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Stereoselective Mannich reaction in the synthesis of diastereomerically pure β-amino ketones

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One of the constant challenges of modern organic synthesis is the formation of a new C-C and C-heteroatom bond in a single step while maintaining the latest ecological and economic requirements of sustainable chemistry. A crucial part of the process is often represented by selecting an appropriate, environmentally friendly, and inexpensive product isolation method. Crystallization belongs to the oldest and most popular separation techniques. Its reaction system's thermodynamic driving forces could empower the course of chemical transformation.

A common choice for the simultaneous C-C and C-N bond formation in the preparation of potentially biologically active molecules is the versatile Mannich reaction employing classical procedures or even asymmetric metal-catalyzed protocols.[1,2] Equally interesting is the possibility of Mannich bases derivatizations providing 1,3-amino alcohols, substituted carbonyl compounds, Michael acceptors or interesting β-lactams.

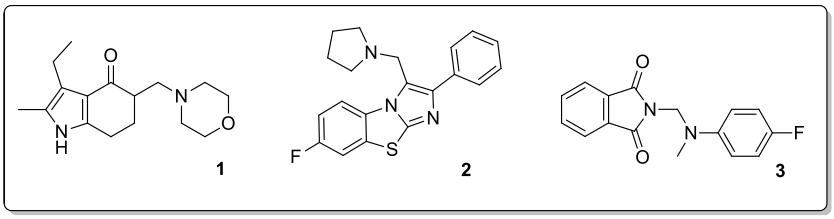

Figure 1: Selected examples of heterocyclic Mannich base compounds[3a-c]

Our research is focused on the stereoselective synthesis of α-substituted Mannich salts. In the first step, the direct three-component Mannich reaction is performed using commercially available reagents in almost stoichiometric ratio. After the crystallization controlled epimerization, desired aromatic, aliphatic and cyclic α-substituted Mannich salts are isolated in high enantio- and diastereomeric purities by simple filtration. The effective chromatography-free protocol is readily scalable (5-110 mmol) and predetermines it for industrial applications.[4]

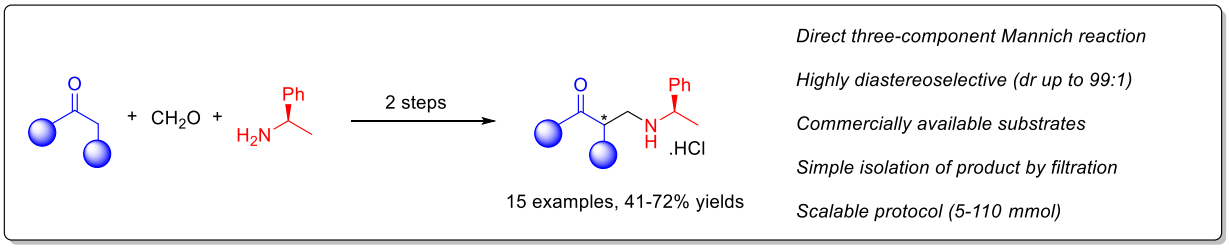

Figure 2: Stereoselective preparation of α-substituted Mannich salts

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