CRIPS Digest

N-heterocyclic carbene- and organic photoredox-catalysed meta-selective acylation of electron-rich arenes

The Friedel-Crafts reaction, one of the most popular organic reactions, has widely been used both in academic laboratories and industry. In Friedel-Crafts acylation reaction, the electrophile acylium cation, generated by an inorganic Lewis acid, is substituted on electron-rich arenes. More importantly, the acyl group is introduced in the ortho- and para-positions to the electron-donating group of aromatic rings. However, meta-selective acylation of electron-rich arenes is a challenging process by this method. In this context, transition metal-catalyzed C-H activation strategy has emerged as a new method for meta-selective functionalization of aromatic rings. However, the method requires rationally designed directing groups and ligands for achieving meta-selectivity. Ohmiya et al. developed the N-heterocyclic carbene (NHC) and organic photoredox cooperative catalytic acylation of electron-rich arenes, which provides exclusive meta-selectivity. The reaction involves a nucleophilic addition of an azolide anion to the aromatic radical cation generated by single electron oxidation of the electron-rich arenes. The catalytic system involves a sequence of single electron oxidation of an electron-rich arene followed by the radical-radical coupling between a ketyl radical and an arene radical cation. This approach does not require any directing group or steric factor required in transition metal catalysis. Unlike conventional approaches such as the Friedel-Crafts acylation, this method follows a different mechanism resulting in precisely opposite regioselectivity (Nat. Synth. 2023, DOI: org/10.1038/s44160-023-00378-4).

A Photochemical Strategy for the Conversion of Nitroarenes into Rigidified Pyrrolidine Analogues

Because of their inherent structural rigidity, saturated bicyclic amines ensure accurate three-dimensional (3D) disposition of exit vectors and their substituents point toward specific areas of chemical space that are often out-of-reach to their conformationally fluxional monocyclic congeners. In this context, 2-azabicyclo[3.2.0]heptanes framework remains unexplored due to a paucity of synthetic methods for its preparation. A modular synthetic strategy that utilizes nitroarenes as feedstocks for the assembly of this framework is developed by Leonori et al. The method uses photochemistry to trigger a dearomative cascade converting the flat benzenoid system into a complex bicyclic pyrroline with full translation of the aromatic substitution pattern into the one of the heterocycles. The process operates at room temperature, tolerates many functionalities, and delivers the high-value 2-azabicyclo[3.2.0] heptanes in one-step. The method features two concomitant photochemical processes that sequentially ring-expand the nitroarene into an azepine followed by folding it into a rigid bicycle pyrroline system by means of singlet nitrene-mediated nitrogen insertion and excited-state -4π electrocyclization. Subsequently, the hydrogenolysis provides the desired bicyclic amines diastereoselectively, wherein the aromatic substitution pattern is translated into the one of the three-dimensional heterocycles. Overall, this platform enables the conversion of nitroarenes into the complex sp3-rich heterocycles of potential interest in drug development (J. Am. Chem. Soc. 2023, ASAP article, DOI: org/10.1021/jacs.3c10863).

Design, synthesis and evaluation of halogenated phenazine antibacterial prodrugs targeting nitroreductase enzymes for activation

Since the end of the antibiotic "golden age" in the late 1960s, very few new classes of antibiotics have entered into the clinic. In addition, numerous problems associated with antibiotic resistance have significantly increased the need for new antibacterial agents with novel modes of action. Therefore, it is important to develop new strategies to combat antibiotic resistance. Huigens et al. reported design, synthesis, and biological study of a new series of nitroarene-based halogenated phenazines (HP) as prodrugs that are designed to utilize a nitroarene trigger to be reduced by nitroreductase enzymes in

bacteria. The strategy relies on the targets nitroreductase (NTR) enzymes found within most bacteria and NTR enzymes are known to reduce nitroarenes to the corresponding aniline products. These HP analogues are highly active against multidrug-resistant bacterial pathogens leveraging intracellular nitroreductase (NTR) enzymes for activation and subsequent release of active HP agents. The sulfonate ester linker present in HP-nitroarene prodrugs (1) allows a straightforward synthesis of HP-nitroarene prodrugs, and (2) facilitates the release of the active drug HP warhead following reduction of the nitroarene to aniline, (which also includes loss of SO2 gas). These compounds were unable to bind iron(II), which is critical for their mode of action and required for mitigating off-target cytotoxicity. Following chemical synthesis, in vitro nitroreductase-promoted release assays and antibacterial assessments were used to characterize the action of HP-N prodrug molecules that led to the identification of HP-1-N as an ideal candidate due to a combination of targeted release by nitroreductase, antibacterial activities, linker stability, and a good cytotoxicity profile. (RSC Med. Chem., 2023, 14, 1472-1481).

Unusual peptide-binding proteins guide pyrroloindoline alkaloid formation in crocagin biosynthesis

Alkaloids are important class of natural products having a common motif hexahydropyrrolo[2,3-b]indole, also referred to as pyrroloindoline. While pyrroloindoline-containing natural products possess diverse and potent bioactivities, their synthesis has presented formidable challenges. An understanding of their biosynthesis may allow access to these valuable molecules by improving synthetic or semi-synthetic routes. Pyrroloindolines are biosynthetically derived from tryptophan using different enzymatic synthetic routes. Peptide natural products have been converted to many highly unusual scaffolds achieved via ribosomally synthesized and post-translationally modified. However, biosynthesis of the intriguing alkaloids crocagins possessing a tetracyclic core structure remains enigmatic. Koehnke et al. demonstrated the use of three proteins, CgnB, CgnC and CgnE for the production of crocagin core from the precursor peptide CgnA through in vitro experiments. The crystal structures of the homologues CgnB and CgnE reveal them to be the founding members of a peptide-binding protein family and allowed the authors to rationalize their distinct functions. The authors further show that the hydrolase CgnD liberates the crocagin core scaffold, which is subsequently N-methylated by CgnL. These insights allow them to propose a biosynthetic route for crocagins. Bioinformatic analyses based on these data led to the discovery of related biosynthetic pathways that may provide access to a structurally diverse family of peptide-derived pyrroloindoline alkaloids. (Nat Chem. 2023, 15, 560-568).