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Facile Access to *N*-Thiazolyl α-Amino Acids from α-Bromo Ketones and α-Amino Acids

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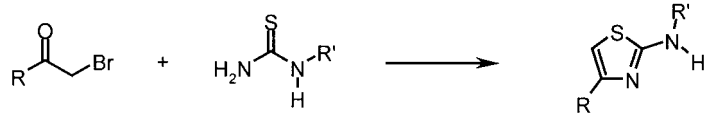
Abstract—*N*-Substituted 2-aminothiazoles are synthesized in a one-pot procedure using readily available α-bromo ketones and amines. This method is compatible with a wide range of functional groups and offers a facile and efficient access to the class of *N*-thiazolyl α-amino acid derivatives.

Introduction

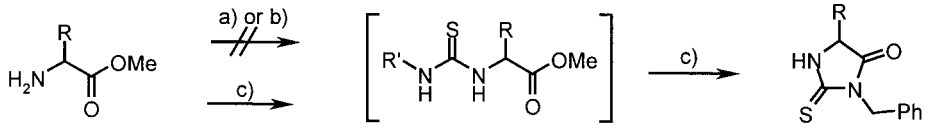
The 2-aminothiazole group is a common functionality in medicinal chemistry.[1] The preferred method for its formation is the classical Hantzsch synthesis.[2] Following the Hantzsch protocol, *N*-monosubstituted thioureas are treated with α-halo ketones to form the *N*-substituted 2-aminothiazole derivative (Scheme 1).

In our laboratory, we were interested in accessing the class of *N*-thiazolyl α-amino acids. With the exception of the corresponding glycine derivatives, not many examples of this compound class exist in the literature.[3] Using different methods, we tried to synthesize the thiourea derivatives of selected amino acids as starting materials for the Hantzsch reaction. In our hands, none of these methods gave the desired compounds: Whereas no reaction occurred with ammonium thiocyanate,[4] reaction with trimethylsilylisothiocyanate[5] led to decomposition. Using benzyl isothiocyanate,[6] we observed further conversion to the corresponding thiohydantoine (Scheme 2). We speculate that such a cyclization reaction may be an intrinsic problem of thiourea derivatives of α-amino acids in general.

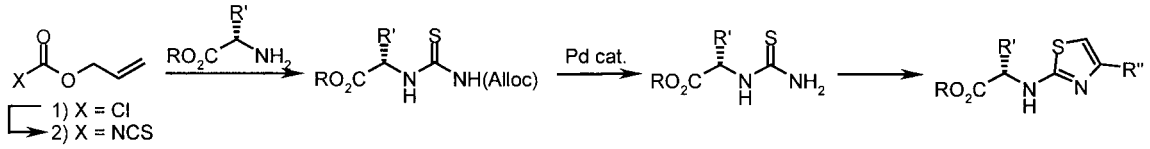
However, in a recent paper, an approach to the formation of the thiourea derivative of an α-amino acids used for a



Scheme 1.



Scheme 2. (a) NH_4SCN; R′=H, (b) Me_3SiNCS; R′=Me_3Si, (c) BnNCS; R′=Bn



Scheme 3.

Keywords: thiazoles; amines; amino acids and derivatives; thiocyanates.

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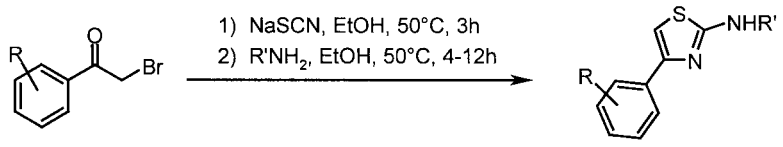
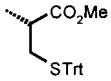
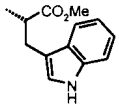
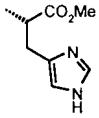
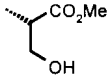
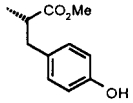
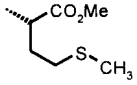
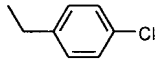
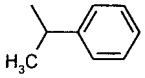
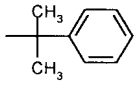
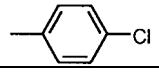
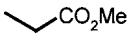
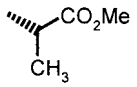
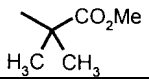


Scheme 4.

Table 1. Reaction products from two selected aryl bromo ketones and various amino acids and amines

	R =	Isolated yield[a] (%)	Melting point (°C)
1		43	131–133
2		45	77–80
3		34	144–148
4		39	156–158
5		32	150–152
6		58	120–123
7		45	78–79
8		31	155–156
9		18	152–154
10		0	–
11		99[b]	204–205
	R =	Isolated yield (%)	Melting point (°C)
12		96[b]	118–120
13		41	109–110
14		0	–

[a] Yields have not been optimized.
[b] No column chromatography required.

subsequent Hantzsch reaction has been described. This method involves a three step procedure using allyloxycarbonyl isothiocyanate.[7] We assume that no cyclization to the thiohydantoine derivative occurs in this case because the allyloxycarbonyl group sufficiently decreases the nucleophilicity of the thiourea nitrogen atom (Scheme 3).

Results

Due to our unfavorable experiences, we preferred to circumvent the synthesis of the thiourea derivatives of α-amino acids required for the Hantzsch reaction by finding a more direct approach for the synthesis of the *N*-thiazolyl α-amino acids. From the literature, it is known that 2-aminothiazoles can be formed from amines and α-thiocyanato ketones. However, under the reaction conditions applied, yields were low in most cases, rendering this method unsatisfactory for general application.[8]

In this report, we present a revised simple one-pot procedure that allows the rapid synthesis of *N*-thiazolyl α-amino acid derivatives and *N*-substituted 2-aminothiazoles in general. The α-bromo ketone is being transformed into the corresponding α-thiocyanato ketone by treating it with sodium thiocyanate in ethanol at 50°C. Subsequent addition of the amino acid ester in the same pot at the same temperature and reaction for 4–12 h yields the corresponding 2-aminothiazole in a clean reaction (Scheme 4).

During the course of our work, an Austrian group independently discovered this method using a slightly different protocol.[9] However, the scope of their work was only focused on aliphatic and aromatic amines and diamines with no additional functional groups. In our work we kept the bromo ketone part constant and focused on varying the amine part. We found that this method is highly compatible with a range of functional groups, e.g. esters, thioethers (Table 1, entry 7), S–S bonds (entry 3), alcohols (entry 5), phenols (entry 6), tertiary and secondary amino groups (entries 2 and 4).

In most cases complete conversion of the starting material was observed, however, a small percentage (15% or less) of byproducts was found. Purification of most aminothiazoles was accomplished by flash chromatography. Due to poor solubility, the reaction product had to be absorbed onto the silica gel, and considerable product loss was observed during chromatography.

Selectivity of the reaction appears to decrease with increasing substitution at the α-C atom of the amine part (see entries 12–14): With α-mono-substituted amines, no side reactions are observed; with α,α-disubstituted amines, reactions are still highly selective; and with α,α,α-trisubstituted amines no reaction occurs. The only tested aniline was converted quantitatively to the product (entry 11). Among the solvents investigated, only ethanol proved to be suitable, in DMF or acetonitrile, the reaction did not proceed.

In summary, we have found a simple procedure for synthesizing the interesting class of *N*-thiazolyl α-amino acids from readily available starting materials. This reaction may find wide application for the laboratory scale and combinatorial synthesis of *N*-substituted 2-aminothiazoles.

Experimental

General

Melting points were obtained on a Gallenkamp melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. HPLC analyses were performed on a Waters Alliance 2690 system (flow: 1 mL/min) with a CC12/4 Nucleosil 100–5C_{18}-HD column (detection: λ=210 nm) and the following gradient program: 2 min 100% H_2O; 10 min 100% H_2O to 100% CH_3CN; 3 min 100% CH_3CN (each solvent with 0.01% HCO_2H added). ^{1}H NMR spectra were recorded on Bruker DPX400 spectrometers in $CDCl_3$ or DMSO-d_6 using the solvent signals as internal references. The chemical shifts are reported in δ (ppm) relative to TMS and the coupling constants (*J*) are given in Hertz (Hz). Electrospray-high resolution mass spectrometry (ESI-HRMS) was performed on a Finnigan-MAT 900 double focusing mass spectrometer. The ESI source was operated in the positive ion mode, spray needle voltage 3.5 kV, nitrogen sheath gas pressure 500 kPa, and the heated metal capillary held at 250°C.

All reactions were monitored by analytical TLC on aluminum backed TLC plates coated with silica gel (Merck Si 60 F_{254}) and visualization of spots was accomplished by UV detection. Column chromatography was carried out using Amicon silica gel (30–70 μm) using a mixture of cyclohexane and ethyl acetate as an eluent.

General procedure for the synthesis of the aminothiazoles 1–14

20.5 mmol of the α-bromo ketone and 1.78 g dry sodium thiocyanate (22.0 mmol) are stirred in 50 mL ethanol for 3 h at 50°C. A solution of 20.5 mmol of the amine (in the case of **3** 10.5 mmol of the amine) in 20 mL ethanol is added at once and the reaction mixture is stirred for 4–12 h (monitoring by TLC). The ethanol is distilled off, and ethyl acetate and water are added. The aqueous phase is extracted twice with ethyl acetate, the combined organic phases are dried with Na_2SO_4, and the solvent is removed in vacuo. In the cases of **10** and **14** no product was obtained. In the cases of **11** and **12** no further purification was needed according to ^{1}H NMR and HPLC analysis. Otherwise, the product was absorbed onto silica gel and purified via column chromatography.

(*S*)-(+)-*N*-[4-(4-Nitro-phenyl)-thiazol-2-yl]-*S*-(triphenyl-methyl)-cysteine methyl ester (1). Purified by flash chromatography on silica gel (cyclohexane/ethylacetate, 6:1 to 4:1) to give 5.13 g, 43% product as a dark yellow solid; mp 131–133°C; $[\alpha]_D^{25}$=+8.5 (*c* 1.0, CH_3CN/H_2O 95:5); HPLC: t_R=13.53 min; TLC (cyclohexane/ethylacetate, 2:1): R_f=0.58; ^{1}H NMR (400 MHz, DMSO-d_6): δ=2.60 (m, 1H, CH_2), 2.71 (m, 1H, CH_2), 3.60 (s, 3H, OCH_3), 4.32 (m, 1H, CH), 7.20–7.33 (m, 15H, Trityl-H), 7.52 (s, 1H, thiazole-H), 7.99 (d, *J*=8.9 Hz, 2H, ArH), 8.26

(d, J=8.9 Hz, 2H, ArH), 8.36 (d, J=7.8 Hz, 1H, NH); ^{13}C NMR (100.4 MHz, $CDCl_3$): δ=33.5, 52.8, 56.3, 67.0, 105.8, 124.0, 126.4, 126.9, 128.0, 129.5, 140.6, 144.3, 146.8, 148.9, 166.6, 171.3; HRMS (ESI) calcd for $[M+H]^+$ $C_{32}H_{28}N_3O_4S_2$ 582.15213, found 582.15253.

(*S*)-(−)-*N*-[4-(4-Nitro-phenyl)-thiazol-2-yl]-tryptophan methyl ester (2). Purified by flash chromatography on silica gel (cyclohexane/ethylacetate, 2:1) to give 3.89 g, 45% product as a yellow solid; mp 77–80°C; $[\alpha]_D^{25}$=−5.47 (*c* 0.95, CH_3CN/H_2O 95:5); HPLC: t_R=11.61 min; TLC (cyclohexane/ethylacetate, 2:1): R_f=0.30; ^{1}H NMR (400 MHz, DMSO-d_6): δ=3.19 (dd, J=14.5 Hz, 8.6 Hz, 1H, CH_2), 3.28 (dd, J=14.5 Hz, 5.8 Hz, 1H, CH_2), 3.61 (s, 3H, OCH_3), 4.70 (m, 1H, CH), 7.49 (s, 1H, thiazole-H), 7.01 (m, 1H, indole-H), 7.08 (m, 1H, indole-H), 7.21 (d, J=2.3 Hz, 1H, indole-H), 7.34 (d, J=7.9 Hz, 1H, indole-H), 7.56 (d, J=7.9 Hz, 1H, indole-H), 8.01 (d, J=9.0 Hz, 2H, ArH), 8.26 (d, J=9.0 Hz, 2H, ArH); ^{13}C NMR (100.4 MHz, $CDCl_3$): δ=27.9, 52.6, 58.4, 105.2, 109.6, 111.4, 118.5, 119.7, 122.3, 123.3, 124.1, 126.5, 127.4, 136.2, 139.7, 146.9, 147.8, 167.8, 172.3; HRMS (ESI) calcd for $[M+H]^+$ $C_{21}H_{19}N_4O_4S$ 423.11270, found 423.11210.

(*S*,*S*)-(+)-*N*,*N*-Bis[4-(4-nitro-phenyl)-thiazol-2-yl]-cystine dimethyl ester (3). Purified by flash chromatography on silica gel (cyclohexane/ethylacetate, 2:1) to give 2.37 g, 34% product as a yellow solid; mp 144–148°C (phase change at 70–80°C); $[\alpha]_D^{25}$=+9.1 (*c* 0.90, CH_3CN/H_2O 95:5); HPLC: t_R=12.25 min; TLC (cyclohexane/ethylacetate, 2:1): R_f=0.26; ^{1}H NMR (400 MHz, DMSO-d_6): δ=3.19 (m, 2H, 2×CH_2), 3.32 (m, 2H, 2×CH_2), 3.69 (s, 6H, 2×OCH_3), 4.82 (m, 2H, 2×CH), 7.41 (s, 2H, 2× thiazole-H), 8.02 (d, J=8.9 Hz, 4H, ArH), 8.19 (d, J= 8.9 Hz, 4H, ArH), 8.36 (d, J=7.9 Hz, 2H, 2×NH); ^{13}C NMR (100.4 MHz, DMSO-d_6): δ=52.1, 56.0, 107.0, 123.7, 126.2, 140.6, 146.0, 147.5, 167.0, 171.2; HRMS (ESI) calcd for $[M+H]^+$ $C_{26}H_{25}N_6O_8S_4$ 677.06168, found 677.06218.

(*S*)-(−)-*N*-[4-(4-Nitro-phenyl)-thiazol-2-yl]-histidine methyl ester (4). Purified by flash chromatography on silica gel (CH_2Cl_2/CH_3OH/17% aq. NH_3, 15:1:0.1) to give 3.00 g, 39% product as a dark yellow solid; mp 156–158°C; $[\alpha]_D^{25}$=−27.2 (*c* 1.03, CH_3CN/H_2O 95:5); HPLC: t_R= 7.24 min; TLC (CH_2Cl_2/CH_3OH/17% aq. NH_3, 15:1:0.1): R_f=0.29; ^{1}H NMR (400 MHz, DMSO-d_6): δ=3.01 (m, 2H, CH_2), 3.63 (s, 3H, OCH_3), 4.68 (m, 1H, CH), 6.87 (s, 1H, imidazole-H), 7.50 (s, 1H, thiazole-H), 7.58 (s, 1H, imidazole-H), 8.04 (d, J=8.9 Hz, 2H, ArH), 8.25 (d, J=8.9 Hz, 2H, ArH); ^{13}C NMR (100.4 MHz, $CDCl_3$, DMSO-d_6): δ=29.5, 51.8, 57.4, 106.1, 123.7, 126.2, 134.7, 140.8, 146.1, 147.8, 167.4, 172.6; HRMS (ESI) calcd for $[M+H]^+$ $C_{16}H_{16}N_5O_4S$ 374.09230, found 374.09230.

(*S*)-(−)-*N*-[4-(4-Nitro-phenyl)-thiazol-2-yl]-serine methyl ester (5). Purified by flash chromatography on silica gel (cyclohexane/ethylacetate 1:1) to give 2.14 g, 32% product as a yellow solid; mp 150–152°C; $[\alpha]_D^{25}$=−69.1 (*c* 1.02, CH_3CN/H_2O 95:5); HPLC: t_R=9.49 min; TLC (CH_2Cl_2/CH_3OH/17% aq. NH_3, 15:1:0.1): R_f=0.49; ^{1}H NMR (400 MHz, DMSO-d_6): δ=3.69 (s, 3H, OCH_3), 3.82 (m, 2H, CH_2), 4.59 (m, 1H, CH), 5.19 (t, J=5.6 Hz, 1H, OH), 7.50 (s, 1H, thiazole-H), 8.04 (d, J=8.9 Hz, 2H, ArH), 8.23 (d, J=8.0 Hz, 1H, NH), 8.25 (d, J=8.9 Hz, 2H, ArH); ^{13}C NMR (100.4 MHz, $CDCl_3$, DMSO-d_6): δ=52.0, 59.5, 61.9, 106.0, 123.7, 126.2, 140.8, 146.2, 147.9, 167.7, 171.5; HRMS (ESI) calcd for $[M+H]^+$ $C_{13}H_{14}N_3O_5S$ 324.06542, found 324.06509.

(*S*)-(+)-*N*-[4-(4-Nitro-phenyl)-thiazol-2-yl]-tyrosine methyl ester (6). Purified by flash chromatography on silica gel (cyclohexane/ethylacetate 2:1) to give 4.75 g, 58% product as an orange-yellow solid; mp 120–123°C; $[\alpha]_D^{25}$=+18.5 (*c* 1.02, CH_3CN/H_2O 95:5); HPLC: t_R=10.66 min; TLC (CH_2Cl_2/CH_3OH/17% aq. NH_3, 15:1:0.1): R_f=0.60; ^{1}H NMR (400 MHz, DMSO-d_6): δ=2.90–3.07 (m, 2H, CH_2), 3.63 (s, 3H, OCH_3), 4.57 (m, 1H, CH), 6.70 (d, J=8.4 Hz, 2H, ArH), 7.08 (d, J=8.4 Hz, 2H, ArH), 7.48 (s, 1H, thiazole-H), 8.03 (d, J=8.9 Hz, 2H, ArH), 8.24 (d, J=8.9 Hz, 2H, ArH), 8.29 (d, J=7.6 Hz, 1H, NH), 9.25 (s, 1H, OH); ^{13}C NMR (100.4 MHz, DMSO-d_6): δ=36.8, 51.8, 58.9, 105.8, 115.3, 123.7, 126.2, 126.9, 130.1, 140.9, 146.2, 148.1, 156.1, 167.4, 172.8; HRMS (ESI) calcd for $[M+H]^+$ $C_{19}H_{18}N_3O_5S$ 400.09672, found 400.09673.

(*S*)-(−)-*N*-[4-(4-Nitro-phenyl)-thiazol-2-yl]-methionine methyl ester (7). Purified by flash chromatography on silica gel (cyclohexane/ethylacetate 5:1) to give 3.38 g, 45% product as an orange solid; mp 78–79°C; $[\alpha]_D^{25}$=−51.23 (*c* 1.14, CH_3CN/H_2O 95:5); HPLC: t_R=11.42 min; TLC (cyclohexane/ethylacetate 2:1): R_f=0.58; ^{1}H NMR (400 MHz, DMSO-d_6): δ=2.04 (m, 2H, CH_2), 2.07 (s, 3H, SCH_3), 2.61 (m, 2H, CH_2), 3.68 (s, 3H, OCH_3), 4.58 (m, 1H, CH), 7.53 (s, 1H, thiazole-H), 8.04 (d, J=8.9 Hz, 2H, ArH), 8.25 (d, J=8.9 Hz, 2H, ArH), 8.29 (d, J=7.6 Hz, 1H, NH); ^{13}C NMR (100.4 MHz, $CDCl_3$): δ=15.5, 30.1, 31.6, 52.7, 56.6, 105.8, 124.0, 126.5, 140.5, 146.8, 149.0, 167.5, 172.9; HRMS (ESI) calcd for $[M+H]^+$ $C_{15}H_{18}N_3O_4S_2$ 368.07388, found 368.07380.

(4-Chloro-benzyl)-[4-(4-nitro-phenyl)-thiazol-2-yl]-amine (8). Purified by flash chromatography on silica gel (cyclohexane/ethylacetate 4:1) to give 2.21 g, 31% product as an orange solid; mp 155–156°C; HPLC: t_R=12.36 min; TLC (cyclohexane/ethylacetate 2:1): R_f=0.47; ^{1}H NMR (400 MHz, DMSO-d_6): δ=4.53 (d, J=5.9 Hz, 2H, CH_2), 7.42 (m, 4H, ArH), 7.49 (s, 1H, thiazole-H), 8.07 (d, J=8.9 Hz, 2H, ArH), 8.24 (d, J=8.9 Hz, 2H, ArH), 8.38 (t, J=5.9 Hz, 1H, NH); ^{13}C NMR (100.4 MHz, DMSO-d_6): δ=47.4, 105.6, 123.7, 126.2, 128.2, 129.2, 132.1, 137.8, 140.9, 146.1, 148.1, 168.5; HRMS (ESI) calcd for $[M+H]^+$ $C_{16}H_{13}ClN_3O_2S$ 346.04170, found 346.04242.

(±)-α-Phenylethyl-[4-(4-nitro-phenyl)-thiazol-2-yl]-amine (9). Purified by flash chromatography on silica gel (cyclohexane/ethylacetate 4:1) to give 1.20 g, 18% product as an ochre to orange solid; mp 152–154°C; HPLC: t_R=12.09 min; TLC (cyclohexane/ethylacetate 2:1): R_f= 0.59; ^{1}H NMR (400 MHz, DMSO-d_6): δ=1.49 (d, J= 6.8 Hz, 3H, CH_3), 4.86 (m, 1H, CH), 7.22 (m, 1H, ArH), 7.34 (m, 2H, ArH), 7.43 (m, 3H, ArH+thiazole-H), 8.03 (d, J=8.9 Hz, 2H, ArH), 8.24 (d, J=8.9 Hz, 2H, ArH), 8.40 (d, J=7.5 Hz, 1H, NH); ^{13}C NMR (100.4 MHz, DMSO-d_6):

δ=23.5, 55.1, 105.2, 124.0, 126.48, 126.50, 127.3, 128.6, 141.3, 144.2, 146.5, 148.7, 168.5; HRMS (ESI) calcd for $[M+H]^+$ $C_{17}H_{16}N_3O_2S$ 326.09627, found 326.09632.

[4-(4-Nitro-phenyl)-thiazol-2-yl]-(4-chloro-phenyl)-amine (11). 6.72 g, 99% product as an orange solid; mp 204–205°C; HPLC: t_R=12.66 min; TLC (cyclohexane/ethylacetate 2:1): R_f=0.42; ^{1}H NMR (400 MHz, DMSO-d_6): δ=7.41 (d, J=9.0 Hz, 2H, ArH), 7.54 (s, 1H, thiazole-H), 7.78 (d, J=9.0 Hz, 2H, ArH), 8.18 (d, J=8.9 Hz, 2H, ArH), 8.29 (d, J=8.9 Hz, 2H, ArH), 10.58 (s, 1H, NH); ^{13}C NMR (100.4 MHz, DMSO-d_6): δ=107.0, 118.4, 123.8, 125.3, 126.4, 128.6, 139.8, 140.5, 146.3, 148.4, 163.3; HRMS (ESI) calcd for $[M+H]^+$ $C_{15}H_{11}ClN_3O_2S$ 332.02605, found 332.02629.

***N*-[4-(2,4-Dichloro-phenyl)-thiazol-2-yl]-glycine methyl ester (12).** 6.22 g, 96% product as an ochre solid; mp 118–120°C; HPLC: t_R=11.74 min; TLC (cyclohexane/ethylacetate 2:1): R_f=0.44; ^{1}H NMR (400 MHz, DMSO-d_6): δ=3.66 (s, 3H, OCH_3), 4.13 (d, J=6.1 Hz, 2H, CH_2), 7.23 (s, 1H, thiazole-H), 7.47 (dd, J=8.5, 2.1 Hz, 1H, ArH), 7.64 (d, J=2.1 Hz, 1H. ArH), 7.87 (d, J=8.5 Hz, 1H, ArH), 8.13 (t, J=6.0 Hz, 1H, NH); ^{13}C NMR (100.4 MHz, $CDCl_3$): δ=46.7, 52.9, 108.0, 127.5, 130.5, 132.1, 132.6, 133.8, 146.8, 166.9, 170.9; HRMS (ESI) calcd for $[M+H]^+$ $C_{12}H_{11}Cl_2N_2O_2S$ 316.99183, found 316.99193.

(*S*)-(−)-*N*-[4-(2,4-Dichloro-phenyl)-thiazol-2-yl]-alanine methyl ester (13). Purified by flash chromatography on silica gel (cyclohexane/ethylacetate 5:1) to give 2.78 g, 41% product as an ochre solid; mp 109–110; $[\alpha]_D^{25}$=−70.1 (*c* 1.03, CH_3CN/H_2O 95:5); HPLC: t_R=12.24 min; TLC (cyclohexane/ethylacetate 2:1): R_f=0.58; ^{1}H NMR (400 MHz, DMSO-d_6): δ=1.40 (d, J=7.1 Hz, 3H, CH_3), 3.65 (s, 3H, OCH_3), 4.39 (m, 1H, CH), 7.23 (s, 1H, thiazole-H), 7.48 (dd, J=8.5, 2.1 Hz, 1H, ArH), 7.64 (d, J=2.1 Hz, 1H, ArH), 7.86 (d, J=8.5 Hz, 1H, ArH), 8.15 (d, J=7.1 Hz, 1H, NH); ^{13}C NMR (100.4 MHz, $CDCl_3$): δ=18.5, 52.6, 53.3, 107.5, 127.1, 130.1, 131.8, 132.2, 133.3, 146.4, 165.9, 173.9; HRMS (ESI) calcd for $[M+H]^+$ $C_{13}H_{13}Cl_2N_2O_2S$ 331.00748, found 331.00746.

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