[4 + 3]Cycloaddition Reactions: Synthesis of 9,10-Dimethoxy-9,10-propanoanthracen-12-ones

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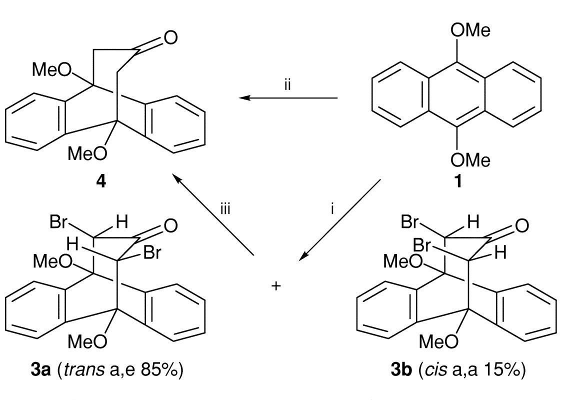
Cycloaddition of 9,10-dimethoxyanthracene (**1**) to tetrabromoacetone (**2a**) under a variety of conditions afforded isomers **3a**,**b**; reductive debromination of **3a**,**b** afforded **4**, while reduction with $NaBH_4$ gave alcohol **6** which on reductive debromination gave olefin **7**; reaction of **1** with **2b** gave isomers **8a**,**b**.

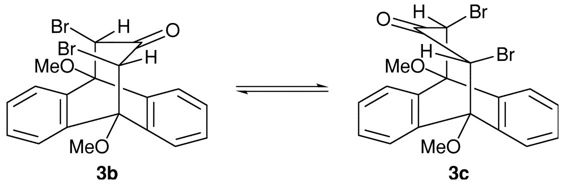
Seven-membered carbocycles are an important class of organic compounds that are of practical and theoretical interest. They are more elusive and have been studied less than their lower homologues, probably because of entropy reasons, ring strain and synthetic difficulties. Before the discovery of the [4 + 3]cycloaddition reaction, methods for preparing seven-membered carbocycles were limited to the enlargement of six-membered rings and some cyclization reactions.[1] The [4 + 3]cycloaddition of reactive three-carbon species with dienes is a convenient and straightforward method for the synthesis of a wide range of seven-membered rings, which cannot easily be prepared by other routes.[2] The [4 + 3]cyclocoupling reaction of allyl cations with 1,3-dienes is an efficient and easy method for the stereoselective synthesis of seven-membered ring compounds. Annulations using these species have provided easy access to a wide range of organic frameworks that have been utilized in the synthesis of natural products, pharmacologically active compounds and key intermediates for various useful organic molecules. Mechanistic and synthetic aspects of the [4 + 3] and [3 + 2]-cycloaddition reactions using allyl cations have been reviewed by Hoffmann,[1] Noyori,[2] Mann[3] and recently Rigby.[4]

9,10-Dimethoxyanthracene (**1**) was prepared according to the literature procedure[11] and allowed to cycloadd to tetrabromoacetone **2a** using Zn–Cu/1,4-dioxane in the presence of Me_3SiCl to afford a mixture of the cycloadducts **3a**–**b** in 24% yield. On cycloaddition of **1** to tetrabromoacetone **2a** using Zn–Cu/1,4-dioxane and ultrasound at 10–20 °C the isomeric cycloadducts **3a**–**b** were also obtained in 40.5% yield [*trans*, *axial equatorial* a,e (**3a**, 85%), and *cis*, *axial axial* a,a (**3b**, 15%), NMR analysis], Scheme 1.

The *cis* isomer of **3b** is flipped into the isomer **3c** as shown in Scheme 2. It is interesting that the ^1H NMR spectrum of the cycloadduct **3b** displays a long-range coupling between H-11 and H-13, in contrast to the usual behavior of planer configured H–C–C–C–H chains.



Scheme 1 *Reagents and conditions*: i, (a) tetrabromoacetone **2a**, Zn–Cu/1,4-dioxane/Me_3SiCl or (b) **2a**, Zn–Cu/1,4-dioxane/ultrasound, 10–20 °C; ii, **2a**, Zn–Cu/1,4-dioxane/ultrasound, 20–50 °C, 9 h; iii, Zn/CuCl/NH_4Cl/MeOH, r.t., 71%



Scheme 2

The MM2 calculation of the conformation **3b** (two possibilities: H-11 and H-13 are *cis*-diequatorial (e,e) or H-11 and H-13 are *cis*-diaxial (a,a) favour the formation of **3c**, where H-11 and H-13 again are *cis*-diequatorial (e,e). The ^1H NMR spectrum (200 MHz, $CDCl_3$) revealed a ^4J coupling of 1.5 Hz for H-11 and H-13. This cannot occur if H-11 and H-13 are not *cis*-diequatorial. MM2 calculations[12] of the isomers **3a**–**c** is in agreement with the ^1H NMR spectroscopic data.

On increasing the reaction temperature (20–50 °C, 9 h), the mixture of 9,10-dimethoxyanthracene (**1**) and tetrabromoacetone (**2a**) afforded the debrominated cycloadduct **4** in 56% yield. The cycloadduct **4** was also obtained, independently by the reduction of the dibromo cycloadducts **3a**–**b** with Zn/CuCl/NH_4Cl/MeOH in 71% yield, Scheme 1.

The cycloadducts **3a**–**b** could not be separated by chromatographic techniques. The ^1H NMR spectra of the *cis*,*trans*-11,13-dibromo-9,10-dimethoxy-9,10-propanoanthracen-12-ones **3a**–**b** were also measured in $CDCl_3$, CD_3CN and in C_6D_6. The results of the isomers **3a**–**c** are listed in Table 1. Formation of the cycloadduct **3c** could be attributed to the flipping of the cycloadduct **3b** in deuterated solvent.

Table 1 Ratios of the isomeric cycloadducts **3a**–**c**

Compound	Isomer	$CDCl_3$	C_6D_6	CD_3CN
3a	a,e	61.34%	61.55%	60.81%
3b	a,a	32.00%	31.76%	31.39%
3c	e,e	06.66%	06.69%	07.80%

When the reaction was carried out under mild conditions (Zn–Cu couple, sonication, 0–15 °C, 3 h) the same isomeric cycloadducts **3a**–**b** were also obtained in very low yield (3.5%), and the ^1H NMR spectra of these isomers in $CDCl_3$ showed the proportions listed in Table 2.

Table 2 Proportions of the isomeric cycloadducts **3a**–**c** in $CDCl_3$

Compound	Proportion (%)
3a (a,e)	71.43
3b (a,a)	22.86
3c (e,e)	5.71

The difference between the ratio of isomers **3a**–**c** in $CDCl_3$ could be attributed to the different reaction time and temperature.

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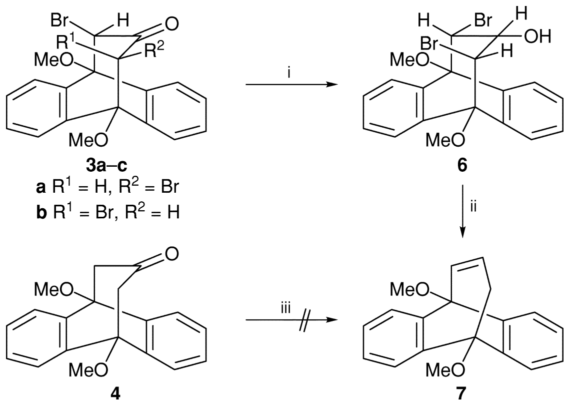
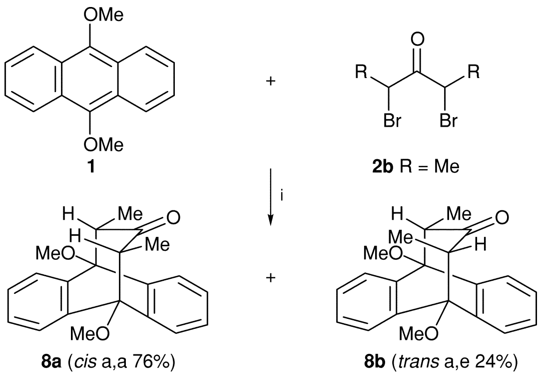


Scheme 4 *Reagents and conditions*: i, NaBH$_4$/Pr^{i}OH, r.t., 24 h, 51.5%; ii, Zn/CuCl/NH$_4$Cl/MeOH, r.t., 14%; iii, Zn/1,2-bis(chlorodimethylsilyl)ethane/THF/ultrasound, 10–20 °C, 6 h, 0%

On reduction of the isomeric cycloadducts **3a**–**b** with NaBH$_4$/isopropanol a racemic mixture of 11,13-dibromo-9,10-dimethoxy-9,10-propanoanthracen-12-ol (**6**) was produced which serves as a starting material for the preparation of the tetracyclic olefin **7**. Reductive debromination of the isomeric alcohol **6** with Zn/Cu/NH$_4$Cl/MeOH gave the tetracyclic olefin **7** in 14% yield. An attempt to directly deoxygenate[13] 9,10-dimethoxy-9,10-propanoanthracen-12-one (**4**) in the hope of obtaining the tetracyclic olefin **7** failed (Scheme 4).



Scheme 5 *Reagents and conditions*: Zn–Cu/Me$_3$SiCl/C$_6$H$_6$/ultrasound, 0–20 °C, 8 h, 21%

According to the general procedure, 9,10-dimethoxyanthracene (**1**) and 2,4-dibromopentan-3-one (**2b**) afforded, after chromatography, two isomeric cycloadducts **8a**–**b** in 21% yield in the ratio *cis* (76%): *trans* (24%) (^{1}H NMR analysis).

Epimerization of the cycladducts **8a**–**b** with MeONa/MeOH at room temperature changed this ratio from 4:1 to 2:1 (^{1}H NMR analysis).[5] The two methyl groups in the adduct **8a** are *cis*-diequatorial e,e and there is no long-range (^4J) coupling (Scheme 5).

Again using the molecular mechanics calculation to show the stereochemistry of the structure of the isomers **8a**–**b** we found that the differences in the MMX are negligible in comparison with the cycloadducts **3a**–**c**. The NMR analysis showed only two isomers in this case in a 4:1 ratio.

Techniques used: TLC, IR, ^{1}H NMR, elemental analysis

References: 13

Schemes: 6

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