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Short Note

1-(Imidazo[1,2-*a*]pyridin-1-ium-1-yl)-2,3,4-trioxocyclobutan-1-ide

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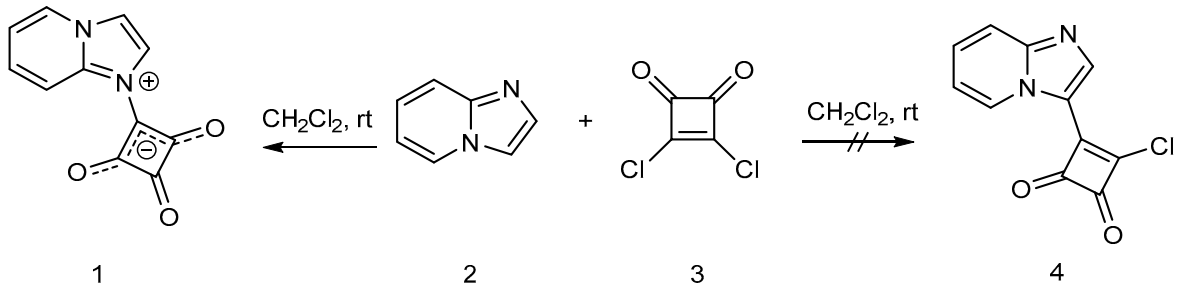
Abstract: 1-(Imidazo[1,2-*a*]pyridin-1-ium-1-yl)-2,3,4-trioxocyclobutan-1-ide was obtained by reaction of squaric acid with imidazo[1,2-*a*]pyridine in acetic anhydride.

Keywords: imidazo[1,2-*a*]pyridine; imidazolium ylide; oxocarbon; squaric acid; X-ray crystallography

1. Introduction

As part of our effort to find new chemotherapeutics for the treatment of malaria, we have prepared a series of bisindolylcyclobutenediones [1] according to a literature procedure [2] by Friedel–Crafts acylation of indoles with squaric acid dichloride (**3**). For this, we needed as starting compounds squarylated indoles, for example, 3-chloro-4-(5-methoxy-1*H*-indol-3-yl)cyclobut-3-ene-1,2-dione [3]. When we tried to extend the procedure to the reaction of 7-azaindole with squaric acid dichloride, we obtained, instead of the expected product, a pyridinium-ylide [4]. Because of this unexpected result, it seemed interesting to study the reaction of imidazo[1,2-*a*]pyridine (**2**) with squaric acid dichloride (**3**). Electrophilic substitution of **2** is expected to occur at the 3-position. The process involves a first activation step through *N*-acylation. Subsequently, the *N*-acyl substituent is shifted to its final position at C-3 [5]. In view of this course of the reaction, we assumed as a result of the reaction the formation of the squarylated imidazopyridine **4** or alternatively of the ylide **1**, formed by *N*-acylation and subsequent spontaneous hydrolysis of the second chloride function (Scheme 1).

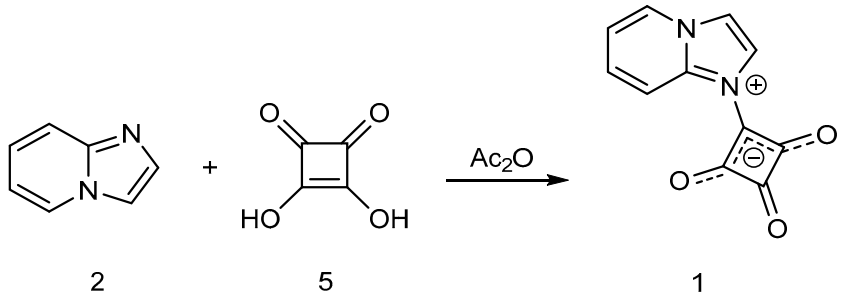


Scheme 1. Synthesis of the title compound **1**.

2. Results and Discussion

The reaction of imidazo[1,2-*a*]pyridine (**2**) with squaric acid dichloride (**3**) afforded only one product, which was identified as the ylide **1**. This reaction course is in accordance with the formation of ylides from imidazole or 1-methylimidazole and squaric acid dichloride [6].

A simple method for the preparation of pyridinium ylides of squaric acid, by heating the starting compounds in acetic anhydride, has been described by Schmidt et al. [7]. Employing this procedure, the reaction of 2-ethyl-4-methylimidazole with squaric acid resulted in the formation of an ylide, which was identified as a candidate to develop a non-linear optical material [8]. By applying this method, **1** was obtained from **2** and squaric acid (**5**) in acetic anhydride (Scheme 2).



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

The structure of **1** was mainly proven by the ^{1}H-NMR spectrum. It displays six signals; hence, an electrophilic substitution cannot have occurred. Furthermore, the mass spectrum shows the molecular ion peak of **1**. Suitable crystals for the X-ray diffraction analysis were obtained by crystallization from glacial acetic acid.

The four-membered ring and three of its immediate substituent atoms (N1, O1, O3) are essentially coplanar (mean dev. 0.01 Å); O2 lies slightly (0.08 Å) outside this plane (Figure 1). The imidazopyridine ring system is also planar (mean dev. 0.01 Å) and subtends an interplanar angle of 11° with the four-membered ring. The short intramolecular contact H10···O3, 2.30 Å, may correspond to a "weak" hydrogen bond; alternatively, it could be imposed by the need to maintain approximate coplanarity for delocalization (cf. the wide bond angles in the atom sequence C3–C4–N1–C11–C10).

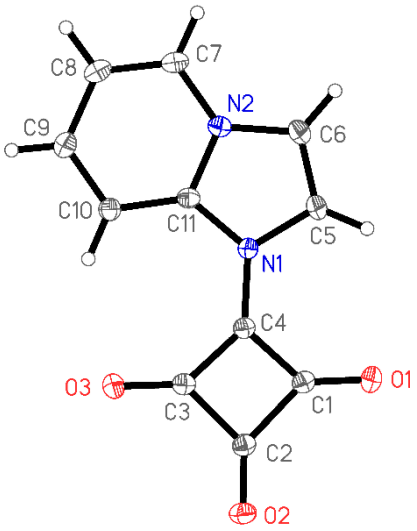


Figure 1. The molecule of compound **1** in the crystal. Ellipsoids represent 50% probability levels. Selected bond lengths (Å) and angles (°): C1–O1 1.2321(14), C1–C4 1.4357(15), C1–C2 1.5230(15), C2–O2 1.2157(14), C2–C3 1.5270(15), C3–O3 1.2271(14), C3–C4 1.4370(15), C4–N1 1.3923(13), C4–C10 1.3742(15); C4–C1–C2 87.83(9), C3–C2–C1 88.70(8), C4–C3–C2 87.63(9), C3–C4–C1 95.83(9), C3–C4–N1 134.95(10), C4–N1–C11 127.44(9), N1–C11–C10 131.86(10).

The Cambridge Database ("Conquest" Version 2.0.0, 2018) contains nine analogous examples of betaine-type molecular squarates with one NC_2 and three "keto" substituents (we note, however,

that the database codes the molecule as a cyclobutene with one C–O single bond, cf. the delocalized formula that we employ in the schemes). Disappointingly, all these structures were measured at room temperature. Furthermore, the two structures most similar to **1**, which are imidazole derivatives [8,9], are rather imprecise; they have *wR*2 values of 0.25 and 0.27, respectively, so that a detailed comparison of molecular dimensions is ruled out. A more precise structure is provided by [10], which has a pyridinium ring at C4. The following common features (using the atom numbering of **1**) are recognizable: The bonds C3–C4 and C1–C4 are significantly shorter than C1–C2 and C2–C3; C2–O2 is slightly shorter than C1–O1 and C3–O3; the angle C3–C4–C1 is some 7 to 10 degrees larger than the other angles of the four-membered ring.

Some related complexes of rare earth metals are known [11].

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, United Kingdom). 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 the 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_m = dead time. Quantification by AUC% method (area under curve).

3.2. Syntheses

Synthesis of 1-(Imidazo[1,2-*a*]pyridin-1-ium-1-yl)-2,3,4-trioxocyclobutan-1-ide (**1**); Method 1

To an ice-cooled solution of squaric acid dichloride (**3**, 0.151 g, 1.00 mmol) in dichloromethane (15 mL) was added a solution of imidazo[1,2-*a*]pyridine (**2**, 0.118 g, 1.00 mmol) in the same solvent (5 mL) with stirring. After stirring for 2 h at room temperature, the precipitate was removed by filtration and washed with ethyl acetate. Crystallization from dimethylformamide yielded a yellow solid (0,137 g, 50%).

Synthesis of 1-(Imidazo[1,2-*a*]pyridin-1-ium-1-yl)-2,3,4-trioxocyclobutan-1-ide (**1**); Method 2

Squaric acid (**5**) (0.114 g, 1.00 mmol) was dissolved in acetic anhydride (15 mL) with stirring and heating to 145 °C. A solution of imidazo[1,2-*a*]pyridine (**2**, 0.118 g, 1.00 mmol) in acetic anhydride (5 mL) was added, and the reaction mixture was refluxed for 1 h at 130 °C. After cooling to room temperature, the precipitate was filtered off and washed with ethyl acetate. Crystallization from glacial acetic acid yielded fine yellow crystals (0.134 g, 57%). The spectroscopic data of this material were identical with those of the compound produced by method 1.

M.p.: 303–304 °C (dec.); MS (EI) *m*/*z* (%): 214 [M$^+$] (3), 158 (100); IR (KBr) (cm^{-1}): 1791, 1719 (C=O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 9.09 (dd, *J* = 1.0, 9.2 Hz, 1H, ArH), 8.97 (dt, *J* = 1.1,

6.7 Hz, 1H, ArH), 8.62 (d, J = 2.3 Hz, 1H, ArH), 8.54 (dd, J = 0.7, 2.3 Hz, 1H, ArH), 8.17 (ddd, J = 1.2, 7.1, 9.2 Hz, 1H, ArH), 7.65 (td, J = 1.1, 7.0 Hz, 1H, ArH); ^{13}C-NMR: (151 MHz, DMSO-d_6) δ (ppm): 209.5 (C), 187.3 (C), 164.6 (C), 136.7 (C), 135.1 (CH), 130.0 (CH), 119.2 (CH), 118.4 (CH), 117.3 (CH), 114.8 (CH); HPLC (AUC %): 99.7% at 254 nm, 97.0% at 280 nm; t_{ms} = 2.31 min; t_m = 1.69 min; Elemental analysis calculated for $C_{11}H_6N_2O_3$: C, 61.69; H, 2.82; N, 13.08; found: C, 61.45; H, 2.61; N, 13.06. The supporting ^{1}H-NMR, ^{13}C-NMR, IR, and mass spectra are presented in the Supplementary Material File.

3.3. X-Ray Structure Determination of **1**

Crystal data: Orthorhombic, *Pbca*, a = 7.01679(13), b = 12.7067(2), c = 19.4234(3) Å, V = 1731.79 Å^3 (at 100 K), Z = 8, D_x = 1.643 Mg m^{-3}, μ = 1.04 mm^{-1}.

A yellow lath-shaped crystal ca. 0.25 × 0.08 × 0.05 mm was mounted in inert oil on a glass fiber and transferred to the cold gas stream of the diffractometer (Oxford Diffraction Nova A using mirror-focused Cu-$K\alpha$ radiation [12]). A total of 59,167 intensities were recorded to $2\theta_{max}$ 152.4°. Absorption corrections were implemented based on multi-scans. The structure was refined anisotropically on F^2 using the program SHELXL-97 [13]. Hydrogens were included using a riding model starting from calculated positions. Final $wR2$ = 0.089 for 146 parameters and all 1811 unique reflections, $R1$ = 0.032 [$I > 2\sigma(I)$], S = 1.07, max. Δρ = 0.34 e Å^{-3}.

Supplementary Materials: The ^{1}H-NMR, ^{13}C-NMR, IR, and mass spectra are available online. CCDC-1916227 contains the complete supplementary crystallographic data, which can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Author Contributions: J.G.: Experimental synthetic work, synthesis planning, literature research, writing of the manuscript; P.G.J.: X-ray structure determination, writing, and proofreading of the manuscript; C.K.: writing of the manuscript.

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

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