

# Synthesis of Methyl 3-Azidothieno[2,3-*b*]pyridine-2-carboxylates and Application of the Huisgen Reaction

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*Dedicated to Professor Willi Kantlehner on the occasion of his 70<sup>th</sup> birthday for his longtime involvement and promotion of the chemistry of iminium salts*

The preparation of new substituted methyl 3-azidothieno[2,3-*b*]pyridine carboxylates by azotization of methyl 3-aminothieno[2,3-*b*]pyridine and subsequent treatment with sodium azide is described. *Via* Huisgen's 1,3-dipolar cycloaddition between substituted alkynes and the prepared azides, methyl 1,2,3-triazolo-thieno[2,3-*b*]pyridine carboxylates have been obtained.

**Key words:** Vilsmeier-Haack-Arnold Reaction, 2-Chloro-3-cyano-pyridines, Thienopyridines, 1,2,3-Triazole

## Introduction

Thieno[2,3-*b*]pyridines have received considerable attention, since they show a wide variety of bioactivities, for example antiviral, antidiabetic, antimicrobial, antitumor, antiparasitic, and neurotropic activities [1–9].

In continuation of synthetic work with aminothieno[2,3-*b*]pyridines previously developed in our laboratory [10], we propose here a new route to methyl 1,2,3-triazolo-thieno[2,3-*b*]pyridine carboxylates. The well-established method for their synthesis is *via* Huisgen's 1,3-dipolar cycloaddition between an alkyne and an organic azide [11, 12].

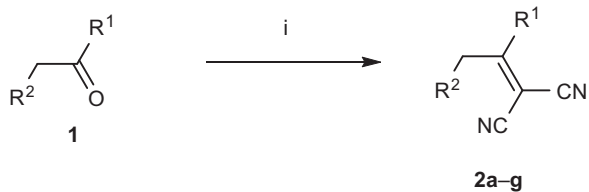
Heterocyclic aromatic azides with electron-deficient aromatic rings have been most widely studied. Such azides are synthesized through nucleophilic substitution of halogen or a similar group by the azide ion. An electron-rich aromatic ring is not suitable for such a reaction. Hence, diazotization of amino derivatives and their conversion into azides by the reaction with sodium azide is the main method for the synthesis of such heteroazides.

## Results and Discussion

In the present work, we describe the synthesis of methyl azidothieno[2,3-*b*]pyridine carboxylates **6** and methyl triazolothieno[2,3-*b*]pyridine carboxylates **8** from methyl 3-aminothieno[2,3-*b*]pyridine carboxylates **5**. The  $\alpha$ -methylene ketones **1** were used as starting materials for the synthesis of thieno[2,3-*b*]pyridines **5**.

The alkylidene malonitriles **2**, prepared by Knoevenagel condensation [13–16] from  $\alpha$ -methylene ketones, served as intermediates for the synthesis of the 2-chloro-3-cyanopyridines **4** (Scheme 1, Table 1).

Treatment of the alkylidene malonitriles with the Vilsmeier-Haack reagent at 70–80 °C led to the formation of 2-chloro-3-cyanopyridines **4** (Scheme 2, Table 2). The cyclization occurred regioselectively at the most active methylene group in  $\gamma$  position of the alkylidene malonitrile **2**, leading to an intermediate I. This intermediate cyclized “*in situ*” to yield 2-chloro-3-cyanopyridines **4**. However, this reaction was accomplished in general with low yields (10–15%). We could increase the yield by adding some natural phos-



Scheme 1. Synthesis of compounds **2**. Reagents and conditions: (i)  $\text{CH}_2(\text{CN})_2$ ,  $\text{CH}_3\text{COONH}_4$ ,  $\text{CH}_3\text{COOH}$ , toluene, reflux, 24 h.

phate (NP) [17] or some phosphate modified by potassium fluoride (KF/NP) to the reaction mixture.

We also used 2-chloro-6-methyl-3-cyanopyridine **4f**. This compound was synthesized from 6-methyl-3-cyanopyridin-2-one [18–29] by treatment with phosphorus oxychloride at 60 °C for 24 h (Scheme 3).

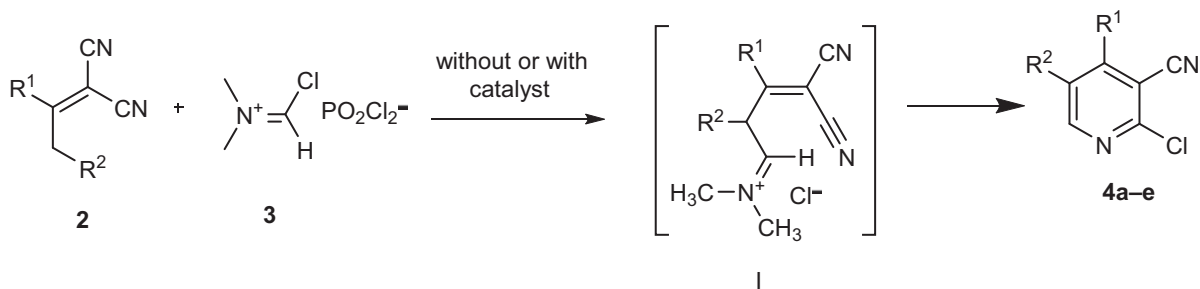
The chlorocyanopyridines **4** were used as intermediates for the synthesis of 3-aminothieno[2,3-*b*]pyridines **5**. Synthesis of the thiophene ring could be accomplished *via* two routes. In route A, condensation with methyl thioglycolate in DMF afforded the  $\text{S}_{\text{N}}\text{Ar}$  product which could be isolated and cyclized in a second step to the 3-amino-2-carbomethoxythiophene **5**. Substitution and cyclization was realized in a one-pot route B by reaction of the 2-chloro-3-cyanopyridine with sodium sulfide and methyl bromoacetate in DMF in the presence of sodium methanolate (Scheme 4, Table 3).

Azidothieno[2,3-*b*]pyridines **6** were obtained by diazotization of the corresponding amino derivatives in 70% sulfuric acid solution upon addition of sodium azide in water to the diazonium salt. The precipitated azides were filtered off (Scheme 5, Table 4). These azido derivatives are light-sensitive. They should be stored in a dark place or used directly for further reactions.

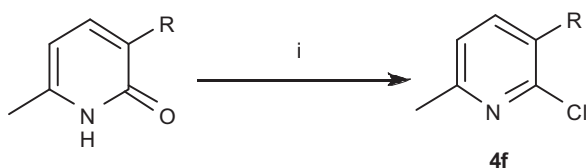
Table 1. Synthesis of alkyldene malononitriles **2**.

Ketone <b>1</b>	Alkyldene malononitrile <b>2</b>	Yield (%)
		83
		90
		74
		45
		51

1,3-Dipolar cycloaddition reactions between 3-azido derivatives **6** and alkynes **7** were run in chloroform in the presence of copper(I) chloride and base. Huisgen's cycloaddition took at least 24 h and the yields were fair to good. The use of copper iodide did



Scheme 2. Synthesis of compounds **4**. Reagents: (i) Vilsmeier-Haack reagent or Vilsmeier-Haack reagent + modified phosphate, 70–80 °C, 3 h.



Scheme 3. Synthesis of **4f**. Reagents and conditions: i)  $\text{POCl}_3$ ,  $60^\circ\text{C}$ , 24 h.

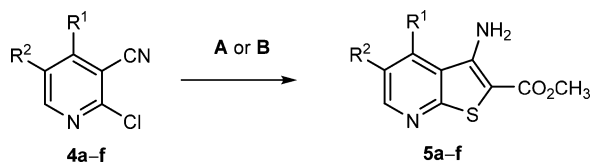
Table 2. Synthesis of 2-chloro-3-cyanopyridines **4**.

Alkylidene malononitrile <b>2</b>		Yield (%)	Yield (%) (KF/NP)
		10	54
		15	56
		8	30
		15	62
		10	–

not lead to the formation of the triazole (Scheme 6, Table 5).

## Conclusion

Starting from simple compounds we prepared functionalized pyridines using a modified Vilsmeier-Haack-Arnold reaction useful for constructing polycyclic heterocyclic compounds.



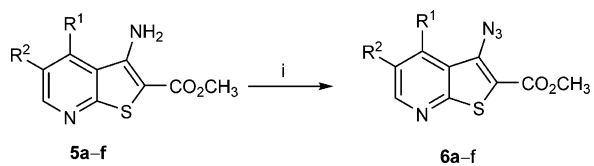
Scheme 4. Synthesis of compounds **5**. Reagents and conditions: A)  $\text{HSCH}_2\text{CO}_2\text{CH}_3$ , DMF,  $\text{K}_2\text{CO}_3$ , r. t., 24 h, MeONa, MeOH, r. t., 1 h; B)  $\text{Na}_2\text{S}\cdot 9\text{H}_2\text{O}$ ,  $\text{BrCH}_2\text{CO}_2\text{CH}_3$ , MeONa, MeOH,  $50^\circ\text{C}$ , 3 h.

Table 3. Synthesis of methyl 3-aminothienopyridine-2-carboxylates **5**.

<b>5</b>	Yield (%)	Method
	60 35	A B
	61 38	A B
	53	A
	85	A
	98	A
	98	A

## Experimental Section

All melting points were measured in open capillary tubes in a Stuart SMP 3 apparatus. NMR spectra were recorded on a Bruker AC 250 (250 MHz) spectrometer in  $\text{CDCl}_3$ ,  $[\text{D}_6]$ acetone or  $[\text{D}_6]$ DMSO. Chemical shifts ( $\delta$ ) are reported in ppm and coupling constants ( $J$ ) in Hz.



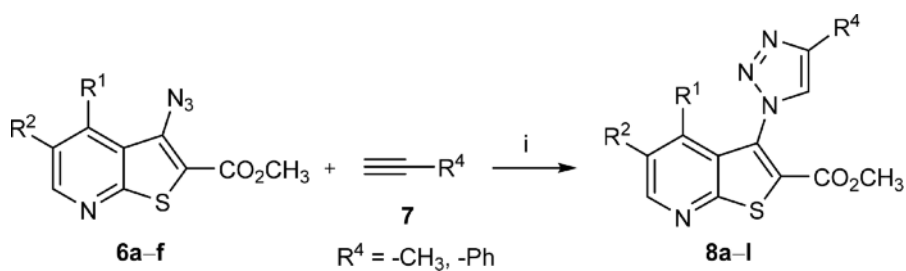
Scheme 5. Synthesis of compounds **6**. Reagents and conditions: i) 1.  $\text{NaNO}_2$ ,  $\text{H}_2\text{SO}_4$ ; 2.  $\text{NaN}_3$ .

Table 4. Synthesis of methyl 3-azidothienopyridine-2-carboxylates **6**.

<b>6</b>	Yield (%)
	53
	67
	47
	58
	37
	63

Table 5. Synthesis of methyl 1,2,3-triazolylthienopyridine-2-carboxylates **8**.

<b>8</b>	Yield (%)
	23
	40
	46
	52
	75
	30



Scheme 6. Synthesis of compounds **8**. Reagents and conditions: i) 2,4-lutidine,  $\text{CuCl}$ ,  $\text{CHCl}_3$ , r. t., 24 h.

Table 5. (Continued.)

8	Yield (%)
<b>g</b>	73
<b>h</b>	65
<b>i</b>	45
<b>j</b>	38
<b>k</b>	93
<b>l</b>	72

*General procedure for the synthesis of alkylidene malononitriles*

These compounds were synthesized according to a known procedure [10].

*General procedure for the synthesis of 2-chloro-3-cyanopyridines 4*

To a flask containing 10 mmol of a gem-dicyanoalkene **1** and 20 mmol (3.0 g) of POCl<sub>3</sub> in DMF (10 mL), 0.1 g of phosphate catalyst (KF/NP) was added, and the mixture was stirred at room temperature for 30 min. Then the bath temperature was slowly raised to 70–80 °C. The reaction mixture was heated for 3 h and after cooling poured into cold water. The formed solid was filtered and recrystallized or purified by column chromatography.

*3-Chloro-6,7-dihydro-5H-cyclopenta[*c*]pyridine-4-carbonitrile (4a)*

Brown solid, m. p. 105 °C (cyclohexane). – <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz, 25 °C): δ = 2.19–2.31 (m, 2H, CH<sub>2</sub>), 2.98–3.04 (t, *J* = 7.5 Hz, 2H, CH<sub>2</sub>), 3.11–3.17 (t, *J* = 7.5 Hz, 2H, CH<sub>2</sub>), 8.38 (s, 1H, H<sub>ar</sub>). – <sup>13</sup>C NMR (CDCl<sub>3</sub>, 250 MHz): δ = 25.00, 25.38, 37.33, 81.62, 112.38, 140.74, 148.17, 162.63, 193.35.

*3-Chloro-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (4b)*

Brown solid, m. p. 126 °C (ethyl acetate-petroleum ether). – <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz, 25 °C): δ = 1.83–1.94 (m, 4H, CH<sub>2</sub>CH<sub>2</sub>), 2.75–2.77 (t, *J* = 2.5 Hz, 2H, CH<sub>2</sub>), 2.93–2.98 (t, *J* = 6.25 Hz, 2H, CH<sub>2</sub>), 8.27 (s, 1H, H<sub>ar</sub>). – <sup>13</sup>C NMR (CDCl<sub>3</sub>, 250 MHz): δ = 21.37, 21.57, 25.70, 28.25, 110.38, 113.92, 139.62, 150.10, 152.43, 153.45.

*2-Chloro-5-methyl-4-phenylnicotinonitrile (4c)*

Orange solid, m. p. 125–127 °C (column chrom., 20% ethyl acetate-cyclohexane). – <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz, 25 °C): δ = 2.19 (s, 3H, CH<sub>3</sub>), 7.28–7.31 (m, 2H, H<sub>ar</sub>), 7.52–7.57 (m, 3H, H<sub>ar</sub>), 8.47 (s, 1H, H<sub>ar</sub>). – <sup>13</sup>C NMR (CDCl<sub>3</sub>, 250 MHz): δ = 16.81, 110.65, 114.36, 128.03, 128.18, 129.78, 131.15, 134.48, 151.02, 152.98, 155.

*2-Chloro-5,6-dihydrobenzo[*ff*]isoquinoline-1-carbonitrile (4d)*

Yellow solid, m. p. 180 °C (column chrom., 20% ethyl acetate-cyclohexane). – <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz, 25 °C): δ = 2.16–2.28 (m, 2H, CH<sub>2</sub>), 3.00–3.06 (t, 2H, *J* = 7.5 Hz, CH<sub>2</sub>), 3.38–3.44 (t, 2H, *J* = 7.5 Hz, CH<sub>2</sub>), 3.98 (s, 3H, CH<sub>3</sub>), 8.56 (s, 1H, H<sub>ar</sub>). – <sup>13</sup>C NMR (CDCl<sub>3</sub>, 250 MHz): δ = 24.14, 28.67, 96.40, 115.19, 117.49, 126.87, 127.18, 128.69, 129.08, 131.68, 140.93, 140.97, 151.37, 160.74.

*2-Chloro-6-methyl-5,6-dihydrobenzo[*ff*]isoquinoline-1-carbonitrile (4e)*

Yellow solid, m. p. 149–151 °C (column chrom., 20% ethyl acetate-cyclohexane). – <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz,

25 °C):  $\delta$  = 0.84–0.87 (m, 3H, CH<sub>3</sub>), 2.68–2.76 (m, 1H, CH), 2.97–3.11 (m, 3H, CH<sub>3</sub>), 7.26–7.50 (m, 3H, H<sub>ar</sub>), 8.44 (s, 2H, H<sub>ar</sub>). – <sup>13</sup>C NMR (CDCl<sub>3</sub>, 250 MHz):  $\delta$  = 18.58, 29.86, 36.26, 105.11, 116.10, 126.79, 127.76, 128.53, 129.60, 130.94, 136.65, 138.31, 147.40, 149.77, 153.23.

*General procedure for the synthesis of methyl aminothienopyridine-2-carboxylates 5*

Chlorocyanopyridine (0.005 mol), methyl thioglycolate (0.01 mol) and potassium carbonate (0.0075 mol) were mixed in 100 mL of DMF. The mixture was stirred for 24 h at room temperature and then poured into ice-water. The precipitated product was filtered off and dried. It was then cyclized by adding it to 0.005 moles of sodium methanolate in 25 mL of methanol. The mixture was stirred for one hour at room temperature and then poured into ice-water. The precipitated product was filtered off, dried and purified by recrystallization from methanol.

*Methyl 1-amino-7,8-dihydro-6H-cyclopenta[d]thieno[2,3-*b*]pyridine-2-carboxylate (5a)*

Yellow solid, yield 60%, m.p. 215 °C. – <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz):  $\delta$  = 2.25–2.34 (m, 2H, CH<sub>2</sub>), 2.99–3.05 (t, 2H, *J* = 7.5 Hz, CH<sub>2</sub>), 3.33–3.39 (t, 2H, *J* = 7.5 Hz, CH<sub>2</sub>), 6.01 (s, 2H, NH<sub>2</sub>), 8.52 (s, 1H, H<sub>ar</sub>). – <sup>13</sup>C NMR (CDCl<sub>3</sub>, 250 MHz):  $\delta$  = 24.83, 29.50, 31.60, 51.59, 97.97, 123.27, 136.24, 146.65, 147.52, 148.74, 158.70, 165.95. – HRMS (APCI): *m/z* = 248.0587 (calcd. 248.0600 for [C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>S<sub>1</sub>+H]<sup>+</sup>).

*Methyl 1-amino-6,7,8,9-tetrahydrothieno[2,3-*c*]isoquinoline-2-carboxylate (5b)*

Yellow solid, m.p. 218 °C. – <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz, 25 °C):  $\delta$  = 1.81–1.95 (m, 4H, CH<sub>2</sub>CH<sub>2</sub>), 2.81–2.86 (t, 2H, *J* = 6.25 Hz, CH<sub>2</sub>), 3.25–3.30 (t, 2H, *J* = 6.25 Hz, CH<sub>2</sub>), 6.23 (s, 2H, NH<sub>2</sub>), 8.32 (s, 1H, H<sub>ar</sub>). – <sup>13</sup>C NMR (CDCl<sub>3</sub>, 250 MHz):  $\delta$  = 26.4, 26.85, 30.94, 31.25, 129.12, 133.51, 136.51, 149.03, 154.69, 156.76, 162.73, 171.82. – HRMS (APCI): *m/z* = 262.0776 (calcd. 262.0800 for [C<sub>13</sub>H<sub>14</sub>N<sub>4</sub>O<sub>2</sub>S<sub>1</sub>+H]<sup>+</sup>).

*Methyl 3-amino-5-methyl-4-phenylthieno[2,3-*b*]pyridine-2-carboxylate (5c)*

Green solid, m.p. 214–216 °C. – <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz, 25 °C):  $\delta$  = 2.31 (s, 3H, CH<sub>3</sub>), 3.80 (s, 3H, CH<sub>3</sub>), 5.43 (s, 2H, NH<sub>2</sub>), 7.30–7.33 (m, 2H, H<sub>ar</sub>), 7.54–7.56 (m, 3H, H<sub>ar</sub>), 8.50 (s, 1H, H<sub>ar</sub>). – <sup>13</sup>C NMR (CDCl<sub>3</sub>, 250 MHz):  $\delta$  = 16.33, 51.51, 96.80, 117.38, 127.22, 129.02, 129.17, 135.49, 145.73, 147.85, 151.70, 159.35, 161.09, 165.92. – HRMS (APCI): *m/z* = 298.0796 (calcd. 298.0800 for [C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>S<sub>1</sub>+H]<sup>+</sup>).

*Methyl 1-amino-6,7-dihydrobenzo[*f*]thieno[2,3-*c*]isoquinoline-2-carboxylate (5d)*

Yellow solid, m.p. 200 °C. – <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz, 25 °C):  $\delta$  = 2.79 (m, 4H, CH<sub>2</sub>CH<sub>2</sub>), 3.77 (s, 3H, CH<sub>3</sub>), 6.24 (s, 2H, NH<sub>2</sub>), 7.38–7.73 (m, 1H, H<sub>ar</sub>), 8.55 (s, 1H, H<sub>ar</sub>). – <sup>13</sup>C NMR (CDCl<sub>3</sub>, 250 MHz):  $\delta$  = 25.83, 29.07, 51.65, 97.38, 126.78, 127.11, 127.42, 128.33, 128.44, 129.20, 129.86, 130.19, 130.79, 131.17, 140.38, 147.50, 166.16. – HRMS (APCI): *m/z* = 310.0806 (calcd. 310.0800 for [C<sub>17</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>S<sub>1</sub>+H]<sup>+</sup>).

*Methyl 1-amino-6,7-dihydro-7-methylbenzo[*f*]thieno[2,3-*c*]isoquinoline-2-carboxylate (5e)*

Yellow solid, m.p. 162–164 °C. – <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz, 25 °C):  $\delta$  = 1.47 (m, 3H, CH<sub>3</sub>), 2.72–2.78 (m, 1H, CH), 3.02–3.08 (m, 2H, CH<sub>2</sub>), 3.91 (s, 3H, CH<sub>3</sub>), 6.23 (s, 2H, NH<sub>2</sub>), 7.37–7.42 (m, 3H, H<sub>ar</sub>), 7.68–7.72 (m, 1H, H<sub>ar</sub>), 8.57 (s, 1H, H<sub>ar</sub>). – <sup>13</sup>C NMR (CDCl<sub>3</sub>, 250 MHz):  $\delta$  = 18.40, 30.53, 36.61, 51.63, 97.36, 119.57, 126.79, 129.17, 129.57, 129.88, 134.77, 138.65, 139.81, 147.65, 148.64, 148.75, 161.17, 166.17. – HRMS (APCI): *m/z* = 324.0932 (calcd. 324.0900 for [C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>S<sub>1</sub>+H]<sup>+</sup>).

*Methyl 3-amino-6-methylthieno[2,3-*b*]pyridine-2-carboxylate (5f)*

Yellow solid, m.p. 182–185 °C. – <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz, 25 °C):  $\delta$  = 2.68 (s, 3H, CH<sub>3</sub>), 3.89 (s, 3H, CH<sub>3</sub>), 5.90 (s, 2H, NH<sub>2</sub>), 7.15–7.18 (d, 1H, *J* = 7.5 Hz, H<sub>ar</sub>), 7.79–7.83 (d, 1H, *J* = 10 Hz, H<sub>ar</sub>). – <sup>13</sup>C NMR (CDCl<sub>3</sub>, 250 MHz):  $\delta$  = 24.81, 51.61, 97.56, 119.21, 122.93, 129.22, 146.36, 160.34, 160.80, 165.89. – HRMS (APCI): *m/z* = 222.0463 (calcd. 222.0500 for [C<sub>10</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>S<sub>1</sub>+H]<sup>+</sup>).

*General procedure for the synthesis of methyl azido-thienopyridine-2-carboxylates 6*

3-Aminothieno[2,3-*b*]pyridine (1.79 mmol) was dissolved in concentrated sulfuric acid (70%, 10 mL) containing ice. When the mixture reached 0 °C, a saturated aqueous solution of sodium nitrite (3 equiv.) was added keeping the temperature below 5 °C. After 10 min, sodium azide (3 equiv.) in 5 mL of water was added dropwise. The solution was left for 30 min at room temperature, and the azide was precipitated in water. The solid was filtered off and washed with water and acetone.

*Methyl 1-azido-7,8-dihydro-6H-cyclopenta[d]thieno[2,3-*b*]pyridine-2-carboxylate (6a)*

Colorless solid, m.p. 137–140 °C. – <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz, 25 °C):  $\delta$  = 2.16–2.28 (m, 2H, CH<sub>2</sub>), 3.00–3.06 (t, 2H, *J* = 7.5 Hz, CH<sub>2</sub>), 3.38–3.44 (t, 2H, *J* = 7.5 Hz, CH<sub>2</sub>), 3.98 (s, 3H, CH<sub>3</sub>), 8.56 (s, 1H, H<sub>ar</sub>). – <sup>13</sup>C NMR

(CDCl<sub>3</sub>, 250 MHz):  $\delta$  = 24.89, 29.92, 32.32, 52.54, 117.10, 125.59, 135.88, 137.58, 147.19, 150.67, 157.00, 162.31. – HRMS (APCI):  $m/z$  = 275.0629 (calcd. 275.0597 for [C<sub>12</sub>H<sub>10</sub>N<sub>4</sub>O<sub>2</sub>S<sub>1</sub>+H]<sup>+</sup>).

*Methyl 1-azido-6,7,8,9-tetrahydrothieno[2,3-*c*]isoquinoline-2-carboxylate (6b)*

Colorless solid, m.p. 133 °C. – <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz, 25 °C):  $\delta$  = 1.81–1.90 (m, 4H, CH<sub>2</sub>CH<sub>2</sub>), 2.83–2.87 (t, 2H,  $J$  = 5 Hz, CH<sub>2</sub>), 3.34–3.36 (t, 2H,  $J$  = 2.5 Hz, CH<sub>2</sub>), 3.90 (s, 3H, CH<sub>3</sub>), 8.5 (s, 1H, H<sub>ar</sub>). – <sup>13</sup>C NMR (CDCl<sub>3</sub>, 250 MHz):  $\delta$  = 21.83, 22.18, 26.67, 26.87, 30.91, 52.54, 117.13, 129.93, 136.79, 144.76, 152.15, 156.94, 162.17. – HRMS (APCI):  $m/z$  = 289.0751 (calcd. 289.0754 for [C<sub>13</sub>H<sub>12</sub>N<sub>4</sub>O<sub>2</sub>S<sub>1</sub>+H]<sup>+</sup>).

*Methyl 3-azido-5-methyl-4-phenylthieno[2,3-*b*]pyridine-2-carboxylate (6c)*

Yellow solid, m.p. 139–143 °C. – <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz, 25 °C):  $\delta$  = 2.17 (s, 3H, CH<sub>3</sub>), 3.95 (s, 3H, CH<sub>3</sub>), 7.18–7.21 (d, 2H,  $J$  = 7.5 Hz, H<sub>ar</sub>), 7.40–7.50 (m, 3H, H<sub>ar</sub>), 8.26 (s, 1H, H<sub>ar</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 250 MHz):  $\delta$  = 16.78, 30.90, 52.61, 118.90, 128.15, 128.17, 129.14, 135.77, 135.94, 146.94, 151.87, 157.28, 161.93, 208.11. – HRMS (APCI):  $m/z$  = 325.0749 (calcd. 325.0750 for [C<sub>16</sub>H<sub>12</sub>N<sub>4</sub>O<sub>2</sub>S<sub>1</sub>+H]<sup>+</sup>).

*Methyl 1-azido-6,7-dihydrobenzo[*f*]thieno[2,3-*c*]isoquinoline-2-carboxylate (6d)*

Yellow solid, m.p. 120–123 °C. – <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz, 25 °C):  $\delta$  = 2.88 (s, 4H, CH<sub>2</sub>CH<sub>2</sub>), 4.00 (s, 3H, CH<sub>3</sub>), 7.38–7.41 (m, 3H, H<sub>ar</sub>), 7.67–7.68 (d, 1H,  $J$  = 2.5 Hz, H<sub>ar</sub>), 8.59 (s, 1H, H<sub>ar</sub>). – <sup>13</sup>C NMR (CDCl<sub>3</sub>, 250 MHz):  $\delta$  = 26.03, 28.82, 52.71, 118.54, 125.83, 127.36, 129.72, 130.20, 131.20, 131.58, 135.75, 139.34, 141.06, 147.75, 149.62, 159.38, 161.99. – HRMS (APCI):  $m/z$  = 337.0756 (calcd. 337.0754 for [C<sub>17</sub>H<sub>12</sub>N<sub>4</sub>O<sub>2</sub>S<sub>1</sub>+H]<sup>+</sup>).

*Methyl 1-azido-6,7-dihydro-7-methylbenzo[*f*]thieno[2,3-*c*]isoquinoline-2-carboxylate (6e)*

Yellow solid, m.p. 145–146 °C. – <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz, 25 °C):  $\delta$  = 1.14–1.17 (d, 3H,  $J$  = 7.5 Hz, CH<sub>3</sub>), 2.71–2.79 (m, 1H, CH), 3.02–3.15 (m, 2H, CH<sub>2</sub>), 4.00 (s, 3H, CH<sub>3</sub>), 7.35–7.39 (m, 3H, H<sub>ar</sub>), 7.65–7.67 (d, 1H,  $J$  = 5 Hz, H<sub>ar</sub>), 8.62 (s, 1H, H<sub>ar</sub>). – <sup>13</sup>C NMR (CDCl<sub>3</sub>, 250 MHz):  $\delta$  = 18.39, 30.65, 36.33, 52.70, 118.56, 125.85, 128.32, 129.58, 129.74, 131.47, 135.74, 135.90, 137.51, 140.31, 149.16, 154.26, 159.24, 161.98. – HRMS (APCI):  $m/z$  = 351.0905 (calcd. 351.0910 for [C<sub>18</sub>H<sub>14</sub>N<sub>4</sub>O<sub>2</sub>S<sub>1</sub>+H]<sup>+</sup>).

*Methyl 3-azido-6-methylthieno[2,3-*b*]pyridine-2-carboxylate (6f)*

Yellow solid, m.p. 112–113 °C. – <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz, 25 °C):  $\delta$  = 2.703 (s, 3H, CH<sub>3</sub>), 3.97 (s, 3H, CH<sub>3</sub>), 7.21–7.25 (d, 1H,  $J$  = 10 Hz, H<sub>ar</sub>), 8.02–8.05 (d, 1H,  $J$  = 7.5 Hz, H<sub>ar</sub>). – <sup>13</sup>C NMR (CDCl<sub>3</sub>, 250 MHz):  $\delta$  = 24.88, 52.55, 116.03, 120.59, 125.89, 131.15, 135.18, 158.88, 160.81, 162.30. – HRMS (APCI):  $m/z$  = 249.0433 (calcd. 249.0441 for [C<sub>10</sub>H<sub>8</sub>N<sub>4</sub>O<sub>2</sub>S<sub>1</sub>+H]<sup>+</sup>).

*General procedure for the synthesis of methyl 1,2,3-triazolylthienopyridine-2-carboxylates 8*

The azide (1.04 mmol) was dissolved in 30 mL of chloroform. The mixture was cooled to 0 °C, and the alkyne (1.2 equiv.) was added. Then, copper(I) chloride (0.05 g) and one drop of 2,4-lutidine were added. The mixture was stirred at room temperature and the reaction monitored by TLC until the disappearance of the starting material. The organic phase was then washed with water, dried and concentrated. The residue was purified by column chromatography (30% ethyl acetate-cyclohexane).

*Methyl 1-(4-propyl-1H-1,2,3-triazol-1-yl)-7,8-dihydro-6H-cyclopenta[*d*]thieno[2,3-*b*]pyridine-2-carboxylate (8a)*

Colorless solid, m.p. 126–128 °C. – <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz, 25 °C):  $\delta$  = 1.01 (t, 3H,  $J$  = 7.5 Hz, CH<sub>3</sub>), 1.75–1.87 (m, 2H, CH<sub>2</sub>), 2.00–2.12 (m, 2H, CH<sub>2</sub>), 2.39–2.45 (t, 2H,  $J$  = 7.5 Hz, CH<sub>2</sub>), 2.83–2.89 (t, 2H,  $J$  = 7.5 Hz, CH<sub>2</sub>), 2.98–3.04 (t, 2H,  $J$  = 7.5 Hz, CH<sub>2</sub>), 3.81 (s, 3H, CH<sub>3</sub>), 7.63 (s, 1H, H<sub>ar</sub>), 8.7 (s, 1H, H). – <sup>13</sup>C NMR (CDCl<sub>3</sub>, 250 MHz):  $\delta$  = 13.62, 21.38, 22.72, 27.52, 30.02, 30.43, 52.91, 124.37, 127.18, 128.40, 130.66, 138.79, 147.26, 147.78, 149.65, 156.80, 160.63. – HRMS (APCI):  $m/z$  = 343.1210 (calcd. 343.1223 for [C<sub>17</sub>H<sub>8</sub>N<sub>4</sub>O<sub>2</sub>S<sub>1</sub>+H]<sup>+</sup>).

*Methyl 1-(4-propyl-1H-1,2,3-triazol-1-yl)-6,7,8,9-tetrahydrothieno[2,3-*c*]isoquinoline-2-carboxylate (8b)*

Yellow solid, m.p. 134–135 °C. – <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz, 25 °C):  $\delta$  = 0.98–1.03 (t, 3H,  $J$  = 6.3 Hz, CH<sub>3</sub>), 1.58–2.15 (m, 8H, -CH<sub>2</sub>-CH<sub>2</sub>-), 2.79–2.88 (m, 4H, -CH<sub>2</sub>-CH<sub>2</sub>-), 3.74 (s, 3H, CH<sub>3</sub>), 7.58 (s, 1H, H<sub>ar</sub>), 8.44 (s, 1H, H<sub>ar</sub>). – <sup>13</sup>C NMR (CDCl<sub>3</sub>, 250 MHz):  $\delta$  = 13.15, 21.60, 21.70, 22.73, 23.09, 26.82, 27.50, 52.88, 77.22, 124.59, 129.13, 130.90, 131.21, 143.42, 148.01, 152.20, 156.67, 160.57. – HRMS (APCI):  $m/z$  = 357.1363 (calcd. 357.1380 for [C<sub>18</sub>H<sub>20</sub>N<sub>4</sub>O<sub>2</sub>S<sub>1</sub>+H]<sup>+</sup>).

*Methyl 5-methyl-4-phenyl-3-(4-propyl-1H-1,2,3-triazol-1-yl)thieno[2,3-*b*]pyridine-2-carboxylate (8c)*

Colorless solid, m. p. 158–160 °C. – <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz, 25 °C): δ = 0.91–0.97 (t, 3H, *J* = 7.5 Hz, CH<sub>3</sub>), 1.49–1.59 (m, 2H, CH<sub>2</sub>), 2.12 (m, 3H, CH<sub>3</sub>), 2.38–2.44 (t, 2H, *J* = 7.5 Hz, CH<sub>2</sub>), 3.73 (s, 3H, CH<sub>3</sub>), 6.80 (s, 1H, H<sub>ar</sub>), 6.88–6.91 (m, 2H, H<sub>ar</sub>), 7.19–7.22 (m, 2H, H<sub>ar</sub>), 8.86 (s, 1H, H<sub>ar</sub>). – <sup>13</sup>C NMR (CDCl<sub>3</sub>, 250 MHz): δ = 13.86, 16.86, 22.08, 27.14, 52.96, 123.25, 126.82, 127.53, 127.65, 128.14, 130.14, 130.50, 130.79, 133.86, 146.07, 146.82, 152.00, 157.04, 160.41. – HRMS (APCI): *m/z* = 393.1381 (calcd. 393.1380 for [C<sub>21</sub>H<sub>20</sub>N<sub>4</sub>O<sub>2</sub>S<sub>1</sub>+H]<sup>+</sup>).

*Methyl 1-(4-propyl-1H-1,2,3-triazol-1-yl)-6,7-dihydrobenzo[*f*]thieno[2,3-*c*]isoquinoline-2-carboxylate (8d)*

Yellow solid, m. p. 162–164 °C. – <sup>1</sup>H NMR ([D<sub>6</sub>]acetone, 250 MHz, 25 °C): δ = 0.88–0.94 (t, 3H, *J* = 7.5 Hz, CH<sub>3</sub>), 1.52–1.61 (m, 2H, CH<sub>2</sub>), 2.53–2.59 (t, 2H, *J* = 7.5 Hz, CH<sub>2</sub>), 2.86 (s, 4H, CH<sub>2</sub>CH<sub>2</sub>), 3.84 (s, 3H, CH<sub>3</sub>), 6.61–6.64 (d, 1H, *J* = 7.5 Hz, H<sub>ar</sub>), 6.74–6.77 (t, 1H, *J* = 3.75 Hz, H<sub>ar</sub>), 7.14–7.21 (t, 1H, *J* = 8.8 Hz, H<sub>ar</sub>), 7.27–7.31 (d, 1H, *J* = 10 Hz, H<sub>ar</sub>), 7.79 (s, 1H, H<sub>ar</sub>), 8.73 (s, 1H, CH). – <sup>13</sup>C NMR (CDCl<sub>3</sub>, 250 MHz): δ = 8.32, 14.06, 23.40, 26.42, 27.52, 28.03, 53.27, 126.28, 126.82, 127.65, 127.99, 128.10, 128.42, 129.79, 129.82, 130.96, 132.23, 139.79, 141.73, 150.53, 159.84, 161.47. – HRMS (APCI): *m/z* = 405.1377 (calcd. 405.1380 for [C<sub>22</sub>H<sub>20</sub>N<sub>4</sub>O<sub>2</sub>S<sub>1</sub>+H]<sup>+</sup>).

*Methyl 7-methyl-1-(4-propyl-1H-1,2,3-triazol-1-yl)-6,7-dihydrobenzo[*f*]thieno[2,3-*c*]isoquinoline-2-carboxylate (8e)*

Colorless solid, m. p. 154–155 °C. – <sup>1</sup>H NMR ([D<sub>6</sub>]acetone, 250 MHz, 25 °C): δ = 0.75–0.80 (t, 3H, *J* = 6.3 Hz, CH<sub>3</sub>), 0.97–0.99 (d, 3H, *J* = 5 Hz, CH<sub>3</sub>), 1.39–1.48 (m, 2H, CH<sub>2</sub>), 2.39–2.45 (t, 2H, *J* = 7.5 Hz, CH<sub>2</sub>), 2.58–2.66 (dd, 1H, *J* = 10.0 Hz, CH), 2.86–3.10 (m, 2H, CH<sub>2</sub>), 3.67 (s, 3H, CH<sub>3</sub>), 6.49–6.52 (d, 1H, *J* = 7.5 Hz, H<sub>ar</sub>), 6.62–6.65 (t, 1H, *J* = 3.8 Hz, H<sub>ar</sub>), 7.02–7.16 (m, 2H, H<sub>ar</sub>), 7.67 (s, 1H, H<sub>ar</sub>), 8.64 (s, 1H, H<sub>ar</sub>). – <sup>13</sup>C NMR ([D<sub>6</sub>]acetone, 250 MHz): δ = 14.06, 18.50, 23.41, 28.04, 31.31, 36.56, 53.24, 124.48, 125.47, 126.87, 127.95, 128.40, 129.12, 129.82, 130.62, 132.40, 137.73, 137.79, 141.03, 147.62, 150.14, 159.79, 161.48. – HRMS (APCI): *m/z* = 419.1531 (calcd. 419.1536 for [C<sub>23</sub>H<sub>23</sub>N<sub>4</sub>O<sub>2</sub>S<sub>1</sub>+H]<sup>+</sup>).

*Methyl 6-methyl-3-(4-propyl-1H-1,2,3-triazol-1-yl)thieno[2,3-*b*]pyridine-2-carboxylate (8f)*

Colorless solid, m. p. 116–118 °C. – <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz, 25 °C): δ = 1.02–1.08 (t, 3H, *J* = 7.5 Hz, CH<sub>3</sub>), 1.75–1.87 (m, 2H, CH<sub>2</sub>), 2.74 (s, 3H, CH<sub>3</sub>), 2.82–2.88

(t, 2H, *J* = 7.5 Hz, CH<sub>2</sub>), 3.88 (s, 3H, CH<sub>3</sub>), 7.28–7.31 (d, 1H, *J* = 7.5 Hz, H<sub>ar</sub>), 7.83 (s, 1H, H<sub>ar</sub>), 7.98–8.02 (d, 1H, *J* = 7.5 Hz, H<sub>ar</sub>). – <sup>13</sup>C NMR (CDCl<sub>3</sub>, 250 MHz): δ = 13.76, 22.59, 24.87, 26.90, 27.55, 52.94, 121.69, 123.19, 124.31, 126.75, 131.20, 132.69, 147.28, 158.74, 160.89. – HRMS (APCI): *m/z* = 317.1068 (calcd. 317.1067 for [C<sub>15</sub>H<sub>16</sub>N<sub>4</sub>O<sub>2</sub>S<sub>1</sub>+H]<sup>+</sup>).

*Methyl 1-(4-phenyl-1H-1,2,3-triazol-1-yl)-7,8-dihydro-6H-cyclopenta[*d*]thieno[2,3-*b*]pyridine-2-carboxylate (8g)*

Colorless solid, m. p. 206–209 °C. – <sup>1</sup>H NMR ([D<sub>6</sub>]acetone, 250 MHz, 25 °C): δ = 2.02–2.11 (m, 2H, CH<sub>2</sub>), 2.48–2.54 (t, 2H, *J* = 7.5 Hz, CH<sub>2</sub>), 2.99–3.05 (t, 2H, *J* = 7.5 Hz, CH<sub>2</sub>), 3.82 (s, 3H, CH<sub>3</sub>), 7.36–7.52 (m, 3H, H<sub>ar</sub>), 7.95–7.99 (dd, 2H, *J* = 5 Hz, 2H, H<sub>ar</sub>), 8.13 (s, 1H, H<sub>ar</sub>), 8.70 (s, 1H, H<sub>ar</sub>). – <sup>13</sup>C NMR ([D<sub>6</sub>]acetone, 250 MHz): δ = 24.67, 30.03, 30.63, 53.04, 123.10, 125.90, 128.54, 128.61, 128.96, 130.04, 130.20, 139.81, 146.90, 147.38, 149.71, 156.76, 158.45, 160.59. – HRMS (APCI): *m/z* = 377.1056 (calcd. 377.1067 for [C<sub>20</sub>H<sub>16</sub>N<sub>4</sub>O<sub>2</sub>S<sub>1</sub>+H]<sup>+</sup>).

*Methyl 1-(4-phenyl-1H-1,2,3-triazol-1-yl)-6,7,8,9-tetrahydrothieno[2,3-*c*]isoquinoline-2-carboxylate (8h)*

Colorless solid, m. p. 229–230 °C. – <sup>1</sup>H NMR ([D<sub>6</sub>]acetone, 250 MHz, 25 °C) δ = 1.62–2.85 (m, 8H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 3.79 (s, 3H, CH<sub>3</sub>), 7.36–7.52 (m, 3H, H<sub>ar</sub>), 7.92–7.99 (dd, 2H, *J* = 8.75 Hz, 2H, H<sub>ar</sub>), 8.099 (s, 1H, H<sub>ar</sub>), 8.47 (s, 1H, H<sub>ar</sub>). – <sup>13</sup>C NMR (CDCl<sub>3</sub>, 250 MHz) δ = 21.56, 21.72, 23.41, 26.84, 52.98, 123.30, 125.89, 127.33, 128.53, 128.95, 129.32, 130.05, 130.77, 131.10, 143.55, 147.58, 152.24, 156.57, 160.48. – HRMS (APCI): *m/z* = 391.1232 (calcd. 391.1223 for [C<sub>21</sub>H<sub>18</sub>N<sub>4</sub>O<sub>2</sub>S<sub>1</sub>+H]<sup>+</sup>).

*Methyl 5-methyl-4-phenyl-3-(4-phenyl-1H-1,2,3-triazol-1-yl)thieno[2,3-*b*]pyridine-2-carboxylate (8i)*

Colorless solid, m. p. 264 °C. – <sup>1</sup>H NMR ([D<sub>6</sub>]DMSO, 250 MHz, 25 °C): δ = 2.37 (s, 3H, CH<sub>3</sub>), 3.69 (s, 3H, CH<sub>3</sub>), 7.01–7.04 (m, 5H, H<sub>ar</sub>), 7.39–7.56 (m, 5H, H<sub>ar</sub>), 8.20 (s, 1H, H<sub>ar</sub>), 8.89 (s, 1H, H<sub>ar</sub>). – <sup>13</sup>C NMR (CDCl<sub>3</sub>, 250 MHz) δ = 16.31, 53.08, 120.35, 124.03, 125.25, 126.06, 127.41, 127.57, 127.65, 128.63, 128.89, 129.98, 130.30, 131.06, 132.36, 133.07, 145.48, 145.73, 152.56, 159.83. – HRMS (APCI): *m/z* = 427.1234 (calcd. 427.1223 for [C<sub>24</sub>H<sub>18</sub>N<sub>4</sub>O<sub>2</sub>S<sub>1</sub>+H]<sup>+</sup>).

*Methyl 1-(4-phenyl-1H-1,2,3-triazol-1-yl)-6,7-dihydrobenzo[*f*]thieno[2,3-*c*]isoquinoline-2-carboxylate (8j)*

Colorless solid, m. p. 259–262 °C. – <sup>1</sup>H NMR ([D<sub>6</sub>]acetone, 250 MHz, 25 °C) δ = 2.88 (s, 4H, CH<sub>2</sub>CH<sub>2</sub>), 3.86 (s, 3H, CH<sub>3</sub>), 6.62–6.75 (m, 2H, H<sub>ar</sub>), 7.03–7.09 (t, 1H, *J* = 7.5 Hz, H<sub>ar</sub>), 7.21–7.24 (d, 2H, *J* = 7.5 Hz,



H<sub>ar</sub>), 7.34–7.41 (m, 2H, H<sub>ar</sub>), 7.44–7.66 (m, Hz, 2H, H<sub>ar</sub>), 7.78 (s, 1H, H<sub>ar</sub>), 8.73 (s, 1H, H<sub>ar</sub>). – <sup>13</sup>C NMR (CDCl<sub>3</sub>, 250 MHz) δ = 26.13, 28.71, 53.08, 124.70, 125.47, 126.05, 126.21, 126.88, 127.49, 128.21, 128.34, 128.44, 128.71, 129.27, 130.05, 130.16, 131.16, 131.20, 132.23, 133.94, 138.53, 141.01, 147.00, 160.82. – HRMS (APCI): *m/z* = 439.1223 (calcd. 439.1223 for [C<sub>25</sub>H<sub>18</sub>N<sub>4</sub>O<sub>2</sub>S<sub>1</sub>+H]<sup>+</sup>).

*Methyl 7-methyl-1-(4-phenyl-1H-1,2,3-triazol-1-yl)-6,7-dihydrobenzo[*f*]thieno[2,3-*c*]isoquinoline-2-carboxylate (8k)*

Colorless solid, m. p. 235–237 °C. – <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz, 25 °C): δ = 1.43 (d, 3H, *J* = 7.5 Hz, CH<sub>3</sub>), 2.71–2.80 (m, 1H, CH), 3.02–3.21 (m, 2H, CH<sub>2</sub>), 3.85 (s, 3H, CH<sub>3</sub>), 6.62–6.65 (d, 1H, *J* = 7.5 Hz, H<sub>ar</sub>), 6.70–6.76 (t, 1H, *J* = 7.5 Hz, H<sub>ar</sub>), 7.07–7.12 (t, 1H, *J* = 6.3 Hz, H<sub>ar</sub>), 7.21–7.23 (d, 1H, *J* = 5.0 Hz, H<sub>ar</sub>), 7.34–7.43 (m, 3H, H<sub>ar</sub>), 7.66–7.68 (d, 2H, *J* = 5.0 Hz, H<sub>ar</sub>), 7.86 (s, 1H, H<sub>ar</sub>), 8.72 (s, 1H, H<sub>ar</sub>). – <sup>13</sup>C NMR (CDCl<sub>3</sub>, 250 MHz): δ = 18.20,

30.71, 36.17, 53.16, 123.08, 124.18, 126.05, 126.27, 126.96, 128.24, 128.43, 128.59, 128.72, 129.20, 129.69, 130.08, 130.55, 136.93, 141.54, 147.30, 147.64, 158.04, 160.63, 174.69. – HRMS (APCI): *m/z* = 453.1382 (calcd. 453.1380 for [C<sub>26</sub>H<sub>20</sub>N<sub>4</sub>O<sub>2</sub>S<sub>1</sub>+H]<sup>+</sup>).

*Methyl 6-methyl-3-(4-phenyl-1H-1,2,3-triazol-1-yl)thieno[2,3-*b*]pyridine-2-carboxylate (8l)*

Yellow solid, m. p. 188.6–189.9 °C. – <sup>1</sup>H NMR ([D<sub>6</sub>]DMSO, 250 MHz, 25 °C): δ = 2.70 (s, 3H, CH<sub>3</sub>), 3.80 (s, 3H, CH<sub>3</sub>), 7.31–7.50 (m, 5H, H<sub>ar</sub>), 7.94–8.04 (m, 2H, H<sub>ar</sub>), 9.15 (s, 1H, H<sub>ar</sub>). – <sup>13</sup>C NMR (CDCl<sub>3</sub>, 250 MHz): δ = 24.35, 53.09, 122.32, 123.67, 124.57, 125.34, 126.05, 128.28, 129.04, 130.03, 130.40, 132.20, 145.97, 157.41, 160.13, 161.22. – HRMS (APCI): *m/z* = 351.0909 (calcd. 351.0910 for [C<sub>18</sub>H<sub>14</sub>N<sub>4</sub>O<sub>2</sub>S<sub>1</sub>+H]<sup>+</sup>).

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