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Short Note

Ethyl 2-[2-(4-Nitrobenzoyl)-1*H*-indol-3-yl]acetate

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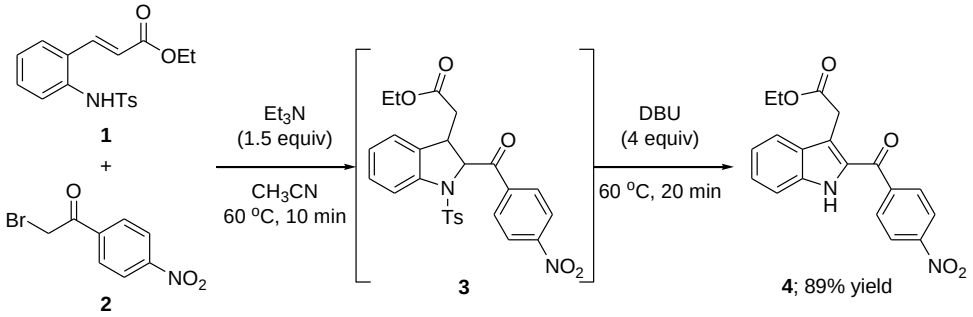
Abstract: Ethyl 2-[2-(4-nitrobenzoyl)-1*H*-indol-3-yl]acetate was prepared in good yield and characterized by the aza-alkylation/intramolecular Michael cascade reaction of (*E*)-ethyl 3-[2-(tosylamino)phenyl]acrylate with 2-bromo-4′′-nitroacetophenone, followed by desulfonative dehydrogenation with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) The structure of the newly synthesized compound was determined using ^{1}H-,^{13}C-NMR, IR and mass spectral data.

Keywords: Indole; Michael reaction; dehydrogenation; cascade reaction

1. Introduction

Indoles are well established as privileged scaffolds, commonly encountered in many biologically active natural products and pharmaceuticals [1–3]. More than 10,000 biologically active indole derivatives have been identified, and more than 200 derivatives are currently known as pharmaceuticals or undergoing clinical trials [4]. Among the indoles, 2-aroyl indole-3-acetic acid derivatives, which are an important subclass of 2,3-disubstituted indoles [5], have attracted attention as a promising pro-drug for anticancer and antitumor activities [6,7]. In continuation of our research interest in 2-aminophenyl α,β-unsaturated carbonyl compounds for the synthesis of highly functionalized indole derivatives [8–10], we report here the preparation of a novel ethyl 2-[2-(4-nitrobenzoyl)-1*H*-indol-3-yl]acetate [11–13].

The synthesis of the title compound **4** was achieved in one-pot, as presented in Scheme 1, which was performed by the aza-alkylation/intramolecular Michael cascade reaction of (*E*)-ethyl 3-[2-(tosylamino)phenyl]acrylate (**1**) with 2-bromo-4′-nitroacetophenone (**2**), followed by desulfonative dehydrogenation. The reaction was carried out in acetonitrile at 60 °C in the presence of triethylamine as a base and provided the indolineinter mediate **3** within 10 min. To the resulting mixture 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was added and gave the desired product in good yield within 20 min. The structure of compound **4** was confirmed by ^{1}H- and ^{13}C-NMR, IR, mass spectral data, and all data are in accordance with the assumed structure.



Scheme 1. Synthesis of ethyl 2-[2-(4-nitrobenzoyl)-1*H*-indol-3-yl]acetate (**4**).

2. Experimental Section

2.1. General Information

All reagents were used as received without further purification. Chromatographic purification of the title compound **4** was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 (Merck, Darmstadt, Germany). Thin-layer chromatography (TLC) (Merck, Darmstadt, Germany) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Developed chromatograms werevisualized by fluorescence quenching and anisaldehyde stain. ^{1}H- and ^{13}C-NMR spectra were recorded on a 400 MHz instrument (Bruker BioSpin GmbH, Karlsruhe, Germany) as noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H-NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C-NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer (Bruker Optics GmbH, Ettlingen, Germany), and reported in terms of frequency of absorption (cm^{-1}). High-resolution mass spectrometry data were recorded on a JEOL JMS-700 MStation mass spectrometer (JEOL, Tokyo, Japan).

*2.2. Syntheis of ethyl 2-[2-(4-nitrobenzoyl)-1H-indol-3-yl]acetate(**4**)*

To a solution of (*E*)-ethyl 3-[2-(tosylamino)phenyl]acrylate (**1**, 35 mg, 0.10 mmol, 1.0 equiv) in CH_3CN (0.5 mL), 2-bromo-4′-nitroacetophenone (**2**, 37 mg, 0.15 mmol) and Et_3N (21 µL, 0.15 mmol,) were added at room temperature. After stirring the resulting mixture for 10 min at 60 °C, DBU (60 µL, 0.40 mmol) was added. The resulting mixture was stirred further for 20 min at 60 °C, and saturated aqueous $NaHCO_3$ was added. The mixture was then extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo.The crude product waspurified on silica gel column chromatography using ethyl acetate and hexane (1/10) as eluents to afford the desired title compound **4** (89%, 31 mg).White solid; m.p. 163–165 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.31 (d, *J* = 8.7 Hz, 2H), 7.85 (d, *J* = 8.7 Hz, 2H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.45–7.34 (m, 2H), 7.19 (ddd, *J* = 8.0, 5.1, 2.8 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.76 (s, 2H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 186.46, 170.80, 149.62, 144.18, 136.83, 131.36, 129.69, 128.16, 127.29, 123.72, 121.30, 121.13, 117.51, 112.44, 61.23, 31.16, 14.17.; IR (film) 3322, 2934, 1722, 1616, 1598, 1522, 1433, 1370, 1331, 1257, 1215, 1170, 1103, 1028, 1008, 990 cm^{-1}; HRMS (EI) *m*/*z* calcd for $[M]^+$ $C_{19}H_{16}N_2O_5$: 352.1059 Found: 352.1051.

Supplementary Materials: ^{1}H- and^{13}C-NMR spectra for compound **4** are available online.

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

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