Organocatalyst-Promoted [3+2] Cycloaddition Reaction of Azomethine Ylides and Olefinic Dipolarophiles

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ABSTRACT

An efficient enantio- and diastereoselective synthesis of substituted pyrrolidines have been reported using tartaric acid as an organocatalyst through [3+2] cycloaddition of azomethine ylides (N-alkylidene glycine esters) and diploarophiles in good-to-excellent yields. We have also used di-p-toluoyl-L-tartaric acid (DTTA) (30% mmol) as an organocatalyst which gives [3+2]-dipolar cycloaddition product along with aza-Michael product by the reaction of dipolarophiles on cycloaddition product. However, DTTA (5% mmol) afforded cycloaddition product as a major product.

Key words: Organocatalysis, Cycloaddition, Dipolarophiles, Micheal reaction, Ylides.

1. INTRODUCTION

The asymmetric [3+2] cycloaddition reaction is one of the most powerful methodologies for enantioselective synthesis of five-membered heterocyclic systems [1]. The asymmetric [3+2] cycloaddition of azomethine ylides and dipolarohiles is of great interest because it allows the preparation of enantiomerically enriched substituted pyrrolidines, which are constituents of various natural products and biologically important compounds [2]. Besides this, pyrrolidines are of much interest in organic chemistry as building blocks and organocatalysts. Asymmetric cycloaddition reactions are very interesting because the absolute configuration of four stereocenters can be controlled simultaneously [3]. The stereoselective synthesis of pyrrolidine derivatives depends on the routes for the synthesis of azomethine ylide and their by influencing the geometry of dipole. In general, the azomethine ylides have been generated by the ring opening of aziridines, 1,2-proton shift of N-arylidene benzylamines, abstraction of the R-proton from iminium salts, or metal complexes of N-alkylidene-R-amino acid esters and related reactions [4-6].

Recently, several examples of the asymmetric cycloaddition of azomethine ylides catalyzed by chiral metal complexes have been reported. The groups of Jørgensen et.al. used hydro cinchonic and Ag, Zhang Schreiber Zhou and Carretero have reported that the reaction of azomethine ylide with dipolarophile in highly enantio- and endoselective in the presence of chiral ZnII–bisoxazolines, AgI–phosphanes, AgI–quinap, Ag–P, N ligands, and Cu Fesulphos, while the groups of Komatsu and Zhang have reported exoselectivity with a Cu–diphosphane complex and P,N ligands as catalyst [7-9].

We wish to report here a metal-free enantio and diastereoselective synthesis of substituted pyrrolidines using tartaric acid as an organocatalyst from N-alkylidene glycine esters and dipolarophiles through [3+2]- cycloaddition. Tartaric acid catalyzes the reaction through the generation of azomethine ylide from α-imino ester. To the best of our knowledge, tartaric acid has not been applied to the cycloaddition reaction between an azomethine ylide and dipolarophile [10-12].

Asymmetric organocatalysis is a very rapidly growing field of research as a result of both the novelty of the concept and the efficiency and

selectivity of many organocatalytic transformations [12-15]. Recently, the use of organocatalysts in organic synthesis has received significant attention due to their eco-friendly nature. Catalytic methods based on metal-free organic molecules (organocatalysis) have evolved as a powerful complement to metal and biocatalysts.

2. EXPERIMENTAL

2.1. Representative Procedure for the Synthesis of Pyrrolidine Derivatives 3a-f

A mixture of α-imine ester 1 (1 mmol) and dipolarophile 2 (1 mmol) were refluxed in ethanol (10 mL) containing tartaric acid (30 mol%). The mixture was refluxed until completion of the reaction as evidenced by TLC. The solvent was removed in vacuo and the crude product was subjected to column chromatography using ethyl acetate: hexane as eluent.

2.2. Spectral Data of 3ba

(2S,3S,5S)-diethyl 5-(2-methoxyphenyl)pyrrolidene-2,4-dicarboxylate 1H NMR (200 MHz, CDCl₃): δ7.24 (m,2H), 6.87 (m,2H), 4.60 (d,J=7.2Hz,1H), 4.25 (q,J=7.1Hz,4Hz), 3.88 (t,1H), 3.76 (s,3H), 3.56 (t,J=7.0Hz,1H), 3.42 (m,1H), 2.32 (m,1H), 1.28 (m,3H), 0.71 (t,J=7.1Hz,3H); 13C NMR (50 MHz, CDCl3) δ174.014, 173.836,157.547, 129.248, 126.693, 126.446, 121.113, 110.841, 61.841, 61.508, 60.918, 60.852, 55.656, 49.714, 34.974, 14.579,14.519; Mass m/z 322(M+Z).

2.3. Spectral Data of 3bc

(2S,4S,5R)-2-ethyl4-methyl5-(2-   methoxyphenyl)-3-phenylpyrrolidine-2,4-dicarboxylate 1H NMR (300 MHz,CDCl₃): δ7.24 (m, 2H), 6.87
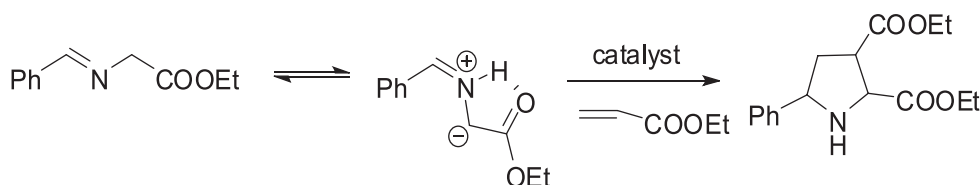
Scheme 1: Proposed organocatalytic [3+2] cycloaddition of azomethine ylide and dipolarophile.

(m, 2H), 4.60 (d,J=7.2Hz,1H), 4.25 (q,J=7.1Hz,4H), 3.88 (t,1H), 3.76 (s,3H), 3.56 (t,J=7.0Hz,1H), 3.42 (m,1H), 2.32 (m,1H), 1.28 (m,3H), 0.71 (t,J=7.1Hz,3H); 13C NMR (50MHz, CDCl3) δ 168.67, 168.35, 155.85, 154.46, 142.5, 127.99, 127.60, 124.83, 119.86, 119.42, 109.94, 94.77, 59.98, 59.56, 57.56, 53.95, 53.74, 46.85, 44.52, 12.44; Mass m/z 384(M+).

2.4. Spectral Data of 3ca

(2S,4S,5R)-diethyl 5-(3- methoxyphenyl)pyrrolidine-2,4-dicarboxylate 1HNMR (200MHz,CDCl3): δ7.20 (m,1H), 6.84 (t,J=7.4Hz,1H), 6.72 (m,2H), 4.45 (d,J=7.6Hz,1H), 4.25 (m,4H), 3.88 (s,1H), 3.71 (s,1H), 3.23 (d,J=7.1Hz,1H), 2.37 (m,2H), 1.25 (t,J=7.2Hz,3H), 0.83 (m,3H); 13CNMR (50MHz,CDCl3): 173.611, 172.862, 159.905, 141.239, 129.525, 119.893, 113.572, 112.960, 96.518, 66.156, 61.553, 60.641, 60.362, 55.549, 50.026, 29.541, 14.642; Mass m/z 322(M+).

3. RESULTS AND DISCUSSION

To develop a new organocatalyst for the generation of azomethine ylides and their cycloaddition reactions, we have developed a procedure to prepare pyrrolidine derivatives through [3+2] cycloaddition of azomethine ylides mediated by tartaric acid. This organocatalyst is responsible for the protonation of α- iminoester to give azomethine ylide and also catalyzes the cycloaddition (Scheme 1). The cyclized product is obtained by the reaction of the azomethine ylide generated from α-imine ester 1a and ethyl acrylate 2a (1:1equivalent) in the presence of tartaric acid in ethanol at 80°C (Scheme 2). This resulted in the formation of endoisomer in the majority (85%) and exoisomer as minor products (15%). The stereochemistry of the cycloadduct was determined by spectroscopic analysis. Both 1H NMR and 13C NMR spectra gave evidence for the formation of the expected structure.

To study the [3+2] cycloaddition of azomethine ylide, we investigated various α -imino esters derived from different aromatic aldehydes. The reactions of α -imino esters (1a–f) with ethyl acrylate (2a) go with high levels of diastereoselectivity and enantioselectivity regardless of the electronic property of the aromatic ring. We carried out the reaction in the presence of various methoxy and hydroxy substituents which showed endo selectivity. The reaction was performed in different solvents, but ethanol was proved to be the best solvent in terms of diastereoselectivity and reaction time (Table 1).

To study the effect of dipolarophile on reaction rate, we investigated that N-alkylidene glycine esters reacted with methyl acrylates, ethyl acrylates, and ethyl cinnamates. In all cases, endo selective products were formed in the majority. The reaction was fast with acrylates and also in high yield but cinnamates gave poor yield. This may be due to the presence of steric hindrance in cinnamates which results in poor reactivity.

The reaction was catalyzed mainly in the presence of two types of organocatalysts, i. e., tartaric acid and (-)-2,3-Di-p-toluoyl-L-tartaric acid (DTTA). Reaction with tartaric acid gave an exclusively pyrrolidine ring and no corresponding Michael adduct (Scheme 1).

Tartaric acid was used in the catalytic amount of 30 mol%. Pka of tartaric acid is 2.98, it catalyzes exclusively cycloaddition reaction between α-imino ester and dipolarophile, and therefore, no Michael product is obtained. (-)-2,3-DTTA showed a unique property. When 5
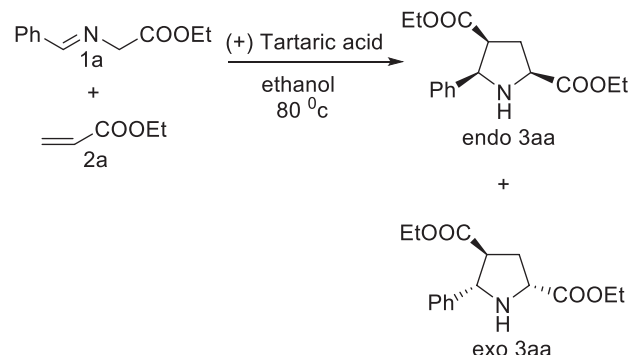
Scheme 2: Tartaric acid catalyzed 1,3 dipolar cycloaddition of azomethine ylide and dipolarophile.

**Table 1:** Effect of catalyst on reaction.

Entry	Catalyst	Mol %	Cycloaddition (%)	Aza-Michael
1	(+) Tartaric acid	5	40	-
2	(+) Tartaric acid	10	50	-
3	(+) Tartaric acid	20	70	-
4	(+) Tartaric acid	30	85	Traces
5	(−) DTTA	5	90	Traces
6	(−) DTTA	20	80	20%
7	(−) DTTA	30	60	40%

DTTA: Di-p-toluoyl-L-tartaric acid

Table 2: Reactions particulars of reaction of dipolarophiles and olefin.

Entry	Imine/ Dipolarophile	Ar	R_1	R_2	Time (h)	Yield	Endo
1	1a/2a	Ph	COOEt	H	8	80	85
2	1b/2a	o-MeOC$_6$H$_5$	COOEt	H	8	75	75
3	1c/2a	m-MeOC$_6$H$_5$	COOEt	H	9	80	85
4	1d/2a	o-HOC$_6$H$_5$	COOEt	H	7	70	60
5	1e/2a	p-HOC$_6$H$_5$	COOEt	H	8	85	70
6	1f/2a	C$_{11}$H$_8$O	COOEt	H	9	70	80
7	1b/2b	o-MeOC$_6$H$_5$	COOMe	H	8	75	85
8	1a/2c	Ph	COOMe	Ph	9	80	70
9	1b/2c	o-MeOC$_6$H$_5$	COOMe	Ph	9	75	65
10	1e/2b	p-HOC$_6$H$_5$	COOMe	H	8	70	70
11	1c/2c	m-MeOC$_6$H$_5$	COOMe	Ph	9	65	75

mol% of catalyst was used 1,3 dipolar cycloaddition occurred in the majority but when 30 mol% of catalyst and 2 mol of dipolarophile were taken cycloaddition along with aza-Michael occurs (Scheme 2). The possible explanation of this can be given as tartaric acid causes protonation of nitrogen of pyrrolidine, therefore, no further Michael addition takes place. However, in the case of DTTA, no protonation
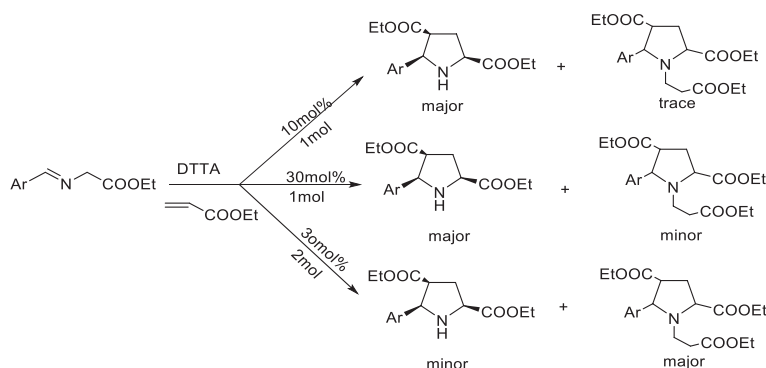
Scheme 3: (-)-2,3-Di-p-toluoyl-L-tartaricacid ((-)DTTA) catalyzed cyclization of azomethine ylide and dipolarophile.

takes place on nitrogen. Thus, due to the presence of lone pairs of electrons on nitrogen, aza-Michael takes place.

1,3 dipolar cycloaddition occurs under mildly basic reaction condition. Polymerization occurs under highly basic conditions instead of cycloaddition. Therefore, in most of the known procedures, weak organic bases were used for deprotonation. Only Na´jera and co-workers have reported the use of KOH/NaOH(10 mol%) in this reaction in the presence of a Lewis acid (i.e., AgOAc) and phase transfer catalyst. It can be argued that tartaric acid catalyzed reaction through protonation of nitrogen of n-alkylidene glycine ester whereas tartrate anion act as a mild base and causes deprotonation of α-imino ester resulting in the formation of azomethine ylide, these species are trapped with electron-deficient olefins resulting in the formation of pyrrolidene.

4. CONCLUSION

We have described a novel and efficient organocatalyzed method for the 1,3-dipolar cycloaddition reaction of azomethine ylides obtained through imine tautomerization with electron-deficient dipolarophile mediated by tartaric acid. This reaction produced the corresponding pyrrolidines in high yield and under mild reaction conditions.

5. ACKNOWLEDGMENT

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Bibliographical Sketch

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