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Short Note

3-Carbamoylmethyl-Indole-1-Carboxylic Acid Ethyl Ester

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Abstract: 3-Carbamoylmethyl-Indole-1-Carboxylic Acid Ethyl Ester (an ethoxycarbonyl derivative of indole-3-acetamide) is obtained by Friedel–Crafts type cyclocondensation of γ-functionalized acetoacetamide in neat polyphosphoric acid.

Keywords: indole; indole-3-acetamide; polyphosphoric acid

1. Introduction

The abundance of indole derivatives in nature makes this heterocycle an attractive target for the synthetic chemists [1]. Many approaches for the synthesis of indoles have been developed over the years and this field of research has been extensively and systematically reviewed [2]. Among the vast number of natural indole derivatives, indole-3-acetic acid occupies a special place with its simple structure and high importance as a plant hormone [3]. The amides of indole-3-acetic acid have similarly attracted significant attention, not only as plant growth regulation agents [4], but also with other biological activities. For example, indole-3-acetamide moiety is present in some spider toxins [5,6], in isoprenylcysteine carboxyl methyltransferase inhibitors [7,8] and in some inhibitors of heme-based dioxygenases [9]. From synthetic point of view, the indole-3-acetamides are most often obtained from the corresponding indole-3-acetic acids [4–6]. An interesting new approach to these compounds is the palladium-catalyzed ketenimination of 2-iodo-*N*-(propa-1,2-dien-1-yl)-anilines [10]. The cyclocondensation of appropriate γ-(*N*-phenyl)-β-keto amides in the presence of a Lewis acid is another approach that has been tried in the past, but with very limited success [11], not least because of the limited availability of the corresponding starting materials.

2. Results

N-protected γ-amino-β-keto amides have recently become easily accessible to us, thanks to a novel methodology developed within our group [12]. This gave us the opportunity to reinvestigate the cyclocondensation approach to indole-3-acetamides and to try the intramolecular Friedel–Crafts reaction on ethoxycarbonyl-protected γ-(*N*-phenyl)-β-keto amide **1** (Scheme 1). We chose to do that in neat polyphosphoric acid—conditions that have previously allowed us to construct six-membered rings and to prepare quinolin-2-ones from similar starting materials [13]. The cyclisation of β-keto amide **1** in PPA proceeded cleanly for 3 h at 80 °C and gave the expected indole-3-acetamide **2** in 80% yield. Compared with the aforementioned synthesis of quinolin-2-ones [13] the reaction here is slower, but nevertheless gives good yield of the indole derivative, with retention of the ethoxycarbonyl group in the newly formed indole ring. Indole-3-acetamide protected in this way could be of use as a building block in the synthesis of more complicated indole derivatives. If necessary, the ethoxycarbonyl group in position 1 of the indole ring can be quantitatively removed at a later stage with the help of *t*-BuNH$_2$ [14].

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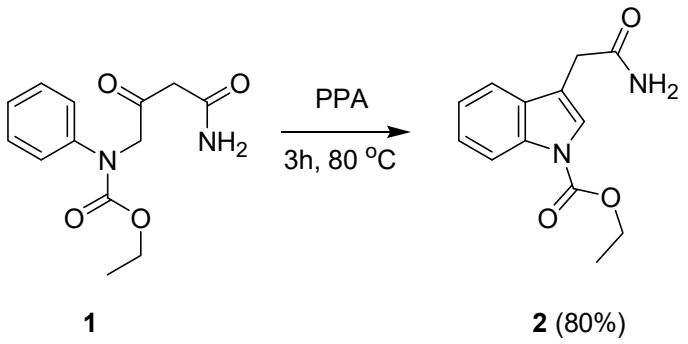

Scheme 1. Synthesis of 3-carbamoylmethyl-indole-1-carboxylic acid ethyl ester.

3. Materials and Methods

The starting material ((3-Carbamoyl-2-oxo-propyl)-phenyl-carbamic acid ethyl ester, **1**) was prepared from acetoacetamide and *N*-phenylglycine according to our previously published method [12]. Polyphosphoric acid (115% H_3PO_4 basis, CAS No. 8017-16-1) was purchased from Sigma-Aldrich, Darmstadt, Germany. NMR spectra were run on a Bruker Avance AV600 (600/150 MHz $^1H/^{13}C$) spectrometer (Bruker, Billerica, MA, USA) at BAS-IOCCP—Sofia and chemical shifts (δ, ppm) are downfield from TMS. Raw and processed NMR spectra in two different solvents are available as supplementary material. High resolution mass spectral measurements were performed on a Thermo Scientific Q Exactive hybrid quadrupole-orbitrap mass spectrometer (Waltham, MA, USA). TLC was conducted on 60 sheets of aluminum-backed Silica gel (Merck) with $KMnO_4$ staining; melting point measurement was conducted on Boetius hot stage apparatus (Carl Zeiss Jena, Germany) and is not corrected.

*Synthesis of 3-Carbamoylmethyl-indole-1-carboxylic acid ethyl ester (***2***):* to 264 mg (1 mmol) of (3-Carbamoyl-2-oxo-propyl)-phenyl-carbamic acid ethyl ester (**1**) in a glass vial was added PPA (5–6 g). The mixture was heated to 80 °C and was stirred intensely until full homogenization (ca. 10 min). The homogenous mixture was left for further 3 h at 80 °C, then the vial was cooled to r.t. with tap water and the contents were rinsed and poured into a glass with 50–70 mL of water. The product was extracted in CH_2Cl_2 (3 × 30 mL), the combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was washed with small amount of diethyl ether to afford compound **2** as a white solid with m.p. 121–122 °C; R_f = 0.55 (Et_2O:MeOH 20:1); ^1H NMR (DMSO-d_6, δ ppm, *J* Hz): 1.39 (t, *J* = 7.0, 3H), 3.50 (s, 2H), 4.43 (q, *J* = 7.0, 2H), 6.99 (br s, 1H), 7.26 (m, 1H), 7.34 (m, 1H), 7.52 (br s, 1H), 7.59 (s, 1H), 7.61 (d, *J* = 7.6, 1H), 8.08 (d, *J* = 7.6, 1H); ^{13}C NMR (DMSO-d_6, δ ppm): 14.7, 32.2, 63.6, 115.1, 116.5, 120.1, 123.1, 124.2, 125.0, 130.7, 135.2, 150.8, 172.0; HRMS (ES+): *m/z* $[M+Na]^+$ calcd for $C_{13}H_{14}N_2NaO_3^+$: 269.0897, found: 269.0895.

Supplementary Materials: The following are available online. S1.PDF—processed ^1H and ^{13}C NMR spectra. S2.zip—Raw NMR data. S3.mol—mol file.

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

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