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Survey reactivity of some *N*-aryl formamides with pentafluoropyridine

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ABSTRACT

Chemo selectivity of some *N*-aryl formamides with pentafluoropyridine under basic conditions in dry THF was investigated. The aromatic nucleophilic substitution of pentafluoropyridine with enol–imines derived from *N*-aryl formamides occurs at the 4-position of pyridine ring by both oxygen and nitrogen site of enol–imines depending on the nature of the aromatic ring substituent; with electron releasing group, nucleophilic attack was accomplished by oxygen atom and with an electron withdrawing group, the reaction of *N*-aryl formamide anions with pentafluoropyridine proceeded via nitrogen site.

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1. Introduction

Polysubstituted pyridines play an important role in organic chemistry, biochemistry, and pharmaceutical chemistry, this reflected in the great number of review articles and monographs for the synthesis and applications of pyridines [1–4]. Polyfluorinated heteroaromatics are used as building blocks and starting materials for the construction of a variety of ring fused systems [5–7] polyfunctional compounds and macrocycles [8,9]. Fluorinated heterocyclic compounds are highly regarded in bioorganic and medicinal chemistry because these compounds encompass unique properties that allow a variety of applications in the synthesis of bioactive compounds [10–12]. The interest in fluoropyridines is explained by their unusual chemical, physical, and biological properties owing to the presence of the strong electron-withdrawing substituents in the aromatic ring [13]. Pentafluoropyridine has a broad and developing chemistry that basically arises from replacement of fluorine atom by aromatic nucleophilic substitution reactions [14]. Reactivity of halogen substituents at 2-, 3-, and 4-positions of pyridine is different toward nucleophiles. The 4- and the 2-positions are most activated toward nucleophilic attack due to the stabilizing influence of the ring nitrogen atom in the transition state [10–12].

Many studies have been carried out on the reaction of perhalogenated compounds with various nucleophiles such as N, O, S, C, and P nucleophiles [15–19]. Regiochemistry of nucleophilic substitution depends on nature of nucleophile, solvent and reaction condition. In our previous work, we showed that the reaction of sodium enolate of ketone, a bidentate nucleophile with pentafluoropyridine selectively proceeds through the attack of oxygen site. This selectivity was illustrated based on hard–hard interaction principle [20].

Formamides are used as important intermediates in organic synthesis. They are useful precursors for synthesis of isocyanides [21], fungicides and herbicides [22], quinolone antibiotics [23], and cancer chemotherapeutic agents [24]. An anion derived from *N*-aryl formamide acts as an ambident nucleophile, which negative charge delocalizes between a nitrogen atom and an oxygen atom. In our last work, we investigated the reaction of pentachloropyridine with *N*-aryl formamides. We showed that the reaction of *N*-aryl formamide anions with pentachloropyridine proceeded from both nitrogen and oxygen site depending on the nature of the aromatic ring substituent [25].

Continuing our research in this area, we would like to report the site selectivity of some N and O bidentate nucleophiles in reaction with pentafluoropyridine.

2. Results and discussion

According to our previous paper [25], Reaction of aromatic amine **1** with formic acid **2** without any solvent in the presence of aminopropyl-silica (APS) **3** as a heterogeneous catalyst using ultrasonic irradiation gave corresponding formamides **3a–i** in 1–5 min and 90–94% isolated yields (Scheme 1). All formamide

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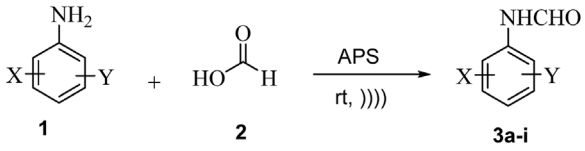
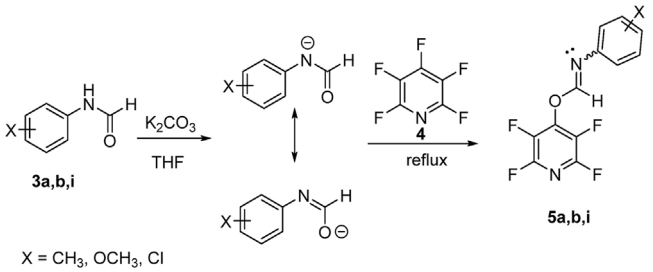


3a: X = *p*-OCH_3, Y = H
3b: X = *p*-CH_3, Y = H
3c: X = *p*-Cl, Y = H
3d: X = *o*-Br, Y = *p*-Br
3e: X = *p*-F, Y = m-Cl
3f: X = *o*-Br, Y = H
3g: X = *m*-NO_2, Y = H
3h: X = *o*-CF_3, Y = H
3i: X = *m*-CF_3, Y = H

Scheme 1. Synthesis of formamides **3a–i** with APS (aminopropyl-silica).

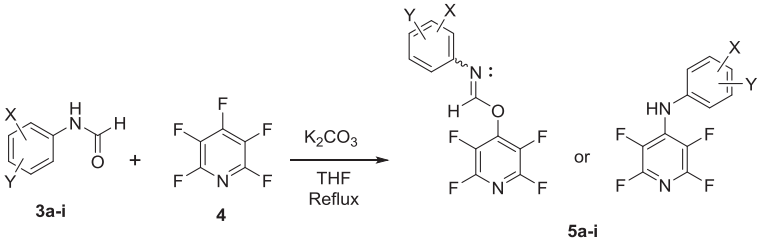


Scheme 2. Reaction of formamide **3a**, **b**, **i** with pentafluoropyridine **4**.

compounds were identified by comparison of their physical and spectral data with those of authentic samples [26–28].

The reaction of pentafluoropyridine **4** with *N*-aryl formamides **3a–i** was carried out in dry THF in the presence of potassium carbonate. The reaction of *N*-(4-methoxyphenyl)formamide **3a** with pentafluoropyridine **4** in the presence of potassium carbonate in dry THF, gave 2,3,5,6-tetrafluoropyridin-4-yl-*N*-(4-methoxyphenyl)-formimidate **5a** (Table 1, Entry 1) after purification using silica gel column chromatography eluted by ethyl acetate/hexane. ^{1}H NMR and ^{19}F NMR analysis confirmed product **5a**. This observation showed that bidentate nucleophile derived from *N*-(4-methoxyphenyl)formamide **3a** reacted with pentafluoropyridine from oxygen site. The electron-donating effect of methoxy group enhanced negative charge density on oxygen by resonance of negative charge on nitrogen atom to oxygen atom, therefore making it more nucleophilic than nitrogen. Two resonances by ^{19}F NMR (−87.1 and −143.5 ppm), indicate displacement of fluorine atom attached to the 4-positions of the pyridine ring. Chemical shifts of fluorine *ortho* and *meta* to ring nitrogen were located at

Table 1
Reaction of aromatic *N*-aryl formamide with pentafluoropyridine



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Entry	Formamide	Product(s)
1	3a	5a, 30%
2	3b	5b, 30%
3	3c	5c, 53%
4	3d	5d, 45%
5	3e	5e, 25%
6	3f	5f, 62%
7	3g	5g, 33%
8	3h	5h, 45%
9	3i	5i, 15%; 5i', 40%

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