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Original Article

Use of natural aminoacids as efficient green catalyst in the synthesis of thiosemicarbazones

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ABSTRACT

In an effort to find improved conditions for the synthesis of medicinally relevant thiosemicarbazones basing our approach on green chemistry approach, we used ten natural alpha aminoacids as nucleophilic catalysts.We therefore hypothetized that aminoacid acid being amphoteric reagent, should be able to boost a reaction submitted to general acid-base catalysis. Using cyclohexanone 4-phenylthiosemicarbazone as target compound for our benchmark reaction, we were able to demonstrate the validity of our hypothesis. A plot of "hydrophobicity/lipophilicity" balance as reflected by logP and the net actual yield does not show any significant correlation, however it is remarkable to note that while L-phenylalanine shows opposite behavior in water (94%) and methanol (24%), glycine – the most concise alpha-amino-acid – performs equally very well in both solvents (95% and 90%, respectively). These green catalysts and specially glycine may be useful in the elaboration of a compound library.

Keywords: Natural alpha-aminoacids - Green efficient catalyst- Nucleophilic catalysis-Thiosemicarbazones

INTRODUCTION

Many enzymes behave as exceptional asymmetric catalysts, performing reactions very effectively and often very selectively [1-4]. In an effort to imitate enzymatic efficiencies, chemists have dived into the natural chiral tool, transforming amino acids into numerous chiral auxiliaries, catalysts, and ligands. In most representative examples, the alpha-amino acid is used purely as a source of chirality and both the amine and acid functionality are altered or even eliminated [5-6].Unmodified amino acids and peptides have been used as catalysts by far much less frequently [7]. Hajos and Wiechert reported the use of proline as a catalyst for the Robinson annellation as early as 1970 [8-9].Wiechert and co-workers indeed at Schering AG reported direct conversion to the target enone. A catalytic quantity of (S)-proline(3 mol%) was sufficient to mediate the aldol cyclization yielding the bicyclic ketol in virtually 100% yield along with a 93% enantiomeric excess.

The idea that a short peptide or even a single amino-acid would be able to function as a pared-down version of an enzyme was first generally met with considerable skepticism in the community of synthetic organic chemists. However, behind enzymatic tactics one can count nucleophilic catalysis, which has been implemented already in the 1960's with great success by Jencks *et al.* [10-12], using rather common laboratory reagents as simple as anilinium chloride. When this approach is employed in conjunction with anchimeric assistance, such as that provided by the potent alpha-effect, a miniaturized version of a molecular motoris produced, which is able to boost a plethora of elementary reactions including the synthesis of thiosemicarbazones, as amply documented by Kassehin *et al.*[13-14]. A key demonstration of this synergetic action using both nucleophic and anchimeric assistance is delivered by sulfanilic acid or anthranilic acid, for instances. Along this line, we recently became interested in using such an approach using water as solvent [15-16]. This

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challenging project was first undertaken using a highly water-soluble catalyst such as sulfamic acid. In order now to render this process even more « green », we explored this feasibility of using common alpha-aminoacids as nucleophic catalysts in the hope that these synthons would also provide an immediate alpha-effect. In this short paper, we summarize our endeavors along this axis.

MATERIALS AND METHODS

Experimental section

General Procedure: Melting points were determined using an Electrothermal melting point apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded at ambient temperature on a AVANCE II BRUKER 400 UltraShield TM spectrometer. Compounds were dissolved in $CDCl_3$ or DMSO-d6 to obtain a 0.1 molar solution. Chemical shifts are expressed in the δ scale with TMS (tetramethylsilane) as internal standard. Thin layer chromatography (TLC) analyses were performed on Merck TLC plates (silica gel, 60 F 254, E. Merck, Darmstadt, ref. 5735). For TLC, all the compounds reported were routinely checked in standard solvent, *i. e.* chloroforme/dichloromethane (4:5, *v/v*). The reverse-phase thin layer chromatography conditions were: HPTLC plates RP-18 F-254 S (Merck), methanol: water (75/25, *v/v*). All compounds reported were found homogenous under such TLC and HPLC conditions.

All reagents were purchased from Acros Organics, Janssen Chimica and Aldrich. All solvents were of the ACS reagent grade (Aldrich). The following procedures are representative of all the synthesis of compounds listed in Tables 1.

Synthesis of cyclohexanone 4-phenylthiosemicarbazone and evaluation of the catalytic efficiency of our aminoacids: Each aminoacid is tested both in methanol and distilled water. Reactions were run in a general rule at 65°C in methanol (50ml) and 100°C in water (50ml) at reflux when the mixture is magnetically stirred. Under those conditions, 500mg of aminoacid is used as catalyst in reaction between stœchiometric quantity of 4-phenylthiosemicarbazide (1.67g, 10mmol) and cyclohexcanone (0.98 g, 10mmol) for 4h, rapidly cooled at 2°C.In methanol, cristals were washed with a diluted solution of hydrochloric acid (0.01 N) to dissolve eventual residue of aminoacid.When reactions are performed in water, cristals form such a rubber which need to be dissolved in ethanol to give solid cristals. **Mp:** 186-188°C (unaffected after recrystallization from methanol), **^{1}H-RMN** ($CDCl_3$) : δ (ppm) : 9.3 (s, 1H, -CSNH-Ph); 8.6 (s, 1H, =NNH-); 7.6 (s, 2H, ortho ArH); 7.3 (s, 2H, meta ArH); 7.2 (s, 1H, para ArH) ; 2.4 (s, 4H, alicyclic H); 1.7 (s, 6H, alicyclic H)

^{13}C-RMN ($CDCl_3$): δ (ppm) : 137.4 (C=S) ; 154.45 (C=N) ; 136.52 (*ipso* C-aromatic); 127.21(*meta* C-aromatic); 124.31 (*para* C-aromatic); 122.61; 33.91; 25.53; 25.37; 24.39; 23.92(C-alicyclic)

RESULTS

In our setting up the experimental planning, we deliberately decided to explore two sets of conditions: a first series of experiments using obviously water and a second set in methanol, a conventional organic solvent which behaves very efficiently the condensation of thiosemicarbazides with aldehydes and ketones. Cyclohexanone and 4-phenylthiosemicarbazide were selected to perform our benchmark reaction (Scheme 1). The latter was chosen because this synthon is a major protagonist in our design of a trypanocidal pharmacophore and also in order to test the value of a hydrophobic effect, which is known as a major reaction-promoting factor in an aqueous environment. The panel of the elected alpha-aminoacids was limited to a mere dozen representatives and spanned over a wide range of side-chains to test likewise the impact of logP and steric effect. As arylthiosemicarbazones derivatives are achiral compounds (exhibiting however *syn* and *anti*-configurations), the chirality of the selected amino-acids was considered as unimportant for our goal.

Table 1. List of intervening alpha-aminoacids as catalyst, corresponding logP values and yields, both in water and methanol

Exp #	Aminoacids		LogP	% yield	
				Water	Methanol
1	Gly	G	-1.39	95	90
2	Pro	P	-0.4	75	36
3	Met	M	-0.67	73	66
4	Leu	L	-0.34	71	81
5	Glu	E	-1.39	65	94
6	Asp	D	-1.67	61	71
7	Trp	W	-0.32	58	50
8	Cys	C	-0.92	31	60
9	Ser	S	-1.75	27	49
10	Phe	F	0.78	23	54

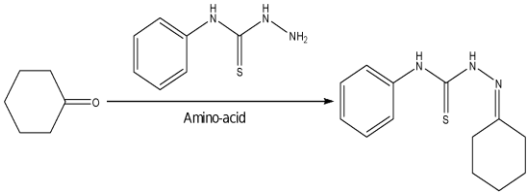
DISCUSSION

A very first rough inspection of the results listed in Table 1 shows at first a contrasted landscape in that each individual aminoacid has got its own specific

behavior with in general a "dichotomic" attitude towards either water or methanol. It is worth noting that the two solvents have indeed a profound impact: for example, L-phenylalanine (Exp #10) provides a modest 23% yield in water while reaches a comfortable 94%! A plot of LogP versus yield (shown in Scheme 4) sheds to some extent light regarding such demeanor.

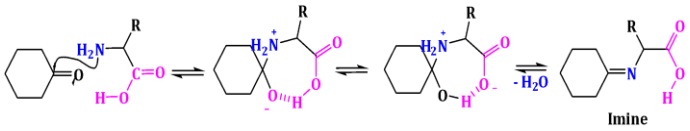
Indeed, while obviously we did not expect a straightforward regular monotonous correlation between "hydrophobicity/lipophilicity" balance and the net end result of each individual synthesis (actual yield), we were eager to see at least some trend but none appears: there is no obvious correlation. In a sense, the behavior seems even to be chaotic at first sight. However, a peculiar result is appealing, it is that of L-phenylalanine (exp. #10). As already noted, this most lipophilic term offers the best yield in absolute in methanol (a solvent less hydrophilic than water) and the tendency is fully invested in plain water.

A most striking result is that of glycine: glycine offers a very good yield both in water and methanol. While this was somewhat expected owing to the the fairly good water solubility of glycine. However, this might constitute a drawback as the 4-phenylthiosemicarbazide species is highly lipophilic (logP = 1.45), which might complicate the mandatory aggregation process to form the final product. There is obviously a high degree of complexity in the yield. One way or another, the cristallinity and solubility concur in particular to the final recovery of the rough material at the end of the process, and altogether to the final yield.

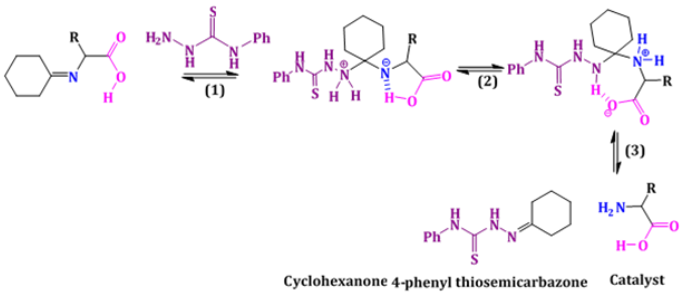


Scheme 1. Condensation of cyclohexanone with 4-phenylthiosemicarbazide (Benchmark Reaction)

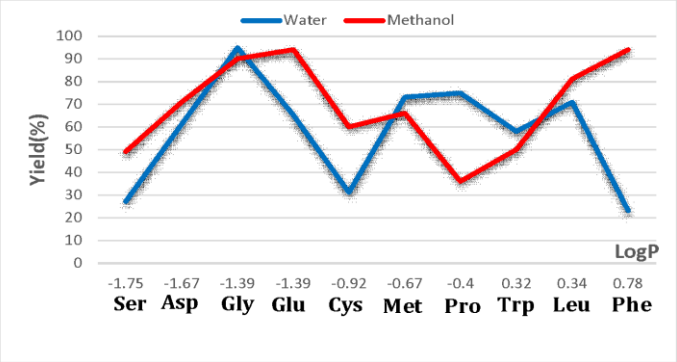
In an effort to somewhat clarify the above point, we designed a detailed reaction mechanism involving the covalent nucleophilic catalysis offered by alpha-aminoacids. This mechanism proposal is shown in the Scheme 2. The scenario can be viewed as the following: initially, a covalent link is established between cyclohexanone and the alpha-aminoacid under the form of an imine function; subsequently, the nucleophilic attack of the thiosemicarbazide species on the intermediate Shiff base results in the final thiosemicarbazone. As it can be seen by inspecting Scheme 3, this last transformation is assisted by the cooperation of the carboxylic acid moiety establishing an important intra-molecular hydrogen bond. The higher segmental mobility of glycine compared to other amino-acids is likely to represent an advantage in establishing the intramolecular hydrogen bond.



Scheme 2. Formation of intermediate imine



Scheme 3. : Thiosemicarbazone formation and catalyst regeneration



Scheme 4. : A plot of Log P versus yield

CONCLUSION

This paper explores the catalytic behavior of some ten alpha-amino-acids in the context of nucleophilic catalysis. These terms were selected to explore a sufficient range of lipophilicity. While a plot of "hydrophobicity/lipophilicity" balance as reflected by logP and the net actual yield does not show any correlation, it is remarkable to notice that while L-phenylalanine shows opposite behavior in water (94%) and methanol (24%), glycine – the most concise alpha-amino-acid – performs equally very well in both solvents (95% and 90%, respectively). A mechanism proposal allows to provide a rational basis for the high performance of glycine in both solvents.

Conflicts of Interest: The authors declare no competing interests.

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