

## An efficient synthesis of tetrahydropyrazolopyridine derivatives by a one-pot tandem multi-component reaction in a green media

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### Abstract

The synthesis of some tetrahydropyrazolopyridine derivatives has been described by a one-pot  $2A + 2B + C + D$  four component reaction of a 1,3-dicarbonyl compound, an aldehyde, hydrazine and ammonium acetate in ethanol as a green media under catalyst-free condition.

**Keywords:** 1,4-Dihydropyridine, dipyrazolopyridine, multi-component reactions, green chemistry

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### Introduction

Green chemistry is a doctrine that inspires chemists to design chemical procedures that minimize the use and production of hazardous materials. In fact, the goal of green chemistry is to reduce and prohibit the pollution of nature and ensure perpetual life on the earth.<sup>1-3</sup>

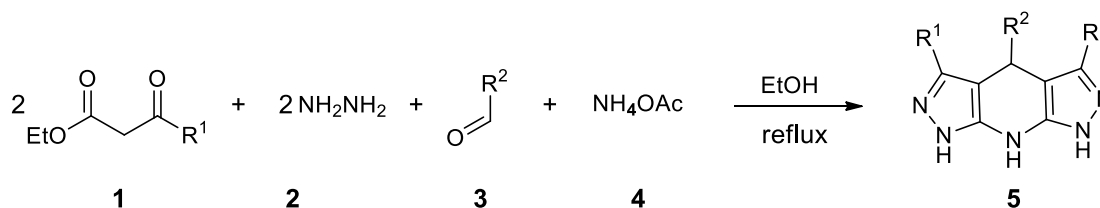
Multi-component reactions (MCRs) require the combination of at least three compounds to generate a product, where all or most of the starting material atoms exist in the final product.<sup>4</sup> The use of MCRs for the synthesis of complex molecules in one pot, is advantageous compared to the classical routes that uses sequential synthesis. Owing to their usefulness for synthesizing drug-like molecules and creating high structural diversity, MCRs play an important role in combinatorial chemistry and industrial chemistry.<sup>5,6</sup> Simple purification, atom economy, convergent character, operational simplicity, elimination of overflow steps are other typical advantages of these reactions.<sup>7</sup>

Since the first example of MCRs reported by Strecker, multi-component reactions have been developed regularly and many useful MCRs such as Mannich, Passerini (three-component

reactions) and Ugi (a four-component reaction) have been reported. The abundance of MCRs decreases as the number of components increases and among them reaction using six or more components are rare.<sup>8</sup>

Owing to their pharmacological and biological properties, 1,4-dihydropyridines (1,4-DHPs) have garnered particular attention in both synthetic and medicinal research.<sup>7</sup> 1,4-DHPs, as a class of calcium modulators, are extensively investigated for their pharmacological activities as antioxidant, anti-tumor, anti-atherosclerosis, anti-diabetes, anti-mutagenic, anti-vasodilator, neuromodulator, hepatoprotector, neuroprotector and memory enhancer.<sup>9</sup> The Hantzsch synthesis, one of the most famous multi-component reactions involving an aldehyde, two equivalents of a  $\beta$ -ketoester and a nitrogen donor such as ammonia or ammonium acetate, is most often used for the construction of 1,4-dihydropyridines.<sup>10</sup> Several modifications have been developed to allow for the synthesis of different 1,4-DHP derivatives.<sup>11</sup>

Pyrazoles exist in some compounds that are used as pharmaceuticals and agrochemicals.<sup>12</sup> Also, fused pyrazoles have fungicidal,<sup>13</sup> herbicidal,<sup>14</sup> virucidal,<sup>15</sup> and insecticidal<sup>16,17</sup> activity and have been used for the treatment of rheumatoid arthritis.<sup>16,18</sup> On account of its variety of biological activity, the chemistry of pyrazoles has attracted much attention and many methods for their synthesis have been extended.<sup>19</sup> Pyrazolopyridines and their derivatives have a wide range of biological activities.<sup>20,21</sup> For example, a number of pyrazolo[3,4-*b*]pyridines exhibit biological activities, including anxiolytic (*e.g.*, trazolam), antiallergic and antihyperthermic properties.<sup>22</sup> The research on organic light emitting diodes (OLEDs) has exploded and progressed considerably in recent years. Dipyrazolopyridines are a new class of fluorescent materials. Preliminary electroluminescence properties were reported in their polymer systems.<sup>23,24</sup>



**Scheme 1.** Synthesis of tetrahydropyrazolopyridine **5**.

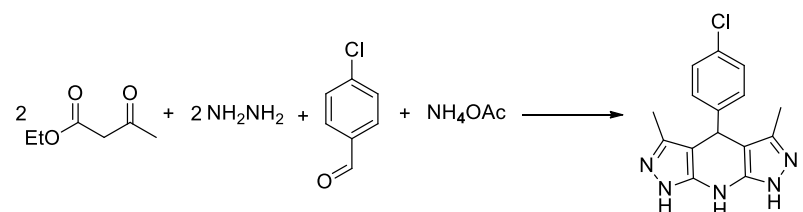
The importance of green chemistry and also the existing attraction in the design and synthesis of heterocyclic compounds through MCRs, motivated us to design a one-pot 2A + 2B + C + D four component reaction for the synthesis of fused pyrazolo-1,4-dihydropyridines under green reaction conditions. Although the synthesis of dipyrazolopyridines starting from pyrazole-containing building blocks has already been reported,<sup>25-27</sup> herein, we introduce the first example of simultaneous assembly of all three heterocyclic rings from four acyclic building blocks. We employed *in situ* preparation of the pyrazolone ring through the reaction between hydrazine and

a  $\beta$ -dicarbonyl compound and subsequent reaction with aldehyde and ammonium acetate (Scheme 1). We note that the *in situ* formation of pyrazolone as pronucleophiles in multicomponent reactions has already been developed.<sup>28-30</sup>

## Results and Discussion

Encouraged by the satisfactory results of our first attempts, the synthesis of the tetrahydropyrazolopyridine **5b** was selected for optimizing the reaction conditions. The optimal reaction conditions for the reaction of 4-chlorobenzaldehyde, hydrazine hydrate, ethyl acetoacetate and ammonium acetate were screened (Table 1) and ethanol was found to be the best solvent for this reaction under reflux and catalyst-free condition.

**Table 1.** Optimization of reaction conditions for the synthesis of tetrahydropyrazolopyridine **5b**



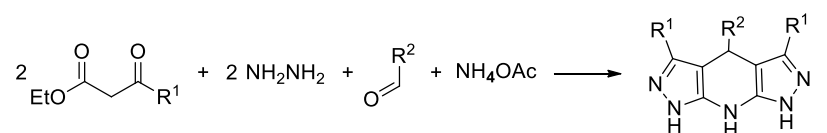
Solvent	Catalyst	Yield (%)	Time (h)
EtOH	-	79	5
H <sub>2</sub> O/EtOH	-	40	6
[Hmim] TFA	-	60	12
H <sub>2</sub> O	p-TSA	36	6
H <sub>2</sub> O	K <sub>2</sub> CO <sub>3</sub>	68	9
H <sub>2</sub> O	Piperidine	43	9

The efficiency of this multicomponent reaction was probed by employing a series of different aldehydes and  $\beta$ -dicarbonyl compounds (Table 2). Aromatic aldehydes bearing electron-withdrawing and electron-donating groups led to the formation of products **5a-5g** in good yields (65-76%). Also heteroaromatic aldehydes such as pyridine carboxaldehydes the use of aliphatic aldehydes such as butyraldehyde led to products **5h** (78%) and **5i** (63%), respectively in good yields, although the use of butyraldehyde gave the product **5j** in a slightly lower yield (60%).

Isatin and acenaphthenquinone were used instead of the aldehyde in this reaction to produce the related spiro-products (**5k-5p**). It became clear that as well as aldehydes, that activated  $\alpha$ -diketones such as these also effectively participate in this reaction and give good yields (Table 3).

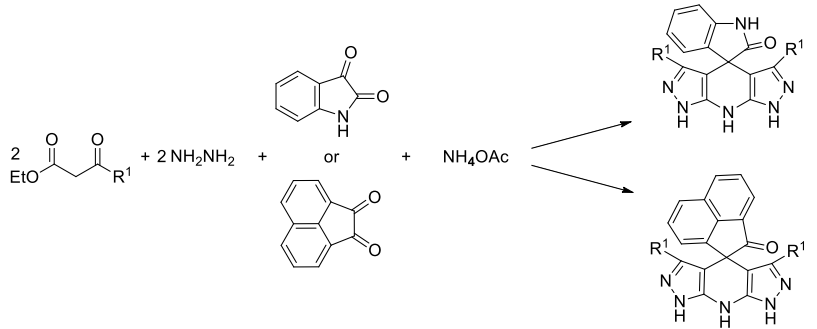
We also used phenylhydrazines and its derivatives instead of hydrazine, and anilines instead of ammonium acetate in this reaction but the desired products were not obtained in any experiments. The products were characterized by NMR ( $^1\text{H}$  and  $^{13}\text{C}$ ), IR and HR-ESIMS analysis. This protocol was shown to be facile, efficient, simple, and environmentally friendly.









**Table 2.** Synthesised products from aldehyde derivatives

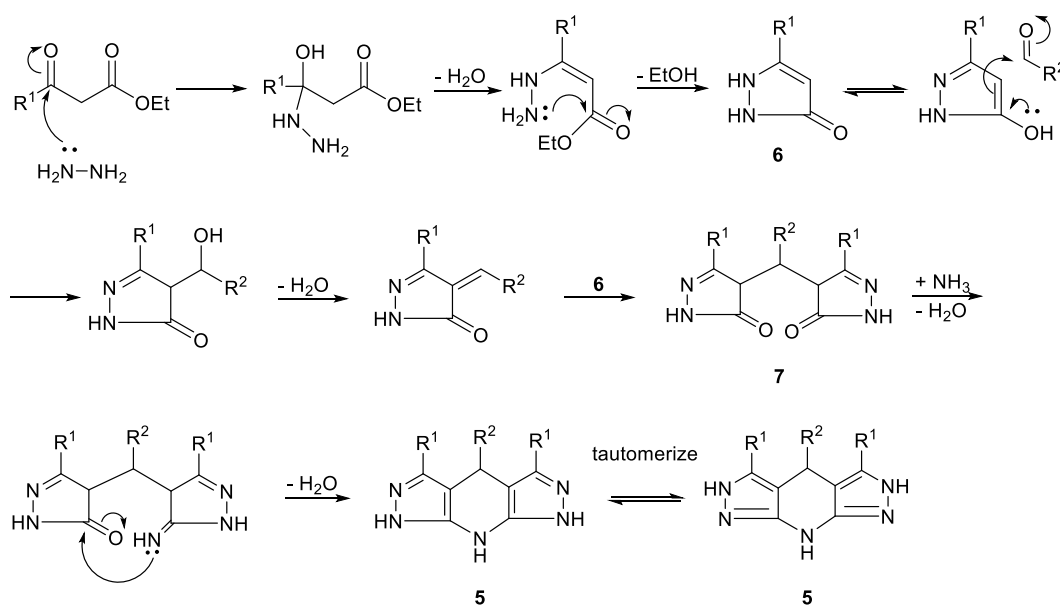


Product	R <sup>1</sup>	R <sup>2</sup>	Yield (%)
<b>5a</b>	Me	3-BrC <sub>6</sub> H <sub>4</sub>	65
<b>5b</b>	Me	4-ClC <sub>6</sub> H <sub>4</sub>	76 <sup>24</sup>
<b>5c</b>	Me	4-Tol	76 <sup>24</sup>
<b>5d</b>	Me	5-Br-2-(Pr-2-ynyloxy)C <sub>6</sub> H <sub>3</sub>	76
<b>5e</b>	Me	5-Me-2-(Pr-2-ynyloxy)C <sub>6</sub> H <sub>3</sub>	75
<b>5f</b>	Et	Ph	72
<b>5g</b>	<i>n</i> -Pr	4-ClC <sub>6</sub> H <sub>4</sub>	75
<b>5h</b>	Me	pyrid-2-yl	78
<b>5i</b>	Me	pyrid-3-yl	63
<b>5j</b>	Me	<i>n</i> -Pr	60

A plausible mechanism for this multi-component process is presented in Scheme 2. The mechanism most likely involves the initial nucleophilic attack of hydrazine on the  $\beta$ -ketoester and subsequent cyclization to form the pyrazolone **6**. In the next step, the reaction can be continued *via* a Knoevenagel condensation followed by attack of the second pyrazolone ring that leads to the formation of **7**. Intermediate **7** has already been reported to be the final product of the reaction of 1-phenyl-3-methyl-5-pyrazolone with an aldehyde.<sup>31,32</sup> Finally, nucleophilic attack of ammonia on intermediate **7** followed by intramolecular cyclization leads to compound **8** which can then tautomerize to form the final product **5**.<sup>33</sup>

**Table 3.** Synthesised products from isatin and acenaphthenquinone


Product	R <sup>1</sup>	 or 	Yield <sup>a</sup> (%)
<b>5k</b>	Me		65
<b>5l</b>	Me		76
<b>5m</b>	Et		76
<b>5n</b>	Et		60
<b>5o</b>	<i>n</i> -Pr		70
<b>5p</b>	<i>n</i> -Pr		76

**Scheme 2.** Plausible mechanism of the reaction.

## Conclusions

In summary, a facile procedure for the synthesis of 3,5-diaryl-4-(aryl/alkyl)-1,4,7,8-tetrahydrodipyrzolo[3,4-*b*:4',3'-*e*]pyridine derivatives has been reported *via* a condensation reaction of a 1,3-dicarbonyl compound, an aldehyde, hydrazine and ammonium acetate in ethanol as a green media under catalyst-free conditions. The versatility of the reaction to allow the formation of a variety of functionalities such as amido, hydroxyl and amino groups make these compounds attractive candidates as precursors for drug discovery, combinatorial chemistry and chemical biology. The simple performance, green and mild conditions, good yields and easy purification of the products are among the advantages of this protocol.

## Experimental Section

**General.** Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. HR-ESIMS spectra were acquired on a Bruker MicroTOF ESI-MS system. IR spectra were recorded on a Shimadzu IR-470 spectrometer.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz, respectively.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were obtained on solutions in DMSO- $d_6$  using TMS as internal standard. Elemental analyses were performed using a Heraeus CHN-O Rapid analyzer.

**General procedure for the synthesis tetrahydropyrzolo[3,4-*b*:4',3'-*e*]pyridine.** A mixture of hydrazine hydrate (2.0 mmol) and  $\beta$ -dicarbonyl compound (2.1 mmol) in EtOH (5 mL) was magnetically stirred for 30 min at *ca.* 25 °C followed by addition of aldehyde (1.0 mmol) and ammonium acetate (4.0 mmol). The reaction mixture was heated at reflux for 4-8 h and then cooled to *ca.* 25 °C and water (10 mL) was added and the resulting mixture was stirred for 30 min. The precipitated product was filtered, washed with water and acetone then dried under vacuum. In most cases no further purification was necessary.

**4-(3-Bromophenyl)-3,5-dimethyl-1,4,7,8-tetrahydrodipyrzolo[3,4-*b*:4',3'-*e*]pyridine (5a).** Yield 65%, mp 245-247 °C; IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3331, 1604, 1468;  $^1\text{H}$  NMR (300.13 MHz, DMSO- $d_6$ ):  $\delta_{\text{H}}$  2.05 (s, 6H, 2CH<sub>3</sub>), 4.81 (s, 1H, CH), 7.09-7.16 (m, 2H, Ar-H), 7.18-7.25 (m, 2H, Ar-H), 11.18-11.51 (br s, 3H, NH);  $^{13}\text{C}$  NMR (75.47 MHz, DMSO- $d_6$ ):  $\delta_{\text{C}}$  10.7 (CH<sub>3</sub>), 32.9 (CH), 104.1 (C-8,12), 121.7, 127.1, 128.8, 130.4, 130.5 (5C, Ar), 140.2 (C-15,16), 146.7 (C-3), 161.4 (C-9,11); HR-MS (ESI) Calcd for C<sub>15</sub>H<sub>14</sub>BrN<sub>5</sub> [M+NH<sub>4</sub>] 361.0771 found 361.0730.

**4-(4-Chlorophenyl)-3,5-dimethyl-1,4,7,8-tetrahydrodipyrzolo[3,4-*b*:4',3'-*e*]pyridine (5b).** Yield 76%, mp 252-254 °C (lit.,<sup>24</sup> 254-256 °C); IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3165, 3100, 1603, 1526;  $^1\text{H}$  NMR (300.13 MHz, DMSO- $d_6$ ):  $\delta_{\text{H}}$  2.01 (s, 6H, 2CH<sub>3</sub>), 4.80 (s, 1H, CH), 7.12 (br s, 2H, Ar-H), 7.25 (br s, 2H, Ar-H), 11.35 (br s, 3H, NH);  $^{13}\text{C}$  NMR (75.47 MHz, DMSO- $d_6$ ):  $\delta_{\text{C}}$  10.8 (CH<sub>3</sub>), 32.6 (CH), 104.3 (C-8,12), 128.1, 129.8, 130.5 (3C, Ar), 140.1 (C-15,16), 142.8 (C-3), 161.4 (C-9,11); HR-MS (ESI) Calcd for C<sub>15</sub>H<sub>14</sub>ClN<sub>5</sub> [M+NH<sub>4</sub>] 317.1276 found 317.1217.

**3,5-Dimethyl-4-(4-methylphenyl)-1,4,7,8-tetrahydrodipyrzolo[3,4-*b*:4',3'-*e*]pyridine (5c).** Yield 76%, mp 239-241 °C (lit.,<sup>24</sup> 244-246 °C); IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3174, 3110, 1605, 1526; <sup>1</sup>H NMR (300.13 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{H}}$  2.07 (s, 6H, 2CH<sub>3</sub>), 2.23 (s, 3H, CH<sub>3</sub>), 4.71 (s, 1H, CH), 7.00-7.04 (m, 4H, Ar-H), 11.06-11.71 (br s, 3H, NH); <sup>13</sup>C NMR (75.47 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{C}}$  10.8 (CH<sub>3</sub>), 21.0 (CH<sub>3</sub>), 32.7 (CH), 104.8 (C-8,12), 127.8, 128.7, 129.3 (3C, Ar), 134.7 (C-15,16), 140.7 (C-3), 161.4 (C-9,11); HR-MS (ESI) Calcd for C<sub>16</sub>H<sub>17</sub>N<sub>5</sub> [M+NH<sub>4</sub>] 297.1822 found 297.1856.

**4-[5-Bromo-2-(prop-2-ynyloxy)phenyl]-3,5-dimethyl-1,4,7,8-tetrahydrodipyrzolo[3,4-*b*:4'3'-*e*]pyridine (5d).** Yield 76%, mp 249-251 °C; IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3366, 3288, 1612; <sup>1</sup>H NMR (300.13 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{H}}$  2.07 (s, 6H, 2CH<sub>3</sub>), 3.58 (s, 1H, (≡CH), 4.77 (s, 2H, CH<sub>2</sub>), 5.00 (s, 1H, CH), 6.89-6.93 (m, 1H, Ar-H), 7.25-7.31 (m, 1H, Ar-H), 7.67 (s, 1H, Ar-H), 11.58-11.62 (br s, 3H, NH); <sup>13</sup>C NMR (75.47 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{C}}$  10.4 (CH<sub>3</sub>), 27.0 (CH), 56.1 (CH<sub>2</sub>), 78.2 (≡CH), 78.9 (≡C), 103.2 (C-2,6), 112.4, 114.3, 129.1, 131.7 (4C, Ar), 135.1 (C-9,10), 140.0 (C-15), 153.2 (C-16), 161.3 (C-3,5); HR-MS (ESI) Calcd for C<sub>19</sub>H<sub>17</sub>BrN<sub>4</sub>O [M+2Na-2H] 417.0586 found 417.0538.

**3,5-Dimethyl-4-[5-methyl-2-(prop-2-ynyloxy)phenyl]-1,4,7,8-tetrahydrodipyrzolo[3,4-*b*:4'3'-*e*]pyridine (5e).** Yield 75%, mp 249-251 °C; IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3366, 3284, 1606, 1490; <sup>1</sup>H NMR (300.13 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{H}}$  2.08 (s, 6H, 2CH<sub>3</sub>), 2.15 (s, 3H, CH<sub>3</sub>), 3.52 (s, 1H, ≡CH), 4.70 (s, 2H, CH<sub>2</sub>), 5.05 (s, 1H, CH), 6.82-6.88 (m, 2H, Ar-H), 7.38 (s, 1H, Ar-H), 11.51 (br s, 3H, NH); <sup>13</sup>C NMR (75.47 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{C}}$  11.0 (2CH<sub>3</sub>), 21.1, (CH<sub>3</sub>), 27.3 (CH), 56.4 (CH<sub>2</sub>), 78.3 (≡CH), 80.1 (≡C), 104.5 (C-2,6), 112.5, 127.3, 129.4, 130.4 (4C, Ar), 132.9 (C-9,10), 140.6 (C-15), 152.4 (C-16), 162.0 (C-3,5); HR-MS (ESI) Calcd for C<sub>20</sub>H<sub>20</sub>N<sub>4</sub>O [M+NH<sub>4</sub>] 351.1926 found 351.1943.

**3,5-Diethyl-4-phenyl-1,4,7,8-tetrahydrodipyrzolo[3,4-*b*:4',3'-*e*]pyridine (5f).** Yield 72%, mp 266-268 °C; IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3391, 1609, 1495; <sup>1</sup>H NMR (300.13 MHz, DMSO-*d*<sub>6</sub>), spectrum at 60 °C:  $\delta_{\text{H}}$  1.10 (t, 6H, *J* 7.2 Hz, 2CH<sub>3</sub>), 2.48-2.55 (m, 4H, 2CH<sub>2</sub>), 4.82 (s, 1H, CH), 7.11-7.20 (m, 5H, Ar-H), 11.20 (br s, 3H, NH); <sup>13</sup>C NMR (75.47 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{C}}$  13.9 (2CH<sub>3</sub>), 18.5 (2CH<sub>2</sub>), 32.9 (CH), 103.9 (C-1,5), 125.8, 127.7, 128.1 (3C, Ar), 143.9 (C-9,10), 145.8 (C-13), 161.6 (C-2,4); HR-MS (ESI) Calcd for C<sub>17</sub>H<sub>19</sub>N<sub>5</sub> [M+NH<sub>4</sub>] 311.1979 found 311.1973.

**4-(4-Chlorophenyl)-3,5-dipropyl-1,4,7,8-tetrahydrodipyrzolo[3,4-*b*:4',3'-*e*]pyridine (5g).** Yield 75%, mp 264 °C (decomp.); IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3352, 1602, 1520; <sup>1</sup>H NMR (300.13 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{H}}$  0.86 (t, 6H, *J* 7.6 Hz, 2CH<sub>3</sub>), 1.42-1.57 (m, 4H, 2CH<sub>2</sub>), 2.48 (t, 4H, *J* 7.6 Hz, 2CH<sub>2</sub>), 4.79 (s, 1H, CH), 7.09 (d, 2H, *J* 8.4 Hz, Ar-H), 7.26 (d, 2H, *J* 8.8 Hz, Ar-H), 11.21-11.74 (br s, 3H, NH); <sup>13</sup>C NMR (75.47 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{C}}$  13.7 (2CH<sub>3</sub>), 22.1 (2CH<sub>2</sub>), 26.6 (2CH<sub>2</sub>), 32.1 (CH), 103.6 (C-1,5), 127.6, 129.2, 130.0 (3C, Ar), 140.1 (C-9,10), 142.5 (C-13), 161.1 (broad, C-2,4); HR-MS (ESI) Calcd for C<sub>19</sub>H<sub>22</sub>ClN<sub>5</sub> [M+NH<sub>4</sub>] 373.1902 found 373.1943.

**3,5-Dimethyl-4-(pyrid-2-yl)-1,4,7,8-tetrahydrodipyrzolo[3,4-*b*:4',3'-*e*]pyridine (5h).** Yield 78%, mp 218 °C (decomp.); IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3178, 3089, 1612, 1465; <sup>1</sup>H NMR (300.13 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\text{H}}$  2.00 (s, 6H, 2CH<sub>3</sub>), 4.94 (s, 1H, CH), 7.15-7.29 (m, 2H, Ar-H), 7.60-7.67

(m, 1H, Ar-H), 8.34-8.38 (m, 1H, Ar-H), 9.74 (br s, 3H, NH);  $^{13}\text{C}$  NMR (75.47 MHz, DMSO- $d_6$ ):  $\delta_{\text{C}}$  10.8 (2CH<sub>3</sub>), 36.6 (CH), 103.5 (C-8,12), 122.0, 122.9, 137.7 (3C, Ar), 140.2 (C-15,16), 148.1 (C-5), 160.7 (C-9,11), 162.4 (C-3); HR-MS (ESI) Calcd for C<sub>14</sub>H<sub>14</sub>N<sub>6</sub> [2M+2Na] 578.2355 found 578.2304.

**3,5-Dimethyl-4-(pyrid-3-yl)-1,4,7,8-tetrahydrodipyrzolo[3,4-*b*:4',3'-*e*]pyridine (5i).** Yield 63%, mp >270 °C; IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3313, 3197, 1604, 1481;  $^1\text{H}$  NMR (300.13 MHz, DMSO- $d_6$ ):  $\delta_{\text{H}}$  2.09 (s, 6H, 2CH<sub>3</sub>), 4.89 (s, 1H, CH), 7.22-7.26 (m, 1H, Ar-H), 7.50-7.54 (m, 1H, Ar-H), 8.30-8.34 (m, 2H, Ar-H), 11.20-11.35 (br s, 3H, NH);  $^{13}\text{C}$  NMR (75.47 MHz, DMSO- $d_6$ ):  $\delta_{\text{C}}$  10.8 (2CH<sub>3</sub>), 31.1 (CH), 103.8 (C-8,12), 123.3, 135.5 (C-3), 139.1 (C-4), 140.1 (C-15,16), 147.0 (C-6), 149.5 (C-4), 161.4 (C-9,11); HR-MS (ESI) Calcd for C<sub>14</sub>H<sub>14</sub>N<sub>6</sub> [2M-H+K] 569.2035 found 569.2069.

**3,5-Dimethyl-4-propyl-1,4,7,8-tetrahydrodipyrzolo[3,4-*b*:4',3'-*e*]pyridine (5j).** Yield 60%, mp 262-264 °C; IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3367, 1621, 1494;  $^1\text{H}$  NMR (300.13 MHz, DMSO- $d_6$ ), spectrum at 60 °C:  $\delta_{\text{H}}$  0.81-0.85 (m, 3H, CH<sub>3</sub>), 1.08-1.12 (m, 2H, CH<sub>2</sub>), 1.78-1.84 (m, 2H, CH<sub>2</sub>), 2.06 (s, 6H, 2CH<sub>3</sub>), 2.40-2.52 (m, 1H, CH), 11.34 (s, 3H, NH),  $^{13}\text{C}$  NMR (75.47 MHz, DMSO- $d_6$ ):  $\delta_{\text{C}}$  10.1 (2CH<sub>3</sub>), 13.6 (CH<sub>3</sub>), 20.7 (2CH<sub>2</sub>), 27.7 (2CH<sub>3</sub>), 33.9 (CH), 105.3 (C-1,5), 138.7 (C-7,12), 161.2 (C-2,4); HR-MS C<sub>12</sub>H<sub>17</sub>N<sub>5</sub> (ESI) Calcd for [M+NH<sub>4</sub>] 249.1484 found 249.1486.

**3,5-Dimethyl-7,8-dihydro-1H-spiro(dipyrzolo[3,4-*b*:4',3'-*e*]pyridine-4,3'-indolin)-2'-one (5k).** Yield 55%, mp 242-244 °C; IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3423, 3251, 1718, 1616, 1519;  $^1\text{H}$  NMR (300.13 MHz, DMSO- $d_6$ ):  $\delta_{\text{H}}$  1.71 (s, 6H, 2CH<sub>3</sub>), 6.76-6.81 (m, 1H, Ar-H), 6.82-6.89 (m, 1H, Ar-H), 7.07-7.18 (m, 2H, Ar-H), 9.81-11.20 (br s, 3H, NH), 10.55 (s, 1H, , NH);  $^{13}\text{C}$  NMR (75.47 MHz, DMSO- $d_6$ ):  $\delta_{\text{C}}$  11.7 (2CH<sub>3</sub>), 49.0 (spiro C), 99.4 (C-1, 5), 109.8, 121.5, 126.8, 128.0, 133.8 (5C, Ar), 137.4 (C-9, 10), 141.5 (C-N), 159.9 (C-2, 4), 181.7 (C=O); HR-MS C<sub>16</sub>H<sub>14</sub>N<sub>6</sub>O (ESI) Calcd for [M+NH<sub>4</sub>] 324.1567 found 324.1510.

**3',5'-Dimethyl-7',8'-dihydro-1'H,2H-spiro(acenaphthylene-1,4'-dipyrzolo[3,4-*b*:4',3'-*e*]pyridin)-2-one (5l).** Yield 40%, mp 232-235 °C; IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3269, 1722, 1604, 1517;  $^1\text{H}$  NMR (300.13 MHz, DMSO- $d_6$ ):  $\delta_{\text{H}}$  1.78-1.82 (s, 6H, 2CH<sub>3</sub>), 7.42-7.70 (m, 1H, Ar-H), 7.52-7.63 (m, 1H, Ar-H), 7.71-7.88 (m, 3H, Ar-H), 8.10-8.30 (m, 1H, Ar-H), 8.86-11.24 (br m, 3H, NH);  $^{13}\text{C}$  NMR (75.47 MHz, DMSO- $d_6$ ):  $\delta_{\text{C}}$  11.4 (2CH<sub>3</sub>), 52.7 (spiro C), 100.3 (C-13, 17), 121.3, 121.9, 123.1, 127.8, 128.5, 130.1, 131.1, 132.8, 137.4 (9C, Ar), 139.7 (C-20, 21), 143.4 (C, Ar), 158.9 (C-14, 16), 203.3 (C=O); HR-MS C<sub>20</sub>H<sub>15</sub>N<sub>5</sub>O (ESI) Calcd for [M+NH<sub>4</sub>] 359.1615 found 359.1639.

**3,5-Diethyl-7,8-dihydro-1H-spiro(dipyrzolo[3,4-*b*:4',3'-*e*]pyridine-4,3'-indolin)-2'-one (5m).** Yield 60%, mp 252-254 °C; IR (KBr) ( $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3320, 1723, 1619, 1510;  $^1\text{H}$  NMR (300.13 MHz, DMSO- $d_6$ ):  $\delta_{\text{H}}$  0.70-0.82 (m, 6H, 2CH<sub>3</sub>), 2.06-2.09 (m, 4H, 2CH<sub>2</sub>), 6.80-6.85 (m, 1H, Ar-H), 6.85-6.88 (m, 1H, Ar-H), 7.11-7.20 (m, 2H, Ar-H), 9.06-11.24 (br s, 3H, NH), 10.67 (s, 1H, NH);  $^{13}\text{C}$  NMR (75.47 MHz, DMSO- $d_6$ ):  $\delta_{\text{C}}$  14.1 (2CH<sub>3</sub>), 18.8 (2CH<sub>2</sub>), 49.4 (spiro C), 98.4 (C-1, 5), 109.9, 121.5, 126.4, 128.2, 133.6 (5C, Ar), 141.8 (C-9, 10), 142.9 (C-N), 159.8 (C-2, 4), 182.3 (C=O); HR-MS C<sub>18</sub>H<sub>18</sub>N<sub>6</sub>O (ESI) Calcd for [M+NH<sub>4</sub>] 352.1880 found 352.1865.



**3',5'-Diethyl-7',8'-dihydro-1'H,2H-spiro(acenaphthylene-1,4'-dipyrzolo[3,4-b:4',3'-e]pyridin)-2-one (5n).** Yield 60%, mp 267-269 °C; IR (KBr) ( $\nu_{\max}/\text{cm}^{-1}$ ): 3461, 3268, 1708, 1597, 1526;  $^1\text{H}$  NMR (300.13 MHz, DMSO- $d_6$ ):  $\delta_{\text{H}}$  0.80-0.91 (m, 6H, 2CH<sub>3</sub>), 2.08-2.22 (m, 4H, 2CH<sub>2</sub>), 7.44 (d, 1H,  $J$  6.8 Hz, Ar-H), 7.58-7.63 (m, 1H, Ar-H), 7.73-7.78 (m, 1H, Ar-H), 7.85-7.90 (m, 2H, Ar-H), 8.21 (d, 1H,  $J$  6.5 Hz, Ar-H), 8.91-11.37 (br m, 3H, NH);  $^{13}\text{C}$  NMR (75.47 MHz, DMSO- $d_6$ ):  $\delta_{\text{C}}$  13.2 (2CH<sub>3</sub>), 18.5 (2CH<sub>2</sub>), 52.9 (spiro C), 99.5 (C-13, 17), 121.4, 121.8, 123.2, 127.9, 128.5, 130.0, 131.2, 132.7, 139.7 (9C, Ar), 143.0 (C-20, 21), 143.3 (C, Ar), 158.0 (C-14, 16), 203.2 (C=O); HR-MS (ESI) Calcd for C<sub>22</sub>H<sub>19</sub>N<sub>5</sub>O [M+NH<sub>4</sub>] 387.1928 found 387.1946.

**3,5-Dipropyl-7,8-dihydro-1H-spiro(dipyrzolo[3,4-b:4',3'-e]pyridine-4,3'-indolin)-2'-one (5o).** Yield 70%, mp 223-225 °C; IR (KBr) ( $\nu_{\max}/\text{cm}^{-1}$ ): 3313, 1706, 1618, 1517;  $^1\text{H}$  NMR (300.13 MHz, DMSO- $d_6$ ):  $\delta_{\text{H}}$  0.62 (br s, 6H, 2CH<sub>3</sub>), 0.85-0.91 (m, 4H, 2CH<sub>2</sub>), 2.04-2.08 (m, 4H, 2CH<sub>2</sub>) 6.84-6.95 (m, 2H, Ar-H), 7.11-7.20 (m, 2H, Ar-H), 9.05-11.32 (br s, 3H, NH), 10.71 (s, 1H, NH);  $^{13}\text{C}$  NMR (75.47 MHz, DMSO- $d_6$ ):  $\delta_{\text{C}}$  14.0 (2CH<sub>3</sub>), 22.9 (2CH<sub>2</sub>), 27.3 (2CH<sub>2</sub>), 49.4 (spiro C), 99, 109.9 (C-1, 5), 121.4, 126.1, 128.1, 132.9 (4C, Ar), 141.6 (C-9, 10), 160 (C-2, 4), 182.6 (C=O); HR-MS (ESI) Calcd for C<sub>20</sub>H<sub>22</sub>N<sub>6</sub>O [M+NH<sub>4</sub>] 380.2193 found 380.2181.

**3',5'-Dipropyl-7',8'-dihydro-1'H,2H-spiro(acenaphthylene-1,4'-dipyrzolo[3,4-b:4',3'-e]pyridine)-2-one (5p).** Yield 76%, mp 284-286 °C; IR (KBr) ( $\nu_{\max}/\text{cm}^{-1}$ ): 3283, 1682, 1596, 1523;  $^1\text{H}$  NMR (300.13 MHz, DMSO- $d_6$ ), spectrum at 60 °C:  $\delta_{\text{H}}$  0.61 (t, 6H,  $J$  7.5 Hz, 2CH<sub>3</sub>), 1.14-1.28 (m, 4H, 2CH<sub>2</sub>), 2.04 (t, 4H,  $J$  7.5 Hz, 2CH<sub>2</sub>), 7.46 (d, 1H,  $J$  6.7 Hz, Ar-H), 7.61-7.66 (m, 1H, Ar-H), 7.75-7.80 (m, 1H, Ar-H), 7.88-7.92 (m, 2H, Ar-H), 8.24 (d, 1H,  $J$  8.0 Hz, Ar-H), 8.85-10.6 (br m, 3H, NH);  $^{13}\text{C}$  NMR (75.47 MHz, DMSO- $d_6$ ):  $\delta_{\text{C}}$  13.7 (2CH<sub>3</sub>), 22.0 (2CH<sub>2</sub>), 27.2 (2CH<sub>2</sub>), 53.3 (spiro C), 99.4 (C-13, 17), 121.7, 121.9, 123.5, 128.0, 128.4, 130.1, 131.4, 132.4, 139.8 (9C, Ar), 141.8 (C-20, 21), 142.9 (C, Ar), 159.1 (C-14, 16), 203.8 (C=O); HR-MS (ESI) Calcd for C<sub>24</sub>H<sub>23</sub>N<sub>5</sub>O [M+NH<sub>4</sub>] 415.2241 found 415.2200.

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## References

1. Tejedor, D.; Garcia-Tellado, F. *Chem. Soc. Rev.* **2007**, *36*, 484-491.  
<http://dx.doi.org/10.1039/b608164a>
2. Weber, L. *Drug Discov. Today* **2002**, *7*, 143-147.  
[http://dx.doi.org/10.1016/S1359-6446\(01\)02090-6](http://dx.doi.org/10.1016/S1359-6446(01)02090-6)
3. Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51-80.

- <http://dx.doi.org/10.2174/0929867033368600>
4. Domling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, 39, 3168-3210.  
[http://dx.doi.org/10.1002/1521-3773\(20000915\)39:18<3168::AID-ANIE3168>3.0.CO;2-U](http://dx.doi.org/10.1002/1521-3773(20000915)39:18<3168::AID-ANIE3168>3.0.CO;2-U)
  5. Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, 39, 79-87.
  6. Dabiri, M.; Salehi, P.; Bahramnejad, M.; Sherafat, F. *J. Comb. Chem.* **2010**, 12, 638-642.  
<http://dx.doi.org/10.1021/cc100043z>
  7. Kappe, C. O. *Eur. J. Med. Chem.* **2000**, 35, 1043-1052.  
[http://dx.doi.org/10.1016/S0223-5234\(00\)01189-2](http://dx.doi.org/10.1016/S0223-5234(00)01189-2)
  8. Domling, A. Ugi, I. *Angew. Chem. Intl. Ed.* **1993**, 32, 563-564.
  9. Varache-Lembège, M.; Nuhrich, A.; Zemb, V.; Devaux, G.; Vacher, P.; Vacher, A. M.; Dufy, B. *Eur. J. Med. Chem.* **1996**, 31, 547-556.  
[http://dx.doi.org/10.1016/0223-5234\(96\)89551-1](http://dx.doi.org/10.1016/0223-5234(96)89551-1)
  10. Hantzsch, A. *Ber. Dtsch. Chem. Ges.* **1881**, 14, 1637-1638.  
<http://dx.doi.org/10.1002/cber.18810140214>
  11. Ghosh, S.; Saikh, F.; Das, J.; Pramanik, A. K. *Tetrahedron Lett.* **2013**, 54, 58-62.  
<http://dx.doi.org/10.1016/j.tetlet.2012.10.079>
  12. Acheson, R. M. *An Introduction to the Chemistry of Heterocyclic Compounds*, 2nd ed.; Wiley: New York, 1967; p. 309.
  13. Pulido, M. L.; Fenyes, J. G. *Eur. Pat. Appl.* 467,708, 1991; *Chem. Abstr.* **1992**, 116, 146150J.
  14. Ohyama H.; One, T., Terakawa, T. *Eur. Pat. Appl* 202,169, 1986; *Chem. Abstr.* **1987**, 106, 33046t.
  15. Zikan, V.; Radl, S.; Smejkal, F.; Zelena, D. *Czech CS* 233445, 1986; *Chem. Abstr.* **1987**, 106, 138437q.
  16. Harlin, W.; Linke, A.; Messer, E. *Deut. Arch. Klin. Med.* **1995**, 201, 690-692; *Chem. Abstr.* **1956**, 50, 11519c.
  17. Roberts, D. A.; Hawkins, D.; Ross, W. *Eur. Pat. Appl.* 403,309, 1991; *Chem. Abstr.* **1991**, 114, 185494c.
  18. Pacousky, V.; Holecek, V. *Casopis Lekaru Ceskych* **1956**, 95, 300-319; *Chem. Abstr.* **1956**, 50, 7306c.
  19. Hanefeld, U.; Rees, C. W.; White, A. J. P.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1*, **1996**, 1545-1552.  
<http://dx.doi.org/10.1039/p19960001545>
  20. Yu, G.; Mason, H.; Wu, X.; Wang, J.; Chong, S.; Dorough, G.; Henwood, A.; Pongrac, R.; Seliger, L.; He, B.; Normandin, D.; Adam, L.; Krupinski, J.; Macor, J. *J. Med. Chem.* **2001**, 44, 1025-1027.  
<http://dx.doi.org/10.1021/jm0155042>
  21. Liu, C.; Li, Z.; Zhao, L.; Shen, L. *Arkivoc*, **2009**, (ii), 258-268.  
<http://dx.doi.org/10.3998/ark.5550190.0010.224>
  22. Chen, Y. L. *WO Pat.* 9534563 A1, 1995; *Chem. Abstr.* **1995**, 124, 232447.

23. Tao, Y. T.; Balasubramaniam, E.; Danel, A.; Tomasik, P. *Appl. Phys. Lett.* **2000**, *77*, 933-935.  
<http://dx.doi.org/10.1063/1.1288811>
24. Tao, Y. T.; Chuen, C. H.; Ko, C. W.; Peng, J. W. *Chem. Mater.* **2002**, *14*, 4256-4261.  
<http://dx.doi.org/10.1021/cm020284h>
25. Sharma, C.; Sharma, S.; Sain, D.; Talesara, G.L. *Indian J. Heterocycl. Chem.* **2008**, *18*, 153-156.
26. Zhao, K.; Lei, M.; Ma, L.; Hu, L. *Monatsh. Chem.* **2011**, *142*, 1169-1173.  
<http://dx.doi.org/10.1007/s00706-011-0565-8>
27. Thakre, W.; Meshram, J. M. *Indian J. Heterocycl. Chem.* **2008**, *18*, 17-20.
28. Vasuki, G.; Kumaravel, K. *Tetrahedron Lett.* **2008**, *49*, 5636-5638.  
<http://dx.doi.org/10.1016/j.tetlet.2008.07.055>
29. Litvinov, Y. M.; Shestopalov, A. A.; Rodinovskaya, L. A.; Shestopalov, A. M. *J. Comb. Chem.* **2009**, *11*, 914-919.  
<http://dx.doi.org/10.1021/cc900076j>
30. Kumaravel, K.; Vasuki, G. *Green. Chem.* **2009**, *11*, 1945-1947.  
<http://dx.doi.org/10.1039/b913838b>
31. Sobhani, S.; Hasaninejad, A.-R.; Maleki, M. F.; Pakdin Parizi, Z. *Synth. Commun.* **2012**, *42*, 2245-2255.  
<http://dx.doi.org/10.1080/00397911.2011.555589>
32. Hasaninejad, A.; Rasekhi Kazerooni, M.; Zare, A. *ACS Sustainable Chem. Eng.* **2013**, *1*, 679-684.  
<http://dx.doi.org/10.1021/sc400081c>
33. Koohshari, M.; Dabiri, M.; Salehi, P. *RSC Adv.* **2014**, *4*, 10660-10671.  
<http://dx.doi.org/10.1039/c3ra47639a>