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Vilsmeier−Haack Reactions of 2-Arylamino-3-acetyl-5,6-dihydro-4*H*-pyrans toward the Synthesis of Highly Substituted Pyridin-2(1*H*)-ones

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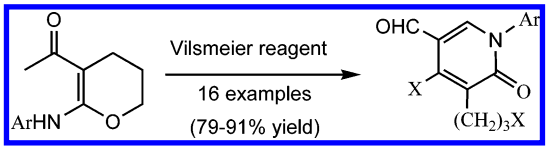
Received July 15, 2007



A facile and efficient one-pot synthesis of highly substituted pyridin-2(1*H*)-ones was developed via Vilsmeier−Haack reactions of readily available enaminones, 2-arylamino-3-acetyl-5,6-dihydro-4*H*-pyrans, and a mechanism involving sequential ring-opening, haloformylation, and intramolecular nucleophilic cyclization reactions is proposed.

Over the past decades, pyridin-2(1*H*)-ones have emerged as an important class of organic heterocycles since they are distributed in numerous natural products and synthetic organic compounds along with diverse useful bioactivities.[1] In particular, they constitute the skeleton of elfamycin antibiotics and the antifungal compound ilicolicin.[2] The pharmacological importance of pyridin-2(1*H*)-ones and their utility as versatile intermediates in the synthesis of a wide variety of nitrogen heterocycles, such as pyridine, piperidine, quinolizidine, and indolizidine alkaloids, have directed considerable research activity toward the construction of the skeleton of such kinds of heterocycles.[3,4] Many synthetic approaches for pyridin-2(1*H*)-ones have been developed involving either the modification of the pre-constructed 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 reactions, intramolecular Dieckmann-type condensation, hetero Diels−Alder reactions, and metal-mediated cycloaddition.[7−10] Each of these approaches represents an important advance toward the objective of a general method for the synthesis of pyridin-2(1*H*)-ones, however, some of them are still severely limited in their use by their lack of generality, the harsh reaction conditions involved, poor yields, a multistep procedure, or the formation of complex mixtures of side products. In light of this, simple and efficient synthetic protocols for the construction of more elaborate and usefully functionalized pyridin-2(1*H*)-ones are still in demand.

On the other hand, the Vilsmeier−Haack reaction associated with its mild reaction condition, commercial viability of the reagents, and improved understanding of the reaction mechanism has been widely used for the formylation of activated aromatic compounds and carbonyl compounds.[11] The versatile reactivity of carbonyl compounds with halomethylene iminium salts and a variety of cyclization reactions leading to heterocyclic compounds induced by the Vilsmeier reagent have been well-documented.[12] In our recent work, we have demonstrated the

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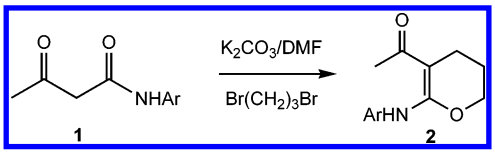
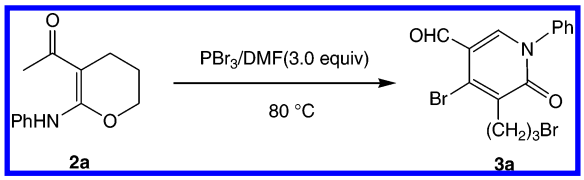
10.1021/jo7015482 CCC: $37.00
Published on Web 10/04/2007

SCHEME 1



SCHEME 2. Vilsmeier−Haack Reaction of 2a



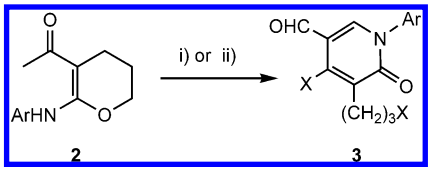
utility of the Vilsmeier reagent in the synthesis of functionalized heterocycles, such as substituted 2*H*-pyrans, pyridines, and pyridin-2(1*H*)-ones.[13] Thus, in connection with the previous work and following with our interest in the synthesis of highly valuable heterocycles from *β*-oxo amide derivatives,[14] we synthesized a series of enaminones (i.e., 2-arylamino-3-acetyl-5,6-dihydro-4*H*-pyrans) and examined their reactivity toward different Vilsmeier reagents. As a result, we report herein a convenient and efficient synthesis of highly substituted pyridin-2(1*H*)-ones **3** via the Vilsmeier−Haack reactions of the readily available 5,6-dihydro-4*H*-pyrans **2**.

The substrates **2** were synthesized from commercially available *β*-oxo amides **1** and 1,3-dibromoethane in the presence of K_2CO_3 in DMF in excellent yields (up to 96%, Scheme 1). With substrates **2** in hands, we selected 2-phenylamino-3-acetyl-5,6-dihydro-4*H*-pyran **2a** as the model compound to examine its behavior under different conditions.

Thus, the reaction of **2a** with the Vilsmeier reagent PBr_3/DMF (3.0 equiv) was first attempted at room temperature. The resulting mixture quickly became viscous and finally turned into a brown solid. Unfortunately, no predominant product was formed as indicated by TLC. With treatment of **2a** with PBr_3/DMF (3.0 equiv) beyond 70 °C, the mixture formed a solution. The reaction proceeded smoothly and furnished a white solid after workup and purification by column chromatography of the resulting mixture. The product was characterized as 4-bromo-5-(3-bromopropyl)-6-oxo-1-phenyl-1,6-dihydropyridine-3-carbaldehyde **3a** (68% yield) on the basis of its spectral and analytical data (Scheme 2). The optimization of the reaction conditions, including reaction temperature and the feed ratio of **2a** and PBr_3/DMF, was then investigated. Series of experiments revealed that 3.0 equiv of PBr_3/DMF was effective for the synthesis of **3a**, and the yield of **3a** reached 91% when the reaction of **2a** with 5.0 equiv of PBr_3/DMF was performed at 80 °C for 1 h (Table 1, entry 1).

Having established the optimal conditions for cyclization, we aimed to determine its scope with respect to the amide motif. Thus, a series of 5,6-dihydro-4*H*-pyrans **2** were subjected to PBr_3/DMF (5.0 equiv) at 80 °C, and some of the results are summarized in Table 1. The efficiency of the cyclization proved

TABLE 1. Vilsmeier−Haack Reactions of 5,6-Dihydro-4*H*-pyrans 2[a]



entry	2	Ar	X	3	yield (%)[b]
1	**2a**	Ph	Br	**3a**	91
2	**2b**	4-MePh	Br	**3b**	84
3	**2c**	4-MeOPh	Br	**3c**	82
4	**2d**	4-ClPh	Br	**3d**	88
5	**2e**	2-MePh	Br	**3e**	85
6	**2f**	2-MeOPh	Br	**3f**	86
7	**2g**	2-ClPh	Br	**3g**	79
8	**2h**	2,4-Me_2Ph	Br	**3h**	89
9	**2a**	Ph	Cl	**3i**	90
10	**2b**	4-MePh	Cl	**3j**	88
11	**2c**	4-MeOPh	Cl	**3k**	81
12	**2d**	4-ClPh	Cl	**3l**	86
13	**2e**	2-MePh	Cl	**3m**	84
14	**2f**	2-MeOPh	Cl	**3n**	86
15	**2g**	2-ClPh	Cl	**3o**	83
16	**2h**	2,4-Me_2Ph	Cl	**3p**	87

[a] Reagents and conditions: (i) For entries 1−8: PBr_3/DMF (5.0 equiv), 80 °C, 0.5−2.0 h. (ii) For entries 9−16: $POCl_3$/DMF (5.0 equiv), 20 °C, 2.0−3.0 h. [b] Isolated yields.

to be suitable for 5,6-dihydro-4*H*-pyrans **2b**−**h** affording the corresponding substituted pyridin-2(1*H*)-ones **3b**−**h** in high yields (Table 1, entries 2−8).

To extend the scope of this protocol, we next examined the pyridin-2(1*H*)-one synthesis from **2** with a different type of Vilsmeier reagent, $POCl_3$/DMF, under the otherwise identical conditions. Thus, the reaction of **2a** with $POCl_3$/DMF (5.0 equiv) was conducted at 80 °C for 2 h, as indicated by TLC for the complete conversion. The reaction furnished a white solid after workup and purification by column chromatography of the resulting mixture. However, the product was characterized as an inseparable mixture containing the corresponding pyridin-2(1*H*)-one of type **3** on the basis of the NMR spectral data. When subjected to room temperature (20 °C), the reaction of **2a** with $POCl_3$/DMF (5.0 equiv) proceeded smoothly, and to our delight, it afforded exclusively 4-chloro-5-(3-chloropropyl)-6-oxo-1-phenyl-1,6-dihydropyridine-3-carbaldehyde **3i** on the basis of spectral and analytical data (Table 1, entry 9). Under identical conditions, the substrates **2b**−**h** rendered successfully the corresponding pyridin-2(1*H*)-ones **3j**−**p** in high yields (Table 1, entries 10−16).

The results shown previously demonstrated the efficiency and synthetic interest of the cyclization reaction with respect to different Vilsmeier reagents and substrates **2** bearing variable aryl amide groups. Although many methods for synthesizing 2(1*H*)-pyridinones have been reported, the halogenated 2(1*H*)-pyridinones starting from acyclic substrates are much less documented.[13c,15] Indeed, halogenated 2(1*H*)-pyridinones are essential since they allow a means of introducing an alkyl or aromatic substituent through transition metal catalysis or

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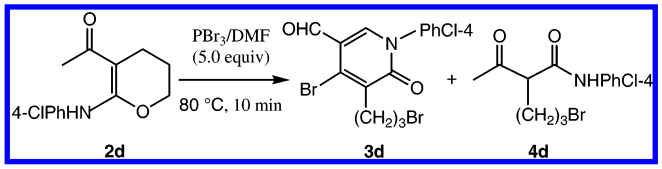
SCHEME 3. Vilsmeier−Haack Reaction of 2d



halogen−metal exchange.[16] It should be noted that the richness of the functionality (e.g., halogen, halogen alkyl, and formyl groups) of the pyridin-2(1*H*)-ones of type **3** 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, hence easily accessing the ring-fused heterocycles.[17]

In contrast with our results, Meth-Cohn and co-workers revealed that the interaction of an acylanilide with the Vilsmeier reagent offered an excellent method for the synthesis of quinolines, pyridines, and related systems,[12h−k] and Amaresh and Perumal achieved the synthesis 2-arylimino-2*H*-pyrancarboxaldehydes via the Vilsmeier−Haack reaction of *β*-oxo amides.[12f] The different results encouraged us to carry out separate experiments to gain insight into the mechanism of the ring-opening/recyclization reaction of **2**. Thus, the reaction of **2d** with the Vilsmeier reagent (PBr_3/DMF, 5.0 equiv) was performed at 80 °C for 10 min and then quenched with brine. Products **3d** and 2-acetyl-5-bromo-*N*-phenylpentanamide **4d** were obtained in 22 and 25% yields, respectively (Scheme 3). It is worthy noting that **4d** could be converted into **3d** in 91% yield upon treatment with PBr_3/DMF under identical conditions.

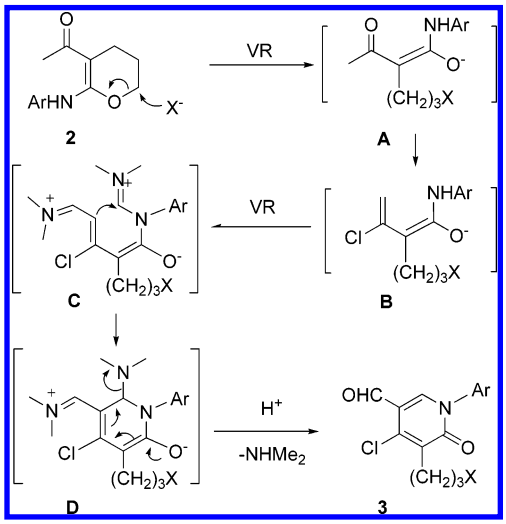
On the basis of all the obtained results combined with our previous studies,[13c] a plausible mechanism for the synthesis of substituted pyridin-2(1*H*)-ones of type **3** is presented in Scheme 4. The overall transformation commences from the ring-opening of **2** mediated by the Vilsmeier reagent to generate enolate **A**, which could be converted into **4** upon treatment with water. Sequential Vilsmeier−Haack reactions of **A** lead to the formation of intermediates **B** and **C**,[12a,g,h] and intramolecular azacyclization reaction of **C** gives the intermediate **D**,[12e,f] which is exclusively converted into substituted pyridin-2(1*H*)-ones of type **3**.[13c]

In summary, a facile and efficient one-pot synthesis of highly substituted pyridin-2(1*H*)-ones of type **3** is developed from the Vilsmeier−Haack reactions of 2-arylamino-3-acetyl-5,6-dihydro-4*H*-pyrans **2**, which involves sequential ring-opening, haloformylation, 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.

Experimental Section

General. All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. The products

SCHEME 4. Plausible Mechanism of Vilsmeier−Haack Reaction of 2



were purified by column chromatography over silica gel. ^{1}H NMR and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively, with TMS as an internal standard at 25 °C. IR spectra (KBr) were recorded on a FTIR spectrophotometer in the range of 400 to 4000 cm^{-1}.

Typical Procedure for the Synthesis of 2-Arylamino-3-acetyl-5,6-dihydro-4*H*-pyranes 2 (2a as an Example). To a well-stirred suspension of *N*-phenyl-3-oxobutanamide **1a** (10 mmol) and anhydrous K_2CO_3 (25 mmol) in DMF (25 mL) at room temperature was added 1,3-dibromopropane (10 mmol) dropwise within 15 min. The mixture was stirred for 6.0 h at room temperature and then poured onto ice−water (100 mL) under stirring. The precipitated solid was collected by filtration, washed with water (3 × 20 mL), and dried in vacuo to afford the product **2a** (2.08 g, yield: 96%).

1-[6-(Phenylamino)-3,4-dihydro-2*H*-pyran-5-yl]ethanone (2a). White solid: mp 65−67 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.95−2.00 (m, 2H), 2.15 (s, 3H), 2.49 (t, J = 6.0 Hz, 2H), 4.24 (t, J = 5.5 Hz, 2H), 7.03−7.06 (m, 1H), 7.25−7.29 (m, 4H), 13.16 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 22.3, 22.6, 27.1, 68.2, 86.4, 122.0, 123.7, 129.1, 138.3, 162.2, 194.4; IR (KBr) 2939, 1630, 1569, 1500, 1466, 1299, 1230, 1133, 1075, 757 cm^{-1}; Anal. calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.74; H, 7.05; N, 6.52.

Typical Procedure for the Synthesis of Pyridin-2(1*H*)-ones 3 (3a as an Example). The Vilsmeier reagent was prepared by adding PBr_3 (8.0 mmol) dropwise to ice cold dry DMF (5 mL) under stirring. The mixture was then stirred for 10−15 min at 0 °C. To the Vilsmeier reagent was added **2a** (2 mmol) as a solution in DMF (20 mL). Then, the mixture was heated to 80 °C and stirred for 1 h. After the staring material was consumed (monitored by TLC), the reaction mixture was poured into water (50 mL). The mixture was extracted with dichloromethane (2 × 30 mL), and the combined organic phase was washed with brine (3 × 30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, petroleum ether/diethyl ether = 5:1) to give **3a** (0.723 g, 91%).

Selected data for **3a**: white solid; mp 89−91 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.14−2.20 (m, 2H), 3.00 (t, J = 7.5 Hz, 2H), 3.51 (t, J = 6.5 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.48−7.55 (m, 3H), 8.10 (s, 1H), 10.11 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 25.6, 25.8, 28.7, 110.9, 121.7, 125.0, 125.1, 128.2, 130.5, 134.8, 136.6, 155.9, 184.3; IR (KBr) 2924, 1683, 1644, 1588, 1455, 1342, 1275, 1013, 671 cm^{-1}; Anal. calcd for $C_{15}H_{13}Br_2NO_2$: C, 45.14; H, 3.28; N, 3.51. Found: C, 45.27; H, 3.38; N, 3.42.

Selected data for **3i**: white solid; mp 86−87 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.08 (m, 2H), 2.96 (t, J = 7.5 Hz, 2H), 3.63 (t,

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J = 6.5 Hz, 2H), 7.35 (d, J = 7.5 Hz, 2H), 7.49−7.54 (m, 3H), 8.12 (s, 1H), 10.14 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 26.2, 30.5, 44.9, 115.0, 126.5, 129.7, 129.8, 130.1, 139.6, 141.4, 143.5, 161.2, 186.8; IR (KBr) 2937, 1692, 1643, 1594, 1543, 1440, 1305, 1204, 1035, 837 cm^{-1}; Anal. calcd for $C_{15}H_{13}Cl_2NO_2$: C, 58.08; H, 4.22; N, 4.52. Found: C, 58.19; H, 4.13; N, 4.63.

Selected data for **4d**: white solid; mp 119−120 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.93−1.95 (m, 2H), 2.05−2.16 (m, 2H), 2.35 (s, 3 H), 3.43−3.48 (m, 2H), 3.54 (t, J = 6.0 Hz, 3H), 7.29 (d, J = 9.0 Hz, 2H), 7.48 (d, J = 9.0 Hz, 2H), 8.39 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 29.5, 29.9, 30.0, 32.7, 60.4, 121.4, 129.2, 129.9, 136.1, 166.3, 208.0; IR (KBr) 3249, 2925, 1722, 1647, 1534, 1489, 1395, 1264, 1162, 1012, 819 cm^{-1}; Anal. calcd for $C_{13}H_{15}BrClNO_2$: C, 46.94; H, 4.55; N, 4.21; Found: C, 46.79; H, 4.48; N, 4.16.

Acknowledgment. Financial support of this research by the National Natural Science Foundation of China (20572013), the Ministry of Education of China (105061), and the Department of Science and Technology of the Jilin Province (20050392) is acknowledged.

Supporting Information Available: Spectral data for **2b**−**h**, **3b**−**h**, **3j**−**p**, and **4d** and NMR spectra copies of **2a**−**h**, **3a**−**p**, and **4d**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO7015482