Synthesis of Substituted γ- and δ-Lactams through Mannich-Type Reactions of Solid-Supported N-Acyliminium Ions - DTU Orbit (03/12/2018)

We report the results of our recent investigations into the reactivity of cyclic solid-supported N-acyliminium ions. An intermolecular Mannich-type transformation of these intermediates was used to generate libraries of substituted lactams. Masked aldehyde building blocks were readily prepared and coupled to peptides immobilized on PEGA800(polyethylene glycol dimethyl acrylamide) resin through an HMBA [4-(hydroxymethyl)benzoic acid] linker. When treated with acid, the aldehyde was cleanly released and condensed with the amide backbone to form a hydroxylactam/N-acyliminium ion, which underwent intermolecular reactions with a series of nucleophilic heterocycles, such as substituted indoles, thiophenes, furans, and electron-rich benzenes. The resulting lactams were formed within a few minutes and in high purities (typically >85%).

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