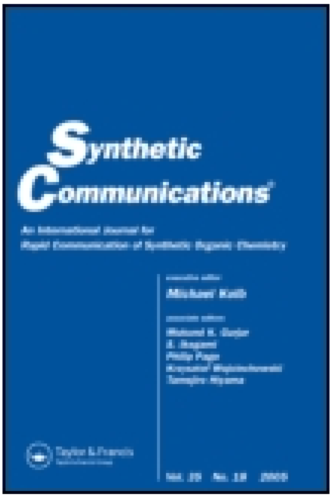

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Oxidative Nuclear Bromination of Substituted 4-Pyridones Using Pyridinium Bromochromate

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OXIDATIVE NUCLEAR BROMINATION OF SUBSTITUTED 4-PYRIDONES USING PYRIDINIUM BROMOCHROMATE

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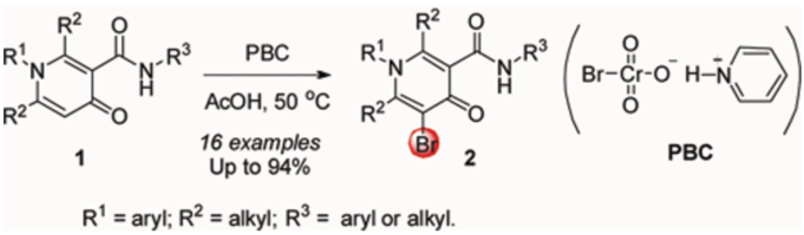
GRAPHICAL ABSTRACT



Abstract *An alternative convenient approach for the bromination of various poly-substituted 4-pyridones has been developed via an oxidative nuclear bromination in the presence of sole pyridinium bromochromate (PBC). The PBC performs the dual role of oxidant and source of* Br^+ *during the process.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

Keywords Bromopyridone; oxidative bromination; oxidative nuclear bromination (ONB); pyridinium bromochromate (PBC); 4-pyridone

INTRODUCTION

Oxidative nuclear halogenation (ONH), essentially subordinate to electrophilic halogenation,[1] is an effective tool to introduce the source of halogens into a variety of organic molecules and thence to many useful halogenated chemical products. Generally, the ONH should be carried out in the presence of oxidant and halogenated

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reagents, and in the process, the halogen cation is generated in situ from halide anions in the presence of oxidant.[2] Oxidative nuclear bromination (ONB), the most commonly used oxidative halogenation, has drawn much attention to the oxidative bromination of aromatic molecules. To date, various methods have been developed using metal bromide salts or an acid in combination with oxidizing agents, including KBr–H_2O_2–$(NH_4)_6Mo_7O_{24} \cdot 4H_2O$,[3] KBr–$NaBO_3 \cdot 4H_2O$,[4] ^{t}BuOBr–zeolite,[5] KBr/LiBr–$(NH_4)_2Ce(NO_3)_6$,[6] NaBr–oxone,[7] and HBr–H_2O_2/^{t}BuOOH.[8] However, the ONB using single bromo reagents, such as PBC, as both the source of Br^+ and an oxidant is relatively rare.[9] A few examples have so far focused on the ONB[3,4,6b,7,10] in the presence of PBC,[11] especially the NBO of aromatic molecules. In 2003, Patwari et al. reported the use of PBC as a *ortho*-selective brominating agent for the phenol compounds.[11a] Yazdanbakhsh and coworkers also successfully achieved γ-picolinium bromochromate (γ-PBC) as a mild, efficient, and highly *para*-selective oxidative mono-brominating reagent for the bromination of substituted aromatic compounds in 2003.[11b] In their cases, the hydroxy or amino group was a necessary part of the aromatic molecules. Using PBC as the brominating reagent was done by Sarrafi's group in 2009. They found that PBC was a highly efficient and selective brominating reagent for the α-monobromination of 1,3-diketones and β-keto-esters in the absence of base, Lewis acid, or other catalysts. In short reaction times, the products could be isolated in good to excellent yields under mild reaction conditions.[11c] Herein, we report our recent efforts on a new and efficient ONB of multiple-substituted 4-pyrindones in the presence of only PBC.

RESULTS AND DISCUSSION

At present, a number of reports[12] and patents[13] reported the bromination of 4-pyridones because they have been identified to have antimalarial activity[12a] and anti-inflammatory activity.[12b] Besides, they are also important intermediates in the synthesis of pharmaceutical molecules (Fig. 1).[12c–e] Commonly, the bromopyridones could be obtained by treating the pyridones with a bromine-containing agent

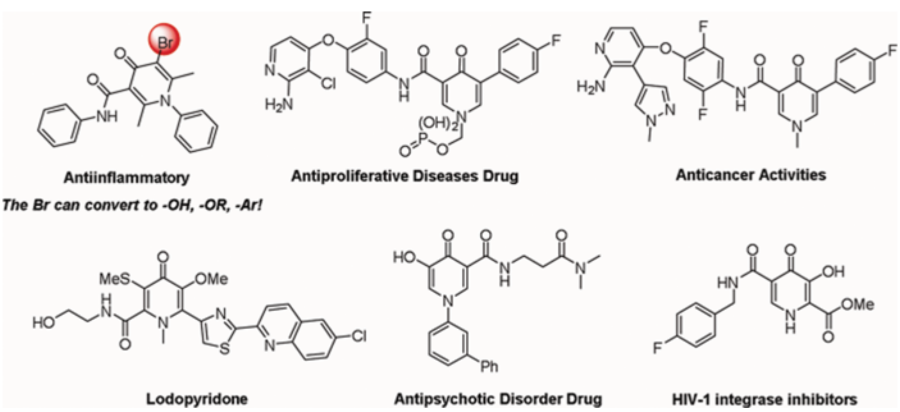
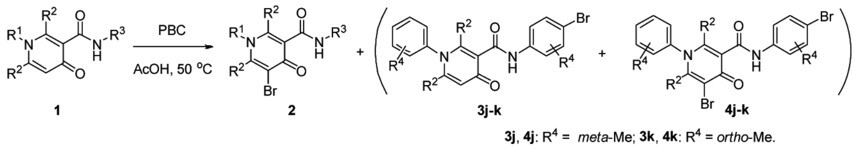


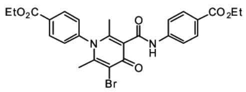
Figure 1. Representative pharmaceutically active molecules partially can be synthesized by bromopyridones. (Figure is provided in color online.)

such as bromine or NBS. Some of these protocols suffered from some poignant drawbacks, such as harsh reaction conditions (high temperature, corrosive, toxic, strong acidity, or basic conditions), unpredictable yields, and poor regioselectivity. Very recently, combined with our research on acetoacetamides in recent years,[14] we successfully achieved a convenient one-pot process for the synthesis of a variety of biologically potent polysubstituted 4-pyridones via a self-condensation of acetoacetamides in the presence of only $Na_2S_2O_8$.[15] We are interested in their bromination at the 5-position because of its importance in the synthesis of some useful drugs (Fig. 1).[16,17] We used ethyl 4-(1-(4-(ethoxycarbonyl)phenyl)-2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxamido)benzoate **1a** as a model for the bromination. After many attempts, we found that ethyl 4-(5-bromo-1-(4-(ethoxycarbonyl)phenyl)-2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxamido)benzoate **2a** could be finally obtained up to 94% by treating **1a** (0.2 mmol) with PBC (1.1 equiv.) in AcOH (1.0 mL) at 50 °C after 3.0 h. If the reaction was performed at a lower temperature (such as room temperature), the reactant could not be completely consumed, even if we prolonged the reaction times, and the same situation occurred in the absence of acetate in CH_2Cl_2 at reflux.

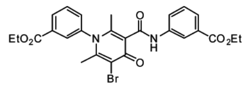
Consequently, we tested the universality of the bromination of 4-pyrindones (Table 1). Notably a variety of substituted 4-pyridones **1a**–**1p** could be easily converted into the corresponding bromopyridones **2a–2p** in the yield of 11–94% in 6.0 h. Various electron-withdrawing groups (EWG) (Cl, COOEt; compounds **2a**–**2f**) and electron-donating groups (EDG) (Me, OMe, OEt; Table 1, compounds **2g**–**2k**) on the aryl group were tolerated in the current transformation. For EDG, the position of the substituents on the aryl group (*para*-, *meta*-, and *ortho*- position) affected the reaction dramatically. *N*-(4-Methylphenyl)pyridine derivative **1i** gave the desired product **2i** in the yield of 76%. When **1j** was used, under the optimization conditions, the reaction was fully disordered and gave 0% **2j**, 76% *N*-(4-bromo-3-methylphenyl)-2,6-dimethyl-4-oxo-1-(*m*-tolyl)-1,4-dihydropyridine-3-carboxamide **3j**, and 14% 5-bromo-*N*-(4-bromo-3-methylphenyl)-2,6-dimethyl-4-oxo-1-(*m*-tolyl)-1,4-dihydropyridine-3-carboxamide **4j** respectively. When the reaction was carried out with **1k**, the mono-brominated product **2k** was obtained in the yield of only 11% along with 47% **3k**, 23% **4k**, and 12% **1k**.[3,6b,7b] Even if the reaction was performed at −10 °C in 1.0 mL CH_2Cl_2, it gave the sole product **3k** in 52% and 45% **1k** was recovered. These results suggested that the reactivity of the phenyl group with EDG on the *meta*- or *ortho*- position in the amide moiety is a little higher than the 4-pyridone ring. A convincing proof for the dibromination occurring on the phenyl of amide moiety rather than on the phenyl of the benzene-pyridone was that we got the only product 5-bromo-2,6-dimethyl-4-oxo-1-(*m*-tolyl)-1,4-dihydropyridine-3-carboxylic acid **5j** via acidic hydrolysis of **4j**. Additionally, **1m** and **1n** were also accepted, thus leading to **2m** and **2n** in the yields of 60% and 91%. While some unidentified complex mixture was generated simultaneously, this made the yield of **2m** slightly less than **2n** and the reaction times also were extended to 6.0 h. For **1o** and **1p**, it showed satisfied efficiency because the bromopyridones **2o** and **2p** were obtained in good yields (83% and 76%, respectively). It is noteworthy that in all tested cases, except **1j** and **1k** where gave the by-products of brominated-4-pyridones **3** and **4**, we did not get any other side-chain *ortho*- or *meta*-brominated by-products,[6b,7b,10a,11a,18] which indicates a strong regioselectivity for the current bromination.

Table 1. ONB of 4-pyridones 1[a,b]

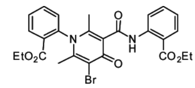




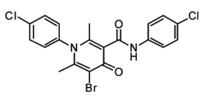
2a: 3.0 h, 94%



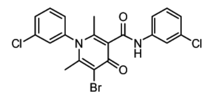
2b: 1.5 h, 89%



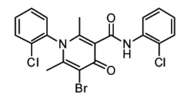
2c: 3.5 h, 91%



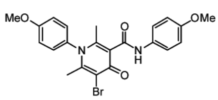
2d: 0.5 h, 84%



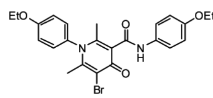
2e: 1.0 h, 78%



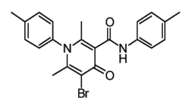
2f: 6.0 h, 73%



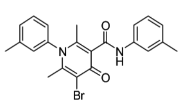
2g: 1.0 h, 87%



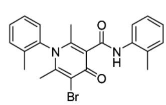
2h: 1.0 h, 80%



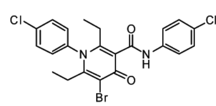
2i: 2.0 h, 76%



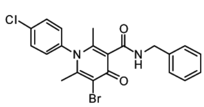
2j: 4.0 h, 0 %[c]



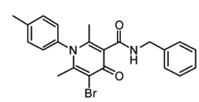
2k: 4.0 h, 11 %[d]



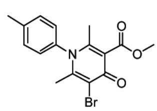
2l: 2.5 h, 88%



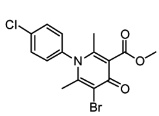
2m: 6.0 h, 60%



2n: 1.5 h, 91%



2o: 1.0 h, 83%



2p: 0.5 h, 76%

[a] All reactions were carried out with **1** (0.2 mmol) and PBC (1.1 equiv.) in AcOH (1.0 mL) at 50 °C in an oil bath.
[b] Isolated yield.
[c] 76% **3j** and 14% **4j** were obtained, and 10% **1j** was recovered.
[d] 47% **3k** and 23% **4k** were obtained, and 12% **1k** was recovered.

EXPERIMENTAL

All reagents were purchased from commercial sources and used without further treatment, unless otherwise indicated. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz at 25 °C) and tetramethylsilane (TMS) was internal standard. Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet), with coupling constants in hertz (Hz). All high-resolution mass spectras (HRMS) were measured on a Bruker MicroTOF mass spectrometer (ESI-oa-TOF). Melting points were measured on a YuHua X-5 apparatus.

Typical Experimental Procedure for the Synthesis of Bromopyridones 2

Multiple-substituted 4-pyrindone derivatives **1** (0.2 mmol), PBC (1.1 equiv.) and AcOH (1.0 mL) were added to a round-bottom flask (25 mL) and then the mixture was well stirred at 50 °C in oil bath. After cooling off, the reaction mixture was poured into 0 °C water (100 mL) and stirred vigorously for 3.0 h when thin-layer chromatography (TLC) monitor **1** was completely consumed or the color of the reaction turned from brown to light green. This suspension was filtered and washed with water (5.0 mL × 3), and then the filter cake was dried under reduced pressure at 40 °C to afford the final product bromopyridones **2**.

Selected Data for 2a

White solid. mp: 212–215 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.62 (s, 1H), 8.31 (d, J = 8.0 Hz, 2H), 8.01 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 4.46 (q, J = 7.2 Hz, 2H), 4.35 (q, J = 7.2 Hz, 2H), 2.49 (s, 3H), 2.26 (s, 3H), 1.44 (t, J = 7.2 Hz, 3H), 1.39 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.30, 165.29, 164.70, 164.29, 147.74, 146.96, 143.33, 143.20, 131.30, 131.09, 130.24, 128.93, 124.48, 123.09, 118.71, 116.24, 61.31, 60.48, 22.44, 19.07, 14.22, 14.11. HRMS (ESI) m/z calcd. for $C_{26}H_{25}BrN_2O_6$ ($[M + Na]^+$): 563.0788, found: 563.0796.

CONCLUSION

In conclusion, an alternative convenient approach for the ONB of poly-substituted 4-pyridone derivatives was successfully achieved with sole PBC in AcOH. The PBC acted as the dual role of oxidant and source of Br^+ during the process. The absence of side-chain brominated products in the vast majority of instances in the reactions suggested the essential effectiveness of the current bromination. All products were constructed efficiently from the readily available 4-pyridones.[15] Furthermore, the synthesized series of bromopyridones **2** could be used as versatile building blocks to construct more useful pharmaceutically active molecules.[12c,12e]

SUPPORTING INFORMATION

Full experimental detail, ^{1}H and ^{13}C NMR spectra, and HRMS can be found via the Supplementary Content section of this article's Web page.

ACKNOWLEDGMENTS

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