Diversity Oriented Synthesis of Pyrrolidines via Natural Carbohydrate Solid Acid Catalyst

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Natural carbohydrate scaffold catalyzed diastereoselective synthesis of functionalized pyrrolidines have been developed via 1,3-dipolar cycloaddition of azomethine ylides derived from α-imino esters with dienes or dipolarophiles. Naturally most abundant carbohydrates, like cellulose and starch, were converted into their sulfuric acid derivative, which are exhibiting efficient catalytic properties, along with excellent cost effectivity and recyclability. The advantages of this methodology are diversity oriented metal free synthesis of functionalized pyrrolidines, mild reaction condition, high diasteroselectivity and yield.

Pyrrolidines are an important class of heterocycles found in numerous natural products,[1] bioactive molecules,[2] organocatalysts,[3] and building blocks in organic synthesis.[1b,4] (Figure 1). In our ongoing research toward the development of diversity oriented synthesis of biologically important heterocycles,[5] we report here diversity-oriented, metal-free synthesis of biologically relevant heterocyclic pyrrolidine scaffolds. In comparison to target-oriented synthesis (TOS), in which the plan is to access precise or dense regions of chemistry space, diversity-oriented synthesis (DOS) populates chemical space mostly with small-molecules having diverse structures and is now considered to be an important tool for lead identification in the area of drug discovery.

The objectives of DOS involve development of pathways leading to the efficient synthesis of collections of small molecules having skeletal and stereochemical diversity with defined coordinates in chemical space. Chemical genetics may benefit from collections of small molecules that are both structurally complex and diverse.[6] Structural diversity is crucial for lead generation in chemical genetics and drug discovery.[7] Diversity-oriented synthesis is a tool to discover new areas of chemical space efficiently. It can be argued that more diverse starting points for lead optimization are presenting scaffolds with superior selectivity profile, compared to narrowly defined chemical libraries.[8] Consequently the efficient construction of pyrrolidine molecules has received significant attention. 1,3-Dipolar cycloaddition of azomethine ylide and dipolarophile is the method of choice for the synthesis of diversity-oriented pyrrolidines or proline derivatives.

Recently, several regio- and diastereoselective synthesis of substituted pyrrolidines via cycloaddition of azomethine ylides have been reported. Scheidt et.al. reported copper(I) salt-catalyzed three-component reaction between an α-diazo ester, an imine, and various alkenes or alkynes with excellent to good diastereoselectivity.[9] Patzel et al.[10] and Toke et al.[11] used AgOAc, LiBr in presence of base, using azomethine ylides with α,β-unsaturated ketones or aryl nitroethylenes to generate substituted pyrrolidines. Che et al. have developed ruthenium porphyrins catalyzed diastereoselective synthesis of substituted pyrrolidine from α-diazoester with *N*-benzylidene imines and alkenes.[12] Interestingly, Jørgensen et. al[13] reported cinchona alkaloids and silver fluoride catalyzed

Table 1. Comparison of CellSA and StarSA in the Synthesis of Pyrrolidines[a]

entry	catalyst	R	diene	R_1	time (h)	yield (%)[b]	endo (%)[c]
1	CellSA	2-NO_2	**2a**	Et	30	70	100
2	StarSA	2-NO_2	**2a**	Et	32	66	76
3	CellSA	3-F	**2a**	Et	28	90	98
4	StarSA	3-F	**2a**	Et	30	75	72
5	CellSA	2-Br	**2a**	Et	24	75	95
6	StarSA	2-Br	**2a**	Et	24	56	70

[a] Reaction conditions: Aromatic α-imino ester **1** (1 mmol), dienes or dipolarophiles **2** (1 mmol), CellSA or StarSA (0.03 g), ethanol (2−3 mL), rt. [b] Isolated yield. [c] Determined by the ^{1}H NMR spectroscopic analysis.

Table 2. Cellulose Sulfuric Acid Catalysed Synthesis of Substituted Pyrrolidines[a]

entry	R	dienes	R_1	time (h)	yield (%)[b]	endo (%)[c]
1	H	**2a$_1$**	Me	28	80	90
2	4-F	**2a$_1$**	Me	30	90	95
3	2-Me	**2a$_1$**	Me	24	85	85
4	4-MeO	**2a**	Me	36	65	95
5	4-F	**2a**	Me	25	85	92
6	2-NO_2	**2a**	Et	30	70	100
7	3-NO_2	**2a**	Et	24	75	100
8	3-F	**2a**	Et	28	90	98
9	2-Br	**2a**	Et	24	75	95
10	4-$PhCH_2O$	**2a**	Et	24	80	95
11	4-$N(CH_3)_2$	**2a**	Et	26	70	90
12	2-Cl	**2a**	Et	24	75	85
13	H	**2a$_2$**	Me	28	75	95
14	4-MeO	**2b**	Me	34	85	90
15	4-Br	**2b**	Me	29	80	90
16	H	**2b$_1$**	Me	30	55	80
17	H	**2c**	Me	30	85	95
18	H	**2d**	Et	34	92	95
19	4-Cl	**2d**	Et	32	85	95

[a] Reaction conditions: aromatic α-imino ester **1** (1 mmol), dienes or dipolarophiles **2** (1 mmol), CellSA (0.03 g), ethanol (2−3 mL), rt. [b] Isolated yield. [c] Determined by the ^{1}H NMR spectroscopic analysis.

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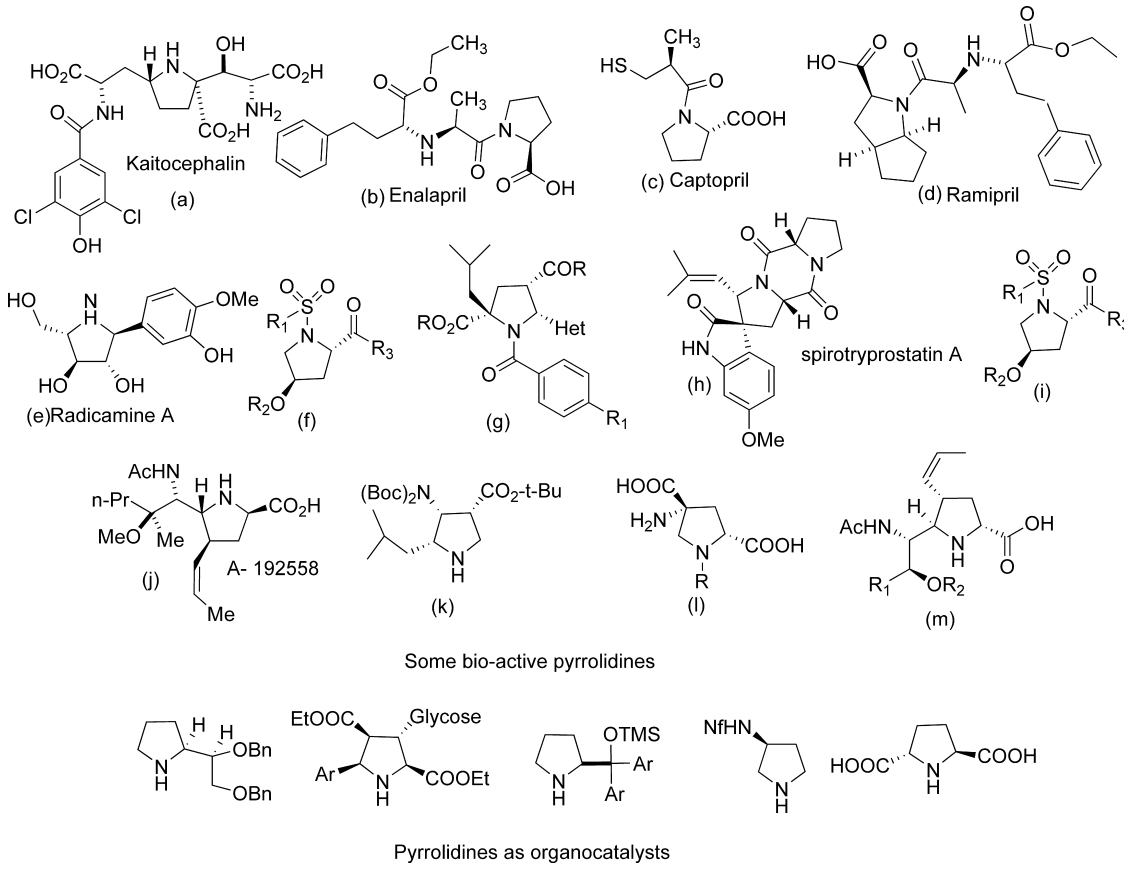


Figure 1. Some important pyrrolidine scaffolds.

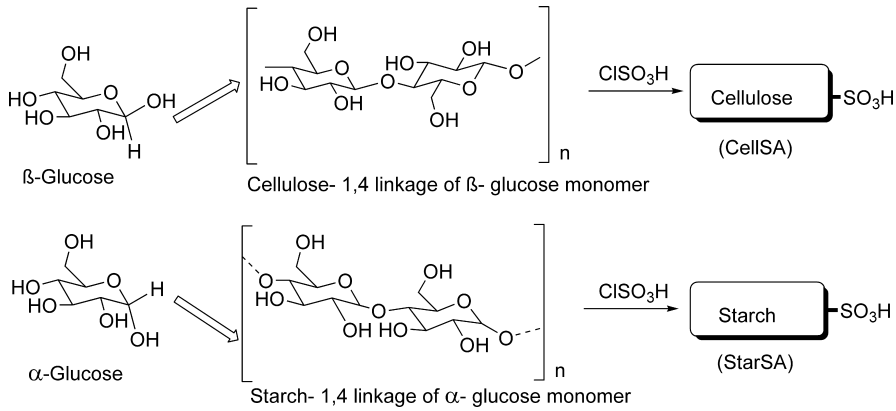


Figure 2. Natural supramolecular carbohydrate acid catalysts.

synthesis of pyrrolidines. All these methods involve metals as catalyst for the synthesis of pyrrolidine derivatives.

We wish to report here a metal-free, diastereoselective and diversity-oriented synthesis of substituted pyrrolidines using cellulose sulfuric acid/starch sulfuric acid as a solid catalyst from α-imino esters and dipolarophiles via 1,3-dipolar cycloaddition.

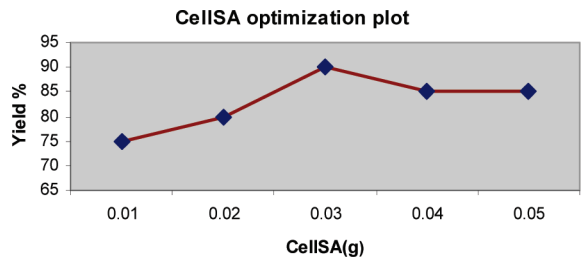


Figure 3. CellSA optimization plot. Reaction conditions: *N*-(3-fluorobenzylidene)-glycine ethyl ester (1 mmol), maleimide (1 mmol), CellSA (0.01−0.05 g), ethanol (2−3 mL), rt.

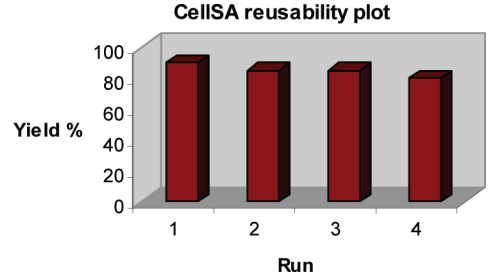
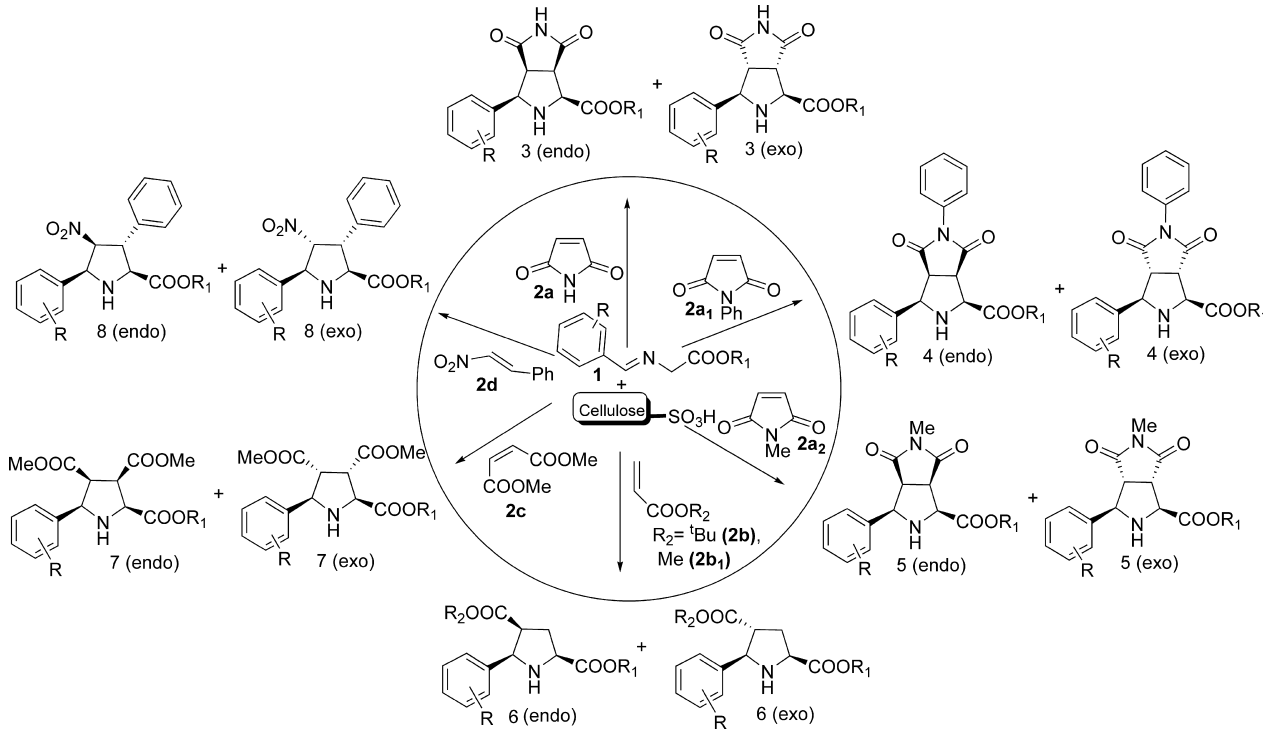


Figure 4. CellSA reusability plot. Reaction conditions: *N*-(3-fluorobenzylidene)-glycine ethyl ester (1 mmol), maleimide (1 mmol), CellSA (0.03 g), ethanol (2−3 mL), rt, 28 h.

Scheme 1. CellSA-Catalysed Synthesis of Subsituted Pyrrolidines



The two most abundant natural supramolecular carbohydrates (NSCar), cellulose and starch molecules are used for catalytic purposes because they are biodegradable, very cost-effective, and renewable resources. To achieve effective catalytic properties, cellulose and starch were converted to their sulfuric acid derivatives (Figure 2).

Cellulose sulfuric acid (CellSA) has an excellent catalytic properties, which are attributed to the high thermal stability and strong acid sites of sulfo functional groups. Cellulose is more appropriate as a support compared to starch because of poor solubility and high stability. CellSA has shown better reusability than starch sulfuric acid (StarSA) for four successive reactions under similar reaction condition without any significant loss in the product yield. In addition, the CellSA-catalyzed reaction has better yield and diastereoselectivity than StarSA for the synthesis of pyrrolidines (Table 1). Thus cellulose sulfuric acid was found to be more efficient catalyst in comparison with starch sulfuric acid for the one-pot synthesis of pyrrolidines.

Recently, cellulose sulfuric acid (CellSA) has emerged as a promising biopolymeric solid support acid catalyst for acid-catalyzed reactions, such as the synthesis of α-aminonitriles, imidazoazines,[14] and tetrahydroquinolines.[15]

Cellulose sulfuric acid is responsible for the protonation of α-imino ester to give azomethine ylide and catalyzes the cycloaddition. The cyclized product is obtained by the reaction of the azomethine ylide generated from α-imino ester **1** and olefinic dipolarophile **2** (1:1) in the presence of cellulose sulfuric acid in ethanol via stirring at room temperature (Scheme 1).

The reaction is highly diastereoselective and generates endoisomer as predominant product. The stereochemistry of the cycloadduct was determined by ^{1}H NMR analysis.

The cellulose sulfuric acid (CellSA) was prepared following a previously reported procedure.[14,15] First cellulose (DEAE for column chromatography, Sigma-Aldrich) in absolute ethanol was treated with chlorosulfonic acid in a slow dropwise addition. The solid obtained was washed with acetonitrile to give cellulose sulfuric acid as white powder. The powder was dried to obtain a fixed weight and used as catalyst after analysis. The number of H^+ site of CellSA determined by acid−base titration and found to be 0.50

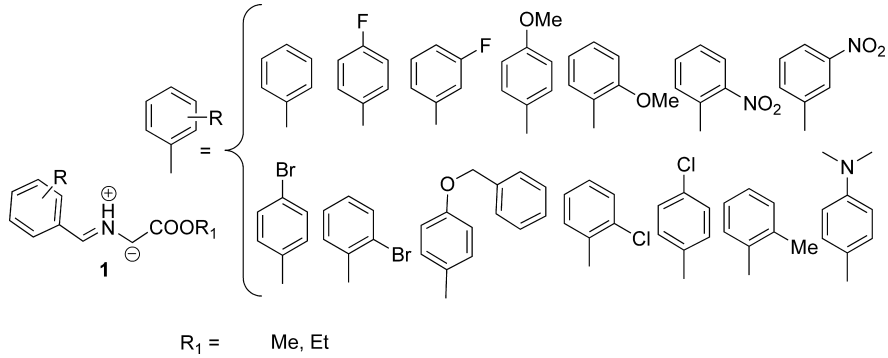


Figure 5. Azomethine ylides.

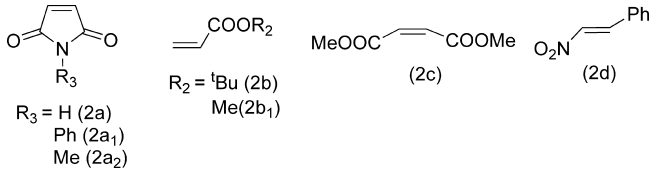


Figure 6. Dienes or dipolarophiles (**2**).

mequiv/g. This value corresponds to about 0.96% of the sulfur content, indicating that most of the sulfur species are in the form of sulfuric acid groups.

The reactions of α-imino esters with olefinic dipolarophiles goes with high levels of diastereoselectivity regardless of the electronic property of the aromatic ring. However presence of a chloro or bromo substituent at the ortho position of α-imino esters accelerated the reaction as reaction completed in almost 24 h (Table 2, entries 9 and 12), whereas lower reactivity was observed when a methoxy group is present at para position of α-imino esters (reaction took place in more than 30 h) (Table 2, entries 4 and 14). The different imino esters reacted smoothly with maleimide and showed high endoselectivity. Acrylates also gave endoadducts as the major products, whereas slightly low reactivity observed with aromatic nitroalkenes may be caused by steric hindrance of aryl ring (reaction completed in more than 30 h) (Table 2, entries 18 and 19).

The catalyst loading was optimized by taking *N*-(3-fluorobenzylidene)-glycine ethyl ester and maleimide as an model reaction in ethanol at rt. Reaction took place in 28 h with 0.03 g of catalyst loading and almost 90% yield was obtained (Table 2, entry 8). Lowering the catalyst loading to 0.01−0.02 g results in 75−80% yield of pyrrolidine with a longer reaction time of more than 40 h, whereas increasing the concentration of catalyst has no significant effect on the yield of the reaction (Figure 3).

One of the advantages of solid acid catalysts is their reusability. Reusability of catalyst was checked under same reaction condition as given above, that is, *N*-(3-fluorobenzylidene)-glycine ethyl ester and maleimide were reacted in ethanol. After completion of reaction, as given in Table 2, entry 8, cellulose sulfuric acid was recovered from the reaction mixture by simple filtration, washed properly with acetone, and dried in oven for 3 h at 70 °C prior to its use in the absence of fresh catalyst. It was observed that catalyst displayed quite good reusability at least four additional times in subsequent reactions under the same reaction conditions without any significant loss in productivity (Figure 4).

We have also studied the effect of temperature on reaction rate. Increasing the reaction temperature to 70−80 °C results in short reaction time (6−7 h) with moderate diastereoselectivity (60% endo product was obtained). To explore 1,3-dipolar cycloaddition and to generate diversity, a number of α-imino esters (Figure 5) were cyclized with different dipolarophiles (Figure 6) in good yields and high diastereoselectvities (only the endo products were observed) (Table 2).

A plausible mechanism for cycloaddition reaction is shown in Figure 7. α-Imino ester coordinates to CellSA, and the azomethine ylide−CellSA complex is generated by protonation of α-imino ester−CellSA complex. The azomethine ylide−CellSA complex reacts with dipolarophile to form diastereoselective pyrrolidine (Figure 7).

In summary, we have developed a novel, metal free, diastereoselective and diversity-oriented synthesis of substituted pyrrolidines catalyzed by cellulose sulfuric acid as natural carbohydrate solid acid catalyst. This process involves avoidance of harsh reaction condition, ecofriendly chemistry, reusable catalyst, high diastereoselectivity, and high yield.

Experimental Section

Preparation of Cellulose or Starch Sulfuric Acid. To a magnetically stirred mixture of 5.00 g of cellulose (DEAE for column chromatography, Sigma-Aldrich) or starch (Merck) in 20 mL of absolute ethanol, 1.00 g of chlorosulfonic acid (9 mmol) was added dropwise at 0 °C over 2 h. HCl gas escaped from the reaction vessel immediately. After the addition was complete, the mixture was stirred for an additional 2 h. After that, the mixture was filtered and washed with 30 mL of acetonitrile and dried at room temperature to obtain 5.20 g of cellulose sulfuric acid as white powder or 5.06 g of starch sulfuric acid as cream powder.

General Procedure for the Synthesis of α-Imino Esters. A suspension of glycine methyl or ethyl ester hydrochloride (1.1 equiv), excess $MgSO_4$, and NEt_3 (1.1 equiv) in CH_2Cl_2 was stirred at rt for 1 h. The aldehyde (1.0 equiv) was added, and the reaction mixture stirred at rt overnight. The $MgSO_4$ was removed by filtration, and the filtrate was washed properly with water. The aqueous phase was extracted with CH_2Cl_2, and the combined organic layers were washed with brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated to give α-imino esters in good yield.

General Procedure for 1,3-Dipolar Cycloaddition. A typical formation of pyrrolidines was carried out by reacting α-imino ester **1** (1 mmol) with olefinic dipolarophile **2** (1 mmol) and 0.03 g of catalyst (CellSA) in ethanol (2−3 mL) under stirring at room temperature. The reaction mixture was stirred until completion of the reaction as evidenced by TLC.

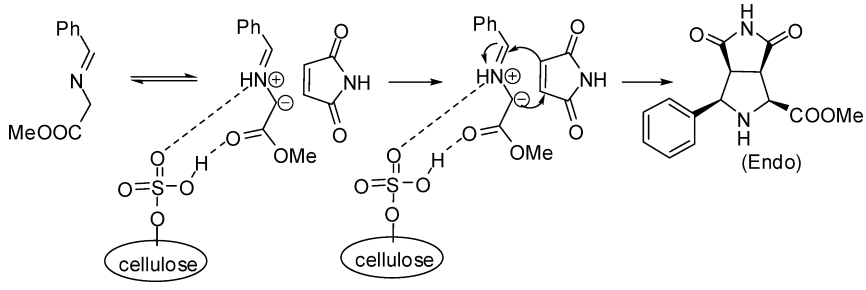


Figure 7. Proposed mechanism of 1,3-dipolar cycloaddition.

Reaction time varies from 24−36 h (Table 2, entry 1−19). The solvent was removed in vacuo, and the crude product was purified by column chromatography through silica gel to give desired product.

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Supporting Information Available. Detailed experimental procedures and compound characterization data for all products. This information is available free of charge via the Internet at http://pubs.acs.org/.

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