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CYCLOCONDENSATION REACTION OF MESOIONIC 4-TRIFLUOROACETYL-1,3-OXAZOLIUM-5-OLATES WITH HYDROXYLAMINE AFFORDING 6-TRIFLUOROMETHYL-5,6-DIHYDRO-4*H*-1,2,4-OXADIAZIN-6-OLS

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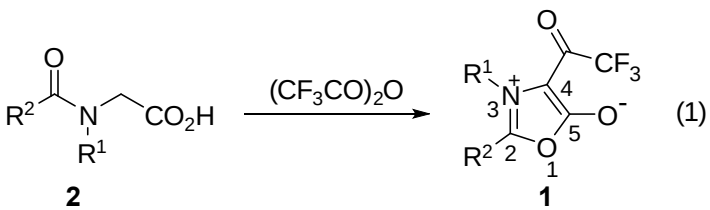
Abstract – Mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates (**1**) undergo tandem addition of hydroxylamine to afford 6-trifluoromethyl-1,2,4-oxadiazin-6-ols (**3**) in high yields.

INTRODUCTION

Trifluoromethyl-substituted heterocyclic compounds continue to receive much attention since many of them sometimes exhibit unique chemical, physiological or physical properties.[1] Therefore, development of new efficient methodologies for the preparation of fluorinated heterocycles is strongly required. One of the most attractive methods for the construction of these heterocyles is based on the use of easily available fluorine-containing building blocks.[2] Recently, we have focused on mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates (**1**) which were easily prepared from *N*-acyl-*N*-alkylglycines (**2**) in a one step through the cyclodehydration by trifluoroacetic anhydride followed by trifluoroacetylation at C-4 position of an intermediary mesoionic 1,3-oxazolium-5-olate (Eq. 1).[3]



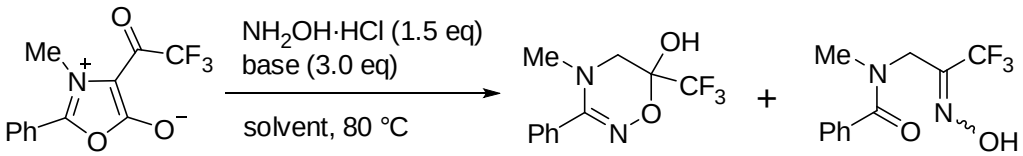
2 **1** (1)

These trifluoroacetylated mesoionic oxazoles (**1**) represent a very reactive system owing to the presence of the electrophilic carbon atoms at C-2, C-5 and trifluoroacetyl group. Therefore, the rich reactivity of **1** can be expected to enable a wide variety of transformation, which makes **1** extremely useful synthons for trifluoromethyl-substituted heterocycles such as imidazoles, pyrazoles, triazines, and pyrroles.[3] In line with this continuing interest, we report the reaction of the mesoionic oxazoles (**1**) with hydroxylamine leading to the formation of 6-trifluoromethyl-1,2,4-oxadiazines in excellent yields. Thus, with the nucleophile, the tandem addition to the C-2 position of the mesoionic ring and to the trifluoromethyl ketone yielded 6-trifluoromethyl-1,2,4-oxadiazines (**3**).

RESULTS AND DISCUSSION

Table 1 shows the results when 4-trifluoroacetyl-1,3-oxazolium-5-olate (**1a**) was allowed to react with hydroxylamine under various conditions. The best result was obtained by the reaction of **1a** (1 mmol) with hydroxylamine hydrochloride (1.5 mmol) in DMF (5 mL) in the presence of sodium acetate (3 mmol) at 80 °C for 3 h: 6-trifluoromethyl-1,2,4-oxadiazine **3a** was isolated in 95% yield (entry 1). The effect of the base on the yield of **3a** was briefly investigated (entries 1, 4, and 7).

Table 1. Condensation of 4-trifluoroacetyl-1,3-oxazolium-5-olate (**1a**) with hydroxylamine under various conditions

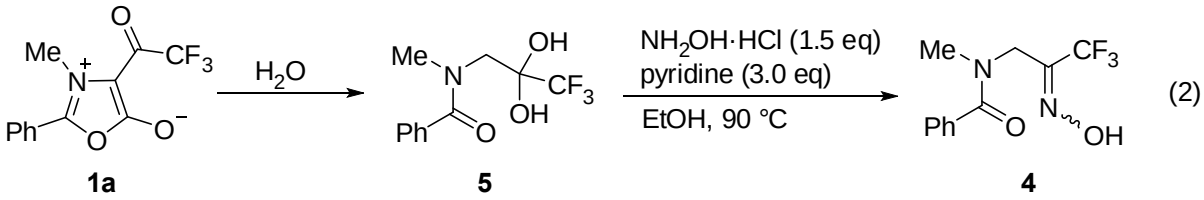


1a **3a** **4**

Entry	Base	Solvent	Time (h)	Yields of products (%)	
				3a	**4**
1	$MeCO_2Na$	DMF	3	95	–
2	$MeCO_2Na$	toluene	3.5	complex mixture	
3	$MeCO_2Na$	1,2-dichloroethane	24	4.5	6
4	K_2CO_3	DMF	3.5	74	–
5	K_2CO_3	toluene	1.5	24	–
6	K_2CO_3	1,2-dichloroethane	24	8	8
7	CF_3CO_2Na	DMF	2	44[a]	22[a]
8	CF_3CO_2Na	1,2-dichloroethane	10	3[b]	7[b]

[a] The yield was determined by ^{1}H NMR. [b] Crude yield.

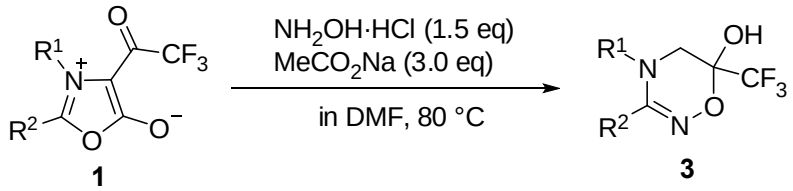
Sodium acetate gave the best yield of **3a** in DMF as a solvent (entry 1). The reaction of **1a** with hydroxylamine could proceed in other solvents, such as toluene and 1,2-dichloroethane, but the conversion was very low. Sometimes, the side product oxime (**4**) was isolated in low yields. The oxime (**4**) was identical with an authentic sample prepared in 74% yield by the reaction of *N*-methyl-*N*-(3,3,3-trifluoro-2,2-dihydroxypropyl)benzamide (**5**),[4] which was obtained by the hydrolysis of **1a**, with hydroxylamine in pyridine-EtOH (Eq. 2).



1a **5** **4** (2)

With the optimized conditions in hand, the scope of the reaction substrates was investigated. The results are summarized in Table 2. The reaction is efficient in both 3-alkyl- and 3-aryl-substituted mesoionic compounds (entries 1, 2, 4, and 5). However, 2-methyl-substituted mesoionic compounds (**1b** and **1d**) gave slightly lower yields compared to 2-aryl-substituted compounds (**1a** and **1e**). 2-*tert*-Butyl-substituted mesoionic compounds (**1c** and **1f**) also gave the desired 1,2,4-oxadiazines (entries 3 and 6).

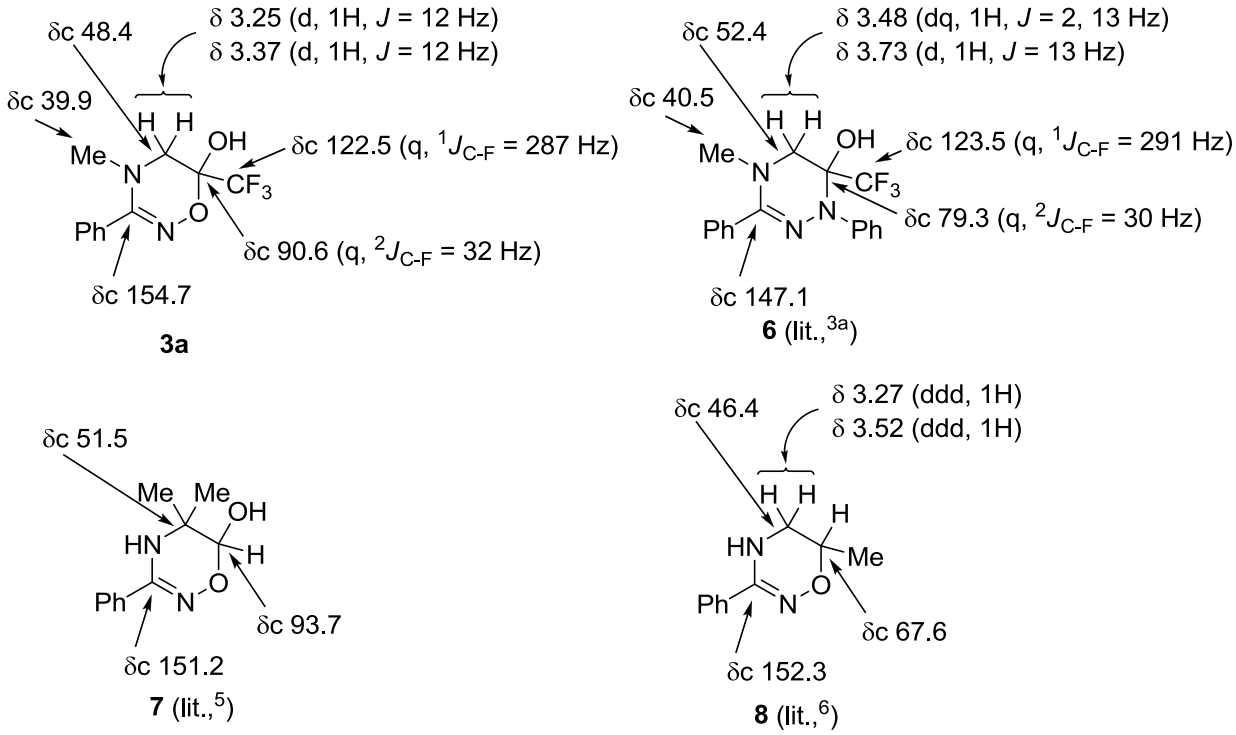
Table 2. Condensation of 4-trifluoroacetyl-1,3-oxazolium-5-olate (**1**) with hydroxylamine



1 **3**

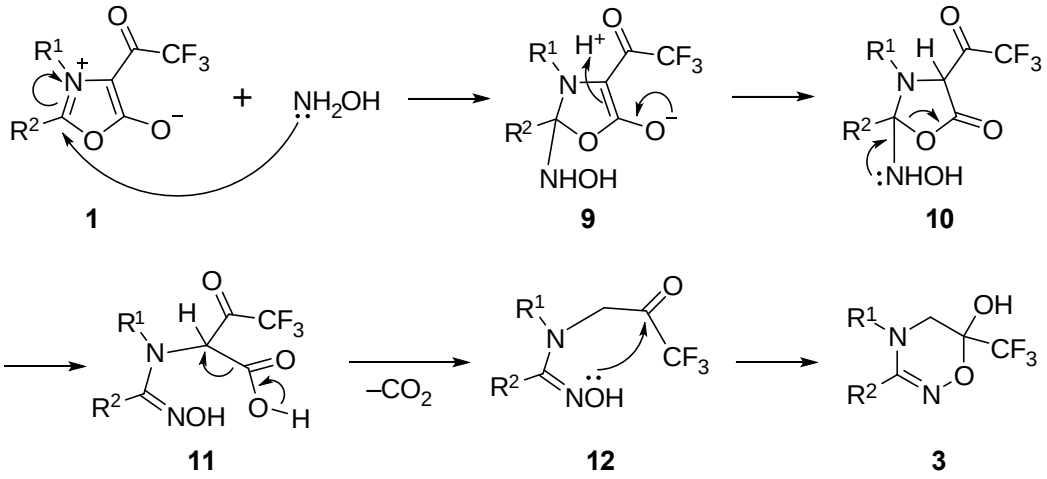
Entry	**1**	R^1	R^2	Time (h)	Yields of **3** (%)
1	**a**	Me	Ph	3	**3a** (95)
2	**b**	Bn	Me	4	**3b** (68)
3	**c**	Ph	*t*-Bu	3	**3c** (97)
4	**d**	Ph	Me	5	**3d** (54)
5	**e**	Ph	Ph	4	**3e** (88)
6	**f**	Me	*t*-Bu	3	**3f** (74)

The structures of **3a-f** are supported by spectral and analytical data. The presence of the CF_3 group in **3a-f** was determined on the basis of long-range ^{13}C-^{19}F coupling. Thus, the carbons of the CF_3 group and C-6 appear at around δ 122.5 ppm (quartet, $^1J_{C\text{-}F}$ = 287 Hz) and δ 90.6 ppm (quartet, $^2J_{C\text{-}F}$ = 32 Hz), respectively. The ^{1}H-NMR spectrum of **3a** exhibited the methylene signal of C-5 at δ 3.25 ppm (d, 1H, J = 12 Hz) and 3.37 ppm (d, 1H, J = 12 Hz). These ^{1}H- and ^{13}C-NMR data are similar to the data for the 6-trifluoromethyl-1,4,5,6-tetrahydro-4-methyl-1,3-diphenyl-1,2,4-triazin-6-ol (**6**),[3a] 5,5-dimethyl-3-phenyl-1,2,4-oxadiazin-6-ol (**7**)[5] and 6-methyl-3-phenyl-1,2,4-oxadiazine (**8**)[6] as shown in Scheme 1.



Scheme 1

A plausible mechanism is described in Scheme 2. Thus, nucleophilic attack of the nitrogen of hydroxylamine on C-2 of **1** gives rise to an adduct (**9**). The scission of the bond of C-2 and O-1 in **10** gives an open-chain intermediate (**11**), which extrudes carbon dioxide to provide the ketone (**12**). Finally, intramolecular cyclization of **12** affords **3**.



Scheme 2

The 1,2,4-oxadiazine compounds possess interesting pharmacological properties such as diuretic, antiphlogistic, peripheral vasodilative, coronary flow increasing, and hypotensive effects.[7] However, the 1,2,4-oxadiazine core belongs to an underutilized class of heterocycles and there are only a handful of methods for the synthesis of 5,6-dihydro-4*H* -1,2,4-oxadiazines: (a) condensation of arylamidoximes and glyoxal,[8] chloroacetyl chloride,[9] ethyl γ-bromoacetoacetate,[10] or 1,2-diaza-1,3-butadienes,[11] (b) reaction of oxazolines and hydroxylamine,[5] and (c) acid-catalyzed isomerization of aziridin-1-yl oximes.[6,12] In spite of the importance of fluorine molecules, 1,2,4-oxadiazines containing trifluoromethyl substituent have not yet been described.

In summary, we developed the first efficient and regiospecific preparation of 6-trifluoromethyl-5,6-dihydro-4*H*-1,2,4-oxadiazines. The method appears to be useful and convenient in terms of the ready accessibility of the starting materials, cheap reagents, operational simplicity, and high overall yields.

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.,[13] mp 102−104 °C). ***N*-Acetyl-*N*-benzylglycine**. mp 118−119 °C (lit.,[14] mp 118−119 °C). ***N*-Phenyl-*N*-pivaloylglycine**. mp 123−124 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (s, 9H, CC*H*$_3$), 4.27 (s, 2H, NC*H*$_2$), 7.36-7.40 (m, 5H, Ar*H*). ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.2, 40.7, 55.1, 128.6, 129.3, 129.5, 143.8, 174.1, 178.7. ***N*-Acetyl-*N*-phenylglycine**. mp 196−198 °C (mp[15] 193−195 °C). ***N*-Benzoyl-*N*-phenylglycine**. mp 126−128 °C (lit.,[13] mp 127−129 °C). ***N*-Methyl-*N*-pivaloylglycine**. mp 75−76 °C (lit.,[4] mp 75−76 °C).

General Procedure for Preparation of 4-Trifluoroacetyl-1,3-oxazolium-5-olates (1): To a stirred suspension of *N*-acyl-*N*-alkylglycine (5.2 mmol) in AcOEt (10 mL) was added TFAA (2.2 mL, 15.6 mmol) at 0 °C, and the solution was stirred at rt for 3 h. To the mixture was added hexane, and the precipitate was collected and recrystallized from hexane/AcOEt to give the product **1**.

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

3-Benzyl-4-trifluoroacetyl-2-methyl-1,3-oxazolium-5-olate (1b).[3a] White crystals, 67% yield. mp 143−144 °C. HRMS (EI) for $C_{13}H_{10}F_3NO_3$ (M^+): Calcd, 285.0613. Found, 258.0626.

2-*tert*-Butyl-4-trifluoroacetyl-3-phenyl-1,3-oxazolium-5-olate (1c). Yellow crystals, 60% yield. mp 174−175 °C. IR (KBr) ν_{max}: 2985, 1880, 1639, 1551, 1357, 1259, 1201, 1148, 831, 779, 734, 705 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (s, 9H, CC*H*$_3$), 7.35–7.37 (m, 2H, Ar*H*), 7.53–7.62 (m, 3H, Ar*H*). ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.5 (C*C*H$_3$), 36.8 (*C*CH$_3$), 97.4, 116.6 (q, $^1J_{C\text{-}F}$ = 289.4 Hz, *C*F$_3$), 126.9, 129.5, 131.1, 134.3, 157.5, 163.3, 166.1 (q, $^2J_{C\text{-}F}$ = 37.3 Hz, *C*CF$_3$). MS *m/z*: 313 (M^+, 66), 58 (100). *Anal.* Calcd for $C_{15}H_{14}F_3NO_3$: C, 57.51; H, 4.50; N, 4.47. Found: C, 57.23; H, 4.62; N, 4.46.

4-Trifluoroacetyl-2-methyl-3-phenyl-1,3-oxazolium-5-olate (1d). White crystals, 90% yield. mp 200−203 °C (lit.,[16] mp 211−212 °C).

4-Trifluoroacetyl-2,3-diphenyl-1,3-oxazolium-5-olate (1e). Yellow crystals, 81% yield. mp 194−196 °C (lit.,[16] mp 194−196 °C).

2-*tert*-Butyl-4-trifluoroacetyl-3-methyl-1,3-oxazolium-5-olate (1f). White crystals, 67% yield. mp 120−121 °C (lit.,[4] mp 120−121 °C).

General Procedure for Synthesis of 6-Trifluoromethyl-1,2,4-oxadiazin-6-ols (3): A mixture of hydroxylamine hydrochloride (104 mg, 1.50 mmol) and sodium acetate (246 mg, 3.00 mmol) in DMF (5 mL) was stirred at 0 °C for 10 min under atmosphere of argon. To the mixture was added

4-trifluoroacetyl-1,3-oxazolium-5-olate **1** (1.00 mmol), and the whole was stirred at 80 °C for an additional several hours. After workup with 10% aqueous Na_2CO_3, the mixture was extracted with AcOEt (x 3). The combined organic layers were washed with brine, dried over anhyd Na_2SO_4, and evaporated. The residue was purified by column chromatography (silica gel, hexane:AcOEt = 2:1) to give the product **3**.

6-Trifluoromethyl-5,6-dihydro-4-methyl-3-phenyl-4*H*-1,2,4-oxadiazin-6-ol (3a). White crystals, 95% yield. mp 163−164 °C ($CHCl_3$-hexane). IR (KBr) ν_{max}: 3032, 1602, 1577, 1413, 1368, 1335, 1272, 1200, 1051, 1024, 979, 770, 704 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 2.86 (s, 3H, NC*H*$_3$), 3.37 (d, *J* = 11.8 Hz, 1H, NC*H*), 3.52 (d, *J* = 11.7 Hz, 1H, NC*H*), 4.85 (br s, 1H, O*H*), 7.41-7.48 (m, 5H, Ar*H*) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ 39.9 (N*C*H$_3$), 48.4 (N*C*H$_2$), 90.6 (q, $^2J_{C\text{-}F}$ = 31.7 Hz, CF_3C), 122.5 (q, $^1J_{C\text{-}F}$ = 287.3 Hz, *C*F$_3$), 128.4, 128.7, 129.8, 131.5, 154.7 (*C*N) ppm. MS *m/z*: 260 (M^+, 100). *Anal.* Calcd for $C_{11}H_{11}F_3N_2O_2$: C, 50.77; H, 4.26; N, 10.77. Found: C, 50.63; H, 4.01; N, 10.70.

4-Benzyl-6-trifluoromethyl-5,6-dihydro-3-methyl-4*H*-1,2,4-oxadiazin-6-ol (3b). White crystals, 68% yield. mp 187−189 °C ($CHCl_3$-hexane). IR (KBr) ν_{max}: 3040, 1614, 1207, 1190 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 2.08 (s, 3H, C*H*$_3$), 3.20 (d, *J* = 11.4 Hz, 1H, NC*H*), 3.39 (d, *J* = 11.5 Hz, 1H, NC*H*), 4.37 (d, *J* = 16.5 Hz, 1H, PhC*H*), 4.62 (d, *J* = 16.6 Hz, 1H, PhC*H*), 6.04 (br s, 1H, O*H*), 7.26-7.27 (m, 2H, Ar*H*), 7.32-7.34 (m, 1H, Ar*H*), 7.38-7.41 (m, 2H, Ar*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 16.6 (*C*H$_3$), 47.0, 54.4, 90.9 (q, $^2J_{C\text{-}F}$ = 32.7 Hz, *C*CF$_3$), 122.1 (q, $^1J_{C\text{-}F}$ = 284.9 Hz, *C*F$_3$), 126.6, 128.0, 129.2, 135.5, 152.4 (*C*N) ppm. MS *m/z*: 274 (M^+, 100). *Anal.* Calcd for $C_{12}H_{13}F_3N_2O_2$: C, 52.56; H, 4.78; N, 10.21. Found: C, 52.22; H, 4.52; N, 10.05.

3-*tert*-Butyl-6-trifluoromethyl-5,6-dihydro-4-phenyl-4*H*-1,2,4-oxadiazin-6-ol (3c). White crystals, 97% yield. mp 156−158 °C ($CHCl_3$-hexane). IR (KBr) ν_{max}: 3161, 2993, 2962, 1562, 1214, 1181, 1145 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.12 (s, 9H, CC*H*$_3$), 3.33 (br s, 1H, O*H*), 3.54 (d, *J* = 12.5 Hz, 1H, NC*H*), 3.58 (d, *J* = 12.4 Hz, 1H, NC*H*), 7.27-7.30 (m, 3H, Ar*H*), 7.35-7.38 (m, 2H, Ar*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 30.2 (C*C*H$_3$), 38.7 (*C*CH$_3$), 51.6 (N*C*H$_3$), 92.2 (q, $^2J_{C\text{-}F}$ = 32.8 Hz, *C*CF$_3$), 121.8 (q, $^1J_{C\text{-}F}$ = 286.4 Hz, *C*F$_3$), 127.5, 128.8, 129.2, 146.2, 160.3 (*C*N) ppm. MS *m/z*: 302 (M^+, 12), 252 (100). *Anal.* Calcd for $C_{14}H_{17}F_3N_2O_2$: C, 55.62; H, 5.67; N, 9.27. Found: C, 55.32; H, 5.74; N, 9.26.

6-Trifluoromethyl-5,6-dihydro-3-methyl-4-phenyl-4*H*-1,2,4-oxadiazin-6-ol (3d). White crystals, 54% yield. mp 169−170 °C ($CHCl_3$-hexane). IR (KBr) ν_{max}: 3071, 3043, 3025, 1616, 1593, 1200, 1179, 1158 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.81 (s, 3H, C*H*$_3$), 3.58 (d, *J* =11.6 Hz, 1H, NC*H*) , 3.76 (d, *J* = 11.6 Hz, 1H, NC*H*), 6.25 (br s, 1H, O*H*), 7.26-7.29 (m, 2H, Ar*H*), 7.35 (m, 1H, Ar*H*), 7.41-7.43 (m, 2H, Ar*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.5 (*C*H$_3$), 50.8 (N*C*H$_2$), 90.6 (q, $^2J_{C\text{-}F}$ =

32.7 Hz, *C*CF_3), 122.2 (q, $^1J_{C\text{-}F}$ = 286.2 Hz, *C*F_3), 127.9, 128.2, 129.9, 142.2, 151.7 (*C*N) ppm. MS *m/z*: 260 (M^+, 100). *Anal.* Calcd for $C_{11}H_{11}F_3N_2O_2$: C, 50.77; H, 4.26; N, 10.77. Found: C, 50.61; H, 4.18; N, 10.74.

6-Trifluoromethyl-5,6-dihydro-3,4-diphenyl-4*H*-1,2,4-oxadiazin-6-ol (3e). White crystals, 88% yield. mp 186−187 °C ($CHCl_3$-hexane). IR (KBr) ν_{max}: 3054, 1590, 1552, 1494, 1359, 1304, 1233, 1203, 1189, 1146, 1088, 1065, 985, 768, 694 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.88 (d, *J* = 12.0 Hz, 1H, NC*H*), 3.96 (d, *J* = 12.0 Hz, 1H, NC*H*), 4.09 (br s, 1H, O*H*), 6.94 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.06 (t, *J* = 7.4 Hz, 1H, Ar*H*), 7.15-7.29 (m, 5H, Ar*H*), 7.38 (d, *J* = 8.5 Hz, 2H, Ar*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 49.8 (N*C*H_2), 92.4 (q, $^2J_{C\text{-}F}$ = 33.0 Hz, CF_3*C*), 121.8 (q, $^1J_{C\text{-}F}$ = 286.5 Hz, *C*F_3), 125.5, 128.2, 129.1, 129.9, 131.1, 144.8, 153.6 (*C*N) ppm. MS *m/z*: 322 (M^+, 100). *Anal.* Calcd for $C_{16}H_{13}F_3N_2O_2$: C, 59.63; H, 4.07; N, 8.69. Found: C, 59.59; H, 3.84; N, 8.72.

3-*tert*-Butyl-6-trifluoromethyl-5,6-tetrahydro-4-methyl-4*H*-1,2,4-oxadiazin-6-ol (3f). White crystals, 74% yield. mp 99−101 °C ($CHCl_3$-hexane). IR (KBr) ν_{max}: 3088, 2996, 1583, 1323, 1185, 1162, 1126, 991 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32 (s, 9H, CCH_3), 3.16 (s, 3H, NCH_3), 3.19 (d, *J* = 11.9 Hz, 1H, NC*H*), 3.36 (d, *J* = 11.9 Hz, 1H, NC*H*), 3.79 (br s, 1H, O*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.8 (C*C*H_3), 36.8 (*C*CH_3), 41.5 (N*C*H_3), 50.7 (N*C*H_2), 90.9 (q, $^2J_{C\text{-}F}$ = 32.7 Hz, *C*CF_3), 122.1 (q, $^1J_{C\text{-}F}$ = 286.3 Hz, *C*F_3), 160.2 (*C*N) ppm. MS *m/z*: 313 (M^+, 66), 58 (100). *Anal.* Calcd for $C_9H_{15}F_3N_2O_2$: C, 45.00; H, 6.29; N, 11.66. Found: C, 44.71; H, 6.19; N, 11.79.

***N*-[3,3,3-Trifluoro-2-(hydroxyimino)propyl]-*N*-methylbenzamide (4)**. Pale yellow crystals. mp 139−141 °C ($CHCl_3$-hexane). IR (KBr) ν_{max}: 2878, 2806, 1598, 1569, 1486, 1409, 1357, 1278, 1189, 1132, 1075, 1007, 736, 708 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.86 (s, 3H, CH_3), 4.40 (br s, 1H, NC*H*), 4.60 (br s, 1H, NC*H*), 7.43-7.46 (m, 5H, Ar*H*), 12.89 (br s, 1H, O*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 37.5 (N*C*H_3), 121.1 (q, $^1J_{C\text{-}F}$ = 273.3 Hz, *C*F_3), 126.6, 128.4, 129.6, 135.6, 143.5 (q, $^2J_{C\text{-}F}$ = 29.8 Hz, *C*CF_3), 170.3 (*C*O) ppm. MS *m/z*: 260 (M^+, 32), 105 (100). *Anal.* Calcd for $C_{11}H_{11}F_3N_2O_2$: C, 55.62; H, 5.67; N, 9.27. Found: C, 55.32; H, 5.74; N, 9.26.

The authentic **4** was prepared by the following method: A mixture of *N*-methyl-*N*-(3,3,3-trifluoro-2,2-dihydroxypropyl)benzamide[4] (263 mg, 1 mmol), hydroxylamine hydrochloride (104 mg, 1.50 mmol) and pyridine (0.25 mL) in EtOH (5 mL) was stirred at 0 °C for 10 min under atmosphere of argon. Then, the whole was stirred at 90 °C for 3 h. After workup with 10% aqueous Na_2CO_3, the mixture was extracted with AcOEt (x 3). The combined organic layers were washed with brine, dried over anhyd Na_2SO_4, and evaporated. The residue was purified by column chromatography (silica gel, hexane:AcOEt=1:2) to give *N*-methyl-*N*-(3,3,3-trifluoro-2-(hydroxyimino)-propyl)benzamide (**4**) (195.0 mg, 74%).

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