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DAKIN-WEST REACTION OF *N*-THIOACYLPROLINES USING TRIFLUOROACETIC ANHYDRIDE: NOVEL ACCESS TO 5-TRIFLUOROMETHYLTHIAZOLES

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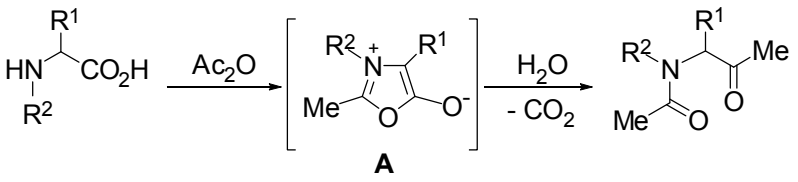
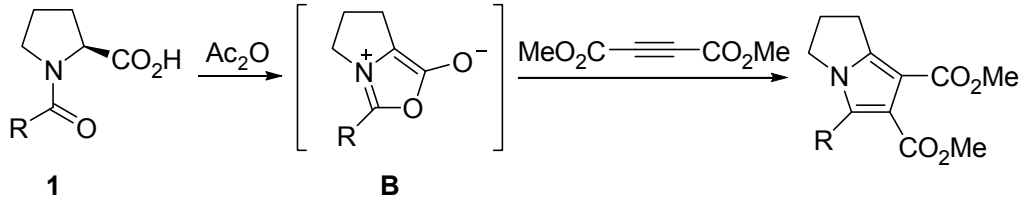
Abstract – The reaction between *N*-thioacylprolines and trifluoroacetic anhydride in the presence of pyridine afforded a good yield of 5-trifluoromethylthiazoles. This reaction proceeded through mesoionic 1,3-thiazolium-5-olates, followed by cleavage of the pyrrolidine ring and the formation of thiazoles, introducing a trifluoromethyl group at position 5 in the thiazole ring.

The Dakin-West (D-W) reaction of α-amino acids was originally performed in acetic anhydride in the presence of pyridine to produce α-acetamido methyl ketones.[1] *Secondary* α-amino acids are also known to undergo the D-W reaction, and this mechanism has been studied in detail.[1a] The D-W reaction involves the condensation of *N*-alkyl-α-amino acids with acetic anhydride in the presence of a base to produce α-acetamido ketones through intermediate mesoionic 1,3-oxazolium-5-olates (münchnone) (**A**) (Eq. 1).



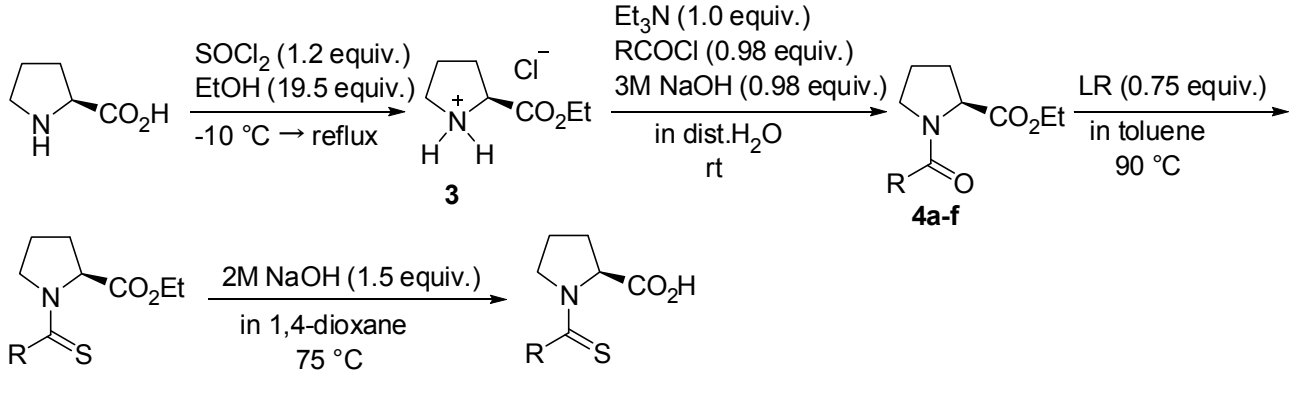
(1)



(2)

However, the D-W reaction of proline or its *N*-acyl derivatives with acetic anhydride does not yield any ketonic products.[1a] On the other hand, a generation of mesoionic oxazolium-5-olates (**B**), formed through the dehydration of *N*-acylprolines (**1**) with acetic anhydride, has been shown to produce 2,3-dihydro-1*H*-pyrrolizine derivatives through the 1,3-dipolar cycloaddition reaction with dimethyl acetylenedicarboxylate (Eq. 2).[2] We previously demonstrated that *N*-acylprolines (**1**) were cyclodehydrated by TFAA to intermediary mesoionic compounds (**B**), which subsequently reacted with TFAA to produce 5-trifluoromethyloxazoles,[3a] trifluoromethylated acyloins,[3b] 3-trifluoroacetyl-4,5-dihydropyrrolidines,[3c] or enol esters[3d] depending on the nature of the *N*-acyl groups and experimental conditions. We have examined the D-W reaction of *N*-thioacylprolines (**1a-f**) with TFAA. 5-Trifluoromethylthiazoles (**2a-f**) could be obtained when the reaction proceeded in the same manner as the D-W reaction of *N*-acylprolines.[3a] We here described the results obtained.

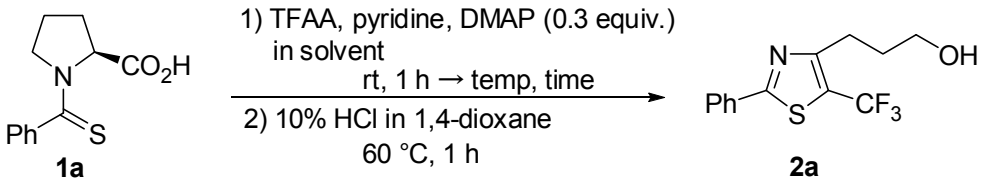
The starting *N*-thioacylprolines (**1a-f**) were prepared from L-proline in four steps with good overall yields (Scheme 1); ester formation (**3** from L-proline), *N*-acylation (**4** from **3**), thionation (**5** from **4**) by Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide; LR) followed by hydrolysis (**1** from **5**). The reaction between the *N*-pivaloylproline ethyl ester (**4f**) and LR produced a low yield of *N*-thiopivaloylproline esters (**5f**) (26%). However, the addition of pyridine (0.38 molar equiv. relative to **4f**) to the reaction mixture increased the yield of **5f** from 26% to 84%.



5a: R=Ph (y. 73% from L-Pro in 3 steps)
5b: 4-ClC_6H_4 (y. 65%)
5c: 4-$MeOC_6H_4$ (y. 62%)
5d: 3,5-$(CF_3)_2C_6H_3$ (y. 60%)
5e: 3,4,5-$(MeO)_3C_6H_2$ (y. 80%)
5f: *t*-Bu (y. 84%)

Scheme 1

Table 1. *N*-Thiobenzoylproline (**1a**) reactions under various conditions



1a **2a**

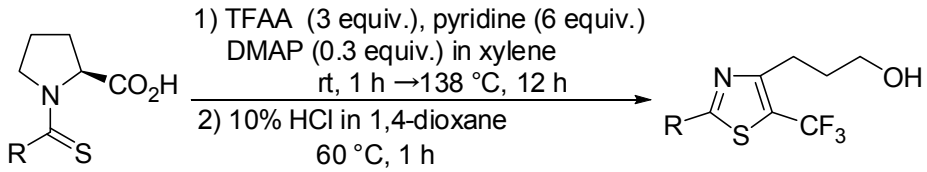
Entry	TFAA (equiv.)	Pyridine (equiv.)	Solvent	Temp. (°C)	Time (h)	Yield (%)[a]
1	3	6	benzene	80	5	6
2	3	6	toluene	110	5	57
3	3	6	xylene	138	5	64
4	3	6	xylene	138	12	79
5	2	4	xylene	138	12	24
6	3	6	DMF	153	5	21

[a] Isolated yields.

Table 1 shows the results obtained when *N*-thiobenzoylproline (**1a**) was reacted with TFAA in the presence of pyridine and 4-*N,N*-dimethylaminopyridine (DMAP) following acid hydrolysis. A higher temperature (entries 1, 2 and 3) and longer reaction time (entries 3 and 4) improved the yield.

The scope of the reaction substrates was investigated using these optimized conditions (Table 1, entry 4). The results obtained are summarized in Table 2. *N*-Thioacyl derivatives (**1a-f**), containing thiobenzoyl or thiopivaloyl groups, were easily transformed to 5-trifluoromethylthiazoles (**2a-f**) with good yields.

Table 2. *N*-Thioacylproline (**1**) reactions



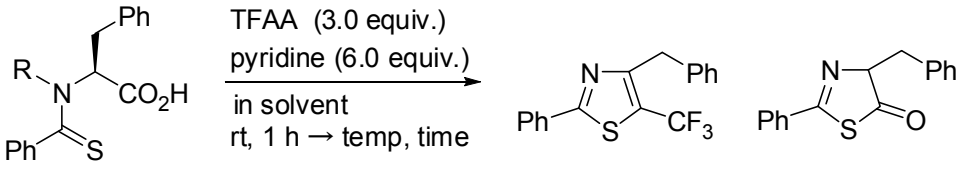
1a-f **2a-f**

Entry	**1**	R	Product	Yield (%)[a]
1	**a**	Ph	**2a**	79
2	**b**	4-ClC_6H_4	**2b**	70
3	**c**	4-$MeOC_6H_4$	**2c**	74
4	**d**	3,5-$(CF_3)_2C_6H_3$	**2d**	75
5	**e**	3,4,5-$(MeO)_3C_6H_2$	**2e**	61
6	**f**	*t*-Bu	**2f**	73

[a] Isolated yields.

We previously described the reaction between *N*-acyl-*N*-benzyl-α-amino acids and TFAA, which produced good yields of 5-trifluoromethyloxazoles.[3a] Therefore, we attempted to react *N*-thiobenzoyl-*N*-benzylphenylalanine (**6**) with TFAA; however, the subsequent yield of 5-trifluoromethylthiazole (**7**) isolated was poor at 10% (Table 3, entries 1 and 2). The main product was 4-benzyl-2-phenylthiazol-5(4*H*)-one (**8**). The yield of **8** increased to 77% in the case of the *N*-(4-methoxybenzyl) derivative **6b** because the *N*-substituent was easily cleaved during the reaction (entry 3). These results indicated that the intermediates 1,3-thiazolium-5-olates cannot undergo the trifluoroacetylation easily at position 4 as compared with the case of the intermediate 1,3-oxazolium-5-olates generated from *N*-acyl-*N*-benzyl-α-amino acids.[3a]

Table 3. D-W reactions of *N*-alkyl-*N*-thiobenzoylalanine derivatives

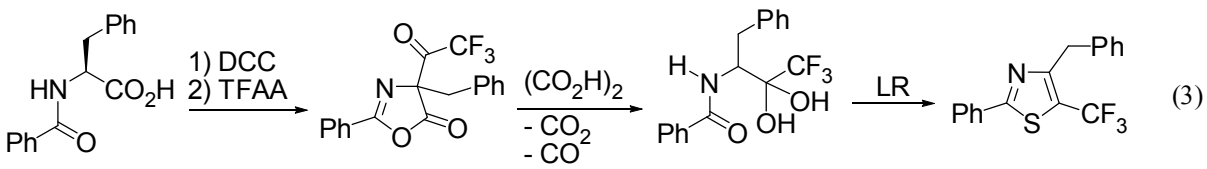


6 **7** **8**

Entry	**1**	R	Solvent	Temp. (°C)	Time (h)	Yield (%)[a]	
						7	**8**
1	**a**	$C_6H_5CH_2$	xylene	138	12	10	49
2	**a**	$C_6H_5CH_2$	toluene	110	12	10	21
3	**b**	4-$MeOC_6H_4CH_2$	toluene	110	15	trace	77

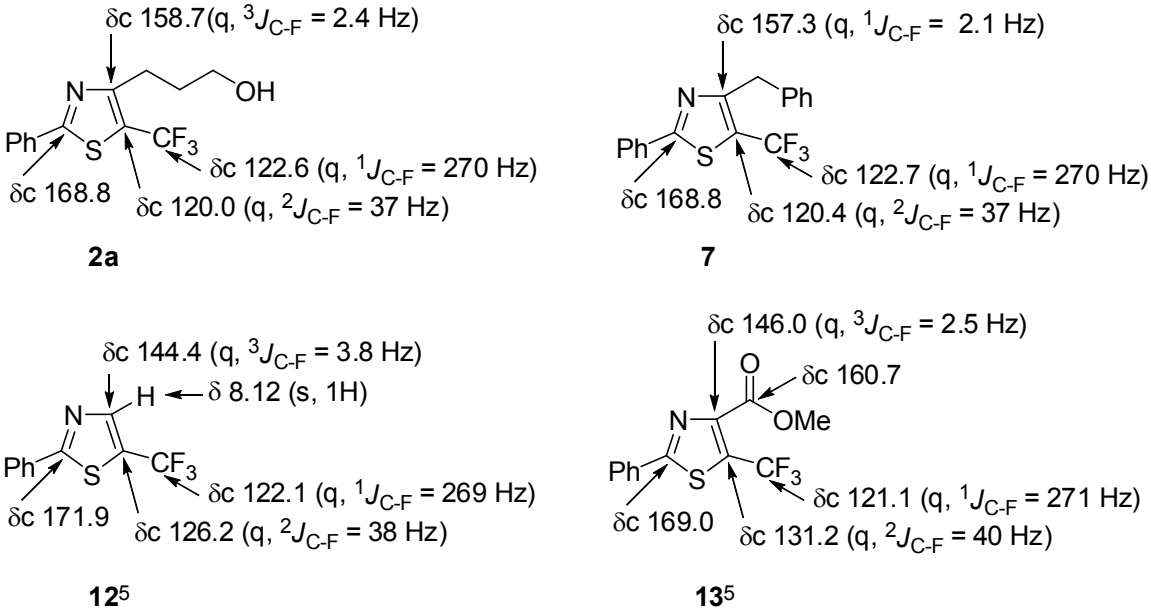
[a] Isolated yields.

Compound **7** was alternatively prepared from *N*-benzoylphenylalanine **9** as shown in equation 3. Thus, **9** was treated with DCC to produce 5(4*H*)-oxazolone, which reacted with TFAA to yield the C-trifluoroacetylated 5(4*H*)-oxazolone **10**. The subsequent hydrolysis and decarboxylation of **10** with oxalic acid produced the hydrated trifluoromethyl ketone **11**.[4] The treatment of **11** with LR provided authentic **7** at a yield of 16%.[5]



9 **10** **11** **7** (3)

As shown in Scheme 2, the ^{13}C NMR spectra of both **7** and **2a** showed each peak of their thiazole rings at the same position. Thus, the carbons at C-2, C-4, and C-5 of the thiazole rings in **7** and **2a** appeared at approximately 169, 158, and 120 ppm, respectively. The structures of **2a-f** were also supported by spectral and analytical data. The presence of the CF_3 group in **2a-f** was determined on the basis of long-range ^{13}C-^{19}F coupling. Thus, the carbons of the CF_3 group and C-5 appeared at approximately δ 123 ppm (quartet, $^1J_{C\text{-}F}$ = 270 Hz) and δ 120 ppm (quartet, $^2J_{C\text{-}F}$ = 37 Hz), respectively. These ^1H- and ^{13}C-NMR data are consistent with those for the 5-trifluoromethylthiazoles **7**, **12**,[5] and **13**[5] (Scheme 2).

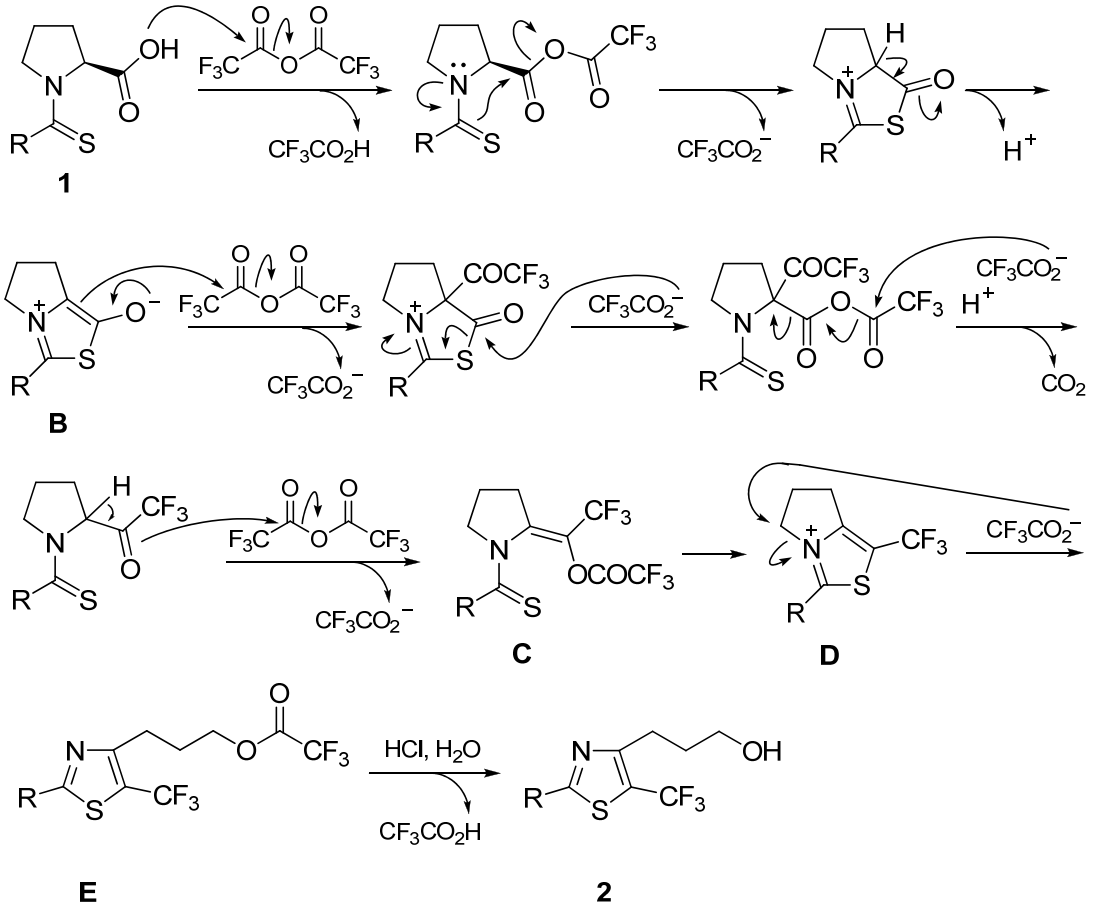


Scheme 2

A plausible mechanism is described in Scheme 3. The reaction involves a mesoionic 1,3-thiazolium-5-olate (**B**) formed through the cyclodehydration of **1** by TFAA. Intermediate **B** undergoes trifluoroacetylation followed by decarboxylation to give the enol trifluoroacetate **C**: a similar mechanism has been postulated in the Dakin-West reaction of *N*-acylproline.[3a] The cyclization of the enol **C** leads to the thiazolium salt **D**. The cleavage of the N-C bond of **D** readily occurs upon an attack of the trifluoroacetate anion because of the hindered 5-5 bicyclic system. As described in a previous study, the formation of **2** could occur through the hydrolysis of **E**.[3a]

Trifluoromethyl-substituted thiazoles may be used as a promising skeleton for the development of medicinal and agrochemical chemistry.[6] 4-Trifluoromethylthiazole derivatives such as metsulfovax and thifuzamide are known fungicides in the agricultural field and several synthetic methods have been reported for the preparation of the 4-trifluoromethylthiazole core.[7] However, few practical procedures

are currently available for the syntheses of 5-trifluoromethylthiazoles.[8] For example, the reaction of 3-(*N*-*tert*-butyl-*N*-methylhydrazono)-1,1,1-trifluoroalkan-2-ones with silica gel to form 5-trifluoromethyl-3-oxazolines, and the subsequent treatment of 5-trifluoromethyl-3-oxazolines with P_2S_5 afforded the corresponding 5-trifluoromethylthiazoles, and this has only been applied in a few cases.[8a] 5,5'-Bistrifluoromethylbisthiazoles were obtained by the reaction of dithioamides with TFAA in moderate yields, in which the products obtained were restricted to 4,4'-bispyridyl substituents.[8b] The unexpected reaction of the 2-dibenzylamino-4,4,4-trifluoro-3-hydroxylbutyric acid ethyl ester with $SOCl_2$ provided 2-phenyl-5-trifluoromethyl-1,3-thiazole-4-carboxylate.[8c] Moody *et al.*[8d] and our group[5] recently reported the practical synthesis of a 2-benzoylamino trifluoromethyl ketone hydrate, which reacted with LR to give 5-trifluoromethylthiazoles.



Scheme 3

In summary, we herein described the novel rearrangement of *N*-thioacylprolines, in which a pyrrolidine ring was cleaved concomitant with the formation of a thiazole ring. In addition, this reaction is a new and easy synthetic procedure for thiazole derivatives with a trifluoromethyl group at position 5. This

method may 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 125 MHz). Both ^{1}H- and ^{13}C-NMR spectral data are reported in parts per million (δ) relative to Me_4Si. The symbols "#1" and "#2" represent two rotamers. 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.

Preparation of *N*-thioacylproline ethyl esters (5a-f): *N*-Acylproline ethyl esters (**4**) were prepared in good yields by Schotten-Baumann reaction of L-proline ethyl ester (**3**) and the appropriate acyl chloride (Scheme 1). A mixture of **4** (4.00 mmol), Lawesson's reagent (3.00 mmol), and pyridine (1.50 mmol) in toluene (20 mL) was heated at 90 °C for 1–5 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 = 10:1 to 2:1) to give **5**.

(*S*)-Ethyl 1-(phenylcarbonothioyl)pyrrolidine-2-carboxylate (5a). Light yellowish needles. 73% yield (3 steps). mp 86 °C (hexane–AcOEt). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (t, *J* = 7.2 Hz, 0.69H, #2), 1.33 (t, *J* = 7.1 Hz, 2.31H, #1), 1.97 (m, 0.77H, #1), 2.05−2.18 (m, 0.69H, #2), 2.18−2.05 (m, 1.54H, #1), 2.31 (m, 0.23H, #2), 2.44 (m, 0.77H, #1), 3.55 (m, 0.77H, #1), 3.66 (m, 0.77H, #1), 3.97−4.09 (m, 0.46H, #2), 4.12 (q, *J* = 7.2 Hz, 0.46H, #2), 4.27 (q, *J* = 7.1 Hz, 1.54H, #1), 4.44 (dd, *J* = 8.5, 2.1 Hz, 0.23H, #2), 5.12 (dd, *J* = 8.7, 5.0 Hz, 0.77H, # 1), 7.22−7.41 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0 ($OCH_2\underline{C}H_3$, #2), 14.2 ($OCH_2\underline{C}H_3$, #1), 22.8 (4-$\underline{C}H_2$, #2), 25.2 (4-$\underline{C}H_2$, #1), 29.7 (3-$\underline{C}H_2$, #1), 31.5 (3-$\underline{C}H_2$, #2), 53.4 (5-$\underline{C}H_2$, #2), 54.1 (5-$\underline{C}H_2$, #1), 61.4 ($O\underline{C}H_2CH_3$, #1), 61.6 ($O\underline{C}H_2CH_3$, #2), 64.7 (2-$\underline{C}$H, #2), 64.9 (2-$\underline{C}$H, #1), 125.4 ($\underline{C}$H, #2), 125.7 ($\underline{C}$H, #1), 128.3 ($\underline{C}$H, #1), 128.4 ($\underline{C}$H, #2), 128.6 ($\underline{C}$H, #2), 128.9 ($\underline{C}$H, #1), 143.6 ($\underline{C}$, #1), 143.9 ($\underline{C}$, #2), 170.4 ($\underline{C}O_2$Et, #1), 170.6 ($\underline{C}O_2$Et, #2), 199.5 ($\underline{C}$=S, #1), 199.8 ($\underline{C}$=S, #2). IR (KBr) cm^{-1}: 2981, 1739, 1463, 1442, 1344, 1284, 1199, 763. MS EI(+) *m/z* (%): 263 ($M^{+\cdot}$, 75), 121 (100). *Anal.* Calcd for $C_{14}H_{17}NO_2S$: C, 63.85; H, 6.51; N, 5.32. Found: C, 63.62;

H, 6.26; N, 5.26.

(*S*)-Ethyl 1-(4-methoxyphenylcarbonothioyl)pyrrolidine-2-carboxylate (5b). Light yellowish needles. 62% yield (3 steps). mp 65−66 °C (hexane−AcOEt). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (t, *J* = 7.1 Hz, 0.66H, #2), 1.32 (t, *J* = 7.1 Hz, 2.34H, #1), 1.96 (m, 0.78H, #1), 2.17−2.06 (m, 0.66H, #2), 2.06−2.17 (m, 1.56H, #1), 2.31 (m, 0.22H, #2), 2.47 (m, 0.78H, #1), 3.62 (m, 0.78H, #1), 3.72 (m, 0.78H, #1), 3.80 (s, 0.66H, #2), 3.82 (s, 2.34H, #1), 3.99−4.09 (m, 0.44H, #2), 4.12 (q, *J* = 7.1 Hz, 0.44H, #2), 4.16 (q, *J* = 7.1 Hz, 1.56H, #1), 4.50 (dd, *J* = 8.4, 2.4 Hz, 0.22H, #2), 5.12 (dd, *J* = 8.5, 5.4 Hz, 0.78H, #1), 6.82 (dt, *J* = 9.3, 2.4 Hz, 0.44H, #2), 6.87 (dt, *J* = 9.3, 2.4 Hz, 1.56H, #1), 7.21 (d, *J* = 9.1 Hz, 0.44H, #2), 7.41 (dt, *J* = 9.3, 2.4 Hz, 1.56H, #1). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1 ($OCH_2\underline{C}H_3$, #2), 14.2 ($OCH_2\underline{C}H_3$, #1), 22.9 (4-$\underline{C}H_2$, #2), 25.3 (4-$\underline{C}H_2$, #1), 29.7 (3-$\underline{C}H_2$, #1), 31.6 (3-$\underline{C}H_2$, #2), 53.7 (5-$\underline{C}H_2$, #2), 54.3 (5-$\underline{C}H_2$, #1), 55.4 ($O\underline{C}H_3$, #2), 55.4 ($O\underline{C}H_3$, #1), 61.4 ($O\underline{C}H_2CH_3$, #1), 61.6 ($O\underline{C}H_2CH_3$, #2), 64.8 (2-$\underline{C}H$, #2), 65.1 (2-$\underline{C}H$, #1), 113.5 ($\underline{C}H$, #1), 113.6 ($\underline{C}H$, #2), 127.3 ($\underline{C}H$, #2), 127.8 ($\underline{C}H$, #1), 136.1 ($\underline{C}$, #1), 136.6 ($\underline{C}$, #2), 159.9 ($\underline{C}$-OCH_3, #1), 160.3 ($\underline{C}$-OCH_3, #2), 170.5 ($\underline{C}O_2Et$, #1), 170.8 ($\underline{C}O_2Et$, #2), 199.4 ($\underline{C}$=S, #1), 200.0 ($\underline{C}$=S, #2). IR (KBr) cm^{-1}: 2977, 1743, 1514, 1457, 1248, 1192, 1173, 1159, 1028, 830. MS EI(+) *m/z* (%): 293 ($M^{+\cdot}$, 88), 151 (100). *Anal.* Calcd for $C_{14}H_{17}NO_2S$: C, 61.41; H, 6.53; N, 4.77. Found: C, 61.49; H, 6.53; N, 4.70.

(*S*)-Ethyl 1-(4-chlorophenylcarbonothioyl)pyrrolidine-2-carboxylate (5c). Light yellowish needles. 65% yield (3 steps). mp 85−86 °C (hexane−AcOEt). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (t, *J* = 7.1 Hz, 0.69H, #2), 1.32 (t, *J* = 7.2 Hz, 2.31H, #1), 1.98 (m, 0.77H, #1), 2.06−2.19 (m, 0.69H, #2), 2.06−2.19 (m, 1.54H, #1), 2.32 (m, 0.23H, #2), 2.43 (m, 0.77H, #1), 3.54 (m, 0.77H, #1), 3.66 (m, 0.77H, #1), 4.01−4.15 (m, 0.88H, #2), 4.23−4.29 (m, 1.54H, #1), 4.41 (dd, *J* = 8.5, 2.4 Hz, 0.23H, #2), 5.10 (dd, *J* = 8.8, 5.2 Hz, 0.77H, #1), 7.19 (dt, *J* = 8.7, 2.2 Hz, 0.46H, #2), 7.29 (dt, *J* = 8.7, 2.0 Hz, 0.46H, #2), 7.32−7.36 (m, 3.08H, #1). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0 ($OCH_2\underline{C}H_3$, #2), 14.2 ($OCH_2\underline{C}H_3$, #1), 22.8 (4-$\underline{C}H_2$, #2), 25.2 (4-$\underline{C}H_2$, #1), 29.7 (3-$\underline{C}H_2$, #1), 31.6 (3-$\underline{C}H_2$, #2), 53.6 (5-$\underline{C}H_2$, #2), 54.1 (5-$\underline{C}H_2$, #1), 61.5 ($O\underline{C}H_2CH_3$, #1), 61.8 ($O\underline{C}H_2CH_3$, #2), 64.7 (2-$\underline{C}H$, #2), 64.9 (2-$\underline{C}H$, #1), 127.0 ($\underline{C}H$, #2), 127.2 ($\underline{C}H$, #1), 128.5 ($\underline{C}H$), 134.6 ($\underline{C}$, #2), 135.0 ($\underline{C}$, #1), 141.9 ($\underline{C}$-Cl, #1), 142.2 ($\underline{C}$-Cl, #2), 170.2 ($\underline{C}O_2Et$, #1), 170.5 ($\underline{C}O_2Et$, #2), 198.1 ($\underline{C}$=S, #1), 198.4 ($\underline{C}$=S, #2). IR (KBr) cm^{-1}: 2979, 1748, 1464, 1444, 1342, 1280, 1192, 1156, 1023, 832, 793, 467. MS EI(+) *m/z* (%): 299 ($M^{+\cdot}$+2, 26), 297 ($M^{+\cdot}$, 69), 157 (43), 155 (100). *Anal.* Calcd for $C_{14}H_{16}ClNO_2S$: C, 56.46; H, 5.42; N, 4.70. Found: C, 56.47; H, 5.60; N, 4.69.

(*S*)-Ethyl 1-(3,5-bis(trifluoromethyl)phenylcarbonothioyl)pyrrolidine-2-carboxylate (5d). Light yellowish needles. 60% yield (3 steps). mp 99−100 °C (hexane-AcOEt). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (t, *J* = 7.1 Hz, 0.69H, #2), 1.31 (t, *J* = 7.1 Hz, 2.31H, #1), 2.04 (m, 0.77H, #1), 2.12−2.24

(m, 0.69H, #2), 2.12−2.24 (m, 1.54H, #1), 2.37 (m, 0.23H, #2), 2.48 (m, 0.77H, #1), 3.51 (m, 0.77H, #1), 3.65 (m, 0.77H, #1), 4.00−4.18 (m, 0.92H, #2), 4.28 (m, 0.23H, #1), 4.23−4.33 (m, 1.54H, #1), 5.10 (dd, J = 8.6, 4.6 Hz, 0.77H, #1), 7.71 (s, 0.46H, #2), 7.82 (s, 0.23H, #2), 7.85 (s, 1.54H, #1), 7.86 (s, 0.77H, #1). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8 ($OCH_2\underline{C}H_3$, #2), 14.2 ($OCH_2\underline{C}H_3$, #1), 22.7 (4-$\underline{C}H_2$, #2), 25.3 (4-$\underline{C}H_2$, #1), 29.6 (3-$\underline{C}H_2$, #1), 31.7 (3-$\underline{C}H_2$, #2), 53.7 (5-$\underline{C}H_2$, #2), 54.2 (5-$\underline{C}H_2$, #1), 61.7 ($O\underline{C}H_2CH_3$, #1), 62.2 ($O\underline{C}H_2CH_3$, #2), 64.9 (2-$\underline{C}H$, #2), 65.0 (2-$\underline{C}H$, #1), 122.3 (m, $\underline{C}$-C-CF_3, #2), 122.6 (m, $\underline{C}$-C-CF_3, #1), 122.9 (q, $\underline{C}F_3$, $^1J_{CF}$ = 273 Hz,), 126.0 (m, $\underline{C}$-C-CF_3), 131.9 (q, $\underline{C}$-CF_3, $^2J_{CF}$ = 33 Hz, #2), 132.0 (q, $\underline{C}$-CF_3, $^2J_{CF}$ = 33 Hz, #1), 144.9 ($\underline{C}$, #1), 145.2 ($\underline{C}$, #2), 169.8 ($\underline{C}O_2Et$, #1), 170.2 ($\underline{C}O_2Et$, #2), 195.1 ($\underline{C}$=S, #1), 195.2 ($\underline{C}$=S, #2). IR (KBr) cm^{-1}: 2988, 2952, 1740, 1485, 1456, 1383, 1280, 1195, 1125, 898. MS EI(+) *m/z* (%): 399 ($M^{+\cdot}$, 45), 58 (100). *Anal.* Calcd for $C_{16}H_{15}F_6NO_2S$: C, 48.12; H, 3.79; N, 3.51. Found: C, 48.06; H, 4.22; N, 3.51.

(*S*)-Ethyl 1-(3,4,5-trimethoxyphenylcarbonothioyl)pyrrolidine-2-carboxylate (5e). Orange amorphous solid. 80% yield (3 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.18 (t, J = 7.1 Hz, 0.72H, #2), 1.34 (t, J = 7.1 Hz, 2.28H, #1), 1.98 (m, 0.76H, #1), 2.07−2.18 (m, 0.72H, #2), 2.07−2.18 (m, 1.52H, #1), 2.30 (m, 0.24H, #2), 2.44 (m, 0.76H, #1), 3.60 (m, 0.76H, #1), 3.69 (m, 0.76H, #1), 3.82 (s, 0.72H, #2), 3.84 (s, 1.44H, #2), 3.84 (s, 2.28H, #1), 3.86 (s, 4.56H, #1), 4.09−4.10 (m, 0.48H, #2), 4.12 (q, J = 7.1 Hz, 0.48H, #2), 4.27 (q, J = 7.1 Hz, 1.52H, #1), 4.45 (dd, J = 7.9, 2.0 Hz, 0.24H, #2), 5.10 (dd, J = 8.7, 5.1 Hz, 0.76H, #1), 6.47 (s, 0.48H, #2), 6.61 (s, 1.52H, #1). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1 ($OCH_2\underline{C}H_3$, #2), 14.2 ($OCH_2\underline{C}H_3$, #1), 22.8 (4-$\underline{C}H_2$, #2), 25.2 (4-$\underline{C}H_2$, #1), 29.7 (3-$\underline{C}H_2$, #1), 31.5 (3-$\underline{C}H_2$, #2), 53.4 (5-$\underline{C}H_2$, #2), 54.2 (5-$\underline{C}H_2$, #1), 56.2 ($O\underline{C}H_3$, #2), 56.3 ($O\underline{C}H_3$, #1), 60.8 ($O\underline{C}H_3$, #2), 60.9 ($O\underline{C}H_3$, #1), 61.5 ($O\underline{C}H_2CH_3$, #1), 61.7 ($O\underline{C}H_2CH_3$, #2), 64.8 (2-$\underline{C}H$, #2), 64.9 (2-$\underline{C}H$, #1), 103.0 ($\underline{C}H$, #2), 103.2 ($\underline{C}H$, #1), 138.2 ($\underline{C}$, #2), 138.6 ($\underline{C}$, #1), 139.0 ($\underline{C}$-OCH_3, #1), 139.3 ($\underline{C}$-OCH_3, #2), 153.1 ($\underline{C}$-OCH_3, #1), 153.1 ($\underline{C}$-OCH_3, #2), 170.5 ($\underline{C}O_2Et$, #1), 171.0 ($\underline{C}O_2Et$, #2), 199.1 ($\underline{C}$=S, #1), 199.4 ($\underline{C}$=S, #2). IR (NaCl) cm^{-1}: 2941, 1742, 1584, 1442, 1341, 1238, 1125, 832. MS EI(+) *m/z* (%): 353 ($M^{+\cdot}$, 42), 195 (100). HRMS EI(+) for $C_{17}H_{23}NO_5S$: Calcd, 353.1297. Found, 353.1287.

(*S*)-Ethyl 1-(2,2-dimethylpropanethioyl)pyrrolidine-2-carboxylate (5f). Colorless oil. 84% yield (3 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (t, J = 7.1 Hz, 3H), 1.43 (s, 9H), 1.94−2.06 (m, 2H), 2.18−2.28 (m, 2H), 3.93−4.03 (m, 2H), 4.18 (q, J = 7.1 Hz, 2H), 5.13 (dd, J = 8.8, 4.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1 ($OCH_2\underline{C}H_3$), 26.0 (4-$\underline{C}H_2$), 27.9 (3-$\underline{C}H_2$), 30.3 (CH_3), 43.7 ($\underline{C}(CH_3)_3$), 53.2 (5-$\underline{C}H_2$), 61.0 ($O\underline{C}H_2CH_3$), 68.6 (2-$\underline{C}H$), 170.8 ($\underline{C}O_2Et$), 211.4 ($\underline{C}$=S). IR (NaCl) cm^{-1}: 2976, 1739, 1409, 1195, 1164, 1023. MS EI(+) *m/z* (%): 243 ($M^{+\cdot}$, 49), 210 (100). HRMS EI(+) for $C_{12}H_{21}NO_2S$: Calcd, 243.1293. Found, 243.1299.

Hydrolysis of Proline Ethyl Ester Derivatives (5): A solution of **5** (2.50 mmol) and 2N NaOH (1.9 mL,

3.75 mmol) in dioxane (5 mL) was heated at 75 °C for 1 h. The reaction mixture was poured into H_2O (50 mL) and washed with Et_2O (50 mL). The aqueous layer was acidified with conc. HCl and extracted with AcOEt (70 mL x 2) followed by standard workup to give the desired acids (**1a-f**) in high yields.

(*S*)-1-(Phenylcarbonothioyl)pyrrolidine-2-carboxylic acid (1a). Yellow amorphous solid. 99% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.01 (m, 1H), 2.14 (m, 1H), 2.31 (m, 1H), 2.47 (m, 1H), 3.56 (m, 0.86H, #1), 3.66 (m, 0.86H, #1), 4.08−4.17 (m, 0.28H, #2), 4.50 (dd, *J* = 8.5, 2.1 Hz, 0.14H, #2), 5.22 (dd, *J* = 8.6, 5.1 Hz, 0.86H, #1), 7.32−7.41 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.2 (4-$\underline{C}H_2$), 29.5 (3-$\underline{C}H_2$), 54.1 (5-$\underline{C}H_2$), 64.6 (2-$\underline{C}$H), 125.7 ($\underline{C}$H), 128.4 ($\underline{C}$H), 129.2 ($\underline{C}$H), 143.3 ($\underline{C}$), 172.8 ($\underline{C}$=S), 200.0 ($\underline{C}O_2$H). IR (KBr) cm^{-1}: 3430, 2979, 2628, 1715, 1449, 1272, 1238, 1158, 760, 699. MS EI(+) *m/z* (%): 235 ($M^{+\cdot}$, 100). HRMS EI(+) for $C_{12}H_{13}NO_2S$: Calcd, 235.0667. Found, 235.0630.

(*S*)-1-(4-Chlorophenylcarbonothioyl)pyrrolidine-2-carboxylic acid (1b). Yellow amorphous solid. 98% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.01 (m, 1H), 2.15 (m, 1H), 2.27 (m, 1H), 2.48 (m, 1H), 3.55 (m, 0.86H, #1), 3.66 (m, 0.86H, #1), 4.09−4.15 (m, 0.28H, #2), 4.48 (m, 0.28H, #2), 5.18 (dd, *J* = 8.4, 5.3 Hz, 0.86H, #1), 7.20−7.35 (m, 4H). ^{13}C NMR (125 MHz, in $CDCl_3$) δ 22.7 (4-$\underline{C}H_2$, #2), 25.2 (4-$\underline{C}H_2$, #1), 29.6 (3-$\underline{C}H_2$, #1), 31.5 (3-$\underline{C}H_2$, #2), 53.4 (5-$\underline{C}H_2$, #2), 54.1 (5-$\underline{C}H_2$, #1), 64.6 (2-$\underline{C}$H, #1), 67.0 (2-$\underline{C}$H, #2), 126.9 ($\underline{C}$H, #2), 127.2 ($\underline{C}$H, #1), 128.6 ($\underline{C}$H, #1), 128.8 ($\underline{C}$H, #2), 134.8 ($\underline{C}$-Cl, #2), 135.2 ($\underline{C}$-Cl, #1), 141.5 ($\underline{C}$, #2), 142.0 ($\underline{C}$, #2), 175.3 ($\underline{C}O_2$H, #1), 175.6 ($\underline{C}O_2$H, #2), 198.4 ($\underline{C}$=S, #1), 198.8 ($\underline{C}$=S, #2). IR (NaCl) cm^{-1}: 2979, 1715, 1444, 1281, 1091, 826, 754. MS EI(+) *m/z* (%): 271 ($M^{+\cdot}$+2, 38), 269 ($M^{+\cdot}$, 100). HRMS EI(+) for $C_{12}H_{12}{}^{35}ClNO_2S$ ($C_{12}H_{12}{}^{37}ClNO_2S$): Calcd, 269.0277 (271.0248). Found, 269.0269 (271.0227).

(*S*)-1-(4-Methoxyphenylcarbonothioyl)pyrrolidine-2-carboxylic acid (1c). Yellowish needles. 98% yield. mp 152−154 °C (hexane−AcOEt). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.99 (m, 1H), 2.12 (m, 1H), 2.29 (m, 1H), 2.45 (m, 1H), 3.61−3.73 (m, 1.72H, #1), 3.79 (s, 0.42H, #2), 3.83 (s, 2.58H, #1), 3.85−4.14 (m, 0.28H, #2), 4.56 (dd, *J* = 8.2, 1.9 Hz, 0.14H, #2), 5.24 (dd, *J* = 8.4, 5.4 Hz, 0.86H, #1), 6.84−6.88 (m, 2H), 7.24 (d, *J* = 8.7 Hz, 0.28H, #2), 7.40 (d, *J* = 8.7 Hz, 1.72H, #1). ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.8 (4-$\underline{C}H_2$, #2), 25.3 (4-$\underline{C}H_2$, #1), 29.6 (3-$\underline{C}H_2$, #1), 31.5 (3-$\underline{C}H_2$, #2), 53.5 (5-$\underline{C}H_2$, #2), 54.3 (5-$\underline{C}H_2$, #1), 55.4 (O$\underline{C}H_3$), 64.4 (2-$\underline{C}$H, #2), 64.9 (2-$\underline{C}$H, #1), 113.5 ($\underline{C}$H, #1), 113.8 ($\underline{C}$H, #2), 127.2 ($\underline{C}$H, #2), 127.9 ($\underline{C}$H, #1), 135.7 ($\underline{C}$, #1), 136.3 ($\underline{C}$, #2), 160.0 ($\underline{C}$-OCH_3, #2), 160.5 ($\underline{C}$-OCH_3, #1), 175.6 ($\underline{C}O_2$H), 199.8 ($\underline{C}$=S). IR (NaCl) cm^{-1}: 2974, 1715, 1605, 1511, 1439, 1249, 1174, 832, 756. MS EI(+) *m/z* (%): 265 ($M^{+\cdot}$, 95), 151 (100). *Anal.* Calcd for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28. Found: C, 58.83; H, 5.83; N, 5.31.

(*S*)-1-(3,5-Bis(trifluoromethyl)phenylcarbonothioyl)pyrrolidine-2-carboxylic acid (1d). Yellow amorphous solid. 98% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.09 (m, 1H), 2.21 (m, 1H), 2.32 (m, 1H),

2.53 (m, 1H), 3.53 (m, 0.91H, #1), 3.66 (m, 0.91H, #1), 4.06−4.20 (m, 0.18H, #2), 4.76 (dd, J = 8.0, 5.2 Hz, 0.09H, #2), 5.17 (dd, J = 8.2, 4.8 Hz, 0.91H, #1), 7.85 (s, 2H), 7.88 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.7 (4-$\underline{C}H_2$, #2), 25.3 (4-$\underline{C}H_2$, #1), 29.6 (3-$\underline{C}H_2$, #1), 31.7 (3-$\underline{C}H_2$, #2), 53.7 (5-$\underline{C}H_2$, #2), 54.2 (5-$\underline{C}H_2$, #1), 64.7 (2-$\underline{C}$H, #1), 67.1 (2-$\underline{C}$H, #2), 122.4 (m, $\underline{C}$-C-CF_3, #2), 122.8 (m, $\underline{C}$-C-CF_3, #1), 122.9 (q, $\underline{C}F_3$, $^1J_{CF}$ = 273 Hz), 126.0 (m, $\underline{C}$-C-CF_3, #1), 127.7 (m, $\underline{C}$-C-CF_3, #2), 144.7 ($\underline{C}$, #1), 132.0 (q, $\underline{C}$-CF_3, $^2J_{CF}$ = 34 Hz), 145.1 ($\underline{C}$, #2), 175.0 ($\underline{C}O_2$H, #1), 175.7 ($\underline{C}O_2$H, #2), 195.5 ($\underline{C}$=S). IR (NaCl) cm^{-1}: 2983, 1719, 1478, 1451, 1379, 1280, 1179,1135. MS EI(+) *m/z* (%): 271 ($M^{+\cdot}$, 72), 257 (100). HRMS EI(+) for $C_{14}H_{11}F_6NO_2S$: Calcd, 374.0414. Found, 371.0410.

(*S*)-1-(3,4,5-Trimethoxyphenylcarbonothioyl)pyrrolidine-2-carboxylic acid (1e). Pale yellow crystals. 80% yield. mp 174–176 °C (hexane−AcOEt). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.96−2.05 (m, 1H), 2.10−2.18 (m, 1H), 2.24−2.31 (m, 1H), 2.44−2.52 (m, 1H), 3.59−3.72 (m, 2H, NCH_2), 3.81, 3.82, 3.84, 3.85, and 3.87 (s, 9H, OCH_3), 4.49 and 5.16 (dd, J = 8.3, 1.9 and 8.6, 5.4 Hz, 1H, NCH), 6.52 and 6.61 (s, 2H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.7 and 25.2 (*C*-4), 29.6 and 31.5 (*C*-3), 53.4 and 54.2 (*C*-5), 55.4, 56.2, 56.3, and 60.9 (O*C*H_3), 64.6 and 64.7 (*C*-2), 103.0 and 103.3 (*Ar*-2), 132.3 and 132.4 (*Ar*-1), 138.6 and 138.7 (*Ar*-4), 153.1 and 153.1 (*Ar*-3), 174.7 and 175.7 (*C*=O), 199.5 (*C*=S). IR (KBr) cm^{-1}: 3309, 2981, 2946, 1741, 1587, 1447, 1413, 1343, 1241, 1171, 1130, 994 826. MS EI(+) *m/z* (%): 325 ($M^{+\cdot}$, 100). *Anal.* Calcd for $C_{15}H_{19}NO_5S$: C, 55.37; H, 5.89; N, 4.30. Found: C, 55.35; H, 6.27; N, 4.28.

(*S*)-1-(2,2-Dimethylpropanethioyl)pyrrolidine-2-carboxylic acid (1f). White solid. 94% yield. mp 160–162 °C (hexane−AcOEt). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29 and 1.43 (s, 9H, CCH_3), 1.96−2.14 (m, 2H), 2.17−2.30 (m, 2H), 3.90−4.05 (m, 2H, NCH_2), 4.61−4.63 and 5.20−5.22 (m, 1H, NCH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.6 and 26.0 (C-4), 27.3 and 27.8 (C-3), 30.3, 43.8, 48.6 and 53.2 (C-5), 67.1 and 68.3 (C-2), 175.4 (C=O), 212.9 (C=S). IR (KBr) cm^{-1}: 2962, 1706, 1410, 1230, 1152, 937. MS EI(+) *m/z* (%): 215 ($M^{+\cdot}$, 47.9), 70 (100). *Anal.* Calcd for $C_{10}H_{17}NO_2S$: C, 55.78; H, 7.96; N, 6.51. Found: C, 55.94; H, 8.21; N, 6.52.

General Procedure for the Reaction of *N*-Thioacylproline with TFAA: To a stirred solution of TFAA (187 μL, 1.35 mmol), pyridine (217 μL, 2.69 mmol), and DMAP (16 mg, 0.14 mmol) in xylene (1 mL) was added the solution of **5** (0.45 mmol) in xylene (1 mL) at 0 °C. The additional amount of xylene (2.5 mL) was added, and the mixture was stirred at rt for 1 h and 138 °C for 12 h. The solvent was evaporated, and the residue was diluted with dioxane (2.7 mL). To the mixture was added 10% aq. HCl (0.9 mL), and the mixture was heated at 60 °C for 3 h. 10% aq. HCl (0.45 mL) was added and the whole was stirred for further 2 h. After workup with water, 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 = 10:1 to 2:1) to give the product **2**.

3-(2-Phenyl-5-(trifluoromethyl)thiazol-4-yl)propan-1-ol (2a). Colorless plate crystals. mp 64−65 °C (hexane−AcOEt). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.04 (quin, J = 6.6 Hz, 2H), 2.63 (br, 1H), 3.05 (t, J = 6.8 Hz, 2H), 3.74 (t, J = 6.1 Hz, 2H), 3.87 (s, 3H), 7.44−7.50 (m, 3H), 7.90 (dd, J = 7.7, 1.4 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.7 (CH_2), 31.6 (CH_2), 62.0 ($\underline{C}H_2OH$), 120.0 (q, F_3C-$\underline{C}$, $^2J_{CF}$ = 37.2 Hz), 122.6 (q, $\underline{C}F_3$, $^1J_{CF}$ = 269.6 Hz), 126.7 ($\underline{C}H$), 129.2 ($\underline{C}H$), 131.2 ($\underline{C}H$), 132.3 ($\underline{C}H$), 158.7 (q, F_3C-C=$\underline{C}$, $^3J_{CF}$ = 2.4 Hz), 168.8 ($\underline{C}$=N). IR (KBr) cm^{-1}: 3335, 2949, 2874, 1545, 1462, 1437, 1361, 1348, 1317, 1168, 1124, 1119, 1062, 1042, 1025, 903.; MS EI(+) *m/z* (%): 287 ($M^{+\cdot}$, 9), 243 (100).; HRMS ESI(+) for $C_{13}H_{12}F_3NOS$: Calcd, 288.0664. Found, 288.0642. *Anal.* Calcd for $C_{13}H_{12}F_3NOS$: C, 54.35; H, 4.21; N, 4.88. Found: C, 54.33; H, 4.26; N, 4.83. UV (EtOH) nm (Abs): 291 (2.65).

3-(2-(4-Methoxyphenyl)-5-(trifluoromethyl)thiazol-4-yl)propan-1-ol (2b). Colorless needles. mp 53−54 °C (hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.78 (br, 1H), 2.03 (quin, J = 6.5 Hz, 2H), 3.04 (tq, J = 7.0 Hz, $^3J_{HF}$ = 1.1 Hz, 2H), 3.74 (t, J = 6.0 Hz, 2H), 3.87 (s, 3H), 6.96 (dd, J = 11.7, 2.9 Hz, 2H), 7.85 (dd, J = 11.7, 2.9 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.8 (CH_2), 31.5 (CH_2), 55.5 ($O\underline{C}H_3$), 62.0 ($\underline{C}H_2OH$), 114.5 ($\underline{C}H$), 118.9 (q, F_3C-$\underline{C}$, $^2J_{CF}$ = 37.1 Hz), 122.7 (q, $\underline{C}F_3$, $^1J_{CF}$ = 269.4 Hz), 125.1 ($\underline{C}$), 128.3 ($\underline{C}H$), 158.4 (q, F_3C-C=$\underline{C}$, $^3J_{CF}$ = 2.1 Hz), 162.1 ($\underline{C}$-OCH_3), 168.8 ($\underline{C}$=N). IR (KBr) cm^{-1}: 3314, 2968, 2943, 2870, 2844, 1607, 1542, 1520, 1456, 1417, 1348, 1305, 1256, 1158, 1110, 1029, 831. MS EI(+) *m/z* (%): 317 ($M^{+\cdot}$, 14), 273 (100). *Anal.* Calcd for $C_{14}H_{14}F_3NO_2S$: C, 52.99; H, 4.45; N, 4.41. Found: C, 52.84; H, 4.41; N, 4.45.

3-(2-(4-Chlorophenyl)-5-(trifluoromethyl)thiazol-4-yl)propan-1-ol (2c). Colorless amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.04 (quin, J = 6.6 Hz, 2H), 2.29 (br, 1H), 3.04 (tq, J = 7.2 Hz, $^3J_{HF}$ = 1.2 Hz, 2H), 3.74 (t, J = 6.1 Hz, 2H), 7.44 (dd, J = 11.1, 2.5 Hz, 2H), 7.85 (dd, J = 11.1, 2.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.7 (CH_2), 31.6 (CH_2), 62.0 ($\underline{C}H_2OH$), 120.3 (q, F_3C-$\underline{C}$, $^2J_{CF}$ = 37.2 Hz), 122.5 (q, $\underline{C}F_3$, $^1J_{CF}$ = 269.7 Hz), 127.9 ($\underline{C}H$), 129.5 ($\underline{C}H$), 130.8 ($\underline{C}$-Cl), 137.4 ($\underline{C}$), 158.9 (q, F_3C-C=$\underline{C}$, $^3J_{CF}$ = 2.1 Hz), 167.4 ($\underline{C}$=N). IR (KBr) cm^{-1}: 3303, 2948, 2869, 1541, 1447, 1348, 1313, 1164, 1117, 1093, 1033, 1014, 833. MS EI(+) *m/z* (%): 323 ($M^{+\cdot}$+2, 4), 321 ($M^{+\cdot}$, 11), 277 (100). HRMS EI(+) for $C_{13}H_{11}ClF_3NOS$: Calcd, 321.0202. Found, 321.0182.

3-(5-(Trifluoromethyl)-2-(3,4,5-trimethoxyphenyl)thiazol-4-yl)propan-1-ol (2d). Colorless needles. mp 105 °C (hexane−AcOEt). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.05 (quin, J = 6.6 Hz, 2H), 3.04 (t, J = 6.9 Hz, 2H), 3.74 (t, J = 6.1 Hz, 2H), 3.91 (s, 3H), 3.94 (s, 6H), 7.12 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.8 (CH_2), 31.7 (CH_2), 56.4 ($O\underline{C}H_3$), 61.0 ($O\underline{C}H_3$), 62.1 ($\underline{C}H_2OH$), 104.7 ($\underline{C}H$), 119.7 (q, F_3C-$\underline{C}$, $^2J_{CF}$ = 37.2 Hz), 122.6 (q, $\underline{C}F_3$, $^1J_{CF}$ = 269.4 Hz), 127.7 ($\underline{C}$), 140.9 ($\underline{C}$-OCH_3), 153.7 ($\underline{C}$-OCH_3), 158.6 (q,

F_3C-C=C, $^3J_{CF}$ = 2.1 Hz), 168.7 (C=N). IR (KBr) cm^{-1}: 3307, 3208, 2934, 2883, 2837, 1586, 1542, 1515, 1460, 1436, 1411, 1352, 1320, 1236, 1148, 1134, 1115, 1063, 1038, 1026, 996. MS EI(+) *m/z* (%): 277 ($M^{+\cdot}$, 9), 61 (100). *Anal.* Calcd for $C_{16}H_{18}F_3NO_4S$: C, 50.92; H, 4.81; N, 3.71. Found: C, 50.79; H, 4.69; N, 3.81.

3-(2-(3,5-Bis(trifluoromethyl)phenyl)-5-(trifluoromethyl)thiazol-4-yl)propan-1-ol (2e). Colorless needles. mp 87−88 °C (hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.71 (br, 1H), 2.08 (quin, *J* = 6.8 Hz, 2H), 3.07 (t, *J* = 7.2 Hz, 2H), 3.76 (t, *J* = 6.2 Hz, 2H), 7.98 (s, 1H), 8.35 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 26.6 (CH_2), 31.9 (CH_2), 62.0 (CH_2OH), 121.9 (q, F_3C-C, $^2J_{CF}$ = 37.9 Hz), 124.3 (CH, $^3J_{CF}$ = 3.6 Hz), 122.2 (q, CF_3, $^1J_{CF}$ = 270.0 Hz), 122.9 (q, CF_3, $^1J_{CF}$ = 273.1 Hz), 126.6 (CH), 126.6 (CH), 132.9 (q, F_3C-C, $^2J_{CF}$ = 33.9 Hz), 134.4 (C), 159.8 (q, F_3C-C=C, $^3J_{CF}$ = 2.8 Hz), 164.9 (C=N). IR (KBr) cm^{-1}: 3291, 2940, 2880, 1539, 1368, 1321, 1284, 1232, 1173, 1136, 1025, 900. MS EI(+) *m/z* (%): 423 ($M^{+\cdot}$, 17), 379 (100). *Anal.* Calcd for $C_{15}H_{10}F_9NOS$: C, 42.56; H, 2.38; N, 3.31. Found: C, 42.73; H, 2.52; N, 3.42.

3-(2-*tert*-Butyl-5-(trifluoromethyl)thiazol-4-yl)propan-1-ol (2f). Light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.96 (quin, *J* = 6.4 Hz, 2H), 2.99 (tq, *J* = 6.8 Hz, $^3J_{HF}$ = 1.1 Hz, 2H,), 3.23 (br, 1H), 3.68 (t, *J* = 5.9 Hz, 2H,). ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.8 (CH_2), 30.6 ($C(CH_3)_3$), 31.3 (CH_2), 38.0 ($C(CH_3)_3$), 62.0 (CH_2OH), 119.1 (q, F_3C-C, $^2J_{CF}$ = 37.2 Hz), 122.7 (q, CF_3, $^1J_{CF}$ = 269.1 Hz), 157.2 (q, F_3C-C=C, $^3J_{CF}$ = 2.4 Hz), 183.5 (C=N). IR (NaCl) cm^{-1}: 3357, 2965, 2871, 1544, 1485, 1346, 1313, 1158, 1124, 1081, 1020. MS EI(+) *m/z* (%): 267 ($M^{+\cdot}$, 12), 223 (100). HRMS EI(+) for $C_{11}H_{16}F_3NOS$: Calcd, 267.0905. Found, 267.0882. UV (EtOH) nm (Abs): 242 (2.85), 219 (2.24).

Ethyl *N*-benzyl-*N*-thiobenzoylphenylalaninate. *N*-Benzoyl-*N*-benzylphenylalanine ethyl ester was prepared in good yield by Schotten-Baumann reaction of *N*-benzylphenylalanine ethyl ester and benzoyl chloride. A mixture of *N*-benzoyl-*N*-benzylphenylalanine ethyl ester (4.00 mmol), Lawesson's reagent (3.00 mmol), and pyridine (1.50 mmol) in toluene (20 mL) was heated at 90 °C for 5.5 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 = 10:1 to 5:1) to give the product. Pale yellow solid. 89% yield. mp 97–99 °C (hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09 and 1.25 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 3.07, 3.17, and 3.49 (dd, *J* = 14.4, 8.3 and 14.3, 6.5 and 14.1, 5.8 Hz, 2H, $ArCH_2C$), 3.59, 3.88, and 4.03–4.15 (dq, dq, and m, *J* = 10.7, 7.2 and 10.7, 7.1 Hz, 2H, CH_2CH_3), 4.68, 5.22, and 5.84 (d, *J* = 15.4, 15.3, and 15.3 Hz, $ArCH_2N$), 4.99 and 6.63 (t, *J* = 7.9 Hz, NCH), 6.82–6.84 (m, 1H, ArH), 7.03–7.05 (m, 2H, ArH), 7.17–7.45 (m, 12H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 14.1, 33.8, 35.7, 51.5, 61.4, 61.8, 65.0, 66.8, 125.4, 127.1, 127.1, 127.4, 127.8, 128.1, 128.3, 128.4, 128.5, 128.6,

128.6, 128.7, 129.5, 129.6, 134.5, 135.8, 137.8, 143.3, 143.8, 168.4, 158.6, 203.0. IR (KBr) cm^{-1}: 3066, 3027, 2980, 1732, 1495, 1476, 1437, 1275, 1258, 1240, 1220, 1055, 765, 746, 701. MS EI(+) *m/z* (%): 403 ($M^{+\cdot}$, 34.4), 121 (100). HRMS (EI) for $C_{25}H_{25}NO_2S$: Calcd, 403.1606. Found, 403.1616.

Preparation of *N*-benzyl-*N*-thiobenzoylphenylalanine (6a). A mixture of ethyl *N*-benzyl-*N*-thiobenzoylphenylalaninate (1.41 g, 3.50 mmol) and 2N aq NaOH (2.6 mL, 5.25 mmol) in dioxane (6.5 mL) was heated at 65 °C for 1 h. The reaction mixture was poured into water and washed with Et_2O. The aqueous layer was acidified with conc. HCl and extracted with AcOEt (x 3). The combined organic layers were washed with brine, dried over anhyd sodium sulfate, and evaporated to give **6a** as yellow amorphous, which was directly used for the next step without further purification.

Yellow amorphous solid. 98% yield. mp 56–58 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.02, 3.17, and 3.48 (dd, *J* = 14.5, 8.5 and 14.5, 6.0 and 14.5, 5.5 Hz, 2H, ArC*H*$_2$C), 4.63, 5.39, and 5.59 (d, *J* = 15.4, 15.5, and 15.4 Hz, 2H, ArC*H*$_2$N), 5.06−5.11 and 6.64 (m, 1H, NC*H*), 6.75 (d, *J* = 7.0 Hz, 1H, Ar*H*), 7.01−7.03 (m, 2H, Ar*H*), 7.15−7.43 (m, 7H, Ar*H*). ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.8, 35.7, 52.5, 64.6, 67.3, 125.7, 127.1, 127.2, 127.4, 127.8, 128.3, 128.4, 128.4, 128.5, 128.6, 128.6, 128.7, 128.8, 129.4, 129.4, 134.1, 135.6, 135.7, 137.2, 143.2, 143.3, 172.9, 173.8, 206.2. IR (KBr) cm^{-1}: 3061, 3029, 1712, 1443, 1225, 754, 698, 418. MS EI(+) *m/z* (%): 375 ($M^{+\cdot}$, 52.4), 91 (100). HRMS (EI) for $C_{23}H_{21}NO_2S$: Calcd, 375.1293. Found, 375.1291.

Ethyl *N*-(4-methoxybenzyl)-*N*-thiobenzoylphenylalaninate. *N*-Benzoyl-*N*-(4-methoxybenzyl)-phenylalanine ethyl ester was prepared in good yield by Schotten-Baumann reaction of *N*-(4-methoxybenzyl)phenylalanine ethyl ester and benzoyl chloride. A mixture of *N*-benzoyl-*N*-(4-methoxybenzyl)phenylalanine ethyl ester (2.00 mmol), Lawesson's reagent (1.50 mmol), and pyridine (0.76 mmol) in toluene (10 mL) was heated at 90 °C for 9 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 = 10:1 to 5:1) to give the product. Pale yellow solid. 83% yield. mp 82–85 °C (hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 and 1.26 (t, *J* = 7.2 and 7.2 Hz, 3H, CH_2C*H*$_3$), 3.06, 3.17, and 3.48 (dd, *J* = 14.5, 8.3 and 14.3, 6.4 and 14.2, 5.6 Hz, 2H, ArC*H*$_2$C), 3.63, 3.91, and 4.05–4.16 (dq, dq, and m, *J* = 10.8, 7.2 and 10.7, 7.1 Hz, 2H, C*H*$_2$CH$_3$), 3.77 and 3.80 (s, 3H, OC*H*$_3$), 4.61, 5.16, and 5.79 (d, *J* = 15.2, 15.1, and 15.0 Hz, 2H, ArC*H*$_2$N), 4.95–4.98 and 6.59 (m, 1H, NC*H*), 6.76 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.82–6.88 (m, 2H, Ar*H*), 6.94 (d, *J* = 8.6 Hz, 2H, Ar*H*), 7.18–7.41 (m, 8H, Ar*H*). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 14.1, 33.6, 35.6, 51.0, 55.3, 55.3, 61.4, 61.8, 64.7, 66.7, 113.7, 113.8, 125.4, 126.2, 127.0, 127.1, 127.7, 128.3, 128.4, 128.6, 128.7, 129.3, 129.5, 129.6, 130.1, 135.9, 137.9, 143.3, 143.8, 159.0, 159.5, 168.4, 168.6, 202.3, 205.7. IR (KBr) cm^{-1}: 2983, 2933, 2897, 2868, 2837, 1732,

1514, 1471, 1252, 1228, 1178, 1033, 763, 700. MS EI(+) *m/z* (%): 433 ($M^{+\cdot}$, 16.1), 121 (100). HRMS (EI) for $C_{26}H_{27}NO_3S$: Calcd, 433.1712. Found: 433.1701

Preparation of *N*-thiobenzoyl-*N*-(4-methoxybenzyl)phenylalanine (6b). A mixture of ethyl *N*-(4-methoxybenzyl)-*N*-thiobenzoylphenylalaninate (663 mg, 1.53 mmol) and 2N aq NaOH (1.15 mL, 2.29 mmol) in dioxane (3.1 mL) was heated at 65 °C for 1 h. The reaction mixture was poured into water and washed with Et_2O. The aqueous layer was acidified with conc. HCl and extracted with AcOEt (x 3). The combined organic layers were washed with brine, dried over anhyd sodium sulfate, and evaporated to give **6b** as yellow amorphous, which was directly used for the next step without further purification. Yellow amorphous solid. 96% yield. mp 61–64 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.03, 3.17, and 3.47 (dd, *J* = 14.3, 8.4 and 14.5, 5.7 and 14.4, 5.2 Hz, 2H, ArC*H*$_2$C), 3.76 (s, 3H, OC*H*$_3$), 4.56, 5.39, and 5.52 (d, *J* = 15.2, 15.1, and 15.0 Hz, 2H, ArC*H*$_2$N), 5.05 and 6.59 (s, 1H, NC*H*), 6.76 (d, *J* = 8.3 Hz, 2H, Ar*H*), 6.92 (d, *J* = 8.3 Hz, 2H, Ar*H*), 7.16–7.40 (m, 10H, Ar*H*). ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.7, 35.6, 52.0, 55.3, 64.2, 67.1, 113.8, 114.0, 125.7, 125.8, 127.1, 127.2, 128.0, 128.3, 128.4, 128.6, 128.7, 128.8, 129.4, 129.4, 130.0, 135.8, 137.3, 143.3, 159.0, 159.6, 172.9, 173.9, 206.1. IR (KBr) cm^{-1}: 3027, 1712, 1514, 1251, 1176, 1032, 761, 699. MS EI(+) *m/z* (%): 405 ($M^{+\cdot}$, 1.9), 121 (100). HRMS (EI) for $C_{24}H_{23}NO_3S$ (M^+): Calcd, 405.1399. Found, 405.1403.

4-Benzyl-2-phenyl-5-(trifluoromethyl)thiazole (7) and 4-benzyl-2-phenylthiazol-5(4*H*)-one (8). **7**: Light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.26 (s, 2H), 7.20−7.23 (m, 2H), 7.28−7.31 (m, 2H), 7.35−7.36 (m, 2H), 7.42−7.45 (m, 3H), 7.92 (dd, *J* = 7.9, 1.7 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.0 (CH_2), 120.4 (q, F_3C-C, $^2J_{CF}$ = 37.0 Hz), 122.7 (q, CF_3, $^1J_{CF}$ = 269.7 Hz), 126.6 (CH), 126.8 (CH), 128.5 (CH), 128.9 (CH), 129.1 (CH), 131.1 (CH), 132.6 (C), 138.0 (C), 157.3 (q, F_3C-C=C, $^3J_{CF}$ = 2.1 Hz), 168.8 (C=N). IR (NaCl) cm^{-1}: 3064, 3031, 2927, 2852, 1537, 1496, 1459, 1435, 1341, 1303, 1157, 1123, 1036, 1027. MS EI(+) *m/z* (%): 319 ($M^{+\cdot}$, 100). HRMS EI(+) for $C_{17}H_{12}F_3NS$: Calcd, 319.0643. Found, 391.0650. **8**: mp 132−133 °C (lit.,[9] mp 138–140 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.21 (dd, *J* = 13.8, 7.0 Hz, 1H), 3.47 (dd, *J* = 13.8, 4.7 Hz, 1H), 5.06 (dd, *J* = 7.0, 4.7 Hz, 1H), 7.12−7.53 (m, 8H), 7.76−7.77 (m, 2H).

Preparation of 4-Benzyl-2-phenyl-5-(trifluoromethyl)thiazole (7). A mixture of **11**[4] (244 mg, 0.76 mmol) and Lawesson's reagent (184 mg, 0.46 mmol) in 1,2-dimethoxyethane (DME, 4 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 **7** as a light yellow oil, 39 mg, 16% yield.

REFERENCES

1. (a) G. L. Buchanan, *Chem. Soc. Rev*., 1988, **17**, 91; (b) M. Kawase, M. Hirabayashi, and S. Saito,

Recent Res. Devel. Org. Chem., 2000, **4**, 283; (c) L. Dalla-Vechia, V. G. Santos, M. N. Godoi, D. Cantillo, C. V. Kappe, M. N. Eberlin, R. O. M. A. de Souza, and L. S. M. Miranda, *Org. Biomol. Chem*., 2012, **10**, 9013.

2. (a) R. Huisgen, H. Gotthardt, H. O. Bayer, and F. C. Schaefer, *Chem. Ber*., 1970, **103**, 2611; (b) F. M. Hershenson, *J. Org. Chem*., 1975, **40**, 1260; (c) I. Lalezeri and E. L. Schwartz, *J. Med. Chem.*, 1988, **31**, 1427.
3. (a) M. Kawase, H. Miyamae, and T. Kurihara, *Chem. Pharm. Bull*., 1998, **46**, 749; (b) M. Kawase, S. Saito, and T. Kurihara, *Chem. Pharm. Bull*., 2000, **48**, 1338; (c) M. Kawase, M. Hirabayashi, H. Koiwai, K. Yamamoto, and H. Miyamae, *Chem. Commun.,* 1998, 641; (d) M. Saeki, Y. Hagimoto, H. Uno, and M. Kawase, *Heterocycles*, 2008, **79**, 821.
4. M. Kolb, B. Neises, and F. Gerhart, *Liebigs Ann. Chem*., 1990, 1.
5. R. Saijo, K. Kurihara, and M. Kawase, *Heterocycles*, 2013, **87**, 2533.
6. R. H. Rynbrandt, E. E. Nishizawa, D. P. Balogoyen, A. R. Mendoza, and K. A. Annis, *J. Med. Chem*., 1981, **24**, 1507.
7. (a) L. F. Lee, F. M. Schleppnik, and R. K. Howe, *J. Heterocycl. Chem.*, 1985, **22**, 1621; (b) M. Moazzam, *Indian J. Chem.*, 1988, **27B**, 1051; (c) K. Burger, K. Geith, and D. Hubl, *Synthesis*, 1988, 189; (d) K. Burger, D. Hubl, and K. Geith, *Synthesis*, 1988, 194; (e) K. Burger, K. Geith, and D. Hubl, *Synthesis*, 1988, 199; (f) M. S. South, *J. Heterocycl. Chem.*, 1991, **28**, 1003 and 1013; (g) G. M. Dubowchik, J. A. Michne, D. Zuev, W. Schwartz, P. M. Scola, C. A. James, E. H. Ruediger, S. S. Pin, K. D. Burris, L. A. Balanda, Q. Gao, D. Wu, L. Fung, T. Fiedler, K. E. Browman, M. T. Taber, and J. Zhang, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3997; (h) C.-L. Liu, Z.-M. Li, and B. Zhong, *J. Fluorine Chem.*, 2004, **125**, 1287; (i) D. Zuev, J. A. Michne, S. S. Pin, J. Zhang, M. T. Taber, and G. M. Dubowchik, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 431; (j) C.-L. Liu, M. Li, H.-W. Chi, C.-Q. Hou, and Z.-M. Li, *J. Fluorine Chem.*, 2006, **127**, 796; (k) C.-L. Lin, Z.-M. Li, and B. Zhong, *J. Fluorine Chem.*, 2006, **127**, 1287.
8. (a) Y. Kamitori, M. Hojo, R. Masuda, M. Wada, and T. Takahashi, *Heterocycles*, 1994, **37**, 153; (b) Y. Martin-Cantalejo, B. Saez, J. Soto, M. J. Villa, and M. F. Brafia, *Synthesis*, 2003, 2211; (c) H.-Z. Jiang, W. Wan, M. Shao, and J. Hao, *Acta Cryst.,* 2008, **E64**, o2004; (d) M. A. Honey, R. Pasceri, W. Lewis, and C. J. Moody, *J. Org. Chem*., 2012, **77**, 1396.
9. Y. Lin and K. K. Andersen, *Eur. J. Org. Chem*., 2002, 557.