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End-group differentiating ozonolysis of furocoumarins

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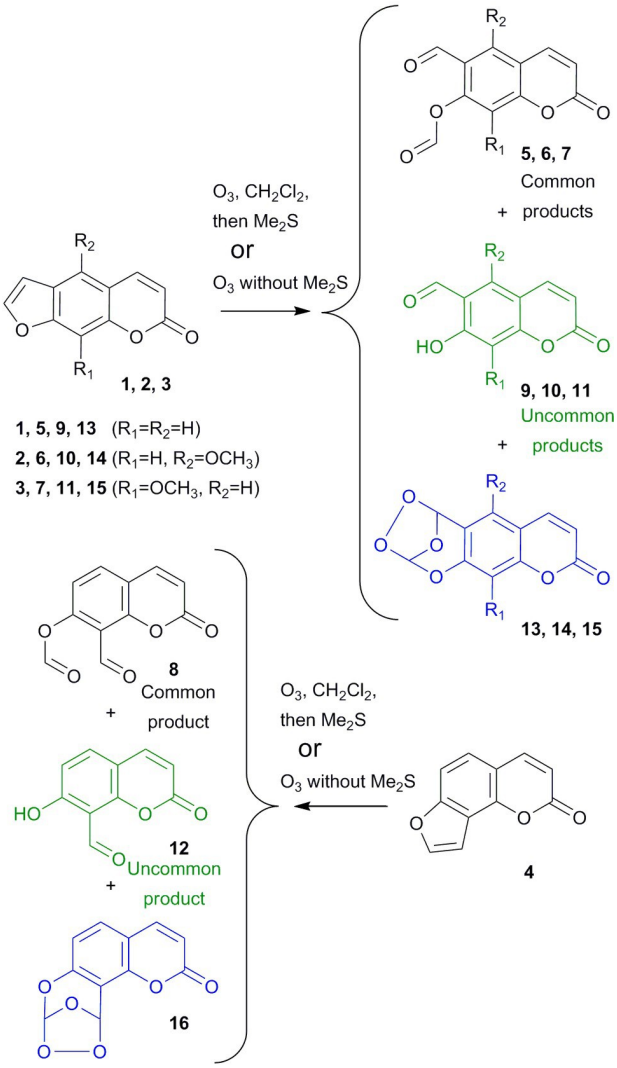
Ozonolysis of furocoumarins followed by reductive work-up yields not only common symmetrical dialdehydes, but also o-formylumbelliferones with moderate-to-high yields. Simultaneous formation of both products is accounted for the transformation of carbonyl oxides – products of primary ozonide ring opening.

Ozonolysis is widely applied in organic synthesis (reviews[1]). Briefly, upon treatment with ozone a double bond oxidatively degrades through the stage of primary ozonide (1,2,3-trioxolane) yielding an aldehyde and a very reactive carbonyl oxide (Criegee intermediate, reviews[2]). In a non-participating solvent, it recomposes with aldehyde to form secondary ozonide (1,2,4-trioxolane), which upon reduction yields two aldehydes or, in the case of cyclic or polycyclic structures, two aldehyde groups within a molecule. This is usually unwanted since it is difficult to treat selectively only one of two aldehyde groups during further compound transformations. Ozonolysis of the terminal double bond with a formation of volatile formaldehyde as a by-product is used to introduce a single aldehyde group (see[3] for the recent examples of this approach). In turn, short-lived carbonyl oxides can be scavenged by a participating solvent (e.g. methanol) resulting in alkoxyhydroxyperoxides, which can be further converted to esters. Thus, double bond ozonolysis may serve as a beneficial approach to introduce into a molecule two different functional groups that can be further independently modified. In complicated syntheses, such simultaneous introduction of two groups may dramatically reduce the number of steps (see[4] for the recent examples). In contrast to reactions yielding symmetrical dialdehydes, such approach was referred to as “end-group differentiating ozonolysis” as proposed originally by Carreira et al.[4e] (also known as “unsymmetrical” or “non-symmetric” ozonolysis in earlier works[4g-i]). Here, we performed the end-group differentiating ozonolysis of furocoumarins, which are known natural photosensitizers and widely used in biomedical chemistry.

o-Formylumbelliferones (o-formyl-7-hydroxycoumarins) were found to be apoptogenic for T lymphoblastic Jurkat cells[5] and are used as fluorescence turn-on probes for homocysteine and cysteine in aqueous solutions at neutral pH[6]. Earlier, it was reported that ozonolysis of 8-methoxypsoralen led to 6-formyl-8-methoxyumbelliferone with moderate yields (see[7] for the examples), and we extended this approach for some other furocoumarins.

Upon ozonolysis of different furocoumarins (Scheme 1, **1–4**) in CH_2Cl_2 at −84°C with subsequent dimethyl sulfide (Me_2S) reductive work-up[‡a], we obtained a mixture of two products[‡b]. The first product is a symmetrical dialdehyde



Scheme 1 Products of furocoumarins' ozonolysis

compound, and the only product expected upon ozonolysis in a non-participating solvent (common product). The second one (an uncommon product) is the respective o-formylumbelliferone initially accounted for as the product of dialdehyde hydrolysis after reductive work-up. We allowed the reaction mixture to stay in the dark at ambient temperature monitoring the conversion of dialdehydes **5–8** to o-formylumbelliferones **9–12**[‡c]. Surprisingly, such a conversion required days or even weeks: in a mixture of **5** and **9** it took one month to convert most of **5** to **9** (see ESI† Figure S1 for NMR kinetics), and the conversion of **6** to **10** took about 8 days. Thus, it is unlikely that

Table 1 Product composition, %.

Ozone followed by Me_2S workup				
	Products			
Source	1,2,4-trioxolane	Formate (common)	Umbelliferone (uncommon)	Formic acid (by-product)
1 (psoralen)	0	63	37	Not found
2 (5-MOP)	0	31	69	present
3 (8-MOP)	0	3	97	Not found
4 (angelicin)	0	12	88	Not found

Ozone without subsequent Me_2S workup				
	Products			
Source	1,2,4-trioxolane	Formate (common)	Umbelliferone (uncommon)	Formic acid (by-product)
1 (psoralen)	45	5	50	Not found
2 (5-MOP)	6	63	31	present
3 (8-MOP)	29	37	34	present
4 (angelicin)	36	4	60	present

[a] Also, see annotated spectra on ESI Figures S2-S5.

o-formylumbelliferones are formed due to hydrolysis of corresponding dialdehydes. Moreover, the slow conversion indicates that o-formylumbelliferones found in the reaction mixture an hour after the end of ozonolysis process are formed simultaneously with dialdehydes. Furthermore, it was noted that the percentage of common and uncommon products depended on the structure of the furocoumarin. Psoralen **1** lacking any substituents mainly provided the common dialdehyde (67%), with only 37% of o-formylumbelliferone. Angular structure (as for angelicin **4**) or methoxy substituents (as for **2** and **3**) promoted unusual product formation, and ozonolysis of 8-methoxypsoralen **3** yielded mainly the uncommon product. Thus, we state the evidence of end-group differentiating ozonolysis in the absence of carbonyl oxide scavengers.

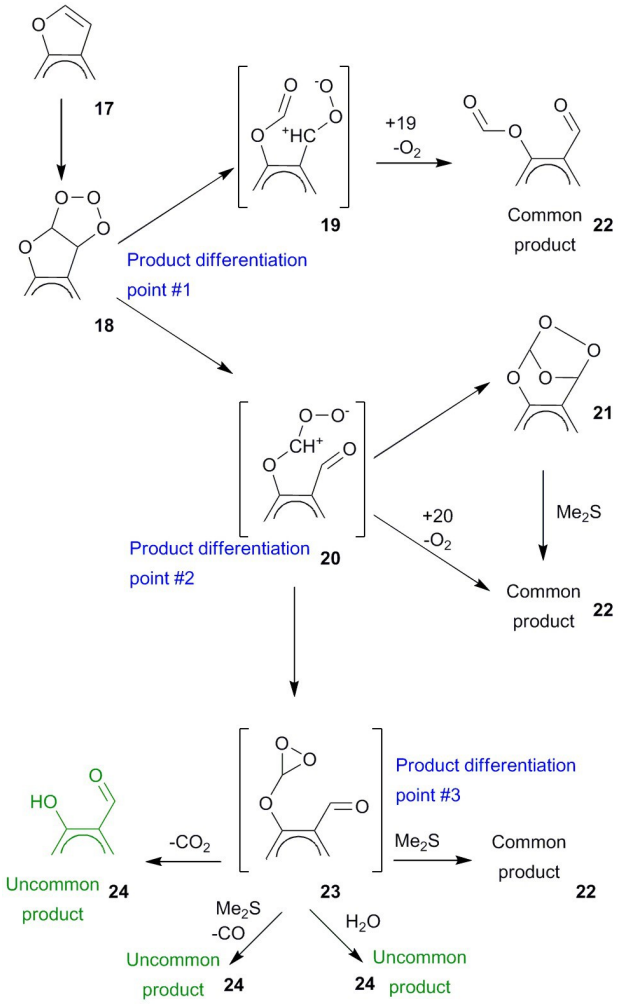
More surprisingly, both umbelliferones and corresponding formates were obtained by ozonolysis of furocoumarins even without the following reductive work-up step, and the reaction mixture further contained the corresponding secondary ozonide[‡d]. After analysis of the product compositions presented in Table 1 we concluded that both products could be formed directly from carbonyl oxide intermediates. These considerations are rationalized on Scheme 2 (only changing parts of molecules are shown; the unfolded schemes for all furocoumarins **1–4** are provided in ESI Schemes S1-S4.

Conventionally, the initial product of ozone 3+2 cycloaddition to a furan **17** double bond is primary ozonide **18**, which is unstable and readily decomposes to an aldehyde and carbonyl oxide. Furocoumarin structure dictates the possibility of two-way opening of primary ozonide which may result in the formation of carbonyl oxides **19** and **20**. Commonly, they recombine with an aldehyde group to secondary ozonide **21**. In the case of carbonyl oxides **19** and **20** the formation of **21** is slowed by the steric hindrance caused by rigidity of the aromatic ring. Moreover, carbonyl oxide **20** unlikely forms **21**, since in that case it should react with an ester[2c]. The secondary ozonides of furocoumarins were stable for several hours on air at ambient temperature, and we obtained their ^{1}H NMR spectra (or full sets of 2D NMR spectra for psoralen **1** and 8-methoxypsoralen **3** secondary ozonides). In the presence of reduction agent the secondary ozonides convert to corresponding common product **22**, thus no traces of the secondary ozonide could be found in reaction mixtures after reductive work-up (see Table 1 and ESI Figures S2-S5).

The slowed formation of **21** due to steric hindrance makes the competitive pathways of carbonyl oxide decomposition possible. Two molecules of carbonyl oxide **19** can interact to form **22** with the release of one O_2 molecule. This type of carbonyl oxide reaction is well-known[2c], while detailed investigations of this reaction are rare due to its high speed (see[8] for the recent study). Furthermore, since the formation of **21** from **19** is unlikely, the bimolecular reaction resulting in formation of **22** and O_2 release becomes predominant for **19**. The carbonyl oxide **20** can also participate in similar reaction. At the same time, the carbonyl oxides can convert to dioxiranes, either photochemically[9a] or thermally as known for the carbonyl oxides with α-methoxy[9b] or α-amino[9c] substituents and for diaryl carbonyl oxides[9d]. Carbonyl oxide **20** has phenyloxy substituent and likely converts to dioxirane **23**. Thus, the formation of dioxirane **23** competes with formation of secondary ozonide **21**. Dioxirane **23** being very labile may readily decompose to uncommon product **24**, both in absence (with CO_2 release) in presence (with CO release) of Me_2S (see[2d] and refs 14, 16, 20–23, and 30–33 cited therein), and we suggest that **23** is most likely to be the product providing the uncommon product **24** even without reduction work-up.

The direction of primary ozonide opening depends mostly on inductive effect of substituents at trioxolane ring. Briefly, in the presence of electron donating group primary ozonide opens with the formation of carbonyl oxide adjacent to that group. On the contrary, the opening in the presence of electron withdrawing group results in the formation of carbonyl oxide located away from that group. This scheme works well in a lot of cases (see[4c] for a recent example), but is not easily applicable in the case of title compounds. Both carbon atoms in trioxolane ring of **18** have electron withdrawing substituents – the furan oxygen atom and benzene ring. In addition, the said substituents depend from each other, and both depend on lactone ring and presence/position of methoxy groups. Notably, in the case of **3**, methoxy group can stabilize carbonyl oxide (see ESI Scheme S3). This is very similar to stabilizing effect of benzyloxy group on carbonyl oxide in sterically hindered intermediates (see Scheme 5[4e]), and explains why ozonolysis of **3** followed by reduction work-up yields almost exclusively uncommon product **11** (see Table 1 and ESI Figure S4), whereas for other furocoumarines such predominance was not noticed.

Thus, there are three product differentiation points governing the product distribution (Scheme 2). The first one is a direction of primary ozonide **18** opening. The second is a way by which carbonyl oxide **20** may further transform either to secondary ozonide **21** or to dioxirane **23**. Finally,



Scheme 2 Proposed mechanism of furocoumarins' ozonolysis

dioxirane **23** can be reduced to common product **22** or decompose to uncommon product **24**, the latter process being dependent on coumarin structure (see ESI unfolded schemes 1-4).

Here, using furocoumarins as a substrate we report a new end-group differentiating ozonolysis reaction lacking common process of carbonyl oxide scavenging and providing o-formylumbelliferones with moderate-to-high yields. The unusual stability of furocoumarins' secondary ozonides made it possible to characterize the product compositions and propose the mechanism of furocoumarin ozonolysis despite the presence of three possible product differentiation points.

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Notes and references

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‡ **(a)** General synthetic procedure: solution of furocoumarin (10−30 mg) in dry CH_2Cl_2 was bubbled with ozone-enriched oxygen at −84°C (ethyl acetate/liquid nitrogen bath) until becoming slightly blue – usually in about 20 min. (At this point reaction mixture could contain yellow precipitate.) After removing excess ozone with a stream of nitrogen (5 min), 50 µl of Me_2S was added, and the reaction mixture was allowed to warm to ambient temperature. The solution was evaporated and re-dissolved in $CDCl_3$ for analysis. **(b)** Compounds lacking R1 substituent (Scheme 1) appeared to be very labile. The mixture of **6** and **10** yields insoluble solid upon storage at 4°C in a week. Being exposed to light, the mixture of **5** and **9** also yields similar insoluble solid, and thus should be processed in dark. While compounds **7** and **8** could be purified by chromatography, compounds **5** and **6** decompose during this procedure. Compounds bearing R1 substituent are stable. **(c)** The sample for NMR kinetics studies was prepared mostly as described in (a). After warming up, it was mixed with equal volume of water and left stirring in the dark. At times, aliquots were collected, evaporated, and re-dissolved in $CDCl_3$ for analysis. **(d)** Ozonolysis without Me_2S work-up was done with following changes as compared to (a). The reaction was run in $CDCl_3$ at -44°C (acetonitrile/liquid nitrogen bath). After bubbling with nitrogen, the reaction mixture was allowed to warm up to ambient temperature. The white precipitate was centrifuged off, and the supernatant was transferred to NMR analysis. The ozonolysis of **3** yields negligible amount of insoluble material, whereas the ozonolysis of **1, 2** and **4** yields sufficient amount of the insoluble material, which considered to be a result of product polymerization. Samples containing trioxolanes were moderately stable, and we were able to get the full set of 2D NMR spectra before product decomposition.

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