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Catalyst-Free Friedel-Crafts Hydroxyalkylation of Imidazo[1,2-α]pyridines with Ethyl Trifluoropyruvate

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A catalyst free Friedel-Crafts (F-C) hydroxyalkylation of imidazo[1,2-α]pyridines with ethyl trifluoropyruvate is herein described using isopropyl ether as a solvent. Electron-donating and electron-withdrawing functional groups at various aromatics positions were well tolerated under our optimized conditions. The method enabled the generation of desired products in moderate to excellent yields under mild conditions, which makes this transformation an attractive, environmentally benign alternative for the synthesis of the target compounds.

Imidazo[1,2-α]pyridine and its derivatives have attracted much attention recently owing to their biological activities[1] such as antiviral[2], anti-inflammatory[3], Anti-tuberculosis[4], antiulcer[5], and antibacterial[6] properties. Remarkable developments have been made on the synthesis of imidazo[1,2-α]pyridine derivatives[7], making a wide range of drugs, including alpidem, olprinone, minodronic acid, zolimidine, necopidem, saripidem and zolpidem, more commercially available (**Figure 1**).

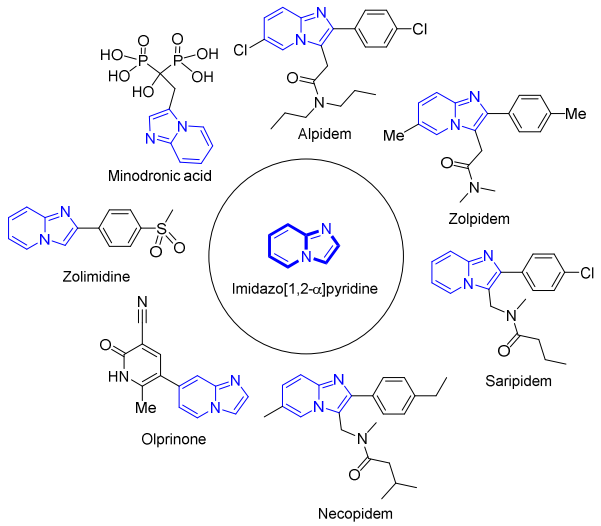
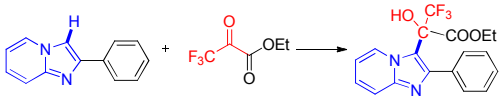


Figure 1. Examples of drugs containing the imidazo[1,2-α]pyridine system.

Fluorinated molecules have the ability to modulate biological functions.[8] The introduction of trifluoromethyl group into drug molecules can bring alteration of their metabolic stability, and

bioavailability.[9] To the best of our knowledge, only a few natural compounds contain fluorine atoms. Despite fluorine atom containing natural products have been reported, compounds with trifluoromethyl group (CF_3) were less investigated. In this regard, state-of-the-art researches have been dedicated to the development of efficient synthesis of CF_3 containing drugs.[10] Using trifluoropyruvates as building block is an appealing route for the trifluoromethylation because no prefunctionalization is required.[11] For examples, Mikami and co-workers reported a catalytic [2+2] cycloaddition of alkyne and trifluoropyruvate for the synthesis of stable oxetenes.[12] Li etc. showed a general and efficient method for the direct alkynylation of trifluoropyruvate and trifluoroacetophenone, which is simple and provides diverse CF_3-substituted tertiary propargyl alcohols in high yields.[13] F-C alkylation of the aromatic and heterocyclic compounds is one of the most important C-C bond-formation reactions.[14] However, the use of Lewis and Brønsted acids generates a large amounts of environmentally toxic waste. To overcome this limitation, catalyst-free F-C hydroxyalkylation reaction has emerged as an alternative strategy with atom economy and environmental benignity. Török and coworkers firstly reported the catalyst-free hydroxyalkylation of indoles with ethyl trifluoropyruvate.[15] Following previous work, the Shibata group introduced environmentally benign solvent Solkane@365mfc as a medium for the F-C reaction.[16] Despite the success of previous work, the development of catalyst-free F-C hydroxyalkylation reaction with improved efficiency is still a long-standing scientific challenge. Herein, we firstly report the high efficiency of catalyst-free F-C hydroxyalkylation of imidazo[1,2-α]pyridines with ethyl trifluoropyruvate in isopropyl ether.

Table 1. Optimization of the reaction conditions.



1a **2a** **3aa**

Entry	Solvent	Time (h)	Yield[a] (%)
1	DCM (2 mL)	24	27
2	DCE (2 mL)	24	62
3	Et_2O (2 mL)	24	84
4	Toluene (2 mL)	24	98
5	Isopropyl ether (2 mL)	24	99
6[b]	Isopropyl ether (2 mL)	24	87
7[c]	Isopropyl ether (2 mL)	24	73
8[d]	Isopropyl ether (2 mL)	24	94
9	Isopropyl ether (1 mL)	24	99
10	Isopropyl ether (1 mL)	10	99
11	Isopropyl ether (1 mL)	8	98
12	Isopropyl ether (1 mL)	6	84

Reaction conditions: Imidazo[1,2-α]pyridines (0.10 mmol), Ethyl trifluoropyruvate (0.20 mmol), room temperature (about 15 °C), Ar atmosphere. [a]Isolated yields. [b]Ethyl trifluoropyruvate (0.15 mmol). [c]Ethyl trifluoropyruvate (0.12 mmol). [d] under air.

In order to screen the optimized conditions, the F-C hydroxyalkyltion of 2-phenylimidazo[1,2-α]pyridine (**1a**) with ethyl trifluoropyruvate (**2a**) was selected as the model reaction under standard condition (**Table 1)**. The desired product **3aa** was isolated in 27% yield at room temperature in dichloromethane (DCM) under Ar for 24 h, and the ratio of **1a/2a** is 1.0/2.0 (**Table 1**, entry 1). Further optimization showed that **3aa** could be obtained in moderate to excellent yields when the solvents 1,2-dichloroethane (DCE), diethyl ether (Et_2O), toluene and isopropyl ether were examined instead (**Table 1**, entries 2 - 5), which highlights the significant influence of solvent on the reaction. When the loading of **2a** decreased to 1.5 equiv. and 1.2 equiv., the yields of **3aa** were reduced to 87% and 73%, respectively (**Table 1**, entries 6 - 7). To access the potential for practical applications, we proceeded the reaction under air condition. To our delightful surprise, the product **3aa** was isolated in 94% yield (**Table 1**, entry 8). It is also noteworthy that **3aa** could be obtained in high yields with shorter reaction time. For example, conversions of 99%, 98% and 84% were observed after 10 h, 8 h and 6 h reaction time (**Table 1**, entries 10 - 12). Under the optimized conditions, we were able to synthesize **3aa** in gram-scale in 98 % yield. The product **3aa** was further confirmed by X-ray diffraction (XRD) (**Figure 2**).

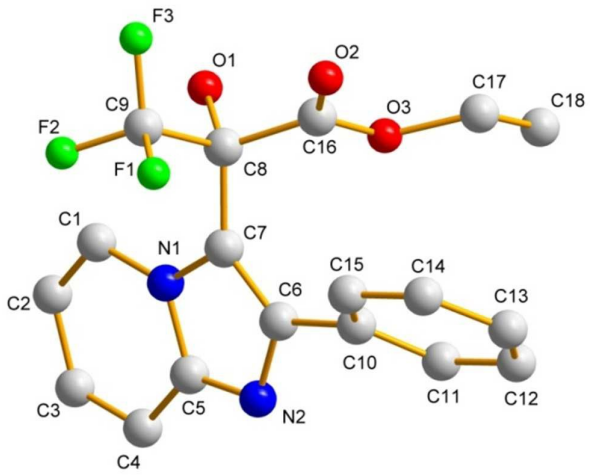
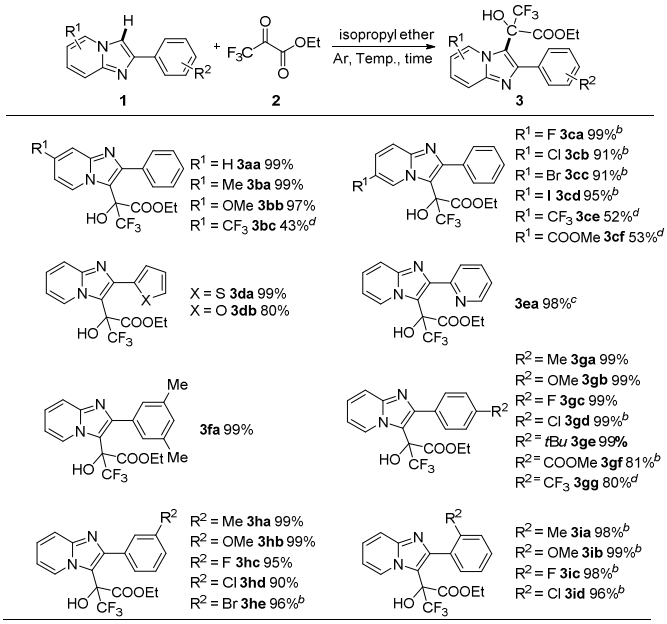


Figure 2. Crystal structure of **3aa**.

To expand the scope of the methodology, the F-C hydroxyalkylation was investigated with different functional groups installed onto the imidazo[1,2-α]pyridine aromatics under our optimized conditions (**Scheme 1)**. The preliminary results demonstrated that the reaction has a high degree of functional group tolerance. Imidazo[1,2-a]pyridines bearing electron-donating groups (Me, OMe) at the pyridine ring could react smoothly at room temperature, and afforded the products **3ba** and **3bb** in excellent yields. It is also remarkable that the presence of electron-withdrawing groups (F,

Cl, Br, I) at the pyridine ring could give products **3ca** - **3cd** in 91% - 99% yields at 60 °C after 24 h. It is not surprising that stronger electron-withdrawing groups (CF_3, COOMe) could tremendously suppress the reaction activity and lead to low yileds of **3bc**(43 %), **3ce**(52 %) and **3cf**(53 %). These results are consistent with the electronic effects of functional groups, which can either increase or decrease the electron density within the double bond and affect the reaction yields. In addition, for the 2-heteroaromatic imidazo[1,2-α]pyridines, the transformation could proceed successfully under mild conditions to obtain **3da**, **3db** and **3ea** in high yields.

Scheme 1. Substrate scopes of catalyst-free F-C hydroxyalkylation of imidazo[1,2-α]pyridines with ethyl trifluoropyruvate in isopropyl ether.[a]



[a]**Reaction conditions:** Imidazo[1,2-α]pyridines (0.10 mmol), Ethyl trifluoropyruvate (0.20 mmol), room temperature (about 15 °C), 10 h, Ar atmosphere. Isolated yields. [b]Carried out at 60 °C for 24 h. [c]Carried out at room temperature (about 15 °C) for 24 h. [d]Carried out at 60 °C for 48 h.

Different substituents on the phenyl ring of 2-phenylimidazo[1,2-a]pyridines were also synthesized and their reactivity were examined. Halides, ester, trifluoromethyl substituents were well tolerated under optimized conditions. From the isolated yields of **3fa**, **3ga – 3gg, 3ha – 3he** and **3ia – 3id,** generally speaking, electronic effect plays the similar role in influencing reaction efficiency as discussed previously. Furthermore, substrates bearing electron-donating groups (Me, OMe) at the *meta* ,and *para* positions of the phenyl ring afforded the desired product easily, while substrates at the *ortho* site needed higher temperature and longer time to reach the same yield level (**3ia** and **3ib**).

In summary, we have developed an efficient method for the synthesis of 3,3,3-trifluoro-2-hydroxy-2-(2-phenylimidazo[1,2-a]pyridin-3-yl)-propionic acid ethyl ester with a high degree of functional group tolerance. The mild reaction conditions (no additive and

catalyst-free) and broad substrate scopes make this proposed method an appealing strategy to synthesize CF_3 containing bioactivity drugs.

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Crystallographic data for compound **3aa** (CCDC 1410234) can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/deposit.

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