The Power of Solvent in Altering the Course of Photorearrangements

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Abstract
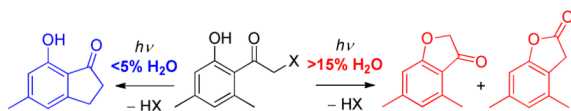
A clean bifurcation between two important photochemical reactions through competition of a triplet state Type II H-abstraction reaction with a photo-Favorskii rearrangement for (*o/p*)-hydroxy-*o*-methylphenacyl esters that depends on the water content of the solvent has been established. The switch from the anhydrous Type II pathway that yields indanones to the aqueous-dependent pathway producing benzofuranones occurs abruptly at low water concentrations (~8%). The surprisingly clean yields suggest that such reactions are synthetically promising.

An intramolecular Type II reaction of alkylphenones, especially 2-methylacetophenoes, produces high yields of photoenols that have been shown to be valuable reactive intermediates.[1] When a leaving group (X) is present in the α-position of 2-alkylacetophenones (**1**), longer-lived (*E*)-photoenols liberate HX to give indanones[2] (**2**; Scheme 1) that can be employed as precursors to elaborate products used in synthetic methodology.[3] Likewise, the photo-Favorskii rearrangement of α-substituted *p*-hydroxyacetophenones (**3**) to *p*-hydroxyphenylacetic acid (**4**), discovered more recently, has enjoyed success in a variety of applications because of its rapid release of nucleofuges (Scheme 1).[4] Both reactions have exhibited very good photochemical efficiencies and are relatively free of side reactions that produce complicated product mixtures. The similarity of the chromophores, the common triplet state origin for reaction, and the extensive understanding of the mechanistic photochemistry[5] have prompted us to explore the intersection of the photochemical pathways to uncover which parameters control the pathway followed by a chromophore common to both.

It is a rare occurrence in organic photochemistry when one can completely and cleanly divert the reaction or rearrangement pathway from a single product type to an alternative

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pathway yielding an entirely different structure by addition of H_2O to the solvent.[3a] Since it is well known that electron donating hydroxy and methoxy groups suppress Type II reactivity[6] and nearly as well known that the photo-Favorskii rearrangement has a strong affinity for water,[4k,7] we assumed that these two reaction pathways might be separated by the water content of the solvent media. In this work, the analogs of 4-hydroxyphenacyl derivatives with good leaving groups necessary for the photo-Favorskii process were fitted with 2-methyl substituent for efficient Type II hydrogen abstraction reaction to compete with the photo-Favorskii rearrangement. As an extension, a similar design, in which the 2-hydroxyphenacyl derivatives were fitted with a 6-methyl group, was also examined.

Synthesis of Phenacyl Esters

4-Hydroxy-2-methyl (**9a–c**) and 2-hydroxy-4,6-dimethylphenacyl (**14**) esters, and the corresponding benzyl (**10**) and methyl (**13**) ethers were prepared by α-bromination of acetophenones **5, 6** and **11** and then S_N2 reaction with formate, acetate, benzoate, or mesylate (Scheme 2). Overall yields ranged from 18% to 50%.

A Comparison of the Photochemistry of 2- and 4-Hydroxy-*o*-methylphenacyl Esters (9a–c, 14), and Their Benzyl (10) and Methyl Ethers (13b)

Solutions (~10 mM) of each of the phenacyl esters in a series of solvents were irradiated at λ = 300 or 313 nm until more than 95% of the starting material had disappeared. All of the esters released the corresponding acid in nearly quantitative yield. The hydroxyphenacyl chromophores were transformed into two distinct solvent-dependent sets of rearranged photoproducts (Scheme 3; Tables 1 and 2). Indanones (**17** and **19**) were formed in low water (<5%) content acetonitrile or benzene. In methanol, **9** gave a complex mixture of unidentified products, which may be due to photoaddition of methanol to the enol.[3a] The ethers **10** and **13b** gave only the indanone products (**18** and **22**) in all solvents; benzocyclobutanol **23** was produced only from **13b**. In contrast, 2-methyl-4-hydroxyphenylacetic acid **15** and 2-methyl-4-hydroxybenzyl alcohol **16** were formed from **9**, while 4,6-dimethylbenzofuran-3(2H)-one **20** and 4,6-dimethylbenzofuran-2(3H)-one **21** were produced from **14** in aqueous-based solutions.

What is clearly apparent is the remarkable influence that water plays in changing the course from classic Type II photochemistry to the photo-Favorskii rearrangement. Phenylacetic acid (**15**), as established earlier,[4a,4c] and dimethylbenzofuranones **20** and **21**, in this study, were formed via the photo-Favorskii rearrangement, whereas the indanones **17, 18, 19**, and **22** were apparently derived from classic Type II photoenolization[2a,b,8] (Scheme 1 and 3).

Figures 1 and 2 further demonstrate that the two competing pathways can be "titrated" by careful addition of water to the reaction media in the photolysis of **9c** and **14**. With **9c**, the reaction efficiencies of the two competing processes coalesced at ~8% aq acetonitrile and **15** and **16** became the sole products when water content reached ~30% in degassed solutions. It is noteworthy that for the irradiations of **14**, the crossover point from the Type II process to photo-Favorskii, where **20/21** replaces **19** as the dominant pathway, was nearly the same.

Anhydrous Media: The Photoenolization Pathway

Photoenolization to isomeric (*E*)- and (*Z*)-dienols from 2-alkylphenones is a well–established, triplet state pathway.[1,5] Strategic positioning of a leaving group α to the carbonyl (**1** Scheme 1) sets the stage for an elimination cascade from the (*E*)-photoenol, whereas the (*Z*)-isomer rapidly reverts to the alkylphenone via 1,5-sigmatropic hydrogen

transfer. The (*E*)-photoenol's longer lifetime is sufficient to permit the release of modest to very good nucleofuges[2,8] generating primarily indanone **2** (Scheme 1) in non-aqueous and nonnucleophilic solvents.[3a] As expected, the presence of either the *o*- or *p*-hydroxy groups on **14** (Scheme 4) and **9**, respectively, did not influence the dominance of the photoenol pathway. The compounds **10** and **13b**, in which the photo-Favorskii pathway was suppressed by replacing the hydroxy with an alkoxy group, also followed the photoenolization pathway. Cyclobutanol **23** along with indanone **22** were formed from **13b** in dry or aqueous acetonitrile, apparently via photoenol **25** (Scheme 4) similar to the cyclobutanols produced from 2,4,6-trialkylphenacyl benzoates.[9]

Phenyl ketones are known to have two nearly isoenergetic triplet states and their relative energies are strongly influenced by both the aryl substituents and the solvent.[10] Electron-donating substituents and polar solvents tend to stabilize the π,π^* state,[11] which is generally far less reactive toward H-atom abstraction than the n,π^* state with its half vacant, non-bonding p orbital on the carbonyl oxygen.[6] To our surprise, **14**, having three electron donating substituents (and largely a π,π^* configuration), still underwent photoenolization in acetonitrile, although the reaction was much less efficient (by a factor of 10 compared with those carried out in aqueous organic solvents).

Aqueous Media: Photo-Favorskii Pathway

In stark contrast to photoenolization, photo-Favorskii rearrangements[4b,c,4g,4i–k] of the 2-alkyl-4-hydroxyphenacyl derivatives **9a–c**, bearing the nucleofuge α to the carbonyl, formed **15** when photolyzed in mixed aqueous organic solvents (Scheme 1). Givens, Wirz, and coworkers recently recounted the vital role that water plays in this rearrangement.[4h,4k] The process relies on a triplet state proton loss from the hydroxy group to solvent water, which is thought to be in concert with solvent assisted release of the nucleofuge forming a triplet biradical intermediate. The biradical relaxes to a putative spirodienedione intermediate (Scheme 1) that either opens to the phenylacetic acid or loses CO to form a quinomethane.

The fact that this process dominates when the water content is significant is not surprising. Both photo-Favorskii and photoenolization transformations are primarily triplet reactions. A triplet lifetime of $\tau = 340$–770 ps[4k] was reported for the 4-hydroxyphenacyl carboxylate analogs, which is nearly an order of magnitude shorter than the triplet ($\tau \sim 3$ ns[2c]) invoked for photoenolization of 2,5-dimethylphenacyl carboxylate. This would imply that the reaction of **9c** in water should favor the photo-Favorskii process. Therefore, decreasing the solvent water content disfavors the photo-Favorskii process and encourages photoenolization which is largely independent of the presence of water.

Even more intriguing are the pathways for formation of **20** and **21**. They were formed in parallel (generally **21** dominates) as the major products in aqueous solvents, although a small amount was also observed in anhydrous solvents (Table 2). We posit that, based on the analogy with the photo-Favorskii reaction, the putative spirodienedione intermediate **26** serves as a common intermediate for both **20** and **21** in the irradiation of **14** (Scheme 4). The proposed ring expansion of the cyclopropanone by nucleophilic attack of the cyclohexadienone carbonyl on either one of the benzylic bonds (blue and red bond scissions) but predominantly on the one attached to the cyclopropanone carbonyl (blue scission) leads to the two products. The rearrangement of **26** to **20** and **21** does not require large amounts of water, i.e. the water assisted ring opening as seen for formation of **15** from **9a–c** is overridden by the intramolecular nature of this novel rearrangement step. These processes are currently under investigation in our laboratories.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.
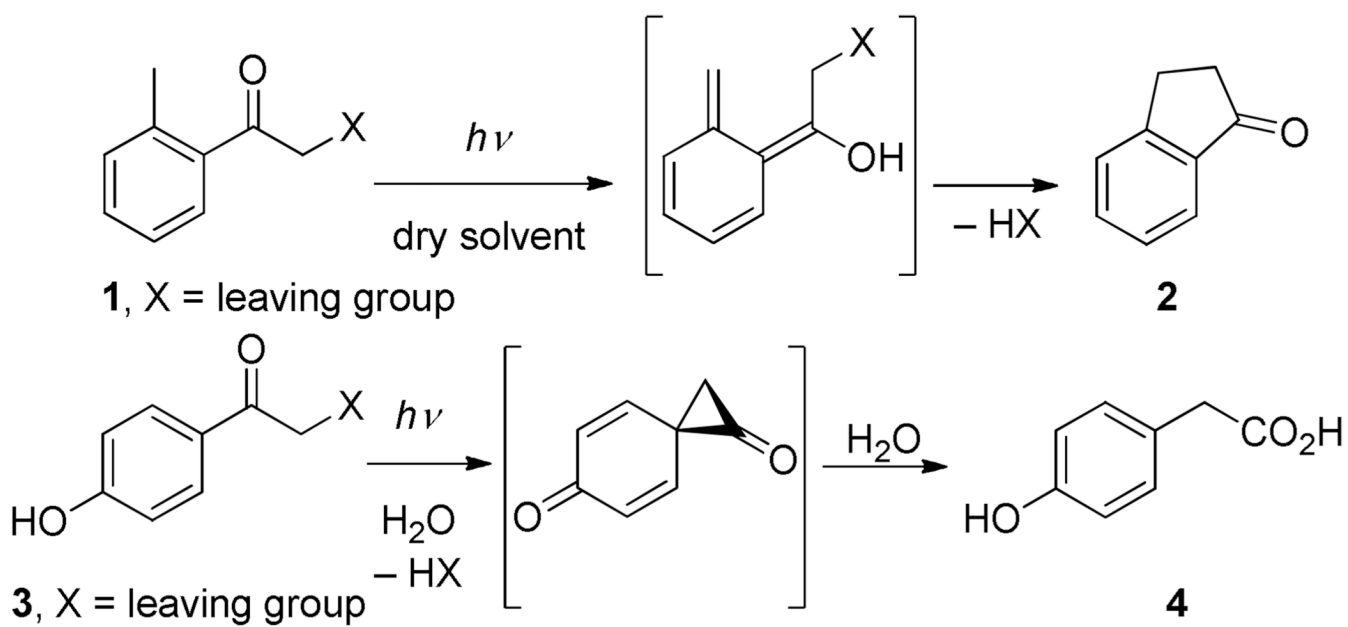
Acknowledgments

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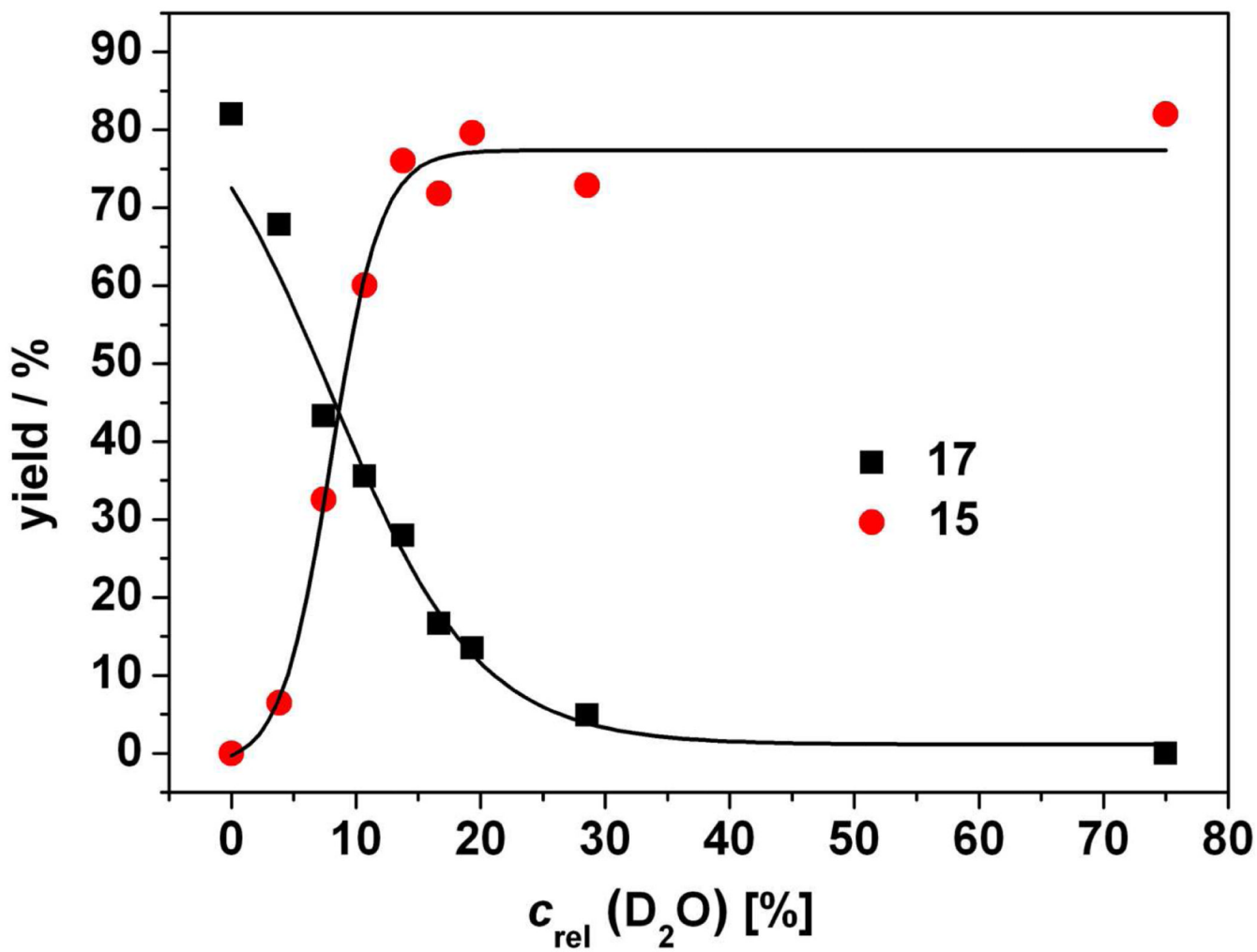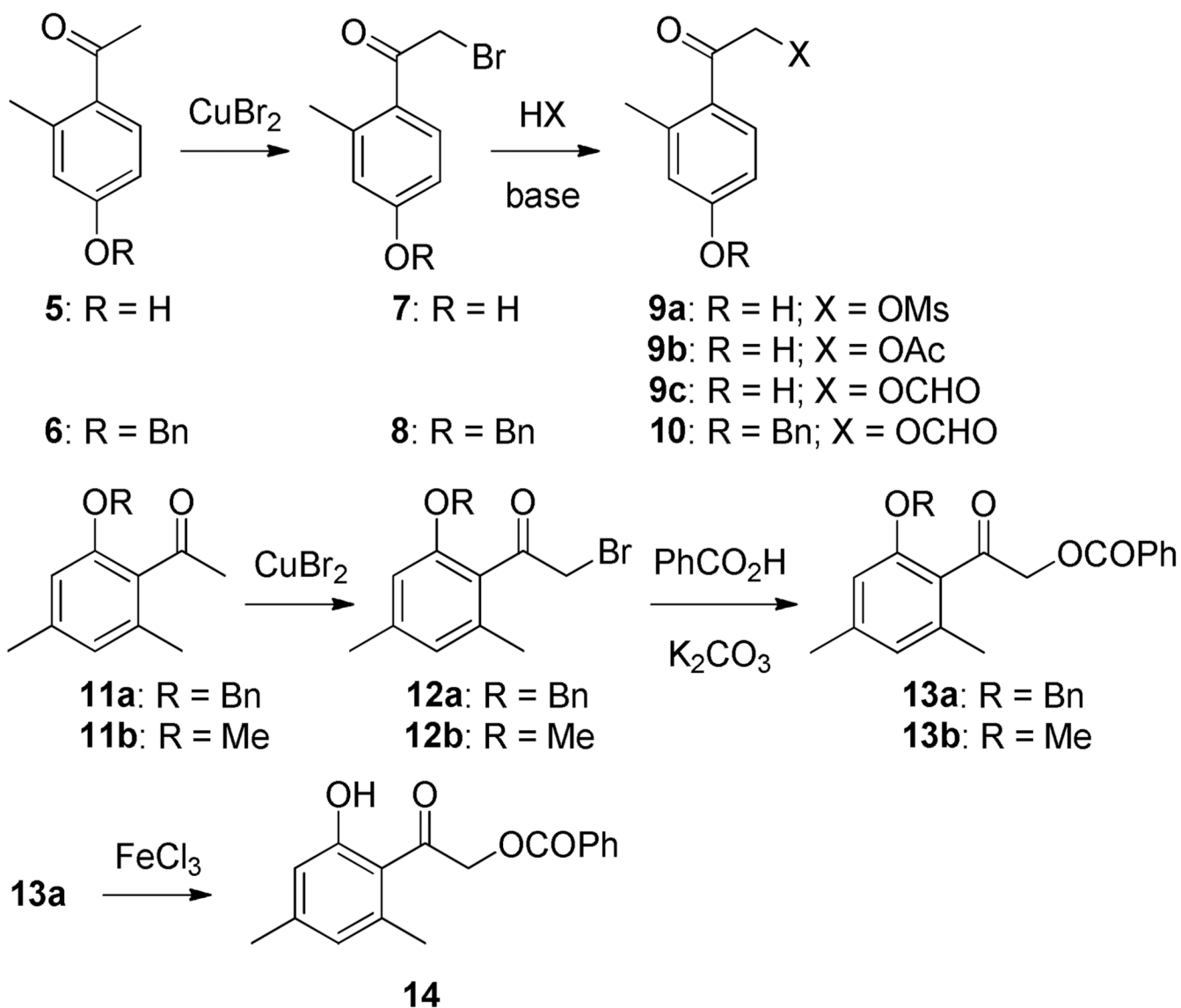
Figure 1.
Yields of **15** (●) and **17** (■) obtained by irradiation of **9c** in aq acetonitrile at $\lambda = 313$ nm. The photochemical conversions were kept between 50 and 70% in all solvent mixtures (and 30% in acetonitrile to avoid secondary reactions). The standard deviation of the mean for each point was <10%.
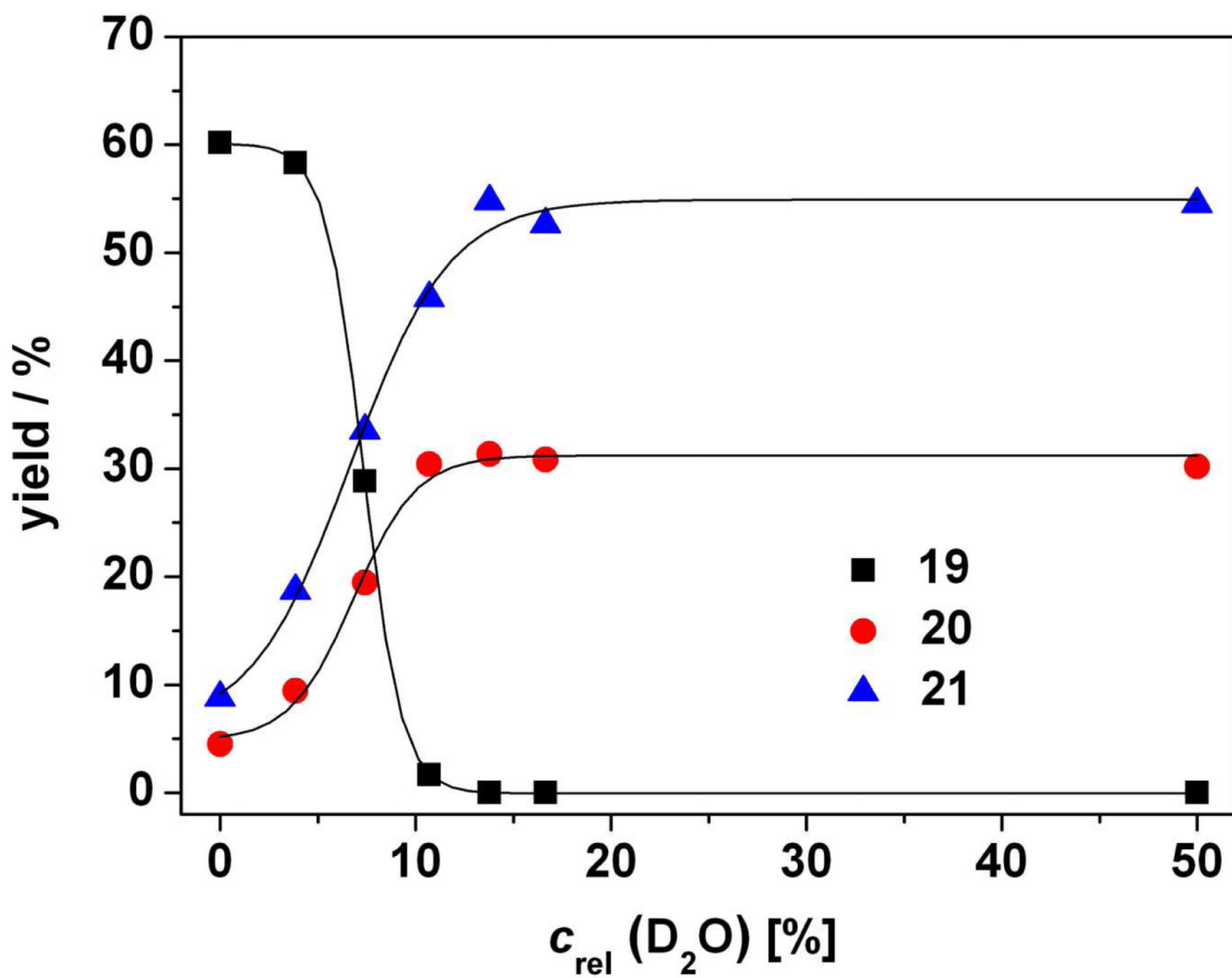
Figure 2.
Yields of **19** (■), **20** (●), and **21** (▲) determined by ^{1}H NMR from irradiation of **14** in aqueous acetonitrile at $\lambda = 313$ nm to > 90% conversion. The standard deviation of the mean for each point was <10%.
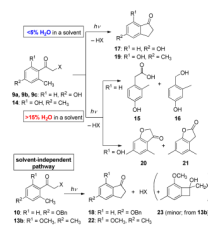
Scheme 1.
Photochemistry of Phenacyl Derivatives

5: R = H

6: R = Bn

7: R = H

8: R = Bn

9a: R = H; X = OMs
9b: R = H; X = OAc
9c: R = H; X = OCHO
10: R = Bn; X = OCHO

11a: R = Bn
11b: R = Me

12a: R = Bn
12b: R = Me

13a: R = Bn
13b: R = Me

14

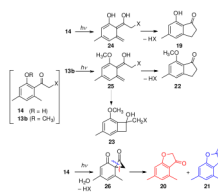**Scheme 2.**
Synthesis of Hydroxy-2-methylphenacyl Esters

Scheme 3.
Photochemistry of **9a–c, 10, 13b**, and **14**

Scheme 4.
Photo-Favorskii and Photoenolization Intermediates

Table 1

Photoproducts Formed by Irradiation of **9a–c** and **10**

compound	solvent (ratio)	chemical yields / % [a]		
		15	**16**	**17 or 18**
9a	H_2O/CH_3CN (3:1)	79	8	_ [b]
9b	H_2O/CH_3CN (3:1)	82	8	_ [b]
9c	H_2O/CH_3CN (3: 1)	80 (80 [c])	9	_ [b]
	CH_3CN or C_6H_6	_ [b]	_ [b]	80 [d] (**17**)
10	H_2O/CH_3CN (1:1)	_ [b]	_ [b]	>80 [d] (**18**)
	C_6H_6	_ [b]	_ [b]	84 [d] (**18**)

[a] Irradiated at $\lambda = 300$ nm in non-degassed solutions to >95% conversion; the chemical yields were determined by ^{1}H NMR and are the average of two measurements.

[b] Not observed.

[c] Isolated yield as the methyl ester of **15** (see Supporting Information).

[d] Indanones **17** and **18** decompose under prolonged irradiation.

Table 2

Photoproducts from Irradiation of **14** and **13b**

compound	solvent (ratio)	chemical yields / %[a]				
		19 or 22	20	21	23	
14	benzene	59 (**19**)	9	8	_[b]	
	CH₃OH	_[b]	28	62	_[b]	
	CH₃CN	60 (**19**)	5	9	_[b]	
	H₂O/CH₃CN (1:1)	_[b]	30	55	_[b]	
13b	benzene	79 (**22**)	_[b]	_[b]	_[b]	
	CH₃CN	65 (**22**)	_[b]	_[b]	15	
	H₂O/CH₃CN (1:1)	41 (**22**)	_[b]	_[b]	13	

[a]Degassed solutions irradiated at λ = 300 nm to >95% conversion. Isolated yields; the average of two measurements.

[b]Not observed.