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Regioselective one-pot synthesis of 1,4-disubstituted 1,2,3-triazole derivatives

Abstract: The one-pot synthesis of novel 1,4-disubstituted 1,2,3-triazole derivatives derived from homopropargyl alcohol backbones has been accomplished. Triazoles are obtained in good yields from a variety of readily available aromatic and aliphatic halides without isolation of potentially unstable organic azide intermediates.

Keywords: homopropargyl alcohols; one-pot synthesis; organic azide; 1,2,3-triazoles.

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Introduction

Triazole-containing compounds show various biological activities including antimicrobial [1, 2], anti-inflammatory [3], antidepressant [4, 5], anticonvulsant [6, 7], antifungal [8, 9], enzyme inhibition [10, 11] activities. 1,2,3-Triazoles have also a wide range applications in industry as anticorrosive agents, dyes, photostabilizers, photographic materials, and agrochemicals [12–14]. Remarkable stability toward metabolic transformations, H-bonding capability, and high dipole moment make triazoles attractive building components [15–17].

In organic chemistry, one-pot multicomponent reactions have received much attention because they minimize the time and cost of the synthesis of highly functional molecules from simple building blocks [18–20]. Moreover, one-pot multicomponent reactions result in better yields, thus minimizing extra operations like isolation, handling, and chromatography.

The Huisgen 1,3-dipolar cycloadditions of azides and alkynes are regioselective, yielding 1,4-disubstituted 1,2,3-triazoles [21]. The regioselective one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles has been reported [22–26]. The advantages of the second method are *in situ* generation of Cu(I) salts needed for the catalysis from the stable Cu(II) sulfate-sodium ascorbate redox system, in addition to the *in situ* generation of a potentially toxic and explosive organic azide without isolation. Only the 1,4-disubstituted isomer can be isolated.

Homopropargyl alcohols are good candidates for the preparation of substituted triazoles. We report herein efficient, safe, and regioselective one-pot synthesis of novel 1,4-disubstituted 1,2,3-triazole derivatives having potential to possess various biological activities.

Results and discussion

The parent homopropargylic alcohols **2a** and **2b**, used as templates in this work for the construction of 1,4-disubstituted 1,2,3-triazoles, were synthesized by the addition reaction of propargyl bromide to aldehydes in the presence of the Zn-Cu couple (Scheme 1).

Terminal acetylenes on homopropargylic alcohol derivatives **2a,b** make them valuable candidates for one-pot synthesis of the target triazole structures. Aliphatic and aromatic azides can easily be generated from the corresponding halides as intermediates used in one-pot method [22–26]. The operational simplicity of this method makes it attractive for wide variety of applications. Initially, 1-phenylbut-3-yn-1-ol **2a** was employed in one-pot, two-step procedure for trapping generated organic azides to afford the corresponding triazole products. Various aromatic and allylic halides were screened under the reported optimized conditions [25] and newl triazole products **3–10** were obtained in good yields (Scheme 2).

1-(2-Thienyl)but-3-yn-1-ol **2b** was also allowed to react with aryl and allyl halides and sodium azide according to the same procedure. New triazole derivatives **11–18** were isolated in good yields (Scheme 2).

Conclusion

New 1,4-disubstituted 1,2,3-triazole derivatives of potential biological activity were synthesized directly from

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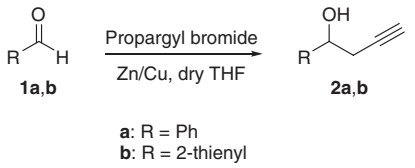
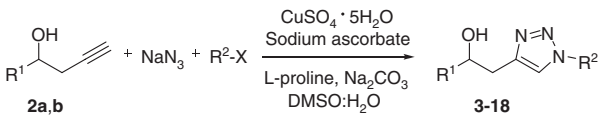


Scheme 1



3: R^1 = Ph; R^2 = Ph
4: R^1 = Ph; R^2 = 4-hydroxyphenyl
5: R^1 = Ph; R^2 = *p*-tolyl
6: R^1 = Ph; R^2 = 1-naphtyl
7: R^1 = Ph; R^2 = 3-pyridinyl
8: R^1 = Ph; R^2 = 3-thiophenyl
9: R^1 = Ph; R^2 = allyl
10: R^1 = Ph; R^2 = Bn
11: R^1 = 2-thienyl; R^2 = Ph
12: R^1 = 2-thienyl; R^2 = 4-hydroxyphenyl
13: R^1 = 2-thienyl; R^2 = *p*-tolyl
14: R^1 = 2-thienyl; R^2 = 1-naphtyl
15: R^1 = 2-thienyl; R^2 = 3-pyridinyl
16: R^1 = 2-thienyl; R^2 = 3-thiophenyl
17: R^1 = 2-thienyl; R^2 = allyl
18: R^1 = 2-thienyl; R^2 = Bn

Scheme 2

homopropargylic alcohols by the reaction with various aryl and allyl halides and sodium azide.

Experimental

General

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ on a Bruker Spectrospin Avance DPX-400 spectrometer. HR mass spectra were obtained on an Agilent Technologies 6224 Accurate-Mass TOF LC/MS instrument at the National Nanotechnology Research Center of Bilkent University (UNAM). Flash column chromatography was performed using thick-walled glass columns with a flash grade (Merck Silica Gel 60). Reactions were monitored by thin layer chromatography (TLC) using precoated silica gel plates (Merck Silica Gel PF-254), visualized by UV light and polymolybden phosphoric acid in ethanol as appropriate.

General procedure for the synthesis of homopropargyl alcohols 2a,b

The Zn-Cu couple preparation was conducted under an oxygen-free environment. Zinc dust (9.54 g, 74 mmol) was suspended in distilled water (10 mL), and the mixture was treated with acidic cupric chloride solution (0.15 M in 5% hydrochloric acid, 22 mL) with vigorous magnetic stirring. When the evolution of the gas ceased, the suspension was filtered and the black solid was washed with water until the wash gave a negative test for chloride with 6% silver nitrate solution. To a stirred mixture of aldehyde **2a,b** (37 mmol) and freshly prepared dry Zn-Cu couple (5.16 g, 40 mmol) in THF (30 mL), propargyl bromide (6 g, 40 mmol, 80 wt% in toluene) was added dropwise at 0°C. The mixture was heated at reflux for 4 h with monitoring by TLC and then hydrolyzed with 1 M HCl (5 mL) and extracted with diethyl ether (3×30 mL). The extract was dried over $MgSO_4$ and concentrated on a rotary evaporator. The crude product (residue) was purified by flash column chromatography using a mixture of ethyl acetate and hexanes.

1-Phenylbut-3-yn-1-ol (2a): Yellow oil; yield 4.33 g (80%); ^{1}H NMR: δ 7.65–6.31 (m, 5H), 4.78 (m, 1H), 3.06 (bs,1H), 2.62–2.40 (m, 2H), 2.08–1.16 (m, 1H); ^{13}C NMR: δ 142.5, 128.5, 128.0, 127.8, 126.1, 125.8, 80.8, 72.3, 71.0, 29.4.

1-(2-Thienyl)but-3-yn-1-ol (2b): Yellow oil; yield 4.12 g (73%); ^{1}H NMR: δ 7.10 (dd, *J* = 1.2 and 5.0 Hz, 1H), 6.88–6.87 (m, 1H), 6.82 (dd, *J* = 3.5 and 5.0 Hz, 1H), 4.90 (t, *J* = 6.2 Hz, 1H), 3.37 (bs,1H), 2.55 (dd, *J* = 2.6 and 6.1 Hz, 2H), 1.96 (t, *J* = 2.6 Hz, 1H); ^{13}C NMR: δ 146.4, 126.7, 125.0, 124.3, 80.5, 71.6, 68.4, 29.4.

General procedure for the synthesis of 1,4-disubstituted 1,2,3-triazoles 3-18

A mixture of an aromatic or aliphatic halide (1 mmol), homopropargyl alcohol (1 mmol), L-proline (24 mg, 0.2 mmol), Na_2CO_3 (24 mg, 0.2 mmol), NaN_3 (65 mg, 1 mmol), sodium ascorbate (20 mg, 0.1 mmol), DMSO/H_2O (18:2, 20 mL), and $CuSO_4$·$5H_2O$ solution (1 M, 0.05 mL) in a 20-mL scintillation vial was stirred overnight at 65°C. The crude mixture was poured into cold dilute NH_4OH solution (30 mL) and extracted with ethyl acetate (4×20 mL). The collected organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash column chromatography using mixtures of ethylacetate and hexanes.

1-Phenyl-2-(1-phenyl-1*H*-1,2,3-triazol-4-yl)ethanol (3): White crystals; yield 244 mg, 92%); mp 120–123°C; ^{1}H NMR: δ 7.66 (s, 1H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.43–7.39 (m, 2H), 7.35–7.31 (m, 2H), 7.28–7.24 (m, 3H), 7.21–7.18 (m, 1H), 5.03 (dd, *J* = 4.9 and 7.6 Hz, 1H), 3.44 (bs, 1H), 3.12–3.10 (m, 2H); ^{13}C NMR: δ 144.5, 142.6, 136.0, 128.7, 127.7, 127.4, 126.6, 124.8, 119.4, 72.1, 34.4. HRMS (ESI-TOF). Calcd for $C_{16}H_{15}N_3O$ $[M+H]^+$: *m/z* 266.12879. Found: *m/z* 266.12903.

4-(4-(2-Hydroxy-2-phenylethyl)-1*H*-1,2,3-triazol-1-yl)phenol (4): Yellow crystals; yield 175 mg (62%); mp 115–116°C. ^{1}H NMR: δ 7.56 (s, 1H), 7.38–7.27 (m, 9H), 5.35–5.33 (m, 1H), 4.99 (bs, 1H), 3.14–3.12 (m, 2H); ^{13}C NMR: δ 144.9, 143.4, 140.4, 128.5, 127.8, 127.7, 125.8, 125.7, 120.3, 106.9, 73.1, 35.3. HRMS (ESI-TOF). Calcd for $C_{16}H_{15}N_3O_2$ $[M+H]^+$: *m/z* 282.12370. Found: *m/z* 282.12484.

1-Phenyl-2-(1-*p*-tolyl-1*H*-1,2,3-triazol-4-yl)ethanol (5): White crystals; yield 136 mg, 49%); mp 130–131°C; ^{1}H NMR: δ 7.62 (s, 1H), 7.48–7.18 (m, 9H), 5.03 (dd, *J* = 4.7 and 7.7 Hz, 1H), 3.50 (bs, 1H), 3.12–3.09 (m, 2H), 2.33 (s, 3H); ^{13}C NMR: δ 145.3, 143.6, 138.8, 134.8, 130.2, 128.5, 127.7, 125.8, 120.4, 73.2, 35.5, 21.1. HRMS (ESI-TOF). Calcd for $C_{17}H_{17}N_3O$ $[M+H]^+$: *m/z* 280.14444. Found: m/z 280.14609.

2-(1-(1-Naphthyl)-1*H*-1,2,3-triazol-4-yl)-1-phenylethanol (6): White crystals; yield 217 mg (69%); mp 118–120°C; ^{1}H NMR: δ 8.00–7.93 (m, 2H), 7.60–7.26 (m, 11H), 5.18–5.22 (m, 1H), 3.57 (bs, 1H), 3.28 (d, *J* = 6.2 Hz, 2H); ^{13}C NMR: δ 144.6, 143.6, 134.1, 133.7, 130.3, 128.4,

128.2, 127.8, 127.6, 127.0, 125.9, 125.0, 123.5, 122.3, 73.3, 35.4. HRMS (ESI-TOF). Calcd for $C_{20}H_{17}N_3O$ $[M+H]^+$: *m/z* 316.14444. Found: m/z 316.14692.

1-Phenyl-2-(1-(3-pyridyl)-1*H*-1,2,3-triazol-4-yl)ethanol (7): White crystals; yield 239 mg (90%); mp 132–134°C; ^{1}H NMR: δ 8.90 (d, *J* = 1.9 Hz, 1H), 8.66–8.64 (m, 1H), 8.12–8.10 (m, 1H), 7.81 (s, 1H), 7.50–7.47 (m, 1H), 7.43–7.27 (m, 5H), 5.14–5.11 (m, 1H), 3.24–3.22 (m, 2H), 2.98 (s, 1H); ^{13}C NMR: δ 149.5, 146.1, 143.6, 141.2, 133.7, 128.5, 128.1, 127.8, 125.8, 124.3, 120.4, 73.0, 35.5. HRMS (ESI-TOF). Calcd for $C_{15}H_{14}N_4O$ $[M+H]^+$: *m/z* 267.12404. Found: *m/z* 267.12701.

1-Phenyl-2-(1-(3-thienyl)-1*H*-1,2,3-triazol-4-yl)ethanol (8): Light yellow crystals; yield 225 mg; (83%) mp 128–130°C; ^{1}H NMR: δ 7.59 (s, 1H), 7.43–7.42 (m, 1H), 7.36–7.32 (m, 4H), 7.29–7.26 (m, 2H), 7.23–7.19 (m, 1H), 5.03 (dd, *J* = 4.8 and 7.8 Hz, 1H), 3.11–3.10 (m, 2H), 3.09 (bs, 1H); ^{13}C NMR: δ 145.1, 143.5, 135.9, 128.5, 127.7, 127.2, 125.8, 120.8, 114.0, 73.2, 35.4. HRMS (ESI-TOF). Calcd for $C_{14}H_{13}N_3OS$ $[M+Na]^+$: *m/z* 294.06715. Found: *m/z* 294.07159.

2-(1-allyl-1*H*-1,2,3-triazol-4-yl)-1-phenylethanol (9): Yellow crystals; yield 170 mg (74%); mp 72–74°C; ^{1}H NMR: δ 7.297.16 (m, 6H), 5.93–5.84 (m, 1H), 5.23 (dd, *J* = 1.0 and 10.2 Hz, 1H), 5.15 (dd, *J* = 0.9 and 17.0 Hz, 1H), 4.95 (dd, *J* = 5.1 and 7.5 Hz, 1H), 4.82 (d, *J* = 6.2 Hz, 2H), 4.25 (bs, 1H), 3.03–3.01 (m, 2H); ^{13}C NMR: δ 145.0, 143.6, 131.2, 128.4, 127.5, 125.8, 122.1, 120.0, 73.1, 52.6, 35.4. HRMS (ESI-TOF). Calcd for $C_{13}H_{15}N_3O$ $[M+H]^+$: *m/z* 230.12879. Found: *m/z* 230.13119.

2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-1-phenylethanol (10): White crystals; yield 180 mg (65%); mp 117–120°C; ^{1}H NMR: δ 7.29–7.10 (m, 11H), 5.39 (s, 2H), 4.96 (dd, *J* = 4.9 and 7.6 Hz, 1H), 3.02–3.00 (m, 2H); ^{13}C NMR: δ 144.1, 142.5, 133.5, 128.1, 127.7, 127.3, 127.0, 126.5, 124.7, 121.1, 72.1, 53.1, 34.4. HRMS (ESI-TOF). Calcd for $C_{17}H_{17}N_3O$ $[M+H]^+$: *m/z* 280.14444. Found: *m/z* 280.14765.

2-(1-Phenyl-1*H*-1,2,3-triazol-4-yl)-1-(2-thienyl)ethanol (11): Yellow crystals; yield 240 mg; (88%); mp 115–118°C; ^{1}H NMR: δ 7.79 (s, 1H), 7.71–7.68 (m, 2H), 7.53–7.49 (m, 2H), 7.45–7.41 (m, 1H), 7.27–7.25 (m, 1H), 7.02–7.00 (m, 1H), 6.98–6.96 (m, 1H), 5.38 (dd, *J* = 4.9 and 7.6 Hz, 1H), 3.66 (bs, 1H), 3.34–3.31 (m, 2H); ^{13}C NMR: δ 147.4, 145.0, 137.0, 129.7, 128.7, 126.7, 124.6, 123.8, 120.5, 120.4, 69.3, 35.6. HRMS (ESI-TOF). Calcd for $C_{14}H_{13}N_3OS$ $[M+H]^+$: *m/z* 272.08521. Found: *m/z* 272.08854.

4-(4-(2-Hydroxy-2-(2-thienyl)ethyl)-1*H*-1,2,3-triazol-1-yl)phenol(12): Yellow crystals; yield 43 mg; (15%) mp 108–110°C; ^{1}H NMR: δ 7.62 (s, 1H), 7.27–7.25 (m, 3H), 6.99–6.95 (m, 4H), 5.39–5.37 (m, 1H), 5.06 (bs, 1H), 2.99 (s, 2H) ^{13}C NMR: δ 146.9, 144.1, 139.5, 129.3, 126.3, 124.3, 123.6, 120.0, 119.1, 106.9, 68.9, 35.1. HRMS (ESI-TOF). Calcd for $C_{14}H_{13}N_3O_2S$ $[M+H]^+$: *m/z* 288.08012. Found: *m/z* 288.08223.

1-(2-Thienyl)-2-(1-*p*-tolyl-1*H*-1,2,3-triazol-4-yl)ethanol (13): Yellow crystals; yield 117 mg (41%); mp 119–121°C; ^{1}H NMR: δ 7.74 (s, 1H), 7.57–7.54 (m, 2H), 7.30–7.27 (m, 2H), 7.25–7.24 (m, 1H), 7.00–6.99 (m, 1H), 6.97–6.95 (m, 1H), 5.36 (dd, *J* = 4.9 and 7.4 Hz, 1H), 3.31–3.29 (m, 2H); ^{13}C NMR: δ 147.6, 144.8, 138.8, 134.7, 130.2, 126.7, 124.5, 123.7, 120.6, 120.3, 69.2, 35.6, 21.1. HRMS (ESI-TOF). Calcd for $C_{15}H_{15}N_3OS$ $[M+H]^+$: *m/z* 286.10092. Found: *m/z* 286.10281.

2-(1-(1-Naphthyl-1*H*-1,2,3-triazol-4-yl)-1-(2-thienyl)ethanol (14): White crystals; yield 239 mg (74%) mp 110–112°C; ^{1}H NMR: δ 8.00–7.92 (m, 2H), 7.68 (s, 1H), 7.58–7.49 (m, 5H), 7.26–7.24 (m, 1H), 7.02–6.96 (m, 2H), 5.47–5.43 (m, 1H), 3.85 (bs, 1H), 3.39 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR: δ 147.6, 144.1, 134.0, 133.6, 130.3, 128.4, 128.2, 127.8, 127.0, 126.7, 125.1, 125.0, 124.6, 123.8, 123.5, 122.3, 69.4, 35.6. HRMS (ESI-TOF). Calcd for $C_{18}H_{15}N_3OS$ $[M+Na]^+$: *m/z* 344.08280. Found: *m/z* 344.08742.

2-(1-(3-Pyridyl)-1*H*-1,2,3-triazol-4-yl)-1-(thiophen-2-yl)ethanol (15): Yellow crystals; yield 177 mg (65%) mp 123–126°C; ^{1}H NMR: δ 8.94–8.93 (m, 1H), 8.67–8.65 (m, 1H), 8.16–8.13 (m, 1H), 7.88 (s, 1H), 7.53–7.49 (m, 1H), 7.28–7.25 (m, 1H), 7.02–7.01 (m, 1H), 6.99–6.96 (m, 1H), 5.40–5.37 (m, 1H), 4.91 (bs, 1H), 3.37–3.34 (m, 2H); ^{13}C NMR: δ 149.4, 147.4, 145.6, 141.0, 133.7, 128.3, 126.7, 124.7, 124.5, 123.9, 120.6, 69.1, 35.6. HRMS (ESI-TOF). Calcd for $C_{13}H_{12}N_4OS$ $[M+Na]^+$: *m/z* 295.06240. Found: *m/z* 295.06733.

1-(2-Thienyl)-2-(1-(3-thienyl)-1*H*-1,2,3-triazol-4-yl)ethanol (16): Yellow crystals; yield 186 mg (67%); mp 124–126°C; ^{1}H NMR: δ 7.72 (s, 1H), 7.51 (s, 1H), 7.43 (s, 2H), 7.27–7.24 (m, 1H), 6.99–6.96 (m, 2H), 5.37–5.35 (m, 1H), 3.68 (bs, 1H), 3.30–3.28 (m, 2H); ^{13}C NMR: δ 144.8, 142.0, 132.3, 124.6, 124.1, 122.1, 121.3, 118.3, 118.2, 111.4, 66.8, 32.9. HRMS (ESI-TOF). Calcd for $C_{12}H_{11}N_3OS_2$ $[M+Na]^+$: *m/z* 300.02357. Found: *m/z* 300.02736.

2-(1-Allyl-1*H*-1,2,3-triazol-4-yl)-1-(2-thienyl)ethanol (17): Yellow crystals; yield 168 mg (71%); mp 69–71°C; ^{1}H NMR: δ 7.33 (s, 1H), 7.23–7.21 (m, 1H), 6.94–6.93 (m, 2H), 6.02–5.92 (m, 1H), 5.33–5.21 (m, 3H), 4.92–4.91 (m, 2H), 3.22–3.21 (m, 2H); ^{13}C NMR: δ 147.7, 144.4, 131.2, 126.5, 124.3, 123.6, 122.3, 119.9, 69.1, 52.5, 35.6. HRMS (ESI-TOF). Calcd for $C_{11}H_{13}N_3OS$ $[M+Na]^+$: *m/z* 258.06715. Found: *m/z* 258.07055.

2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-1-(2-thienyl)ethanol (18): Yellow crystals; yield 200 mg (70%); mp 112–114°C; ^{1}H NMR: δ 7.38–7.34 (m, 3H), 7.23–7.20 (m, 4H), 6.93–6.92 (m, 2H), 5.49 (d, *J* = 2.6 Hz, 2H), 5.29 (dd, *J* = 5.1 and 6.9 Hz, 1H), 3.20–3.18 (m, 2H); ^{13}C NMR: δ 147.3, 144.8, 134.6, 129.1, 128.7, 128.0, 126.6, 124.5, 123.6, 122.1, 69.4, 54.1, 35.5. HRMS (ESI-TOF). Calcd for $C_{15}H_{15}N_3OS$ $[M+Na]^+$: *m/z* 308.08280. Found: *m/z* 308.08695.

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