Pergamon

Tetrahedron 58 (2002) 891–896

TETRAHEDRON

Ozonolyses of 1-alkyl-substituted 1-*tert*-butylethylenes and highly methylated methylenecycloalkanes. The influence of the substituent steric bulk on the direction of cleavage of the primary ozonides

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Received 17 October 2001; accepted 26 November 2001

Abstract—Ozonolyses of 1-alkyl-substituted 1-*tert*-butylethylenes and of highly methylated methylenecycloalkanes were conducted in the presence of trifluoroacetophenone (**7**) in ether. The ozonolysis of 2,2,6-trimethyl-1-methylenecyclohexane provided only the crossed-ozonide **10** derived from capture of formaldehyde *O*-oxide with the ketone **7** in 42% yield, while in the case of the relevant 2,2,5-trimethyl-1-methylenecyclopentane the alternative crossed-ozonide **15e** derived from cycloaddition of 2,2,5-trimethylcyclopentanone *O*-oxide with the ketone **7** was the sole isolable product. The total energies of two possible cycloreversion processes for the primary ozonide **12c** and for **12e**, calculated at B3LYP/6-31G**//B3LYP/3-21G* level of theory, seem to reproduce the observed difference in the regio-chemistry of fragmentation between these two primary ozonides. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

Extensive investigation of the mechanism of alkene ozonolysis has confirmed the essential features of the pathway originally proposed by Criegee.[1] Much of the current interest in this process centers on the factors affecting the direction of cleavage of the primary ozonide (PO; 1,2,3-trioxolane).[2] Three factors have been found to play an important role, i.e. the electron-donating effect of the alkyl substituent attached to the C–C double bond (Markovnikov effect),[3] the electron-withdrawing effect of the hetero-atom substituent at the allylic position,[4] and the steric effect of the allylic dialkyl substituents.[5] The most clear-cut example indicating the importance of the latest factor is the ozonolysis of 1,5,5-trimethylcyclopentene.[5c] Of two possible carbonyl oxide intermediates, only the less-hindered aldehyde oxide, with the geminal methyl groups remote from the carbonyl oxide group, is exclusively produced. Thus, in this case the steric effect of the allylic dimethyl groups seems to overcome the electronic effect of the methyl substituent at C-1. In contrast, ozonolysis of 1-methylcyclopentene proceeds mainly by the corresponding ketone oxide.[3b] To obtain further insight into the origin of the substituent steric effects, we have conducted the ozonolyses of a series of 1-alkyl-substituted 1-*tert*-butylethylenes **1a–c** and of methylenecycloalkanes, **11a–d** and **17**, in the presence of trifluoroacetophenone in ether and have determined in each case the ratios of two possible crossed-ozonides.

2. Results and discussion

2.1. Ozonolysis of 1-alkyl-substituted 1-*tert*-butylethylenes

Ozonolysis of 1-*tert*-butyl-1-methylethylene (**1a**) in ether gave the normal ozonide **9a** in a yield of 36%. When the same reaction was repeated in the presence of trifluoroacetophenone (**7**), however, the formation of the ozonide **9a** was completely suppressed and instead, only the crossed-ozonide **8a** derived from the cycloaddition of *tert*-butyl methyl ketone *O*-oxide (**3a**) with the ketone **7** was obtained in 60% yield (Table 1 and Scheme 1). This suggests that (i) the direction of cleavage of PO **2a** is very selective, affording exclusively the ketone oxide **3a** and (ii) the reaction of the ketone *O*-oxide **3a** with the reactive ketone **7** is much faster than that with formaldehyde **4**. From the ozonolysis of 1-*tert*-butyl-1-isopropylethylene (**1b**) in the presence of **7** was obtained the crossed-ozonide **8b** (56%). In the case of 1,1-di-*tert*-butylethylene (**1c**), however, the ^{1}H NMR spectra of the crude reaction mixture showed that only the alternative cross-ozonide **10**, derived

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Keywords: ozonolysis; direction of cleavage of primary ozonide; steric effect.

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PII: S0040-4020(01)01183-8

Table 1. Ozonolysis of 1-alkyl-substituted *tert*-butylethylenes and highly methylated methylenecycloalkanes

Substrate	Additive[a]	Products (% yield)
1a		**9a** (36)
1a	$PhCOCF_3$	**8a** (60)
1b		**9b** (48)
1b	$PhCOCF_3$	**8b** (56)
1c		**5c** (45)
1c	$PhCOCF_3$	**10** (44)[b]
11a		**16a** (81)
11a	$PhCOCF_3$	**15a** (59)
11b		**16b** (75)
11b	$PhCOCF_3$	**15b** (65)
11c		**14c** (56)
11c	$PhCOCF_3$	**10** (42)[b], **14c** (75)
11d		**14d** (76)
11d	$PhCOCF_3$	**10** (42)[b], **14d** (80)
11e		**16e** (53)[c]
11e	$PhCOCF_3$	**15e** (59)[d]

Reaction with 1 equiv. of ozone in diethyl ether at -70°C.

[a] The reaction was conducted in the presence of 1 equiv. of trifluoroacetophenone.

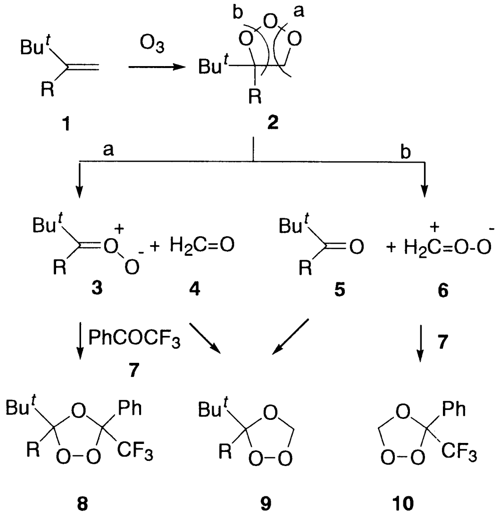
[b] The yields of the ozonide **10** determined by the ^{1}H NMR spectra of the crude product mixture were 67% from **1c**, 83% from **11c**, and 83% from **11d**, respectively.

[c] The ^{1}H NMR spectra of the crude product mixture showed that **16e** was produced in 80% yield.

[d] ^{1}H NMR spectra of the crude product mixture showed that **15e** was produced in 80% yield.

from cycloaddition of formaldehyde *O*-oxide (**6**) to the ketone **7**, was produced in 67% yield (Scheme 1). Since the ozonide **10** was volatile, the isolated yield was only 44% (Table 1, see footnote).

These results clearly demonstrate that for a series of 1-alkyl-substituted 1-*tert*-butylethylenes **1a**–**c**, the electronic and/or steric effects of the alkyl substituents play an important role in determining the direction of cleavage of the corresponding PO **2a**–**c**. It would be reasonable to expect that, on the basis of the electronic considerations, the formation of the corresponding ketone *O*-oxide **3** should be favored, whereas a preponderance of formaldehyde *O*-oxide (**6**) would arise from the influence of steric effects. Exclusive formation of the crossed-ozonides **8a**,**b** from alkenes **1a**,**b** suggests that for these substrates the electronic effects of the alkyl-substituents are decisive, thereby providing predominantly the pairs of the ketone *O*-oxides **3a**,**b** and formaldehyde (**4**) (path a in Scheme 1). In the case of highly congested di-*tert*-butylethylene (**1c**), however, the steric effect of two *tert*-butyl groups determines the regiochemistry of the PO cleavage such that the sterically less-congested formaldehyde *O*-oxide (**6**) is exclusively produced (path b in Scheme 1). In the case of **1a**,**c** the difference in total energies between two cleavage pathways, determined by the quantum chemical calculations at B3LYP/6-31G**//B3LYP/3-21G* level of theory,[6] is consistent with these conclusions (Table 2). In the alkene **1a** the pathway a leading to the formation of the corresponding ketone *O*-oxides **3a** is more exothermic (15.1 kJ/mol). In contrast, the alternative pathway b is more favorable (7.4 kJ/mol) in the case of the sterically most-congested di-*tert*-butylethylene (**1c**). However, the DFT calculations could not reproduce the result for the behavior of **1b**; the calculation suggests the predominance of path b (5.4 kJ/mol), while the experimental result demonstrates the predominant contribution of the alternative path a. At present, we can not offer proper explanation for this discrepancy.



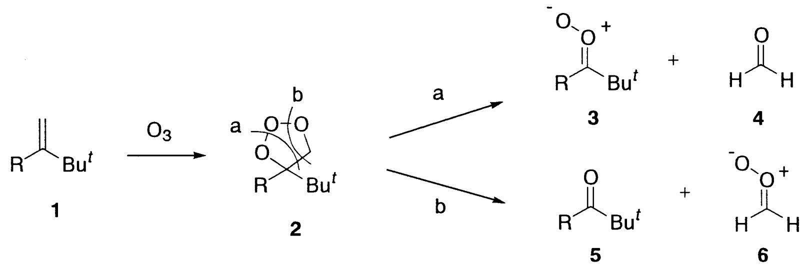
Scheme 1. (a) R=Me; (b) R=isopropl; (c) R=*tert*-butyl.

2.2. Ozonolyses of highly-methylated methylene-cycloalkanes

As expected from the substituent electronic effects, ozonolysis of methylenecyclohexane (**11a**) in the presence of trifluoroacetophenone (**7**) in ether proceeded mainly by cyclohexanone *O*-oxide (**13a**) and as the sole isolable product, the crossed-ozonide **15a** was obtained in 59% yield (Table 1 and Scheme 2). From 2,2-dialkyl-substituted 1-methylenecyclohexane **11b** also, the corresponding crossed-ozonide **15b** derived from cycloaddition of the ketone *O*-oxides **13b** and the ketone **7** was exclusively produced. The presence of additional methyl group(s) at C-6, however, altered dramatically the regiochemistry of PO cleavage. Ozonolyses of 2,2,6-trimethyl-1-methylenecyclohexane (**11c**) and 2,2,6,6-tetramethyl-1-methylenecyclohexane (**11d**) gave exclusively the alternative crossed-ozonide **10** derived from capture of formaldehyde *O*-oxide (**6**) by the ketone **7**. Thus, in the ozonolyses of substrates **11c**,**d** the steric effects of the additional methyl substituent(s) seem to be important in determining the direction of cleavage of PO.

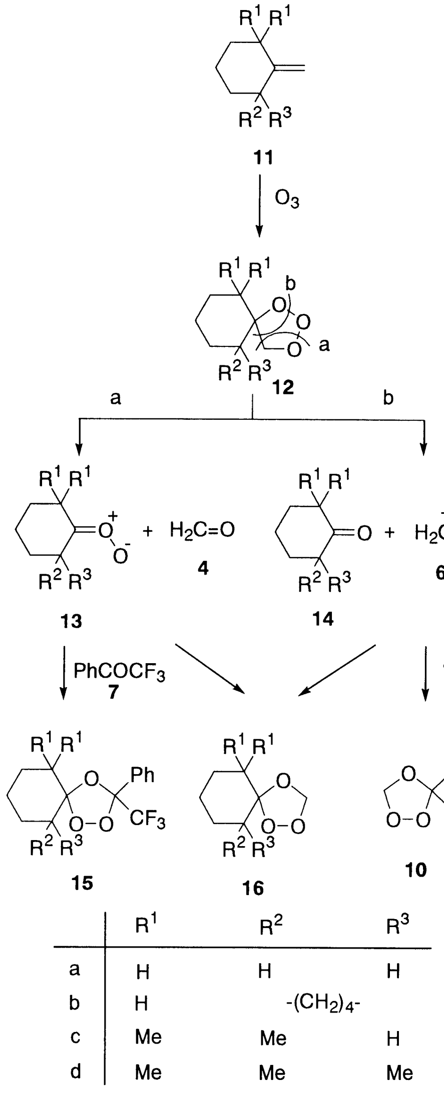
If consideration is given to the behavior of 1,1-di-*tert*-butylethylene (**1c**), the result for the highly crowded methylenecyclohexane **11d** is understandable.[5] Less easily understood is the fact that the substitution pattern of 2,2,6-trimethyl-1-methylenecyclohexane (**11c**) is very similar to that of 1-*tert*-butyl-1-isopropylethylene (**1b**) and nevertheless, the regiochemistry of the PO cleavage is quite different between two PO, **12c** and **2b**. As an approach to understanding this apparent discrepancy, ozonolysis of 2,2,5-trimethyl-1-methylenecyclopentane (**11e**) was conducted in the presence of trifluoroacetophenone (**7**). Surprisingly, the sole isolable product was the crossed-ozonide **15e** derived from the cycloaddition of the ketone *O*-oxide **13e** and the ketone **7**, suggesting that in this case the substituent electronic effects overcome the steric effect of the methyl substituent at C-5

Table 2. The difference in heats of two cycloreversion processes for primary ozonides, **2a–c**, respectively



R	**2**	**3**	**3**+**4** (path a)	**5**	**5**+**6** (path b)
Me	−500.674911 hartree (44.0 kJ/mol)	−386.189269 hartree	−500.691689 hartree (0 kJ/mol)	−311.111119 hartree	−500.685933 hartree
^{i}Pr	−579.298819 hartree (50.1 kJ/mol)	−464.813413 hartree	−579.316641 hartree (5.4 kJ/mol)	−389.743092 hartree	−579.317906 hartree (0 kJ/mol)
^{t}Bu	−618.602473 hartree (57.0 kJ/mol)	−504.119943 hartree	−618.621363 hartree (7.4 kJ/mol)	−429.049360 hartree	−618.624174 hartree (0 kJ/mol)

Heats of formation of **4** and **6** were −144.502420 and −189.574814 hartree, respectively.

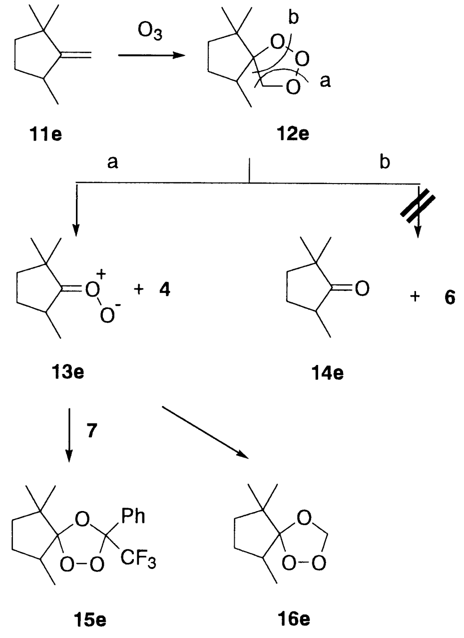


	R^1	R^2	R^3
a	H	H	H
b	H	-(CH$_2$)$_4$-	
c	Me	Me	H
d	Me	Me	Me

Scheme 2.

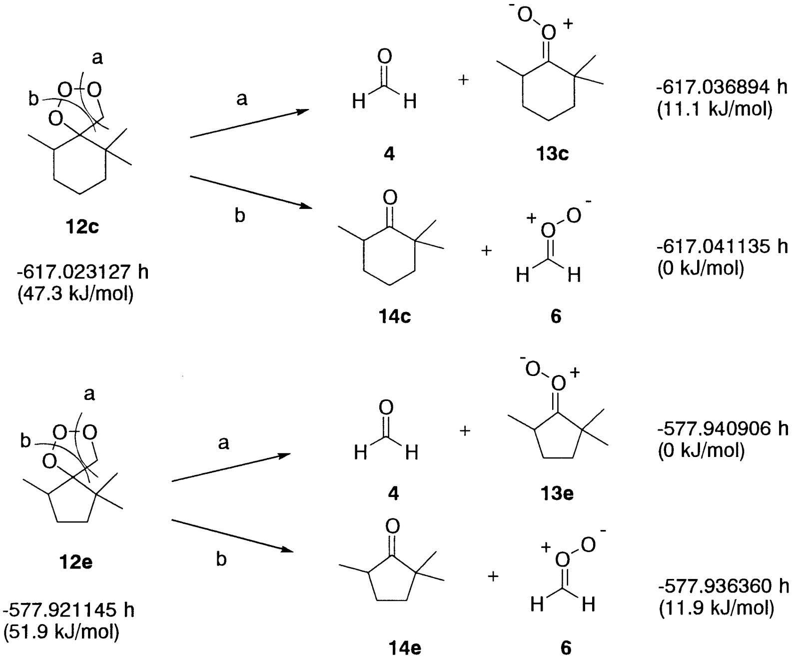
(Table 1 and Scheme 3). In connection with this, ozonolysis of the methylenecyclopentane **11e** in ether in the absence of the ketone **7** was found to give the normal ozonide **16e** in a high yield of 80%, suggesting that the cycloaddition of the ketone *O*-oxide **1e** with formaldehyde (**4**) proceeds smoothly. In contrast, under the similar conditions the ozonolysis of the methylenecyclohexane **11c** did not yield the normal ozonide **16c** and instead, the ketone **14c** was isolated in 56% yield. This implies that the sterically congested ketone **14c** has a negligible reactivity even toward the small and reactive formaldehyde *O*-oxide (**6**). Exactly the same trend was observed for the sterically most-congested methylenecyclohexane **11d**.

To understand the remarkable difference in behavior between the two substrates, **11c** and **11e**, the difference in total energies between two cycloreversion processes were



Scheme 3.

Table 3. The difference in heats of two cycloreversion processes for primary ozonides, **12c** and **12e**, respectively



examined in each case by the quantum chemical calculations at B3LYP/6-31G**//B3LYP/3-21G* level of theory. (Table 3). In the case of PO **12c** path b leading to the formation of formaldehyde *O*-oxide (**6**) and ketone **14c** was more favorable than the alternative pathway a leading to the ketone *O*-oxide **13c** and formaldehyde (**4**). In contrast, exactly a reverse trend was observed for PO **12e**. Thus, path a leading to the ketone *O*-oxide **13e** and **4** was more favorable than the alternative pathway b leading to a pair of the ketone **14e** and **6**. These results are clearly consistent with the experimental observations. The dramatic ring-size effect (cyclohexanone *O*-oxide **13c** and cyclopentane *O*-oxide **13e**) on the energy difference can be reasonably explained by the steric effect (Fig. 1). In the case of **13c** a severe repulsion (1,3-allylic strain) between the oxygen and the methyl group, which are located in almost the same plane, would be expected. Alternatively, in **13e** the steric repulsion seems to be negligible, as can be visualized in the calculated structure (Fig. 1).

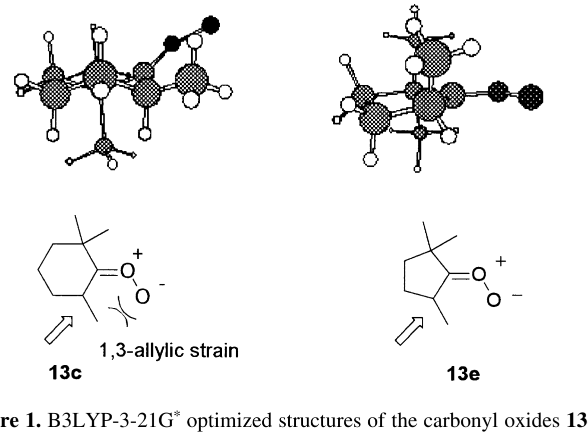


Figure 1. B3LYP-3-21G* optimized structures of the carbonyl oxides **13c** and **13e**.

3. Conclusion

The ozonolyses of 1-alkyl-substituted 1-*tert*-butylethylenes and of highly methylated methylenecylcloalkanes, together with the former observations,[5] demonstrate that the steric effect of the allylic alkyl groups plays an important role in determining the direction of cleavage of PO such that the formation of the electronically less-favored but sterically more-favored carbonyl oxide predominates. However, the remarkable difference in the regiochemistry of the PO cleavage observed between 2,2,6-trimethyl-1-methylenecyclohexane and 2,2,5-trimethyl-1-methylenecyclopentane suggests that the extent of appearance of the steric effect would be significantly influenced by the apparently minor change in the structure of substrates.

4. Experimental

4.1. General procedures

^{1}H and^{13}C NMR spectra were obtained in $CDCl_3$ (unless otherwise noted) with $SiMe_4$ standard. The method of ozonolysis was previously described.[7] The alkenes **1b**,[8] **1c**,[9] and **11b**,[10] **11c**,[9] **11d**,[11] were prepared from the corresponding ketones **5b**,[12] **5c**,[12] and **14b**,[13] **14c**,[14] **14d**[15] by the reported methods. 2,2,5-Trimethyl-1-methylenecyclopentane (**11e**) was prepared as follows.[10] To dry dimethyl sulfoxide (30 mL) was added 1.58 g of sodium hydride followed by 13.6 g (38 mmol) of methyltripheylphosphonium bromide. This mixture was stirred at 50–55°C for 1 h before 4.0 g (32 mmol) of 2,2,5-trimethylcyclopentanone[16] was added as a solution in 20 mL dimethyl sulfoxide. After the mixture was stirred at 55°C overnight, it was added to 50 mL of water and extracted four times with pentane. The pentane extracts were combined, washed with saturated brine, and then dried over $MgSO_4$. The pentane was removed by distillation and the residue was distilled under reduced pressure to give 1.2 g (31%) of 2,2,5-trimethyl-1-methylenecyclopentane (**11e**): colorless oil, bp 80°C (20 mmHg); ^{1}H NMR δ 1.03 (3H, s), 1.08 (3H, s), 1.09 (3H, d, J=7 Hz), 1.2–1.6 (4H, m), 1.8–1.9 (1H, m), 4.74 (1H, d, J=2 Hz), 4.78 (1H, d, J=2 Hz); ^{13}C NMR δ 19.75, 29.88, 29.96, 31.99, 39.26, 40.11, 42.39, 101.89, 167.40. Anal. Calcd for C_9H_{16}: C, 87.0; H, 13.0. Found: C, 87.0; H, 13.1.

4.2. Ozonolysis of 1-alkyl-substituted 1-*tert*-butylethylenes 1a–c in ether

The ozonolysis of 1-*tert*-butyl-1-methylethylene (**1a**) is representative. To a solution of an ethylene **1a** (196 mg, 2.00 mmol) in diethyl ether (20 mL) was passed a slow stream of ozone (1 equiv.) at −70°C. After evaporation of the solvent, the crude products were separated by column chromatography on silica gel (column, 2×50 cm; 20 g of silica gel). Elution with ether–hexane (1:20, v/v) gave ozonide **9a** (106 mg, 36%).

4.2.1. 3-*tert*-Butyl-3-methyl-1,2,4-trioxolane (9a). Colorless oil; ^{1}H NMR δ 1.00 (9H, s), 1.35 (3H, s), 4.88 (1H, s), 5.15 (1H, s); ^{13}C NMR δ 19.57, 25.41, 37.70, 94.28, 113.35. Anal. Calcd for $C_7H_{14}O_3$; C, 57.5; H 9.65. Found: C, 57.7; H, 9.6.

4.2.2. 3-*tert*-Butyl-3-isopropyl-1,2,4-trioxolane (9b). Colorless oil; ^{1}H NMR δ 0.98 (6H, d, J=3 Hz), 1.10 (9H, s), 2.0–2.3 (1H, m), 4.93 (1H, s), 5.10 (1H, s); ^{13}C NMR δ 18.56, 20.08, 25.86, 32.24, 39.66, 94.23, 114.03. Anal. Calcd for $C_9H_{18}O_3$: C, 62.0; H, 10.4. Found: C, 62.0; H, 10.6.

4.3. Ozonolysis of 1-alkyl-substituted 1-*tert*-butylethylenes 1a–c in the presence of trifluoroacetophenone in ether

Ozonolysis of 1-*tert*-butyl-1-methylethylene (**1a**) is representative. To a solution of an alkene **1a** (196 mg, 2.00 mmol) and trifluoroacetophenone (348 mg, 2 mmol) in diethyl ether (20 mL) was passed a slow stream of ozone (1 equiv.) at −70°C. After evaporation of the solvent, the products were separated by column chromatography on silica gel (elution with ether–hexane, 1:20). As the first fraction, the ozonide **8a** (348 mg, 60%) was eluted.

4.3.1. 3-*tert*-Butyl-3-methyl-5-phenyl-5-trifluoromethyl-1,2,4-trioxolane (8a). Colorless oil; ^{1}H NMR δ 1.13 (9H, s), 1.25 (3H, s), 7.3–7.7 (5H, m). Anal. Calcd for $C_{14}H_{17}F_3O_3$: C, 57.9; H, 5.9. Found: C, 58.2; H, 6.2.

4.3.2. 3-*tert*-Butyl-3-isopropyl-5-phenyl-5-trifluoromethyl-1,2,4-trioxolane (8b). Colorless oil; ^{1}H NMR δ 0.63 (3H, d, J=7 Hz), 0.90 (3H, d, J=7 Hz), 1.15 (9H, s), 2.27 (1H, septet, J=7 Hz), 7.3–7.8 (5H, m); ^{13}C NMR δ 18.24, 19.00, 20.36, 26.18, 28.16, 32.60, 39.26, 103.16 (q, J=33 Hz), 121.74 (q, J=288 Hz), 126.82, 128.01, 129.84, 132.44. Anal. Calcd for $C_{16}H_{21}F_3O_3$: C, 60.4; H, 6.7. Found: C, 60.1; H, 6.7.

4.3.3. 3-Phenyl-3-trifluoromethyl-1,2,4-trioxolane (10). Colorless oil; ^{1}H NMR δ 5.13 (1H, s), 5.45 (1H, s), 7.3–7.7 (5H, m); ^{13}C NMR δ 95.56, 103.03 (q, J=34 Hz), 121.49 (q, J=289 Hz), 126.77, 128.73, 129.08, 130.58, 135.51. Anal. Calcd for $C_9H_7F_3O_3$: C, 49.1; H, 3.2. Found: C, 49.0; H, 3.0.

4.4. Ozonolysis of methylenecycloalkanes in ether

Ozonolysis of methylenecyclohexane (**11a**) is representative. To a diethyl ether solution (20 mL) of an alkene **11a** (192 mg, 2.00 mmol) was passed a slow stream of ozone (1 equiv.) at −70°C. After evaporation of the solvent, the products were separated by column chromatography on silica gel. Elution with ether–hexane (1:20; v/v) gave the ozonide **16a** (234 mg, 81%).

4.4.1. 1,2,4-Trioxaspiro[4.5]decane (16a). Colorless oil; ^{1}H NMR δ 1.2–1.8 (10H, m), 5.27 (2H, s); ^{13}C NMR δ 23.94, 24.91, 33.94, 93.75, 108.89. Anal. Calcd for $C_7H_{12}O_3$: C, 58.3; H, 8.4. Found: C, 58.2; H, 8.4.

4.4.2. 1,2,4-Trioxadispiro[4.0.4.4]tetradecane (16b). Colorless oil; ^{1}H NMR δ 1.2–2.1 (16H, m), 5.01 (1H, s), 5.22 (1H, s); ^{13}C NMR δ 21.57, 23.18, 25.25, 25.41, 32.69, 33.64, 33.96, 35.40, 36.89, 94.41, 112.53. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.6; H, 9.2. Found: C, 66.8; H, 9.1.

4.4.3. 6,6,9-Trimethyl-1,2,4-trioxaspiro[4.4]nonane (16e). Colorless oil; ^{1}H NMR δ 0.98 (3H, s), 0.99 (3H, d, J=7 Hz), 1.07 (3H, s), 1.4–1.6 (4H, m), 1.8–1.9 (1H, m), 5.04 (1H, s), 5.11 (1H, s); ^{13}C NMR δ 22.70, 25.88, 27.51, 31.63, 36.84, 38.90, 43.16, 94.00, 118.06. Anal. Calcd for $C_9H_{16}O_3$: C, 62.8; H, 9.4. Found: C, 62.6; H, 9.6.

4.5. Ozonolysis of methylenecycloalkanes in the presence of trifluoroacetophenone

Ozonolysis of methylenecyclohexane (**11a**) is representative. After treating a diethyl ether solution (20 mL) of an alkene **11a** (160 mg, 1.67 mmol) and trifluoroacetophenone (291 mg, 1.67 mmol) with ozone (1 equiv.) at −70°C, the crude products were separated by column chromatography on silica gel. The first fraction (elution with ether–hexane, 1:20) contained the ozonide **15a** (285 mg, 59%).

4.5.1. 3-Phenyl-3-trifluoromethyl-1,2,4-trioxaspiro[4.5]decane (15a). Colorless oil; ^{1}H NMR δ 1.3–2.2 (10H, m), 7.3–7.8 (5H, m); ^{13}C NMR δ 23.38, 23.92, 24.69, 31.77, 33.93, 103.27 (q, J=34 Hz), 113.08, 121.69 (q, J=288 Hz), 126.61, 128.27, 130.21, 132.09, 135.49. Anal. Calcd for $C_{14}H_{15}F_3O_3$: C, 58.3; H, 5.3. Found: C, 58.6; H, 5.4.

4.5.2. 3-Phenyl-3-trifluoromethyl-1,2,4-trioxadispiro[4.0.4.4]tetradecane (a 2:1 mixture of two isomers) (15b). Colorless oil; ^{1}H NMR δ 1.0–2.3 (16H, m), 7.3–7.8 (5H, m); ^{13}C NMR δ major isomer: 21.69, 22.79, 25.05, 25.38, 31.29, 33.10, 33.98, 36.88, 48.09, 103.02 (q, J=34 Hz), 116.73, 121.65 (q, J=288 Hz), 126.51, 128.05, 128.14, 130.01, 133.14; minor isomer: ^{13}C NMR δ 21.46, 23.13, 25.14, 25.25, 31.81, 33.25, 34.54, 37.02, 48.86, 103.59 (q, J=34 Hz), 117.93, 121.36 (q, J=287 Hz), 126.51, 127.04, 128.14, 129.92, 133.53. Anal. Calcd for $C_{18}H_{21}F_3O_3$: C, 63.2; H, 6.2. Found: C, 63.3; H, 6.5.

4.5.3. 3-Phenyl-3-trifluoromethyl-6,6,9-trimethyl-1,2,4-trioxaspiro[4.4]nonane (15e). Colorless oil; ^{1}H NMR δ 1.06 (3H, s), 1.10 (3H, d, J=7 Hz), 1.23 (3H, s), 1.5–1.7 (4H, m), 1.8–1.9 (1H, m), 7.4–7.6 (5H, m); ^{13}C NMR δ 22.41, 25.50, 28.75, 31.70, 38.38, 41.63, 43.43, 102.88 (q, J=33 Hz), 121.18 (q, J=289 Hz), 122.05, 126.79, 128.17, 128.25, 130.15, 132.29. Anal. Calcd for $C_{16}H_{19}F_3O_3$: C, 60.8; H, 6.1. Found: C, 60.5; H, 6.0.

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