

2,5-Dimethylphenacyl as a New Photoreleasable Protecting Group for Carboxylic Acids

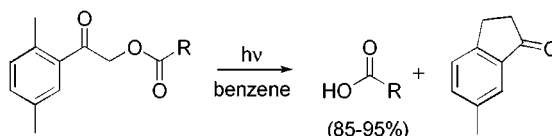
Petr Klán,* Miroslav Zabadal, and Dominik Heger

Department of Organic Chemistry, Faculty of Science, Masaryk University,
Kotlarska 2, 611 37 Brno, Czech Republic

klan@sci.muni.cz

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ABSTRACT



The 2,5-dimethylphenacyl chromophore, a new photoremovable protecting group for carboxylic acids, is proposed. Direct photolysis of various 2,5-dimethylphenacyl esters in benzene or methanol at 254–366 nm leads to the formation of the corresponding carboxylic acids in almost quantitative isolated yields. The photodeprotection is based on efficient intramolecular hydrogen abstraction without the necessity of introducing a photosensitizer.

There has been long-standing interest in photoreleasable protecting groups, especially in terms of their applications in various multistep organic syntheses or in biochemistry.¹ The *o*-nitrobenzyl group, for example, is among the most widely used.²

The photochemical release of phosphates and carboxylic acids from the *p*-methoxyphenacyl esters has already been reported.³ In the past three years, the photochemistry of phenacyl and *p*-hydroxyphenacyl chromophores has received considerable attention. Falvey and co-workers reported that photolysis of electron-donating photosensitizers in the presence of various phenacyl derivatives resulted in release of the corresponding carboxylic acids,⁴ alcohols, and phos-

phates⁵ in high yields. In addition, efficient photolysis of phenacyl esters in the presence of hydrogen atom donors has been described.⁶ Givens et al. proposed the *p*-hydroxyphenacyl group as an aqueous soluble, photoremovable, protecting group for amino acids, peptides,⁷ and phosphates.⁸ Irradiation of those esters in the presence of water at 300–350 nm triggered release of the corresponding acids with high efficiency and at the same time resulted in formation of biochemically benign byproducts. Recently, a mechanism in which the primary photochemical step involves the singlet excited state has been proposed.⁹ There are also a number of nonphotochemical deprotection methods for the phenacyl group described in the literature.¹⁰

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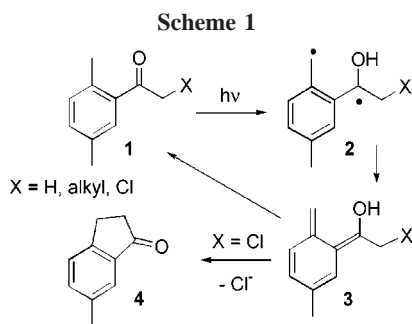
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It is well-known that aryl ketones with *o*-alkyl groups undergo an efficient photoinduced enolization (Scheme 1).¹¹

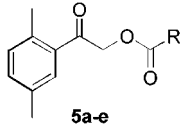


The reaction of **1** (X = H, alkyl) involves triplet excited ketone formation, which is followed by intramolecular hydrogen abstraction yielding the biradical **2** and consequently the triplet photoenol **3**.¹² In the absence of trapping agents, photoenols decay by reverse hydrogen transfer to regenerate the ketone. On the other hand, α -chloro-2',5'-dimethylacetophenone (**1**, X = Cl) can lead to methylindanone **4** as has been reported by Bergmark et al.¹³

Now we wish to report on the photochemistry of 2,5-dimethylphenacyl (DMP) esters of carboxylic acids. We were intrigued by the possibility that carboxylic acids might be effectively released as a consequence of intramolecular hydrogen abstraction; thus the DMP chromophore would be a "self-photoreleasable" protecting group, i.e., without necessity to introduce any photosensitizer or hydrogen atom donor. The photochemistry of the DMP esters has been investigated in terms of solvent and wavelength influence.

The esters (**5a–e**) were synthesized by refluxing a mixture of α -chloro-2',5'-dimethylacetophenone,¹⁴ the sodium salt of the corresponding acid (1.2–2 equiv), sodium iodide (1.2 equiv), and triethylamine (1.2 equiv) in acetone and then purifying the product by recrystallization or column chromatography. The chemical yields are shown in Table 1.

Table 1. Synthesis of DMP Esters

 5a–e		
R	ester	yield (%)
CH ₃	5a	84
C ₆ H ₅	5b	95
C ₆ H ₅ CH ₂	5c	84
<i>n</i> -pentadecyl	5d	69
<i>N</i> -(<i>tert</i> -butoxycarbonyl)-L-phenylalanine	5e	51

The corresponding carboxylic acids were obtained in nearly quantitative isolated yields (Table 2) when irradiated according to the representative procedure: $\sim 5 \times 10^{-3}$ M

Table 2. Photolysis of DMP Esters

ester	solvent	wavelength (nm)	yield (%) ^a
5a	benzene	>280	85 ^b
5b	benzene	>280	86
5b	methanol	>254	92
5c	benzene	>280	91
5d	benzene	>280	95
5e	benzene	>280	90

^a Isolated yields of the crude acids (>95% purity). ^b Determined by GC.

solution of the DMP ester in benzene or methanol (~ 250 mL) was irradiated in a quartz immersion well reactor using a 125 W medium-pressure Hg lamp (>254 nm experiments) or irradiated through a 2 mm borosilicate glass filter (>280 nm experiments) over 5 h. Irradiation was stopped when conversion reached at least 96% (GC). For reactions in benzene, the acid was isolated by washing with an Na₂CO₃ solution. The alkaline layer was then acidified with dilute HCl, and the product was extracted into dichloromethane. For reactions in methanol, solvent was evaporated, the residue was dissolved in dichloromethane, and the following extraction proceeded in a similar manner to that described above. The crude acids were analyzed by GC, GC/MS, and NMR, and the data were compared to those of the authentic samples. The purity of the product was always found to be higher than 95%.

We isolated and analyzed all significant photoproducts. 6-Methyl-1-indanone (**4**)¹⁵ was practically the only photoproduct found, in addition to the carboxylic acid, in nonpolar benzene (Scheme 2). This parallels Bergmark's results obtained by irradiation of α -chloro-2',5'-dimethylacetophenone in benzene as previously mentioned.¹³ The reaction obviously proceeds through triplet excited ester **6** and 1,4-biradical **7**, which loses the corresponding carboxylic acid in the subsequent step of a possibly concerted rearrangement of the enol. However, photosolvolysis seems to be a dominant pathway when photolysis is accomplished in nucleophilic methanol. Thus, along with indanone **4**, 2-(methoxymethyl)-5-methylacetophenone (**8**)¹⁶ was isolated in high yields.

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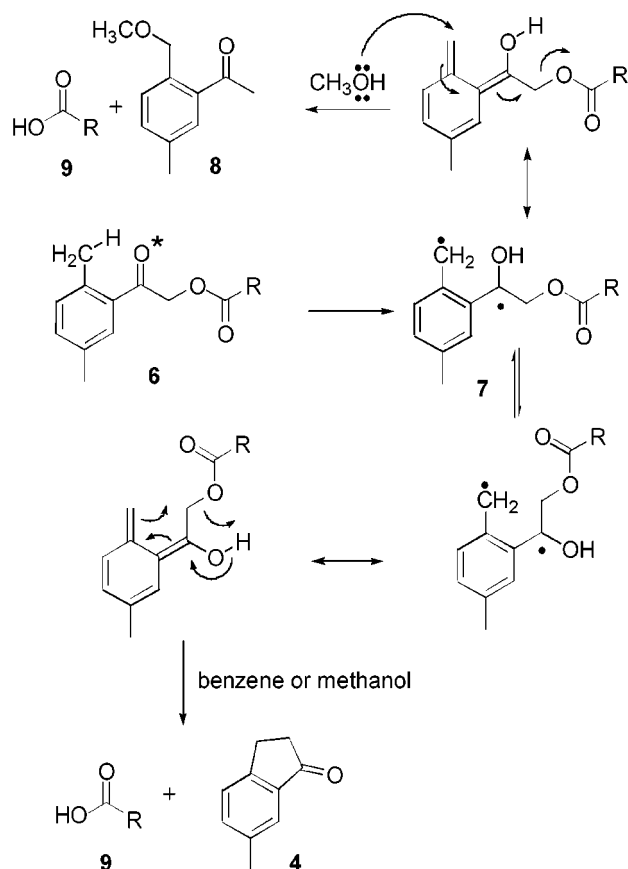
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(14) 2,5-Dimethyl- α -chloroacetophenone was synthesized according to ref 13.

(15) Mp (from petroleum ether) 48–51 °C. ¹H NMR (300 MHz, CDCl₃) δ (ppm) 2.40 (s, 3H), 2.65–2.69 (m, 2H), 3.08 (t, J = 5.8 Hz, 2H), 7.35 (d, J = 7.9 Hz, 1H), 7.40 (dd, J_1 = 7.9 Hz, J_2 = 1.5 Hz, 1H), 7.55 (broad s, 1H). ¹³C NMR (75.5 MHz, CDCl₃) δ (ppm) 21.1, 25.4, 36.6, 123.7, 126.4, 135.9, 137.2, 137.3, 152.5, 207.1. MS (EI) m/z 146 (M⁺), 118, 115, 103, 91. Anal. Calcd for C₁₀H₁₀O: C, 82.16; H, 6.89. Found: C, 82.39; H, 6.92.

(16) Mp. 31–32 °C. ¹H NMR (300 MHz, CDCl₃) δ (ppm) 2.39 (s, 3H), 2.57 (s, 3H), 3.42 (s, 3H), 4.70 (s, 2H), 7.29 (t, J_1 = 7.9 Hz, J_2 = 8.2 Hz, 1H), 7.50 (d, J = 5.8 Hz, 2H); ¹³C NMR (75.5 MHz, CDCl₃) δ (ppm) 21.0, 29.2, 58.6, 72.6, 128.0, 129.9, 132.5, 136.3, 136.6, 136.7, 201.6. MS (EI) m/z 178 (M⁺), 163, 147, 117, 91. Anal. Calcd for C₁₁H₁₄O₂: C, 74.13; H, 7.92. Found: C, 73.91; H, 7.96.

Scheme 2



In quantum yield measurements, benzene or methanol solutions (0.005 M) of **5b** and **5c** were irradiated simultaneously with valerophenone solutions used as an actinometer¹⁷ at >366 nm.¹⁸ The reaction conversion was kept under 20% to avoid interference from the photoproducts. The low concentrations also reduced the probability of energy transfer during a solution encounter as well as intermolecular reactions. It is expected that intramolecular triplet energy transfer in **5b** and **5c** (with the phenylacetic and benzoic chromophores, respectively) is endothermic and thus negligible.¹⁹ The results from our as well as Bergmark's¹³ quantum yield measurements are listed in Table 3. The values for both

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(18) Samples in Pyrex tubes were degassed in three freeze–pump–thaw cycles before being sealed and were irradiated in a “merry-go-round” apparatus immersed in a water bath. The 366 nm band from a medium-pressure 125 W Telslamp mercury lamp was isolated by filtration with Corning CS 0-52 and CS 7-37 filters.

Table 3. Quantum Yields in Benzene at >366 nm

ester	Φ
1 (X = Cl)	0.11 ^a
5b	0.23 ^b
5c	0.18 ^b

^a From ref 13. ^b Quantum yields for the ester degradation. The reproducibility was $\pm 9\%$.

5b and **5c** in benzene were found to be higher approximately by a factor of 2 than that of **1** (X = Cl). Initially, we anticipated an opposite tendency since the carboxylate is a poorer leaving group than chloride and there might be a higher probability of reverse hydrogen transfer in **7** causing a drop in the quantum yield. A quantum yield of $\sim 20\%$ makes our DMP chromophore as photochemically efficient as the α -phenyl-*o*-nitrobenzyl moiety.²⁰ On the other hand, an unexpected decrease in quantum yields by a factor of approximately 1.5 in methanol compared to that of benzene was found, and it will be examined thoroughly in the forthcoming research.

In conclusion, we propose a new type of photoreleasable protecting group (photochemical switch)¹ for carboxylic acids, the 2,5-dimethylphenacyl chromophore, which afford almost quantitative yields of deprotection. Practical applications perfectly fulfill all the criteria for the good protecting group in organic synthesis: very high yields of deprotection, high photochemical efficiency, a possibility of using wavelengths in the broad range of 254–366 nm thanks to the absorption characteristics of the group, good stability, and simplicity of the experiment. Furthermore, similar to some other groups (e.g., 2-nitrobenzyl² or 7-nitroindolyl²¹), the DMP group is “self-removable” because the photoreaction is intramolecular. Our future research is directed at other DMP derivatives than carboxylic acid esters as well as at a detailed kinetic analysis of this reaction.

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