Synthesis of Nonenolizing 2-Acylcyclohex-2-enones

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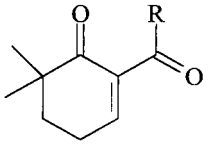
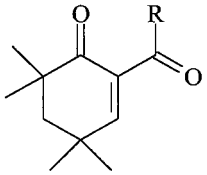
Cyclohexanones **2b** and **2c** represent the first examples of nonenolizing 2-acylcyclohex-2-enones, as they bear H-atoms neither at C(4) or C(6) of the enone ring, nor at the C-atom vicinal to the exocyclic carbonyl group. While the CF_3CO group in **2b** (and the Ac group in **2a**) are coplanar to the enone double bonds, the pivaloyl group in **2c**, for steric reasons, is out of plane. Compounds **2** exhibit a pronounced sluggishness in both thermal and light-induced bimolecular reactions.

Introduction. – 2-Acylcyclohex-2-enones are highly reactive due to the additional electron-withdrawing group at the C(α)-atom and are therefore, potential valuable synthons as *Michael* acceptors [1]. Unfortunately, the compounds described in the literature up to 1998 are all unstable to acid and base, readily isomerizing to dienolic tautomers [2–4]. We have recently reported preliminary results on the photochemical behavior of 2-acyl-6,6-dimethylcyclohex-2-enones **1** [5][6]. On dealing with these compounds, we observed that the Ac and CF_3CO derivatives **1a** and **1b** are (still) sensible to acid and base, while the pivaloyl compound **1c** does not undergo any noticeable enolization. Here, we report on the synthesis and properties of three novel 2-acyl-4,4,6,6-tetramethylcyclohex-2-enones **2**, wherein the 'acidic' H-atoms at *both* C(4) and C(6) have been replaced by Me groups.



1

a R = CH_3
b R = CF_3
c R = *t*-Bu

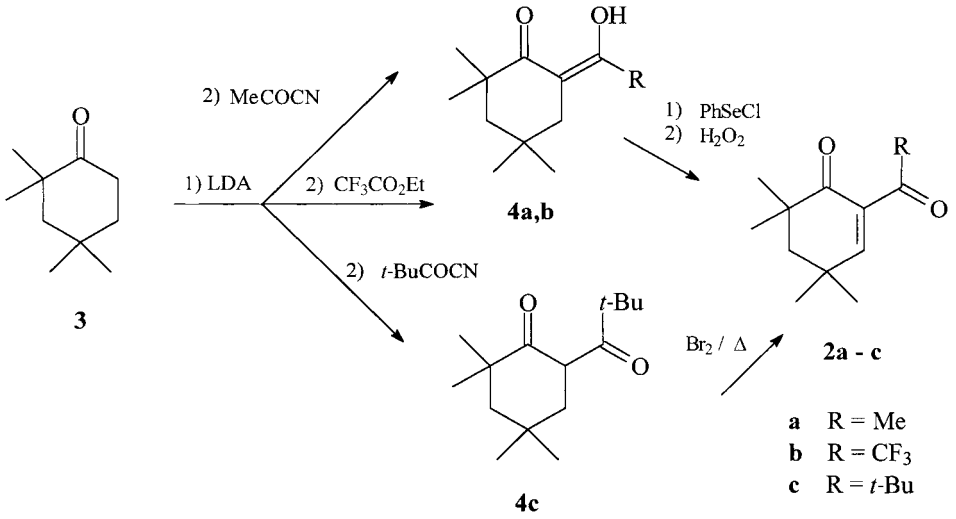


2

Results and Discussion. – The synthesis of compounds **2** involves *C*-acylation of 2,2,4,4-tetramethylcyclohexanone (**3**) and subsequent dehydrogenation of compounds **4**. For **4a** and **4b**, both enols, this is achieved by treatment with PhSeCl and then (oxidative) elimination of phenylseleninic acid. For diketone **4c**, a bromination/dehydrobromination sequence turned out to be more convenient, the elimination of HBr already occurring in boiling CCl_4 (*Scheme 1*).

A comparison of the chemical shifts of both C(3) and H–C(3) in the NMR spectra of compounds **2** shows that, in both **2a** and **2b**, the exocyclic acyl group is coplanar with the enone C=C bonds (δ(C) $\approx$ 162, δ(H) $\approx$ 7.21 ppm in $CDCl_3$), while, in **2c**, the

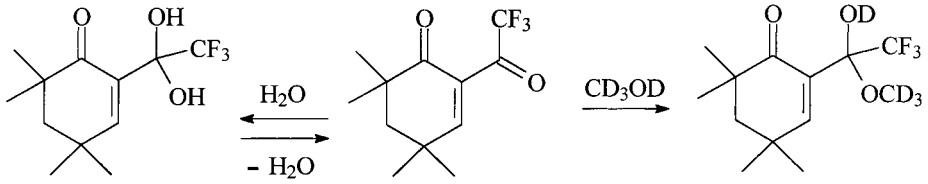
Scheme 1



pivaloyl group is not (δ(C) = 148 ppm, δ(H) = 6.29 ppm in $CDCl_3$), the chemical shift of the olefinic H-atom now corresponding to that of 2,4,4,6,6-pentamethylcyclohex-2-enone (δ(H) ≈ 6.25 ppm [7]). In contrast to the UV spectra of **2b** and **2c**, an additional absorption band at $\lambda_{max} \approx 282$ nm in C_6H_{12} is present in the spectrum of **2a**, most probably due to the presence of 1–2% of the dienolic tautomer 2-(1-hydroxyethenyl)-4,4,6,6-tetramethylcyclohex-2-enone.

Trifluoroacetyl enone **2b** readily adds H_2O or MeOH to afford hydrate **5** and hemiacetal **6**, respectively (*Scheme 2*). The quantitative formation of these C=O addition products becomes evident from the NMR spectra in either CD_3CN/D_2O 9:1 or in CD_3OD, as, in both solvents, the signal of the C-atom adjacent to the CF_3 group is shifted from 185 ppm (C=O) to values around 95 ppm, and also because the signals of the diastereotopic methylene-H-atoms of **6** appear as an *AB* part of an *ABX* pattern, and the Me groups give four distinct signals.

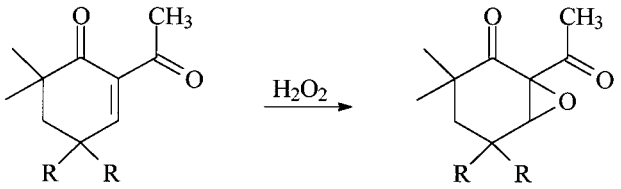
Scheme 2



The additional kinetically stabilizing effect of geminal dimethyl substitution at C(4) is reflected in a pronounced sluggishness in (bimolecular) reactivity of compounds **2**, *e.g.*, in the rate of epoxidation of **2a** *vs.* **1a** with neutral H_2O_2 according to [8][9]. While

the latter compound is quantitatively converted to oxabicycloheptanone **7**, only 15% of **8** is obtained from **2a** in the same period of time (*Scheme 3*). Also, irradiation of **2a** or **2b** in the presence of either 2-methylbut-1-en-3-yne or 2,3-dimethylbut-2-ene does not lead to the formation of any cycloadducts, but merely to slow (monomolecular) degradation, in contrast to **1a** or **1b**, which react efficiently [5] with both hydrocarbons. And again similarly, **2c**, in contrast to **1c** [6], does not react with the solvent on irradiation in i-PrOH.

Scheme 3



1a R = H **7** R = H

2a R = Me **8** R = Me

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Experimental Part

1. *General. 2,2,4,4-Tetramethylcyclohexanone* (**3**) was synthesized according to [10]. Anal. GC: 30-m *SE 30* cap. column. UV Spectra: in cyclohexane in nm (log ε). ^{1}H- and ^{13}C-NMR Spectra: at 500 and 125.8 MHz, resp.; chemical shifts in ppm rel. to TMS (=0 ppm). MS: at 70 eV; in *m/z* (rel. intensity in %).

2. *Acylation of* **3**: *Preparation of Cyclohexanones* **4**. To a soln. of (i-Pr)$_2$NH (2.9 g, 2.84 mmol) in 200 ml of THF at $-10°$ were added during 30 min 1.6M BuLi in hexane (18 ml, 28.4 mmol), then, during 30 min, a soln. of **3** (4 g, 25.8 mmol) in 40 ml of THF, and finally a soln. of the acylating agent (either AcCN, CF_3COOEt, or *t*-BuCOCN; 28.4 mmol) in 20 ml THF. Stirring was continued for 30 min, and the mixture was allowed to warm to r.t. Then, 200 ml of H_2O was added, the mixture was extracted three times with 20 ml of Et_2O, and the org. phase was washed with sat. aq. NaCl soln. and dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by chromatography on SiO_2.

2-(1-Hydroxyethylidene)-4,4,6,6-tetramethylcyclohexanone (**4a**). Pentane/Et_2O 4:1: 2.42 g (48%). Light yellow liquid. ^{1}H-NMR ($CDCl_3$): 16.41 (*s*); 2.14 (*s*, 3 H); 2.13 (*s*, 2 H); 1.47 (*s*, 2 H); 1.22 (*s*, 6 H); 1.05 (*s*, 6 H). ^{13}C-NMR ($CDCl_3$): 197.7 (*s*); 189.4 (*s*); 104.4 (*s*); 50.8 (*t*); 39.3 (*t*); 37.0 (*s*); 30.0 (*s*); 29.4 (*q*); 29.3 (*q*); 25.0 (*q*). MS: 196 (30, $M^{+\cdot}$), *43*.

4,4,6,6-Tetramethyl-2-(2,2,2-trifluoro-1-hydroxyethylidene)cyclohexanone (**4b**). Pentane/Et_2O 4:1: 3.52 g (54%). Dark yellow liquid. ^{1}H-NMR ($CDCl_3$): 15.70 (*s*); 2.27 (*s*, 2 H); 1.52 (*s*, 2 H); 1.26 (*s*, 6 H); 1.01 (*s*, 6 H). ^{13}C-NMR ($CDCl_3$): 197.9 (*s*); 177.5 (*q*, J = 34); 118.8 (*q*, J = 286); 103.1 (*s*); 50.2 (*t*); 38.23 (*s*); 36.3 (*t*); 29.8 (s); 29.6 (*q*); 28.9 (*q*). MS: 250 (30, $M^{+\cdot}$), *41*.

2-(2,2-Dimethylpropanoyl)-4,4,6,6-tetramethylcyclohexanone (**4c**). Pentane/Et_2O 9:1: 2.44 g (41%). M.p. 89–91°. ^{1}H-NMR ($CDCl_3$): 4.34 (*dd*, J = 5.1, 13.7); 2.11 (*t*, J = 11.7); 1.62 (*m*, 3 H); 1.29 (*s*, 3 H); 1.25 (*s*, 3 H); 1.12 (*s*, 9 H); 1.06 (*s*, 3 H); 1.01 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$): 213.8 (s); 213.2 (*s*); 53.1 (*t*); 50.2 (*d*); 45.2 (*s*); 45.1 (*s*); 42.7 (*t*); 30.3 (*s*); 27.8 (*q*); 27.7 (*q*); 27.3 (*q*); 25.7 (*q*). MS: 238 (2, $M^{+\cdot}$), *57*.

3. *Dehydrogenation of* **4**: *Preparation of Cyclohexanones* **2**. a) *Preparation of* **2a** *and* **2b**. To a suspension of NaH (340 mg, 14 mmol) in 40 ml of THF at 0° was added slowly a soln. of either **4a** or **4b** (0.01 mol) in 20 ml of THF. After stirring for 30 min, a soln. of PhSeCl (1.91 g, 0.01 mol) in 20 ml of THF was added, and stirring was

continued for another 30 min. The mixture was then poured into 20 ml of Et_2O, 20 ml of pentane, and 10 ml of sat. aq. $NaHCO_3$ soln. The aq. phase was further extracted with 20 ml of Et_2O/pentane 1:1. The combined org. phases were washed with NaCl aq. and dried ($MgSO_4$). The solvent was evaporated, the residue was dissolved in 50 ml of CH_2Cl_2, the soln. was cooled to 0°, and then 2 ml of 30% H_2O_2, dissolved in 10 ml H_2O, was added. The mixture was then stirred for 1 h and allowed to warm to r.t., washed with sat. aq. $NaHCO_3$ and dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by chromatography (SiO_2).

2-Acetyl-4,4,6,6-tetramethylcyclohex-2-enone (**2a**). Pentane/Et_2O 4:1: 1.74 g (89%). Light yellow oil. UV: 228 (4.01), 286 (2.35), 320 (1.90). ^{1}H-NMR ($CDCl_3$): 7.20 (*s*); 2.43 (*s*, 3 H); 1.80 (*s*, 2 H); 1.24 (*s*, 6 H); 1.20 (*s*, 6 H). ^{13}C-NMR ($CDCl_3$): 202.9 (*s*); 198.5 (*s*); 161.5 (*d*); 136.7 (*s*); 49.8 (*t*); 43.2 (*s*); 33.8 (*s*); 30.9 (*q*); 30.6 (*q*); 27.9 (*q*). MS: 194 (10, $M^{+\bullet}$), *43*.

4,4,6,6-Tetramethyl-2-(trifluoroacetyl)cyclohex-2-enone (**2b**). Pentane/Et_2O 4:1 and drying for 12 h over molecular sieves (4 Å): 1.36 g (55%). Light yellow oil. UV: 230 (4.21), 321 (1.98). ^{1}H-NMR ($CDCl_3$): 7.20 (*s*); 1.85 (*s*, 2 H); 1.28 (*s*, 6 H); 1.19 (*s*, 6 H). ^{13}C-NMR ($CDCl_3$): 199.9 (*s*); 15.2 (*q*, $J = 33$); 163.4 (*d*); 132.7 (*s*); 124.3 (*q*, $J = 289$); 48.5 (*t*); 42.4 (*s*); 33.5 (*s*); 30.1 (*q*); 26.5 (*q*). MS: 248 (5, $M^{+\bullet}$), *123*.

b) *Preparation of* **2c**. To a refluxing soln. of **4c** (2.38 g, 0.01 mol) in 50 ml of CCl_4 was added dropwise a soln. of Br_2 (1.60 g, 0.01 mol) in 10 ml of CCl_4. The mixture was then refluxed for 2 more h. After cooling to r.t., the solvent was evaporated, and the residue was purified by chromatography (SiO_2; pentane/Et_2O 9:1) to afford 2.04 g (90%) of *2-(2,2-Dimethylpropanoyl)-4,4,6,6-tetramethylcyclohex-2-enone* (**2c**). M.p. 83–85°. UV: 223 (4.21), 315 (2.19). ^{1}H-NMR ($CDCl_3$): 6.29 (*s*); 1.85 (*s*, 2 H); 1.21 (*s*, 6 H); 1.20 (*s*, 6 H); 1.16 (*s*, 6 H). ^{13}C-NMR ($CDCl_3$): 207.1 (*s*); 197.2 (*s*); 148.0 (*d*); 133.2 (*s*); 44.0 (*t*); 39.8 (*s*); 36.6 (*s*); 27.8 (*s*); 25.6 (*q*); 22.3 (*q*); 21.9 (*q*). MS: 236 (3, $M^{+\bullet}$), *179*.

4. *Preparation of Carbonylhydrate* **5**. A soln. of **2b** (24.8 mg, 0.1 mmol) in 10 ml of H_2O-sat. Et_2O was stirred for 6 h at r.t., and, thereafter, the solvent was evaporated to afford 26 mg (98%) of *2-(1,1-dihydroxy-2,2,2-trifluoroethyl)-4,4,6,6-tetramethylcyclohex-2-enone* (**5**). M.p. 73–75°. ^{1}H-NMR ($CDCl_3$): 7.15 (*s*); 5.65 (*s*, 2 OH); 1.81 (*s*, 2 H); 1.20 (*s*, 6 H); 1.17 (*s*, 6 H). ^{13}C-NMR ($CDCl_3$): 208.1 (*s*); 161.1 (*d*); 127.4 (*s*); 124.1 (*q*, $J =$ 289); 95.2 (*q*, $J = 33$); 48.1 (*t*); 42.0 (*s*); 32.9 (*s*); 30.5 (*q*); 26.9 (*q*). UV: 230 (4.21), 321 (1.98).

5. *Characterization of Hemiacetal* **6** *by its* ^{1}*H-NMR Spectrum*. Data for **2c** in CD_3OD: 7.08 (*dd*, $J = 0.5, 1.0$); 1.91 (*dd*, $J = 0.5, 13.0$); 1.87 (*dd*, $J = 1.0, 13.0$); 1.28 (*s*, 3 H); 1.26 (*s*, 3 H); 1.22 (*s*, 3 H); 1.18 (*s*, 3 H).

6. *Formation of Epoxides* **7** *and* **8**. To a soln. of **1a** or **2a** (1 mmol) in 10 ml of MeCN was added 30% H_2O_2 (0.5 ml, 4.5 mmol), and the mixture was stirred at r.t. for 3 h. The same quantity H_2O_2 was added, and stirring was continued over night. The soln. was poured into 30 ml of 10% aq. $NaHSO_3$, and then extracted 3 × with 10 ml of CH_2Cl_2. The combined org. phases were dried ($MgSO_4$), and the solvent was evaporated.

1-Acetyl-3,3-dimethyl-7-oxabicyclo[4.1.0]heptan-2-one (**7**): 165 mg (91%). Light yellow liquid. ^{1}H-NMR ($CDCl_3$): 3.54 (*t*, $J = 2.0$); 2.25 (*dddd*, $J = 2.0, 2.5, 5.0, 15.2$); 2.20 (*s*, 3 H); 2.10 (*dddd*, $J = 2.0, 5.0, 13.0, 15.2$); 1.77 (*ddd*, $J = 5.0, 13.0, 13.2$); 1.42 (*ddd*, $J = 2.0, 5.0, 13.2$); 1.18 (*s*, 3 H); 1.17 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$): 203.1 (*s*); 201.2 (*s*); 59.4 (*s*); 57.2 (*d*); 40.3 (*s*); 27.3 (*t*); 24.9 (*q*); 22.1 (*q*); 20.8 (*q*); 18.4 (*t*). MS: 182 (5, $M^{+\bullet}$); *55*.

Under these experimental conditions, a 1:5 mixture (GC/MS) of *1-Acetyl-3,3,5,5-tetramethyl-7-oxabicyclo[4.1.0]heptan-2-one* (**8**; MS: 210 (7, $M^{+\bullet}$), *43*) and **2a** was obtained, which was not separated.

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