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HETEROCYCLIZATION OF 4-TRIFLUOROACETYL-1,3-OXAZOLIUM-5-OLATES WITH 1,4-*BIS*-NUCLEOPHILES

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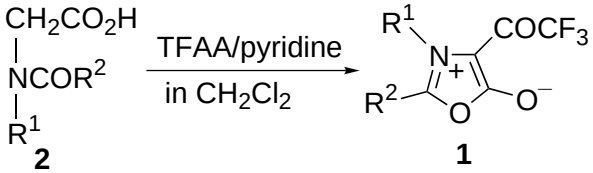
Abstract - Reactions of aromatic 1,4-*bis*-nucleophiles such as *o*-phenylenediamine and *o*-aminothiophenol, with mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates (**1**) gave regiospecifically seven member trifluoromethylated heterocycles such as 1,5-benzodiazepines (**3**) and 1,5-benzothiazepines (**4**). The reaction with *o*-aminophenol afforded non-cyclized products (**5**). The structures of **3**, **4**, and **5** were established by X-Ray diffraction analysis.

During our studies on the chemistry of mesoionic 1,3-oxazolium-5-olates (munchnones),[1] we have focused on mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates (**1**) as useful synthons for trifluoromethyl-substituted heterocycles.[2] These reactions proceed through the regioselective attack of the nucleophiles such as amidines,[2a, f] ammonia,[2b, g] phenylhydrazine,[2c] and amino-malonate [2e] on **1**, depending on the nature of the nucleophiles and the reaction conditions.
Recent studies have also demonstrated that munchnones are useful synthons for heterocycles in combinatorial chemistry. Thus, the 1,3-dipolar cycloaddition of polymer-bound munchnones with a variety of alkynes has been developed to produce a library of up to 10^8 different pyrroles.[3] The solid-phase synthesis of imidazoles is reported to utilize a munchnone cycloaddition to aryltosylimines.[4] The reaction of **1** with amidines [2a] has also been applied to a combinatorial solid-phase synthesis to prepare a library of two hundred 5-trifluoroacetylimidazoles by Hamper *et al*.[5] Thus, munchnone chemistries are suitable to develop new synthesis in combinatorial chemistry.
In this study, we examined the question which position of **1** would be attacked by aromatic 1,4-*bis*-nucleophiles such as *o*-phenylenediamine, *o*-aminothiophenol, and *o*-aminophenol.

Reactions of **1** with *o*-phenylenediamine

The 4-trifluoroacetyl-1,3-oxazolium-5-olates (**1a-e**) have been prepared by the reaction of *N*-

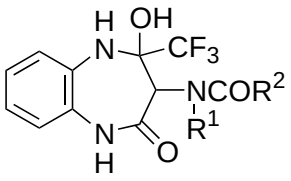


a: R^1=Me, R^2=4-$MeOC_6H_4$
b: R^1=Me, R^2=Me
c: R^1=Bn, R^2=Me
d: R^1=Ph, R^2=Me
e: R^1=Me, R^2=Ph

Table 1. Reaction of **1a** with *o*-phenylenediamine.[a]

Entry	Solvent	Conditions	Yield of **3a** (%)
1	CH_2Cl_2	rt for 24 h	91
2	$ClCH_2CH_2Cl$	rt for 24 h	73
3	DMF	rt for 24 h	66
4	DMF	rt for 0.5 h, 80°C for 2 h	51
5	benzene	rt for 0.5 h, 80°C for 2 h	59

[a] The reactions were carried out on a 1 mmol scale.



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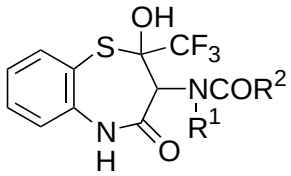
a: R^1=Me, R^2=4-$MeOC_6H_4$
b: R^1=Me, R^2=Me
c: R^1=Bn, R^2=Me
d: R^1=Ph, R^2=Me
e: R^1=Me, R^2=Ph



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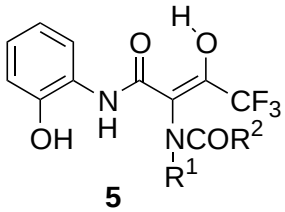
a: R^1=Me, R^2=4-$MeOC_6H_4$
b: R^1=Me, R^2=Me
c: R^1=Bn, R^2=Me
d: R^1=Ph, R^2=Me



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a: R^1=Me, R^2=4-$MeOC_6H_4$
b: R^1=Me, R^2=Me
c: R^1=Bn, R^2=Me
d: R^1=Ph, R^2=Me

Table 2. Reactions of mesoionic **1** with nucleophiles.

Entry	Starting material	Nucleophiles (equiv)	Solvent	Conditions	Products, Yield (%)
1	**1a**	*o*-phenylenediamine (1.05)	CH_2Cl_2	rt for 24 h	**3a** (91)
2	**1b**	*o*-phenylenediamine (1.05)	CH_2Cl_2	rt for 24 h	**3b** (80)
3	**1c**	*o*-phenylenediamine (1.05)	CH_2Cl_2	rt for 24 h	**3c** (89)
4	**1d**	*o*-phenylenediamine (1.02)	CH_2Cl_2	rt for 24 h	-[a]
5	**1e**	*o*-phenylenediamine (1.02)	CH_2Cl_2	rt for 6 h	**3e** (98)
6	**1a**	*o*-aminothiophenol (1.2)	benzene	rt for 0.5 h, 80°C for 3 h	**4a** (93)
7	**1b**	*o*-aminothiophenol (1.2)	benzene	rt for 0.5 h, 80°C for 1 h	**4b** (81)
8	**1c**	*o*-aminothiophenol (1.2)	benzene	rt for 0.5 h, 80°C for 1 h	**4c** (86)
9	**1d**	*o*-aminothiophenol (1.2)	benzene	rt for 0.5 h, 80°C for 1 h	**4d** (82)
10	**1a**	*o*-aminophenol (1.2)	CH_2Cl_2	rt for 72 h	**5a** (78)
11	**1b**	*o*-aminophenol (1.05)	CH_2Cl_2	rt for 24 h	**5b** (70)
12	**1c**	*o*-aminophenol (1.2)	CH_2Cl_2	rt for 24 h	**5c** (75)
13	**1d**	*o*-aminophenol (1.2)	CH_2Cl_2	rt for 6 h	**5d** (77)

[a] complex mixture.

acyl-*N*-alkylglycines (**2a-e**) with trifluoroacetic anhydride (TFAA). Table 1 shows the results when **1a** was allowed to react with *o*-phenylenediamine under various conditions. The reaction proceeded smoothly at room temperature. However, the higher temperature lowered the yield. The best result was obtained when CH_2Cl_2 was used as a solvent. *o*-Phenylenediamine reacted with 4-trifluoroacetyl-1,3-oxazolium-5-olates (**1a-c, e**) to produce in good yields 1,5-benzodiazepine derivatives (**3a-c, e**), introduced both a trifluoromethyl and amido groups in the diazepine segment (Table 2). This shows that the nucleophile exclusively condenses on both of the C-5 and the trifluoroacetyl function with opening of the mesoionic ring. However, reaction of **1d** with *o*-phenylenediamine gave only complex mixture. The structures were confirmed by elemental analyses, ^{1}H and ^{13}C NMR, MS, and IR spectroscopy (Tables 3, 4, and 5). The ^{1}H NMR spectrum of **3** exhibited the methine signal of H-3 at around 5.6 ppm (singlet). Three peaks at 6.27, 7.68, and 10.18 ppm of **3a** were exchangeable with D_2O. The carbons of CF_3 and C-4 appear at around 125 ppm (quartet, $^1J_{C\text{-}F}$=289-294 ppm) and 92 ppm (quartet, $^2J_{C\text{-}F}$ =27-28 Hz), respectively. The structure of **3e** was unequivocally confirmed by the X-Ray analysis (Figure 1).

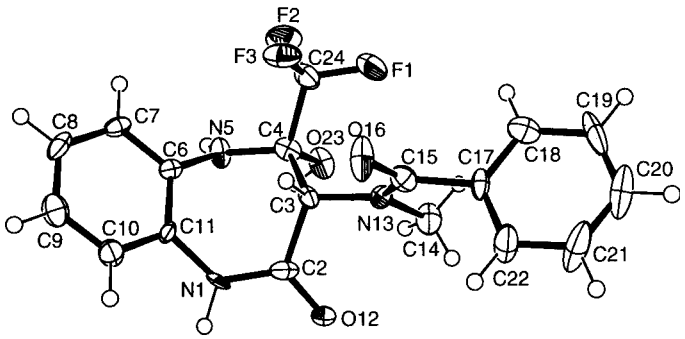

Figure 1. X-Ray structure drawing of **3e**.

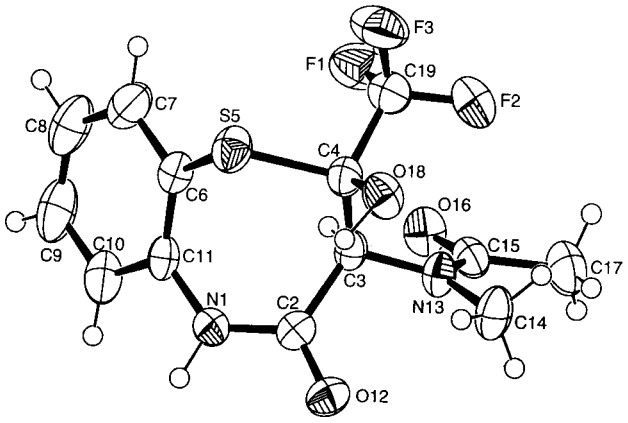

Figure 2. X-Ray structure drawing of **4b**.

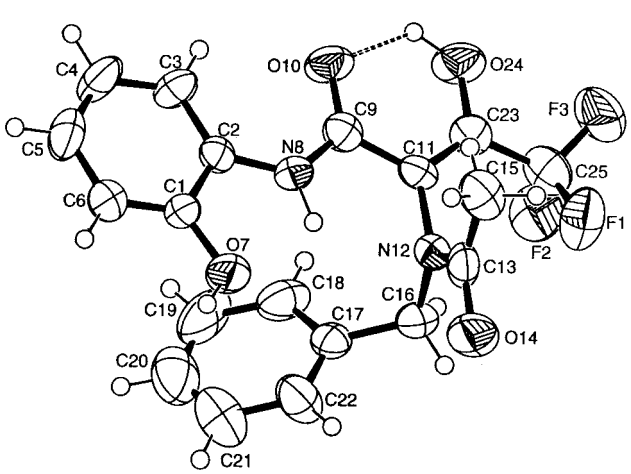

Figure 3. X-Ray structure drawing of **5c**.

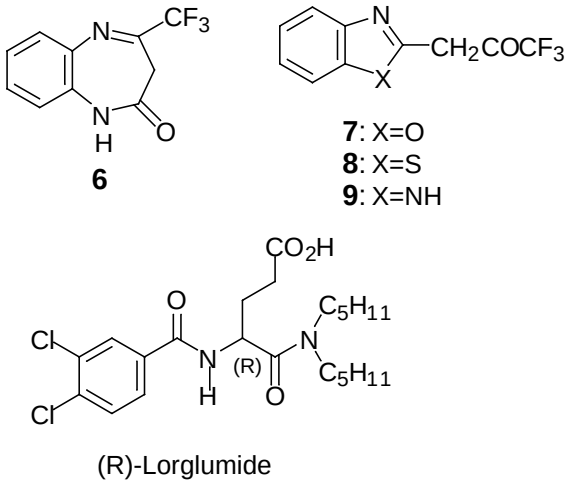

Figure 4. Structures of the related compounds

Reactions of **1** with *o*-aminothiophenol

The reaction of **1a-d** with *o*-aminothiophenol also took place to produce 1,5-benzothiazepine derivatives (**4a-d**) in good yields (Table 2). The reaction was complete at 80 °C. As the same as *o*-phenylenediamine, the amino and thiol fuction of *o*-aminothiophenol condensed at C-5 and trifluoroacetyl group, respectively. The structure of **4b** was also determined by the X-Ray analysis (Figure 2).

Reactions of **1** with *o*-aminophenol

We have also studied heterocyclizations with *o*-aminophenol. As we found, mesoionic **1a-d** reacted with *o*-aminophenol to give a product (**5a-d**) derived from a condensation reaction between the amino group of *o*-aminophenol and the C-5 of **1** (Table 2). Methanolic solution of **5a** turned violet in color on addition of a few drops of iron(III) chloride solution, thus confirming the phenol group of the products. The phenolic hydroxyl group of the adduct (**5**) is not nucleophilic enough to give the corresponding 1,5-benzoxazepine derivatives, which were not isolated in these reactions. Structural assignments were made on the basis of analytical and spectroscopic data (Tables 3 and 4) and the structure was secured by single-crystal X-Ray diffraction analysis of **5c** (Figure 3). The X-Ray analysis of **5c** indicates that the enolic form is stabilized by resonace and by the formation of an intramolecular hydrogen bond.

1,5-Benzodiazepine,[6] 1,5-benzothiazepine [7] and the related derivatives constitute an important class of heterocyclic compounds and many thousands of them have been synthesized as potential drugs. The benzodiazepine derivatives have been well documented as nonpeptide cholecystokinin (CCK) agonists and antagonists, which have potential as therapeutic agents for treating both peptic ulcers and CNS disorders.[8] The selected compounds (**3a-c**, **4a**, **4c** and **5a**) and related compounds (**6**-**9**) (Figure 4) were screened for CCK-A antagonistic activity, but were inactive at 1 x 10^{-5} M concentration, compared with lorglumide (IC_{50} = 2.4 x 10^{-7} M), a specific antagonist of CCK-8.

In conclusion, mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates (**1**), readily available from *N*-acyl-*N*-alkylglycines and TFAA, reacted with *o*-phenylenediamine or *o*-aminophenol giving 1,5-benzodiazepines (**3**) and 1,5-benzothiazepines (**4**) which were introduced by the trifluoromethyl group at 4 position and amido group at 3-position. The method appears to be useful and convenient in terms of the ready accessibility of the starting materials, cheap reagents, and operational simplicity.

EXPERIMENTAL

Mps were determined on a Yanagimoto hot-stage apparatus and are uncorrected. ^{1}H NMR spectra were measured at 500 MHz with tetramethylsilane (Me_4Si) as an internal reference and DMSO-d_6 as the solvent. J-Values are given in Hz. IR spectra were recorded on a JASCO IR810 spectrophotometer. Only pertinent IR peaks are given. MS spectra (electron impact:

70 eV) were measured with a JEOL JMS-DS300 spectrometer. For column chromatography, SiO_2 (Merk, Art 9385) was used.

4-Trifluoroacetyl-2-(4'-methoxyphenyl)-3-methyl-1,3-oxazolium-5-olate (**1a**) was synthesized in 86% yield by the reaction of *N*-(4'-methoxybenzoyl)-*N*-methylglycine[9] with TFAA as described previously.[2g] **1a**: mp 142.5-144.5 °C (AcOEt-hexane), Anal. Calcd for $C_{13}H_{10}NO_4F_3$: C, 51.84; H, 3.35; N, 4.65. Found: C, 51.86; H, 3.42; N, 4.62. MS m/z 301 (M^+, 17), 135 (100); IR $\upsilon_{max/nujol}$ (cm^{-1}) 1630, 1780; ^1H NMR ($CDCl_3$) δ 3.90 (s, 3H), 4.06 (s, 3H), 7.06 (d, 2H, *J*=9.0), 7.69 (d, 2H, *J*=9.0). 4-Trifluoroacetyl-2,3-dimethyl-1,3-oxazolium-5-olate (**1b**) [10] and 4-trifluoromethyl-1*H*-1,5-benzodiazepin-2(3H)-one (**6**) [11] were prepared by the reported method. Compounds (**1c-e**)[2g] and (**7-9**)[12] were previously prepared.

General Procedure for the Reaction of 1 with *o*-Phenylenediamine, *o*-Aminothiophenol or *o*-Aminophenol. A mixture of **1** (1 mmol) and the nucleophile (1.02-1.2 mmol) in 5 mL of the indicated solvent (Table 2) was stirred under the conditions described in Table 2. The reaction mixture was diluted with 5 mL of hexane and allowed to stand for 3-5 h in an ice bath. The precipitate was then filtered, dried and crystallized to give the corresponding product (Table 3).

Table 3. Physical and analytical data of new compounds.

Compound	Formula	Mp (solvent)[a]	Analysis (%) Found (Calculated) C	H	N	IR, $\nu_{max/nujol}$ (cm^{-1})	MS, m/z (%), M^+ and base peak
3a	$C_{19}H_{18}N_3O_4F_3$	171-173 (A-H)	55.96 (55.75)	4.64 (4.43)	10.31 (10.26)	1610, 1680, 3300	409 (3) 135
3b	$C_{13}H_{14}N_3O_3F_3$	156-157 (A-H)	49.14 (49.22)	4.44 (4.45)	13.29 (13.24)	1625, 1690, 3270	317 (18) 108
3c	$C_{19}H_{18}N_3O_3F_3$	161-163 (A)	57.94 (58.01)	4.61 (4.61)	10.61 (10.68)	1625, 1675, 3400	393 (25) 91
3e	$C_{18}H_{16}N_3O_3F_3$	189-190 (A-H)	56.97 (56.99)	4.32 (4.25)	11.01 (11.08)	1615, 1680, 3400	379 (10) 105
4a	$C_{19}H_{17}N_2O_3F_3S$	188-189 (A)	53.27 (53.52)	4.20 (4.02)	6.32 (6.57)	1610, 1675, 3050-3230	426 (52) 135
4b	$C_{13}H_{13}N_2O_3F_3S$	155-157 (E)	46.95 (46.71)	4.11 (3.92)	8.43 (8.38)	1625, 1690, 3120	334 (6) 152
4c	$C_{19}H_{17}N_2O_3F_3S$	154-156 (C-H)	55.20 (55.60)	4.26 (4.17)	6.66 (6.83)	1625, 1670, 3100	410 (6) 91
4d	$C_{18}H_{15}N_2O_3F_3S$	171-173 (E)	54.29 (54.54)	3.99 (3.81)	7.07 (7.07)	1630, 1690, 3180	396 (6) 203
5a	$C_{19}H_{17}N_2O_5F_3$	183-185 (A)	410.1085 (410.1089)			1620, 3370 (br)	410 (2) 135
5b	$C_{13}H_{13}N_2O_4F_3$	162-163 (C-H)	48.89 (49.06)	4.09 (4.12)	9.00 (8.80)	1600, 1670, 3320, 3400	318 (4) 109
5c	$C_{19}H_{17}N_2O_4F_3$	171-173 (E)	57.98 (57.87)	4.53 (4.34)	7.05 (7.10)	1595, 1640, 3220 (br), 3360	394 (9) 91
5d	$C_{18}H_{15}N_2O_4F_3$	195-198 (A)	362.0865[b] (362.0878)			1625, 2700 -3600 (br)	362 (0.2, M^+-H_2O)[b] 106

[a] A=AcOEt, E=EtOH, C=CH_2Cl_2, H=hexane. [b] Calcd for $C_{18}H_{13}N_2O_3F_3$ (M^+-H_2O)

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

Compound	^{1}H NMR (500 MHz) δ
3a	3.28 (s, 3H), 3.77 (s, 3H), 5.56 (s, 1H), 6.27 (s, 1H), 6.98 (d, 2H, *J*=8.9), 7.01-7.11 (m, 4H), 7.27 (d, 2H, *J*=8.9), 7.68 (s, 1H), 10.18 (s, 1H)
3b	1.97 (s, 3H), 3.30 (s, 3H), 5.63 (s, 1H), 6.20 (s, 1H), 6.96-7.07 (m, 4H), 7.53 (s, 1H), 10.11 (s, 1H)
3c	1.62 (s, 3H), 4.53 (d, 1H, *J*=17.4), 5.59 (d, 1H, *J*=17.4), 5.84 (s, 1H), 6.21 (s, 1H), 6.99-7.09 (m, 4H), 7.17-7.23 (m, 2H), 7.27-7.30 (m, 3H), 7.78 (s, 1H), 10.12 (s, 1H)
3e[a]	3.23 + 3.32 (s, 3H), 4.50 + 5.65 (s, 1H), 6.11 + 6.30 (s,1H), 6.80-6.87 + 7.03-7.11 (m, 4H), 6.94-6.97 + 7.25-7.29 (m, 2H), 7.19-7.21 + 7.43-7.45 (m, 3H), 7.71 + 7.72 (s, 1H), 10.22 + 10.23 (s, 1H)
4a[a]	3.32 (s, 3H), 3.66 + 3.76 (s, 3H), 4.57 + 5.61 (s, 1H), 6.66 + 6.96 (d, 2H, *J*=8.6), 6.83 + 7.25 (d, 2H, *J*=8.6), 7.02 + 7.25 (t, 1H, *J*=7.6), 7.20 (d, 1H, *J*=7.6), 7.39 + 7.53 (t, 1H, *J*=7.6), 7.58 (d, 1H, *J*=7.6), 8.90 (s, 1H), 10.54 + 10.61 (s, 1H)
4b	1.93 (s, 3H), 3.33 (s, 3H), 5.73 (s, 1H), 7.18 (d, 1H, *J*=7.7), 7.22 (t, 1H, *J*=7.7), 7.50 (t, 1H, *J*=7.7), 7.55 (d, 1H, *J*=7.7), 8.73 (s, 1H), 10.47 (s, 1H)
4c[a]	1.57 + 1.61 (s, 3H), 4.55 (d, 1H, *J*=17.1), 5.54 + 5.80 (d, 1H, *J*=17.1), 5.74 + 6.08 (s, 1H), 7.16-7.21 (m, 3H), 7.23-7.31 (m, 4H), 7.50 (t, 1H, *J*=7.5), 7.59 (d, 1H, *J*=7.5), 8.84 + 9.05 (s, 1H), 10.56 + 10.65 (s, 1H)
4d[a]	1.72 (s, 3H), 7.11-7.19 (m, 3H), 7.31-7.38 (m, 5H), 7.45 (t, 1H, *J*=7.6), 7.53 (d, 1H, *J*=7.6), 10.70 (s, 1H)
5a	3.01 (s, 3H), 3.69 (s, 3H), 6.70 (t, 2H, *J*=7.5), 6.76 (d, 2H, *J*=8.9), 6.80 (d, 1H, *J*=7.5), 7.31 (d, 2H, *J*=8.9), 7.69 (d, 1H, *J*=7.5), 9.00-9.50 (br, 1H), 10.49 (br s, 1H), 12.16 (br s, 1H)
5b	2.06 (s, 3H), 3.06 (s, 3H), 6.77 (d, 1H, *J*=7.3), 6.87 (d, 1H, *J*=7.9), 6.91 (d, 1H, *J*=7.6), 8.04 (d, 1H, *J*=7.9), 9.74 (s, 1H), 9.96 (br s, 1H), 10.84 (s, 1H)
5c	2.24 (s, 3H), 4.52 (d, 1H, *J*=13.9), 4.59 (d, 1H, *J*=13.9), 6.74 (t, 1H, *J*=7.5), 6.86 (d, 1H, *J*=8.2), 6.95 (t, 1H, *J*=7.9), 7.20-7.40 (m, 5H), 7.95 (d, 1H, *J*=7.7), 9.70 (s, 1H), 9.90 (br s, 1H), 10.81 (br s, 1H)
5d	2.00 (s, 3H), 6.70-6.73 (m, 2H), 6.82-6.83 (m, 2H), 6.99 (t, 1H, *J*=7.3 Hz), 7.19 (t, 2H, *J*=7.8), 7.29 (d, 2H, *J*=7.6), 7.84 (d, 1H, *J*=7.6), 10.26 (s, 1H), 12.40 (s, 1H)

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

Crystal data for 3e [13]

($C_{18}H_{16}N_3O_3F_3$) FW=379.34, mp 189-190 ˚C. Monoclinic $P2_1/a$, a=7.2109(2), b=17.3810(7), c=14.1745(5) Å, β = 99.818(1) °, V=1750.51(9) Å^3, μ(Mo Kα)= 0.120 cm^{-1} using 0.20×0.12×0.08 mm colorless platelet crystal by Rigaku Rapid ($-9 \leqq h \leqq 9$, $-22 \leqq k \leqq 22$, $-18 \leqq l \leqq 18$ with θ max=27.48 °). Final R and Rw were 0.068 and 0.025, respectively, for 2452 independent reflections with $F^2 \geqq \sigma(F^2)$, S=1.506, final (Δ/σ)max = 0.033, $\Delta\rho$ max=0.57, $\Delta\rho$ min= -0.69 e Å^{-3}.

Crystal data for 4b [13]

($C_{13}H_{13}N_2O_3F_3S$) FW=334.32, mp 155-157 ˚C. Tetragonal $I4_1/a$, a=20.547(1), c=13.7786(9) Å, V=5817.2(5) Å^3, μ(Mo Kα)= 0.271 cm^{-1} using 0.5×0.2×0.2 mm colorless prismatic crystal by Rigaku Rapid ($-27 \leqq h \leqq 27$, $-27 \leqq k \leqq 27$, $-17 \leqq l \leqq 18$ with θ max=28.69 °). Absorption correction was applied (Tmin=0.428 and Tmax=0.947). Final R and Rw were 0.044 and 0.035, respectively, for 1979 independent reflections with $F^2 \geqq \sigma(F^2)$, S=0.806, final (Δ/σ)max = 0.003, $\Delta\rho$ max=0.68, $\Delta\rho$ min= -0.58 e Å^{-3}.

Table 5. ^{13}C NMR data of new compounds.

Compound	^{13}CNMR (127 MHz) δ
3a	37.5 (CH_3), 52.7 (CH), 55.3 (CH_3), 92.3 (C, $^2J_{CF}$=27), 113.7 (CH), 121.4 (CH), 123.4 (CH), 123.5 (CH), 125.1 (C), 126.25 (CF_3, $^1J_{CF}$=289), 127.6 (CH), 128.8 (C), 131.1 (C), 135.8 (C), 160.4 (C), 167.9 (C), 171.7 (C)
3b	21.5 (CH_3), 35.0 (CH_3), 51.6 (CH), 91.8 (C, $^2J_{CF}$=27), 121.3 (CH), 123.1 (CH), 123.2 (CH), 123.6 (CF_3, $^1J_{CF}$=294), 125.0 (CH), 130.7 (C), 135.8 (C), 168.1 (C), 171.4 (C)
3c	22.7 (CH_3), 51.5 (CH_2), 52.7 (CH), 92.3 (C, $^2J_{CF}$=28), 121.4 (CH), 123.5 (CH), 123.6 (CH), 123.8 (CF_3, $^1J_{CF}$=296), 125.2 (CH), 126.3 (CH), 126.8 (CH), 128.0 (CH), 131.1 (C), 136.1 (C), 140.3 (C), 167.3 (C), 173.0 (C)
3e[a]	32.8 + 37.3 (CH_3), 52.4 + 58.7 (CH), 92.3 (C, $^2J_{CF}$=28), 121.2 + 121.4 (CH), 123.1 + 123.4 (CH), 123.3 + 123.5 (CH), 125.1 + 125.2 (CH), 126.2 (CF_3, $^1J_{CF}$=294), 125.5 +126.4 (CH), 128.3 + 128.6 (CH), 129.3 +129.7 (CH), 130.5 + 131.0 (C), 135.4 + 135.8 (C), 135.6 +135.9 (C), 167.7 +167.8 (C), 171.2 + 171.9 (C)
4a[a]	37.4 (CH_3), 52.3 (CH), 55.2 + 55.3 (CH_3), 90.2 (C, $^2J_{CF}$=32),113.7 + 113.8 (CH), 122.8 (CH), 124.3 (CH), 124.8 (CF_3, $^1J_{CF}$=285), 126.0 (CH), 127.1 + 127.2 (C), 128.9 (CH), 131.0 + 131.5 (C), 134.4 + 134.7 (C), 141.1 + 141.9 (C), 159.7 + 160.5 (C), 167.7 + 168.3 (C), 171.1 + 171.6 (C)
4b	21.5 (CH_3), 34.9 (CH_3), 50.7 (CH), 91.9 (C, $^2J_{CF}$=29), 122.7 (CH), 124.2 (CF_3, $^1J_{CF}$=287), 124.3 (C), 125.9 (CH), 131.4 (CH), 134.6 (CH), 141.9 (C), 168.2 (C), 171.3 (C)
4c[a]	22.4 (CH_3), 50.6 (CH), 50.8 (CH_2), 92.5 (C, $^2J_{CF}$=32), 122.8 (CH), 124.2 (CF_3, $^1J_{CF}$=296), 124.6 (CH), 126.0 (CH), 126.2 (CH), 126.3 (CH), 128.1 (CH), 131.5 (CH), 134.8 (CH), 140.3 (CH), 141.7 + 141.9 (CH), 167.2 + 167.3 (C), 172.6 (C)
4d[a]	23.7 + 23.8 (CH_3), 54.9 + 57.9 (CH), 90.9 (C, $^2J_{CF}$=32), 122.6 (CH), 123.9 (CH), 124.4 (CF_3, $^1J_{CF}$=288), 126.1 (CH), 128.5 (C), 128.6 (CH), 131.7 (CH), 134.8 (CH), 140.7 (C), 141.7 (C), 141.8 (CH), 166.2 + 166.3 (C), 166.3 + 166.4 (C)

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

Crystal data for 5c [13]

($C_{19}H_{17}N_2O_4F_3$) FW=394.35, mp 171-173 ˚C. Orthorhombic Pbca, a=25.5873(8), b=15.483(2), c=9.3807(5) Å, V=3716.3(3) Å^3, μ(Mo Kα)= 0.119 cm^{-1} using 0.40×0.35×0.10 mm colorless platelet crystal by Rigaku Rapid (-32≦h≦33, -20≦k≦20, -12≦l≦12 with θmax=27.48°). Final R and Rw were 0.048 and 0.113, respectively, for 2363 independent reflections with $F^2 \geqq \sigma(F^2)$, S=3.146, final (Δ/σ)max = 0.015, $\Delta\rho$max=0.39, $\Delta\rho$min= -0.42 e Å^{-3}.

Pepsinogen release: Chief cells from the rat stomach were prepared by a Percoll (Amercham Pharmacia Biotech, Uppsala, Sweden) gradient centrifugation after dispersing from a everted sacs of the stomach with Dispase I (1 kU/ml) (Godo Shusei Co., Tokyo, Japan). The cells were cultured in a mixture of Dulbecco's modified Eagle's minimum essential medium and Ham's F-12 (1:1) containing 10% fetal calf serum on collagen coated plastic dishes at 37 ˚C in a CO_2 incubator as described.[14] After replacing the medium, the cells were incubated with CCK-8 (1 x 10^{-8} M) and various concentrations of lorglumide or tested compounds (1 x 10^{-5} M) for 30 min at 37 ˚C in a CO_2 incubator. The concentration of pepsinogen was measured by the avidin-biotin complex enzyme-linked immunosorbent assay (abcELISA).

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