Molbank **2013**, M808; doi:10.3390/M808

OPEN ACCESS

molbank

ISSN 1422-8599

www.mdpi.com/journal/molbank

Short Note

6-[5-Chloro-2-(trifluoromethyl)phenyl]-3-fluoro-2-methylpyridine

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Received: 10 July 2013 / Accepted: 17 September 2013 / Published: 25 September 2013

Abstract: Suzuki coupling reaction of 5-fluoro-6-methylpyridin-2-ylboronic acid (1) with 4-chloro-2-iodo-1-(trifluoromethyl)benzene (2) in the presence of dikis and K_2CO_3 produce C-C coupled new title compound 6-(5-chloro-2-(trifluoromethyl)phenyl)-3-fluoro-2-methylpyridine (3). The structure of the newly synthesized compound has been confirmed by IR, ^{1}H-NMR, ^{13}C-NMR, LC-MS and CHN analysis.

Keywords: Suzuki coupling; 5-fluoro-6-methylpyridin-2-ylboronic acid; 4-chloro-2-iodo-1-(trifluoromethyl)benzene; bis(triphenylphosphine)palladium(II) dichloride (dikis); 1,4-dioxane

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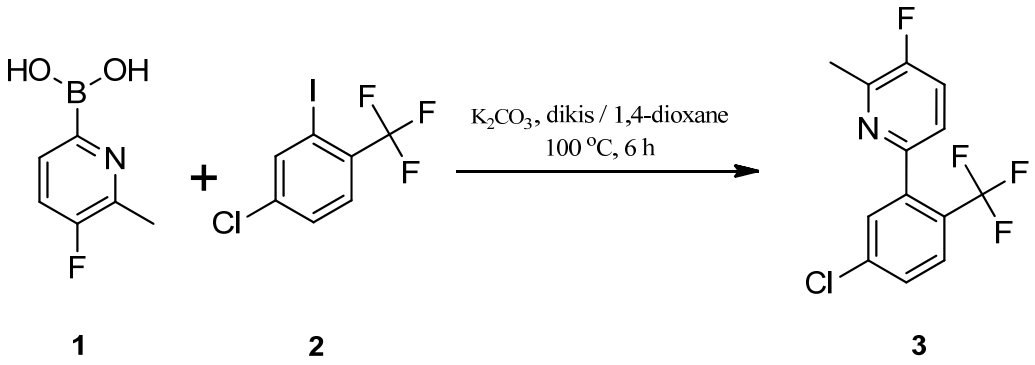
The fluorine atom plays a very important role in the chemical and biological field [1]. After nitrogen, fluorine occupies the position of the second most important hetero atom in life science research. Overall 10%–15% of newly synthesised pharmaceutical drugs and 30%–40% of newly registered agrochemicals contain one or more fluorine atom.[2] Generally, halogenated heterocyclic compounds like pyridine and pyrimidine derivatives are associated with antibacterial [3,4], antioxidant [5], antitumor [6,7], anticancer, fungicidal [8] and anti-inflammatory agents [9]. Some of the halogenated pyridines are used as anti-colorectal cancer compounds [10], anti-hypoglycemic and antihypertensive agents [11]. Due to the wide application of fluorinated pyridines and potency of fluorine atom, it was thought worthwhile to prepare a new fluorinated pyridine.

Experimental

All reagents were purchased from commercial sources and used without further purification. Melting point was determined in one end open capillary tube on a liquid paraffin bath and was not corrected. Reaction was carried out under an inert nitrogen atmosphere. Mass spectra, ^{1}H-NMR and ^{13}C-NMR spectra were recorded for the compound on Agilent Mass spectrometer, Bruker Avance II (399.65 MHz, ^{1}H-NMR; 100.50 MHz, ^{13}C-NMR) instruments, respectively. Chemical shifts were reported in parts per million (ppm) using tetramethylsilane (TMS) as an internal standard and Elemental (C, H and N) analysis was performed on an Elementar vario MICRO cube.

Scheme 1. Synthetic route for the title compound, 6-[5-chloro-2-(trifluoromethyl)phenyl]-3-fluoro-2-methylpyridine (**3**).



1 **2** **3**

Synthesis of 6-[5-Chloro-2-(trifluoromethyl)phenyl]-3-fluoro-2-methylpyridine (**3**)

The title compound (**3**) was synthesized according to a known procedure reported for the synthesis of isomeric compound 6-[4-chloro-2-(trifluoromethyl)phenyl]-3-fluoro-2-methylpyridine [12] (Scheme 1.). A mixture of 5-fluoro-6-methylpyridin-2-ylboronic acid (**1**) (1.0 g, 6.49 mmol), 1,4-dioxane (16 mL) and water (8 mL) was prepared in a round bottom flask at room temperature under nitrogen atmosphere. The reaction mixture was degassed with argon for 15 min, K_2CO_3 (1.34 g, 9.74 mmol) and Bis(triphenylphosphine)palladium(II) dichloride (dikis) (0.22 g, 0.32 mmol) were added and degassed for 25 min. To this solution, 4-chloro-2-iodo-1-(trifluoromethyl)benzene (**2**) (1.95 g, 6.49 mmol) was added and the reaction mixture was heated for 6 h at 100 °C. It was allowed to cool to room temperature and diluted with ethyl acetate, filtered over celite, washed with ethyl acetate. The filtrate was washed with water and brine solution. Organic layer was dried over anhydrous $MgSO_4$ and concentrated to give the crude product which was further purified by column chromatography using petroleum ether and ethyl acetate (7:3) as eluent to get the title compound (**3**) as a white solid with $R_f = 0.64$.

Yield: 1.6 g (86%).

Melting point: 141–143 °C.

MS: *m/z*: 290.2 ($M^+ + 1$).

IR: ν_{max}/cm^{-1}: 3091–2957 (aromatic C-H stretching), 1314–1221 (CF_3 stretching), 1618 and 1431 (C=C stretching).

^{1}H-NMR ($CDCl_3$) δ ppm: 7.74 (d, *J* = 1.9 Hz 1H, Ar-H), 7.58 (dd, *J* = 8.3 Hz and *J* = 1.9 Hz 1H, Ar-H), 7.44–7.34 (m, 2H, Ar-H), 7.24–7.21 (m, 1H, Ar-H), 2.57 (d, *J* = 2.7, 3H, Ar-CH_3).

^{13}C-NMR (DMSO-d_6): δ ppm: 158.6, 156.1, 151.5, 146.5, 137.8, 134.5, 133.0, 131.6, 126.6 CF_3, 124.5, 122.6, 121.8, 17.9.

Elemental analysis: Calculated for: $C_{13}H_8ClF_4N$: C, 53.91%; H, 2.78%; N, 4.84%. Found: C, 53.89%; H, 2.76%; N, 4.83%.

Acknowledgments

We gratefully acknowledge the guidance by S.C. Sharma, Former Vice Chancellor, Tumkur University, Tumkur.

Conflicts of Interest

The authors declare no conflict of interest.

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