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Short Note

4-[5-(3,5-Difluorophenyl)furan-2-yl]-2,3,7-triazaspiro[4.5]dec-3-en-1-one Hydrochloride

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Abstract: A novel route for the synthesis of new spirocyclic derivative is developed. The present work involves the synthesis of title compound **3** by Suzuki coupling of 3,5-difluorophenyl boronic acid with *tert*-butyl 1-(5-bromofuran-2-yl)-4-oxo-2,3,7-triazaspiro[4.5]dec-1-ene-7-carboxylate (**2**), which in turn prepared from the ethyl nipecotate (**1**). Newly prepared spirocyclic derivative (**3**) is characterized by IR, NMR and mass spectral data.

Keywords: spirocyclic; pyrazolone; Suzuki coupling; ethyl nipecotate

Introduction

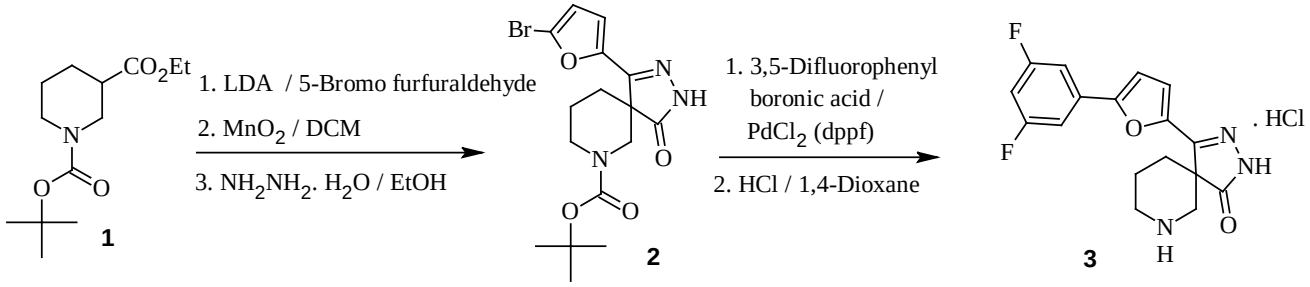
The spiro framework is an important subunit in a vast number of natural products such as alkaloid: (−)-sibirine, fused tetracyclic lycopodium alkaloid: nankakurine-A, several spongistatins: β-vetivone, acorenone B, fredericamycin and Shizuca-acordienol [1,2]. Many spirocyclic compounds have been found to display *inter alia* antiinflammatory [3] and herbicidal activity [4] or act as aromatase inhibitors [5]. Moreover, the unique structural features of spirocyclics have been used for the synthesis of new ligands and catalysts such as spirobisoxazolines, SPINOL, SPINOL-derived phosphoric acids *etc.* [6–8]. Due to their unique structural properties, several methodologies have been reported

for the synthesis of spiro compounds [9–11]. In view of the biological importance of spirocycles and in continuation of our effort on the synthesis of new spirocyclic derivatives [12,13], a new spirocyclic derivative was synthesized and characterized.

Results and Discussion

The title compound, 4-[5-(3,5-difluorophenyl)furan-2-yl]-2,3,7-triazaspiro[4.5]dec-3-en-1-one hydrochloride (**3**), was prepared by the $PdCl_2$ (dppf) catalyzed Suzuki coupling of *tert*-butyl 1-(5-bromofuran-2-yl)-4-oxo-2,3,7-triazaspiro[4.5]dec-1-ene-7-carboxylate (**2**) with 3,5-difluorophenyl boronic acid followed by deprotection of Boc group (Scheme 1). The intermediate **2**, a bromo substituted derivative of *tert*-butyl 1-(furan-2-yl)-4-oxo-2,3,7-triazaspiro[4.5]dec-1-ene-7-carboxylate, was prepared by using 5-bromo-2-furaldehyde as described in our earlier work [12]. The final product **3** was well characterized by using NMR, IR and mass spectral data.

Scheme 1. Synthesis of 4-[5-(3,5-difluorophenyl)furan-2-yl]-2,3,7-triazaspiro[4.5]dec-3-en-1-one hydrochloride.



The IR spectrum of compound (**3**) showed a wide absorption band at 3425 cm^{-1} due to the presence of NH in the molecule. The absorption band at 1708 cm^{-1} is due to the stretching of amide carbonyl group. In the ^{1}H-NMR spectrum, the signals of the respective protons of the title compound (**3**) were verified on the basis of their chemical shifts, multiplicities and coupling constants. A singlet observed at δ 12.18 ppm was due to the proton of piperidine NH. Another singlet observed at δ 9.70 ppm was due to the proton of pyrazolone NH. The two furyl protons appeared as two doublets at δ 7.43 and 7.46 ppm. The eight protons of piperidine ring resonated in the region δ 1.8–3.6 ppm as different signals due to chemical non-equivalence of these protons. The mass spectrum showed a molecular ion peak at *m/z* 332 corresponding to (M^+−HCl)+1 as the HCl gets instantly dissociated in the mass spectral conditions. Elemental analysis and ^{13}C-NMR spectrum also gave satisfactory results for the title compound.

Experimental

Melting point was taken in open capillary tube and was uncorrected. The purity of the compound was confirmed by thin layer chromatography using Merck silica gel 60 F_{254} coated aluminium plates. IR spectrum was recorded on Shimadzu-FTIR Infrared spectrometer in KBr (ν_{max} in cm^{-1}). ^{1}H-NMR (400 MHz) spectrum was recorded on a Varian 400 spectrometer, with 5 mm PABBO BB-1H TUBES and ^{13}C-NMR (100 MHz) spectrum was recorded for approximately 0.03 M solutions in CD_3OD at

100 MHz with TMS as internal standard. All exchangeable protons were confirmed by addition of D_2O. LCMS was obtained using Agilent 1200 series LC and Micromass zQ spectrometer. Elemental analysis was carried out by using VARIO EL-III (Elementar Analysensysteme GmBH).

The synthesis of *tert*-butyl 1-(furan-2-yl)-4-oxo-2,3,7-triazaspiro[4.5]dec-1-ene-7-carboxylate was described in our earlier work [12]. Intermediate (**2**) was prepared by following the same procedure using 5-bromo-2-furaldehyde instead of 2-furaldehyde.

To a solution of **2** (0.3 g, 0.755 mmol) in 1,2-dimethoxyethane (2 mL), 3,5-difluorophenyl boronic acid (0.143 g, 0.9 mmol) was added followed by Na_2CO_3 solution (0.24 g, 2.264 mmol). After passing nitrogen to the reaction mass for 30 min, $PdCl_2$ (dppf) (0.124 g, 0.152 mmol) was added and heated to 80 °C and maintained for 4 h. After the completion of reaction as indicated by TLC, the reaction mixture was concentrated to afford the crude material which was purified by column chromatography. The isolated product was reacted with HCl in 1,4-dioxane [14] to afford the title compound. Yield was 123 mg, 44%.

Melting point: 193–200 °C.

LCMS: *m/z* = 332, $(M^+ - HCl)+1$.

IR (KBr): ν_{max} (cm^{-1}), 3424 (NH), 3087 (Ar-H), 1708 (pyrazolone C=O), 1588 (C=N), 1213 (C-F).

^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm, 1.76 (d, 1H, Piperidine-H, *J* = 14 Hz), 1.88 (d, 1H, Piperidine-H, *J* = 13.6 Hz), 2.20 (m, 3H, Piperidine-H), 3.61 (d, 1H, Piperidine-H, *J* = 13.2Hz), 7.24 (m, 2H, 3,5-Difluorophenyl-H), 7.43 (d, 2H, Furyl-H, *J* = 4 Hz), 7.46 (d, 2H, Furyl-H, *J* = 3.6 Hz), 7.51 (d, 1H, 3,5-Difluorophenyl-H), 7.74 (broad s, 1H, HCl, D_2O exchangeable), 9.70 (s, 1H, Pyrazolone-NH, D_2O exchangeable), 12.18 (s, 1H, Piperidine-NH, D_2O exchangeable).

^{13}C-NMR (100 MHz, CD_3OD): δ ppm, 15.62, 26.84, 43.1, 44.48, 66.2 (Piperidine C's), 102.5, 106.1, 108.9, 113.5, 132.1, 145.1, 149.1 (Ar-C), 152.9 (C=N), 161.91 (C-F), 164 (C-F), 177.6 (Pyrazolone C=O).

Elemental analysis: Calculated for $C_{17}H_{16}ClF_2N_3O_2$, C, 55.52%; H, 4.38%; N, 11.43%; Found: C, 55.49%; H, 4.42%; N, 11.38%.

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