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I_2/CuO-catalyzed tandem cyclization strategy for one-pot synthesis of substituted 2-aminothiozole from easily available aromatic ketones/α,β-unsaturated ketones and thiourea

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ABSTRACT

A concise and efficient one-pot process from easily available methyl ketones/unsaturated methyl ketones and thiourea was developed for the synthesis of 2-aminothiazoles under the media of I_2/CuO. The method can highly stereoselectivity obtain the E-isomers of 4-ethenyl-2-aminothiazoles (**5a**–**f**). All these target molecules were characterized by NMR, HRMS and IR spectra. Furthermore, the target compounds **3c** and **5b** were further determined by X-ray crystallographic analysis.

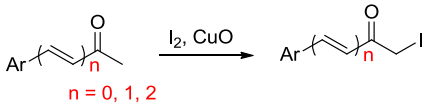
1. Introduction

Thiazole as useful structural element plays an important role in nature and has broad applications in the field of agriculture and medicinal chemistry.[1] Thiazole ring is a main structural motif of many natural compounds such as vitamin B1 (thiamine), penicillin and carboxylase.

Moreover 2-aminothiazoles as important precursors have been employed in the preparation of different important drugs required for the treatment of allergies, hypertension, inflammation, schizophrenia, bacterial, and HIV infections.[2] Therefore, much attention has been paid to the synthesis of 2-aminothiazoles, for which the general approaches include condensation of α-bromoketone with thiourea,[3] the reaction of α-thiocyanato carbonyl compounds with aromatic or aliphatic aminehydrochlorides,[4] treatment of stylene and thiourea with NBS[5] and condensation of aromatic ketone and thiourea with solid supported catalyst or heterogeneous catalyst.[6]

In recent years, tandem, multicomponent, and one-pot reactions have attracted much attention as powerful and useful synthetic tools in synthetic chemistry and drug discovery. These reactions, by virtue of their atom-economy, reducing the number of operations, and saving reagents, energy, time, and labour, have been used in many chemical transformations.[7]

In our previous studies, we proposed a novel method for the synthesis of α-iodo ketones and α,β-unsaturated α′-iodo ketones (Scheme 1) on the basis of aromatic ketones and α,β-unsaturated ketones under the media of I_2/CuO.[8] Moreover, α-halogenation ketones as important precursors have been employed in the preparation of various heterocycles.[9] Therefore, we considered the possibility of catalyzing aromatic ketones in situ obtained α-iodo ketones, which can react with thiourea in one-pot to afford 2-aminothiazole under the media of I_2/CuO. If successful, this would simplify the synthetic steps, and develop a novel synthetic method for the synthesis of 2-amino-4-arylthiazole and 2-amino-4-ethenylthiazole derivatives.



Scheme 1. Synthesis of α-iodo ketones and α,β-unsaturated α′-iodo ketones on the basis of aromatic ketones and α,β-unsaturated ketones under the media of I_2/CuO.

Herein, we present a concise, rapid and efficient method for preparation of substituted 2-aminothiazole from easily available aromatic ketones and thiourea. In addition, this method can also synthesize 2-amino-4-ethenylthiazole derivatives efficiently.

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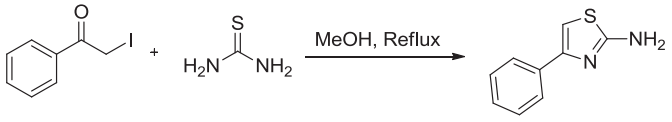
2. Results and discussion

To initiate our study, we first tested the reaction of α-iodo ketone with thiourea in MeOH at reflux. To our delight, the product was obtained in 95% yield (Scheme 2).

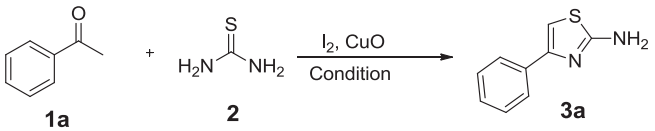


Scheme 2. Formation of 2-amino-4-arylthiazole via the condensation of α-iodo ketone with thiourea in MeOH at reflux.

With the success in obtaining substituted 2-aminothiazole from phenacyl iodine with thiourea, we wondered whether it would be possible to integrate the two processes (Schemes 1 and 2) in a one-pot reaction. Therefore, we optimized the reaction conditions for the formation of 2-aminothiazole with aryl methyl ketones (**1a**) and thiourea (**2**) as substrates (Table 1). Various solvents were first examined. The product was not obtained when acetonitrile (MeCN), tetrahydrofuran (THF), toluene or dimethylformamide (DMF) was used as solvent. It was notable, however, that this transformation occurred smoothly in MeOH, with 88% yield. And product **3a** was obtained in moderate to good yields using methanol, propanol and butanol as solvents. However, no reaction occurred in *tert*-butanol in the conditions. It was obvious that ethanol was the optimal solvent in the reaction. Next, the molar ratio of substrate, I_2 and CuO was also optimized. When the molar ratio of n(**1a**)/n(**2**)/n(CuO)/$n(I_2)$ was varied from 1:1:1:1 to 1:1.1:1.1:1.1 (entries 6, 10–12), the reaction afforded the product **3a** in 86–90% yield in ethanol at reflux. It was obvious that n(**1a**)/n(**2**)/$n(I_2)$/n(CuO)=1:1:1.1:1.1 is the optimal condition. Finally, the effect of reaction temperature on the yield of the product **3a** was also examined. The experiment result indicates that 78 °C is the optimal temperature.

To assess the generality of this method and to evaluate the electronic influence of the aromatic ring substituents, a series of other aromatic ketones **1b**–**m** were examined under the optimal conditions (Table 2). While the benzene rings bore electron-donating groups (e.g., 4-Me, 4-OMe, 2,4-OMe_2), the corresponding products **3b**–**e** were obtained in good yields (85–92%, entries 2–5, Table 2). And when the benzene rings substituted with electron-withdrawing groups (e.g., 4-Cl, 4-Br, 3-NO_2, 4-Ph), the corresponding products **3b**–**k** were obtained in moderate to good yields (48–80%, entries 6–9, Table 2). It should be noted that an electron-donating substituent on the benzene ring caused a considerable increase in the yield. 2-Naphthyl methyl ketone (**1k**) also gave satisfying result. To our great satisfaction, sensitive hydroxy group (OH) was not affected under these mild reaction conditions, and the expected product **3k** was obtained in 50% yield. Encouraged by the results obtained with aryl methyl ketones, we turned our attention to the heteroaryl ketones. The heterocycle, including furan (**1l**) and thiophen (**1m**), did not affect the overall efficiency, and the corresponding products **3l** and **3m** were obtained in 75% and 72% yields, respectively.

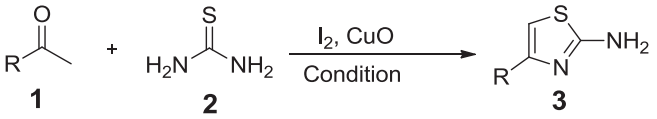
Table 1
Effect of solvent, temperature and molar ratio of n(**1a**)/n(**2**)/$n(I_2)$/n(CuO) on the yield of **3a**



Entry	Solvent/(°C)	n(**1a**)/n(**2**)/$n(I_2)$/n(CuO)	Yield[a] (%)
1	MeCN/82	1:1:1:1	0[b]
2	THF/66	1:1:1:1	0[b]
3	DMF/90	1:1:1:1	0[b]
4	Toluene/111	1:1:1:1	0[b]
5	MeOH/65	1:1:1:1	85
6	EtOH/78	1:1:1:1	88
7	PrOH/97	1:1:1:1	75
8	BuOH/118	1:1:1:1	70
9	*t*-BuOH/83	1:1:1:1	0[b]
10	EtOH/78	1:1:1.1:1	90
11	EtOH78	1:1:1.5:1.5	88
12	EtOH/78	1:1.1:1.1:1.1	86
13	EtOH/65	1:1:1.1:1.1	75
14	EtOH/55	1:1:1.1:1.1	50

[a] Isolated yield.
[b] No reaction.

Table 2
Formation of 2-amino-4-arylthiazole via the tandem reaction of methyl ketones and thiourea under the media of I_2/CuO[a]



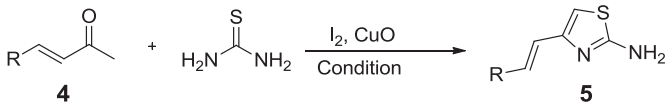
Entry	Substrates (R=)	Product	Yield[b] (%)
1	C_6H_5 (**1a**)	**3a**	90
2	4-Me–C_6H_5 (**1b**)	**3b**	88
3	4-Me–OC_6H_5 (**1c**)	**3c**	92
4	3,4-OCH_2O–C_6H_5 (**1d**)	**3d**	85
5	2,4-OMe_2–C_6H_5 (**1e**)	**3e**	86
6	4-Cl–C_6H_5 (**1f**)	**3f**	80
7	4-Br–C_6H_5 (**1g**)	**3g**	72
8	3-O_2N–C_6H_5 (**1h**)	**3h**	48
9	4-Ph–C_6H_5 (**1i**)	**3i**	68
10	2-Naph–C_6H_5 (**1j**)	**3j**	65
11	4-HO–C_6H_5 (**1k**)	**3k**	50
12	2-Furan–C_6H_5 (**1l**)	**3l**	75
13	2-Thinyl–C_6H_5 (**1m**)	**3m**	72

[a] Standard conditions: n(**1**)/n(**2**)/$n(I_2)$/n(CuO)=1:1:1.1:1.1, T=78 °C.
[b] Isolated yield.

To further expand scope of the ketone, unsaturated methyl ketones such as **4a**–**f** were also investigated.[10] Under the optimal conditions, the corresponding ethenyl 2-aminothiazoles could be obtained with a slightly lower yield of 45–63%. The possible reason for the low yield was that C=C bond reduced the conjugate effect of aromatic cycles and acetyl group. So, the α-iodination was not easy to achieve in the first step. For further investigation, the reactions with unsaturated methyl ketones such as benzalacetone (**4g**) and 4-phenylbut-3-yn-2-one (**4h**) could not afford the desired product. It should be noted that an electron-donating substituent on the benzene ring caused a considerable increase in the yield than an electron-withdrawing substituent, which was consistent with aryl methyl ketones. In all cases, only the thermodynamically stable *E*-isomers were obtained. It has a high stereoselectivity (Table 3).

After successful exploration of the scope of the reaction towards reactants, the aromatic ketones/α,β-unsaturated ketones and thiourea, we turned our attention to other types of ketones and thioureas. Accordingly, the substituted *N*-methylthiourea was investigated; all the aromatic ketones smoothly underwent the transformation with *N*-methylthiourea to provide the *N*-methyl aminothiazoles (**7a**–**c**) in good yields (70–78% yields, Table 4). Next, 1,3-diketone (1,3-bis(4-methoxyphenyl)propane-1,3-dione) was also investigated, the desired product was obtained in 72% yield. In addition, the scope of the reaction was further demonstrated by reacting β-ketoesters (**6e**–**j**) under the optimized conditions. The results collected (Table 4) point out the facts that both

Table 3
Formation of 2-amino-4-ethenylthiazoles via the tandem reaction of α,β-unsaturated methyl ketones[a]



Entry	Substrates (R=)	Product	Isolated yield[b] (%)	trans[c] (%)
1	C_6H_5 (**4a**)	**5a**	60	>99
2	4-Me–C_6H_5 (**4b**)	**5b**	58	>99
3	4-MeO–C_6H_5 (**4c**)	**5c**	62	>99
4	3,4-$(MeO)_2$–C_6H_5(**4d**)	**5d**	63	>99
5	4-NO_2–C_6H_5 (**4e**)	**5e**	45	>99
6	3-NO_2–C_6H_5 (**4f**)	**5f**	48	>99
7	(*E*)-C_6H_5–CH=CH– (**4g**)	**5g**	0[d]	—
8	C_6H_5–CH≡CH– (**4h**)	**5h**	0[d]	—

[a] Standard conditions: n(**1**)/n(**2**)/$n(I_2)$/n(CuO)=1:1:1.1:1.1, T=78 °C.
[b] Isolated yield.
[c] Determined by ^{1}H NMR of the crude product.
[d] No reaction occurred.

Supplementary data page 7) and **5b** [11] were further determined by X-ray crystallographic analysis. In the crystal structure of compound **5b**, the bond distance of C8–C9 and the torsion angle of C(5)–C(8)–C(9)–C(10) are 1.32 Å and −179.69°, respectively, which supports the *E*-configuration of the olefin **5b** (Fig. 1).

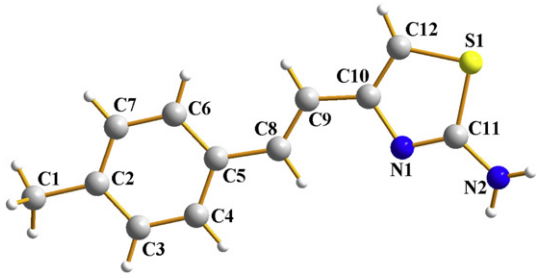
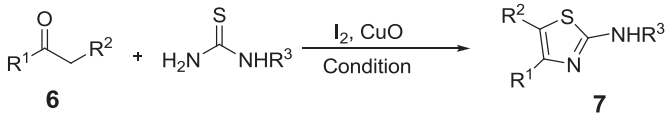
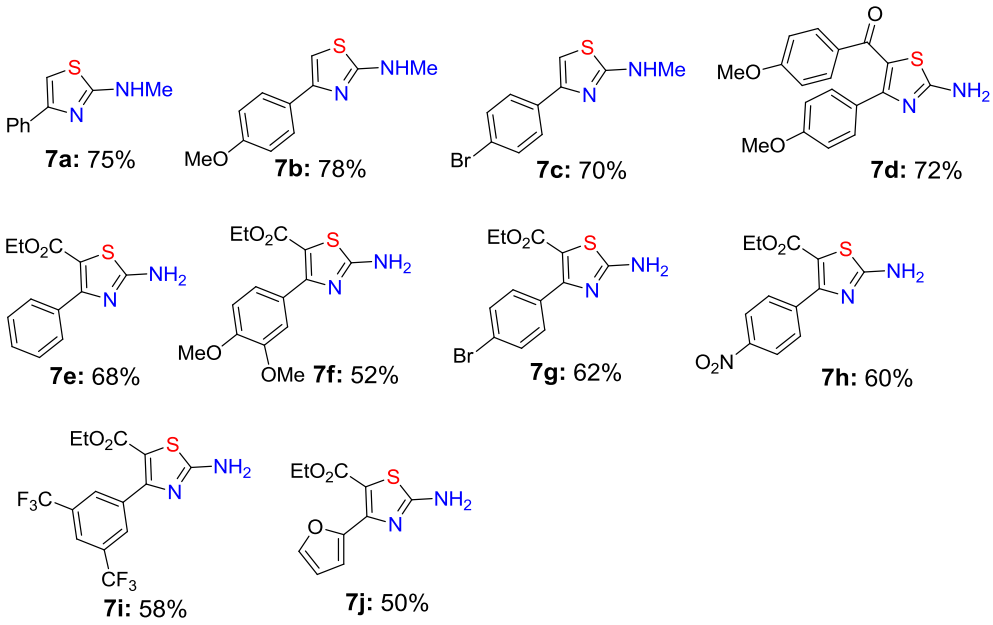


Fig. 1. The X-ray crystal structure of compound **5b**.

Table 4
Scope of ketones and thioureas[a,b]



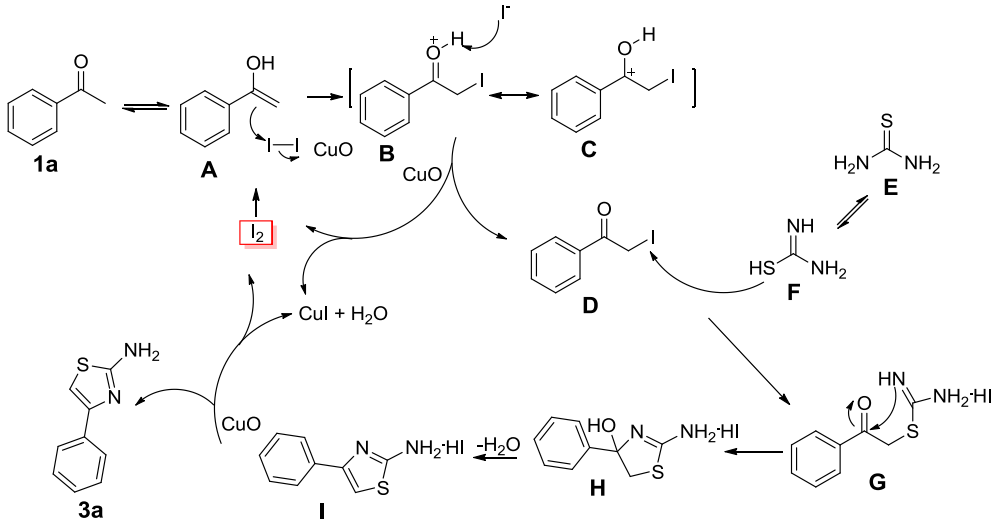


[a] Standard conditions: n(**6**)/n(**2**)/$n(I_2)$/n(CuO)=1:1:1.1:1.1, T=78 °C.
[b] Isolated yield.

electron-withdrawing and electron-donating groups at aromatic cycles are tolerated. To our great satisfaction, the heterocycle (furan) was not affected under these mild reaction conditions, and the expected product **7j** was obtained in 50% yield. Other aliphatic ketones (3,3-dimethylbutan-2-one, 3-methylbutan-2-one and butan-2-one), hexamethylketone and hexamethyldiketone were also investigated under the optimal conditions. Unfortunately, the reaction could not be performed.

All these target molecules were characterized by NMR, MS and IR spectra. Furthermore, the target compounds **3c** (See

A possible mechanism of the present reaction could be described as follows using acetophenone (**1a**) as an example (Scheme 3): Initially, the acetophenone **1a** undergoes the formation of enolate ion **A** under basic conditions, and **A** converts to **B** or its enolizational isomer **C** in the media of I_2 and CuO. Subsequently, CuO catalyses **B** converting to **D**, CuI, H_2O and regenerated I_2. Then, **G** is obtained undergoing intermolecular nucleophilic substitute of **D** with thiourea enolizational isomer **F**. **G** undergoing an intramolecular nucleophilic addition transforms into **H**, which converts to **I** via dehydration. Finally, intermediate **I** undergoes neutralization reaction



Scheme 3. The proposed mechanism for the transformation.

to furnish the desired product in the presence of CuO. In addition, regenerated I_2 can catalyse the transformation of **A** to **B** again.

3. Conclusion

In conclusion, a concise and efficient one-pot process from easily available methyl ketones/unsaturated methyl ketones, 1,3-diketone, β-ketoesters and thioureas was developed for the synthesis of 2-aminothiazoles under the media of I_2/CuO. In addition, the method can highly stereoselectivity obtain the E-isomers of 4-ethenyl-2-aminothiazoles (**5a**–**f**). Further application of this methodology for the synthesis of various heterocyclic compounds is under way in our laboratory.

4. Experimental

4.1. General method

All aryl methyl ketones (**1a**–**m**), thiourea (**2**) and other reagents were obtained from commercial suppliers and used without further purification. TLC analysis was performed using pre-coated glass plates. Column chromatography was performed using silica gel (200–300 mesh). IR spectra were recorded on a Perkin–Elmer PE-983 infrared spectrometer as KBr pellets with absorption in cm^{-1}. NMR spectra were recorded on a Varian Mercury 400 or 600 MHz spectrometer. Chemical shifts are reported in ppm, relative to the internal standard of tetramethylsilane (TMS). HRMS were obtained on a Bruker 7-tesla FT-ICR MS equipped with an electrospray source. The X-ray crystal structure determinations of **1a** and **5a** were obtained on a Bruker SMART APEX CCD system.

4.2. General procedure for preparation of 3 and 5 (3a as an example)

A mixture of acetophenone **1a** (120 mg, 1 mmol), iodine (279.2 mg, 1.1 mmol), and CuO (88 mg, 1.1 mmol) in anhydrous ethanol (30 mL) was heated at reflux, after disappearance of the reactant (1–12 h, monitored by TLC), thiourea **2** (76 mg, 1 mmol) was added and the mixture was refluxed for 1 h. After that, the solvent was removed under reduce pressure, and added 50 mL water to the residue, then extracted with EtOAc three times (3×50 mL). The extract was washed with 10% $Na_2S_2O_3$ then a small amount 5% NaOH solution, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel using petroleum ether/EtOAc as the eluent to give the expected products **3a** in 90% yield.

4.3. Spectroscopic data

*4.3.1. 4-Phenylthiazol-2-amine (**3a**).* IR (KBr): 3434, 3248, 3113, 1598, 1516, 1481, 1440, 1330, 1306, 1199, 1070, 1038, 1021 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ=7.75 (d, J=7.8 Hz, 2H), 7.36–7.38 (t, J=7.8 Hz, 2H), 7.27–7.29 (t, J=7.8 Hz, 1H), 5.49 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=167.5, 151.1, 134.6, 128.6, 127.7, 126.0, 102.7; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_9H_9N_2S$: 177.0418; found: 177.0477.

*4.3.2. 4-p-Tolylthiazol-2-amine (**3b**).* IR (KBr): 3453, 3298, 3117, 1637, 1538, 1521, 1489, 1333, 1037 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ=7.64 (d, J=8.4 Hz, 2H), 7.17 (d, J=8.4 Hz, 2H), 6.62 (s, 1H), 5.54 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=167.7, 151.2, 137.4, 131.9, 129.2, 125.8, 101.7, 21.2; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{10}H_{11}N_2S$: 191.0637; found: 191.0632.

*4.3.3. 4-(4-Methoxyphenyl)thiazol-2-amine (**3c**).* IR (KBr): 3438, 3267, 3117, 2964, 2934, 2834, 1626, 1606, 1537, 1519, 1492, 1290, 1245, 1177, 1035 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ=7.73 (d, J=9.0 Hz, 2H), 7.01 (s, 2H), 6.93 (d, J=9.0 Hz, 2H), 3.78 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=168.2, 158.7, 149.9, 128.0, 127.0, 114.0, 100.0, 55.2; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{10}H_{11}N_2SO$: 207.0587; found: 207.0581.

*4.3.4. 4-(1,3-Dihydroisobenzofuran-5-yl)thiazol-2-amine (**3d**).* IR (KBr): 3431, 3298, 3122, 2900, 1639, 1539, 1498, 1481, 1449, 1331, 1291, 1242, 1195, 1122, 1039 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ=7.38 (s, 2H), 7.08 (s, 2H), 6.91–6.95 (m, 2H), 6.07 (s, 2H), 3.48 (s, 2H); ^{13}C NMR (150 MHz, DMSO-d_6): δ=168.1, 149.5, 147.5, 146.4, 129.5, 119.4, 108.3, 105.9, 101.0, 100.1; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{11}H_{13}N_2O_2S$: 237.0692; found: 237.0690.

*4.3.5. 4-(2,4-Dimethoxyphenyl)thiazol-2-amine (**3e**).* IR (KBr): 3382, 3287, 3113, 2924, 1609, 1579, 1533, 1463, 1434, 1291, 1211, 1160, 1127, 1069, 1050 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ=7.94 (d, J=8.4 Hz, 1H), 7.25 (s, 1H), 6.51–6.54 (m, 2H), 5.31 (s, 2H), 3.87 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=165.8, 160.0, 157.8,

146.5, 130.5, 116.6, 105.2, 104.4, 98.7, 55.3; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{11}H_{13}N_2O_2S$: 237.0692; found: 237.0690.

*4.3.6. 4-(4-Chlorophenyl)thiazol-2-amine (**3f**).* IR (KBr): 3438, 3283, 3112, 1633, 1534, 1476, 1401, 1338, 1088 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ=7.83 (d, J=9.0 Hz, 2H), 7.43 (d, J=9.0 Hz, 2H), 6.90 (s, 2H), 7.06 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=168.6, 148.6, 133.7, 131.8, 128.7, 127.4, 102.5; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_9H_8N_2SCl$: 211.0091; found: 211.0086.

*4.3.7. 4-(4-Bromophenyl)thiazol-2-amine (**3g**).* IR (KBr): 3428, 3282, 3111, 2926, 1633, 1534, 1472, 1396, 1336, 1198, 1068, 1037, 1006 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ=7.76 (d, J=8.4 Hz, 2H), 7.56 (d, J=8.4 Hz, 2H), 7.16 (s, 2H), 7.07 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=168.5, 148.8, 134.2, 131.5, 127.7, 120.3, 102.6; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_9H_8N_2SBr$: 254.9586; found: 254.9583.

*4.3.8. 4-(3-Nitrophenyl)thiazol-2-amine (**3h**).* IR (KBr): 3423, 3291, 3110, 1636, 1537, 1514, 1473, 1344, 1259, 1205, 1050 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ=8.63 (s, 1H), 8.25 (d, J=7.8 Hz, 1H), 8.12 (d, J=7.8 Hz, 1H), 7.67–7.69 (t, J=7.8 Hz, 1H), 7.35 (s, 1H), 7.25 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=168.6, 148.3, 147.5, 136.4, 131.6, 130.1, 121.8, 120.0, 104.3; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_7H_7N_2OS$: 222.0332; found: 222.0332.

*4.3.9. 4-([1,1′-Biphenyl]-4-yl)thiazol-2-amine (**3i**).* IR (KBr): 3438, 3289, 3109, 1631, 1524, 1480, 1405, 1332, 1306, 1198, 1041 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ=7.91 (d, J=8.4 Hz, 2H), 7.68–7.73 (m, 4H), 7.46–7.48 (t, J=7.8 Hz, 2H), 7.35–7.39 (t, J=7.8 Hz, 1H), 7.12 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=168.3, 149.6, 139.8, 138.8, 134.1, 129.0, 127.5, 126.8, 126.5, 126.2, 101.9; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{13}N_2S$: 253.0794; found: 253.0790.

*4.3.10. 4-(Naphthalen-2-yl)thiazol-2-amine (**3j**).* IR (KBr): 3423, 3248, 3111, 2925, 2856, 1599, 1525, 1494, 1361, 1321, 1182, 1037 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ=8.36 (s, 1H), 7.89–7.98 (m, 5H), 7.49–7.53 (m, 2H), 7.18 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=168.3, 149.8, 133.3, 132.3, 128.2, 128.0, 127.6, 126.4, 126.0, 124.1, 102.5; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{11}N_2S$: 227.0637; found: 222.0632.

*4.3.11. 4-(2-Aminothiazol-4-yl)phenol (**3k**).* IR (KBr): 3449, 3304, 3199, 3120, 2654, 2588, 1622, 1539, 1515, 1436, 1339, 1265, 1245, 1180, 1033 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ=9.58 (s, 1H), 7.64 (s, 2H), 7.07 (s, 2H), 6.81 (s, 2H), 6.73 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=168.3, 156.9, 149.9, 127.1, 126.3, 115.4, 98.8; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_9H_9N_2OS$: 193.0430; found: 193.0427.

*4.3.12. 4-(Furan-2-yl)thiazol-2-amine (**3l**).* IR (KBr): 3436, 3271, 3106, 2960, 1627, 1527, 1453, 1389, 1333, 1204, 1150, 1047, 1008 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ=7.64 (s, 1H), 7.14 (s, 2H), 6.74 (s, 1H), 6.54 (d, J=4.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=168.7, 150.6, 142.2, 141.8, 111.6, 106.0, 100.6; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_7H_7N_2OS$: 167.0274; found: 167.0270.

*4.3.13. 4-(Thiophen-2-yl)thiazol-2-amine (**3m**).* IR (KBr): 3425, 3269, 3100, 2928, 1622, 1551, 1520, 1364, 1317, 1285, 1186, 1079, 1050 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ=7.31 (d, J=3.0 Hz, 1H), 7.21 (d, J=4.8 Hz, 1H), 7.01–7.02 (t, J=4.2 Hz, 1H), 5.54 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=167.7, 145.4, 138.6, 127.6, 124.5, 123.4, 123.3, 101.3; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_7H_7N_2S_2$: 183.0045; found: 183.0042.

*4.3.14. (E)-4-Styrylthiazol-2-amine (**5a**).* IR (KBr): 3478, 3377, 3287, 3092, 3024, 1636, 1599, 1538, 1522, 1444, 1343, 1292, 1124, 1072, 960 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ=7.48 (d, J=7.2 Hz, 2H), 7.32–7.34 (t, J=7.8 Hz, 2H), 7.24 (d, J=16.2 Hz, 1H), 8.86 (d, J=16.2 Hz, 1H), 5.24 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=167.3, 150.2, 137.1, 130.3, 128.6, 127.6, 126.5, 121.4, 106.6; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{11}H_{11}N_2S$: 203.0637; found: 203.0634.

*4.3.15. (E)-4-(4-Methylstyryl)thiazol-2-amine (**5b**).* IR (KBr): 3410, 3282, 3112, 3019, 2918, 1616, 1533, 1512, 1352, 1295, 1124, 967 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ=7.36–7.37 (d, J=6.6 Hz, 2H), 7.19–7.22 (d, J=15.6 Hz, 1H), 7.13–7.14 (d, J=6.6 Hz, 2H), 6.80–6.83 (d, J=15.6 Hz, 1H), 5.31 (s, 2H), 2.34 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=167.4, 150.3, 137.4, 134.3, 130.2, 129.3, 126.4, 120.5, 106.1, 21.2; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{13}N_2OS$: 233.0743; found: 233.0743.

*4.3.16. (E)-4-(4-Methoxystyryl)thiazol-2-amine (**5c**).* IR (KBr): 3428, 3267, 3118, 2962, 2931, 2836, 1624, 1603, 1535, 1514, 1417, 1347, 1304, 1266, 1239, 1176, 1110, 1024, 963 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ=7.41 (d, J=8.4 Hz, 2H), 7.12–7.20 (d, J=15.6 Hz, 1H), 6.86–6.88 (d, J=7.8 Hz, 2H), 6.72–6.75 (d, J=15.6 Hz, 1H), 5.25 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=167.3, 159.2, 150.2, 129.8, 128.8, 127.7, 119.3, 114.0, 105.5, 89.6, 55.2; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{13}N_2OS$: 233.0743; found: 233.0743.

*4.3.17. (E)-4-(3,4-Dimethoxystyryl)thiazol-2-amine (**5d**).* IR (KBr): 3415, 3292, 3146, 3109, 2967, 2932, 2833, 1631, 1538, 1514, 1495, 1462, 1417, 1349, 1260, 1221, 1156, 1135, 1026 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ=7.17–7.19 (d, J=16.8 Hz, 1H), 7.02–7.03 (d, J=6.6, Hz, 2H), 6.83–6.84 (d, J=8.4 Hz, 1H), 6.74–6.76 (d, J=16.8 Hz, 1H), 6.39 (s, 1H), 5.29 (s, 2H), 3.91 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=167.4, 150.3, 148.9, 148.8, 130.0, 119.9, 119.7, 111.0, 108.5, 105.7, 55.8; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{13}N_2OS$: 233.0743; found: 233.0743.

*4.3.18. (E)-4-(4-Nitrostyryl)thiazol-2-amine (**5e**).* IR (KBr): 3418, 2959, 2925, 2854, 1726, 1628, 1589, 1514, 1340, 1288, 1106, 1075 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ=8.18–8.20 (d, J=8.4 Hz, 2H), 7.77–7.78 (d, J=8.4 Hz, 2H), 7.23–7.26 (d, J=15.6 Hz, 1H), 7.15–7.18 (d, J=15.6 Hz, 1H), 6.82 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=168.2, 149.3, 145.9, 144.3, 129.5, 127.0, 126.3, 124.1, 109.6; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{13}N_2OS$: 233.0743; found: 233.0743.

*4.3.19. (E)-4-(3-Nitrostyryl)thiazol-2-amine (**5f**).* IR (KBr): 3407, 3103, 2926, 1725, 1633, 1536, 1519, 1350, 1125 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ=8.33 (s, 1H), 8.07–8.08 (q, J=7.8 Hz, 1H), 7.96–7.97 (d, J=7.8 Hz, 1H), 7.63–7.65 (t, J=7.8 Hz, 1H), 7.20–7.23 (d, J=15.6 Hz, 1H), 7.15–7.18 (d, J=15.6 Hz, 1H), 7.10 (s, 2H), 6.76 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=168.3, 149.3, 148.5, 139.3, 132.8, 130.4, 126.3, 125.5, 121.8, 120.3, 108.5; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{13}N_2OS$: 233.0743; found: 233.0743.

*4.3.20. N-Methyl-4-phenylthiazol-2-amine (**7a**).* IR (KBr): 3444, 3225, 3116, 2918, 1588, 1482, 1403, 1330, 1072, 1059 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.78 (d, J=7.2 Hz, 2H), 7.35–7.39 (t, J=7.2 Hz, 2H), 7.29 (s, 1H), 6.92 (s, 2H), 6.66 (s, 1H), 2.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.5, 151.6, 135.1, 128.5, 127.6, 126.0, 100.4, 32.2; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{10}H_{11}N_2S$: 191.06375; found: 191.06313.

*4.3.21. 4-(4-Methoxyphenyl)-N-methylthiazol-2-amine (**7b**).* IR (KBr): 3275, 3111, 2923, 1715, 1578, 1534, 1492, 1463, 1396, 1330, 1303, 1251, 1182, 1108, 1055, 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.68 (d, J=8.8 Hz, 2H), 6.90 (d, J=8.4 Hz, 2H), 6.83 (s, 1H), 6.53 (s, 1H), 3.82 (s, 3H), 2.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.3,

127.6, 127.3, 113.9, 98.6, 55.2, 32.2; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{11}H_{13}N_2OS$: 221.07431; found: 211.0738.

*4.3.22. 4-(4-Bromophenyl)-N-methylthiazol-2-amine (**7c**).* IR (KBr): 3443, 3265, 1581, 1567, 1474, 1451, 1394, 1325, 1268, 1121, 1071, 1008 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.65 (d, J=8.8 Hz, 2H), 7.49 (d, J=8.4 Hz, 2H), 6.68 (s, 1H), 6.35 (s, 1H), 2.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.3, 150.3, 133.8, 131.6, 127.6, 121.5, 101.1, 32.2; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{10}H_{10}BrN_2S$: 268.97426; found: 268.97392.

*4.3.23. (2-Amino-4-(4-methoxyphenyl)thiazol-5-yl)(4-methoxyphenyl)methanone (**7d**).* IR (KBr): 3310, 3071, 2961, 2833, 1709, 1643, 1606, 1585, 1568, 1510, 1471, 1433, 1330, 1299, 1248, 1172, 1124, 1071, 1033 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ=7.90 (s, 2H), 7.42 (d, J=7.6 Hz, 2H), 7.24 (d, J=7.6 Hz, 2H), 6.72 (d, J=7.6 Hz, 2H), 6.68 (d, J=7.6 Hz, 2H), 3.72 (s, 3H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ=186.4, 170.2, 161.8, 159.3, 131.0, 113.1, 112.9, 55.3, 55.1; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{18}H_{17}N_2O_3S$: 341.09544; found: 341.09510.

*4.3.24. Ethyl 2-amino-4-phenylthiazole-5-carboxylate (**7e**).* IR (KBr): 3396, 3285, 3095, 2979, 1658, 1635, 1516, 1481, 1448, 1369, 1340, 1303, 1170, 1091 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ=7.89 (s, 2H), 7.66–7.69 (m, 2H), 7.37–7.39 (m, 2H), 4.09–4.13 (m, 2H), 1.13–1.17 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO): δ=170.0, 161.2, 158.8, 134.7, 129.7, 128.7, 127.3, 108.5, 60.1, 14.1; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{13}O_2N_2S$: 249.06922; found: 249.06878.

*4.3.25. Ethyl 2-amino-4-(3,4-dimethoxyphenyl)thiazole-5-carboxylate (**7f**).* IR (KBr): 3366, 3112, 2971, 2939, 1705, 1639, 1520, 1302, 1255, 1228, 1183, 1138, 1076, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.35 (d, J=8.8 Hz, 1H), 7.31 (s, 1H), 6.90 (d, J=8.0 Hz, 1H), 5.85 (s, 2H), 4.19–4.24 (q, J=14.0 Hz, 2H), 3.92 (s, 6H), 1.25–1.28 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO): δ=168.82, 161.71, 158.45, 149.74, 126.61, 122.96, 112.89, 110.84, 110.11, 60.79, 55.90, 55.85, 14.28; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{17}O_4N_2S$: 309.09035; found: 309.09021.

*4.3.26. Ethyl 2-amino-4-(4-bromophenyl)thiazole-5-carboxylate (**7g**).* IR (KBr): 3413, 3289, 3107, 1984, 1668, 1642, 1524, 1478, 1394, 1368, 1309, 1170, 1091, 1013 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ=7.90 (s, 2H), 7.60 (s, 4H), 4.08–4.12 (m, 2H), 1.15–1.18 (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO): δ=175.16, 166.23, 162.50, 138.90, 136.92, 135.51, 127.14, 113.8, 65.36, 19.28; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{12}BrF_6O_2N_2S$: 328.97974; found: 328.97726.

*4.3.27. Ethyl 2-amino-4-(4-nitrophenyl)thiazole-5-carboxylate (**7h**).* IR (KBr): 3411, 3128, 1707, 1648, 1600, 1519, 1482, 1346, 1279, 1159, 1113, 1071 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ=8.24 (s, 2H), 7.91 (s, 4H), 4.11 (s, 2H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ=170.2, 160.9, 155.7, 147.2, 140.9, 131.0, 122.6, 60.5, 14.0; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{12}N_3O_4S$: 294.05430; found: 294.05400.

*4.3.28. Ethyl 2-amino-4-(3,5-bis(trifluoromethyl)phenyl)thiazole-5-carboxylate (**7i**).* IR (KBr): 3368, 3139, 1662, 1645, 1516, 1464, 1380, 1308, 1278, 1168, 1130, 1080, 1017 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ=8.37 (d, J=6.8 Hz, 2H), 8.12 (s, 1H), 8.05 (d, J=7.6 Hz, 2H), 4.11–4.16 (m, 2H), 1.12–1.21 (m, 3H); ^{13}C NMR (100 MHz, DMSO): δ=170.4, 160.9, 154.3, 136.7, 130.4, 129.7, 129.4, 124.7, 122.0, 110.6, 60.6, 13.8; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{11}F_6O_2N_2S$: 385.04399; found: 385.04359.

*4.3.29. Ethyl 2-amino-4-(furan-2-yl)thiazole-5-carboxylate (**7j**).* IR (KBr): 3452, 3270, 3115, 1699, 1631, 1511, 1478, 1302, 1273, 1170, 1145, 1119, 107.3, 1020 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ=7.75 (s, 1H), 7.53 (s, 1H), 6.53 (s, 1H), 6.04 (s, 2H), 4.29 (br, 2H), 1.33–1.36 (br, 3H); ^{13}C NMR (100 MHz, DMSO): δ=169.2, 147.9, 143.1, 115.2, 111.9, 60.9, 29.5, 14.4; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{10}H_{11}O_3N_2S$: 239.04849; found: 239.04811.

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Supplementary data

Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2011.10.074. These data include MOL files and InChiKeys of the most important compounds described in this article.

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10. Compounds **5a**–**5f** were synthesized via condensation of aromatic aldehyde and acetone in the presence of NaOH. See: Drake, N. L.; Allen, P., Jr. *Org. Synth. Coll.*; John Wiley & Sons: London, 1941; Vol. 1, pp 77–78.
11. Crystal structure data for macrocycle **5b**: CCDC 834646. $C_{48}H_{48}N_8S_4$, chemical formula weight: 865.18, monoclinic, space group $P2(1)/n$, a=14.3676(16), b=17.231(2), c=18.422(2) Å; α=90.000°, β=92.679(2)°, γ=90.00°, U=4555.8(9) $Å^3$, T=200(2) K, Z=4, DC=1.261 Mg/M^3, μ=0.252 mm^{-1}, λ=0.71073 Å, $F(000)$ 1824, crystal size 0.16×0.12×0.10 mm^3, 8458 independent reflections[R(int)=0.0380], reflections collected 24,747, refinement method: full-matrix least-squares on F^2: goodness-of-fit on F^2 1.183, final R indices [$I>2\sigma(I)$], $R1$=0.0734, $wR2$=0.1544, largest diff. peak and hole 0.321 $Å^{-3}$ and −0.206 e $Å^{-3}$.