

Short Note

3-Chloro-4-(5-methoxy-1*H*-indol-3-yl)cyclobut-3-ene-1,2-dione

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Received: 18 April 2013 / Accepted: 10 July 2013 / Published: 22 July 2013

Abstract: The indole ring system is a prominent partial structure of several protein kinase inhibitor families. The title compound is the first example of a 5-substituted indolyl squaryl chloride with free indole nitrogen. It has been synthesized by reaction of 5-methoxyindole with squaric acid dichloride in diethyl ether and its IR, ¹H-NMR, ¹³C-NMR, MS, UV and HPLC data are presented. This compound may prove to be a rather useful building block for the preparation of various derivatives for biological studies.

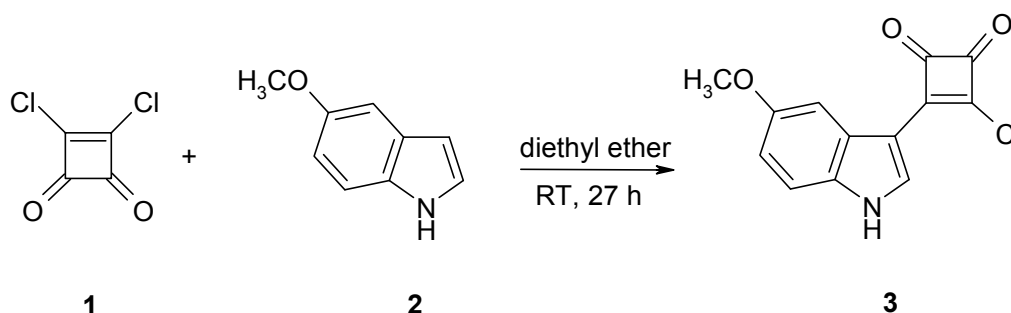
Keywords: Friedel-Crafts acylation; indole; squaric acid dichloride

The indole ring system is a prominent partial structure of several protein kinase inhibitor families, e.g., bisindolylmaleimides (BIMs) [1], staurosporine analogues [2], and paullones [3,4]. With the aim to develop protein kinase inhibitors based on novel scaffolds by structure-guided design methods [5] we were interested to combine the indole ring system with squaric acid derived structure elements. The latter have recently been highlighted as “unusual” chemical structures with high potential for drug development [6]. A review of the literature revealed that only few squarylated indoles are described [7–9]. Only a single study mentioned a 3-chloro-4-(1*H*-indol-3-yl)cyclobut-3-ene-1,2-dione unsubstituted at the indole nitrogen [10]. We here report the detailed synthesis procedure of the title compound **3** as first example of a 5-substituted indolylchlorocyclobutenedione with free indole nitrogen. This compound may prove to be a rather useful building block for the preparation of various derivatives for biological studies.

According to the high reactivity of the indole ring system for electrophilic attack in 3-position, the synthesis was carried out by means of a Friedel-Crafts acylation reaction from 5-methoxyindole (**2**)

and squaric acid dichloride (**1**) in anhydrous diethyl ether in the absence of a Lewis acid catalyst affording the product in moderate to good yields. The reason for using anhydrous diethyl ether was the good solubility of the reactants in this solvent and the fact that the product precipitated readily from the reaction mixture. The electron donating properties of the indole ring diminish the reactivity of the remaining chloride in the product compound, enabling a convenient preparation, isolation and purification of the product. Side-products resulting from a 2+1-reaction of the starting materials or from hydrolysis of the product were not observed.

Scheme 1. Synthesis of 3-chloro-4-(5-methoxy-1*H*-indol-3-yl)cyclobut-3-ene-1,2-dione.



Experimental

General

Melting points were determined in open-glass capillaries on an electric variable heater (Electrothermal IA 9100). FT-IR absorption spectra were recorded on a Thermo Nicolet FT-IR 200 spectrometer using KBr pellets. ¹H-NMR and ¹³C-NMR spectra were recorded on a Bruker Avance DRX-400 (NMR laboratories of the Chemical Institutes of the Technische Universität Braunschweig) using DMSO-*d*₆ as solvent. Chemical shifts are reported as parts per million (ppm) downfield from TMS used as an internal standard. Elemental analyses were recorded on a CE Instruments FlashEA® 1112 Elemental Analyzer. The reactions were monitored by TLC (Macherey-Nagel Polygram SIL G/UV₂₅₄) using a mixture of ethyl acetate and petroleum ether (2:1) as eluent. Mass spectra were recorded on a MAT 95 XL spectrometer (ThermoFinnigan MAT, Bremen, Germany, department of mass spectrometry of the Chemical Institutes of the Technische Universität Braunschweig). HPLC analyses were performed on a Merck Hitachi LaChrom Elite system (pump: L-2130, DAD detector: L-2450; autosampler: L-2200; column: Merck LiChroCART 125-4, LiChrospher 100 RP-18 (5 μm); eluent: acetonitrile/water (50:50), elution rate 1.000 mL/min; detection wavelength: 254 nm and 280 nm; overall run time: 15 min); *t*_{ms} = total retention time, *t*_s = dead time. UV absorption spectra (200 to 600 nm) were recorded on a PU 8700 UV/VIS Spectrophotometer in DMF.

3-Chloro-4-(5-methoxy-1H-indol-3-yl)cyclobut-3-ene-1,2-dione (3)

To squaric acid dichloride (**1**) (151 mg, 1.00 mmol) dissolved in anhydrous diethyl ether (10 mL) was added a solution of 5-methoxyindole (**2**) (147 mg, 1.00 mmol) in the same solvent (5 mL). After stirring for 27 h at room temperature the resulting precipitate was filtered and washed twice with diethyl ether (5 mL). Crystallization from CHCl₃/DMF yielded 0.222 g (74.4 %) of a green solid.

Melting point: 202–207 °C (dec.)

UV (DMF): $\lambda_{\max}$ (log ϵ = 4.26) 365 nm; $\lambda_{\max}$ (log ϵ = 4.19) 266 nm.

MS (EI) m/z (%): 261 [M^+] (48), 205 (100).

IR (KBr) (cm⁻¹): 3464 (N-H), 1776/1740 (C=O).

¹H-NMR (400 MHz, DMSO-*d*₆) δ (ppm): 12.27 (s, 1H, NH), 8.15 (d, 1H, J = 3.0 Hz), 7.85 (d, 1H, J = 2.5 Hz), 7.44 (d, 1H, J = 8.8 Hz), 6.90 (dd, 1H, J = 2.5, 8.8 Hz), 3.80 (s, 3H).

¹³C-NMR (100 MHz, DMSO-*d*₆) δ (ppm): 192.8, 192.3, 171.3, 154.9, 131.5, 125.7, 105.8 (C quat., one C not detectable due to signal overlapping), 129.4, 113.2, 112.6, 104.0 (C tert.), 55.3 (CH₃).

HPLC (AUC %): 99.6% at 254 nm, 99.6% at 280 nm; t_{ms} = 3.26 min; t_s = 1.69 min.

Elemental analysis calculated for C₁₃H₈ClNO₃ (261.02): C, 59.67%; H, 3.08%; N, 5.35%; found: C, 59.55%; H, 2.98%; N, 5.29%.

Acknowledgements

The authors are grateful to B. Babic, S. Meyer and P. Reich for technical assistance.

Conflict of Interest

The authors declare no conflict of interest.

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