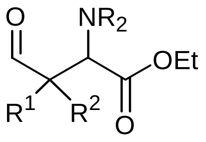
Modern Alternatives of the Mannich Reaction for the Aminoalkylation of Aldehydes, Nitroalkanes and cyclic Dienes

Stefan Piper

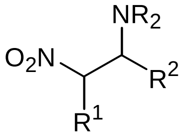
The Mannich reaction (Carl Mannich, 1877 - 1947), or more general the α-amino alkylation of carbonyl compounds is one of the eminent preparative C-C bond-forming reactions in organic chemistry. The products, β-amino ketones (Mannich bases) and their derivatives afford a variety of interesting applications. Among these the preparation of agents for medicine is still of capital importance.

However, the conventional Mannich reaction is generally fraught with serious drawbacks such as drastic reaction conditions (high temperature, long reaction time, use of protic solvents) leading to objectionable by-products. Substrates unemployed so far were used in our group for the consequent enhancements of the Mannich reaction to develop modern versions of the Mannich reaction. We have disclosed, that the aminoalkylation of enamines and imines with ternary iminium salts provides the corresponding Mannich bases in excellent yields and diastereoselectivities. Our interest is currently directed towards aminoalkylation of such nucleophiles that have not or just restricted been used under the conditions of the classical Mannich reaction.

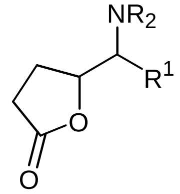
Within the scope of this work, the synthesis of β-formyl-α-aminocarboxylates **1**, α-amino-nitroalkanes **2**, γ-(dialkylamino-arylmethyl)-γ-dihydro-furan-2-ones **3** and γ-arylidenbutenolides **4** is shown.



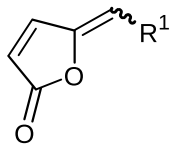
1



2



3



4

All products synthesised feature the addition of nucleophiles to iminium salts. Preformed and *in situ* generated iminium salts are used.

For the first time, β-formyl-α-aminocarboxylates **1** have been systematically synthesised and characterised. Reduction of α-amino-nitroalkanes **2** provides 1,2-diamines. The γ-(dialkylamino-arylmethyl)-γ-dihydro-furan-2-ones **3** can be synthesised in high regioselectivities by aminoalkylation of (Furan-2-yloxy)-trimethyl-silane (vinylogous Mannich reaction) and subsequent hydration. Thus, the γ-arylidenbutenolides **4** can be synthesised as well. These products just as the Mannich bases and their derivatives afford a variety of interesting applications. The preparation of pharmaceuticals and natural products is by far of particular importance. In addition there are applications for plant-protection, in coatings and polymer chemistry for dyes, surface active compounds, curing and cross linking agents.

New compounds are currently tested in consideration of their suitability as synthetic building blocks in the preparation of new pharmaceuticals.