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# Functionalization of non-activated C–H bonds in ketones and imines with $HF/SbF_5/CCl_4$

Sébastien Thibaudeau, Agnès Martin-Mingot, Marie-Paule Jouannetaud* and J. C. Jacquesy

*Laboratoire 'Synthèse et Réactivité des Substances Naturelles', UMR 6514, 40, Avenue du Recteur Pineau, F-86022 Poitiers Cedex, France*

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**Abstract**—Reaction of cyclic ketones **2**–**6** and imines **15**–**17** in $HF/SbF_5$ in presence of $CCl_4$ yield hydroxy or fluoroderivatives, hydride abstraction occurring at a site located far from the functional group. Whereas ketones **2**–**5** yield only hydroxy derivatives, through cyclic carboxonium ion, imines **15**, **16** N-protonated in the media conditions give only fluoroderivatives **18**, **19**, respectively, after quenching with HF–pyridine. Ring contraction is operative when starting from large membered ring ketones **24** and **25**, and imine **26**, leading to a mixture of hydroxy or fluoro cyclohexanones and/or cycloheptanones. © 2002 Published by Elsevier Science Ltd.

## 1. Introduction

Functionalization of non-activated C–H bonds remains a major challenge in organic chemistry. As shown by Olah and co-workers, functionalization of σ-bonds can be carried out with superacids (or their salts) by protolysis or by reaction with electrophiles: halogens, protonated ozone, hydrogen peroxide, chloromethyl ions, or nitronium and nitrosonium ions.[1–9] These results have been accounted for by Olah who developed the concept of σ basicity of C–C or C–H bond sharing its electron pair with an electrophile, through a two-electron-three centre bonded intermediate or transition state.[10] Functionalized substrates being protonated in superacids, reaction with an electrophile will occur at a rich electron site far from the protonated functional group.[11] We wish to report here the hydroxylation or fluorination of various ketones and imines in $HF–SbF_5$ in presence of $CCl_4$.

## 2. Results and discussion

### 2.1. Reaction of acyclic ketones and imines in $HF/SbF_5/CCl_4$

The results reported in Tables 1 and 2 show that most substrates yield hydroxy and/or fluoro derivatives, which after flash-chromatography over silica gel, have been identified by NMR spectroscopy. Firstly it should be pointed out that no reaction was observed in $HF/SbF_5$ in the same experimental conditions (except with imines leading to the corresponding ketones) after hydrolysis. The observed reactivity of the substrates in $HF/SbF_5/CCl_4$ can be accounted for by hydride abstraction by the electrophilic trichloromethyl cation $CCl_3^+$.[12,13] The surprising hydride abstractive power of this ion has been assumed by Olah to be due to protosolvatation or complexation by the Lewis acid $SbF_5$, leading to a 'superelectrophile' (Fig. 1).[14]

**Table 1**. Reaction of ketones with $HF/SbF_5/CCl_4$

| Entry | Substrate | Temperature (°C) | Time (min) | Quenching conditions | Products (%) |
|---|---|---|---|---|---|
| 1 | **1** | −30 | 30 | A or B | No reaction |
| 2 | **2** | −30 | 5 | A or B | **8**+**9** (67) (1/3 ratio) |
| 3 | **2** | 0 | 30 | A or B | **10** (44) |
| 4 | **3** | −30 | 10 | A or B | **10** (82) |
| 5 | **4** | −30 | 5 | A or B | **11** (80) |
| 6 | **5** | −30 | 5 | A or B | **11** (92) |
| 7 | **6** | −30 | 3 | A | **13** (50)+**12** (12) |
| 8 | **6** | −30 | 3 | B | **13** (32)+**12** (20) |
| 9 | **7** | −30 | 30 | A | No reaction |

*Keywords*: ketones; imines; iminium.

* Corresponding author. Tel.: +33-5-49-453-859; fax: +33-5-49-453-501; e-mail: marie.paule.jouannetaud@univ-poitiers.fr

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**Table 2**. Reaction of imines in $HF/SbF_5/CCl_4$

| Entry | Substrate | Temperature (°C) | Time (min) | Quenching conditions | Products (%) |
|---|---|---|---|---|---|
| 1 | **14** | −30 | 30 | A or B | **1** (qqtive) |
| 2 | **15** | 0 | 30 | A | **10** (21)+**18** (46)+**2** (9) |
| 3 | **15** | 0 | 30 | B | **18** (68) |
| 4 | **16** | −30 | 30 | A | **11** (14)+**19** (24) |
| 5 | **16** | −30 | 30 | B | **19** (67) |
| 6 | **17** | −30 | 30 | A | **13** (20)+**12** (20) |
| 7 | **17** | −30 | 30 | B | **13** (19)+**12** (36) |

(a) $HF/SbF_5$/substrate molar ratio 20/1/0.05; (b) quenching conditions: A: $Na_2CO_3$/ice/$H_2O$; B: (1) excess PPHF (HF/pyridine molar ratio 70/30) at reaction temperature for 15 min, (2) $Na_2CO_3$/ice/$H_2O$.

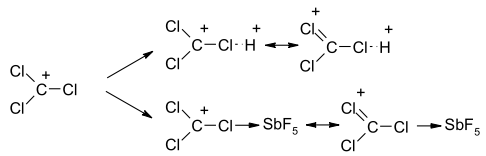
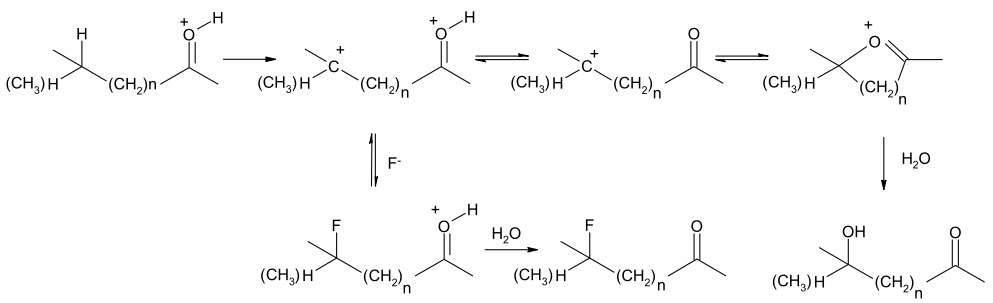


**Figure 1.**

Imines and ketones are N and O-protonated, respectively, in superacids.[15,16] As a result, hydride abstraction by the electrophile occurs at the more reactive C–H bond, far located from the protonated functional group. With a straight chain, hydride abstraction at the (ω-1) position yields a secondary ion which may isomerize to a tertiary one. Except for ketones **1** and **7** which are too deactivated to react, all other ketones yield hydroxy and/or fluoro derivatives (Table 1).[11] Ketones **2**–**5** give only hydroxy derivatives, whatever the quenching conditions are. This implies intermediacy of a five or six-membered ring carboxonium ion, preventing the substrate from fluorination (Scheme 1).[17] Hydrolysis only leads to hydroxy derivatives **8**–**11** (Fig. 2).

Starting from ketone **6**, formation of a seven-membered ring carboxonium ion is more difficult, favoring equilibrium with the diprotonated species which can be trapped by fluoride ion. Reaction with HF–pyridine (PPHF) slightly improves the yield of fluoro derivative **12**, besides alcohol **13**. It should be pointed out that fluorination in the reaction conditions is a reversible process. Fluoro derivative **12**, placed again in the reaction conditions ($HF/SbF_5/CCl_4$) yields compounds **12** and **13**, with similar yields than from **6**.

Very different results were obtained when starting from the corresponding imines (Table 2). If, as expected imine **14** is too deactivated to react, conducting only to ketone **1** after hydrolysis of the corresponding iminium ion, imines **15**–**17**



**Scheme 1.**

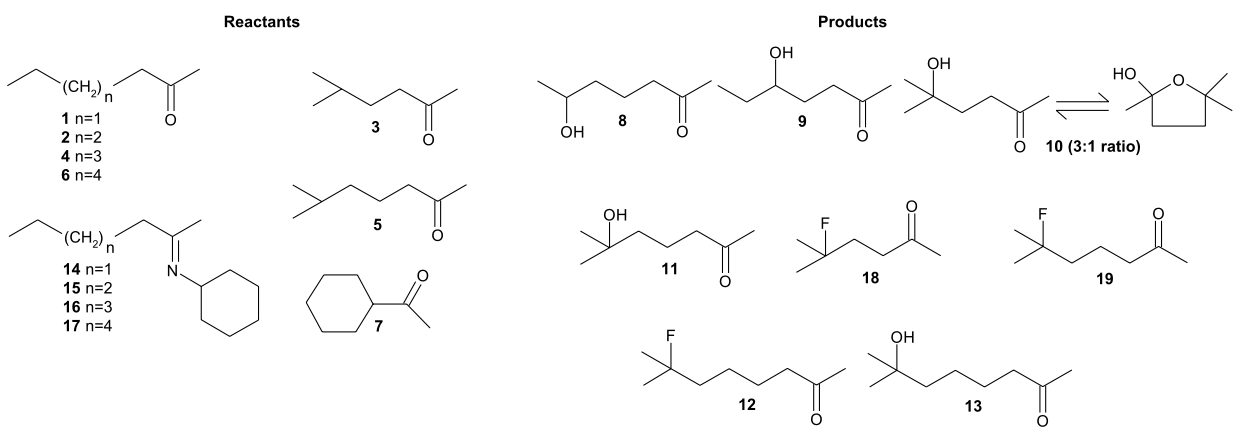
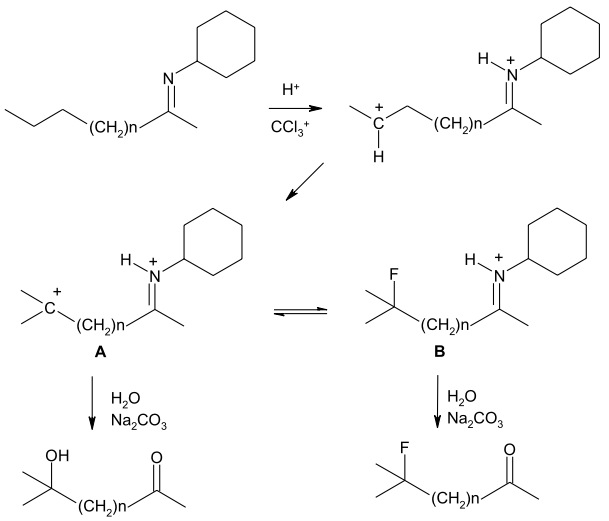



**Figure 2.**



**Scheme 2.**

always yield fluoroketones, besides hydroxy derivatives. These results can be explained by the intermediary of the N-protonated imine, less prone to deprotonation than the corresponding protonated ketone, and therefore preventing the formation of the cyclic iminium ion (Scheme 2).

As expected, treatment of the reaction medium with PPHF yields the sole fluoro derivatives **18** and **19** in good yields. Starting from the imine **17**, quenching with PPHF only slightly improves the yield of compound **12**. This result might reflect the equilibrium between ions A and B, the repulsive interaction between the positive charges in ion A (separated by four methylene groups) being minimal in this case.

It appears that the imino group could be used as a 'protecting group' for ketone function, preventing the formation of a cyclic carboxonium ion. After hydrolysis, the latter only leads to the hydroxy compounds(s), whereas iminium ion, acting as a 'protected ketone', yields the corresponding fluorinated derivative after quenching by PPHF. This selective novel reaction of functionalization in superacidic media could be extended to cyclic imines and ketones as reported below.

## 2.2. Reaction of cyclic ketones 20–25 and imine 26 in $HF/SbF_5/CCl_4$

The results reported in Table 3 show that the reactivity is very sensitive to the structure of the substrates.

Cyclic ketone **20** is unreactive in the reaction conditions, the δ-methylene group being probably deactivated by the cumulative effect of the ring arms. On the other hand hydride abstraction being easier from an isopropyl group, 4-isopropylcyclohexanone **21** leads to compounds **27** and **28** and to the sole fluoro derivative **27** in the presence of PPHF.

This result, conducting to a 5-fluoro (or hydroxy) ketone, when compared to other reaction of ketone **4** leading only to the δ-hydroxy derivative through a cyclic carboxonium ion, implies that the intermediate is an opened ion **35**, more favoured than the strained cyclic carboxonium ion **36** (Fig. 3).

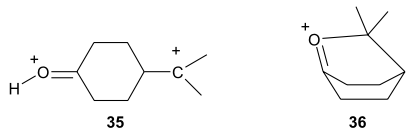


**Figure 3.**

Table 3 shows that if cycloheptanone **22** is unreactive, ketones **23** give only complex mixtures, and rearranged hydroxy and fluoroderivatives are obtained when ketones **24** and **25** are reacted (Fig. 4).

**2.2.1. Reaction of cycloundecanone 24.** Starting from ketone **24**, the structure of the products is very sensitive to reaction time. It appears that cycloheptanones **29** and **30** are the primary products, their precursors isomerizing for longer reaction time into those of cyclohexanones **31** and **32**. The first step implies a hydride abstraction at C-6 to give ion **37**, as far as possible from the protonated carbonyl group (Scheme 3). Successive ring contractions, involving protonated cyclopropane, will finally yield ion **42**. To minimize the repulsive interaction of the positive charges, ion **42** isomerizes to the more stable tertiary ion **43**, precursor of compounds **29** and **30**. Ion **43** can undergo a novel ring

**Table 3**. Reaction of cyclic ketones and imines in $HF/SbF_5/CCl_4$

| Entry | Substrate | Temperature (°C) | Time | Quenching conditions | Products (%) |
|---|---|---|---|---|---|
| 1 | **20** | −30 | 45 min | A | No reaction |
| 2 | **21** | −30 | 2 min | A | **27** (60)+**28** (20) |
| 3 | **21** | −30 | 2 min | B | **27** (75) |
| 4 | **22** | 0 | 15 min | A | No reaction |
| 5 | **23** | 0 | 15 min | A | Complex mixture |
| 6 | **24** | −30 | 10 s | A | **29**+**30** (11) (molar ratio 3/2) |
| 7 | **24** | 0 | 15 min | A | **29** (6)+**30** (11)+**31** (6)+**32** (17) |
| 8 | **24** | 0 | 60 min | A | **31** (9)+**32** (23) |
| 9 | **25** | 0 | 15 min | A | **33** (17)+**34** (36, 5) |
| 10 | **25** | 0 | 15 min | B | **33** (13)+**34** (29) |
| 11 | **26** | 0 | 15 min | A | **33** (19,5)+**34** (12) |
| 12 | **26** | 0 | 15 min | B | **33** (20)+**34** (10) |

(a) $HF/SbF_5$/substrate molar ratio 20/1/0.05; (b) quenching conditions: A: $Na_2CO_3$/ice/$H_2O$; B: (1) excess PPHF (HF/pyridine molar ratio 70/30) at reaction temperature for 15 min, (2) $Na_2CO_3$/ice/$H_2O$.

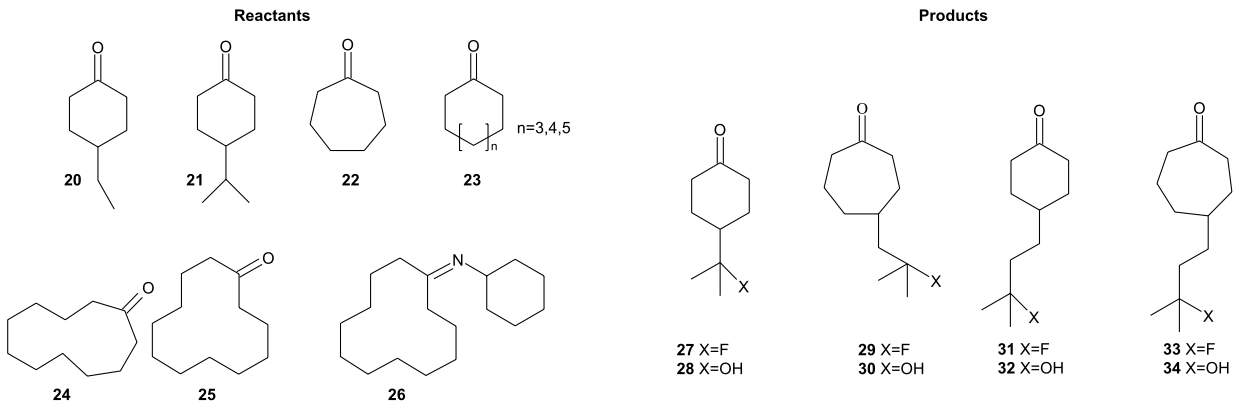
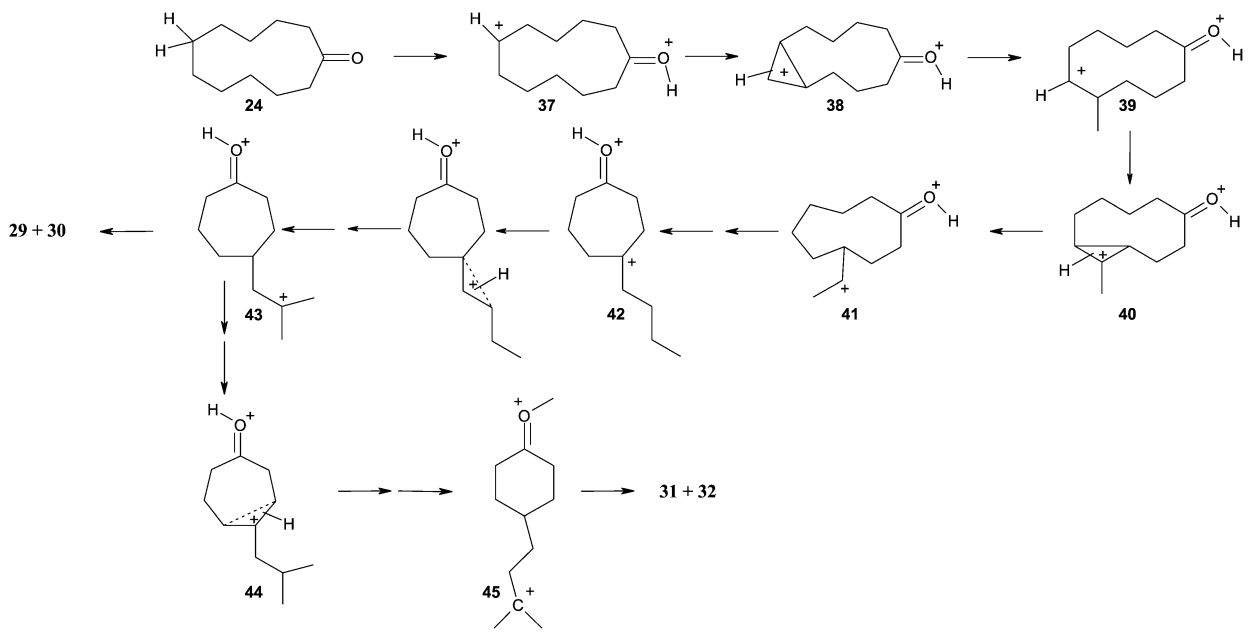



**Figure 4.**




**Scheme 3.**

contraction through ion **44** to ion **45**, precursor of cyclohexanones **31** and **32**.

Our results have to be compared with those previously published on the ring contraction of cycloalkyl cation in superacids.[18–20] Starting from 1-chloroundecane, in $SbF_5$/$SO_2ClF$ at −84°C Sorensen obtained the 1-methylcyclodecyl cation **46**[18] (Fig. 5).

On the other hand, cycloundecanol when dissolved in

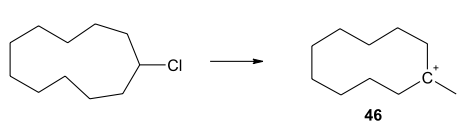



**Figure 5.**

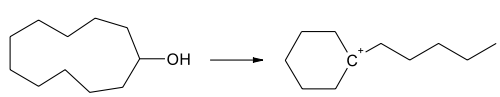



**Figure 6.**

$FSO_3H–SbF_5–SO_2ClF$ at −78°C yields the 1-*n*-pentylcyclohexyl tertiary cation[20] (Fig. 6).

The more pronounced rearrangement observed in our study when starting from cycloundecanone **24** in HF/$SbF_5$/$CCl_4$ can be accounted for by the repulsive interaction of the protonated carbonyle and the carbonium ion in the intermediate(s).

**2.2.2. Reaction of cyclododecanone 25 and imine 26.** A similar mechanism can be proposed for the formation of cycloheptanones **33** and **34** from ketone **25** and imine **26**. Formation of the corresponding cyclohexanones is not observed, reflecting the stability of the ions precursors of ketones **33** and **34**, in which the interaction of the positive charges should be small.

Surprisingly the **34/33** ratio is about 3 when starting from ketone **25**, and about 0.5 with imine **26**. Starting from ketone **25**, we cannot completely rule out intermediacy of a large-membered ring carboxonium ion precursor of the hydroxy ketone.

To conclude, hydroxylation or fluorination of non-activated bonds of various acyclic or cyclic ketones and imines can be carried out in superacid in presence of carbon tetrachloride. Hydride abstraction by the activated trichloromethyl ion occurs at a site far from the protonated carbonyle or iminium.

Starting from ketones, formation of a five or six-membered carboxonium ion accounts for the formation of hydroxy derivatives after hydrolysis. On the other hand, the corresponding imines, N-protonated in the reaction conditions, yield hydroxy or fluoroderivatives after trapping of the intermediate acyclic carbenium ion.

With large-membered ring ketones and imines, ring contraction is operative leading to functionalizated fluoro or hydroxy cyclohexanones or cycloheptanones, the driving force being the repulsive interaction of the positive charges in the intermediate ions.

## 3. Experimental

### 3.1. General methods

The authors draw the reader's attention to the dangerous features of superacidic chemistry. Handling of hydrogen fluoride and antimony pentafluoride must be done by experienced chemists with all the necessary safety arrangements in place.

Reactions are carried out in sealed Teflon® flask with a magnetic stirring. No further precaution have to be taken to prevent mixture from moiety (test reaction worked out in anhydrous conditions lead as expected to the same results).

Yields refer to isolated pure products. NMR spectra were recorded on Bruker-300 spectrometer using chloroform-d solvent, TMS was used as internal standard. Flash chromatography were carried out on silica gel (Matrex® 60A/20–45 μm) and MS were recorded on INCOS 50.

### 3.2. Preparation of imines substrates

Imines were prepared by azeotropic distillation of water with Dean–Stark apparatus, from a mixture of cyclohexylamine (240 mmol), ketone (80 mmol), and anhydrous benzene and *p*-tolyl sulfonic acid (catalytic). After neutralisation and extraction ($CH_2Cl_2$), imines were distilled. Yields are quantitative.

### 3.3. Typical procedure for reaction in superacids

To a mixture of $SbF_5$ (0.041 mol) and HF (0.300 mol) at reaction temperature, were added substrate (2 mmol) and $CCl_4$ (1.2 equiv.). The reaction mixture was stirred at reaction temperature for required time. The reaction mixture was neutralised on water/ice (150 mL) and sodium carbonate (80 g) (quenching condition A). When quenching conditions are B, 5 mL of HF/pyridine (molar ratio 70/30) were added on reaction mixture, stirred for 15 min, followed by neutralisation as quenching A. The reaction mixture was worked-up by the usual manner (extraction with $CH_2Cl_2$, then dry on magnesium sulphate) and products were isolated by column chromatography over $SiO_2$. Fluoroderivatives were eluted by EtOAc/P. ether: 5/95, and hydroxyderivatives by EtOAc/P. ether: 50/50.

### 3.4. Reaction of acyclic ketones and imines

**3.4.1. 6-Hydroxyheptan-2-one (8) and 5-hydroxyheptan-2-one (9).** Obtained as a mixture (molar ratio 1/3), from ketone **2** (quenching condition A) yield 67%. Alcohols are not separable, so they are acetylated. The acetylated derivatives are separated by semi-preparative HPLC: column SI 100, eluent EtOAc/*n*-hexane: 10/90, flow: 10 mL/min, refractive detector.

*6-(Methylacetoxy) heptan-2-one (**8′**).* $^1$H NMR ($CDCl_3$) $\delta$ 1.21 (d, $^3J$=6.1 Hz, 3H, $CH_3$, H-7), 1.56 (m, 4H, $2CH_2$, H-4 and H-5), 2.14 (s, 3H, $CH_3$, H-1), 2.14 (s, 3H, $CH_3$ acetate), 2.46 (t, $^3J$=9.0 Hz, 2H, $CH_2$, H-3), 4.89 (m, 1H, CH, H-6). $^{13}$C NMR ($CDCl_3$) $\delta$ 19.5 ($CH_2$, C-4), 19.8 ($2CH_3$, C-7), 21.2 ($CH_3$ acetate), 29.8 ($CH_3$, C-1), 35.3 ($CH_2$, C-5), 43.2 ($CH_2$, C-3), 70.4 (CH, C-6), 170.6 (C=O acetate), 208.2 (C=O, C-2). MS; *m/z* (%): 129 (8); 113 (100); 97 (54). HRMS: $C_9H_{16}O_3$ ($-COCH_3$) calculated: 129.09155, measured: 129.09100.

*5-(Methylacetoxy) heptan-2-one (**9′**).* $^1$H NMR ($CDCl_3$) $\delta$ 0.89 (t, $^3J$=8.0 Hz, 3H, $CH_3$, H-7), 1.57 (m, 2H, $CH_2$, H-6), 1.81 (m, 2H, $CH_2$, H-4), 2.05 (s, 3H, $CH_3$, H-1), 2.15 (s, 3H, $CH_3$ acetate), 2.47 (t, $^3J$=7.1 Hz, 2H, $CH_2$, H-3), 4.78 (m, 1H, CH, H-5). $^{13}$C NMR ($CDCl_3$) $\delta$ 9.4 ($CH_3$, C-7), 27.0 and 27.5 ($2CH_2$, C-4 and C-6), 29.7 ($CH_3$, C-1), 39.4 ($CH_2$, C-3), 74.7 (CH, C-5), 170.7 (C=O acetate), 207.5 (C=O, C-2). MS; *m/z* (%): 129 (32); 115 (50); 113 (100). HRMS: $C_9H_{16}O_3$ ($-COCH_3$) calculated: 129.09155, measured: 129.09100.

**3.4.2. 5-Hydroxyisoheptan-2-one and 2-hydroxy-2,5,5-trimethyl tetrahydrofurane (10).** Obtained as a mixture (molar ratio 3/1) from ketone **3** (quenching condition A or B) yield 82%.

*5-Hydroxyisoheptan-2-one.* $^1$H NMR ($CDCl_3$) $\delta$ 1.22 (s, 6H, $2CH_3$, H-6), 1.75 (t, $^3J$=7.0 Hz, 2H, $CH_2$, H-4), 2.18 (s, 3H, $CH_3$, H-1), 2.59 (t, $^3J$=7.1 Hz, 2H, $CH_2$, H-3), 3.32 (sl, 1H, OH). $^{13}$C NMR ($CDCl_3$) $\delta$ 29.1 ($2CH_3$, C-6), 29.7 (C-1), 36.7 ($CH_2$, C-3), 38.6 ($CH_2$, C-4), 69.7 ($CH_2$, C-5), 209.4 (C=O).

*2-Hydroxy-2,5,5-trimethyltetrahydrofurane.* $^1$H NMR ($CDCl_3$) $\delta$ 1.21 (s, 3H, $CH_3$, H-5′ or H-5″), 1.38 (s, 3H, $CH_3$, H-5′ or H-5″), 1.51 (s, 3H, $CH_3$, H-2′), 2.05 (t, $^3J$=6.1 Hz, 2H, $CH_2$, H-3). $^{13}$C NMR ($CDCl_3$) $\delta$ 28.1 and 28.5 ($2CH_3$, C-5′), 30.1 ($CH_3$, C-2′), 37.5 and 38.2 ($2CH_2$, C-3 and C-4), 82.2 (C-5), 105.0 (C-2). MS; *m/z* (%): 115 (70); 113 (30); 97 (80); 72 (70); 59 (100).

**3.4.3. 6-Hydroxyisooctan-2-one (11).** Obtained from ketone **3** (quenching condition A) yield 92%. $^1$H NMR ($CDCl_3$) $\delta$ 1.20 (s, 6H, $2CH_3$, H-7), 1.45 (t, $^3J$=4.9 Hz, 2H, $CH_2$, H-5), 1.61 (m, 2H, $CH_2$, H-4), 2.15 (s, 3H, $CH_3$, H-1), 2.47 (t, $^3J$=6.8 Hz, 2H, $CH_2$, H-3), 3.28 (sl, 1H, OH). $^{13}$C NMR ($CDCl_3$) $\delta$ 18.6 ($CH_3$, C-1), 29.2 ($2CH_3$, C-7), 29.8

($CH_2$, C-4), 43.1 and 43.9 ($2CH_2$, C-3 and C-5), 70.7 (C-6), 208.7 (C=O, C-2). MS; *m/z* (%): 129 (20); 126 (10); 116 (40); 111 (40); 71 (50); 58 (100). HRMS: $C_8H_{16}O_2-CH_3$ calculated: 129.09155, measured: 129.09160.

**3.4.4. 7-Fluoroisononan-2-one (12).** Obtained from ketone **6** (quenching condition B) yield 20%. $^1$H NMR ($CDCl_3$) $\delta$ 1.32 (d, $^3J_{HF}$=22 Hz, 6H, $2CH_3$, H-8), 1.56 (m, 6H, $3CH_2$, H-4, H-5 and H-6), 2.14 (s, 3H, $CH_3$, H-1), 2.46 (t, $^3J$=6.9 Hz, 2H, $CH_2$, H-3). $^{13}$C NMR ($CDCl_3$) $\delta$ 23.5 (d, $^3J$=5.1 Hz, $CH_2$, C-5), 24.0 (s, $CH_3$, C-1), 26.6 (d, $^2J$=24.2 Hz, $2CH_3$, C-8), 29.9 (s, $CH_2$, C-4), 41.2 (d, $^2J$=22.9 Hz, $CH_2$, C-6), 43.6 (s, $CH_2$, C-3), 95.5 (d, $J_{CF}$=162.1 Hz, C-F, C-7), 209.0 (C=O, C-2). MS; *m/z* (%): 141 (10); 140 (16); 122 (20); 97 (30); 82 (100). HRMS: $C_9H_{17}OF-HF$ calculated: 140.12011, measured: 140.12020. $C_9H_{17}OF$ (160.23): calculated C 67.48, H 10.69; found C 37.03, H 10.80.

**3.4.5. 7-Hydroxyisononan-2-one (13).** Obtained from ketone **6** (quenching condition A) yield 50%. $^1$H NMR ($CDCl_3$) $\delta$ 1.20 (s, 6H, $2CH_3$, H-8), 1.44 (m, 6H, $3CH_2$, H-4, H-5 and H-6), 2.14 (s, 3H, $CH_3$, H-1), 2,22 (sl, 1H, OH), 2.46 (t, $^3J$=6.7 Hz, 2H, $CH_2$, H-3). $^{13}$C NMR ($CDCl_3$) $\delta$ 23.7 and 24.2 ($CH_2$, C-4 and C-5), 29.0 ($2CH_3$, C-8), 29.6 ($CH_3$, C-1), 43.4 and 43.5 ($2CH_2$, C-3 and C-6), 70.5 (C–OH, C-7), 208.9 (C=O, C-2). MS; *m/z* (%): 143 (8); 140 (7); 125 (40); 100 (40); 71 (64); 58 (100). HRMS: $C_9H_{18}O_2-H_2O$ calculated: 140.12011, measured: 140,12000.

**3.4.6. 5-Fluoroisoheptan-2-one (18).** Obtained from imine **15** (quenching condition B) yield 68%. $^1$H NMR ($CDCl_3$) $\delta$ 1.33 (d, $^3J_{HF}$=21.0 Hz, 6H, $2CH_3$, H-6), 1.85 (m, 2H, $CH_2$, H-4), 2.16 (s, 3H, $CH_3$, H-1), 2.57 (t, $^3J$=8.1 Hz, 2H, $CH_2$, H-3). $^{13}$C NMR ($CDCl_3$) $\delta$ 26.6 (d, $^2J$=23.9 Hz, $2CH_3$, C-6), 29.9 (s, $CH_3$, C-1), 34.5 (d, $^2J$=23.0 Hz, $CH_2$, C-4), 38.0 (d, $^3J$=3.1 Hz, $CH_2$, C-3), 94.7 (d, $J_{CF}$=165.1 Hz, C-F, C-5), 208.1 (s, C=O, C-2). HRMS: $C_6H_{10}OF$, M−Me calculated: 117.07157, measured: 117.0709.

**3.4.7. 6-Fluoroisooctan-2-one (19).** Obtained from imine **16** (quenching condition B) yield 69%. $^1$H NMR ($CDCl_3$) $\delta$ 1.34 (d, $^3J_{HF}$=21.0 Hz, 6H, $2CH_3$, H-7), 1.64 (m, 4H, $2CH_2$, H-4 and H-5), 2.14 (s, 3H, $CH_3$, H-1), 2.47 (t, $^3J$=7.1 Hz, 2H, $CH_2$, H-3). $^{13}$C NMR ($CDCl_3$) $\delta$ 18.2 (d, $^3J$=5.3 Hz, $CH_2$, C-4), 26.5 (d, $^2J$=24.8 Hz, $2CH_3$, C-7), 29.9 (s, $CH_3$, C-1), 40.5 (d, $^2J$=22.1 Hz, $CH_2$, C-5), 43.5 (s, $CH_2$, C-3), 95.4 (d, $J_{CF}$=150.0 Hz, C-F, C-6), 208.6 (s, C=O, C-2). HRMS: $C_8H_{14}O$, M−HF calculated: 126.10447, measured: 126.1054.

### 3.5. Reaction of cyclic ketones and imines

**3.5.1. 1′-Fluoro-4-isopropylcyclohexanone (27).** Obtained from ketone **21** (quenching condition B) yield 60%. $^1$H NMR ($CDCl_3$) $\delta$ 1.36 (d, $^3J_{HF}$=22.6 Hz, 6H, $2CH_3$, H-2′), 1.58 (m, 2H, 1H-3 and 1H-5), 2.02 (m, 1H, H-4), 2.14 (m, 2H, 1H-3 and 1H-5), 2.36 (m, 4H, H-2 and H-6). $^{13}$C NMR ($CDCl_3$) $\delta$ 24.4 (d, $^2J$=25.1 Hz, $2CH_3$, C-2′), 27.1 (d, $^3J$=6.1 Hz, $2CH_2$, C-3 and C-5), 40.5 (s, $2CH_2$, C-2 and C-6), 45,9 (d, $^2J$=22.7 Hz, CH, C-4), 96.6 (d, $J_{CF}$=167.1 Hz, C-F, C-1′), 210.6 (s, C=O, C-1). MS; *m/z* (%): 158 (10); 138 (8), 130 (20); 84 (47); 69 (100). HRMS: $C_9H_{15}FO$ calculated: 158.11069, measured: 158.11070.

**3.5.2. 1′-Hydroxy-4-isopropylcyclohexanone (28).**[21] Obtained from ketone **21** (quenching condition A) yield 20% $^1$H NMR ($CDCl_3$) $\delta$ 1.25 (s, 6H, $2CH_3$, H-2′), 1.55 (m, 2H, 1H-3 and 1H-5), 1.81 (m, 1H, H-4), 2.20 (m, 2H, 1H-3 and 1H-5), 2.40 (m, 4H, H-2 and H-6). $^{13}$C NMR ($CDCl_3$) $\delta$ 26.9 ($2CH_3$, C-2′), 27.3 ($2CH_2$, C-3 and C-5), 40.7 ($2CH_2$, C-2 and C-6), 47.1 (CH, C-4), 72.0 (C–OH, C-1′), 212.6 (C=O, C-1). MS; *m/z* (%): 156 (10); 138 (20); 98 (68); 82 (58); 69 (100).

**3.5.3. 4-[2-Fluoro-2-methyl]propylcycloheptanone (29) and 4-[3-fluoro-3-methyl]butylcyclohexanone (31).** Obtained as a mixture (ratio molar 50/50) from ketone **24** (quenching condition A) yield 12%.

*4-[2-Fluoro-2-methyl]propylcycloheptanone (**29**).* $^1$H NMR ($CDCl_3$) $\delta$ 1.38 (d, $^3J_{HF}$=21.2 Hz, 6H, $2CH_3$, H-3′), 1.30–2.6 (m, 13H). $^{13}$C NMR ($CDCl_3$) $\delta$ 22.8 (s, $CH_2$, C-6), 27.1 and 27.3 (2d, $^2J$=25.3 Hz, $2CH_3$, C-3′), 31.3 (d, $^4J$=1.9 Hz, $CH_2$, C-3), 37.2 (s, CH, C-4), 37.8 (d, $^4J$=2.1 Hz, $CH_2$, C-5), 42.1 and 43.6 (s, $2CH_2$, C-2 and C-7), 47.6 (d, $^2J$=21.5 Hz, $CH_2$, C-1′), 95.7 (d, $J_{CF}$=162.7 Hz, C-F, C-2′), 215.0 (s, C=O, C-1).

*4-[3-Fluoro-3-methyl]butylcyclohexanone (**31**).* $^1$H NMR ($CDCl_3$) $\delta$ 1.35 (d, $^3J_{HF}$=21.4 Hz, 6H, $2CH_3$, H-4′), 1.30–2.60 (m, 13H). $^{13}$C NMR ($CDCl_3$) $\delta$ 26.6 (d, $^2J$=25.0 Hz, $2CH_3$, C-4′), 29.5 (d, $^3J$=5.1 Hz, $CH_2$, C-1′), 32.6 (s, $2CH_2$, C-3 and C-5), 36.3 (s, CH, C-4), 39.1 (d, $^2J$=22,5 Hz, $CH_2$, C-2′), 40,7 (s, $2CH_2$, C-2 and C-6), 95.5 (d, $J_{CF}$=162,1 Hz, C-F, C-3′), 212.2 (s, C=O, C-1). MS; *m/z* (%): 186 (68); 165 (7); 149 (27); 109 (29); 95 (34); 81 (30); 55 (100). HRMS: $C_{11}H_{19}FO$ calculated: 186.14199, measured: 186.14180.

**3.5.4. 4-[2-Hydroxy-2-methyl]propylcycloheptanone (30) and 4-[3-hydroxy-3-methyl]butylcyclohexanone (32).** Obtained as a mixture (ratio molar 38/62) from ketone **24** (quenching condition A) yield 28%. Compounds **30** and **32** are separated by semi-preparative HPLC: column SI 100, Eluent AcOEt/*n*-hexane: 35/65 flow: 10 mL/min, refractive detector.

*4-[2-Hydroxy-2-methyl]propylcycloheptanone (**30**).* $^1$H NMR ($CDCl_3$) $\delta$ 1.25 (s, 6H, $2CH_3$, H-3′), 1.40–2.10 (m, 9H, H-3, H-4, H-5, H-6 and H-1′), 2.40–2,25 (m, 4H, H-2 and H-7). $^{13}$C NMR ($CDCl_3$) $\delta$ 23.0 ($CH_2$, C-6), 29.9 and 30.1 ($2CH_3$, C-3′), 32.1 ($CH_2$, C-3), 37.5 (CH, C-4), 38,6 ($CH_2$, C-5), 42.3 and 43.7 ($2CH_2$, C-2 and C-7), 50.2 ($CH_2$, C-1′), 71.4 (C–OH, C-2′), 215.0 (C=O, C-1). MS; *m/z* (%): 184 (2); 167 (39); 109 (75); 96 (58); 83 (56); 69 (70); 56 (100). HRMS: $C_{11}H_{20}O_2$ calculated: 184.14633, measured: 184.14730.

*4-[3-Hydroxy-3-methyl]butylcyclohexanone (**32**).* $^1$H NMR ($CDCl_3$) $\delta$ 1.23 (s, 6H, $2CH_3$, H-4′), 1.32–1.50 (m, 4H, H-3 and H-5), 1.50–1.60 (m, 2H, H-1′), 1.70 (m, 1H, H-4), 2.00–2.15 (m, 2H, H-2′), 2.30–2.40 (m, 4H, H-2 and H-6). $^{13}$C NMR ($CDCl_3$) $\delta$ 29.2 ($2CH_3$, C-4′), 30.0 ($CH_2$, C-1′), 32.7 ($2CH_2$, C-3 and C-5), 36.5 (CH, C-4), 40.7 ($2CH_2$, C-2

and C-6), 41.4 ($CH_2$, C-2′), 70.9 (C–OH, C-3′), 212.5 (C=O, C-1). MS; *m/z* (%):184 (2); 167 (34); 126 (28); 109 (74); 96 (58); 82 (50); 69 (68); 56 (100). HRMS: $C_{11}H_{20}O_2$ calculated: 184.14633, measured: 184.14630.

**3.5.5. 4-[3-Fluoro-3-methyl]butylcycloheptanone (33).** Obtained from imine **26** (quenching condition B) yield 20%. $^1$H NMR ($CDCl_3$) $\delta$ 1.34 (d, $^3J_{HF}$=20.0 Hz, 6H, $2CH_3$, H-4′), 1.40–2.10 (m, 12H), 2.50 (m, 4H, $2CH_2$, H-2 and H-7). $^{13}$C NMR ($CDCl_3$) $\delta$ 22.6 (s, $CH_2$, C-6), 26.5 (2d, $^2J$=24.4 Hz, $2CH_3$, C-4′), 30.1 (s, $CH_2$, C-3), 30.8 (d, $^3J$=5.1 Hz, $CH_2$, C-1′), 36.2 (s, $1CH_2$, C-5), 38.9 (d, $^2J$=22.9 Hz, $CH_2$, C-2′), 41.4 (s, CH, C-4), 42.1 (s, $CH_2$, C-2), 43.6 (s, $CH_2$, C-7), 95.2 (d, $J_{CF}$=167.1 Hz, C-F, C-3′), 214.5 (s, C=O, C-1). MS; *m/z* (%): 200 (20); 180 (18); 165 (20); 124 (56); 110 (90); 96 (70); 82 (85); 69 (100). HRMS: $C_{12}H_{21}FO$ calculated: 200.15764, measured: 200,15650.

**3.5.6. 4-[3-Hydroxy-3-methyl]butylcycloheptanone (34).** Obtained from ketone **25** (quenching condition A) yield 36.5% $^1$H NMR ($CDCl_3$) $\delta$ 1.20 (s, 6H, $2CH_3$, H-4′), 1.25–2.10 (m, 12H), 2.49 (m, 4H, H-2 and H-7). $^{13}$C NMR ($CDCl_3$) $\delta$ 22.8 ($CH_2$, C-6), 29.0 ($2CH_3$, C-4′), 30.0 ($CH_2$, C-3), 31.3 ($CH_2$, C-1′), 36.3 ($CH_2$, C-5), 41.1 ($CH_2$, C-2′), 41.5 (CH, C-4), 42.0 ($CH_2$, C-2), 43.6 ($CH_2$, C-7), 70.6 (C–OH, C-3′), 215.4 (C=O, C-1). MS; *m/z* (%): 198 (1); 180 (24); 165 (30); 147 (37); 125 (30); 11 (74); 97 (64); 83 (56); 69 (68); 59 (100). HRMS: $C_{12}H_{22}O_2$ (FAB: $MLi^+$) calculated: 205.17798, measured: 205.17720.

## References


1. Olah, G. A.; Prakash, S.; Sommer, J. *Science* **1979**, *206*, 13–20.
2. Olah, G. A.; Prakash, S.; Sommer, J. *Superacids*; Wiley-Interscience: New York, 1985.
3. Olah, G. A.; Mo, Y. K. *J. Am. Chem. Soc.* **1972**, *94*, 6864–6865.
4. Olah, G. A.; Renner, R.; Schilling, P.; Mo, Y. K. *J. Am. Chem. Soc.* **1973**, *95*, 7680–7686.
5. Culmann, J. C.; Sommer, J. *J. Chem. Soc., Chem. Commun.* **1992**, 481–483.
6. Olah, G. A.; Parker, D. G.; Yoneda, N. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 909–931.
7. Olah, G. A.; Lin, H. C. *J. Am. Chem. Soc.* **1971**, *63*, 1259–1261.
8. Olah, G. A.; Gupta, B. G. B. *J. Org. Chem.* **1980**, *45*, 3532–3533.
9. Olah, G. A.; Shih, J.; Singh, B. P.; Gupta, B. G. P. *J. Org. Chem.* **1983**, *48*, 3356–3358.
10. Olah, G. A. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 173–212.
11. Preliminary report: Martin, A.; Jouannetaud, M. P.; Jacquesy, J. C. *Tetrahedron Lett.* **1996**, *37*, 2967–2970.
12. Olah, G. A.; Heiliger, L.; Prakash, G. K. S. *J. Am. Chem. Soc.* **1989**, *111*, 8020–8021.
13. Culmann, J. C.; Simon, M.; Sommer, J. *J. Chem. Soc., Chem. Commun.* **1990**, 1098–1100.
14. Olah, G. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 767–788.
15. Olah, G. A.; Kreinbühe, P. *J. Am. Chem. Soc.* **1967**, *89*, 4756–4759.
16. Olah, G. A.; Cahin, M.; O'Brien, D. H. *J. Am. Chem. Soc.* **1967**, *89*, 3568–3590.
17. Brower, D. M.; Kiffen, A. A. *Recl. Trav. Chim. Pays-Bas* **1973**, *92*, 906–914.
18. Kirchen, R. P.; Sorensen, T. S. *J. Am. Chem. Soc.* **1979**, *101*, 3240–3243.
19. Kirchen, R. P.; Sorensen, T. S.; Wagstaff, K. E. *J. Am. Chem. Soc.* **1978**, *100*, 5134–5140.
20. Olah, G. A.; Kelly, D. L.; Johanson, R. G. *J. Am. Chem. Soc.* **1970**, *92*, 4137–4139.
21. Cawley, J. J.; Spaziano, V. T. *Tetrahedron Lett.* **1973**, *47*, 4719–4722.