

Short Note

***N*-(3,4-Dimethoxyphenyl)-4-oxo-2,3,7-triazaspiro[4.5]dec-1-ene-1-carboxamide Hydrochloride**

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Received: 29 May 2012 / Accepted: 3 August 2012 / Published: 8 August 2012

Abstract: A simple and novel route for synthesis of new spirocyclic amide derivative is developed. The present work involves the oxidative cleavage of *tert*-butyl 1-(furan-2-yl)-4-oxo-2,3,7-triazaspiro[4.5]dec-1-ene-7-carboxylate **1** followed by the amine coupling and deprotection of Boc.

Keywords: spirocyclic; pyrazolone; oxidation; amide

Introduction

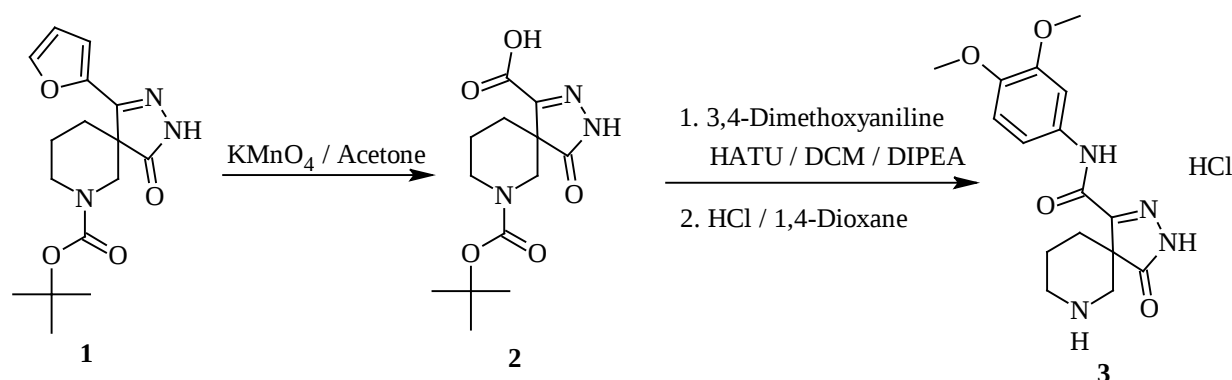
Spirocyclic structures are found in wide range of natural compounds isolated from various sources. Spiro compounds are known to be PDE7 inhibitors and have a number of therapeutic applications in the treatment of pain, especially neuropathic pain. They are useful for arresting cell growth and apoptosis of neoplastic cells, thereby useful in anticancer treatment [1,2]. The spiro functionality shown in many phytochemicals, such as in alkaloids, lactones, terpenoids, and clinically valuable compounds has been known for a long time. At present, spirocyclic compounds play a very important role in many fields such as chiral medicine, chiral LCD materials, macromolecule bulking agent and biological pesticides [3–5]. Due to those promising biological activities of spirocyclic compounds and

in continuation of our work on synthesis of spirocyclic derivatives [6], it was decided to prepare a new spirocyclic amide derivative.

Results and Discussion

The title compound, *N*-(3,4-dimethoxyphenyl)-4-oxo-2,3,7-triazaspiro[4.5]dec-1-ene-1-carboxamide hydrochloride (**3**), was prepared by the coupling of 7-(*tert*-butoxycarbonyl)-4-oxo-2,3,7-triazaspiro[4.5]dec-1-ene-1-carboxylic acid (**2**) with 3,4-dimethoxyaniline using *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) followed by deprotection of Boc group using HCl in 1,4-dioxane (Scheme 1). The intermediate **2** was in turn prepared by the oxidative cleavage of *tert*-butyl 1-(furan-2-yl)-4-oxo-2,3,7-triazaspiro[4.5]dec-1-ene-7-carboxylate **1**. The final product **3** was well characterized by using NMR, IR and mass spectral data.

Scheme 1. Synthesis of *N*-(3,4-dimethoxyphenyl)-4-oxo-2,3,7-triazaspiro[4.5]dec-1-ene-1-carboxamide hydrochloride.



The IR spectrum of compound (**3**) showed a wide absorption band at 3378 cm^{-1} due to the presence of NH groups in the molecule. Two sharp bands at 1731 and 1660 cm^{-1} were due to pyrazolone carbonyl and amide carbonyl group respectively. In ^1H -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 12.50 ppm was due to the proton of amide NH. Another singlet observed at δ 10.49 ppm was due to the proton of pyrazolone NH. A broad singlet appeared in the region δ 8.50–8.70 ppm was due to piperidine NH. Signals due to two methoxy groups appeared as singlets at δ 3.85 and 3.86 ppm. The eight protons of piperidine ring resonated in the region δ 1.90–3.66 ppm as different signals due to chemical non-equivalence of these protons. The mass spectrum showed a molecular ion peak at m/z 333.2 corresponding to $[(\text{M}^+ - \text{HCl}) + \text{H}]$ 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 an open capillary tube and was uncorrected. The purity of the compound was confirmed by thin layer chromatography using Merck silica gel 60 F₂₅₄ coated aluminium plates. IR spectrum was recorded on Shimadzu-FTIR Infrared spectrometer in KBr (ν_{max} in cm^{-1}). ^1H -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 oxidation of **1** with potassium permanganate in acetone medium yielded 7-(*tert*-butoxycarbonyl)-4-oxo-2,3,7-triazaspiro[4.5]dec-1-ene-1-carboxylic acid (**2**) [7].

To a solution of **2** (0.15 g, 0.5 mmol) in DMF (2 mL), DIPEA (0.3 mL, 1.5 mmol) was added at 0–5 °C followed by 3,4-dimethoxyaniline (0.081 g, 0.53 mmol). After stirring at 0–5 °C for 15 min, HATU (0.23 g, 0.6 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 [8] to afford the title compound. Yield was 87 mg, 47%.

Melting point: 224–230 °C.

LCMS: $m/z = 333.2$, $[(\text{M}^+ - \text{HCl}) + \text{H}]$.

IR (KBr): ν_{max} (cm^{-1}), 3378 (NH), 2998 (Ar-H), 2944 (aliphatic CH), 1731 (pyrazolone C=O), 1660 (amide C=O).

^1H -NMR (400 MHz, CD_3OD): δ ppm, 1.90 (m, 1H, piperidine-H), 2.10 (m, 3H, piperidine-H), 3.30 (m, 2H, piperidine-H), 3.40 (m, 1H, piperidine-H), 3.66 (m, 1H, piperidine-H), 3.85 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 6.94 (d, 1H, Ar-H, $J = 8.8$ Hz), 7.26 (dd, 1H, Ar-H, $J = 2.4$ Hz, $J = 8.8$ Hz), 7.43 (d, 1H, Ar-H, $J = 2.4$ Hz), 8.50 (s, broad, 1H, piperidine NH, D_2O exchangeable), 10.49 (s, 1H, pyrazolone NH, D_2O exchangeable), 12.50 (s, 1H, CONH, D_2O exchangeable).

^{13}C -NMR (100 MHz, CD_3OD): δ ppm, 19.02, 29.49, 44.78, 45.87 (piperidine C's), 56.55 (OCH_3), 56.74 (OCH_3), 68.13 (quaternary spirocyclic C), 107.09, 113.17, 114.66, 132.10, 148.13, 150.50 (Ar-C), 155.30 (pyrazolone-C), 160.84 (amide C=O), 178.53 (pyrazolone CO).

Elemental analysis: Calculated for $\text{C}_{16}\text{H}_{21}\text{ClN}_4\text{O}_4$, C, 52.10%; H, 5.74%; N, 15.19 %; Found: C, 52.05%; H, 5.76%; N, 15.16%.

Acknowledgments

RS thanks Aurigene Discovery Technologies Limited and Mangalore University for research facilities.

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