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Short Note

(*E*)-1-(2,5-Dimethylphenyl)-3-phenylprop-2-en-1-one

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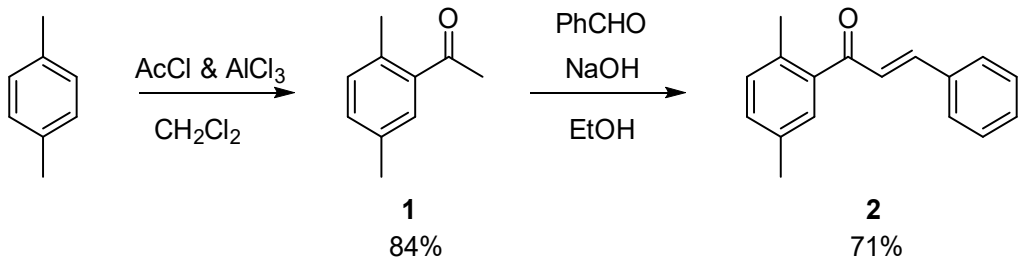
Abstract: X-ray crystallography has been used to characterize the title compound for the first time; ^{1}H NMR, ^{13}C NMR and IR spectroscopic data have also been updated from earlier reports. We also report the melting point of the title compound.

Keywords: aldol condensation; X-ray crystallography; NMR; chalcones

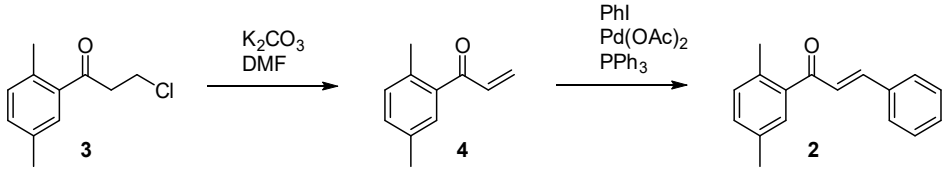
1. Introduction

Friedel–Crafts acylation of 1,4-dimethylbenzene affords ketone **1** as the sole product [1]. Ketone **1** may then be efficiently converted to chalcone **2** via a Claisen–Schmidt reaction [2] with benzaldehyde in the presence of sodium hydroxide (Scheme 1).



Scheme 1. Friedel–Crafts acylation of p-xylene to afford 1-(2,5-dimethylphenyl)ethan-1-one (**1**) and subsequent aldol condensation with benzaldehyde to afford the title compound (**2**).

Most of the literature's procedures to prepare (*E*)-1-(2,5-Dimethylphenyl)-3-phenylprop-2-en-1-one (**2**) use Friedel–Crafts conditions ($AlCl_3$, Ac_2O) to prepare ketone **1** followed by the aldol condensation with benzaldehyde to from **2** [1], however, an alternative route has also been reported [3]. Scheme 2 illustrates a recent route to **2** that involves the in-situ formation of ketone **4** by the base-mediated elimination of HCl from compound **3**. Ketone **4** is formed in the presence of palladium(II) acetate; this allows a subsequent Heck reaction of iodobenzene with ketone **4** to proceed with the efficient formation of chalcone **2** (84% yield reported).



Scheme 2. In situ formation of compound **4** and subsequent Heck reaction with iodobenzene to form chalcone **2**.

Compound **2** has found uses as a precursor in organic synthesis; two recent examples are highlighted in Schemes 3 and 4. Chalcone **2** can be readily epoxidized in basic hydrogen

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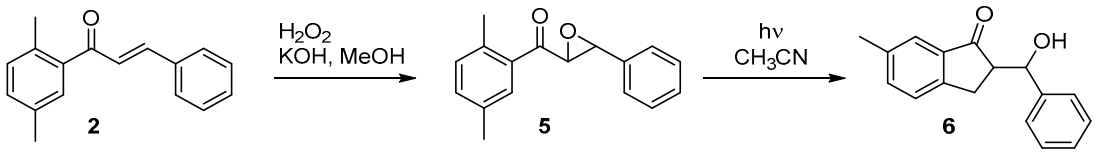
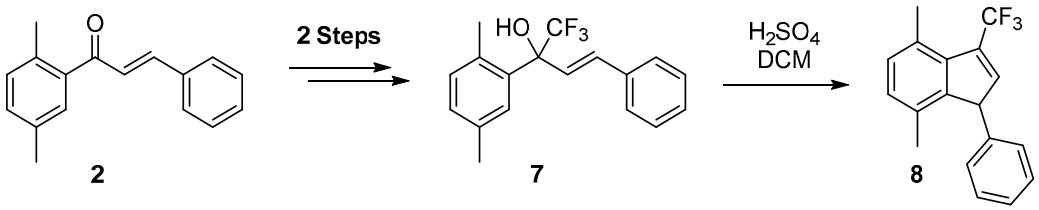
peroxide to form epoxide **5**; the subsequent irradiation of **5** with UV light affords the corresponding β-hydroxy functionalized indanone **6** [1].



Scheme 3. Conversion of chalcone **2** to trifluoromethyl indanone **6**.

Chalcone **2** can be readily converted to **7** by a trifluoromethylation/desilylation sequence; the treatment of **7** with sulfuric acid then affords the corresponding trifluoromethyl indene **8** [4].



Scheme 4. Conversion of chalcone **2** to trifluoromethyl indene **8**.

2. Results

Ketone **1** readily reacts with benzaldehyde under basic conditions to form chalcone **2**; the reaction is usually complete within 30 min. Compound **2** has been previously reported as a yellow oil in the literature [5], and although other publications do report a pale yellow solid, they do not report a melting point [3]. Upon leaving the yellow oil of **2** to stand for 24−48 h, we observed the formation of large yellow crystals (Figure 1). The crystals were washed with cold ethanol and dried *in vacuo*. The melting point was determined to be 51−53 °C (see Video S1).

Figure 1. Crystals of **2**.

The ^{1}H NMR spectrum (see Supporting Information Figure S7) of chalcone **2** provides useful evidence for the *E* configuration of the alkene double bond. The H8–H9 (numbering in Figure 6) coupling constant ($^3J_{HH}$) has been found to be 16.0 Hz. This value is within the range predicted by the Karplus equation [6] for *E*-configured alkenes. Furthermore, crystals of **2** were of suitable quality for single-crystal X-ray diffraction and confirmed the expected structure of **2** (Figure 2). The molecule is planar from the phenyl ring to the ketone (mean deviation from plane of 0.092 Å), indicative of conjugation. The xylyl group does not take

part in the conjugation, as it is forced out of that plane by the steric clash between ketone and the *ortho* methyl group [torsion C2–C1–C7–C8 40.9(4)].

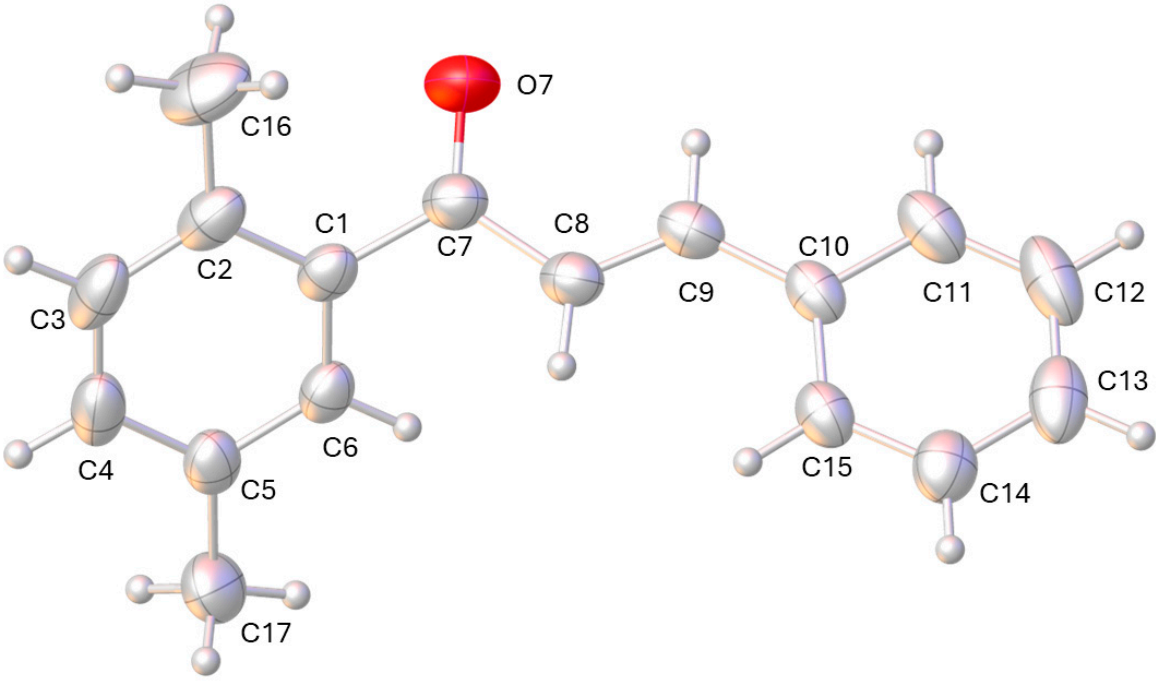


Figure 2. The molecular structure of **2**. The anisotropic displacement ellipsoids of non-hydrogen atoms are set at the 50% probability level.

The bond lengths are all comparable to chalcone (CSD code BZYACO), with the C8–C9 bond length being 1.326(3) Å (cf. 1.319(6) Å) and the C7–O7 bond being 1.222(3) Å in **2** and 1.204(6) Å in chalcone [7]. The major difference between the structure of **2** and that of chalcone is the dihedral angle between the two aromatic rings. In chalcone, the two phenyl rings are nearly coplanar, with a small 11.35° angle between the mean planes. However, in **2**, the angle between the mean planes of the phenyl and xylyl rings is much larger at 56.23(6)°. This can be attributed to the *ortho*-methyl group (C16) imposing some steric demands around the carbonyl group, preventing it from lying essentially coplanar with the styrene part of the molecule (Figure 3).

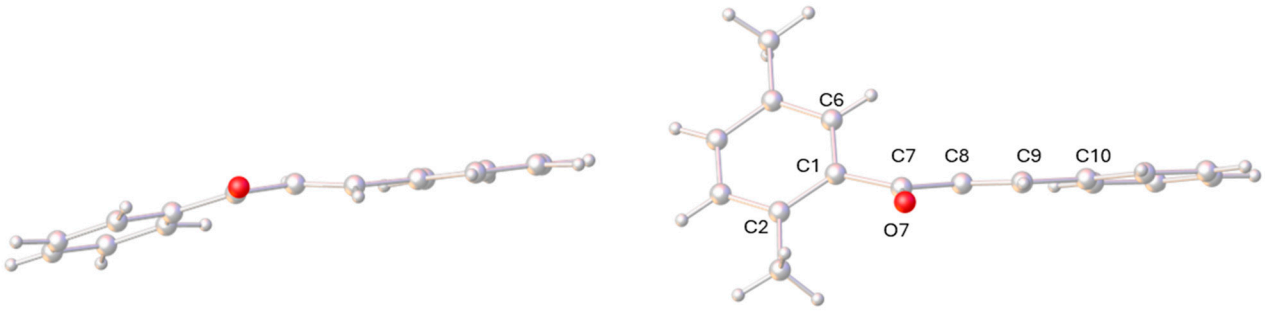


Figure 3. Ball and stick images of chalcone (**left**) and **2** (**right**) showing the differences between the dihedral angles of the two aromatic rings.

There is a weak hydrogen bond of 2.638 Å between the carbonyl oxygen (O7) and the hydrogen (H17b) from the *meta*-methyl group on the xylyl ring. This results in the formation of 1D helical chains along the *c*-axis, as shown in Figure 4.

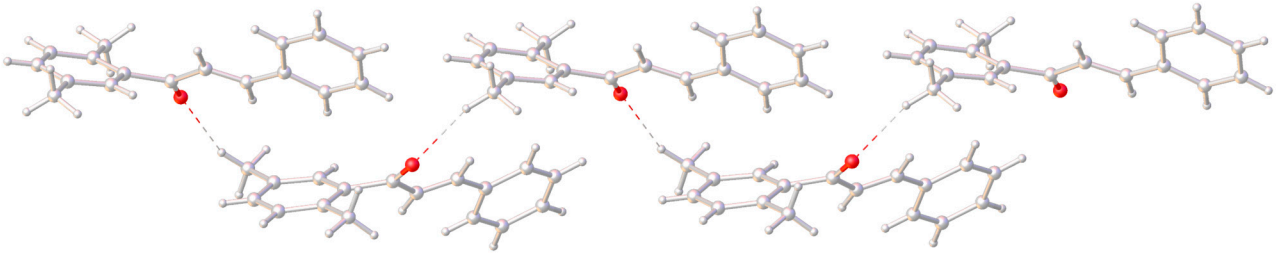


Figure 4. The 1D helical chains formed along the c-axis in **2** by the C=O···H interaction.

Perhaps surprisingly, the only structurally similar motif reported in the CSD, outside of its incorporation into cyclophanes, is in 1-(2,5-dimethylphenyl)-3-oxy-3-phenylprop-2-en-1-onato(difluoro) boron (CSD code WAQPEM) (Figure 5) [8]. The diketone backbone in WAQPEM is essentially planar as the angles between the mean planes of the phenyl and xylyl rings are much smaller than those of **2** at 19.9° and 19.7° (for the two molecules in the asymmetric unit). This is due to the coordination with the boron allowing for delocalization across the backbone.

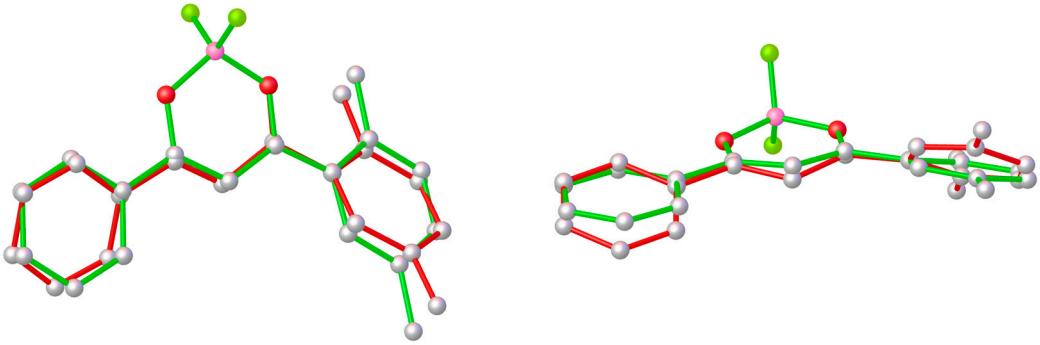
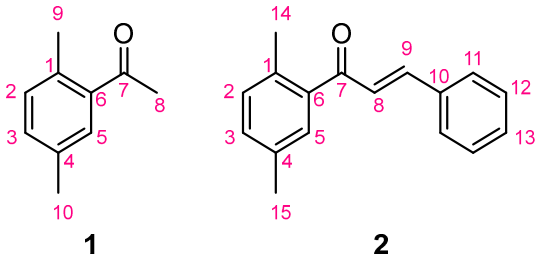


Figure 5. Two views of an overlay of **2** (red) and WAQPEM (green).

3. Materials and Methods

All synthetic manipulations were performed in air. Glassware was dried in an oven (ca. 110 °C) prior to use. Solvents and chemicals were used as provided without further purification. IR spectra were recorded on a Perkin Elmer Spectrum Two instrument with a DTGS detector and a diamond ATR attachment. The HRMS data were acquired from the University of St Andrews Mass Spectrometry Service. All NMR spectra were recorded using a Bruker Avance II 400 (MHz) spectrometer at 20 °C. The ^{13}C NMR spectrum was recorded using the DEPTQ-135 pulse sequence with broadband proton decoupling. Assignments were made in conjunction with selected 2D NMR experiments. Tetramethylsilane was used as an external standard (δ_H, δ_C 0.00 ppm). Residual solvent peaks were also used for secondary calibration ($CDCl_3$ δ_H 7.260 ppm; δ_C 77.160 ppm). Chemical shifts (δ) are given in parts per million (ppm) relative to the TMS peak. NMR Spectra were analyzed using the MestReNova software package (version 14). The numbering scheme for the NMR assignment is shown in Figure 6.



1 **2**

Figure 6. NMR numbering schemes for compounds **1** and **2**.

*3.1. Synthesis of 1-(2,5-Dimethylphenyl)ethan-1-one (**1**)*

The following is adapted from a procedure in the literature [1]. In a three-necked flask equipped with an addition funnel and a reflux condenser, aluminum chloride (9.34 g, 70 mmol) was combined with dichloromethane (20 mL) with continuous stirring. The suspension was cooled to 0 °C using an ice/water bath. A solution of acetyl chloride (5.0 mL, 5.50 g, 70 mmol) in dichloromethane (10 mL) was added dropwise over 15 min. Then, a solution of *p*-xylene (6.2 mL, 5.32 g, 50 mmol) in dichloromethane (12 mL) was added dropwise over 30 min. After addition, the solution was warmed to ambient conditions and allowed to stir for a further 30 min. The mixture was poured into a mix of ice (ca. 40 g) and conc. hydrochloric acid (12 mL) and stirred for 25 min. The organic layer was separated and the aqueous layer washed with dichloromethane (3 × 15 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (2 × 15 mL) then dried over sodium sulfate. The solvent was removed in vacuo to afford **1** as a pale-yellow oil (6.23 g, 84%). The NMR data agree with the literature procedure: ^{1}H NMR: (400.3 MHz, $CDCl_3$) δ_H 7.49 (1H, s, H-5), 7.19 (1H, d, $^{3}J_{HH}$ 7.8 Hz, H-3), 7.13 (1H, d, $^{3}J_{HH}$ 7.8 Hz, H-2), 2.57 (3H, s, H-8), 2.48 (3H, s, H-9), 2.36 (3H, s, H-10). ^{13}C DEPTQ NMR (100.7 MHz, $CDCl_3$) δ_C 202.1 (s, qC-7), 137.8 (s, qC-1), 135.33 (s, qC-4fff), 135.30 (s, qC-6), 132.3 (s, C-3), 132.1 (s, C-2), 130.0 (s, C-5), 29.7 (s, C-8), 21.2 (s, C-9), 21.0 (s, C-10). IR ν_{max} (ATR/cm^{-1}) 3025w (ν_{CH}), 2926w (ν_{CH}), 1679vs ($\nu_{C=O}$), 1354s, 1256s, 1188s, 953m, 816s, 615s.

*3.2. Synthesis of 1-(2,5-Dimethylphenyl)-3-phenylprop-2-en-1-one (**2**)*

The following is adapted from a procedure in the literature [2]. Compound **1** (2.22 g, 15 mmol) was dissolved in 95% ethanol (15 mL) and benzaldehyde (1.55 mL, 1.61 g, 15 mmol) was added in one portion. With continuous stirring, a sodium hydroxide solution (3 mL, 8.33 $molL^{-1}$, 25 mmol) was added dropwise to the reaction mixture over 2–3 min. Stirring was continued for a further 30 min. The solution was poured onto ice (ca. 45 g) and dichloromethane (50 mL) was added. The organic layer was separated, and the aqueous layer washed with dichloromethane (3 × 10 mL). The combined organic layers were dried over sodium sulfate. The volatiles were removed in vacuo to afford a yellow oil. The addition of diethyl ether (3 mL) promoted crystallization of the oil over 24–48 h, affording bright yellow crystals of 2 suitable for X-ray diffraction (2.53 g, 71%) (Mp. 51−53 °C). The NMR data agree with the literature procedure: ^{1}H NMR: (400.3 MHz, $CDCl_3$) δ_H 7.60−7.55 (2H, m, H-11), 7.48 (1H, d, $^{3}J_{HH}$ 16.0 Hz, H-9), 7.42−7.38 (3H, m, H-12,13), 7.30 (1H, s, H-5), 7.22−7.16 (2H, m, H-2,3), 7.14 (1H, d, $^{3}J_{HH}$ 16.0 Hz, H-8), 2.40 (3H, s, H-14), 2.37 (3H, s, H-15). ^{13}C DEPTQ NMR (100.7 MHz, $CDCl_3$) δ_C 196.9 (s, qC-7), 145.8 (s, C-9), 139.2 (s, qC-1), 135.2 (s, qC-4), 134.8 (s, qC-10), 133.8 (s, qC-6), 131.3 (s, C-2,3), 130.7 (s, C-13), 129.1 (s, C-12), 128.7 (s, C-5), 128.5 (s, C-11), 126.9 (s, C-8), 21.0 (s, C-15), 19.9 (s, C-14). IR ν_{max} (ATR/cm^{-1}) 3061w (ν_{CH}), 2926w (ν_{CH}), 1666vs ($\nu_{C=O}$), 1597vs ($\nu_{C=C}$), 1447m, 1328s, 1168s, 984vs, 775vs, 696vs, 564m.

X-ray diffraction data for compound **2** were collected at 173 K using a Rigaku FR-X Ultra-high Brilliance Microfocus RA generator/confocal optics [Mo Kα radiation (λ = 0.71073 Å)] with an XtaLAB P200 diffractometer. Intensity data were collected (using a calculated strategy) and processed (including correction for Lorentz, polarization and absorption) using CrysAlisPro [9]. The structure was solved by dual-space methods (SHELXT) [10] and refined by full-matrix least-squares against F^2 (SHELXL-2019/3) [11]. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were refined using a riding model. All calculations were performed using the Olex2 interface [12].

Crystal data for **2**: $C_{17}H_{16}O$ (M = 236.30 $gmol^{-1}$), orthorhombic, space group $P2_12_12_1$ (no. 19), a = 7.3103(3), b = 13.6107(4), c = 13.4970(4) Å, vol. = 1342.94(8) $Å^3$, Z = 4, ρ_{calc} (gcm^{-3}) = 1.169, 15,416 reflections measured, 3212 unique (R_{int} = 0.0594), which were used in all calculations. The final R_1 [I > 2σ(I)] was 0.0449 and wR_2 (all data) was 0.1180.

Supplementary Materials: Figures S1–S12: spectroscopic data of compounds **1** and **2**. Video S1: melting point of **2**.

Author Contributions: All synthetic steps and preliminary analysis were carried out by B.A.C. and D.B.C. collected the X-ray data, and solved the structure. B.A.C. and I.A.S. collected the other spectroscopic data and designed the study. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: CCDC 2368767 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.

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

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