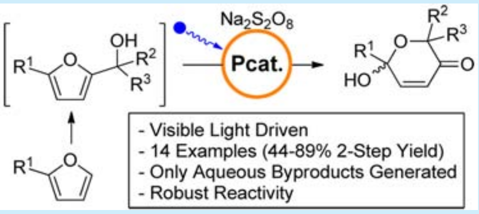
Visible-Light-Mediated Achmatowicz Rearrangement

Matthew B. Plutschack,† Peter H. Seeberger,†,‡ and Kerry Gilmore*,†

†Department of Biomolecular Systems, Max-Planck Institute of Colloids and Interfaces, Am Mühlenberg 1, 14476 Potsdam, Germany
‡Institute of Chemistry and Biochemistry, Department of Biology, Chemistry and Pharmacy, Freie Universität Berlin, Arnimallee 22, 14195 Berlin, Germany

Supporting Information

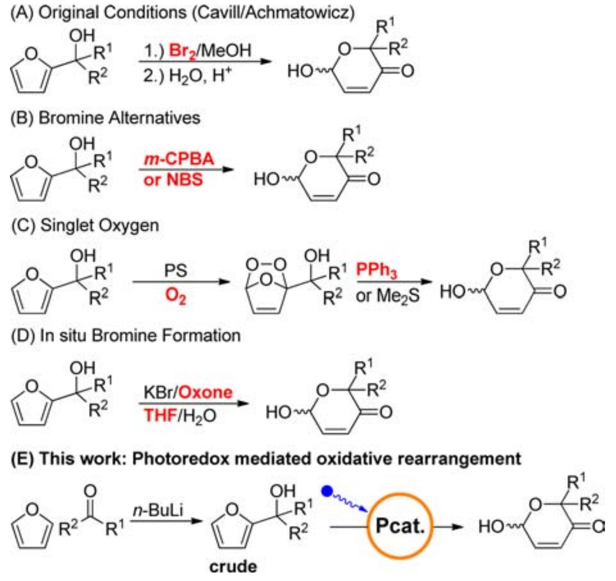
ABSTRACT: Visible-light-mediated photoredox catalysis is a viable method to access highly reactive intermediates from cheap, readily available, and shelf-stable reagents to perform clean chemical transformations. Here, we report the first photoredox-catalyzed Achmatowicz reaction of furfuryl alcohol derivatives to produce functionalized dihydropyranones while only forming easily separable $NaHSO_4$ as a byproduct. The water solubility of the byproduct facilitates direct Boc-protection of the resulting hemiacetal without the need for column purification. The reaction is very robust and permits the use of various aqueous solutions and light sources including sunlight.



The furan ring serves as a precursor to 1,4-dicarbonyls,[1] cyclopentanones,[2] and carboxylic acids,[3] in organic synthesis. Its molecular complexity can be readily increased via Diels–Alder chemistry.[4] Furfuryl alcohols, a class of 2-substituted furan molecules, are a precursor to highly ornamented dihydropyranones via the Achmatowicz rearrangement.[5]

The rearrangement of furfuryl alcohols to dihydropyranones, first reported by Cavill et al.[6] and later popularized by Achmatowicz,[7] relies on stoichiometric bromine in methanol, followed by a separate acid catalyzed hydrolysis step (Scheme 1A). To avoid the use of elemental bromine, alternative methods were developed employing either *meta*-chloroperbenzoic acid (*m*-CPBA)[8] or the bromine surrogate *N*-bromosuccinimide (NBS)[9] (Scheme 1B). However, these reaction conditions produce stoichiometric amounts of organic byproducts. Singlet oxygen, produced with the help of a photosensitizer, is trapped by the furan moiety via a Diels–Alder-type reaction to form a trioxolane intermediate that necessitates the use of stoichiometric triphenylphosphine[10] or dimethyl sulfide[11] for selective decomposition (Scheme 1C).[12] Oxone with catalytic amounts of bromide can affect the transformation.[13] While the water solubility of the oxidant byproducts greatly facilitated purification and demonstrated greater sustainability than the aforementioned conditions, the method requires low temperatures and exhibits diminished yields unless tetrahydrofuran (THF) is employed as solvent (Scheme 1D), presenting a safety risk due to its proclivity to form peroxides.

Scheme 1. Oxidative Rearrangement of Furfuryl Alcohols[20]



Similar to photosensitized reactions, visible light photoredox catalysis is an attractive method of activation, as solar energy is the most abundant renewable energy source and a traceless reagent.[14] Polypyridyl complexes are applied as photoredox catalysts to a wide range of transformations in different fields.[15] In the context of this work, tris(bipyridine)ruthenium(II) $[Ru(bpy)_3]^{2+}$ has been used extensively in combination with sodium persulfate for the photoinduced oxidation of water.[16] However, this combination has found limited applications in the field of organic chemistry.[17,18] We hypothesized that persulfate radicals, selectively generated using $[Ru(bpy)_3]^{2+}$, could represent a nonflammable, less toxic, and affordable stoichiometric oxidant to generate dihydropyranones while producing water-separable byproducts in industrially suitable solvents (Scheme 1E).[19]

In the course of our initial studies we found that the stability of 2-substituted furfuryl alcohols varied greatly. Therefore, we sought to develop a two-step process toward dihydropyranones.

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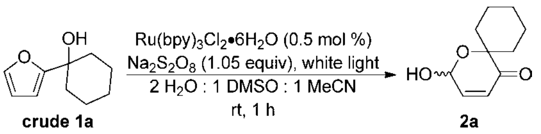
The high yielding, clean reaction of lithiated furan with carbonyls was exploited to generate crude substituted furfuryl alcohols to be utilized directly in the designed photoredox reaction.

Treatment of freshly distilled furan with *n*-butyllithium generated the 2-lithiated species, which was trapped using cyclohexanone. Aqueous workup and concentration afforded crude furfuryl alcohol **1a**, which was taken up in a DMSO/MeCN mixture (1:1), combined with sodium persulfate (1.05 equiv) and $Ru(bpy)_3Cl_2·6H_2O$ (0.5 mol %) in water, and degassed with argon. This solution was irradiated with white light (red/green/blue LEDs), and complete conversion was observed in 1 h (Table 1, entry 1). This three-solvent mixture is necessary because water/DMSO mixtures led to the visibly poor solubility of some furfuryl alcohol substrates, and water/MeCN mixtures led to poor solubility of the persulfate salt. Additionally, solvent mixtures consisting of low proportions of water reacted slower, in good agreement with reports of lower yields of $[Ru(bpy)_3]^{3+}$ with organic cosolvents.[21] Control studies excluding the photocatalyst, light source, or oxidant resulted in little to no conversion (Table 1, entries 2−4). Using oxone as the oxidant led to no detectable product, and in combination with $Ru(bpy)_3Cl_2·6H_2O$ and light, a less than 1:10 product/starting material ratio was observed.

Table 1. Photoredox Mediated Achmatowicz Rearrangement[a]



entry	oxidant (equiv)	catalyst (mol %)	light	1a:2a
1	**1.05**	**0.5**	**white**	**0:1**
2	1.05	none	white	1:trace
3	1.05	0.5	none	1:0
4	none	0.5	white	1:0
5	1.05 oxone	none	none	1:0[b]
6	1.05 oxone	0.5	white	10:1[b]

[a] Reactions were performed on a 0.5 mmol scale of crude material with respect to the starting carbonyl compound. Starting material (**1a**) to product (**2a**) ratios were determined by ^1H NMR analysis of 0.1 mL of the crude reaction mixture in 0.4 mL of d6-DMSO; small quantities are indicated by trace (<1:20). See Supporting Information for detailed reaction procedures. [b] An unknown side product (s.p.) was observed in appreciable amounts (see Supporting Information).

Certain photoredox reactions are highly influenced by the color or intensity of the light source, the nature of the solvent, and the presence of oxygen.[22] Table 2 summarizes our attempts to test the sensitivity of the developed conditions. Both white light (red/green/blue) and blue light work well (Table 2, entry 1), and the reaction even gives full conversion using the October sunlight in northern Germany (Table 2, entry 2). Aqueous contaminants are well tolerated, as full conversion was observed in both unfiltered seawater (a sustainable reaction medium) and beer (Table 2, entries 3 and 4). The persulfate source and purity is also flexible. Commercial hair bleach contains ammonium, potassium, and sodium persulfates, and when used in excess, no discernible difference in the reaction is observed (Table 2, entries 5 and 6). However, the reaction was sensitive to the organic solvent. Substitution of acetonitrile and dimethyl sulfoxide with ethanol resulted in a 1:1.7 mixture of starting material and product with considerable amounts of side products observed (Table 2, entry 7). Finally, complete conversion was observed when the reaction was performed without degassing, however, with the formation of 5-hydroxy-2(5*H*)-furanone in a 1:6.7 ratio with the product (Table 2, entry 8). $Ru(bpy)_3Cl_2·6H_2O$ is a known photosensitizer for singlet oxygen production[23] and responsible for the formation of this side product due to decomposition of a trioxolane intermediate.[24]

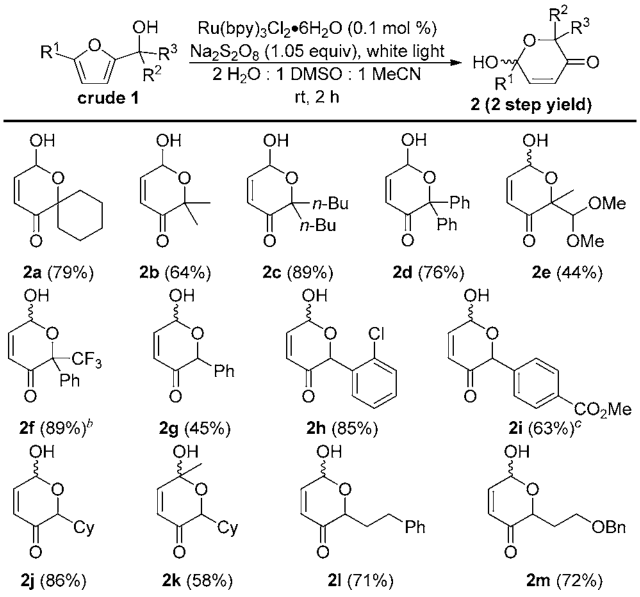
Table 2. Reaction Robustness and Sustainability[a]

entry	oxidant	solvent a/b/c	light	1a:2a
1	$Na_2S_2O_8$	a/b/c	blue	trace:1
2	$Na_2S_2O_8$	a/b/c	sunlight	0:1
3	$Na_2S_2O_8$	seawater/b/c	white	0:1
4	$Na_2S_2O_8$	beer/b/c	white	0:1
5	hair bleach	a/b/c	white	1:3.6
6	hair bleach[b]	a/b/c	white	0:1
7	$Na_2S_2O_8$	a/EtOH	white	1:1.7[c]
8[d]	$Na_2S_2O_8$	a/b/c	white	0:1[e]

[a] Reactions were performed using 0.5 mmol of compound **1a** with a 2 water (a):1 DMSO (b):1 acetonitrile (c) solvent ratio; starting material (**1a**) to product (**2a**) ratios were determined by ^1H NMR analysis of 0.1 mL of the crude reaction mixture in 0.4 mL of d6-DMSO after 1 h. Small quantities are indicated by trace (<1:20). See Supporting Information for detailed reaction procedures. [b] The reaction was run with 3.5 equiv of hair bleach. [c] Side products observed (see Supporting Information). [d] The reaction mixture was not degassed. [e] A side product was observed (see Supporting Information).

With robust reaction conditions in hand, the substrate scope of this two-step procedure was examined (Scheme 2). Generally,

Scheme 2. Photoredox Mediated Achmatowicz Rearrangement: Substrate Scope[a]

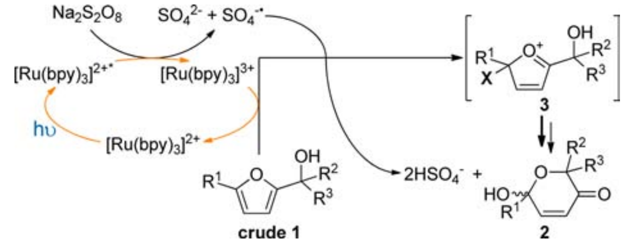


[a] Furan and *n*-BuLi were reacted, followed by addition of 2 mmol of the corresponding carbonyl compound. After overnight reaction and aqueous workup, crude furfuryl alcohol **1** was taken up in 4 mL of a 1 MeCN:1 DMSO mixture and combined with a 4 mL aqueous solution of 1.05 equiv of $Na_2S_2O_8$ and 0.1 mol % $Ru(bpy)_3Cl_2·6H_2O$. After degassing and 2 h of white light irradiation, the reaction mixture was worked up and purified by column chromatography. Two-step isolated yields are reported. See Supporting Information for detailed reaction procedures. [b] The reaction required 6 h. [c] See Supporting Information for the preparation of **1i**.

the desired product was obtained in very good to excellent isolated yields over two steps. Substrate **1g** suffered from unselective reactivity, where the α,β-unsaturated cyclopentanone (Piancatelli product) was isolated in 14% yield.[2b] The conditions tolerated aromatic halides (**1h**) and esters (**1i**), yielding the product in 85% and 65% yield, respectively. Compound **2k** was isolated as a white solid in just 58% yield due to the instability of the more thermodynamically favorable keto-form (see Supporting Information for details). Protected alcohol **2m** was obtained in 72% yield, with no isolated side products suggesting no oxidative cleavage of the benzyl group.

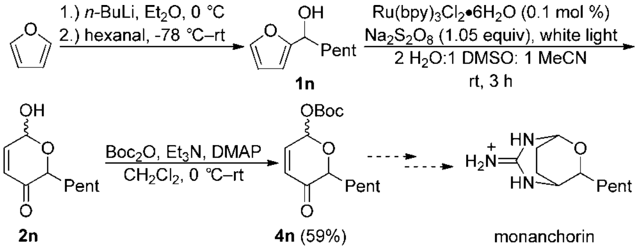
Stern–Volmer analysis[25] revealed an oxidative quenching pathway, where $[Ru(bpy)_3]^{2+*}$ is quenched by persulfate to generate sulfate and a sulfate radical (Scheme 3). We propose that the oxidation of the furan ring closes the catalytic cycle, and subsequent combination with the sulfate radical generates intermediate **3**, where **x** is either SO_4^- or the hydrolyzed sulfate (**x** = OH). Addition of water to the oxocarbenium, followed by the loss of **x**, furnishes the product **2**. No intermediates were observed by mass spectrometry or NMR spectroscopy, suggesting these structures are short-lived.

Scheme 3. Proposed Mechanism for the Photoredox Mediated Achmatowicz Rearrangement



To showcase the benefits of the developed Achmatowicz conditions, we targeted Boc-protected dihydropyranone **2n**, an intermediate in the de novo synthesis of monanchorin (Scheme 4).[26] Lithiation of furan, followed by trapping with hexanal and aqueous workup, yielded furfuryl alcohol **1n**. This crude material was subjected to our photoredox conditions, which cleanly provided dihydropyranone **2n** after another aqueous workup. Protection of the crude hemiacetal was achieved using di-*tert*-butyl dicarbonate, triethylamine, and catalytic *N*,*N*-dimethylpyridin-4-amine. After a third aqueous workup followed by column chromatography, Boc-protected dihydropyranone **4n** was obtained in 59% yield over three steps (average of 84% yield per step).

Scheme 4. Formal Synthesis of Monanchorin



In summary, we describe the first photoredox mediated Achmatowicz rearrangement, providing a range of dihydropyranones in fair to excellent yields over two steps. The use of $Ru(bpy)_3Cl_2·6H_2O$ and sodium persulfate represents a robust and sustainable combination for this transformation, working with various light sources (including sunlight) and aqueous impurities. Finally, we were able to use our conditions in a three-step, one-column formal synthesis of monanchorin. Current efforts in our laboratory are being directed toward applying this photocatalyst/oxidant combination to other bromine-mediated rearrangements and oxidations.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03237.

General information, reactor setup, experimental procedures, and compound characterization data (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: kerry.gilmore@mpikg.mpg.de.

ORCID

Kerry Gilmore: 0000-0001-9897-6017

Notes

The authors declare no competing financial interest.

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