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Amine-catalyzed cascade reactions of ketoses with 1,3-dicarbonyl compounds

Celin Richter, Benjamin Voigt and Rainer Mahrwald*

An amine-catalyzed cascade reaction of ketoses with 1,3-dicarbonyl compounds is described. Several highly chemoselective reactions are operating in this novel cascade. The operationally simple protocol allows a stereoselective access to optically active carbon chain elongated ketoses.

Due to their biological activity chain elongated carbohydrates – so called higher carbohydrates - have gained considerable importance in biochemistry, medicinal chemistry and pharmacology. The synthesis of defined configured elongated carbohydrates remains a challenge in carbohydrate chemistry. Although many methods exist to synthesize higher carbohydrates they are hampered by low yields, poor stereoselectivity and at the end by problematic isolation processes.1

Recently we have reported several highly selective organocatalyzed cascade reactions to access elongated carbohydrates. Based on an amine-catalyzed Knoevenagel-reaction 1,3-dicarbonyl compounds were successfully reacted with unprotected and unactivated aldoses in operationally simple protocols.2 In conjunction with these processes we envisioned reactions of 1,3-dicarbonyl compounds with unprotected ketoses. Initial reactions of acetylacetone with acetone or several methylketones in the presence of amines failed, no reactions were observed. Surprisingly, a clear and nearly quantitative reaction was observed when using with hydroxyacetone instead of acetone in these reactions (Scheme 1, 3a: 83%). This result indicates an extremely strong supporting character of the hydroxyl groups during this reaction. The reaction is performed at room temperature for approximately 24 h and is catalyzed by tertiary amines. After an intensive optimization water emerged as the best solvent. DBU was used as the optimal catalyst (20 mol%).

Scheme 1 Amine-catalyzed cascade reaction of acetylacetone and hydroxyacetone.

The acetate 3a is a product of an amine-catalyzed intramolecular cascade reaction. An initial Knoevenagel addition is followed by the formation of a cyclic hemiketal. A subsequent intramolecular retroaldol type reaction generates the acetate 3a with high yields. Support for this suggested mechanism is given by several similar observations reported in the literature.3,4

In a first series we tested the application and scope of 1,3-dicarbonyl compounds. To this end we reacted hydroxyacetone with several different 1,3-dicarbonyl compounds. The results of this investigation are summarized in Scheme 2.

Scheme 2 Amine-catalyzed reactions of hydroxyacetone with 1,3-dicarbonyl compounds; reaction conditions: 20 mol% DBU, rt, water 72 h.

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1 Humboldt-University, Institute of Chemistry, Brook-Taylor Str. 2, 12489 Berlin, Germany, rainer.mahrwald@rz.hu-berlin.de
2 Address here.
3 Address here.
4 Footnotes relating to the title and/or authors should appear here. Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x
The yields of products depend mainly on the bulkiness of substituents R<sup>1</sup> and R<sup>2</sup>. High yields were observed when used with acetylacetone, whereas by deployment of dibenzoylmethane 2c the expected benzoate 3c was isolated with only low yields (8%). In reactions of hydroxyacetone with diphenyl-pentane-trione 2d the expected benzoate 3d was isolated with moderate yields (29%).

With unsymmetrical benzoylacetone 2b a mixture of acetate 3b and benzoate 4b was isolated with an overall yield of 64%.

Based on these results we tested the application and scope of several hydroxylated ketones. To this end we reacted dihydroxyacetone with acetylacetone and benzoylacetone. A clear reaction was observed when used with benzoylacetone 2b. The acetate 6b was isolated with 75% yield. The corresponding benzoate was detected to only a small extent (yield: < 3%). On the other hand, using acetylacetone in reactions with dihydroxyacetone a mixture of acyclic acetate 6a and the corresponding cyclic acetates 7a and 7b (anomers) was isolated in an overall yield of 72%. A homogenous reaction product is obtained, when the crude reaction mixture was acetylated with acetic anhydride and pyridine. Under these conditions the diacetate of 6a was isolated as the only product with 72% yield.

To get more information about this new cascade transformation we reacted L-erythrulose 8 with acetylacetone. Again a clear reaction was observed under the described conditions. The unusually substituted ketose 9 was isolated as a single stereoisomer with 22% yield (Scheme 4).

The exceptionally high chemo- as well as stereoselectivity observed in this reaction based on several highly selective reactions which are operating in this cascade. The high chemoselectivity can be explained by the following considerations depicted in Scheme 5. The two primary alcohol functionalities of the intermediate structure A formed by the Knoevenagel addition can cyclize to either of the hemiketals B or C. Retroaldol type reaction of hemiketal B yield furanoid structures of type D, which were not observed in these reactions. The formation of hemiketal C gives access to pyranoid structures of type E, which was the only product detected in these reactions (Scheme 5). Further support for these considerations is given by the failed reaction of acetylacetone with β-hydroxybutanone instead of hydroxyacetone. No reaction was observed with this substrate under the discussed conditions.
Amine-catalyzed chain elongation of ketones with acetylacetone.

The preferred formation of the hemiketal with the primary hydroxyl group yields the intermediate syn-H (as discussed above). A subsequent retroaldol type reaction yields the acetate syn-K. Again the preferred cyclization with the primary hydroxyl group gives an access to the product 9, which was detected as the only one product in these reactions (Scheme 6).

Scheme 6 Stereochimical path of the cascade reaction of L-erythrulose and acetylacetone.

In a last series we reacted several unprotected ketoses with acetylacetone to demonstrate the utility of this operationally simple cascade reaction. Longer reaction times (up to 8 days) and equimolar amounts of DBU proved necessary in these transformations. The products were isolated again with extreme high degrees of stereoselectivities. In all cases only one single stereoisomer was detected. For a better isolation as well as structure elucidation the products were converted into their corresponding acetates 13-18. When used with an excess of acetic anhydride and pyridine (3 equivalent acetic anhydride and pyridine) the acyclic forms of the chain elongated carbohydrates were obtained. Interestingly, the acyclic structure of acetate 15 (from D-tagatose) is not accessible by this procedure. Even disaccharides can be used as substrates in these transformations. Reactions of

acetylacetone with isomaltoolose (1,6-D-glucopyranosyl-D-fructose) gives an access to the chain elongated methyl ketone 18 (Scheme 7). When used with disaccharides like lactulose or maltulose, no reactions were observed. These 1,4-linked disaccharides cannot form the terminal pyranoid hemiketal structure (lactulose: 1,4-galactopyranosyl-D-fructose, maltulose: 1,4-glucopyranosyl-D-fructose). Thus, these results support the proposed reaction mechanism depicted in Scheme 6.

Scheme 7 Amine-catalyzed chain-elongation of ketoses with acetylacetone; reaction conditions: 1 equ. DBU, rt, water, 8 d.

These novel amine-catalyzed transformations have not been reported in the literature so far. A similar although intermolecular process was reported by Lubineau et al. The authors described a direct cascade reaction of unprotected carbohydrates with acetylacetone in aqueous alkali media. By application of this method an access to different mixtures of furanoid- and pyranoid-structures of α- and β-configured C-glycosides were obtained. This Knoevenagel / Michael / retroaldol cascade is carried out at high temperature (60 - 90°C) and is associated with the loss of a C2-fragment of the starting 1,3-dicarbonyl component (when used with acetylacetone). This methodology has been used in several transformations to synthesize configurative required C-glycosides. For an overview of this development see reference 9.

In summary we have developed an amine-catalyzed cascade reaction of ketoses with 1,3-dicarbonyl compounds. This operationally simple protocol allows an access to carbon-chain elongated ketoses. High stereoselectivities were observed in these novel reactions – only a single stereoisomer was detected in these transformations. Further investigations of this new reaction are under way.

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Notes and references

4 Most of these authors describe this step as a retro-Claissen process. Since the Claisen process is a reaction between two carboxylic esters, we prefer to use the term retroaldol type reaction. In addition, the intramolecular version of Claissen reaction is called Dieckmann condensation.
5 See Supporting informations


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**Diagram:**

1. DBU, water, rt
2. excess Ac₂O, pyridine

38% $\alpha >$50%