Tetrahedron Letters 57 (2016) 3902–3907

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Stereochemistry of hexachlorocyclopentadiene [4+2]-cycloaddition to 2-substituted 4,7-dihydro-1,3-dioxepins

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ARTICLE INFO

Article history:
Received 19 May 2016
Revised 1 July 2016
Accepted 7 July 2016
Available online 9 July 2016

Keywords:
Diels–Alder reaction
[4+2]-Cycloaddition
Microwave irradiation
π-Facial selectivity
4,7-Dihydro-1,3-dioxepins

ABSTRACT

Experimental investigation of hexachlorocyclopentadiene [4+2]-cycloaddition to 2-substituted 4,7-dihydro-1,3-dioxepins revealed an atypical stereochemical effect. Clear experimental evidence was obtained that more bulky C2 substituents favour the thermodynamically and sterically less favourable *endo*-isomers. The possible reasons for such behaviour are secondary interactions of the highest occupied and lowest unoccupied orbitals in the transition state for *endo*-cycloaddition, diastereotopic solvation and coordination of the attacking diene reagent to the acetal oxygens. The reaction stereoselectivity also depends on the solvent nature and reaction temperature. We have also found that microwave irradiation significantly influences the [4+2]-cycloaddition yields and stereochemistry, though the nature of the underlying effects remains unclear.

Introduction

Synthetic intermediates containing the 1,3-dioxepin fragment with chiral substituents at positions 4 and 5 are of significant interest for the design of biologically active drug-like compounds and agrochemicals.[1] Thus, such intermediates were used in the enantiocontrolled syntheses of P2-ligands for HIV-1 protease inhibition,[1a] cathepsin K inhibitors for the treatment of osteoporosis,[1b] antidiabetic compounds,[1c] the antibacterial indolmycin,[1d] (±)-samin, a general furofuran lignin precursor,[1e] hypoglycaemic agents,[1f] the anti-inflammatory drugs *S*-naproxen and *S*-ibuprofen,[1g] as well as GABA antagonists with insecticidal action.[1h] The chiral *exo*- and *endo*-isomers of 4-phenyl-3,5,8-trioxabicyclo[5.1.0]octanes were used in our previous work as precursors for the synthesis of stereoisomeric compounds, which possessed fungicidal activity dependent on the configuration of the stereocentres at positions 4 and 5 of the 1,3-diozepane ring.[1i] Considering the rich bioactivity potential of compounds containing the 1,3-dioxepin moiety with controlled stereochemistry of the chiral centres, our group has developed and described a range of synthetic approaches based on the reaction of various reactants with 2-substituted 4,7-dihydro-1,3-dioxepins, leading to different cyclic *exo*- and *endo*-adducts.[2] In particular, [4+2]-cycloaddition of hexachlorocyclopentadiene (HCCPD) to 2-substituted 4,7-dihydro-1,3-dioxepins under high pressure (5300 atm) was studied.[2d]

As a continuation of this experimental and theoretical work, we have directed our effort to the search for more convenient synthetic methods and an in-depth analysis of factors influencing the stereochemistry of this interesting reaction type. In this work, we studied the following experimental factors influencing the reaction stereochemistry: reaction media including solvent-free conditions, temperature, microwave irradiation and the nature of the 2-substituent in the 4,7-dihydro-1,3-dioxepin ring.

Results and discussion

Chemistry

2-Substituted 4,7-dihydro-1,3-dioxepins **Ia–e** used in this work represent relevant and useful models of diastereotopic dienophiles for studying the stereochemistry of the [4+2]-cycloaddition process.[2d] HCCPD was chosen as a diene which readily undergoes the Diels–Alder reaction to give a variety of adducts that have been commercialized as pesticides (e.g., aldrin, bromodan, chlordane, endrin). The cycloaddition reactions (Scheme 1) were performed under a variety of experimental conditions. Our aim

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http://dx.doi.org/10.1016/j.tetlet.2016.07.023
0040-4039/