

Short Note

2'-[(4-Fluorophenyl)carbonyl]-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indole-3,3'-pyrrolizin]-2(1H)-one

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Abstract: A new spiro[indole-3,3'-pyrrolizine] derivative is regioselectively synthesized by the straightforward multicomponent reaction of 1-(4-fluorophenyl)-3-phenylprop-2-en-1-one, isatin and L-proline without any catalyst. The structure of the newly synthesized compound is characterized by IR, NMR, UV-visible and mass spectral data. The compound is also screened for its reducing power assay.

Keywords: spiro[indole-3,3'-pyrrolizine]; 1-(4-fluorophenyl)-3-phenylprop-2-en-1-one; isatin; L-proline; reducing power assay

Introduction

Among the various nitrogen-containing heterocycles, functionalized pyrrolidine, pyrrolizidine and oxindole alkaloids have become important synthetic targets as they constitute classes of compounds with significant biological activity [1]. Several natural alkaloids and pharmacological agents, contain spiro-oxindole system e.g., spirotryprostatin A, isopteropodine and pteropodine, which have shown important biological activity with potential use in antibacterial, antiprotozoal, and anticancer activities [2]. Spiropyrrrolizine oxindoles are important synthetic targets and several reports of such syntheses exist [3,4]. Such new heterocyclic scaffolds can be prepared by the intermolecular 1,3-dipolar cycloaddition reaction of azomethine ylide with olefinic and acetylenic dipolarophiles [5].

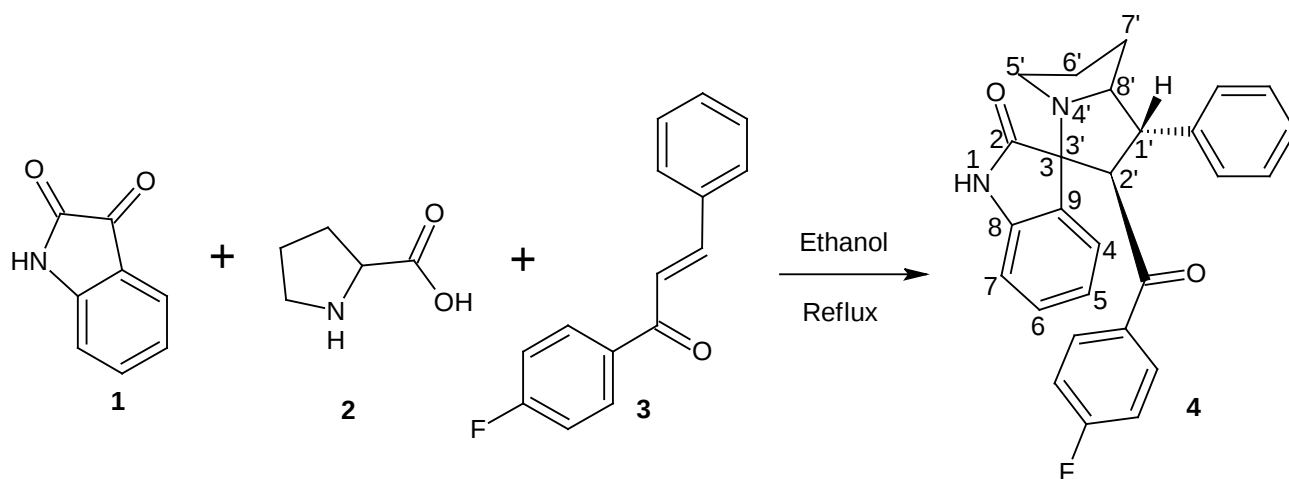
Chalcones constitute an important family of substances belonging to flavonoids, a large group of natural and synthetic products with interesting physicochemical properties, biological activity and structural characteristics [6]. Chalcones are highly reactive substances of varied nature. The basic skeleton of chalcones which possess α,β -unsaturated carbonyl group is useful as the starting material for the synthesis of various biodynamic heterocyclic compounds such as pyrazolines, isoxazolines, pyridines, pyrimidines, benzodiazepines and cyclohexenone derivatives [7–11]. In addition, multicomponent reactions of chalcones with various components yield 2,4,6-triaryl pyridines [12], spiro pyrrolizines [13–15], cyanopyridines [16] *etc.*

In continuation of our work on the synthesis of diverse chalcone derivatives [17,18] and in view of the pharmaceutical importance of spiro pyrrolizines, in this paper we describe the synthesis of new spiro[indole-3,3'-pyrrolizine] derivative derived from 1-(4-fluorophenyl)-3-phenylprop-2-en-1-one.

Results and Discussion

Refluxing a solution of 1-(4-fluorophenyl)-3-phenylprop-2-en-1-one (**3**) in ethanol with isatin (**1**) and L-proline (**2**) afforded the title compound (**4**) (Scheme 1). The 1,3-dipolar cycloaddition of isatin (**1**) and L-proline (**2**) could generate *in situ* azomethine ylides, which was then reacted with dipolarophile chalcone (**3**) to afford regioselectively the spiro[indole-3,3'-pyrrolizine] derivative **4** [14,15]. The structure of the title compound **4** was determined by IR, NMR, UV-visble and mass spectral data.

Scheme 1. Synthesis of 2'-[(4-fluorophenyl)carbonyl]-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indole-3,3'-pyrrolizin]-2(1*H*)-one, **4**.



The IR spectrum of the title compound **4** showed an absorption band at $3,194\text{ cm}^{-1}$ indicated the presence of indole NH. Furthermore, a sharp strong absorption band was noticed at $1,734\text{ cm}^{-1}$ for (4-fluorophenyl)carbonyl group and another strong absorption band was assigned to the amide carbonyl group at $1,676\text{ cm}^{-1}$. The ^1H -NMR spectrum showed a singlet at $\delta\ 7.50\text{ ppm}$ due to the presence of NH proton in the indole ring. A doublet appeared at $\delta\ 4.86\text{ ppm}$ ($J = 11.2\text{ Hz}$) integrating for a single aliphatic proton attached to the C-2' of the pyrrolizine ring. A triplet appeared at 3.86 ppm ($J = 10.8\text{ Hz}$) was integrating for the proton attached to C-1' of pyrrolizine ring. The signals due to aromatic protons of compound **4** merged in the region $\delta\ 6.56\text{--}7.48\text{ ppm}$ as multiplets. ^{13}C -NMR spectrum showed signals at $\delta\ 195.56$ and 180.05 ppm due to the keto and amide carbonyl carbons. The

signals due to aromatic carbons were appeared at δ 110.23–164.48 ppm while that of hexahydro-pyrrolizine carbons at δ 27.39–73.71 ppm, among which δ 73.71 ppm was due to the spiro carbon. Due to the *para*-fluoro substituent in one of the phenyl rings, three phenyl carbon signals of this ring in ^{13}C -NMR spectrum, the signals were split into doublets due to 2, 3 and 4 bond coupling with ^{19}F . DEPT 135 spectrum of compound **4** exhibited -ve signals at δ 26.68, 29.54, 47.49 ppm which could be attributed to methylene C-5', C-6' and C-7' carbons of pyrrolizine ring. The signals for C-1', C-2' and C-8' carbons of pyrrolizine ring appeared as +ve signals at δ 52.08, 63.09, 71.52 ppm. Mass spectrum showed a molecular ion peak at m/z 427.1 ($\text{M}^+ + 1$, 92.56% at RT = 0.987 min) corresponding to the molecular formula of $\text{C}_{27}\text{H}_{23}\text{FN}_2\text{O}_2$. UV-visible spectra showed a maximum absorption peak at 260 nm. Elemental analysis also gave satisfactory results for the title compound.

The compound was screened for its reducing power assay according to the method described by Oyaizu [19]. The EC_{50} value for the title compound **4** was comparable with the standard, ellagic acid. The good reducing power capacity of this compound might be due to the presence of free NH group in the molecule

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 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 and DEPT-135 (100 MHz) spectra were recorded at 100 MHz with TMS as internal standard. 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). A UV-Visible spectrophotometer (SHIMADZU, Model No.: UV-2550) with 1 cm matched quartz cells was used for the absorbance measurements.

A mixture of isatin **1** (0.01 mol, 1.4 g), L-proline **2** (0.01 mol, 1.15 g) and 1-(4-fluorophenyl)-3-phenylprop-2-en-1-one **3** (0.01 mol, 2.26 g) in ethanol was refluxed for 24 h. After the completion of reaction, as indicated by TLC, the reaction mixture was cooled to room temperature and quenched with ice cold water. The resulting precipitate was filtered and recrystallized from methanol. Yield was 82%.

Melting point: 178–182 °C.

LCMS: m/z = 427.1 ($\text{M}^+ + 1$).

IR (KBr): ν_{max} (cm^{-1}), 3194 (NH), 3078 (ArH), 2962, 2868 (Aliphatic CH), 1734 ((4-fluorophenyl)carbonyl), 1676 (amide carbonyl), 1597, 1469 (Ar C=C), 1236 (C-F).

^1H -NMR (400 MHz, CDCl_3): δ ppm, 1.69 (m, 2H, protons attached to C-7' of pyrrolizine ring), 1.85 (m, 2H, protons attached to C-6' of pyrrolizine ring), 1.99 (m, 1H, proton attached to C-8' of pyrrolizine ring), 2.60 (m, 2H, proton attached to C-5' of pyrrolizine ring), 3.86 (t, 2H, J = 10.8 Hz, proton attached to C-1' of pyrrolizine ring), 4.86 (d, 1H, J = 11.2 Hz, proton attached to C-2' of pyrrolizine ring), 6.56–7.48 (m, 13H, Ar-H), 7.50 (s, 1H, NH).

^{13}C -NMR (100 MHz, CDCl_3 , δ ppm): 27.39, 30.83, 48.55, 53.15, 64.58, 72.26, 73.71, 110.23, 115.41, (d), 122.62, 127.30, 127.85, 128.32, 128.95, 129.79, 130.75 (d), 133.65, 139.73, 140.59, 164.48 (d) (Aromatic C's), 180.05 (amide C=O), 195.56 (keto C=O). ^{13}C DEPT-135 NMR (100 MHz, $\text{DMSO}-d_6$, δ ppm): 26.68, 29.54, 47.49 (-ve, CH_2), 52.08, 63.09, 71.52 (+ve, CH), 109.55, 115.22 (d), 121.03, 126.68, 127.24, 127.68, 128.56, 129.26, 130.33(d) (Aromatic C's).

UV/Vis (ethanol): λ_{max} (ϵ): 260 nm (18905).

TLC (Hexane: Ethyl acetate, 3:1 v/v): R_f = 0.60.

Elemental analysis: Calculated for $\text{C}_{27}\text{H}_{23}\text{FN}_2\text{O}_2$, C, 76.04%; H, 5.44%; N, 6.57%; Found: C, 76.06%; H, 5.48%; N, 6.51%.

Reducing Power Assay

The reducing power of the synthesized compound was determined according to the method described by Oyaizu [19]. A sample of concentration 500 $\mu\text{g/mL}$ in DMSO (1 mL) was mixed with phosphate buffer (2.5 mL, 0.2 M, pH 6.6) and potassium ferricyanide (2.5 mL, 1% solution). The mixture was incubated at 50 $^\circ\text{C}$ for 20 min. After which 10% trichloroacetic acid (2.5 mL) was added to the mixture, which was then centrifuged for 10 min. The upper layer of solution (2.5 mL) was mixed with distilled water (2.5 mL) and FeCl_3 (0.5 mL, 0.1%) and then the absorbance at 700 nm was measured using a spectrophotometer. The EC_{50} value for the synthesized compound **4** was $3,164.55 \pm 0.42$ while that of standard (ellagic acid) was $3,048.78 \pm 0.26$.

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