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Short Note

1-(2,3,5,6-Tetramethylphenyl)ethan-1-one

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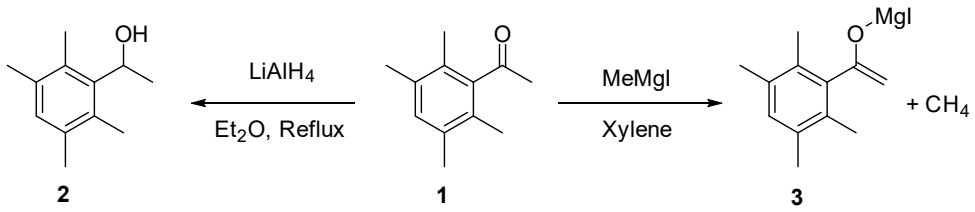
Abstract: X-ray crystallography was used to characterize 1-(2,3,5,6-tetramethylphenyl)ethan-1-one (acetyldurene) for the first time.

Keywords: acetyldurene; Friedel–Crafts acetylation; bulky substituents

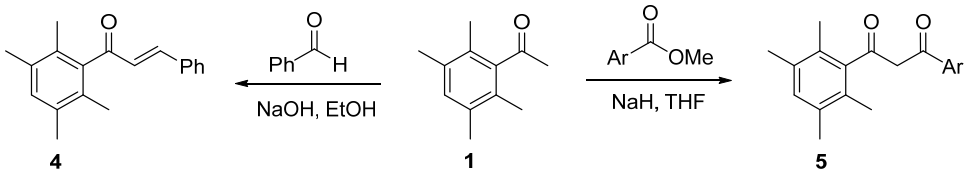
1. Introduction

1-(2,3,5,6-Tetramethylphenyl)ethan-1-one, "acetyldurene" **1** is a versatile starting material in many reaction sequences, since both the ketone group can be functionalised, and the aromatic ring can react with electrophilic reagents. However, the reactivity of **1** is significantly different to simpler acetophenone derivatives. In common with pentamethylphenyl ketones [1], the carbonyl group of **1** is unreactive to the addition of nucleophiles due to the shielding effect of the 2,6-methyl substituents. It is possible to reduce **1** to the corresponding alcohol (**2**) using $LiAlH_4$, although less reactive hydride reducing agents are ineffective [2] (Scheme 1). Furthermore, the reaction of Grignard reagents with **1** does not usually lead to the 1,2-nucleophilic addition product; instead, a magnesium enolate (**3**) is formed [3] (Scheme 1).



Scheme 1. The reaction of **1** with $LiAlH_4$ affording alcohol **2** and the reaction with Grignard regents to give enol **3**.

Ketone **1** can also be deprotonated by other strong bases; for example, **1** can undergo an aldol reaction sequence in the presence of sodium hydroxide in ethanol to form chalcone **4** [4] (Scheme 2). Ketone **1** can also be converted to 1,3-diketone products (**5**) when deprotonated with sodium hydride and then reacted with an aryl methyl ester [5] (Scheme 2).



Scheme 2. Formation of chalcone (**4**) and 1,3-diketone (**5**) products from **1**.

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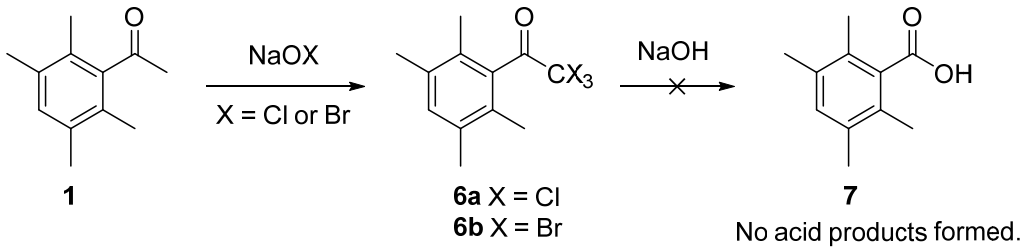
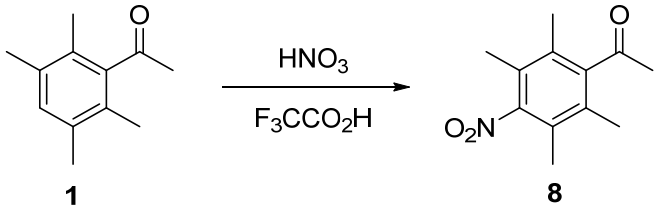
The reactivity of **1** in haloform reactions is particularly noteworthy, since it demonstrates the ability to manipulate the acetyl CH_3 and unreactive nature of the carbonyl group toward nucleophiles. This reaction sequence has been studied in detail by Gray, Walker, and Fuson [6]. It was reported that **1** could be converted to the trichloro (**6a**) and tribromo (**6b**) ketones in good yields, although the reactions required 2–5 days to reach completion (Scheme 3). Attempts were made to convert **6a** and **6b** to carboxylic acid **7** by heating the trihaloketones in 40% sodium hydroxide for several hours. All attempts to transform **6a** and **6b** to carboxylic acid reportedly failed yield any product; in the case of **6a**, the starting material was recovered from the reaction mixture.

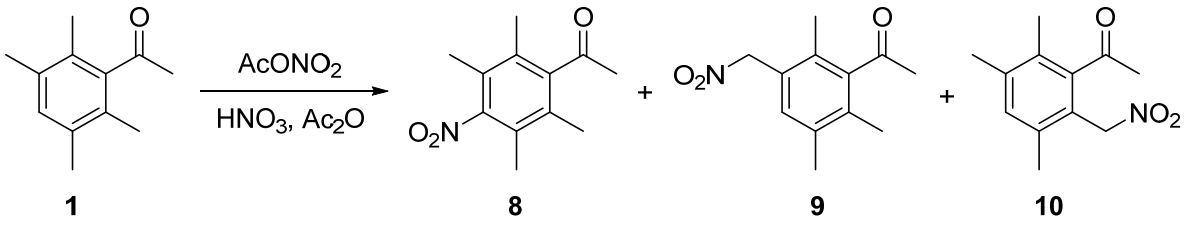


Scheme 3. The attempted haloform reaction using **1,** with **6** being the sole product.

There is a single reaction site for electrophilic aromatic substitutions reactions to occur, and a limited number of examples of such reactions have been reported. The electrophilic addition of halogens to the aromatic ring is currently unknown. Instead, the halogenated compounds are usually prepared by Friedel–Crafts acetylation of the corresponding halogenated durene derivative [7]. There are, however, reports of successful nitration reactions of ketone **1** [8,9]. Nitration of **1** to afford nitro derivative **8** was achieved by reaction of the ketone in 70% nitric acid in trifluoroacetic acid [9] (Scheme 4). **1** has also been reported to undergo nitration in the presence of acetyl nitrate at 0 °C (generated from a mixture of acetic anhydride and fuming nitric acid) [9]. These more forcing conditions result in a complex mixture of products, which includes nitro compound **8** and the products resulting from the nitration of individual ring methyl groups (**9** and **10**) (Scheme 5).



Scheme 4. Nitration of **1** to afford **8** in nitric acid and trifluoroacetic acid.

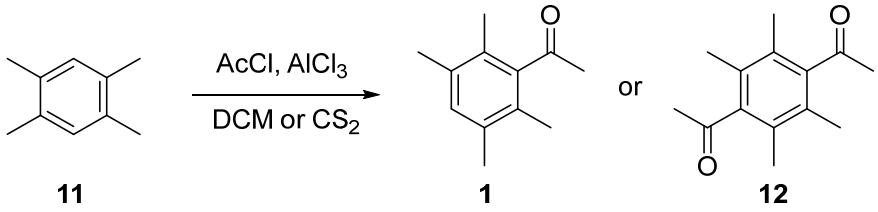


Scheme 5. Nitration of **1** affording multiple products (**8**, **9**, and **10**).

2. Results and Discussion

*2.1. Synthesis of **1***

Ketone **1** (1-(2,3,5,6-Tetramethylphenyl)ethan-1-one) is usually prepared by Friedel–Crafts acetylation of durene (**11**) (Scheme 6). Control of the reaction conditions is required to ensure only compound **1** is formed, since it is possible to obtain the diacetylated derivative **12** as a byproduct. Compound **1** is favoured if the "Perrier method" is used; this approach requires that durene be added to a mixture of acetyl chloride/aluminium chloride in dichloromethane [10] or carbon disulfide [11]. A detailed study of the acylation conditions was conducted by Andreou, Bulbulian, and Gore in 1980 [12]. This work demonstrated that the diacetylated product **12** was most likely to be formed if an excess of aluminium trichloride relative to the amount of acetyl chloride was used.



Scheme 6. The formation of acetyldurene (**1**) and diacetyldurene (**12**).

It was also postulated that the acetyl group of **1** does not exert a strong electron-withdrawing effect on the aromatic ring. This effect was attributed to the acetyl substituent being forced to rotate to a "near orthogonal position" and, therefore, reduce the ability to be conjugated with the aromatic ring [12].

2.2. NMR and IR Spectroscopy

The ^{1}H and ^{13}C DEPTQ NMR spectra (see Figures S1 and S2 in the Supporting Information) of **1** provide evidence that acylation has taken place. The appearance of the highly deshielded peak at δ_C 210.0 ppm clarifies the inclusion of the acetyl group. There is an upfield shift associated with the *ortho* and *meta* methyl groups from δ_H 2.24 ppm in **11** to 2.20 and 2.09 ppm in **1**. The infrared spectrum shows the characteristic carbonyl stretching band at 1691 cm^{-1} for **1**, which is slightly shifted from that of acetophenone (1686 cm^{-1}).

2.3. X-Ray Crystallography

Crystals of **1** of suitable quality for single-crystal X-ray diffraction were obtained by slow evaporation of an acetone solution (Figure 1). The molecular structure is as expected confirming the mono-acylation of durene has taken place.

A noteworthy feature of the structure is that the carbonyl group and the mean plane of the tetramethylphenyl ring are not coplanar, with an angle of 68.07(17)° between the C2−C7 plane and the C8−C1−C2−O1 plane. This is in contrast with acetophenone (CSD code ACETPH), which has an equivalent angle of 3.69° (Figure 2) [13]. This observed angle strongly indicates that there is very little conjugation between the phenyl ring and the carbonyl group due to the steric effects of the *ortho* methyl groups. Furthermore, more significant twisting is observed in dipropiodurene (CSD code MEHJOZ), which has an angle of 86.24° between the ketone and xylene ring [14] (Figure 2).

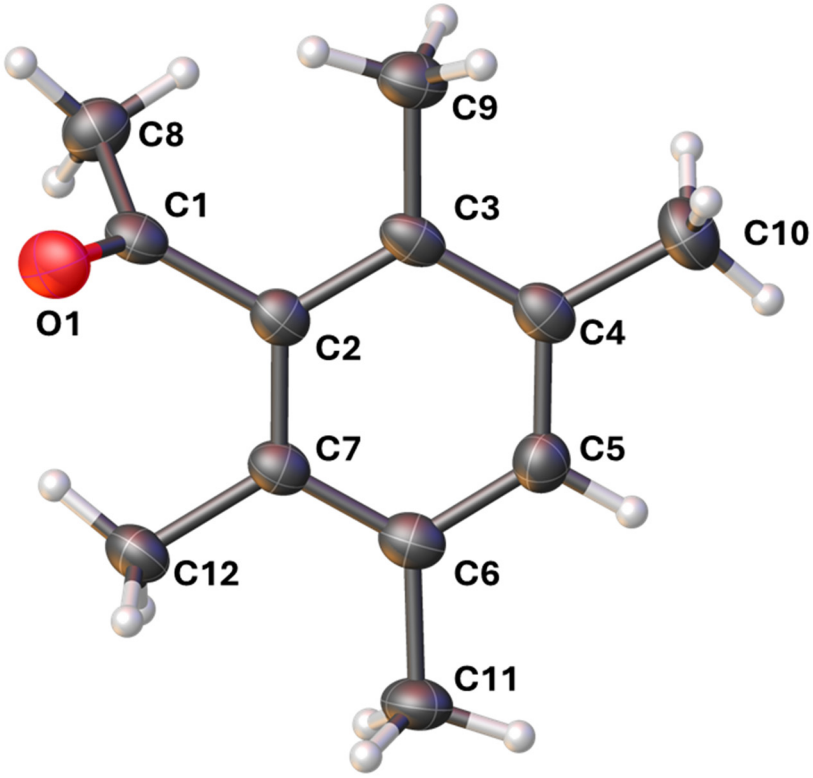


Figure 1. The molecular structure of **1**. The anisotropic displacement ellipsoids of non-hydrogen atoms are set at the 50% probability level.

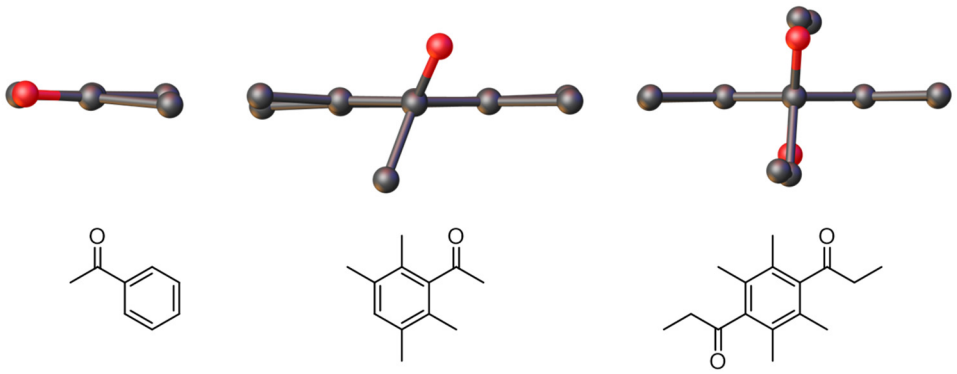


Figure 2. View along the mean aromatic ring plane of ACEPTH (**left**), **1** (**centre**), and MEHJOZ (**right**).

The C−C ring bond lengths observed in **1** are all typical and comparable to acetophenone. There is also no difference in the carbonyl bond. In **1,** the C1−O1 bond length is 1.212(6) Å, compared to acetophenone at 1.216(2) Å.

There are non-classical C-H···O hydrogen bonds between O1 and H9C (2.582 Å) which form one-dimensional chains running along the along the *a*-axis (Figure 3). Adjacent chains pack with the ketones in proximity, giving rise to a layered appearance.

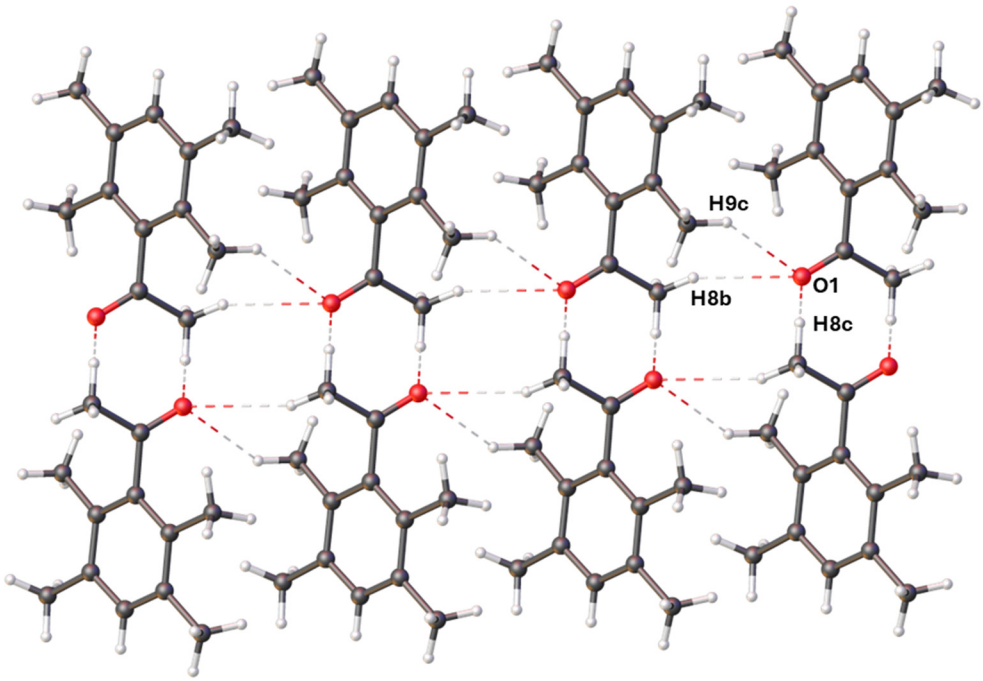


Figure 3. View of the C-H··· hydrogen bonds in **1** between O1 and H9c, forming chains along the *a*-axis.

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 (Bruker, Billerica, MA, USA). All NMR spectra were recorded using a Bruker Avance II 400 (MHz) spectrometer at 20 °C (Bruker, Billerica, MA, USA). The ^{13}C NMR spectrum was recorded using the DEPTQ-135 pulse sequence with broadband proton decoupling. Tetramethylsilane was used as an internal standard (δ_H, δ_C 0.00 ppm). Chemical shifts (δ) are given in parts per million (ppm) relative to the TMS peak. Spectra were analysed using the MestReNova software package (Santiago de Compostela, Spain) (version 14).

3.1. Synthesis of 1-(2,3,5,6-Tetramethylphenyl)ethan-1-one (1)

A suspension of aluminium chloride (9.34 g, 70 mmol) in dichloromethane (70 mL) was prepared and cooled in an ice/water bath. To this, acetyl chloride (5.50 g, 5.0 mL, 70 mmol) in dichloromethane (10 mL) was added dropwise over 15 min. After a further 10 min of stirring, a solution of 1,2,4,5-tetramethylbenzene (6.71 g, 50 mmol) in dichloromethane (80 mL) was added dropwise over 30 min to the $AlCl_3$/AcCl mixture, turning the mixture dark yellow and, eventually, orange. Stirring was maintained at ambient conditions for a further 24 h. The reaction mixture was added to ice (50 g) and conc. hydrochloric acid (20 mL), at which point, the solution turned colourless. The organic layer was separated, and the aqueous layer was washed with dichloromethane (2 × 50 mL). The organic layers were combined, washed with aqueous brine (2 × 40 mL), then aqueous sodium bicarbonate solution (3 × 30 mL), and dried over sodium sulfate. The volatiles were removed in vacuo to afford a white powder (8.46 g, 96%) (M.p. 72−73 °C from X-ray suitable crystals).

^{1}H NMR (400.3 MHz, $CDCl_3$) 6.95 (1H, s, *p*-H), 2.46 (3H, s, C(O)Me), 2.21 (6H, s, *m*-CH_3), 2.09 (6H, s, *o*-CH_3). ^{13}C DEPTQ (100.6 MHz, $CDCl_3$) δ_C 210.0 (s, C=O), 143.2 (s, *ipso*-C), 134.5 (s, *o*-CMe), 131.6 (s, *p*-CH), 127.7 (s, *m*-CMe), 32.9 (s, COMe), 19.6 (s, *m*-CMe),

16.0 (s, *o*-C<u>Me</u>). Infrared (IR) ν_{max} (ATR/cm^{-1}) 3004w (ν_{C-H}), 2961w (ν_{C-H}) 1691vs ($\nu_{C=O}$), 1465 m, 1349 s, 1160 s, 995 m, 870 m, 622 m, 570 m.

3.2. X-Ray Crystallography Experimental Details

X-ray diffraction data for compound **1** were collected at 173 K using a Rigaku FR-X Ultrahigh Brilliance Microfocus RA generator/confocal optics [Mo Kα radiation (λ = 0.71073 Å)] with XtaLAB P200 diffractometer (Rigaku Corporation, Tokyo, Japan). Intensity data were collected (using a calculated strategy) and processed (including correction for Lorentz, polarization, and absorption) using CrysAlisPro [15]. The structure was solved by dual-space methods (SHELXT [16]) and refined by full-matrix least squares against F^2 (SHELXL-2019/3 [17]). Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were refined using a riding model. Crystals were affected by non-merohedral twinning, showing a twin law of [−0.9992 0.0005 −0.0002 −0.0005 −0.9995 0.0003 −0.5578 0.0108 0.9998], representing a 179.97° rotation about the [0.00 0.00 1.00] reciprocal-space axis, and a refined twin fraction of 0.301(3). The twinned data were processed within CrysAlisPro, generating an HKLF5-format file for structure refinement. All calculations were performed using the Olex2 interface [18].

Crystal data for **1**: $C_{12}H_{16}O$, M = 176.25, T = 173 K, triclinic, space group $P\bar{1}$ (no. 2), a = 5.5814(6), b = 6.0070(5), c = 15.212(3) Å, α = 89.286(10), β = 84.102(11), γ = 81.997(8)°, Vol. = 502.36(11) Å^3, Z = 2, 8970 reflections measured, 3230 unique (R_{int} = 0.0643), which were used in all calculations. The final $R1$ [$I > 2\sigma(I)$] was 0.0726, and wR_2 (all data) was 0.2127.

Supplementary Materials: Figures S1–S3: Spectroscopic data for **1**.

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

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Data Availability Statement: CCDC 2410206 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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