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

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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 neurotopic 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 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

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 α-methylene ketones 1 were used as starting materials for the synthesis of thieno[2,3-b]pyridines 5.

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

Treatment of the alkylidene malononitriles 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 γ position of the alkylidene malononitrile 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) CH₂(CN)₂, CH₃COONH₄, CH₃COOH, toluene, reflux, 24 h.

phosphate (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 S_NAr 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 diazotation 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 2. Synthesis of 2-chloro-3-cyanopyridines 4.

<table>
<thead>
<tr>
<th>Alkylidene malononitrile 2</th>
<th>Yield (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC-CN</td>
<td>2a</td>
<td>10</td>
</tr>
<tr>
<td>NC-CN</td>
<td>2b</td>
<td>15</td>
</tr>
<tr>
<td>NC-CN</td>
<td>2c</td>
<td>8</td>
</tr>
<tr>
<td>NC-CN</td>
<td>2d</td>
<td>15</td>
</tr>
<tr>
<td>NC-CN</td>
<td>2e</td>
<td>10</td>
</tr>
</tbody>
</table>

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.

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

<table>
<thead>
<tr>
<th>5</th>
<th>Yield (%)</th>
<th>Method</th>
</tr>
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<tr>
<td>a</td>
<td>60</td>
<td>A</td>
</tr>
<tr>
<td>b</td>
<td>35</td>
<td>B</td>
</tr>
<tr>
<td>c</td>
<td>61</td>
<td>A</td>
</tr>
<tr>
<td>d</td>
<td>38</td>
<td>B</td>
</tr>
<tr>
<td>e</td>
<td>53</td>
<td>A</td>
</tr>
<tr>
<td>f</td>
<td>98</td>
<td>A</td>
</tr>
</tbody>
</table>

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 CDCl₃, [D₆]acetone or [D₆]DMSO. Chemical shifts (δ) are reported in ppm and coupling constants (J) in Hz.

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

<table>
<thead>
<tr>
<th></th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>53</td>
</tr>
<tr>
<td>b</td>
<td>67</td>
</tr>
<tr>
<td>c</td>
<td>47</td>
</tr>
<tr>
<td>d</td>
<td>58</td>
</tr>
<tr>
<td>e</td>
<td>37</td>
</tr>
<tr>
<td>f</td>
<td>63</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th></th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>23</td>
</tr>
<tr>
<td>b</td>
<td>40</td>
</tr>
<tr>
<td>c</td>
<td>46</td>
</tr>
<tr>
<td>d</td>
<td>52</td>
</tr>
<tr>
<td>e</td>
<td>75</td>
</tr>
<tr>
<td>f</td>
<td>30</td>
</tr>
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Table 5. (Continued.)

<table>
<thead>
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<th>Yield (%)</th>
<th>Compound Structure</th>
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<td>73</td>
<td><img src="image" alt="Compound g" /></td>
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<tr>
<td>65</td>
<td><img src="image" alt="Compound h" /></td>
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<tr>
<td>45</td>
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<td>38</td>
<td><img src="image" alt="Compound j" /></td>
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<tr>
<td>93</td>
<td><img src="image" alt="Compound k" /></td>
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</table>

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 POCl3 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). – 1H NMR (CDCl3, 250 MHz, 25 °C): δ = 2.19 – 2.31 (m, 2H, CH2), 2.98 – 3.04 (t, J = 7.5 Hz, 2H, CH2), 3.11 – 3.17 (t, J = 7.5 Hz, 2H, CH2), 8.38 (s, 1H, H-ar). – 13C NMR (CDCl3, 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). – 1H NMR (CDCl3, 250 MHz, 25 °C): δ = 1.83 – 1.94 (m, 4H, CH2CH2), 2.75 – 2.77 (t, J = 2.5 Hz, 2H, CH2), 2.93 – 2.98 (t, J = 6.25 Hz, 2H, CH2), 8.27 (s, 1H, H-ar). – 13C NMR (CDCl3, 250 MHz): δ = 21.37, 21.57, 25.70, 28.25, 31.08, 113.92, 139.62, 140.10, 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). – 1H NMR (CDCl3, 250 MHz, 25 °C): δ = 2.19 (s, 3H, CH3), 7.28 – 7.31 (m, 2H, H-ar), 7.52 – 7.57 (m, 3H, H-ar), 8.47 (s, 1H, H-ar). – 13C NMR (CDCl3, 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[f]isoquinoline-1-carbonitrile (4d)

Yellow solid, m. p. 180 °C (column chrom., 20% ethyl acetate-cyclohexane). – 1H NMR (CDCl3, 250 MHz, 25 °C): δ = 2.16 – 2.28 (m, 2H, CH2), 3.00 – 3.06 (t, 2H, J = 7.5 Hz, CH2), 3.38 – 3.44 (t, 2H, J = 7.5 Hz, CH2), 3.98 (s, 3H, CH3), 8.56 (s, 1H, H-ar). – 13C NMR (CDCl3, 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[f]isoquinoline-1-carbonitrile (4e)

Yellow solid, m. p. 149 – 151 °C (column chrom., 20% ethyl acetate-cyclohexane). – 1H NMR (CDCl3, 250 MHz,
8.44 (s, 2H, H_2).


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. – 1H NMR (CDCl_3, 250 MHz): δ = 2.25 – 2.34 (m, 2H, CH_2), 2.99 – 3.05 (t, 2H, J = 7.5 Hz, CH_2), 3.33 – 3.39 (t, 2H, J = 7.5 Hz, CH_2), 6.01 (s, 2H, NH), 8.52 (s, 1H, H_2). – 13C NMR (CDCl_3, 250 MHz): δ = 24.83, 29.50, 31.60, 51.59, 97.97, 123.27, 136.24, 146.65, 147.74, 158.70, 165.95. – HRMS (APCI): m/z = 248.0587 (calcd. 248.0600 for [C_7H_10N_2O_2S]_+).

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

Yellow solid, m. p. 218°C. – 1H NMR (CDCl_3, 250 MHz, 25°C): δ = 1.81 – 1.95 (m, 4H, CH_2CH_2), 2.81 – 2.86 (t, 2H, J = 6.25 Hz, CH_2), 3.25 – 3.30 (t, 2H, J = 6.25 Hz, CH_2), 6.23 (s, 2H, NH), 8.32 (s, 1H, H_2). – 13C NMR (CDCl_3, 250 MHz): δ = 26.4, 26.85, 30.94, 31.25, 129.12, 133.51, 136.51, 143.09, 154.69, 162.73, 171.82. – HRMS (APCI): m/z = 262.0776 (calcd. 262.0800 for [C_14H_12N_2O_2S]_+).

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

Green solid, m. p. 214 – 216°C. – 1H NMR (CDCl_3, 250 MHz, 25°C): δ = 2.31 (s, 3H, CH_3), 3.80 (s, 3H, CH_3), 5.43 (s, 2H, NH_2), 7.30 – 7.33 (m, 2H, H_2), 7.54 – 7.56 (m, 3H, H_2), 8.50 (s, 1H, H_3). – 13C NMR (CDCl_3, 250 MHz): δ = 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_16H_14N_2O_2S]_+).
Methyl 1-azido-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline-2-carboxylate (6b)

Colorless solid, m.p. 133 °C. – 1H NMR (CDCl3, 250 MHz; δ = 2.17 (s, 3H, CH3), 7.16 – 7.21 (d, 2H, J = 7.5 Hz, H5a), 7.40 – 7.50 (m, 3H, H4, H6a), 8.26 (s, 1H, H3) – 13C NMR (CDCl3, 250 MHz): δ = 16.78, 30.90, 52.61, 118.90, 128.15, 128.17, 129.14, 135.77, 135.94, 146.94, 159.15, 154.87, 156.83, 161.93, 208.11. – HRMS (APCI); m/z = 289.0751 (calcd. 289.0754 for [C16H12N2O2S2+H]+).

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

Yellow solid, m.p. 139 – 143 °C. – 1H NMR (CDCl3, 250 MHz; δ = 2.17 (s, 3H, CH3), 7.16 – 7.21 (d, 2H, J = 7.5 Hz, H5a), 7.40 – 7.50 (m, 3H, H4, H6a), 8.26 (s, 1H, H3) – 13C NMR (CDCl3, 250 MHz): δ = 16.78, 30.90, 52.61, 118.90, 128.15, 128.17, 129.14, 135.77, 135.94, 146.94, 159.15, 154.87, 156.83, 161.93, 208.11. – HRMS (APCI); m/z = 325.0749 (calcd. 325.0750 for [C16H12N2O2S2+H]+).

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

Yellow solid, m.p. 120 – 123 °C. – 1H NMR (CDCl3, 250 MHz; δ = 2.88 (s, 4H, CH2CH2), 4.00 (s, 3H, CH3), 7.38 – 7.41 (m, 3H, H4, H6a), 7.67 – 7.68 (d, 1H, J = 2.5 Hz, H5a), 8.59 (s, 1H, H3) – 13C NMR (CDCl3, 250 MHz): δ = 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 [C17H12N2O2S2+H]+).

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

Yellow solid, m.p. 145 – 146 °C. – 1H NMR (CDCl3, 250 MHz; δ = 1.14 – 1.17 (d, 3H, J = 7.5 Hz, CH3), 2.71 – 2.79 (m, 1H, CH2), 3.02 – 3.15 (m, 2H, CH2), 4.00 (s, 3H, CH3), 7.35 – 7.39 (m, 3H, H4, H6a), 7.65 – 7.67 (d, 1H, J = 5 Hz, H5a), 8.62 (s, 1H, H3) – 13C NMR (CDCl3, 250 MHz): δ = 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 [C18H14N2O2S2+H]+).

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

Yellow solid, m.p. 121 – 123 °C. – 1H NMR (CDCl3, 250 MHz; δ = 2.09 (s, 3H, CH3), 3.97 (s, 3H, CH3), 7.21 – 7.25 (d, 1H, J = 10 Hz, H4), 8.02 – 8.05 (d, 1H, J = 7.5 Hz, H5). – 13C NMR (CDCl3, 250 MHz): δ = 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 [C10H8N2O2S2+H]+).

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

The azide (1.04 mmol) was dissolved in 30 mL of chloroform. The mixture was cooled to 0 °C, and the alkyn (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. – 1H NMR (CDCl3, 250 MHz; δ = 1.01 (t, 3H, J = 7.5 Hz, CH3), 1.75 – 1.87 (m, 2H, CH2), 2.00 – 2.12 (m, 2H, CH2), 2.39 – 2.45 (t, 2H, J = 7.5 Hz, CH2), 2.83 – 2.89 (t, 2H, J = 7.5 Hz, CH2) 2.98 – 3.04 (t, 2H, J = 7.5 Hz, CH2), 3.81 (s, 3H, CH3), 7.63 (s, 1H, H4a), 8.7 (s, 1H, H6). – 13C NMR (CDCl3, 250 MHz): δ = 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 = 343.1223 (calcd. 343.1223 for [C17H16N2O2S2+H]+).

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. – 1H NMR (CDCl3, 250 MHz; δ = 0.98 – 1.03 (t, 3H, J = 6.3 Hz, CH3), 1.58 – 2.15 (m, 8H, -CH2-CH2-), 2.79 – 2.88 (m, 4H, -CH2-CH2-), 3.74 (s, 3H, CH3), 7.58 (s, 1H, H4a), 8.44 (s, 1H, H6a). – 13C NMR (CDCl3, 250 MHz): δ = 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 = 357.1362 (calcd. 357.1380 for [C18H20N2O2S2+H]+).
Methyl 5-methyl-4-phenyl-3-(4-propyl-1H-1,2,3-triazol-1-yl)thieno[2,3-b]pyridine-2-carboxylate (8e)

Colorless solid, m.p. 158 – 160 °C. – 1H NMR (CDCl3, 250 MHz, 25 °C): δ = 0.88 – 0.94 (t, 3H, J = 7.5 Hz, CH3), 1.52 – 1.61 (m, 2H, CH2), 2.53 – 2.59 (t, 2H, J = 7.5 Hz, CH2), 2.86 (s, 4H, CH2CH3), 3.84 (s, 3H, CH3), 6.61 – 6.64 (d, 1H, J = 7.5 Hz, Hα), 6.74 – 6.77 (t, 1H, J = 3.75 Hz, Hδa), 7.14 – 7.21 (t, 1H, J = 8.8 Hz, Hβ), 7.27 – 7.31 (d, 1H, J = 10 Hz, Hα), 7.79 (s, 1H, Hγ), 8.73 (s, 1H, CH). – 13C NMR (CDCl3, 250 MHz): δ = 37.77, 30.03, 30.63, 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 = 405.1380 for [C15H16N4O2S1+H]+.

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

Yellow solid, m.p. 162 – 164 °C. – 1H NMR ([D6]acetone, 250 MHz, 25 °C): δ = 0.88 – 0.94 (t, 3H, J = 7.5 Hz, CH3), 1.52 – 1.61 (m, 2H, CH2), 2.53 – 2.59 (t, 2H, J = 7.5 Hz, CH2), 2.86 (s, 4H, CH2CH3), 3.84 (s, 3H, CH3), 6.61 – 6.64 (d, 1H, J = 7.5 Hz, Hα), 6.74 – 6.77 (t, 1H, J = 3.75 Hz, Hδa), 7.14 – 7.21 (t, 1H, J = 8.8 Hz, Hβ), 7.27 – 7.31 (d, 1H, J = 10 Hz, Hα), 7.79 (s, 1H, Hγ), 8.73 (s, 1H, CH). – 13C NMR (CDCl3, 250 MHz): δ = 37.77, 30.03, 30.63, 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 = 405.1380 for [C22H20N4O2S1+H]+.

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

Colorless solid, m.p. 154 – 155 °C. – 1H NMR ([D6]acetone, 250 MHz, 25 °C): δ = 0.75 – 0.80 (t, 3H, J = 6.3 Hz, CH3), 0.97 – 0.99 (d, 3H, J = 5.5 Hz, CH3), 1.39 – 1.48 (m, 2H, CH2), 2.39 – 2.45 (t, 2H, J = 7.5 Hz, CH3), 2.58 – 2.66 (dd, 1H, J = 10.0 Hz, CH2), 2.86 – 3.10 (m, 2H, CH2), 3.67 (s, 3H, CH3), 6.49 – 6.52 (d, 1H, J = 7.5 Hz, Hα), 6.62 – 6.65 (t, 1H, J = 3.8 Hz, Hβ), 7.02 – 7.16 (m, 2H, Hα), 7.67 (s, 1H, Hγ), 8.64 (s, 1H, Hδ). – 13C NMR ([D6]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 = 427.1234 (calcd. 427.1223 for [C15H16N4O2S1+H]+).

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

Colorless solid, m.p. 264 – 266 °C. – 1H NMR ([D6]DMSO, 250 MHz, 25 °C): δ = 2.37 (s, 3H, CH3), 3.69 (s, 3H, CH3), 7.01 – 7.04 (m, 5H, Hα), 7.39 – 7.56 (m, 5H, Hβ), 8.20 (s, 1H, Hδ). – 13C NMR ([D6]DMSO, 250 MHz): δ = 16.31, 53.08, 120.35, 124.03, 125.25, 126.06, 127.41, 127.57, 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 = 431.1232 (calcd. 431.1223 for [C15H16N4O2S1+H]+).

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

Colorless solid, m.p. 259 – 262 °C. – 1H NMR ([D6]acetone, 250 MHz, 25 °C): δ = 2.88 (s, 4H, CH2CH3), 3.86 (s, 3H, CH3), 6.62 – 6.75 (m, 2H, Hα), 7.03 – 7.09 (t, 1H, J = 7.5 Hz, Hβ), 7.21 – 7.24 (d, 2H, J = 7.5 Hz, Hγ).
H$_{ar}$). 7.34–7.41 (m, 2H, H$_{ar}$), 7.44–7.66 (m, Hz, 2H, H$_{ar}$), 7.78 (s, 1H, H$_{ar}$), 8.73 (s, 1H, H$_{ar}$) – $^{13}$C NMR (CDCl$_3$, 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 (calcld. 439.1223 for [C$_{25}$H$_{16}$N$_2$O$_2$S$_1$+H]$^+$).

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

Colorless solid, m.p. 235–237°C. – $^1$H NMR (CDCl$_3$, 250 MHz, 25°C): δ = 1.43 (d, 3H, J = 7.5 Hz, CH$_3$), 2.71 – 2.80 (m, 1H, CH), 3.02 – 3.21 (2H, CH$_2$), 3.85 (s, 3H, CH$_3$), 6.62 – 6.65 (d, 1H, J = 7.5 Hz, H$_{ar}$), 6.70 – 6.76 (t, 1H, J = 7.5 Hz, H$_{ar}$), 7.07 – 7.12 (t, 1H, J = 6.3 Hz, H$_{ar}$), 7.21 – 7.23 (d, 1H, J = 5.0 Hz, H$_{ar}$), 7.34 – 7.43 (m, 3H, H$_{ar}$), 7.66 – 7.68 (d, 2H, J = 5.0 Hz, H$_{ar}$), 7.86 (s, 1H, H$_{ar}$), 8.72 (s, 1H, H$_{ar}$). – $^{13}$C NMR (CDCl$_3$, 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 (calcld. 453.1380 for [C$_{26}$H$_{20}$N$_2$O$_2$S$_1$+H]$^+$).

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

Yellow solid, m.p. 188.6–189.9°C. – $^1$H NMR (CD$_3$) DMSO, 250 MHz, 25°C): δ = 2.70 (s, 3H, CH$_3$), 3.80 (s, 3H, CH$_3$), 7.31 – 7.50 (m, 5H, H$_{ar}$), 7.94 – 8.04 (m, 2H, H$_{ar}$), 9.15 (s, 1H, H$_{ar}$). – $^{13}$C NMR (CDCl$_3$, 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 (calcld. 351.0910 for [C$_{18}$H$_{14}$N$_2$O$_2$S$_1$+H]$^+$).

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