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Regioselective Syntheses of 2- and 4-Formylpyrido[2,1-*b*]benzoxazoles

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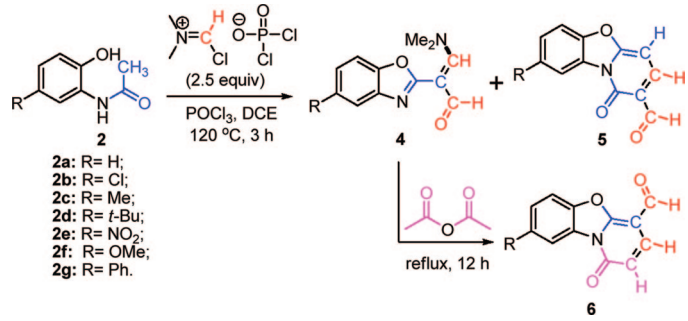

o-Acetaminophenols (**2**) reacted with Vilsmeier reagent under Meth-Cohn conditions to yield 2-formylpyrido[2,1-*b*]benzoxazoles (**5**) unexpectedly besides the known compounds 2-(benzoxazol-2′-yl)-3-dimethylaminoacroleins (**4**). Refluxing **4** in acetic anhydride gave 4-formylpyrido[2,1-*b*]benzoxazoles (**6**), an isomer of **5**. Both **5a** and **6a** were structurally characterized by X-ray crystallography. A mechanism for the formation of **5** involving sequential chlorination, dimerization, intramolecular elimination of HCl to form the oxazole ring, formylation twice, and regioselective intramolecular nucleophilic cyclization to construct the pyridone ring is proposed.

Introduction

Pyrido[2,1-*b*]benzoxazoles have attracted many chemists' and pharmacologists' attention in recent years due to their potential bioactivities, such as antitumor, antiviral, and antimicrobial, etc.[1] Despite the synthetic and pharmacological importance of pyrido[2,1-*b*]benzoxazoles, few methods are known for the synthesis of these compounds. To our knowledge, only two routes leading to such types of compounds have been described in the literature. One of them is involved in the reactions of 2-substituted benzoxazoles with 1,3-dicarbonyl or equivalent compounds.[2] The other approach employs heating ethyl 2-(benzoxazol-2′-yl)-3-dimethylaminoacrylate with acetic anhydride or diketene.[3] Each of these approaches represents an important advance toward the objective of a general method for the synthesis of pyrido[2,1-*b*]benzoxazoles. However, they are still more or less limited in their use by their lack of generality, poor yields, or a multistep procedure needed in obtaining the starting materials. Moreover, the structures of those pyrido[2,1-*b*]benzoxazoles prepared using the known methods are somewhat monotonous, as they always have a substituted group on the 4-position without exception. In addition, most of them usually bear two or three substituted groups on the pyridone ring, which may bring inconvenience to their further structural modification toward various functionalized compounds. In light of this, simple and regioselective synthetic protocols for the construction

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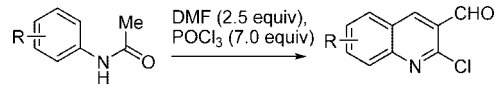
of more modifiable, elaborate, and usefully functionalized pyrido[2,1-*b*]benzoxazoles are strongly in demand.

On the other hand, the Vilsmeier reaction, one of the most useful synthetic methods for the introduction of one or more formyl groups into electron-rich aromatic and heteroaromatic compounds since its discovery by Vilsmeier and Haack,[4,5] has also shown great usefulness in the construction of a large number of heterocyclic systems,[6] such as pyridines,[7]pyridones,[7h,8] pyrroles,[9] pyrans,[10] pyrones,[7c,11] pyrimidines,[12] pyrazoles,[13] oxazoles,[13a,14] quinolines,[15] and so on.[16] Among them, the Meth-Cohn quinoline synthesis, which involves the conversation of acylanilides into 2-chloro-3-substituted quinolines by the action of Vilsmeier reagent in hot $POCl_3$ solution, is of particular interest because of its ease of operation, wide general applicability, and the great importance of the products.[17] Notably, a large range of acetanilides, both activated and unactivated, have been explored under the original or modified reaction conditions, giving cyclization products in moderate to good yields (Scheme 1).[18]

SCHEME 1. Meth-Cohn Quinoline Synthesis



R= H, 2-Me, 3-Me, 4-Me, 2-OMe, 3-OMe, 4-OMe, 2-Cl, 3-Cl, 4-Cl, 4-Br, 2-NO_2, 3-NO_2, 4-NO_2, 2-Et

When the substituted group R on acetanilide is *o*-hydroxy, namely, the substrate is *o*-acetaminophenol (**2a**), the product might be 2-chloro-8-hydroxyquinoline-3-carbaldehyde according to Meth-Cohn's procedure, but no one has put it into practice up to now. A previous report by Chandramohan in 1972 revealed that *o*-acetaminophenol reacted with Vilsmeier reagent in DMF at 60 °C to give 2-(benzoxazol-2′-yl)-3-dimethylaminoacrolein (**4a**).[19] In connection with our interest in porphyrin-based red-light emission materials,[20] we attempted to prepare this fascinating 8-hydroxyquinolinecarbaldehyde via the Meth-Cohn method. To our surprise, no desired 8-hydroxyquinolinecarbaldehyde was detected, but an unexpected product 2-formylpyrido[2,1-*b*]benzoxazole (**5a**) was obtained in addition to the known compound **4a** (Scheme 2). During the course of elucidating the structure of **5a**, its isomer, 4-formylpyrido[2,1-*b*]benzoxazole (**6a**), was also synthesized. Herein we present the results.

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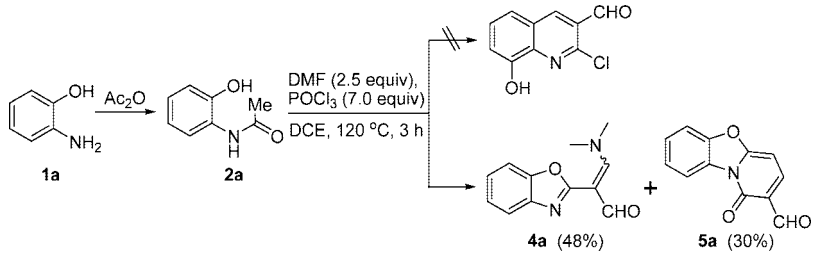
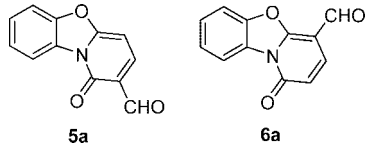
SCHEME 2. Reaction of *o*-Acetaminophenol (2a) with Vilsmeier Reagent



SCHEME 3. Two Proposed Structures for the Minor Product of the Reaction of 2a with Vilsmeier Reagent



Results and Discussion

Synthesis and Characterization of 2-Formylpyrido[2,1-*b*]-benzoxazoles. The starting material, *o*-acetaminophenol (**2a**), was prepared by adding acetic anhydride dropwise to a suspension of *o*-aminophenol (**1a**) in water (Scheme 2). Consequently, the Vilsmeier reaction was carried out according to Meth-Cohn's procedure.[17d] Crude products were purified by flash chromatography on silica gel. Elution with CH_2Cl_2 afforded a pale yellow band as the minor product (yield 30%), which showed strong blue fluorescence upon irradiation with 365 nm light on TLC. After elution with EtOAc, a yellow fraction was isolated as the major product (yield 48%). Spectroscopic characterization of the major product identified its structure as the known **4a**, which was further confirmed by its melting point.

In contrast with the major product, it was rather troublesome to elucidate the structure of the minor product. The combination of its MS, ^{1}H NMR, ^{13}C NMR, and elemental analysis revealed its formula as $C_{12}H_7NO_3$, which was also confirmed by HRMS. On the basis of the above spectra, mainly ^{1}H NMR and ^{13}C NMR, two isomers, 2-formylpyrido[2,1-*b*]benzoxazole (**5a**) and 4-formylpyrido[2,1-*b*]benzoxazole (**6a**) (Scheme 3), were considered to be the most possible structures. Nevertheless, it was still difficult to distinguish them, although it could be performed in theory by HMBC spectroanalysis, but in fact it seemed not credible enough due to its poor solubility in common deuterated solvents.

At the same time, we noted that **6a** might can be constructed starting from **4a** according to Kato's procedure.[3] Thus, **4a** was refluxed in acetic anhydride to give a yellow solid. With these two compounds in hand, we were able to compare their various spectra. Each pair of spectra, including MS, ^{1}H NMR, ^{13}C NMR, and IR, all showed extreme similarity with only slight differences (Figures S16, S17, S30, and S31 in the Supporting Information). On the other hand, fortunately, single crystals of the two isomers suitable for single-crystal X-ray diffraction analysis were obtained by slowly diffusing petroleum ether into their $CHCl_3$ solution (Figure 1).[21,22] Thus, the structure of the minor product had been elucidated as 2-formylpyrido[2,1-*b*]-benzoxazole (**5a**), and the synthesis of its isomer 4-formylpyrido[2,1-*b*]benzoxazole (**6a**) had also been achieved during this process.

After identification of the product structures, the reaction conditions, i.e., reaction solvents, reaction temperature, reaction time, and the feed ratio of substrate and Vilsmeier reagent, were investigated. 4-*tert*-Butyl-2-acetamidophenol (**2d**) was chosen as a model compound due to its good solubility in common organic solvents. The results are summarized in Table 1. Under the original reaction conditions, 2-formyl-8-*tert*-butylpyrido-[2,1-*b*]benzoxazole (**5d**) can be synthesized in 54% yield (entry 2, Table 1). Reducing the amount of Vilsmeier reagent from 2.5 to 1.0 equiv led to a sharp decrease of **5d** but a great increase of 2-methyl-5-*tert*-butylbenzoxazole (**3d**) (entry 1, Table 1). Raising Vilsmeier reagent's amount to 4.5 equiv had little effect on the reaction yield (compare entries 2 and 3 in Table 1). 2-(5′-*tert*-Butylbenzoxazol-2′-yl)-3-dimethylaminoacrolein (**4d**) was nearly the sole product when the reaction solvent was replaced by DMF (entry 4, Table 1), which is in accordance with the literature.[19] Temperature had a big influence on the reaction. Sometimes when the oil bath temperature was varied, but only a small change happened in inner temperature, the result was very different (compare entries 5 and 6 in Table 1). A screen of reaction temperature along with refluxing solvents demonstrated that the formation of **5d** occurred more efficiently in higher temperature (entries 2, 5−7, and 11, Table 1) and 1,2-dichloroethane (DCE) was a proper cosolvent. Since excess $POCl_3$ played a vital role in Meth-Cohn quinoline synthesis,[17d] various amounts of $POCl_3$ were then examined (entries 2, 8−10, and 12, Table 1). The results revealed that addition of 9 equiv of $POCl_3$ gave the best yield of **5d**. All of these results suggested that a combination of 2.5 equiv of DMF, 9.0 equiv of $POCl_3$, and *o*-acetamidophenol in DCE at 120 °C for 3 h was the most effective system for the synthesis of 2-formylpyrido[2,1-*b*]-benzoxazole.

In order to explore the effect of the substituents on the phenyl ring in the reaction of *o*-acetaminophenols with Vilsmeier reagent, a series of substrates with diverse electronic properties were then investigated. As illustrated in Table 2, under the optimal conditions, various *o*-acetaminophenols could be converted into the corresponding 2-formylpyrido[2,1-*b*]benzoxazoles except the one bearing a nitro group (entry 9, Table 2). Notably, while the majority of substrates had a better yield of 2-formylpyrido[2,1-*b*]benzoxazoles (**5**) by adding 9 equiv of $POCl_3$ rather than 7 equiv of $POCl_3$, the yield of **5a** was much higher when 7 equiv of $POCl_3$ was added. Generally speaking, the results demonstrated that the reactivity of a substrate with

(21) Crystal data for **5a**: $C_{12}H_7NO_3$, M = 213.19, monoclinic, space group $P2(1)/c$, a = 9.0473(15) Å, b = 7.9725(13) Å, c = 13.064(2) Å, α = 90°, β = 96.046(3)°, γ = 90°, V = 937.0(3) Å^3, T = 292(2) K, Z = 4, D_c = 1.511 g cm^{-3}, μ(Mo Kα) = 0.111 mm^{-1}, 5368 reflections measured, 2050 unique which were used in all calculations. R_1 (all data) = 0.0688. R_1 = 0.0496. CCDC 689518.

(22) Crystal data for **6a**: $C_{12}H_7NO_3$, M = 213.19, triclinic, space group P-1, a = 7.9660(18) Å, b = 9.582(2) Å, c = 13.056(3) Å, α = 72.118(4)°, β = 85.884(4)°, γ = 75.818(4)°, V = 919.4(4) Å^3, T = 293(2) K, Z = 4, D_c = 1.540 g cm^{-3}, μ(Mo Kα) = 0.113 mm^{-1}, 3539 reflections measured, 2790 unique which were used in all calculations. R_1 (all data) = 0.0591. R_1 = 0.0502. CCDC 689517.

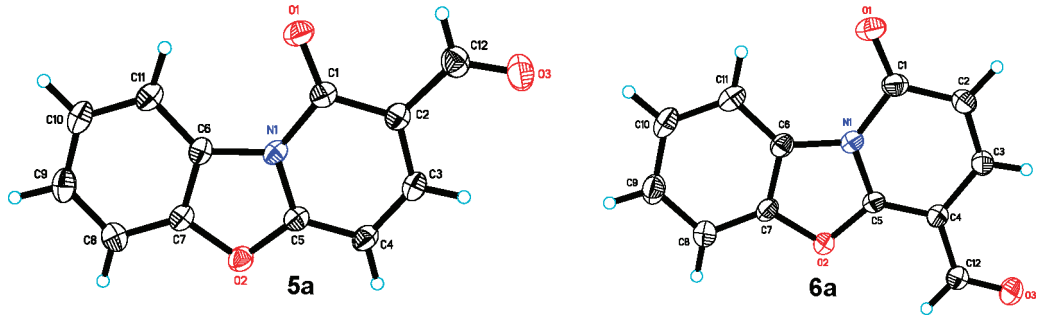
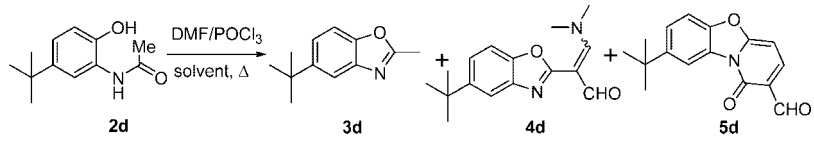


FIGURE 1. ORTEP drawing of **5a** and **6a**.

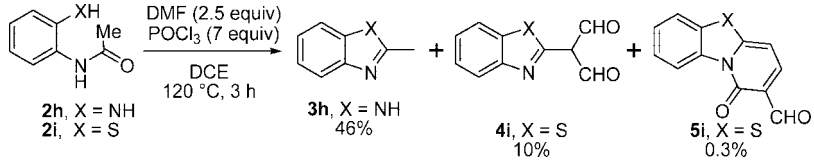
TABLE 1. Optimization of Conditions for the Vilsmeier Reaction of *o*-Acetamidophenol 2d[a]



						yield[d] (%)		
entry	DMF (equiv)	$POCl_3$ (equiv)	refluxing solvent	t_o[b] (t_i[c]) (°C)	T (h)	**3d**	**4d**	**5d**[e]
1	1.0	7.0	DCE	120 ± 2 (93 ± 1)	3	50	45	2
2	2.5	7.0	DCE	120 ± 2 (93 ± 1)	3	trace	38	54
3	4.5	11.0	DCE	120 ± 2 (93 ± 1)	3	trace	41	50
4	solvent	2.5	DMF	120 ± 2	3	trace	94	
5[f]	2.5	7.0	$CHCl_3$	80 ± 2 (73 ± 1)	3	38	27	7
6[g]	2.5	7.0	$CHCl_3$	100 ± 2 (75 ± 1)	3	32	30	20
7	2.5	7.0	DCE	100 ± 2 (87 ± 1)	3	26	34	32
8	2.5	3.0	DCE	120 ± 2 (93 ± 1)	3	trace	93	
9	2.5	5.0	DCE	120 ± 2 (93 ± 1)	3	trace	44	48
10	2.5	9.0	DCE	120 ± 2 (93 ± 1)	3	trace	34	58
11	2.5	9.0	PhCl	160 ± 2 (123 ± 1)	3		36	56
12	2.5	11.0	DCE	120 ± 2 (93 ± 1)	3	trace	38	53
13	2.5	9.0	DCE	120 ± 2 (93 ± 1)	2	trace	42	50
14	2.5	9.0	DCE	120 ± 2 (93 ± 1)	4	trace	36	56

[a] Reactions were carried out with **2d** (2.07 g, 10 mmol, 1.0 equiv) and 10 mL of refluxing solvent. Trace 5-*tert*-butylbenzoxazole (**7d**) was obtained unless otherwise noted. [b] Oil bath temperature. [c] Inner temperature. [d] Isolated yields. [e] Based on the assumption that one molecular **5d** consumes two molecular **2d**. [f] 20% **7d** was obtained. [g] 10% **7d** was obtained.

SCHEME 4. Vilsmeier Reaction of 2h and 2i



an electron-donating group on the 4-position is much higher than that with an electron-withdrawing one. However, it should be noted that when the substituent group is phenyl, the yield of 8-phenyl-2-formylpyrido[2,1-*b*]benzoxazole (**5g**) is 2% (entry 11, Table 2), which is even lower than the corresponding chloride (10%) (entry 6, Table 2) under the same conditions.

To further determine its scope and limitations, the reaction was then examined by changing the hydroxyl group of the substrates **2**. Thus, *N*-(2-aminophenyl)acetamide (**2h**) and *N*-(2-mercaptophenyl)acetamide (**2i**) were subjected to DMF (2.5 equiv)/$POCl_3$ (7 equiv) in DCE at 120 °C for 3 h (Scheme 4). Unfortunately, the corresponding 2-formylpyrido[2,1-*b*]benzimidazole had not been detected when **2h** was used as a substrate, and the main product was 2-methylbenzimidazole (**3h**). Only trace 2-formylpyrido[2,1-*b*]benzothiazole (**5i**) was obtained when **2i** was used.

Synthesis of 4-Formylpyrido[2,1-*b*]benzoxazoles. In 1979, Kato et al. described a convenient approach to ethyl pyrido-[2,1-*b*]benzoxazole-4-carboxylate by refluxing ethyl 2-(benzoxazol-2′-yl)-3-dimethylaminoacrylate in acetic anhydride.[3] Previously, we have demonstrated that 4-formylpyrido[2,1-*b*]-benzoxazole (**6a**) can also be synthesized by using this method starting from 2-(benzoxazol-2′-yl)-3-dimethylaminoacrolein (**4a**). During the course of optimizing the conditions for the Vilsmeier reaction of **2d**, we found that 2-(benzoxazol-2′-yl)-3-dimethylaminoacrolein (**4d**) could be prepared in high yield by reacting **2d** with Vilsmeier reagent in either DMF or DCE (entries 4 and 8, Table 1). Thus, various 2-(benzoxazol-2′-yl)-3-dimethylaminoacroleins (**4**) were prepared and subjected to cyclization, and 4-formylpyrido[2,1-*b*]benzoxazoles (**6**) bearing different substituents on the 8-position were obtained, as listed in Table 3. The results that the yields of the cyclization products with an electron-donating group are higher than that with an electron-withdrawing one is in good agreement with the initial electrophilic addition of an acetyl group onto the nitrogen of imine.[3]

Mechanisitic Consideration. Just as Chandramohan's report that *o*-acetaminophenol **2a** cyclized to 2-methylbenzoxazole (**3a**)

SCHEME 5. Synthesis and Vilsmeier Reaction of 2-Methylbenzoxazole (3a)

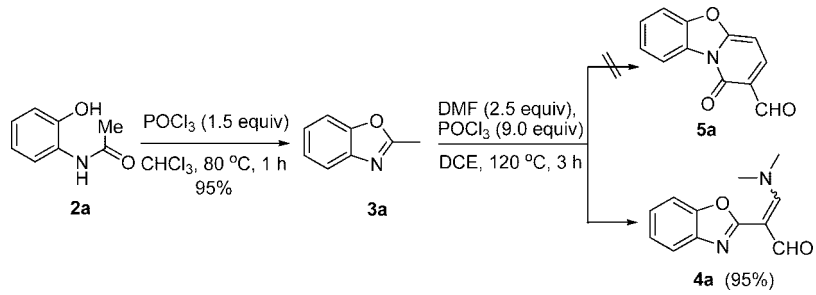
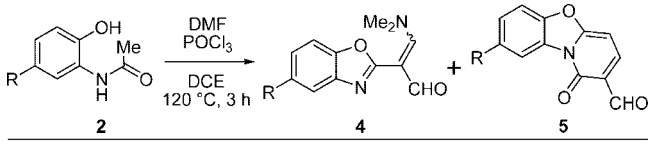


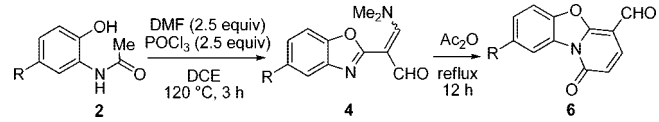
TABLE 2. Synthesis of 2-Formylpyrido[2,1-*b*]benzoxazoles (5)[a]



entry	substrate **2**	R	yield[b] (%) **4**		**5**[c]	
1[d]	**2a**	H	**4a**	52	**5a**	20
2[d]	**2b**	Cl	**4b**	40	**5b**	26
3[d]	**2c**	Me	**4c**	40	**5c**	46
4[d]	**2d**	*t*-Bu	**4d**	36	**5d**	58
5[e]	**2a**	H	**4a**	48	**5a**	30
6[e]	**2b**	Cl	**4b**	58	**5b**	10
7[e]	**2c**	Me	**4c**	42	**5c**	40
8[e]	**2d**	*t*-Bu	**4d**	38	**5d**	54
9[e]	**2e**	NO_2	**4e**	90	**5e**	0
10[e]	**2f**	OMe	**4f**		**5f**	64
11[e,f]	**2g**	Ph	**4g**	30	**5g**	2

[a] Trace 2-methylbenzoxazoles (**3**) were also obtained. [b] Isolated yields. [c] Based on the assumption that one molecular **5** consumes two molecular **2**. [d] DMF (2.5 equiv), $POCl_3$ (9.0 equiv), DCE, 120 °C, 3 h. [e] DMF (2.5 equiv), $POCl_3$ (7.0 equiv), DCE, 120 °C, 3 h. [f] 5-Phenylbenzoxazole (**7g**) was obtained in 17% yield.

TABLE 3. Synthesis of 4-Formylpyrido[2,1-*b*]benzoxazoles (6)



entry	substrate	R	yield[a] (%) **4**		**6**		total
1	**2a**	H	**4a**	93	**6a**	61	57
2	**2b**	Cl	**4b**	91	**6b**	53	48
3	**2c**	Me	**4c**	92	**6c**	67	62
4	**2d**	*t*-Bu	**4d**	93	**6d**	73	68
5	**2e**	NO_2	**4e**	93	**6e**	32	30
6	**2g**	Ph	**4g**	92	**6g**	64	59

[a] Isolated yield.

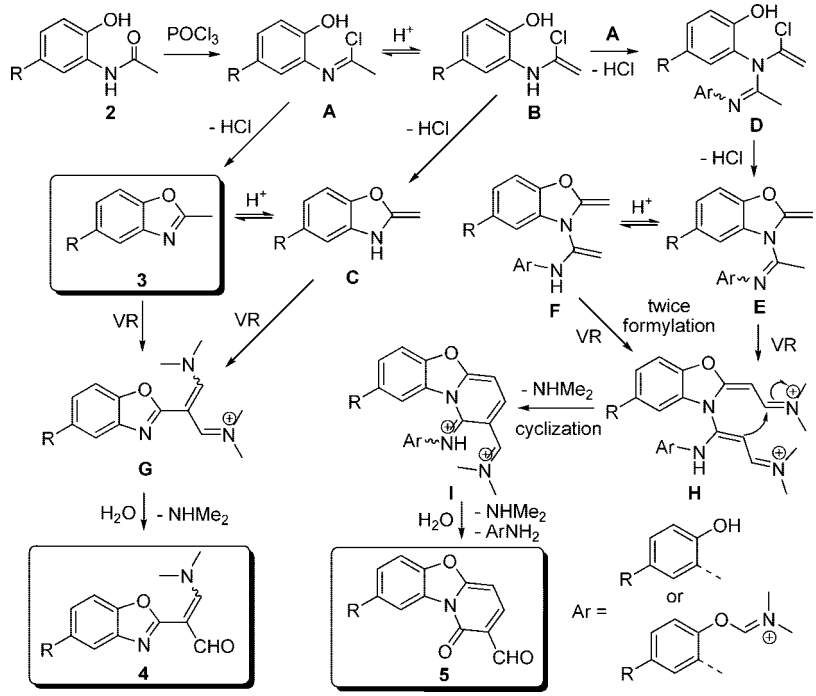
in situ under Vilsmeier conditions,[19] 2-methylbenzoxazoles were also obtained under Vilsmeier−Meth-Cohn conditions (Tables 1 and 2). Under optimized conditions, **3a** can be prepared in 95% yield by refluxing **2a** with 1.5 equiv of $POCl_3$ in chloroform. Importantly, when **3a** was used as a substrate under the above optimized Vilsmeier−Meth-Cohn conditions, no 2-formylpyrido[2,1-*b*]benzoxazole (**5a**) was formed; only **4a** was produced in 95% yield (Scheme 5). Apparently, the mechanism of the formation of **4a** under Vilsmeier−Meth-Cohn conditions is identical to that reported in literature.[19]

Considering that there are four more carbon atoms in 2-formylpyrido[2,1-*b*]benzoxazoles **5** than the starting material *o*-acetaminophenols **2**, and it is almost hard to believe that all of the four connected carbon atoms derive from Vilsmeier reagent, we presumed that part of these carbon atoms came from another molecular **2**. In other words, the formation of one molecular **5** needs 2 equiv of the starting material **2** (as noted as footnote *e* in Table 1 and footnote *c* in Table 2). It is worth noting that dimerization was previously observed and described in Meth-Cohn quinoline synthesis when 2-methoxyacetanilide was used as a substrate.[23]Taking into account that the reaction conditions under which **5** were formed are nearly identical to those of Meth-Cohn quinoline synthesis and, moreover, the two reactions demonstrated a similar substituent effect, we suggest that the formation of **5** follows a similar mechanistic pathway to the Meth-Cohn quinoline synthesis.

On the basis of the above experimental results together with the related reports,[17d,19,23] a possible mechanism for the formation of **4** and **5** is proposed and depicted in Scheme 6. Initially, **2** is converted into imidoyl chloride **A** and enamine **B** by the action of hot $POCl_3$.[17d,23] Then, intramolecular elimination of HCl of **A** and **B** leads to the formation of **3** and **C**, respectively, which undergo formylation twice by Vilsmeier regent (VR) and finally hydrolysis to afford **4**. Simultaneously, imidoyl chloride **A** reacts with its tautomer enamine **B** to eliminate HCl intermolecularly, leading to the formation of a dimeric imidoyl chloride **D**, which sequentially undergoes intramolecular elimination of HCl to construct the oxazole ring, formylation twice, regioselective intramolecular nucleophilic cyclization to form the pyridone ring, and finally hydrolysis to afford **5**. However, it should be mentioned that the phenolic hydroxyl group on those intermediates (such as **E**, **F**, **H**, and **I**, etc.) during the formation of **5** might also be involved in this reaction, which can be formylated by the Vilsmeier reagent[24] and further undergo cyclization (for details, see Scheme 1 in the Supporting Information). As a result, in addition to **5**, the hydrolysis products of **I** are varied.

The two processes, i.e., intramolecular and intermolecular elimination of HCl of **A** and **B**, are competitive. When products derived from one process (namely **3** and **4**) increase, products derived from another process (**5**) decrease, which can be seen

SCHEME 6. Proposed Mechanisms for the Formation of 4 and 5



in Table 1. Electron-donating groups on the 4-position of *o*-acetaminophenols make the intermediate **B** more nucleophilic and thus more easily *N*-acylated by the imidoyl chloride **A** to produce enamidines **D**,[23] which finally leads to the formation of **5**. If the substituent is too large, such as phenyl, some of the intermediates formed during the formation of **5** would be too bulky to be stabilized, and then the process becomes difficult to proceed and the yields of **5** subsequently decrease. Similar to the Meth-Cohn quinoline synthesis,[17d] the presence of excess $POCl_3$ is essential to maintain a strong acid environment, which enables the acid-catalyzed imine−enamine tautomerism, such as **A** and **B**, **3** and **C**, **E** and **F**, and so on. Regioselectivity in cyclization of **H** to **I** might can be attributed to the fact that the nucleophilicity of enamine is higher than that of enol ether.

Conclusion

In summary, we have demonstrated a novel and simple synthesis of 2-formylpyrido[2,1-*b*]benzoxazoles via one-pot reaction of *o*-acetaminophenols with Vilsmeier reagents. Easy availability of the starting materials and ready modificability of the products make this protocol very attractive. On the other hand, 4-formylpyrido[2,1-*b*]benzoxazoles were synthesized in moderate to good yield from *o*-acetaminophenols via a two-step procedure. The formyl group present on both isomers opens up the possibility of carrying out a diverse range of functional group transformations, which may find great utility in further exploration.

Experimental Section

General Procedure for Preparation of the Starting Material *o*-Acetaminophenols (2). To a vigorously stirred suspension of *o*-aminophenols (**1**) (10 mmol, 1.0 equiv) in 10 mL of water was added dropwise 1.1 mL of acetic anhydride (11 mmol, 1.1 equiv), and stirring was continued for 30 min after the addition was complete. The mixture was filtered through a Buchner funnel, and the solid obtained was dried in vacuo. The crude product was used directly in the next step without further purification.

***o*-Acetaminophenol (2a):** yield 95% (1.43 g); white solid; mp 208.5−209.0 °C (lit.[25] mp 209 °C); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 8.66 (s, 1H, OH), 7.44 (bs, 1H, NH), 7.12−7.17 (m, 1H, ArH), 6.97−7.04 (m, 2H, ArH), 6.84−6.89 (m, 1H, ArH), 2.28 (s, 3H, CH_3); GCMS (EI, 70 eV) *m*/*z* 151 (M^+, 21), 133 ($M^+ - H_2O$, 7), 109 ($M^+ - CH_2CO$, 100), 80 (26), 63 (4), 53 (8), 43 (18).

General Procedure for Preparation of 2-Methylbenzoxazoles (3). To a 50 mL flask equipped with a condenser and an anhydrous $CaCl_2$ dried tube were added *o*-acetaminophenols (**2**) (10 mmol, 1.0 equiv), 1.38 mL of $POCl_3$ (15 mmol, 1.5 equiv), and 5 mL of chloroform, and the mixture was refluxed until the solid completely disappeared for ca. 1 h. After being cooled to room temperature, the reaction mixture was diluted with 10 mL of CH_2Cl_2, poured into 10 mL of ice−water followed by basification with 5 mol L^{-1} of aq NaOH to adjust the pH value of the solution to 8, and extracted with CH_2Cl_2 (10 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the corresponding crude product, which was purified by flash chromatography (silica gel, 300−400 mesh) using CH_2Cl_2 as eluent to give pure product.

2-Methylbenzoxazole (3a): yield 95% (1.26 g); yellow liquid;[26] ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.57 (dd, J = 6.6, 3.0 Hz, 1 H, ArH), 7.39 (dd, J = 6.0, 3.2 Hz, 1 H, ArH), 7.19−7.22 (m, 2 H, ArH), 2.56 (s, 3 H, CH_3); GCMS (EI, 70 eV) *m*/*z* 133 (M^+, 100), 104 (19), 92 (7), 78 (15), 63 (23), 51 (5), 38 (6).

General Procedure for the Vilsmeier Reaction of *o*-Acetaminophenols (2) in Hot $POCl_3$. To a 50 mL three-necked flask equipped with a thermometer, a condenser, and an anhydrous $CaCl_2$ dried tube were added 1.92 mL of DMF (25 mmol, 2.5 equiv) and 10 mL of DCE, and the mixture was cooled in an ice bath. $POCl_3$ (7.0 or 9.0 equiv) was added dropwise with stirring to

(23) Meth-Cohn, O.; Westwood, K. T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2089–2092.
(24) Morimura, S.; Horiuchi, H.; Murayama, K. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2189–2190.
(25) De Luca, L.; Giacomelli, G.; Porcheddu, A. *J. Org. Chem.* **2002**, *67*, 6272–6274.
(26) Schweizer, E. E.; Goff, S. D. *J. Org. Chem.* **1978**, *43*, 2972–2976.

maintain the temperature below 0 °C. To this solution was added *o*-acetaminophenols (**2**) (10 mmol, 1.0 equiv), and after 30 min, the solution was heated at 120 °C for 3 h. After being cooled to room temperature, the reaction mixture was diluted with 10 mL of CH_2Cl_2, poured into 10 mL of ice−water, followed by basification with 5 mol L^{-1} of aq NaOH to adjust the pH value of the solution to 8, and extracted with CH_2Cl_2 (30 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude product, which was purified by flash chromatography (silica gel, 300−400 mesh) using first CH_2Cl_2 as eluent to give 2-formylpyrido[2,1-*b*]benzoxazoles (**5**) and then ethyl acetate (containing 1% Et_3N) to give 2-(benzoxazol-2′-yl)-3-dimethylaminoacroleins (**4**).

2-(Benzoxazol-2′-yl)-3-dimethylaminoacrolein (4a): yield 48% (1.04 g); pale yellow crystal; mp 113.8−115.6 °C(lit.[19] mp 114−116 °C); UV−vis (CH_2Cl_2) λ_{max} (log ε) 288 (4.32), 331 (4.10) nm; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 9.57 (bs, 1 H, CHO), 7.81 (bs, 1 H, C*H*NMe_2), 7.67 (bs, 1 H, 4′-H), 7.50 (d, J = 4.4 Hz, 1 H, 7′-H), 7.28−7.30 (m, 2 H, 5′-H and 6′-H), 3.35 (bs, 3 H, NCH_3), 3.00 (bs, 3 H, NCH_3); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 187.43 (CHO), 155.72 (*C*$HN(CH_3)_2$), 150.26 (2′-C), 141.71 (7′*a*-C), 124.18 (5′-C and 6′-C), 119.19 (4′-C), 110.20 (7′-C), 47.89 (CH_3), 41.60 (CH_3); IR (KBr) 1658, 1618, 1601, 1562, 1454, 1404, 1281, 1242, 1188, 1117, 1086, 1007, 922, 812, 754 cm^{-1}; GCMS (EI, 70 eV) *m*/*z* 216 (M^+, 64), 199 (M^+ − OH, 9), 188 (M^+ − CO, 100), 173 (M^+ − NCH_3CH_2, 28), 160 (M^+ − CO − $2CH_2$, 13), 146 (M^+ − CO − NCH_2CH_2, 41), 144 (M^+ − CO − NCH_3CH_3, 33), 133 (M^+ − CO − $CNCH_2CH_3$, 42), 120 (12), 108 (10), 93 (14), 81 (89), 63 (19), 52 (7), 42 (31), 39 (13); HRMS (MALDI) calcd for $C_{12}H_{12}N_2O_2$ 216.0893, found 216.0892. Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.52; H, 5.61; N, 12.84.

2-Formylpyrido[2,1-*b*]benzoxazole (5a): yield 30% (320 mg); yellow crystal; mp 247.0−248.5 °C; UV−vis (CH_2Cl_2) λ_{max} (log ε) 226 (3.92), 255 (4.03), 379 (4.31), 388 (4.33) nm; ^{1}H NMR (400 MHz, DMSO-d_6, TMS) δ 10.15 (s, 1 H, CHO), 8.51 (dd, J = 7.8, 1.0 Hz, 1 H, 9-H), 8.27 (d, J = 8.4 Hz, 1 H, 3-H), 7.90 (d, J = 8.4 Hz, 1 H, 6-H), 7.65 (td, J = 8.0, 0.8 Hz, 1 H, 7-H), 7.60 (td, J = 8.0, 0.6 Hz, 1 H, 8-H), 6.78 (d, J = 8.4 Hz, 1 H, 4-H); ^{13}C NMR (100 MHz, DMSO-d_6, TMS) δ 187.09 (CHO), 158.93 (4*a*-C), 157.63 (1-C), 146.75 (3-C), 143.13 (5*a*-C), 127.60 (2-C), 126.79 (9*a*-C), 125.61 (7-C), 116.35 (9-C), 115.99 (8-C), 111.47 (6-C), 87.91 (4-C); IR (KBr) 2924, 1672 (CO), 1631, 1583, 1527, 1464, 1398, 1342, 1277, 1190, 1142, 1074, 768, 754 cm^{-1}; GCMS (EI, 70 eV) *m*/*z* 213 (M^+, 25), 185 (M^+ − CO, 90), 157 (M^+ − 2CO, 100), 129 (M^+ − 2CO − C_2H_4, 26), 102 (21), 73 (12), 63 (22), 51 (12), 39 (22); HRMS (MALDI) calcd for $C_{12}H_7NO_3$ 213.0420, found 213.0418. Anal. Calcd for $C_{12}H_7NO_3$: C, 67.61; H, 3.31; N, 6.57. Found: C, 67.71; H, 3.53; N, 6.46.

General Procedure for the Vilsmeier Reaction of *o*-Acetaminophenols (2) in DCE. To a 50 mL three-necked flask equipped with a thermometer, a condenser, and an anhydrous $CaCl_2$ dried tube were added 1.92 mL of DMF (25 mmol, 2.5 equiv) and 10 mL of DCE, and the mixture was cooled in an ice bath. $POCl_3$ (2.33 mL, 25 mmol, 2.5 equiv) was added dropwise with stirring to maintain the temperature below 0 °C. To this solution was added *o*-acetaminophenols (**2**) (10 mmol, 1.0 equiv), and after 30 min, the solution was heated at 120 °C for 3 h. After being cooled to room temperature, the reaction mixture was diluted with 10 mL of CH_2Cl_2, poured into 10 mL of ice−water, followed by basification with 5 mol L^{-1} of aq NaOH to adjust the pH value of the solution to 8, and extracted with CH_2Cl_2 (30 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude product, which was purified by flash chromatography (silica gel, 300−400 mesh) using ethyl acetate (containing 1% Et_3N) as eluent to give 2-(benzoxazol-2′-yl)-3-dimethylaminoacroleins (**4**).

General Procedure for Preparation of 4-Formylpyrido[2,1-*b*]-benzoxazoles (6). To a 50 mL flask equipped with a condenser and an anhydrous $CaCl_2$ dried tube were added 2-(benzoxazol-2′-yl)-3-dimethylaminoacroleins (**4**) (5 mmol) and 10 mL of acetic anhydride, and the mixture was refluxed with stirring for 12 h. After being cooled to room temperature, the reaction mixture was concentrated under reduced pressure to yield the crude product, which was purified by flash chromatography (silica gel, 300−400 mesh) using CH_2Cl_2 as eluent to give pure product.

4-Formylpyrido[2,1-*b*]benzoxazole (6a): yield 61% (650 mg); pale yellow crystal; mp 202.5−203.5 °C; UV−vis (CH_2Cl_2) λ_{max} (log ε) 230 (4.13), 300 (4.50), 327 (4.19), 343 (4.07) nm; ^{1}H NMR (400 MHz, DMSO-d_6, TMS) δ 10.01 (s, 1 H, CHO), 8.43 (dd, J = 8.0, 0.8 Hz, 1 H, 9-H), 8.07 (d, J = 9.2 Hz, 1 H, 3-H), 7.91 (d, J = 8.0 Hz, 1 H, 6-H), 7.64 (td, J = 8.0, 1.6 Hz, 1 H, 7-H), 7.57 (td, J = 8.0, 1.2 Hz, 1 H, 8-H), 6.39 (d, J = 9.6 Hz, 1 H, 2-H); ^{13}C NMR (100 MHz, DMSO-d_6, TMS) δ 182.90 (CHO), 158.87 (4*a*-C), 156.80 (1-C), 146.48 (5*a*-C), 138.18 (3-C), 127.52 (7-C), 126.19 (9*a*-C), 125.67 (8-C), 116.16 (9-C), 111.39 (2-C), 110.66 (6-C), 89.81 (4-C); IR (KBr) 1674 (CHO), 1658 (CON), 1604, 1533, 1462, 1419, 1371, 1284, 1246, 1196, 1111, 1080, 1030, 829, 760, 744 cm^{-1}; MS (EI, 70 eV) *m*/*z* 213 (M^+, 100), 185 (M^+ − CO, 11), 184 (M^+ − CHO, 14), 157 (M^+ − 2CO, 85), 129 (M^+ − 2CO − C_2H_4, 19), 102 (16), 78 (10), 63 (17), 51 (11), 39 (15); HRMS (MALDI) calcd for $C_{12}H_7NO_3$ 213.0420, found 213.0424. Anal. Calcd for $C_{12}H_7NO_3$: C, 67.61; H, 3.31; N, 6.57. Found: C, 67.49; H, 3.53; N, 6.41.

Acknowledgment. We are grateful for financial support from the National Natural Science Foundation of China (Nos. 20272076, 20772146, and D20032010). We also thank Associate Professor J. Sun for the resolution of the X-ray crystal structures.

Supporting Information Available: Experimental details, spectral characterization data for **2**−**6**, NMR spectra copies of **5** and **6**, and MS and IR spectra as well as crystallographic data for **5a** and **6a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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