Tetrahedron Letters 153 (2024) 155369

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis of (bicyclo[2.2.0]hex-1-yl)methanal and Arrhenius parameters for thermal rearrangement: Radical stabilizing effect of aldehyde substituents on highly strained C—C bonds

Anita Nowienski [a], Murray G. Rosenberg [b], Udo H. Brinker [c,d,*]

[a] Department of Chemistry, Ruhr-University Bochum, Universitätsstr. 150, 44801 Bochum, Germany
[b] 216 Harry L Dr., Johnson City, NY 13790, United States
[c] Department of Chemistry, The State University of New York at Binghamton, P. O. Box 6000, Binghamton, NY 13902, United States
[d] Institute of Organic Chemistry, University of Vienna, Währinger Str. 38, 1090 Vienna, Austria

ARTICLE INFO

Keywords:
Bicyclo[2.2.0]hexanes
Aldehyde synthesis
Swern oxidation
Thermolysis
Arrhenius parameters
1,4-Diradicals
Radical stabilization energy

ABSTRACT

Bicyclo[2.2.0]hexane rearranges to hexa-1,5-diene via the cyclohexane-1,4-diyl diradical. The 1-formyl substituted derivative was sought to evaluate the effect of a CHO-group on the rate of rearrangement. (Bicyclo[2.2.0]hex-1-yl)methanal was prepared for the first time in a multistep synthesis starting from hexachlorocyclopentadiene. The pivotal last step was achieved by Swern oxidation of (bicyclo[2.2.0]hex-1-yl) methanol at $T = -60$ °C. The carbon skeleton of the alcohol precursor remains intact under those conditions. Thermolysis of the aldehyde to 2-methylenehex-5-enal follows a first-order rate law between $T = 322.85–361.51$ K ($T_{avg} = 343.30$ K). Seven rate constants k_T were used to plot log k_T vs. $1/T$, which provided the Arrhenius parameters for the rearrangement: activation energy (E_a) = 25.4 ± 1.0 kcal/mol and pre-exponential factor (A_{343}) = 1.66×10^{12} s^{-1}. The E_a is 10.6 kcal/mol below that of the unsubstituted archetype bicyclo[2.2.0] hexane. This sizable change in E_a reflects the radical stabilization energy of the CHO-group in 1-formylcyclohexane-1,4-diyl.

Introduction

Bicyclo[2.2.0]hexane (**1**) [1] opens to hexa-1,5-diene (**3**) upon thermolysis (Scheme 1).[2–5] The mechanism for **1**→**3** was established from detailed kinetics experiments and advanced computations.[2–7] The twist-boat conformation of cyclohexane-1,4-diyl (**2**) is formed after the C1–C4 bond of **1** is homolyzed.[6] It cannot form diene **3** directly, however, because C1 and C4 are too far from the C2–C3 and C5–C6 bonds (Scheme 1). Instead, the fate of **2** depends on its conformation.[6,7] The twist-boat form of **2** mediates the automeric ring-inversion **1**⇌**1** but it is the chair form of **2** that opens to **3**. This part of the mechanism is shared by the automeric Cope rearrangement **3**⇌**3**, which proceeds via chair **2**(Scheme 1).[6–11].

Alkyl groups placed on C1 of **1** increase thermal ring-opening rates.[12,13] This decrease in reaction activation energy (E_a) is due to σ-bond inductive donation (+*I* effect). We hypothesize that a stabilizing CHO-group placed on C1 of **1** will further reduce the E_a, due to π-electron resonance delocalization (+*R* effect), [14] and further increase the rate of thermal ring-opening. (Bicyclo[2.2.0]hex-1-yl)methanal (**4**) has been computed to be stable, [15] so a multistep synthesis leading to **4** should be promising. Once thermolyzed, aldehyde **4** would generate 1-formylcyclohexane-1,4-diyl (**5**) (Scheme 2) in the way that **1** generates **2** (Scheme 1), assuming the same ring-opening mechanism. Stabilization of **5** by its CHO-group should noticeably decrease the E_a for **4**→**6** compared to that for **1**→**3** (E_a = 36.0 kcal/mol).[2] The change in E_a (ΔE_a) serves as an estimate of the substituent's radical stabilization energy (RSE), which is the difference between a radical's thermodynamic and kinetic bond dissociation energy (BDE).[7] Tables of empirically based RSE values for various substituents can be found elsewhere.[16,17].

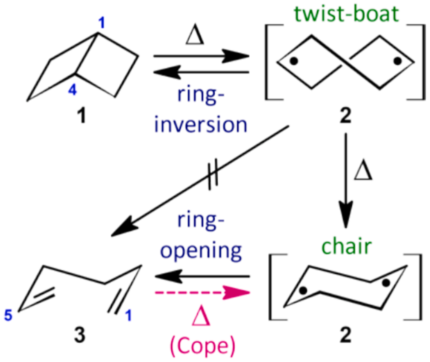
Materials and methods

Several 1-substituted bicyclo[2.2.0]hexanes have been synthesized to date but few have been thermolyzed for kinetics analyses.[13,18–20] So, a multistep synthesis giving (bicyclo[2.2.0]hex-1-yl)methanal (**4**)

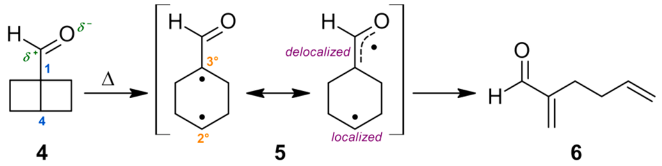
---

* Corresponding author.
E-mail addresses: udo.brinker@univie.ac.at, ubrinker@binghamton.edu (U.H. Brinker).

https://doi.org/10.1016/j.tetlet.2024.155369
Received 9 October 2024; Received in revised form 8 November 2024; Accepted 11 November 2024



Scheme 1. Generation and fate of cyclohexane-1,4-diyl (**2**).



Scheme 2. Proposed radical stabilization of C1 of 1-formylcyclohexane-1,4-diyl (**5**).

was implemented (Scheme 3; see Supplementary data). Retrosynthesis of aldehyde **4** hinged on preparing the precursor (bicyclo[2.2.0]hex-1-yl)methanol (**15**) [19,21–23] (Scheme 3).[20–28] So, we followed the proven methods of Gassman and of Dauben to prepare alcohol **15** (Scheme 3).[21,25] Reaction of hexachlorocyclopentadiene (**7**) with a methanolic solution of KOH gave 1,2,3,4-tetrachloro-5,5-dimethoxycyclopenta-1,3-diene (**8**) [25] in 52% yield. Diels–Alder cycloaddition of **8** with ethene at $T = 197$ °C provided 1,2,3,4-tetrachloro-7,7-dimethoxybicyclo[2.2.1]hept-2-ene (**9**) in 16% yield.[21,25,26] Next, **9** was hydrogenated in the presence of a Pd catalyst and Et_3N to give 1,4-dichloro-7,7-dimethoxybicyclo[2.2.1]heptane (**10**) [21] in 63% yield and 98% purity. Then a one-pot synthesis bypassing ketone **11** was followed to make (4-chlorobicyclo[2.2.0]hex-1-yl)methanoic acid (**12**), [20,21,23] which was obtained from **10** in 48% yield. Next, carboxylic acid **12** was esterified at room temperature using diazomethane in Et_2O to form methyl (4-chlorobicyclo[2.2.0]hex-1-yl)methanoate (**13**) in 96% yield and 98% purity. The reduction of methyl ester **13** with $LiAlH_4$ in Et_2O at $T = 0$ °C provided alcohol **14** in 71% yield after subliming the crude product. The dechlorination of **14** with Na metal in the presence of *tert*-BuOH formed the isomeric alcohols **15** and (spiro[2.3]hex-4-yl) methanol (**16**) in a 90.3:9.7 ratio, according to analytical GC. This is an improvement over the original method,[21] which gave a 72:28 ratio. Alcohol **15** was isolated in 44% yield and 98% purity after workup using preparative GC. All that remained was to oxidize **15** to **4**, but an exact procedure was unknown. We were mainly concerned with possible side reactions, such as over-oxidation of **15** or cleavage of its labile C1–C4 bond.

Results

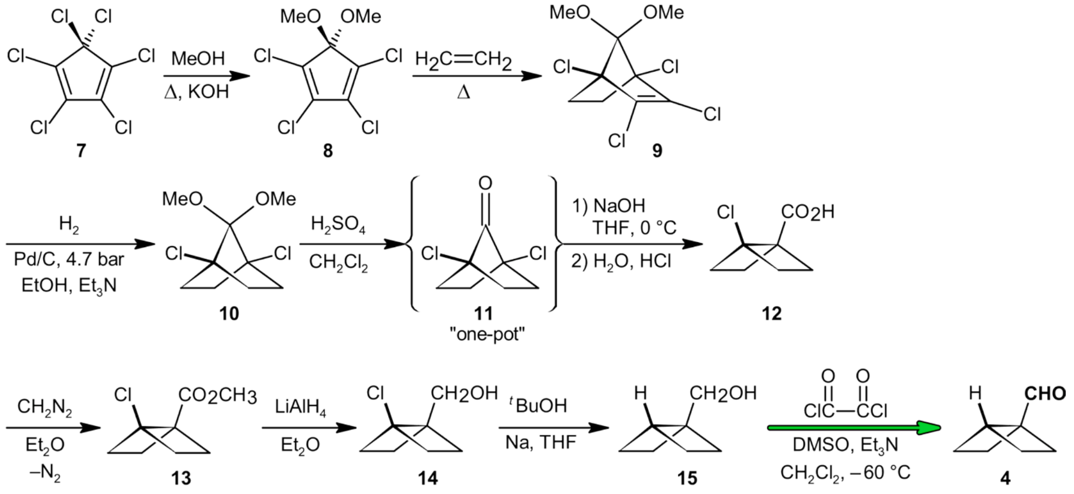
We found that the nonacidic conditions of oxalyl chloride/Et_3N and low temperatures ($T = -60$ °C) were necessary to oxidize **15** to **4** successfully (Scheme 3).[27,28] The Swern oxidation produced aldehyde **4** in 87.4% purity. The impurity is attributed to residual Et_3N. The structure of **4** and the presence of its characteristic CHO-group were determined using spectroscopy (see Supplementary data). Comparison of the NMR signals of **4** with precursor **15** shows that the bicyclo[2.2.0]hexane skeleton remains intact during **15**→**4** (Scheme 3). Aldehyde **4** is thermolabile and could not be purified by preparative GC. Only 2-methylenehex-5-enal (**6**) was isolated (Scheme 2). The structure of **6** was verified using spectroscopy.

Samples of **4** were dissolved in benzene-d_6 doped with an internal standard in order to study the rate of **4**→**6**. Aliquots ($V = 10$ μL) were sealed in glass melting-point tubes. A temperature range (ΔT) of ca. 40 Celsius degrees was necessary to ensure reliable data. Each sample was thermolyzed in an oven by heating it at the temperature designated in Table 1. A dry-ice/acetone bath was used to freeze the sample's reaction progress before restoring it to room temperature. The remaining amount of **4**, compared to the internal standard, was monitored using analytical GC. The decrease in the initial $[\mathbf{4}]_0$ over time (t) was recorded (see

Table 1
Empirical rate constants (k_T) for rearrangement **4** → **6**.

T[a] (°C)	($k_T \pm \sigma$) ($\times 10^{-5}$ s^{-1})
49.70	1.17 ± 0.08
59.14	2.71 ± 0.07
65.50	5.60 ± 0.22
71.30	11.11 ± 0.67
74.32	14.70 ± 1.47
82.70	55.07 ± 1.89
88.36	61.81 ± 3.16

[a] $T_{avg} = 70.15$ °C (343.30 K).



Scheme 3. Multistep synthesis of (bicyclo[2.2.0]hex-1-yl)methanal (**4**).

Supplementary data) and graphed according to eq (1) to give the first-order plot in Figure 1, which uses a logarithmic scale to represent the exponential decay of **4** over the range Δ*T*. The slope of each line represents rate-constant *k* at that specific *T* (i.e., k_T). Values and standard deviations (σ) are compiled in Table 1. The results support a unimolecular rearrangement **4**→**6** within the Δ*T* used.

$$\ln\left(\frac{[\mathbf{4}]}{[\mathbf{4}]_0}\right) = -kt \tag{1}$$

The integrated form of the Arrhenius equation is presented in eq (2). The seven k_T and *T* values in Table 1 were used to graph eq (2) (Figure 2). The Arrhenius parameters E_a and *A* are obtained from eq (2), which defines a line with slope $E_a/(-2.303\ R)$ and vertical intercept of log *A*. Extrapolation of the line defined by eq (2) to the vertical axis gives log *A*, which is 12.2 (Figure 2). The value of *A* is $10^{(\log A)}$ s^{-1}, or 1.66 × 10^{12} s^{-1}. The line's slope corresponds to an E_a of 25.4±1.0 kcal/mol. These values are most valid for the average temperature used (T_{avg} = 343.30 K) and may be compared with those already reported in Table 2. The Eyring parameters activation enthalpy ($\Delta H^{\ddagger}$), activation entropy ($\Delta S^{\ddagger}$), and activation free energy ($\Delta G^{\ddagger}$) at $T = 343.3$ K are 24.8 kcal/mol, –4.89 × 10^{-3} (kcal/mol)/K (i.e., –4.9 eu), and 26.4 kcal/mol, respectively. Note that $\Delta S^{\ddagger}$ for **4**→**6** is modestly negative despite fragmentation of the strained C1–C4 bond. This may reflect increased symmetry in the transition state for **1**→**3**.[6,7]

$$\log k_T = -\frac{E_a}{2.303\ R}\left(\frac{1}{T}\right) + \log A_T \tag{2}$$

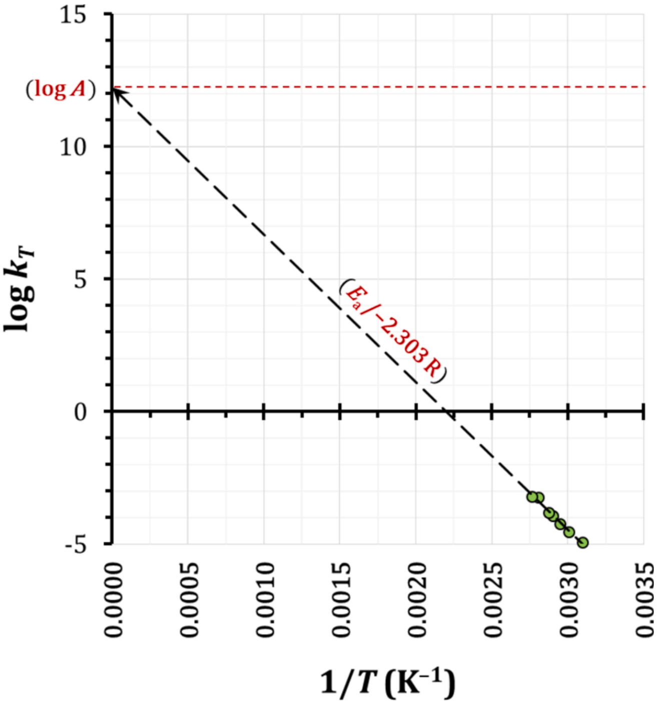
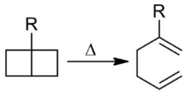


Figure 2. First-order Arrhenius equation plot for **4** → **6**: E_a = 25.4 ± 1.0 kcal/mol and log *A* = 12.2.

Table 2
Arrhenius parameters for bicyclo[2.2.0]hexanes.

	**E_a**(kcal/mol)	**log *A***
–R = –H [a]	36.0	13.4
= –CO_2Me [b]	29.4	12.2
= –**CHO** [c]	**25.4**	**12.2**

[a] Ref. 2. [b]Ref. 13. [c]This work.

Discussion

The rearrangement **1**→**3** is driven by the release of a copious amount of strain energy (E_s). In fact, **1** ($\Delta_f H^{\circ}$ = 29.8 kcal/mol) [29] has a computed E_s of 54.1 kcal/mol. [30] This is about twice that of cyclobutane (**17**; E_s = 26.5 kcal/mol). [31] Indeed, the difference between the C—C bond homolysis E_a of **17** and that of **1** is 26.5 kcal/mol (cf. Table 3). Unlike **1**→**3**, rearrangement **4**→**6** is also driven by π-electron resonance delocalization within diradical intermediate **5** (Scheme 2). The E_a barrier for ring-opening **1**→**3** is 36.0 kcal/mol,[2,3] while that for **4**→**6** is only 25.4 kcal/mol (Table 2, Table 3). The ΔE_a for bicyclic systems **1** vs. **4** of –10.6 kcal/mol is in accord with that already reported for monocyclic systems **17** [32] vs. cyclobutylmethanal (**18**), [33] for which ΔE_a is –9.2 kcal/mol (Table 3). The ΔE_a of –10.6 kcal/mol is tantamount to the RSE of the CHO-group vs. an H atom (Table 3). The reduction in E_a for **4**→**6** (Scheme 2), compared to that for unsubstituted prototype **1**→**3** (Scheme 1), is due to the RSE imparted by the –CH=O group positioned at C1 of **1**. The weak C1–C4 bond of **1** is even weaker in **4**. So, thermolysis of **4** is well underway at a temperature lower than that needed for **1**→**3**. It must be pointed out that the –CH=O group is almost as stabilizing as the –CH=CH_2 group (RSE = –12.6 kcal/mol).[17] The difference of 2 kcal/mol is ostensibly due to destabilizing σ-inductive withdrawal (i.e., –*I* effect) from the CHO-group's O atom (Scheme 2). A sample of RSE values for 3°-C-centered radicals is listed in Table 4.[17]

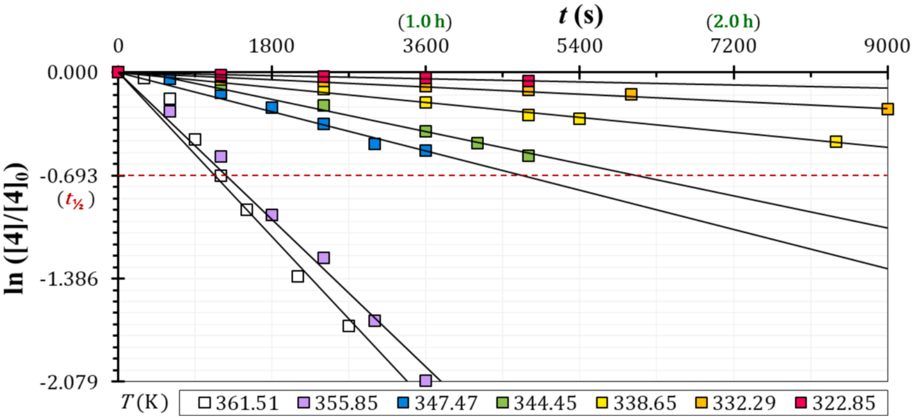
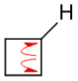
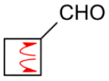
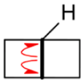
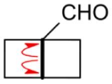


Figure 1. Plots for the first-order decay of (bicyclo[2.2.0]hex-1-yl)methanal (**4**) at different temperatures *T* provide the corresponding rate constants k_T needed for an Arrhenius equation plot.

Table 3
Arrhenius parameters for cyclic aldehydes 18 and 4 compared to corresponding cycloalkanes 17 and 1.

Compound	E_a(kcal/mol)	log *A*	*A* (s^{-1})
 **17**[a]	62.5	15.6	3.98×10^{15}
 **18**[b]	53.3	14.4	2.51×10^{14}
$\Delta E_a =$	**–9.2**		
 **1**[c]	36.0	13.4	2.52×10^{13}
 **4**[d]	25.4	12.2	1.66×10^{12}
$\Delta E_a =$	**–10.6**		

[a] Ref. 32. [b]Ref. 33. [c]Ref. 2. [d]This work.

Table 4
Radical stabilization energy (RSE) for some 3°-C radicals.[a]

Substituent–R	RSE (kcal/mol)
–Me	[0]
$–CO_2Et$	–2.8
–C≡N	–3.4
–Bz	–6.0
–Ph	–8.4
–CH = O[b]	**–10.6**
$–CH = CH_2$	–12.6

[a] Ref. 17. [b]This work.

Conclusion

(Bicyclo[2.2.0]hex-1-yl)methanal (**4**) was synthesized for the first time from (bicyclo[2.2.0]hex-1-yl)methanol (**15**) by using Swern oxidation conditions at $T = –60$ °C. Thermolysis of **4** between $T = 322.85–361.51$ K gives 2-methylenehex-5-enal (**6**) in a first-order reaction. The Arrhenius parameters were determined: $E_a = 25.4 \pm 1.0$ kcal/mol and $\log A_{343} = 12.2$. There is a 50-fold rate increase over the temperature range used. The radical stabilization energy (RSE) imparted by a –CH=O group positioned at C1 of bicyclo[2.2.0]hexane (**1**) was determined to be –10.6 kcal/mol. This is in line with the value of –9.2 kcal/mol already reported for cyclobutane (**17**). It also approaches the RSE for the $–CH=CH_2$ group of –12.6 kcal/mol. The marked decrease in E_a with **4** compared to that of unsubstituted **1** indicates that 1-formylbicyclo[2.2.0]hexa-1,4-diyl (**5**) is stabilized due to the combined presence of π-electron resonance delocalization between C1 and the CHO-group and the increased ordinality of C1 from a 2°-C radical center in diradical **2** to a 3°-C one in **5**.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Anita Nowienski: Writing – original draft, Investigation, Data curation. **Murray G. Rosenberg:** Writing – review & editing, Data curation. **Udo H. Brinker:** Writing – review & editing, Data curation, Conceptualization, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2024.155369.

Data availability

Data will be made available on request.

References

[1] S. Cremer, R. Srinivasan, Tetrahedron Lett. 1 (1960) 24–27, https://doi.org/10.1016/S0040-4039(01)99367-0.
[2] C. Steel, R. Zand, P. Hurwitz, S.G. Cohen, J. Am. Chem. Soc. 86 (1964) 679–684, https://doi.org/10.1021/ja01058a027.
[3] M.J. Goldstein, M.S. Benzon, J. Am. Chem. Soc. 94 (1972) 5119–5121, https://doi.org/10.1021/ja00769a075.
[4] M.J. Goldstein, M.S. Benzon, J. Am. Chem. Soc. 94 (1972) 7147–7149, https://doi.org/10.1021/ja00775a046.
[5] E.N. Cain, Tetrahedron Lett. 12 (1971) 1865–1868, https://doi.org/10.1016/S0040-4039(01)87483-9.
[6] D.A. Hrovat, W.T. Borden, J. Am. Chem. Soc. 123 (2001) 4069–4072, https://doi.org/10.1021/ja004209o.
[7] B.K. Carpenter. In: Z. Rappoport, J.F. Liebman, eds. The Chemistry of Cyclobutanes. S. Patai, Z. Rappoport, eds. Patai's Chemistry of Functional Groups. Wiley: New York, 2005, Chapter 20, 923–954. ISBN: 9780470864005.
[8] W.v.E. Doering, W.R. Roth, Tetrahedron. 18 (1962) 67–74, https://doi.org/10.1016/0040-4020(62)80025-8.
[9] J.J. Gajewski, N.D. Conrad, J. Am. Chem. Soc. 100 (1978) 6268–6269, https://doi.org/10.1021/ja00487a071.
[10] J.L. Mackey, Z. Yang, K.N. Houk, Chem. Phys. Lett. 683 (2017) 253–257, https://doi.org/10.1016/j.cplett.2017.03.011.
[11] K.-J. Su, J.-L. Mieusset, V.B. Arion, L. Brecker, U.H. Brinker, Org. Lett. 9 (2007) 113–115, https://doi.org/10.1021/ol0626793.
[12] E.N. Cain, R.K. Solly, J. Am. Chem. Soc. 95 (1973) 7884–7885, https://doi.org/10.1021/ja00804a063.
[13] W. Kirmse, P. Sandkühler, Liebigs Ann. Chem. (1981) 1394–1406, https://doi.org/10.1002/jlac.198119810808 (Ger.).
[14] M.L. Poutsma, J. Org. Chem. 76 (2011) 270–276, https://doi.org/10.1021/jo102097n.
[15] M.A. Forman, B.C. Zanoni, E.C. Chopko, P.J. Carroll, Struct. Chem. 9 (1998) 27–32, https://doi.org/10.1023/A:1022431514386.
[16] F.G. Bordwell, X.-M. Zhang, Acc. Chem. Res. 26 (1993) 510–517, https://doi.org/10.1021/ar00033a009.
[17] J.J. Brocks, H.-D. Beckhaus, A.L.J. Beckwith, C. Rüchardt, J. Org. Chem. 63 (1998) 1935–1943, https://doi.org/10.1021/jo971940d.
[18] E.N. Cain, R.K. Solly, J. Am. Chem. Soc. 95 (1973) 4791–4796, https://doi.org/10.1021/ja00796a004.
[19] D.C. Owsley, J.J. Bloomfield, J. Am. Chem. Soc. 93 (1971) 782–784, https://doi.org/10.1021/ja00732a042.
[20] K.V. Scherer Jr, Tetrahedron Lett. 7 (1966) 5685–5689, https://doi.org/10.1016/S0040-4039(01)84178-2.
[21] W.G. Dauben, J.L. Chitwood, K.V. Scherer Jr, J. Am. Chem. Soc. 90 (1968) 1014–1020, https://doi.org/10.1021/ja01006a029.
[22] F. Arndt, Org. Synth. 15 (1935) 3–5, https://doi.org/10.15227/orgsyn.015.0003.
[23] W.C. Fong, R. Thomas, K.V. Scherer Jr, Tetrahedron Lett. 12 (1971) 3789–3790, https://doi.org/10.1016/S0040-4039(01)97289-2.
[24] R.N. McDonald, C.A. Curi, Tetrahedron Lett. 17 (1976) 1423–1426, https://doi.org/10.1016/S0040-4039(00)71273-1.
[25] P.G. Gassman, J.L. Marshall, Org. Synth. 48 (1968) 68–71, https://doi.org/10.15227/orgsyn.048.0068.
[26] P.G. Gassman, P.G. Pape, J. Org. Chem. 29 (1964) 160–163, https://doi.org/10.1021/jo01024a037.
[27] A.J. Mancuso, D.S. Brownfain, D. Swern, J. Org. Chem. 44 (1979) 4148–4150, https://doi.org/10.1021/jo01337a028.
[28] E.J. Leopold, Org. Synth. 64 (1986) 164–174 (cf. Part A). https://doi.org/10.15227/orgsyn.064.0164.
[29] W.R. Roth, O. Adamczak, R. Breuckmann, H.-W. Lennartz, R. Boese. Chem Ber. 124 (1991) 2499–2521. (Ger.) https://doi.org/10.1002/cber.19911241121.
[30] P.R. Rablen, Chemistry 2 (2020) 347–360, https://doi.org/10.3390/chemistry2020022.

[31] K.B. Wiberg. In: Z. Rappoport, J. F. Liebman, eds. The Chemistry of Cyclobutanes. S. Patai, Z. Rappoport, eds. Patai's Chemistry of Functional Groups. Wiley: New York, 2005, Chapter 1, 1–15. ISBN: 9780470864005.

[32] C.T. Genaux, F. Kern, W.D. Walters, J. Am. Chem. Soc. 75 (1953) 6196–6199, https://doi.org/10.1021/ja01120a025.

[33] B.C. Roquitte, W.D. Walters, J. Am. Chem. Soc. 84 (1962) 4049–4052, https://doi.org/10.1021/ja00880a015.