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Current diversity of cyclic anhydrides for the Castagnoli-Cushman-type formal cycloaddition reactions: prospects and challenges

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Abstract: The diversity of dicarboxylic acid anhydrides employable in the Castagsnoli-Cushman reaction (CCR) was traditionally thought to be limited to the classical succinic and glutaric anhydrides – as well as to its remarkably more reactive counterpart, homophthalic anhydride. The diversity of the lactam products resulting from this extremely powerful, three-component reaction could have been perceived as somewhat limited and the reaction itself may have often been associated with forcing temperatures (thereby limiting, in public mind, the functional group tolerance that this reaction is capable of displaying). In this Digest we aim to provide a glimpse of the remarkable advancements the diversity of the anhydride component for the CCR has taken, summarize the consequences these advancements may have for the scope and applicability of the reaction and pencil in some directions this exciting area of organic chemistry could be taking in the near future, particularly based on the current efforts in our group.

Keywords: scaffold-oriented synthesis, multicomponent reactions, acylations, nucleophilic addition, heterocyclic diversity, lactams.

First described by Castagnoli in 1969, the reaction of imines **1** (formed in situ or in a separate step) with either succinic (**2**)[1a] or glutaric anhydride (**3**),[1b] provided convenient access to densely functionalized pyrrolidones (**4**) or piperidones (**5**), respectively, which are prevalent motifs encountered in the natural product realm and in synthetic pharmaceuticals (Scheme 1).[2] The apparent disadvantages of this reaction (which we term the Castagnoli-Cushman reaction, or CCR,[3] to acknowledge the persons primarily responsible for its discovery) were the prolonged heating in highly boiling hydrocarbon solvents (often leading to tar formation) and the somewhat limited scope, particularly, with respect to the dicarboxylic anhydride component. In the next 40 years or so, the reaction followed a long evolutionary path, particularly in the latter aspect. In this Digest, we aim to provide a brief overview of main milestones achieved in expanding the diversity of the anhydride inputs for the CCR and sketch out some recent contributions from our laboratory. It is not our goal to provide a comprehensive review of the scope and applicability of