



Construction of dihydropyran-bridged macrocycles by inverse-electron-demand Diels–Alder reaction



Xiaomei Dong, Qingxia Wang, Qian Zhang, Shuai Xu, Zhihong Wang*

State Key Laboratory and Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, PR China

ARTICLE INFO

Article history:

Received 28 August 2013

Received in revised form 22 October 2013

Accepted 31 October 2013

Available online 6 November 2013

Keywords:

Dihydropyran-bridged macrocycles
Inverse-electron-demand Diels–Alder reaction
Lewis acid catalysis

ABSTRACT

A variety of dihydropyran-bridged macrocyclic structures were constructed by the inverse-electron-demand Diels–Alder reaction of 2-oxo-4-aryl-but-3-enoates. Controlling of the tether length and the position of the activating substituent in the substrates would guide the reaction to the formation of four different types of polycyclic frames, namely bicyclic [*n*.3.1], bicyclic [*n*.2.2], tricyclic [*n*.3.1.1], and tricyclic [*n*.2.2.2] macrocycles. The intermolecular/intramolecular selectivity of the Diels–Alder reaction was virtually governed by the tether length. The reactions were carried out rapidly under mild conditions, and offered a practical method for creating bridged polycyclic structures with large rings from acyclic precursors.

© 2013 Elsevier Ltd. All rights reserved.

1. Introduction

Macrocycles, no matter being isolated from natural sources or chemically synthesized, possess particular charm because of their known occurrence in many attention-getting fields such as bio-recognition,^{1,2} drug development,^{3,4} supramolecular chemistry,^{5–7} chemosensing,⁸ and catalysis.^{9,10} Thus substantial efforts have been made in developing synthetic methods for this intriguing class of compounds and a variety of means have proved their effectiveness, such as multicomponent reactions,^{11,12} ring-closing metathesis,^{13,14} metal- or anion-directed formations,^{15–17} as well as enzyme-catalyzed¹⁸ and DNA-templated synthesis.^{19,20} While impressive progress has been made in building monocyclic or fused bicyclic macrocycles, little work has been devoted to creating bridged polycyclic structures with large rings. Thus it would be conceptually attractive to develop a method for the relatively facile construction of these complex polycyclic systems from acyclic precursors.

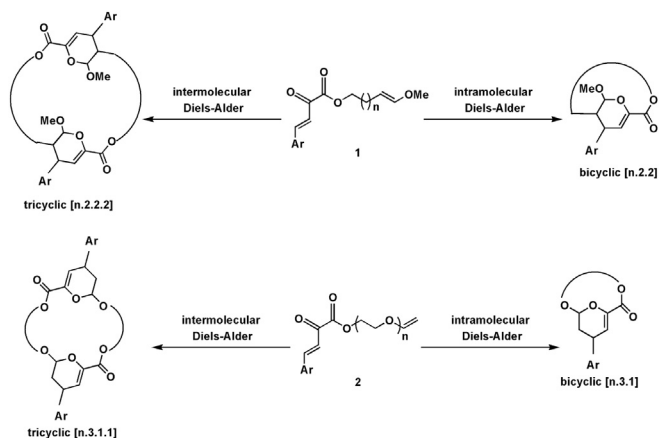
In a series of pioneer works, Shea and co-workers have demonstrated the capacity of the type 2 intramolecular Diels–Alder reaction for constructing bridged bicyclic medium rings from open chain substrates^{21–25} and studied the origins of regio- and stereochemistry.²⁶ Taking account of the existing literature as well as the well-known fact that the regioselectivity of Diels–Alder reaction is affected by the position of electron-donating or electron-withdrawing groups, we have reason to believe that with proper

tether length and appropriate positioning of activating groups, acyclic starting materials containing both diene and dienophile moieties may participate in inter- or intramolecular Diels–Alder reaction, providing bridged polycyclic macrocycles with a variety of structural modes. Herein we report the construction of a series of bridged bicyclic and tricyclic macrocycles by inverse-electron-demand hetero Diels–Alder reaction of 2-oxo-4-aryl-but-3-enoates.

2. Results and discussion

In general, the regioselectivity of the inverse-electron-demand hetero Diels–Alder reaction of 2-oxobut-3-enoates is guided by the location of the activating groups on the dienophiles. The electron-donating group prefers an *ortho* orientation with respect to the oxygen atom in the products in order to gain the strongest interaction between the centers on the frontier orbitals having the largest orbital coefficients. Thus by positioning the activating groups on the different side of the double bond in the dienophile moiety, a variation in the ring-closing position is attained. For this purpose, two series of substrates were designed. Substrate **1** in Scheme 1 has an 'exo' methoxy group, and in a reaction leading this substituent to the position *ortho* to oxygen, a bicyclic [*n*.2.2] or a tricyclic [*n*.2.2.2] frame will be formed, depending on the tether length in the substrates. When the oxygen-containing part is in an 'endo' position, like that in substrate **2** in Scheme 1, locating of this electron-donating group at the proper position will lead to the generation of a bicyclic [*n*.3.1] or a tricyclic [*n*.3.1.1] molecule.

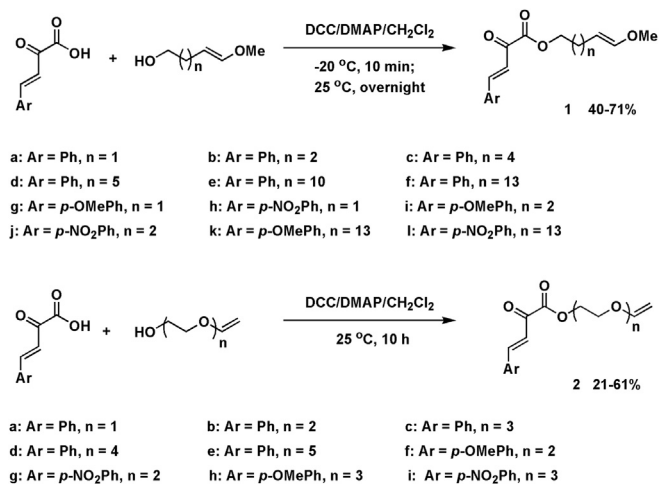
* Corresponding author. E-mail address: zhihongwang@nankai.edu.cn (Z. Wang).



Scheme 1. Designed construction of bridged polycyclic macrocycles by hetero Diels–Alder reaction of 2-oxo-but-3-enates.

2.1. Synthesis of substrates

In order to create bridged polycyclic structures from open chain starting materials by Diels–Alder reaction, it is essential to introduce both diene and dienophile moieties into a single molecule of substrate. This aim was fulfilled in the esterification between 2-oxo-4-aryl-but-3-enoic acids and primary alcohols having alkoxy-substituted alkenes on the other end of the chain (**Scheme 2**). The introduction of ester connection plays triple roles here. First, the electron-withdrawing ester group effectively activates the oxodiene for the inverse-electron-demand Diels–Alder reaction; second, esterification allows the combination of a variety of acids and alcohols, making the synthesis of substrates and the following Diels–Alder reaction more generalized; and third, the ester-containing oxodienes are responsible for the generation of pyran-based macrolide structures, which is also an interesting class of compounds.^{27,28}



Scheme 2. Synthesis of substrates.

The length of the chain connecting the diene and dienophile moieties varied in a certain range to enable us to examine the influence of tether length on the intermolecular/intramolecular selectivity of the Diels–Alder reaction. The electronic effect was studied by introducing typical electron-withdrawing nitro group or electron-donating methoxy group into the phenyl ring. Ethylene

glycol units were chosen to form the tether in substrate **2** mainly for two reasons. First, the incorporation of the unit allows convenient elongation of the tether; and second, the repetition of the ethylene glycol units in the substrates, once finally being exhibited in the Diels–Alder products, may provide a practical method for the formation of crown-ether-like molecules with various ring sizes.

2.2. Optimization of reaction conditions

Optimization of Diels–Alder reaction conditions was carried out, choosing **1c** as model substrate since it has a medium tether length thus would be representative in understanding the intermolecular/intramolecular selectivity of the reaction as well as examining whether the reaction is controllable to yield a dominant product. Initial tests at room temperature employing SnCl₄ as catalyst (entries 1 and 2 in **Table 1**) gave us a mixture of dimerized, trimerized, and tetramerized products, even when a highly diluted solution at a concentration of 0.001 M was used. The products were extremely close in solubility and polarity and disabled effective separation with regular techniques, indicating that milder conditions were required to guide the reaction to a major product. Reducing the temperature (entry 3) partially alleviated the problem but was still not able to simplify the reaction to a primary product. Only when the catalyst loading was reduced at the same time (entry 4), trimerization and tetramerization died away and product **3c** could be cleanly isolated. However, further cut in catalyst loading (entry 5) caused an adverse impact on the yield.

The formation of Diels–Alder adduct was primarily judged from the disappearance of olefinic protons in **1c** at 7.85, 7.34, 6.27 (*Z*-isomer of substrate) and 5.87 (*E*-isomer of substrate), and 4.70 ppm, respectively, in ¹H NMR, associated with the appearance of the only olefinic proton in **3c** at 6.35 ppm (**Fig. 1**). Though NMR alone could not provide verification whether the reaction occurred in an intermolecular or an intramolecular way, either could it differentiate a dimer of the substrate from a trimer or tetramer, since all these compounds would have similar chemical environments for the nuclei and thus markedly resembling spectra. Fortunately, mass spectra could give decisive results here, which ascertained an intermolecular reaction between two substrate molecules in the particular case of **3c**. Thus a combination of NMR and HRMS spectra was employed later in the investigation on the reaction selectivity.

It is well-known that in the synthesis of macrocycles the concentration of substrate may largely affect the reaction. To understand the influence here, the initial concentration of the substrate was tested in a range of 10⁻¹ to 10⁻⁴ mol/L (entries 6–8). An initial concentration of 0.1 mol/L of substrate resumed the formation of large amount of trimerized and tetramerized products, probably due both to the easy approach among molecules and the increase in the concentration of catalyst. Lowering the concentration to 0.01 mol/L enabled the separation of dimerized product, but in a quite low yield. Unfortunately, further dilution to a concentration of 1 × 10⁻⁴ mol/L did not help as we hoped, which could be the result of an unduly low concentration of catalyst.

The SnCl₄-catalyzed reaction with proper concentration of substrate and catalyst succeeded in providing dimerized product as major product, however some unidentified by-products, which were proved not to be the trimerized and tetramerized products formed as well in the reaction. As a result, the isolated yields of the reactions are not high, as a sacrifice for purity in the purification by flash column. In an effort to improve the reaction, some other commonly used Lewis acids were also tested (entries 9–16), including Eu(fod)₃, which has been proven to be highly effective catalyst for inverse-electron-demand Diels–Alder reactions,²⁹ but none of the examined catalysts surpassed SnCl₄ in this particular case. The substrate was also subject to conditions of thermal Diels–Alder reaction (entry 17) and photoreaction (entry 18) to explore

Download English Version:

<https://daneshyari.com/en/article/5217274>

Download Persian Version:

<https://daneshyari.com/article/5217274>

[Daneshyari.com](https://daneshyari.com)