Abstract

Aryl nitrenes and *p*-arynes as biochemical and synthetic tools

Reactive organic molecules/intermediates like azides and benzynes have been exploited in organic synthesis and also in biology. Amongst these, chemical probes based on photoaffinity labeling (PAL) are powerful chemical tools for understanding complex biological systems through labeling and detection of disease-causing proteins in biomedical research, chemical proteomics and drug discovery. Conventional design of PAL probe requires synthetically challenging procedure and often the overall steric size of the probe restricts its applicability *in vivo*. Photolysis of aryl azides produces aryl nitrene intermediates which can readily cross-link with protein residues. Azidonaphthalimide- based probes offer dual advantage of inducing cross-linking by photo-irradiation which also results in fluorescence enhancement after conversion to the amino-derivative. Exploiting these, we have developed a universal template which can ideally be used for targeting any protein simplifying the design of probes for different proteins. The thesis also concentrated on another reactive intermediate, namely the *p*-arynes generated during Bergman cyclization and explored their synthetic potential as nucleophile capture. The regioselectivity during nucleophile addition was achieved in *p*-arynes derived from naphthalene enediynes using hydrogen acting as a steric element to block the trajectory of the attacking nucleophile.

The thesis comprised five chapters with **Chapter 1** providing a concise review on nitrene and *p*-aryne intermediates, and on photoaffinity chemical probes. **Chapter 2** describes the design and synthesis of the azidonaphthalimide templates that have been elaborated to make PAL probes for successful capturing of human carbonic anhydrase II (HCA II) and penicillin binding proteins (PBP-5). In **Chapter 3**, the same template has been used in the synthesis of PAL probes for detecting plasmid-encoding carbapenem-resistant metallo-beta-lactamases (PCM BL), a superbug family enzyme, at nanomolar level *via* in-gel fluorescence technique. In **Chapter 4**, we have shown the versatility of the template in the inhibitor screening for HCA II *via* cross-linking and in-gel fluorescence. In **Chapter 5**, experiments have been carried out for obtaining regioselectivity in nucleophilic addition to naphthalene enediynes by exploiting the steric effect of bay-region hydrogen to produce tetrahydro naphtho isoquinoline derivatives which showed impressive DNA intercalating properties.

Keywords: Reactive intermediate, aryl azide, *p*-arynes, photoaffinity probe, inhibitor screening, Bergman cyclization, regioselectivity, tetrahydro isoquinoline.