## The Beckmann Rearrangement Executed by Visible-Light-Driven Generation of Vilsmeier–Haack Reagent

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**Abstract:** A new and efficient approach for the Beckmann rearrangement is reported. The protocol involves eosin Y catalyzed, visible-light-mediated in situ formation of the Vilsmeier–Haack reagent from  $CBr_4$  and a catalytic amount of DMF for activation of ketoximes at room temperature. The method is operationally simple and avoids the need for any corrosive, water-sensitive reagents and elevated temperatures.

Key words: visible light, eosin Y, photoredox, Beckmann rearrangement, amides

Nature's ability to accomplish photosynthesis utilizing sunlight has inspired the development of a number of synthetically important visible-light-mediated photoredox catalytic processes. Due to the deleterious effects and side reactions associated with the use of high-energy UV light,<sup>1</sup> visible-light-mediated photoredox catalysis has emerged as a new technique for developing new methodologies. MacMillan<sup>2a</sup> and Yoon<sup>2b</sup> groups have demonstrated that the use of photocatalysts such as Ru(bpy)<sub>3</sub>Cl<sub>2</sub> (bpy = 2.2'-bipyridine) and  $Ir(dtbbpy)_3Cl (dtbbpy = 4.4'$ di-tert-butyl-2,2'-bipyridine) is capable of initiating powerful transformations, both for the target-oriented organic synthesis and methodology development.<sup>2</sup> Very recently, Stephenson et al. have opened a new opportunity for the activation of hydroxyl functionality employing a visiblelight-mediated photocatalytic process.<sup>3</sup> The resulting transformation of alcohols to halides<sup>3a</sup> or carboxylic acids to anhydrides<sup>3b</sup> proceeds through the oxidative quenching of the excited organometallic catalyst Ru(bpy)<sub>3</sub><sup>2+</sup> to provide the strong oxidant  $\operatorname{Ru}(bpy)_2^{3+}$ .

However, the utilization of ruthenium and iridium complexes suffers from disadvantages such as potential toxicity, low sustainability, high cost, and problematic removal of their undesirable traces from products, especially in the case of drugs and drug intermediates. Recently, metal-free organic dyes have shown enough promise for their application as photocatalysts in visible-light-mediated photoredox reactions<sup>4</sup> and offer a superior alternative to transition-metal photocatalysts because they are inexpensive, easy to handle, and eco-friendly. It has been reported that similar to the chemistry of  $Ru^{2+*}$  (\* = excited state) both reductive and oxidative quenching are known for the excited triplet state <sup>3</sup>EY\* of eosin Y (EY).<sup>5</sup> However, the

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oxidative quenching of <sup>3</sup>EY\* has found very limited application in organic synthesis<sup>6</sup> as compared to its reductive quenching.<sup>4,7</sup> On the basis of the earlier reports on the successful application of EY as a photocatalyst<sup>4</sup> coupled with further exploitation of its oxidative quenching, it has been selected as an organophotoredox catalyst for the present study.

The Beckmann rearrangement continues to be a strategically useful tool for the synthesis of amides and lactams from the corresponding oximes since its discovery in 1886.<sup>8</sup> A large amount of strong acids and dehydrating agents at an elevated temperature have been traditionally used to bring about this rearrangement, which leads to large amount of waste and serious corrosion problems and precludes its application to sensitive substrates. In order to make the rearrangement economically and environmentally viable, several methods have been recently developed and claimed to be organocatalytic.9 Very recently, these methods have been a subject of ingenious discussion on the point whether they are actually organocatalytic or merely self-propagating.<sup>10</sup> Thus, there is still a wide scope for investigations on convenient and more rational methods to execute the Beckmann rearrangement.

After careful consideration of the above facts and our continued efforts for the development of new organocatalytic processes,<sup>7c,9c,d,11</sup> we sought to explore and establish an efficient and operationally simple Beckmann rearrangement. The present novel design of the Beckmann rearrangement is inspired by the recent work of Stephenson et al.<sup>3</sup> and it utilizes EY as a photocatalyst instead of Ru(bpy)<sub>3</sub>Cl<sub>2</sub> (Scheme 1). An in situ generated Vilsmeier-Haack reagent from DMF is a well-studied species for effecting the Beckmann rearrangement in a stoichiometric amount, thus we envisaged that the rearrangement could be rendered catalytic with respect to DMF. After some preliminary experimentation, we were able to realize that the present visible-light-driven Beckmann rearrangement could be effected through the Vilsmeier-Haack reagent with a catalytic amount of DMF.

The Beckmann rearrangement of a model substrate 4-methoxyacetophenone oxime (1a) was performed by using EY as a photocatalyst, CBr<sub>4</sub> as an oxidative quencher, and a catalytic amount of DMF in MeCN under irradiation with visible light for the screening process (Table 1). Among the different light sources used, viz. green LEDs (light-emitting diodes,  $\lambda_{max} = 535$  nm, 2.6 W, 161 lm), CFL (18 W), and daylight, green LEDs were found to be



Scheme 1 Visible-light-mediated activation of hydroxyl groups

the best in terms of yield and reaction time (Table 1, entries 1-5 vs 6 and 7). This result encouraged us to carry out a series of control experiments (Table 1), which indicated that in the absence of any of the reagents/reaction parameters, no product formation was detected (Table 1, entries 8–11).

 
 Table 1
 Screening and Control Experiments for the Visible-Light-Driven Beckmann Rearrangement<sup>a</sup>

MeO—		eosin Y, DMF MeCN, CBr <sub>4</sub> visible light r.t., 10–48 h				
Entry	Visible light	Eosin Y (mol%)	CBr <sub>4</sub> (equiv)	DMF (mol%)	Time (h)	Yield (%) <sup>b</sup>
1	green LED <sup>c</sup>	2	3	20	14	96
2	green LED	2	2	20	14	96
3	green LED	2	1	20	18	58 <sup>d</sup>
4	green LED	2	1	20	30	58 <sup>d</sup>
5	green LED	2	2	20	10	85
6	CFL (18 W) <sup>e</sup>	2	2	20	48	39
7	daylight	2	2	20	48	24
8	green LED	0	2	20	48	n.r.
9	green LED	2	0	20	48	n.r.
10	green LED	2	2	0	48	n.r.
11	in the dark	5	2	20	48	n.r.

<sup>a</sup> The reaction was conducted with **1a** (1.0 mmol) in MeCN (3 mL) under a nitrogen atmosphere for each entry.

<sup>b</sup> Isolated yield after aqueous workup followed by column chromatography; n.r. = no reaction.

<sup>c</sup> Green LEDs 2.6 W, 161 lm (for details, see the Supporting Information) were used for irradiation at 2 cm distance from the reaction mixture with its temperature not exceeding to 25 °C.

<sup>d</sup> 37% of **1a** was recovered.

<sup>e</sup> 18 W CFL (compact fluorescent lamp, Philips, 6500 K, 1010 lm, 85 mA) was used for irradiation.

Next, we optimized reaction conditions with respect to catalyst loading and solvent (Table 2). The yield was significantly decreased with decreasing eosin Y from 2 mol% to 1 mol% (Table 2, entry 2 vs. 3); whilst it was not affected by increasing the catalyst loading from 2 mol% to 5 mol% (Table 2, entry 1 vs. 2). Thus, the optimum catalyst loading of eosin Y was found to be 2 mol%. The optimum catalytic amount of DMF was found to be 20 mol%, because decreasing its amount from 30 mol% to 20 mol% did not affect the yield (Table 2, entry 2 vs. 4); whilst decreasing the amount from 20 mol% to 15 mol% significantly decreased the yield (Table 2, entry 4 vs. 5). Under the optimized catalyst loading different solvent media were tested, and among all the tested solvents (MeCN, DCE, THF, and MeNO<sub>2</sub>), MeCN was the best (Table 2, entry 4). The highest yield (96%) was obtained in the case of MeCN (Table 2), hence it was used as solvent throughout the present study.

Table 2 Optimization of Catalyst Loading and Solvent<sup>a,b</sup>

MeO→	1a N-	OH eosin solver greer r.t., 1-	Y, DMF ht, CBr <sub>4</sub>	MeO-	−NH →
Entry	Eosin Y (mol%)	DMF (mol%)	Solvent	Time (h)	Yield (%) <sup>c</sup>

2	(mol%)	(mol%)		(h)	(%) <sup>c</sup>
1	5	30	MeCN	14	96
2	2	30	MeCN	14	96
3	1	30	MeCN	14	67
4	2	20	MeCN	14	96
5	2	15	MeCN	14	71
6	2	20	DCE	18	76
7	2	20	THF	20	60
8	2	20	MeNO <sub>2</sub>	15	78

<sup>a</sup> The reaction was carried out with **1a** (1.0 mmol) and CBr<sub>4</sub> (2.0 mmol) in solvent (3 mL) under a nitrogen atmosphere for each entry. <sup>b</sup> Green LEDs 2.6 W, 161 lm (for details, see the Supporting Information) were used for irradiation at 2 cm distance from the reaction mixture with its temperature not exceeding to 25 °C.

<sup>c</sup> Isolated yield after aqueous workup followed by column chromatography.

With the optimized reaction conditions in hand, the functional-group compatibility and scope of the present photocatalytic protocol were demonstrated across a range of aromatic, aliphatic acyclic, and aliphatic cyclic oximes (Table 3). The presence of an electron-withdrawing group in the aryl moiety of an oxime appears to decrease the yield (Table 3, entry 3 vs. entries 6–10), while the yield is enhanced in case of the presence of an electron-donating group (Table 3, entry 3 vs. entries 1, 2, 4, and 5). A variety of functional groups such as OMe, OH, Br, and NO<sub>2</sub> are compatible with the present protocol for the Beckmann rearrangement. The industrially important  $\varepsilon$ -caprolactam could also be obtained in good yield (Table 3, entry 13).

On the basis of our observations and the literature reports,<sup>3-7</sup> a plausible pathway for the conversion of **1** into **2** through the Beckmann rearrangement is depicted in Scheme 2. The photoredox catalyst EY is excited on absorption of visible light, and its more stable triplet state <sup>3</sup>EY\* undergoes oxidative quenching by single-electron transfer (SET) to CBr<sub>4</sub> and generates 'CBr<sub>3</sub>, which reacts with DMF to form radical **5**. Then, SET from the radical **5** to EY<sup>++</sup> gives iminium ion **6** to complete the redox cycle. Iminium ion **6** is converted into Vilsmeier–Haack reagent **4**, which reacts with the hydroxyl group of oxime **1** to form imidoyl bromide **7** through **3**. Furthermore, COBr<sub>2</sub> formed as a byproduct in the reaction pathway reacts with

DMF to generate **4** as reported earlier.<sup>12</sup> Aqueous workup of the reaction mixture containing **7** gives the desired product **2**. As mentioned in Table 1 (entries 3 and 4), the yield of Beckmann rearrangement product **2a** was drastically reduced on decreasing the amount of CBr<sub>4</sub> from two equivalents to one equivalent, that is, on decreasing the amount of **6**, which generates the Vilsmeier–Haack reagent **4** and the intermediate **3** leading to the product **2**. This shows that the rearrangement is not self-propagating instead it is catalytic with respect to DMF, as depicted in Scheme 2. Had the reaction been self-propagating, it would have not proceeded to give the yield of only 58% with the recovery of 37% of oxime **1a** (Table 1, entries 2 vs. 3 and 4). Furthermore, DMF could be recovered up to 94% after the reaction.

 Table 3
 Generality and Scope of the Visible-Light-Driven Beckmann Rearrangement<sup>a</sup>



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	eosin Y (2 mol%), DMF (20 mol%), CBr <sub>4</sub> (2.0 eo	quiv) 0 B <sup>1</sup>		
R <sup>2</sup> OH 1	MeCN, green LEDs, r.t., 12–18 h	R <sup>2</sup> N <sup>-11</sup> 2		
Entry	Ketoxime 1	Product 2	Time (h)	Yield (%) <sup>b,c</sup>
8	O2N	$O_2N$	18	80
9	O <sub>2</sub> N	$\begin{array}{c} 2\mathbf{i} \\ 0_2 \mathbf{N} \\ \end{array} \\ \begin{array}{c} H \\ \mathbf{N} \\ \mathbf{O} \\ \mathbf{O} \end{array}$	18	85
10		i	18	77
11	N OH		14	85
12	N OH		14	84
13			12	78
14	М ОН	2m NH	12	89
15	N OH	2n	12	88
16	N_OH	20 $H$ $0$ $2p$	16	91

<sup>a</sup> Reaction conditions: **1** (1.0 mmol); eosin Y (2 mol%); CBr<sub>4</sub> (2.0 equiv), DMF (20 mol%) in MeCN (3 mL), irradiation with green LEDs under a nitrogen atmosphere.<sup>13</sup>

<sup>b</sup> Isolated yield after aqueous workup followed by column chromatography.

<sup>c</sup> For the characterization data of compounds **2**, see the Supporting Information.



Scheme 2 Plausible mechanistic pathway of visible-light-driven Beckmann rearrangement

In conclusion, we have disclosed an efficient Beckmann rearrangement involving activation of ketoximes by the Vilsmeier–Haack reagent, which is in situ generated by an eosin Y catalyzed, visible-light-driven reaction of  $CBr_4$  and a catalytic amount of DMF in MeCN at room temperature. This operationally simple protocol offers a superior alternative to the existing methods because it avoids the need for corrosive, water-sensitive reagents and elevated temperatures. Moreover, the rearrangement is catalytic with respect to DMF and it is not self-propagating.

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**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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## (13) General Procedure for the Visible-Light-Driven Beckmann Rearrangement A mixture of ketoxime 1 (1.0 mmol) CBr. (2.0 equip

A mixture of ketoxime 1 (1.0 mmol),  $CBr_4$  (2.0 equiv), eosin Y (2 mol%), DMF (20 mol%), and MeCN (3 mL) was taken in an oven-dried round-bottom flask and irradiated with green LEDs while stirring under a nitrogen atmosphere. After completion of the reaction as indicated by TLC, it was quenched with sat. aq NaHCO<sub>3</sub> (10 mL) and extracted with EtOAc ( $3 \times 10$  mL). The organic phase was dried over anhydrous MgSO<sub>4</sub> and concentrated under reduced pressure to yield the crude product, which was purified by silica gel column chromatography (EtOAc-hexane) to give the corresponding amide 2 in high yield. All the products are known compounds and were characterized by comparison of their mp, TLC, <sup>1</sup>H NMR, <sup>13</sup>C NMR, and MS data with authentic samples obtained commercially or prepared by literature methods.<sup>7d,8d,9c,10a,14</sup> The characterization data of the synthesized compounds 2 are summarized in the Supporting Information with relevant references.

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