HETEROCYCLES, Vol. 87, No. 12, 2013, pp. 2533 - 2553. © 2013 The Japan Institute of Heterocyclic Chemistry
Received, 12th September, 2013, Accepted, 23rd October, 2013, Published online, 1st November, 2013
DOI: 10.3987/COM-13-12838

4-TRIFLUOROACETYL-2-PHENYLOXAZOL-5-ONE: VERSATILE TEMPLATE FOR SYNTHESES OF TRIFLUOROMETHYL-SUBSTITUTED HETEROCYCLES

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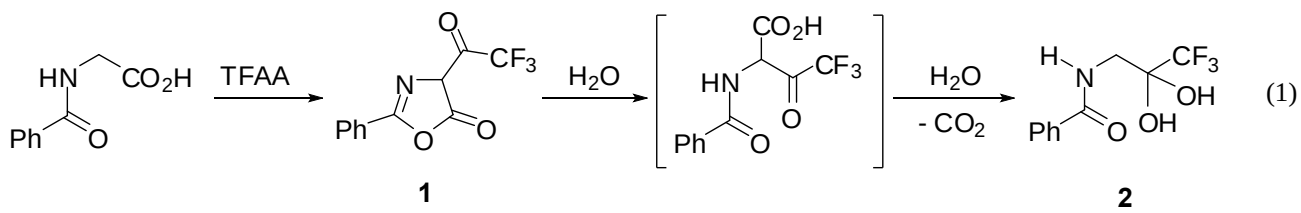
Abstract – 4-Trifluoroacetyl-2-phenyloxazol-5-one (**1**) is a versatile template for the synthesis of various trifluoromethyl-substituted heterocycles. Cyclocondesation of **1** with hydroxylamine and hydrazine afforded isoxazole and pyrazole, respectively. Another key protocol involves nucleophilic ring opening of **1** with H_2O or MeOH to give α-amido trifluoromethyl ketones which are transformed into trifluoromethyl-substituted thiazoles, oxazoles, imidazoles, pyrazoles, and pyrimidines.

INTRODUCTION

We are looking for a convenient route to a series of CF_3-substituted heterocycles[1] and since we required access to moderate quantities of compounds of this type for subsequent library synthesis,[2] the development of a more flexible approach to such structures was therefore investigated.

One of the key issues in organo-fluorine chemistry is the availability of suitably functionalized fluorinated building blocks to be used of more complex fluorinated molecular structures.[3]



1 **2** (1)

4-Trifluoroacetyl-2-phenyloxazol-5-one (4-trifluoroacetylazlactone) **1** is expected to constitute a very promising, highly reactive, yet easy-to-handle class of fluorinated building blocks. Compound **1** can be prepared in a one-step by the reaction of *N*-benzoylglycine and trifluoroacetic anhydride (TFAA) in a

high yield (Eq. 1).[4] However, the reactivity of compound **1** is nearly unexplored and **1** is involved as an intermediate in the Dakin-West reaction of *N*-benzoylglycine with TFAA and undergoes hydrolysis and subsequent decarbonylation to lead the trifluoromethyl ketone hydrate **2** (Eq. 1).[5]

In view of the unique biological properties displayed by many trifluoromethylated heterocyclic compounds[1] and in the course of our studies on the reactivities of mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates **3**,[6] we have focused our attention on the structurally related **1** as a novel fluorinated building block. Because **1** exists in three tautomeric forms **A**, **B** and **C**, in which the last one is structurally related to mesoionic **3** (Figure 1).

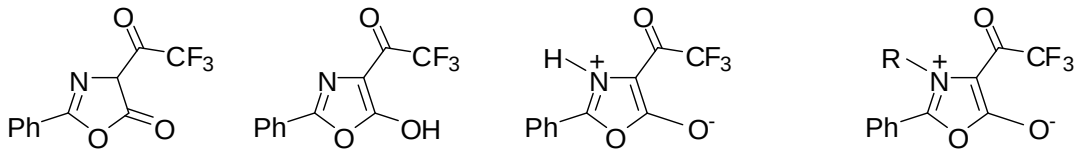


Figure 1

In this context, we decided to study the interaction of **1** with *N*- and *O*-nucleophiles such as NH_2NH_2, $PhNHNH_2$, NH_2OH, H_2O, and MeOH, in heterocyclic construction. We now report the use of **1** in the synthesis of a wide range of trifluoromethyl-substituted pyrazoles, isoxazoles, oxazoles, thiazoles, imidazoles and pyrimidines.

RESULTS AND DISCUSSION

The reactivity of 4-trifluoroacetylazlactone **1** is nearly unexplored, as one paper describing hydrolysis of **1** has been reported so far.[4] In principle, the addition of nucleophiles to **1** can a priori be expected to occur at three different positions (C-2, C-5, or COCF3). Therefore, we have now investigated the reaction of **1** and *N*-nucleophiles such as hydroxylamine, hydrazine, and phenylhydrazine which, being *bis*-nucleophilic in nature, may attack on any one of the electrophilic centers of **1**.

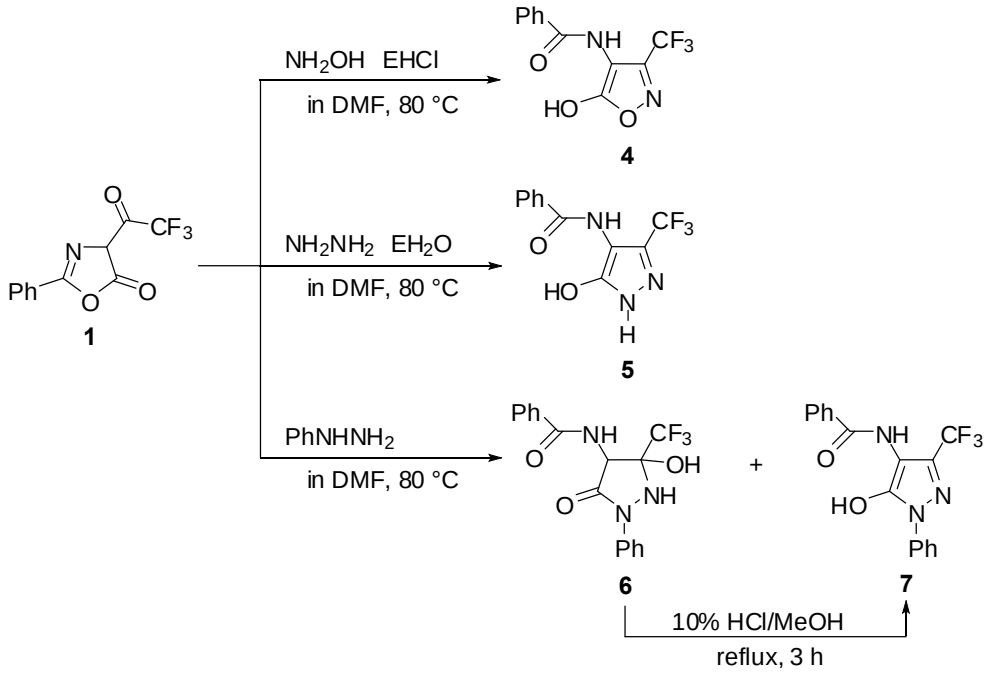
Treatment of **1** with hydroxylamine HCl (1.5 equiv) in the presence of AcONa (3 equiv) in DMF at 80 °C furnished 3-trifluoromethylisoxazole **4** in 82% yield (Table 1, entry 3). In the absence of a base to liberate the hydroxylamine from their hydrochloride salt, no desired product was observed (entry 1). Three equiv. of hydroxylamine HCl result in lower yields (entry 2).

Compound **1** reacted with hydrazine hydrate with the formation of 3-trifluoromethylpyrazole **5** (entries 4-7). At higher equiv. of hydrazine hydrate led to higher yields of product. The use of 5 equiv. of hydrazine hydrate increased the yield to 84% (entry 6).

Condensation of **1** with phenylhydrazine afforded regioselectivity. Pyrazinone **6** was obtained as the

major product, accompanying the formation of 1-phenyl-3-trifluoromethyl-5-hydroxypyrazole **7** (entry 8). Acid-catalyzed dehydration of **6** yielded the corresponding **7** in 81% yield. The structures of **4**, **5**, **6**, and **7** were unambiguously characterized by a careful analysis of the ^{13}C-NMR spectra (Scheme 2). In the ^{13}C-NMR spectra of **7**, pyrazole ring carbon atoms C3, C4, and C5 appear at 137.1 (^{2}J = 36 Hz), 99.1, and 149.9 ppm, respectively. These ^{13}C-NMR data of **6** and **7** are similar to the data for the related compounds **6x** and **7x** (Figure 2).[7]

Table 1. Reactions of 1 with bis-nucleophiles



Entry	Bis-nucleophiles (equiv.)	Base (equiv.)	Time (h)	Products (%)
1	$NH_2OH{\cdot}HCl$ (3)	none	3	**4** (0)
2	$NH_2OH{\cdot}HCl$ (3)	AcONa (3)	3	**4** (57)
3	$NH_2OH{\cdot}HCl$ (1.5)	AcONa (3)	3	**4** (82)
4	$NH_2NH_2{\cdot}H_2O$ (1.5)	none	3	**5** (20)
5	$NH_2NH_2{\cdot}H_2O$ (3)	none	3	**5** (70)
6	$NH_2NH_2{\cdot}H_2O$ (5)	none	3	**5** (84)
7	$NH_2NH_2{\cdot}H_2O$ (10)	none	3	**5** (78)
8	$PhNHNH_2$ (1.5)	none	4	**6** (62)[a]

[a] Plus **7** (10%).

In addition, the reactions are regiospecific in the synthesis of isoxazole **4** and pyrazinone **6**. The first step of the reaction always proceeds *via* attack of the more nucleophilic atom (NH_2) in hydroxylamine and phenylhydrazine to the trifluoroacetyl group. The second step is the attack of hydroxyl group (hydroxylamine) or phenyl-substituted amino group (phenylhydazine) to the lactone furnishing the compounds **4** and **6**, respectively.

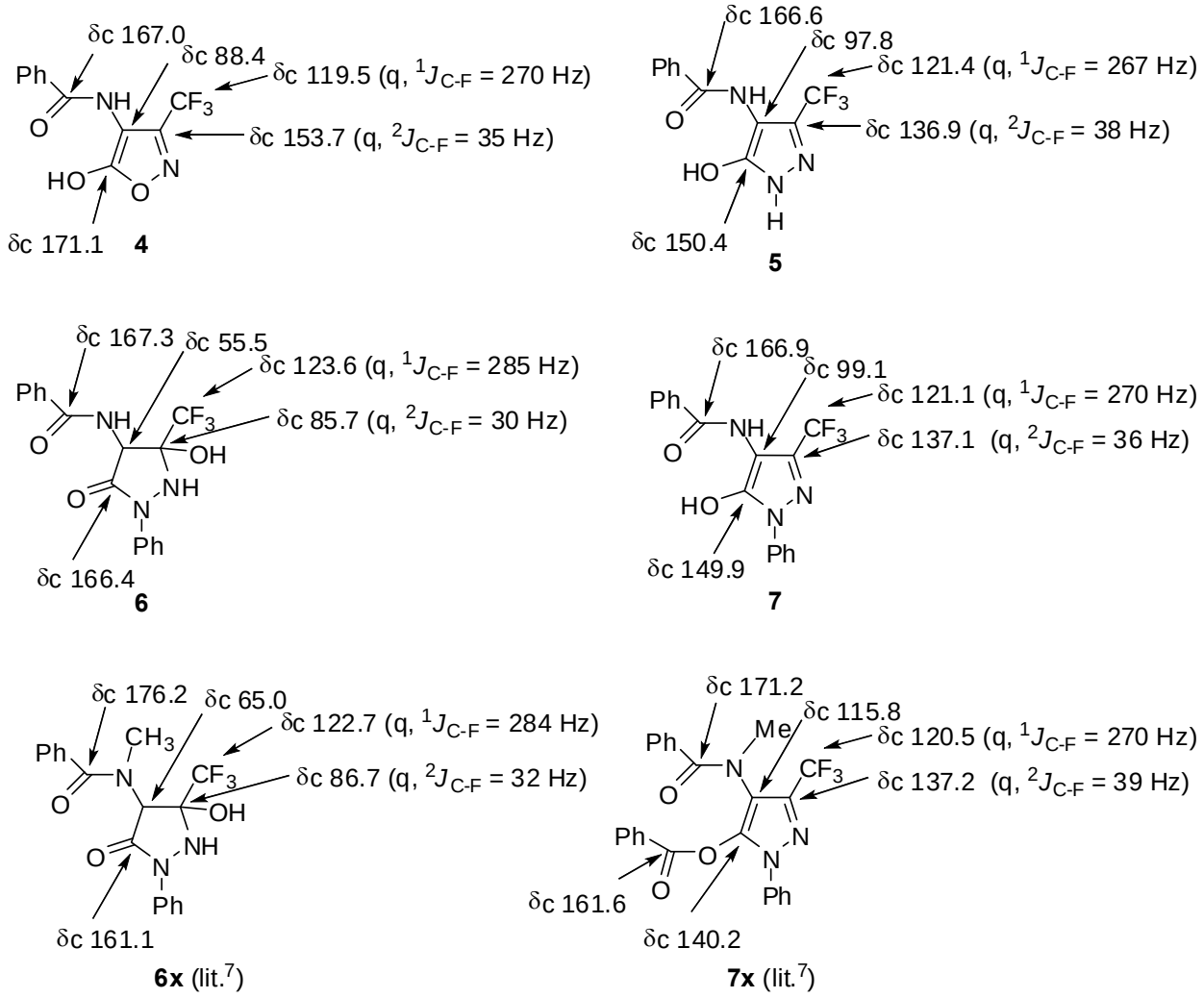
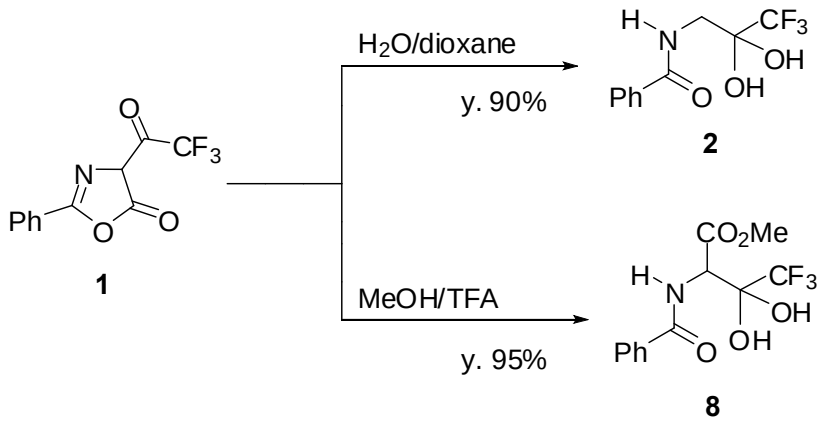


Figure 2

We next investigated ring-opening of the oxazolone ring in **1** by *O*-nucleophiles such as H_2O and MeOH (Eq. 2). Hydrolysis of 4-trifluoroacetylazlactone **1** to afford 2-benzoylamino trifluoromethyl ketone hydrate **2** is already reported.[4]



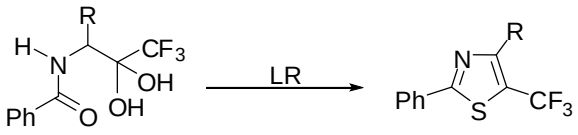
(2)

We have synthesized **2** in improved yield of 90% by slight modification of the original report. Thus, the reaction mixture was refluxed in 1,4-dioxane and H_2O (3:2) for 15 min (Eq. 2). On the other hand, to our best knowledge, reaction of **1** with alcohol was not reported. The methanolysis of **1** was performed in MeOH in the presence of trifluoroacetic acid (TFA) and the product **8** was obtained in 95% yield. These trifluoromethyl ketones readily form covalent hydrates **2** and **8**, as observed from ^{13}C NMR spectra. A characteristic feature of the ^{13}C NMR spectra of **2** and **8** in DMSO-d_6 is the appearance of a quartet at around 92 ppm (^2J = 30-31 Hz) for the hydrated carbon signals.

The non-fluorinated 2-acylamino ketones constitute interesting building blocks for further functionalization by various reactions.[8] Indeed such substrates are well-known synthons in the synthesis of azoles such as imidazoles, thiazoles, and oxazoles. Consequently, such trifluoromethylated compounds **2** and **8** should constitute very useful building blocks as starting materials in the synthesis of fluorinated molecules. Syntheses of 2-acylamino trifluoromethyl ketones were also reported by several research groups[9]; however, no attempts were made for further synthetic application of **2** as a fluorine building block for CF_3-substituted heterocycles. Therefore, their synthetic potential has not been fully explored. A close look at the structure of **8** reveals that the compound **8** contains a carbon substituted with three different reactive functional groups such as $COCF_3$, CO_2Me, and NHCOPh.

Recently, Moody and co-workers reported that ethyl esters of type **8** were obtained through the rhodium-catalyzed reaction of trifluoroacetyl diazoketoester and benzamides in low yields (32-43%), accompanying side products.[10] Several examples of subsequent cyclizations afforded CF_3-substituted oxazoles, imidazoles, and thiazoles. Obviously, our strategy provides a more simple, facile and high-yielding route to this type of compounds **8**. In our study we have chosen two compounds **2** and **8** as our readily available substrates for CF_3-substituted heterocycles.

Table 2. Formation of thiazoles



2: R=H
8: R=CO_2Me

9: R=H
10: R=CO_2Me

Entry	Compound	Solvent	LR (equiv.)	Temp (°C)	Time (h)	Yields (%)
1	**2**	DME	0.6	105	24	**9** (70)
2	**2**	xylene	0.6	158	12	**9** (58)
3	**2**	diglyme	0.6	170	12	**9** (59)
4	**2**	diglyme	0.6	170	24	**9** (69)
5	**2**	DME	1.2	103	12	**9** (60)
6	**8**	DME	0.6	105	12	**10** (78)

As expected, the treatment of both compounds **2** and **8** with Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide; LR) gave the cyclized 5-trifluoromethylthiazoles **9** and **10**, respectively (Table 2).[11] Among the solvents investigated (entries 1-3), DME is found to be the solvent of choice for the transformation. 0.6 Equivalents of LR is adequate for the conversion of **2** to **9** (entry 1). When 1.2 equiv of LR was used, the yield of **9** dropped (entry 5). Based on these results and the previous literature,[11] the reaction is likely to involve initial thionation of the amide **2** to the corresponding thioamide which undergoes intramolecular cyclization.

Table 3. Formation of oxazoles

2: R=H
8: R=CO_2Me

11: R=H
12: R=CO_2Me

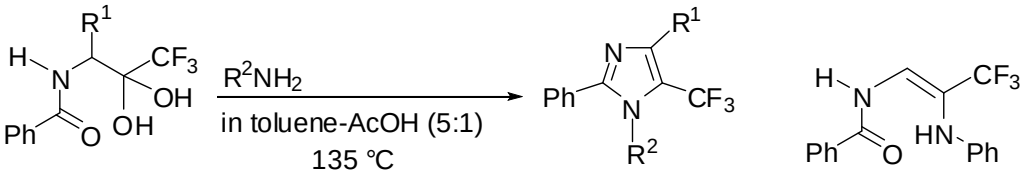
Entry	Compound	Solvent	Reagent	Time (h)	Temp (°C)	Yields of products (%)
1	**2**	toluene	phosphoryl chloride	3	80	**11** (0)
2	**2**	-	sulfuric acid	3	80	**11** (0)
3	**2**	toluene	polyphosphoric acid	6	160	**11** (0)
4	**2**	toluene	phosphorus(V) oxide	6	160	**11** (14)
5	**2**	DCE	$PPh_3{\cdot}I_2{\cdot}Et_3N$	5	rt	**11** (0)
6	**8**	DCE	$PPh_3{\cdot}I_2{\cdot}Et_3N$	4	rt	**12** (20)
7	**8**	DCE	$PPh_3{\cdot}I_2{\cdot}Et_3N$	14	rt	**12** (68)
8	**8**	toluene	phosphorus(V) oxide	6	160	**12** (27)
9	**8**	DMF	phosphoryl chloride	16	rt	**12** (14)

Historically, the cyclodehydration of 2-acylamino ketones, known as the Robinson-Gabriel reaction, is one of the most widely used synthesis of substituted oxazoles. The conversion has been accomplished using cyclodehydrating agents such as phosphoryl chloride, sulfuric acid, polyphosphoric acid, or phosphorus pentoxide. We surveyed a series of conditions that could affect cyclodehydration of **2** to yield **11** and the results are summarized in the Table 3. Thus, $POCl_3$, H_2SO_4 and PPA gave completely negative results (entries 1, 2, and 3), whereas P_2O_5 in toluene at 160 °C yielded the expected oxazole **11** in a low yield (14%) (entry 4). In 1993, Wipf and Miller introduced a new protocol based on the use of triphenylphosphine/iodine in the presence of triethylamine.[12] Cyclodehydration of **2** with Ph_3P-I_2-Et_3N under Wipf's condition resulted in negative results (entry 5). However, treatment of **8** with Ph_3P-I_2-Et_3N under Wipf's condition provided the desired oxazole **12**[13] in 68% yield (entry 7). These differences indicated that an ester substituent attached to 2-posion of the ketones **8** is necessary for the

oxazole formation using Wipf's protocol. It has been suggested that the variation in yield of the product is large by the difference in a substituent group.[12] The cyclodehydration of **8** to **12** could also be effected by P_2O_5 and $POCl_3$ in low yields (entries 8 and 9).

Next, several examples of imidazole formation were studied: simply treating both compounds **2** and **8** with ammonia or primary amines in a solution of toluene and AcOH (5:1) gave the 5-trifluoromethylimidazoles **13a**-**e** and **14a**,**b** in 36-84% yields (Table 4, entries 1-8, 11, and 12). The reactions were monitored by TLC and the optimal reaction time and temperature were determined. The yields of the products depended on the structure of amines. The reactions of **2** with aniline gave the enamide **15**, before undergoing cyclodehydration to the 1,2-diphenylimidazole **13e** (entry 9). The Z-stereochemistry of **15** was determined by the nuclear Overhauser effect (NOE) of the amido proton caused by irradiation of the aromatic protons (Figure 3).

Table 4. Formation of imidazoles



2: R^1=H
8: R^1=CO_2Me

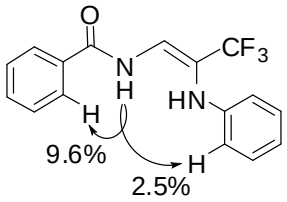
13a-e: R^1=H
14a-b: R^1=CO_2Me

15

Entry	Compound	R^1	R^2	Amine (equiv.)	Time (h)	Yields of products (%)
1	**2**	H	H	NH_4OAc (3)	8	**13a** (72)
2	**2**	H	H	NH_4OAc (10)	8	**13a** (68)
3	**2**	H	Me	$MeNH_2$·HCl (3)	8	**13b** (63)
4	**2**	H	Me	$MeNH_2$·HCl (10)	8	**13b** (84)
5	**2**	H	*n*-C_6H_{13}	hexylamine (3)	8	**13c** (79)
6	**2**	H	*n*-C_6H_{13}	hexylamine (10)	8	**13c** (75)
7	**2**	H	$PhCH_2$	benzylamine (3)	8	**13d** (24)
8	**2**	H	$PhCH_2$	benzylamine (10)	8	**13d** (36)
9	**2**	H	Ph	aniline (3)	2	**15** (72)
10[a]	**2**	H	Ph	aniline (3)	24	**13e** (45)
11	**8**	CO_2Me	H	NH_4OAc (3)	8	**14a** (45)
12	**8**	CO_2Me	Me	$MeNH_2$·HCl (3)	48	**14b** (65)

[a] $POCl_3$ (2 equiv.) was used instead of AcOH.

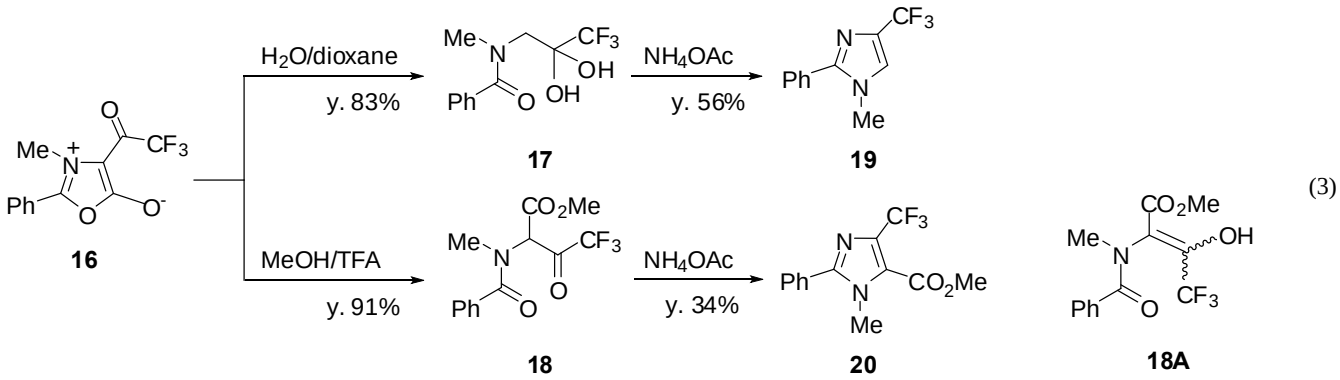
The conversion of **15** to **13e** were only moderate (up to 20%) in spite of several reactions tried. Fortunately, **13e** was directly obtained from **2** in 45% yield when the reaction was performed in the presence of $POCl_3$ instead of AcOH (entry 10).



15

Figure 3. NOE experiments in 15

The reactions of the α-amido ketone **8** with ammonium acetate and methylamine also afforded the corresponding 5-trifluoromethylimidazoles **14a** and **b** in moderate yields, respectively (entries 11 and 12).



(3)

The isomeric 4-trifluoromethylimidazoles **19** and **20** were prepared by the reactions of **17** and **18**, respectively, with ammonium acetate in moderate yields, in which both **17** and **18** were obtained by the reactions of mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olate **16** with H_2O or MeOH, respectively (Eq. 3). The ^{13}C NMR spectrum of **17** contained a hydrated carbon signal appearing at 93 ppm (quartet, $^2J_{C\text{-}F}$ = 31 Hz). However, the hydrated carbon signal was not observed in **18** which was present in an enol form **18A**, based on a quartet at 159 ppm ($^2J_{C\text{-}F}$ = 32 Hz) in the ^{13}C NMR spectrum. Previously, the 4-trifluoromethylimidazole **19** was synthesized from the reaction of mesoionic **16** with ammonium acetate, followed by dehydration of an intermediate.[14]

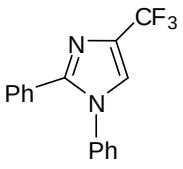
The ^{13}C-NMR spectra of 5-trifluoromethylimidazoles **13b-e** exhibited the carbon signals of C-4 at around 131 ppm (quartet, $^3J_{C\text{-}F}$ = 2-5 Hz) and C-5 at around 123 ppm (quartet, $^2J_{C\text{-}F}$ = 39 Hz). In isomeric 1-methyl-2-phenyl-4-trifluoromethylimidazoles (**19**), 1,2-diphenyl-4-trifluoromethylimidazole (**21**),[14] and 1-benzyl-2-phenyl-4-trifluoromethylimidazole (**22**),[14] the carbons of C-4 and C5 appeared at around 132 ppm (quartet, $^2J_{C\text{-}F}$ = 39 Hz) and 122 ppm (quartet, $^3J_{C\text{-}F}$ = 4 Hz), respectively. Both 4-methoxycarbonyl-5-trifluoromethylimidazoles (**14b** and **20**) showed similar ^{13}C-NMR spectra of **13b** and **19**. In the case of the 1-methyl-5-trifluoromethylimidazoles (**13b** and **14b**), we observed four-bond fluorine coupling to the 1-methyl carbon (Table 5).

Table 5. ^{13}C NMR data of 4- and 5-trifluoromethylimidazoles

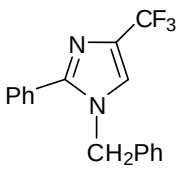
Compound	CF_3	C-2	C-4	C-5	1-methyl
13a	122.0 (q) ($^1J_{C\text{-}F}$ = 266 Hz)	150.0	133.0 (q) ($^2J_{C\text{-}F}$ = 43 Hz)	119.3 (q) ($^3J_{C\text{-}F}$ = 4.3 Hz)	-
1-Methyl series					
19	121.8 (q) ($^1J_{C\text{-}F}$ = 265 Hz)	149.1	131.4 (q) ($^2J_{C\text{-}F}$ = 39 Hz)	121.8 (q) ($^3J_{C\text{-}F}$ = 3.8 Hz)	34.8
13b	121.2 (q) ($^1J_{C\text{-}F}$ = 265 Hz)	151.7	130.6 (q) ($^3J_{C\text{-}F}$ = 2.3 Hz)	122.8 (q) ($^2J_{C\text{-}F}$ = 39 Hz)	32.7 (q) ($^4J_{C\text{-}F}$ = 1.4 Hz)
1-Phenyl series					
21[a]	121.7 (q) ($^1J_{C\text{-}F}$ = 267 Hz)	148.0	132.3 (q) ($^2J_{C\text{-}F}$ = 39 Hz)	122.2 (q) ($^3J_{C\text{-}F}$ = 4.0 Hz)	-
13e	120.5 (q) ($^1J_{C\text{-}F}$ = 265 Hz)	151.0	130.9 (q) ($^3J_{C\text{-}F}$ = 4.9 Hz)	124.5 (q) ($^2J_{C\text{-}F}$ = 39 Hz)	-
1-Benzyl series					
22[a]	121.7 (q) ($^1J_{C\text{-}F}$ = 267 Hz)	149.3	131.9 (q) ($^2J_{C\text{-}F}$ = 39 Hz)	120.6 (q) ($^3J_{C\text{-}F}$ = 4.0 Hz)	-
13d	120.9 (q) ($^1J_{C\text{-}F}$ = 265 Hz)	152.3	131.4(q) ($^3J_{C\text{-}F}$ = 3.6 Hz)	122.8 (q) ($^2J_{C\text{-}F}$ = 39 Hz)	-
14a	121.8 (q) ($^1J_{C\text{-}F}$ = 267 Hz)	148.4	135.6(q) ($^2J_{C\text{-}F}$ = 39 Hz)	121.8 (q) ($^3J_{C\text{-}F}$ = 2.5 Hz)	-
1-Methyl-4-methoxycarbonyl series					
20	121.0 (q) ($^1J_{C\text{-}F}$ = 267 Hz)	150.7	136.3(q) ($^2J_{C\text{-}F}$ = 39 Hz)	122.3 (q) ($^3J_{C\text{-}F}$ = 2.3 Hz)	34.9
14b	120.2 (q) ($^1J_{C\text{-}F}$ = 268 Hz)	150.7	133.7[b]	124.4 (q) ($^2J_{C\text{-}F}$ = 41 Hz)	34.3 (q) ($^4J_{C\text{-}F}$ = 3.4 Hz)

[a] The ^{13}C NMR data of **21** and **22** were obtained from the literature.[14]

[b] $^3J_{C\text{-}F}$ coupling was not observed.



21 (lit.[14])

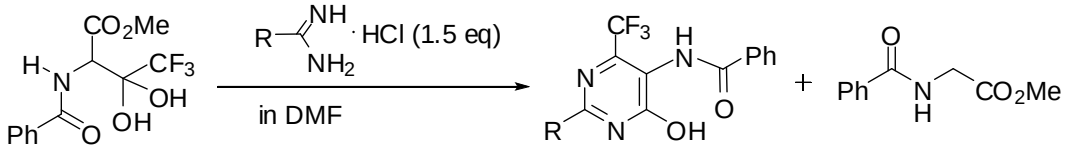


22 (lit.[14])

These data suggested that both imidazoles **13a** and **14a** are predominantly present as tautomeric 4-trifluoromethylimidazoles. According to Kamitori's work, **13a** is also suggested to be predominatly present as 4-trifluoromethylimidazole, based of *ab initio* calculation.[15]

In order to explore another utility of **8** as β-keto esters in the synthesis of trifluoromethyl heterocycles, we next investigated its reaction with amidines. The cyclizations did not take place without using a base to liberate the amidines from their hydrochloride salts (Table 6, entry 1). Thus, cyclocondensation reactions of **8** with amidines in the presence of AcONa afforded the 6-trifluoromethylpyrimidines (**23**), which was accompanied by unexpected by-product, *N*-benzoylglycine methyl ester (**24**). Several attempts to reduce the side product **24** were performed. The reaction temperature and AcONa equivalents have an effect on the outcome of this reaction. The reaction using 3 equiv AcONa at 100 °C provided a 62% of **23a**, accompanying by **24** (36%) (entry 3). Under similar conditions, formamidine and acetamidine afforded the corresponding pyrimidines **23b** and **c** in 44% and 46% yields, respectively (entries 6 and 7).

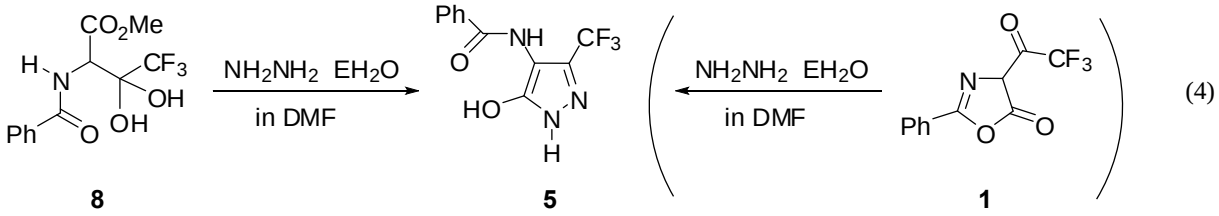
Table 6. Reactions of 8 with amidines



8 **23** **24**

Entry	R	Base (equiv.)	Temp (°C)	Time (h)	Yields of products (%)	
					23	**24**
1	Ph	none	80	3	NR	
2	Ph	$MeCO_2Na$ (3)	rt	24	**23a** (24)	23
3	Ph	$MeCO_2Na$ (3)	100	1.5	**23a** (62)	36
4	Ph	$MeCO_2Na$ (3)	120	1.5	**23a** (35)	60
5	Ph	$MeCO_2Na$ (1.5)	100	1.5	**23a** (48)	51
6	H	$MeCO_2Na$ (3)	100	1.5	**23b** (44)	52
7	Me	$MeCO_2Na$ (3)	100	1.5	**23c** (46)	48

During these reactions, we observed the formation of **24** which involves the loss of CF_3CO group. The reactions involving the loss of CF_3CO moiety are rarely reported in the literature.[16] The observed de-trifluoroacetylation reaction could occur in the presence of base, because no reaction was observed upon treating **8** with amidine at 80 °C in the absence of base and the starting material was quantitatively recovered.



8 **5** **1** (4)

Finally, we examined a reaction of **8** with hydrazine hydrate. The product **5** was obtained in 80% yield and identical with the product **5** obtained from **1** and hydrazine hydrate (Eq. 4).

In conclusion, we have found that hydroxylamine or hydrazine reacts with **1** mainly by the ring opening-ring closure (RORC) sequence and furnish the pyrazoles and isoxazoles, respectively. Facile ring opening of **1** by *O*-nucleophiles further prompted us to envisage efficient synthetic transformations based on these open-chain amide adducts such as **2** and **8** providing ready access to structurally diverse trifluoromethyl-substituted heterocycles.

EXPERIMENTAL

All melting points were determined using a Yanagimoto hot-stage melting point apparatus and are uncorrected. ^{1}H-NMR spectra were measured on Bruker AVANCE500 spectrometer with tetramethylsilane (Me_4Si) as an internal reference and $CDCl_3$ as the solvent. ^{13}C-NMR spectra were obtained on a Bruker AVANCE500 spectrometer (at 126 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 FT/IR-4100 spectrometer. Low- and high-resolution MS were obtained with a JEOL JMS-GC mate Ⅱ spectrometer with a direct inlet system at 70 eV. Elemental analyses were carried out in the microanalytical laboratory of Ehime University. Standard work-up 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 employing the reported method. ***N*-Benzoyl-*N*-methylglycine**. mp 101−104 °C (lit.,[14] mp 102−104 °C).

4-Trifluoroacetyl-3-methyl-2-phenyl-1,3-oxazolium-5-olate (16). Pale yellow crystals, 87% yield. mp 161−163 °C (AcOEt–hexane) (lit.,[14] mp 162−163 °C).

4-Trifluoroacetyl-5-hydroxy-2-phenyloxazole (1). To a stirred suspension of hippuric acid (2.00 g, 11.2 mmol) in acetone (20 mL) was added trifluoroacetic anhydride (4.65 mL, 33.5 mmol) at 0 °C under atmosphere of argon, and the solution was stirred overnight. After workup with water, the precipitate was collected and washed with water to give **1** as pink crystals, 2.56 g, 89% yield. mp 221–222 °C (dec.) (acetone–H_2O) (lit.,[4] mp 227–231 °C (dec.)). IR (KBr) ν_{max}: 3437, 3040, 2910, 1824, 1577, 1496, 1457, 1389, 1235, 1188, 1173, 1156, 815, 716, 697, 679 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.37-7.45 (m, 3H, Ar*H*), 7.76–7.83 (m, 2H, Ar*H*) ppm.

***N*-(3,3,3-Trifluoro-2,2-dihydroxypropyl)benzamide (2)**. A mixture of **1** (4.90 g, 19.1 mmol), 1,4-dioxane (28.8 mL) and water (18 mL) was heated at reflux for 15 min. After evaporated and basified with 10% sodium carbonate, the mixture was extracted with AcOEt (x 3). The combined organic layers were washed with brine, dried over anhyd sodium sulfate, and evaporated. The residue

was purified by column chromatography (silica gel, hexane:AcOEt = 1:1) to give **2** as white crystals, 4.28 g, 90% yield. mp 107−110 °C (MeOH–H_2O) (lit.,[4] mp 107−109 °C). IR (KBr) ν_{max}: 3368, 1627, 1604, 1567, 1436, 1415, 1343, 1320, 1294, 1249, 1201, 1172, 1141, 1105, 976, 943, 728, 715, 700, 632, 616 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 3.62 (d, J = 6.0 Hz, 2H, NCH_2), 7.24 (s, 2H, O*H*), 7.48–7.51 (m, 2H, Ar*H*), 7.55–7.59 (m, 1H, Ar*H*), 7.86–7.89 (m, 2H, Ar*H*), 8.53 (t, J = 5.9 Hz, 1H, N*H*) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 44.0, 92.3 (q, $^2J_{C\text{-}F}$ = 29.9 Hz), 123.6 (q, $^1J_{C\text{-}F}$ = 290.0 Hz, *C*F_3), 127.4, 128.3, 131.6, 133.7, 167.9 ppm.

***N*-(3-Trifluoromethyl-5-hydroxyisoxazol-4-yl)benzamide (4)**. To a stirred mixture of hydroxylamine hydrochloride (104 mg, 1.50 mmol) and sodium acetate (246 mg, 3.00 mmol) in DMF (5 mL) was added **1** (257 mg, 1.00 mmol) at 0 °C under atmosphere of argon, and the whole was heated at 80 °C for 3 h. After acidified with 10% HCl, the mixture was extracted with AcOEt (x 3). The combined organic layers were washed with brine, dried over anhyd sodium sulfate, and evaporated. The residue was purified by column chromatography (silica gel, hexane:AcOEt = 1:2 to 0:1) to give **4** as a pale pink hard gum, 223 mg, 82% yield. IR (neat) ν_{max}: 3281, 3066, 2923, 1651, 1515, 1485, 1192, 1152, 1004, 715, 651, 495 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 7.50–7.53 (m, 2H, Ar*H*), 7.57–7.60 (m, 1H, Ar*H*), 7.90–7.96 (m, 2H, Ar*H*), 9.55 (s, 1H, N*H*), 10.22 (br s, 1H, O*H*) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 88.4, 119.5 (q, $^1J_{C\text{-}F}$ = 270.1 Hz, *C*F_3), 127.6, 128.4, 131.8, 133.3, 153.7 (q, $^2J_{C\text{-}F}$ = 34.9 Hz), 167.0, 171.1 ppm. MS *m/z*: 272 (M^+, 51), 105 (100). HRMS (EI) for $C_{11}H_7F_3N_2O_3$ (M^+): Calcd, 272.0409. Found, 272.0405.

***N*-(3-Trifluoromethyl-5-hydroxy-1*H*-pyrazol-4-yl)benzamide (5)**. To a stirred solution of **1** (257 mg, 1.00 mmol) in DMF (5 mL) was added hydrazine monohydrate (250 mg, 5.00 mmol) at 0 °C under atmosphere of argon, and the whole was heated at 80 °C for 3 h. After acidified with 10% HCl, the mixture was extracted with AcOEt (x 3). The combined organic layers were washed with brine, dried over anhyd sodium sulfate, and evaporated. The residue was purified by column chromatography (silica gel, hexane:AcOEt = 2:1 to 1:2) to give **5** as white crystals, 228 mg, 84% yield. mp 188−189 °C (AcOEt-hexane). IR (KBr) ν_{max}: 3309, 3268, 3161, 3037, 2756, 2601, 1643, 1616, 1573, 1523, 1496, 1319, 1287, 1195, 1144, 1119, 1013, 1003, 717, 689 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 7.50 (t, J = 7.3 Hz, 2H, Ar*H*), 7.57 (t, J = 7.3 Hz, 1H, Ar*H*), 7.94 (t, J = 7.1 Hz, 2H, Ar*H*), 9.39 (s, 1H, CON*H*), 11.15 (s, 1H, N*H*), 12.95 (s, 1H, O*H*) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 97.8 (*C*-4), 121.4 (q, $^1J_{C\text{-}F}$ = 266.7 Hz, *C*F_3), 127.7 (Ar), 128.2 (Ar), 131.5 (Ar), 134.0 (Ar), 136.9 (q, $^2J_{C\text{-}F}$ = 37.5 Hz, *C*-4), 150.4 (*C*-5), 166.6 (*C*ONH) ppm. MS *m/z*: 271 (M^+, 35), 105 (100). *Anal.* Calcd for $C_{11}H_8F_3N_3O_2$: C, 48.72; H, 2.97; N, 15.49. Fond: C, 48.52; H, 3.27; N, 15.71.

***N*-(3-Trifluoromethyl-3-hydroxy-5-oxo-1-phenylpyrazolidin-4-yl)benzamide (6)**. To a stirred solution

of **1** (257 mg, 1.00 mmol) in DMF (5 mL) was added phenylhydrazine (140 μL, 1.50 mmol) at 0 °C under atmosphere of argon, and the whole was heated at 80 °C for 4 h. After workup with water, the mixture was extracted with AcOEt (x 3). The combined organic layers were washed with brine, dried over anhyd sodium sulfate, and evaporated. The residue was purified by column chromatography (silica gel, hexane:AcOEt = 1:2) to give **6** as white crystals, 245 mg, 67% yield. mp 130−132 °C ($CHCl_3$–hexane). IR (KBr) ν_{max}: 3422, 3400, 3243, 3069, 3035, 2929, 1700, 1652, 1598, 1580, 1526, 1491 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 5.53 (d, J = 9.3 Hz, 1H, 4-C*H*), 7.18 (t, J = 7.5 Hz, 1H, Ar*H*), 7.24 (s, 1H, NH), 7.42 (t, J = 7.5 Hz, 2H, Ar*H*), 7.50 (t, J = 7.3 Hz, 2H, Ar*H*), 7.59 (t, J = 7.3 Hz, 1H, Ar*H*), 7.74 (s, 1H, OH), 7.81 (dd, J = 8.7 Hz, 2H, Ar*H*), 7.94 (d, J = 7.0 Hz, 2H, Ar*H*), 8.80 (d, J = 9.3 Hz, 1H, CON*H*) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 55.5 (*C*-4), 85.7 (q, $^2J_{C\text{-}F}$ = 29.9 Hz, *C*-3), 118.7 (Ar), 123.6 (q, $^1J_{C\text{-}F}$ = 285.4 Hz, *C*F_3), 124.9 (Ar), 128.2 (Ar), 128.8 (Ar), 129.1 (Ar), 132.3 (Ar), 133.6 (Ar), 139.1 (Ar), 166.4 (*C*-5), 167.3 (s, *C*ONH) ppm. MS *m/z*: 365 (M^+, 4), 105 (100). *Anal.* Calcd for $C_{17}H_{14}F_3N_3O_3$: C, 55.89; H, 3.86; N, 11.50. Found: C, 55.61; H, 3.73; N, 11.40.

***N*-(3-Trifluoromethyl-5-hydroxy-1-phenyl-1*H*-pyrazol-4-yl)benzamide (7)**. To a stirred solution of **6** (205 mg, 0.562 mmol) in MeOH (2 mL) was added 10% aq HCl (2 mL) at rt, and the mixture was stirred for 3 h. After workup with water, the mixture was extracted with AcOEt (x 3). The combined organic layers were washed with brine, dried over anhyd sodium sulfate, and evaporated. The residue was purified by column chromatography (silica gel, hexane:AcOEt = 1:1) to give **7** as pale yellow crystals, 158 mg, 81% yield. mp 108–110 °C ($CHCl_3$–hexane). IR (KBr) ν_{max}: 3305, 3077, 3035, 1623, 1551, 1524, 1479, 1342, 1311, 1178, 1148, 1125, 1008, 761, 714, 693, 642 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 7.42 (t, J = 7.4 Hz, 1H, Ar*H*), 7.51–7.61 (m, 5H, Ar*H*), 7.75 (d, 2H, J = 7.5 Hz, Ar*H*), 7.98 (d, 2H, J = 7.5 Hz, Ar), 9.57 (s, 1H, N*H*), 12.48 (s, 1H, O*H*) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 99.1 (*C*-4), 121.1 (q, $^1J_{C\text{-}F}$ = 269.8 Hz, *C*F_3), 122.1, 127.3, 127.7, 128.3, 129.2, 131.6, 133.8, 137.1 (q, $^2J_{C\text{-}F}$ = 35.6 Hz, *C*-3), 137.9, 149.9 (*C*-5), 166.9 (*C*ONH) ppm. MS *m/z*: 347 (M^+, 41), 105 (100). *Anal.* Calcd for $C_{17}H_{12}F_3N_3O_2$: C, 58.79; H, 3.48; N, 12.10. Fond: C, 58.56; H, 3.27; N, 12.11.

Methyl 2-(benzamido)-4,4,4-trifluoro-3,3-dihydroxybutanoate (8). To a stirred solution of **1** (1.29g, 5.00 mmol) in MeOH (15 mL) was added trifluoroacetic acid (0.37 mL, 1.00 mmol) at 0 °C under atmosphere of argon, and the whole was stirred at rt for 5 h. After removal of the solvent, the residue was purified by column chromatography (silica gel, hexane:AcOEt = 1:1) to give **8** as a white solid, 1.46 g, 95% yield. mp 93–95 °C (MeOH–H_2O). IR (KBr) ν_{max}: 3505, 3373, 3138, 2971, 1762, 1637, 1535, 1408, 1346, 1250, 1185, 1140, 1108, 1072, 973, 733, 708, 696, 624, 614 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 3.70 (s, 3H, OCH_3), 5.02 (d, J = 9.0 Hz, 1H, C*H*), 7.52 (t, J = 7.5 Hz, 2H, Ar*H*), 7.59 (t, J = 7.5 Hz, 1H, Ar*H*), 7.67 (br s, 2H, OH), 7.88 (d, J = 7.0 Hz, 2H, Ar*H*), 8.28 (d, J = 9.0 Hz, 1H, N*H*) ppm.

^{13}C NMR (125 MHz, DMSO-d_6) δ 52.1, 55.9, 92.5 (q, $^{2}J_{C\text{-}F}$ = 30.9 Hz, *C*CF_3), 123.0 (q, $^{1}J_{C\text{-}F}$ = 288.1 Hz, *C*F_3), 127.3, 128.5, 131.9, 133.2, 166.2, 168.5 ppm. MS *m/z*: 289 ([M–H_2O]$^+$, 2.4), 105 (100). *Anal.* Calcd for $C_{12}H_{12}F_3NO_5$: C, 46.91; H, 3.94; N, 4.56. Found: C, 46.93; H, 3.94; N, 4.60.

5-Trifluoromethyl-2-phenylthiazole (9). A mixture of **2** (249 mg, 1.00 mmol) and Lawesson's reagent (243 mg, 0.600 mmol) in 1,2-dimethoxyethane (DME, 5 mL) was heated at reflux under atmosphere of argon for 24 h. After removal of solvent, the residue was purified by column chromatography (silica gel, hexane:AcOEt = 9:1) to give **9** as white crystals, 160 mg, 70% yield. mp 45−47 °C (MeOH-H_2O). IR (KBr) ν_{max}: 3065, 1532, 1455, 1432, 1329, 1314, 1299, 1153, 1135, 1117, 1029, 763, 687, 635 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.51 (m, 3H, Ar*H*), 7.96–7.97 (m, 2H, Ar*H*), 8.12 (s, 1H, *H*-4) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 122.1 (q, $^{1}J_{C\text{-}F}$ = 268.9 Hz, *C*F_3), 126.2 (q, $^{2}J_{C\text{-}F}$ = 38.2 Hz, *C*-5), 126.9 (Ar), 129,2 (Ar), 131.3 (Ar), 132.5 (Ar), 144.4 (q, $^{3}J_{C\text{-}F}$ = 3.8 Hz, *C*-4), 171.9 (*C*-2) ppm. MS *m/z*: 229 (M$^+$, 100). *Anal.* Calcd for $C_{10}H_6F_3NS$: C, 52.40; H, 2.64; N, 6.11. Fond: C, 52.32; H, 2.89; N, 6.16.

Methyl 5-trifluoromethyl-2-phenylthiazole-4-carboxylate (10). A mixture of **8** (308 mg, 1.00 mmol) and Lawesson's reagent (243 mg, 0.600 mmol) in DME (5 mL) was heated at reflux under atmosphere of argon for 12 h. After removal of solvent, the residue was purified by column chromatography (silica gel, hexane:AcOEt = 9:1) to give **10** as white crystals, 224 mg, 78% yield. mp 68–69 °C (MeOH–H_2O). IR (KBr) ν_{max}: 3046, 2953, 1728, 1526, 1462, 1440, 1372, 1345, 1314, 1295, 1243, 1157, 1138, 1030, 1001, 972, 793, 765, 747, 687, 650 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.02 (s, 3H, OCH_3), 7.47–7.54 (m, 3H, Ar*H*), 7.98 (d, *J* = 7.5 Hz, 2H, Ar*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 53.0, 121.1 (q, $^{1}J_{C\text{-}F}$ = 270.7 Hz, *C*F_3), 127.1, 129.3, 131.2 (q, $^{2}J_{C\text{-}F}$ = 40.1 Hz, *C*-5), 131.6, 131.8, 146.0 (q, $^{3}J_{C\text{-}F}$ = 2.5 Hz, *C*-4), 160.7, 169.0 (*C*-2) ppm. MS *m/z*: 287 (M$^+$, 100). *Anal.* Calcd for $C_{12}H_8F_3NO_2S$: C, 50.17; H, 2.81; N, 4.88. Fond: C, 50.06; H, 3.04; N, 5.01.

5-Trifluoromethyl-2-phenyloxazole (11). A mixture of **2** (249 mg, 1.00 mmol) and phosphorus(V) oxide (278 mg, 1.00 mmol) in toluene was heated at reflux with Dean–Stark trap under atmosphere of argon for 7 h. After workup with 10% aq sodium carbonate, the mixture was extracted with AcOEt (x 3). The combined organic layers were washed with brine, dried over anhyd sodium sulfate, and evaporated. The residue was purified by column chromatography (silica gel, hexane:AcOEt = 9:1) to give **11** as a colorless oil, 30 mg, 14% yield. IR (neat) ν_{max}: 3066, 1365, 1325, 1179, 1136, 1110, 964, 926 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50–7.55 (m, 4H, Ar*H*, *H*-4), 8.08–8.10 (m, 2H, Ar*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 119.0 (q, $^{1}J_{C\text{-}F}$ = 266.3 Hz, *C*F_3), 126.1, 127.1, 129.0, 129.4 (q, $^{3}J_{C\text{-}F}$ = 2.6 Hz, *C*-4), 131.7, 139.6 (q, $^{2}J_{C\text{-}F}$ = 43.9 Hz, *C*-5), 163.7 ppm. MS *m/z*: 213 (M$^+$, 13), 105 (100). HRMS (EI) for $C_{10}H_6F_3NO$ (M$^+$): Calcd, 213.0402. Found, 213.0396.

Methyl 5-trifluoromethyl-2-phenyloxazole-4-carboxylate (12). To a mixture of triphenylphosphine

(157 mg, 0.600 mmol) and iodine (152 mg, 0.600 mmol) in 1,2-dichloroethane (DCE, 20 mL) was added a solution of **8** (92 mg, 0.300 mmol) and triethylamine (167 μL, 1.20 mmol) in DCE (5 mL) at rt under atmosphere of argon. The whole was stirred for 14 h and evaporated. The residue was purified by column chromatography (silica gel, hexane:AcOEt = 10:1) to give **12** as a white powder, 111 mg, 68% yield. mp 80–82 °C (MeOH–H_2O) (lit.,[13] mp 80.7−82.3 °C). IR (KBr) ν_{max}: 2968, 1752, 1601, 1562, 1490, 1481, 1450, 1428, 1377, 1322, 1311, 1277, 1186, 1168, 1148, 1081, 1068, 1035, 1023, 951, 810, 751, 715, 691 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 4.01 (s, 3H, OC*H*$_3$), 7.50–7.58 (m, 3H, Ar*H*), 8.13–8.15 (m, 2H, Ar*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 53.0, 118.3 (q, $^1J_{C\text{-}F}$ = 268.1 Hz, *C*F$_3$), 125.1, 127.4, 129.1, 132.4, 133.3 (q, $^3J_{C\text{-}F}$ = 1.9 Hz, *C*-4), 142.1 (q, $^2J_{C\text{-}F}$ = 44.3 Hz, *C*-5), 159.9, 162.0 ppm. MS *m/z*: 271 (M^+, 100). *Anal.* Calcd for $C_{12}H_8F_3NO_3$: C, 53.15; H, 2.97; N, 5.16. Fond: C, 53.07; H, 2.73; N, 5.40.

General procedure for the synthesis of 5-trifluoromethyl-1*H*-imidazoles (13a–d). A mixture of **2** (249 mg, 1.00 mmol) and amine (3 or 10 equiv) in toluene (5 mL) and acetic acid (1 mL) was heated at 135 °C for 8 h under atmosphere of argon. After evaporated and basified with 10% sodium carbonate, the mixture was extracted with AcOEt (x 3). The combined organic layers were washed with brine, dried over anhyd sodium sulfate, and evaporated. The residue was purified by column chromatography (silica gel, hexane:AcOEt = 4:1) to give **13a**–**d**.

4-Trifluoromethyl-2-phenyl-1*H*-imidazole (13a). White solid, 72% yield. mp 210−212 °C (MeOH–H_2O) (lit.,[15] mp 212−213 °C). IR (KBr) ν_{max}: 2758, 1589, 1548, 1487, 1461, 1408, 1360, 1182, 1160, 1138, 1119, 945, 808, 730, 695, 686 cm^{-1}. ^1H NMR (500 MHz, CD_3OD) δ 7.41–7.49 (m, 3H, Ar*H*), 7.62 (s, 1H, *H*-5), 7.90 (d, *J* = 7.5 Hz, 2H, Ar*H*) ppm. ^{13}C NMR (125 MHz, CD_3OD) δ 119.3 (q, $^3J_{C\text{-}F}$ = 4.3 Hz, *C*-5), 123.4 (q, $^1J_{C\text{-}F}$ = 266.0 Hz, *C*F$_3$), 127.0, 130.1, 130.5, 130.7, 133.0 (q, $^2J_{C\text{-}F}$ = 42.8 Hz, *C*-4), 150.0 ppm. MS *m/z*: 212 (M^+, 100).

5-Trifluoromethyl-1-methyl-2-phenyl-1*H*-imidazole (13b). White solid, 84% yield. mp 122−124 °C (MeOH–H_2O) (lit.,[17] mp 118−120 °C). IR (KBr) ν_{max}: 3073, 3008, 2969, 1562, 1475, 1456, 1412, 1376, 1312, 1282, 1249, 1225, 1167, 1147, 1120, 1099, 1078, 1077, 936, 850, 775, 749, 729, 717, 700, 679 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 3.77 (s, 3H, Me-*H)*, 7.49–7.50 (m, 4H, Ar-*H*, *H*-4), 7.59–7.60 (m, 2H, Ar*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.7 (q, $^4J_{C\text{-}F}$ = 1.4 Hz, N*C*H$_3$) , 121.8 (q, $^1J_{C\text{-}F}$ = 265.3 Hz, *C*F$_3$), 122.8 (q, $^2J_{C\text{-}F}$ = 38.9 Hz, *C*-5), 128.7, 128.9, 129.3, 129.5, 130.6 (q, $^3J_{C\text{-}F}$ = 2.3 Hz, *C*-4), 151.7 ppm. MS *m/z*: 226 (M^+, 80), 225 (100).

5-Trifluoromethyl-1-*n*-hexyl-2-phenyl-1*H*-imidazole (13c). Pale yellow oil, 79% yield. IR (neat) ν_{max}: 2932, 1563, 1462, 1447, 1420, 1323, 1242, 1159, 1057, 776, 700 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.82 (t, *J* = 7.1 Hz, 3H, C*H*$_3$), 1.11–1.26 (m, 6H, C*H*$_2$C*H*$_2$C*H*$_2$), 1.63–1.69 (m, 2H, C*H*$_2$), 4.08 (t,

J = 8.0 Hz, 2H, NCH_2), 7.48–7.52 (m, 4H, Ar*H* and *H*-4), 7.55–7.58 (m, 2H, Ar*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 22.2, 26.0, 30.5, 30.8, 45.9, 121.2 (q, $^1J_{C\text{-}F}$ = 270.6 Hz, *C*F_3), 122.1 (q, $^2J_{C\text{-}F}$ = 32.9 Hz, *C*-5), 128.7, 129.1, 129.7, 130.1, 131.0 (q, $^3J_{C\text{-}F}$ = 3.6 Hz, *C*-4), 151.6 ppm. MS *m/z*: 296 (M^+, 43), 252 (100). HRMS (EI) for $C_{16}H_{19}F_3N_2$ (M^+): Calcd, 296.1500. Found, 296.1511.

1-Benzyl-5-trifluoromethyl-2-phenyl-1*H*-imidazole (13d). Yellow solid, 36% yield. mp 80−82 °C (MeOH–H_2O). IR (KBr) ν_{max}: 3060, 1557, 1456, 1444, 1417, 1362, 1321, 1255, 1178, 1164, 1154, 1110, 1058, 983, 869, 776, 744, 724, 698, 680 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.34 (s, 2H, ArCH_2), 6.92–6.94 (m, 2H, Ar*H*), 7.26–7.32 (m, 3*H*, Ar*H*), 7.36–7.39 (m, 3*H*, Ar*H*), 7.41–7.44 (m, 2*H*, Ar*H*), 7.47–7.48 (m, 1*H*, *H*-4) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 49.0, 120.9 (q, $^1J_{C\text{-}F}$ = 265.4 Hz, *C*F_3), 122.8 (q, $^2J_{C\text{-}F}$ = 39.1 Hz, *C*-5), 125.6, 127.8, 128.7, 128.8, 129.3, 129.6, 129.9, 136.6, 131.4 (q, $^3J_{C\text{-}F}$ = 3.6 Hz, *C*-4), 152.3 ppm. MS *m/z*: 302 (M^+, 35), 91 (100). *Anal.* Calcd for $C_{17}H_{13}F_3N_2$: C, 67.54; H, 4.33; N, 9.27. Found: C, 67.44; H, 4.16; N, 9.15.

5-Trifluoromethyl-1,2-diphenyl-1*H*-imidazole (13e). To a stirred solution of **2** (249 mg, 1.00 mmol) in toluene (1 mL) was added aniline (273 μL, 3.00 mmol) and phosphoryl chloride (186 μL, 2.00 mmol) at rt under atmosphere of argon, and the mixture was heated at 135 °C for 24 h. After evaporated and acidified with 2% HCl, the mixture was extracted with AcOEt (x 3). The combined organic layers were washed with brine, dried over anhyd sodium sulfate, and evaporated. The residue was purified by column chromatography (silica gel, hexane:AcOEt = 9:1) to give **13e** as a white solid, 130 mg, 45% yield. mp 115−116 °C (MeOH–H_2O). IR (KBr) ν_{max}: 3058, 2923, 1561, 1496, 1442, 1417, 1292, 1200, 1165, 1109, 664 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.69–7.15 (m, 5H, Ar*H*), 7.17–7.30 (m, 2H, Ar*H*), 7.35–7.37 (m, 3H, Ar*H*), 7.63 (s, 1H, N*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 120.5 (q, $^1J_{C\text{-}F}$ = 265.4 Hz, *C*F_3), 124.5 (q, $^2J_{C\text{-}F}$ = 38.8 Hz, *C*-5), 128.1, 128.3, 128.8, 129.0, 129.3, 129.5, 129.8, 130.9 (q, $^3J_{C\text{-}F}$ = 4.9 Hz, *C*-4), 135.7, 151.0 ppm. MS *m/z*: 288 (M^+, 100). *Anal.* Calcd for $C_{16}H_{11}F_3N_2$: C, 66.66; H, 3.85; N, 9.72. Found: C, 66.71; H, 3.94; N, 9.50.

General procedure for the synthesis of methyl 5-trifluoromethyl-1*H*-imidazole-4-carboxylates (14a–b). A mixture of **8** (307 mg, 1.00 mmol) and amine (3 or 10 equiv) in toluene (5 mL) and acetic acid (1 mL) was heated at 135 °C for 8 or 48 h under atmosphere of argon. After evaporated and basified with 10% sodium carbonate, the mixture was extracted with AcOEt (x 3). The combined organic layers were washed with brine, dried over anhyd sodium sulfate, and evaporated. The residue was purified by column chromatography (silica gel, hexane:AcOEt = 4:1) to give **14a–b**.

Methyl 4-trifluoromethyl-2-phenyl-1*H*-imidazole-4-carboxylate (14a). White solid, 49% yield. mp 184−185 °C (MeOH–H_2O). IR (KBr) ν_{max}: 3296, 2962, 1542, 1463, 1450, 1300, 1277, 1210, 1165, 1155, 1139, 1055, 961, 785, 694 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.98 (s, 3H, CH_3), 7.48–7.50 (m,

3H, Ar*H*), 7.93–7.95 (m, 2H, Ar*H*), 10.46 (s, 1H, N*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.2, 121.8 (q, $^1J_{C\text{-}F}$ = 267.2 Hz, *C*F_3), 121.8 (q, $^3J_{C\text{-}F}$ = 2.5 Hz, *C*-4), 126.8, 126.9, 128.6, 129.9, 135.6 (q, $^2J_{C\text{-}F}$ = 38.8 Hz, *C*-5), 148.4, 159.2 ppm. MS *m/z*: 270 (M^+, 72), 238 (100). *Anal.* Calcd for $C_{12}H_9F_3N_2O_2$: C, 53.34; H, 3.36; N, 10.37. Found: C, 53.50; H, 3.54; N, 10.43.

Methyl 5-trifluoromethyl-1-methyl-2-phenyl-1*H*-imidazole-4-carboxylate (14b). Pale yellow oil, 65% yield. IR (neat) ν_{max}: 2954, 2847, 1563, 1408, 1458, 1438, 1402, 1336, 1289, 1213, 1186, 1161, 1121, 1086, 1056, 1030, 826, 777, 701, 448 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.79 (s, 3H, NCH_3), 3.95 (s, 3H, OCH_3), 7.49–7.52 (m, 3H, Ar*H*), 7.57–7.59 (m, 2H, Ar*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.3 (q, $^4J_{C\text{-}F}$ = 3.4 Hz, N*C*H_3), 52.4, 120.2 (q, $^1J_{C\text{-}F}$ = 267.7 Hz, *C*F_3), 124.4 (q, $^2J_{C\text{-}F}$ = 40.5 Hz, *C*-5), 128.2, 128.7, 129.7, 130.2, 133.7 (*C*-4), 150.7, 161.9 ppm. MS *m/z*: 284 (M^+, 100). HRMS (EI) for $C_{13}H_{11}F_3N_2O_2$ (M^+): Calcd, 284.0773. Found, 284.0786.

***N*-(3,3,3-Trifluoro-2-(phenylamino)prop-1-enyl)benzamide (15)**. To a stirred solution of **2** (996 mg, 4.00 mmol) in xylene (20 mL) and acetic acid (4 mL) was added aniline (1.09 mL, 12.0 mmol) at rt under atmosphere of argon, and the whole was heated at 135 °C for 8 h. After evaporated and acidified with 10% HCl, the mixture was extracted with AcOEt (x 3). The combined organic layers were washed with brine, dried over anhyd sodium sulfate, and evaporated. The residue was purified by column chromatography (silica gel, hexane:AcOEt = 9:1) to give **15** as a brown oil, 955 mg, 78% yield. IR (neat) ν_{max}: 3296, 3069, 1729, 1602, 1497, 1368, 1249, 1200, 712 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.16 (br s, 1H, ArN*H*), 6.74 (d, *J* = 7.7 Hz, 2H, NAr*H*-2), 6.88 (t, *J* = 7.4 Hz, 1H, NAr*H*-4), 7.24 (dt, *J* = 7.4, 1.2 Hz, 2H, NAr*H*-3), 7.30 (t, *J* = 7.6 Hz, 2H, COAr*H*-3), 7.45 (t, *J* = 7.5 Hz, 1H, COAr*H*-4), 7.49 (dd, *J* = 8.2, 1.2 Hz, 2H, COAr*H*-2), 7.73 (dd, *J* = 11.2, 0.8 Hz, 1H, C*H*), 7.93 (d, *J* = 11.0 Hz, 1H, CON*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 111.3 (q, $^2J_{C\text{-}F}$ = 34.3 Hz, CF_3C), 114.6 (NAr*C*-2), 120.5 (NAr*C*-4), 122.9 (q, $^3J_{C\text{-}F}$ = 4.5 Hz, *C*H), 123.0 (q, $^1J_{C\text{-}F}$ = 271.0 Hz, *C*F_3), 127.3 (COAr*C*-2), 128.9 (COAr*C*-3), 129.8 (NAr*C*-3), 132.2 (COAr*C*-1), 132.8 (COAr*C*-4), 142.9 (NAr*C*-1), 164.4 (*C*O) ppm. MS *m/z*: 306 (M^+, 57), 105 (100). HRMS (EI) for $C_{16}H_{13}F_3N_2O$ (M^+): Calcd, 306.0980. Found, 306.0973.

Conversion of 15 to 13e: To a stirred solution of **15** (100 mg, 0.327 mmol) in toluene (2 mL) was added phosphoryl chloride (61 mL, 0.654 mmol) at rt under atmosphere of argon, and the mixture was stirred for 2 h. After evaporated and basified with 20% sodium carbonate, the mixture was extracted with AcOEt (x 3). The combined organic layers were washed with brine, dried over anhyd sodium sulfate, and evaporated. The residue was purified by column chromatography (silica gel, hexane:AcOEt = 9:1) to give **13e** as a brown solid, 19 mg, 20% yield.

***N*-Methyl-*N*-(3,3,3-trifluoro-2,2-dihydroxypropyl)benzamide (17)**. To a stirred solution of **16** (3.00 g,

10.3 mmol) in 1,4-dioxane (18 mL) was added water (9 mL) at rt, and the mixture was heated at 110 °C for 15 min. After evaporated and basified with 10% sodium carbonate, the mixture was extracted with AcOEt (x 3). The combined organic layers were washed with brine, dried over anhyd sodium sulfate, and evaporated. The residue was purified by column chromatography (silica gel, hexane:AcOEt = 4:1) to give **17** as a yellow powder, 2.25 g, 83% yield. mp 85–87 °C ($CHCl_3$–hexane) (lit.,[18] mp 90−92 °C). IR (KBr) ν_{max}: 3290, 3069, 2500, 1596, 1575, 1509, 1482, 1460, 1436, 1409, 1372, 1297, 1226, 1174, 1146, 1128, 1103, 1076, 1017, 939, 805, 792, 728, 706, 692, 572, 432 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 3.07 and 3.14 (s, 3H, NC*H*$_3$), 3.89 and 4.66 (s, 2H, C*H*$_2$), 5.70 (s, 1H, O*H*), 7.43-7.50 (s, 5H, Ar*H*) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 34.7, 51.1, 92.8 (q, $^2J_{C\text{-}F}$ = 30.8 Hz, *C*CF_3), 123.5 (q, $^1J_{C\text{-}F}$ = 292.4 Hz, *C*F_3), 126.9, 128.3, 129.6, 132.8, 172.0 ppm.

Methyl 2-(*N*-methylbenzamido)-4,4,4-trifluoro-3,3-dihydroxybutanoate (18). A solution of **16** (272 mg, 1.00 mmol) in MeOH (3 mL) was stirred at rt for 4 h. After removal of the solvent, the residue was purified by column chromatography (silica gel, hexane: AcOEt = 1:1) to give **18** as a yellow oil, 276 mg, 91% yield. IR (neat) ν_{max}: 3434, 3028, 2832, 2673, 2566, 1751, 1676, 1602, 1583, 1454, 1423, 1325, 1295, 1203, 1181, 1130, 1072, 1025, 929, 802, 701, 683, 665, 602, 547, 517 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 2.58 and 2.61 (s, 3H, NC*H*$_3$), 3.78 and 3.99 (s, 3H, OC*H*$_3$), 7.48–7.51 (m, 2H, Ar*H*), 7.60–7.63 (m, 1H, Ar*H*), 7.95–7.97 (m, 2H, Ar*H*) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 32.5, 48.0, 52.5, 117.0 (q, $^1J_{C\text{-}F}$ = 298.6 Hz, *C*F_3), 128.5, 129.2, 130.8, 132.7, 158.7 (q, $^2J_{C\text{-}F}$ = 31.7 Hz, *C*CF_3), 167.3, 168.1 ppm. MS *m/z*: 303 (M^+, 8), 60 (100). HRMS (EI) for $C_{13}H_{12}F_3NO_4$ (M^+): Calcd, 303.0718. Found, 303.0707.

4-Trifluoromethyl-1-methyl-2-phenylimidazole (19). A mixture of **17** (263 mg, 1.00 mmol) and ammonium acetate (770 mg, 10.0 mmol) in toluene (5 mL) and acetic acid (1 mL) was heated at 135 °C for 8 h under atmosphere of argon. After evaporated and basified with 10% sodium carbonate, the mixture was extracted with AcOEt (x 3). The combined organic layers were washed with brine, dried over anhyd sodium sulfate, and evaporated. The residue was purified by column chromatography (silica gel, hexane:AcOEt = 4:1) to give **19** as a white solid, 127 mg, 56% yield. mp 56–57 °C (hexane) (lit.,[14] mp 59–60 °C). IR (KBr) ν_{max}: 2957, 2925, 1584, 1476, 1398, 1371, 1251, 1209, 1155, 1114, 1099, 1075, 1048, 962, 799, 776, 730, 710, 703, 681 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 3.77 (s, 3H, NC*H*$_3$), 7.31–7.49 (m, 4H, Ar*H* and *H*-4), 7.62–7.64 (m, 2H, Ar*H*) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 34.8, 121.8 (q, $^1J_{C\text{-}F}$ = 265.3 Hz, *C*F_3), 121.8 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, *C*-4), 128.7, 128.9, 129.3, 129.5, 131.4 (q, $^2J_{C\text{-}F}$ = 38.5 Hz, *C*-5), 149.1 ppm. MS *m/z*: 226 (M^+, 100), 225 (M^+, 100).

Methyl 4-trifluoromethyl-1-methyl-2-phenyl-1*H*-imidazole-5-carboxylate (20). A mixture of **18** (307 mg, 1.01 mmol) and ammonium acetate (770 mg, 10.0 mmol) in toluene (5 mL) and acetic acid (1

mL) was heated at 135 °C for 8 h under atmosphere of argon. After evaporated and basified with 20% sodium carbonate, the mixture was extracted with AcOEt (x 3). The combined organic layers were washed with brine, dried over anhyd sodium sulfate, and evaporated. The residue was purified by column chromatography (silica gel, hexane:AcOEt = 4:1) to give **20** as a white solid, 98 mg, 34% yield. mp 84–85 °C (MeOH–H_2O). IR (KBr) ν_{max}: 2959, 2703, 1725, 1692, 1642, 1542, 1442, 1410, 1367, 1349, 1293, 1259, 1213, 1162, 1136, 1051, 447 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 3.94 and 3.96 (s, 3H, NC*H*$_3$ and OC*H*$_3$), 7.59–7.61 (m, 2H, Ar*H*), 7.50 (m, 3H, Ar*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.9, 52.3, 121.0 (q, $^1J_{C\text{-}F}$ = 267.2 Hz, *C*F$_3$), 122.3 (q, $^3J_{C\text{-}F}$ = 2.3 Hz, *C*-5), 128.5, 128.8, 129.5, 130.2, 136.3 (q, $^2J_{C\text{-}F}$ = 38.6 Hz, *C*-4), 150.7, 160.0 ppm. MS *m/z*: 284 (M^+, 100). *Anal.* Calcd for $C_{13}H_{11}F_3N_2O_2$: C, 54.93; H, 3.90; N, 9.86. Found: C, 55.06; H, 3.74; N,9.86.

***N*-(4-Trifluoromethyl-6-hydroxy-2-phenylpyrimidin-5-yl)benzamide (23a) and Methyl 2-(benzamide)acetate (24)**. To a mixture of benzamidine hydrochloride (235 mg, 1.50 mmol) and sodium acetate (246 mg, 3.00 mmol) in DMF (6 mL) was added **8** (307 mg, 1.00 mmol) at 0 °C under atmosphere of argon, and the whole was heated at 100 °C for 1.5 h. After workup with satd aq ammonium chloride, the mixture was extracted with AcOEt (x 3). The combined organic layers were washed with brine, dried over anhyd sodium sulfate, and evaporated. The residue was washed with cold *tert*-butyl methyl ether to give **23a** as a white solid, 223 mg, 62% yield. The mother liquor was concentrated and washed with the same solvent to give **24** as a pale yellow crystals, 64 mg, 36% yield. **23a**: mp >300 °C ($CHCl_3$–hexane). IR (KBr) ν_{max}: 3223, 3068, 2975, 1685, 1655, 1604, 1558, 1507, 1486, 1405, 1315, 1289, 1202, 1185, 1139, 987, 720, 691 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 7.56–7.65 (m, 6H, Ar*H*), 7.96–8.00 (m, 2H, Ar*H*), 8.17 (s, 2H, Ar*H*), 9.98 (s, 1H, CON*H*), 13.65 (s, 1H, O*H*) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 120.9 (q, $^1J_{C\text{-}F}$ = 274.6 Hz, *C*F$_3$), 123.1, 127.8, 128.0, 128.5, 128.8, 131.1, 132.0, 132.4, 133.2, 146.5, 156.2, 160.9, 162.3, 166.2 ppm. MS *m/z*: 359 (M^+, 18) 105 (100). *Anal.* Calcd for $C_{18}H_{12}F_3N_3O_2$: C, 60.17; H, 3.37; N, 11.69. Found: C, 60.36; H, 3.51; N, 11.41. **24**: mp 77–80 °C (lit.,[19] mp 82–83 °C). IR (KBr) ν_{max}: 3223, 3068, 2975, 1685, 1655, 1604, 1558, 1507, 1486, 1405, 1315, 1289, 1202, 1185, 1139, 987, 720, 691 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 3.81 (s, 3H, COOC*H*$_3$), 4.26 (d, *J* = 5.0 Hz, 2H, C*H*$_2$), 6.68 (br s, 1H, N*H*), 7.44 (t, *J* = 7.3 Hz, 2H, Ar*H*), 7.52 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.82 (d, *J* = 7.1 Hz, 2H, Ar*H*) ppm.

***N*-(4-Trifluoromethyl-6-hydroxypyrimidin-5-yl)benzamide (23b) and 24**. To a mixture of formamidine hydrochloride (120 mg, 1.50 mmol) and sodium acetate (246 mg, 3.00 mmol) in DMF (6 mL) was added **8** (307 mg, 1.00 mmol) at 0 °C under atmosphere of argon, and the whole was heated at 100 °C for 1.5 h. After workup with satd aq ammonium chloride, the mixture was extracted with AcOEt (x 3). The combined organic layers were washed with brine, dried over anhyd sodium sulfate, and

evaporated. The residue was purified by column chromatography (silica gel, hexane:AcOEt = 1:1) to give **24**, 93 mg, 52% yield. Further elution with tha same solvent gave **23b** as a white solid, 125 mg, 44% yield. **23b**: mp >300 °C ($CHCl_3$–hexane). IR (KBr) ν_{max}: 3218, 3155, 2931, 1718, 1628, 1577, 1562, 1525, 1488, 1427, 1389, 1352, 1296, 1247, 1200, 1142, 969, 819, 806, 717, 688, 640 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 7.53–7.64 (m, 3H, Ar*H*), 7.94–7.96 (m, 2H, Ar*H*), 8.37 (s, 1H, *H*-2), 9.92 (s, 1H, CON*H*), 13.44 (s, 1H, O*H*) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 120.9 (q, $^1J_{C\text{-}F}$ = 274.6 Hz, *C*F_3), 125.6, 127.7, 128.5, 132.1, 133.1, 146.5 (q, $^2J_{C\text{-}F}$ = 31.7 Hz, *C*CF_3), 149.1, 159.1, 166.1 ppm. MS *m/z*: 283 (M^+, 51), 105 (100). *Anal.* Calcd for $C_{12}H_8F_3N_3O_2$: C, 50.89; H, 2.85; N, 14.84. Found: C, 50.72; H, 2.96; N, 14.72.

***N*-(4-Trifluoromethyl-6-hydroxy-2-methylpyrimidin-5-yl)benzamide (23c) and 24**. To a mixture of acetamidine hydrochloride (142 mg, 1.50 mmol) and sodium acetate (246 mg, 3.00 mmol) in DMF (6 mL) was added **8** (307 mg, 1.00 mmol) at 0 °C under atmosphere of argon, and the whole was heated at 100 °C for 1.5 h. After workup with satd aq ammonium chloride, the mixture was extracted with AcOEt (x 3). The combined organic layers were washed with brine, dried over anhyd sodium sulfate, and evaporated. The residue was purified by column chromatography (silica gel, hexane:AcOEt = 1:1) to give **24**, 86 mg, 48% yield. Further elution with tha same solvent gave **23c** as a white solid, 137 mg, 46% yield. **23c**: mp 290–295 °C ($CHCl_3$–hexane). IR (KBr) ν_{max}: 255, 3218, 1715, 1627, 1574, 1531, 1513, 1486, 1446, 1405, 1303, 1290, 1238, 1223, 1200, 1183, 1169, 1131, 1046, 721, 690 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 2,40 (s, 3H, CH_3), 7.52–7.64 (m, 3H, Ar*H*), 7.94–7.96 (m, 2H, Ar*H*), 9.83 (s, 1H, CON*H*), 13.29 (s, 1H, O*H*) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 21.1, 120.9 (q, $^1J_{C\text{-}F}$ = 274.6 Hz, *C*F_3), 122.7, 127.7, 128.4, 131.9, 133.2, 146.4 (q, $^2J_{C\text{-}F}$ = 31.4 Hz, *C*CF_3), 158.9, 160.0, 166.1 ppm. MS *m/z*: 297 (M^+, 36), 105 (100). *Anal.* Calcd for $C_{13}H_{10}F_3N_3O_2$: C, 52.53; H, 3.39; N, 14.14. Found: C, 52.68; H, 3.48; N, 14.20.

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