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Reactions of carboxyl derivatives of camphor with sulphur tetrafluoride

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Abstract

Treatment of a mixture of *endo*- and *exo*-(1R)-3-camphorcarboxylic acid (**1**) with sulphur tetrafluoride gave initially, (1R)-3-(fluoroformyl)camphor (**2**) and (1R)-2,2-difluoro-3-(fluoroformyl)bornane (**3**) but after prolonged reaction time, a mixture of *endo*- and *exo*-(1R)-3-(trifluoromethyl)camphor (**4**) was obtained, albeit in low yield. Carboxylic groups in (1S)-ketopinic and (1R)-*trans*-isoketopinic acids (**5**) and (**9**) were found to be resistant towards SF_4 such that at ambient temperature only corresponding acid fluorides (**6**) and (**10**) were obtained but under forced conditions fluorination of the carbocyclic ring carbonyl group occurred affording, respectively, (1S)-2,2-difluoro-1-fluoroformyl-7,7-dimethylbicyclo[2,2,1]heptane (**7**) and (1R)-2,2-difluoro-*trans*-7-fluoroformyl-1,7-dimethylbicyclo[2,2,1]heptane (**11**). Hydrolysis of **7** and **11** gave the corresponding acids **8** and **12**.

Keywords: 3-Camphorcarboxylic acid; Ketopinic acid; Isoketopinic acid; Fluorination; Sulphur tetrafluoride; (1R)-3-(Trifluoromethyl)camphor; (1S)-2,2-difluoro-7,7-dimethylbicyclo[2,2,1]heptane-1-carboxylic acid; (1R)-2,2-difluoro-1,7-dimethylbicyclo[2,2,1]heptane-*trans*-7-carboxylic acid

1. Introduction

Terpenes are versatile, chiral and enantiopure staring materials in natural product synthesis [1]. In the preceding papers we reported that a sulphur tetrafluoride fluorination of (1R,3S)-(+)-camphoric acid [2,3] and (1S,4R)-(−)-camphanic acid [4] proceeds selectively, i.e. only sterically less hindered carboxyl groups were converted into trifluoromethyl groups: (1R,3S)-(+)-3-(trifluoromethyl)-camphonanic acid and (1S,4R)-(−)-3-oxa-4-(trifluoromethyl)-camphor were obtained, respectively, in good yields. These compounds were converted into a number of new trifluoromethyl derivatives with the defined steric configuration. The present paper reports results of the continued study on fluorination of carboxyl derivatives of camphor.

2. Results and discussion

In contrast to the earlier reported reactions of camphoric and camphanic acids with SF_4 which gave good yields of trifluoromethyl derivatives [2–4], fluorination of (1R)-3-camphor-carboxylic acid (**1**) was less successful. Treatment of **1** (*endo*/*exo*=ca. 3:1) with SF_4 at ambient temperature for 24 h resulted mostly in conversion of the carboxylic group into a fluoroformyl group and, to much less extent in fluorination of the carbonyl group; a mixture of (1R)-3-(fluoroformyl)camphor (**2**) and (1R)-2,2-difluoro-3-(fluoroformyl)bornane (**3**) in a 10:1.6 ratio was formed almost quantitatively. When the reaction was run for a prolonged time (7 days) a dark oily tar was formed from which, after treatment with aqueous alkaline solution a mixture of *endo*- and *exo*-(1R)-3-(trifluoromethyl)camphor (**4**) was isolated but only in ca. 18% yield. The *endo*/*exo* ratio of **4** was roughly the same as that of the starting acid **1** thus confirming retention of the configuration at the carbon atom C-3 during the fluorination reaction. The *endo* and *exo* configurations of the CF_3 group in **4** (and of the COOH group in **1**) were unambiguously assigned from their ^1H NMR spectra: in the *endo* form a coupling between H-3 and H-4 protons appears which is absent in the *exo* form. The coupling constants (J=4.6 and 0 Hz, respectively) are in agreement with values obtained by semiempirical modelling (MOPAC 6, PCMODEL).

The long reaction time did not gave detectable amount of pentafluorobornane which should result from the fluorination of both carboxylic and keto groups; probably steric crowding in compound **3** prohibits further fluorination.

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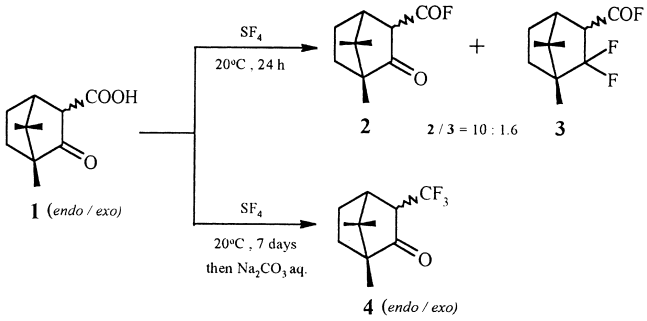
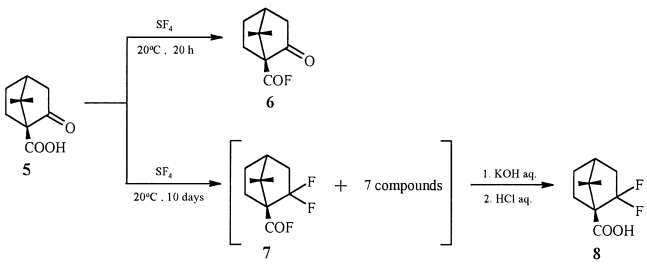
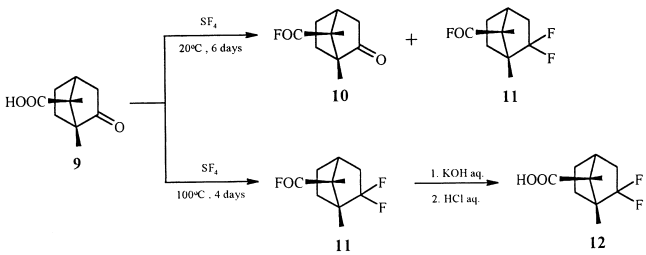


Interestingly, introduction of the CF_3 group into a camphor molecule drastically changes its physical properties. In contrast to unsubstituted camphor, which is a high melting crystalline solid (mp ca. 180°C), 3-(trifluoromethyl)camphor (**4**) is at room temperature a viscous oil.

The carboxylic groups in ketopinic acid (**5**) and isoketopinic acid (**9**) were found to be unexpectedly unreactive towards SF_4. Thus, treatment of the acid **5** with SF_4 at room temperature overnight gave ketopinoyl fluoride (**6**) almost quantitatively and as the only product. When the reaction time was prolonged to 10 days a complex mixture was formed with 2,2-difluoro-1-fluoroformyl-7,7-dimethylbicyclo[2,2,1]heptane (**7**) being the main product (GC-MS identification). The latter was isolated, after hydrolysis, as 2,2-difluoro-7,7-dimethylbicyclo-[2,2,1]heptane-1-carboxylic acid (**8**).



Isoketopinic acid (**9**) appears to be even less reactive than ketopinic acid (**5**); the reaction conducted for 6 days at room temperature gave isoketopinoyl fluoride (**10**) and 2,2-difluoro-7-fluoroformyl-1,7-dimethylbicyclo[2,2,1]heptane (**11**) in a 3.5:1 ratio. In contrast to **5**, which when reacted at elevated temperatures produced only black tar, acid **9** was successfully fluorinated at 100°C to give acid fluoride (**11**) almost quantitatively. Hydrolysis of the crude reaction mixture afforded 2,2-difluoro-1,7-dimethylbicyclo[2,2,1]-heptane-7-carboxylic acid (**12**) in a 86 % yield.



It appears that carboxylic groups in acids **5** and **9** are even less reactive towards SF_4 than the carbonyl group at the highly sterically crowded position 2 of the bornane molecule. In both above cases the carboxylic groups are bound to tertiary carbon atoms. Similarly low reactivity was previously reported for α-branched aliphatic acids, e.g. trimethylacetic, isobutyric and others [5,6].

3. Experimental

Melting points were determined in capillaries and boiling points were measured during distillation; both are uncorrected. ^1H and ^{19}F NMR spectra were recorded with a Varian Gemini 200 spectrometer at 200 and 188 MHz, respectively. Chemical shifts are quoted in ppm from internal TMS for ^1H (positive downfield) and from internal $CFCl_3$ (positive upfield). The crude mixture of products was analysed with a Shimadzu GC-14A Chromatograph using a 3.5 m×2 mm column packed with 5% silicone oil SE-52 on Chromosorb G. GC-MS analyses were performed with a Hewlett-Packard 5890 apparatus using a 30 m capillary column coated with a HP-5 oil. Mass spectra of pure compounds were obtained with an AMD-604 spectrometer and IR spectra with a Perkin-Elmer Spectrum 2000 instrument. Optical rotations were measured at ambient temperature with a JASCO DIP-360 polarimeter using a 100 mm cell.

3.1. Starting materials

Sulphur tetrafluoride was a technical grade commercial product (Air Products, USA).

(1R)-3-camphorcarboxylic acid (**1**) was synthesizsed from (1R)-(+)-camphor by following the literature procedure [7]; according to the ^1H NMR analysis a 3:1 mixture of *endo* and *exo* forms was obtained, mp 124–126°C (Lit. 128°C for the *endo* form [7]); $[\alpha]_D$=+41.2 (c=10, MeOH).

(1S)-(+)-ketopinic acid (**5**) was prepared by oxidation of (1S)-(+)-10-camphorsulphonyl chloride [8]; mp 232–233°C (Lit. 237–240°C [9]); $[\alpha]_D$=+26.1 (c=10, MeOH), in agreement with literature data [10].

(1R)-*trans*-isoketopinic acid (**9**) was prepared in six stages from (1R)-(+)-camphor. Camphor was brominated, first to *endo*-3-bromocamphor then to 3,8-dibromocamphor which was debrominated to 8-bromocamphor [11]. The next three steps involved a conversion of 8-bromocamphor to 8-acetylcamphor followed by hydrolysis to 8-hydroxycamphor [12,13] and oxidation of the latter [13]; mp 252–255°C (Lit. 257–258°C [14]).

3.2. Reactions of carboxylic acids with sulphur tetrafluoride

3.2.1. General procedure

An acid was placed in a 30 ml capacity stainless steel autoclave fitted with a needle valve, the autoclave was

cooled in an acetone-dry ice bath, evacuated, then sulphur tetrafluoride was condensed into it. The autoclave was mechanically agitated at ambient temperature (ca. 20°C) for the required time. After completion of the reaction, gaseous products were let off (excess SF_4, SOF_2, HF), the residue was dissolved in CH_2Cl_2, agitated overnight with dry sodium fluoride (removal of HF) then the solvent was removed on a rotary evaporator to give a crude mixture of products.

3.2.2. Reactions of (1R)-3-camphorcarboxylic acid (*1*) with SF_4

3.2.2.1. Preparation of compounds 2 and 3. The acid (2.0 g, 10 mmol) was reacted with SF_4 (3.5 g, 30 mmol) at ambient temperature for 24 h and worked up as in Section 3.2.1. GC-MS analysis of the crude product (1.8 g, dark oil) showed the presence of compounds **2** and **3** in a 10:1.6 ratio. IR (film) ν (cm^{-1}): 1833.7 (vs, COF); 1755.3 (vs, CO).

(1R)-3-(fluoroformyl)camphor (**2**): GLC yield: 78%. GC-MS *m/z* (rel. int., ion): 198 (trace, M^+); 152 [35, $(M-COF)^+$]; 109 (50, $C_8H_{13}^+$); 108 (30); 95 (100, $C_7H_{11}^+$); 83 ($C_6H_{11}^+$); 81 ($C_6H_9^+$); 67 (50, $C_5H_7^+$); 55 (45, $C_4H_7^+$); 41 (75, $C_3H_5^+$).

(1R)-2,2-difluoro-3-(fluoroformyl)bornane (**3**): GLC yield: 11%. GC-MS *m/z* (rel. int., ion): 220 (10, M^+); 200 [20, $(M-HF)^+$]; 153 [20, $(M-HF-COF)^+$]; 132 (30, $C_6H_6F_2O^+$); 117 ($C_5H_3F_2O^+$); 103 (100, $C_4HF_2O^+$); 90 (40, $C_3F_2O^+$); 77 (40, $C_3H_3F_2^+$); 51 (20, CHF_2^+).

*3.2.2.2. Preparation of endo- and exo-(1R)-3-(trifluoromethyl)camphor (**4**).* The acid (2.0 g, 10 mmol) was reacted with SF_4 (3.5 g, 30 mmol) at ambient temperature for 7 days and worked up as in Section 3.2.1. A solution of crude product in CH_2Cl_2 was decanted from NaF and vigorously shaken with saturated aqueous Na_2CO_3, then with water and dried over $MgSO_4$. A dark residue obtained after removal of the solvent (1.4 g) was vacuum distilled to give a colourless oil possessing a irritant terpenic odour. This oil was found by GC-MS, ^1H and ^{19}F NMR analyses to be a mixture of *endo* and *exo* isomers of 4 in a ca. 3:1 ratio. Yield: 0.41 g (18.6%). Bp 78°C/5 Torr. IR (film) ν (cm^{-1}): 1758.1 (vs, CO). $[\alpha]_D^{20}=+28.2$ ($c=5$, MeOH). Analysis: Found: C, 60.0; H, 7.0; F, 25.8%. Calculated for $C_{11}H_{15}F_3O$ (220.23): C, 59.99; H, 6.86; F, 25.88%.

endo-(1R)-3-(trifluoromethyl)camphor (**4a**):^1H NMR (200 MHz, in $CDCl_3$) δ: 0.90 (s, CH_3); 0.96 (s, CH_3); 1.04 (s, CH_3); 1.45–1.9 (m, 4H); 2.38 (t, $^3J_{HH}$=ca. 4.5 Hz, 1H); 3.14 (qdd, $^3J_{HF}=10.5$ Hz, $^3J_{HH}=4.6$ Hz, $^5J_{HH}=1.0$ Hz, 1H) ppm. ^{19}F NMR (188 MHz, in $CDCl_3$) δ: 61.9 (d, $^3J_{HF}=10.5$ Hz, CF_3). GC-MS *m/z* (rel. int., ion): 220 (10, M^+); 205 [1, $(M-CH_3)^+$]; 192 [2, $(M-CO)^+$]; 177 [25, $(M-Me-CO)^+$]; 108 (20, $C_8H_{12}^+$); 95 (40, $C_7H_{11}^+$); 83 (100, $C_6H_{11}^+$); 69 (90, CF_3^+); 55 (80, $C_4H_7^+$); 41 (95, $C_3H_5^+$).

exo-(1R)-3-(trifluoromethyl)camphor (**4b**): ^1H NMR (200 MHz, in $CDCl_3$) δ: 0.90 (s, CH_3); 0.96 (s, CH_3); 0.99 (s, CH_3); 1.45–1.9 (m, 4H); 2.43 (d, $^3J_{HH}=4.1$ Hz, 1H); 2.72 (q, $^3J_{HF}=11.3$ Hz, 1H) ppm. ^{19}F NMR (188 MHz, in $CDCl_3$) δ: 60.8 (d, $^3J_{HF}=11.3$ Hz, CF_3). GC-MS: identical with *endo* isomer.

3.2.3. Reactions of (1S)-(+)-ketopinic acid (*5*) with SF_4

*3.2.3.1. Preparation of (1S)-ketopinoyl fluoride (**6**).* (1S)-(+)-ketopinic acid (1.82 g, 10 mmol) and SF_4 (7 g, 65 mmol) were reacted at ambient temperature for 20 h and worked up as in Section 3.2.1. Evaporation of the solvent gave a colourless and odourless crystalline product. GLC analysis showed basically one component. Yield: 1.73 g (95%). GLC purity>92%. IR (CCl_4) (cm^{-1}): 1831 (vs, COF); 1757.8 (vs, CO). MS (70 eV) *m/e* (rel. int., ion): 184 (86, M^+); 169 [57, $(M-CH_3)^+$]; 164 [100, $(M-HF)^+$]; 141 [27, $(M-CO-CH_3)^+$]; 136 [41, $(M-HF-CO)^+$].

*3.2.3.2. Preparation of (1S)-(+)-2,2-difluoro-7,7-dimethylbicyclo[2,2,1]heptane-1-carboxylic acid (**8**).* (1S)-(+)-ketopinic acid (1.82 g, 10 mmol) and SF_4 (7 g, 65 mmol) were reacted at ambient temperature for 10 days and worked up as in Section 3.2.1 to give a dark oil (2.2 g). GC-MS analysis revealed the presence of eight components with highest *m/e* ions: 208 ($C_{10}H_{15}F_3O$, one minor component), 206 ($C_{10}H_{13}F_3O$, two compounds), 246 ($C_{10}H_{12}F_6$, two compounds), 228 ($C_{10}H_{13}F_5$, two compounds) and 278 (probably $C_{10}H_{12}F_6S$). The oil was dissolved in *n*-hexane (20 ml) and agitated with 5% aqueous KOH for 2 h. GC-MS showed the disappearance of one component with molecular ion 206 (compound **7**, the most abundant one). The aqueous layer was separated, boiled for a few minutes with charcoal and filtered. Acidification with concentrated hydrochloric acid gave a white–gray precipitate which was filtered off and recrystallised from *n*-hexane/$CHCl_3$ (2:1) to give colourless crystals. Yield: 0.27 g (13%). Mp ca. 260°C (subl.). IR (nujol) (cm^{-1}): 1708.6 (vs, CO). $[\alpha]_D=+8.8$ ($c=1.4$, MeOH).

Analysis: Found, C, 58.6; H, 7.0; F, 18.6%. $C_{10}H_{14}F_2O_2$ (204.22) requires: C, 58.8; H, 6.9; F, 18.6 %. ^1H NMR (200 MHz, in DMSO): 1.06 (s, CH_3); 1.15 (d, $^5J_{HF}=2.5$ Hz, CH_3); 1.28 (complex, 1H); 1.65–2.0 (complex, 5H); 2.28–2.45 (complex, 1H); 12.55 (broad s, COOH) ppm. ^{19}F NMR (188 MHz, in DMSO): AB system centered at 83.5 ($J_{AB}=225$ Hz) ppm.

MS (70 eV) *m/e* (rel. int., ion): 204 (<1, M^+); 184 [72, $(M-HF)^+$]; 169 [23, $(M-HF-CH_3)^+$]; 142 (41, $C_7H_7FO_2^+$); 141 [83, $(M-F-CO_2)^+$]; 140 [69, $(M-HF-CO_2)^+$]; 139 [100, $(M-HF-CO_2H)^+$]; 125 [31, $(M-HF-CO_2-CH_3)^+$]; 97 (52, $C_7H_{13}^+$); 83 (27, $C_6H_{11}^+$); 77 (25, $C_3H_3F_2^+$); 55 (24, $C_4H_7^+$); 43 (18, $C_3H_7^+$); 41 (26, $C_3H_5^+$).

*3.2.4. Reactions of (1R)-trans-isoketopinic acid (**9**) with SF_4*

3.2.4.1. Preparation of compounds 10 and 11. (1R)-*trans*-Isoketopinic acid (0.9 g, 5 mmol) and SF_4 (2 g, 20 mol) were reacted at ambient temperature for 6 days and worked up as in Section 3.2.1. A colourless crystalline product was obtained. GC-MS analysis (in Et_2O solution) showed two components in a 3.5:1 ratio which were identified, respectively, as isoketopinoyl fluoride (**10**) [*m/e* 184 M^+; 156 $(M-CO)^+$] and (1R)-2,2-difluoro-7-fluorocarbonyl-1,7-dimethyl-bicyclo[2.2.1]heptane (**11**) [*m/e* 206 M^+; 186 $(M-HF)^+$]. IR (**10** and **11** in CCl_4) (cm^{-1}): 1837.3 (vs, COF); 1755.0 (vs, CO). Total yield: 0.9 g (ca. 96%).

*3.2.4.2. Preparation of (1R)-2,2-difluoro-7-fluorocarbonyl-1,7-dimethylbicyclo- [2,2,1]heptane (**11**).* (1R)-*trans*-Isoketopinic acid (0.9 g, 5 mmol) and SF_4 (3.5 g, 32 mmol) were reacted at 100°C for 4 days (96 h) to give a yellow crystalline solid which was shown by GLC to be 92% pure **11**. Analytical, colourless sample was obtained by recrystallisation from acetone with charcoal added. Yield: 0.95 g (85%); 0.4 g (40%) after recrystal-lisation. Mp ca. 165–170°C (intense sublimation). IR (CCl_4) ν (cm^{-1}): 1837.3 (vs, COF). Analysis: Found: C, 58.0; H, 6.5; F, 27.7%. $C_{10}H_{13}F_3O$ (206.21) requires: C, 58.25; H, 35; F, 27.64 %. ^{1}H NMR (200 MHz, in $CDCl_3$) δ: 1.25 (t, J=1.5 Hz, CH_3); 1.38 (d, J=2.1 Hz, CH_3); 1.4–2.0 (complex, 5H); 2.2–2.5 (complex, 2H) ppm. ^{19}F NMR (188 MHz, in $CDCl_3$) δ: −34.4 (d, J=1.9 Hz, COF); 89.1 and 107.8 (AB system, J_{AB}=229 Hz, CF_2) ppm. MS (70 eV) *m/e* (rel. int., ion): 206 (6, M^+); 191 [6, $(M-CH_3)^+$]; 187 [12, $(M-F)^+$]; 186 [100, $(M-HF)^+$]; 171 [22, $(M-HF-CH_3)^+$]; 166 [37, $(M-2HF)^+$]; 159 [82 $(M-COF)^+$]; 146 [58, $(M-3HF)^+$]; 139 [$(M-COF-HF)^+$], 127 (63); 119 [77, $(M-COF-2HF)^+$]; 111 (98); 77 (38, $C_3H_3F_2^+$); 55 (22, $C_4H_5^+$); 41 (17, $C_3H_5^+$).

*3.2.4.3. Preparation of (1R)-(−)-2,2-difluoro-1,7-dimethylbicyclo[2,2,1]heptan-trans-7-carboxylic acid (**12**).* (1R)-*trans*-isoketopinic acid (0.39 g, 2.17 mmol) and SF_4 (3.5 g, 32 mmol) were reacted under conditions as in Section 3.2.4.2. The solid product was dissolved in ether (5 ml), the solution was added to 10% aqueous KOH and a two-phase mixture was vigorously stirred overnight then charcoal was added, the mixture was boiled for a while and filtered while hot. Acidification of the filtrate gave a white precipitate which was filtered off, washed with water and dried under vacuo over P_4O_{10}. Analytical sample was obtained by recrystallization from hexane. Yield: 0.38 g (86%). Mp ca. 220°C (subl.). IR (nujol) ν (cm^{-1}): 1704.2 (vs, COOH). $[\alpha]_D^{20}$=−14.5 (c=5, MeOH).

Analysis: Found: C, 58.6; H, 6.2; F, 18.55%. $C_{10}H_{14}F_2O_2$ (204.22) requires: C, 58.8; H, 6.1; F, 18.6%. ^{1}H NMR (200 MHz, in DMSO-d_6) δ: 1.15 (d, J=0.3 Hz, CH_3); 1.18 (d, J=2.3 Hz, CH_3); 1.2–1.4 (complex, 1H); 1.4–1.9 (complex, 4H); 2.29 (m, 1H): 12.4 (broad, COOH) ppm.

^{19}F NMR (188 MHz, in DMSO-d_6) δ: 89.0 and 107.3 (AB system, J_{AB}=228 Hz, CF_2) ppm. GC-MS (rel. int., ion): 282 (3, M^+); 263 [10, $(M-F)^+$]; 213 [100, $(M-CF_3)^+$].

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