Convenient Synthesis of 5-Trifluoroacetylated Imidazoles by Ring Transformation of Mesoionic 1,3-Oxazolium-5-olates

Masami KAWASE* and Setsuo SAITO

Faculty of Pharmaceutical Sciences, Josai University, 1–1 Keyakidai, Sakado, Saitama 350–0295, Japan.
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Mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates (1), obtained from the reaction of *N*-acyl-*N*-alkylglycines (2) with trifluoroacetic anhydride, react with amidines to give 5-trifluoroacetylimidazoles (3) in moderate yield. The novel ring transformations of 1 into 3 occur *via* an initial attack of amidines on the C-2 position of the ring.

Key words: imidazole; 1,3-oxazolium-5-olate; trifluoroacetyl compound; ring transformation; trifluoroacetic anhydride

Trifluoromethyl ketones are interesting compounds in the design of enzyme inhibitors.[1)] The concept of mimicking tetrahedral transition states of enzyme-mediated peptide bond hydrolysis previously led to the successful design and synthesis of trifluoroacetyl compounds as a promising class of proteinase inhibitors.[1)] Recently, we have reported that heteroaromatic and aromatic trifluoromethyl ketones show interesting biological activities such as bactericidal activity[2a)] and apoptosis-induced cytotoxic activity.[2b)] However, there appear to be few practical procedures available for the synthesis of trifluoroacetyl substituted heterocycles, such as imidazoles and pyridines.[3)] Generally, heterocycles, which are electron deficient, are resistant to electrophilic substitution reactions, such as Friedel–Crafts acylation.[4)] Hence, an effective method for the synthesis of trifluoroacetylated heteroaromatic compounds is required.

Although the imidazole ring is an important residue and fluorinated systems are much sought after by medicinal and agricultural chemists,[5)] trifluoroacetyl substituted imidazoles remain rare compounds.

In the course of our studies on the reactivities of mesoionic 1,3-oxazolium-5-olates,[6)] we have focused on 4-trifluoroacetyl-1,3-oxazolium-5-olates (**1**) as useful synthons for trifluoromethyl-substituted heterocycles.[7)] Compound **1** could easily be prepared from *N*-acyl-*N*-alkylglycines **2** with trifluoroacetic anhydride (TFAA).[8)] In general, the mesoionic 1,3-oxazolium-5-olates are too unstable to be isolated and are utilized *in situ*.[6)] However, compound **1** with 4-trifluoroacetyl group can be isolated and stored for several months. It is reported that compound **1** showed high reactivity towards nucleophilic reagents such as H_2O, EtOH, and AcOH, bringing about ring-opening reactions.[8)] These reactions occur *via* an initial attack of a nucleophile on the C-5 position of the ring.[7d)] We have been interested in the reactions of **1** with *N*-nucleophiles such as amidines,[7a)] ammonia,[7b)] hydrazines,[7c)] and aminomalonate.[7e)] In principle, nucleophilic reagents can be expected to be added to one of the three electrophilic centers at C-2, C-5, and $COCF_3$ in **1**. We now present a full account of the reactions of **1** with amidines[7a)] and the new synthesis of 5-trifluoroacetylimidazoles **3**.

Results and Discussion

The 4-trifluoroacetyl-1,3-oxazolium-5-olates (**1a**—**d**) required for this study have been prepared by the reaction of *N*-acyl-*N*-alkylglycines (**2a**—**d**) with TFAA. The derivatives employed in this study, along with the products (**3a**—**h**, **4a**—**f**, **5a**—**b**), are summarized in Chart 1. Table 1 shows the results when 4-trifluoroacetyl-1,3-oxazolium-5-olate (**1a**) was allowed to react with formamidine under various conditions. The best result was obtained by the reaction of **1a** (1 mmol) with formamidine hydrochloride (1.5 mmol) in *N*,*N*-dimethylformamide (DMF) (5 ml) in the presence of potassium carbonate (1.5 mmol) at 70 °C for 2 h: 5-trifluoroacetylimidazole **3a** and dihydroimidazole **4a** were isolated in 63% and 19% yields, respectively (Table 1, run 5). Various substituted 4-trifluoroacetyl-1,3-oxazolium-5-olates **1a**—**d** were subjected to a reaction under the optimum conditions and the results are listed in Table 2. In all reactions examined, 4,5-dihydroimidazoles **4a**—**f** were isolated as side products, whose mechanism of formation is discussed later. In runs 7 and 8, **5a** and **5b** were also isolated, possibly formed *via* hydrolysis of the mesoionic 1,3-oxazolium-5-olates **1**.

A one-pot conversion of **2** to **3** also proceeded successfully. Thus, **2a** reacted with TFAA in CH_2Cl_2 to give **1a**, which was directly subjected to the ring transformation reaction to yield **3a** in 68% yield (Table 2, run 2). The one-pot procedure gave slightly higher yield. When acetamidine or benzamidine was used instead of formamidine, 4-methyl- and 4-phenylimidazole derivatives (**3e**, **3f**) were obtained in good yield, respectively (Table 2, runs 6, 7). Pentafluoropropionic and heptafluorobutyric anhydride also reacted readily with *N*-benzoyl-*N*-methylglycine **2a** to yield 5-pentafluoropropionyl- (**3g**) and 5-heptafluorobutyrylimidazole (**3h**) by the one-pot procedure in good yield, respectively (Table 2, runs 8, 9, Chart 1).

The structure of **3a**—**f** is supported by spectral and analytical data. The presence of the $COCF_3$ group in **3a**—**f** was determined on the basis of long-range ^{13}C–^{19}F coupling. Thus, the carbons of the $COCF_3$ group appear at around δ 116 ppm (quartet, $^1J_{C\text{-}F}$=280—290 Hz) and δ 170 ppm (quartet, $^2J_{C\text{-}F}$= 37—38 Hz). The ultimate proof of the structure of **3a** rests upon its conversion into the known[9)] 5-formyl-1-methyl-2-phenylimidazole (**8**), as shown in Chart 2. Thus, treatment of **3a** with NaH followed by ethyl iodide afforded an ethyl ester (**6**).[10)] In this reaction, compound **7** of formula $C_{15}H_{14}F_6N_2O$ was also isolated as a side product. The ^1H-NMR spectrum of **7** contained a signal of ethoxy protons, whereas the IR spectrum of **7** showed no carbonyl group. MS and analytical data indicated the existence of two trifluoromethyl groups, while the ^{13}C-NMR spectrum indicated only one trifluoromethyl group at δ 122 ppm (quartet, $^1J_{C\text{-}F}$=293 Hz). The reduction with $LiAlH_4$ of the ester **6**, followed by oxidation

* To whom correspondence should be addressed.

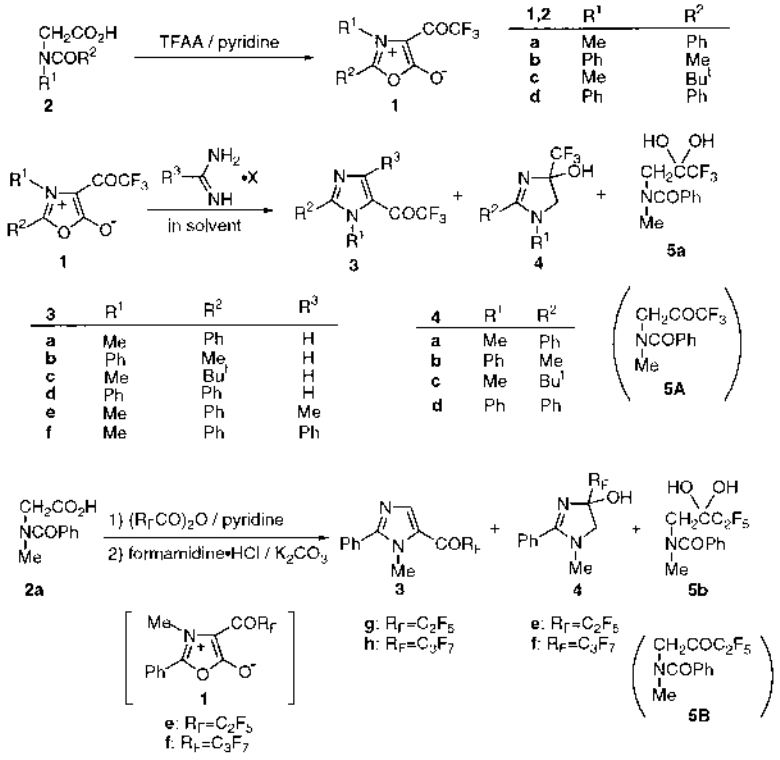

Chart 1

Table 1. Reactions of **1a** with Formamidine·X[a]

Run	X	Base (eq)[b]	Solvent	Product (%)		
				3a	**4a**	**5a**
1	HCl	None	Dioxane	5	9	74
2	HCl	Et_3N (3)	Dioxane	43	7	3
3	HCl	Pyridine (3)	Dioxane	9	—	81
4	HCl	K_2CO_3 (1.5)	Dioxane	42	10	3
5	HCl	K_2CO_3 (1.5)	DMF	63	19	—
6	HCl	K_2CO_3 (1.5)	$CHCl_3$	31	6	19
7	AcOH	K_2CO_3 (1.5)	DMF	55	38	—
8	AcOH	None	Dioxane	40	18	—

a) The reactions were carried out on a 1 mmol scale at 70 °C for 2 h. *b*) Eq refers to molar equivalents with respect to **1a**.

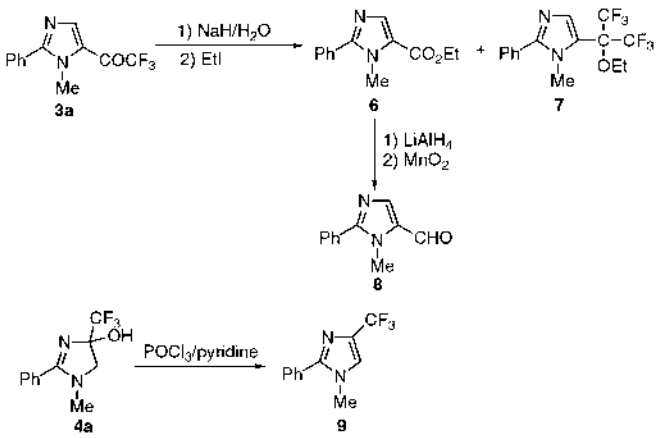

Chart 2

Table 2. Reactions of Mesoionic Compounds (**1**) or *N*-Acyl-*N*-alkylglycine (**2**) with Formamidine·HCl

Run	Starting material	Product (yield, %)
1	**1a**	**3a** (63), **4a** (19)
2	**2a**[a]	**3a** (68), **4a** (15)
3	**1b**	**3b** (55), **4b** (14)
4	**1c**	**3c** (49), **4c** (15)
5	**1d**	**3d** (54), **4d** (11)
6[b]	**1a**	**3e** (46), **4a** (16)
7[c]	**1a**	**3f** (55), **4a** (25), **5a** (4)
8[d]	**2a**[a]	**3g** (60), **4e** (14), **5b** (11)
9[e]	**2a**[a]	**3h** (56), **4f** (20)

a) Yields refer to the one-pot procedure using **2a**. *b*) Acetamidine·HCl was used instead of formamidine. *c*) Benzamidine·HCl was used instead of formamidine. *d*) Pentafluoropropionic anhydride was used instead of TFAA in a one-pot conversion procedure. *e*) Heptafluorobutyric anhydride was used instead of TFAA in a one-pot conversion procedure.

of the resulting alcohol with MnO_2, leads the known[9] 5-formyl-1-methyl-2-phenylimidazole **8** in a high overall yield.

The structure of **4a**—**f** was also deduced from spectroscopic data, and dehydration of **4a** with $POCl_3$ and pyridine[11] gave the known[12] 4-trifluoromethyl-1-methyl-2-phenylimidazole (**9**) in 88% yield (Chart 2).

The IR spectra of **5** did not exhibit an absorption band due to the trifluoroacetyl form (**5A** and **5B**), but a band represented the hydrated form. The ^{13}C-NMR spectra of **5a** and **5b** contained hydrated carbon signals appearing at 94.42 ($^2J_{C\text{-}F}$=32 Hz) and 95.50 ($^2J_{C\text{-}F}$=27 Hz), respectively.

Mechanistic Consideration The novel ring transformation of **1** into imidazoles **3** may proceed through an initial attack of amidines on the C-2 position of the ring. This involves direct displacement of the O(1)–C(5) portion by a N–C fragment of the amidines, which corresponds with 1,3-

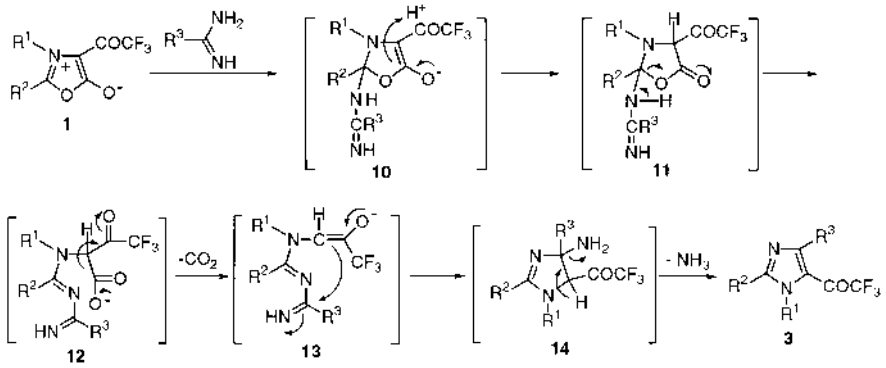

Chart 3

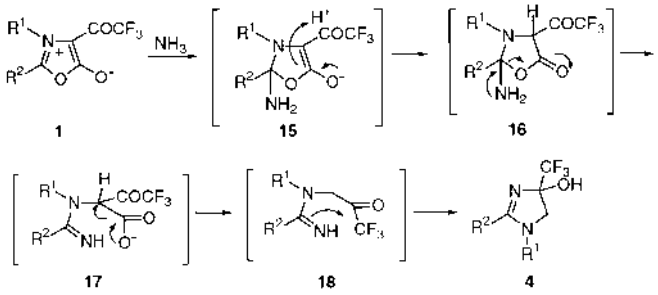

Chart 4

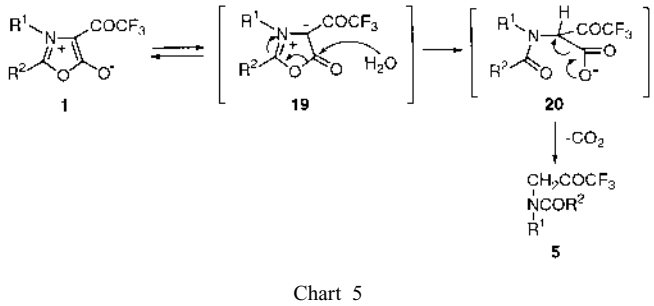

Chart 5

dipolar cycloaddition of munchnones with nitriles to afford imidazoles.[13] However, the cycloaddition has limited synthetic applicability, for only electron-deficient nitriles can react as dipolarophiles, and only one case using 2,4-diphenyl-1,3-oxazolium-5-olates as a dipole has been recorded.[13] On the other hand, the analogous reaction of a munchnone with a tosylimine to provide an imidazole has been also reported.[14]

As shown in Chart 3, a nucleophilic attack of amidines on the C-2 position of **1** affords an adduct (**10**) which is converted to **11**. The intermediate **11** gives an open-chain intermediate **12**, which is then decarboxylated to afford an enolate anion (**13**). The intermediate **13** can undergo cyclization to give **14**, which loses ammonia leading to the imidazoles **3**. A similar reactivity of amidines which extrudes ammonia has been postulated in their reactions with benzoins[15] or cyanohydrins[16] to give oxazoles.

A plausible mechanism of the formation of **4** and **5** is suggested in Charts 4 and 5, respectively. Compound **4** is not formed by the reaction of **5** with ammonia, because the reaction of **5a** with ammonium acetate did not afford the expected **4a**. However, the same reaction of **2a** with ammonium acetate gave **4a** in a high yield. Thus, a nucleophilic attack of ammonia, which was generated during the reaction, on C-2 of **1** gives rise to the adduct **15**. The scission of the O(1)–C(2) bond of **16** gives an open-chain intermediate **17**, which extrudes carbon dioxide to provide the ketone **18**. Finally, intramolecular cyclization of **18** affords dihydroimidazoles **4**. The formation of **5** might be formed through the hydrolysis of the keto form **19**, which is probably in equilibium with **1**.

In summary, we devised an easy method of accessing 5-trifluoroacetylimidazole derivatives which are otherwise difficult to obtain. The principle advantage of using mesoionic oxazoles **1** is the great variety of substituents available for R^1 and R^2. This flexibility in the type of substituents in the mesoionic ring will be reflected in the corresponding substitution of the resulting imidazole. The trifluoroacetyl group at the 5-position serves as a handle for further elaborations, therefore making a variety of functionalized imidazoles accessible.

Experimental

General Methods All melting points were determined using a Yanagimoto hot-stage melting point apparatus and are uncorrected. ^{1}H-NMR spectra were measured on either a JEOL JNM-PMX60SI, JNM-FX270, or JNM-GSX500 spectrometer with tetramethylsilane (Me_4Si) as an internal reference and $CDCl_3$ as the solvent. ^{13}C-NMR spectra were obtained on a JEOL JNM-FX270 or JNM-GSX500 spectrometer (at 68 or 127 MHz). Both ^{1}H- and ^{13}C-NMR spectral data are reported in parts per million (δ) relative to Me_4Si. 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. Elemental analyses were carried out in the microanalytical laboratory of this university. Standard workup means that the organic layers were finally dried over Na_2SO_4, filtered, and concentrated *in vacuo* below 45 °C using a rotary evaporator.

Materials The following compounds were prepared by reported procedures: *N*-Benzoyl-*N*-methylglycine (**2a**): mp 101—104 °C (mp[17] 102—104 °C). *N*-Acetyl-*N*-phenylglycine (**2b**): mp 196—198 °C (mp[17] 193—195 °C). *N*-Methyl-*N*-pivaloylglycine (**2c**): Yield 91%. mp 75—76 °C (benzene–hexane). ^{1}H-NMR (60 MHz) δ: 1.30 (9H, s), 3.18 (3H, s), 4.25 (2H, s), 10.13 (1H, br s). IR (Nujol) cm^{-1}: 2500—300, 1680, 1620. MS *m/z*: 173 (M^+, 3%), 57 (100). High-resolution MS: Calcd for $C_8H_{15}NO_3$: 173.1053. Found: 173.1045. *N*-Benzoyl-*N*-phenylglycine (**2d**): mp 190—193 °C (mp[17] 193—195 °C).

General Procedure for the Preparation of 4-Trifluoroacetyl-1,3-oxazolium-5-olates (1) TFAA (11 ml, 78 mmol) was added to a stirred solution of *N*-acyl-*N*-alkylglycine (26 mmol) in CH_2Cl_2 (50 ml) at 0 °C for 10 min. The mixture was stirred at 25 °C for 3 h and then extracted with CH_2Cl_2 (80 ml×2). The extract was washed successively with 3% HCl, H_2O, 1% Na_2CO_3, and H_2O. After the standard workup, the residue was recrystallized from CH_2Cl_2–hexane to give the 4-trifluoroacetyl-1,3-oxazolium-5-olates (**1**).

3-Methyl-2-phenyl-4-trifluoroacetyl-1,3-oxazolium-5-olate (**1a**): Yield 92%. mp 161—163 °C (mp[8b] 162—163 °C). 2-Methyl-3-phenyl-4-trifluoroacetyl-1,3-oxazolium-5-olate (**1b**): Yield 78%. mp 200—203 °C (mp[8b] 211—212 °C). 2-*tert*-Butyl-3-methyl-4-trifluoroacetyl-1,3-oxazolium-5-olate (**1c**): Yield 94%. mp 120—121 °C (benzene–hexane). IR (Nujol) cm^{-1}: 1800, 1630. ^{1}H-NMR (270 MHz) δ: 1.52 (9H, s), 4.08 (3H, s). ^{13}C-NMR ($CDCl_3$, 68 MHz) δ: 27.43 (CH_3), 35.26 (C), 36.26 (C), 36.27 (CH_3), 96.69 (C), 116.84 (CF_3, $^1J_{C\text{-}F}$=289.0 Hz), 157.82 (C), 162.69 (C), 167.15 (C, $^2J_{C\text{-}F}$=37.4 Hz). MS *m/z*: 251 (M^+, 22%), 105 (100%). *Anal.* Calcd for $C_{10}H_{12}F_3NO_3$: C, 47.81; H, 4.81; N, 5.58. Found: C, 47.87; H, 4.76; N, 5.63. 2,3-Diphenyl-4-trifluoroacetyl-1,3-oxazolium-5-olate (**1d**): Yield 81%. mp 194—196 °C (mp[8b] 194—196 °C).

General Procedure for the Reactions of 4-Trifluoroacetyl-1,3-oxazolium-5-olates (1) with Amidines A solution of **1** (1.5 mmol), an amidine (2.2 mmol), and potassium carbonate (207 mg, 2.2 mmol) in dry DMF (5 ml) was stirred at 70 °C for 2 h. The mixture was diluted with AcOEt (40 ml) and H_2O (30 ml). After the standard workup, the residue was purified by column chromatography on silica gel with EtOAc–hexane to give the products (**3**, **4**, and/or **5**).

1-Methyl-2-phenyl-5-trifluoroacetylimidazole (**3a**) and 4-Hydroxy-1-methyl-2-phenyl-4-trifluoromethyl-4,5-dihydroimidazole (**4a**): **3a**; 63% yield from the less polar fraction (EtOAc : hexane=1 : 1), mp 107—108 °C (hexane). IR (Nujol) cm^{-1}: 1680. ^{1}H-NMR (500 MHz) δ: 4.00 (3H, s), 7.51—7.54 (3H, br s), 7.61—7.66 (2H, br s), 8.15 (1H, s). ^{13}C-NMR (127 MHz) δ: 35.23 (CH_3), 116.56 (CF_3, $^1J_{C\text{-}F}$=291 Hz), 126.34 (C), 128.31 (C), 128.94 (CH), 129.45 (CH), 130.66 (CH), 143.31 (CH, $^3J_{C\text{-}F}$=5.2 Hz), 156.16 (C), 170.79 (C, $^2J_{C\text{-}F}$=37 Hz). MS *m/z*: 254 (M^+, 100%). *Anal.* Calcd for $C_{12}H_9F_3N_2O$: C, 56.70; H, 3.57; N, 11.02. Found: C, 56.75; H, 3.55; N, 11.11. **4a**; 19% yield from the more polar fraction (EtOAc : hexane=1 : 1), mp 196—198 °C (Et_2O). IR (Nujol) cm^{-1}: 2400—3300 (br). ^{1}H-NMR (500 MHz) δ: 2.91 (3H, s), 3.56 (1H, d, *J*=11.7 Hz), 3.70 (1H, d, *J*=11.7 Hz), 7.41—7.48 (3H, m), 7.53—7.56 (2H, m). ^{13}C-NMR (127 MHz) δ: 34.60 (CH_3), 59.73 (CH_2), 94.01 (C, $^2J_{C\text{-}F}$=31 Hz), 124.24 (CF_3, $^1J_{C\text{-}F}$=286 Hz), 128.44 (CH), 128.52 (CH), 128.59 (C), 130.81 (CH), 169.71 (C). MS *m/z*: 244 (M^+, 10%), 91 (100%). *Anal.* Calcd for $C_{11}H_{11}F_3N_2O$: C, 54.10; H, 4.54; N, 11.47. Found: C, 53.98; H, 4.65; N, 11.27.

2-Methyl-1-phenyl-5-trifluoroacetylimidazole (**3b**) and 4-Hydroxy-2-methyl-1-phenyl-4-trifluoromethyl-4,5-dihydroimidazole (**4b**): **3b**; 55% yield from the less polar fraction (EtOAc : hexane=1 : 1), oil. IR (oil) cm^{-1}: 1700. ^{1}H-NMR (500 MHz) δ: 2.30 (3H, s), 7.19—7.22 (2H, m), 7.51—7.56 (3H, m), 8.06 (1H, q, *J*=1.8 Hz). ^{13}C-NMR (127 MHz) δ: 13.89 (CH_3), 116.39 (CF_3, $^1J_{C\text{-}F}$=291 Hz), 126.41 (CH), 126.77 (CH), 129.67 (CH), 129.70 (CH), 136.01 (C), 142.48 (C, $^3J_{C\text{-}F}$=5.2 Hz), 154.92 (C), 169.11 (C, $^2J_{C\text{-}F}$=37 Hz). MS *m/z*: 254 (M^+, 58%), 185 (100%). High-resolution MS: Calcd for $C_{12}H_9F_3N_2O$: 254.0667. Found: 254.0661. **4b**; 14% yield from the more polar fraction (EtOAc : hexane=1 : 1), mp 201—202 °C (Et_2O). IR (Nujol) cm^{-1}: 2400—3300. ^{1}H-NMR (500 MHz) δ: 2.05 (3H, s), 3.92 (1H, d, *J*=11.0 Hz), 4.09 (1H, d, *J*=11.0 Hz), 7.17 (2H, d, *J*=8.5 Hz), 7.27 (1H, t, *J*=7.6 Hz), 7.41 (2H, t, *J*=7.6 Hz). ^{13}C-NMR (127 MHz) δ: 14.69 (CH_3), 59.55 (CH_2), 93.49 (C, $^2J_{C\text{-}F}$=32 Hz), 124.37 (CF_3, $^1J_{C\text{-}F}$=285 Hz), 124.69 (CH), 126.77 (CH), 129.61 (CH), 138.79 (C), 166.03 (C). MS *m/z*: 244 (M^+, 17%), 106 (100%). *Anal.* Calcd for $C_{11}H_{11}F_3N_2O$: C, 54.10; H, 4.54; N, 11.47. Found: C, 54.20; H, 4.61; N, 11.48.

2-*tert*-Butyl-1-methyl-5-trifluoroacetylimidazole (**3c**) and 2-*tert*-Butyl-4-hydroxy-1-methyl-4-trifluoromethyl-4,5-dihydroimidazole (**4c**): **3c**; 49% yield from the less polar fraction (EtOAc : hexane=1 : 2), mp 38—40 °C (hexane). IR (Nujol) cm^{-1}: 1685. ^{1}H-NMR (500 MHz) δ: 1.51 (9H, s), 4.07 (3H, s), 7.94 (1H, q, *J*=2.1 Hz). ^{13}C-NMR (127 MHz) δ: 28.94 ($CH_3\times3$), 33.97 (C), 35.09 (CH_3), 116.57 (CF_3, $^1J_{C\text{-}F}$=291 Hz), 126.29 (CH), 142.16 (C, $^3J_{C\text{-}F}$=5.2 Hz), 163.34 (C), 170.56 (C, $^2J_{C\text{-}F}$=37 Hz). MS *m/z*: 234 (M^+, 20%), 219 (100%). High-resolution MS: Calcd for $C_{10}H_{13}F_3N_2O$: 234.0980. Found: 234.0964. **4c**; 15% yield from the more polar fraction (EtOAc : hexane=1 : 1), mp 155—157 °C (Et_2O). IR (Nujol) cm^{-1}: 2400—3400. ^{1}H-NMR (500 MHz) δ: 1.30 (9H, s), 3.07 (3H, s), 3.43 (1H, dq, *J*=1.2, 11.6 Hz), 3.64 (1H, d, *J*=11.6 Hz). ^{13}C-NMR (127 MHz) δ: 28.04 ($CH_3\times3$), 33.69 (C), 34.93 (CH_3), 60.55 (CH_2), 92.75 (C, $^2J_{C\text{-}F}$=31 Hz), 124.48 (CF_3, $^1J_{C\text{-}F}$=286 Hz), 175.58 (C). MS *m/z*: 224 (M^+, 3%), 191 (100%). *Anal.* Calcd for $C_9H_{15}F_3N_2O$: C, 48.21; H, 6.74; N, 12.49. Found: C, 48.23; H, 6.64; N, 12.52.

1,2-Diphenyl-5-trifluoroacetylimidazole (**3d**) and 1,2-Diphenyl-4-hydroxy-4-trifluoromethyl-4,5-dihydroimidazole (**4d**): **3d**; 54% yield from the less polar fraction (EtOAc : hexane=1 : 2), mp 134—136 °C (Et_2O). IR (Nujol) cm^{-1}: 1680. ^{1}H-NMR (500 MHz) δ: 7.24—7.27 (4H, m), 7.33—7.36 (1H, m), 7.40—7.45 (2H, m), 7.46—7.51 (3H, m), 8.24 (1H, q, *J*=1.8 Hz). ^{13}C-NMR (127 MHz) δ: 116.40 (CF_3, $^1J_{C\text{-}F}$=291 Hz), 127.04 (C), 127.62 (CH), 128.23 (C), 128.44 (CH), 129.29 (CH), 129.51 (CH), 129.69 (CH), 130.26 (CH), 136.48 (C), 143.09 (C, $^3J_{C\text{-}F}$=4.1 Hz), 154.77 (C), 169.41 (C, $^2J_{C\text{-}F}$=37 Hz). MS *m/z*: 316 (M^+, 100%). *Anal.* Calcd for $C_{17}H_{11}F_3N_2O$: C, 64.56; H, 3.51; N, 8.86. Found: C, 64.65; H, 3.57; N, 8.88. **4d**; 11% yield from the more polar fraction (EtOAc : hexane=1 : 1), mp 174—175 °C (Et_2O). IR (Nujol) cm^{-1}: 2500—3300. ^{1}H-NMR (500 MHz) δ: 4.09 (1H, d, *J*=11.6 Hz), 4.13 (1H, d, *J*=11.6 Hz), 6.85 (2H, d, *J*=7.9 Hz), 7.10 (1H, t, *J*=7.6 Hz), 7.20 (2H, t, *J*=7.9 Hz), 7.30 (2H, t, *J*=7.6 Hz), 7.40 (1H, t, *J*=7.6 Hz), 7.49 (2H, d, *J*=7.6 Hz), 8.08 (1H, br s). ^{13}C-NMR (127 MHz) δ: 60.68 (CH_2), 93.98 (C, $^2J_{C\text{-}F}$=31 Hz), 124.04 (CF_3, $^1J_{C\text{-}F}$=285 Hz), 124.39 (CH), 125.71 (CH), 128.28 (CH), 128.82 (C), 129.14 (CH), 129.17 (CH), 131.05 (CH), 140.66 (C), 166.49 (C). MS *m/z*: 306 (M^+, 15%), 106 (100%). *Anal.* Calcd for $C_{16}H_{13}F_3N_2O$: C, 62.74; H, 4.28; N, 9.15. Found: C, 62.88; H, 4.40; N 9.08.

1,4-Dimethyl-2-phenyl-5-trifluoroacetylimidazole (**3e**) and **4a**: **3e**; 55% yield from the less polar fraction (EtOAc : hexane=1 : 2), mp 88—89 °C (hexane). IR (Nujol) cm^{-1}: 1660. ^{1}H-NMR (500 MHz) δ: 2.61 (3H, q, *J*=1.8 Hz), 3.89 (s, 3H), 7.51—7.54 (m, 3H), 7.62—7.64 (m, 2H). ^{13}C-NMR (127 MHz) δ: 16.39 (C, $^3J_{C\text{-}F}$=5.1 Hz), 36.14 (CH_3), 116.40 (CF_3, $^1J_{C\text{-}F}$=289 Hz), 124.45 (C), 128.52 (C), 128.87 (CH), 129.48 (CH), 130.48 (CH), 151.93 (C), 154.59 (C), 171.12 (C, $^2J_{C\text{-}F}$=37 Hz). MS *m/z*: 268 (M^+, 79%), 199 (100%). *Anal.* Calcd for $C_{13}H_{11}F_3N_2O$: C, 58.21; H, 4.13; N, 10.44. Found: C, 57.95; H, 4.28; N, 10.56. **4a**; 16% yield from the more polar fraction (EtOAc : hexane=1 : 1).

2,4-Diphenyl-1-methyl-5-trifluoroacetylimidazole (**3f**), **4a** and *N*-Methyl-*N*-[1-(3,3,3-trifluoro-2,2-dihydroxy)propyl]benzamide (**5a**): **3f**; 55% yield from the less polar fraction (EtOAc : hexane=1 : 1), oil. IR (Nujol) cm^{-1}: 1670. ^{1}H-NMR (500 MHz) δ: 3.91 (3H, s), 7.41—7.44 (3H, m), 7.51—7.53 (5H, m), 7.68—7.72 (2H, m). ^{13}C-NMR (127 MHz) δ: 35.55 (CH_3), 115.75 (CF_3, $^1J_{C\text{-}F}$=290 Hz), 124.17 (C), 128.00 (CH), 128.56 (C), 128.84 (CH), 129.13 (CH), 129.48 (CH), 129.66 (CH), 130.48 (CH), 133.95 (C), 153.70 (C), 154.21 (C), 174.35 (C, $^2J_{C\text{-}F}$=38 Hz). MS *m/z*: 330 (M^+, 78%), 261 (100%). High-resolution MS: Calcd for $C_{18}H_{13}F_3N_2O$: 330.0980. Found: 330.0982. **5a**; 4% yield from the more polar fraction (EtOAc : hexane=1 : 1), mp 90—92 °C (Et_2O–hexane). IR (Nujol) cm^{-1}: 3280, 1600. ^{1}H-NMR (500 MHz) δ: 3.18 (3H, s), 3.88 (2H, s), 5.96 (2H, br s), 7.42—7.46 (2H, m), 7.4—7.51 (3H, m). ^{13}C-NMR (127 MHz) δ: 41.26 (CH_2), 52.92 (CH_3), 94.42 (C, $^2J_{C\text{-}F}$=32 Hz), 122.87 (CF_3, $^1J_{C\text{-}F}$=288 Hz), 127.46 (CH), 128.53 (CH), 130.80 (CH), 133.86 (C), 175.72 (C). CI-MS *m/z*: 246 (M^+-H_2O+1, 100%). *Anal.* Calcd for $C_{11}H_{12}F_3NO_3$: C, 50.20; H, 4.60; N, 5.32. Found: C, 50.40; H, 4.66; N, 5.37. **4a**; 25% yield from the most polar fraction (EtOAc : hexane=1 : 1).

One-Pot Procedure for the Conversion of *N*-Acyl-*N*-alkylglycine (2) to Imidazoles (3) TFAA (0.64 ml, 4.5 mmol) was added to a stirred solution of *N*-acyl-*N*-alkylglycine (1.5 mmol) in dry CH_2Cl_2 (4 ml) at 0 °C. The mixture was stirred at 25 °C for 3 h and the solvents were evaporated to dryness. The residue was dissolved in dry DMF (6 ml), and K_2CO_3 (304 mg, 2.2 mmol) and formamidine·HCl (182 mg, 2.2 mmol) were added to the DMF solution at 0 °C. The mixture was stirred at 70 °C for 2 h. After the standard workup, the residue was purified by column chromatography on silica gel with EtOAc–hexane to give the products (**3**, **4** and/or **5**).

1-Methyl-5-pentafluoropropionyl-2-phenylimidazole (**3g**), 4-Hydroxy-1-methyl-4-pentafluoroethyl-2-phenyl-4,5-dihydroimidazole (**4e**), and *N*-Methyl-*N*-[1-(2,2-dihydroxy-3,3,4,4,4-pentafluoro)butyl]benzamide (**5b**): **3g**; 60% yield from the less polar fraction (EtOAc : hexane=1 : 2), mp 95—96 °C (Et_2O–hexane). IR (Nujol) cm^{-1}: 1670. ^{1}H-NMR (500 MHz) δ: 4.00 (3H, s), 7.53—7.55 (3H, m), 7.65—7.67 (2H, m), 8.19 (1H, t, *J*=2.6 Hz). ^{13}C-NMR (127 MHz) δ: 35.46 (CH_3), 108—120 (CF_2CF_3), 127.39 (CH), 128.25 (CH), 128.96 (CH), 129.51 (CH), 130.73 (C), 143.66 (C, $^3J_{C\text{-}F}$=8.3 Hz), 156.18 (C), 172.96 (C, $^2J_{C\text{-}F}$=27 Hz). MS *m/z*: 304 (M^+, 71%), 185 (100%). *Anal.* Calcd for $C_{13}H_9F_5N_2O$: C, 51.33; H, 2.98; N, 9.21. Found: C, 51.33; H, 3.04; N, 9.34. **4e**; 14% yield from the more polar fraction (EtOAc : hexane=1 : 1), mp 183—186 °C (Et_2O). IR (Nujol) cm^{-1}: 2400—3200. ^{1}H-NMR (500 MHz) δ: 2.93 (3H, s), 3.64 (1H, d, *J*=11.9 Hz), 3.69 (1H, d, *J*=11.9 Hz), 7.44 (2H, t, *J*=7.3 Hz), 7.49 (1H, t, *J*=7.3 Hz), 7.55 (2H, d, *J*=7.3 Hz). ^{13}C-NMR (127 MHz) δ: 34.56 (CH_3), 60.19 (CH_2), 94.00 (C, $^2J_{C\text{-}F}$=27 Hz), 105—115 (CF_2CF_3), 128.50 (CH), 128.58 (CH), 129.00 (C), 130.96 (CH), 169.57 (C). MS *m/z*: 294 (M^+, 0.4%), 276 (100%). *Anal.* Calcd for $C_{12}H_{11}F_5N_2O$: C, 48.99; H, 3.77; N, 9.52. Found: C, 48.81; H, 3.86; N, 9.66. **5b**; 11% yield from the most polar fraction (EtOAc : hexane=1 : 1), oil. IR (oil) cm^{-1}: 3360, 1600. ^{1}H-NMR (500 MHz) δ: 3.05 (3H, s), 3.19+3.90 (1H, s), 4.69 (2H, s), 7.26—7.50 (3H, m), 8.08—8.10 (2H, m). ^{13}C-NMR (127 MHz) δ: 38.65 (CH_3), 53.28 (CH_2), 95.50 (C, $^2J_{C\text{-}F}$=

27 Hz), 110—120 (CF_2CF_3), 127.25 (CH), 128.39 (CH), 130.06 (CH), 133.49 (C), 171.08 (C). MS *m/z*: 276 (M^+-H_2O-F, 100%).

5-Heptafluorobutyryl-1-methyl-2-phenylimidazole (**3h**) and 4-Heptafluoropropyl-4-hydroxy-1-methyl-2-phenyl-4,5-dihydroimidazole (**4f**): **3h**; 56% yield from the less polar fraction (EtOAc : hexane=1 : 2), mp 72—73 °C (hexane). IR (Nujol) cm^{-1}: 1660. ^{1}H-NMR (500 MHz) δ: 4.00 (3H, s), 7.52—7.55 (3H, m), 7.65—7.68 (2H, m), 8.16 (1H, br s). ^{13}C-NMR (127 MHz) δ: 35.53 (CH_3), 105—120 ($CF_2CF_2CF_3$), 128.17 (CH), 128.24 (CH), 128.96 (CH), 129.53 (CH), 130.75 (C), 143.85 (C, $^3J_{C\text{-}F}$=8.3 Hz), 156.20 (C), 172.66 (C, $^2J_{C\text{-}F}$=27 Hz). MS *m/z*: 354 (M^+, 61%), 185 (100%). *Anal.* Calcd for $C_{14}H_9F_7N_2O$: C, 47.47; H, 2.56; N, 7.91. Found: C, 47.20; H, 2.67; N, 8.15. **4f**; 20% yield from the more polar fraction (EtOAc : hexane=1 : 1), mp 188—189 °C (Et_2O). IR (Nujol) cm^{-1}: 2450—3100. ^{1}H-NMR (500 MHz) δ: 2.91 (3H, s), 3.60—3.66 (2H, m), 7.43 (2H, t, *J*=7.3 Hz), 7.48 (1H, t, *J*=7.3 Hz), 7.53 (2H, d, *J*=7.0 Hz). ^{13}C-NMR (127 MHz) δ: 34.54 (CH_3), 60.26 (CH_2), 95.10 (C, $^2J_{C\text{-}F}$=28 Hz), 110—120 ($CF_2CF_2CF_3$), 128.46 (CH), 128.56 (CH), 128.71 (C), 130.85 (CH), 169.65 (C). CI-MS *m/z*: 345 (M^++1, 20%), 327 (100%). *Anal.* Calcd for $C_{13}H_{11}F_7N_2O$: C, 45.36; H, 3.22; N, 8.14. Found: C, 45.16; H, 3.31; N, 8.30.

Ethyl 1-Methyl-2-phenyl-1*H*-imidazole-5-carboxylate (6) and 5-[2′-(2-Ethoxy-1,1,1,3,3,3-heptafluoropropyl)]-1-methyl-2-phenylimidazole (7) A solution of **3a** (196 mg, 0.77 mmol) in DMF (1 ml) was added to a stirred mixture of NaH (60%) (124 mg, 3.1 mmol) in DMF (2 ml) at 0 °C, and the mixture was stirred at 60 °C for 0.5 h. After the reaction, a solution of EtI (0.25 ml, 3.1 mmol) in DMF (2 ml) was added to the reaction mixture and the mixture was stirred at 80 °C for 0.5 h. After the standard workup, the residue was purified by column chromatography on silica gel with EtOAc–hexane (1 : 2) to give **6** (110 mg, 62%) and **7** (11 mg, 4%). **6**: The less polar fraction, mp 83—84 °C (Et_2O–hexane). IR (Nujol) cm^{-1}: 1705. ^{1}H-NMR (500 MHz) δ: 1.39 (3H, t, *J*=7.2 Hz), 3.95 (3H, s), 4.35 (2H, q, *J*=7.2 Hz), 7.46—7.50 (3H, m), 7.60—7.63 (2H, m), 7.84 (1H, s). ^{13}C-NMR (127 MHz) δ: 14.39 (CH_3), 34.19 (CH_3), 60.41 (CH_2), 124.22 (C), 128.65 (CH), 129.31 (CH), 129.59 (CH), 129.74 (C), 137.18 (CH), 152.63 (C), 160.76 (C). MS *m/z*: 230 (M^+, 100%). *Anal.* Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.72; H, 6.32; N, 12.06. **7**: The more polar fraction, mp 79—80 °C (hexane). IR (Nujol) cm^{-1}: 1660. ^{1}H-NMR (500 MHz) δ: 1.35 (3H, dt, *J*=1.8, 7.0 Hz), 3.74 (2H, q, *J*=6.7 Hz), 3.79 (3H, s), 7.39 (1H, s), 7.46—7.49 (3H, m), 7.61—7.62 (2H, m). ^{13}C-NMR (127 MHz) δ: 15.04 (CH_3), 34.14 (CH_3), 62.98 (CH_2), 80.63 (C), 119.05 (CH), 122.20 (CF_3, $^1J_{C\text{-}F}$=293 Hz), 128.64 (CH), 129.44 (CH), 129.51 (CH), 130.01 (C), 133.58 (C), 152.13 (C). MS *m/z*: 352 (M^+, 57%), 255 (100%). *Anal.* Calcd for $C_{15}H_{14}F_6N_2O$: C, 51.14; H, 4.01; N, 7.95. Found: C, 51.13; H, 4.08; N, 8.05.

1-Methyl-2-phenyl-1*H*-imidazole-5-carboxaldehyde (8) A solution of ethyl ester (**6**) (196 mg, 0.85 mmol) in dry tetrahydrofuran (THF) (5 ml) was added to a suspension of lithium aluminum hydride (LAH) (65 mg, 1.7 mmol) in dry THF (3 ml) at 0 °C and the mixture was stirred at 25 °C for 3 h. The reaction was quenched with $Na_2SO_4\cdot 10H_2O$ (5 g) and filtrated through a Celite pad and washed with AcOEt (30 ml). The filtrate was evaporated to dryness and the residue was dissolved in dry CH_2Cl_2 (6 ml). MnO_2 (739 mg, 8.5 mmol) was added to the solution and the mixture was stirred at 25 °C for 3 h. The mixture was filtered through a Celite pad and the filtrate was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with EtOAc–hexane (1 : 1) to give **8** (140 mg, 88%). **8**: mp 92—94 °C (Et_2O–hexane) (mp[9] 94—95 °C). IR (Nujol) cm^{-1}: 1665. ^{1}H-NMR (500 MHz) δ: 4.01 (3H, s), 7.50—7.53 (3H, m), 7.65—7.68 (2H, m), 7.88 (1H, s), 9.78 (1H, s). ^{13}C-NMR (127 MHz) δ: 34.46 (CH_3), 128.74 (C), 128.80 (CH), 129.27 (CH), 130.16 (CH), 132.79 (C), 143.63 (CH), 154.39 (C), 179.36 (C). MS *m/z*: 186 (M^+, 100%).

1-Methyl-2-phenyl-4-trifluoromethylimidazole (9) $POCl_3$ (0.23 ml, 2.5 mmol) was added to a stirred solution of **4a** (251 mg, 1.0 mmol) in pyridine (0.73 ml, 9.0 mmol) at 0 °C and the mixture was heated at 90 °C for 2 h. The solvent was evaporated to dryness and the residue was extracted with AcOEt (40 ml×2). After the standard workup, the residue was purified by column chromatography on silica gel with EtOAc–hexane (1 : 5) to give **9** (198 mg, 88%). **9**: mp 59—60 °C (hexane) (mp[12] 61.5—62.5 °C). IR (Nujol) cm^{-1}: 1585. ^{1}H-NMR (500 MHz) δ: 3.76 (3H, s), 7.31 (1H, s), 7.45—7.48 (3H, m), 7.61—7.63 (2H, m). ^{13}C-NMR (127 MHz) δ: 34.82 (CH_3), 121.74 (CH, $^3J_{C\text{-}F}$=4.1 Hz), 121.77 (CF_3, $^1J_{C\text{-}F}$=267 Hz), 128.69 (CH), 128.95 (CH), 129.27 (C), 129.54 (CH), 131.56 (C, $^2J_{C\text{-}F}$=39 Hz), 149.06 (s). MS *m/z*: 226 (M^+, 100%).

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