

Short Note

3-(1*H*-Indol-3-yl)-4-(morpholin-4-yl)cyclobut-3-ene-1,2-dione

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Abstract: 3-(1*H*-Indol-3-yl)-4-(morpholin-4-yl)cyclobut-3-ene-1,2-dione was obtained in good yields (72–82%) by nucleophilic substitution of 3-chloro-4-(1*H*-indol-3-yl)cyclobut-3-ene-1,2-dione with morpholine.

Keywords: indole; squaryl amide; morpholine

The indole ring system is a widespread structural motif in a variety of biologically active species [1]. While it is obvious to use such a privileged structure as a template for further drug development, it has been suggested that medicinal chemists should direct their attention to “unusual scaffolds” for the sake of novelty and originality [2]. Along these lines, a number of studies report novel bioactive compounds comprising a combination of the indole core with less common motifs such as 2,5-diazabicyclo[2.2.1]heptanes [3], benzazepinones [4–6], epoxides [7], and aroylhydrazides [8]. The squaric acid diamide structure was recently highlighted as an unusual medicinal chemistry scaffold of high potential [2,9]. Surprisingly there are only scattered examples in the literature in which the indole and the squaramide scaffold are combined [10–12]. A survey of the literature revealed only a single study describing the synthesis of indolylsquaryl amides [13]. We here report the preparation of the title compound as the first example of an indolylsquaryl amide unsubstituted at the indole nitrogen. A 1,2-disubstituted analog of the compound is mentioned in the literature without reporting analytical data [13].

In order to establish suitable reaction conditions various ratios of **1** and **2** were stirred in different solvents under reflux (scheme 1, Table 1). The best yields were obtained with ethanol as solvent and a 1:2.2 ratio of **1** and **2**. Exchanging ethanol for acetonitrile did not lead to better results. Furthermore, the replacement of one equivalent of morpholine (**2**) by triethylamine also failed to provide higher yields. The reaction with a 1:1 ratio of **1** and **2** afforded lower yields and unreacted educt **1**. The product precipitated from the reaction mixture and was collected by simple filtration. The work-up of the filtrate increased the yield only by 3–6%. The optimized procedure furnished satisfactory yields of a crystalline product that proved to be stable under ambient storage conditions.

Scheme 1. Synthesis of the title compound **3**.

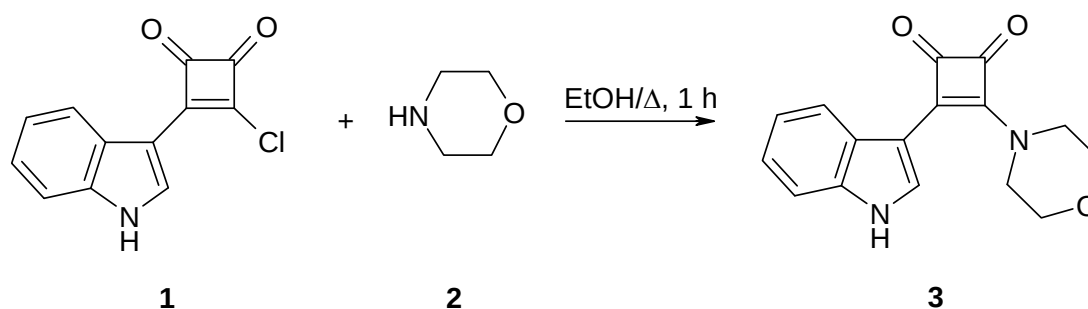


Table 1. Conditons and reagents for optimization of synthesis procedure.

Run	Molar Ratio indolylsquarylchloride (1):morpholine (2)	Moles triethylamine	Solvent	Yield [%]
1	1:1	0	ethanol	46.2
2	1:2.2	0	ethanol	82.3
3	1:1	1	ethanol	70.5
4	1:1	0	acetonitrile	47.2
5	1:2.2	0	acetonitrile	73.2
6	1:1	1	acetonitrile	65.3

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. ¹HNMR and ¹³CNMR 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. The elemental analysis was recorded on a CE Instruments FlashEA[®] 1112 Elemental Analyzer. The reaction was monitored by TLC (Macherey-Nagel Polygram SIL G/UV₂₅₄) using ethyl acetate as eluent. The mass spectrum was recorded on a ThermoFisher Scientific LTQ-Orbitrap Velos (department of mass spectrometry of the Chemical Institutes of the Technische Universität Braunschweig). HPLC was 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 μ m); eluent: acetonitrile/water (30:70), 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.

3-Chloro-4-(1*H*-indol-3-yl)cyclobut-3-ene-1,2-dione (**1**) was synthesized by chlorosquarylation of indole according to the procedure described in lit. [13]. Morpholine was purchased from a commercial supplier and distilled at atmospheric pressure prior to use.

3-(1*H*-Indol-3-yl)-4-(morpholin-4-yl)cyclobut-3-ene-1,2-dione (**3**)

3-Chloro-4-(1*H*-indol-3-yl)cyclobut-3-ene-1,2-dione (**1**) (0.231 g; 1.00 mmol) was added to a solution of morpholine (**2**) (0.192 g; 2.20 mmol) in ethanol (15 mL). This suspension was stirred for 1 h under reflux. After storage at room temperature for 24 h the mixture was filtered through a paper filter. The residue was crystallized from ethanol (99.6%) to yield yellow crystals (0.20–0.23 g; 72–82%; $n = 3$).

Mp: 264–265 °C (dec.).

MS (EI, rel. intensity) m/z : 282.1 [M^+] (30), 226.1 (100).

IR (KBr) (cm^{-1}): 3428 (N-H), 3125 (C-H, arom.), 2916 (C-H, aliph.), 1777 and 1708 (C=O), 1590 (C=C, arom.).

^1H -NMR (400 MHz, DMSO- d_6) δ (ppm): 3.7–3.8 (m, 4H, CH_2), 3.86 (br. s, 4H, CH_2), 7.14 (ddd, 1H, $J = 1.1, 7.1, 8.1$ Hz, CH arom.), 7.21 (ddd, 1H, $J = 1.2, 7.1, 8.2$ Hz, CH arom.), 7.47 (dt, 1H, $J = 8.0, 0.9$ Hz, CH arom.), 7.73 (d, 1H, $J = 2.8$ Hz, CH arom.), 7.91 (dd, 1H, $J = 0.5, 7.8$ Hz, CH arom.), 12.00 (s, 1H, NH).

^{13}C -NMR (100 MHz, DMSO- d_6) δ (ppm): 47.5 (2 C, CH_2), 65.9 (2 C, CH_2), 105.0 (C quat.), 112.0 (CH), 120.3 (CH), 121.6 (CH), 122.5 (CH), 125.6 (C quat.), 127.5 (CH), 136.3 (C quat.), 161.1 (C quat.), 176.3 (C quat.), 188.1 (C quat.), 191.2 (C quat.).

HPLC (AUC %): 99.4% at 254 nm, 99.9% at 280 nm; $t_{ms} = 4.03$ min; t_s (DMSO) = 1.00 min.

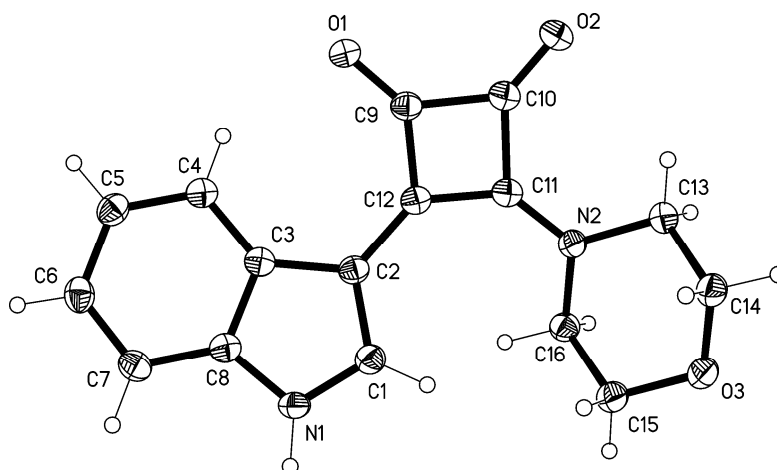
Anal. calculated for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_3$: C, 68.08; H, 5.00; N, 9.92. Found: C, 68.10; H, 4.87; N, 9.79.

X-Ray Structure Determination of **3**

Crystal data: Triclinic, space group $P\bar{1}$, $a = 6.8488(5)$, $b = 8.1491(6)$, $c = 12.2500(8)$ Å, $\alpha = 73.888(7)$, $\beta = 75.955(6)$, $\gamma = 89.166(6)$, $V = 636.18(8)$ Å³, $Z = 2$, $D_x = 1.474$ Mg m⁻³. Data collection: A yellow lath $0.30 \times 0.08 \times 0.04$ mm was mounted on an Oxford Diffraction diffractometer. A total of 19988 intensities were registered using Cu $K\alpha$ radiation to 2θ 152°. The crystal was twinned by 180° rotation about the x axis. Only non-overlapped reflections were used, resulting in a completeness of 92%. Structure refinement: The structure was refined anisotropically on F^2 using the program SHELXL-97 [14]. The NH hydrogen was refined freely; other H were included using a riding model starting from calculated positions. The final $wR2$ was 0.103 for 194 parameters

and 2427 unique reflections, with a conventional $R1$ of 0.038; $S = 1.06$, max. $\Delta\rho = 0.2 \text{ e } \text{\AA}^{-3}$. Complete data have been deposited at the Cambridge Crystallographic Data Centre under the number CCDC-882817. These data can be obtained free of charge from www.ccdc.cam.ac.uk/data_request/cif.

Figure 1. The molecule of compound **3** in the crystal. Ellipsoids represent 50% probability levels.



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