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Short Note

3-(4-Fluorophenyl)-*N*-[4-(4-furan-2-yl-1-oxo-2,3,7-triazaspiro[4.5]dec-3-en-2-yl)phenyl]propionamide Hydrochloride

Rajagopalan Srinivasan [1,2], Badiadka Narayana [1,*], Seranthimata Samshuddin [1] and Balladka Kunhanna Sarojini [3]

[1] Department of Studies in Chemistry, Mangalore University, Mangalagangotri-574 199, Karnataka, India

[2] Aurigene Discovery Technologies Limited, Electronics city, Phase-II, Bangalore-560 100, Karnataka, India

[3] Research Department of Chemistry, P. A College of Engineering, Nadupadavu, Mangalore 574153, Karnataka, India

***** Author to whom correspondence should be addressed; E-Mail: nbadiadka@yahoo.co.uk.

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Abstract: A simple and novel route for the synthesis of new spirocyclic propionamide derivative is developed. The present work involves *N*-arylation of pyrazolone (**1**) using copper(I) iodide catalyst followed by reduction to give amine (**2**). The coupling of **2** with 3-(4-fluorophenyl)propionic acid and deprotection of Boc group yields the title compound (**3**).

Keywords: spirocyclic; pyrazolone; reduction; *N*-arylation; amide coupling

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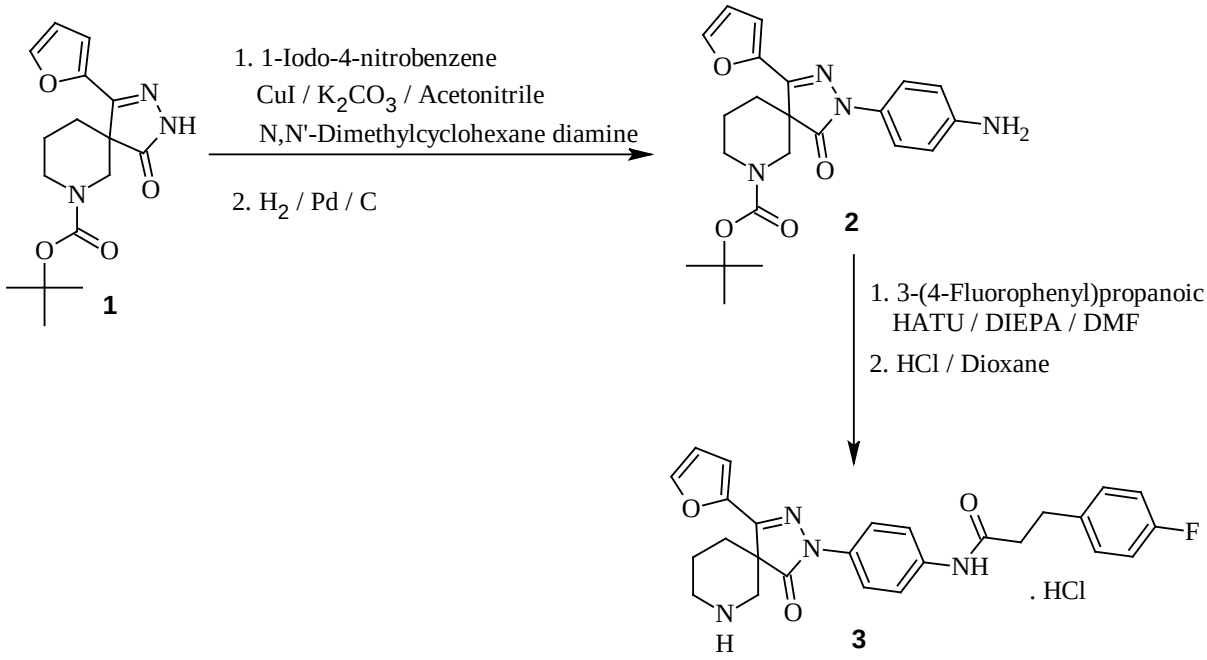
Introduction

Spirocyclic structures are found in wide range of natural compounds isolated from various sources [1,2]. These compounds play a very important role in many fields like chiral medicine, chiral LCD materials, macromolecule bulking agents and biological pesticides [3–5]. In continuation of our work on synthesis of spirocyclic derivatives [6,7], a new spirocyclic amide derivative was synthesized and characterized.

Results and Discussion

The title compound, 3-(4-fluorophenyl)-*N*-[4-(4-furan-2-yl-1-oxo-2,3,7-triazaspiro[4.5]dec-3-en-2-yl)phenyl]propionamide hydrochloride (**3**) was prepared by the coupling of *tert*-butyl 3-(4-aminophenyl)-1-(furan-2-yl)-4-oxo-2,3,7-triazaspiro[4.5]dec-1-ene-7-carboxylate (**2**) with 3-(4-fluorophenyl)-propionic acid using HATU followed by deprotection of Boc group using HCl in 1,4-dioxane (Scheme 1). The intermediate **2** in turn prepared by *N*-arylation of *tert*-butyl 1-(furan-2-yl)-4-oxo-2,3,7-triazaspiro[4.5]dec-1-ene-7-carboxylate (**1**) using copper(I) iodide catalyst followed by reduction. The final product **3** was well characterized by using NMR, IR and mass spectral data.

Scheme 1. Synthesis of 3-(4-fluorophenyl)-*N*-[4-(4-furan-2-yl-1-oxo-2,3,7-triazaspiro[4.5]dec-3-en-2-yl)phenyl]propionamide hydrochloride, **3**.



The IR spectrum of compound **3** showed a broad absorption band at 3,424 cm^{-1} due to the presence of NH in the molecule. Two sharp bands appeared at 1,697 and 1,603 cm^{-1} was due to pyrazolone carbonyl and amide carbonyl group respectively. In ^{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 10.16 ppm was due to the amide NH. Another singlet observed at δ 9.85 ppm was due to the piperidine NH which was D_2O exchangeable. All the aromatic protons resonated in the region δ 6.8–8.0 ppm. Protons of two methylene groups appeared at δ 2.88 and 2.60 ppm respectively as triplets. The eight protons of the piperidine ring resonated in the region δ 1.8–3.8 ppm as multiplets due to chemical non-equivalence of these protons. The mass spectrum showed a molecular ion peak at *m/z* 461 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 (**1**) was described in our earlier work [6]. The reaction of **1** with 1-iodo-4-nitrobenzene under copper(I) iodide catalyzed condition followed by the reduction of the nitro compound using Pd/C afforded the intermediate **2** [8].

To a solution of **2** (0.250 g, 0.609 mmol) in DMF (2 mL), DIPEA (0.3 mL, 1.8 mmol) was added at 0–5 °C followed by 3-(4-fluorophenyl)propionic acid (0.102 g, 0.609 mmol). After stirring at 0–5 °C for 15 min, HATU (0.277 g, 0.73 mmol) was added and stirring continued at ambient temperature for 6 h. After the completion of reaction as indicated by TLC, the reaction mixture was quenched into crushed ice and filtered. The solid product was reacted with HCl in 1,4-dioxane [9] to afford the title compound. Yield was 160 mg, 53%.

Melting point: 210–220 °C.

LCMS: *m/z* = 461, (M^+-HCl) + 1.

IR (KBr): ν_{max} (cm^{-1}), 3424 (NH), 1697 (pyrazolone C=O), 1603 (amide C=O), 1535 (C=N), 1222 (C-F).

^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm, 1.8 (d, 1H, Piperidine-H, *J* = 8.4 Hz), 2.1 (d, 1H, Piperidine-H, *J* = 8.4 Hz), 2.2 (m, 2H, Piperidine-H), 2.6 (t, 2H, CH_2, *J* = 7.6 Hz), 2.88 (t, 2H, CH_2, *J* = 7.6 Hz), 3.2 (m, 3H, Piperidine-H), 3.85 (d, 1H, Piperidine-H, *J* = 12.8 Hz), 6.8 (m, 1H, Furyl-H), 7.1 (t, 2H, 4-Fluorophenyl-H, *J* = 8.8 Hz), 7.3 (dd, 2H, 4-Fluorophenyl-H, *J* = 5.6 Hz, 8.4 Hz), 7.5 (d, 1H, Furyl-H, *J* = 1.6 Hz), 7.7 (2d, 4H, Aryl-H, *J* = 9.2 Hz), 7.8 (m, 1H, HCl, D_2O exchangeable), 8.0 (d, 1H, Furyl-H, *J* = 1.6 Hz), 9.85 (s,1H, Piperidine-NH, D_2O exchangeable), 10.16 (s, 1H, amide-NH).

^{13}C-NMR (100 MHz, CD_3OD): δ ppm, 17.68, 28.82, 44.95, 46.19, 50,10 (Piperidine C's), 31.92, 39.80, 113.56, 114.11, 115.97, 116.19, 121.14, 121.53, 131.1, 131.17, 134.75, 137.89, 138.13, 146.94 (C=N), 151.31 (Aryl C-F), 173.47 (Pyrazolone C=O), 175.02 (Amide C=O).

Elemental analysis: Calculated for $C_{26}H_{25}FN_4O_3$, C, 67.81%; H, 5.47%; N, 12.17%; Found: C, 67.75%; H, 5.44%; N,12.13%.

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