Late-Stage Peptide Modifications through S-imination enable Chemoselective Installation of free-NH Sulfilimines and Sulfoximines

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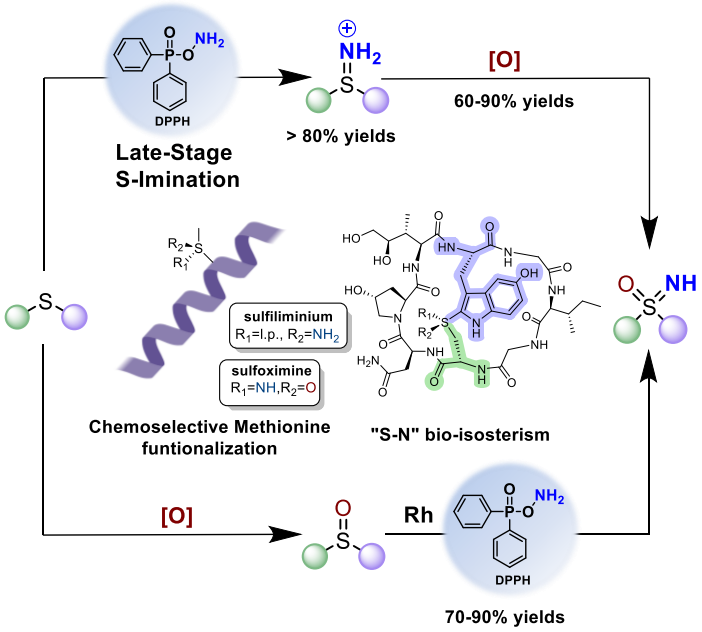
Sulfilimines, the mono aza-analogues of sulfoxides have sparked acute interest in the fields of chemistry and biology with the discovery of a S=N crosslink in collagen IV. They serve as potential bioconjugation handles, bioisosteric pharmacophores, and are precursors to medicinally relevant S(VI) scaffolds. S-imination strategies to access sulfilimines have been employed for methionine (Met) functionalization in peptides and proteins for conjugation and also for chemoproteomic profiling of Met.[1-3] Herein, we report the use of diphenylphosphinylhydroxylamine (DPPH) for S-imination to access sulfiliminium salts and sulfoximines under safe, mild, metal-free, and bio-molecule-compatible conditions with excellent chemoselectivity, broad functional group tolerance, and applicability in late-stage derivatization. These S-imination methods afforded successful chemoselective installation of sulfiliminium and sulfoximine scaffolds on clinically relevant methionine, buthionine, and also on complex peptides such as cholecystokinin and bombesin. α-amanitin is a sulfoxide bearing bicyclic octapeptide which is a potent inhibitor of RNA polymerase II, explored as a payload in targeted cancer therapy.[4] DPPH mediated S-imination renders late-stage synthetic access to sulfilimine, sulfoximine, and sulfondiimine amatoxins; and cytotoxicity assays were employed to address their potential bioisosterism. Collectively, these results attest to the robustness of this S-imination strategy for chemoselective installation of versatile sulfilimine and sulfoximine scaffolds on peptides.



References

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