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LED lighting as a simple, inexpensive, and sustainable alternative for Wolff rearrangements†

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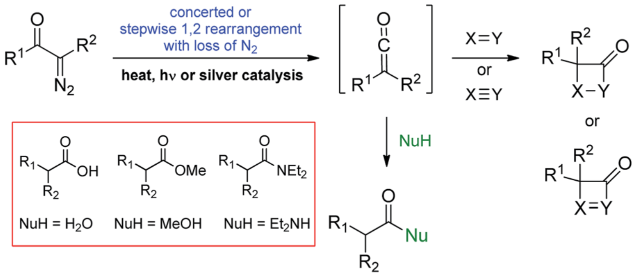
The Wolff rearrangement is one of the best methods for chain homologation. However, it still suffers from many drawbacks with respect to its practical execution in the laboratory. We wish to demonstrate the use of commercial LED lamps as a sustainable alternative for the classic experimental protocols typically used for Wolff rearrangements.

Introduction

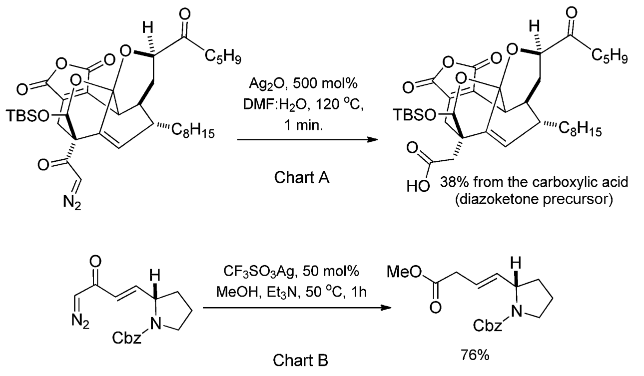
The Wolff rearrangement is a useful transformation in chemistry consisting of a 1,2-rearrangement from diazoketones to ketenes.[1–9] These ketenes, in the course of the reaction, can react with various nucleophiles (Arndt–Eistert homologation) or unsaturated compounds to provide carboxylic acid derivatives or cycloadducts, respectively (Scheme 1). Discovered by Ludwig Wolff in 1902,[10] this rearrangement was not well explored until 1930 when general methods to prepare diazoketones were developed.[11,12]



Scheme 1 General scheme for the Wolff rearrangement, showing its application in synthesis.

Initially, Ludwig Wolff found that heating solutions of select diazoketones to temperatures above 100 °C,[10] or use of freshly prepared silver(I)oxide in basic media,[13] were suitable for carrying out the transformation. Nowadays, thermolysis is generally avoided as it cannot be applied to sensitive substrates and is usually accompanied by formation of many undesired products. As a result, silver(I) salts[14–22] (particularly silver benzoate) and photolysis[23–32] have been the methods of choice. In the case of silver salts, the main disadvantage is the cost and need of high catalyst loadings (20–50 mol%). Experimental protocols can also require slow addition of the catalyst and heating for complete substrate consumption. For some substrates, super-stoichiometric amounts or high loadings of expensive silver salts must be employed, as described in the works of Nicolaou[33] and Burtoloso[34] (Scheme 2, Charts A and B, respectively).

Contrary to reactions with silver catalysts, photolysis benefits from mild reaction conditions and high yields of Wolff rearrangement products.[1] However, a major limitation of photolysis



Scheme 2 Two examples that excess of the catalyst or expensive silver salts need to be employed for the Wolff rearrangement to occur satisfactorily.

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is the use of special medium- and high-pressure xenon and mercury arc lamps. These lamps are expensive, energy consuming, and emit large amounts of heat. A sustainable alternative for the photochemical Wolff rearrangement utilizing commercially available light sources has yet to be investigated in great detail. Although two single examples[24,29,35] are described in the literature for the Wolff rearrangement employing a compact fluorescent lamp (CFL) in flow systems, to the best of our knowledge, no study is described using light emitting diode (LED) lamps. In the last few years, the use of LED lamps is increasing exponentially as a durable and energy-saving light source[36] when compared to the traditional CFL and incandescent lamps. The impact of LED lamps as a sustainable and important source of light resulted in the 2014 Nobel Prize in physics to Isamu Akasaki, Hiroshi Amano, and Shuji Nakamura for the discovery of the blue LED light.

As a part of our ongoing studies in the chemistry of diazoketones, we decided to investigate the outcome of the Wolff rearrangement in the presence of LED light. Not only we will demonstrate that these sources of light are efficient to carry out this rearrangement, but also that this method can be applied to several structurally different substrates under mild conditions with practical execution in the laboratory.

Results and discussion

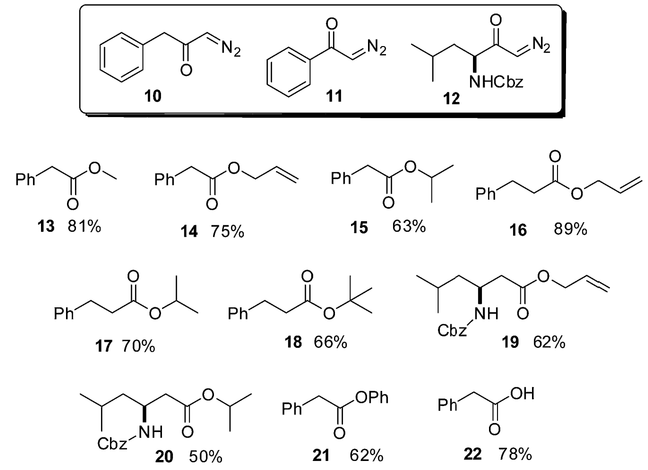


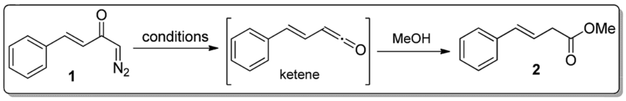
Fig. 1 The use of different substrates and oxygen nucleophiles for the Wolff rearrangement.

We began our work by evaluating the ability of five different white CFL and LED lamps to perform the Wolff rearrangement from diazoketone **1** in MeOH (Arndt–Eistert homologation) to obtain methyl ester **2** (Table 1). Diazoketone **1** was chosen as a model substrate since it is known to provide good results when classical conditions for the Wolff rearrangement are employed[37,38] (entries 1 and 2, Table 1). This would permit a fair comparison between the methods. As depicted in Table 1, medium potency CFL and LED lamps are needed for total consumption of **1** and to provide quantitative yields of ester **2** after 24 h (entries 4 and 7, respectively). It is also worth noting that while the CFLs caused considerable heating of the reaction solution, this was not observed when the LED lamps were employed.

After determining that the 18 W white LED lamp was the best source of light to carry out the Wolff rearrangements, we evaluated the reaction between diazoketone **1** and various hydroxyl nucleophiles. These included hindered isopropyl, *t*-butyl and menthyl alcohols, as well as allyl alcohol, benzyl alcohol, phenol, and water. As illustrated in Scheme 3, the reaction of **1** with all of these structurally different hydroxyl nucleophiles led to isolated yields of the corresponding esters in the range of 63–100%. Even when weakly nucleophilic phenol and highly hindered *t*-butyl alcohol were used, a 63% yield was obtained for compounds **8** and **4**.

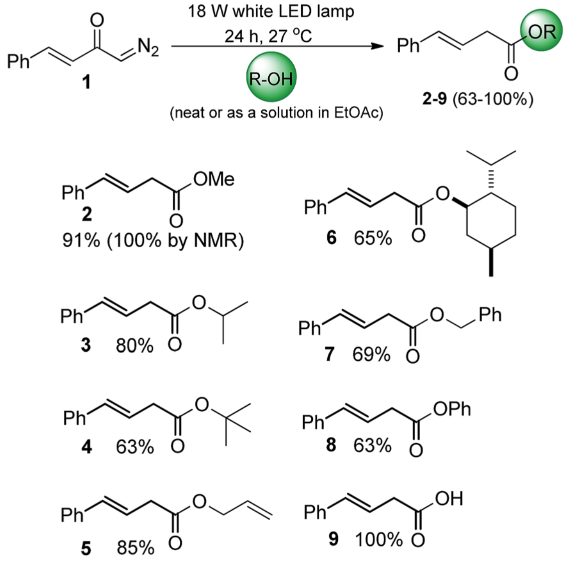
With the exception of water and solid nucleophiles, where a solution of the nucleophile in ethyl acetate was employed, the

Table 1 Wolff rearrangement using CFL and LED lamps as the light source



Entry	Conditions	Color temperature	Yield[a] (%)	Temperature of reaction solution after 24 h
1 (ref. 37)	20 mol% AgOBz, Et_3N, MeOH, 50 °C, 1 h	—	63	—
2 (ref. 38)	300 W high pressure Xe arc lamp, 4 h	6000 K	98	30 °C
3[b]	White CFL 15 W lamp, 24 h	6500 K	65	38 °C
4[b]	White CFL 45 W lamp, 24 h	6500 K	92	40 °C
5[b]	White CFL 25 W lamp, 24 h	2700 K	83	39 °C
6[b]	White LED 5 W lamp, 24 h	2700 K	10	27 °C
7[b]	White LED 18 W lamp, 24 h	2700 K	100	27 °C
8[b]	Without lamp (blank)	—	0	27 °C

[a] Yields determined by NMR with 1,2,4,5-tetramethylbenzene as an internal standard. [b] 0.05 M in MeOH at 27 °C. Reactions were carried out with 10 mg of **1**.



Scheme 3 The photochemical Wolff rearrangement from **1** in the presence of various oxygen nucleophiles.

reactions were carried out using the nucleophile as solvent. Alcohols are claimed to be one of the greenest solvents[39] and could be easily recovered from the reaction in high purity. During the course of this evaluation, another study revealed that the concentration of the reaction solution is crucial for high performance. For example, a 100% yield of **2** was obtained when solutions in the order of 0.025–0.05 M were used, whereas only 49% was obtained in a 0.5 M solution after 24 hours. However, longer reaction times (48 h) can permit the use of more concentrated solutions. For the procedures employing ethyl acetate as the solvent, 10 equivalents of the alcohol is necessary to guarantee high yields of product.

Next, we decided to investigate the synthetic utility of this photochemical method in the presence of other diazoketones. Diazoketones **10–12** were prepared and irradiated with the 18 W white LED lamp in the presence of several alcohols. For this study, hindered-, aryl-, chiral- and amino acid-derived diazoketones were employed, providing the corresponding esters and acids **13–22** in 50–89% isolated yields (Fig. 1). It is well known that α-amino acid-derived diazoketones are important precursors for the preparation of β-amino acids and esters *via* the Wolff rearrangement. Another point that deserves attention is that no significant change in the chemical yield was observed by increasing the scale of the reaction. For example, experiments with 0.2 and 2.0 mmol of diazoketone **11** furnished 81% and 78% of compound **13**, respectively.

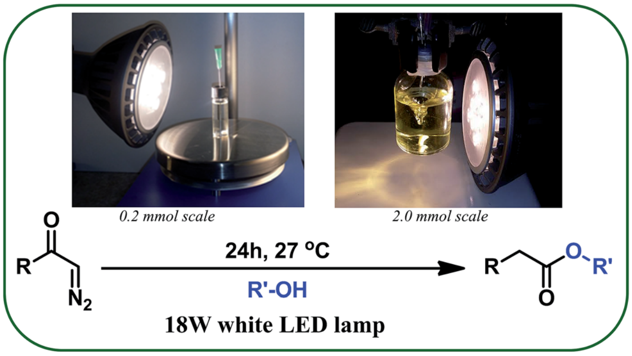
Conclusions

In conclusion, we have demonstrated the use of simple, commercially available LED lamps as a practical and sustainable alternative for carrying out Wolff rearrangements. This method is broad with respect to the alcohol nucleophile and diazoketone providing moderate to excellent yields of the desired Arndt–Eistert homologation products. Moreover, this method could be applied to other nucleophiles as the experimental procedure requires only the preparation of a solution of the diazoketone and nucleophile. This new protocol avoids the use of expensive and energy consuming Hg and Xe medium and high pressure arc lamps as well as tedious experimental procedures involving the use of expensive silver salts.

Experimental

General procedures for photochemical Wolff rearrangement with LEDs

Method A: using alcohols as solvent.



In a 4 mL vial, diazoketones (0.174 mmol) were dissolved in 3.5 mL of desired alcohol. The vial was closed with a cap and a needle added (to vent the nitrogen gas formed during the reaction). Next, the light yellow diazoketone solution was irradiated with a Philips Master LEDspot PAR 38 MV Dimmable (18 W, 2700 K, 50–60 Hz typ, 90 mA) lamp for 24 h under magnetic stirring at room temperature (nitrogen gas evolution observed; the solution tends to become colorless with the consumption of the diazoketone). After the reaction was complete, the solvent was removed with a rotary evaporator. Purification by flash column chromatography afforded the ester products. The schematic setup of the experiment is described above.

Method B: using ethyl acetate as solvent. In a 4 mL vial, diazoketones (0.174 mmol) were dissolved in 3.5 mL of dry EtOAc (MeCN can be also used as solvent) followed by the addition of 10 equiv. of desired alcohol. The resulting solution was irradiated with a Philips Master LEDspot PAR 38 MV Dimmable (18 W, 2700 K, 50–60 Hz typ, 90 mA) lamp for 24 h under magnetic stirring at room temperature (nitrogen gas evolution observed). After the reaction was complete, the solvent was evaporated in rotary evaporator. Purification, when necessary, was performed by flash column chromatography to afford the desired products.

Acknowledgements

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