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Short Communication

Novel synthetic approach to fluoro- and amido-disubstituted 3-hydroxypyridin-4-ones

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ABSTRACT

Starting from fluoropyridines as a building block, with chelating functional groups being introduced, several fluoro- and amido-disubstituted 3-hydroxypyridin-4-ones have been synthesized with the intention of improving the pharmaceutical profile of 3-hydroxypyridin-4-ones.

1. Introduction

3-Hydroxypyridin-4-ones (HPOs) are currently one of the main candidates for the development of orally active iron chelators [1]. They are also one of the two general classes of molecules having been reported to possess potential for the treatment of neurodegenerative diseases [2]. Dimethyl-3-hydroxypyridin-4-one (deferiprone) has been used clinically as an orally active iron chelator for treating transfusion-induced iron overload for over a period of 20 years [3]. It has been reported to be effective and safe in the reversal of oxidative stress in the neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD) and Friedreich's ataxia (FA) [4–6]. The efficacy of deferiprone is limited by extensive metabolism in the liver and therefore a relatively high dose is required to maintain iron overloaded patients in negative iron balance [7]. In addition, deferiprone is not particularly efficient at crossing the blood–brain barrier [8].

An introduction of fluorine into an organic molecule can significantly improve the chemical and biological properties, such as its metabolic stability, bioavailability, selective reactivity and receptor binding interactions [9]. In fact, the role of fluorine in drug design has been frequently reviewed [10–12]. It is clear that fluorine plays an increasingly important role in the design of pharmaceuticals.

Many synthetic methods to introduce a fluorine atom directly into the pyridine-4-one ring have been attempted but all have failed [13]. Schlosser's group has reported that fluoropyridines can be readily and site selectively metalated by using different lithium reagents. Subsequent reaction with a suitable electrophile achieves the target product [14,15]. This approach subverts our conventional approach and has directed us to redesign synthetic pathways of fluorinated 3-hydroxypyridin-4-ones. It is possible to obtain the target products by starting with a fluorine-containing precursor and then introducing chelating functional groups. As an introduction of an electron-withdrawing group on the pyridinone ring can decrease pK_a value of the 3-pyridinone oxygen atom and correspondingly result enhanced metal stability constant [16,17], we would like to report fluorinated HPOs in this present paper which contain another functional group, the amido group, in order to enhance the pFe^{3+} value and possibly also the metabolic stability of the ligands [16,18].

2. Results and discussion

The novel synthetic route to 2-fluoro-5-amido substituted 3-hydroxypyridin-4-one is summarized in Scheme 1. It starts from the commercially available 2-fluoropyridine (**1**). Due to the strong inductive effect of fluorine atom at C2, the starting material

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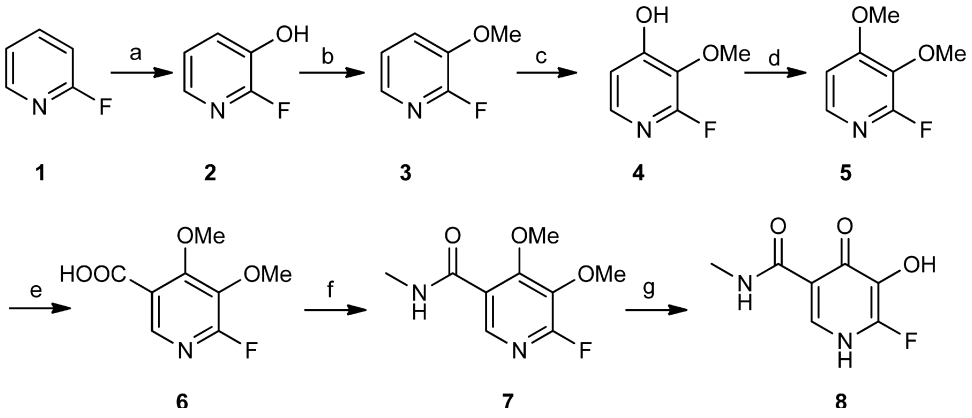
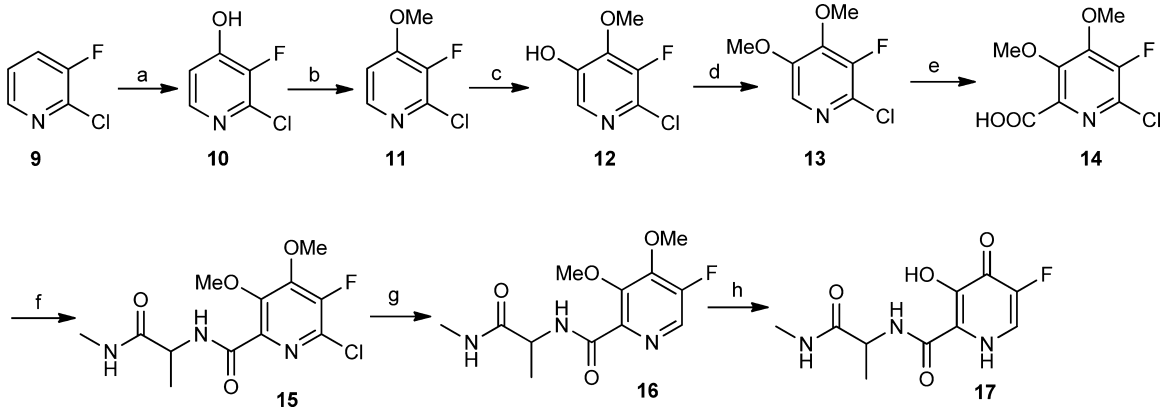


Scheme 1. Synthesis of 2-fluoro-5-amido substituted 3-hydroxypyridin-4-one. (a) (1) LDA, THF, −75 °C, 2 h, (2) $B(OMe)_3$, −75 °C, 2 h, (3) CH_3CO_3H, 0 °C, 1 h, 92%; (b) K_2CO_3/MeI/acetone, reflux overnight, 95%; (c) (1) LTMP, THF, −75 °C, 20 h; (2) $B(OMe)_3$, −75 °C, 2 h, (3) CH_3CO_3H, 0 °C, 1 h, 87%; (d) K_2CO_3/MeI/acetone, reflux overnight, 40%; (e) (1) LTMP, THF, −75 °C, 20 h; (2) dry ice, thaw to r.t., 87%; (f) DCC/NHS/$MeNH_2$, r.t., overnight, 67%; (g) BBr_3, 0 °C to r.t., overnight, 70%.

undergoes lithiation at the *ortho*-position (C3) by lithium diisopripylamide (LDA). The lithiated fluoropyridine was trapped with trimethylborate, followed by *in situ* reaction with peracetic acid to afford 2-fluoro-3-hydroxypyridine (**2**). The hydroxy group of compound **2** needs to be protected before lithiation and a simple methyl group was introduced by reacting compound **2** with methyl iodide in the presence of potassium carbonate. When we attempted to lithiate compound **3** using LDA, no product was isolated. This may be due to the relatively weaker inductive effect of methoxy group at *ortho*-position (C3) as compared to that of the fluorine atom. Therefore, a stronger metalation reagent lithium 2,2,6,6-tetramethylpiperidide (LTMP) was investigated. The resulting lithiated intermediate was again trapped with trimethylborate and oxidized by peracetic acid to afford 2-fluoro-4-hydroxy-3-methoxypyridine (**4**). Compound **4** can react with MeI/K_2CO_3 to afford two isomers due to its two resonance forms. To minimize the formation of the N-methyl isomer, polar solvents such as methanol were avoided as they favor polar products. When compound **5** was lithiated with LTMP, the lithiation only occurs at C5, due to neighboring group assistance. The resulting lithiating intermediate was trapped with dry ice to afford 5-carboxy-3,4-dimethoxy-2-fluoropyridine (**6**). The carboxyl group of compound **6** was activated with dicyclohexylcarbodiimide (DCC)/N-hydroxy succinimide (NHS), followed by coupling with methylamine to afford compound **7**. The methyl protecting group was then readily removed using BBr_3 to form the corresponding target iron chelator **8**.

The synthesis of 2-amido-5-fluoro substituted 3-hydroxypyridin-4-one is outlined in Scheme 2. Although 3-fluoropyridine is commercial available, the lithiation of 3-fluoropyridine derivatives readily occurs at C2 due to the neighboring fluorine effect. To avoid this, 2-chloro-3-fluoropyridine (**9**) was selected as a building block, where C2 is blocked by chlorine. A similar procedure as that outlined in Scheme 1 led to the formation of 2-chloro-3-fluoro-4-hydroxypyridine (**10**). Subsequent to the conversion of the hydroxyl function to the methoxy group, another hydroxyl group was introduced at C5, adjacent to the 4-methoxy group. To obtain compound **14**, the 5-hydroxy group of compound **12** required protection. The resulting compound **13** was lithiated at C6 and trapped with dry ice. The carboxy group of compound **14** is readily converted to amido group by activation with DCC/NHS followed by amine coupling. To remove the 6-chloro group of compound **15**, hydrogenation in the presence of Pd/C was adopted to afford **16** in quantitative yield. This procedure does not influence the methoxy groups which were readily removed by BBr_3 to obtain the target product **17**.

In comparison with the 1-nonsubstituted HPOs, an introduction of alkyl group at N1 can dramatically influence its physiochemical properties such as pK_as and iron affinity constants [18]. To introduce an additional alkyl group at N1 of the 2-amido-5-fluoro substituted HPOs, compound **16′** was reacted with ethyl iodide in acetone overnight to afford 1-ethyl substituted compound **18** (Scheme 3). The phenomenon may be explained by a mechanism which involves the production of an intermediate 1-alkyl



Scheme 2. Synthesis of 2-amido-5-fluoro substituted 3-hydroxypyridin-4-one. (a) (1) LDA, THF, −75 °C, 2 h, (2) $B(OMe)_3$, −75 °C, 2 h, (3) CH_3CO_3H, 0 °C, 1 h, 80%; (b) K_2CO_3/MeI/acetone, reflux overnight, 52%; (c) (1) LTMP, THF, −75 °C, 20 h; (2) $B(OMe)_3$, −75 °C, 2 h, (3) CH_3CO_3H, 0 °C, 1 h, 96%; (d) K_2CO_3/MeI/acetone, reflux overnight, 97%; (e) (1) LTMP, THF, −75 °C, 20 h; (2) dry ice, thaw to r.t., 89%; (f) DCC/NHS/$MeNHCOCH(Me)NH_2$, r.t., overnight, 58%; (g) Pd/H_2/Et_3N, 85%; (h) BBr_3, 0 °C to r.t., overnight, 63%.