Carbohydrate Research 389 (2014) 50–56

Contents lists available at ScienceDirect

Carbohydrate Research

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

Preparation of new type of organocatalysts having a carbohydrate scaffold ☆

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ARTICLE INFO

Article history:
Received 18 September 2013
Received in revised form 5 December 2013
Accepted 6 December 2013
Available online 31 January 2014

Keywords:
Bifunctional organocatalysts
Thiourea–amine type catalysts
Carbohydrate scaffold
Michael addition

ABSTRACT

The synthesis of nine new, bifunctional organocatalysts having carbohydrate scaffolds has been accomplished. In these catalysts both of the catalytic amino and thiourea functions are directly attached to a carbohydrate core. The activities of the newly prepared catalysts were tested in a Michael addition.

1. Introduction

In recent years, organocatalysis, the acceleration of various chemical reactions by catalytic amounts of organic molecules, emerged as one of the rapidly developing areas of organic chemistry.[1] With the aid of organocatalysis a large number of chemical reactions could then be performed in stereoselective manner. Particularly great attention has been paid to the development of new, efficient catalysts. A special class of these catalysts is the so called bifunctional organocatalysts in which H-bond donor and Lewis base functionalities are combined in a single asymmetric molecular scaffold. Several different bifunctional catalysts have been designed, synthesized, and tested. Most of these molecules have a combination of thiourea and amine groups as catalytic functionalities which are presented on a single chemical entity. The very first example of these catalysts has been described by Takemoto[2] in this molecule the catalytic centers are connected to a cyclohexane scaffold (compound **A**, Fig. 1). Later some different chiral scaffolds such as binaphtyl[3] or cinchona alkaloids[4] (compounds **B** and **C**, Fig. 1) were investigated and the catalysts based on these scaffolds showed promising results in asymmetric synthesis, particularly, in catalyzing Michael and aza-Henry reactions.

To date only a limited number of scaffolds have been used to synthesize bifunctional organocatalysts. Monosaccharides as commercially available, inexpensive molecules of diverse chirality can be considered as obvious candidates for chiral scaffolds. Organocatalysts based on a D-glucosamine scaffold carrying urea and imine as catalytic functionalities were described by Kunz in 2007.[5] Enantioselective Strecker and Mannich reactions were performed using these catalysts.[5]

Thiourea–amine type bifunctional organocatalysts containing a monosaccharide unit were prepared and their catalytic activities were investigated recently.[6] In these cases, the carbohydrate moiety was located on the periphery of the catalyst molecule and not in-between the two catalytic centers (compounds **D** and **E**, Fig. 2). To our knowledge there is only one example in the literature where a monosaccharide residue was used as a scaffold to connect thiourea and amine functionalities thereby defining the selectivity of the catalyzed reaction (compound **F**, Fig. 2).[7] In this study the use of urea derivatives, however, provided higher yields and selectivity than the corresponding thiourea derivative.[7] Up to now, there are no examples of bifunctional thiourea-amine organocatalysts where the core scaffold is a monosaccharide unit and the use of the catalyst results in high yield and high enantioselectivity catalyzing a chemical reaction.

We have initiated the preparation of new—bifunctional—thiourea–amine catalysts starting from D-glucose. In these molecules the two catalytic centers are connected with a carbohydrate residue. Using these catalysts the enantioselectivity of the catalyzed reaction will be influenced only by the carbohydrate moiety. The possible effect arising from carbohydrate chirality

☆ Presented at the 17th European Carbohydrate Symposium, Tel-Aviv, Israel, July 7–11, 2013, as poster July 7th P1.

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http://dx.doi.org/10.1016/j.carres.2013.12.026
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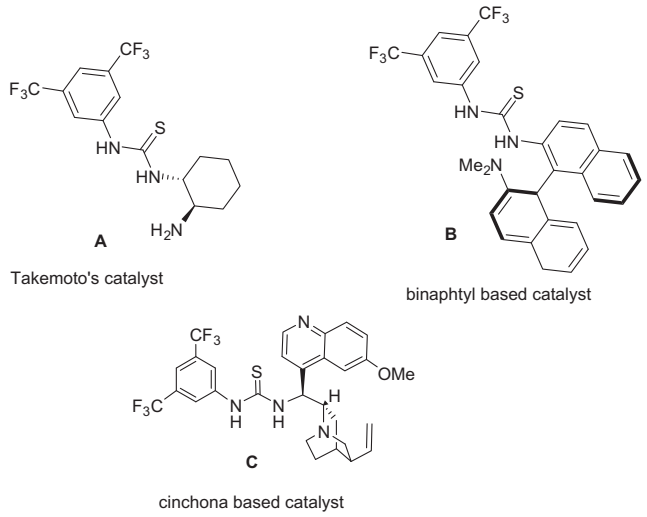


Figure 1. Representative examples of bifunctional organocatalysts.

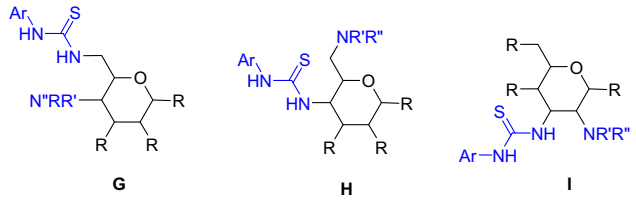
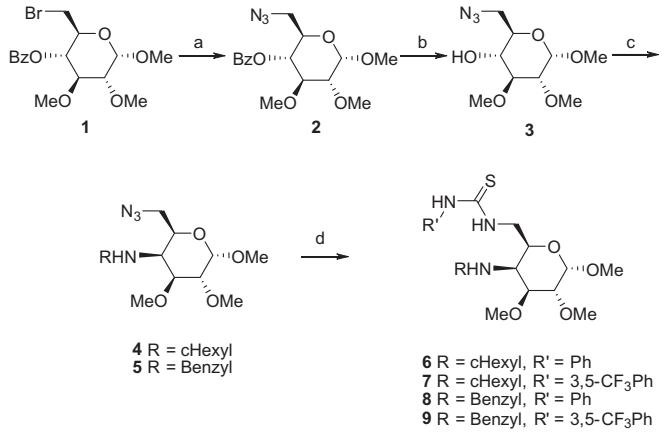


Figure 3. General structures of the targeted organocatalysts.



Scheme 1. Reagents and conditions: (a) NaN_3, DMF, 70 °C, 6 h, 94%; (b) NaOMe, MeOH, rt, 1 h, 80%; (c) (i) Tf_2O, pyridine, CH_2Cl_2, 0 °C, 2 h, (ii) amine, DMF, 45 °C, 10 h, 50–70%; (d) (i) propanedithiol, MeOH, rt, 48 h (**6** and **7**), or PPh_3, H_2O, THF, 80 °C, (**8** and **9**), (ii) isothiocyanate, MeOH, rt, 4 h, 30–50%.

was taken into consideration in the design, by placing the catalytic groups at various positions of the carbohydrate scaffold. Thus the synthesis of molecules having the amino and thioureido groups in positions 4 and 6 (**G** and **H**, Fig. 3), or in positions 2 and 3 (**I**, Fig. 3), respectively, was planned. The catalytic groups are distanced by three carbon–carbon bonds in the first case, whereas they are separated by two C–C bonds in the latter. In the case of **G** and **H**, the synthetic route was designed to afford both the 4-amino-6-thioureido (**G**) and the 6-amino-4-thioureido (**H**) derivatives from the same starting material.

2. Results and discussion

For the preparation of the targeted catalysts having the catalytic groups in the 4 and 6 positions, methyl 4-*O*-benzoyl-6-bromo-6-deoxy-2,3-di-*O*-methyl-α-D-glucopyranoside[8] (**1**, Scheme 1) was selected as starting material which is easily available from commercial methyl α-D-glucopyranoside in a few steps in high yields.

The synthesis of the 4-amino-6-thioureido type compounds started with the preparation of the 6-azido derivative (**2**). Reaction of compound **1** with sodium azide in DMF at elevated temperature resulted in the formation of the 6-azido derivative (→**2**, Scheme 1) in almost quantitative yield. The benzoate protecting group from compound **2** was removed with NaOMe in MeOH affording derivative **3** in high yield. 4-Amino derivatives were prepared by S_N2 replacement with primary amines via the 4-*O*-triflate in a one-pot manner. Treatment of **3** with triflic anhydride in CH_2Cl_2 in the presence of pyridine at 0 °C afforded the crude 4-*O*-triflate, which was reacted directly with cyclohexylamine or benzylamine in the solvent mixture of CH_2Cl_2/DMF to yield the 4-cyclohexylamino (**4**) and 4-benzylamino (**5**) derivatives, respectively. The azido function of compound **4** was reduced to amine with propanedithiol in methanol[9] and the 6-amino derivative was reacted with phenyl isothiocyanate (**4** → **6**) or 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**4** → **7**) affording the bifunctional organocatalyst candidates.

For the reduction of azido function of compound **5**, the use of triphenylphosphine was found more advantageous, as reduction with propanedithiol resulted in impurities which were difficult to separate from the amino derivative. The amino derivative of compound **5** was reacted with phenyl isothiocyanate or 3,5-bis(trifluoromethyl)phenyl isothiocyanate affording derivatives **8** and **9**, respectively.

For the preparation of the 6-amino-4-thioureido type target molecule nucleophilic substitution of the bromo function of compound **1** with piperidine was performed to afford **10** in high yield (Scheme 2). This reaction was significantly slower than the substitution of **1** with sodium azide. The removal of the benzoate protecting group from **10** by Zemplén's method required elevated temperature, but afforded compound **11** in good yield. The azido function was introduced at position **4** by S_N2 reaction via a triflate intermediate. Treatment of **11** with Tf_2O, as described for **4**, followed by reaction of the crude with sodium azide in DMF

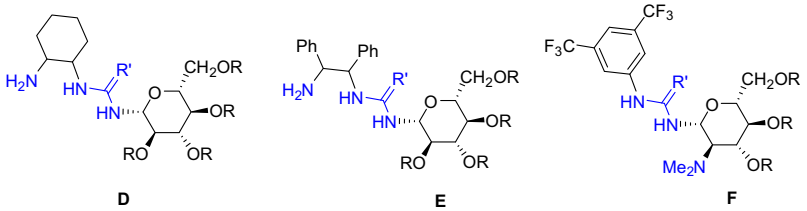


Figure 2. Monosaccharide-containing bifunctional organocatalysts.