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Editorial

Photochemical synthesis and group transfer reactions of azoxy compounds

Azoxy compounds are extensively utilized in various fields, including dyes, polymerization inhibitors. Their high nitrogen and oxygen content make them ideal for use as energy storage materials [1–4]. Additionally, azoxy functional groups are found in various natural products. In 1949, chemists successfully isolated natural congener of azoxy compounds from cycads, marking a significant discovery. Subsequently, azoxy compounds were also discovered in mushrooms, sponges, and soil-dwelling bacteria, showing promising pharmaceutical activity, including antimicrobial, antifungal or antibacterial agents (Scheme 1) [5].

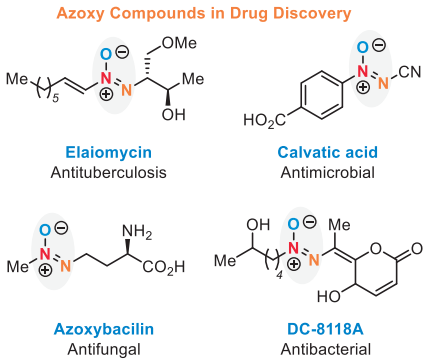
From a synthetic perspective, the current methods for synthesizing azoxy compounds are often costly, inefficient, and not environmentally sustainable [6]. Traditional techniques involve the oxidative coupling of amines or the reductive coupling of nitro compounds to produce symmetric azoxy compounds. However, these methods did not address the synthesis of asymmetric azoxy compounds, further restricting their potential applications.

Recently, Xuan and Koenigs utilized nitroso compounds as triplet nitrene capture reagents for synthesizing a range of sulfonyl-protected azoxy compounds [7]. Furthermore, they employed sulfonyl-protected azoxy compound as a transfer reagent for the azoxy functional group, enabling the functionalization of C(sp^3)-H bonds in ethers as solvent or the bifunctionalization of vinyl ethers as solvent through the homolytic cleavage of the N-S bond under visible light irradiation. This innovative approach allowed for the synthesis of a diverse range of asymmetric azoxy compounds. Notably, the reaction conditions are mild, without resorting to photocatalysts or additives, and proceed efficiently solely under visible light exposure (Scheme 2).

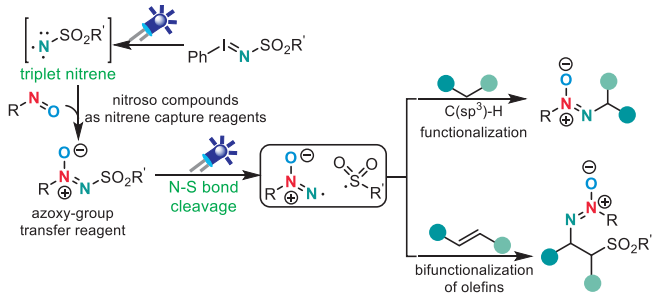
The photochemical synthesis [8,9] of sulfonyl-protected azoxy compounds is not limited to nitrosoarenes, demonstrating good functional group tolerance towards 2-nitrosopyridine and alkyl nitroso compounds. Additionally, researchers successfully utilized this method to modify active molecules such as ibuprofen, cholesterol, and propofol, providing valuable strategies for the later modification of drug molecules and natural products.

During the optimization of reaction conditions, a significant decrease in the yield of the desired azoxy compound was observed when using THF as the solvent. Further controlled experiments demonstrated that sulfonyl-protected azoxy compounds could undergo an azoxy functional group transfer reaction with THF under visible light irradiation. Moreover, it was found that this strategy was not limited to various types of cyclic ethers, but also applicable to chain ethers such as diethyl ether and tetrahydrothiophene. The authors proposed that this phenomenon might be due to the homocleavage of N-S bonds in sulfonyl-protected azoxy compounds under visible light irradiation, leading to the formation of diradical intermediates.

In order to gain a deeper understanding of this solvent-dependent reaction, the researchers conducted a comprehensive investigation into the reaction mechanism. They proposed a potential reaction mechanism based on control experiments, UV absorption spectra, radical capture experiments, EPR studies, and DFT calculations. The results indicate that when THF is used as a solvent, sulfonyl-protected azoxy compounds can generate N-centered and S-centered radicals through homolytic cleavage of N-S bonds



Scheme 1. Azoxy compounds in drug discovery.



Scheme 2. Photochemical synthesis and azoxy group transfer reactions of azoxy compounds.

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under visible light irradiation. The S-centered radical then reacts with a hydrogen atom at the α position of THF, forming a new C-centered radical. Subsequently, the desired product of azoxy functional group transfer was obtained through the coupling of C-center and N-center radicals.

Following the identification of a diradical intermediate in the reaction mechanism, the authors explored the potential of sulfonyl-protected azoxy compounds as difunctionalization reagents. These compounds demonstrated effectiveness in the difunctionalization of alkenes, albeit with a restricted substrate scope limited to alkenyl ethers or alkenyl sulfides. The authors suggest that this limited scope could be attributed to the role of S or O atoms in stabilizing free radical intermediates.

Xuan and Koenigs have successfully synthesized a range of sulfonyl-protected azoxy compounds by utilizing nitroso compounds as triplet nitrene capture reagents. Subsequently, with a single visible light irradiation, the authors utilized these sulfonyl-protected azoxy compounds to achieve a series of azoxy functional group transfer reactions. This approach presents a new pathway for the synthesis of asymmetric azoxy compounds, with potential implications in synthetic chemistry and drug development.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Mei Peng: Data curation, Conceptualization. **Wei-Min He:** Writing – review & editing, Supervision.

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