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Tetrahedron 62 (2006) 6405–6411
Tetrahedron

Synthesis of 1,4,5-trisubstituted-1,2,3-triazoles by copper-catalyzed cycloaddition-coupling of azides and terminal alkynes

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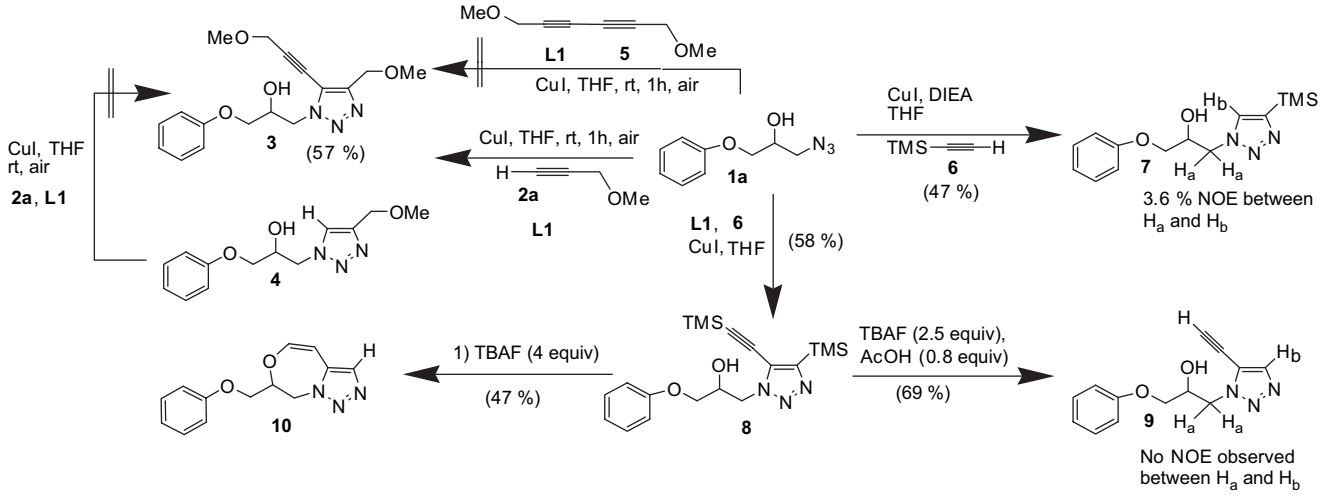
Received 10 February 2006; revised 1 April 2006; accepted 6 April 2006
Available online 12 May 2006

Abstract—Primary, secondary, and aromatic azides undergo 1,3 dipolar cycloaddition-coupling with an excess of alkyne in the presence of $Cu(CH_3CN)_4PF_6$ as catalyst, *N*,*N*,*N*′-trimethylethylenediamine as ligand, molecular oxygen, and 4-methoxymorpholine *N*-oxide (NMO) as co-oxidant to afford 1,4,5-trisubstituted-1,2,3-triazoles.

1. Introduction

1,2,3-Triazoles have received significant attention as biologically important heterocycles.[1] These compounds are typically prepared by thermal cycloaddition of azides and alkynes to afford a mixture of 1,4- and 1,5-disubstituted isomers.[2] Alternative methods have been developed to gain regioselectivity such as the use of push–pull alkenes containing a leaving group.[3] Recent publications from Sharpless and co-workers,[4] Meldal and co-workers,[5] and others[6] have reported copper(I) catalysis for regioselective cycloaddition of terminal alkynes and azides to afford exclusively 1,4-disubstituted-1,2,3-triazoles. Our interest in this methodology involved applications to diversify resin-bound alkynes.[7] Based on previous studies, we employed amine ligands in order to increase the solubility of copper(I).[8] However, treatment of hydroxy azide **1a** and alkyne **2a** (Scheme 1) with CuI and *N*,*N*-dimethylethylenediamine **L1** (Fig. 1) as ligand led unexpectedly to the production of 5-alkynyl-1,2,3-triazole **3**. Sharpless and co-workers have also observed these derivatives in the direct synthesis of trisubstituted triazoles via addition of bromomagnesium acetylides to azides.[9] In this communication, we report the regioselective formation of 1,4,5-trisubstituted-1,2,3-triazoles via copper-catalyzed cycloaddition-coupling and our initial studies concerning the scope and limitation of the process.



Scheme 1.

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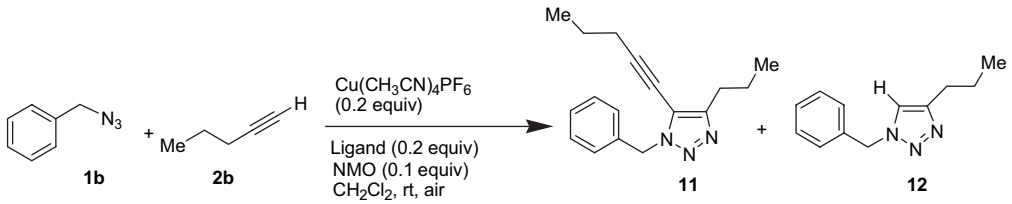
doi:10.1016/j.tet.2006.04.025



Scheme 2.

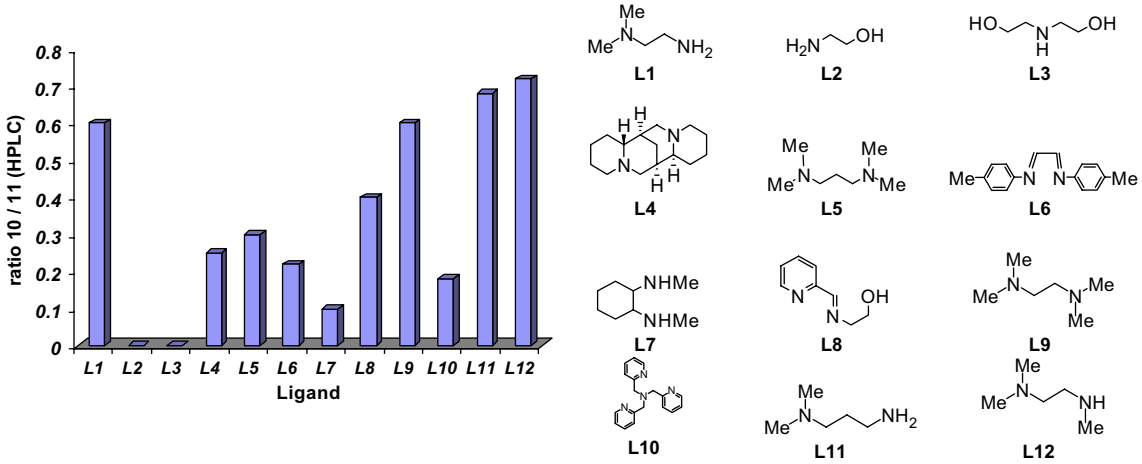
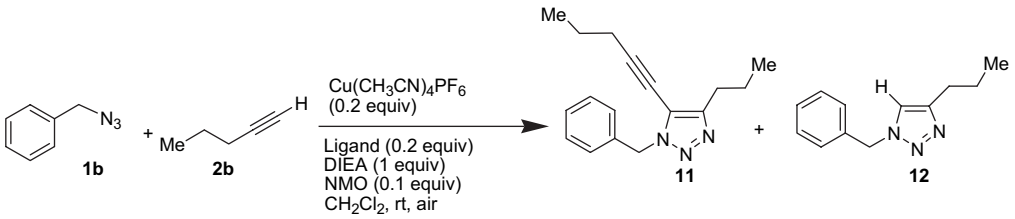


Figure 1. Parallel ligand evaluation. Ratio of **11/12** determined by HPLC analysis (gradient: 70:30 to 30:70 water/acetonitrile in 10 min) using evaporative light scattering detection (ELSD).

2. Results and discussion

We first conducted control experiments to define the requirements for copper source and alkyne coupling partner. Initial studies found that Cu(II) sources (e.g., $CuCl_2$) were not effective for cycloaddition-coupling of **1a** and **2a**. In addition, when Cu(I) or both Cu(I) and Cu(II) catalysts were used under oxygen-free conditions, only 1,4-disubstituted triazole **4** was observed. These results indicate that the presence of both Cu(I) and Cu(II) in an oxygen atmosphere maybe necessary for the production of **3**. Because the oxidative coupling of terminal alkynes (Glaser reaction) is also conducted using similar conditions (Hay's conditions),[10] we reasoned that the product **3** maybe formed by an initial Glaser coupling and subsequent 1,3-dipolar cycloaddition. However, treatment of 1,6-dimethoxyhexa-2,4-diyne[11] **5** and hydroxy azide **1a** with CuI and *N*,*N*-dimethylethylenediamine **L1** led to no reaction.[12] An alternative pathway may involve initial formation of 1,4-disubstituted triazole **4** and subsequent insertion of a second equivalent of alkyne at C5. Treatment of disubstituted triazole **4** with alkyne **2a** in the presence of CuI and *N*,*N*-dimethylethylenediamine **L1** led to no reaction. This result indicates that 1,4-disubstituted triazole **4** is not likely a discrete intermediate en route to 1,4,5-trisubstituted triazole **3**. The regioselectivity of the cycloaddition-coupling process was verified by the experiments outlined in Scheme 1. Copper(I)-mediated cycloaddition[4] of hydroxy azide **1a** and trimethylsilyl acetylene **6** afforded 1,4-triazole **7** (47%). The regiochemistry of **7** was confirmed using NOE difference NMR spectroscopy (3.6% NOE from the C5 vinyl hydrogen to the indicated methylene). Treatment of **1a** with **6**, **L1**, and CuI (THF, rt, and 8 h) afforded 1,4,5-trisubstituted triazole **8** (58%). Desilylation of **8** with tetrabutylammonium fluoride (TBAF) (1 equiv) buffered with acetic acid afforded 1,2,3-triazole **9** (69%), which did not have a corresponding NOE between the vinylic and methylene hydrogens. Interestingly, desilylation of **8** with TBAF (4 equiv, unbuffered) produced triazole oxepin **10** through 7-*endo*-*dig* cyclization.[13]

Further optimization of reaction conditions indicated that the copper source and oxygen diffusion were important factors for the reaction.[14] Tetrakisacetonitrile copper(I)hexafluorophosphate was found to be the most effective copper catalyst examined; use of an amine oxide as co-oxidant minimized the complication of direct delivery of oxygen[15] possibly by facilitating formation of high valent copper intermediates.[16] Reaction optimization (data not shown) indicated that a 2:1 ratio of Cu(I)/*N*-methylmorpholine oxide (NMO) afforded 1,4,5-trisubstituted triazole **3** in optimal yield (64%). Parallel evaluation of amino ligands[8] was next conducted in order to define structural requirements for formation of trisubstituted versus disubstituted triazoles using benzyl azide **1b** and pentyne **2b** as substrates (Scheme 2). We found that the nature of the diamine ligand had a pronounced effect on the ability to facilitate the formation of triazole **11** (Fig. 1). Interestingly, the presence of N–H functionality on the ligand favored **11** as the major product (ligands **L11** and **L12**), whereas peralkylated ligands increased selectivity toward the disubstituted product **12** (**L4** and **L10**) and hydroxyl amine ligands **L2** and **L3** led to no reaction. Further optimization using ligands **L5**, **L9**, **L11**, and **L12** was performed (Scheme 2 and Fig. 2). We found that addition of 1 equiv of Hünig's base (DIEA) at rt noticeably improved the ratio of **11/12**, optimally using **L12** (*N*,*N*,*N*′-trimethylethylenediamine) as ligand (Scheme 3). Additionally, a control experiment was



Scheme 3.

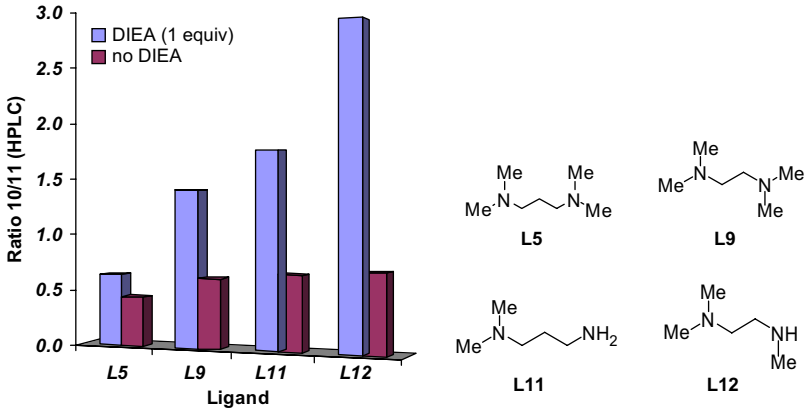


Figure 2. Parallel evaluation of selected ligands in presence of Hünig's base (DIEA, 1 equiv). Ratio of **11/12** determined by HPLC analysis (gradient: 70:30 to 30:70 water/acetonitrile in 10 min) using evaporative light scattering detection (ELSD).

performed without diamine ligand **L12**, reasoning that it might be possible that the added DIEA may also serve as a ligand. Although, the reaction went to completion under these conditions, the ratio of trisubstituted/disubstituted triazole for this reaction was significantly decreased (1:1).

We next investigated the cycloaddition-coupling using a number of azide and alkyne substrates using the optimized conditions in which DIEA (1 equiv) was included (Table 1 and Scheme 4). In many cases, lower isolated yields were likely due to competing Glaser coupling (diyne formation, entries 5, 6, and 7) and cycloaddition to afford 1,4-disubstituted triazoles without further alkynylation. Higher selectivity for the formation of trisubstituted triazoles was observed using a β-hydroxy azide (entries 1 and 2). Stabilization of a putative vinyl copper intermediate by hydroxyl chelation may account for this selectivity (Fig. 3).[17]

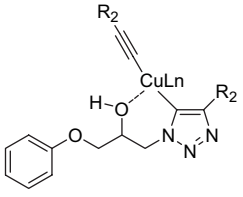


Figure 3.

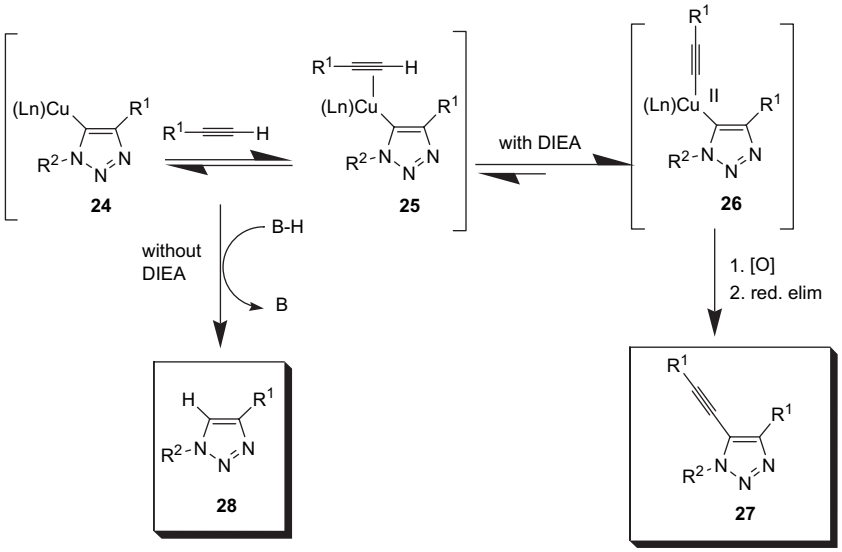
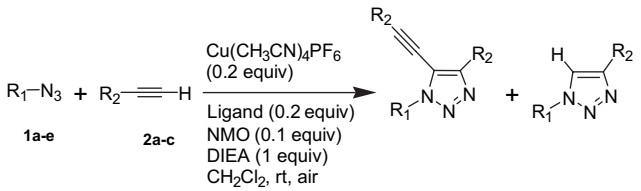


Figure 4.

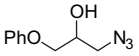
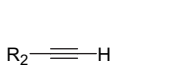
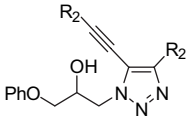
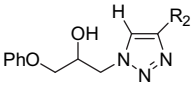
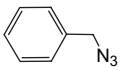
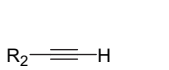
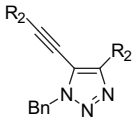
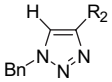
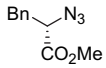
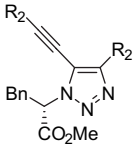
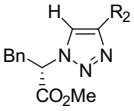
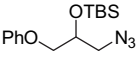
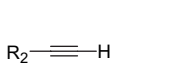
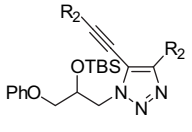
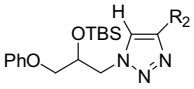
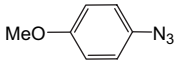
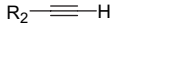
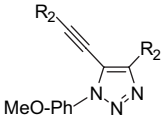
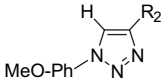


Scheme 4.

Blocking accessibility of the oxygen by silylation resulted in a decreased yield of 1,4,5-trisubstituted triazole (entry 7) reinforcing the lower selectivity generally observed for azides lacking a β-chelating group (entries 1 and 7).

Although it is not possible to define a detailed reaction mechanism at this stage,[18] the cycloaddition-coupling likely proceeds via formation of a Cu(II) intermediate such as **24** (Fig. 4). The role of the amine oxide maybe to oxidize **24** to a Cu(III) species to facilitate reductive elimination and regeneration of Cu(I).[19] The addition of Hünig's base may help the deprotonation step of a putative π Cu–acetylide complex **25** to σ-Cu–acetylide intermediate **26**. As described in a recent mechanistic study, the general mechanism shown in Figure 4 may involve binuclear or multinuclear copper complexes. Additional mechanistic studies to determine the nature of the copper acetylide undergoing cycloaddition and possible involvement of dicopper–dioxo complexes[20] are currently under investigation.

Table 1. Synthesis of 1,4,5-trisubstituted-1,2,3-triazoles by copper-catalyzed cycloaddition-coupling of azide (**1a–e**) and alkynes (**2a–c**)

Entry	Azide	Alkyne	Product (yield (%))[a]	
				
1	**1a**	R_2=MeOCH$_2$ **2a**	**3** (68)[b]	**4** (32)
2	**1a**	R_2=*n*Pr **2b**	**13** (57)[b]	**14** (25)
				
3	**1b**	R_2=*n*Pr **2b**	**11** (61)	**12** (23)
4	**1b**	R_2=Ph **2c**	**15** (42)[a]	**16** (46)
				
5	**1c**	R_2=MeOCH$_2$ **2a**	**17** (55)	**18** (24)
6	**1c**	R_2=*n*Pr **2b**	**19** (55)	**20** (31)
				
7	**1d**	R_2=MeOCH$_2$ **2a**	**21** (31)	**22** (45)
				
8	**1e**	R_2=MeOCH$_2$ **2a**	**23** (49)[a]	**24** (32)

[a] Reactions were conducted with 0.4 equiv of Cu(CH$_3$CN)$_4$PF$_6$ and 0.4 equiv of *N*,*N*,*N*′-trimethylethylenediamine **L12**.
[b] Reactions were conducted with 0.3 equiv of Cu(CH$_3$CN)$_4$PF$_6$ and 0.3 equiv of *N*,*N*,*N*′-trimethylethylenediamine **L12**.

3. Conclusion

In summary, we have developed a dipolar cycloaddition-coupling process, which affords 1,4,5-trisubstituted-1,2,3-triazoles in a regioselective manner. The selectivity for trisubstituted triazole synthesis was shown to be dependent on the nature of the diamine ligand. Preliminary results indicate that a broad scope of azides and terminal alkynes maybe employed to prepare highly functionalized 1,4,5-trisubstituted-1,2,3-triazoles.[21] Further applications of the cycloaddition-coupling process are currently under investigation and will be reported in due course.

4. Experimental

4.1. General

Column chromatography was performed on silica gel (60–120 mesh size). Infrared resonance spectra were recorded on a Nicolet Impact 400 FTIR. ^{1}H (400 MHz) NMR spectra were recorded in $CDCl_3$ on a Varian spectrometer. HRMS were obtained on a Finnegan MAT-90 spectrometer. Optical rotations were recorded on an AUTOPOL III digital polarimeter at 589 nm, and are recorded as $[\alpha]_D$ (concentration in grams/100 mL solvent).

4.1.1. Preparation of two-layer Hydromatrix columns. To a 1 mL Isolute HM-N cartridge (Biotage, 800-0100-CM) was added 1 mL of 1 M EDTA and the cartridge was allowed to stand for 10 min. Volume of loose Celite® (1 mL) (C566 18/60, Celite Corporation) was then conditioned with 1 mL of 1 N HCl and allowed to stand for 10 min. The acidic material was layered onto the pre-packed Isolute cartridge and used for workup as described in the general procedure for the preparation of 1,4,5-trisubstituted-1,2,3-triazoles.

4.2. Experimental procedures

4.2.1. Attempted cycloaddition using dimethoxyhexa-2,4-diyne. To a solution of azido alcohol **1a** (100 mg, 0.53 mmol) in THF was added 21 mg of CuI (0.11 mmol) followed by 14 μL (0.11 mmol) of *N*,*N*,*N*′-trimethylethylenediamine. To the stirred solution was added 109 mg (0.795 mmol) of dimethoxyhexa-2,4-diyne **5**. The reaction was stirred at rt for 6 h. No conversion of starting material was observed.

4.2.2. Attempted alkynylation of 1,4-disubstituted-1,2,3-triazole (4). To a solution of disubstituted triazole **4** (50 mg, 0.19 mmol) in THF was added CuI (7 mg, 0.03 mmol) followed by 4 μL (0.03 mmol) of *N*,*N*,*N*′-trimethylethylenediamine. To the stirred solution was added 32 μL (27 mg, 0.38 mmol) of **2a**. The reaction was stirred at rt for 9 h. No conversion of starting material was observed.

4.2.3. Synthesis of 1-phenoxy-3-(4-trimethylsilyl-[1,2,3]-triazol-1-yl)-propan-2-ol (7). To a solution of azido alcohol **1a** (100 mg, 0.53 mmol) in THF was added 21 mg of CuI (0.11 mmol) followed by 460 μL (2.65 mmol) of diisopropylethylamine. To the stirred solution was added 82 μL (0.58 mmol) of trimethylsilyl acetylene **6**. The solution became yellow and a slight precipitate formed after 30 min. The reaction was stirred at rt for 12 h, the mixture was filtered, and the solvent was removed in vacuo. Flash chromatography (silica, 60:40 hexane/EtOAc) afforded 75 mg (0.26 mmol, 48%) of **7** as an amorphous solid (mp=80–83 °C). IR ν_{max} (film) 3216.1, 2955.9, 1599.4, 1587.9, 1496.1, 1247.7 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (1H, s), 7.28 (2H, t, J=7.6 Hz), 6.98 (1H, t), 6.86 (2H, d, J=8.4 Hz), 4.65 (1H, dd, J=3.6, 10.4 Hz), 4.54 (1H, dd, J=6.8, 7.2 Hz), 4.41 (1H, m), 3.98 (2H, d, J=5.6 Hz), 0.23 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 131.2, 130.0, 121.9, 114.9, 69.2, 69.1, 52.8, −0.93; HRMS (CI/NH_3) m/z calculated for $C_{14}H_{21}N_3O_2Si$, 291.1403; found, 291.1393.

4.2.4. Synthesis of 1-phenoxy-3-(4-trimethylsilanyl-5-trimethylsilanylethynyl-[1,2,3]triazol-1-yl)-propan-2-ol (8). Prepared according to the general procedure using 100 mg (0.53 mmol) of azido alcohol **1a**, 152 μL (1.5 mmol) of trimethylsilyl acetylene **6**, 41 mg (0.11 mmol) of tetrakisacetonitrile copper(I)hexafluorophosphate, 14 μL (0.11 mmol) of *N*,*N*,*N*′-trimethylethylenediamine, and 6 mg (0.053 mmol) of NMO. Flash chromatography (silica, 70:30 hexane/EtOAc) afforded 120 mg (0.3 mmol, 58%) of triazole **8** as an amorphous solid (mp=73–75 °C). IR ν_{max} (film) 3263.7, 2958.3, 2166.8, 1599.8, 1588.1, 1496.3, 1413.2, 1249.9 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (2H, t, J=8.4 Hz), 6.95 (1H, t, J=7.6 Hz), 6.87 (2H, d, J=8.4 Hz), 4.67–4.50 (3H, overlap), 4.08–3.96 (2H, m), 3.39 (1H, d, J=5.2 Hz), 0.34 (3H, s), 0.24 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 130.1, 121.9, 114.9, 70.2, 69.7, 69.3, 69.0, 68.7, 53.7, 51.4, 46.3, −0.33, −1.4; HRMS (CI/NH_3) m/z calculated for $C_{19}H_{29}N_3O_2Si_2$, 387.1798; found, 388.1865 (M+H).

4.2.5. Preparation of 1-(5-ethynyl-[1,2,3]triazol-1-yl)-3-phenoxy-propan-2-ol (9). To a solution of 40 mg (0.03 mmol) of bis-TMS triazole **8** in 0.5 mL of THF was added 6 μL of AcOH followed by 300 μL (0.075 mmol) of 1.0 M tetrabutylammonium fluoride in THF. The reaction was stirred for 6 h at rt and the solvent was removed in vacuo. Flash chromatography (silica, 50:50 hexane/EtOAc) afforded 20 mg (0.082 mmol, 69%) of **9** as a colorless oil. IR ν_{max} (film) 3279.9, 2919.1, 2850.4, 1599.3, 1588.1, 1496.7, 1244.6 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (1H, s), 7.28 (2H, t, J=8.8 Hz), 6.98 (1H, t, J=7.2 Hz), 6.89 (2H, d, J=8.4 Hz), 4.73–4.62 (2H, m), 4.53 (1H, dd, J=6, 5.2 Hz), 3.65 (1H, s), 3.00 (1H, d, J=6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6, 132.7, 125.1, 117.3, 110.0, 94.5, 71.6, 62.5, 48.5; HRMS (CI/NH_3) m/z calculated for $C_{13}H_{13}N_3O_2$, 243.1008; found, 244.1105 (M+H).

4.2.6. Preparation of 7-phenoxymethyl-4,5,7,8-tetrahydro-6-oxa-1,2,8a-triaza-azulene (10). Bis-TMS triazole **7** (60 mg, 0.18 mmol) was dissolved in 1 mL of THF. To this was added 700 μL of 1.0 M tetrabutylammonium fluoride in THF. The reaction was stirred for 12 h at rt and the solvent was removed in vacuo. Flash chromatography (silica, 70:30 hexane/EtOAc) afforded 24 mg (0.099 mmol, 53%) of bicyclic triazole **10** as a colorless oil. IR ν_{max} (film) 2928.8, 1656.1, 1650.1, 1598.8, 1587.8, 1494.6, 1304.2, 1243.5 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (1H, s), 7.30 (2H, t, J=8.0 Hz), 6.99 (1H, t, J=7.2 Hz), 6.91 (2H, d, J=8.4 Hz), 6.59 (1H, d, J=7.6 Hz), 5.56 (1H, d, J=7.6 Hz), 5.52 (1H, m), 4.53–4.45 (3H, overlap),

4.31 (1H, dd, J=3.6, 6.4 Hz), 4.17 (1H, dd, J=4.8, 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.4, 141.8, 127.5, 125.2, 117.3, 110.0, 84.5, 71.6, 62.5, 48.5; HRMS (CI/NH_3) m/z calculated for $C_{13}H_{13}N_3O_2$, 243.1008; found, 243.1018.

4.3. General procedure for the preparation of 1,4,5-trisubstituted-1,2,3-triazoles

Tetrakisacetonitrile copper(I)hexafluorophosphate (0.05 mmol) was placed in a 110 mL miniblock XT reaction vessel (Mettler Toledo Autochem) and dissolved in 2 mL of CH_2Cl_2 (15×45 mm) with the vessel open to the atmosphere. *N*,*N*,*N*′-Trimethylethylenediamine (6.3 μL, 0.05 mmol) was then added to afford a purple solution. A solution of azide **1a–e** (0.26 mmol) and alkyne **2a–c** (0.55 mmol) in 1 mL of CH_2Cl_2 was then added. After 5 min NMO (0.025 mmol) was added and the resulting green solution was stirred for 20 min at rt. The solution was transferred to a two-layer Hydromatrix column (see Section 4.1.1). After washing the Hydromatrix column with CH_2Cl_2 (5 mL), the solution was concentrated in vacuo to afford a yellow oil. Purification via flash chromatography (30:70 hexane/EtOAc) afforded trisubstituted triazole as a colorless oil.

4.4. Characterization data

4.4.1. 1-[4-Methoxymethyl-5-(3-methoxy-prop-1-ynyl)-[1,2,3]-triazol-1-yl]-3-phenoxy-propan-2-ol (3). Colorless oil; IR ν_{max} (film) 3367.0, 2924.3, 2819.4, 1600.0, 1491.3, 1448.5, 1359.2, 1293.2, 1246.6, 1099.1, 834.9, 761.2 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (1H, d, J=8 Hz), 7.27 (1H, d, J=7.4 Hz), 6.97 (1H, t, J=7.4 Hz), 6.87 (2H, d, J=8 Hz), 4.60–4.70 (2H, m), 4.55 (2H, s), 4.49–4.51 (1H, m), 4.39 (2H, s), 4.29 (2H, s), 3.90–4.10 (1H, m), 3.40 (3H, s), 3.38 (3H, s), 3.10–3.11 (1H, d, J=6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6, 142.3, 125.1, 117.0, 116.6, 109.9, 94.1, 66.0, 64.2, 63.9, 60.1, 55.5, 53.8, 46.9; HRMS (CI/NH_3) m/z calculated for $C_{17}H_{21}N_3O_4$, 331.1532; found, 332.1580 (M+H).

4.4.2. 1-(4-Methoxymethyl-[1,2,3]-triazol-1-yl)-3-phenoxy-propan-2-ol (4). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (1H, s), 7.28 (1H, d, J=8.4 Hz), 7.26 (1H, d, J=7.2 Hz), 6.98 (1H, t, J=7.2 Hz), 6.87 (2H, d, J=8.4 Hz), 4.68–4.69 (1H, dd, J=3.2, 14 Hz), 4.56 (2H, s), 4.55–4.49 (1H, dd, J=6.8, 14 Hz), 4.45–4.43 (1H, m), 4.00–3.96 (1H, dd, J=5.2, 9.6 Hz), 3.94–3.90 (1H, dd, J=6, 9.6 Hz), 3.39 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8, 140.7, 125.1, 119.4, 117.1, 110.2, 64.4, 64.3, 61.3, 53.6, 48.3; HRMS (CI/NH_3) m/z calculated for $C_{13}H_{17}N_3O_3$, 263.1270; found, 264.1362 (M+H).

4.4.3. 1-Benzyl-4-methoxymethyl-5-(3-methoxy-prop-1-ynyl)-1*H*-[1,2,3]-triazole (11). Colorless oil; IR ν_{max} (film) 2996.9, 2926.1, 2823.3, 1731.9, 1565.4, 1501.6, 1459.1, 1363.4, 1186.2, 1097.6, 895.7 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (5H, s), 5.56 (2H, s), 4.56 (2H, s), 4.35 (2H, s), 3.40 (3H, s), 3.37 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7, 129.9, 124.4, 124.1, 123.9, 123.5, 93.9, 66.5, 60.2, 55.6, 53.8, 53.3, 48.3; HRMS (CI/NH_3) m/z calculated for $C_{15}H_{17}N_3O_2$, 271.1321; found, 272.1428 (M+H).

4.4.4. 1-(5-Pent-1-ynyl-4-propyl-[1,2,3]-triazol-1-yl)-3-phenoxy-propan-2-ol (13). Colorless oil; IR ν_{max} (film) 3246.6, 2959.2, 2920.4, 2862.1, 1592.3, 1580.6, 1495.1, 1444.6, 1242.7, 1048.6, 831.1, 741.8, 687.4 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (1H, t, J=8.4 Hz), 7.26 (1H, d, J=7.2 Hz), 6.97 (1H, t, J=7.2 Hz), 6.88 (2H, d, J=8.4 Hz), 4.46–4.62 (3H, m), 4.02–4.05 (1H, dd, J=5.6, 9.6 Hz), 3.97–3.93 (1H, dd, J=5.6, 9.6 Hz), 3.17 (1H, d, J=5.2 Hz), 2.66 (2H, t, J=7.6 Hz), 2.40 (2H, t, J=7.2 Hz), 1.71 (2H, sextet, J=7.6 Hz), 1.61 (2H, sextet, J=7.2 Hz), 1.02 (3H, t, J=7.6 Hz), 0.93 (3H, t, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7, 145.4, 125.1, 116.9, 116.1, 109.9, 98.8, 64.3, 63.9, 61.3, 46.5, 22.8, 17.5, 17.1, 16.9, 9.1, 8.8; HRMS (CI/NH_3) m/z calculated for $C_{19}H_{25}N_3O_2$, 327.1947; found, 328.2018 (M+H).

4.4.5. 1-Benzyl-5-pent-1-ynyl-4-propyl-1*H*-[1,2,3]-triazole (15). Colorless oil; IR ν_{max} (film) 3033.2, 3962.1, 2933.4, 2872.2, 1558.4, 1496.9, 1456.2, 1429.5, 1338.7, 731.9 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.2–7.4 (5H, m), 5.48 (1H, s), 2.66 (2H, t, J=7.2 Hz,), 2.41 (2H, t, J=7 Hz), 1.71 (2H, sextet, J=7.2 Hz), 1.59 (2H, sextet, J=7 Hz), 0.98 (3H, t, J=7.2 Hz), 0.93 (3H, t, J=7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8, 130.7, 124.2, 123.7, 123.4, 98.4, 61.8, 47.8, 22.9, 17.6, 17.1, 16.9, 9.1, 8.8; HRMS (CI/NH_3) m/z calculated for $C_{17}H_{21}N_3$, 267.1735; found, 267.1719.

4.4.6. 2-[4-Methoxymethyl-5-(3-methoxy-prop-1-ynyl)-[1,2,3]-triazol-1-yl]-3-phenyl-propionic acid methyl ester (17). Colorless oil; $[\alpha]_D^{22}$ −36.0 (c 0.1, $CHCl_3$); IR ν_{max} (film) 2954.4, 2926.1, 2844.5, 1746.1, 1629.1, 1498.1, 1448.4, 1264.2, 1264.2, 1214.6, 1101.2 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17–7.18 (3H, m), 7.02–7.04 (2H, m), 5.46–5.42 (1H, q, J=5.3 Hz), 4.51 (2H, s), 4.30 (2H, s), 3.75 (3H, s), 3.62–3.64 (2H, m), 3.38 (3H, s), 3.30 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5, 130.9, 124.4, 124.2, 123.5, 122.8, 65.9, 60.0, 58.6, 55.5, 53.5, 53.3, 48.6, 32.4; HRMS (CI/NH_3) m/z calculated for $C_{18}H_{21}N_3O_4$, 343.1532; found, 344.1606 (M+H).

4.4.7. 2-(5-Pent-1-ynyl-4-propyl-[1,2,3]-triazol-1-yl)-3-phenyl-propionic acid methyl ester (19). Colorless oil; $[\alpha]_D^{22}$ −53.5 (c 0.5, $CHCl_3$); IR ν_{max} (film) 3060.2, 3025.2, 2951.5, 2928.1, 2846.6, 2217.5, 1452.4, 1429.1, 1335.9, 1277.7, 1262.1, 1219.5, 986.4, 772.8, 749.5, 687.4 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16–7.27 (3H, dd, J=1.6, 7.6 Hz), 7.00–7.02 (2H, dd, J=1.6, 7.6 Hz), 5.36–5.40 (1H, dd, J=6, 9.2 Hz), 3.73 (3H, s), 3.62–3.66 (2H, m), 2.61 (2H, t, J=7.4 Hz), 2.38 (2H, t, J=7.6 Hz), 1.66 (2H, sextet, J=7.4 Hz), 1.58 (2H, sextet, J=7.6 Hz), 0.99 (3H, t, J=7.4 Hz), 0.86 (3H, t, J=7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 145.2, 131.3, 124.5, 124.3, 124.1, 122.6, 98.9, 61.3, 58.2, 48.4, 32.4, 22.6, 17.5, 17.1, 16.9, 8.9, 8.8; HRMS (CI/NH_3) m/z calculated for $C_{20}H_{25}N_3O_2$, 339.1947; found, 340.1997 (M+H).

4.4.8. 1-[2-(*tert*-Butyl-dimethyl-silanyloxy)-3-phenoxy-propyl]-4-methoxymethyl-5-(3-methoxy-prop-1-ynyl)-1*H*-[1,2,3]-triazole (21). Colorless oil; IR ν_{max} (film) 2928.2, 2850.5, 1592.2, 1487.4, 1452.4, 1246.6, 1095.1, 834.9, 772.8 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (1H, d, J=8.4 Hz), 7.26 (1H, d, J=7.2 Hz), 6.96 (1H, t, J=7.2 Hz), 6.87

(2H, d, J=8.4 Hz), 4.66–4.62 (1H, dd, J=4.4, 13.2 Hz), 4.56 (2H, s), 4.50–4.45 (1H, dd, J=7.6, 13.2 Hz), 4.32 (2H, s), 3.99–3.92 (3H, m), 3.42 (3H, s), 3.38 (3H, s), 0 (3H, s), −0.2 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8, 142.3, 125.1, 116.7, 109.9, 93.7, 72.8, 65.4, 65.0, 60.1, 55.6, 53.6, 53.3, 47.9, 21.0, 20.9, 132, −9.6, −10.1; HRMS (CI/NH_3) m/z calculated for $C_{23}H_{35}N_3O_4Si$, 445.2397; found, 446.2462 (M+H).

4.4.9. 4-Methoxymethyl-5-(3-methoxy-prop-1-ynyl)-1-(4-methoxy-phenyl)-1*H*-[1,2,3]-triazole (23). Colorless oil; IR ν_{max} (film) 2932.1, 1751.5, 1592.2, 1518.3, 1258.3, 1099.1, 834.9, 737.9, 675.7 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (2H, d, J=9.2 Hz), 7.00 (2H, d, J=9.2 Hz), 4.63 (2H, s), 4.31 (2H, s), 3.86 (3H, s), 3.45 (3H, s), 3.36 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 143.1, 120.6, 120.5, 109.9, 93.4, 88.4, 67.1, 60.2, 55.6, 53.9, 53.3, 51.0; HRMS (CI/NH_3) m/z calculated for $C_{15}H_{17}N_3O_3$, 287.1270; found, 288.1319 (M+H).

Acknowledgements

We thank Professors Sean Elliott, Scott Schaus (Boston University), and Valery Fokin (Scripps Research Institute) for helpful discussions. Financial support for this project from Boston University and Boehringer Ingelheim Pharmaceuticals, Inc. (Ridgefield, CT) is gratefully acknowledged. We thank Bristol-Myers Squibb for an unrestricted Grant in Synthetic Organic Chemistry (J.A.P.), Novartis Pharma AG for research support, and Mettler Toledo Autochem for assistance with reaction blocks.

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