SHORT REPORT

Reaction of hydroxyl-quinoline with pentafluoropyridin

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Abstract

Reaction of pentafluoropyridine with 2 or 8-hydroxyl-quinoline under basic conditions in acetonitrile gives 4-oxy quinoline 2,3,5,6-tetrafluoropyridine derivatives in good yields. All the compounds were characterized using ¹H, ¹³C, ¹⁹F-NMR and MS spectroscopy.

Keywords: Pentafluoropyridine, Synthesis, Hydroxyl-quinoline, ¹⁹F-NMR

Background

The unique properties of fluorine atom make organofluorine compounds find many different applications, ranging from pharmaceuticals and agrochemicals to advanced materials and polymers. Circa 20 % of pharmaceuticals contain a fluorine atom (Hunter 2010; Champagne et al. 2015). The fluorinated groups in these systems lead to remarkable changes in their physical properties, chemical reactivity, and physiological activity (Iwao 2009). Pentafluoropyridine, as one of the simplest members of electron-deficient species of perfluoroheteroaromatic compounds, has been investigated into since the early 1960s (Fox et al. 2013). The most important reaction of pentafluoropyridines involves the replacement of the para-fluorine atom by nucleophilic reagents for the synthesis of new organofluorine compounds, such as heterocyclic and macrocyclic perfluoro systems (Cartwright et al. 2010; Chambers et al. 2005; Ranjbar-Karimi et al. 2015). In this paper, we have recently reported the reaction of pentafluoropyridine with hydroxyl-quinoline. This allows the synthesis of a wide range of 4-substituted 2,3,5,6-tetrafluoropyridine (Additional file 1).

Results and discussion

In this short report, we describe nucleophilic substitution of pentafluoropyridine with 2 or 8-hydroxyl-quinoline and how the resulting products of 4-quinoline-perfluoropyridine derivatives. Reaction of pentafluoropyridine 1 with 2-hydroxyl quinoline 2 under basic conditions (NaHCO₃) in acetonitrile at reflux temperature gave a single product of 2-(perfluoropyridin-4-yloxy)quinoline 2a (Fig. 1). In 2-hydroxyl quinoline 2, the hydroxyl group deprotonate by base and attacks at the most active para position of pentafluoropyridine to give 2a.

The structures of 2a were characterized by ¹⁹F, ¹H, ¹³C NMR and mass spectra. In ¹⁹F NMR spectroscopy of 2a observed two peaks for fluorine’s, a peak is observed as multiple at δ = −86.4 for fluorine atom located in the ortho position towards the ring nitrogen and also, a multiple is remarked at up field δ = −154.8 for fluorine atom located in the meta position towards the ring nitrogen.

The two resonances by ¹⁹F NMR and their chemical shift of them indicate that displacement of fluorine atoms attached to the para position of pyridine ring. In the ¹H NMR spectrum of compound 2a, the aromatic proton resonances were observed as doublets at δ = 7.01–8.01 ppm. Other spectroscopic techniques were consistent with the structures proposed. The mass spectrum of 2a compound displayed molecular ion peaks at peak (M-1) at m/z = 293, and any initial fragmentation involved the loss of the other molecules which is consistent with the proposed structure.

Also, we examined the reaction of pentafluoropyridine 1 with 8-hydroxyl quinoline 3 in the presence of sodium hydrogen carbonate in CH₃CN as a solvent gave 8-(perfluoropyridin-4-yloxy) quinoline 3a (Fig. 2). In basic condition, hydroxyl group of the quinoline deprotonation...
and attack to Para position of pentafluoropyridine and elimination of 4-fluor pyridine ring to give 3a. The purification of 3a was achieved by column chromatography using ethyl acetate/n-hexane (1:8).

8-(perfluoropyridin-4-yloxy) quinoline 3a (0.23 g, 80 %) as brown solid; mp 180 °C; 1H NMR (DMSO): δ (ppm) 6.84–7.92 (6H, m, Ar–H). 19F NMR (CDCl₃): δ (ppm) −65.7 (2F, m, F−2,6), −139.1 (2F, m, F−3,5). 13C NMR (CDCl₃): δ (ppm) 110.9, 112.6, 113.3, 122.3, 123.3, 128.7, 130.8, 148.2, 156.0, 161.1, 163.9, 165.1 MS (EI), m/z (%)= 294 (M⁺) 282, 275, 268, 227, 167, 122, 101, 85, 58, 43.

**Additional file**

Additional file 1. 1H, 13C, 19F-NMR and MS spectra of the compounds.

**Authors’ contributions**

All authors (KB, MTM and RH) read and approved the final manuscript. Analysis and interpretation of data: by KB and RH. Drafting of manuscript: KB. Critical revision: MTM. All authors read and approved the final manuscript.

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**Competing interests**

The reaction of pentafluoropyridine with hydroxyl-quinoline give perfluoro-heteroaromatic derivatives in good yields and high regioselectivity. The attractive of this protocol are cleaner reaction, non-toxic catalyst and solvent which makes it a useful process for the preparation of 4-oxy quinoline-tetrafluoropyridine. The all authors (KB, MTM and RH) declare that they have no competing interests.

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