

Constructing 4-hydroxythiazole-5-carboxamide building blocks in one pot

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Received mm-dd-yyyy

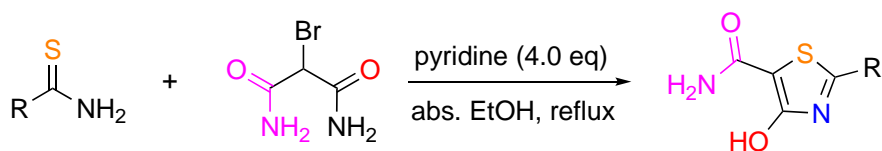
Accepted Manuscript mm-dd-yyyy

Published on line mm-dd-yyyy

Dates to be inserted by editorial office

Abstract

4-Hydroxythiazole-5-carboxamide units have been found in many bioactive compounds. However, the yield for its overall synthetic method is as low as 10%, which limits its further broad application in novel drug discovery. Herein, we report a concise method to prepare 4-hydroxythiazole-5-carboxamides using a thioamide and monobromomalonamide (2-bromopropanediamide) in one-step with good-to-excellent yields.

7 examples
yields up to 91%

Keywords: 4-Hydroxythiazole-5-carboxamide, one-pot, monobromomalonamide (2-bromopropanediamide), thioamide

Introduction

4-Hydroxythiazole-5-carboxamide has attracted rising attention recently, owing to the discovery that compounds with this motif show significant activity as transient receptor potential cation channel subfamily M member 8 (TRPM8) antagonists,^{1,2} proteasome inhibitors,³ antifungal succinate dehydrogenase Inhibitors,⁴ 11 β -hydroxysteroid dehydrogenase Type I inhibitors,⁵ GSK-3 inhibitors,⁶ et al. All these drug targets are directly related with somatic pain and ocular pain,¹ inflammation, ischemia, cancer,^{3,7} obesity,^{5,8} neurodegenerative disease^{9,10} treatment. For example, 2-(4-chlorophenyl)-4-(methoxymethoxy)-1,3-thiazole-5-carboxamide^{1,11} (**1**) (Figure 1) is reported to be a selective antagonist of TRPM8, 4-hydroxy-2-(pyridin-4-yl)thiazole-5-carboxamide (**2**) an inhibitor of the serine/threonine protein kinase Cdc7 in cancer cells.⁷ Also, 4-phenoxythiazol-5-carboxamides were developed into highly potent TGR5 (Takeda G-protein-coupled receptor 5) agonist, represented by (4-cyclopropyl-3,4-dihydro-1(2*H*)-quinoxaliny)[4-(2,6-dichlorophenoxy)-2-methyl-5-thiazolyl]methanone (**3**) the EC₅₀ of hTGR5 is 1.1 nm.⁸ 2-[2-(Cyclopropanecarbonylamino)pyridin-4-yl]-4-(cyclopropylmethoxy)-1,3-thiazole-5-carboxamide (**4**, thiazolypyridines) emerges as a highly selective GSK-3 β inhibitor.⁶ Besides as drug candidates, 4-hydroxythiazole-5-carboxamides are also found in antifungal succinate dehydrogenase inhibitors as potential novel fungicide candidates.⁴

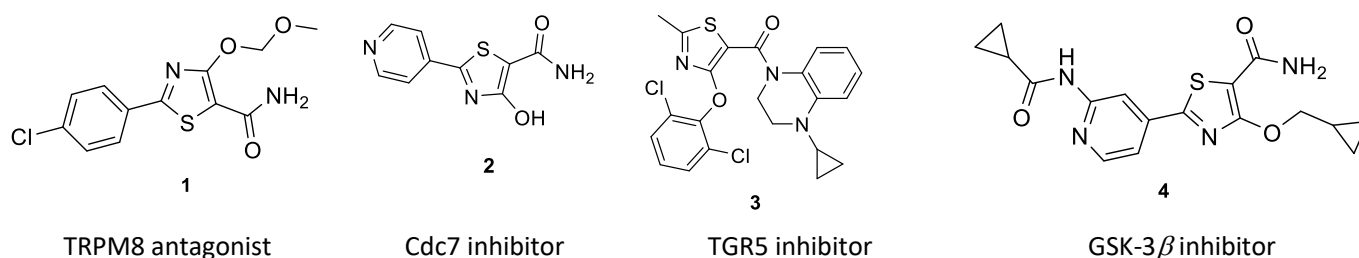
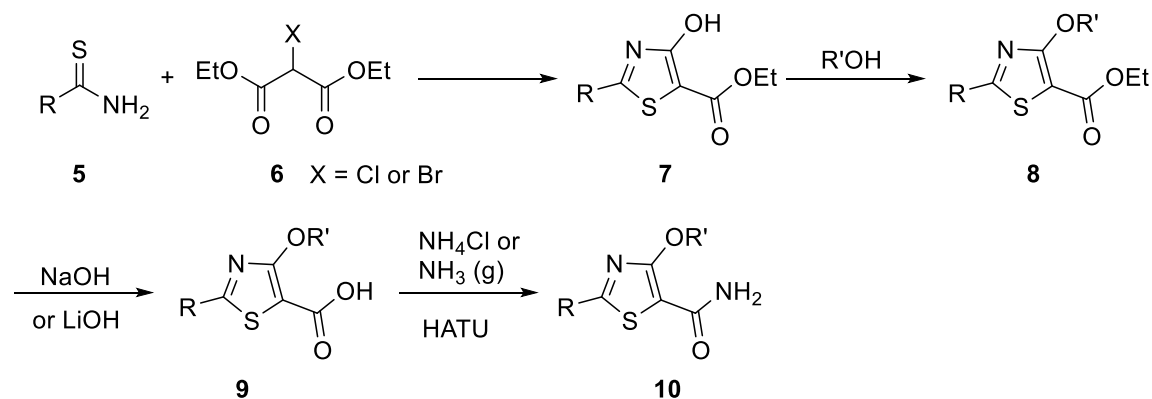


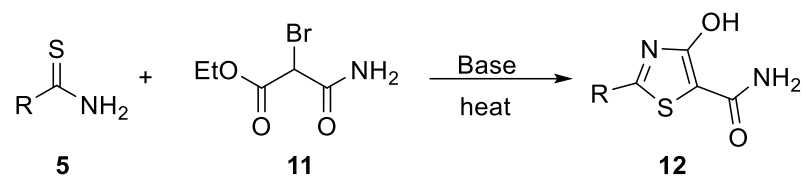
Figure 1. Bioactive compounds containing a 4-hydroxythiazole-5-carboxamide motif.

However, known methods to construct 4-hydroxythiazole-5-carboxamides are far from satisfactory. In general, they can be divided into two types, although both started with a carbothioamide. For method A,⁶ diethyl halomalonate (**6**) was condensed with a thioamide to generate thiazole (**7**), the newly generated hydroxyl group was alkylated, followed by hydrolysis of the ester to form free carboxylic acid (**9**), and finally, thiazolecarboxamide (**10**) was constructed via amidating the carboxylic acid with ammonia (g) or ammonium chloride. In total, there are four steps. For method B,⁷ a thiazolecarboxamide (**12**) was achieved in one step via condensation of a thioamide and ethyl 3-amino-2-bromo-3-oxopropanoate (**11**), however, the yield was only 3% (one example⁷ reported).

Method A:



Method B:

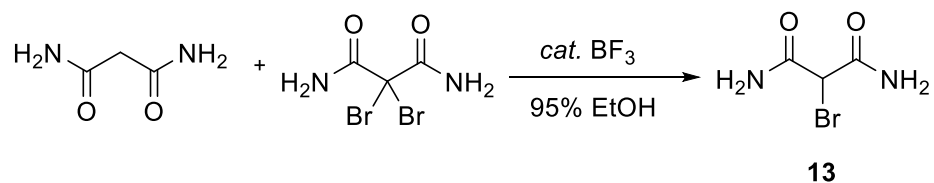


Scheme 1. Known methods for preparation of 4-hydroxythiazole-5-carboxamide motifs.

Results and Discussion

In our endeavors to prepare bioactive molecules containing 4-hydroxythiazole-5-carboxamides, it was necessary for us to find an efficient method. Theoretically, this could be achieved in one step by condensing a thioamide (**5**) with monobromomalonamide (**13**) in a 1:1 ratio (Scheme 2). Compared to method B, monobromomalonamide (**13**) is a much easier and cheaper building block, so we set off to explore our idea.

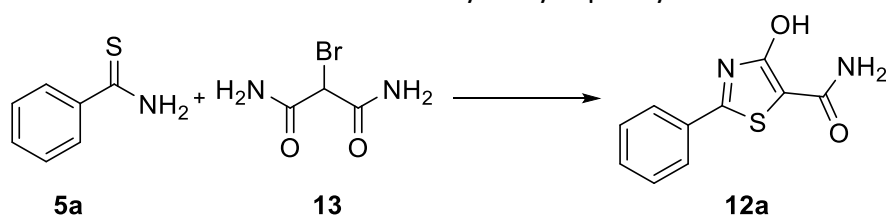
Monobromomalonamide (**13**) was prepared by Hata's procedure¹² (Scheme 2).



Scheme 2. Hata's procedure for preparation of monobromomalonamide (2-bromopropanediamide).

Using thiobenzamide (**5a**) as the model substrate, we screened one-pot conditions and the results are listed in Table 1.

Table 1. Optimization of conditions^a for formation of 4-hydroxy-2-phenylthiazole-5-carboxamide formation.



Entry	Solvent	Base (eq.)	Monobromo-malonamide (eq.)	Yield ^b
1	abs. EtOH	pyridine (2.0 eq)	1.0	47%
2	abs. EtOH	pyridine (4.0 eq)	1.0	91%
3	abs. EtOH	pyridine (4.0 eq)	2.0	83%
4	MeOH	pyridine (4.0 eq)	1.0	86%
5	<i>n</i> -PrOH	pyridine (4.0 eq)	1.1	61%
6	DMF	pyridine (4.0 eq)	1.0	19%
7	abs. EtOH	Et_3N (4.0 eq)	1.0	0

8	abs. EtOH	imidazole (4.0 eq)	1.0	0
9	abs. EtOH	K ₂ CO ₃ (anhy., 4.0 eq)	1.0	0
10	abs. EtOH	NaOAc (4.0 eq)	1.0	19%

Monobromomalonamide (0.75 mmol, 1.0 eq or 1.50 mmol, 2.0 eq.) was suspended in the solvent (10 mL), to which thiobenzamide (0.75 mmol) was added. Then, base (1.50 mmol, 2.0 eq or 3.00 mmol, 4.0 eq.) was added to the mixture. The reacting mixture was heated in 100 °C in an oil bath for 4 h in an atmosphere of N₂; yields are as isolated

Initially, using a 1:1 ratio of thiobenzamide to monobromomalonamide and 2.0 eq. of pyridine, 47% of 4-hydroxy-2-phenylthiazole-5-carboxamide (**12a**) was obtained (Table 1, entry 1). After two more equivalents of pyridine were added, an excellent yield was achieved (entry 2). Addition of one more equivalent of **13** did not generate a better yield, indeed the yield was slightly decreased (entry 3). The product is prone to precipitate during the reaction, which is in favor of the reaction, according to *Le Chatelier's* principle. When stronger base Et₃N or imidazole was used (*pK_a* is 10.75, 6.95, 5.21 for Et₃NH⁺, imidazolium and pyridinium respectively), no desired product was detected at all. This means strong basicity disfavors the reaction (entries 7 and 8). Inorganic bases also disfavor the reaction, poor solubility is an issue (entries 9 and 10). As a result, the optimized conditions are: thiobenzamide and monobromomalonamide (1.0 eq) heated to reflux in abs. ethanol, under the basic conditions provided by pyridine (4.0 eq.) for four hours.

With the optimized conditions in hand, we set off to explore the scope of substrates, and the results are shown in Table 2.

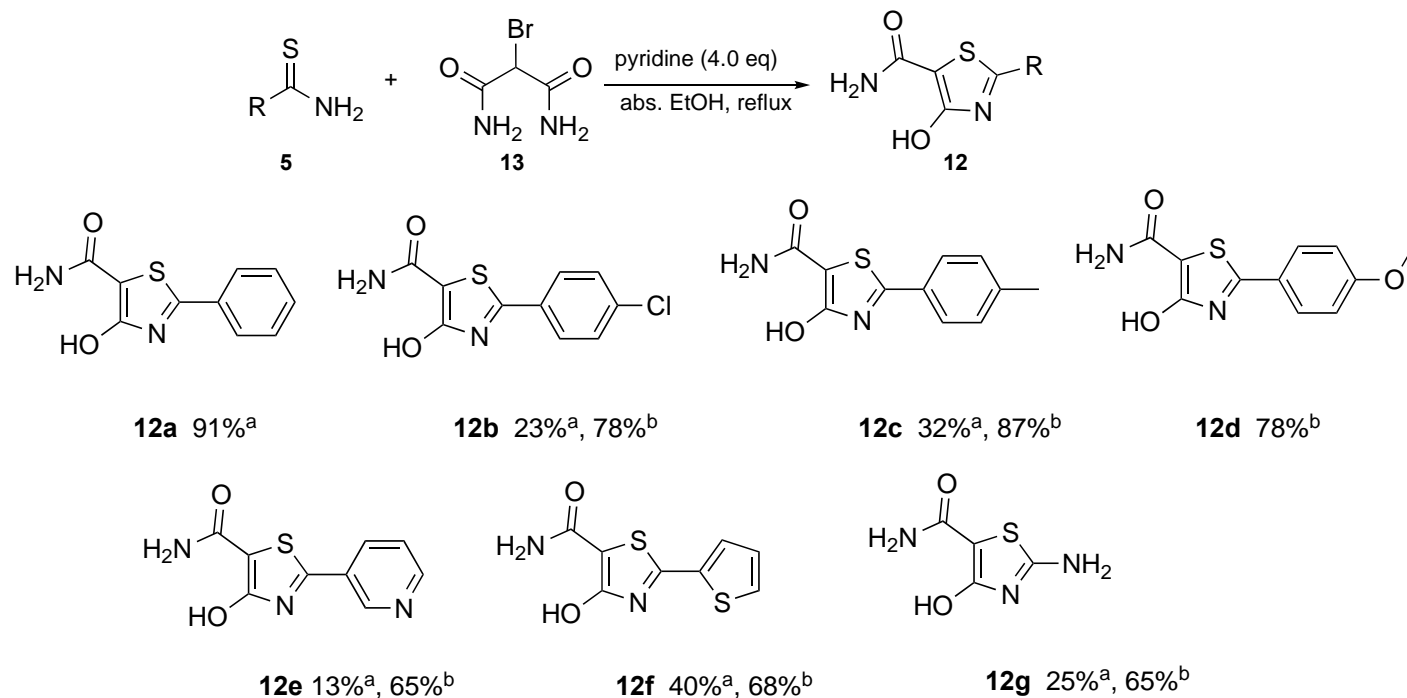
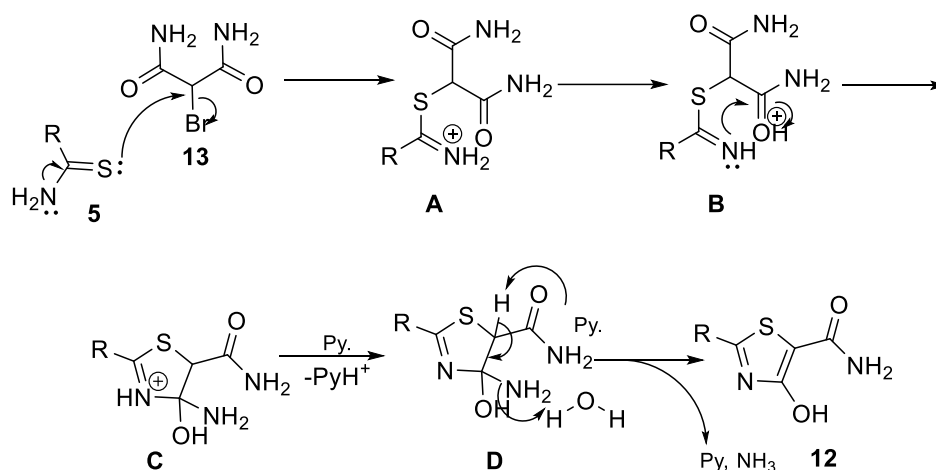


Table 2. Reaction scope of 4-hydroxythiazole-5-carboxamide synthesis in one-pot.^a

a. Reaction conditions: thiobenzamide (**5**) and monobromomalonamide (**13**, 1.0 eq) and pyridine (4.0 eq.) were dissolved in EtOH and the mixture was refluxed for 4 h under an atmosphere of N₂. The yields are as isolated. b. 1:5 Ratio of thiobenzamide (**5**) and monobromomalonamide (**13**) is applied.

This method applies to a rather broad scope of thioamides with good to excellent yields. Especially for thiobenzamides and the substrate on phenyl group is compatible with chloro-, methoxy- or methyl- groups (**5a**, **5b**, **5c** and **5d**). In terms of heteroaromatic thioamides, like thionicotinamide (**5e**) and thiophene-2-carbothioamide (**5f**), also gave good yields. Thiourea (**5g**) also worked in this conditions and gave a good yield. Except for thiobenzamide (**5a**) and monobromomalonamide (**13**) ratio of 1:1, the other six examples (**5b-5g**) all needed more equivalents of the thiobenzamides to give high yields. We conjecture that this might be because of low solubility and high electrophilicity of **13**, therefore, thioamides with low activity need excess of **13**. We have tried 2, 4 and 5 equiv. of **13** for substrate **12e**, but only 5 equiv. gave a good yield. Similarly, a 1:5 ratio of **13** to thioamide gave better yield than 1:1 ratio for **12b-d** and **12g**.

A plausible mechanism is shown in Scheme 3. Firstly, thioamide (**5**) attacks monobromomalonamide (**13**) via S_N2 reaction to form a new C-S bond in intermediate **A**. Then intramolecular cyclization via nitrogen/carbonyl attack forms intermediate **C**. After deprotonation of the α -carbon of the amide, ammonia is released and 4-hydroxythiazole-5-carboxamide (**12**) is generated.



Scheme 3. Plausible mechanism for formation of 4-hydroxythiazole-5-carboxamide in one-pot.

Conclusions

A one-pot method to form the 4-hydroxythiazole-5-carboxamide motif has been developed, which is to heat a mixture of a thioamides and monobromomalonamide under basic condition in absolute ethanol. The scope of substrates covers thiobenzamides, heteroaromatic thioamides, and thiourea. However, still some thioamides did not work in this conditions, like thioacetamide. This method offers a user-friendly alternative for building compounds comprising a 4-hydroxythiazole-5-carboxamide, and paves the way for developing such bioactive compounds into novel drugs.

Experimental Section

General. Solvents were analytical grade and used without further purification. The reactions were carried out in standard laboratory glassware. Melting points were recorded on a Binocular micro-melting point instrument from Beijing Taike Instrument Corporation. Infrared spectra were recorded on a Nicolet Avatar 370 DTGS equipment. ^1H NMR & ^{13}C NMR spectra were recorded on a Bruker AV500 or a Varian 400MR equipment. MS data was recorded on AB SCIEX X500R QTOF.

General procedure for preparation of 4-hydroxythiazole-5-carboxamides. To a 25 mL round-bottom flask, monobromomalonamide (120 mg, 0.66 mmol, 1.0 eq.) was added, followed by abs. EtOH (10 mL). To the solution, thiobenzamide (91 mg, 0.66 mmol) and anhyd. pyridine (220 mL, 224 mg, 2.829 mmol, 4.28 eq.) were added and the mixture was heated at reflux for 4 h. After cooling down to rt, the suspension was filtered to afford a yellow solid (86 mg, 0.39 mmol), and the filtrate was concentrated and purified via flash chromatography to afford a yellow solid (46 mg, 0.21 mmol), the overall yield being 91%. (Note : a. ratio of thioamide and monobromomalonamide is 1 :1. b . ratio of thiamide of monobromomalonamide is 1 :5))

4-hydroxy-2-phenylthiazole-5-carboxamide (12a). Yellow solid (132 mg, 0.60 mmol), yield 91%^a. Mp 245-247 °C. $R_f = 0.35$ (DCM-MeOH, 5:1). ^1H NMR (400 MHz, TFA-d) δ 7.79 (d, J 7.8 Hz, 2H, 2-Ph-H-3'&5'), 7.67 (t, J 7.5 Hz, 1H, 2-Ph-H-4'), 7.53 (t, J 7.7 Hz, 2H, 2-Ph-H-2'&6'), 3.79 (s, 2H, CONH₂). ^{13}C NMR (101 MHz, TFA-d) δ 170.3, 136.3, 130.4, 126.6, 124.9, 115.9, 113.1. IR (KBr pellet) ν_{max} 3437, 3279, 3151, 1642, 1544, 1479, 1380, 1119, 764, 681 cm^{-1} . MS (ESI) m/z (%) = 221.0 ([M+H]⁺).

2-(4-Chlorophenyl)-4-hydroxythiazole-5-carboxamide (12b). Pale yellow powder (52 mg, 0.204 mmol), yield 78%^b. Mp >300 °C (dec). $R_f = 0.41$ (DCM-MeOH, 5:1). ^1H NMR (400 MHz, DMSO- d_6) δ 12.90 (br s, 1H, OH), 7.92 (d, J 8.0 Hz, 2H, 2-Ph-H-3'&5'), 7.59 (d, J 8.0 Hz, 2H, 2-Ph-H-2'&6'), 7.59 (br s, 1H, CONH_a), 7.24 (br s, 1H, CONH_b). ^{13}C NMR (101 MHz, DMSO- d_6) δ 164.1, 162.9, 162.5, 135.7, 131.3, 129.4, 127.5, 104.6. IR (KBr pellet) ν_{max} 3427, 3287, 3169, 1645, 1544, 1430, 1361, 1094, 828 cm^{-1} . HRMS calc. for C₁₀H₈ClN₂O₂S⁺ 254.9990, found 254.9986.

4-Hydroxy-2-(4-methylphenyl)thiazole-5-carboxamide (12c). Yellow solid (58 mg, 0.25 mmol), yield 87%^b. Mp 268-270 °C. $R_f = 0.40$ (DCM-MeOH, 5:1). ^1H NMR (400 MHz, TFA-d) δ 7.70 (d, J 8.0 Hz, 2H, 2-Ph-H-3'&5'), 7.36 (d, J 6.8 Hz, 2H, 2-Ph-H-2'&6'), 2.37 (s, 3H, CH₃). ^{13}C NMR (101 MHz, TFA-d) δ 170.7, 149.8, 131.3, 126.9, 122.3, 20.5. IR (KBr pellet) ν_{max} 3736, 3432, 3287, 3165, 1542, 1485, 1433, 1359, 817 cm^{-1} . ESI-HRMS: calcd. For C₁₁H₁₁N₂O₂S ([M+H]⁺) 235.0536; found 235.0538.

4-Hydroxy-2-(4-methoxyphenyl)thiazole-5-carboxamide (12d). Yellow solid (51 mg, 0.20 mmol), yield 78%^a. Mp 279-280 °C. $R_f = 0.47$ (DCM-MeOH, 5:1). ^1H NMR (400 MHz, TFA-d) δ 7.75 (d, J 8.7 Hz, 2H, 2-Ph-H-3'&5'), 7.01 (d, J 8.7 Hz, 2H, 2-Ph-H-2'&6'), 3.81 (s, 3H, CH₃). ^{13}C NMR (101 MHz, TFA-d) δ 170.1, 167.0, 129.5, 117.6, 116.2, 55.4. IR (KBr, pellet) ν_{max} 3433, 3147, 1609, 1580, 1415, 1267, 1178, 829 cm^{-1} . TOF-HRMS calcd. for C₁₁H₈NO₃S⁺ ([M-NH₃+H]⁺) 234.0219, found 234.0215.

4-Hydroxy-2-(3-pyridyl)thiazole-5-carboxamide (12e). Yellow solid (49 mg, 0.22 mmol), yield 65%^b. Mp >297 °C (dec). $R_f = 0.42$ (DCM-MeOH, 2:1). ^1H NMR (400 MHz, TFA-d) δ 9.27 (s, 1H, pyridyl-H-2'), 8.90 (d, J 8.3 Hz, 1H, pyridyl-H-6'), 8.86 (d, J 5.9 Hz, 1H, pyridyl-H-4'), 8.14 (dd, J 8.3, 5.9 Hz, 1H, pyridyl-H-5'). ^{13}C NMR (101 MHz, TFA-d) δ 164.6, 161.6, 160.8, 144.3, 142.9, 139.4, 132.3, 128.7. IR (KBr pellet) ν_{max} 3442, 3145, 1669, 1617, 1448, 1426, 1118, 694 cm^{-1} . ESI-HRMS: calcd. For C₉H₈N₃O₂S ([M+H]⁺) 222.0332; found 222.0335.

4-Hydroxy-2-(3-thienyl)thiazole-5-carboxamide (12f). Yellow solid (52 mg, 0.23 mmol), yield 68%^b. Mp >258 °C (dec). $R_f = 0.31$ (DCM-MeOH, 5:1). ^1H NMR (400 MHz, TFA-d) δ 7.92 (d, J 4.0 Hz, 1H, thienyl-H-3'), 7.86 (d, J 4.9 Hz, 1H, thienyl-H-5'), 7.24 (t, J 4.6 Hz, 1H, thienyl-H-4'). ^{13}C NMR (101 MHz, TFA-d) δ 166.3, 163.2, 163.0,

136.9, 134.0, 130.4, 127.5, 91.1. IR (KBr pellet) ν_{\max} 3436, 3274, 1636, 1533, 1446, 1363, 1119, 697 cm^{-1} . ESI-HRMS: calcd. For $\text{C}_8\text{H}_7\text{N}_2\text{O}_2\text{S}_2$ ($[\text{M}+\text{H}]^+$) 226.9943; found 226.9947.

2-Amino-4-hydroxythiazole-5-carboxamide (12g). Yellow solid (41 mg, 0.26 mmol), yield 65%^b. Mp >236 °C (dec). R_f = 0.38 (DCM-MeOH, 5:1). ^1H NMR (400 MHz, DMSO- d_6) δ 9.17 (s, 1H, CONH_a), 8.93 (s, 1H, CONH_b), 7.71 (s, 1H, NH_a), 7.40 (s, 1H, NH_b), 4.03 (s, 1H, OH). ^{13}C NMR (101 MHz, DMSO- d_6) δ 184.8, 182.1, 167.0. IR (KBr pellet) ν_{\max} 3392, 3250, 3046, 1675, 1621, 1485 cm^{-1} . TOF-HRMS calcd. For $\text{C}_4\text{H}_5\text{N}_3\text{O}_2\text{S}$ ($[\text{M}+\text{H}]^+$) 160.0175, found 160.0178.

Acknowledgements

This project is supported by National Key R&D Program of China (No. 2018YFE0208600) and Jiangsu University Postdoctoral daily funding funds (No. 5363000742).

Supplementary Material

Full experimental details, IR, ^1H NMR, and ^{13}C NMR data for this article can be accessed on the [publisher's website](#).

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