Synthesis of oxa-bridged derivatives from Diels–Alder bis-adducts of butadiene and 1,2,3,4-tetrahalo-5,5-dimethoxycyclopentadiene

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Abstract

Bis-adducts of 1,2,3,4-tetrahalo-5,5-dimethoxycyclopentadiene and 1,3-butadiene, generated in situ from 3-sulfolene, have been synthesized in excellent yield. Ruthenium catalyzed oxidation of the bis-adducts followed by a one-pot transformation of the resulting α-diketone furnished oxa-bridged compounds. Unambiguous stereochemical assignments of both diastereomeric series are reported.

Introduction

3-Sulfolene is a nonflammable, nontoxic, nonhygroscopic and stable crystalline solid and is a convenient equivalent for gaseous 1,3-butadiene [1-3] and is commonly used for in situ generation of 1,3-butadiene as the diene component in Diels–Alder reactions. We and other groups have demonstrated the utility of cyclic dienes for the synthesis of 2:1 Diels–Alder bis-adducts with 1,2,3,4-tetrahalo-5,5-dimethoxycyclopentadiene 1 [4-7]. In the case of cyclic dienes (or trienes) such as cyclohexa-1,4-diene and cycloheptatriene, endo-syn-endo diastereomer 2 is formed exclusively, whilst cyclopentadiene and furan yield solely endo-anti-endo diastereomer 3 (Scheme 1). In continuation of our interest in the Diels–Alder bis-adducts of 1,2,3,4-tetrahalo-5,5-dimethoxycyclopentadienes 1 and their applications [8-14], we envisaged employing 1,3-butadiene as bis-dienophile component. Herein we report the synthesis of bis-adducts of 1,2,3,4-tetrahalo-5,5-dimethoxycyclopentadiene and butadiene followed by their transformation to oxa-bridged compounds. The stereochemistry of the diastereomeric products was also unequivocally established.

We were interested in exploring the previously overlooked stereochemical outcome of the Diels–Alder reaction between 1a and 1,3-butadiene [15,16]. The bis-adduct obtained from 1a and gaseous 1,3-butadiene was previously assigned as “endo, exo-bis(7,7-dimethoxy-1,2,3,4-tetrachloronorborn-2-en-5-yl)” [16].
In our reinvestigation we used 3-sulfolene as a 1,3-butadiene source to prepare both the mono- and bis-adducts. The two diastereomeric bis-adducts were separated and the relative stereochemistry was established by single crystal X-ray diffraction and \(^1\)H NMR spectroscopy. The bis-adducts were further transformed into bis-diketones by means of supported ruthenium catalyzed oxidation. Finally, the two diastereomeric norbornyl α-diketones from the chloro as well as the bromo series were each converted to the corresponding oxa-bridged compounds [7].

**Results and Discussion**

For the preparation of the 2:1 adducts, 2 equivalents of 1,2,3,4-tetrachlorodimethoxycyclopentadiene 1a and one equivalent of 3-sulfolene were heated at 140–150 °C for 69 h in a sealed tube. The reaction mixture was purified by silica gel chromatography to afford the mono-adduct 4 in 7% yield as an inseparable mixture of endo and exo isomers [16] (endo:exo = 90:10, as determined by \(^1\)H NMR spectroscopy) and the two diastereomeric bis-adducts 5 and 6 as a 1:1 mixture in 92% yield (Scheme 2).

The assignment for the exo-isomer 4 is based on the H5-endo methine signal at 2.48 ppm which appears as a triplet of doublets. The corresponding H5-exo methine proton for endo-isomer 4 appeared at 3.2 ppm. The bis-adducts 5 and 6 were successfully separated by preparative HPLC [17]. Adduct 5, a colourless crystalline compound with melting point 176–178 °C, displayed two singlets at 3.54 and 3.51 ppm for the methoxy groups, a multiplet at 2.45–2.42 ppm for two methine protons and another multiplet at 2.37–2.31 ppm for four methylene protons in its \(^1\)H NMR spectrum. In the \(^{13}\)C NMR spectrum, the methine carbon atoms appeared at 47.6 ppm, and the methylene carbon atoms at 41.4 ppm. By contrast, the diastereomer 6, a colorless solid with melting point 182–184 °C showed two singlets at 3.57 and 3.50 ppm for methoxy groups, a doublet of doublets at 2.96 ppm for methine protons and two doublets of doublets at 2.33 and 1.34 ppm for the methylene protons in its \(^1\)H NMR spectrum. In the \(^{13}\)C NMR spectrum of 6, the methine carbon atoms appeared at 43.7 ppm and the methylene carbons at 35.9 ppm.

The bis-adducts 5 and 6 were smoothly transformed to the corresponding bis-α-diketones 7 and 9 in excellent yield with a supported ruthenium catalyst (Ru-LDH) and NaIO\(_4\) as stoichiometric co-oxidant, a methodology developed in our laboratory [18,19]. Previously, we reported a smooth one-pot transformation of norbornyl α-diketones to the corresponding oxa-bridged derivatives [7], but our initial attempts to transform the bis-diketones 7 and 9 to bis-oxa-bridged compounds 8 and 10 using this strategy did not give the desired result. However, when the reaction was carried out in presence of the phase transfer catalyst TBHSO\(_4\) the bis-oxa-bridged compounds 8 and 10 were obtained (after esterification with diazomethane) in 31 and 37%, respectively (Scheme 3).

The relative stereochemistry in 8 was unambiguously established by the single crystal X-ray analysis (Figure 1) [20]. Working backwards, the structures of the adduct 5, the bis-diketone 7 were confirmed unequivocally.

We next turned our attention to the bromo analogue 1b in order to see if the overall yield of the bis-oxa-bridged derivatives 8...
and 10 could be improved. We were also interested to see if any bromo derivative, corresponding to the diastereomer 6 in the chloro series, would furnish crystals suitable for X-ray analysis. The Diels–Alder reaction between 1,2,3,4-tetrabromo-5,5-dimethoxycyclopentadiene 1b and 3-sulfolene under the same experimental conditions as described for the chloro-analogue furnished mono-adduct 11 (endo:exo = 91:9) and bis-adducts 12 and 13 (Scheme 4). The bis-adducts 12 and 13 were separated by preparative HPLC.

The bis-adducts 12 and 13 were converted in excellent yields to the corresponding bis-α-diketones 14 and 15 (Scheme 5). Bis-diketone 14 was treated first with alkaline H$_2$O$_2$ and then with additional NaOH (60 equiv) at 60 °C followed by esterification with diazomethane to obtain the oxa-bridged compound 8 in 42% yield. Bis-diketone 15 was transformed into 10 in 39% yield by a similar method. Unlike the bis-diketones in chloro
Scheme 5: Synthesis of bis-oxa-bridged compounds 8 and 10 from bis-diketones 14 and 15.

series (7 and 9), which required a phase transfer reagent (TBHSO₄), the bromo bis-diketones 14 and 15 underwent transformation to the bis-oxa-bridged derivative 8 and 10 under the usual procedure previously reported from our laboratory [7] (Scheme 5). Although the yields in the final step were moderate (42 and 39%), this corresponds to 63–65% per oxa-bridge formed which is gratifying considering the number of intermediates involved and possible side reactions.

Unfortunately, neither 13 nor 15 gave crystals suitable for X-ray analysis. However, unambiguous assignment was possible from the diagnostic chemical shifts and coupling constants observed for methine (H₅) and methylene (H₆ and H₆') protons of bis-adducts 6 and 13 (Figure 2). The appearance of H₅ at ~3 ppm with characteristic coupling constants of ~9 and ~4 Hz to H₆ and H₆', respectively, unequivocally supports the assigned structures. These values are consistent with several endo-substituted derivatives (R = alkyl-like groups) reported by us [9] and others [21,22]. The observed selectivity is in agreement with the strong endo-selectivity displayed by diene 1.

From the above results it is clear that the diastereomeric bis-adducts 5, 6 and 12, 13 are formed via endo-endo addition. The proposed transition states for the formation of bis-adducts are shown in Figure 3. The initial endo-mono adduct (4 or 11) gives rise to two possible endo-transition states leading to 5, 6 or 12, 13. The corresponding exo-transition states suffer from severe steric congestion due to the bulky R group and are consequently unfavorable.

Figure 2: ¹H NMR chemical shifts (in parentheses) and coupling constants (J) for the three interacting protons (H₅, H₆, and H₆'; for the sake of convenience, numbering sequence of mono-adducts is adopted) of the bis-adducts 6 and 13.

Figure 3: Transition state models for the bis-adduct formation.
unfavorable. Similar steric considerations rule out the participation of an initially formed minor exo-mono adduct (4 or 11) to participate further in the reaction to give bis-adducts, thus ruling out the formation of diastereomers via exo-endo addition.

**Conclusion**

In conclusion, we have demonstrated that the Diels–Alder reaction between I (diene component) and 1,3-butadiene (bis-dienophile component) proceeds via endo-endo addition mode to give a 1:1 mixture of diastereomeric bis-adducts. The diastereomeric bis-adducts were separated and transformed into bis-oxa-bridged compounds. The relative stereochemistry of the products was unambiguously established by single crystal X-ray diffraction and NMR spectroscopy.

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**Supporting Information**

**Supporting Information File 1**

General methods, experimental procedures and analytical data for new compounds.

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