Tandem addition-cyclization reaction catalyzed by ytterbium chloride: An efficient one-step synthesis of 2-amino-4*H*-3,1-benzothiazine

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A clean, efficient method to synthesize 2-amino-4*H*-3,1-benzothiazines by ytterbium chloride-catalyzed tandem addition-cyclization reaction of *o*-aminocinnamate and isothiocyanates under solvent-free conditions is developed.

2-amino-3,1-benzothiazine, ytterbium chloride, catalysis, tandem reaction

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3,1-Benzothiazine skeleton is present in many natural and synthetic biologically active materials. While 3,1-benzothiazines are well studied [1–9] and widely applied in pharmaceutical and biochemical fields [5,10–13], some of their functionalized derivatives such as 2-amino-4*H*-3,1-benzothiazines also possess interesting biological properties [14–17] and have attracted increasing attention. For example, it was recently found that 2-(4-piperidinamino)-4*H*-3,1-benzothiazines (Figure 1, **A**) show considerable cytoprotective properties toward the heart or neurons [16]. More recently, amidine, thiourea and guanidine derivatives of 2-amino-3,1-benzothiazine (Figure 1, **B**) were used as novel pharmacological agents for the treatment of neurodegenerative pathologies such as cerebral ischemia, neurodegeneration induced by cranial trauma, and Alzheimer's disease [17]. Encouraged by the potential applications of 2-amino-4*H*-3,1-benzothiazines, some research groups dedicated their effort to developing efficient methods for the synthesis of this type of compound. As a consequence, several approaches to prepare 2-amino-4*H*-3,1-benzothiazines have been reported [18–31], and most of which are based on the reactions of aromatic amines or thioureas bearing a halo-methyl or hydroxymethyl substituent in the *ortho* position

Figure 1 Potential pharmacological agents containing a 2-amino-3,1-benzothiazine core.

of the aromatic ring. We noticed that a strong Bronsted acid [18–22] or noble metal catalyst [23,24] was required for a smooth reaction in most cases. At the same time, heating under reflux in organic solvents, complex and inaccessible substrates, and multistep reaction processes appeared to be essential conditions to obtain satisfactory results. Therefore, further development of novel catalysts and relevant processes of high efficiency to synthesize 2-amino-4*H*-3,1-benzothiazine in a simple and clean manner remains of great interest.

Over the past decades, notable progress has been made in the use of lanthanide reagents as catalysts in organic synthesis. Lanthanides are nontoxic and relatively abundant in nature, and the success in developing many useful reactions efficiently catalyzed by lanthanide compounds is attributed

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to the unique features of lanthanide centers such as high electrophilicity, variable metal ion radius and tunable coordination patterns. As a continuation of our interest in the applications of lanthanide-catalyzed carbon-nitrogen and carbon-phosphorus bond-forming reactions [32–40] for the construction of heterocycles, we investigated the effectiveness of lanthanide chlorides as catalysts for carbon-sulfur bond-forming reactions. Herein, a highly efficient process affording 2-amino-4*H*-3,1-benzothiazines by lanthanide chloride-catalyzed tandem addition-cyclization reaction of *o*-aminocinnamate and isothiocyanates is presented.

1 Experimental

1.1 General remarks

Lanthanide chlorides were synthesized according to the method described by Taylor and Carter [41]. Melting points were uncorrected. ^1H and ^{13}C NMR spectra were obtained on Varian INOVA-400 and System-300 spectrometers using tetramethylsilane (TMS) as an internal reference. IR spectra were obtained on a Nicolet FT-IR 1000 spectrophotometer. HRMS data were recorded on a Micromass GCT instrument.

1.2 General procedure

A mixture of ethyl *o*-aminocinnamate (1 mmol), isothiocyanate (1.2 mmol) and ytterbium trichloride (0.025 mmol) was stirred at the desired temperature for the given time. Water was added, and the mixture was extracted with EtOAc. The combined organic layers were dried with anhydrous Na_2SO_4 , concentrated in vacuo, and purified by chromatography on silica gel [eluent: EtOAc/petroleum ether (60–90°C) 1:10] to afford the desired 2-amino-4*H*-3,1-benzothiazine.

Ethyl 2-(2-(phenylamino)-4*H*-benzo[*d*][1,3]thiazin-4-yl)acetate (**3a**). mp 113–114°C; ^1H NMR (400 MHz, CDCl_3) δ 7.57 (d, $J=8.0$ Hz, 2H), 7.36–7.27 (m, 3H), 7.22–7.16 (m, 2H), 7.09 (t, $J=7.2$ Hz, 2H), 6.71 (br s, 1H), 4.51 (dd, $J=8.8$, 6.4 Hz, 1H), 4.14 (q, $J=7.2$ Hz, 2H), 2.83 (dd, $J=16.0$, 8.8 Hz, 1H), 2.75 (dd, $J=16.0$, 6.4 Hz, 1H), 1.22 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 170.7, 149.6, 143.1, 141.8, 129.4, 129.1, 126.9, 124.5, 124.3, 124.0, 122.8, 121.2, 61.3, 42.0, 40.7, 14.6; IR (KBr) ν 691, 757, 1494, 1576, 1732, 2973 cm^{-1} ; HRMS calcd. for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$ 326.1089, found 326.1095.

Ethyl 2-(2-(phenylimino)-2,4-dihydro-1*H*-benzo[*d*][1,3]thiazin-4-yl)acetate (**4a**). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.54 (br s, 1H), 7.97–7.79 (m, 2H), 7.33–7.21 (m, 4H), 7.13–6.99 (m, 3H), 4.59 (t, $J=7.6$ Hz, 1H), 4.07 (q, $J=7.2$ Hz, 2H), 2.75 (dd, $J=16.0$, 6.4 Hz, 1H), 2.68 (dd, $J=16.0$, 9.6 Hz, 1H), 1.16 (t, $J=7.2$ Hz, 3H).

Ethyl 2-(2-(4-fluorophenylamino)-4*H*-benzo[*d*][1,3]thiazin-

4-yl)acetate (**3b**). mp 112–114°C; ^1H NMR (400 MHz, CDCl_3) δ 7.43–7.40 (m, 2H), 7.24 (d, $J=7.6$ Hz, 1H), 7.16 (d, $J=7.2$ Hz, 1H), 7.10–7.00 (m, 4H), 6.40 (br s, 1H), 4.50 (t, $J=7.6$ Hz, 1H), 4.13 (q, $J=7.2$ Hz, 2H), 2.84 (dd, $J=16.0$, 8.8 Hz, 1H), 2.76 (dd, $J=16.0$, 6.4 Hz, 1H), 1.22 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 170.2, 160.7, 157.5, 150.5, 141.7, 138.5, 128.6, 126.4, 123.8, 122.7, 115.6, 115.3, 60.9, 41.5, 40.2, 14.1; IR (KBr) ν 752, 837, 1149, 1226, 1300, 1439, 1504, 1581, 1736, 2985 cm^{-1} ; HRMS calcd. for $\text{C}_{18}\text{H}_{17}\text{FN}_2\text{O}_2\text{S}$ 344.0995, found 344.0995.

Ethyl 2-(2-(4-chlorophenylimino)-2,4-dihydro-1*H*-benzo[*d*][1,3]thiazin-4-yl)acetate (**4c**). mp 130–132°C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.72 (br s, 1H), 7.96 (m, 2H), 7.37 (d, $J=8.4$ Hz, 2H), 7.31–7.23 (m, 2H), 7.16–7.07 (m, 2H), 4.63 (t, $J=7.6$ Hz, 1H), 4.07 (q, $J=7.2$ Hz, 2H), 2.76 (dd, $J=16.0$, 6.0 Hz, 1H), 2.69 (dd, $J=16.0$, 8.8 Hz, 1H), 1.17 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 170.7, 149.9, 142.4, 141.1, 129.4, 129.2, 128.9, 127.0, 124.7, 123.7, 122.7, 122.5, 61.4, 42.0, 40.7, 14.6; IR (KBr) ν 741, 844, 1092, 1337, 1485, 1575, 1730, 2911 cm^{-1} ; HRMS calcd. for $\text{C}_{18}\text{H}_{17}\text{ClN}_2\text{O}_2\text{S}$ 360.0699, found 360.0698.

Ethyl 2-(2-(4-bromophenylamino)-4*H*-benzo[*d*][1,3]thiazin-4-yl)acetate (**3d**). mp 130–132°C; ^1H NMR (400 MHz, CDCl_3) δ 7.45–7.40 (m, 4H), 7.30–7.28 (m, 1H), 7.17–7.07 (m, 3H), 6.95 (br s, 1H), 4.51 (dd, $J=8.8$, 6.4 Hz, 1H), 4.14 (q, $J=7.2$ Hz, 2H), 2.83 (dd, $J=16.0$, 8.8 Hz, 1H), 2.75 (dd, $J=16.0$, 6.4 Hz, 1H), 1.22 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 170.7, 150.0, 142.3, 141.7, 132.3, 129.2, 127.0, 124.6, 123.6, 122.9, 122.7, 116.6, 61.5, 42.0, 40.7, 14.6; IR (KBr) ν 742, 841, 1337, 1562, 1728, 2926 cm^{-1} ; HRMS calcd. for $\text{C}_{18}\text{H}_{17}\text{BrN}_2\text{O}_2\text{S}$ 404.0194, found 404.0200.

Ethyl 2-(2-(4-nitrophenylamino)-4*H*-benzo[*d*][1,3]thiazin-4-yl)acetate (**3e**). mp 156–156.5°C; ^1H NMR (400 MHz, CDCl_3) δ 8.14 (d, $J=9.2$ Hz, 2H), 7.63 (d, $J=8.4$ Hz, 2H), 7.27–7.23 (m, 1H), 7.15–7.05 (m, 3H), 4.48 (dd, $J=8.8$, 6.8 Hz, 1H), 4.08 (q, $J=7.2$ Hz, 2H), 2.77 (dd, $J=16.0$, 8.8 Hz, 1H), 2.68 (dd, $J=16.4$, 6.4 Hz, 1H), 1.16 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 170.0, 148.6, 147.7, 142.6, 141.5, 128.9, 126.6, 125.4, 125.0, 123.8, 122.0, 119.7, 61.1, 41.6, 40.2, 14.1; IR (KBr) ν 749, 848, 1226, 1304, 1331, 1407, 1449, 1502, 1558, 1582, 1719, 2983 cm^{-1} ; HRMS calcd. for $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_4\text{S}$ 371.0940, found 371.0943.

Ethyl 2-(2-(4-nitrophenylimino)-2,4-dihydro-1*H*-benzo[*d*][1,3]thiazin-4-yl)acetate (**4e**). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.25 (br s, 1H), 8.24–8.15 (m, 4H), 7.35–7.14 (m, 4H), 4.68 (dd, $J=8.8$, 6.4 Hz, 1H), 4.07 (q, $J=7.2$ Hz, 2H), 2.77 (dd, $J=16.0$, 6.4 Hz, 1H), 2.70 (dd, $J=16.0$, 8.8 Hz, 1H), 1.17 (t, $J=7.2$ Hz, 3H).

Ethyl 2-(2-(3-chlorophenylamino)-4*H*-benzo[*d*][1,3]thiazin-4-yl)acetate (**3f**). mp 107–109°C; ^1H NMR (400 MHz, CDCl_3) δ 7.74–7.69 (m, 1H), 7.33–7.29 (m, 2H), 7.24–7.04 (m, 5H), 6.76 (br s, 1H), 4.52 (dd, $J=8.8$, 6.8 Hz, 1H), 4.15 (q, $J=7.2$ Hz, 2H), 2.83 (dd, $J=16.0$, 8.8 Hz, 1H), 2.75 (dd, $J=16.0$, 6.4 Hz, 1H), 1.23 (t, $J=7.2$ Hz, 3H); ^{13}C NMR

(75 MHz, CDCl₃) δ 170.7, 150.3, 144.1, 142.0, 134.9, 130.3, 129.2, 127.0, 124.6, 124.0, 123.4, 122.7, 121.4, 119.4, 61.5, 42.0, 40.7, 14.6; IR (KBr) ν 700, 756, 779, 879, 1043, 1240, 1307, 1439, 1466, 1499, 1574, 1721, 2980 cm⁻¹; HRMS calcd. for C₁₈H₁₇ClN₂O₂S 360.0699, found 360.0706.

Ethyl 2-(2-(3-chlorophenylimino)-2,4-dihydro-1*H*-benzo[d][1,3]thiazin-4-yl)acetate (**4f**). ¹H NMR (400 MHz, DMSO-d₆) δ 9.74 (br s, 1H), 8.17–7.05 (m, 8H), 4.62 (t, *J*=7.2 Hz, 1H), 4.07 (q, *J*=7.2 Hz, 2H), 2.75 (dd, *J*=15.6, 6.0 Hz, 1H), 2.67 (dd, *J*=15.6, 8.8 Hz, 1H), 1.16 (t, *J*=6.8 Hz, 3H).

Ethyl 2-(2-(3-methoxyphenylimino)-4*H*-benzo[d][1,3]thiazin-4-yl)acetate (**3g**). mp 87–89°C; ¹H NMR (400 MHz, CDCl₃) δ 7.38 (s, 1H), 7.28–6.94 (m, 6H), 6.64 (d, *J*=8.0 Hz, 1H), 4.50 (t, *J*=7.6 Hz, 1H), 4.13 (q, *J*=7.2 Hz, 2H), 3.82 (s, 3H), 2.84 (dd, *J*=16.0, 8.4 Hz, 1H), 2.75 (dd, *J*=16.0, 6.8 Hz, 1H), 1.22 (t, *J*=7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 170.1, 159.8, 150.0, 143.2, 141.8, 129.3, 128.4, 126.3, 123.7, 123.0, 122.2, 113.2, 109.3, 106.6, 60.7, 55.0, 41.4, 40.0, 14.0; IR (KBr) ν 748, 775, 864, 1049, 1192, 1234, 1303, 1435, 1496, 1581, 1727, 2962 cm⁻¹; HRMS calcd. for C₁₉H₂₀N₂O₃S 356.1195, found 356.1189.

Ethyl 2-(2-(3-methoxyphenylimino)-2,4-dihydro-1*H*-benzo[d][1,3]thiazin-4-yl)acetate (**4g**). ¹H NMR (400 MHz, DMSO-d₆) δ 9.56 (br s, 1H), 7.79–7.25 (m, 3H), 7.23–7.17 (m, 2H), 7.13–7.07 (m, 2H), 6.60–6.58 (m, 1H), 4.60 (t, *J*=7.6 Hz, 1H), 4.06 (q, *J*=7.2 Hz, 2H), 3.76 (s, 3H), 2.75 (dd, *J*=15.6, 6.4 Hz, 1H), 2.67 (dd, *J*=15.6, 8.8 Hz, 1H), 1.16 (t, *J*=7.2 Hz, 3H).

Ethyl 2-(2-(*p*-toluidino)-4*H*-benzo[d][1,3]thiazin-4-yl)acetate (**3h**). mp 116–119°C; ¹H NMR (400 MHz, CDCl₃) δ 7.43 (d, *J*=8.0 Hz, 2H), 7.30–7.28 (m, 1H), 7.20–7.05 (m, 5H), 6.66 (br s, 1H), 4.50 (t, *J*=7.6 Hz, 1H), 4.13 (q, *J*=7.2 Hz, 2H), 2.82 (dd, *J*=16.0, 8.4 Hz, 1H), 2.74 (dd, *J*=16.0, 6.4 Hz, 1H), 2.33 (s, 3H), 1.22 (t, *J*=7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 170.8, 150.0, 143.1, 139.4, 133.7, 129.8, 129.0, 126.9, 124.2, 124.0, 122.8, 121.5, 61.3, 42.0, 40.7, 21.3, 14.6; IR (KBr) ν 748, 833, 1244, 1300, 1438, 1465, 1504, 1581, 1730, 2968 cm⁻¹; HRMS calcd. for C₁₉H₂₀N₂O₂S 340.1245, found 340.1245.

Ethyl 2-(2-(4-methoxyphenylimino)-4*H*-benzo[d][1,3]thiazin-4-yl)acetate (**3i**). mp 107–109°C; ¹H NMR (400 MHz, CDCl₃) δ 7.41 (d, *J*=8.4 Hz, 2H), 7.28–7.24 (m, 1H), 7.16–7.04 (m, 3H), 6.88 (d, *J*=8.8 Hz, 2H), 4.49 (dd, *J*=8.0, 6.8 Hz, 1H), 4.13 (q, *J*=7.2 Hz, 2H), 3.81 (s, 3H), 2.83 (dd, *J*=16.0, 8.4 Hz, 1H), 2.75 (dd, *J*=16.0, 6.8 Hz, 1H), 1.22 (t, *J*=7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 170.8, 156.6, 150.7, 143.1, 135.0, 129.0, 126.9, 124.1, 123.9, 123.5, 122.8, 114.5, 61.3, 55.9, 42.0, 40.7, 14.6; IR (KBr) ν 752, 829, 1028, 1199, 1240, 1298, 1441, 1504, 1581, 1734, 2984 cm⁻¹; HRMS calcd. for C₁₉H₂₀N₂O₃S 356.1195, found 356.1199.

Ethyl 2-(2-(4-methoxyphenylimino)-2,4-dihydro-1*H*-benzo[d][1,3]thiazin-4-yl)acetate (**4i**). ¹H NMR (400 MHz, DMSO-d₆) δ 9.43 (br s, 1H), 7.78 (m, 2H), 7.27–7.20 (m, 2H),

7.09–7.02 (m, 2H), 6.90 (d, *J*=8.8 Hz, 2H), 4.58 (dd, *J*=8.8, 6.8 Hz, 1H), 4.07 (q, *J*=7.2 Hz, 2H), 3.74 (s, 3H), 2.75 (dd, *J*=15.6, 6.8 Hz, 1H), 2.67 (dd, *J*=15.6, 8.8 Hz, 1H), 1.17 (t, *J*=7.2 Hz, 3H).

Ethyl 2-(2-(2-fluorophenylamino)-4*H*-benzo[d][1,3]thiazin-4-yl)acetate (**3j**). mp 127–128.5°C; ¹H NMR (400 MHz, CDCl₃) δ 8.37 (br s, 1H), 7.31–6.99 (m, 8H), 4.52 (dd, *J*=8.4, 6.8 Hz, 1H), 4.15 (q, *J*=7.2 Hz, 2H), 2.85 (dd, *J*=16.4, 8.8 Hz, 1H), 2.76 (dd, *J*=16.0, 6.4 Hz, 1H), 1.23 (t, *J*=7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 170.2, 154.4, 151.2, 149.7, 149.2, 141.9, 128.6, 126.5, 124.3, 123.6, 122.5, 122.3, 115.1, 114.8, 60.9, 41.4, 40.2, 14.1; IR (KBr) ν 752, 775, 1226, 1249, 1300, 1435, 1497, 1581, 1724, 2977 cm⁻¹; HRMS calcd. for C₁₈H₁₇FN₂O₂S 344.0995, found 344.0997.

Ethyl 2-(2-(2-chlorophenylamino)-4*H*-benzo[d][1,3]thiazin-4-yl)acetate (**3k**). mp 132–132.5°C; ¹H NMR (300 MHz, CDCl₃) δ 8.42 (br s, 1H), 7.40–7.28 (m, 3H), 7.21–6.98 (m, 5H), 4.53 (dd, *J*=8.7, 6.9 Hz, 1H), 4.20–4.09 (m, *J*=7.2 Hz, 2H), 2.86 (dd, *J*=16.2, 8.7 Hz, 1H), 2.76 (dd, *J*=15.6, 6.6 Hz, 1H), 1.23 (t, *J*=7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 170.6, 150.8, 141.8, 140.2, 129.7, 129.1, 127.9, 127.0, 124.9, 124.6, 124.5, 123.3, 123.0, 122.8, 61.3, 41.9, 40.6, 14.6; IR (KBr) ν 749, 1035, 1240, 1340, 1496, 1574, 1724, 2921 cm⁻¹; HRMS calcd. for C₁₈H₁₇ClN₂O₂S 360.0699, found 360.0694.

Ethyl 2-(2-(cyclohexylamino)-4*H*-benzo[d][1,3]thiazin-4-yl)acetate (**3l**). mp 93.5–95.5°C; ¹H NMR (400 MHz, CDCl₃) δ 7.25–6.99 (m, 4H), 4.59 (br s, 1H), 4.43 (dd, *J*=8.4, 6.8 Hz, 1H), 4.14 (q, *J*=7.2 Hz, 2H), 4.07–3.97 (m, 1H), 2.75 (dd, *J*=16.0, 8.8 Hz, 1H), 2.69 (dd, *J*=16.0, 6.4 Hz, 1H), 2.15–1.13 (m, 13H); ¹³C NMR (75 MHz, CDCl₃) δ 170.9, 151.0, 145.3, 128.9, 126.7, 125.4, 123.7, 122.7, 61.2, 51.5, 41.8, 40.6, 34.1, 33.5, 26.1, 25.3, 25.2, 14.6; IR (KBr) ν 761, 1220, 1488, 1574, 1728, 2936, 3391 cm⁻¹; HRMS calcd. for C₁₈H₂₄N₂O₂S 332.1559, found 332.1550.

Ethyl 2-(2-(cyclohexylimino)-2,4-dihydro-1*H*-benzo[d][1,3]thiazin-4-yl)acetate (**4l**). ¹H NMR (400 MHz, DMSO-d₆) δ 7.26 (d, *J*=6.4 Hz, 1H), 7.18–7.11 (m, 2H), 6.94–6.92 (m, 2H), 4.43 (t, *J*=7.6 Hz, 1H), 4.05 (q, *J*=6.8 Hz, 2H), 3.97–3.89 (m, 1H), 2.68–2.55 (m, 2H), 1.99–1.11 (m, 13H).

Ethyl 2-(2-(methylamino)-4*H*-benzo[d][1,3]thiazin-4-yl)acetate (**3m**). mp 138–140°C; ¹H NMR (400 MHz, CDCl₃) δ 7.27–7.24 (m, 1H), 7.17 (d, *J*=8.0 Hz, 1H), 7.12 (d, *J*=7.2 Hz, 1H), 7.02 (t, *J*=7.2 Hz, 1H), 4.43 (t, *J*=7.6 Hz, 1H), 4.14 (q, *J*=7.2 Hz, 2H), 3.09 (s, 3H), 2.75 (dd, *J*=16.0, 8.8 Hz, 1H), 2.68 (dd, *J*=16.0, 6.8 Hz, 1H), 1.23 (t, *J*=7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 170.4, 152.0, 144.7, 128.5, 126.3, 125.1, 123.4, 122.3, 60.8, 41.5, 40.1, 29.3, 14.1; IR (KBr) ν 761, 1221, 1411, 1450, 1478, 1604, 1730, 2889, 2975 cm⁻¹; HRMS calcd. for C₁₃H₁₆N₂O₂S 264.0932, found 265.1005.

Ethyl 2-(2-(methylimino)-2,4-dihydro-1*H*-benzo[d][1,3]thiazin-4-yl)acetate (**4m**). ¹H NMR (400 MHz, DMSO-d₆) δ 7.33 (br s, 1H), 7.20–7.12 (m, 2H), 6.98–6.92 (m, 2H), 4.45

(dd, $J=8.8, 6.4$ Hz, 1H), 4.05 (q, $J=7.2$ Hz, 2H), 2.87 (d, $J=4.0$ Hz, 3H), 2.65 (dd, $J=15.6, 6.4$ Hz, 1H), 2.56 (dd, $J=16.0, 8.8$ Hz, 1H), 1.15 (t, $J=7.2$ Hz, 3H).

2 Results and discussion

In an initial experiment, ethyl *o*-aminocinnamate (**1**) was reacted with phenyl isothiocyanate (**2a**) (Scheme 1) in the presence of 10 mol% of ytterbium chloride (YbCl_3), a readily available and economical lanthanide Lewis acid. After work up, a compound was isolated in quantitative yield (99%) and high purity as judged by HPLC. The results of X-ray diffraction analysis of a single crystal of this compound [42] (Figure 2) indicated that the product was the expected ethyl 2-(2-(phenylimino)-4*H*-benzo[*d*][1,3]thiazin-4-yl)acetate (**3a**). However, after careful identification, it was found that the

average C1-N1 bond distance of 1.363 Å was longer than the C1-N2 bond length of 1.288 Å. According to the literature [43,44], the typical length of a C–N bond is 1.339 Å, while that of a C=N double bond is 1.279 Å. Thus, the structure of the product in crystalline state is actually 2-(2-(phenylimino)-2,4-dihydro-1*H*-benzo[*d*][1,3]thiazin-4-yl)acetate (**4a**), in which the C=N double bond is exocyclic. To confirm the structure of the product, ^1H NMR spectra recorded in different deuterated solvents were studied. The compound produces a signal at δ 6.7 in CDCl_3 , which is in accord with the chemical shift of the exocyclic N–H group [20,21] in **3a**. Meanwhile, the signal of the N–H group in the ^1H NMR spectrum recorded in $\text{DMSO}-d_6$ appears at δ 9.5, correlating with the corresponding value of the proton of the endocyclic N–H group [31,45,46] in **4a**. These findings suggest that the product present in both $\text{DMSO}-d_6$ and the single crystal is **4a**. When the crystal dissolves in CDCl_3 , it

Scheme 1

Figure 2 X-ray crystal structure of **4a**.

readily undergoes tautomeric transformation from **4a** into **3a**. It can be confirmed that solvent conditions play an important role in affecting the tautomeric equilibrium. This result is slightly different from that obtained by Shabarov and coworkers [22]. Interestingly, another type of cyclization product **5** (Scheme 1), which can be formed through an intramolecular *N*-nucleophilic attack rather than *S*-nucleophilic attack, was not observed.

Various conditions including time, temperature, catalyst loading, and the molar ratio of the respective substrates were then screened to optimize this catalytic system. The results are listed in Table 1. Use of 2.5 mol% of YbCl₃ is sufficient to give the product in 99% yield, and a slight excess of isothiocyanate promotes conversion. Thus, reaction conditions of 2.5 mol% catalyst at 50°C for 4 h were used for the following studies.

A series of metal chlorides were used as Lewis acids to assess the influence of the central metal ion on catalytic activity. Inferior results were observed when traditional Lewis acids such as ZnCl₂ and FeCl₃ were used. A progressive decrease in the ionic radii of Ln(III) from the light rare earth La to heavy rare earth Yb had a significant influence

on the reaction. The order of catalytic activity of these lanthanide ions is simply the reverse of their ionic radii. As a result, YbCl₃ was chosen as a representative lanthanide source for carrying out the following studies.

To our delight, this Lewis acid-catalyzed reaction proceeded under mild, simple, and clean conditions. First, no solvent is required during the reaction, which not only negates the use of auxiliary reagents that may be toxic or flammable but also simplifies the operation. Second, the reaction works well under an air atmosphere (entry 6), so the steps of drying and protection, which are usually essential for most of the reactions involving lanthanide compounds, are unnecessary. As a result, this procedure is an efficient, convenient and environmentally friendly protocol for the synthesis of 2-amino-4*H*-3,1-benzothiazines.

The reaction scope of this YbCl₃ catalytic system and its tolerance toward functional groups were explored using various isothiocyanates (Scheme 2). As shown in Table 2, all of the reactions with *ortho*-, *meta*- and *para*-substituted aryl isothiocyanates proceeded smoothly and afforded the expected products in good to excellent yields. Both electronic and steric effects were observed. The electron-donating group (EDG)-substituted aryl isothiocyanates (*para*-substituted, entries 8 and 9) required increased temperature (70°C) to realize yields close to those containing electron-withdrawing substituents (entries 2–5). For example, *p*-chlorophenyl isothiocyanate (**2c**) reacted with **1** at 50°C leading to the corresponding product in 95% yield, whereas *p*-methoxyphenyl isothiocyanate (**2i**) achieved the same yield only when the reaction was carried out at 70°C. Increased temperature was also necessary for *ortho*-substituted aryl isothiocyanates (entries 10 and 11) to achieve the desired yields, indicating an obvious steric effect. The reaction encountered some difficulties when alkyl isothiocyanates with different steric hindrance (entries 12 and 13) were used as substrates. Methyl isothiocyanate worked well at 70°C, realizing a yield similar to those of EDG-substituted aryl isothiocyanates. However, sterically hindered cyclohexyl isothiocyanate gave a relatively lower yield despite extending the reaction time to 48 h.

The high efficiency of the reaction compelled us to deduce a plausible mechanism. It was considered that the required 2-amino-4*H*-3,1-benzothiazine can be formed *via* a three-step sequence (Scheme 3). The first step of the reaction is the formation of thiourea **C**, which can be detected and

Table 1 Condition screening for the reaction of **1** with **2a**^{a)}

Entry	Catalyst (mol%)	Molar ratio (1 : 2a)	Time (h)	Temp. (°C)	Yield (%)
1	–	1:1.2	4	50	0
2	YbCl ₃ (10)	1:2	4	50	99
3	YbCl ₃ (10)	1:2	3	50	84
4	YbCl ₃ (2.5)	1:2	4	50	99
5	YbCl ₃ (1)	1:2	4	50	90
6	YbCl ₃ (2.5)	1:1.2	4	50	99(99) ^{b)}
7	YbCl ₃ (2.5)	1:1	4	50	95
8	YbCl ₃ (2.5)	1:1.2	4	40	71
9	ErCl ₃ (2.5)	1:1.2	4	50	95
10	GdCl ₃ (2.5)	1:1.2	4	50	32
11	SmCl ₃ (2.5)	1:1.2	4	50	24
12	LaCl ₃ (2.5)	1:1.2	4	50	10
13	ZnCl ₂ (2.5)	1:1.2	4	50	33
14	FeCl ₃ (2.5)	1:1.2	4	50	6

a) Reactions were carried out under solvent-free conditions. b) The reaction was performed under an air atmosphere.

Scheme 2

Table 2 YbCl₃-catalyzed reaction of **1** with various isothiocyanates^{a)}

Entry	R	Temp. (°C)	Time (h)	Product	Yield (%)
1	Ph	50	4	3a+4a	99
2	<i>p</i> -FC ₆ H ₄	50	4	3b+4b	91
3	<i>p</i> -ClC ₆ H ₄	50	4	3c+4c	95
4	<i>p</i> -BrC ₆ H ₄	50	4	3d+4d	88
5	<i>p</i> -NO ₂ C ₆ H ₄	50	4	3e+4e	91
6	<i>m</i> -ClC ₆ H ₄	50	4	3f+4f	99
7	<i>m</i> -MeOC ₆ H ₄	50	4	3g+4g	96
8	<i>p</i> -MeC ₆ H ₄	70	4	3h+4h	96
9	<i>p</i> -MeOC ₆ H ₄	70	4	3i+4i	95
10	<i>o</i> -FC ₆ H ₄	70	4	3j+4j	96
11	<i>o</i> -ClC ₆ H ₄	70	4	3k+4k	96
12	<i>c</i> -hexyl	70	48	3l+4l	74
13	CH ₃	70	4	3m+4m	91(91) ^{b)}

a) Typical reaction conditions: **1**:isothiocyanate=1:1.2, 2.5 mol% YbCl₃, solvent-free. b) The reaction was performed at 50°C for 15 h.

isolated during the reaction, through the addition of the aromatic amino group to the isothiocyanate. Then, cyclization of **C** takes place *via* an intramolecular Michael addition of the S-terminal of thiourea to the lanthanide-activated α,β -unsaturated ester, leading to intermediate **D**. Finally, an intramolecular hydride transfer forms the target 2-amino-4*H*-3,1-benzothiazine and releases the active Ln(III) catalyst.

3 Conclusions

In conclusion, an efficient method to synthesize 2-amino-

4*H*-3,1-benzothiazines by YbCl₃-catalyzed addition-cyclization reaction of *o*-aminocinnamate with isothiocyanates under solvent-free conditions has been developed. This tandem reaction is clean and can be handled easily. The environmentally friendly features of this catalytic procedure make it a practical and environmentally acceptable method for the synthesis of 2-amino-4*H*-3,1-benzothiazines.

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Scheme 3

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