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

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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 phosphates⁵ 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

References


It is well-known that aryl ketones with o-alkyl groups undergo an efficient photoinduced enolization (Scheme 1).\textsuperscript{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.\textsuperscript{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 methyl-indanone 4 as has been reported by Bergmark et al.\textsuperscript{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 effectively released as a consequence of intramolecular hydrogen abstraction yielding the biradical 7, which loses the corresponding carboxylic acid in the subsequent step of a possibly concerted rearrangement of the enol. However, photooxidolysis seems to be a dominant pathway when photolysis is accomplished in the absence of any photosensitizer or hydrogen atom donor.

We isolated and analyzed all significant photoproducts. 6-Methyl-1-indanone (4)\textsuperscript{15} was practically the only photoprocess 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.\textsuperscript{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, photooxidolysis seems to be a dominant pathway when photolysis is accomplished in nucleophilic methanol. Thus, along with indanone 4, 2-(methoxymethyl)-5-methylacetophenone (8)\textsuperscript{16} was isolated in high yields.


\textsuperscript{14} 2,5-Dimethyl-α-chloracetophenone was synthesized according to ref 13.\textsuperscript{13}

\textsuperscript{15} (15) Mp (from petroleum ether) 48–51 °C. \textsuperscript{1H} NMR (300 MHz, CDCl\textsubscript{3}), δ (ppm) 2.40 (s, 3H), 2.65–2.69 (2H, 2H), 7.35 (d, J = 7.9 Hz, 1H), 7.40 (dd, J\textsubscript{1} = 7.9 Hz, J\textsubscript{2} = 1.5 Hz, 1H), 7.55 (broad s, 1H). \textsuperscript{13C} NMR (75.5 MHz, CDCl\textsubscript{3}), δ (ppm) 21.1, 25.4, 36.6, 123.7, 126.4, 135.9, 137.2, 137.3, 152.5, 201.6. MS (EI) m/z: 146 (M\textsuperscript{+}), 118, 113, 103, 91, 84. Anal. Calcd for C\textsubscript{10}H\textsubscript{10}O: C, 82.16; H, 6.89. Found: C, 82.39; H, 6.92.

\textsuperscript{16} (16) Mp. 31–32 °C. \textsuperscript{1H} NMR (300 MHz, CDCl\textsubscript{3}), δ (ppm) 2.39 (s, 3H), 2.57 (s, 3H), 3.42 (s, 3H), 4.70 (s, 2H), 7.29 (t, J = 7.9 Hz, J\textsubscript{2} = 8.2 Hz, 1H), 7.50 (d, J = 5.8 Hz, 2H). \textsuperscript{13C} NMR (75.5 MHz, CDCl\textsubscript{3}), 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\textsuperscript{+}), 163, 147, 117, 91. Anal. Calcd for C\textsubscript{11}H\textsubscript{14}O\textsubscript{2}: C, 74.13; H, 6.92.

The corresponding carboxylic acids were obtained in nearly quantitative isolated yields (Table 2) when irradiated according to the representative procedure: a ~5 × 10\textsuperscript{-3} M 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 Na\textsubscript{2}CO\textsubscript{3} 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.
In quantum yield measurements, benzene or methanol solutions (0.005 M) of 5b and 5c were irradiated simultaneously with valerophenone solutions used as an actinometer\(^{17}\) 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’s\(^{13}\) quantum yield measurements are listed in Table 3. The values for both 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 \(~20\%) makes our DMP chromophore as photochemically efficient as the \(\alpha\)-phenyl-\(\omega\)-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-nitrobenzyl\(^2\) or 7-nitroindolyl\(^21\)), 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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\(^{(18)}\) 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 Teslamp mercury lamp was isolated by filtration with Corning CS 0-52 and CS 7-37 filters.

