SHORT COMMUNICATION

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Decarboxylative Mannich Reactions

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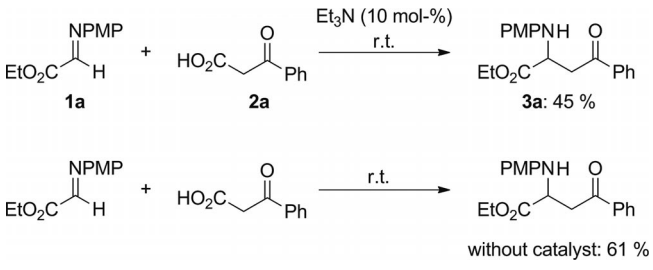
p-Methoxyphenylimines obtained from enolizable aldehydes react in the absence of catalysts at room temperature with β-keto carboxylic acids through a decarboxylative Mannich reaction. The Mannich products were obtained with a high degree of *anti* selectivity. By use of chiral oxygen-containing aldehydes, operationally simple access to aminohydroxylated polyketide substructures is possible.

Introduction

Nature generates carbon–carbon bonds under very mild conditions by using various different methods for activating substrates. Decarboxylation[1] is one activation mode that allows C–C bonds to be constructed simultaneously under physiological conditions. This mild and operationally simple transformation is found as a key step in the aldol processes of polyketides[2] and carbohydrate[3] biochemical pathways. Moreover, decarboxylative Mannich reactions are also known and play an important role in nature in the construction of alkaloids with a defined configuration. Prominent examples of this transformation are the biosyntheses of pyrrolidine-containing alkaloids of the tropane series, including tropinone, calystegine, and atropine. The simplicity and logic of these natural transformations have challenged synthetic chemists for a long time. An overview of developments in this area has been published,[4] as have reports of metal-catalyzed decarboxylative Mannich reactions.[5] Also, organocatalytic solutions of this transformation have been attempted. To this end, malonic acid half thioesters were treated with imines of aromatic aldehydes in the presence of stoichiometric or catalytic amounts of tertiary amines.[6] Amine-catalyzed symmetric decarboxylative Mannich reactions in the total syntheses of natural products were reported early on,[7] but only three examples became known as organocatalyzed asymmetric decarboxylative Mannich reactions. Ricci et al. described reactions of malonic acid half thioesters with imines in the presence of cinchona alkaloids. The corresponding β-amino thioesters were obtained with *ee* values up to 79%.[8] Tan and coworkers used chiral bicyclic guanidines as catalysts in the decarboxylative Mannich reactions of *N*-tosyl imines of aromatic aldehydes to obtain the corresponding β-amino thioesters with high degrees of enantioselectivity.[9] Lu and co-workers described decarboxylative Mannich reactions of aromatic imines in the presence of chiral thioureas.[10] During our ongoing studies in the field of amine-catalyzed direct aldol additions, we successfully developed a direct amine-catalyzed decarboxylative aldol addition of β- and α-keto carboxylic acids with enolizable aldehydes.[11] Following these results, we attempted a decarboxylative Mannich reaction under similar reaction conditions. The results of this investigation are described below.

Results and Discussion

In initial experiments, compound **1a**, which is the *p*-methoxyphenylimine (PMP-imine) of ethyl glyoxylate, was treated with benzoyl acetic acid (**2a**) in the presence of a catalytic amount of a tertiary amine (10 mol-%). PMP-protected β-amino ketone **3a** was isolated in moderate yield (45%). Upon decreasing the amount of catalyst, an increase in the yield was observed. In the absence of a catalyst, a high yield was detected in a clean reaction at room temperature (61%, Scheme 1). Similar results were obtained for catalyst-free aldol additions with 1,3-dicarbonyl compounds.[12]



Scheme 1. Decarboxylative Mannich reaction of benzoyl acetic acid (**2a**) and imine **1a**.

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A competitive decarboxylation of the starting β-keto carboxylic acid initiated by the tertiary amine with a higher rate of formation than C–C bond formation is assumed. Detection of varying amounts of acetophenone depending on the amount of the tertiary amine used in the reaction supports this theory. Moreover, quantitative decarboxylation of the β-keto carboxylic acid in the presence of a catalytic amount of the tertiary amine within 15 min at room temperature was detected independently by NMR spectroscopy. Systematic investigations with other tertiary amines yielded the same results.

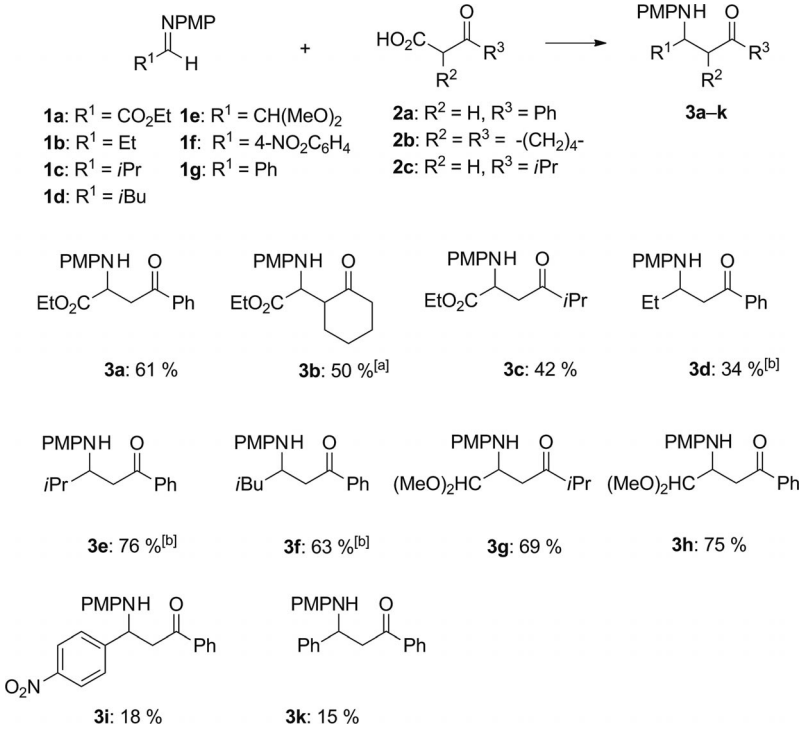
This competitive decarboxylation of the β-keto carboxylic acid was detected at room temperature as well as at –40 °C. Also, when *N*-tosyl imine was used instead of *p*-PMP-imine, an uncatalyzed decarboxylative Mannich reaction was detected, although to a lesser extent. The basicity of the imine is clearly strong enough to induce the decarboxylation of the starting β-keto carboxylic acids.

To explore the scope and limitations of the uncatalyzed Mannich reaction, *p*-PMP-imines **1a**–**g** were treated in a first series with β-keto carboxylic acids **2a**–**c**. The PMP-imines were produced by optimized literature reports[13] and were used without further purification in the subsequent Mannich reaction. As a result of the variable stabilities of the different imines, three optimized protocols for the Mannich reaction were elaborated according to the nature of the R^1 substituent. Imines **1b**–**d** of enolizable aldehydes proved to be the most problematic substrates in the course of this reaction (R^1 = Et, *i*Pr, *i*Bu). Because of their reactivity, they tend to undergo undesired side reactions, which leads to reduced yields, even in a catalyst-free and neutral medium.[14] For this reason, imines **1b**–**d** of enolizable aldehydes were formed and treated at –40 °C with β-keto carboxylic acids, whereas imines **1a** and **1f**–**g** (non-enolizable aldehydes) were used at room temperature. Imines **1h**–**n** of oxygen-containing, chiral aldehydes were formed at 0 °C and used at room temperature. The reactions were monitored by thin-layer chromatography and were mostly complete after 1–2 h. The results of the investigations with imines **1a**–**g** are depicted in Scheme 2.

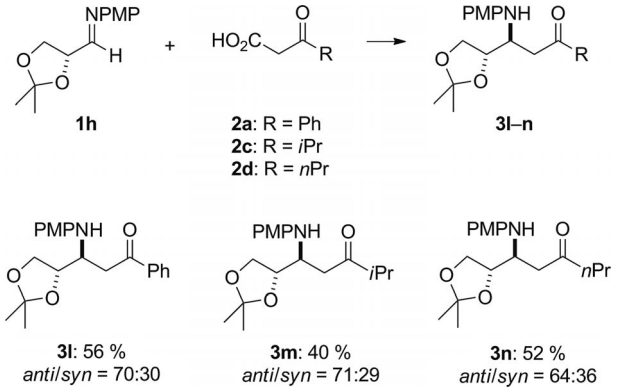
Accounts of the synthesis of optically pure Mannich adducts through the direct decarboxylative Mannich reactions of the imines of enolizable aldehydes have not been reported.[15] Thus, by using the imines of chiral enolizable aldehydes, access to optically pure, β-amino ketones with a defined configuration is possible. In preliminary experiments, we treated **1h**, which is the imine of glyceraldehyde, with differently substituted β-keto carboxylic acids **2a**, **2c**, and **2d** (Scheme 3).

Completion of the reaction was observed after 60 min at room temperature. PMP-protected β-amino ketones **3l**–**n** were obtained as a diastereomeric mixture. A slight *anti* selectivity was detected. Separation by column chromatography yielded diastereoisomers **3l** and **3m** in optically pure form. Racemization of the starting chiral aldehydes was not detected under these reaction conditions.

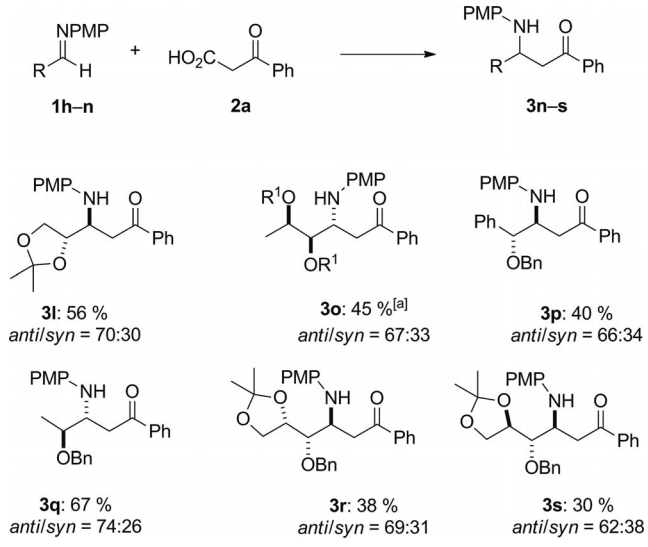
By further investigations, we extended this transformation. To demonstrate the broad scope of this operationally simple protocol, we treated imines **1h**–**n**, obtained from different chiral aldehydes, with **2a**. Results of these investigations are depicted in Scheme 4.



Scheme 2. Catalyst-free decarboxylative Mannich reaction. Reaction conditions: dichloromethane, r.t. [a] *syn*/*anti* = 45:55. [b] Reaction conditions: dichloromethane, –40 °C.



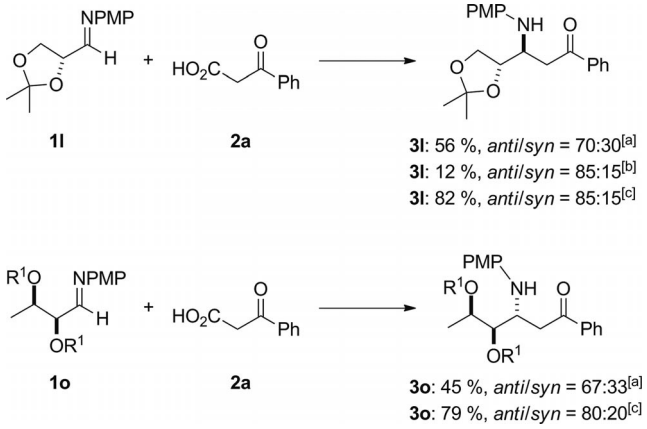
Scheme 3. Decarboxylative Mannich reactions of PMP-imine **1h**. Reaction conditions: dichloromethane, r.t.



Scheme 4. Direct decarboxylative Mannich reaction of benzoyl acetic acid (**2a**) with chiral imines. Reaction conditions: dichloromethane, 0 °C. [a] Reaction conditions: r.t., $R^1 = CMe_2$.

Reactions were carried out at 0 °C and were mostly complete after 1–2 h. Mannich products **3l**–**s** were isolated in moderate to good yields. A reasonable *anti*-diastereoselectivity was obtained. Racemization was not observed during these reactions. Diastereomeric Mannich adducts **3l**–**s** were isolated in enantiopure form.

By additional investigations several details were identified that are responsible for the reduction in both the yield and the stereoselectivity. To overcome the moderate stereoselectivities, imines **1l** and **1o** were treated with **2a** at –15 °C. Longer reaction times were required for full conversion under these conditions. Indeed, the stereoselectivities were significantly enhanced, but the yields were greatly reduced. For the reaction with imine **1l**, the yield decreased from 56% at 0 °C to 12% at –15 °C (compare conditions b in Scheme 5 with those of Scheme 4). A retro-Michael reaction was suspected, which could be operative under these conditions.[16] For that reason, an excess amount of the corresponding imine was used in these experiments, and the reaction mixtures were quenched at –15 °C. Under these conditions, the Mannich products were obtained with high yields and stereoselectivities (Scheme 5).



Scheme 5. Optimization of the reaction conditions. [a] Reaction conditions: dichloromethane, 0 °C. [b] Reaction conditions: dichloromethane, –15 °C. [c] Reaction conditions: dichloromethane, –15 °C, **1l** (2 equiv.).

The high *anti* selectivity can be explained by Felkin–Anh considerations. The steric demand of the R^1 substituent (dioxolane ring) favors model **A** to yield the *anti*-configured Mannich product (Figure 1).

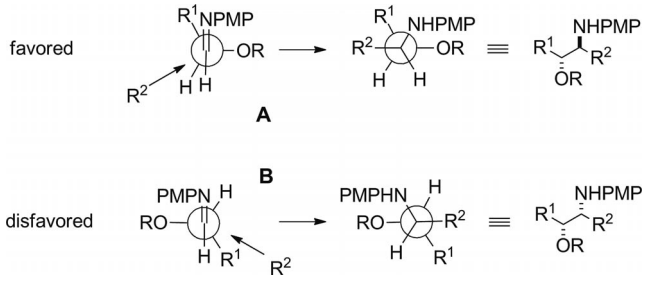
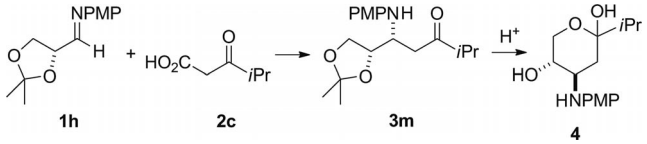


Figure 1. Felkin–Anh models.

To demonstrate the utility of this transformation in the total synthesis of carbohydrate derivatives, protected *syn*-configured Mannich adduct **3m** was converted into 2-deoxy-3-aminoketose **4** (Scheme 6).



Scheme 6. Synthesis of 2-deoxy-3-aminoketoses.

This can be easily accomplished by deprotection of acetal *syn*-**3m** followed by spontaneous cyclization to give compound **4**. NMR spectroscopic experiments revealed the existence of an acyclic and a cyclic pyranoid structure in about a 1:1 ratio. For structural elucidation, see the Supporting Information.[13]

Conclusions

In conclusion, we have described the catalyst-free decarboxylative Mannich reaction of PMP-protected imines with β-keto acids. Furthermore, insight into the mechanism and configurative course of this reaction is given. Important is the existence of a retro-Michael process, which requires reaction and workup conditions to isolate the products in high yields with high stereoselectivities. This operationally simple protocol provides very easy access to aminohydroxylated carbohydrate derivatives with a defined configuration. Further investigations of an asymmetric and catalytic version of this transformation are under way.

Experimental Section

General Procedure: A solution of isopropylidene-protected D-glyceraldehyde (**1l**; 348 mg, 2.68 mmol) in dichloromethane (40 mL) was cooled to 0 °C. After the successive addition of $MgSO_4$ (5.0 g) and *p*-anisidine (300 mg, 2.41 mmol, 0.9 equiv.), the mixture was stirred for 30–60 min. The formation of the imine was monitored by TLC. After full conversion of the aldehyde into the corresponding imine, the suspension was filtered, cooled to –15 °C, and benzoyl acetic acid (**2a**; 220 mg, 1.34 mmol) was added to the filtrate. The reaction mixture was stirred for 2–3 h while monitoring the reaction by TLC. After the reaction was complete, the reaction mixture was quenched at –15 °C and extracted with saturated aqueous NH_4Cl solution (3×). The organic layer was separated, dried (Na_2SO_4), and filtered, and the solvent was removed in vacuo. The residue was purified by column chromatography (hexane/ethyl acetate, 95:5) to yield product **3l** (702 mg, 82%, *antilsyn* = 85:15).

Supporting Information (see footnote on the first page of this article): Full experimental procedures, characterization data, and copies of the $^1H/^{13}C$ NMR spectra of all new compounds.

Acknowledgments

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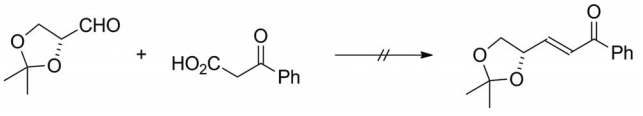
[15] With the sole exception of ref.[8], Ricci and co-worker have used cyclohexylcarboxaldehyde and hydrocinnamaldehyde in these transformations. The corresponding Mannich products were isolated with moderate enantioselectivities.
[16] This assumption was supported by the following observations. The corresponding α,β-unsaturated ketones were detected to a more or less substantial extent. Furthermore, reactions of the corresponding aldehydes with **2a** do not yield α,β-unsaturated ketones under these conditions.



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