Synthesis of 1,2,3-Triazoles by Cycloadditions of Azides with Enol Ethers

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Abstract: 1,2,3-Triazoles were prepared in good to modest yields by cycloaddition of alkyl azides onto enol ethers under solventless conditions. The reaction can access ring-fused triazoles that are unavailable by azide-alkyne cycloadditions and is easily scalable. The 1,2,3-triazole products bear functionality that may be readily derivatized.

Key words: azides, cycloadditions, heterocycles, nitrogen, regioselectivity

1,2,3-Triazoles and their benzofused analogs have been investigated for numerous uses including halide synthons **1**,[1] antiviral nucleoside analogues **2**,[2,3] antifungals **3**,[4] and transition metal ligands **4**[5] (Figure 1).

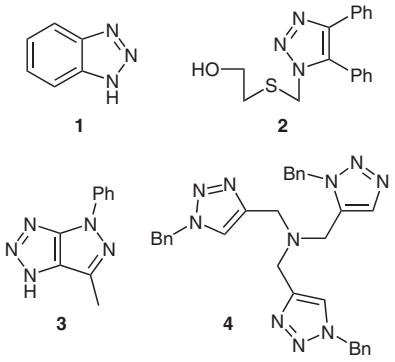
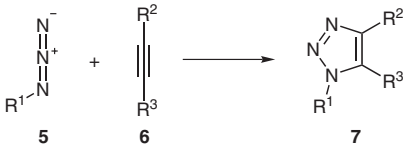


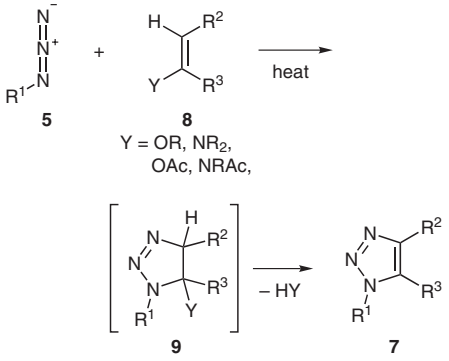
Figure 1 1,2,3-Triazoles and their benzofused analogs

The predominant method for preparing 1,2,3-triazoles **7** is the 1,3-dipolar cycloaddition of an azide **5** onto an alkyne **6** (Scheme 1).[6]



Scheme 1

This well-explored route receives continual interest because of the utility of 1,2,3-triazoles.[7,8] A less explored route to 1,2,3-triazoles is the cycloaddition of azides **5** onto alkenes **8** bearing a leaving group (Scheme 2).



Scheme 2

Alkenes of type **8** have the same oxidation state as alkynes and can serve as alkyne synthons. Cycloadditions of **8** with azides afford 1,2,3-triazoline intermediates **9** which lose HY to aromatize the ring. Alkene dipolarophiles studied in this reaction include enol ethers,[9–13] enamines,[10,14–18] vinylogous amides,[19,20] vinyl amides,[21] and vinyl sulfoxides.[22,23] While azide cycloadditions onto alkenes typically require higher temperatures than alkynes,[24] alkene dipolarophiles do possess advantages. First, alkenes of type **8** are often made from carbonyl compounds and may be prepared with a broader range of functionality than alkynes. Second, the electronegative Y-group that is lost in the reaction may serve as a traceless means of controlling the regiochemistry of the cycloaddition.[10]

Of the alkenes investigated as alkyne synthons, enamines **8** (Y = NR_2) have received the most attention.[10,14–18] One drawback to the synthesis of triazoles by enamines is the stability of the 5-amino-1,2,3-triazoline intermediates **9** (Y = NR_2).[10,14] Loss of the amino group from the 5-position can be slow, and decomposition of the triazoline ring frequently competes with triazole formation. Side reactions include aziridine formation[25,26] and diazonium ion rearrangements.[10] The use of enamides **8** (Y = NRAc) in place of enamines facilitates loss of the nitrogen in the 5-position,[21] but enamides are typically less convenient to prepare than enamines.

To address the shortcomings of azide–enamine cycloadditions, we investigated cycloadditions of azides onto enol ethers **8** (Y = OR). Azide–enol ether cycloadditions are relatively unexplored relative to azide–enamine cycloadditions. The starting azides used in this study are available by standard S_N2 replacement of alkyl halides or the ring-opening of epoxides with sodium azide according to liter-

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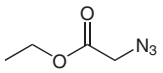
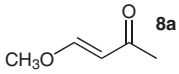
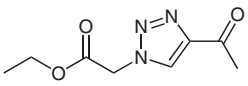
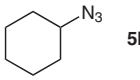
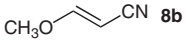
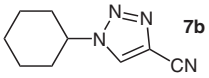
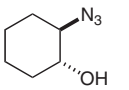
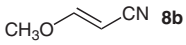
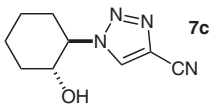
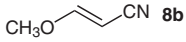
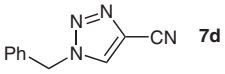
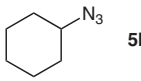
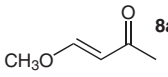
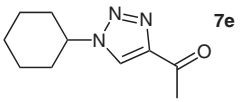
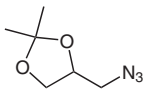
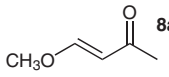
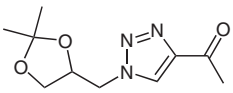
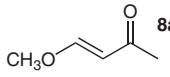
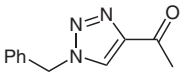
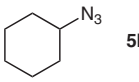
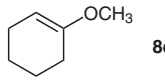
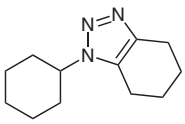
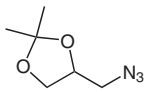
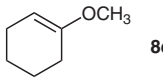
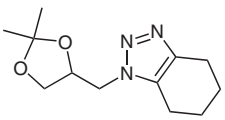
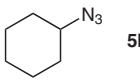
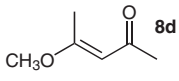
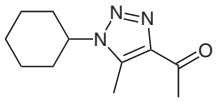
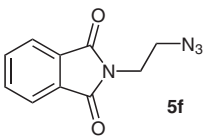
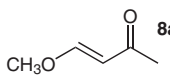
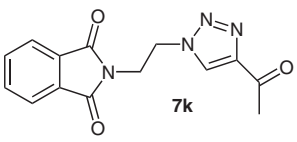
ature procedures.[27–30] Similarly, enol ethers used are available either commercially or by published procedures.[31–33]

Since alkenes of enol ethers are less electron-rich than enamine alkenes, they react less quickly than enamines in azide cycloadditions.[10] To increase the cycloaddition rate, the azide–enol ether cycloadditions were performed at 200 °C in a sealed tube without solvent. Under these conditions almost all the cycloadditions were complete within six hours. The reactions were monitored by GC analysis and most showed very clean conversion to the desired triazole product. The results are summarized in Table 1.

Despite concerns over the stability and safety of azides, azides, especially alkyl azides, may be readily prepared, purified, and reacted without difficulty or incident.[34] The use of sealed tubes for the cycloadditions is unrelated to azide stability. The sealed tubes minimize loss of volatile starting materials during the high reaction temperatures. Pressure build-up during the reactions is primarily due to the loss of methanol from the initial triazoline cycloadducts. No evidence of azide decomposition was observed.

The cycloaddition yields are modest to good. The reaction tolerates a range of functionality including esters, alcohols, ketones, imides, and nitriles. Despite the high reac-

Table 1 Cycloadditions of Azides **5** and Enol Ethers **8** (Y = OR) to form 1,2,3-Triazoles **7** (Scheme 1)

Entry	Azide **5**	Enol ether **8**	1,2,3-Triazole **7**	Yield (%)[a]
1	 **5a**	 **8a**	 **7a**	72
2	 **5b**	 **8b**	 **7b**	62
3	 **5c**	 **8b**	 **7c**	49
4	 **5d**	 **8b**	 **7d**	67[b]
5	 **5b**	 **8a**	 **7e**	62
6	 **5e**	 **8a**	 **7f**	68
7	 **5d**	 **8a**	 **7g**	78
8	 **5b**	 **8c**	 **7h**	68
9	 **5e**	 **8c**	 **7i**	51
10	 **5b**	 **8d**	 **7j**	60
11	 **5f**	 **8a**	 **7k**	66

[a] Isolated yields following column chromatography or recrystallization.
[b] Crude reaction mixture contained a 10:1 mixture of regioisomers.

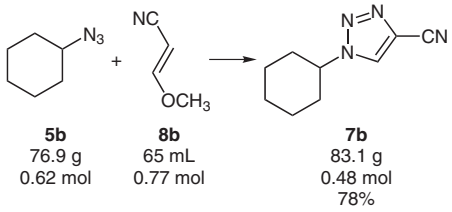
tion temperature, the ethyl ester of triazole **7a** showed almost no transesterification by methanol liberated from the enol ether (Table 1, Entry 1). The reaction accommodates modest steric congestion in the form of branching on the azide-bearing carbon and substitution of the enol ether alkene. Electronically, both simple enol ethers and captodative alkenes undergo cycloaddition.

The reaction presumably follows a concerted 1,3-dipolar cycloaddition mechanism to generate a 1,2,3-triazoline intermediate **9** (Y = OR),[10] although the putative intermediate was not directly observed. Under the high temperature conditions the triazoline loses an alcohol to form the aromatic triazole product **7** (Scheme 2).

The reactions were highly regioselective with only the cycloaddition of benzyl azide (**5d**) and 3-methoxyprop-2-enenitrile (**8b**) showing significant amounts of a second regioisomer (Table 1, Entry 4). In this instance the regioselectivity of the crude mixture was approximately 10:1 with the minor regioisomer being removed by recrystallization. Where applicable, regiochemical assignments are based on upon X-ray crystallographic evidence from related cycloadditions performed by Zhu[13] and are consistent with FMO analysis.[35]

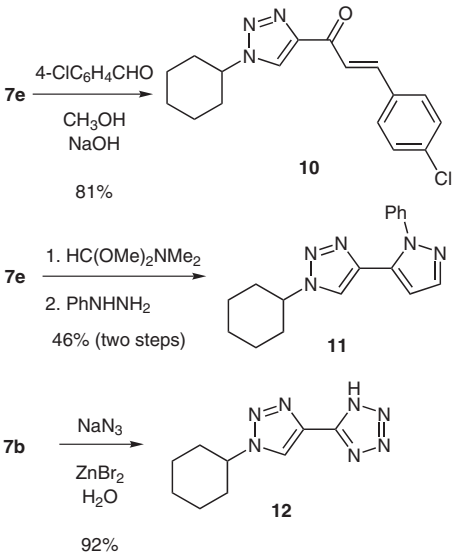
Two noteworthy products are triazoles **7h** and **7i** (Table 1, Entries 8 and 9). Ring-fused triazoles of this type are not available by standard azide–alkyne cycloadditions. Attempts to use enamines derived from cyclic ketones to form ring-fused triazoles have given mixed results. In some cases cyclic enamines successfully react with azides to afford ring-fused triazoles,[16,17] while triazoline decomposition products predominate in other instances.[10,25,26]

Most reactions in Table 1 were performed on less than a 10 mmol scale in sealed vials or pressure tubes. The reaction can be run on a large scale without resorting to heavy-walled glassware and elevated pressures. A cycloaddition between cyclohexyl azide (**5b**) and 3-methoxyprop-2-enenitrile (**8b**) was performed on a 0.6 mol scale in a heated round-bottom flask open to the atmosphere. Methanol, a side-product of the reaction, was removed by distillation as it was formed. The crude product was directly recrystallized in the reaction flask to afford the desired product **7b** in 78% yield (Scheme 3).



Scheme 3

Triazoles from azide–enol ether cycloadditions bear functionality that may be further derivatized (Scheme 4). The 4-acetyl group of cycloadduct **7e** readily undergoes an aldol condensation to form an α,β-unsaturated ketone **10** in high yield.[36] Likewise, the 4-acetyl group of **7e** may be used to append a pyrazole ring **11** through a two-step protocol using the dimethyl acetal of DMF followed by phenylhydrazine.[37] The 4-cyano substituent of triazole **7b** reacts with sodium azide to form a tetrazole ring **12** in excellent yield following the procedure of Sharpless.[38]



Scheme 4

In conclusion, the cycloaddition of azides onto enol ethers provides a direct, efficient, and scalable route to 1,2,3-triazoles. This reaction is able to generate triazoles that are inaccessible by traditional azide-alkyne cycloadditions and avoids complications of 5-amino-1,2,3-triazoline decomposition that can accompany azide-enamine cycloadditions. The products of azide-enol ether cycloadditions incorporate functional groups that are amenable to further derivatization of the triazole products.

NMR spectra were recorded on a JEOL JNM-ECP 400 MHz spectrometer. Chemical shifts are reported in ppm (δ) relative to TMS as an internal standard. IR spectra were recorded on a MIDAC Series M spectrometer. MS (EI) were recorded with a Varian 3800 Gas Chromatograph-Saturn 2000 Mass Spectrometer system operating at 11.7 eV. Melting ranges were taken on an Electrothermal MelTemp and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc. of Knoxville, TN and Quantitative Technologies, Inc. of Whitehouse, NJ. Merck precoated silica gel 60 F_{254} plates were used for TLC, and Merck 60 for column chromatography. Chromatography solvents were mixed on a v/v basis. Cyclohexyl azide (**5b**),[27] *trans*-2-azidocyclohexanol (**5c**),[28] ethyl 2-azidoethanoate (**5a**),[29] benzyl azide (**5d**),[27] *N*-(2-azidoethyl)phthalimide (**5f**),[30] and 4-azidomethyl-2,2-dimethyl-1,3-dioxolane (**5e**),[31] 1-methoxycyclohexene (**8c**),[32] and 4-methoxypent-3-en-2-one (**8d**)[33] were prepared according to literature procedures. All other reagents were purchased from commercial sources and used without purification. Cycloadditions performed on less than a 5 mmol scale were performed in round-bottom screw-cap vials (Fisher 14-959-35C). Larger scale cycloadditions were performed in a heavy-walled pressure tube (Ace 8608-07) unless otherwise specified.

1,2,3-Triazoles 7; General Procedure

The azide **5** (1.0 equiv) and enol ether **8** (1.1–1.2 equiv) were combined neat and sealed in a vial and heated to 200 °C in a sand bath

(**Caution!** high pressure from alcohol generation). The reaction was monitored for disappearance of azide by GC analysis. The crude reaction mixture was directly chromatographed or recrystallized without an aqueous extraction (Table 1).

Ethyl 2-(4-Acetyl-1*H*-1,2,3-triazol-1-yl)acetate (7a)
White solid by column chromatography; yield: 0.53 g (72%); mp 79–80 °C; R_f 0.37 (EtOAc–hexanes, 1:1).

IR (film): 3145, 2996, 1749, 1686, 1530, 1208 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.26 (s, 1 H), 5.25 (s, 2 H), 4.28 (q, 2 H, *J* = 7.2 Hz), 2.70 (s, 3 H), 1.31 (t, 3 H, *J* = 7.1 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.5, 165.6, 148.2, 126.9, 62.6, 50.9, 27.1, 13.9.

MS (EI): *m*/*z* (%) = 198 (35, [M^+ + 1]), 169 (48), 154 (51), 126 (98), 97 (35), 96 (37), 54 (43), 53 (31), 43 (100).

Anal. Calcd for $C_8H_{11}N_3O_3$: C, 48.73; H, 5.62; N, 21.31. Found: C, 48.75; H, 5.67; N, 21.20.

1-Cyclohexyl-1*H*-1,2,3-triazole-4-carbonitrile (7b)
General Procedure: White solid by recrystallization from MeOH–H_2O; yield: 1.10 g (62%); mp 110 °C; R_f 0.32 (EtOAc–hexanes, 1:1).

Large-Scale Procedure: Cyclohexyl azide (**5b**; 76.9 g, 0.62 mmol, 1.00 equiv) and 3-methoxyprop-2-enenitrile (**8b**; 65 mL, 0.77 mmol, 1.2 equiv) were mixed neat in a 250 mL flask equipped with a distillation head and heated with a 200 °C sand bath. After 5 h, no azide remained based on GC analysis. The reaction mixture solidified upon cooling to r.t. Recrystallization from MeOH–H_2O (5:1, 350 mL) afforded the product; light brown solid; yield: 83.1 g (78%).

IR (film): 3124, 2945, 2858, 2247, 1454, 1266, 1239, 1210 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.05 (s, 1 H), 4.54 (tt, 1 H, *J* = 11.7, 3.8 Hz), 2.26 (d, 2 H, *J* = 11.9 Hz), 1.97 (dt, 2 H, *J* = 13.9, 7.0 Hz), 1.72–1.83 (m, 3 H), 1.50 (tq, 2 H, *J* = 12.9, 3.5 Hz), 1.33 (tt, 1 H, *J* = 12.8, 3.7 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 127.3, 120.6, 111.6, 61.1, 33.3, 24.9, 24.8.

MS (EI): *m*/*z* (%) = 177 (100, [M^+ + 1]), 176 (16), 83 (15), 82 (30), 67 (36), 55 (40).

Anal. Calcd for $C_9H_{12}N_4$: C, 61.34; H, 6.86; N, 31.79. Found: C, 61.45; H, 6.97; N, 31.43.

1-[(1*R,2*R**)-2-Hydroxycyclohexyl]-1*H*-1,2,3-triazole-4-carbonitrile (7c)**
Pale yellow solid by chromatography; yield: 0.38 g (49%); mp 124–125 °C; R_f 0.24 (EtOAc–hexanes, 2:3).

IR (film): 3433, 3131, 2940, 2868, 2255, 1444, 1236, 1042 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.14 (s, 1 H), 4.22 (ddd, 1 H, *J* = 12.5, 9.6, 4.4 Hz), 3.96 (dt, 1 H, *J* = 9.7, 4.8 Hz), 2.38 (br s, 1 H), 2.29–2.17 (m, 2 H), 2.04 (dq, 1 H, *J* = 12.7, 3.7 Hz), 1.98–1.84 (m, 2 H), 1.55–1.37 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 129.9, 120.4, 111.5, 72.5, 67.7, 34.3, 31.3, 24.5, 23.8.

MS (EI): *m*/*z* (%) = 193 (100, [M^+ + 1]), 164 (32), 163 (59), 122 (17), 121 (33), 107 (18), 80 (16), 67 (17), 43 (15), 41 (16).

Anal. Calcd for $C_9H_{12}N_4O$: C, 56.24; H, 6.29; N, 29.15. Found: C, 56.25; H, 6.19; N, 28.94.

1-Benzyl-1*H*-1,2,3-triazole-4-carbonitrile (7d)
White solid by column chromatography; yield: 0.57 g (67%); mp 77–78 °C; R_f 0.60 (EtOAc–hexanes, 1:1).

IR (film): 3149, 2240, 1520, 1496, 1454, 1236 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.94 (s, 1 H), 7.45–7.40 (m, 3 H), 7.33–7.28 (m, 2 H), 5.61 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.8, 129.5, 129.5, 129.2, 128.3, 121.4, 111.3, 54.8.

MS (EI): *m*/*z* (%) = 184 (17, [M^+]), 155 (39), 129 (15), 104 (13), 91 (100), 78 (10), 77 (10), 65 (35), 51 (16), 50 (13).

Anal. Calcd for $C_{10}H_8N_4$: C, 65.21; H, 4.38; N, 30.42. Found: C, 65.32; H, 4.46; N, 30.21.

1-(1-Cyclohexyl-1*H*-1,2,3-triazol-4-yl)ethanone (7e)
Cream-colored solid by recrystallization from MeOH–H_2O; yield: 4.5 g (72%); mp 116 °C; R_f 0.32 (EtOAc:–hexanes, 1:1).

IR (film): 3099, 2932, 2857, 1687, 1451 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.09 (s, 1 H), 4.51 (tt, 1 H, *J* = 11.7, 3.9 Hz), 2.70 (s, 3 H), 2.24 (d, 2 H, *J* = 12.8 Hz), 1.95 (dt, 2 H, *J* = 13.7, 3.1 Hz), 1.83–1.69 (m, 3 H), 1.49 (tq, 2 H, *J* = 12.9, 3.5 Hz), 1.30 (tq, 1 H, *J* = 12.8, 3.5 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.1, 147.7, 123.1, 60.4, 33.4, 27.1, 25.0, 24.9.

MS (EI): *m*/*z* (%) = 194 (100, [M^+ + 1]), 165 (20), 150 (28), 122 (22), 83 (39), 55 (46), 43 (20).

Anal. Calcd for $C_{10}H_{15}N_3O$: C, 62.15; H, 7.82; N, 21.74. Found: C, 62.26; H, 7.97; N, 21.76.

1-{1-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]-1*H*-1,2,3-triazol-4-yl}ethanone (7f)
White solid by column chromatography; yield: 0.40 g (68%); mp 111–112 °C; R_f 0.27 (EtOAc–hexanes, 3:1).

IR (film): 3100, 2989, 1683, 1374, 1253, 1198, 1062, 1049, 1042 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.23 (s, 1 H), 4.69–4.59 (m, 1 H), 4.53–4.42 (m, 2 H), 4.20–4.13 (m, 1 H), 3.80–3.74 (m, 1 H), 2.70 (s, 3 H), 1.39 (s, 3 H), 1.34 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.8, 148.1, 126.7, 110.4, 73.6, 66.2, 52.7, 27.2, 26.7, 25.0.

MS (EI): *m*/*z* (%) = 226 (89, [M^+ + 1]), 210 (100), 167 (43), 150 (23), 101 (32), 73 (15), 43 (79), 41 (17).

Anal. Calcd for $C_{10}H_{15}N_3O_3$: C, 53.32; H, 6.71; N, 18.66. Found: C, 53.36; H, 6.67; N, 18.61.

1-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)ethanone (7g)
Orange-yellow solid by recrystallization from MeOH–H_2O; yield: 0.64 g (78%); mp 88–89 °C (Lit.[39] mp 90 °C); R_f 0.32 (EtOAc–hexanes, 2:3).

IR (film): 3111, 1683, 1530, 1208 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.95 (s, 1 H), 7.42–7.38 (m, 3 H), 7.32–7.28 (m, 2 H), 5.57 (s, 2 H), 2.68 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.9, 148.4, 133.6, 129.3, 129.2, 128.3, 125.2, 54.5, 27.1.

MS (EI): *m*/*z* (%) = 202 (13, [M^+ + 1]), 173 (13), 172 (64), 158 (20), 130 (22), 91 (100), 65 (32).

Anal. Calcd for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.74; H, 5.50; N, 20.63.

1-Cyclohexyl-4,5,6,7-tetrahydro-1*H*-benzo[*d*][1,2,3]triazole (7h)
Cream-colored solid by column chromatography; yield: 0.52 g (68%); mp 106–108 °C; R_f 0.17 (EtOAc–hexanes, 1:1).

IR (film): 2934, 2861, 1582, 1447, 1287, 1211 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.12 (tt, 1 H, *J* = 10.6, 4.8 Hz), 2.74 (t, 2 H, *J* = 5.9 Hz), 2.63 (t, 2 H, *J* = 5.9 Hz), 2.06–1.71 (m, 11 H), 1.48–1.23 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.9, 130.7, 58.2, 32.5, 25.4, 25.0, 22.6, 22.4, 21.8, 20.3.

MS (EI): *m*/*z* (%) 206 (45, [M$^+$ + 1]), 205 (72), 124 (16), 95 (100), 94 (49), 68 (58), 67 (66), 55 (66), 41 (26).

Anal. Calcd for $C_{12}H_{19}N_3$: C, 70.20; H, 9.33; N, 20.47. Found: C, 70.35; H, 9.34; N, 20.41.

4,5,6,7-Tetrahydro-1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-1*H*-benzo[*d*][1,2,3]triazole (7i)

Orange-yellow solid by column chromatography; yield: 0.18 g (51%); mp 86–87 °C; R_f 0.27 (EtOAc–hexanes, 1:1).

IR (film): 2985 (m), 2938 (s), 2859 (m), 1586 (w), 1443 (m), 1376 (m), 1212 (s), 1158 (m), 1057 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.48 (quint, 1 H, *J* = 5.7 Hz), 4.38 (dd, 1 H, *J* = 14.1, 4.9 Hz), 4.28 (dd, 1 H, *J* = 14.1, 5.7 Hz), 4.13 (dd, 1 H, *J* = 8.8, 6.2 Hz), 3.88 (dd, 1 H, *J* = 8.8, 5.8 Hz), 2.77–2.71 (m, 2 H), 2.70–2.63 (m, 2 H), 1.90–1.77 (m, 4 H), 1.34 (s, 3 H), 1.33 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.2, 132.9, 109.9, 74.5, 66.7, 49.7, 26.5, 25.2, 22.6, 22.4, 21.8, 20.2.

MS (EI): *m*/*z* (%) = 238 (98, [M$^+$ + 1]), 237 (65), 222 (86), 179 (81), 162 (39), 122 (65), 108 (77), 95 (43), 81 (44), 79 (44), 67 (65), 43 (100), 41 (43).

Anal. Calcd for $C_{12}H_{19}N_3O_2$: C, 60.74; H, 8.07; N, 17.71. Found: C, 60.82; H, 8.26; N, 17.53.

1-(1-Cyclohexyl-5-methyl-1*H*-1,2,3-triazol-4-yl)ethanone (7j)

White solid by column chromatography; yield: 0.28 g (60%); mp 76–77 °C; R_f 0.21 (EtOAc–hexanes, 1:9).

IR (film): 2936, 2859, 1681, 1561, 1452, 1422, 1388, 1363, 1280, 1179 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.13 (tt, 1 H, *J* = 11.4, 4.2 Hz), 2.69 (s, 3 H), 2.59 (s, 3 H), 2.14–1.94 (m, 6 H), 1.82–1.74 (m, 1 H), 1.51–1.28 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.7, 143.2, 135.5, 57.8, 32.5, 27.7, 25.3, 24.9, 8.9.

MS (EI): *m*/*z* (%) = 207 (10, [M$^+$]), 164 (57), 137 (11), 136 (100), 126 (34), 108 (16), 97 (33), 94 (15), 83 (24), 82 (25), 81 (10), 68 (17), 67 (39), 55 (63), 54 (32), 53 (12), 43 (37), 42 (18), 41 (20).

Anal. Calcd for $C_{11}H_{17}N_3O$: C, 63.74; H, 8.27; N, 20.27. Found: C, 63.86; H, 8.48; N, 19.93.

2-[2-(4-Acetyl-1*H*-1,2,3-triazol-1-yl)ethyl]isoindoline-1,3-dione (7k)

Light brown solid by recrystallization from MeCN–MeOH; yield: 0.48 g (66%); mp 212–214 °C; R_f 0.25 (EtOAc–hexanes, 1:1).

IR (film): 3092, 1773, 1707, 1680, 1532, 1360, 1221, 1045 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.85 (s, 1 H), 7.90–7.82 (m, 4 H), 4.74–4.66 (m, 2 H), 4.09–4.01 (m, 2 H), 2.51 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.6, 167.4, 147.0, 134.6, 131.4, 127.9, 123.2, 48.1, 37.8, 27.1.

MS (EI): *m*/*z* (%) = 285 (14, [M$^+$ + 1]), 256 (15), 241 (32), 174 (15), 175 (100), 161 (18), 160 (75), 147 (37), 133 (39), 130 (53), 129 (23), 109 (57), 105 (24), 104 (29), 102 (14), 77 (33), 76 (33), 54 (18), 53 (14), 51 (14), 50 (27), 43 (38).

Anal. Calcd for $C_{14}H_{12}N_4O_3$: C, 59.15; H, 4.25; N, 19.71. Found: C, 59.21; H, 4.24; N, 19.68.

(*E*)-3-(4-Chlorophenyl)-1-(1-cyclohexyl-1*H*-1,2,3-triazol-4-yl)prop-2-en-1-one (10)

Following the procedure of Kulp,[36] **7e** (390 mg, 2.0 mmol, 1.0 equiv) and 4-chlorobenzaldehyde (290 mg, 2.1 mmol, 1.0 equiv) were dissolved in MeOH (10 mL). Aq 40% NaOH (200 μL) was added, and the mixture was stirred for 10 min at 40 °C. Precipitation of the product was completed by adding H_2O (5 mL) and cooling the mixture to r.t. The product was filtered and recrystallized from 1:1 MeOH–MeCN; white solid; yield: 0.52 g (81%); mp 178–180 °C; R_f 0.26 (EtOAc–hexanes, 1:3).

IR (film): 3131, 2929, 2853, 1662, 1602, 1567, 1525, 1490, 1184 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (s, 1 H), 7.92 (s, 2 H), 7.64 (d, 2 H, *J* = 8.8 Hz), 7.40 (d, 2 H, *J* = 8.4 Hz), 4.54 (tt, 1 H, *J* = 11.7, 3.8 Hz), 2.27 (d, 2 H, *J* = 11.4 Hz), 2.00–1.92 (m, 2 H), 1.84–1.70 (m, 3 H), 1.50 (tq, 2 H, *J* = 13.1, 3.3 Hz), 1.31 (tq, 1 H, *J* = 12.8, 3.5 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.0, 148.1, 142.9, 136.6, 133.3, 129.9, 129.2, 124.3, 122.8, 60.5, 33.5, 25.03, 24.98.

MS (EI): *m*/*z* (%) = 317 (79, [M$^+$ + 1]), 316 (70), 315 (61), 253 (64), 205 (44), 178 (53), 170 (47), 115 (26), 55 (66), 43 (100).

Anal. Calcd for $C_{17}H_{18}ClN_3O$: C, 64.66; H, 5.75; N, 13.31. Found: C, 64.45; H, 5.87; N, 13.42.

1-Cyclohexyl-4-(1-phenylpyrazol-5-yl)-1*H*-1,2,3-triazole (11)

Following the procedure of Penning and Talley,[37] **7e** (500 mg, 2.6 mmol, 1.00 equiv), dimethyl acetal of DMF (370 mg, 2.8 mmol, 1.1 equiv), and *p*-TsOH (10 mg) were mixed neat and heated to 175 °C with stirring. After 1 h, all **7e** had been consumed based on GC analysis. Solid phenylhydrazine hydrochloride (380 mg, 2.60 mmol, 1.00 equiv) was added, and the reaction heated for 45 min at 200 °C. The reaction was cooled to r.t., H_2O (30 mL) was added, and the mixture was stirred to precipitate the product. The crude, dark solid was filtered and recrystallized from 7:1 MeOH–H_2O to afford the product; cream-colored solid; yield: 0.35 g (46%); mp 121–122 °C; R_f 0.32 (EtOAc–hexanes, 1:3).

IR (film): 2936, 2858, 1598, 1503, 1452, 1390 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, 1 H, *J* = 1.8 Hz), 7.49–7.37 (m, 5 H), 6.92 (s, 1 H), 6.88 (d, 1 H, *J* = 1.8 Hz), 4.35 (tt, 1 H, *J* = 11.5, 3.8 Hz), 2.11 (m, 2 H), 1.87 (dt, 2 H, *J* = 13.6, 3.1 Hz), 1.76–1.69 (m, 1 H), 1.60 (dq, 2 H, *J* = 12.3, 3.3 Hz), 1.41 (tq, 2 H, *J* = 12.9, 3.5 Hz), 1.22 (tq, 1 H, *J* = 12.8, 3.5 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.4, 139.8, 137.7, 134.3, 129.0, 128.5, 126.0, 119.1, 107.3, 66.1, 33.3, 24.94, 24.89.

MS (EI): *m*/*z* (%) = 294 (59, [M$^+$ + 1]), 293 (81), 292 (100), 265 (71), 183 (84), 169 (33), 168 (49), 156 (53), 155 (36), 55 (42).

Anal. Calcd for $C_{17}H_{19}N_5$: C, 69.60; H, 6.53; N, 23.87. Found: C, 69.32; H, 6.51; N, 23.86.

5-(1-Cyclohexyl-1*H*-1,2,3-triazol-4-yl)-1*H*-tetrazole (12)

Following the procedure of Sharpless,[38] **7b** (3.48 g, 20.0 mmol, 1.00 equiv), NaN_3 (1.46 g, 22.5 mmol, and 1.12 equiv), and $ZnBr_2$ (4.50 g, 20.0, 1.00 equiv) were dissolved in H_2O (40 mL) and refluxed. After 24 h, the reaction was diluted with EtOAc (100 mL), CH_2Cl_2 (100 mL), and 3 M HCl (30 mL) to dissolve all solids. The organic layer was separated and concentrated in vacuo. Aq 0.25 M NaOH (200 mL) was added, and the resulting suspension was filtered. The filtrate was acidified with 3 M HCl (40 mL) to afford a precipitate. The precipitate was filtered and dried in an oven at 100 °C to give the product; white solid; yield: 4.0 g (92%); mp 227 °C (dec.); R_f 0.18 (EtOAc).

IR (Nujol): 3149, 3087, 1643, 988 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.00 (s, 1 H), 4.64 (tt, 1 H, *J* = 11.5, 3.8 Hz), 2.19–2.09 (m, 2 H), 1.93–1.79 (m, 4 H), 1.70 (br d, 1 H, *J* = 12.8 Hz), 1.46 (tq, 2 H, *J* = 13.3, 3.1 Hz), 1.27 (tq, 1 H, *J* = 12.7, 3.3 Hz).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 148.6, 133.0, 123.7, 59.7, 32.7, 24.60, 24.57.

Anal. Calcd for $C_9H_{13}N_7$: C, 49.30; H, 5.98; N, 44.72. Found: C, 49.14; H, 5.83; N, 44.32.

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