

REGULAR ARTICLE

A theoretical study on the reaction mechanisms and stereoselectivities of NHC-catalyzed [2 + 2] cycloaddition of ketene with C=N double bond of isothiocyanate

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Received 7 Aug 2016; Accepted (in revised version) 30 Aug 2016

Abstract: In this work, three possible mechanisms, including mechanisms A and B associated with the stereoselective [2 + 2] cycloaddition product and mechanism C associated with the [2 + 2 + 2] cycloaddition product, have been investigated for N-heterocyclic carbenes (NHCs) catalyzed cycloadditions of ketenes with isothiocyanates by using density functional theory (DFT). Our calculated results suggest that the mechanism A is the most energy favorable pathway, which contains three steps, i.e. (1) the nucleophilic attack on the ketene by NHC catalyst for the formation of enolate intermediate, (2) regioselective [2 + 2] cycloaddition of the enolate intermediate with isothiocyanate, and (3) the dissociation of the NHC catalyst from the thioxo- β -lactam product. Notably, the [2 + 2] cycloaddition step is proved to be both the rate- and stereoselectivity-determining step. Moreover, the reaction pathway associated with the R configuration is the most favorable pathway and leads to the major product, which is in good agreement with the experimental results. The mechanistic insights obtained in the present study should be valuable for the rational design of more efficient organocatalytic cycloadditions for the synthesis of heterocycle compounds with high selectivities.

AMS subject classifications: 92E99

Keywords: DFT, NHC, [2 + 2] Cycloaddition, Stereoselectivity

1. Introduction

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In modern synthetic and organic chemistry, it is a critical and challenging goal to design highly stereoselective and region-specific reactions. Notably, organocatalysis is playing more and more important role in asymmetric synthesis. Since the first report of the isolation and characterization of a free N-heterocyclic carbene (NHC), [1] NHCs have been successfully and widely applied as the ligands of organometallic catalysts. [2-5] Afterwards, the excellent performances of NHCs have been uncovered for acting as one of the most powerful organocatalysts in asymmetric reactions, such as the cross-benzoin, Stetter, annulation, homoenolate, [1, 6-16] and cycloaddition (i.e., [2 + 2], [17-22] [2 + 2 + 2], [23] [4 + 2], [24-27] cycloadditions) reactions, which can afford a facile and also effective route to obtain various heterocyclic skeletons. Due to the special reactivities and wide applications of NHC-catalyzed [2 + 2] cycloadditions of ketenes and C = X (X = O, CH₂, and NH), their theoretical studies [28-30] have also attracted more and more attention.

Recent reports show that the Lewis base organocatalysts (especially for N-heterocyclic carbenes) can improve the stereoselectivity of the ketene cycloaddition reaction significantly. For instance, the remarkable work of NHC-catalyzed [2 + 2] cycloaddition reactions of ketenes with isothiocyanates (**Scheme 1**) were firstly published by Ye's group. [20] To the best of our knowledge, the reaction mechanisms are still ambiguous, and which step is the stereoselectivity-determining step and which factor is the decisive one for the stereoselectivity in this kind of reaction remain unclear. In this work, we mainly focused on some issues still unsettled: (1) Which reactant (**R1** or **R2**) can react with **Cat** firstly? (2) Which processes are the rate- and stereoselectivity-determining step? (3) Why is the R-isomer the major product? (4) Why does the [2 + 2] cycloaddition rather than other cycloadditions (such as [2 + 2 + 2] cycloaddition) favorably occur? With these questions as motivation, the present work will pursue a theoretical investigation on the title reaction to clarify the actually reaction mechanism and the above questions. And we believe that the mechanistic information should be important for understanding the NHC-catalyzed [2 + 2] cycloaddition reactions and providing novel insights into recognizing this kind of reaction in detail.

In this work, the [2 + 2] cycloaddition of aryl(alkyl)ketene **R1** with PNP-isothiocyanate **R2** promoted by NHC catalyst to give the corresponding major β -lactone **PR** (up to 85% yield) with 97% ee (**Scheme 1**) has been chosen as the object of the theoretical investigation. As shown in **Scheme 1**, it should be noted that the "R/S" represents the chirality of C3 atom in the stationary points involved in the reaction. The reaction mechanisms were studied using density functional theory, which has been widely used in the studies of the reaction mechanisms.