Convenient Synthesis of α -Trifluoromethylated Acyloins from α -Hydroxy or α -Amino Acids

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α -Trifluoromethylated acyloins (2 and 6) have been prepared from α -hydroxy acids (1), *N*-acylprolines (5) or *N*-acyl-*N*-alkyl α -amino acids (8) by novel transformation reactions with trifluoroacetic anhydride (TFAA) in the presence of pyridine. The former reaction of 1 could proceed through mesoionic 1,3-dioxolium-4-olates, whereas the latter two reactions of α -amino acids (5 and 8) could involve mesoionic 1,3-oxazolium-5-olates. The reaction of 1 with TFAA shows more potential for practical applications because of the ready availability of the starting materials and ease of manipulation.

Key words acyloin; trifluoromethyl; α -hydroxy ketone; mesoionic compound; trifluoroacetic anhydride

Organic compounds containing fluorine possess special chemical properties¹⁾ and hence often exhibit an interesting physiological profile.²⁾ Among them, molecules bearing a trifluoromethyl (CF₃) group are of great interest. This has stimulated intensive research and many reliable methods are now available to introduce the CF₃ moiety into organic substrates.³⁾ Ideally, the fluorinated building block should be easy to handle and relatively readily available. This could mean that the material is available commercially, or can be synthesized from an appropriate compound *via* a short reaction sequence. The reagents should be inexpensive and carry the required CF₃ group.

α -Hydroxy ketones or acyloins are very useful synthons for a variety of organic synthesis,⁴⁾ while their fluorine-containing analogues, *e.g.* α -trifluoromethylated acyloins have not been easily accessible in spite of their potential building blocks for CF₃-substituted compounds.⁵⁾ Four reactions for the formation of CF₃-acyloins have been recorded: 1) hydrolysis of 3-bromo-1,1,1-trifluoro-3-phenylpropanone with aq. Na₂CO₃ to afford CF₃-acyloin as one example,⁶⁾ 2) hydrolytic ring cleavage of 6-trifluoromethyl-1,3,4-oxadiazine derivatives obtained from benzaldehyde,⁷⁾ 3) hydrolysis of α -amino CF₃-ketones during the purification by chromatography on SiO₂, resulting in a mixture of regioisomeric α -hydroxy ketones⁸⁾ and 4) acid hydrolysis of α -amido CF₃-ketone to give CF₃-acyloin as one example.⁹⁾ However, these reactions are limited by the fact that only benzoyl derivatives are accessible or they need too many steps to be efficient in a building block strategy.

Following our first publication¹⁰⁾ on the use of trifluoroacetic anhydride (TFAA) as a useful reagent¹¹⁾ for the introduction of the CF₃ group into organic compounds, we were interested in other reactions of TFAA leading to new CF₃-substituted compounds¹²⁾ and started a study on the interaction of TFAA with α -hydroxy acids (1),¹³⁾ *N*-acylprolines (5), or *N*-acyl-*N*-alkyl α -amino acids (8).¹⁴⁾ We now present a full account of these reactions and a new synthesis of CF₃-acyloin derivatives in good yields.

Results and Discussion

Reactions of α -Hydroxy Acids (1) with TFAA A reaction of simple carboxylic acids with TFAA to yield the corre-

sponding trifluoromethyl ketones is not known. However, it is reported that some carboxylic acid chlorides were converted to trifluoromethyl ketones by reaction with pyridine and TFAA, in which the intermediate ketenes undergo the trifluoroacetylation.¹⁵⁾ We examined a reaction of mandelic acid (1a) with TFAA in detail, and the results are presented in Table 1. Thus, the reaction of 1a with TFAA in the presence of pyridine results in the formation of CF₃-acyloin (2a) in 87% yield. Pyridine was essential, and the absence of the base lowered the yield (run 1). High temperature (80 °C) was needed to obtain a high yield of 2a, the reaction at room temperature reducing the yield (9%) (runs 2, 3 and 4). Other α -hydroxy acids (1b–f) were subjected to the reaction under optimum conditions and the results are listed in Table 2. *O*-Acetylmandelic acid (1b) gave 2a in a good yield, whereas *O*-benzoylmandelic acid (1c) gave 2a and 3a in 41% and 42% yields, respectively. However, *O*-methylmandelic acid (1d) and α -methylmandelic acid failed to give the corre-

Table 1. Reactions of Mandelic Acid (1a) with TFAA in Benzene^{a)}

Run	Base (eq) ^{b)}	Conditions	Yield of 2a (%)
1	None	Reflux, 6 h	5
2	Pyridine (6)	r. t., 24 h	9
3	Pyridine (6)	Reflux, 1 h	43
4	Pyridine (6)	Reflux, 3 h	87

a) The reactions were carried out on a 2 mmol scale. b) Eq. refers to molar equivalents with respect to 1a.

Table 2. Reactions of α -Hydroxy Acids (1) with TFAA

Run	1	Product (yield, %)
1	a	2a (87)
2	b	2a (88)
3	c	2a (41), 3a (42)
4	d	— ^{a)}
5	e	2b (71)
6	f	2c (42)
7 ^{b)}	a	4a (84)
8 ^{c)}	a	4b (66)

a) Methyl benzoate was isolated in 41% yield. b) Pentafluoropropionic anhydride was used instead of TFAA. c) Heptafluorobutyric anhydride was used instead of TFAA.

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sponding trifluoroacetyl compounds. In the reaction of **1d**, we obtained in 41% yield the methyl benzoate, which might be formed through decarboxylative oxygenation involving autoxidation.

Pentafluoropropionic and heptafluorobutyric anhydride also reacted readily with **1a** to yield the corresponding α -pentafluoroethyl- (**4a**) or α -heptafluoropropyl-substituted acyloins (**4b**) in good yield, respectively.

The structures of **2** and **3** are supported by spectral and analytical data. The assignments of the carbon signals in **2a** were performed on the basis on the long-range ^{13}C – ^{19}F coupling. Thus, $^1J_{\text{C-F}}$ and $^2J_{\text{C-F}}$ are measured in ^1H -decoupled ^{13}C -NMR spectra: at around δ 123 (CF_3 , $^1J_{\text{C-F}}$ = 285 Hz) and δ 71 (CH , $^2J_{\text{C-F}}$ = 31 Hz).

Reactions of *N*-Acylprolines (5**) or *N*-Acyl-*N*-alkylamino Acids (**8**) with TFAA** The reaction of α -amino acids and acetic anhydride in the presence of a base to give α -acetaminoalkyl ketones is known as the Dakin–West (D–W) reaction.¹⁶ Likewise, the D–W reaction of α -amino acids with TFAA yields the corresponding α -amido CF_3 -ketones, which have attracted much interest as an important class of inhibitors of a variety of hydrolytic enzymes.¹⁷ Recently, we have reported that the D–W reaction of *N*-alkoxycarbonyl-*N*-alkyl α -amino acids with TFAA affords the corresponding CF_3 -ketones.¹⁸ However, our early discovery¹⁰ of the unusual formation of 5- CF_3 -oxazoles (**9**) from *N*-acylprolines (**5**) or *N*-acyl-*N*-alkylamino acids (**8**) and TFAA under the D–W reaction conditions prompted us to investigate in detail the D–W reaction of *N*-acyl-*N*-alkyl- α -amino acids (**5** and **8**) with TFAA. We have now found that the reaction of **5** or **8** with TFAA affords CF_3 -acyloins (**2** and **6**) as the main products. According to a previous report,¹⁰ the reaction was carried out by the addition of TFAA at 0 °C to a solution of *N*-acylprolines (**5**) in benzene in the presence of pyridine to give 5- CF_3 -oxazole derivative (**9**) in good yield. In contrast, when the addition of TFAA was performed at 100 °C, the results were quite different. Thus, TFAA was added to a refluxing solution of **5a** and pyridine in benzene and the mixture was further refluxed for 1 h. After usual work-up, the compound **6a** was isolated in 88% yield. The reason why the reaction affords a completely different product depending on the reaction temperature is still unclear. However, several *N*-acyl derivatives (**5b**–**d**) were easily converted to the acyloins (**6b**–**d**) in good yields (Table 3, runs 2–4). The reaction is generally applicable to not only *N*-acylprolines (**5**) but also other *N*-acyl-*N*-alkylamino acids (**8**), as shown in Table 3. In the case of **8c**, the temperature at addition of TFAA does not have a profound effect on the product distribution (Table 3, runs 7 and 8). Among the three *N*-alkyl groups examined (Me, Et, and benzyl), use of the Me group proved to give the best result (Table 3, runs 7, 9, and 11).

Transformation of acyloins (**2**) to oxazoles (**10**) is possible (Chart 2).¹⁹ Thus, reactions of acyloins (**2b** or **6a**) with formamide at 105 °C afforded the corresponding 5- CF_3 -oxazoles (**10a** and **b**) in 47% and 27% yields, respectively.

Mechanistic Consideration Plausible mechanisms of the reactions of α -hydroxy acids (**1**) and *N*-acyl amino acids (**5** and **8**) are suggested in Charts 3, 4, and 5, respectively. The reaction of α -hydroxy acids (**1**) could involve mesoionic 1,3-dioxolium-4-olates (**12**), whose existence was supported by the following facts: 1) α -hydroxy carboxylic acid (**1a**), *O*-

Table 3. Reactions of *N*-Acyl-*N*-alkyl- α -amino Acids with TFAA

Run	Amino acid	Method ^{a)}	Product (yield, %)
1	5a	A	6a (88)
2	5b	A	6b (85)
3	5c	A	6c (81)
4	5d	A	6d (62)+ 7 (12)
5	8a	A	2a (68)+ 3a (8)+ 9a (12)
6	8b	A	2a (30)+ 3a (4)+ 9a (41)
7	8c	A	2b (54)+ 3b (11)+ 9b (5)
8	8c	B	2b (50)+ 3b (14)+ 9b (13)
9	8d	A	2b (27)+ 3b (23)+ 9b (1)
10	8d	B	2b (17)+ 3b (43)+ 9b (16)
11	8e	A	2b (41)+ 3b (10)+ 9b (33)
12 ^{b)}	8e	B	9b (88)
13 ^{c)}	8f	A	3c (43)+ 9c (2)
14	8g	A	3d (23)+ 9d (5)

a) Methods A and B are described in the experimental. b) Literature data.¹⁰

c) No isolation of **2d** is probably due to the loss during extraction because the product may be water-soluble.

acetylmandelic acid (**1b**), and *O*-benzoylmandelic acid (**1c**), which can form the mesoionic intermediates, gave the expected product, 2) neither *O*-methylmandelic acid (**1d**) nor α -methylmandelic acid can form the mesoionic intermediate and failed to give the corresponding CF_3 -ketones. These results also showed that the mechanism of the reaction of α -hydroxy acids (**1**) with TFAA did not consist with those of the Hunsdiecker reaction²⁰ or the reaction of carboxylic acid chlorides with pyridine and TFAA to afford CF_3 -ketones via ketene intermediates.¹⁵ The existence of the mesoionic intermediate (**12**) was postulated for the first time in the 1,3-dipolar cycloaddition reaction with olefinic dipolarophiles.²¹ The conversion of **12** to **2** appears to proceed in a similar mechanism to that described in the case of the D–W reaction of *N*-acyl-*N*-alkyl α -amino acids.^{10,16}

Several observations help to delineate the gross mechanistic details of the way **8** is converted to **2** and **3**, respectively (Chart 4). First, in the reaction of **8e**, benzoic acid (40%), benzylamine (35%, isolated as an *N*-acetyl derivative) and benzyl alcohol (13%) were isolated as the acidic and basic fractions after extraction of the products. Second, it was proved that **2a** and **3a** were not the direct reaction products, but they were formed after hydrolysis of the reaction mixture. On the other hand, oxazole (**9a**) was formed before the acid hydrolysis. Third, it was also proved that **2a** was not derived from the hydrolysis of **3a**, because **3a** was recovered unchanged under the same reaction conditions as **8e**. The reaction involves mesoionic 1,3-oxazolium-5-olates (**18**), commonly known as munchnones, formed through the cyclodehydration of **8** by TFAA. In Chart 4, the key intermediate oxazolium ion (**19**), the postulated common intermediate for the formation of oxazoles,¹⁰ could have three sites which could be attacked by the trifluoroacetate anion. Further addition of the trifluoroacetate anion to intermediate **20** could lead to **21**, and acid hydrolysis of **21** via α -amino trifluoromethyl ketones (**22**) may account for the formation of **2**. In the case of *N*-acylprolines (**5**), the formation of **6** could be through hydrolysis of **25** as described in Chart 5.

In summary, our methods make this class of compounds readily accessible for study as building blocks for the synthesis of fluorine-containing compounds. Recently, three methods for the preparation of α -hydroxy- α -trifluoromethyl car-

Chart 1

Chart 2

bonyl compounds have been devised: 1) the addition of formaldehyde *N,N*-dialkylhydrazones to trifluoromethyl ketones, followed by hydrazone cleavage,²²⁾ 2) Friedel-Crafts type reactions of trifluoropyruvamides to give trifluoromethylated glycolic acid derivatives²³⁾ and 3) Grignard reactions of trifluoropyruvamides.²⁴⁾ Recently, we have found that the CF₃-acyloins (**2a, b**) induce apoptotic cell death in human oral tumor cell lines and could be a lead compound of anticancer agents.²⁵⁾ The reactions of α -hydroxy acids **1** show more potential for practical applications because of the ready availability of the starting materials and ease of manipulation.

Experimental

General Methods All melting points were determined using a Yanagimoto hot-stage melting point apparatus and are uncorrected. ¹H-NMR spectra were measured on either a JEOL JNM-PMX60SI, JNM-FX270, or JNM-GSX500 spectrometer with tetramethylsilane (Me₄Si) as an internal reference and CDCl₃ as the solvent. ¹³C-NMR spectra were obtained on a JEOL JNM-FX270 or JNM-GSX500 spectrometer (at 68 or 127 MHz). Both ¹H- and ¹³C-NMR spectral data are reported in parts per million (δ) relative to Me₄Si. Infrared (IR) spectra were recorded on a JASCO IR810 spectrometer. Low- and high-resolution MS were obtained with a JEOL JMS-DX300 spectrometer with a direct inlet system at 70 eV. Combustion analyses were carried out in the microanalytical laboratory of this university. Standard workup means that the organic layers were finally dried over Na₂SO₄, filtered, and concentrated *in vacuo* below 45 °C using a rotary evaporator. In the preparation of *N*-acyl-*N*-alkyl- α -amino acids (**5** and **8**), L-Ala, L-Ileu, L-Phe, DL-phenylglycine, and L-Pro were used as the starting materials.

Materials The following compounds were prepared by reported procedures²⁶⁾: *O*-Acetylmandelic acid (**1b**): mp 50–52 °C (mp²⁶⁾ 52 °C). *O*-Benzoylmandelic acid (**1c**): mp 114–115 °C (mp²⁶⁾ 114–115 °C). The following compounds were previously synthesized and used in this study as the starting materials¹⁰⁾: *N*-benzoylproline (**5a**): mp 155–157 °C; *N*-(4-methoxybenzoyl)proline (**5b**): mp 105–108 °C; *N*-(4-chlorobenzoyl)proline (**5c**): mp 122–125 °C; *N*-pivaloylproline (**5d**): mp 131–132 °C; *N*-benzoyl-*N*-methylphenylglycine (**8a**): mp 120–122 °C; *N*-benzoyl-*N*-benzylphenylalanine (**8b**): mp 114–116 °C; *N*-benzoyl-*N*-methylphenylalanine (**8c**): mp 137–138 °C; *N*-benzoyl-*N*-ethylphenylalanine (**8d**): mp 162–164 °C; *N*-benzoyl-*N*-benzylphenylalanine (**8e**): mp 114–116 °C; *N*-benzoyl-*N*-methylphenylalanine (**8f**): mp 131–132 °C.

***N*-Benzoyl-*N*-methylisoleucine (**8g**)** This was obtained according to a conventional method¹⁰⁾: Oil. IR (oil) cm⁻¹: 3000 (br), 1730, 1635. ¹H-NMR (500 MHz) δ : 0.75–0.88+0.93–1.10 (m, 3H), 1.01+1.09 (d, 3H,

Chart 3

Chart 4

Chart 5

249.1364. Found: 249.1362.

The following compounds are commercially available: **1a**, **1d**, **1e**, **1f**, and α -methylmandelic acid.

General Procedure for the Reactions of α -Hydroxy Acids with TFAA

TFAA (1.2 ml, 8 mmol) was added to a stirred solution of α -hydroxy acid (**1**) (2 mmol) and pyridine (0.97 ml, 12 mmol) in dry benzene (7 ml) at room temperature under Ar atmosphere and the mixture was refluxed for 3 h. Then, 5% HCl (5 ml) was added to the mixture and the solution was stirred at 60 °C for 10 min. After standard workup, the crude product was purified by column chromatography on silica gel eluting with EtOAc–hexane (1 : 4) to give the products (**2** and/or **3**). The results are summarized in Table 2.

3,3,3-Trifluoro-2-hydroxy-1-phenyl-1-propanone (2a): mp 80–81 °C (benzene) (mp⁶) 80.5–82.5 °C). IR (Nujol) cm^{-1} : 3370, 1685. ¹H-NMR (500 MHz) δ : 4.00–4.40 (br, 1H), 5.40 (q, 1H, $J=5.8$ Hz), 7.40–7.71 (m, 3H), 7.98 (m, 2H). ¹³C-NMR (126 MHz) δ : 70.97 (CH, $^2J_{\text{C-F}}=31$ Hz), 123.34 (CF₃, $^1J_{\text{C-F}}=285$ Hz), 129.03 (CH), 129.50 (CH), 133.35 (C), 135.34 (CH), 193.10 (C). CI-MS m/z : 205 ($M^+ + 1$, 100%).

4,4,4-Trifluoro-3-hydroxy-1-phenyl-2-butanone (2b): mp 95–96 °C (benzene–hexane). IR (Nujol) cm^{-1} : 3420, 3350, 1735. ¹H-NMR (500 MHz) δ : 3.61–4.08 (br, 1H), 3.93 (d, 1H, $J=16.3$ Hz), 4.04 (d, 1H, $J=16.3$ Hz), 4.60 (q, 1H, $J=7.4$ Hz), 7.18–7.21 (m, 2H), 7.31–7.37 (m, 3H). ¹³C-NMR (126 MHz) δ : 46.41 (CH₂), 73.82 (CH, $^2J_{\text{C-F}}=31$ Hz), 122.50 (CF₃, $^1J_{\text{C-F}}=284$ Hz), 127.89 (C), 129.10 (CH), 129.54 (CH), 131.49 (C), 200.61 (C). MS m/z : 218 (M^+ , 6%), 91 (100%). Anal. Calcd for C₁₀H₉F₃O₂: C,

$J=6.9$ Hz), 1.20–1.65 (m, 2H), 1.95–2.30 (m, 1H), 2.99+3.06 (s, 3H), 4.71–4.84 (m, 1H), 7.35–7.80 (m, 5H), 7.55–8.10 (br, 1H). MS m/z : 249 (M^+ , 0.4%), 105 (100%). High-resolution MS: Calcd for C₁₄H₁₉NO₃:

55.05; H, 4.16. Found: C, 54.95; H, 4.26.

1,1,1-Trifluoro-2-hydroxy-3-nonane (**2c**): Oil. IR (oil) cm^{-1} : 3450, 1725. ^1H -NMR (500 MHz) δ : 0.89 (t, 3H, $J=7.0$ Hz), 1.23—1.37 (m, 6H), 1.62—1.72 (m, 2H), 2.58—2.76 (m, 2H), 4.00—4.20 (br, 1H), 4.50 (q, 1H, $J=7.5$ Hz). ^{13}C -NMR (126 MHz) δ : 13.99 (CH_3), 22.45 (CH_2), 23.27 (CH_2), 28.62 (CH_2), 31.45 (CH_2), 39.73 (CH_2 , $^2J_{\text{C-F}}=2$ Hz), 74.81 (CH, $^2J_{\text{C-F}}=31$ Hz), 122.53 (CF_3 , $^1J_{\text{C-F}}=283$ Hz), 203.08 (C). CI-MS m/z : 213 (M^+ , 1, 79%), 113 (100%).

2-Benzoyloxy-3,3,3-trifluoro-1-phenyl-1-propanone (**3a**): mp 87—88 °C (Et₂O-hexane). IR (Nujol) cm^{-1} : 1750, 1700. ^1H -NMR (500 MHz) δ : 6.52—6.57 (m, 1H), 7.47—7.62 (m, 4H), 7.62—7.68 (m, 2H), 8.03—8.14 (m, 4H). ^{13}C -NMR (126 MHz) δ : 71.29 (CH, $^2J_{\text{C-F}}=32$ Hz), 121.87 (CF_3 , $^1J_{\text{C-F}}=282$ Hz), 127.73 (C $\times$ 2), 128.69 (CH), 128.97 (CH $\times$ 2), 130.29 (CH), 134.26 (CH), 134.58 (CH), 164.66 (C), 188.36 (C). MS m/z : 308 (M^+ , 0.1%), 105 (100%). High-resolution MS: Calcd for $\text{C}_{16}\text{H}_{11}\text{F}_3\text{O}_3$: 308.0660. Found: 308.0670.

3,3,4,4,4-Pentafluoro-2-hydroxy-1-phenyl-1-butanone (4a) The procedure was the same as described above, except that TFAA was replaced with pentafluoropropionic anhydride: Yield 84%, oil. IR (oil) cm^{-1} : 3450, 1690. ^1H -NMR (500 MHz) δ : 3.81—4.22 (br, 1H), 5.52 (dd, 1H, $J=2.8$, 19.5 Hz), 7.54 (t, 2H, $J=8.1$ Hz), 7.70 (t, 1H, $J=8.1$ Hz), 7.96 (d, 2H, $J=8.1$ Hz). ^{13}C -NMR (126 MHz) δ : 69.81 (CH, $^2J_{\text{C-F}}=25$, 28 Hz), 110—120 (CF_2CF_3), 129.03 (CH), 129.46+129.48 (CH), 133.93 (C), 135.33 (CH), 193.52 (C). MS m/z : 253 (M^+ —1, 28%), 105 (100%).

3,3,4,4,5,5,5-Heptafluoro-2-hydroxy-1-phenyl-1-pentanone (4b) The procedure was the same as described above, except that TFAA was replaced with heptafluorobutyric anhydride: Yield 66%, oil. IR (oil) cm^{-1} : 3450, 1685. ^1H -NMR (500 MHz) δ : 4.28 (d, 1H, $J=8.6$ Hz), 5.60 (dd, 1H, $J=8.6$, 20.5 Hz), 7.54 (t, 2H, $J=7.8$ Hz), 7.69 (t, 1H, $J=7.8$ Hz), 7.96 (d, 2H, $J=7.8$ Hz). ^{13}C -NMR (126 MHz) δ : 69.74 (CH, $^2J_{\text{C-F}}=24$, 28 Hz), 105—120 ($\text{CF}_2\text{CF}_2\text{CF}_3$), 129.08 (CH), 129.42+129.44 (CH), 134.12 (C), 135.32 (CH), 193.52 (C). CI-MS m/z : 305 (M^+ +1, 52%), 105 (100%).

General Procedures for the Reactions of *N*-Acylprolines (5) or *N*-Acyl-*N*-alkylamino Acids (8) with TFAA Method A: TFAA (0.64 ml, 4.5 mmol) was added to a refluxing solution of **5** or **8** (1.5 mmol) and pyridine (0.73 ml, 9 mmol) in dry benzene (6 ml) at 100 °C and the mixture was refluxed for 1 h. Then, 5% HCl (6 ml) was added to the mixture and the solution was stirred at 60 °C for 30 min. After standard workup, the crude product was purified by column chromatography on silica gel eluting with EtOAc-hexane (1 : 4) to give the products (**2**, **3** and/or **9**).

Method B: Compound **5** or **8** (1.5 mmol) was added to a stirred solution of TFAA (0.64 ml, 4.5 mmol) and pyridine (0.73 ml, 9 mmol) in dry benzene (6 ml) at 0 °C and the mixture was stirred at 25 °C for 3 h, then refluxed for 5 h. After the reaction, 5% HCl (6 ml) was added to the mixture and the solution was stirred at 60 °C for 30 min. After standard workup, the crude product was purified by column chromatography on silica gel eluting with EtOAc-hexane (1 : 4) to give the products (**2**, **3** and/or **9**). The results are summarized in Table 3.

3-Benzoyloxy-4,4,4-trifluoro-1-phenyl-2-butanone (**3b**): mp 63—64 °C (hexane). IR (Nujol) cm^{-1} : 1745, 1735. ^1H -NMR (270 MHz) δ : 3.98 (d, 2H, $J=2$ Hz), 5.79 (q, 1H, $J=7.4$ Hz), 7.15—7.19 (m, 2H), 7.27—7.35 (m, 3H), 7.46—7.52 (m, 2H), 7.61—7.68 (m, 1H), 8.07—8.11 (m, 2H). ^{13}C -NMR (68 MHz) δ : 46.85 (CH_2), 74.14 (CH, $^2J_{\text{C-F}}=31$ Hz), 121.77 (CF_3 , $^1J_{\text{C-F}}=282$ Hz), 127.58 (CH), 123.77 (CH), 129.69 (CH), 130.28 (CH $\times$ 2), 131.63 (C), 134.37 (CH), 164.44 (C), 196.19 (C). MS m/z : 322 (M^+ , 1.8%), 91 (100%). Anal. Calcd for $\text{C}_{17}\text{H}_{13}\text{F}_3\text{O}_3$: C, 63.36; H, 4.07. Found: C, 63.24; H, 4.06.

3-Benzoyloxy-4,4,4-trifluoro-2-butanone (**3c**): Oil. IR (oil) cm^{-1} : 1740 (br), 1730, 1640. ^1H -NMR (270 MHz) δ : 2.38 (s, 3H), 5.67 (q, 1H, $J=7.4$ Hz), 7.50 (t, 2H, $J=7.5$ Hz), 7.66 (t, 1H, $J=7.5$ Hz), 8.12 (d, 2H, $J=7.5$ Hz). ^{13}C -NMR (68 MHz) δ : 27.39 (CH_3), 74.96 (CH, $^2J_{\text{C-F}}=32$ Hz), 121.75 (CF_3 , $^1J_{\text{C-F}}=282$ Hz), 127.71 (C), 128.81 (CH), 130.26 (CH), 134.40 (CH), 164.56 (C), 196.16 (C). MS m/z : 246 (M^+ , 9%), 105 (100%). High-resolution MS: Calcd for $\text{C}_{17}\text{H}_9\text{F}_3\text{O}_3$: 246.0503. Found: 246.0475.

2-Benzoyloxy-1,1,1-trifluoro-4-methyl-3-hexanone (**3d**): mp 34—35 °C (hexane). IR (Nujol) cm^{-1} : 1745, 1735. ^1H -NMR (500 MHz) δ : 0.86+0.96 (t, 3H, $J=7.4$ Hz), 1.11+1.24 (d, 3H, $J=7.1$ Hz), 1.36—1.44+1.45—1.52 (m, 1H), 1.71—1.78+1.83—1.90 (m, 1H), 2.84—2.91 (m, 1H), 5.82—5.87 (m, 1H), 7.49—7.52 (m, 2H), 7.63—7.66 (m, 1H), 8.12+8.13 (d, 2H, $J=7.6$ Hz). ^{13}C -NMR (126 MHz) δ : 11.31+11.47 (CH_3), 15.06+16.57 (CH_3), 25.23+26.18 (CH_2), 44.83+45.26 (CH_2), 73.61+73.96 (CH, $^2J_{\text{C-F}}=32$ Hz), 121.85+121.89 (CF_3 , $^1J_{\text{C-F}}=281$ Hz), 127.85+127.87 (C), 128.76 (CH), 130.23 (CH), 134.28 (CH), 164.42+164.44 (C), 202.33+202.40 (C). CI-MS m/z : 289 (M^+ +1, 7%), 105 (100%). Anal. Calcd for

$\text{C}_{14}\text{H}_{15}\text{F}_3\text{O}_3$: C, 58.33; H, 5.24. Found: C, 58.17; H, 5.40. The multiplicity of ^1H and ^{13}C NMR peaks is due to the diastereomer of **3d**.

1,1,1-Trifluoro-2-hydroxy-6-pivaloamido-3-hexanone (**6d**): Oil. IR (oil) cm^{-1} : 3350 (br), 1730, 1640. ^1H -NMR (270 MHz) δ : 1.18 (s, 9H), 1.78—1.94 (m, 2H), 2.61—2.83 (m, 2H), 3.16—3.30 (m, 2H), 4.53 (q, 1H, $J=7.4$ Hz), 4.90—5.00 (br, 1H), 6.07 (br s, 1H). ^{13}C -NMR (68 MHz) δ : 24.82 (CH_2), 28.72 (C), 29.03 (CH_3), 37.89 (CH_2), 40.20 (CH_2), 76.77 (CH, $^2J_{\text{C-F}}=31$ Hz), 124.30 (CF_3 , $^1J_{\text{C-F}}=283$ Hz), 181.28 (C), 205.42 (C). MS m/z : 269 (M^+ , 5%), 57 (100%). High-resolution MS: Calcd for $\text{C}_{11}\text{H}_{18}\text{F}_3\text{O}_3$: 269.1239. Found: 269.1239.

The following products were identified by comparison of the IR and ^1H -NMR spectral data with those of authentic samples¹⁰: 6-Benzamido-1,1,1-trifluoro-2-hydroxy-3-hexanone (**6a**); 1,1,1-trifluoro-2-hydroxy-6-(4-methoxybenzamido)-3-hexanone (**6b**); 6-(4-chlorobenzamido)-1,1,1-trifluoro-2-hydroxy-3-hexanone (**6c**); 3-(2-*tert*-butyl-5-trifluoromethylloxazol-4-yl)propanol (**7**); 5-trifluoromethyl-2,4-diphenyloxazole (**9a**); 4-benzyl-5-trifluoromethyl-2-phenyloxazole (**9b**); 5-trifluoromethyl-4-methyl-2-phenyloxazole (**9c**); 4-*sec*-butyl-5-trifluoromethyl-2-phenyloxazole (**9d**).

General Procedures for the Reactions of Acyloins with Formamide A solution of acyloin (**2b** or **6a**) (1 mmol) in formamide (0.9 ml, 20 mmol) containing $\text{c.H}_2\text{SO}_4$ (0.2 ml, 2 mmol) was heated at 105 °C for 3 h. The mixture was diluted with Et₂O (40 ml) and 1% Na_2CO_3 (30 ml). After standard workup, the crude product was purified by column chromatography on silica gel eluting with EtOAc-hexane (1 : 1) to give the products (**10a**, **b**).

4-Benzyl-5-trifluoromethylloxazole (**10a**): Yield 41%, oil. IR (oil) cm^{-1} : 1630. ^1H -NMR (270 MHz) δ : 4.00 (s, 2H), 7.22—7.33 (m, 5H), 7.83 (s, 1H). ^{13}C -NMR (68 MHz) δ : 32.01 (CH_2), 119.71 (CF_3 , $^1J_{\text{C-F}}=268$ Hz), 126.96 (CH), 128.75 (CH), 129.14 (CH), 133.78 (C, $^2J_{\text{C-F}}=42$ Hz), 137.02 (C), 140.95 (C), 151.40 (C). MS m/z : 227 (M^+ , 100%). High-resolution MS: Calcd for $\text{C}_{11}\text{H}_8\text{NF}_3\text{O}$: 227.0558. Found: 227.0548.

4-(3'-Benzamidopropyl)-5-trifluoromethylloxazole (**10b**): Yield 27%, mp 87—88 °C (Et₂O-hexane). IR (Nujol) cm^{-1} : 3300, 1625. ^1H -NMR (270 MHz) δ : 1.94—2.05 (m, 2H), 2.78 (t, 2H, $J=6.9$ Hz), 3.45—3.52 (m, 2H), 6.80 (br s, 1H), 7.38—7.51 (m, 3H), 7.56—7.80 (m, 2H), 7.89 (s, 1H). ^{13}C -NMR (68 MHz) δ : 23.09 (CH_2), 28.07 (CH_2), 39.13 (CH_2), 119.65 (CF_3 , $^1J_{\text{C-F}}=268$ Hz), 126.94 (CH), 128.57 (CH), 131.70 (CH), 133.80 (CH, $^2J_{\text{C-F}}=42$ Hz), 134.70 (C), 141.39 (C), 151.29 (C), 167.72 (C). MS m/z : 298 (M^+ , 8%), 105 (100%). Anal. Calcd for $\text{C}_{14}\text{H}_{13}\text{N}_2\text{F}_3\text{O}_2$: C, 56.38; H, 4.39; N, 9.39. Found: C, 56.42; H, 4.49; N, 9.28.

References and Notes

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