A New Approach to Nitrones through Cascade Reaction of Nitro Compounds Enabled by Visible-Light Photoredox Catalysis

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Visible-light-induced photoredox catalysis has received considerable attention lately and has been used as a key strategy in organic synthesis. Nevertheless, visible light photoredox catalytic reactions of nitroalkanes are particularly scarce, and most examples have been conducted on nitroaromatic compounds. Recently, a new synthesis of oximes through photoredox catalysis of nitro compounds (mainly primary nitroalkanes) by the synergistic actions of visible-light irradiation and Lewis acid promoted dehydration was reported (*Org. Lett.* 2013, 15, 2660).

The group of Professor Bor-Cherng Hong at the National Chung Cheng University (Taiwan) has now developed a concise visible-light-induced photocatalytic conversion of nitro compounds carrying various functionalities into nitrone derivatives in high yield. According to the authors, this paper represents the first example of visible-light-induced photocatalytic conversion of nitroalkanes into nitrones. “This one-pot method not only represents a mild and concise process which adds to the repertoire of nitrone formation methodologies but also demonstrates a proof of concept of the synergistic action of photoredox catalytic cycles and condensation processes,” said Professor Hong. “The cross-condensation method had not been possible previously by assistance of Hünig’s base (DIPEA, N,N-diisopropylethylamine), but in this case, we achieved this transformation with the addition of DIPIBA (N,N-diisopropylisobutylamine) as the sacrificial electron donor. The use of a Hünig’s base surrogate provides a new pathway for photoredox catalysis which was previously not accessible. The structures of the products were unambiguously confirmed by single-crystal X-ray crystallographic analyses.”

Nitroalkanes, which are known as synthetic chameleons, are able to undergo transformation to a variety of functionalities and have received much attention in organic chemistry. Professor Hong said: “The visible-light-induced photocatalytic reaction of nitroalkanes that we described provides a mild and direct protocol for the synthesis of nitrones. Given the importance of the nitrone functionality in synthetic and medicinal chemistry, this mild and efficient reaction method could constitute a useful protocol with broad applications in chemical synthesis.”

The discovery of this novel reaction occurred serendipitously, revealed Professor Hong. In fact, during the course of a study combining organocatalysis with photoredox catalysis, Ms. Chang observed that a visible-light-induced photoredox-catalyzed reaction of nitroalkane 1 afforded an unexpected product (2a) bearing a CHCH₃ substituent. Professor Hong remarked: “However, with only the NMR spectra in hand, the exact structure of the product and the mechanism remained elusive. At least two questions arose from this noteworthy observation: (1) where does the CHCH₂ group come from? and: (2) how did the transformation occur and how can it be controlled for a better yield? To answer the first question, the same reaction was conducted with the replacement of DIPEA by Bu₃N, followed by a 15-hour irradiation to give the corresponding photoadduct carrying a CH(CH₂)₂CH₃ group, although in lower yield (33%) and with recovery of a certain amount of starting compound 1. “These results implied that the alkyl fragment on the photoadduct came from the alkylamine additive,” explained Professor Hong, continuing: “Nevertheless, the exact structure of the photoadduct remained unknown. For a period of time, we thought it might be an alkylimine, especially because the original mass spectra gave the daughter ion M-16 as the false molecular ion peak. However, we remained skeptical about this structural assignment since imines should not have such a high polarity as the photoadduct we obtained. In addition, in contrast with the instability of imines, the photoadducts we obtained were quite stable. Later, we found out that these compounds were not oximes either.”
In short, the bona fide structure of the photoadducts remained unknown at that time, and many structure-elucidation efforts, including re-crystallization in order to produce a single crystal for X-ray analysis, were in vain. The two unexpected products were eventually left in the refrigerator for a long time. Professor Hong said: “In the meantime, Mr. Lin expanded the exploration of this chemistry and undertook extensive experimental endeavors in order to optimize the reaction conditions and explore the reaction scope as well as provide more analogues for structure elucidation.” A few months after Ms. Chang’s graduation in 2013, Professor Hong took the photoadducts which Ms. Chang prepared and managed to carry out the crystallization process successfully. Professor Hong concluded: “Fortunately, the single crystals of compound 2b, prepared from the Bu₃N additive, were obtained; the structure of photoadduct 2b could therefore be unambiguously assigned by X-ray crystal structure analysis. The project was then advanced by refocusing on the photocatalysis of nitroalkanes to nitrones. This clearly demonstrates once again that research progress benefits from the power and synergy of team work.”

With regard to future prospects and developments, the one-pot and cascade asymmetric organocatalysis/photocatalysis/dipolar cycloaddition, as well as the exploration of its application in natural products synthesis, are currently under active investigation.
About the authors

C.-W. Lin was born in Changhua (Taiwan) in 1982. He received his BSc in chemistry from National Tsing Hua University (Taiwan) in 2004 and his MSc in organic chemistry from National Changhua University of Education (Taiwan) in 2009. He is currently a PhD student in the Department of Chemistry and Biochemistry, NCCU, under the guidance of Professor Hong. His research interests are the development of new methodologies for catalysis and their application to natural product synthesis.

B.-C. Hong was born in Changhua (Taiwan) in 1962. He graduated with a BSc from Tunghai University (Taiwan) in 1984 and received his MSc from National Taiwan University in 1986 (working with Professor Jim-Min Fang). After the two-year mandatory military service, he went to The University of Chicago (USA) for graduate studies where he obtained his PhD degree under the guidance of Professor J. D. Winkler in 1992. Immediately after graduating, he joined the group of Professor E. J. Corey as a postdoctoral fellow at Harvard University (USA) from January 1993 to July 1994. He was appointed as an Associate Professor at National Chung Cheng University in August 1994, established his research group, and was promoted to Full Professor in 1999. His current research interests are focused on the development of novel annulation methodologies, especially with organocatalysts or photocatalysts, and natural products synthesis.

W.-C. Chang was born in Taipei (Taiwan) in 1988. After receiving her BSc in chemistry from Chung Yuan Christian University (Taiwan) in 2011, she joined Professor Hong’s research group as a graduate student at NCCU and received her MSc in 2013. Currently, she is a research scientist in a pharmaceutical company.

Dr. G.-H. Lee graduated with a BSc in chemistry from Chinese Culture University (Taiwan) and received his MSc from the same university in applied chemistry and his PhD in organic and polymeric materials from National Taipei University of Technology (Taiwan). He is currently a senior crystallographic specialist in the X-ray Diffraction Laboratory at Instrumentation Center, National Taiwan University.