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Short Note

2′,7′-Dimethyl-3*H*-spiro[isobenzofuran-1,9′-xanthen]-3-one

Brian A. Chalmers, Aidan P. McKay, David B. Cordes, Iain L. J. Patterson, Nadiia Vladymyrova and Iain A. Smellie *

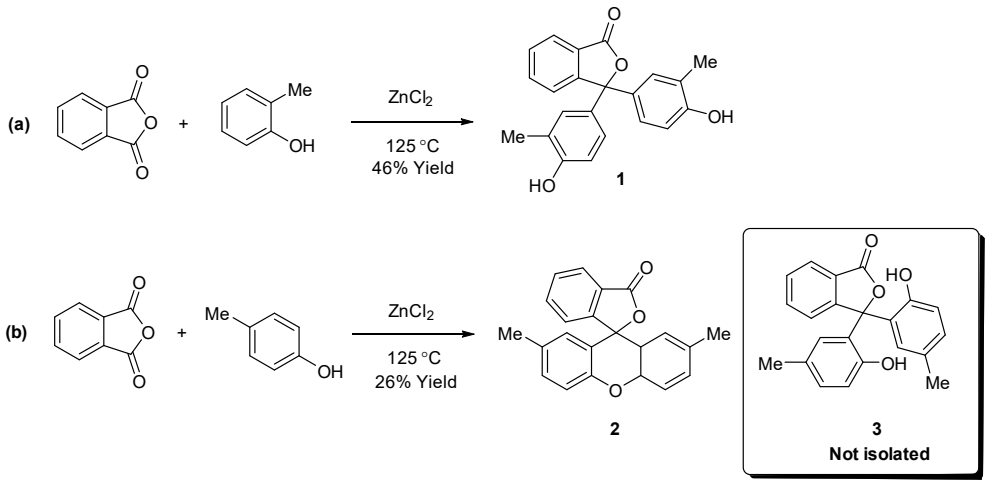
EaStCHEM School of Chemistry, University of St Andrews, North Haugh, St Andrews, Fife KY16 9ST, UK; bac8@st-andrews.ac.uk (B.A.C.); apm31@st-andrews.ac.uk (A.P.M.); dbc21@st-andrews.ac.uk (D.B.C.); iljp@st-andrews.ac.uk (I.L.J.P.); nv33@st-andrews.ac.uk (N.V.)
* Correspondence: ias10@st-andrews.ac.uk; Tel.: +44-1334-463845

Abstract: A synthetic route to 2′,7′-dimethyl-3*H*-spiro[isobenzofuran-1,9′-xanthen]-3-one has been described using methanesulfonic acid in place of reagents described in protocols from the early 20th century. A full NMR assignment has been made and X-ray crystallography has been used to characterise the title compound for the first time.

Keywords: heterocycle synthesis; X-ray structure; NMR spectra; IR spectrum

1. Introduction

Reactions of phenols with phthalic anhydride under strongly acidic conditions has long been known as a general method for the preparation of phenolphthalein-based dyes (3,3-bis(4-hydroxyaryl)isobenzofuran-1(3*H*)-ones) [1,2]. For example, it is known that heating 2-methylphenol with a mixture of phthalic anhydride and zinc chloride affords cresolphthalein (3,3-bis(4-hydroxy-3-methylphenyl)isobenzofuran-1(3*H*)-one **1**) [3]; this compound is often used as an acid-base indicator [1,2]. It has also been reported that the use of 4-methylphenol under the same conditions results in the formation of fluoran **2** as the product rather than an isomer (**3**) of cresolphthalein (Scheme 1) [3]. These results align with an earlier study that found that fluoran **2** is the product of strongly heating a mixture of phthalic anhydride, 4-methylphenol, and boric acid [4].



Scheme 1. Reaction of phthalic anhydride with (**a**) 2-methylphenol and (**b**) 4-methylphenol mixed with $ZnCl_2$ at 125 °C for 8 h.

Alternative methods for the preparation of phenolphthalein analogues have become available since the original studies that were conducted in the early 20th century. In re-

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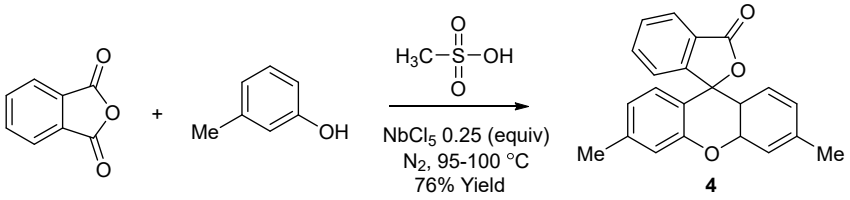
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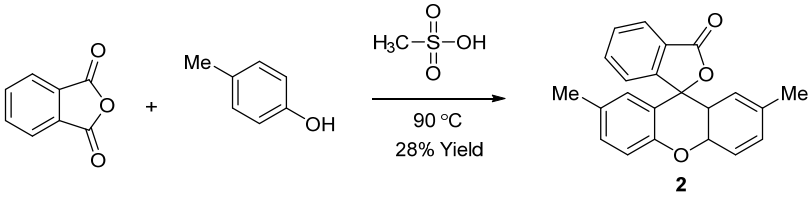
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cent years, methanesulfonic acid and methanesulfonic acid/niobium(V) chloride mixtures have been found to be useful replacements for concentrated sulfuric acid and mixtures containing zinc chloride or aluminium chloride [1,5]. Methanesulfonic acid is a readily available replacement for concentrated sulfuric acid, it is liquid at room temperature, and it is a less potent oxidising agent than concentrated sulfuric acid. Classical methods for the synthesis of 3,3-bis(4-hydroxyaryl)isobenzofuran-1(3*H*)-ones (such as **1**) and corresponding xanthene derivatives often require temperatures significantly greater than 100 °C; in contrast, the same reactions in methanesulfonic acid often readily proceed when heated below 100 °C [1,5]. The reaction of 2-substituted phenols with phthalic anhydride in hot methanesulfonic acid affords the corresponding 3,3-bis(4-hydroxyaryl)isobenzofuran-1(3*H*)-one products in good yield [1]. Furthermore, it has been shown that the reaction of 3-substituted phenols with phthalic anhydride in hot methanesulfonic acid (containing 0.25 equivalents of niobium(V) chloride) affords fluoran **4** (Scheme 2) rather than 3,3-bis(2-hydroxy-4-methylphenyl)isobenzofuran-1(3*H*)-one [6].



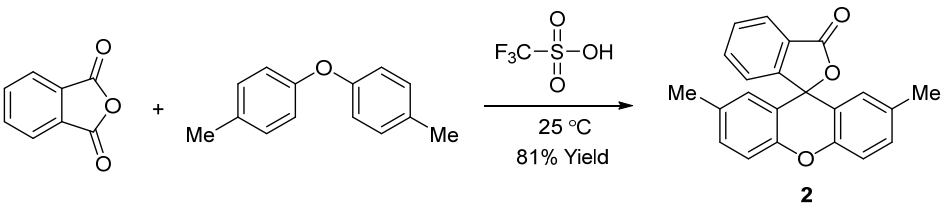
Scheme 2. Reaction of phthalic anhydride with 3-methylphenol to form fluoran **4**.

In this work, we describe a short study to examine whether 2′,7′-dimethyl-3*H*-spiro[isobenzofuran-1,9′-xanthen]-3-one (**2**) or 3,3-bis(2-hydroxy-5-methylphenyl)isobenzofuran-1(3*H*)-one (**3**) is the isolable product from the reaction of phthalic anhydride and 4-methylphenol under milder conditions than reported in older studies [3,4]. Our findings align with the outcome of closely related reactions from the earlier 20th century; fluoran **2** was the sole isolated product (Scheme 3), and this compound has been characterised using X-ray crystallography for the first time.



Scheme 3. Reaction of phthalic anhydride with 4-methylphenol to form fluoran **2**.

Fluoran **2** can be made by other methods; for example, a recent study has demonstrated that compound **2** can be produced from the reaction of phthalic anhydride with 4,4′-oxybis(methylbenzene) (di-*p*-tolyl ether) in the presence of trifluoromethanesulfonic acid (Scheme 4) [7]. The reaction pathway has been investigated by *in situ* NMR experiments and computational (DFT) studies; these conditions can also be used to prepare a selection of spirocyclic xanthene products.



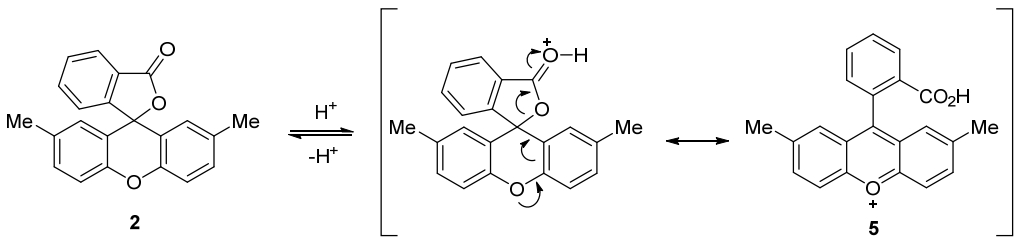
Scheme 4. Reaction of phthalic anhydride with 4,4′-oxybis(methylbenzene) to form fluoran **2**.

2. Results

2.1. Synthesis and Spectroscopy

The reaction of 4-methylphenol with phthalic anhydride in hot methanesulfonic acid (90 °C) proceeds over 4 h. The crude product is then easily isolated by filtration after the reaction is quenched with water and sodium bicarbonate. The crude material is usually obtained as a tan coloured solid; however, it can readily be recrystallized from hot acetone. The melting point was determined to be 251–253 °C; this observation is consistent with earlier studies [3,4]. The isolated yield in this case is 28%, this is very similar to the results reported by Copisarow in 1920; in that instance, fluoran **2** was obtained in 26% yield [3]. It is apparent from our work that heating the reagents in methanesulfonic acid does not offer a significant improvement in terms of % yield from the earlier protocol [3]. It is likely that the reaction did not procced to completion and that unreacted phthalic anhydride and 4-methylphenol were removed during the purification steps. Most previous reports of fluoran **2** were published prior to the introduction of modern spectroscopic techniques; however, there is one recent paper that includes ^{1}H and ^{13}C NMR spectra [7]. In this work, a full assignment of the structure has been made using 2D NMR techniques, and a full set of assigned spectra is provided in the supporting information document (Supporting Information—Figures S1–S5). The ATR-IR spectrum of fluoran **2** has also been obtained (Supporting Information—Figure S6); this shows a distinctive signal at 1756.8 cm^{-1} consistent with the γ-lactone carbonyl group [8].

In contrast to cresolphthalein (**1**) [1], fluoran **2** is insoluble in aqueous solutions of sodium hydroxide and the solution does not become red/pink in colour. However, a report from 1902 suggested fluoran **2** is reactive under acidic conditions, since it would likely exist as oxonium ion **5** in concentrated sulfuric acid (98%) [9]. The observation at the time was that the addition of concentrated sulfuric acid to fluoran **2** afforded a clear yellow solution. This outcome was attributed to the formation of the conjugated resonance stabilised species such as **5** (Scheme 5). Our results align with the original observation regarding the colour of the strongly acidic solution, and it was found that the solution emits yellow light when illuminated with a 405 nm violet laser (Figure 1).



Scheme 5. Reaction of fluoran **2** in concentrated sulfuric acid.

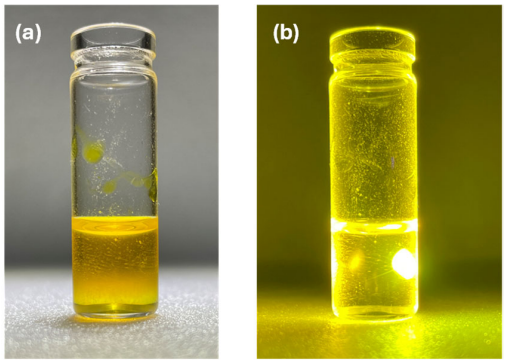


Figure 1. A sample fluoran **2** dissolved in concentrated sulfuric acid (**a**) illuminated in ambient light; (**b**) illuminated with a 405 nm violet laser.

2.2. The Crystal Structure of **2**

Crystals of **2** suitable for X-ray diffraction were isolated by the slow cooling of a saturated solution of **2** in dimethyl sulfoxide. The data confirm the structure of **2** is in agreement with the spectroscopic assignment.

The structure shows (Figure 2) only slight distortion from the ideal tetrahedral angles at the spiro carbon (C3), ranging from the smallest angle of 101.94(9)° in the constrained isobenzofuranone ring (C4−C3−O2), to 114.14(9)°. The C−O bond lengths are of typical length, 1.3608(14) and 1.4912(13) Å, and the C=O distance is typical of isobenzofuranones at 1.2026(14) Å. Unsurprisingly, given the linkage of the two rings at the spiro carbon, the xanthene group adopts a planar conformation (mean deviation from plane 0.037 Å). The interplanar angle between the xanthene and isobenzofuranone rings is 87.679(14)°.

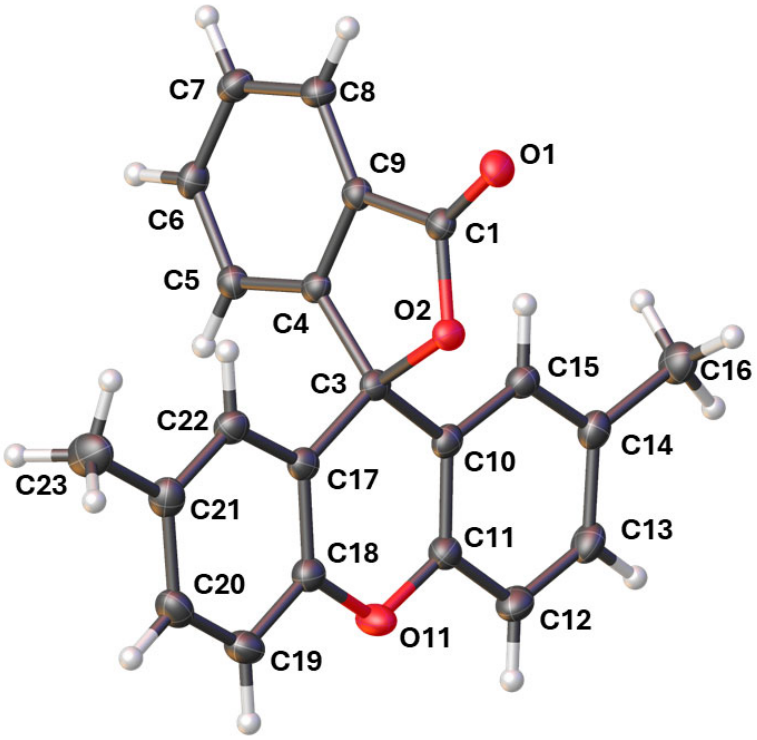


Figure 2. The molecular structure of **2**. The anisotropic displacement ellipsoids of non-hydrogen atoms are set at the 50% probability level.

The structure displays several non-classical intermolecular CH···O interactions. A pair of interactions are found between both H6 and H7 with O2 at H···O distances of 2.65 and 2.55 Å (C···O separations of 3.2503(14) and 3.1986(15) Å), respectively, resulting in 1D chains running along the crystallographic *a*-axis (Figure 3). Two sets of dimer-forming CH···O interaction are also seen; between H5 and O11 and between H22 and O1, at H···O distances of 2.45 Å (C···O separations of 3.3715(15) and 3.3875(15) Å) (Figure 4). The dimer-forming interactions result in the chains of molecules being linked into two-dimensional sheets in the *ab*-plane (Figure 3).

In summary, the first X-ray crystal structure of 2′,7′-Dimethyl-3*H*-spiro[isobenzofuran-1,9′-xanthen]-3-one (**2**) has been obtained and full ^{1}H and ^{13}C NMR assignments have been made. The title compound was prepared by heating a mixture of phthalic anhydride, 4-methylphenol, and methanesulfonic acid. This method produces results that align with studies conducted in the early 20th century that employed more forcing conditions to prepare fluoran **2**.

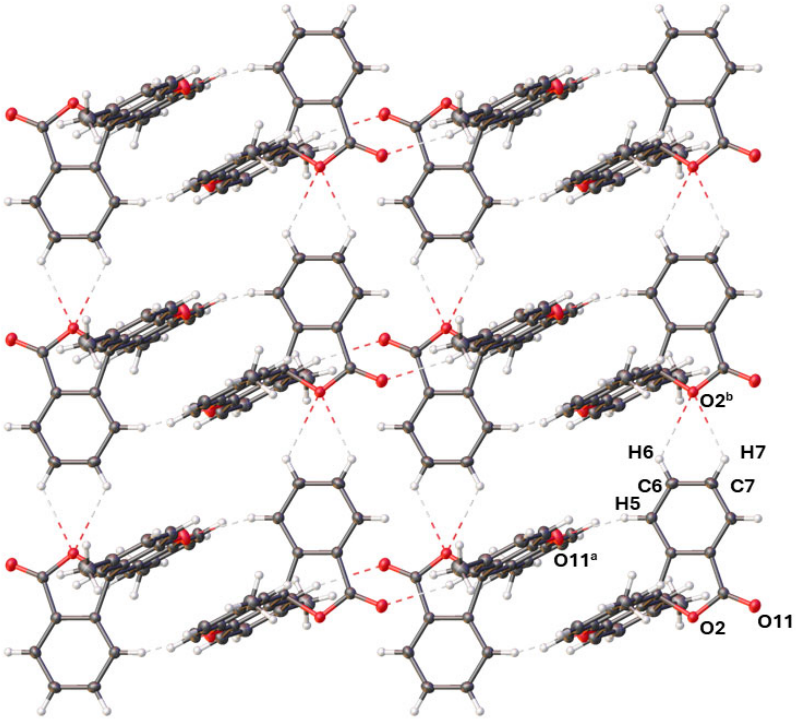


Figure 3. A view of the structure of **2** showing hydrogen-bonded chains running along the *a*-axis.

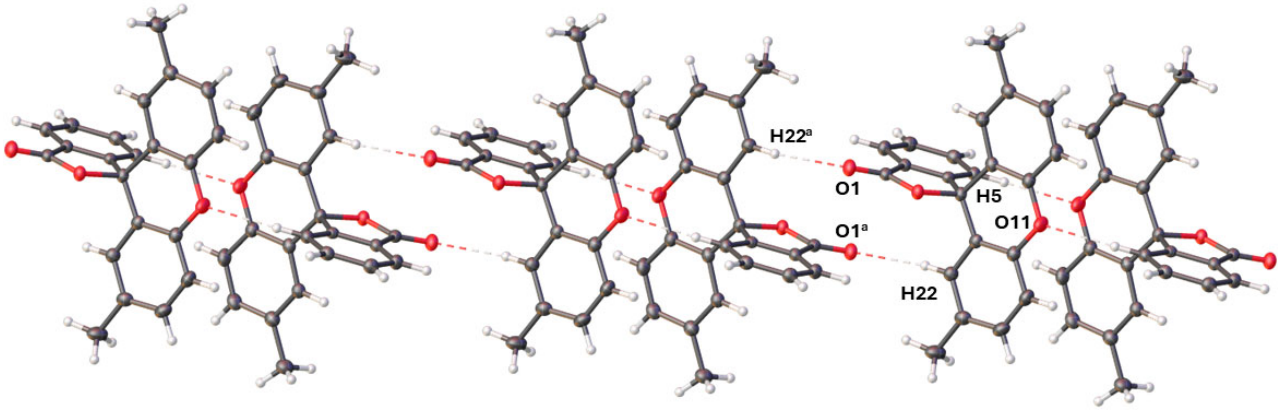


Figure 4. Alternative view of **2** showing the other intermolecular interactions.

3. Experimental Section

Melting points were recorded on an Stuart Scientific SMP3 melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet Summit FTIR instrument with Everest diamond ATR accessory. NMR spectra were obtained for ^{1}H at 400 MHz and for ^{13}C at 100 MHz using a Bruker AVIII_HD 400 instrument. Spectra were run at 25 °C in d_6-DMSO. Chemical shifts are reported in ppm to the high frequency of the reference, and coupling constants *J* are reported in Hz. The HRMS data were acquired from the University of St Andrews Mass Spectrometry Service.

2′,7′-Dimethyl-3H-spiro[isobenzofuran-1,9′-xanthen]-3-one

A stirred mixture of 4-methylphenol (0.36 g, 3.3 mmol) and phthalic anhydride (0.30 g, 2.0 mmol) in methanesulfonic acid (1.00 g, 0.68 mL, 10.0 mmol) was heated to 90 °C in a boiling tube for 4 h. Upon cooling to room temperature, water (20 mL) was added, and the resulting mixture was triturated with a glass rod until a tan-coloured solid was formed. The supernatant liquid was neutralised by the portionwise addition of solid sodium bicarbonate.

The crude product was filtered off under suction, washed with water (2 × 5 mL), and recrystallized from acetone. A colourless crystalline solid was formed; this was filtered off under suction and washed with ice-cold acetone (2 × 2 mL) to afford product **2** (0.15 g, 28%), mp 251–253 °C (lit. [4] 250–252 °C). IR (ATR) 3059.4, 3016.8 (ArCH), 2920.3 (CH_3), 1756.8 (C=O), 1610.5, 1486.3, 1106.7 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO); 8.06 (1H, ddd, *J* = 7.4 Hz, 1.4, 0.8 Hz, ArH), 7.80 (1H, td, *J* = 7.5, 1.4 Hz, ArH), 7.75 (1H, td, *J* = 7.5, 1.1 Hz, ArH), 7.29–7.33 (4H, m, ArH), 7.27 (1H, dt, *J* = 7.5, 0.9 Hz) ArH), 6.60 (2H, dt, *J* = 1.7, 0.9 Hz, ArH), 2.17 (6H, s, CH_3); ^{13}C NMR (100 MHz, d_6-DMSO); 169.3 (C=O), 153.5 (ArCq), 148.9 (ArCq), 136.4 (ArCH), 133.6 (ArCq), 132.3 (ArCH), 130.8 (ArCH), 127.7 (ArCH), 125.7 (ArCq), 125.5 (ArCH), 124.4 (ArCH), 118.7 (ArCq), 117.4 (ArCH), 82.2 (Cq), and 20.6 (CH_3). HRMS (ESI+) *m/z* (%) Calcd. for $C_{22}H_{16}O_3Na$ 351.0992, found 351.0998 [M+Na] (100).

Colourless X-ray quality crystals of **2** were grown by slow cooling of a sample dissolved in dimethyl sulfoxide.

X-ray Structure Determination of 2

X-ray diffraction data were collected at 100 K using a Rigaku MM-007HF High Brilliance Microfocus RA generator/confocal optics with XtaLAB P200 diffractometer [Cu Kα radiation (λ = 1.54187 Å), Tokyo, Japan]. Data were collected (using a calculated strategy) and processed (including correction for Lorentz, polarisation, and absorption) using CrysAlisPro [10]. The structure was solved by dual-space methods (SHELXT) [11] and refined by full-matrix least squares against F^2 (SHELXL-2019/3) [12]. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were refined using a riding model. All calculations were performed using the Olex2 interface [13].

Crystal data for $C_{22}H_{16}O_3$, M = 328.35 g mol^{-1}, colourless plate, crystal dimensions 0.15 × 0.05 × 0.01 mm, monoclinic, space group $P2_1/n$ (No. 14), a = 7.72260(6), b = 12.79542(10), c = 16.74757(13) Å, β = 91.3986(7) °, V = 1654.40(2) $Å^3$, Z = 4, D_{calc} = 1.318 g cm^{-3}, T = 100 K, 31,448 reflections measured, 3426 unique (R_{int} = 0.0644), which were used in all calculations. The final R_1 [$I > 2\sigma(I)$] was 0.0426 and wR_2 (all data) was 0.1227, with a goodness of fit on F^2 of 1.095. Data have been deposited at the Cambridge Crystallographic Data Centre as CCDC 2441124. The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/structures.

Supplementary Materials: The following supporting information are available online. Figure S1: ^1H-NMR spectrum of **2**; Figure S2: ^1H-^1H COSY 2D H-H correlation NMR spectrum of **2**; Figure S3: ^{13}C DEPTQ NMR spectrum of **2**; Figure S4: ^1H-^{13}C HSQC 2D H-C correlation NMR spectrum of **2**; Figure S5: ^1H-^{13}C HMBC 2D H-C correlation NMR spectrum of **2**; Figure S6: IR spectrum of **2**; Figure S7: ESI-mass spectrum of **2**; CIF file for compound **2**.

Author Contributions: Synthetic steps, crystallisation trials, and preliminary analysis have been conducted by N.V., I.A.S. and I.L.J.P.; A.P.M. and D.B.C. collected the Xray data and solved the structure; I.A.S. and B.A.C. wrote the paper. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: CCDC 2441124 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

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

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