Supporting Information

One-flask synthesis of 1,3,5-trisubstituted 1,2,4-triazoles from nitriles and hydrazonoyl chlorides via 1,3-dipolar cycloaddition†

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<u>Table of Contents:</u> <u>Page</u>

Experimental Section

All chemicals were reagent grade and used as purchased. All reactions were carried out under argon or nitrogen atmosphere and monitored by TLC. Flash column chromatography was carried out on silica gel (230–400 mesh). Analytical thin-layer chromatography (TLC) was performed on precoated plates (silica gel 60 F-254) purchased from Merck Inc. Mixtures of ethyl acetate and hexanes were used as eluants. Infrared (IR) spectra were measured on a Bomem Michelson Series FT-IR spectrometer. The wavenumbers reported are referenced to the polystyrene absorption at 1601 cm^{-1}. Absorption intensities are recorded by the following abbreviations: s, strong; m, medium; w, weak. Proton NMR spectra were obtained on a Bruker (200 MHz or 500 MHz) spectrometer by use of $CDCl_3$ as solvent. Carbon-13 NMR spectra were obtained on a Bruker (50 MHz or 125 MHz) spectrometer by used of $CDCl_3$ as solvent. Carbon-13 chemical shifts are referenced to the center of the $CDCl_3$ triplet (δ 77.0 ppm). Multiplicities are recorded by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; *J*, coupling constant (Hz). ESI-MS spectra were obtained from an Applied Biosystems API 300 mass spectrometer. High-resolution mass spectra were obtained from a JEOL JMS-HX110 mass spectrometer. Elemental analyses were carried out on a Heraeus CHN–O RAPID element analyzer.

Standard Procedure for the One-Flask Synthesis of 1,3,5-Trisubstituted 1,2,4-Triazoles 4a–s and 8a–b. Nitriles **5a**–**i** (1.0 mmol, 1.0 equiv) was mixed with ethanol (1.0 mL) and dichloromethane (2.0 mL). The solution was slowly saturated with HCl(g) in a rate of ~1 bubble/min for 6.0 h.[1] After the corresponding imidate ethyl ester hydrochloride was formed, the reaction mixture was concentrated under reduced pressure. The residue was added with a toluene solution containing hydrazonoyl hydrochlorides (**3a**–**i** or **7a**–**b**, 1.0 mmol, 1.0 equiv) and triethylamine (3.0 mmol, 3.0

equiv), and heated at reflux for 5.0 h. The reaction mixture was concentrated, added with water (10 mL), and extracted with CH_2Cl_2 (3 × 30 mL). The organic layer was washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give the corresponding 1,3,5-trisubstituted 1,2,4-triazoles **4a**–**s** and **8a**–**b** in 56–98% yields. The spectroscopic data of compounds **4a**–**c**, **4e**–**h**, and **4s** were consistent with our previously reported.[2]

1-(4-Methylphenyl)-3-methoxycarbonyl-5-methyl-1,2,4-triazole (4d). Yield: 56%; yellow liquid; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.41 (s, 3 H, CH_3), 2.52 (s, 3 H, CH_3), 3.98 (s, 3 H, CH_3), 7.29 (d, 2 H, J = 8.5 Hz, ArH), 7.32 (d, 2 H, J = 8.5 Hz, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.08, 21.17, 52.69, 124.69 (2 × CH), 130.03 (2 × CH), 134.22, 139.83, 153.36, 154.03, 160.38; IR (diffuse reflectance) 3441 (m), 2924 (m), 2353 (m), 1735 (s, C=O), 1666 (m), 1381 (m), 1219 (m), 1141 (m), 1026 (m), 825 (m) cm^{-1}; MS (ESI) m/z 232 (M + H)$^+$; Anal. Calcd for $C_{12}H_{13}N_3O_2$; C: 62.33; H: 5.67; N: 18.17, Found: C: 62.32; H: 5.69; N: 18.19.

1-(4-Chlorophenyl)-3-methoxycarbonyl-5-ethyl-1,2,4-triazole (4i). Yield: 93%; brown solids; mp 101–102 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.28 (t, 3 H, J = 7.5 Hz, CH_3), 2.80 (q, 2 H, J = 7.5 Hz, CH_2), 3.92 (s, 3 H , CH_3), 7.39 (d, 2 H, J = 8.5 Hz, ArH), 7.45 (d, 2 H, J = 8.5 Hz, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.30, 19.58, 52.12, 125.86 (2 × CH), 129.17 (2 × CH), 134.56, 134.98, 153.25, 158.45, 159.65; IR (diffuse reflectance) 3456 (m), 2985 (m), 1735 (s, C=O), 1635 (m), 1496 (m), 1219 (m), 1141 (m), 1010 (m), 840 (m), 732 (m) cm^{-1}; ESI-MS m/z 265 (M + H)$^+$; Anal. Calcd for $C_{12}H_{12}Cl\ N_3O_2$; C: 54.25; H: 4.55; N: 15.82, Found: C: 54.28; H: 4.52; N: 15.83.

1-(4-Chlorophenyl)-3-methoxycarbonyl-5-isopropyl-1,2,4-triazole (4j). Yield: 98%; yellow liquid; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.30 (d, 6 H, J = 7.0 Hz), 3.09

(septet, 1 H, $J = 7.0$ Hz, CH), 3.95 (s, 3 H , CH_3), 7.36 (d, 2 H, $J = 8.5$ Hz, ArH), 7.47 (d, 2 H, $J = 8.5$ Hz, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.06 (2 × CH), 25.70, 52.44, 126.64 (2 × CH), 129.49 (2 × CH), 134.84, 135.55, 153.67, 160.02, 162.76; IR (diffuse reflectance) 3448 (m), 2978 (m), 1743 (s, C=O), 1635 (m), 1496 (m), 1373 (m), 1219 (m), 1010 (m), 840 (m), 748 (m) cm^{-1}; ESI-MS *m*/*z* 279 (M + H)$^+$; Anal. Calcd for $C_{13}H_{14}Cl\ N_3O_2$; C: 55.82; H: 5.04; N: 15.02, Found: C: 55.81; H: 5.06; N: 15.03.

1-(4-Chlorophenyl)-3-methoxycarbonyl-5-*n*-butyl-1,2,4-triazole (4k). Yield: 76%; brown liquid; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.85 (t, 3 H, $J = 7.0$ Hz, CH_3), 1.22–1.32 (m, 2 H, CH_2), 1.71–1.74 (m, 2 H, CH_2), 2.78 (t, 2 H, $J = 8.0$ Hz, CH_2), 3.99 (s, 3 H, CH_3), 7.38 (d, 2 H, $J = 7.5$ Hz, ArH), 7.49 (d, 2 H, $J = 7.5$ Hz, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.53, 22.25, 26.25, 29.72, 52.82, 126.57 (2 × CH), 129.78 (2 × CH), 135.17, 135.81, 154.00, 158.26, 160.30; IR (diffuse reflectance) 3448 (m), 2353 (m), 1735 (s, C=O), 1635 (m), 1489 (m), 1404 (m), 1219 (m), 1141 (m), 956 (m), 833 (m), 732 (m) cm^{-1}; ESI-MS *m*/*z* 293 (M + H)$^+$; Anal. Calcd for $C_{14}H_{16}Cl\ N_3O_2$; C: 57.27; H: 5.49; N: 14.30, Found: C: 57.29; H: 5.50; N: 14.31.

1-(4-Chlorophenyl)-3-methoxycarbonyl-5-cyclopentyl-1,2,4-triazole (4l). Yield: 57%; brown liquid; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.58–1.61 (m, 2 H), 1.87–1.88 (m, 2 H), 1.97–1.99 (m, 4 H), 3.07 (quintet, 1 H, $J = 8.5$ Hz, CH), 3.99 (s, 3 H, CH_3), 7.38 (d, 2 H, $J = 8.5$ Hz, ArH), 7.49 (d, 2 H, $J = 8.5$ Hz, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.73 (2 × CH), 32.98 (2 × CH), 36.38, 52.83, 126.98 (2 × CH), 129.76 (2 × CH), 135.31, 135.88, 154.04, 160.46, 162.31; IR (diffuse reflectance) 3053 (m), 2920 (m), 1739 (s, C=O), 1500 (m), 1481 (m), 1217 (m), 1134 (m), 1091 (m), 1012 (m), 837 (m) cm^{-1}; ESI-MS *m*/*z* 305 (M + H)$^+$; Anal. Calcd for $C_{15}H_{16}ClN_3O_2$; C: 58.92; H: 5.27; N: 13.74, Found: C: 58.91; H: 5.25; N: 13.75.

1-(4-Chlorophenyl)-3-methoxycarbonyl-5-phenyl-1,2,4-triazole (4m). Yield: 86%;

yellow solids; mp 139–140 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.00 (s, 3 H, CH_3), 7.24–7.50 (m, 9 H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.83, 126.41 (2 × CH), 126.62, 128.67 (2 × CH), 129.01 (2 × CH), 129.66 (2 × CH), 130.75, 135.52, 135.95, 154.34, 155.62, 160.12; IR (diffuse reflectance) 3448 (m), 2916 (m), 1743 (s, C=O), 1635 (m), 1496 (m), 1465 (m), 1219 (m), 1172 (m), 987 (m), 840 (m), 694 (m) cm^{-1}; ESI-MS *m/z* 313 $(M + H)^+$; Anal. Calcd for $C_{16}H_{12}ClN_3O_2$; C: 61.25; H: 3.86; N: 13.39, Found: C: 61.23; H: 3.89; N: 13.42.

1-(4-Chlorophenyl)-3-methoxycarbonyl-5-(2-furyl)-1,2,4-triazole (4n). Yield: 61%; yellow solids; mp 175–176 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.99 (s, 3 H, CH_3), 6.45 (q, 1 H, J = 1.5 Hz, furyl–H), 6.85 (d, 1 H, J = 3.5 Hz, furyl–H), 7.38–7.40 (m, 3 H, ArH), 7.46 (d, 2 H, J = 9.0 Hz, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.91, 111.93, 114.52, 127.25 (2 × CH), 129.47 (2 × CH), 135.82, 136.08, 141.25, 144.99, 147.62, 154.52, 159.91; IR (diffuse reflectance) 3448 (m), 2954 (m), 1743 (s, C=O), 1635 (m), 1496 (m), 1396 (m), 1226 (m), 1018 (m), 848 (m), 763 (m) cm^{-1}; ESI-MS *m/z* 304 $(M + H)^+$; Anal. Calcd for $C_{14}H_{10}Cl\,N_3O_3$; C: 55.37; H: 3.32; N: 13.84, Found: C: 55.35; H: 3.35; N: 13.87.

1-(4-Chlorophenyl)-3-methoxycarbonyl-5-(2-thienyl)-1,2,4-triazole (4o). Yield: 82%; brown solids; mp 139–140 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.01 (s, 3 H, CH_3), 6.98 (dd, 1 H, J = 4.0 Hz, 4.5 Hz, thienyl–H), 7.20 (d, 1 H, J = 4.0 Hz, thienyl–H), 7.42 (d, 1 H, J = 4.5 Hz, thienyl–H), 7.42 (d, 2 H, J = 8.5 Hz, ArH), 7.49 (d, 2 H, J = 8.5 Hz, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.91, 127.67, 127.77, 127.96 (2 × CH), 129.98 (3 × CH), 130.24, 135.54, 136.70, 151.35, 154.37, 160.04; IR (diffuse reflectance) 3448 (m), 2954 (m), 1736 (s, C=O), 1635 (m), 1558 (m), 1404 (m), 1219 (m), 1165 (m), 956 (m), 840 (m), 732 (m) cm^{-1}; ESI-MS *m/z* 319 $(M + H)^+$; Anal. Calcd for $C_{14}H_{10}ClN_3O_2S$; C: 52.59; H: 3.15; N: 13.14, Found: C: 52.56; H: 3.17; N: 13.14.

1-(4-Chlorophenyl)-3-methoxycarbonyl-5-(2-pyrrolyl)-1,2,4-triazole (4p). Yield: 56%; brown solids; mp 200–201 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.02 (s, 3 H, CH_3), 5.87–5.88 (m, 1 H, ArH), 6.11–6.12 (m, 1 H, ArH), 6.92–6.93 (m, 1 H, ArH), 7.46 (d, 2 H, J = 9.0 Hz, ArH), 7.52 (d, 2 H, J = 9.0 Hz, ArH), 9.61 (br, 1 H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.96, 110.52, 111.51, 118.12, 121.90, 127.95 (2 × CH), 129.98 (2 × CH), 135.91, 136.57, 150.15, 153.88, 160.33; IR (diffuse reflectance) 3261 (m), 2954 (m), 1737 (s, C=O), 1598 (m), 1498 (m), 1390 (m), 1220 (s), 1087 (m), 1004 (m), 914 (m) cm^{-1}; ESI-MS m/z 302 $(M + H)^+$; Anal. Calcd for $C_{14}H_{11}ClN_4O_2$; C: 55.55; H: 3.66; N: 18.51, Found: C: 55.54; H: 3.68; N: 18.52.

1-(2-Trifluorophenyl)-3-methoxycarbonyl-5-(2-pyrrolyl)-1,2,4-triazole (4q). Yield: 43%; brown solids; mp 90–91 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.97 (s, 3 H, CH_3), 5.40–5.43 (m, 1 H, ArH), 6.01–6.03 (m, 1 H, ArH), 6.88–6.89 (m, 1 H, ArH), 7.48–7.50 (m, 1 H, ArH), 7.73–7.75 (m, 2 H, ArH), 7.88–7.90 (m, 1 H, ArH), 9.99 (br, 1 H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.80, 110.36, 111.21, 117.95, 122.03, 127.90, 127.92, 127.93 (CF_3), 128.18 (CF_3), 128.43 (CF_3), 128.69 (CF_3), 130.27, 131.36, 133.38, 134.90, 151.48, 153.75, 160.20; IR (diffuse reflectance) 2360 (m), 1743 (s, C=O), 1604 (m), 1496 (m), 1388 (m), 1319 (s), 1226 (m), 1180 (m), 1033 (m) cm^{-1}; ESI-MS m/z 336 $(M + H)^+$; Anal. Calcd for $C_{15}H_{11}F_3N_4O_2$; C: 53.58; H: 3.30; N: 16.66, Found: C: 53.61; H: 3.31; N: 16.63.

1-(3-Trifluorophenyl)-3-methoxycarbonyl-5-(2-pyrrolyl)-1,2,4-triazole (4r). Yield: 44%; brown solid; mp 159–160 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.00 (s, 3 H, CH_3), 5.83–5.84 (m, 1 H), 6.09–6.10 (m, 1 H), 6.93–6.93 (m, 1 H), 7.68 (t, 1 H, J = 8.0 Hz, ArH), 7.74 (d, 1 H, J = 8.0 Hz, ArH), 7.83 (d, 1 H, J = 7.5 Hz, ArH), 7.84 (s, 1 H, ArH), 9.98 (br, 1 H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.93, 110.48, 111.47, 117.75, 122.26, 123.79, 123.82, 127.13, 129.88, 130.34, 132.03 (CF_3), 132.30 (CF_3), 132.57 (CF_3), 132.83 (CF_3), 137.91, 150.24, 154.02, 160.15; IR (diffuse reflectance) 3336 (m), 1741 (s, C=O), 1498 (m), 1390 (m), 1367 (m), 1276 (m), 1130 (m), 1095 (m), 1070 (m) cm^{-1}; ESI-MS *m/z* 336 $(M + H)^+$; Anal. Calcd for $C_{15}H_{11}F_3N_4O_2$; C: 53.58; H: 3.30; N: 16.66, Found: C: 53.61; H: 3.31; N: 16.63.

1-(4-Trifluorophenyl)-3-ethyloxycarbonyl-5-methyl-1,2,4-triazole (8a). Yield: 81%; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.42 (t, 3 H, *J* = 7.10 Hz, CH_3), 2.59 (s, 3 H , CH_3), 4.47 (q, 2 H, *J* = 7.10 Hz, CH_2), 7.64 (d, 2 H, *J* = 8.40 Hz, ArH), 7.79 (d, 2 H, *J* = 8.40 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.40, 14.25, 62.13, 124.29, 126.76, 126.83, 131.23 (CF_3), 131.47 (CF_3), 131.89 (CF_3), 132.55 (CF_3), 139.48, 154.10, 154.42, 159.67; IR (diffuse reflectance) 2924 (m), 1735 (s, C=O), 1612 (m), 1519 (m), 1473 (m), 1211 (m), 1126 (m), 1064 (m), 848 (m), 671 (m) cm^{-1}.

1-Phenyl-3-ethanone-5-methyl-1,2,4-triazole (8b). Yield: 79%; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.56 (s, 3 H, CH_3), 2.67 (s, 3 H, CH_3), 7.25–7.55 (m, 5 H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.19, 27.00, 124.73, 129.60 (2 × CH), 136.77, 154.17, 159.30, 191.45; IR (diffuse reflectance) 2920 (m), 1701 (s, C=O), 1504 (m), 1458 (m), 1354 (m), 1141 (m), 910 (m) cm^{-1}.

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