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Diastereoselective synthesis of glycosylated prolines as α-glucosidase inhibitors and organocatalyst in asymmetric aldol reaction☆

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Abstract—1,3-Dipolar cycloaddition of azomethine ylides and glycosyl E-olefins in presence of LDA led to diastereoselective formation of C-glycosylated proline esters. The selected esters on regioselective hydrolysis with LiOH gave C-glycosyl prolines. Few of the proline esters exhibited very good α-glucosidase inhibitory activity. The organocatalytic activity of the proline derivatives in a prototype Aldol reaction has also been investigated.

Dipolar cycloaddition reactions has found many useful synthetic applications both in solution- and solid-phase synthesis particularly with respect to the preparation of compounds with new chiral centres.[1,2] This approach towards asymmetric synthesis is of major importance in both the pharmaceutical and agricultural industries. 1,3-Dipolar cycloaddition reactions, in general, are of paramount importance for the construction of polyfunctionalised five membered cyclic rings.[2] Application of azomethine ylides and alkenes in such dipolar reactions has been extensively used for the synthesis of pyrrolidines and many alkaloids as chemotherapeutics or chiral catalysts or as building blocks in organic synthesis.[3] Highly substituted pyrrolidines are known for their glucosidase inhibitory activity and consequently possess potent antiviral, antibacterial, antidiabetic and anticancer activities.[4] Glycosylated prolines as constituent of hydroxyproline-rich plant glycoproteins (HRGPs)[5] impart them many biological functions in plants. The main thrust in this area is to generate enantioriched compounds in a single step with minimum number of reagents used. Asymmetric catalysis or application of at least one chiral substrate in such reaction led to generate optically active compounds in enantioselective or diastereoselective manner.[6]

Although the enantioselective cycloaddition and pericyclic reactions via organometallic asymmetric catalysis have played a pivotal role in this area yet, the application of chiral organometallic catalyst sometimes is undesired due to metallic impurity associated with the final products limiting the utility in the synthesis of chemotherapeutics.[7]

Azomethine ylides have principally been generated by the reaction of an amine with an aldehyde to form an iminium species, which under experimental condition led to the formation of carbanion in situ, as they are very labile. Asymmetric 1,3-dipolar cycloaddition with azomethine ylide and dienophile has been achieved[8] via any of the three strategies; (a) by attaching a chiral auxiliary to the imino or to the electron withdrawing group of the dipole (b) by attaching chiral auxiliary to the electron withdrawing group of the alkene or (c) by employing a chiral Lewis acid which chelates both the substrates. It is believed that like other cycloaddition reactions, 1,3-dipolar cycloaddition is also a concerted process and proceeds via Woodward Hoffmann Rule. Pure *E*-α, β-unsaturated esters or ketones with chiral substituent at the γ-position were employed in regioselective and diastereoselective cycloaddition to get the pyrrolidine derivatives.[9,10]

Keywords: Glycosyl prolines; 1,3-Dipolar cycloaddition; α-Glucosidase; Tetrasubstituted pyrrolidines.
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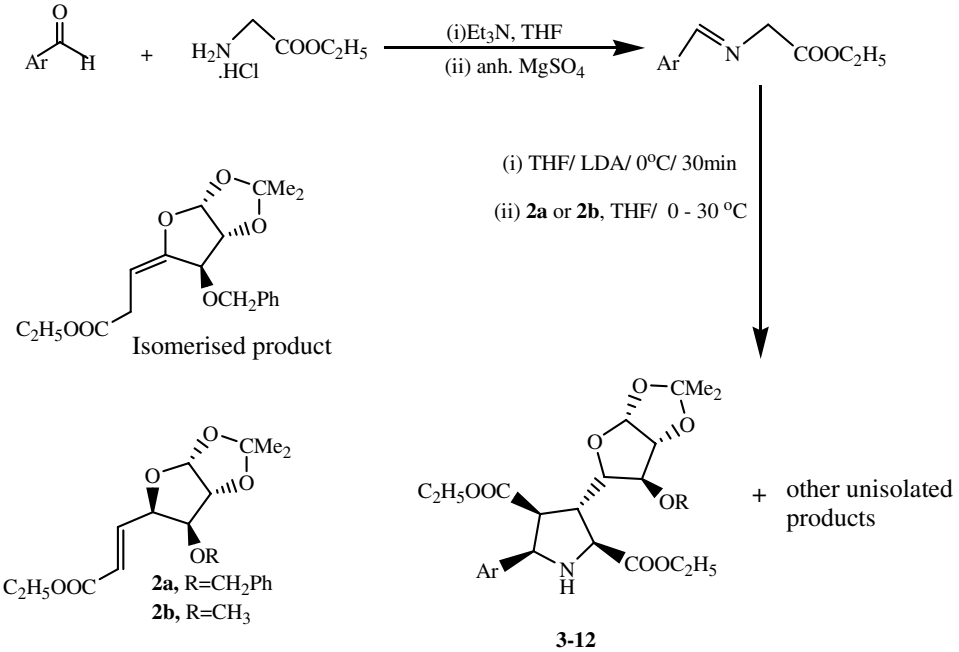
Keeping in mind the above facts and in continuation of our effort to develop α-glucosidase inhibitors[11,12] and new organocatalysts[13] from simple sugars we were interested to synthesize functionalized chiral pyrrolidines and see their α-glucosidase inhibitory activity and catalytic efficiency in organic synthesis. Thus, the present communication deals with the 1,3-dipolar cycloaddition of different azomethine ylides and chiral alkenes bearing 1,2-*O*-isopropylidene-β-L-*threo*-pentofuranosyl sugar moiety at the γ-position.

To start with [(3-nitro-benzylidene)-amino]-acetic acid ethyl ester (**1a**) was prepared by reaction of 3-nitrobenzaldehyde and ethyl glycinate in presence of anhy. $MgSO_4$. The azomethine ylide of **1a** was generated in situ by reacting it with lithium diisopropyl amide in anhydrous tetrahydrofuran at 0 °C for half an hour. The ylide, so generated, on reaction with ethyl-1,2-*O*-isopropylidene-3-*O*-benzyl-β-L-*threo*-hept-5-eno-furanosyl uronate (**2a**) led to the formation of the required tetrasubstituted pyrrolidine (**3**) as major product along with small amount of un-reacted starting materials **1a** and **2a** as observed on TLC plate. The major product was isolated by column chromatography and was characterized as ethyl (2*S*,3*S*,4*S*,5*R*)-3-(1,2-*O*-isopropylidene-3-*O*-benzyl-β-L-*threo*-furanos-4-yl)-5-(3-nitrophenyl)-pyrrolidine-2,4-dicarboxylate (**3**) on the basis of its spectroscopic data and microanalysis. The stereochemistry in compound **3** was speculated on the basis of literature precedents and the mechanism involved in this reaction.[8–10] It has earlier been reported[9] that in such cycloadditions involving a chiral dienophile and azomethine ylide the relative orientation of substituents at C2/C3 and C3/C4 is *anti* and at C4/C5 is *syn* in major isomers of the reaction products. In ^{1}H NMR spectrum of compound **3**, the coupling constant $J_{4,5}$ was found to be 8.2 Hz, while $J_{3,4}$ was <1.0 Hz indicating *syn* and *anti* orientation of substituents at C4/C5 and C3/C4 as observed earlier in such a study.[14] It has been proved[8–10] that this stereochemistry is attained via regiospecific *endo* cycloaddition of the dipole to the *E* configured dipolarophiles in the ester series. It is appropriate to mention here that we did carry out above reaction under different experimental conditions (Table 1) including the use of DBU/LiBr as mentioned earlier[9,10] and after 6 h of reaction only the β,γ-unsaturated ester[15] was isolated as the major product of the reaction along with a small amount of the desired product (TLC).

Similarly, reaction with [(3-chloro-benzylidene)-amino]-acetic acid ethyl ester (**1b**), [(4-bromo-benzylidene)-amino]-acetic acid ethyl ester (**1c**), [(3-pyridyl-methylidene)-amino]-acetic acid ethyl ester (**1d**), [(2,5-dichloro-benzylidene)-amino]-acetic acid ethyl ester (**1e**) and

Table 1. Synthesis of tetrasubstituted pyrrolidines from chiral olefinic ester and benzylidene glycinate under different reaction conditions

Alkene	Benzylidene glycinate	Ar	R	Catalyst	Time (h)	Temp (°C)	Yield
2a	**1a**	3-Nitrophenyl	CH_2Ph	DBU/LiBr	6	25–80	Isomerised product
2a	**1a**	3-Nitrophenyl	CH_2Ph	Et_3N/LiBr	8	25	No reaction
2a	**1a**	3-Nitrophenyl	CH_2Ph	LDA	4	0–30	70%
2a	**1a**	3-Nitrophenyl	CH_2Ph	LDA	4	−78	72%



Scheme 1. Synthesis of tetrasubstituted prolines.

[(4-fluoro-benzylidene)-amino]-acetic acid ethyl ester (**1f**) with ethyl-1,2-*O*-isopropylidene-3-*O*-benzyl-β-L-*threo*-hept-5-eno-furanosyl uronate (**2a**) separately led to formation of respective tetrasubstituted prolines (**4**–**8**) as major products along with un-reacted olefins and azomethylidenes (Scheme 1).

The other glycosyl olefin, ethyl-3-*O*-methyl-1,2-*O*-isopropylidene-β-L-*threo*-hept-5-eno-furanosyl uronate (**2b**) was similarly reacted with [(4-bromo-benzylidene)-amino]-acetic acid ethyl ester (**1c**), [(3-pyridyl-methylidene)-amino]-acetic acid ethyl ester (**1d**), [(3-nitro-benzylidene)-amino]-acetic acid ethyl ester (**1a**) and [(4-chloro-benzylidene)-amino]-acetic acid ethyl ester (**1g**) separately to give the respective tetrasubstituted pyrrolidines diastereoselectively (**9**–**12**) in moderate to good yields (Table 2). The structures of all the products were established on the basis of spectroscopic data.

Formation of the above major product could be rationalized on the basis of Houk's transition state model (**A**) where the preferred diastereotopic facial attack of the *W* shaped dipoles to the chiral dipolarophile takes place. The major product arises from the transition state **I** in which the largest group (β-L-threose) occupies the anti position with respect to the incoming dipole, while the smallest group, hydrogen, present outside the crowded region. As shown in model **A** the ylide attacks *Re*/*Re* face of the olefinic ester and the attack is quite similar to nitrile oxide cycloaddition,[16] where the β-L-threose occupies the stereoelectronically favoured 'inside position' and the smallest group 'H' is at the more sterically demanding outside position. The relative and absolute stereochemistry in the products obtained was speculated on the basis of transition state model and earlier reports[6,10] on such 1,3-dipolar cycloaddition of chiral olefin and azomethine ylide (Fig. 1).

As many proline derivatives are known to catalyze a number of organic reactions we were interested to prepare tetrasubstituted analogs and see their catalytic ability. Thus, above tetrasubstituted prolines (**3**–**7**) having 2,4-carbethoxy substituents were treated with one equivalent of LiOH in THF to give compounds **13**–**17** in good yields. To our pleasant finding only 2-carbethoxy group was regioselectively hydrolysed in all these compounds leading to respective tetrasubstituted pyrrolidines with 2-carboxyl group. The regioselective hydrolysis of 2-carbethoxy group may be explained in terms of sterically hindered approach of LiOH to the 4-carbethoxy group and chelation controlled facile delivery of the required OH group to the carbonyl carbon of 2-carbethoxy group

Table 2. Synthesis of tetrasubstituted pyrrolidines from chiral olefinic esters and benzylidene glycinate

Alkene	Benzylidene glycinate	Ar	R	Product	Time (h)	Yield (%)
2a	**1a**	3-Nitrophenyl	CH_2Ph	**3**	4	80
2a	**1b**	3-Chlorophenyl	CH_2Ph	**4**	4	85
2a	**1c**	4-Bromophenyl	CH_2Ph	**5**	4	80
2a	**1d**	3-Pyridyl	CH_2Ph	**6**	4	80
2a	**1e**	2,5-Dichlorophenyl	CH_2Ph	**7**	3	80
2a	**1f**	4-Fluorophenyl	CH_2Ph	**8**	3	70
2b	**1c**	4-Bromophenyl	CH_3	**9**	3	75
2b	**1d**	3-Pyridyl	CH_3	**10**	3	70
2b	**1a**	3-Nitrophenyl	CH_3	**11**	3	80
2b	**1g**	4-Chlorophenyl	CH_3	**12**	3	78

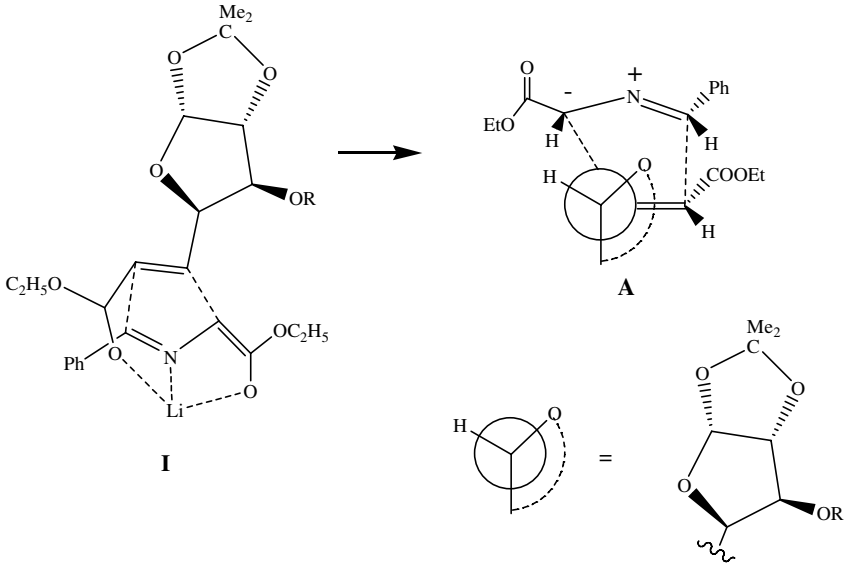


Figure 1. Transition state model for cycloaddition.

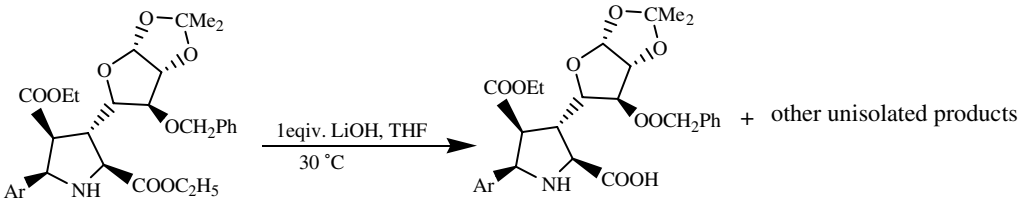
as lithium chelates with ring nitrogen and carbonyl oxygen of carbethoxy group (Scheme 2).

Inspired by the work of List et al.[17] asymmetric aldol reaction catalyzed by prolines we have studied the catalytic activity of these prolines **13**–**17** in one such reaction of acetone and 3-nitrobenzaldehyde. Thus, reaction of 3-nitrobenzaldehyde with acetone in presence of 20 mol% of the above proline derivatives **13**–**17** separately led to the formation of aldol product **18** in varying yield (65–85%) and enantioselection (10–90%) (Scheme 3). Enantioselection in aldol product was determined by HPLC, using Chiradex column, and 9:1 MeCN–water as eluent. Proline derivative **17** gave best (90%) enantioselection. Reactions with all the catalysts were performed under identical reaction condition. 10 mol% of the catalysts resulted in lower yield of the reaction product.

The compounds synthesized were evaluated against the isolated α-glucosidase from rat intestine following earlier protocol.[18,19] As evident from Table 3 all the compounds screened inhibited glucosidase enzyme ranging from 5% to 82.7% at the only concentration of 100 μM used in the present study. A closure look into α-glucosidase inhibitory activity reveals that among these compounds, compounds having 3-*O*-benzyl substituent (**3**–**8**) in the sugar moiety are more active than those with 3-*O*-methyl substituent in glycofuranose (**9**–**12**). Further, among compounds having 3-*O*-benzyl substituent compounds with nitro, chloro or bromo groups at various positions in 5-phenyl ring have good inhibition (65–82% inhibition) of the enzyme. A similar compound having 4-fluoro substituent is comparatively less active (43% inhibition). Substitution of phenyl ring at C-5 with pyridyl group results in drastic loss of activity. Furthermore, all the compounds with 3-*O*-methyl sub-

Table 3. α-Glucosidase inhibitory activity of tetrasubstituted prolines

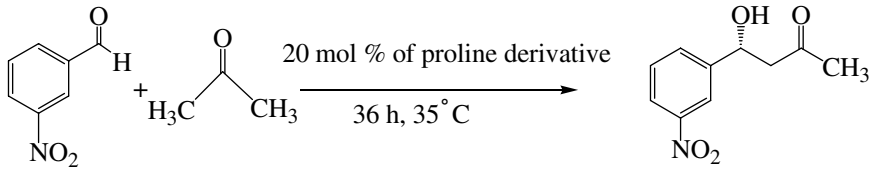
Compound	% α-glucosidase inhibition (100 μM)	IC_{50} (μM)	K_i (μM)
3	82.7	61	33
4	65.5	96	79
5	79.3	64	36
6	29.3	ND	ND
7	67.2	99	65
8	43.1	75	40
9	26.8	ND	ND
10	17.1	ND	ND
11	14.6	ND	ND
12	21.1	ND	ND
13	10.3	ND	ND
14	24.1	ND	ND
15	8.1	ND	ND
16	5.1	ND	ND
17	10.5	ND	ND
Acarbose	39.0	ND	ND



3-7 **13-17**

Compounds	*Ar*	*% yield*
13	3-nitro-phenyl	80
14	3-chloro-phenyl	85
15	4-bromo-phenyl	80
16	3-pyridyl	75
17	2,5-dichloro-phenyl	80

Scheme 2. Synthesis of 2-carboxypyrrolidines.



18

Catalyst	*% yield*	*% ee*
13	85	20
14	70	80
15	85	55
16	65	10
17	86	90

Scheme 3. Direct asymmetric Aldol reaction of 3-nitrobenzaldehyde and acetone.

stituent are very poor inhibitor of the enzyme. Replacement of 2-carbethoxy substituent with carboxyl (**13**–**17**) always results in drastic loss in inhibitory potential. The best compound of the series (**3**) inhibited the rat intestinal α-glucosidase up to the extent of 82.7%, while the standard drug acarbose used in this study has only 39% inhibition.

In summary, we have developed a diastereoselective synthesis of tetrasubstituted glycosyl pyrrolidines by 1,3-dipolar cycloaddition of azomethine ylides and glycosyl olefins. The compounds displayed α-glucosidase inhibitory activity. The catalytic potential of these prolines in asymmetric aldol reaction has also been demonstrated.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2006.12.002.

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