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Short Note

4-Amino-5-benzoyl-1-benzyl-2-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)-1*H*-pyrrole-3-carbonitrile

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Abstract: The title compound, 4-amino-5-benzoyl-1-benzyl-2-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)- 1*H*-pyrrole-3-carbonitrile, was synthesized for the first time in a 40% yield by the reaction of *N*-benzyl-3-imino-5,6,7,8-tetrahydro-3*H*-pyrrolo[1,2-*a*]indol-1-amine and 1-chloroacetophenone in a K_2CO_3/MeCN system (reflux, 6 h). The product was characterized by ^{1}H-NMR, ^{13}C-NMR, IR spectroscopy, and elemental analysis.

Keywords: 2,2′-bipyrroles; 1-amino-3-imino-3*H*-pyrrolizine; 1-chloroacetophenone; K_2CO_3/MeCN system

1. Introduction

4-Amino-5-benzoyl-1-benzyl-2-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)-1*H*-pyrrole-3-carbonitrile **1** belongs to the class of 2,2′-bipyrroles, which are of interest as basic building blocks for the synthesis of pyrrolic macrocycles and natural products, such as prodigiosins, promising biomolecules with many potential applications [1,2]. 2,2′-Bipyrroles are extensively employed for the design of many synthetic porphyrinoids [3,4], which are used as anion binding agents [5], ion chemosensors [6], antitumor agents [7,8], and photosentizers for the photodynamic therapy (PDT) [9] as well as for conducting polymers [10]. 2,2′-Bipyrroles with electron-withdrawing benzoyl groups are highly polarized, which induces dipole−dipole interaction, π−π stacking, and hydrogen-bonding interaction leading to unique self-assemblies to functional materials [3,11,12]. Such features of bipyrroles impart interesting properties to porphyrinoids [13], and therefore their synthesis attracts ever-growing interest of the synthetic community. The methods for the preparation of 2,2′-bipyrroles, including the most common Ullmann coupling of α-halogenated pyrroles, Lewis-acid-catalyzed pyrrolinone condensation, and oxidative dimerization of pyrroles, are summarized in the reviews [1,3,4].

2. Result

4-Amino-5-benzoyl-1-benzyl-2-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)-1*H*-pyrrole-3-carbonitrile (**1**) was synthesized according to our previously developed method [14,15] by the reaction of easily available 1-benzyl-3-imino-5,6,7,8-tetrahydro-3*H*-pyrrolo-[1,2-*a*]indol-1-amine (**2**) and 1-chloroacetophenone in K_2CO_3/MeCN system (reflux, 6 h) (Scheme 1). These conditions were proved to be suitable for the synthesis of the target product and ensured its yield of 40%.

The mechanism of compound **1** formation can be rationalized as depicted in Scheme 2. Initially, 1-benzyl-3-imino-5,6,7,8-tetrahydro-3*H*-pyrrolo[1,2-*a*]indol-1-amine (**2**) is alkylated with 1-chloroacetophenone to form the corresponding ketone **A**. The latter undergo the proton abstraction from the active CH_2 group, then carbanion **B** thus obtained intramolecularly attacks the nitrile's electrophilic carbon with simultaneous the pyrrolizine

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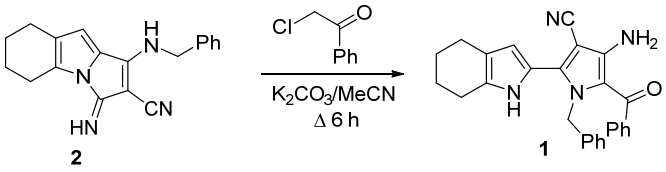
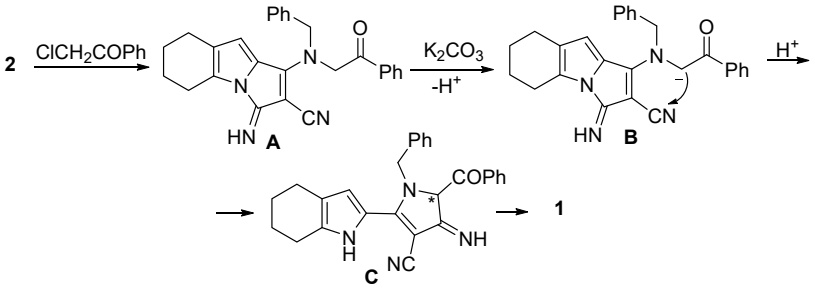
ring-opening and formation of iminopyrroline **C** with chiral center. Its further aromatization via the proton transfer from asymmetric carbon atom to imino-group finishes this process.



Scheme 1. Synthesis of 4-amino-5-benzoyl-1-benzyl-2-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)- 1*H*-pyrrole-3-carbonitrile (**1**).



Scheme 2. Possible mechanism of 2,2′-bipyrrole **1** formation.

The structure and composition of the synthesized 2,2′-bipyrrole **1** were confirmed by ^{1}H, ^{13}C NMR, IR spectroscopy (see Supplementary Materials). Elemental analysis establishes the chemical formula of compound **1**.

Thus, we synthesized new 2,2′-bipyrrole, 4-amino-5-benzoyl-1-benzyl-2- (4,5,6,7-tetrahydro-1*H*-indol-2-yl)-1*H*-pyrrole-3-carbonitrile, which, in addition to the benzoyl group, has amino and nitrile functions located in neighboring positions. The obtain polyfunctionalized bipyrrole represents a possible intermediate for the synthesis of novel purine analogs that can further expand synthetic application of this compound.

3. Materials and Methods

NMR spectra were recorded on a Bruker DPX-400 spectrometer (Bruker, Billerica, MA, USA) (400.1 MHz for ^{1}H and 100.6 MHz for ^{13}C) in $CDCl_3$. The internal standards were HMDS (for ^{1}H) and the residual solvent signals (for ^{13}C). Coupling constants (*J*) were measured from one-dimensional spectra, and multiplicities were abbreviated as follows: s (singlet), br. s (broad singlet), d (doublet), and m (multiplet). IR spectra were recorded on a two-beam Bruker Vertex 70 spectrometer (Bruker, Billerica, MA, USA), in a KBr pellet. Elemental analyses (C, H, N) were performed on an EA FLASH 1112 Series (CHN Analyzer) instrument (Thermo Finnigan, Italy). Melting points (uncorrected) were measured using a Stuart Scientific melting point SMP3 apparatus.

Synthesis of 4-amino-5-benzoyl-1-benzyl-2-(4,5,6,7-tetrahydro-1H-indol-2-yl)- 1H-pyrrole-3-carbonitrile (**1**)**.** The mixture of 1-benzyl-3-imino-5,6,7,8-tetrahydro-3*H*-pyrrolo[1,2-*a*]indol-1-amine (**2**) (154 mg, 0.51 mmol), K_2CO_3 (95 mg, 0.61 mmol) and 1-chloroacetophenone (106 mg, 0.77 mmol) in MeCN (8 mL) was refluxed for 6 h. After cooling the reaction mixture to room temperature, the precipitate was filtered off and washed with MeCN (3 × 3 mL). The filtrate was concentrated under reduced pressure. By column chromatography of the residue (Al_2O_3, eluent *n*-hexane and systems of *n*-hexane/diethyl ether gradient from 4:1 to 1:4) 2,2′-bipyrrole **1** was obtained (84 mg, 40%) as yellow crystals, mp 198–200 °C (*n*-hexane). IR spectrum (KBr), ν, cm^{-1}: 3476, 3414, 3339, 3229, 3080, 2923, 2849, 2218, 1601, 1570, 1499, 1463, 1430, 1367, 1293, 1237, 1148, 1076, 1004, 809, 738, 698. ^{1}H NMR ($CDCl_3$, ppm): δ 8.27 (br. s, 1H, NH), 7.49–7.45 (m, 3H, Ho,p, COPh), 7.41–7.37 (m, 2H, Hm, COPh), 7.21–7.18 (m, 3H, Hm,p, CH_2Ph), 6.80–6.79 (m, 2H, Ho, CH_2Ph), 6.26 (d, *J* = 2.1 Hz, 1H, H-3), 5.39 (s, 2H, CH_2, C$\underline{H_2}$Ph), 4.51 (br. s, 2H, NH_2), 2.57–2.54 (m, 2H, CH_2-7), 2.47–2.44

(m, 2H, CH_2-4), 1.82–1.76 (m, 2H, CH_2-6), 1.74–1.68 (m, 2H, CH_2-5). ^{13}C NMR ($CDCl_3$, ppm): 184.2 (C=O), 147.2 (C-4), 140.4 (Ci, PhCO), 140.2 (Cp), 137.5 (Ci, $PhCH_2$), 132.3 (C-7a), 131.4 (Cp, PhCO), 128.9 (2C, m, PhCO), 128.7 (2C, m, $PhCH_2$), 127.9 (2C, o, PhCO), 127.5 (Cp, $PhCH_2$), 126.1 (2C, o, $PhCH_2$), 119.8 (C-3a), 116.8 (CN), 116.7 (C-5), 115.8 (C-2′), 112.5 (C-3′), 80.9 (C-3), 51.2 ($\underline{C}H_2Ph$), 23.4, 23.0, 22.8, 22.7 (CH_2-4,5,6,7). Anal. calcd. for $C_{27}H_{24}N_4O$ (%): C, 77.12; H, 5.75; N, 13.32. Found (%): C, 77.28; H, 5.57; N, 13.46.

Supplementary Materials: The followings can be downloaded online. Copies of ^{1}H NMR, ^{13}C NMR, IR spectra.

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