

## Efficient three-component synthesis of *N*-alkyl-3,6-diaryl-[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-amines under solvent-free condition

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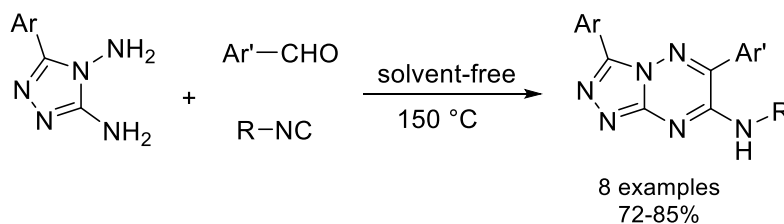
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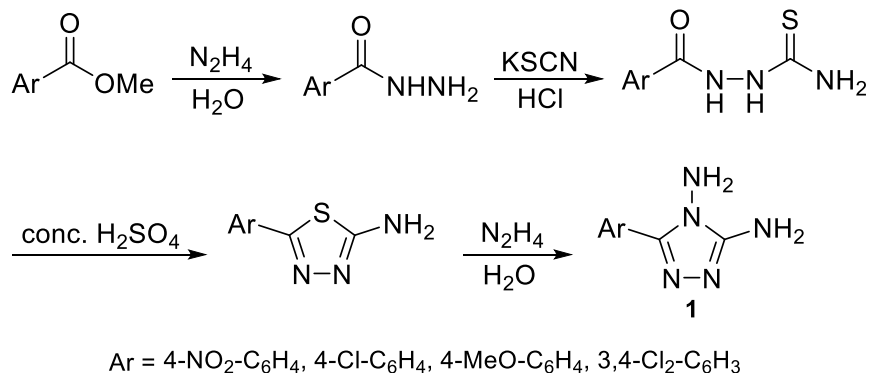
### Abstract

A simple, efficient and environment-friendly approach is described for the synthesis of *N*-alkyl-3,6-diaryl-[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-amines based on three-component reaction between 5-aryl-4*H*-1,2,4-triazole-3,4-diamine, isocyanide and aldehyde under solvent-free condition. The products are obtained in moderate to good yields and are in a state of high purity.



**Keywords:** Three-component reaction, *N*-Alkyl-3,6-diaryl-[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-amines, 5-aryl-4*H*-1,2,4-triazole-3,4-diamine, isocyanide, aldehyde





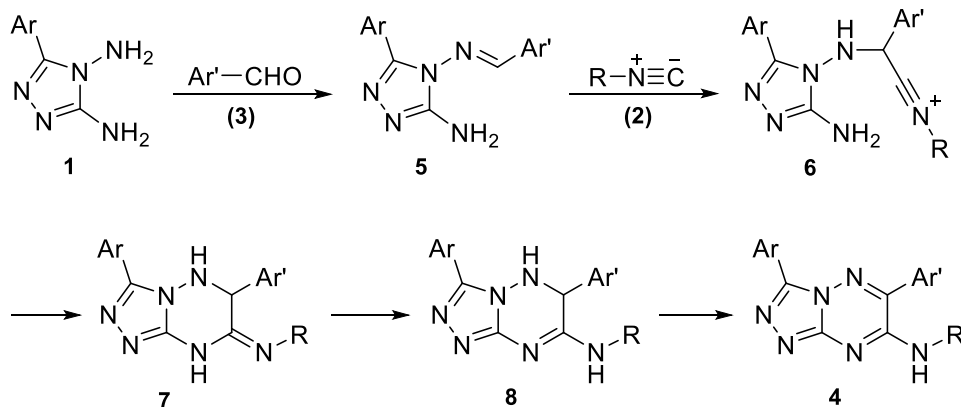
**Scheme 2.** Three-component synthesis of the *N*-alkyl-3,6-diaryl-[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-amines.

**Table 1.** Synthesis of *N*-alkyl-3,6-diaryl-[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-amines

| Product   | Ar   | Ar'  | R            | Yield (%) <sup>a</sup> |
|-----------|--|--|--------------|------------------------|
| <b>4a</b> | 4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>   | C <sub>6</sub> H <sub>5</sub>                    | <i>t</i> -Bu | 72                     |
| <b>4b</b> | 4-Cl-C <sub>6</sub> H <sub>4</sub>                 | 2-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> | <i>t</i> -Bu | 75                     |
| <b>4c</b> | 4-MeO-C <sub>6</sub> H <sub>4</sub>                | 3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> | Cyclohexyl   | 82                     |
| <b>4d</b> | 4-Cl-C <sub>6</sub> H <sub>4</sub>                 | C <sub>6</sub> H <sub>5</sub>                    | Cyclohexyl   | 85                     |
| <b>4e</b> | 4-Cl-C <sub>6</sub> H <sub>4</sub>                 | 3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> | Cyclohexyl   | 78                     |
| <b>4f</b> | 4-Cl-C <sub>6</sub> H <sub>4</sub>                 | 2-Cl-C <sub>6</sub> H <sub>4</sub>               | Cyclohexyl   | 74                     |
| <b>4g</b> | 4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>   | 2-Cl-C <sub>6</sub> H <sub>4</sub>               | Cyclohexyl   | 80                     |
| <b>4h</b> | 3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> | 3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> | Cyclohexyl   | 78                     |

<sup>a</sup> Yield of isolated products.

To explain the formation of *N*-alkyl-3,6-diaryl-[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-amines **4**, a plausible reaction mechanism is proposed in Scheme 3. Initially, due to the stronger nucleophilicity of the amino group at position 4 of the five-member ring in contrast to the amino group at position 3,<sup>[39,40]</sup> it is reasonable to assume that imine intermediate **5** is formed by condensation of 5-aryl-4*H*-1,2,4-triazole-3,4-diamine **1** with aldehyde **3**. Then, the nucleophilic addition of isocyanide **2** to this intermediate results in formation of intermediate **6**, which undergoes the intramolecular cyclization of amino group with triple bond followed by tautomerization and aerobic oxidation affords the *N*-alkyl-3,6-diaryl-[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-amines **4** (Scheme 2).



**Scheme 3.** Plausible mechanism for synthesis of the *N*-alkyl-3,6-diaryl-[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-amines.

## Conclusions

In conclusion, a straightforward and eco-friendly approach for the synthesis of *N*-alkyl-3,6-diaryl-[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-amines based on three-component reaction between 5-aryl-4*H*-1,2,4-triazole-3,4-diamine, isocyanide and aldehyde under solvent-free condition is described. The simplicity of starting materials, moderate to good yields of the products and use of solvent-free conditions are the main advantages of this method.

## Experimental Section

**General.** All chemicals were purchased from Merck and Fluka companies. All yields refer to isolated products. IR spectra were recorded on a Shimadzu IR-460 spectrometer. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker, Rheinstetten, Germany (at 500 and 400 MHz) NMR spectrometer using tetramethylsilane (TMS) as internal standard. Elemental analyses for C, H and N were performed using a Heraeus CHN-O-Rapid analyzer. Melting points were determined in a capillary tube and are not corrected. The progress of reaction was followed with TLC using silica gel SILG/UV 254 and 365 plates. All products are known compounds and their structures were deduced by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy as well as elemental analysis.

**General procedure for the preparation of products 4a–4h.** A mixture of appropriate 5-aryl-4*H*-1,2,4-triazole-3,4-diamine **1** (1.0 mmol), isocyanide **2** (1.0 mmol), and aldehyde **3** (1.0 mmol) was stirred in a sealed vessel at 150 °C under solvent-free condition for 4–9 h. After reaction completion (TLC), the reaction mixture was cooled to room temperature and the crude product was purified by column chromatography on silica gel using hexane–EtOAc (4:1) as eluent to afford products **4a–4h** (Table 1).

***N*-(*tert*-butyl)-3-(4-nitrophenyl)-6-phenyl-[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-amine (4a).** White solid, mp 218–220 °C; IR (KBr): 3379, 2936, 2875, 1628, 1500, 1548, 1423, 1366cm<sup>-1</sup>. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 500 MHz): δ 0.99 (s, 9H), 4.65 (s, 1H), 7.19–7.22 (m, 3H), 7.51 (d, *J* 9.0 Hz), 8.05 (d, *J* 8.0 Hz), 8.51 (d, *J* 8.0 Hz) ppm; <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 125 MHz): δ 29.9, 59.9, 118.2, 121.5, 121.7, 124.3, 124.5, 127.5, 127.6, 128.4, 128.5, 132.0, 136.3, 149.3 ppm; Anal. Calcd for C<sub>20</sub>H<sub>19</sub>N<sub>7</sub>O<sub>2</sub>: C, 61.69; H, 4.92; N, 25.18. Found: C, 61.61; H, 4.90; N, 25.16.

***N*-(*tert*-butyl)-3-(4-chlorophenyl)-6-(2-tolyl)-[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7-amine (4b):** White solid, mp 224–226 °C; IR (KBr): 3370, 2930, 2852, 1601, 1570, 1565, 1489, 1382 cm<sup>-1</sup>. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 500 MHz): δ 0.99 (s, 9H), 2.32 (s, 1H), 4.56 (s, 1H), 6.85 (t, *J* 7.0 Hz), 7.15 (t, *J* 7.0 Hz), 7.19 (d, *J* 8.0 Hz, 2H), 7.44 (d, *J* 7.0 Hz, 1H), 8.05 (d, *J* 8.0 Hz, 2H), 8.38 (d, *J* 7.0 Hz, 1H) ppm; <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 125 MHz): δ 20.8, 30.0, 55.6,

116.3, 123.5, 123.8, 123.9, 124.0, 127.5, 127.6, 128.3, 128.4, 129.2, 132.4, 135.9, 137.9, 140.8 ppm; Anal. Calcd for C<sub>21</sub>H<sub>21</sub>ClN<sub>6</sub>: C, 64.20; H, 5.39; Cl, 9.02; N, 21.39. Found: C, 64.11; H, 5.30; Cl, 8.96; N, 21.23.

**N-cyclohexyl-3-(4-methoxyphenyl)-6-(3-nitrophenyl)-[1,2,4]triazolo[4,3-b][1,2,4]triazin-7-amine (4c):** Pale yellow solid, mp 188–190 °C; IR (KBr): 3277, 2944, 2856, 1654, 1527, 1530, 1428, 1338 cm<sup>-1</sup>. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 500 MHz): δ 1.08–1.70 (m, 10H), 2.81–2.84 (m, 1H), 4.00 (s, 3H), 4.79 (d, *J* 6.0 Hz, 1H), 7.17 (d, *J* 7.5 Hz, 1H), 7.28 (d, *J* 7.5 Hz, 1H), 7.40 (t, *J* 7.5 Hz, 1H), 7.51 (d, *J* 8.0 Hz, 2H), 8.13 (t, *J* 7.5 Hz, 1H), 8.33 (s, 1H) ppm; <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 125 MHz): δ 24.3, 25.3, 33.4, 49.8, 56.2, 111.3, 111.5, 116.2, 123.2, 123.9, 124.9, 125.3, 127.7, 129.6, 130.0, 130.6, 134.2, 136.6, 143.1, 157.1 ppm; Anal. Calcd for C<sub>23</sub>H<sub>23</sub>N<sub>7</sub>O<sub>3</sub>: C, 62.01; H, 5.20; N, 22.01; Found: C, 61.92; H, 5.12; N, 21.93.

**3-(4-chlorophenyl)-N-cyclohexyl-6-phenyl-[1,2,4]triazolo[4,3-b][1,2,4]triazin-7-amine (4d):** White solid, mp 212–214 °C; IR (KBr): 3294, 2973, 2844, 1600, 1528, 1483, 1351 cm<sup>-1</sup>. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 500 MHz): δ 0.91–1.59 (m, 10H), 2.68–2.73 (m, 1H), 4.53 (s, 1H), 7.16 (m, 2H), 7.39–7.44 (m, 2H), 7.50–7.58 (m, 3H), 8.43 (d, *J* 8.0 Hz, 2H) ppm; <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 125 MHz): δ 24.0, 25.2, 32.9, 54.5, 118.6, 120.5, 120.7, 123.5, 126.5, 126.7, 127.4, 129.3, 132.3, 132.9, 133.8, 137.9 ppm; Anal. Calcd for C<sub>22</sub>H<sub>21</sub>ClN<sub>6</sub>: C, 65.26; H, 5.23; Cl, 8.76; N, 20.76. Found: C, 65.21; H, 5.15; Cl, 8.70; N, 20.71.

**3-(4-chlorophenyl)-N-cyclohexyl-6-(3-nitrophenyl)-[1,2,4]triazolo[4,3-b][1,2,4]triazin-7-amine (4e):** White solid, mp 185–187 °C; IR (KBr): 3270, 2900, 2810, 1628, 1544, 1525, 1489, 1366 cm<sup>-1</sup>. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 500 MHz): δ 1.09–1.71 (m, 10H), 2.80–2.82 (m, 1H), 4.78 (d, *J* = 6.0 Hz, 1H), 7.09 (d, *J* 7.5 Hz, 1H), 7.18–7.31 (m, 3H), 7.34 (d, *J* 7.5 Hz, 1H), 7.51 (d, *J* 8.0 Hz, 2H), 8.13 (d, *J* 7.5 Hz, 1H), 8.33 (s, 1H) ppm; <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 125 MHz): δ 24.4, 25.3, 33.4, 52.8, 114.5, 117.2, 118.5, 120.8, 124.3, 124.6, 124.6, 127.7, 127.9, 128.1, 128.7, 157.3, 160.0 ppm; ; Anal. Calcd for C<sub>22</sub>H<sub>20</sub>ClN<sub>7</sub>O<sub>2</sub>: C, 58.73; H, 4.48; Cl, 7.88; N, 21.79. Found: C, 58.66; H, 4.41; Cl, 7.80; N, 21.71.

**6-(2-chlorophenyl)-3-(4-chlorophenyl)-N-cyclohexyl-[1,2,4]triazolo[4,3-b][1,2,4]triazin-7-amine (4f):** Yellow solid, mp 190–192 °C; IR (KBr): 3230, 2917, 2860, 1625, 1587, 1555, 1364 cm<sup>-1</sup>. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 500 MHz): δ 1.09–1.72 (m, 10H), 2.79 (m, 1H), 4.68 (d, *J* 6.0 Hz, 1H), 6.84 (t, *J* 7.5 Hz, 1H), 7.07 (d, *J* 7.5 Hz, 1H), 7.14 (t, *J* 7.5 Hz, 1H), 7.27 (d, *J* 8.0 Hz, 2H), 7.42 (d, *J* 7.5 Hz, 1H), 7.87 (d, *J* 8.0 Hz, 1H) ppm; <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 125 MHz): δ 24.4, 25.3, 33.4, 52.0, 111.0, 114.4, 116.4, 121.3, 123.1, 123.4, 124.6, 127.7, 130.1, 131.6, 135.3, 140.3, 157.1 ppm; Anal. Calcd for C<sub>22</sub>H<sub>20</sub>Cl<sub>2</sub>N<sub>6</sub>: C, 60.14; H, 4.59; Cl, 16.14; N, 19.13. Found: C, 60.04; H, 4.43; Cl, 16.01; N, 19.02.

**6-(2-chlorophenyl)-N-cyclohexyl-3-(4-nitrophenyl)-[1,2,4]triazolo[4,3-b][1,2,4]triazin-7-amine (4g):** White solid, mp 202–204 °C; IR (KBr): 3285, 2900, 2827, 1615, 1577, 1515, 1479, 1365 cm<sup>-1</sup>. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 500 MHz): δ 1.12–1.79 (m, 10H), 2.85–2.90 (m, 1H), 4.98 (s, 1H), 7.23 (t, *J* 7.5 Hz, 1H), 7.52 (d, *J* 7.5 Hz, 1H), 7.73 (t, *J* 7.5 Hz, 1H), 8.11 (d, *J* 8.0 Hz, 2H), 8.36 (d, *J* 7.5 Hz, 1H), 8.66 (d, *J* 8.0 Hz, 2H) ppm; <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 125 MHz): δ 24.4, 25.3, 33.5, 56.7, 116.8, 117.0, 121.1, 121.1, 123.5, 123.6, 124.4, 124.6, 129.7, 132.0, 132.2, 136.3, 140.7, 148.1 ppm; Anal. Calcd for C<sub>22</sub>H<sub>20</sub>ClN<sub>7</sub>O<sub>2</sub>: C, 58.73; H, 4.48; Cl, 7.88; N, 21.79. Found: C, 58.67; H, 4.40; Cl, 7.74; N, 21.68.

**N-cyclohexyl-3-(3,4-dichlorophenyl)-6-(3-nitrophenyl)-[1,2,4]triazolo[4,3-b][1,2,4]triazin-7-amine (4h):** White solid, mp 217–219 °C; IR (KBr): 3280, 2925, 2847, 1615, 1577, 1535, 1479, 1360 cm<sup>-1</sup>. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 500 MHz): δ 1.11–1.78 (m, 10H), 2.84–2.88 (m, 1H), 5.05 (s, 1H), 7.26 (d, *J* 9.5 Hz, 1H), 7.58 (d, *J* 9.5 Hz, 1H), 7.74 (t, *J* 8.0 Hz, 1H), 8.14 (d, *J* 8.0 Hz, 1H), 8.57 (s, 1H), 8.63 (d, *J* 8.0 Hz, 1H) 9.09 (d, *J* 8.0 Hz, 1H) ppm; <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 125 MHz): δ 24.5, 25.2, 33.5, 56.9, 119.0, 120.3, 120.6, 121.2, 121.3, 125.1, 127.8, 129.8, 132.0, 132.1, 132.7, 135.9, 139.0, 148.1 ppm; Anal. Calcd for C<sub>22</sub>H<sub>19</sub>Cl<sub>2</sub>N<sub>7</sub>O<sub>2</sub>: C, 54.56; H, 3.95; Cl, 14.64; N, 20.24. Found: C, 54.48; H, 3.83; Cl, 14.53; N, 20.17.

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## Supplementary Material

General information, General procedure for the preparation of products **4a-4h**, Characterization data for compounds **4a-4h**, Copies of  $^1\text{H}$  and  $^{13}\text{C}$  NMR Spectra.

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