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1,2-Addition of TMS-CF_3 and TMS-CN to sterically crowded 2,2,4,4-tetramethyl-1,3-cyclobutanedione and related studies[1†]

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Abstract

Cyanotrimethylsilane (TMS-CN) and (trifluoromethyl)trimethylsilane (TMS-CF_3) add smoothly to carbonyl groups of sterically congested 2,2,4,4-tetramethyl-1,3-cyclobutanedione (**1**). Depending on the ratio of reagents used, respective mono- and bis-adducts were obtained in good yields. In contrast, reactions with such nucleophiles as methylmagnesium bromide and methyllithium give exclusively open-chain products including a novel hydroperoxide (**18**) whose structure was unequivocally characterized by X-ray crstallography.

1. Introduction

2,2,4,4-Tetramethyl-1,3-cyclobutanedione (1) was reported for the first time by Wedekind and Weissange at the beginning of this century.[2] It is a well-known building block for the synthesis of sterically congested systems.[3–6] A convenient method for its synthesis consists of in situ dimerization of dimethylketene generated from isobutyryl chloride and triethylamine.[7]

In spite of high steric hindrance, the carbonyl groups in **1** react easily with diverse nucleophiles to give products with either the cyclobutane ring intact or are converted into open-chain derivatives. Typical conversions with amines can afford both types of products and the course of reaction was shown to depend on the nucleophilicity/basicity of the amine used. Generally, ammonia and aliphatic amines are able to cleave the cyclobutane ring resulting in the formation of ketoamides of type **2** (XR = NHR, NR_2). Less basic aromatic amines afford, in a typical addition – elimination reaction, imine derivatives of type **3**.[8–13] Later reports showed that aliphatic amines can also be used to prepare cyclic imines **3** (R=Alk) but the reaction must be performed in the presence of titanium (IV) chloride.[14,15] Moreover, under these conditions, the diimine with very bulky *t*-butyl substituents (R=*t*-Bu) could be obtained in good yield.[14] Alcohols and phenols easily cleave the cyclobutane ring to provide the corresponding 2,2,4-trimethyl-3-oxovalerate **2** (X=OR, OAr).[16] Contrasting results were reported for the reactions of **1** with organometallic reagents. Wedekind and Miller[17] claim to have obtained 1,3-diethyl-2,2,4,4-tetramethyl-1,3-

† Dedicated to Prof. S. C. Bhattacharyya.

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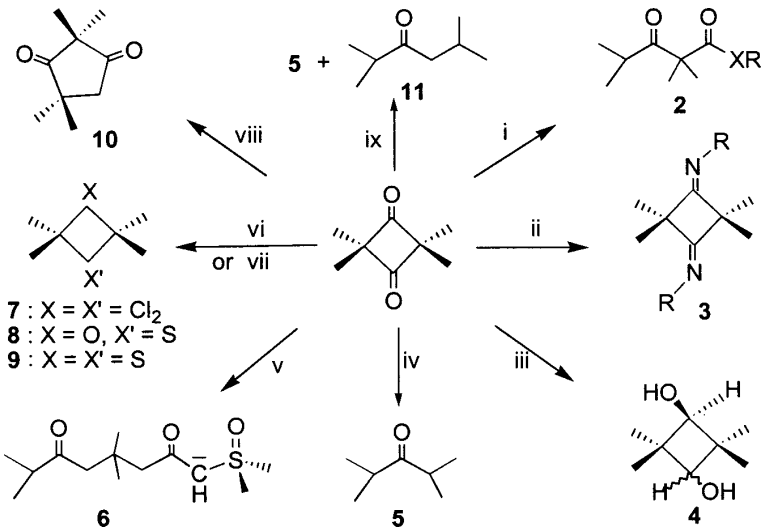


i) RXH (X = NH or O); ii) Ar-NH_2 or R-NH_2/$TiCl_4$ (RT=Ar or Alk); iii) H_2/cat.; iv) C_6H_5MgBr; v) $(CH_3)_2S{=}CH_2$; vi) PCl_5 or vii) P_2S_5; viii) CH_2N_2; ix) Zn/AcOH.

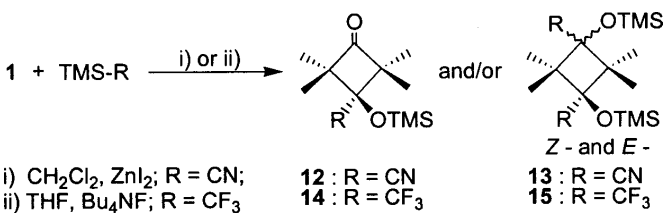
cyclobutanediol as the product upon reaction with ethylmagnesium bromide. Subsequent studies, however, showed that it was not possible to obtain cyclic alcohols from **1** with Grignard reagents. Erickson and Kitchens[18] described the open-chain ketone (**5**) as the main product isolated after reaction with phenylmagnesium bromide under similar reaction conditions. Dimethylsulfonium methylide [$(CH_3)_2S(O)^+CH_2^-$] was reported to open the cyclobutanone ring of **1** and after an intramolecular H-migration, a new ylide **6** was the only product formed in this clean conversion.[19] Reaction of **1** with phosphorus pentachloride, however, gave the expected tetrachlorocyclobutane **7**[20] which after treatment with lithium can be effectively converted into bicyclo[1.1.0]butane.[21] Reaction of **1** with phosphorus pentasulfide in pyridine solution offers an easy entry to sulfur analogues **8** and **9** without ring opening.[22–24] Diazomethane undergoes a smooth 1,3-dipolar cycloaddition to thiocarbonyl groups in thioketones **8** and **9** without the destruction of cyclobutane ring and new sulfur-nitrogen heterocycles are the products.[4,22–25] Parent dione **1** reacts with diazomethane in a different way giving synthetically useful 2,2,5,5-tetramethyl-1,3-cyclopentanedione **10** as the only product after N_2-elimination and ring expansion.[26] Catalytic hydrogenations of **1** gave a mixture of isomeric 2,2,4,4-tetramethyl-1,3-cyclobutanediols (**4**) in good yields,[27] while newly reported reduction with metallic zinc results in the formation of open-chain ketones **5** and/or **11**.[28]

Previously, we have found that the fluorine-anion-induced addition of (trifluoromethyl)-trimethylsilane (TMS-CF_3) to carbonyl groups in ketones and aldehydes offers a very attractive entry to trifluoromethylated secondary and tertiary alcohols.[29–31] This prompted us to extend our studies to the reaction of **1** towards TMS-CF_3 as well as other silylated nucleophiles such as cyanotrimethylsilane (TMS-CN), allyltrimethylsilane ($CH_2{=}CHCH_2TMS$) and trimethylsilyl isocyanate (TMS-NCO). The nature of ring-opened products upon the addition of methylmagnesium bromide and methyllithium to **1** was also ascertained.

2. Results and discussion

2.1. *Reaction with silylated nucleophilic reagents*

Cyanotrimethylsilane (TMS-CN) is a powerful source of CN^- (or NC^-)[32] and its additions to saturated and unsaturated carbonyl compounds has a special importance in organic synthesis.[33] Now, TMS-CN has been treated with **1** in the presence of zinc iodide as a catalyst (Scheme 1). At room temperature the only product isolated was the 1:1 adduct **(12)** obtained upon exclusive 1,2-addition. In ^{13}C NMR spectrum the unconverted carbonyl group was identified as a singlet at δ ^{13}C 216.4 and the signal of the cyano group was found at δ ^{13}C 118.3. When the reaction mixture of **1** with 2 mol. equiv. of TMS-CN was heated for a longer period of time, the *bis*-adduct **13** was the main product. After distillative work-up and separation of **12** as a lower boiling fraction, bis-adduct **13** was identified as a 2:1 mixture of geometrical isomers in favor of sterically less hindered *E*-**13**. Both isomers were characterized based on the spectral data that differ in a characteristic manner due to the different symmetry elements in both molecules. ^1H NMR spectrum of *E*-**13** showed the presence of only one singlet for the four equivalent CH_3-groups anchored to the cyclobutane ring (δ ^1H 1.25) and for *Z*-**13** the same groups appeared as two singlets, 6H each, at δ ^1H 1.06 and 1.46, respectively.



Scheme 1.

Trifluoromethyltrimethylsilane (TMS-CF_3) adds easily to carbonyl groups under fluoride-anion-catalyzed reactions and is generally described as a 'nucleophilic trifluoromethylating reagent'.[31] In our initial experiments, the addition of TMS-CF_3 to **1** was carried out in the presence of commercial tetrabutylammonium fluoride (TBAF) (available in THF solution). The reaction went to completion at room temperature within several hours to afford mono- and bis-adducts (**14** and **15**) in 2:1 approximate ratio. After distillative separation of both the products, bis-adduct **15** was identified in ^{19}F NMR spectrum as a 1:6 mixture of *Z*- and *E*-isomers. In order to reduce the amount of TMS-CF_3 decomposed by water notoriously present in commercial THF solution of TBAF,[34] we dried it[29] by using activated molecular sieves. This reduced the amount of undesired water in the reaction mixture and enhanced the catalytic activity of TBAF. Predried solution of the catalyst in THF showed much higher activity and no evolution of gaseous trifluoromethane (generated *in situ* by the hydrolysis of TMS-CF_3) from the reaction mixture has been observed.[35] Under these conditions, the addition of TMS-CF_3 to **1** took place instantenously and only the ratio of the reagents determined the nature of the adduct obtained. With almost equimolar amount of **1** and TMS-CF_3 (a slight excess of TMS-CF_3 is, however, still needed), the mono-adduct **14** was the only product. Increasing the amount of TMS-CF_3 resulted in the formation of the bis-adduct **15** as a 1:2 mixture of *Z*- and *E*-isomers. Adducts **14** and **15** differ sufficiently in their boiling points and similar to the adducts of **1** with TMS-CN, could be easily separated by fractional distillation.

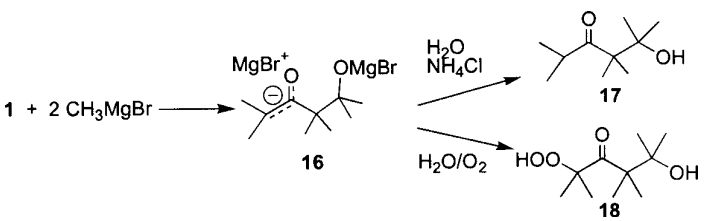
All further attempts to separate the mixture of isomeric *Z*- and *E*-**15** using either distillation or chromatographic methods (TLC, column chromatography) were, however, unsuccessful. Characteristic differences in the NMR spectra, of *Z*- and *E*-**15** result from the different symmetry of their molecules. In the ^{13}C NMR of *Z*-**15**, two pairs of nonequivalent CH_3 groups give two signals at δ ^{13}C 19.6 and 23.5, respectively. A possible 'through space' interaction between CF_3- and CH_3- groups generates a small coupling constant J_{CF} = 3.2 Hz. In *E*-**15**, all the four CH_3 groups are equivalent and their broadened signal appeared in the decoupled ^{13}C NMR spectrum at δ ^{13}C 21.5. In ^{19}F NMR spectra, however, both isomers gave only one CF_3 signal (due to accidental equivalence).

Based on the ^{1}H and ^{19}F NMR spectra of crude reaction mixtures, it is clear that in the reactions with TMS-CF_3 no open-chain products were formed. It is noteworthy that the addition products of TMS-CN and TMS-CF_3 to dione **1** preserve the trimethylsilyl ether moiety even after the aqueous work-up with dilute hydrochloric acid. No attempts were made to desilylate the ethers into free alcohols.

Other silylated nucleophiles studied were allyltrimethylsilane and trimethylsilyl isocyanate (TMS-NCO). Both are known to add to carbonyl groups under fluoride ion catalysis.[36] However, all our attempts to react either allyltrimethylsilane or TMS-NCO with **1**, even in the presence of freshly activated molecular sieves and after 48 h at ambient temperature, failed and no discernible addition products were observed. Heating of the reaction mixtures in THF resulted in decomposition and formation of tarry products.

2.2. *Alkylation of **1** with organometallic reagents*

In earlier study by Erickson and Kitchens,[18] the reaction of **1** with Grignard reagents took place only at elevated temperature and resulted in the formation of some open-chain products after a cascade of reactions. Looking for a possible route to achieve mild additions of methylmagnesium bromide or methyllithium to **1** that could result in alkylated cyclobutanediols, we investigated the course of reactions at low temperature and in different solvents. Dione **1** was reacted with a fourfold excess of methylmagnesium bromide (CH_3MgBr) at 0ºC using diethyl ether or tetrahydrofuran as solvents. From the reaction mixture we isolated two open-chain products **17** and **18**. Hydroxyketone **17** was identical with a product described earlier by Erickson and Kitchens,[18] but hydroperoxide **18** (isolated in 20% yield) was unprecedented (Scheme 2).



Scheme 2.

Dione **1** is able to add 2 mol/equiv. of CH_3MgBr with the preservation of one carbonyl group. Addition occurs stepwise and the reaction with the first molecule of organometallic reagent must generate the open-chain anion in which only one carbonyl group is available to react with the next

molecule of CH_3MgBr. The same hydroxyketone **17** was also the only product isolated from reaction of **1** with methyllithium in etheral solution.

The route to hydroperoxide **18** must lead by deprotonation and oxidation of **17**. Enolizable ketones are known to give hydroperoxides and a proposal of the mechanism of this interesting reaction involves the autooxidation of ketone-anion by a radical chain process.[37] A possible oxygen source may involve that the work-up procedure responsible for the formation of **18** involving a secondary reaction of an unstable organometallic intermediate **16**. Compared with the usual methods of synthesis of hydroperoxides, the formation of **18** under extremely mild conditions is interesting but such analogies in the chemistry of alkylhydroperoxides already exist.[38,39] **18** is a remarkably stable, crystalline compound with a narrow melting point of 110ºC that melts without decomposition. Isolated in a pure form, it could be stored conveniently in a refrigerator without decomposition.

Compound **18** crystallized from pentane as colorless needles in the orthorhombic space group Pbca, with a = 12.427(2) Å, b = 12.077(2) Å, c = 15.106(2) Å (volume 2267.1(6) Å^3), Z = 8. The X-ray data were collected at 163 K up to a 2θ maximum at 95.0º. The structure was solved with direct method and refined to a final agreement factor of R = 5.33%. Hydroperoxide group -O-O-H shows a *trans*-planar conformation with the dihydral angles ϕ=121.1º; the bond length between both oxygen atoms -O-O- was found to be 1.465(4) Å and agrees with typical value found in other hydroperoxides.[25] On the other hand, hydroxy group H-O- and the carbonyl function at C(2) are located almost in the same plane and show clearly *cis*-orientation along which an intramolecular hydrogen bond between the oxygen and hydrogen atoms exists; the distance between two atoms was found to be 1.64 Å.

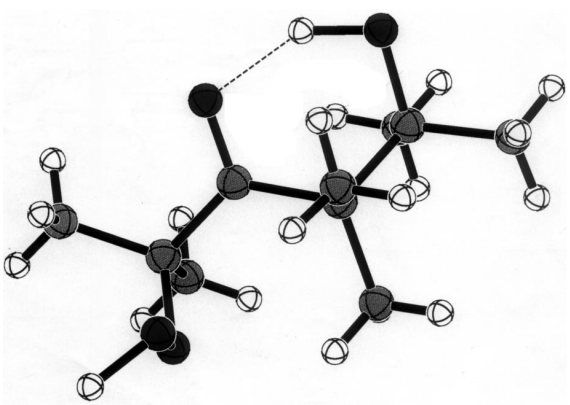


FIG.1. X-ray structure of hydroperoxide **18** (ORTEP plot).

Further attempts were also made to obtain alkylated diols from **1** and other organometallic reagents. Using *N*,*N*,*N*',*N*'-tetramethylethylenediamine (TMEDA) as a cosolvent for the reaction with methyllithium, we, however, isolated **17** again as the only product. A similar result was obtained when methylmagnesium bromide was reacted with **1** in a heterogeneous mixture, in pentane. In this case, **17** was isolated in 56% yield. All these experiments seem to suggest that the retro-aldol-cleavage cannot be suppressed in the reactions of **1** with organometallic reagents.

Finally, we tested the reaction of **1** with methyltitanium tris(isopropoxide) [$CH_3Ti(O\text{-}i\text{-}Pr)_3$] which is known as a nonbasic, nucleophilic reagent capable of adding to aldehydes and ketones with a very high chemo- and stereoselectivity.[40] At room temperature, no reaction took place. The subsequent heating of the THF-solution for 15 h resulted in decomposition of starting material, probably via formation of ring-opened products similar to those postulated by Erickson and Kitchens.[18]

3. Conclusions

Sterically crowded 2,2,4,4-tetramethyl-1,3-cyclobutanedione (**1**) was shown to react smoothly with TMS-CN and TMS-CF_3 to give 1, 2-mono- and bis-adducts, depending on the molar ratio of reagents used. The addition of TMS-CF_3 to dione **1** is the first example of a successful alkylation of **1** which afforded products with intact cyclobutane ring. Activated molecular sieves improved significantly the catalytic activity of commercial solution of tetrabutylammonium fluoride by diminishing the amount of water. Dione **1** undergoes a retro-aldol-cleavage upon nucleophilic attack by methylmagnesium bromide and methyllithium even at low temperature.

4. Experimental

Melting points are uncorrected. NMR spectra were recorded on a Varian VXR-200 (200 MHz) and Varian Unity-300 (300 MHz); chemical shifts are given in δ(ppm) and coupling constants (J) in Hz. Tetramethylsilane has been used as a standard for ^1H and ^{13}C, and trichlorofluoromethane $CFCl_3$ was used as a reference for ^{19}F NMR spectra. IR spectra were taken on a Nicolet FT-IR 800-SX as KBr pellets or liquid films on NaCl plates. Mass spectra were registered on a Hewlett-Packard GC/MS 5890/5971A, a Finnigan MAT INCOS 50 and at the Mass Spectrometry Facility, University of California at Riverside. Elemental analyses were performed at the Galbraith Laboratories Inc., Knoxville, Tenessee.

(Trifluoromethyl)trimethylsilane (TMS-CF_3) was synthesized from bromotrifluoromethane and chlorotrimethylsilane according to a modified procedure.[41] Other starting materials were obtained from commercial suppliers and used without further purification. THF and ether were distilled over sodium/benzophenone, pentane from P_2O_5, TMEDA over KOH, and CH_2Cl_2 over CaH_2 immediately prior to use. Pyridine and ethanol were used as received. Reactions were carried out under nitrogen or argon atmosphere. Commercial solution of tetrabutylammonium fluoride (TBAF) in THF (1M concentration) was purchased from Aldrich.

X-ray diffraction analyses were performed on a Siemens P4/RA diffractometer using CuKα radiation (l = 1.54178 Å) with a highly oriented graphite crystal monochromator. Structural solution and refinements were done using the Siemens SHELXS-86 program[42] and the full-matrix least squares method.

4.1. *3-Cyano-2,2,4,4-tetramethyl-3-trimethylsiloxycyclobutanone (**12**)*

A solution of TMS-CN (298 mg, 3 mmol) and dione **1** (140 mg, 1 mmol) in 5 ml dichloromethane was added dropwise at 0ºC to a magnetically stirred solution of zinc iodide (64 mg, 0.2 mmol) in 5 ml dichloromethane. The stirring was continued for 48 h at ambient temperature. After quenching the reaction mixture with $KHCO_3$ solution, the aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were washed with $KHCO_3$ solution and dried over $MgSO_4$. The solvent was evaporated in vacuum and the residue was distilled in Kugelrohr at 90ºC/20 torr to

give 97 mg (41%) **12** as a colorless liquid; ^{1}H NMR (CD_2Cl_2) δ 0.29 (s, 9H, $Si(CH_3)_3$), 1.17 (s, 6H, CH_3), 1.37 (s, 6H, CH_3); ^{13}C NMR (CD_2Cl_2) δ 0.72 ($Si(CH_3)_3$), 18.4 (CH_3), 22.0 (CH_3), 65.5 (*C*$(CH_3)_2$), 75.0 (*C*(CN)OTMS), 118.3 (CN), 216.4 (CO); IR (neat) 2971, 2298, 2188 (CN), 1777 (C=O), 1382, 1027 (Si-O), 950, 874, 839 (Si-CH_3) cm^{-1}; MS (CI, NH_3) *m*/*e*(%) 257 (37.1) [$M(NH_4)^+$], 242 (7.3), 196 (10.5), 187 (10.6), 169 (26.1), 141 (21.2), 90 (74.7), 70 (100) [$(CH_3)_2CO$]; HRMS calc. for $C_{12}H_{25}N_2O_2Si$ [$M(NH_4)^+$] *m*/*e* 257.1678, found 257.1685.

4.2. *1,3-Bis(trimethylsiloxy)-1,3-dicyano-2,2,4,4-tetramethylcyclobutane (**13**)*

A solution of TMS-CN (688 mg, 6.9 mmol) and dione (**1**) (445 mg, 3.2 mmol) in 5 ml dichloromethane was added dropwise at 0ºC to a stirred solution of zinc iodide (160 mg, 0.5 mmol) dissolved in 5 ml dichloromethane. Stirring was continued at ambient temperature for 24 h and after this time a new portion of zinc iodide (109 mg, 0.34 mmol) was added. The reaction mixture was heated under reflux for 4 h followed by stirring for another 48 h at ambient temperature. The reaction mixture was quenched with $KHCO_3$ solution (15 ml). The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were washed with $KHCO_3$ solution and dried over $MgSO_4$. The solvent was evaporated in vacuum and the oily residue was distilled in vacuum, in Kugelrohr to give first a portion of **12** at 90ºC/20 torr (203 mg, 27%) and subsequently **13** isolated as a colorless, thick oil at 130ºC/20 torr (yield 433 mg, 40%). Based on ^{1}H NMR spectrum, **13** formed 1:2 mixture of *Z*- and *E*- isomers.

Z-**13**: ^{1}H NMR (CD_2Cl_2) δ 0.24 (s, 18H, $Si(CH_3)_3$), 1.06 (s, 6H, CH_3), 1.46 (s, 6H, CH_3); ^{13}C NMR (CD_2Cl_2) δ 0.80 ($Si(CH_3)_3$), 18.2 (CH_3), 22.0 (CH_3), 50.3 (*C*$(CH_3)_2$), 75.9 (*C*(CN)OTMS), 118.4 (CN).

E-**13**: ^{1}H NMR (CD_2Cl_2) δ 0.25 (s, 18H, $Si(CH_3)_3$), 1.25 (s, 12H, CH_3); ^{13}C NMR (CD_2Cl_2) δ 0.90 ($Si(CH_3)_3$), 25.6 (CH_3), 50.1 (*C*$(CH_3)_2$), 76.3 (*C*(CN)OTMS), 117.7 (CN).

Mixture of *Z*- and *E*-isomers: IR (Film) 2962, 2232, 1386, 1008 cm^{-1}. MS (DCI, NH_3) *m*/*e* (%) 357 (27.4), 356 (100) [$M(NH_4)^+$], 312 (17.6) [M^+-CN], 242 (63.9), 169 (97.6), 141 (68.8), 90 (51.6), 70 (79.0); Anal. calc. for $C_{16}H_{30}N_2O_2Si_2$ (338.6): C 56.76; H 8.93, N 8.27; found: C 56.84, H 8.76, N 8.12.

4.3. *2,2,4,4-Tetramethyl-3-trifluoromethyl-3-trimethylsiloxycyclobutanone (**14**)*

A solution of dione **1** (280 mg, 2 mmol) and TMS-CF_3 (355 mg, 2.5 mmol) in 2 ml dry THF was placed under nitrogen atmosphere and ca. 300 mg of fresh activated molecular sieves 4Å were added.[43] Flask was closed with a rubber septum and the mixture was stirred at ambient temperature for 2 h.

Dilute solution of TBAF (0.5 ml of commercial 1M solution in THF was diluted with 2 ml dry THF) was placed in another 10 ml Schlenk flask under magnetic stirring bar and similarly as described earlier, ca. 300 mg of fresh activated molecular sieves 4Å were added. The flask was closed with a rubber septum and the TBAF solution was stirred magnetically for 2 h. After this time, a portion of 0.25 ml of predried solution containing ca. 0.05 mmol TBAF was taken via syringe and added dropwise to the solution of **1** cooled with an external water/ice bath. No evolution of gaseous products was observed and after 2 min a sample of the reaction solution was taken via syringe to check the progress of the reaction by ^{19}F NMR. A small excess of TMS-CF_3 was

observed, singlet at δ ^{19}F 62.24, followed by a peak at δ ^{19}F 67.70 assigned to the newly formed mono-adduct **14**. Similar examination after 1 h showed virtually the same ratio of both the components of the reaction mixture. After dilution with 20 ml dichloromethane, the reaction mixture was shaken with three portions (each 20 ml) of water, organic phase was separated, dried over magnesium sulfate and the solvent was evaporated in vacuum to give 450 mg of a colorless oil which after microdistillation at 95–97ºC/20 torr afforded 420 mg (74%) of analytically pure **14**: ^{1}H NMR ($CDCl_3$) δ 0.18 (q, J_{HF} = 0.6 Hz, 9H, $Si(CH_3)_3$), 1.23 (q, J_{HF} = 1.8 Hz, 6H, CH_3), 1.26 (s, 6H, CH_3); ^{13}C NMR ($CDCl_3$): δ 1.4 (q, J_{CF} = 1.8 Hz, $Si(CH_3)_3$), 18.8 (q, J_{CF} = 3.2 Hz, CH_3), 22.1 (CH_3), 63.0 ($C(CH_3)_2$), 79.9 (q, $^2J_{CF}$ = 28.1 Hz, C-CF_3), 125.6 (q, $^1J_{CF}$ = 284.4 Hz, CF_3); ^{19}F NMR ($CDCl_3$) δ 67.7 (2 CF_3). IR (Film) 2971, 1783 (C = O), 1472, 1256 ($Si(CH_3)_3$), 1026 (Si-O), 874, 839 ($Si(CH_3)_3$) cm^{-1}; MS (EI, 70 eV) *m*/*e*(%) 267 (4.3), 213 (6.9), 212 (52.7) [M^+-$(CH_3)_2CCO$], 120 (38.8), 77 (40.9), 70 (100) [$(CH_3)_2CCO^+$]. Anal. calc. for $C_{12}H_{21}F_3O_2Si$ (282.4): C 51.04, H 7.50; found: C 49.51, H 7.02.

4.4. *1,3-Bis(trifluoromethyl)-1,3-bis(trimethylsiloxy)-2,2,4,4-tetramethylcyclobutane (**15**)*

Reaction was performed identically as described above for the mono-adduct **14** but in this run reaction solution was prepared from 140 mg (1 mmol) of the dione **1** and 427 mg (3 mmol) of TMS-CF_3. The same amounts of activated molecular sieves (ca. 300 mg for each solution) were used in order to dry the TBAF-commercial solution and the same amount of catalyst was added to initiate the reaction. After 5 min of reaction, the reaction mixture was subjected to aqueous work-up and after extraction, drying and evaporation of the solvent, 390 mg of crude product in a form of a thick, colorless oil was obtained; according to ^{19}F NMR no mono adduct **14** was formed under these conditions. The same spectrum showed that the crude bis-adduct **15** is a mixture of *Z*- and *E*-isomers in a 1:2 ratio. Microdistillation at 125–130ºC/20 torr afforded 348 mg (yield 82%) **15** as the unchanged 1:2-mixture of *Z/E*- isomers.

Z-isomer: ^{1}H NMR ($CDCl_3$) δ 0.20 (brs, 18H, $Si(CH_3)_3$), 1.07 (s, 6H, CH_3), 1.26 (m, 6H, CH_3); ^{13}C NMR ($CDCl_3$) δ 1.40 (q, J_{CF} = 1.8 Hz, $Si(CH_3)_3$), 19.6 (sept, J_{CF} = 2.7 Hz, CH_3), 23.5 (CH_3), 48.8 ($C(CH_3)_2$), 81.2 (q, $^2J_{CF}$ = 27.8 Hz, C-CF_3), 125.4 (q, $^1J_{CF}$ = 286.4 Hz, CF_3); ^{19}F NMR ($CDCl_3$) δ 67.34 (2 CF_3).

E-isomer: ^{1}H NMR ($CDCl_3$) δ 0.14 (brs, 18H, $Si(CH_3)_3$), 1.17 (q, J_{HF} = 2.4 Hz, 12H, CH_3); ^{13}C NMR ($CDCl_3$) δ 1.5 (q, J_{CF} = 1.8 Hz, $Si(CH_3)_3$), 21.5 (m, CH_3), 48.9 ($C(CH_3)_2$), 81.2 (q, $^2J_{CF}$ = 27.8 Hz, C CF_3), 125.2 (q, $^1J_{CF}$ = 285.5 Hz, CF_3); ^{19}F NMR ($CDCl_3$) δ 67.52 (2 CF_3);

Mixture of isomers: IR (Film) 2957, 1485, 1255 ($Si(CH_3)_3$), 1172, 1019 (Si-O), 867, 839 ($Si(CH_3)_3$) cm^{-1}; MS (EI, 70 eV) *m*/*e*(%) 212 (100), 197 (26.9), 143 (19.9), 120 (32.8), 101 (9.1), 77 (67.4). Anal. calc. for $C_{16}H_{30}F_6O_2Si_2$ (424.6): C 45.26, H 7.12, found: C 45.31, H 6.88.

4.5. *Reactions with methylmagnesium bromide and methyllithium*

a) *Reactions in THF or ether:* Dione **1** (1.0 g, 7.1 mmol) was dissolved in THF or ether and cooled down to either 0 or –20ºC. Methylmagnesium bromide (9.5 ml of commercial 3M solution in ether, 28.6 mmol) was added over a period of 10 min and the reaction mixture stirred for 1–2 h at low temperature before warming up to room temperature. After additional 2 h of stirring, the reaction mixture was quenched with aq. NH_4Cl solution, the aqueous layer was extracted with ether and the combined organic extracts were dried over $MgSO_4$. The solvent was distilled off

and the residue was distilled under reduced pressure in Kugelrohr to yield **17** (709 mg, 58%) and **18** as the residue, which was purified by extraction with pentane to give 290 mg of pure **18** (20%) as a crystalline solid with m. p. 110ºC.

Reaction with methyllithium (2.2 equiv., 1.4 M in ether) was performed in a similar manner to yield 306 mg (25%) **17** and 30 mg (2%) **18**, respectively.

b) *Reaction with MeLi/TMEDA*: Dione **1** (1.0 g, 7.13 mmol) dissolved in 7 ml THF was mixed with 10.9 g (94.1 mmol) TMEDA and to this solution, cooled with an external water/ice bath, an ethereal solution of methyllithium (11.20 ml, 1.4 M in ether, 15.7 mmol) was added dropwise so that the temperature did not exceed 0–3ºC. The reaction mixture was stirred for 90 min, quenched with NH_4Cl solution and the aqueous layer was extracted with ether. The combined organic extracts were dried over $MgSO_4$ and treated as described above. **17** (551 mg, 45%) was separated as the only product.

c) *Reaction with methylmagnesium bromide in pentane*: Commercial solution of methyl-magnesium bromide in ether (5 ml of commercial 3M solution, 15 mmol) was stirred vigorously at 0ºC and 45 ml of pentane was added in portions to yield a white precipitate that was mixed by vigorous stirring. Dione **1** (500 mg, 3.6 mmol) was added in portions to this suspension and stirring was continued for another 3 h at 0ºC. After this time the reaction mixture was quenched with a saturated ammonium chloride solution and the aqueous layer was extracted with ether. The combined organic extracts were dried over $MgSO_4$ and treated as described above to yield **17** (346 mg, 56%) as the only product.

*5-Hydroxy-2,4,4,5-tetramethyl-3-hexanone (**17**)*: b. p. 59ºC/0.6 torr; (lit.,[12] b. p. 71–71.5ºC/3 torr); ^{1}H NMR ($CDCl_3$) δ 1.00 (d, 6H, J = 6.7 Hz, $CH(CH_3)_2$), 1.11 (s, 6H, CH_3), 1.20 (s, 6H, CH_3), 3.11 (sept, 1H, J = 6.7 Hz, $CH(CH_3)_2$), 4.29 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 19.6, 20.9, 25.5, 35.6, 53.6, 74.4, 224.5 (C = O); IR (neat) 3478 (OH), 2971, 1679 (C = O), 1457, 1374, 1144, 1019, 985, 950 cm^{-1}; MS (CI, CH_4) *m/e* (%) 173 (14) [MH^+], 155 (25) [M^+-OH], 115 (24), 114 (14), 97 (15), 71 (100) [$C_4H_7O^+$]. HRMS calc. for $C_{10}H_{21}O_2$ [MH^+] *m*/*e* 173.1542, found 173.1541. Anal. calc. for $C_{10}H_{20}O_2$ (172.3): C, 69.70; H, 11.70; found: C, 69.64; H, 11.80.

2-Hydroperoxy-5-hydroxy-2,4,4,5-tetramethyl-3-hexanone (***18***): m. p. 110ºC (pentane); ^{1}H NMR ($CDCl_3$) δ 1.15 (s, 6H, CH_3), 1.35 (s, 6H, CH_3), 1.40 (s, 6H, CH_3), 4.47 (brs, 1H, OH), 10.43 (brs, 1H, OOH); ^{13}C NMR ($CDCl_3$) δ 22.0, 23.6, 25.8, 54.70, 76.5, 90.8, 220.4 (C=O); IR (KBr) 3194, 3083, 2861, 1652 (C=O), 1319, 992 cm^{-1} ; MS (CI, NH_3) *m/e*(%) 222 (96.4) [$M(NH_4)^+$], 205 (100) [MH^+], 204 (12.3) [M^+], 189 (21.8) [M^+-CH_3], 187 (47.6) [M^+-OH], 171 (28.1) [M^+-OOH], 164 (24.6) [M^+-OOH-OH], 100 (29.3) [$C_6H_{12}O^+$], 84 (90.0) [$C_6H_{12}^+$], 71 (54.0); HRMS calc. for $C_{10}H_{21}O_4$ [MH^+] *m*/*e* 205.1440, found 205.1432; Anal. calc. for $C_{10}H_{20}O_4$ (204.3): C 58.80, H, 9.87; found: C 58.99, H 9.79.

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