Tetrahedron 72 (2016) 592–598

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A comprehensive investigation and optimisation on the proteinogenic amino acid catalysed homo aldol condensation

Karoline A. Ostrowski, Dominik Lichte, Moritz Stuck, Andreas J. Vorholt *

Department of Bio- and Chemical Engineering, TU Dortmund, Emil-Figgestr. 66, 44227 Dortmund, Germany

ARTICLE INFO

Article history:
Received 27 August 2015
Received in revised form 25 November 2015
Accepted 30 November 2015
Available online 5 December 2015

Keywords:
Aldol condensation
Aldehyde
Organocatalysis
Amino acid

ABSTRACT

A systematic investigation regarding the application of catalytic amounts of all 20 proteinogenic amino acids in the homo aldol condensation of aldehydes is described obtaining excellent yields of the desired α,β-unsaturated aldehyde. These investigations proved the basic amino acids, lysine and arginine, are effective as organocatalysts, if comparably low concentrations are applied. Through the stepwise and systematic condition alteration, the reaction could be optimised and successfully transferred to other substrates with longer, branched or functionalised alkyl chains. The highest yields are observed with tryptophan as organocatalyst in only 1 h reaction time with TONs of up to 27.

1. Introduction

The aldol reaction is a C–C bond forming reaction between aldehydes and/or ketones and was already described in the 19th century.[1] The aldol condensation of aldehydes is a very effective tool, gaining α,β-unsaturated aldehydes, which can be used in further organic reactions, especially in the dienamine catalysis[2] or in tandem catalyses.[3]

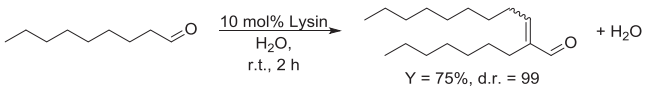
In industry, the homo aldol condensation (HAC) is an essential reaction step to form the precursor 2-ethylhex-2-enal from butanal, which is used in the synthesis of different plasticisers, for example, DEHP=bis(2-ethylhexyl)phthalate. The latter has the highest market share of 54% regarding the global plasticiser consumption.[4] Therein, butanal undergoes a base catalysed homo aldol condensation to 2-ethylhex-2-enal in a sodium hydroxide solution.

Besides the base catalysed homo aldol condensation of aldehydes in industry,[5] further investigations and catalyst developments were made with organic metal salts (2,4,6-trimethylphenoxymagnesium bromide),[6] transition metal complexes,[7] electrolysis,[8] acids,[9] amines,[10] amine/acid mixtures[11] and immobilised amines on silica.[12]

Amino acids occupy a special position in organocatalysis having an amine and an acid function in their molecular structure. An advantage of applying amino acids is given by their ubiquitous existence being precursors of proteins.[13] They are easily accessible and have no GHS hazard statements. Therefore, they can be described as green reagents, if applied in chemical reactions.[14]

The first amino acid catalysed HAC was carried out with alanine as catalyst and acetaldehyde as substrate.[15] Later, only scattered examples were dealing with the amino acid catalysed HAC of aldehydes.[16] The multiple homo aldol condensation of acetaldehyde with proline led to 2,4-hexadienal, which was not investigated intensively and was formed in 5% yield after two aldol condensation steps with 3 equiv of acetaldehyde.[16a] A kinetic study with arginine, glycine, serine, alanine and proline[16b,c] revealed a complex kinetic behaviour, if arginine was used as catalyst in the HAC of acetaldehyde, which can form higher aldol condensation products. Therein, large rate constants were observed with a maximum at small catalyst concentrations, due to the transition from a first order reaction into a second order reaction. The second order reaction is limiting the aldol condensation.

An environmentally friendly, green (water as solvent or no solvent) and transferable method to other substrates was established, wherein 10 mol % of lysine catalyses the HAC of aldehydes with unfunctionalised alkyl chains up to C_9-aldehydes in moderate to good yields of 46–75%. The application of arginine as catalyst was not pursued any further in this case, since only a yield of 24% was obtained. Therein, a turnover number (TON) up to 7.5 and a turnover frequency (TOF) up to 3.75 h^{-1} was achieved for unfunctionalised aldehydes[16d] (Scheme 1).



Scheme 1. Established homo aldol condensation (HAC).[16d]

* Corresponding author. Tel.: +49 231 755 2313; fax: +49 231 755 2311; e-mail address: andreas.vorholt@bci.tu-dortmund.de (A.J. Vorholt).

http://dx.doi.org/10.1016/j.tet.2015.11.069
0040-4020/

Amino acids can be used in the cross aldol condensation, which is described by an intermolecular aldol condensation between different substrates. With proline–triethylamine as catalyst, a ketone C-glycoside undergoes the aldol condensation with different ketones and aromatic aldehydes.[17]

Furthermore, an aldol condensation allows the generation of a stereo centre depending on the initial substrates. The application of enantiopure organocatalysts in an intramolecular aldol condensation enables asymmetric organocatalyses leading to products with high enantiomeric excesses. The first examples were given with steroid cyclodione backbones as substrates and amino acids as catalysts. Therein, L-proline, L-alanine and L-phenylalanine were applied as organocatalysts and $HClO_4$ as additive simulating the dehydration.[18] Later, this reaction was extended to other product derivatives and up to 14 proteinogenic amino acids were compared with each other regarding their catalytic activities, reaction times, yields and enantiomeric excesses in the intramolecular aldol condensation. The 'organocatalyst' was used equimolar to the substrate with $HClO_4$ as additive.[19]

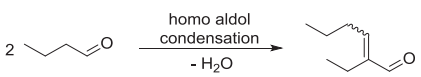
In the beginning of this millennium, first investigations towards the asymmetric cross aldol addition with amino acids have been made. The cross aldol addition of acetone with aldehydes is catalysed with 30 mol % L-proline[20] in DMSO achieving very high yields and enantiomeric excess. This protocol was extended to α-unsubstituted substrates as aldehydes.[21] The cross aldol addition between aldehydes in DMF with 10 mol % L-proline at low temperatures led to comparable results.[22] Therefore, proline has an exceptional position in organocatalysis, since a lot of organocatalysts are based on the five-membered ring structure of proline.[23]

The cross aldol addition between ketones and aldehydes was extended to primary amino acids[24] using 20 mol % catalyst, for example, isoleucine, with long reaction times of 7 d[25] or 30 mol % catalyst, for example, valine, with very high yields and also long reaction times of 3 d.[26]

In this publication we fill the gap by giving a comprehensive overview on the reactivity of all 20 proteinogenic amino acids at same reaction conditions in the homo aldol condensation (HAC) of aldehydes. This systematic investigation enables a direct comparison between each amino acid, which was not possible yet, due to a scattered data set.[16] The model substrate butanal was chosen as linear alkyl aldehyde with an industrial background being an important precursor for plasticisers. From this data, we established a general method for the homo aldol condensation with different substrates using simple, green, mild and environmentally friendly conditions. Short reaction times (down to 1 h), amino acids as green catalysts with low catalyst loading (down to 3.33 mol %) and ethanol as a green solvent, which can be removed easily, were employed. Excellent yields, with high TONs and TOFs, were obtained if compared to other amino acid catalysed aldol reactions, which needed long reaction times in questionable solvents, for example, DMF.[27]

2. Results and discussion

We set our focus on the homo aldol condensation of unmodified aldehydes as starting material (Scheme 2). In all experiments the *trans* aldol condensate of butanal was the major product with a *trans/cis* ratio of >20.



Scheme 2. Homo aldol condensation of butanal.

For a better overview and a separate assessment we divide the investigated 20 proteinogenic amino acids in five groups, which are displayed in Fig. 1. We used them as drawn, since their L-form is easily commercially available.

2.1. Systematic investigation of all 20 amino acids

We wanted to use simple conditions with only a few reagents, which can be easily removed and are non-toxic. The established reaction system should be transferable to other substrates, wherefore we used ethanol to ensure a homogenous solution of polar and non-polar reagents. Furthermore, we are already thinking about future developments using this homo aldol condensation as a tool for more complex conversions in, for example, tandem catalyses,[28] wherefore a simple reaction system is desirable for having more changing options.

In the first part of our investigation, different catalytic amounts between 1.67 and 20 mol % of each amino acid were employed in the homo aldol condensation of butanal for a better comparability regarding their catalytic activity as organocatalysts by not using them in stoichiometric amounts.

Aromatic amino acids are characterised by aromatic groups in their side chain. The results of applying aromatic amino acids, Group II (Fig. 1), is given in Fig. 2 displaying observed yields over catalyst concentration. Tryptophan (indol side chain) and phenylalanine (phenyl side chain) already led to excellent yields, if only 3.33 mol % were used. This is a great catalyst amount, since other publications regarding the amino acid catalysed aldol reaction are dealing with higher catalyst concentrations of 20–30 mol %. A quantitative yield was observed, if 20 mol % tryptophan was used. Nevertheless, it is quite astonishing why no conversion could be observed, if tyrosine was applied. The only difference to phenylalanine is given by the phenol group. Presumably, tyrosine is active at higher concentrations (from approx. 30 mol %) needing higher reaction times. This is strengthened due to the investigation regarding the cross aldol addition of ketones with aldehydes. While 20 mol % tyrosine gave only traces of the product after 7 d,[25] a moderate yield of the cross aldol product was obtained after 53 h by applying 30 mol % of tyrosine.[26b]

An interesting trend is given in the aldol catalysed reaction with basic amino acids from Group V (Fig. 1) displayed in Fig. 3. These amino acids have further basic functionalities in their side chain. Experiments with histidine (imidazole side chain) as catalyst showed a general trend: the more catalyst is applied, the more yield can be observed with 29% yield at a concentration of 20 mol % catalyst. On the other hand, lysine (primary amino side chain) and arginine (guanidine side chain) as catalysts led to a maximum regarding the obtained yield, which resulted in high yields at low catalyst amounts. Lysine has its maximum at 3.33 mol % giving 82% yield and arginine at 6.67 mol % giving 85% yield. The results of arginine in the homo aldol condensation of butanal are in good agreement with the kinetic studies of Córdova and co-workers regarding the homo aldol condensation of acetaldehyde.[16b,c] Therein, the rate constants are varying with the concentration of the amino acid arginine. At low concentrations the rate constant is described by the first order, which is increasing linearly with the catalyst concentration and limited by the enamine formation. At higher concentrations, the reaction is described by the second order, which is limiting the overall reaction speed leading to lower yields controlled by the C–C bond formation. With arginine as catalyst, the transition from the first to the second order was reached at quite low catalyst amounts. In this publication, we could proof the same tendency with lysine as organocatalyst and with the application of longer chain aldehydes.