Pergamon

Tetrahedron Letters 41 (2000) 6923–6927

TETRAHEDRON LETTERS

A facile entry into a stable functionalized bis(methylene)cyclobutene system

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Received 9 March 2000; revised 27 June 2000; accepted 5 July 2000

Abstract

A parameter for the stabilization of the 3,4-bis(methylene)cyclobutene system has been identified. Appropriate functionalized derivatives, stable even in solution, have been conveniently prepared by tandem double [2,3]-sigmatropic rearrangement of conjugated dipropargylic sulfenates to diallenic disulfoxides and spontaneous cyclization of the latter. Stereochemical aspects are presented. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: acetylenes; allenes; cyclization; cyclobutenes; sulfur compounds.

The conjugated triene functionality in a 3,4-bis(methylene)cyclobutene (**1**) not fused to an aromatic system is unique, and interesting in that its reactivity may be expected to be ruled by a shunning of anti-aromatic cyclobutadiene products or intermediates.[1] Despite the anticipated selectivity as regards reaction pathways, and despite the variegated synthetic potential of such structures, the literature on their chemistry is surprisingly limited, and there is a paucity of reports on derivatives of **1** bearing synthetically useful functional groups.[2] The marked tendency of such compounds to polymerize or suffer air oxidation in solution is apparently at fault.[1,3–5] We postulated that these phenomena are not to be blamed on thermodynamic instability alone. In fact, **1** and its derivatives are of lower energy than the diallenes from which they are usually prepared. [The diallene is most often accessed by a high temperature Cope rearrangement of a 1,5-hexadiyne, and under these conditions it is not isolated since its ring closure is faster than its formation[4,5] (Fig. 1).] Rather, it seemed that it is the relatively large charge separation within the structure (μ of **1**$\approx$0.616 D)[6] which is the basis of the kinetic instability. The polarization is presumably one which shifts electronic charge towards the exocyclic methylenes so as to escape the energy penalty of cyclic 4*e* anti-aromaticity. Electron-withdrawing anion-stabilizing

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PII: S0040-4039(00)01148-5

substituents (EWGs) on the exocyclic carbons should therefore, we concluded, stabilize the system. Perusal of the literature showed that this reasoning and corollaries rationalize the chemistry of substituted 3,4-bis(methylene)cyclobutenes and explain why some 1,2,4,5-hexatetraenes readily cyclize to the former, whereas other do not.[2,7–9] Furthermore, the conclusion withstood the additional experimental test to which we subjected it. By extending our previously discovered facile low-temperature rearrangement of propargylic sulfenates to allenic sulfoxides[10] to dipropargylic systems, we succeeded in treading a new and convenient path to conjugated diallenes bearing EWGs (sulfoxides) at their extremities (Fig. 2). In accord with the rationale promulgated above, these cyclized spontaneously to stable 3,4-bis(methylene)cyclobutenes, which did not suffer polymerization or auto-oxidation even in solution.

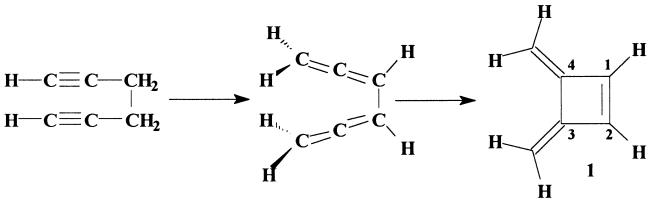


Figure 1.

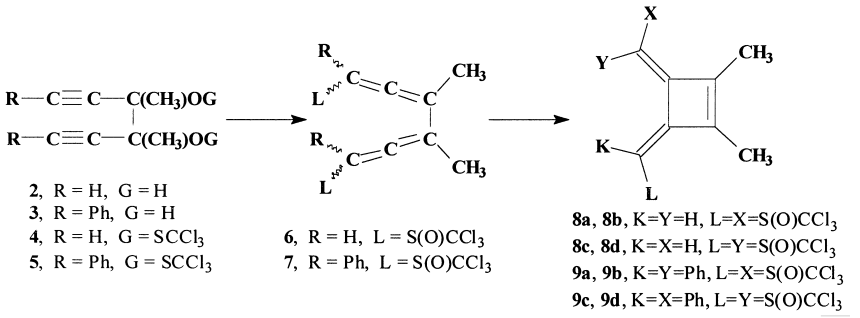


Figure 2.

Specifically, we report herein the simple preparation and characterization of stereoisomers of two derivatives of **1**, 3,4-bis(trichloromethanesulfinylmethylidene)cyclobutene (**8**) and 3,4-bis(phenyltrichloromethanesulfinylmethylidene)cyclobutene (**9**). It should be noted that the pendant sulfoxide groups are also convenient substituents for further transformations.

The desired diols **2** and **3** were prepared by standard procedures, each as an approximately equimolar mixture of the *meso* and *racemic* forms.[11] Flash chromatography (silica gel, EtOAc: hexane, 1:5 v/v) separated the diastereomers of **3**, **3a** (mp 122–124°C) and **3b** (mp 68–70°C), but not those of **2**. Each of diols **2** (*racemate* plus *meso*), **3a** and **3b** was reacted in dry CH_2Cl_2 solution under nitrogen at –78°C with trichloromethanesulfenyl chloride and triethylamine. Following 30 min at –78°C and rapid work-up, examination of the crude reaction products by NMR showed that in no case were there any remains of the first formed propargyl sulfenate esters **4** or **5**. These had completely rearranged to the diallenic disulfoxides (**6**, **7**) and in part further cyclized to 3,4-bis(methylene)cyclobutenes (**8**, **9**) (Fig. 2), as detailed below.

About 78% of the crude product derived from **2** were cyclobutenes **8**, and we were unable to isolate the remaining diallene **6** (~22%)[12] because of its continuing transformation to **8**. Work-up and flash chromatography after total conversion of **6** led to the isolation of four isomeric 3,4-bis(methylene)cyclobutenes, **8a–d** (Table 1).[13]

Table 1
Some NMR data of bis(methylene)cyclobutenes **8** and **9**

	δ ^{1}H				δ ^{13}C							
	CH		**C**H$_3$		**C**H$_3$		**C**S		**C**=CS		**C**CH$_3$	
	E	*Z*	*E*	*Z*	*E*	*Z*	*E*	*Z*	*E*	*Z*	*E*	*Z*
8a	6.05	-	2.27	-	14.17	-	109.49	-	155.35	-	161.54	-
8b	6.01	-	2.27	-	14.44	-	109.28	-	155.39	-	161.75	-
8c	5.97	6.34	2.28	2.09	14.67	10.87	110.05	114.04	154.89	155.76	161.94	161.36
8d	5.94	6.36	2.28	2.11	14.60	10.93	110.38	114.24	155.02	155.47	162.05	161.29
9a	-	-	2.39	-	16.02	-	107.71	-	153.12	-	159.95	-
9b	-	-	2.41	-	16.22	-	108.61	-	152.49	-	160.68	-
9c	-	-	2.33	1.45	16.18	12.54	124.46	126.38	154.86	151.98	161.51	160.11
9d	-	-	2.33	1.34	16.47	12.47	125.07	127.99	153.96	152.37	162.35	160.05

The crude product from **3a** no longer contained diallene, and upon chromatographic separation yielded approximately equal amounts of **9a** and **9b** (total yield 82%; Table 1).[13] In contrast, the crude product derived from **3b**, even after 1 h at –78°C, was still the diallene **7**.[14] However, in CH_2Cl_2 solution at ambient temperature (ca. 3.5 h), **7** transformed to a mixture of cyclobutenes **9c** and **9d**, accompanied by a little polymer. Chromatographic separation yielded pure **9c** and **9d** (Table 1).[13]

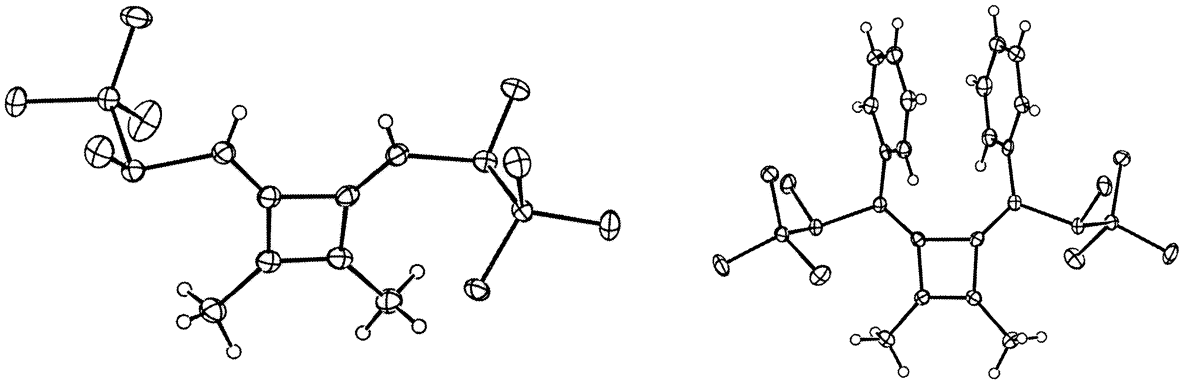
In **8** (or **9**), each of the exocyclic double bonds could independently have an *E* or a *Z* substitution pattern. Additionally, the two sulfur atoms are chiral centers. Ten stereoisomers are therefore possible, and they divide into two *meso* compounds and four *racemates*. These are listed in Table 2. In the event, and as stated above, only four of the six were obtained in each system, **8** and **9**, and in differing yields.

Table 2
Stereochemical isomers of **8** and **9**

	$C_{(3)}$=C----S(O)		$C_{(4)}$=C-----S(O)		*rac/meso*	Corresponds to	
(i)	*Z*	(*R*/*S*)	*E*	(*R*/*S*)	*rac*	{**8d** or **8c**},	{**9d** or **9c**}
(ii)	*Z*	(*R*/*S*)	*E*	(*S*/*R*)	*rac*	{**8c** or **8d**},	{**9c** or **9d**}
(iii)	*E*	(*R*/*S*)	*E*	(*R*/*S*)	*rac*	**8a**	**9a**
(iv)	*E*	(*R*/*S*)	*E*	(*S*/*R*)	*meso*	**8b**	**9b**
(v)	*Z*	(*R*/*S*)	*Z*	(*R*/*S*)	*rac*	-	-
(vi)	*Z*	(*R*/*S*)	*Z*	(*S*/*R*)	*meso*	-	-

The structures of **8a** and **9a** were established unequivocally by X-ray crystallography (Fig. 3). Clearly, both exocyclic double bonds in each are *E*, and the configuration of both sulfur atoms in each is the same. They are therefore *racemates*. The NMR data of **8b** and **9b** show that they too are symmetrical (only one signal for each type of hydrogen and carbon), and the chemical shifts are similar to those of **8a** and **9a**, respectively. Thus, the relevant double bonds in each are also

E,*E*, with **8b** differing from **8a**, and **9b** from **9a**, in the configurations of the sulfoxide groups only. By elimination (Table 2), **8b** and **9b** must be *meso*. In contrast to the foregoing, compounds **8c**, **8d**, **9c** and **9d** all have two absorptions in their NMR spectra for each type of hydrogen and carbon, showing that the two halves of each are dissimilar. This is consistent with one exocyclic double bond in each being *E*, and the other *Z*, the difference in structure within each pair (**8c**/**8d**; **9c**/**9d**) being restricted to the sulfoxide configurations. The proton resonances of C-1 and C-2 pedant methyl groups of **9a** and **9b** are at δ ~2.4. In these *E*,*E*-compounds, both phenyl groups are at the mouth of the 'bay' formed by the exocyclic double bonds, and distanced from the said methyl groups. In the *E*,*Z*-compounds **9c** and **9d** the methyl resonances are at δ 2.33 and 1.34/1.45 (see Table 1). The latter value may be assigned to the methyl group shielded by the proximate phenyl on the *Z* exocyclic double bond.



8a **9a**

Figure 3. Crystal structures of compounds **8a** and **9a**

By similar comparison of the methyl group resonance in the series **8a**–**d** (and also **9a**,**b**), it may be argued that those with δ 2.09 (in **8c**) and 2.11 (in **8d**) are ones proximate to the *Z* double bond, in accord with connectivity determinations by 2D NMR. The steric congestion created in the placement of one phenyl group and one $-S(O)CCl_3$ group in the 'bay' regions of **9c** and **9d** is presumably responsible for slowing the cyclization of the diallene **7** (derived from **3b**) and permitting competing polymerization. No product in which both exocyclic double bonds have *Z* configuration was isolated in either series. Such a structure would require both trichloromethylsulfinyl groups to occupy positions in the 'bay' area, and this is precluded by their steric requirements.

The steric structures of **8a**–**d** and **9a**–**d** detailed above are in keeping with expectations based on the known suprafacial nature of the [2,3]-sigmatropic rearrangement of β,γ-unsaturated sulfenate esters,[15] and the known conrotatory path of the ring closure of diallenes to 3,4-bis(methylene)-cyclobutenes.[3,4,9,16] Not having as yet irrefutable experimental evidence regarding the stereochemistries of the sulfoxide functions in **8c**, **8d**, **9c** and **9d**, we desist from tentative assignments based on conceivable mechanistic steric arguments only.

In conclusion, we note that the present approach utilizes a convenient low-temperature conversion of readily accessible bis(propargylic alcohols) to obtain surprisingly stable disulfoxide substituted 3,4-bis(methylene)cyclobutenes. Methodologies for the synthetic exploitation of the extremely versatile sulfoxide function are well known. Structures of the type presented herein await their profitable utilization.

We are currently engaged in further application and extension of the rational and the simple methodology presented above to the preparation of otherwise substituted stable derivatives of **1**. Their availability will enable our planned investigations of the chemistry of this unique system and its synthetic utilization.

Acknowledgements

The financial support of this study by the Israel Science Foundations is gratefully acknowledged.

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12. Compound **6**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.01 (6H, d, 1.5 Hz), 6.52 (2H, q, 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.30 (CH_3), 99.54 (CH), 106.7 (CCl_3), 108.5 (C-3,4), 206.60 (C-2,5).
13. All compounds for which mp's are reported were recrystallized from ethyl acetate–hexane mixtures and gave satisfactory HRMS and IR spectra. NMR spectra were determined in $CDCl_3$ solution, for ^{1}H at 300 MHz and for ^{13}C at 75 MHz. Assignments are on the basis of 2D NMR. Compound **8a**: mp 168–169°C (24%); **8b**, mp 58–60°C (6%); **8c**, mp 146–148°C (25%); **8d**, mp 80–82°C (4%); **9a**, mp 164–165°C (42%); **9b**, mp 158–159°C (40%); **9c**, mp 128–130°C (15%); **9d**, mp 164–166°C (13%).
14. Compound **7**, hexane-insoluble colorless crystals, mp 124–126°C, isolated yield 63%; ^{1}H NMR δ 2.05 (6H, s), 7.43 (10H, m); ^{13}C NMR δ 16.94 (CH_3), 109.27 (CCl_3), 113.39 (C-3,4), 118.16 (C-1,6), 129.21, 127.84 (arom C), 206.06 (C-2,5).
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