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Short Note

N-[2-(1*H*-Indol-3-yl)ethyl]-2-(4-isobutylphenyl)propanamide

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Abstract: The compound in the title was prepared by reaction between tryptamine and ibuprofen using *N*,*N*′-dicyclohexylcarbodiimide as a "dehydrating" reagent. The structure of the newly synthesized compound was determined by nuclear magnetic resonance (NMR) (^{1}H-NMR and ^{13}C-NMR), UV, IR, and mass spectral data.

Keywords: tryptamine; Ibuprofen; DCC; amide

1. Introduction

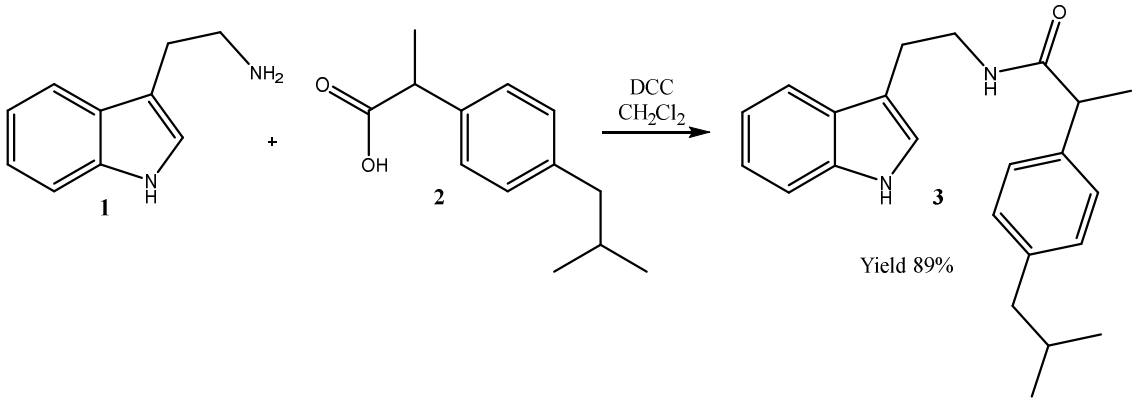
2-Arylpropanoic acids are an important class of non-steroidal anti-inflammatory drugs (NSAIDs) [1]. They are widely used for the treatment of various types of arthritis and musculoskeletal disorders [2–7]. One of the most widely used NSAIDs is ibuprofen (**2**) or 2-(4-isobutylphenyl) propionic acid, well known for its analgesic, antipyretic, and anti-inflammatory properties [8,9]. On the other hand, tryptamine (**1**) and its derivatives are known for their vast array of biological activities [10–18]. Because of the importance of amides for the pharmaceutical industry, a coupling between ibuprofen with tryptamine via amide bond formation was achieved to obtain *N*-[2-(1*H*-indol-3-yl)ethyl]-2-(4-isobutylphenyl)propanamide (**3**).

2. Results

In this paper, we report the successful synthesis of *N*-[2-(1*H*-indol-3-yl)ethyl]-2-(4-isobutylphenyl) propanamide (**3**) as shown in Scheme 1.

A convenient method for the preparation of amides is through *N*,*N*′-dicyclohexylcarbodiimide (DCC) mediated coupling between amines and carboxylic acids. DCC is a dehydrating agent commonly used for the preparation of esters, amides, and anhydrides. It is commercially available as a white crystalline substance with a low melting point of 34–35 °C. DCC reacts with the carboxyl group of ibuprofen to produce an activated acylating agent that reacts with the amino group of the other molecule to form an amide bond.

The obtained compound was identified by melting point, ^{1}H- and ^{13}C-NMR, UV, IR and HRMS spectra. The obtained spectra can be seen at the supplementary information file.



Scheme 1. Synthesis of *N*-[2-(1*H*-indol-3-yl)ethyl]-2-(4-isobutylphenyl)propanamide (**3**).

Compound **3** was obtained as a white solid with an 89% yield, its melting point was recorded at 93–95 °C. The UV spectrum exhibited absorption maxima λ_{max} 221, 280 nm. The mass of the compound in the HRMS spectrum was found to be m/z = 349.2264 $[M+H]^+$ (calcd: 349.2274).

3. Materials and Methods

All reagents and chemicals were purchased from commercial sources (Sigma-Aldrich S.A., Sofia, Bulgaria) and used as received. The melting points were determined on a Boetius hot stage apparatus and are uncorrected. The spectral data were recorded on a Bruker Avance II+600 spectrometer (BAS-IOCCP, Sofia, Bulgaria). ^{1}H-NMR and ^{13}C-NMR spectra for compound **3** were taken in $CDCl_3$ at 600 MHz and at 150.9 MHz, respectively. Chemical shifts are given in ppm relative to tetramethylsilane (TMS) (δ = 0.00 ppm) as an internal standard and the coupling constants are indicated in Hz. The NMR spectra were recorded at room temperature (ac. 295 K). Mass analyses were carried out on a Q Exactive Plus mass spectrometer (ThermoFisher Scientific) equipped with a heated electrospray ionization (HESI-II) probe (ThermoScientific) (Medical University of Sofia, Sofia, Bulgaria). TLC was carried out on precoated 0.2 mm Fluka silica gel 60 plates, using diethyl ether/*n*-hexane = 1/1 as chromatographic system.

Synthesis of N-[2-(1H-Indol-3-yl)ethyl]-2-(4-isobutylphenyl)propanamide (**3**)

N,*N*′-dicyclohexylcarbodiimide (1 mmol) was added to a solution of ibuprofen (1 mmol) in CH_2Cl_2. The reaction mixture was stirred at room temperature for 10 min. After the addition of tryptamine (1 mmol) the reaction mixture was stirred for 50 min and formation of white crystalline dicyclohexylurea was observed and then separated by filtration over a sintered glass filter. The filtrate was washed with diluted hydrochloric acid, saturated solution of Na_2CO_3, and brine. The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure.

N-[2-(1H-Indol-3-yl)ethyl]-2-(4-isobutylphenyl)propanamide (**3**). White solid (m.p. 93–98 °C), Yield 89%, ^{1}H-NMR (600 MHz, $CDCl_3$) δ ppm 8.08 (s, 1H), 7.45 (d, J = 7.9 Hz, 1H), 7.27 (dd, J = 8.2, 0.7 Hz, 1H), 7.11 (ddd, J = 16.3, 8.6, 5.0 Hz, 1H), 7.04–7.01 (m, 3H), 6.99–6.97 (m, 2H), 5.39 (s, 1H), 3.47 (dq, J = 12.9, 6.5 Hz, 1H), 3.43–3.35 (m, 2H), 2.84–2.74 (m, 2H), 2.37 (dd, J = 7.2, 2.6 Hz, 2H), 1.80–1.73 (m, 1H), 1.40 (d, J = 7.2 Hz, 3H), 1.29–1.22 (m, 1H), 0.83 (s, 3H), 0.82 (s, 3H); ^{13}C-NMR (151 MHz, $CDCl_3$) δ ppm 174.46, 140.61, 138.58, 136.34, 129.54 overlapped (2×CHAr), 127.39 overlapped (2×CHAr), 127.24, 126.92, 122.08, 119.40, 118.69, 112.79, 111.23, 46.81, 45.03, 39.78, 30.24, 25.16, 22.43 overlapped (2×CH_3), 18.47. λ_{max}, MeOH: 221, 280 nm. HRMS (ESI) m/z calcd for $C_{23}H_{29}N_2O$ m/z = 349.2274 $[M+H]^+$, found 349.2264. IR(KBr) ν_{max}, cm^{-1}: 699, 734, 768, 779, 810, 846 γ(C_{sp^2}-H); 1383 δ_s (CH_3); 1456, 1567, 1641, 1654 ν(C=C); 1672, 1701 ν(C=O); 2856 ν(CH_2); 2923 ν_{as}(CH_2); 2954, ν_{as}(CH_3); 3019, 3049, 3093 ν(C_{sp^2}-H); 3294 ν(N-H).

Supplementary Materials: The following are available online. Figure S1: ^{1}H-NMR spectrum of compound **3**, Figure S2: ^{13}C-NMR spectrum of compound **3**, Figure S3: UV spectrum of compound **3**, Figure S3: UV spectrum of compound **3**, Figure S5: IR spectrum of compound **3**.

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Conflicts of Interest: The authors declare no conflict of interest.

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