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Synthesis and photolysis studies of carboxylic esters of 2-hydroxy-1,2,2-triphenylethanone: a novel tandem photocyclisation

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Abstract—Carboxylic esters of 2-hydroxy-1,2,2-triphenylethanone can be prepared in good yield by reaction between 2-chloro-1,2,2-triphenylethanone and a carboxylic acid in the presence of silver carbonate and silver tetrafluoroborate. Irradiation of the ester with a medium pressure mercury lamp results in a rapid and quantitative photolysis to afford the carboxylic acid and benzo[*b*]phenanthro[9,10-*d*]furan. \bigcirc 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

Photolabile protecting groups are of increasing interest. They have found application in the synthesis of complex organic molecules,¹ the preparation of spatiallyaddressable arrays of macromolecules,² microlithography³ and the photorelease of biomolecules. The latter area in particular is a very fertile one, where biomolecules rapidly released from a 'caged' form are used to initiate a biological reaction that may be studied by fast X-ray diffraction,⁴ infra red spectroscopy,⁵ voltage clamp, patch clamp or other physiological recording techniques.⁶ The two most commonly employed photolabile protecting groups for carboxylic acids are those derived from 2-nitrobenzyl alcohol7 and benzoin.⁸ The former suffers a number of drawbacks, not least of which are relatively slow release kinetics and the production of electrophilic nitroso aldehydes and ketones as photolytic by products. These can cause undesirable side reactions, and also undergo facile dimerisation to diazo compounds which are very efficient light screens, leading to a reduction in the efficiency of deprotection as the photolysis proceeds. Benzoin esters overcome a number of these drawbacks, and their photolysis proceeds rapidly with a high quantum vield. However esterification of a chiral acid produces an undesirable mixture of diastereoisomers due to the chirality inherent in the benzoin moiety, leading to difficulties in purification and the problem of carrying

diastereoisomers through subsequent reactions. Enantiopure benzoin is expensive, and moreover the direct esterification of carboxylic acids with benzoin itself requires relatively vigorous conditions not applicable to all substrates. The photolytic properties of esters of 2-hydroxy-1,2,2-triphenylethanone 1 have not been examined, although the corresponding carbamates have been shown to liberate amines upon irradiation.⁹ The mechanism for this photocleavage process is unknown, but the available data do not support a benzoin-like photolysis and rather suggest that several competing pathways are in operation. We were interested to see whether the esters would liberate the corresponding carboxylic acid on irradiation, thereby providing an achiral alternative to benzoin as a photolabile acid protecting group.

2. Results and discussion

Grignard reaction between phenyl magnesium bromide and benzil afforded 2-hydroxy-1,2,2-triphenylethanone **1** (40%). As anticipated, esterification of this very hindered alcohol required forcing conditions. For example the acetate **4a** was prepared in a 70% yield by heating **1** and acetic anhydride for 4 days in refluxing pyridine, and so we sought a milder method which would be applicable to a wider range of substrates. The success of our earlier synthesis of benzoin esters based upon the displacement of bromide anion from desyl bromide by a cesium carboxylate suggested to us that a similar process could provide a facile route to the desired esters.¹⁰

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Ohwada and Shudo have demonstrated that the chloride **2** undergoes silver assisted ionisation in dichloromethane solution at -60° C to afford around 50% of the corresponding cation.¹¹ Addition of water trapped the cation to yield the alcohol **1** along with recovered chloride. We anticipated that trapping of the cation by a carboxylic acid or a carboxylate anion would afford the corresponding ester. The chloride **2** was prepared in 64% yield from the alcohol **1** by reaction with thionyl chloride in pyridine.¹² Disappointingly, treatment of **2** in dichloromethane solution at -60° C with 2 equiv. of silver acetate returned unreacted starting material. However addition of 2 equiv. of silver tetrafluoroborate to the -60° C solution resulted in a 92% yield of the acetate ester **4a** after only 30 min.

Pre-forming the silver carboxylate is inconvenient in the majority of cases, and so we examined whether acetic acid could be employed directly in the transformation. Treatment of chloride **2** with 2 equiv. each of silver tetrafluoroborate and acetic acid resulted in sluggish formation of the acetate **4a** in a modest 37% yield. Addition of cesium carbonate as base suppressed the reaction completely, possibly due to the insolubility of the cesium carboxylate. Silver carbonate on the other hand gave a much improved 75% yield of ester **4a**, and warming the reaction to 0°C increased the yield to 89% (Scheme 1).

To explore the scope of the reaction a range of carboxylic acids were employed (Table 1). The optimised protocol, suitable for the more hindered acids, involved reaction at -60° C for 1 h, followed by 1–2 h at 0°C. Isolated yields of the esters were typically 70–80% (Table 1). A number of chiral carboxylic acids were esterified, acids **3e–g**. By contrast with benzoin esters of chiral acids,¹⁰ purification and NMR analysis of the 2-hydroxy-1,2,2-triphenylethanone esters was not complicated by the presence of diastereoisomers.

The esters were irradiated using a 400 W medium pressure mercury lamp in methanol or ethanol solution, or in a mixed solvent system of ethanol and acetonitrile, without precautions to exclude air. Photolysis was rapid and quantitative as judged by TLC and NMR, and recovered yields of carboxylic acid were all high (Table 1). In the case of the chiral esters 4e-g, the stereochemical integrity of the carboxylic acid was not compromised by the protection-deprotection sequence, as judged by the optical rotation of the recovered acid. Interestingly the side product from the photolysis was benzo[b]phenanthro[9,10-d]furan 5, identified by observation of a parent ion at m/z 268 in the EI⁺ mass spectrum, and by comparison of the UV spectrum with that from an authentic sample.¹³ It is postulated that 5 results from a novel tandem photolysis process (Scheme 2). It is proposed that initial benzoin-like photolysis produces 2,3-diphenylbenzofuran 6, which undergoes photochemical cyclisation to 7; aerial oxidation re-aromatises the system to yield 5. Photochemical cyclisation of compounds related to 6 have previously been reported.14

Figure 1 shows the UV spectra of a sample of acetate **4a** in ethanol, recorded before irradiation and after irradiation for 1 min and 18 min with a 16 W medium pressure mercury lamp. The spectra appear to be consistent with the postulated tandem photolysis processes.



Scheme 1.

Table I.	Ta	ble	1.
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Acid		Ester	Yield of ester (%)	Recovery of acid following photolysis (%)
3a	Acetic	4a	89	88
3b	Propanoic	4b	73	86
3c	Hexanoic	4c	74	91
3d	Benzoic	4d	54	86
3e	(R)-(+)-Citronellic	4 e	74	82
3f	(-)-Menthoxyacetic	4f	77	86
3g	(R)- $(-)$ - O -Acetylmandelic	4g	74	89
3h	3-Methylbutanoic	4h	71	90



Figure 1.

Initial benzoin-like photolysis gives a rapid build up of 2,3-diphenylbenzofuran **6**, evident by an increased absorption at around 300 nm in the spectrum recorded after 1 min.¹⁵ Spectra recorded over the next 5 min (not shown) are complex, indicating the presence of at least two species. On prolonged irradiation benzo[*b*]-phenanthro[9,10-*d*]furan **5** clearly emerges, and after 18 min **5** is the sole species evident in the UV spectrum.¹⁶

In conclusion, we have identified 2-hydroxy-1,2,2triphenylethanone **1** as a new photolabile protecting group for carboxylic acids, which may be attached in good yield under mild reaction conditions. Photolytic deprotection to produce the carboxylic acid proceeds rapidly and in excellent yield, with the protecting group undergoing a novel tandem photocyclisation process to afford benzo[*b*]phenanthro[9,10-*d*]furan **5**.

3. Experimental

Typical esterification procedure: To a solution of propanoic acid (75 μ L, 1.0 mmol) in anhydrous dichloromethane (15 mL) at -60°C was added silver carbonate (276 mg, 1.0 mmol). The suspension was stirred for 20 min before 2-chloro-1,2,2-triphenylethanone **2** (153 mg, 0.5 mmol) was added, followed by silver tetrafluoroborate (195 mg, 1.0 mmol). After stirring at -60°C for 1 h the reaction mixture was removed to an ice bath for a further 1–2 h,

until the reaction was judged to be complete by TLC. The reaction mixture was quenched by addition of water (10 mL) and then filtered through a small pad of celite to remove silver salts. The aqueous phase was extracted with dichloromethane (2×10 mL) and the combined organic phases were dried with anhydrous MgSO₄ and reduced in vacuo. Purification by flash column chromatography using petroleum ether (40-60°C) and diethyl ether (9:1) yielded 4b as a colourless solid (126 mg, 73%); mp 146–149°C; $R_f = 0.33$; $v_{max}(neat)/cm^{-1}$ 1698 (C=O), 1744 (ester C=O) and 2859–3061 (aromatic CH); $\delta_{\rm H}$ (300 MHz, CDCl₃) 0.93 $(3H, t, J=7.7, CH_3)$, 2.29 $(2H, q, J=7.7, CH_2)$ and 7.27–7.72 (15H, m, $3 \times C_6 H_5$); δ_C (75 MHz, CDCl₃) 9.17 (CH₃), 28.55 (CH₂), 89.17 ((C₆H₅)₂C-), 127.94 (CH), 128.39 (CH), 128.70 (CH), 129.51 (CH), 132.27 (CH), 137.12 (C⁴), 140.25 (C⁴), 172.80 (-CO₂-) and 196.06 (C₆H₅CO-); m/z (ES) 367 (92%, $[M+Na]^+$) and 271 (100%, [Ph₂CCOPh]⁺); Found (ES) [*M*+Na]⁺, 367.1315. $C_{23}H_{20}O_{3}Na$ requires 367.1310.

Photolysis procedure: A solution of ester 4 (0.10 mmol) in a mixture of ethanol and acetonitrile (1:1, 10 mL) was placed in a borosilicate glass tube and exposed to a 400 W medium pressure mercury lamp.¹⁷ On complete photolysis (10–15 min, as judged by TLC) the solvent was removed in vacuo and the residue partitioned between dichloromethane (10 mL) and saturated sodium hydrogen carbonate solution (2×10 mL). The

aqueous phase was acidified to pH 2 with 2 M HCl and extracted with dichloromethane (2×10 mL). The organic phase was dried with anhydrous MgSO₄ and reduced in vacuo to yield the pure acid **3**.

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