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Controlled Light-Induced Release of Volatile Aldehydes and Ketones by Photofragmentation of 2-Oxo-(2-phenyl)acetates

Barbara Levrand and Andreas Herrmann*

Abstract: The light-induced controlled release of fragrances from photolabile 2-oxo-(2-phenyl)acetates *via* Norrish Type II photofragmentation was evaluated by irradiation of the precursors in different solvents and on cotton in a typical fabric softener application. The desired photooxidation was found to work efficiently in water-based systems, and it tolerates the presence of oxygen. The formation of a certain amount of alcohol besides the desired aldehyde or ketone was attributed to further reaction of the photochemically released carbonyl compound, rather than to ester hydrolysis in an aqueous environment.

Keywords: Delivery systems · Fragrances · Keto esters · Photooxidations · Triggered release

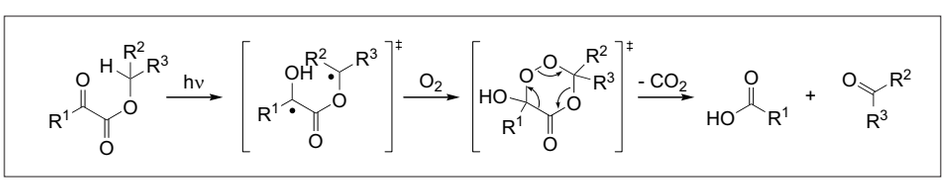
1. Introduction

Natural outdoor sunlight is an important energy source for numerous biological processes. Historically, it also served as the reaction trigger for the development of the first photochemical reactions. Today, with the availability of modern photochemical equipment, preparative syntheses are rarely carried out by photoirradiation with natural daylight, but rather with lamps emitting light at specific wavelengths and at a high intensity.[1] Up to now, photochemical processes have mainly been used in functional group protection for organic synthesis,[2] for various applications in bioorganic systems[3] or drug discovery[4] and, only recently, they have also been applied to the controlled release of volatiles in various applications of functional perfumery.[5,6] As a consequence of their high volatility, fragrances easily evaporate and can thus only be perceived for a limited period of time. On the other hand, this evaporation takes place from surfaces which are generally exposed to ambient daylight, and thus photoresponsive fragrance delivery systems seem to be particularly appropriate to control the release of volatile compounds. The design of suitable precursor structures, so-called 'profragrances' has become an important area of research in the flavour and fragrance industry.[6]

To be efficient for the release of fragrances, photochemical delivery systems have to respond to the relatively low light intensities of ambient daylight and to work in the presence of oxygen in polar solutions, preferentially in water. A typical reaction fulfilling these requirements is the Norrish Type II photoreaction of carbonyl derivatives,[5,7] with 2-oxoacetates (α-keto esters) being particularly relevant in this context.[8–11] In the presence of oxygen, these latter release aldehydes or ketones together with a carboxylic acid in a photooxidation pathway, as illustrated in Scheme 1.[12] As aldehydes tend to be relatively unstable in various applications of functional perfumery, this class of compounds is of particular interest for release from photolabile profragrances. Both, alkyl and aryl 2-oxoacetates were found to work efficiently for the release of different fragrance aldehydes and ketones.[8–11] Given the ready commercial availability of 2-oxo-(2-phenyl)acetic acid (= phenylglyoxylic acid) (**1**) and its methyl or ethyl esters (**2** and **3**), the present work focuses on the development of 2-oxo-(2-phenyl)acetates as photolabile delivery systems in functional perfumery.

2. Results and Discussion

As a first step, the synthesis of 2-oxo-(2-phenyl)acetates **4**–**7** (Scheme 2) was attempted by transesterification of **2** (or **3**) with 3-(4-*tert*-butylphenyl)-2-methylpropanol (obtained by reduction of Lilial®



Scheme 1. Mechanism for the photochemical release of aldehydes and ketones from 2-oxo-(2-phenyl)acetates in the presence of oxygen[12]

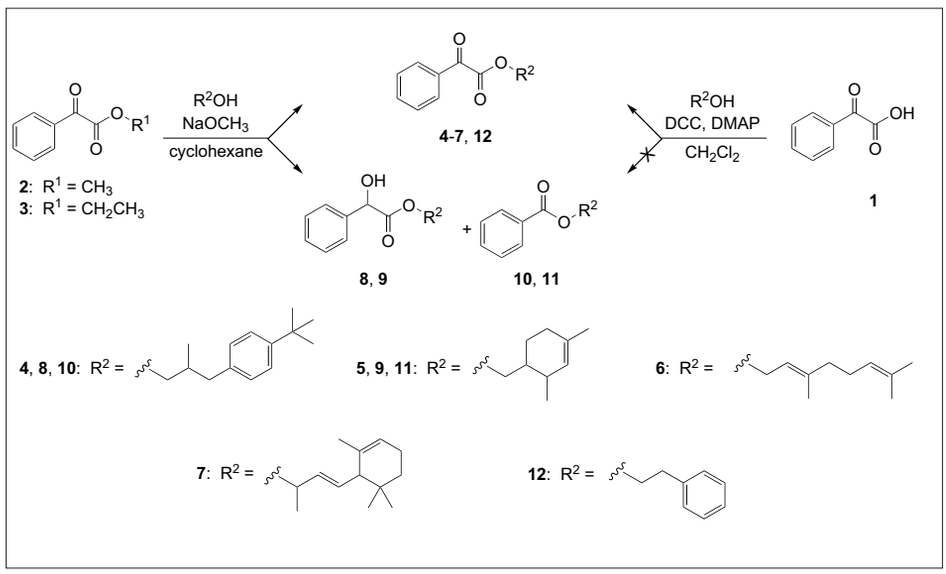
*Correspondence: Dr. A. Herrmann
Firmenich SA
Division Recherche et Développement
B. P. 239
CH-1211 Genève 8
Tel.: +41 22 780 34 74
Fax: +41 22 780 33 34
E-Mail: andreas.herrmann@firmenich.com

with $LiAlH_4$ in ether), Floralol®, geraniol and α-ionol, respectively, in the presence of a small amount of sodium methoxide in refluxing cyclohexane. Surprisingly, under these conditions 3-(4-*tert*-butylphenyl)-2-methylpropanol and Floralol® did not afford the desired keto esters **4** and **5**, but a mixture of α-hydroxy esters **8** and **9** together with benzoates **10** and **11**, respectively (presumably as the result of a redox process), whereas oxo(phenyl)acetates **6** and **7** were formed as expected from geraniol and α-ionol (Scheme 2). The formation of the α-hydroxy ester was also observed in the reaction of hexylcinnamic alcohol with ethyl ester **3**, but this reaction pathway was not further investigated[13] as 2-oxo-(2-phenyl)acetates **4**, **5** and **12** (Scheme 2) can be easily prepared from **1** using *N,N'*-dicyclohexylcarbodiimide (DCC) as described in the literature.[14]

The release of the different aldehydes and ketones from their respective precursors was investigated in undegassed solution by irradiation with a xenon lamp (Heraeus Suntest CPS at 460 W/m^2)[15] or outdoor sunlight (Table). *Ca.* 8 mM solutions of the different 2-oxo-(2-phenyl)acetates **4**–**7** and **12** in the indicated solvent were prepared by adding 1 ml of a 0.01 M solution of decanol (which was used as an internal standard for the GC analysis) to 5 ml of a 0.01 M solution of the 2-oxo-(2-phenyl)acetate. These solutions were then irradiated for 3 h in 10 ml volumetric Pyrex glass flasks and analysed by GC and GC/MS as described previously[9,10,16]. In each case a control experiment was performed in the dark.

The data in the Table show that all compounds afforded the desired aldehydes or ketones after only 3 h of irradiation. Comparable amounts of fragrances were released upon irradiation with the xenon lamp or natural outdoor sunlight. The lower yields of aldehydes or ketones (and higher yields of remaining starting material) obtained for the irradiation in 2-propanol, as compared to toluene or acetonitrile as solvent, suggest that the reaction proceeds more slowly in polar solution.

To evaluate the performance of the delivery systems under more realistic application conditions, we performed dynamic headspace analyses on small cotton sheets that had previously been treated with a fabric softener containing the 2-oxo-(2-phenyl)acetate or a molar equivalent of the aldehyde or ketone to be released as the reference sample. In a typical experiment, either 0.39% of **6** or 0.14% of citral (serving as the reference) were thus weighed into 1.8 g of the fabric softener formulation, respectively, and filled up to *ca.* 600 ml with (demineralised) tap water. Then one pre-washed cotton sheet (12 x 12 cm) was added to each sample and manually stirred for 3 min, left standing for another 2 min and then wrung out, while ensuring a constant amount of residual water. The sheets were each put into a home-made headspace sampling cell (*ca.* 160 ml of volume), thermostatted at 25 °C and irradiated with a xenon lamp at *ca.* 108500 lux. A constant flow of air (*ca.* 200 ml/min, filtered through activated charcoal and passed through a tube of $CaCl_2$ to remove the humidity from the ambient air) was continuously pumped across the headspace cell. After equilibrating the system for 15 min, the volatiles were adsorbed onto a clean Tenax® cartridge for 5 min, and the sampling was repeated 6–8 times at constant time intervals (every 50 min). After the experiment the Tenax® car-



Scheme 2. Preparation of 2-oxo-(2-phenyl)acetates **4**–**7** and **12**

Table. Amount of fragrance aldehydes and ketones released and quantity of remaining starting material (in brackets, rounded to ± 5%) after photoirradiation of 2-oxo-(2-phenyl)acetates in undegassed solution for 3 h. All numbers are average values of three samples.

N°	Name of Released Compound	Light Source	Yield of Released Aldehyde or Ketone and Amount of Remaining Starting Material (in brackets) [mol-%]					
			Toluene		2-Propanol		Acetonitrile	
4	Lilial®	xenon	39	(10)	8	(35)	53	(<5)
		sunlight	n.d.	n.d.	8	(30)	70	(5)
5	Triplal®	xenon	10	(10)	4	(35)	16	(10)
		sunlight	10	(5)	n.d.	n.d.	6	(5)
6	*trans*/*cis*-Citral	xenon	10/10	(5)	3/3	(25)	6/7	(5)
		sunlight	10/9	(<5)	2/2	(25)	8/9	(5)
7	α-Ionone	xenon	13	(5)	2	(30)	32	(<5)
		sunlight	11	(5)	n.d.	n.d.	24	(<5)
12	Phenylacetic aldehyde	xenon	51	(10)	n.d.	n.d.	53	(<5)
		sunlight	41	(15)	n.d.	n.d.	21	(<5)

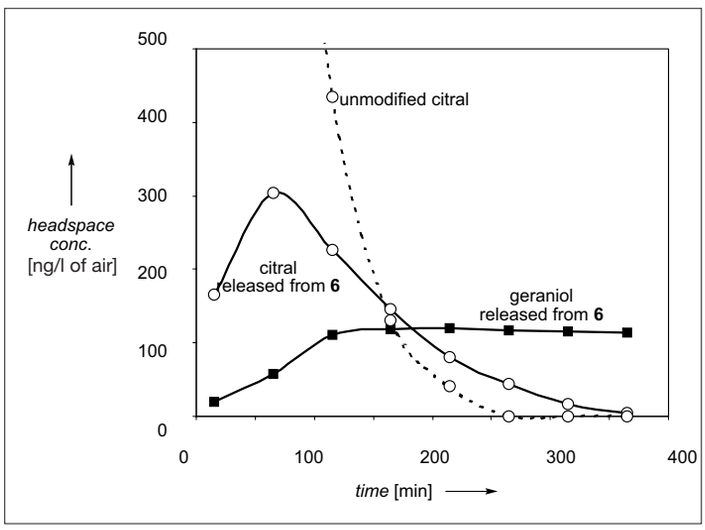


Fig. Headspace concentrations of unmodified citral (---○---, data from measurement with NaCl) and of citral (—●—) and geraniol (—■—) released from precursor **6** by irradiation with a xenon lamp (108500 lux, data from measurement with $CaCl_2$)

tridges were thermally desorbed and the amount of trapped volatiles quantified by GC analysis by calibration with an external standard.

The results obtained are depicted in the Fig. The amount of citral released from **6** first increased and then constantly decreased after reaching a maximum after 1 h, whereas the headspace concentration of the citral of the reference sample decreased continuously. The headspace concentration curve of the reference sample crosses the one of the citral released from the precursor after *ca.* 150 min, thus showing the expected slow release effect. Similar results were also obtained in a second experiment, when the humidity of the air was kept at about 75% (using a saturated solution of NaCl instead of the $CaCl_2$ tube).

Besides the desired citral, a certain amount of geraniol was also detected in the headspace of the irradiated sample. As 2-oxo-(2-phenyl)acetates are relatively labile to ester hydrolysis this seems unsurprising at first view. Partial hydrolysis of the precursors could always give rise to a certain amount of alcohol, especially if the compounds are exposed to acidic or alkaline aqueous media. However, it is interesting to note that the release of the alcohol seems to depend on the light intensity of irradiation (as also shown in other cases) and that no evidence for alcohol formation was obtained either upon irradiation of the precursors in solution or in a series of other water-based applications such as all-purpose cleaner films on glass or hair conditioners on hair. The formation of alcohol thus seems to be restricted to fabric softeners.

If one considers the shape of the curve corresponding to the citral released from **6** together with that of the geraniol formed in the reaction, they closely resemble the ones expected for stepwise, consecutive reactions. The photochemical formation of citral from the precursor at constant light intensity would give rise to an initially increasing headspace concentration of the aldehyde. The fact that a maximum is reached, followed by a slow decrease of the aldehyde concentration and, a concurrent increase of the alcohol concentration could suggest that the latter was (at least partially) generated from the former under the given reaction conditions. This could also explain the dependency of alcohol formation on the light intensity. Whether the formation of geraniol is due to a reduction of the aldehyde in the reaction medium or the result of a photochemical pathway remains unexplained. As many other parameters such as matrix effects of the surfactant may have to be considered, further experimental investigations are required to support our preliminary data.

3. Conclusion

Due to their ease of preparation from inexpensive starting materials, 2-oxo-(2-phenyl)acetates were found to be very efficient delivery systems for the controlled release of volatile aldehydes and ketones. Photoirradiation with outdoor sunlight or a xenon lamp in the presence of oxygen released the desired aldehydes and ketones in solution, as well as on cotton in a fabric softener application. In contrast to irradiations in solution or in other types of practical applications, the oxo(phenyl)acetates release a certain amount of the corresponding alcohol with the desired aldehyde (or ketone) after being deposited on cotton from a fabric softener formulation. The evolution of the headspace concentrations of the photochemically released aldehyde and the formation of the corresponding alcohol suggest a consecutive multistep reaction as a possible explanation for the observed data. However, additional experiments will be required to support this hypothesis. As the alcohol formed in the photoreaction is also a perfumery alcohol with a similar olfactive descriptor as the corresponding aldehyde, the released mixture of the two compounds is well appreciated by the perfumers.

4. Experimental Section

General

The preparation of precursor **6** and the photoirradiations in solution were carried out as described previously.[10,16] All new compounds were fully characterised by UV/Vis, IR and NMR spectroscopy as well as by mass spectrometry.

Synthesis of 2-Oxo-(2-phenyl)acetates under DCC Coupling Conditions

A solution of **1**, DMAP (0.1 equiv.) and alcohol (1.8 equiv.) in dichloromethane (*ca.* 100 ml for 45 mmol of **1**) was cooled in an ice-bath before a solution of DCC (1.2 equiv.) in dichloromethane (*ca.* 40 ml for 40 mmol of DCC) was added during 15–40 min. The reaction mixture was stirred for 10–15 min at 0 °C, then at 20 °C for several hours. The precipitate was filtered off and the filtrate taken up in ether, washed with water (3x), HCl (10%, 3x), and a saturated solution of Na_2CO_3 (3x). The organic layer was dried (Na_2SO_4), concentrated and chromatographed (SiO_2, heptane/ether 8:2) to give the target compound.

4 (91%): ^{1}H-NMR (360 MHz, $CDCl_3$): 8.05–7.97 (*m*, 2 H); 7.71–7.62 (*m*, 1 H); 7.58–7.47 (*m*, 2 H); 7.34–7.26 (*m*, 2 H); 7.13–7.05 (*m*, 2 H); 4.29 (*ABX*, *J* = 10.7, 5.9, 1 H); 4.21 (*ABX*, *J* = 10.7, 6.3, 1 H); 2.73 (*ABX*, *J* = 13.6, 6.5, 1 H); 2.51 (*ABX*, *J* = 13.6, 7.5, 1 H); 2.33–2.17 (*m*, 1 H); 1.31 (*s*, 9 H); 1.01 (*d*, *J* = 6.7, 3 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 186.44 (*s*); 164.08 (*s*); 149.01 (*s*); 136.32 (*s*); 134.92 (*d*); 132.48 (*s*); 130.01 (*d*); 128.93 (*d*); 128.78 (*d*); 125.28 (*d*); 70.23 (*t*); 39.04 (*t*); 34.49 (*d*); 34.38 (*s*); 31.38 (*q*); 16.79 (*q*).

5 (93%): ^{1}H-NMR (360 MHz, $CDCl_3$): 8.04–7.96 (*m*, 2 H); 7.70–7.61 (*m*, 1 H); 7.51 (*t*, *J* = 7.7, 2 H); 5.36–5.29 (*m*, 1 H); 4.32 (*dd*, *J* = 7.7, 1.4, 2 H); 2.45–2.31 (*m*, 1 H); 2.21–2.09 (*m*, 1 H); 2.06–1.84 (*m*, 2 H); 1.69–1.41 (*m*, 2 H); 1.64 (*s*, 3 H); 0.91 (*d*, *J* = 7.1, 3 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$, major isomer): 186.52 (*s*); 164.18 (*s*); 134.90 (*d*); 133.06 (*s*); 132.48 (*s*); 129.97 (*d*); 128.92 (*d*); 126.50 (*d*); 67.98 (*t*); 35.91

(*d*); 30.56 (*d*); 29.21 (*t*); 23.47 (*q*); 21.23 (*t*); 15.67 (*q*).

12 (95%): ^{1}H-NMR (360 MHz, $CDCl_3$): 7.89–7.82 (*m*, 2 H); 7.66–7.58 (*m*, 1 H); 4.49–7.40 (*m*, 2 H); 7.36–7.20 (*m*, 5 H); 4.62 (*t*, *J* = 7.1, 2 H); 3.08 (*t*, *J* = 6.9, 2 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 186.28 (*s*); 163.72 (*s*); 136.96 (*s*); 134.87 (*d*); 132.32 (*s*); 130.02 (*d*); 129.01 (*d*); 128.85 (*d*); 128.68 (*d*); 126.86 (*d*); 66.40 (*t*); 34.93 (*t*).

Synthesis of 2-Oxo-(2-phenyl)acetates by Transesterification

A solution of **2**, alcohol (1.2 equiv.) and 1 ml of $NaOCH_3$ (30% in methanol) in cyclohexane (*ca*. 150 ml for 40 mmol of **2**) was heated under reflux for 112 h. After cooling to room temperature the reaction mixture was taken up in ether, washed with water (2x), dried (Na_2SO_4), filtered and concentrated. Column chromatography (SiO_2, heptane/ether 95:5) afforded the product.

7 (76%): ^{1}H-NMR (360 MHz, $CDCl_3$): 7.97 (*d*, *J* = 7.5, 2 H); 7.64 (*t*, *J* = 7.5, 1 H); 7.49 (*t*, *J* = 7.7, 2 H); 5.76–5.48 (*m*, 3 H); 5.43 (*s*, br., 1 H); 2.14 (*d*, *J* = 9.1, 1 H); 2.00 (*s*, br., 2 H); 1.58 (*s,* 3 H); 1.51–1.34 (*m*, 1 H); 1.47 (*dd*, *J* = 6.3, 2.0, 3 H); 1.23–1.14 (*m*, 1 H); 0.90 (*s*, 3 H); 0.83 (*d*, *J* = 5.9, 3 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 186.69 (*s*), 163.48 (*s*), 136.17 (*d*); 135.97 (*d*); 134.78 (*d*); 133.28 (*s*); 132.55 (*s*); 129.97 (*d*); 129.80 (*d*); 128.85 (*d*); 121.53 (*d*); 74.09 (*d*); 73.95 (*d*); 53.97 (*d*); 53.94 (*d*); 32.03 (*s*); 31.98 (*s*); 31.54 (*t*); 31.37 (*t*); 27.56 (*q*); 27.41 (*q*); 26.96 (*q*); 26.86 (*q*); 23.02 (*t*); 22.84 (*q*); 22.77 (*q*); 20.54 (*q*).

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