basis of all of the results obtained together with our previous studies,[14,15] a plausible mechanism for the cyclization of enaminone **1** is presented in Scheme 4. The overall transformation commences from the halogenation of **1**, mediated by Vilsmeier reagent (VR),[23,24] to generate enolate **A** that can be transformed into compound **4** upon treatment with water. Activated by the adjacent enolate and aryl groups, the amino group of **A** undergoes Vilsmeier−Haack reaction to generate intermediate **B**. An intramolecular cyclization reaction of **B** gives intermediate **C**, which sheds dimethylamine to afford intermediate **D**. In another pathway, further formylation of intermediate **B** leads to the formation of intermediate **E**, followed by an intramolecular cyclization to **F**. At high temperature, 125 °C for example, **F** undergoes deformylation to give **D** also. Upon treatment with water, **D** is finally converted into the pyridin-2(1*H*)-one of type **2**, whereas **F** is converted into the pyridin-2(1*H*)-one of type **3**.

SCHEME 4. Plausible Mechanism of the Reaction of Enaminones 1 under Vilsmeier Conditions



In summary, a facile and efficient one-pot synthesis of halogenated pyridin-2(1*H*)-ones of type **2** is developed from the Vilsmeier reactions of enaminones **1**, which involves sequential halogenation, formylation, and intramolecular nucleophilic cyclization reactions. The simple execution, readily available substrates, mild conditions, high yields, and wide range of synthetic potential of the products make this protocol very attractive. Synthetic transformations using the functionalized pyridin-2(1*H*)-ones **2** as scaffolds are currently under investigation in our laboratory.

Experimental Section

Typical Procedure for the Synthesis of Substituted Pyridin-2(1*H*)-ones 2. Synthesis of 2a1. The Vilsmeier reagent was prepared by adding PBr_3 (8.0 mmol) dropwise into ice-cold dry DMF (5 mL) under stirring. The mixture was then stirred for 15 min at 0 °C. To the above Vilsmeier reagent was added **1a** (2.0 mmol) as a solution in DMF (20 mL). The mixture was heated to 125 °C and stirred for 1.0 h. After cooling to room temperature, the resulting mixture was poured into saturated aqueous NaCl (100 mL), which was extracted with dichloromethane (3 × 30 mL). The combined organic phase was washed with water, dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The crude product was purified by flash silica gel chromatography (petroleum ether/ethyl acetate = 4:1, v/v) to give **2a1** as a white solid (68%): mp 187−189 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.40 (d, J = 7.0 Hz, 1H), 7.37 (d, J = 7.0 Hz, 2H), 7.49−7.54 (m, 4H), 10.40 (s, 1H); ^{13}C NMR

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(100 MHz, $CDCl_3$): δ 109.6, 122.0, 126.2, 129.4, 129.6, 139.1, 141.8, 150.5, 161.4, 188.4. Anal. Calcd for $C_{12}H_8BrNO_2$: C, 51.83; H, 2.90; N, 5.04. Found: C, 51.64; H, 2.97; N, 5.12.

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Supporting Information Available: Experimental details, full characterization data, and copies of NMR spectra for compounds **1**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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