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Short Note

Methyl 9-(1-methyl-1H-indol-3-yl)-9-oxononanoate

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Abstract: Methyl 9-(1-methyl-1*H*-indol-3-yl)-9-oxononanoate was synthesized using Friedel–Crafts acylation between *N*-methyl indole and methyl 9-chloro-9-oxononanoate. The structure of the newly synthesized compound was elucidated using ^{1}H-NMR, ^{13}C-NMR, NOESY-1D, ESI-MS, FT-IR, and UV-Vis spectroscopy.

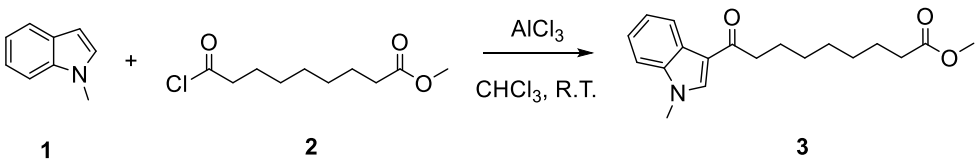
Keywords: indole; azelaic acid; acylation; Friedel–Crafts

1. Introduction

Friedel–Crafts acylation [1–4] is one of the most used reactions in organic synthesis to attach an acyl group to an aromatic ring. It occurs with a plethora of aromatics and heteroaromatics; the keto derivative produced can be, in turn, subjected to many transformations. Friedel–Crafts acylation on 1-substituted indoles occurs regioselectively on the 3-position and the products are key structural units in alkaloids, drugs, and pharmaceuticals, including anticancer agents [5–7]. Recently, antiproliferative activity against a panel of human cancer cell lines has been showed using hybrid compounds bearing a heterocyclic moiety (i.e., pyridinyl-, pyrimidinyl-, and benzothiazolyl-) connected to an azelayl chain [8,9]. Herein, we report the synthesis of a new hybrid of possible interest as an anticancer agent, namely methyl 9-(1-methyl-1*H*-indol-3-yl)-9-oxononanoate, obtained using Friedel–Crafts acylation between *N*-methyl indole and methyl 9-chloro-9-oxononanoate.

2. Results

The synthesis of methyl 9-(1-methyl-1*H*-indol-3-yl)-9-oxononanoate (**3**) was performed using Friedel–Crafts acylation in chloroform at room temperature on *N*-methyl indole (**1**) with methyl 9-chloro-9-oxononanoate (**2**) in an equimolar amount and in the presence of $AlCl_3$ (Scheme 1). The reaction course was monitored using thin layer chromatography (TLC) that showed the presence of compound **3** together with other unidentified by-products. At the end of the reaction, the product was purified and recovered in a 40% yield using column chromatography on silica gel with a mixture of light petroleum and diethyl ether, 3/7 *v*/*v* ratio, as the eluent. The newly synthesized compound was characterized using ^{1}H-NMR, ^{13}C-NMR, DEPT, NOESY-1D, ESI-MS, FT-IR, and UV-Vis spectroscopy.



1 **2** **3**

Scheme 1. Synthesis of methyl 9-(1-methyl-1*H*-indol-3-yl)-9-oxononanoate (**3**).

In particular, the diagnostics to ascertain the structure of compound **3** were: the presence of the IR bands at ν = 1725 cm^{-1} and 1642 cm^{-1} due to ester and carbonyl stretching modes, respectively, and the NOESY-1D experiment (see Supplementary Materials Figure S4). In the

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latter case, when irradiating the signal at 7.71 ppm (CH adjacent to the nitrogen atom of the heterocyclic indole ring), a positive NOE effect was recorded with the methyl group bound to the nitrogen atom and the methylene in the alpha position to the carbonyl group.

3. Materials and Methods

The ^{1}H-NMR, ^{13}C-NMR, NOESY-1D and DEPT (Distortionless Enhancement by Polarization Transfer) spectra were recorded on an Inova 600 (Varian, Palo Alto, CA, USA) spectrometer operating at 600 MHz (for ^{1}H-NMR) and at 150 MHz (for ^{13}C-NMR). The chemical shifts are referenced to the solvent for ^{1}H and ^{13}C-NMR (δ = 7.26 ppm and δ = 77.0 ppm, respectively, for $CDCl_3$). The signal multiplicities were established using DEPT experiments. The chemical shifts were measured in δ (ppm). The *J* values are provided in Hertz. The electron spray ionization mass spectra (ESI-MS) were recorded using a WATERS 2Q 4000 instrument (Waters Corporation, Milford, MA, USA). The IR spectra were recorded on a Perkin Elmer FT-IR Mod. 1600 spectrophotometer (Perkin Elmer, Waltham, MA, USA). The UV/Vis spectra were recorded on a PerkinElmer Lambda 12 spectrophotometer (Perkin Elmer, Waltham, MA, USA), at 20 °C in $CDCl_3$ and in quartz cells (path length cell: 1 cm). The melting points (m.p.) were measured on Büchi 535 apparatus (Büchi, Flawil, Switzerland). The chromatographic purifications (FC) were carried out on glass columns packed with silica gel (Merck grade 9385, 230−400 mesh particle size, 60 Å pore size) at medium pressure (Merck & Co., Readington, NJ, USA). Thin layer chromatography (TLC) was performed on silica gel 60 F_{254}-coated aluminum foils (Fluka, Buchs, Switzerland). The methyl 9-chloro-9-oxononanoate was prepared as previously reported [8], while the *N*-methyl indole was purchased by Sigma-Aldrich (Milan, Italy), as well as all the other reagents and solvents used.

*Methyl 9-(1-methyl-1H-indol-3-yl)-9-oxononanoate (**3**)*

The methyl 9-chloro-9-oxononanoate (**2**) (110 mg, 0.5 mmol) was dissolved in chloroform (5 mL) in a round bottomed flask then $AlCl_3$ (80 mg, 0.6 mmol) was introduced. The mixture was magnetically stirred for 15 min then the *N*-methyl indole (**1**, 65.5 mg, 0.5 mmol) was added. The reaction course was monitored using TLC (eluent diethyl ether/petroleum ether 8/2). After 3 h, the reaction was quenched with water (5 mL) then 10% aq. $NaHCO_3$ was added until the pH~8. After extraction with CH_2Cl_2, the organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated 'in vacuo'. The purification of the residue using a chromatography column on silica gel (eluent diethyl ether/petroleum ether 7/3) provided pure product isolated in 40% (63 mg).

Red solid, m.p.: 43.4–44.9 °C; ^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ, ppm: 8.40–8.37 (m, 1H, aromatic C<u>H</u>), 7.72 (s, 1H, aromatic C<u>H</u>), 7.35–7.28 (m, 3H, aromatic C<u>H</u>), 3.84 (s, 3H, C<u>H$_3$</u>N), 3.66 (s, 3H, COOC<u>H$_3$</u>), 2.82 (t, *J* = 7.5 Hz, 2H, C<u>H$_2$</u>CON), 2.30 (t, *J* = 7.6 Hz, 2H, C<u>H$_2$</u>COOCH$_3$), 1.80–1.74 (m, 2H, C<u>H$_2$</u>CH$_2$CON), 1.66–1.59 (m, 2H, C<u>H$_2$</u>CH$_2$COOCH$_3$), 1.44–1.30 (m, 6H, aliphatic C<u>H$_2$</u>); ^{13}C-NMR: (150 MHz, $CDCl_3$, 25 °C) δ, ppm: 195.9 (C), 174.3 (C), 137.4 (C), 135.2 (CH), 126.3 (C), 123.2 (CH), 122.6 (CH), 122.5 (CH), 116.6 (C), 109.5 (CH), 51.4 (CH_3), 39.8 (CH_2), 34.0 (CH_2), 33.4 (CH_3), 29.3 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 25.1 (CH_2), 24.9 (CH_2); FT-IR ($CDCl_3$) ν (cm^{-1}): 3012, 2933, 2860, 1725, 1642, 1526, 1470, 1377, 1215, 1080; UV-Vis λ_{max} = 243 nm, 300 nm; ESI-MS (*m*/*z*): 316 $[M + H]^+$, 338 $[M + Na]^+$, 354 $[M + K]^+$; Elemental Analysis for $C_{19}H_{25}NO_3$, Calculated C, 72.35; H, 7.99; N, 4.44; found C, 72.38; H, 7.97; N, 4.42.

Supplementary Materials: The following are available online: Figure S1. 1H-NMR spectrum in CDCl3 of compound **3**; Figure S2. 13C-NMR spectrum in CDCl3 of compound **3**; Figure S3. DEPT spectrum in CDCl3 of compound **3**; Figure S4. NOESY-1D spectrum for compound **3**; Figure S5. ESI-MS spectrum of compound **3**; Figure S6. FT-IR spectrum in CDCl3 of compound **3**; Figure S7. UV-Vis spectrum in CDCl3 of compound **3**.

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

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