

Facile Access to a Variety of 2,5-Biaryl-1,2,4-triazol-3-ones via Regioselective N-Arylation of Triazolones

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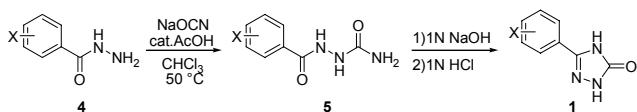
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General Considerations

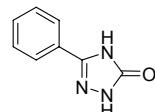
Reagents. Benzohydrazide, 4-methoxybenzoic acid, *m*-toluic acid, *p*-toluic hydrazide, *m*-anis hydrazide, methyl Iodide, sodium cyanate, K₂CO₃, Copper (I) Iodide and ligands were purchased from Aldrich. 3,4-(Methylenedioxyl)benzoic acid was purchased from TCI. 3-Iodobenzonitrile was purchased from TCI and the others aryl iodides were purchased from Aldrich. Hydrazine monohydrate was purchased from Junsei. DMF was purchased from J. T. Baker and used after distillation. Flash chromatography was performed on Silica gel 60 (70 - 230 mesh, Merck) and TLC was performed on silica gel 60 F₂₅₄ glass plate (Merck).

Analytical methods. Non-aqueous reactions were carried out in oven-dried glassware under nitrogen. ¹H NMR (500 MHz) and ¹³C NMR (125 MHz) spectra were recorded on a Varian 500 NMR spectrometer with chemical shifts reported in ppm relative to residual solvent peaks or to TMS as the internal standard. HPLC was conducted on a Hewlett Packard Series 1100 system using ZORBAX ECLIPS C₁₈ column (3 × 50 mm). Electrospray ionization (ESI) mass spectrometry (MS) experiments were performed on Agilent Technologies 6130 Quadrupole mass spectrometer at 4000 V emitter voltage. Yields refer to isolated yields of compounds greater than 95% pure as determined by ¹H NMR and HPLC analyses. All compounds were characterized by ¹H NMR and ¹³C NMR.

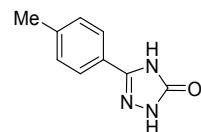
Preparation of Aryltriazolones¹



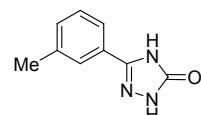
General procedure. To a suspension of 4 (1.0 equiv.) and sodiumcyanate (1.5 equiv.) in chloroform was added acetic acid and the reaction mixture was stirred at 50 °C for 14 h. The reaction mixture was cooled to room temperature and the precipitated solid (**5**) was filtered, washed with distilled water, and air dried. **5** was used for the following cyclization without further purification. A solution of **5** (1.0 equiv.) in 1.0 N NaOH (2.0 equiv.) was refluxed for 7 h. The reaction mixture was cooled to room temperature, acidified to pH 6 - 7 with 1.0 N HCl solution. The precipitated solid (**1**) was collected, washed with distilled water and dried under vacuum-oven.



5-Phenyl-2H-1,2,4-triazol-3(4H)-one (1a): Using the general procedure, benzohydrazide **4a** (5.5 g, 40.4 mmol) was reacted with sodiumcyanate (3.9 g, 60.6 mmol) to furnish the compound **5a** as a white solid (7.2 g, 99%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.13 (bs, 1H), 7.98 (s, 1H), 7.90-7.82 (m, 2H), 7.55-7.39 (m, 3H), 6.04 (s, 2H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 166.7, 159.9, 133.7, 132.1, 128.9, 128.2. **5a** (7.2 g, 40.2 mmol) was reacted in aqueous 1 N NaOH (80.5 mL) to furnish compound **1a** as a white solid (2.16 g, 33%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.01 (bs, 1H), 8.00 (s, 1H), 7.78 (dd, *J* = 7.5, 1.5 Hz, 2H), 7.51-7.40 (m, 3H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 157.1, 145.8, 130.5, 129.6, 127.8, 125.4. MS (ESI) *m/z*: 162.0 (M+H)⁺

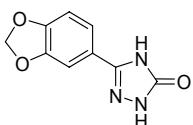


5-p-Tolyl-2H-1,2,4-triazol-3(4H)-one (1b): Using the general procedure, *p*-toluic hydrazide **4b** (3.0 g, 19.9 mmol) was reacted with sodiumcyanate (1.9 g, 29.9 mmol) to furnish the compound **5b** as a white solid (3.7 g, 95%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.99 (bs, 1H), 7.84 (s, 1H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 7.5 Hz, 2H), 6.00 (s, 2H), 2.35 (s, 3H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 166.8, 159.9, 142.2, 130.7, 129.5, 128.2, 21.7. **5b** (3.54 g, 18.3 mmol) was reacted in aqueous 1 N NaOH (36.6 mL) to furnish the compound **1b** as a white solid (1.1g, 34%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.94 (bs, 1H), 11.59 (s, 1H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 2H), 2.33 (s, 3H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 157.0, 145.8, 140.2, 130.1, 125.4, 125.1, 21.6. MS (ESI) *m/z*: 176.0 (M+H)⁺

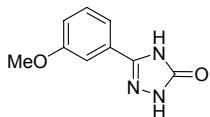


5-m-Tolyl-2H-1,2,4-triazol-3(4H)-one (1c): Using the general

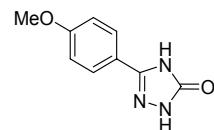
procedure, 3-methylbenzohydrazide **4c** (2.4 g, 16.2 mmol) was reacted with sodiumcyanate (1.6 g, 24.4 mmol) to furnish the compound as a white solid **5c** (2.9 g, 93%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.04 (bs, 1H), 7.87 (s, 1H), 7.70 (s, 1H), 7.65 (d, *J* = 6.5 Hz, 1H), 7.34 (d, *J* = 6.5 Hz, 2H), 6.00 (s, 2H), 2.35 (s, 3H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 171.1, 167.1, 159.8, 138.2, 133.4, 132.8, 128.9, 125.3, 21.6. **5c** (1.5 g, 7.7 mmol) was reacted in aqueous 1 N NaOH (15.4 mL) to furnish the compound **1c** as a white solid (0.7 g, 52%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.96 (bs, 1H), 11.64 (s, 1H), 7.61 (s, 1H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.35 (t, *J* = 7.3 Hz, 1H), 7.25 (d, *J* = 7.5 Hz, 1H), 2.33 (s, 3H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 157.0, 145.8, 138.9, 131.2, 129.5, 127.7, 125.9, 122.7, 21.7. MS (ESI) *m/z* : 176.0 (M+H)⁺



5-(3,4-(Methylenedioxyl)benzoyl)-2H-1,2,4-triazol-3(4H)-one (1d): Using the general procedure, 3,4-(methylenedioxyl) benzohydrazide **4d** (1.25 g, 6.9 mmol) was reacted with sodiumcyanate (0.7 g, 10.3 mmol) to furnish the compound **5d** as a white solid (1.43 g, 93%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.00 (s, 1H), 7.97 (s, 1H), 7.48 (t, *J* = 1.5, 8.0 Hz, 1H), 7.42 (d, *J* = 1.5 Hz, 1H), 7.00 (d, *J* = 8.5 Hz, 1H), 6.10 (s, 2H), 6.08 (s, 2H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 174.1, 166.1, 150.6, 147.9, 127.4, 123.4, 108.6, 102.4, 23.7. **5d** (1.42 g, 6.35 mmol) was reacted in 1 N NaOH (12.8 mL) to furnish the compound **1d** as a white solid (0.56 g, 43%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.88 (bs, 1H), 11.55 (s, 1H), 7.29-7.27 (m, 2H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.07 (s, 2H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 157.0, 149.3, 148.5, 145.5, 121.8, 119.9, 109.3, 105.5, 102.3. MS (ESI) *m/z* : 206.0 (M+H)⁺

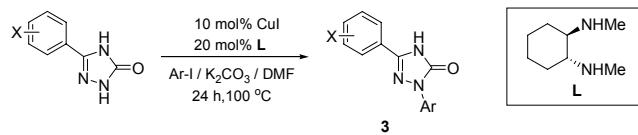


5-(3-Methoxyphenyl)-2H-1,2,4-triazol-3(4H)-one (1e): Using the general procedure, *m*-anis hydrazide **4e** (3.0 g, 18.0 mmol) was reacted with sodiumcyanate (1.7 g, 27.0 mmol) to furnish the compound **5e** as a white solid (3.5 g, 92%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.11 (bs, 1H), 7.88 (s, 1H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.44 (s, 1H), 7.38, (t, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 6.02 (s, 2H), 3.80 (s, 3H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 166.8, 159.9, 159.7, 134.8, 130.1, 120.5, 118.2, 113.3, 56.0. **5e** (3.4 g, 16.2 mmol) was reacted in aqueous 1 N NaOH (32.4 mL) to furnish the compound **1e** as a white solid (1.85 g, 60%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.01 (bs, 1H), 11.68 (s, 1H), 7.41-7.30 (m, 3H), 7.04-6.97 (m, 1H), 3.79 (s, 3H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 164.9, 161.7, 150.3, 135.5, 133.7, 122.4, 121.1, 115.4, 60.6. MS (ESI) *m/z* : 192.0 (M+H)⁺

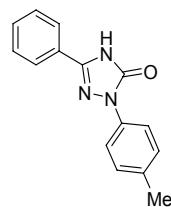


5-(4-Methoxyphenyl)-2H-1,2,4-triazol-3(4H)-one (1f): Using the general procedure, 3-methoxybenzohydrazide **4f** (1.0 g, 6.2 mmol) was reacted with sodiumcyanate (0.6 g, 9.3 mmol) to furnish the compound **5f** as a white solid (1.3 g, 99%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.98 (bs, 1H), 7.86 (d, *J* = 8.5 Hz, 2H), 7.81 (s, 1H), 7.00 (d, *J* = 8.5 Hz, 2H), 6.00 (s, 2H), 3.81 (s, 3H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 166.5, 162.5, 160.0, 130.1, 125.6, 114.2, 56.0. **5f** (1.3 g, 6.15 mmol) was reacted in aqueous 1 N NaOH (12.3 mL) to furnish the compound **1f** as a white solid (0.48 g, 40%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.88 (bs, 1H), 11.51 (s, 1H), 7.71 (d, *J* = 8.5 Hz, 2H), 7.02 (d, *J* = 8.5 Hz, 2H), 3.78 (s, 3H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 161.1, 157.1, 145.7, 128.0, 120.3, 115.0, 60.0. MS (ESI) *m/z*: 192.0 (M+H)⁺

N-Arylation of Aryltriazolones

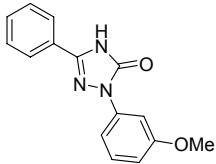


General procedure. To a suspension of aryltriazolone (0.5 mmol), CuI (9.5 mg, 0.05 mmol) and K₂CO₃ (207 mg, 1.5 mmol) in anhydrous DMF (1.0 mL) under N₂ was added aryl iodide (1.0 mmol) followed by *trans*-*N,N'*-dimethylcyclohexane-1,2-diamine (13 μ L, 0.1 mmol) and the reaction mixture was stirred at 100 °C for 24 h. The reaction mixture was cooled to room temperature, quenched with water (10 mL) and extracted with ethyl acetate (30 mL × 3). The combined organic layer was washed with water, brine, dried over MgSO₄, and the solvent was evaporated under vacuum. The crude product was recrystallized from ethyl acetate or purified by flash column chromatography (*n*-hexane : ethyl acetate).

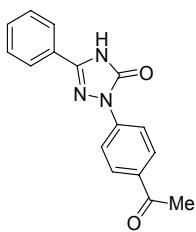


5-Phenyl-2-p-tolyl-2H-1,2,4-triazol-3(4H)-one (3a): Using the general procedure, **1a** (81 mg, 0.5 mmol) was reacted with 4-iodotoluene (218 mg, 1.0 mmol). Purification of the crude product by flash column chromatography (*n*-hexane : ethyl acetate = 3 : 7 to 1 : 1) afforded **3a** as a white solid (118 mg, 94%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.64 (bs, 1H), 7.95-7.89 (m, 2H), 7.87 (d, *J* = 8.5 Hz, 2H), 7.58-7.48 (m, 3H), 7.27 (d, *J* = 8.0 Hz, 2H), 2.33 (s, 3H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 153.6, 145.3, 136.2, 134.8, 131.2, 130.1, 129.8,

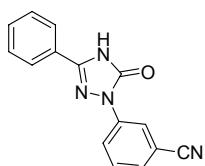
126.9, 125.9, 118.8, 21.2 . MS (ESI) m/z : 252.0 ($M+H$)⁺



2-(3-Methoxyphenyl)-5-phenyl-2H-1,2,4-triazol-3(4H)-one (3b): Using the general procedure, **1a** (81 mg, 0.5 mmol) was reacted with 3-iodoanisole (119 μ L, 1.0 mmol). Recrystallization of the crude product from ethyl acetate and the flash column chromatography (*n*-hexane : ethyl acetate = 3 : 7 to 1 : 1) of the mother liquid afforded **3b** as a white solid (122 mg, 91%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.70 (bs, 1H), 7.96-7.90 (m, 2H), 7.65-7.58 (m, 2H), 7.58-7.51 (m, 1H), 7.38 (t, *J* = 8.0 Hz, 1H), 6.82 (dd, *J* = 1.5, 8.0 Hz, 1H), 3.81 (s, 3H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 160.4, 153.6, 145.4, 139.6, 131.4, 130.7, 129.8, 126.8, 126.0, 111.1, 110.9, 104.4, 55.9. MS (ESI) m/z : 268.0 ($M+H$)⁺

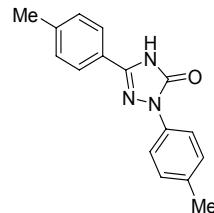


2-(4-Acetylphenyl)-5-phenyl-2H-1,2,4-triazol-3(4H)-one (3c): Using the general procedure, **1a** (81 mg, 0.5 mmol) was reacted with 4-iodoacetophenone (246 mg, 1.0 mmol). Recrystallization of the crude product from ethyl acetate and the flash column chromatography (*n*-hexane : ethyl acetate = 3 : 7 to 1 : 1) of the mother liquid afforded **3c** as a yellow solid (139 mg, 99%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.80 (bs, 1H), 8.18 (d, *J* = 7.5 Hz, 2H), 8.09 (d, *J* = 8.5 Hz, 2H), 8.01-7.90 (m, 2H), 7.62-7.52 (m, 3H), 2.59 (s, 3H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 197.4, 153.9, 146.5, 142.2, 133.6, 131.6, 130.3, 129.8, 126.7, 126.2, 117.8, 27.3. MS (ESI) m/z : 280.0 ($M+H$)⁺

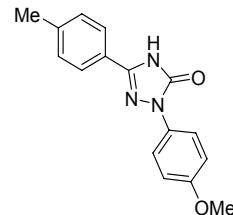


3-(5-Oxo-3-phenyl-4,5-dihydro-1,2,4-triazol-1-yl)benzonitrile (3d): Using the general procedure, **1a** (81 mg, 0.5 mmol) was reacted with 3-iodobenzonitrile (229 mg, 1.0 mmol). Recrystallization of the crude product from ethyl acetate and the flash column chromatography (*n*-hexane : ethyl acetate = 3 : 7 to 1 : 1) of the mother liquid afforded **3d** as a white solid (129.9

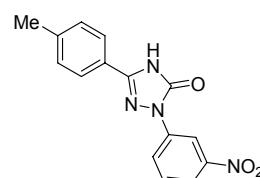
mg, 99%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.86 (bs, 1H), 8.40 (s, 1H), 8.33 (td, *J* = 2.0, 4.5 Hz, 1H), 7.99-7.92 (m, 2H), 7.71 (d, *J* = 5.0 Hz, 2H), 7.60-7.53 (m, 3H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 153.6, 146.3, 139.0, 131.6, 131.3, 129.7, 128.9, 126.5, 126.2, 122.7, 121.1, 119.1, 112.6. MS (ESI) m/z : 263.0 ($M+H$)⁺



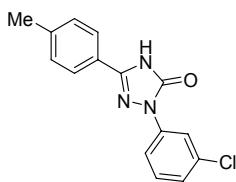
2,5-Di-p-tolyl-2H-1,2,4-triazol-3(4H)-one (3e): Using the general procedure, **1b** (88 mg, 0.5 mmol) was reacted with 4-iodotoluene (218 mg, 1.0 mmol). Purification of the crude product by flash column chromatography (*n*-hexane : ethyl acetate = 3 : 7 to 1 : 1) afforded **3e** as a white solid (132 mg, 99%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.60 (bs, 1H), 7.87 (d, *J* = 8.5 Hz, 2H), 7.80 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 2H), 2.37 (s, 3H), 2.33 (s, 3H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 153.6, 145.5, 141.1, 136.2, 134.6, 130.3, 130.1, 125.9, 124.2, 118.7, 21.7, 21.2. MS (ESI) m/z : 266.0 ($M+H$)⁺



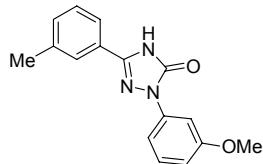
2-(4-Methoxyphenyl)-5-p-tolyl-2H-1,2,4-triazol-3(4H)-one (3f): Using the general procedure, **1b** (88 mg, 0.5 mmol) was reacted with 4-iodoanisole (234 mg, 1.0 mmol). Recrystallization of the crude product from ethyl acetate and the flash column chromatography (*n*-hexane : ethyl acetate = 3 : 7 to 1 : 1) of the mother liquid afforded **3f** as a pale yellow solid (113 mg, 81%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.53 (bs, 1H), 7.86 (d, *J* = 8.5 Hz, 2H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 7.5 Hz, 2H), 7.36 (d, *J* = 9.5 Hz, 2H), 3.79 (s, 3H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 157.2, 153.5, 145.2, 141.0, 131.8, 130.3, 125.8, 124.2, 120.6, 114.8, 56.0, 21.7. MS (ESI) m/z : 282.0 ($M+H$)⁺



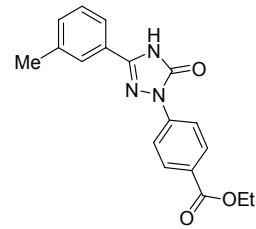
2-(3-Nitrophenyl)-5-p-tolyl-2*H*-1,2,4-triazol-3(4*H*)-one (3g**):** Using the general procedure, **1b** (88 mg, 0.5 mmol) was reacted with 1-iodo-3-nitrobenzene (249 mg, 1.0 mmol). Recrystallization of the crude product from ethyl acetate and the flash column chromatography (*n*-hexane : ethyl acetate = 3 : 7 to 1 : 1) of the mother liquid afforded **3g** as a white solid (147 mg, 99%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.80 (bs, 1H), 8.84 (s, 1H), 8.39 (td, *J* = 0.75, 8.3 Hz, 1H), 8.05 (td, *J* = 1.0, 8.5 Hz, 1H), 7.81 (d, *J* = 7.5 Hz, 2H), 7.75 (t, *J* = 8.3 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 2.36 (s, 3H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 153.8, 148.8, 146.6, 141.6, 139.3, 131.4, 130.4, 126.1, 124.1, 123.7, 119.8, 112.4, 21.7. MS (ESI) *m/z* : 297.0 (M+H)⁺



1-(3-Chlorophenyl)-3-p-tolyl-1*H*-1,2,4-triazol-5(4*H*)-one (3h**):** Using the general procedure, **1b** (88 mg, 0.5 mmol) was reacted with 3-chloroiodobenzene (124 μL, 1.0 mmol). Recrystallization of the crude product from ethyl acetate and the flash column chromatography (*n*-hexane : ethyl acetate = 3 : 7 to 1 : 1) of the mother liquid afforded **3h** as a white solid (139 mg, 97%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.71 (bs, 1H), 8.09 (s, 1H), 7.97 (d, *J* = 8.0, 1H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 7.5 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 1H), 2.38 (s, 3H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 153.7, 146.1, 141.4, 139.7, 134.1, 131.5, 130.3, 126.1, 125.1, 123.9, 117.8, 116.8, 21.7. MS (ESI) *m/z* : 287.0 (M+H)⁺



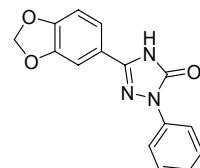
2-(3-Methoxyphenyl)-5-m-tolyl-2*H*-1,2,4-triazol-3(4*H*)-one (3i**):** Using the general procedure, **1c** (88 mg, 0.5 mmol) was reacted with 3-iodoanisole (119 μL, 1.0 mmol). Recrystallization of the crude product from ethyl acetate and the flash column chromatography (*n*-hexane : ethyl acetate = 3 : 7 to 1 : 1) of the mother liquid afforded **3i** as a white solid (108 mg, 77%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.62 (bs, 1H), 7.77 (s, 1H), 7.71 (d, *J* = 7.5 Hz, 1H), 7.62 (s, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 7.3 Hz, 1H), 7.39-7.38 (m, 2H), 6.82 (d, *J* = 8.0 Hz, 1H), 3.81 (s, 3H), 2.39 (s, 3H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 160.4, 153.6, 145.5, 139.6, 139.1, 132.0, 130.7, 129.7, 126.7, 126.4, 123.3, 111.1, 110.9, 104.4, 55.9, 21.7. MS (ESI) *m/z* : 282.0 (M+H)⁺



Ethyl 4-(5-oxo-3-m-tolyl-4,5-dihydro-1,2,4-triazol-1-yl)benzoate (3j**):** Using the general procedure, **1c** (88 mg, 0.5 mmol) was reacted with ethyl-4-iodobenzoate (167 μL, 1.0 mmol). Recrystallization of the crude product from ethyl acetate and the flash column chromatography (*n*-hexane : ethyl acetate = 3 : 7 to 1 : 1) of the mother liquid afforded **3j** as a white solid (169 mg, 92%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.64 (bs, 1H), 8.17 (d, *J* = 9.0 Hz, 2H), 8.26 (d, *J* = 8.5 Hz, 2H), 7.77 (d, 1H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 7.5 Hz, 1H), 4.30 (q, *J* = 7.0 Hz, 1H), 2.37 (s, 3H), 1.31 (t, *J* = 7.0 Hz, 3H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 166.0, 155.2, 148.0, 142.6, 139.0, 131.9, 131.0, 129.6, 127.5, 126.6, 125.9, 123.4, 117.7, 61.3, 21.7, 14.9. MS (ESI) *m/z* : 324.0 (M+H)⁺

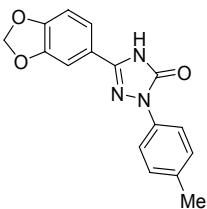


3-(5-Oxo-3-m-tolyl-4,5-dihydro-1,2,4-triazol-1-yl)benzonitrile (3k**):** Using the general procedure, **1c** (88 mg, 0.5 mmol) was reacted with 3-iodobenzonitrile (229 mg, 1.0 mmol). Recrystallization of the crude product from ethyl acetate and the flash column chromatography (*n*-hexane : ethyl acetate = 3 : 7 to 1 : 1) of the mother liquid afforded **3k** as a white solid (138 mg, 99%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.74 (bs, 1H), 8.4 (s, 1H), 8.35-8.29 (m, 1H), 7.81 (s, 1H), 7.78-7.78 (m, 3H), 7.44 (t, *J* = 7.3 Hz, 1H), 7.37 (d, *J* = 7.5 Hz, 1H), 2.39 (s, 3H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 153.8, 146.4, 139.1, 132.2, 131.3, 129.6, 128.8, 126.5, 123.3, 122.8, 121.1, 119.1, 112.6, 21.6. MS (ESI) *m/z* : 277.0 (M+H)⁺

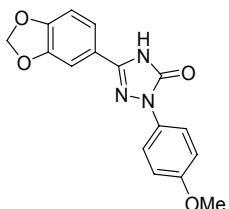


5-((3,4-(Methylenedioxy)benzoyl)-2-phenyl-2*H*-1,2,4-triazol-3(4*H*)-one (3l**):** Using the general procedure, **1d** (103 mg, 0.5 mmol) was reacted with phenyl iodide (112 μL, 1.0 mmol). Recrystallization of the crude product from ethyl acetate and the flash column chromatography (*n*-hexane : ethyl acetate = 3 : 7 to 1 : 1) of the mother liquid afforded **3l** as a white solid

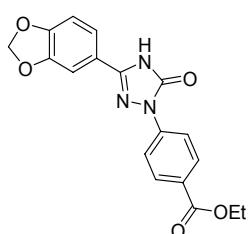
(140 mg, 99%). ^1H NMR (500 MHz, DMSO- d_6) δ 12.51 (bs, 1H), 7.97 (d, J = 8.5 Hz, 2H), 7.46–7.42 (m, 4H), 7.21 (t, J = 7.5 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H), 6.11 (s, 2H). ^{13}C NMR (125 MHz, DMSO- d_6) δ 153.6, 150.0, 148.6, 145.3, 138.5, 129.7, 125.5, 120.7, 118.6, 109.5, 105.9, 102.5. MS (ESI) m/z : 282.0 (M+H) $^+$



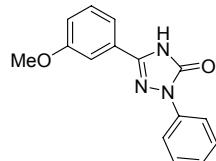
5-((3,4-(Methylenedioxyl)benzoyl)-2-p-tolyl-2H-1,2,4-triazol-3(4H)-one (3m): Using the general procedure, **1d** (103 mg, 0.5 mmol) was reacted with 4-iodotoluene (218 mg, 1.0 mmol). Purification of the crude product by flash column chromatography (*n*-hexane : ethyl acetate = 3 : 7 to 1 : 1) afforded **3m** as a white solid (136 mg, 92%). ^1H NMR (500 MHz, DMSO- d_6) δ 12.47 (bs, 1H), 7.85 (d, J = 8.5 Hz, 2H), 7.42 (m, 2H), 7.25 (d, J = 8.5 Hz, 2H), 7.07 (d, J = 8.0 Hz, 1H), 6.11 (s, 2H), 2.31 (s, 3H). ^{13}C NMR (125 MHz, DMSO- d_6) δ 153.5, 149.9, 148.6, 145.1, 136.2, 134.6, 130.1, 120.8, 120.6, 118.6, 109.5, 105.9, 102.5, 21.2. MS (ESI) m/z : 296.0 (M+H) $^+$



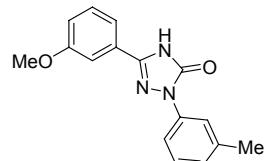
5-((3,4-(Methylenedioxyl)benzoyl)-2-(4-methoxyphenyl)-2H-1,2,4-triazol-3(4H)-one (3n): Using the general procedure, **1d** (103 mg, 0.5 mmol) was reacted with 4-iodoanisole (234 mg, 1.0 mmol). Recrystallization of the crude product from ethyl acetate and the flash column chromatography (*n*-hexane : ethyl acetate = 3 : 7 to 1 : 1) of the mother liquid afforded **3n** as a white solid (105 mg, 68%). ^1H NMR (500 MHz, DMSO- d_6) δ 12.46 (bs, 1H), 7.84 (d, J = 9.0 Hz, 2H), 7.41 (d, J = 8.0 Hz, 1H), 7.40 (s, 1H), 7.07 (d, J = 8.0 Hz, 1H), 7.02 (d, J = 9.0 Hz, 2H), 6.11 (s, 2H), 3.77 (s, 3H). ^{13}C NMR (125 MHz, DMSO- d_6) δ 161.9, 158.2, 154.6, 153.4, 149.7, 136.6, 125.6, 125.3, 119.5, 114.2, 110.6, 107.2, 60.7. MS (ESI) m/z : 312.0 (M+H) $^+$



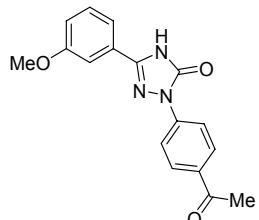
Ethyl 4-(3,4-(Methylenedioxyl)benzoyl)-5-oxo-4,5-dihydro-1,2,4-triazol-1-ylbenzoate (3o): Using the general procedure, **1d** (103 mg, 0.5 mmol) was reacted with ethyl-4-iodobenzoate (167 μL , 1.0 mmol). Recrystallization of the crude product from ethyl acetate and the flash column chromatography (*n*-hexane : ethyl acetate = 3 : 7 to 1 : 1) of the mother liquid afforded **3o** as a white solid (158 mg, 89%). ^1H NMR (500 MHz, DMSO- d_6) δ 12.66 (bs, 1H), 8.14 (d, J = 9.0 Hz, 2H), 8.04 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.0 Hz, 1H), 7.42 (s, 1H), 7.08 (d, J = 8.5 Hz, 1H), 6.13 (s, 2H), 4.31 (q, J = 7.0 Hz, 2H), 1.33 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, DMSO- d_6) δ 165.9, 153.6, 150.2, 148.7, 146.1, 142.2, 131.0, 126.2, 121.0, 120.4, 117.7, 109.5, 106.0, 102.6, 61.4, 14.9. MS (ESI) m/z : 354.0 (M+H) $^+$



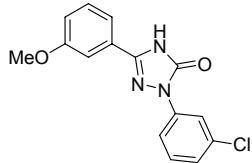
5-(3-Methoxyphenyl)-2-phenyl-2H-1,2,4-triazol-3(4H)-one (3p): Using the general procedure, **1e** (96 mg, 0.5 mmol) was reacted with phenyl iodide (112 μL , 1.0 mmol). Purification of the crude product by recrystallization and flash column chromatography (*n*-hexane : ethyl acetate = 3 : 7 to 1 : 1) afforded **3p** as a white solid (123.8 mg, 93%). ^1H NMR (500 MHz, DMSO- d_6) δ 12.64 (bs, 1H), 7.99 (d, J = 8.0 Hz, 2H), 7.51–7.41 (m, 5H), 7.23 (t, J = 7.3 Hz, 1H), 7.09 (d, J = 8.5 Hz, 1H), 3.82 (s, 1H). ^{13}C NMR (125 MHz, DMSO- d_6) δ 160.3, 153.8, 145.6, 138.5, 131.0, 129.7, 128.2, 125.6, 118.7, 118.2, 117.1, 111.2, 56.0. MS (ESI) m/z : 268.0 (M+H) $^+$



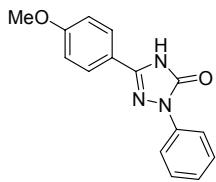
5-(3-Methoxyphenyl)-2-m-tolyl-2H-1,2,4-triazol-3(4H)-one (3q): Using the general procedure, **4e** (96 mg, 0.5 mmol) was reacted with 3-iodotoluene (128.0 μL , 1.0 mmol). Purification of the crude product by flash column chromatography (*n*-hexane : ethyl acetate = 3 : 7 to 1 : 1) afforded **3q** as a pale yellow solid (130 mg, 89%). ^1H NMR (500 MHz, DMSO- d_6) δ 12.67 (bs, 1H), 7.84 (s, 1H), 7.80 (d, J = 8.5 Hz, 1H), 7.52 (d, J = 7.5 Hz, 1H), 7.47 (d, J = 3.0 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H), 7.10 (d, J = 8.0 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 3.84 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (125 MHz, DMSO- d_6) δ 160.3, 153.7, 145.4, 139.1, 138.5, 131.0, 129.5, 128.2, 126.3, 119.2, 118.2, 117.1, 115.9, 111.2, 56.0, 21.9. MS (ESI) m/z : 282.0 (M+H) $^+$



2-(4-Acetylphenyl)-5-(3-methoxyphenyl)-2*H*-1,2,4-triazol-3(4*H*)-one (3r**):** Using the general procedure, **1e** (96 mg, 0.5 mmol) was reacted with 4-iodoacetophenone (246 mg, 1.0 mmol). Purification of the crude product by recrystallization and flash column chromatography (*n*-hexane : ethyl acetate = 3 : 7 to 1 : 1) afforded **3s** as a white solid (154 mg, 99%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.78 (bs, 1H), 8.15 (d, *J* = 8.5 Hz, 2H), 8.06 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 6.0 Hz, 1H), 7.47 (s, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 3.83 (s, 3H), 2.57 (s, 3H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 197.4, 160.3, 153.8, 146.3, 142.1, 133.6, 131.0, 130.3, 127.8, 118.4, 117.8, 117.4, 111.4, 56.1, 27.3. MS (ESI) *m/z* : 310.0 (M+H)⁺

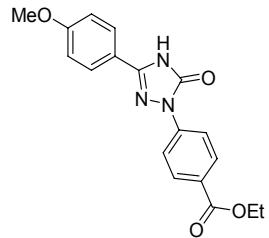


2-(3-Chlorophenyl)-5-(3-methoxyphenyl)-2*H*-1,2,4-triazol-3(4*H*)-one (3s**):** Using the general procedure, **1e** (96 mg, 0.5 mmol) was reacted with 3-chloroiodobenzene (124 μL, 1.0 mmol). Recrystallization of the crude product from ethyl acetate and the flash column chromatography (*n*-hexane : ethyl acetate = 3 : 7 to 1 : 1) of the mother liquid afforded **3t** as a white solid (151 mg, 99%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.78 (bs, 1H), 8.10 (s, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.53-7.46, (m, 4H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 3.84 (s, 1H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 160.3, 153.6, 145.9, 139.7, 134.2, 131.5, 131.0, 127.8, 125.2, 118.3, 118.0, 117.4, 116.9, 111.3, 56.1. MS (ESI) *m/z* : 301.9 (M+H)⁺



5-(4-Methoxyphenyl)-2-phenyl-2*H*-1,2,4-triazol-3(4*H*)-one

(3t): Using the general procedure, **1f** (96 mg, 0.5 mmol) was reacted with phenyl iodide (111.5 μL, 1.0 mmol). Recrystallization of the crude product from ethyl acetate and the flash column chromatography (*n*-hexane : ethyl acetate = 3 : 7 to 1 : 1) of the mother liquid afforded **3u** as a white solid (123.8 mg, 93%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.55 (bs, 1H), 7.98 (d, *J* = 8.0 Hz, 2H), 7.85 (d, *J* = 8.5 Hz, 2H), 7.46 (t, *J* = 8.0 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.10 (d, *J* = 9.0 Hz, 2H), 3.82 (d, 3H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 161.7, 153.7, 145.6, 138.6, 129.7, 127.7, 125.4, 119.3, 118.6, 115.2, 56.1, 40.8. MS (ESI) *m/z* : 268.0 (M+H)⁺



Ethyl 4-(3-(4-methoxyphenyl)-5-oxo-4,5-dihydro-1,2,4-triazol-1-yl)benzoate (3u**):** Using the general procedure, **1f** (96 mg, 0.5 mmol) was reacted with ethyl-4-iodobenzoate (166.7 μL, 1.0 mmol). Recrystallization of the crude product from ethyl acetate and the flash column chromatography (*n*-hexane : ethyl acetate = 3 : 7 to 1 : 1) of the mother liquid afforded **3v** as a white solid (133.1 mg, 79%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.66 (bs, 1H), 8.16 (d, *J* = 8.5 Hz, 2H), 8.04 (d, *J* = 8.5 Hz, 2H), 7.87 (d, *J* = 8.5 Hz, 2H), 7.10 (d, *J* = 8.5 Hz, 2H), 4.31 (q, *J* = 7.0 Hz, 2H), 3.83 (s, 3H), 1.33 (t, *J* = 7.0 Hz, 3H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 166.0, 161.8, 154.5, 147.0, 142.5, 131.1, 127.9, 125.9, 119.4, 117.7, 115.2, 61.3, 56.1, 14.9. MS (ESI) *m/z* : 340.0 (M+H)⁺

References

1. Mazzone, G.; Puglisi, G.; Corsaro, A.; Panico, A.; Bonina, F.; Amico-Roxas, M.; Caruso, A.; Trombadore, S. *Eur. J. Med. Chem.* **1986**, 21, 277.