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Short Note

2,3,4-Trioxo-1-(1*H*-pyrrolo[2,3-*b*]pyridin-7-ium-7yl)-cyclobutan-1-ide

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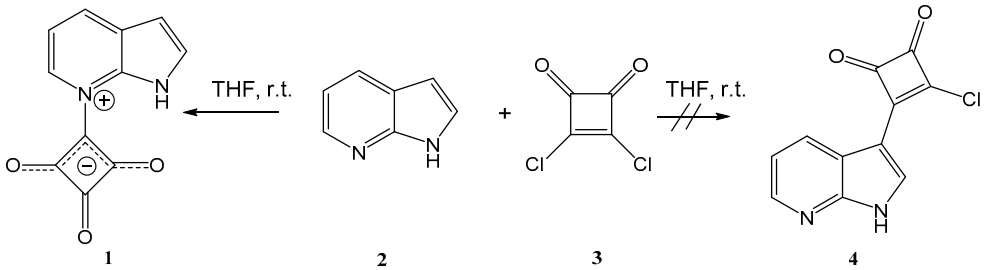
Abstract: 2,3,4-Trioxo-1-(1*H*-pyrrolo[2,3-*b*]pyridin-7-ium-7-yl)-cyclobutan-1-ide was obtained by reaction of squaric acid with 7-azaindole in acetic anhydride.

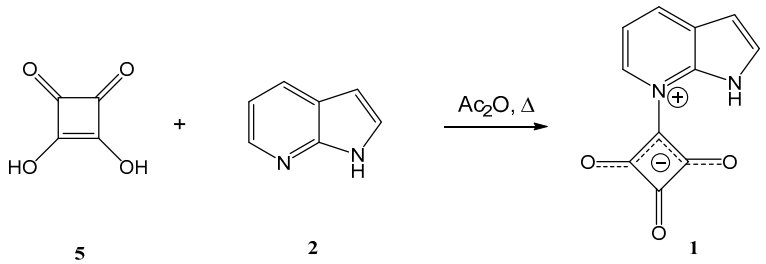
Keywords: azaindole; betaine; oxocarbon; pyridinium ylide; squaric acid

1. Introduction

Manifold derivatives of squaric acid have been reported in the literature for their biological activity, e.g., squaramides as protein kinase inhibitors [1] and 3,4-diarylcyclobutene-1,2-diones as antiproliferative compounds [2]. In addition, squaramides have a high impact in asymmetric organocatalysis [3]. With the aim to develop novel squaric acid derived structures for screening purposes, we prepared several squarylated indoles [4] according to a literature procedure [5] by Friedel-Crafts acylation of indoles with squaric acid dichloride (**3**), for example, 3-chloro-4-(5-methoxy-1*H*-indol-3-yl)cyclobut-3-ene-1,2-dione [6]. Upon the attempted synthesis of the squarylated 7-azaindole **4** from 7-azaindole (**2**) and squaric acid dichloride (**3**), the mesoionic title compound **1** was produced (Scheme 1). This result is in accordance with the reaction of squaric acid dichloride with pyridines in the presence of water yielding pyridinium ylides [7,8]. In order to prove the structure of **1**, we synthesized the compound independently from **2** and squaric acid (**5**) employing a procedure described by Schmidt et al. [9] (Scheme 2).



Scheme 1. Attempted synthesis of the squarylated azaindole **4**.



5 2 1

Scheme 2. Independent synthesis of the title compound **1**.

2. Results and Discussion

The linkage of the four-membered ring with the pyridine-N of the azaindole in **1** was proven by two-dimensional NMR techniques (see Supplementary Materials). The ^{1}H-NMR spectrum shows a sharp singlet at 13.37 ppm compatible with the indole-NH. In the H,H COSY-spectrum, this NH-signal exhibits a correlation with the signal at 7.98 ppm (H-2), which is coupled with the H-3-signal at 6.97 ppm. Furthermore, H-5 appears at 7.74 ppm and shows a correlation with H-4 at 8.75 ppm and H-6 at 9.19 ppm. Additionally, a H,C-HMBC spectrum was made. It displays a correlation between C-1 of the four-membered ring at 165.4 ppm and H-6 at 9.19 ppm.

3. Materials and Methods

3.1. Instrumentation

Melting points were determined in open-glass capillaries on an electric variable heater (Electrothermal IA 9100, Bibby Scientific, Stone, UK). FT-IR absorption spectra were recorded on a Thermo Nicolet FT-IR 200 spectrometer (Thermo Nicolet, Madison, WI, USA) using KBr pellets. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance AV II-600 spectrometer (Bruker Corporation, Billerica, MA, USA, 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 Flash EA® 1112 Elemental Analyzer (Thermo Quest, San Jose, CA, USA). The reactions were monitored by TLC (Polygram SIL G/UV$_{254}$, Macherey-Nagel, Düren, Germany) using a mixture of ethyl acetate and petroleum ether (2:1) as eluent. Mass spectra were recorded on a MAT 95 XL spectrometer (Thermo Finnigan 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) (Merck, Darmstadt, Germany); eluent: acetonitrile/water (10:90), 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.

3.2. Syntheses

3.2.1. Synthesis of 2,3,4-trioxo-1-(1*H*-pyrrolo[2,3-*b*]pyridin-7-ium-7-yl)-cyclobutan-1-ide (**1**); Method 1

To a solution of squaric acid dichloride (**3**, 0.151 g, 1.00 mmol) in tetrahydrofuran (20 mL) was added a solution of 7-azaindole (**2**, 0.354 g, 3.00 mmol) in the same solvent (20 mL) with stirring at room temperature. After stirring for 30 min at room temperature, the precipitate was removed by filtration and washed with ethanol. Crystallization from glacial acetic acid yielded a yellow solid (0.051 g, 24%).

3.2.2. Synthesis of 2,3,4-trioxo-1-(1*H*-pyrrolo[2,3-*b*]pyridin-7-ium-7-yl)cyclobutan-1-ide (**1**); Method 2

Squaric acid (**5**) (0.114 g, 1.00 mmol) was dissolved in acetic anhydride (10 mL) with stirring and heating to reflux. A solution of 7-azaindole (**2**, 0.118 g, 1.00 mmol) in acetic anhydride (5 mL)

was added and the reaction mixture was refluxed for 30 min. After cooling to room temperature, the precipitate was filtered off and washed with ethanol. Crystallization from glacial acetic acid yielded a yellow solid (0.075 g, 35%). The spectroscopic data of this material were identical with the results obtained with the compound produced by Method 1.

Melting point: 330–335 °C (dec.); MS (EI) m/z(%): 214.1 [M^+] (1), 118.1 (100); IR (KBr) (cm^{-1}): 3422, 3096, 1795, 1734, 1625, 1575; ^{1}H-NMR (600 MHz, DMSO-d_6) δ (ppm): 13.37 (s, 1H, NH), 9.19 (ddd, J = 0.5, 1.0, 6.4 Hz, 1H, ArH), 8.75 (dt, J = 0.8, 7.8 Hz, 1H, ArH), 7.98 (dd, J = 2.3, 3.6 Hz, 1H, ArH), 7.74 (dd, J = 6.4, 7.8 Hz, 1H, ArH), 6.97 (dd, J = 1.9, 3.5 Hz, 1H, ArH); ^{13}C-NMR: (151 MHz, DMSO-d_6) δ (ppm): 103.4, 116.5, 128.3, 130.1, 138.2 (CH), 126.9, 136.3, 165.4, 188.0 (2C), 207.0 (C); HPLC (AUC %): 100.0% at 254 nm, 100.0% at 280 nm; t_{ms} = 7.06 min; t_s = 1.69 min; Elemental analysis calculated for $C_{11}H_6N_2O_3$: C, 61.69; H, 2.82; N, 13.08; found: C, 61.70; H, 2.63; N, 12.98.

Supplementary Materials: The following are available online: Figure S1: ^{1}H-NMR, Figure S2: ^{13}C-NMR, Figure S3. H,H-COSY, Figure S4. H,C-HMBC, Figure S5. H,N-HMBC, Figure S6. IR, Figure S7: mass spectrum.

Author Contributions: D.H.L.: synthesis planning, literature research, experimental synthetic work, HPLC, IR, MS, and NMR interpretation; C.K.: literature research, writing of manuscript; J.G.: experimental synthetic work, synthesis planning, literature research, NMR interpretation, writing of manuscript.

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

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