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A Facile and Efficient Synthesis of Polyfunctionalized Pyridin-2(1*H*)-ones from *β*-Oxo Amides under Vilsmeier Conditions

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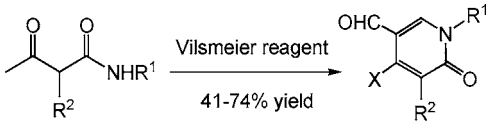
ABSTRACT



R^1 = aryl, alkyl; R^2 = Alkyl, H; X = Br, Cl

A facile and efficient one-pot synthesis of polysubstituted pyridin-2(1*H*)-ones from a variety of *β*-oxo amides under Vilsmeier conditions is described, and a mechanism involving sequential halogenation, formylation and intramolecular nucleophilic cyclization is proposed.

The vast number of bioactive natural products and pharmaceutical drugs based on the pyridin-2(1*H*)-one ring system, such as elfamycin and ilicolicin, have become very important in the area of natural product and pharmacetical chemistry.[1,2] 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 involving pyridinium salt chemistry,[5] Guareschi−Thorpe reaction,[6] Dieckmann-type condensation,[7] hetero Diels−Alder reaction,[8] and metal-mediated cycloaddition.[9] Other notable methods starting from polarized ketene *S*,*S*- and *N*,*N*-acetals were reported.[10] However, many of the established approaches are still severely limited in their use by the lack of substrate scope and selectivity, the harsh

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(1) (a) Elbein, A. D.; Molyneux, R. J. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1981; Vol. 5, p 1. (b) Li, Q.; Mitscher, L. A.; Shen, L. L. *Med. Res. Rev.* **2000**, *20*, 231. (c) Nagarajan, M.; Xiao, X. S.; Antony, S.; Kohlhagen, G.; Pommier, Y.; Cushman, M. *J. Med. Chem.* **2003**, *46*, 5712.

(2) (a) Dolle, R. E.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1985**, *107*, 1691. (b) Cox, R. J.; O'Hagan, D. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2537.

(3) (a) Jones, G. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 5, p 167. (b) Scriven, E. F. V. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 2.

(4) (a) Torres, M.; Gil, S.; Parra, M. *Curr. Org. Chem.* **2005**, *9*, 1757. (b) Jayasinghe, L.; Abbas, H. K.; Jacob, M. R.; Herath, W. H. M. W.; Nanayakkara, N. P. D. *J. Nat. Prod* **2006**, *69*, 439. (c) Angibaud, P. R.; Venet, M. G.; Filliers, W.; Broeckx, R; Ligny, Y. A.; Muller, P.; Poncelet, V. S.; End, D. W. *Eur. J. Org. Chem.* **2004**, 479. (d) Litvinov, V. P. *Russ. Chem. Rev.* **2003**, *72*, 69.

(5) (a) Comins, D. L.; Saha, J. K. *J. Org. Chem.* **1996**, *61*, 9623. (b) Du, W. *Tetrahedron*, **2003**, *59*, 8649. (c) Comins, D. L.; Gao, J. L. *Tetrahedron Lett.* **1994**, *35*, 2819. (d) Hu, T.; Li, C. *Org. Lett.* **2005**, *7*, 2035. (e) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem. Eur. J.* **2004**, *10*, 5607.

(6) (a) Baron, H.; Renfry, H.; Thorpe, J. *J. Chem. Soc.* **1904**, *85*, 1726. (b) Aggarwal, V.; Sing, G.; Ila, H.; Junjappa, H. *Synthesis* **1982**, 214.

(7) Chung, K. H.; Cho, K. Y.; Asami, Y.; Takahashi, N.; Yoshida, S. *Heterocycles* **1991**, *32*, 4040.

(8) (a) Robin, A.; Julienne, K.; Meslin, J. C.; Deniaud, D. *Tetrahedron Lett.* **2004**, *45*, 9557. (b) Sainte, F.; Serckx-Poncin, B.; Hesbain-Frisque, A.; Ghosez, L. *J. Am. Chem. Soc.* **1982**, *104*, 1428.

(9) (a) Varela, J. A.; Saa, C. *Chem. Rev.* **2003**, *103*, 3787. (b) Yamamoto, Y.; Takagishi, H.; Itoh, K. *Org. Lett.* **2001**, *3*, 2117. (c) Padwa, A.; Sheehan, S. M.; Straub, C. S. *J. Org. Chem.* **1999**, *64*, 8648. (d) Padwa, A.; Heidelbaugh, T. M.; Kuethe, J. T. *J. Org. Chem.* **2000**, *65*, 2368.

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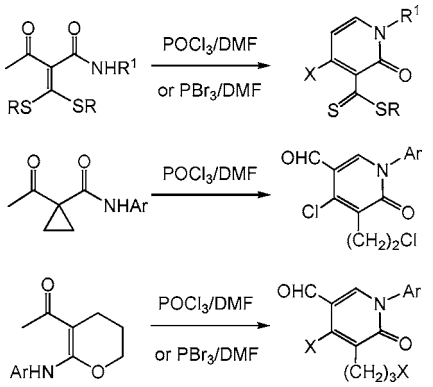
reaction conditions involved, or the multistep procedure required. Therefore, to match the increasing scientific and practical demands, it is still of continued interest and great importance to explore simple and efficient synthetic approaches for the construction of pyridin-2(1*H*)-ones, especially those with wide applicability to achieve more elaborate and flexible substitution patterns.

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.[11] Unfortunately, the most available approaches for accessing pyridin-2(1*H*)-ones are not general for the preparation of halogenated pyridin-2(1*H*)-ones. To date, the direct synthesis of such halogenated heterocycles from acyclic substrates is much less documented.[12] Chen et al. recently reported the synthesis of 4-halogenated pyridin-2(1*H*)-ones from α-oxo ketene *S*,*S*-acetals (Scheme 1).[13]

Scheme 1. Synthesis of Halogenated Pyridin-2(1*H*)-ones via Vilsmeier−Haack Reactions

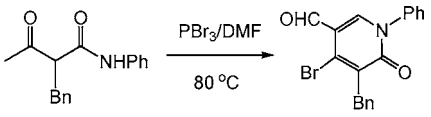


During the course of our studies on Vilsmeier−Haack reactions,[14] we developed a facile one-pot synthesis of halogenated pyridin-2(1*H*)-ones from either cyclopropyl amides or cyclic enaminones under Vilsmeier conditions (Scheme 1).[15] The significance of the protocol relies on the combination of construction of the pyridin-2(1*H*)-one skeleton and creation of its dense substitution patterns. In connection with these studies and the aim to extend the substrate scope and further clarify the mechanism involved, we examined the reactions of a variety of *β*-oxo amides under different Vilsmeier conditions. By this research, we achieved a facile and efficient synthesis of polysubstituted pyridin-2(1*H*)-ones in good to high yields. Herein, we report our experimental results and present a proposed mechanism for the cyclization.

The substrates, α-monosubstituted *β*-oxo amides **1**, were prepared from commercially available α-unsubstituted *β*-oxo amides and alkyl bromides in the presence of K_2CO_3 in high yields. A few of the alkylation products **1** were purified and characterized with the help of spectral and analytical data, whereas in the subsequent reactions, they are used as obtained without further purification.

Thus, the Vilsmeier cyclization of 2-benzyl-3-oxo-*N*-phenyl butanamide **1a** was initially attempted. Upon treatment of **1a** with Vilsmeier reagent PBr_3/DMF (3.0 equiv) below 60 °C, the resulting mixture quickly became viscous, and finally turned into a brown solid. Unfortunately, no major product could be isolated from the intractable reaction mixture. When **1a** was heated with PBr_3/DMF (3.0 equiv) at 70 °C for 3.0 h, the reaction proceeded smoothly as indicated by TLC and furnished a white solid after workup and purification by column chromatography of the resulting reaction mixture. From the spectral and analytical data, the exclusive product was characterized as 5-benzyl-4-bromo-6-oxo-1-phenyl-1,6-dihydropyridine-3-carbaldeh-yde **2a1** (Scheme 2). The reaction conditions, including reaction

Scheme 2. Reaction of **1a** with $POCl_3$/DMF



temperature and the feed ratio of **1a** and PBr_3/DMF, were then investigated. A series of experiments revealed that 3.0 equiv of PBr_3/DMF was effective for the synthesis of **2a1**, and the optimal results were obtained when the reaction of **1a** was carried with 5.0 equiv of PBr_3/DMF at 80 °C for 2.0 h, whereby the yield of **2a1** reached 71% (Table 1, entry 1).

Having established the optimal conditions for the cyclization, we intended to determine its scope with respect to the amide motif. Thus, a series of α-benzyl *β*-oxo amides **1b**−**e** 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 to be suitable for **1b**−**e** bearing variable aryl and alkyl amide groups affording the corresponding substituted pyridin-2(1*H*)-ones **2b1**−**e1** in good yields (Table 1, entries 2−5). The versatility of this facile pyridin-2(1*H*)-one synthesis was evaluated by performing the Vilsmeier reaction on *β*-oxo amides **1f**−**o** with different

(10) (a) Anabha, E. R.; Asokan, C. V. *Synthesis* **2006**, 151. (b) Chakrabarti, S.; Panda, K.; Misara, N. C.; Ila, H.; Junjappa, H. *Synlett* **2005**, 1437. (c) Mahata, P. K.; Syam, Kumar, U. K.; Sriram, V.; Ila, H.; Junjappa, H. *Tetrahedron* **2003**, *59*, 2631.

(11) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Choi, W. B.; Houpis, I. N.; Churchill, H.; Molina, O.; Lynch, J. E.; Volante, R. P.; Reider, P. J.; King, A. O. *Tetrahedron Lett.* **1995**, *36*, 4571. (c) Houpis, I. N.; Choi, W. B.; Reider, P. J.; Molina, O.; Churchill, H.; Lynch, J.; Volante, R. P. *Tetrahedron Lett.* **1994**, *35*, 9355.

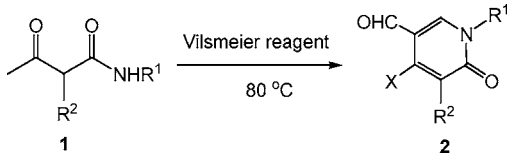
(12) (a) Marcoux, J.-F.; Marcotte, F.-A.; Wu, J.; Dormer, P. G.; Davies, I. W.; Hughes, D.; Reider, P. J. *J. Org. Chem.* **2001**, *66*, 4194. (b) Agami, C.; Dechoux, L.; Hebbe, S.; Moulinas, J. *Synthesis* **2002**, 79. (c) Adams, J.; Hardin, A.; Vounatsos, F. *J. Org. Chem.* **2006**, *71*, 9895.

(13) Chen, L.; Zhao, Y.; Liu, Q.; Cheng, C.; Piao, C. *J. Org. Chem.* **2007**, *72*, 9259.

(14) (a) Sun, S.; Liu, Y.; Liu, Q.; Zhao, Y.; Dong, D. *Synlett* **2004**, 1731. (b) Liu, Y.; Dong, D.; Liu, Q.; Qi, Y.; Wang, Z. *Org. Biomol. Chem.* **2004**, *2*, 28. (c) Dong, D.; Liu, Y.; Zhao, Y.; Qi, Y.; Wang, Z. Liu, Q. *Synthesis* **2005**, 85.

(15) (a) Pan, W.; Dong, D.; Wang, K.; Zhang, J.; Wu, R.; Xiang, D.; Liu, Q. *Org. Lett.* **2007**, *9*, 2421. (b) Xiang, D.; Yang, Y.; Zhang, R.; Liang, Y.; Pan, W.; Huang, J.; Dong, D. *J. Org. Chem.* **2007**, *72*, 8693.

Table 1. Vilsmeier−Haack Reaction of β-Oxo Amides **1**[a]



1 **2**

entry	**1**	R^1	R^2	X	**2**	yield[b] (%)
1	**1a**	Ph	Bn	Br	**2a1**	71
2	**1b**	4-MePh	Bn	Br	**2b1**	67
3	**1c**	4-MeOPh	Bn	Br	**2c1**	54
4	**1d**	4-ClPh	Bn	Br	**2d1**	74
5	**1e**	Me	Bn	Br	**2e1**	62
6	**1f**	Ph	Me	Br	**2f1**	68
7	**1g**	4-MePh	Me	Br	**2g1**	65
8	**1h**	4-MeOPh	Me	Br	**2h1**	53
9	**1i**	2-MePh	Me	Br	**2i1**	41
10	**1j**	Ph	allyl	Br	**2j1**	69
11	**1k**	4-MePh	allyl	Br	**2k1**	63
12	**1l**	4-MeOPh	allyl	Br	**2l1**	58
13	**1m**	Ph	CH_2COOEt	Br	**2m1**	70
14	**1n**	4-MePh	CH_2COOEt	Br	**2n1**	72
15	**1o**	4-MeOPh	CH_2COOEt	Br	**2o1**	55
16	**1a**	Ph	Bn	Cl	**2a2**	68
17	**1b**	4-MePh	Bn	Cl	**2b2**	63
18	**1c**	4-MeOPh	Bn	Cl	**2c2**	60
19	**1d**	4-ClPh	Bn	Cl	**2d2**	73
20	**1f**	Ph	Me	Cl	**2f2**	71

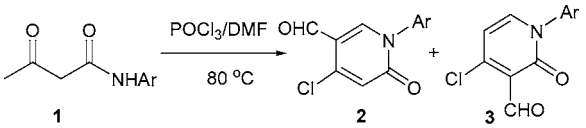
[a] Reagents and conditions: **1** (1.0 mmol), $POCl_3$/DMF or PBr_3/DMF (5.0 mmol), 80 °C, 2.0−3.0 h. [b] Isolated yields.

substituted groups, e.g., methyl, allyl, and ethyl methylene carboxy (−CH_2COOEt), at α position. All the reactions of **1f-o** with Vilsmeier reagent, PBr_3/DMF, proceeded smoothly to give the corresponding substituted pyridin-2(1*H*)-ones **2f1**−**o1** in moderate to good yields (Table 1, entries 6−15). Lower yield was observed in the case of **1i** (Table 1, entry 9), which might stem from the steric hindered effect of the ortho-substituted methyl group on the benzene ring of aryl amide.

The protocol was next extended for the synthesis of 4-chloropyridin-2(1*H*)-ones by subjecting β-oxo amides **1** to the cyclization with a different type of Vilsmeier reagent, $POCl_3$/DMF. Thus, the reaction of **1a** with $POCl_3$/DMF (5.0 equiv) was conducted at 80 °C for 2.0 h. Workup and purification of the resulting mixture afforded only one product, which was characterized as 5-benzyl-4-chloro-6-oxo-1-phenyl-1,6-dihydropyridine-3-carbaldehyde (**2a2**) on the basis of the spectral and analytical data (Table 1, entry 16). Similarly, β-oxo amides **1b**−**d** and **1f** underwent rapid spontaneous Vilsmeier cyclization to furnish the respective substituted pyridin-2(1*H*)-ones **2** in good yields (Table 1, entry 17−20). The results shown above have demonstrated the efficiency and interest of the cyclization reaction for the synthesis of halogenated pyridin-2(1*H*)-ones **2** with respect to substrates **1** bearing variable amide and α-alkyl functional groups, i.e., R^1 and R^2.

In contrast with our results, Amaresh and co-workers investigated the Vilsmeier−Haack reaction of β-oxo amides and reported that two isomeric 2-arylimino-4-chloro-2*H*-pyrancarboxaldehydes were obtained.[16] These studies inspired us to recheck the reaction of α-unsubstituted β-oxo amides **1** under Vilsmeier conditions. Thus, the reaction of 3-oxo-*N*-phenylbutanamide **1p** was performed with $POCl_3$/DMF at 80 °C for 2.0 h. As indicated by TLC, two main products were formed. Workup and purification of the resulting reaction mixture furnished two products, which surprisingly were characterized as 4-chloro-6-oxo-1-phenyl-1,6-dihydropyridine-3-carbaldehyde (**2p2**) and 4-chloro-2-oxo-1-phenyl-1,2-dihydropyridine-3-carbaldehyde (**3p2**) on the basis of the spectral and analytical data (Scheme 3). The

Scheme 3. Reactions of **1p/1q** with $POCl_3$/DMF



1 **2** **3**

substrate **1**	Ar	**2** (yield %)	**3** (yield %)
1p	Ph	**2p2** (37)	**3p2** (32)
1q	4-MePh	**2q2** (35)	**3q2** (30)

structure of **2p2** was further confirmed by the X-ray single-crystal analysis (Figure 1). Comparison of NMR spectra

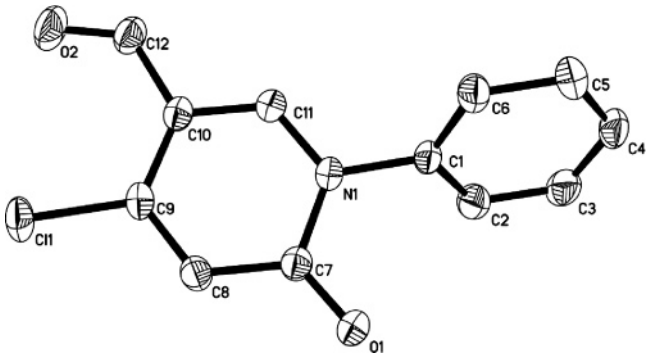


Figure 1. ORTEP drawing of **2p2**.

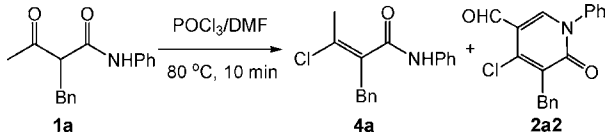
between **2p2** and **3p2** led us further confirm the structure of **3p2** without difficulty. In the ^{1}H NMR spectra, **2p2** displayed three single peaks at δ 6.73, 8.19, and 10.08, respectively, which were assigned to 5-H, 2-H, and 3-formyl hydrogen of pyridin-2(1*H*)-one ring. With respect to **3p2**, two single peaks disappeared, while two doublet peaks (J = 7.0 Hz) were observed, one at δ 6.40 for 5-H and another at δ 7.36 for 6-H. The single peak at δ 10.39 was assigned to the 3-formyl hydrogen of **3p2**. In the ^{13}C NMR spectra of **3p2**, the peak for the 3-formyl carbon appeared at δ 188.5.

(16) Amaresh, R. R.; Perumal, P. T. *Tetrahedron* **1999**, *55*, 8083.

Additionally, from mass spectrometry analysis, same molecular ion peaks were observed for **2p2** and **3p2** (233.6-$[M]^+$). This is consistent with the NMR results, and confirms that **2p2** and **3p2** are a pair of isomers. In the same fashion, chlorogenated pyridin-2(1*H*)-ones **2q2** and **3q2** were obtained in 35% and 30% yields, respectively (Scheme 3). The results reveal that the cyclization efficiency of α-unsubstituted *β*-oxo amides **1** to **2** is suitable, and therefore the previous report by Amaresh and co-workers on the structural identity and proposed mechanism seems to be ambiguous.[16]

To gain insight into the mechanism of the cyclization, a separate experiment was conducted. The reaction of **1a** with 5.0 equiv of Vilsmeier reagent ($POCl_3$/DMF) was performed at 80 °C for 10 min and then quenched with water. Compounds **4a** and **2a2** were obtained in 47% and 25% yields, respectively (Scheme 4).

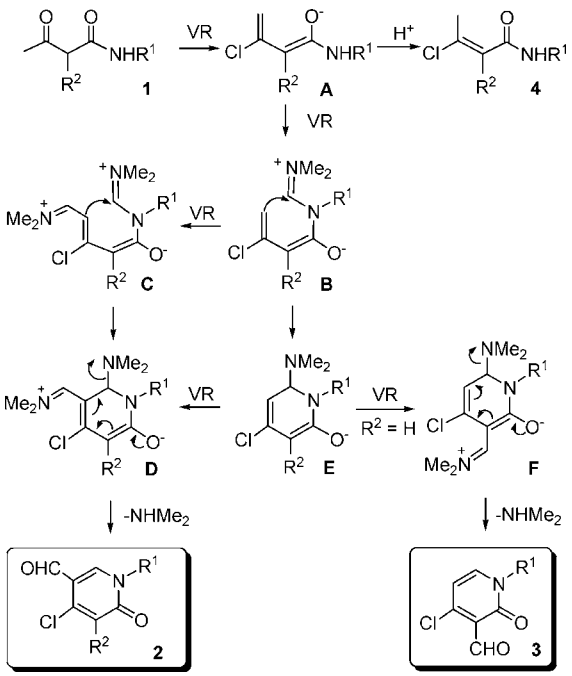
Scheme 4. Reaction of **1a** with $POCl_3$/DMF



On the basis of all 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 5. The overall transformation commences from the halogenation of **1**, mediated by Vilsmeier reagent, to generate enolate **A**, which can be converted into compound **4** upon treatment with water. Activated by the adjacent enolate, sequential Vilsmeier−Haack reactions of the acetyl group of **A** leads 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**. In another pathway, intermediate **B** undergoes intramolecular aza-cyclization to **E**, which also can be transformed into intermediate **D** and finally to **2**. When R^2 is H, a competitive, regioselective formylation occurs on **E** to give intermediates **D** and **F**, the latter leads the formation of pyridin-2(1*H*)-ones of type **3**.

(17) (a) Marson, C. M. *Tetrahedron* **1992**, *48*, 3659. (b) Thomas, A. D.; Asokan, C. V. *Tetrahedron* **2004**, *60*, 5069.

Scheme 5. Plausible Mechanism of the Vilsmeier−Haack Reaction of *β*-Oxo Amides **1**



In summary, a facile and efficient one-pot synthesis of polyfunctionalized pyridin-2(1*H*)-ones of types **2** and **3** has been developed from the Vilsmeier−Haack reaction of readily available α-monosubstituted/unsubstituted *β*-oxo amides **1**, which involves sequential halogenation, formylation, and intramolecular nucleophilic cyclization reactions. This protocol is associated with readily available starting materials, mild conditions, high yields, a wide range of substrate scope, dense and flexible substitution patterns, and important synthetic potential of the final products.

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

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