THE DAKIN-WEST REACTION OF *N*-ACYL-1,2,3,4-TETRAHYDROISOQUINOLINE-1-CARBOXYLIC ACIDS USING TRIFLUOROACETIC ANHYDRIDE: STRUCTURAL REVISION FOR THE UNEXPECTED PRODUCT

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Abstract --- The Dakin-West reaction of *N*-pivaloyl- and *N*-benzoyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids (**1a-e**) with trifluoroacetic anhydride yielded unexpectedly 1-(1-acyloxy-2,2,2-trifluoroethyl)-3,4-dihydroisoquinoline derivatives (**3a-e**) in good yields. Among of the products (**3**), the structure of **3b** has been confirmed by X-Ray crystallography. The carbamate derivatives (**1h**, **i**) gave 1-trifluoroacetyl-*N*-acyl-1,2,3,4-tetrahydroisoquinolines (**4e**, **f**), the Dakin-West reaction products, as a main product. The reaction of *N*-acetyl derivative (**1g**) produced completely different type of the product (**5**).

The reaction of α-amino acids with acetic anhydride in the presence of a base to give α-acetamidoalkyl ketones is known as the Dakin-West (D-W) reaction.[1] Recently, the D-W reaction employing trifluoroacetic anhydride (TFAA) has gained renewed interest in the preparation of trifluoromethyl ketones,[2] an important class of inhibitors for a variety of hydrolytic enzymes.[3] We have previously communicated that the reaction of *N*-acyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids (**1**) with TFAA afforded 2-trifluoromethyl-3-benzazepine derivatives (**2**) under the D-W reaction conditions.[4] However, during investigation dealing with chemical transformation of the product, their chemical behavior arose doubts on the correctness of the proposed 3-benzazepinone ring structure. This prompted a re-examination of the structure of the unexpected product and we now report full details of the reaction of *N*-acyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids (**1**) with TFAA and X-Ray crystallography of the product (**3b**).

The *N*-acyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids (**1**) required for this study have been prepared by the literature method.[5] Treatment of *N*-pivaloyl derivative (**1a**)[5] with an excess of TFAA in CH_2Cl_2 in the presence of pyridine at room temperature resulted in the formation of a single product (**3a**) in a high yield, the structure of which was previously

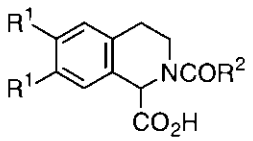
Table 1. Reaction of **1a** with TFAA.[a]

Entry	Reagents: TFAA (equiv.)[b]	Reagents: Base (equiv)[b]	Yield of **3a** (%)
1	3	pyridine (6)	50
2	5	pyridine (10)	98
3	5	—	45
4	5	DMAP (0.2)	77

[a] The reactions were carried out on a 1 mmol scale at 25 °C for 12 h in benzene. [b] Equiv. refers to molar equivalents with respect to **1a**.

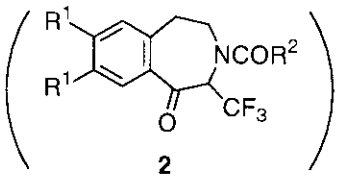
Table 2. Reactions of isoquinolines (**1**) with TFAA in the presence of pyridine.

Entry	Compound	Products, Yield (%)
1	**1a**	**3a** (98)
2	**1b**	**3b** (92)
3	**1c**	**3c** (61) + **4a** (28)
4	**1d**	**3d** (58) + **4b** (15)
5	**1e**	**3e** (52) + **4c** (24)
6	**1f**	**4d** (55)
7	**1g**	**5** (28)
8	**1h**	**4e** (61) + **6** (17)
9	**1i**	**4f** (47)



1

a: R^1=H, R^2=Bu^t
b: R^1=MeO, R^2=Bu^t
c: R^1=H, R^2=Ph
d: R^1=H, R^2=4-ClC$_6$H$_4$
e: R^1=H, R^2=4-MeOC$_6$H$_4$
f: R^1=MeO, R^2=2,4,6-Me$_3$C$_6$H$_2$
g: R^1=H, R^2=Me
h: R^1=H, R^2=OEt
i: R^1=H, R^2=OBn



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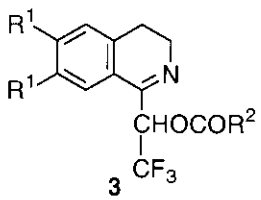
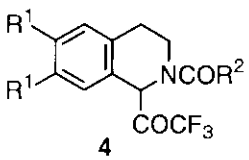


3

a: R^1=H, R^2=Bu^t
b: R^1=MeO, R^2=Bu^t
c: R^1=H, R^2=Ph
d: R^1=H, R^2=4-ClC$_6$H$_4$
e: R^1=H, R^2=4-MeOC$_6$H$_4$



4

a: R^1=H, R^2=Ph
b R^1=H, R^2=4-ClC$_6$H$_4$
c: R^1=H, R^2=4-MeOC$_6$H$_4$
d: R^1=MeO, R^2=2,4,6-Me$_3$C$_6$H$_2$
e: R^1=H, R^2=OEt
f: R^1=H, R^2=OBn

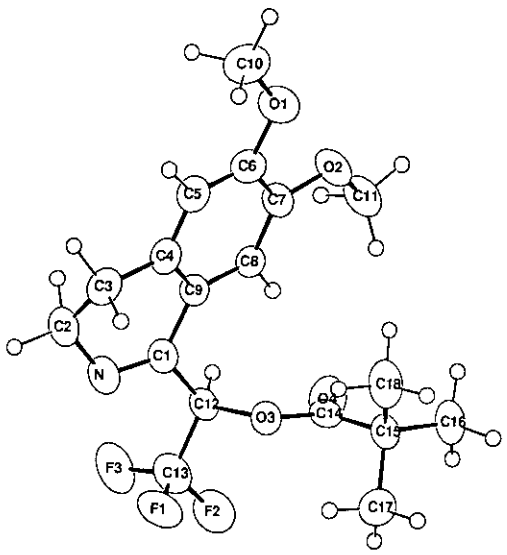
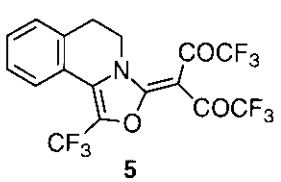


Figure 1. X-Ray structure drawing of 3b



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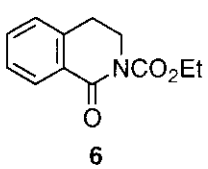


6

assigned to 3-benzazepine derivative (**2**) by the elemental analysis and spectral data.[4] However, the structure proposed previously has been found to be incorrect on the basis of the X-Ray crystallographic determination. The X-Ray structure drawing of 1-(1-pivaloxy-2,2,2-trifluoroethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (**3b**) is shown in Figure 1. The precise assignments of the carbon signals in **3a** were performed by ^{1}H-^{13}C shift correlated 2D NMR (COSY) and ^{1}H-^{13}C long-range COSY (COLOC) spectral analysis. In particular, the imine carbon signal at δ 158.8 was correlated with the 9-H signal at δ 7.61 in the COLOC spectrum ($^{3}J_{C\text{-}H}$). Furthermore, due to the presence of the CF_3 group, $J_{C\text{-}F}$ is easily measured in ^{1}H-decoupled ^{13}C NMR spectra. Thus, the carbon of CF_3 group appears at δ 123.0 ppm (quartet, $^{1}J_{C\text{-}F}$=277.8 Hz) and the 1-acyloxymethyl carbon appears at δ 70.9 ppm (quartet, $^{2}J_{C\text{-}F}$=32.4 Hz). The ^{1}H NMR spectrum of **3a** contained the $CHCF_3$ signal appeared at δ 6.28 (quartet, J=6.9 Hz). In the reactions of the *N*-pivaloyl derivatives (**1a** and **b**), the D-W reaction products, a trifluoromethyl ketones (**4**), were not isolated.

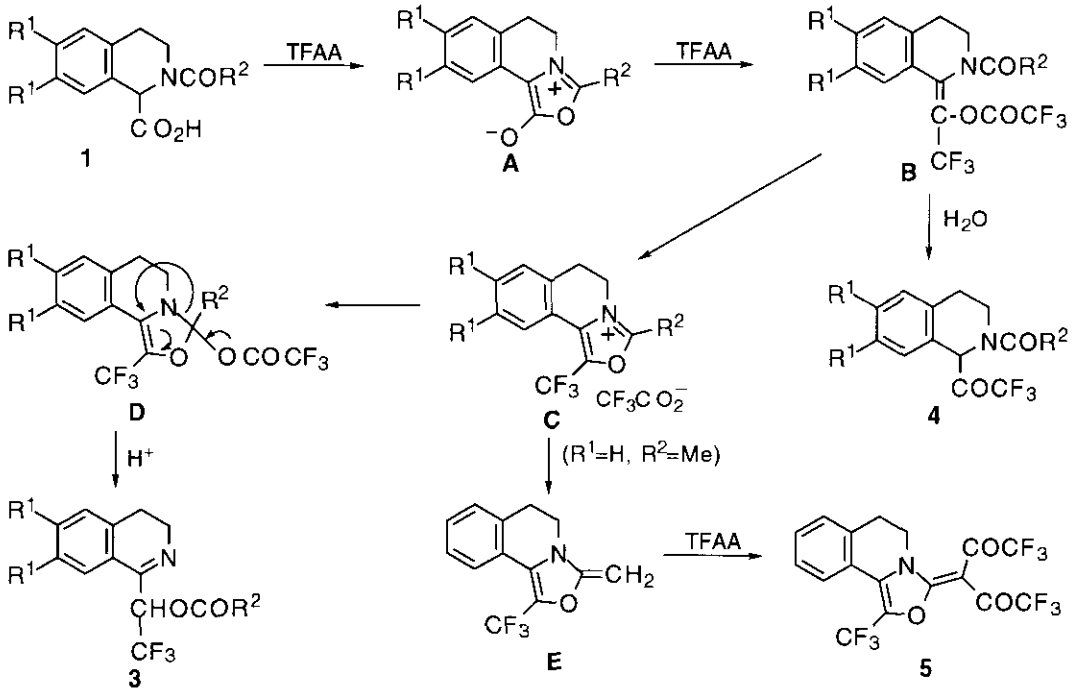
The influence of several parameters on the yield of reaction of **1a** to give **3a** was investigated to find the optimum conditions and to gain insight into the mechanism of the formation of **3a**. The results are summarized in Table 1. As shown in Table 1, pyridine was not essential to the reaction (Entries 2 and 3). However, the absence of base lowered the yield (45%). 5 equiv. of TFAA with respect to **1a** were needed to obtain a high yield of the product (**3a**) (Entries 1 and 2). Several *N*-acyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids (**1a-i**) were subjected to reaction under the optimum conditions (Table 1, Entry 2) and the results are listed in Table 2.

The reaction of *N*-benzoyl derivatives (**1c-e**) with TFAA under the optimized condition afforded the 1-acyloxymethyl-3,4-dihydroisoquinolines (**3c-e**) in 52-62% yield, together with trifluoroacetyl derivatives (**4a-c**) (15-28%), the products of the D-W reaction. However, **1f** gave only the trifluoroacetyl compound (**4d**) in 55% yield. The ^{1}H NMR spectra of **4a-d** showed a singlet at around δ 6.10 ppm attributed to the H-1. In the ^{13}C NMR spectra of **4a-d**, the C-1 carbon atom appears at around δ 60.0 ppm and the trifluoromethylcarbonyl carbon atom appears at around δ 187.0 ppm ($^{2}J_{C\text{-}F}$=32-33 Hz). The IR spectrum of **4a-d** showed the presence of C=O group (1760 cm^{-1}) and amide carbonyl group (1610-1620 cm^{-1}).

From the reaction between *N*-acetyl derivative (**1g**) and TFAA, a compound (28%) of formula $C_{17}H_8NO_3F_9$ was only isolated. The structure (**5**) was determined by spectral data. The ^{1}H NMR spectrum of **5** contained no signal of the methyl protons of the acetyl group and indicated two methylene and four aromatic protons. The ^{13}C NMR spectrum exhibited only fifteen carbon signals, which account for the existence of the two identical carbons (indicative of the existence of two trifluoroacetyl groups), because MS and analytical data indicated the existence of three trifluoromethyl groups, while ^{13}C NMR spectrum indicated only two different trifluoromethyl groups at δ 116.8 ($^{1}J_{CF}$=290.2 Hz) and 118.0 ppm ($^{1}J_{CF}$=270.3 Hz).

Treatment of *N*-alkoxycarbonyl derivatives (**1h** and **i**) with TFAA did not lead to the expected dihydroisoquinoline derivative (**3**) but instead furnished the 1-trifluoroacetyl derivatives (**4e** or **f**) in moderate yields. In the case of *N*-ethoxycarbonyl derivative (**1h**), 1-isoquinolone (**6**)

(17%) was also isolated which might be formed *via* autoxidation of the mesoionic 1,3-oxazolium-5-olate (**A**).[5]



Scheme 1

A plausible mechanism for the formation of **3**, **4**, and **5** is suggested in Scheme 1. The reaction involves a mesoionic 1,3-oxazolium-5-olate (**A**) formed through the cyclodehydration of **1** by TFAA. Intermediate (**A**) undergoes trifluoroacetylation followed by decarboxylation to give the enol trifluoroacetate (**B**). Hydrolysis of **B** leads to the trifluoromethyl ketones (**4**), which are products of the D-W reaction. It was observed that **4a** yielded **3a** in 56% yield under the same reaction conditions as **1c**, whose experiment supports the existence of intermediate (**B**), the enol form of the trifluoromethyl ketones (**4**). Cyclization of **B** gives the oxazolium salt (**C**) whose existence is supported by the isolation of **5** in the reaction of **1g**. Furthermore, intermediary oxazolium salt (**C**) has been posturated in the reactions of *N*-alkyl-*N*-acyl-α-amino acids with TFAA in the presence of pyridine.[6] Intermediate (**C**)(R^2=Me), bearing α-hydrogens, isomerizes to **E** which undergoes trifluoroacetylation. A similar type of bis-trifluoroacetylation has been reported in the reaction of other vinyl ethers with TFAA in the presence of pyridine.[7] However, as the R^2 group does not possess α-hydrogens, the isomerization of **C** is no longer possible. Therefore, nucleophilic attack of trifluoroacetate anion on **C** gives rise to an adduct (**D**) which is converted to **3** by a novel rearrangement. A similar rearrangement was reported in the oxidation of 1-methylenedihydroisoquinoline

enamides with lead tetraacetate to give 1-hydroxymethyl-3,4-dihydroisoquinolines.[8]
In summary, the reaction of *N*-acyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids (**1**) with TFAA to give the 1-(1-acyloxy-2,2,2-trifluoroethyl)-3,4-dihydroisoquinoline derivatives (**3**) is general with *N*-pivaloyl and *N*-aroyl derivatives bearing no α-hydrogens. Of the various *N*-acyl groups, the pivaloyl gave the highest yield of the product (**3**). On the other hand, the *N*-alkoxycarbonyl derivatives afforded mainly the D-W reaction product (**4**). The *N*-acetyl derivative (**1f**) produced completely different type of the product (**5**).

EXPERIMENTAL

Mps and bps were determined on a Yanagimoto hot-stage apparatus and Kugelrohr distillation apparatus, respectively, and are uncorrected. ^{1}H NMR spectra were measured at 60, 270, or 500 MHz with tetramethylsilane (Me_4Si) as an internal reference and $CDCl_3$ as the solvent. J-Values are given in Hz. IR spectra were recorded on a JASCO IR810 spectrophotometer. Only pertinent IR peaks are given. MS spectra (electron impact: 70 eV) were measured with a JEOL JMS-DS300 spectrometer. For column chromatography, SiO_2 (Merk, Art 9385) was used.
Compounds (**1a**), (**1b**), (**1c**), and (**1g**) were prepared by reported procedures.[5] 2-(4-Chlorobenzoyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (**1d**) and 2-(4-methoxybenzoyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (**1e**) were prepared in good yields by Schotten-Baumann reaction of 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid[9] with the appropriate acid chlorides: **1d**: mp 162-164 °C (AcOEt), Anal. Calcd for $C_{17}H_{14}NO_3Cl$: C, 64.76; H, 4.47; N, 4.44. Found: C, 64.42; H, 4.56; N, 4.10. ^{1}H NMR (270 MHz) δ 2.90-2.96 (m, 2H), 3.73-3.79 (m, 2H), 5.97 (s, 1H), 7.16-7.48 (m, 6H), 7.60-7.63 (m, 1H), 7.98-8.02 (m, 1H). **1e**: HRMS Calcd for $C_{18}H_{17}NO_4$: 311.1158, Found 311.1161. ^{1}H NMR (270 MHz) δ 2.92-3.01 (m, 2H), 3.70-3.85 (m, 2H), 5.94 (s, 1H), 6.94 (d, 2H, J=8.9), 7.17-7.26 (m, 4H), 7.51 (d, 2H, J=8.9). Ethyl ester of 2-(2,4,6-timethylbenzoyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (**1f**) was prepared in 76% yield by Schotten-Baumann reaction of ethyl 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylate[10] with 2,4,6-trimethylbenzoyl chloride: Ethyl 2-(2,4,6-timethylbenzoyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxylate: HRMS Calcd for $C_{24}H_{29}NO_5$: 411.2045, Found 411.2045. ^{1}H NMR (60 MHz) δ 1.32 (t, 3H, J=7.0), 2.17 (s, 3H), 2.28 (s, 3H), 2.32 (s, 3H), 2.57-2.95 (m, 2H), 3.33-3.77 (m, 2H), 3.82 (s, 3H), 3.88 (s, 3H), 4.25 (q, 2H, J=7.0), 6.17 (s, 1H), 6.58 (s, 1H), 6.87 (s, 2H), 7.12 (s, 1H). Ethyl esters of 2-ethoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (**1h**) and 2-benzyloxycarbonyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (**1i**) were prepared in good yields by Schotten-Baumann reaction of ethyl 1,2,3,4-tetrahydroisoquinoline-1-carboxylate[5] with the appropiate chlorocarbonate: Ethyl 2-ethoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate: bp_6 174-176 °C, Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 65.01; H, 6.94; N, 4.76. ^{1}H NMR (60 MHz) δ 1.23 (t, 3H, J=7.0), 1.25 (t, 3H, J=7.0), 2.70-3.10

(m, 2H), 3.67-4.08 (m, 2H), 4.15 (q, 2H, J=7.0), 4.20 (q, 2H, J=7.0), 5.50+5.56 (s, 1H), 7.00-7.65 (m, 4H). Ethyl 2-benzyloxycarbonyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate: bp_2 230 °C (bath temperature), Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.98; H, 6.31; N, 4.01. ^{1}H NMR (60 MHz) δ 1.17 (t, 3H, J=7.0), 2.73-3.07 (m, 2H), 3.67-4.38 (m, 4H), 5.17 (s, 2H), 5.47-5.70 (m, 1H), 7.00-7.60 (m, 9H). Hydrolyses of the above esters with 2N NaOH gave the corresponding carboxylic acids (**1f**, **1h**, and **1i**) in good yields: **1f**: HRMS Calcd for $C_{22}H_{25}NO_5$: 383.1732, Found 383.1729. ^{1}H NMR (270 MHz) δ 2.16 and 2.21 (s, 3H), 2.28 and 2.29 (s, 6H), 2.71-2.77 (m, 2H), 3.44-3.64 (m, 2H), 3.85 and 3.87 (s, 3H), 3.88 and 3.89 (s, 3H), 6.04 (s, 1H), 6.60 and 6.61 (s, 1H), 6.85 and 6.87 (s, 2H), 7.10 (s, 1H). **1h**: $bp_{2.5}$ 174-176 °C (bath temperature), Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.88; H, 6.02; N, 5.68. ^{1}H NMR (60 MHz) δ 1.25 (t, 3H, J=7.0), 2.67-3.13 (m, 2H), 3.63-3.97 (m, 2H), 4.17 (q, 2H, J=7.0), 5.55 (br s, 1H), 7.07-7.63 (m, 4H), 9.75 (br s, 1H). **1i**: mp 134-135 °C (dicyclohexylamine salt)(EtOH), Anal. Calcd for $C_{18}H_{17}NO_4 \cdot C_{12}H_{23}N$: C, 73.14; H, 8.18; N, 5.69. Found: C, 73.17; H, 7.96; N, 5.42. ^{1}H NMR (500 MHz) δ 2.82-3.01 (m, 2H), 3.74-3.87 (m, 2H), 5.10-5.22 (m, 2H), 5.55 and 5.63 (s, 1H), 7.14-7.50 (m, 9H). The multiplicity of the signals of **1f** and **1i** is due to hindered rotation around the amide bond.

General Procedure for the Reaction of *N*-Acyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic Acids (1a-i) with TFAA: TFAA (0.71 mL, 5 mmol) was added to a solution of an *N*-acyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic Acid (**1**) (1 mmol) and pyridine (0.81 mL, 10 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C under an Ar atmosphere and the mixture was stirred at rt for 12 h. The reaction mixture was diluted with 1% HCl (20 mL) with cooling and extracted with EtOAc (30 mL x 2). The combined extracts were washed successively with brine (30 mL), 3% Na_2CO_3 (30 mL), and brine (30 mL). The organic solvent was dried over Na_2SO_4 and concentrated under reduced pressure at 45 °C using a rotary evaporator. The residue was chromatographed on a column of silica gel with AcOEt-hexane (1:3) as the eluent to give the product. The results are summarized in Table 2. Analytical and physical data of all products are presented in Tables 3 and 4.

X-Ray Analysis of 3a

$C_{18}H_{22}NO_4F_3$ F.W.=373, mp 62-63 °C (hexane).

Crystal data: a=9.572(2)Å, b=11.392(2)Å, c=9.441(2)Å, α=107.61(1)°, β=103.13(2)°, γ=99.77(2)°, V=923.4(3)Å^3, triclinic, $P\bar{1}$, Z=2, D_x=1.343 g/cm^3, F(000)=392, μ(CuKα)=9.48 cm^{-1}. The diffraction experiment was carried out using a colorless transparent single crystal with dimension of 0.5 x 0.4 x 0.1 mm. The diffractometer Rigaku AFC-5 was used with graphite-monochromated Cu Kα radiation (λ=1.5417 Å). The unit cell dimensions were determined from 37 2θ values in the range of 30<2θ<36°. 3344 unique reflections (3≤θ≤140°) were measured, of which 2555 with $F_o \geq 3\sigma(F_o)$ were considered as observed. The structure was solved by the direct method. The refinement of atomic parameters assuming anisotropic thermal displacement were applied for all non-H atoms, while H-atoms were fixed at

Table 3. Physical and analytical data of new compounds.

Compound	Formula	mp (solvent)[a] or bp (Torr)[b] (°C)	Analysis (%) Found (calculated) C	H	N	IR, ν_{max} (cm^{-1})	MS, m/z (%), M^+ and base peak
3a	$C_{16}H_{18}NO_2F_3$	150 (3)	61.13 (61.34)	5.60 (5.79)	4.25 (4.47)	1750, 1633	313 (3.5) 229
3b	$C_{18}H_{22}NO_4F_3$	62-63 (H)	57.96 (57.90)	5.99 (5.94)	3.73 (3.75)	1750, 1640	373 (100)
3c	$C_{18}H_{14}NO_2F_3$	185 (2)	64.64 (64.86)	4.51 (4.23)	4.14 (4.20)	1735, 1630	333 (14) 256
3d	$C_{18}H_{13}NO_2F_3Cl$	185 (1)	58.55 (58.79)	3.35 (3.56)	4.00 (4.00)	1735, 1630	367 (35)+369 (13) (3:1), 211
3e	$C_{19}H_{16}NO_3F_3$	91-92 (H)	62.64 (62.81)	4.50 (4.44)	3.57 (3.86)	1720, 1630	363 (18) 135
4a	$C_{18}H_{14}NO_2F_3$	131-132 (A-H)	64.84 (64.86)	4.31 (4.23)	4.08 (4.20)	1760, 1615	333 (1.1) 105
4b	$C_{18}H_{13}NO_2F_3Cl$	150 (1)	367.0587 (367.0586)			1760, 1740, 1620	367 (6.6)+369 (2.2)(3:1), 139
4c	$C_{19}H_{16}NO_3F_3$	114-115 (E-H)	62.84 (62.81)	4.62 (4.44)	3.68 (3.57)	1755, 1610	363 (1.9) 135
4d	$C_{21}H_{20}NO_2F_3$	oil	435.1657 (435.1670)			1760, 1605	435 (12) 147
4e	$C_{14}H_{14}NO_3F_3$	135 (1)	56.05 (55.82)	4.39 (4.68)	4.81 (4.65)	1765, 1700	302 (M^++1, 100)[c]
4f	$C_{19}H_{16}NO_3F_3$	195 (1)	62.95 (62.81)	4.36 (4.44)	3.84 (3.86)	1765, 1700	364 (M^++1, 77) 91[c]
5	$C_{17}H_8NO_3F_9$	174-175 (A-H)	45.67 (45.86)	2.01 (1.81)	3.37 (3.15)	1675, 1665, 1630	445 (38) 376
6	$C_{12}H_{13}NO_3$	145 (1)	66.00 (65.74)	5.93 (5.98)	6.20 (6.39)	1765, 1715	219 (48) 118

[a] A=AcOEt, E=Et_2O, H=hexane. [b] Bp refers to the bath temperature in a Kugelrohr apparatus. [c] CIMS.

Table 4. ^1H and ^{13}C NMR data of new compounds.

Compound	^1H NMR (270 MHz) δ	^{13}C NMR (67.8 MHz) δ
3a	1.23 (s, 9H), 2.67-2.74 (m, 2H), 3.62-3.74 (m, 1H), 3.85-3.96 (m, 1H), 6.28 (q, 1H, J=6.9), 7.20 (d, 1H, J=7.3), 7.34 (dt, 1H, J=1.4, 7.3), 7.36 (dt, 1H, J=1.4, 7.3), 7.61 (d, 1H, J=7.3)	25.62 (CH_2), 26.86 (CH_3), 38.84 (C), 47.33 (CH_2), 70.89 (CH, $^2J_{CF}$=32.4), 122.99 (CF_3, $^1J_{CF}$=277.8), 125.03 (CH), 126.74 (C), 127.03 (CH), 127.80 (CH), 131.36 (CH), 137.36 (C), 158.83 (C), 176.46 (C)
3b	1.24 (s, 9H), 2.62-2.69 (m, 2H), 3.67-3.76 (m, 1H), 3.77-3.86 (m, 1H), 3.90 (s, 3H), 3.92 (s, 3H), 6.27 (q, 1H, J=6.9), 6.72 (s, 1H), 7.16 (s, 1H)	25.34 (CH_2), 26.92 (CH_3), 38.91 (C), 47.44 (CH_2), 55.98 (CH_3), 56.13 (CH_3), 71.37 (CH, $^2J_{CF}$=32.4), 108.75 (CH), 110.51 (CH), 119.46 (C), 123.07 (CF_3, $^1J_{CF}$=281.5), 132.06 (C), 147.48 (C), 151.44 (C), 158.20 (C), 176.45 (C)
3c	2.65-2.81 (m, 2H), 3.60-3.72 (m, 1H), 3.89-4.00 (m, 1H), 6.55 (q, 1H, J=6.9), 7.20 (d, 1H, J=7.4), 7.36 (dt, 2H, J=2.0, 7.4), 7.45 (t, 2H, J=7.4), 7.59 (t, 1H, J=7.4), 7.72 (d, 1H, J=7.4), 8.12 (d, 2H, J=7.4)	25.63 (CH_2), 47.38 (CH_3), 71.12 (CH, $^2J_{CF}$=32.3), 123.05 (CF_3, $^1J_{CF}$=281.5), 124.90 (CH), 126.94 (C), 127.20 (CH), 127.87 (CH), 128.46 (C), 128.63 (CH), 130.24 (CH), 131.47 (CH), 133.93 (CH), 137.96 (C), 158.72 (C), 164.67 (C)

Table 4. (Continued).

Compound	^{1}H NMR (270 MHz) δ	^{13}C NMR (67.8 MHz) δ
3d	2.63-2.81 (m, 2H), 3.59-3.71 (m, 1H), 3.90-4.00 (m, 1H), 6.53 (q, 1H, J=6.9), 7.21 (d, 1H, J=7.4), 7.33 (t, 1H, J=7.4), 7.38 (t, 1H, J=7.4), 7.42 (d, 2H, J=8.4), 7.69 (d, 1H, J=7.4), 8.05 (d, 2H, J=8.4)	25.62 (CH_2), 47.38 (CH_3), 71.09 (CH, $^2J_{CF}$=32.4), 122.94 (CF_3, $^1J_{CF}$=281.5), 124.76 (CH), 126.90 (C), 127.21 (CH), 127.93 (CH), 129.01 (CH), 129.45 (C), 131.52 (CH), 131.60 (CH), 137.94 (C), 140.54 (C), 158.50 (C), 163.85 (C)
3e	2.65-2.75 (m, 2H), 3.57-3.70 (m, 1H), 3.84 (s, 3H), 3.88-3.99 (m, 1H), 6.52 (q, 1H, J=6.9), 6.92 (d, 2H, J=8.9), 7.20 (d, 1H, J=7.4), 7.29-7.41 (m, 2H), 7.73 (d, 1H, J=7.4), 8.08 (d, 2H, J=8.9)	25.65 (CH_2), 47.38 (CH_3), 55.48 (CH_3), 70.89 (CH, $^2J_{CF}$=32.4), 113.92 (CHx2), 120.72 (C), 123.12 (CF_3, $^1J_{CF}$=281.5), 124.94 (CH), 126.99 (C), 127.16 (CH), 127.84 (CH), 131.40 (CH), 132.40 (CHx2), 137.94 (C), 158.88 (C), 164.22 (C), 164.33 (C)
4a	2.71-2.79 (m, 1H), 3.10-3.22 (m, 1H), 3.44-3.54 (m, 1H), 3.94-4.04 (m, 1H), 6.13 (s, 1H), 7.19-7.24 (m, 1H), 7.29-7.32 (m, 2H), 7.37-7.51 (m, 6H)	29.78 (CH_2), 45.82 (CH_2), 59.94 (CH), 115.95 (CF_3, $^1J_{CF}$=293.7), 127.42 (CH), 127.62 (CH), 127.91 (C), 128.26 (CH), 128.59 (CH), 128.83 (CH), 128.96 (CH), 130.81 (CH), 134.18 (C), 136.55 (C), 171.37 (C), 187.69 (C, $^2J_{CF}$=33.7)
4b	2.73-2.91 (m, 1H), 3.11-3.33 (m, 1H), 3.46-3.59 (m, 1H), 3.95-4.03 (m, 1H), 6.13 (s, 1H), 7.21-7.55 (m, 8H)	29.72 (CH_2), 45.93 (CH_2), 60.01 (CH), 116.00 (CF_3, $^1J_{CF}$=286.5), 127.53 (CH), 128.31 (C), 128.81 (CH), 128.92 (CH), 129.01 (CH), 129.10 (CH), 129.16 (CH), 132.55 (C), 136.46 (C), 137.06 (C), 170.32 (C), 187.60 (C, $^2J_{CF}$=33.7)
4c	2.74-2.82 (m, 1H), 3.14-3.26 (m, 1H), 3.51-3.60 (m, 1H), 3.83 (s, 3H), 4.06-4.13 (m, 1H), 6.08 (s, 1H), 6.94 (d, 2H, J=8.9), 7.21-7.52 (m, 4H), 7.50 (d, 2H, J=8.9)	29.96 (CH_2), 46.12 (CH_2), 55.43 (CH_3), 59.98 (CH), 113.85 (CH), 116.03 (CF_3, $^1J_{CF}$=286.5), 126.11 (C), 127.38 (CH), 128.26 (CH), 128.75 (CH), 128.90 (CH), 129.89 (CH), 132.44 (C), 136.64 (C), 161.72 (C), 171.13 (C), 187.50 (C, $^2J_{CF}$=33.7)
4d	2.17 (s, 3H), 2.24 (s, 3H), 2.28 (s, 3H), 2.51-2.71 (m, 1H), 3.00-3.21 (m, 2H), 3.66-3.72 (m, 1H), 3.86 (s, 3H), 3.88 (s, 3H), 6.15 (s, 1H), 6.70 (s, 1H), 6.73-6.87 (m, 3H)	18.46 (CH_3), 18.87 (CH_3), 21.11 (CH_3), 29.25 (CH_2), 43.82 (CH_2), 55.98 (CH_3), 56.11 (CH_3), 58.68 (CH), 110.88 (CH), 117.76 (CH), 115.95 (CF_3, $^1J_{CF}$=293.7), 119.46 (C), 128.28 (CH), 128.63 (CH), 129.08 (C), 131.74 (C), 133.71 (C), 134.70 (C), 138.86 (C), 148.34 (C), 149.42 (C), 171.73 (C), 187.99 (C, $^2J_{CF}$=33.6)
4e[a]	1.23-1.33 (m, 3H), 2.77-2.87 (m, 1H), 2.99-3.11 (m, 1H), 3.27-3.42 (m, 1H), 4.07-4.26 (m, 3H), 5.96+6.01 (s, 1H), 7.21-7.34 (m, 4H)	14.30+14.61 (CH_3), 28.68+28.84 (CH_2), 41.49+41.57 (CH_2), 60.84 (CH), 62.45 (CH_2), 115.76 (CF_3, $^1J_{CF}$=292.8), 127.21 (CH), 127.80 (C), 128.22+128.39 (CH), 128.68+129.14 (CH), 129.01 (CH), 136.62+136.97 (C), 154.77+156.24 (C), 189.32 (C, $^2J_{CF}$= 32.4)
4f[a]	2.73-2.87 (m, 1H), 2.97-3.09 (m, 1H), 3.29-3.44 (m, 1H), 4.10-4.18 (m, 1H), 5.14-5.21 (m, 2H), 5.97+6.05 (s, 1H), 7.20-7.36 (m, 9H)	28.53+28.73 (CH_2), 41.60+41.75 (CH_2), 60.95+61.02 (CH_2), 68.06+68.19 (CH), 116.00 (CF_3, $^1J_{CF}$=290.5), 127.10+127.20 (CH), 127.27 (CH), 127.65 (C), 128.04+128.31 (CH), 128.42 (CH), 128.61 (CH), 128.90+129.10 (CH), 129.21 (CH), 136.09 (C), 136.58+136.91 (C), 154.61+156.04 (C), 189.50 (C, $^2J_{CF}$=32.5)
5	3.23 (t, 2H, J=6.5), 3.94 (t, 2H, J=6.5), 7.49 (d, 1H, J=7.9), 7.55 (t, 1H, J= 7.9), 7.63 (t, 1H, J=7.9), 7.73 (d, 1H, J=7.9)	28.12 (CH_2), 45.20 (CH_2), 87.14 (C), 116.82 (CF_3x2, $^1J_{CF}$=290.2), 118.00 (CF_3, $^1J_{CF}$=270.3),119.07 (C), 127.83 (CH), 127.86 (CH), 128.99 (CH), 129.03 (CH), 130.39 (C), 132.68 (CH), 134.13 (C), 164.30 (C), 175.09 (Cx2, $^2J_{CF}$=36.1)
6	1.40 (t, 3H, J=6.9), 3.02 (t, 2H, J=6.4), 4.07 (t, 2H, J=6.4), 4.38 (q, 2H, J=6.9), 7.22 (d, 1H, J=7.9), 7.36 (t, 1H, J=7.9), 7.48 (t, 1H, J=7.9), 8.16 (d, 1H, J=7.9)	14.32 (CH_3), 28.29 (CH_2), 44.68 (CH_2), 63.37 (CH_2), 127.25 (CH),127.32 (CH), 129.14 (C), 129.73 (CH), 133.10 (CH), 139.59 (C), 154.59 (C), 163.83 (C)

[a] The multiplicity of the signals suggests two conformers due to hindered rotation around the amide bond.

Table 5. Atomic coodinates of non-H atoms with estimated isotropic thermal parameters for **3a**.

atom	x/a	y/b	z/c	Ueqiv	atom	x/a	y/b	z/c	Ueqiv
C1	-.0740(4)	.7830(4)	.2334(4)	.042(2)	C11	.3563(5)	.8338(4)	-.0179(5)	.063(2)
N	-.1968(4)	.7872(3)	.2606(4)	.056(2)	C12	-.0223(4)	.6620(4)	.2260(4)	.043(2)
C2	-.2486(5)	.9014(4)	.2599(5)	.063(2)	C13	-.1163(6)	.5685(5)	.2729(6)	.065(3)
C3	-.1250(5)	1.0240(4)	.3256(5)	.055(2)	F1	-.1254(3)	.6162(2)	.4165(3)	.081(1)
C4	-.0025(4)	1.0053(4)	.2531(4)	.044(2)	F2	-.0563(3)	.4688(2)	.2657(3)	.090(2)
C5	.0859(5)	1.1072(4)	.2325(5)	.048(2)	F3	-.2536(3)	.5203(2)	.1750(3)	.086(1)
C6	.1963(5)	1.0868(4)	.1639(5)	.046(2)	O3	.1234(3)	.7014(2)	.3388(3)	.043(1)
C7	.2205(4)	.9647(4)	.1132(4)	.043(2)	C14	.2312(5)	.6491(4)	.2907(5)	.042(2)
C8	.1348(4)	.8651(3)	.1345(4)	.040(2)	O4	.2103(3)	.5743(3)	.1629(3)	.063(2)
C9	.0221(4)	.8854(3)	.2048(4)	.038(2)	C15	.3752(4)	.6985(4)	.4245(5)	.045(2)
O1	.2865(3)	1.1790(3)	.1355(3)	.063(1)	C16	.4969(4)	.6465(4)	.3660(5)	.064(2)
C10	.2561(5)	1.3025(4)	.1701(5)	.069(2)	C17	.3479(5)	.6534(4)	.5568(5)	.072(2)
O2	.3323(3)	.9558(2)	.0459(3)	.057(1)	C18	.4197(4)	.8432(4)	.4814(5)	.068(2)

Ueqiv. = 1 / 3 (U_{11} + U_{22} + U_{33})

Table 6. Selected bond lengths (Å) and angles (°), and dihedral angles (°) for **3a**.

C1-N	1.264(6)	O1-C10	1.440(5)	C9-C1-N-C2	1.5(5)
C1-C9	1.489(6)	O2-C11	1.418(5)	C12-C1-N-C2	-177.1(3)
C1-C12	1.529(6)	C12-C13	1.510(7)	N-C1-C9-C4	18.8(5)
N-C2	1.471(6)	C12-O3	1.451(4)	N-C1-C9-C8	-162.1(4)
C2-C3	1.522(5)	C13-F1	1.328(6)	C12-C1-C9-C4	-162.6(3)
C3-C4	1.500(7)	C13-F2	1.348(6)	C12-C1-C9-C8	16.5(5)
C4-C5	1.407(6)	C13-F3	1.334(5)	N-C1-C12-C13	-7.6(5)
C4-C9	1.382(6)	O3-C14	1.372(5)	N-C1-C12-O3	-123.9(3)
C5-C6	1.375(7)	C14-O4	1.196(5)	C9-C1-C12-C13	173.7(3)
C6-C7	1.405(6)	C14-C15	1.526(5)	C9-C1-C12-O3	57.4(4)
C6-O1	1.374(5)	C15-C16	1.530(6)	C1-N-C2-C3	-36.1(5)
C7-C8	1.378(6)	C15-C17	1.544(7)	N-C2-C3-C4	48.9(5)
C7-O2	1.365(5)	C15-C18	1.519(5)	C2-C3-C4-C5	149.7(4)
C8-C9	1.406(6)			C2-C3-C4-C9	-29.7(5)
				C6-C7-C8-C9	.9(5)
N-C1-C9	125.1(4)	C7-O2-C11	118.4(3)	C8-C7-O2-C11	5.0(5)
N-C1-C12	117.2(4)	C1-C12-C13	114.8(4)	C7-C8-C9-C4	-.2(5)
C9-C1-C12	117.7(4)	C1-C12-O3	106.8(2)	C1-C12-C13-F1	-58.5(5)
C1-N-C2	116.6(4)	C13-C12-O3	105.3(4)	C1-C12-C13-F2	-178.2(3)
N-C2-C3	114.0(3)	C12-C13-F1	114.0(3)	C1-C12-C13-F3	65.0(5)
C2-C3-C4	109.9(3)	C12-C13-F2	108.7(4)	O3-C12-C13-F1	58.7(5)
C3-C4-C5	121.1(4)	C12-C13-F3	112.0(5)	O3-C12-C13-F2	-60.9(4)
C3-C4-C9	119.0(4)	F1-C13-F2	107.2(5)	C1-C12-O3-C14	-134.0(4)
C5-C4-C9	119.9(4)	F1-C13-F3	108.4(4)	C13-C12-O3-C14	103.5(4)
C4-C5-C6	119.8(4)	F2-C13-F3	106.0(3)	C12-O3-C14-O4	-.1(6)
C5-C6-C7	120.4(4)	C12-O3-C14	116.8(3)	O3-C14-C15-C17	63.1(4)
C5-C6-O1	124.3(4)	O3-C14-O4	123.5(3)	O3-C14-C15-C18	-56.7(5)
C7-C6-O1	115.2(4)	O3-C14-C15	109.7(3)	O4-C14-C15-C16	5.2(7)
C6-C7-C8	119.8(4)	O4-C14-C15	126.8(4)	O4-C14-C15-C17	-115.5(5)
C6-C7-O2	115.2(4)	C14-C15-C16	109.0(3)	O4-C14-C15-C18	124.7(5)
C8-C7-O2	124.9(4)	C14-C15-C17	108.3(3)		
C7-C8-C9	120.0(4)	C14-C15-C18	109.0(4)		

calculated position with an isotropic thermal parameter 1.25 and 1.5 times of that of the host atom for sp^2 and sp^3 carbons, respectively. The final R value is 0.064 (R_w=0.048, S=6.611). The minimum and maximum peaks on the final difference Fourier map were -0.3 and 0.3*e* Å^{-3}. All the calculations were carried out using *Xtal* 3.2[11] on a Hewlett Packerd 735/125 of Josai University. Atomic parameters, bond lengths, and angles are collected in Tables 5 and 6.

REFERENCES

1. G. L. Buchanan, *Chem. Soc. Rev.*, 1988, **17**, 91.
2. J. -P. Bégué and D. Bonnet-Delpon, *Tetrahedron*, 1991, **47**, 3207 and references cited therein: for recent development in the preparation of trifluoromethyl ketones: P. D. Edwards, *Tetrahedron Lett.*, 1992, **33**, 4279; J. Boivin, L. El Kaim, and S. Z. Zard, *Tetrahedron*, 1995, **51**, 2573; C. W. Derstine, D. N. Smith, and J. A. Katzenellenbogen, *Tetrahedron Lett.*, 1997, **38**, 4359.
3. B. Imperiali and R. H. Abeles, *Biochemistry*, 1986, **25**, 3760; A. Szekacs, P. P. Halarnkar, M. M. Olmstead, K. A. Prag, and B. D. Hammock, *Chem. Res. Toxicol.*, 1990, **3**, 325; R. S. Garigipati, G. Seibel, R. J. Mayer, B. Bolognese, M. McCord, L. A. Marshall, and J. L. Adams, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 1421; M. W. Walter, R. M. Adlington, J. E. Baldwin, and C. J. Schofield, *Tetrahedron*, 1997, **53**, 7275.
4. M. Kawase, *J. Chem. Soc., Chem. Commun.*, **1992**, 1076.
5. M. Kawase, *Chem. Pharm. Bull.*, 1997, **45**, 1248.
6. M. Kawase, *Tetrahedron Lett.*, 1994, **35**, 149; M. Kawase, S. Saito, H. Kikuchi, and H. Miyamae, *Heterocycles*, 1997, **45**, 2185.
7. M. Hojo, R. Masuda, and E. Okada, *Synthesis*, **1990**, 347; M. Hojo, R. Masuda, Y. Kamitori, and E. Okada, *J. Org. Chem.*, 1991, **56**, 1975.
8. G. R. Lenz, R. A. Lessor, P. W. Rafalko, and Z. Kosarych, *J. Chem. Soc., Perkin Trans.* 1, **1993**, 745.
9. W. Solomon, *J. Chem. Soc.*, **1947**, 129.
10. A. Grüssner, E. Jaeger, J. Hellerbach, and O. Schnider, *Helv. Chim. Acta*, 1959, **42**, 2431.
11. S. R. Hall and J. M. Stewart, *Xtal* 3.2. Univs. of Western Australia, Australia and Maryland, USA.

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