Inorganica Chimica Acta 363 (2010) 2520–2525

Contents lists available at ScienceDirect

Inorganica Chimica Acta

journal homepage: www.elsevier.com/locate/ica

Rhenium tricarbonyl complexes of 1-benzyl-4-(5-bipyridyl)-1H-1,2,3-triazoles

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ARTICLE INFO

Article history:
Received 20 January 2010
Received in revised form 10 April 2010
Accepted 13 April 2010
Available online 20 April 2010

Keywords:
Cu(I) catalyzed [3+2] cycloaddition reactions
Rhenium complexes
Bipyridine complexes

ABSTRACT

Copper(I) catalyzed [3+2] cycloaddition reactions between 5-ethynylbipyridine and benzyl, *p*-methylbenzyl, or *m*-bromobenzyl azides yields the corresponding 1-benzyl-4-(5-bipyridyl)-1H-1,2,3-triazoles **1**–**3**. Reaction between **1**–**3** and $[NEt_4]_2[Re(CO)_3Br_3]$ yields the [1-benzyl-4-(5-bipyridyl)-1H-1,2,3-triazole]$Re(CO)_3Br$ complexes **4**–**6**. The $Re(CO)_3Br$ complexes of 5- and 6-ethynylbipyridine complexes (**7**–**8**) are prepared in a similar fashion. Cycloaddition reactions between **7** and benzyl azide yields mixtures of **4** and unreacted starting material.

1. Introduction

The coordination chemistry of rhenium is relevant to the biomedical community since rhenium compounds can be used as models for analogous ^{99m}Tc complexes useful in a broad range of imaging applications [1,2]. Coordination compounds containing radioactive isotopes of rhenium (e.g. ^{186}Re and ^{188}Re) have also been investigated as therapeutic agents for bone and other cancer [2b,3]. A recurrent theme in this research is the ongoing search for bifunctional chelating agents (BFCA) [2], which consist of a targeting molecule, a linker and a chelating ligand for the metal or radionuclide. The targeting molecule can include hormones [4], peptides [5], fatty acids [6], and carbohydrates [7]. Among the linkers that have been explored are hydrocarbon chains [4], polyethers [8] and polypeptides [2,5]. Amino acids [9], pyridyl amines [10], thioethers [11], phosphates [12] and peptide nucleic acids [13] have all been reported as chelating groups for Re and Tc in BFCA's. From the perspective of chemical synthesis, the preparation of BFCA's should proceed rapidly, in high yield and with a minimum number of steps. The coordination of the metal should be the final step and have a large formation constant.

Bipyridines are known to be excellent chelating ligands for a wide range of transition metals. We have been exploring the chemistry of 5-ethynylbipyridine in copper-catalyzed [3+2] cycloaddition reactions with organic azides as a potentially versatile route to BFCA's. In this paper we report on the synthesis and characterization of 1-benzyl-4-(5-bipyridyl)-1H-1,2,3-triazoles derived from copper-catalyzed reactions of 5-ethynylbipyridine and three substituted benzyl azides as a "proof of concept" for future efforts toward the preparation of BFCA's bearing the bipyridyl moiety as the chelating ligand (Scheme 1). We also describe the synthesis and characterization of rhenium carbonyl derivatives of the new triazole ligands as well as our explorations of copper-catalyzed "click" chemistry of (ethynylbipyridine)$Re(CO)_3Br$ coordination compounds.

2. Experimental

Bromobipyridines [14], ethynylbipyridines [15] organic azides [16] and $[NEt_4]_2Re(CO)_3Br_3$ [17] were prepared by literature procedures. Elemental analyses (C, H, N) were performed by Columbia Analytical Services, Inc. NMR spectra were recorded at 300 and 400 MHz for ^1H and 75.4 and 100.7 MHz for $^{13}C\{^1H\}$ on a Varian Mercury VX300 and Varian Mercury VX400 spectrometers. Proton chemical shifts are reported relative to residual protons in the solvent ($CHCl_3$ at δ 7.24 ppm, $CHDCl_2$ or CD_3COCD_2H at δ 2.05 ppm) referenced to TMS at 0.00 ppm. Proton decoupled carbon chemical shifts are reported relative to solvent ($CDCl_3$ t at δ 77.0 ppm and CD_2Cl_2 m at δ 55.61 ppm) referenced to TMS at 0.00 ppm. IR spectra were recorded from evaporated solutions on KBr plates on a Bruker ATR FTIR spectrometer from 625 to 4000 cm^{-1}. UV/vis spectra were recorded as CH_2Cl_2 solutions on a Thermo Biomate 3S spectrometer between 300 and 500 nm.

2.1. 1-Benzyl-4-(5-bipyridyl)-1H-1,2,3-triazole (*1*)

Copper sulfate pentahydrate (370 mg, 1.48 mmol) and 601 mg (3.03 mmol) sodium ascorbate are added to a solution of 265 mg (1.59 mmol) 5-ethynyl-2,2′-bipyridine and 318 mg (2.39 mmol)

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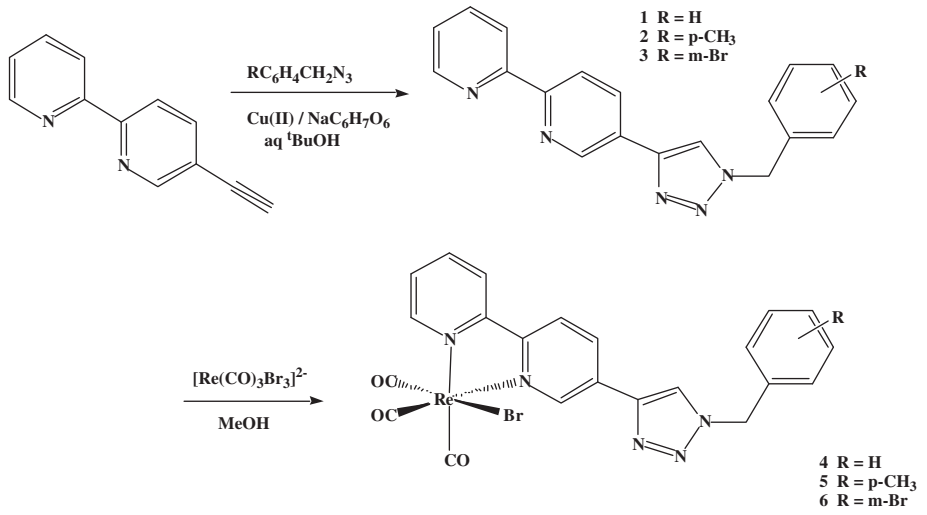
doi:10.1016/j.ica.2010.04.019



Scheme 1.

benzyl azide in 10 mL 1:1 ^{t}butanol:water at ambient temperature. Initially, the mixture is brown but turns green upon stirring. After 3 h the green mixture is poured into 150 mL aqueous ammonia (9 M) precipitating a solid. Extraction with 3 × 50 mL CH_2Cl_2 dissolved the solid and yields a yellow organic layer and a blue aqueous solution of $Cu(NH_3)_4^{2+}$. The CH_2Cl_2 extracts were combined and washed with 2 × 50 mL 9 M aqueous ammonia, dried over sodium sulfate, filtered and evaporated to an off-white solid. Re-crystallization from hot ethyl acetate yielded 260 mg (54%) of 1-benzyl-4-(5-bipyridyl)-1H-1,2,3-triazole (**1**).

M.p. 197–198 °C. *Anal.* Calc. for $C_{19}H_{15}N_5$: C, 72.83; H, 4.82; N, 22.35. Found: C, 73.32; H, 4.82; N, 22.48%. Analytical data for **1** are high for % C, but the combination of spectroscopy and conversion of **1** to analytically pure **4** confirm the identity of **1**.

^{1}H (300 MHz, $CDCl_3$): δ 5.62 s (2H, CH_2), 7.31 m (3H), 7.40 m (3H), 7.79 s (1H), 7.82 t (J = 9.6 Hz, 1H), 8.27 dt (J = 9.6, 1 Hz, 1H), 8.40 d (J = 8.4 Hz, 1H), 8.45 d (J = 7.2 Hz, 1H), 8.68 d (J = 3.9 Hz, 1H), 9.06 m (1H).

^{13}C{^{1}H} (75.4 MHz, $CDCl_3$): δ 54.87, 119.96, 121.11, 123.74, 126.56, 128.11, 128.92, 129.22, 133.78, 134.34, 136.89, 145.16, 149.18, 150.45, 155.58.

IR (KBr) 677 m, 711 s, 744 s, 794 m, 821 w, 846 w, 859 w, 924 w, 975 m, 1021 w, 1033 m, 1048 w, 1072 w, 1085 w, 1128 w, 1194 m, 1225 m, 1339 w, 1376 w, 1434 m, 1448 m, 1493 w, 1531 w, 1570 w, 1585 w.

UV/vis (CH_2Cl_2) λ_{max} = 305 (ε = 22,600) nm.

The procedure above uses a stoichiometric amount of $CuSO_4{\cdot}5H_2O$. Reactions using catalytic (10–20 mol%) amounts of copper and longer reaction times (1–2 days) produce **1** in lower yields. Chromatography on silica using 2:1 CH_2Cl_2:ethyl acetate as the eluent is required to obtain pure **1**. Heating at 60 °C for 3 h failed to increase yields of **1** in the presence of catalytic amounts of copper sulfate.

2.2. 1-(p-Methylbenzyl)-4-(5-bipyridyl)-1H-1,2,3-triazole (**2**)

Using the procedure described for **1**, reaction of 261 mg (1.57 mmol) 5-ethynyl-2,2′-bipyridine, 269 mg (2.39 mmol) *p*-methylbenzyl azide, 459 mg, (1.84 mmol) $CuSO_4{\cdot}5H_2O$ and 698 mg (3.52 mmol) sodium ascorbate in 10 mL 1:1 ^{t}butanol:water at ambient temperature followed by re-crystallization from hot ethyl acetate yielded 138 mg (38%) of analytically pure 1-(*p*-methylbenzyl)-4-(5-bipyridyl)-1H-1,2,3-triazole (**2**).

M.p. 181–183 °C. *Anal.* Calc. for $C_{20}H_{17}N_5$: C, 73.38; H, 5.23; N, 21.39. Found: C, 73.49; H, 5.10; N, 21.07%.

^{1}H (300 MHz, $CDCl_3$): δ 2.39 s (3H, CH_3), 5.56 s (2H, CH_2), 7.31 m (1H), 7.75 s (1H), 7.81 td (J = 1.8, 7.5 Hz, 2H), 8.25 dd (J = 2.1, 8.1 Hz, 2H), 8.42 two overlapping d (J = 8.7 Hz, 4H), 8.68 d (1H), 9.05 m (1H).

^{13}C{^{1}H} (75.4 MHz, $CDCl_3$): δ 21.16, 54.17, 119.86, 121.03, 123.5, 128.18, 129.87, 130.15, 131.28, 133.76, 136.90, 138.91, 155.43.

IR (KBr) 641 w, 678 w, 691 w, 747 s, 782 w, 795 w, 830 w, 848 w, 970 m, 1022 w, 1061 w, 1093, 1145 w, 1190 w, 1220 w, 1343 w, 1387 w, 1429 m, 1455 m, 1507 w, 1516 w, 1539 w, 1558 w, 1575 m, 1651 w cm^{-1}.

UV/vis (CH_2Cl_2) λ_{max} = 305 (ε = 32,500) nm.

2.3. 1-(m-Bromobenzyl)-4-(5-bipyridyl)-1H-1,2,3-triazole (**3**)

Using the procedure described for **1**, reaction of 265 mg (1.59 mmol) 5-ethynyl-2,2′-bipyridine, 365 mg (1.72 mmol) *m*-bromobenzyl azide, 394 mg, (1.45 mmol) $CuSO_4{\cdot}5H_2O$ and 583 mg (2.94 mmol) sodium ascorbate in 10 mL 1:1 ^{t}butanol:water at ambient temperature followed by re-crystallization from hot ethyl acetate yielded 283 mg (47%) of analytically pure 1-*m*-bromobenzyl-4-(5-bipyridyl)-1H-1,2,3-triazole (**3**).

M.p. 188–190 °C. *Anal.* Calc. for $C_{19}H_{15}N_5Br$: C, 58.18; H, 3.60; N, 17.85. Found: C, 58.46; H, 3.66; N, 17.34%.

^{1}H (300 MHz, $CDCl_3$): δ 5.58 s (2H, CH_2), 7.28 m (3H), 7.32 m (1H), 7.50 s (1H), 7.82 s (2H), 8.27 dd (J = 2.1, 8.4 Hz, 1H), 8.41 d (J = 8.4 Hz, 1H), 8.68 d (J = 4.5 Hz, 1H), 8.70 s (1H) 9.07 s (1H).

IR (KBr) 659 w, 671 w, 679 w, 754 w, 762 w, 775 s, 807 s, 856 w, 994 w, 1046 s, 1071 m, 1082 w, 1155 w, 1199 w, 1258 w, 1297 w, 1342 w, 1358 w, 1426 m, 1465 w, 1572 m, 1598 m cm^{-1}.

UV/vis (CH_2Cl_2) λ_{max} = 248 (ε = 26,300) nm.

2.4. fac-[1-Benzyl-4-(5-bipyridyl)-1H-1,2,3-triazole]Re(CO)$_3$Br (**4**)

A mixture of 238 mg (0.31 mmol) $[NEt_4]_2[Re(CO)_3Br_3]$ and 51.6 mg (0.17 mmol) **1** in 20 mL methanol was refluxed for 1 h precipitating a yellow solid. The product was collected by filtering, washed with 20 mL water and dried. 88.8 mg (80% yield) of *fac*-[1-benzyl-4-(5-bipyridyl)-1H-1,2,3-triazole]Re(CO)$_3$Br (**4**) was isolated as a bright yellow powder.

M.p. 193–195 °C. *Anal.* Calc. for $C_{22}H_{15}N_5O_3BrRe$: C, 39.83; H, 2.28; N, 10.55. Found: C, 39.47; H, 2.40; N, 10.47%.

^1H (300 MHz, CD_3COCD_3): δ 5.76 s (2H, CH_2), 7.4 m (5H), 7.78 tm (1H), 8.83 tm (1H), 8.72 m (3H), 8.86 s (1H), 9.13 dm (1H), 9.59 m (1H) (400 MHz, CD_2Cl_2): δ 5.56 s (2H, CH_2), 7.29 m (2H), 7.34 m (3H), 7.95 s (1H), 7.99 t (J = 8.0 Hz, 1H), 8.15 m (2H), 8.43 d (J = 8.8 Hz, 1H), 8.95 d (J = 5.2 Hz, 1H), 9.27 s (1H).

$^{13}C\{^1H\}$ (100.7 MHz, CD_2Cl_2): δ 56.65, 123.96, 125.44, 125.66, 129.10, 130.31, 131.10, 131.37, 132.72, 136.51, 137.42, 141.29, 144.32, 151.88, 155.27, 156.40, 157.46, 191.02, 199.27.

IR (KBr) 2017 vs (ν_{CO}), 1936 sh, s (ν_{CO}), 1887 vs (ν_{CO}), 640 w, 694 m, 720 w, 757 m, 791 m, 812 m, 858 w, 899 w, 913 w, 979 w, 1039 w, 1071 w, 1115 w, 1144 w, 1172 w, 1190 w, 1206 w, 1231 w, 1313 w, 1393 w, 1435 m, 1454 m, 1470 m, 1495 w, 1540 w, 1558 w, 1602 m cm^{-1}.

UV/vis (CH_2Cl_2) λ_{max} = 265 (ε = 18,450), 326 (ε = 27,200), 398 (ε = 3450) nm.

2.5. *fac-[1-{p-Methylbenzyl}-4-(5-bipyridyl)-1H-1,2,3-triazole]Re(CO)$_3$Br (**5**)*

A mixture of 235 mg (0.31 mmol) $[NEt_4]_2[Re(CO)_3Br_3]$ and 54.3 mg (0.17 mmol) **2** in 20 mL methanol was refluxed for 1 h precipitating a yellow solid. The product was collected by filtering, washed with 20 mL water and dried. 80.6 mg (70% yield) of *fac*-[1-{*p*-methylbenzyl}-4-(5-bipyridyl)-1H-1,2,3-triazole]Re(CO)$_3$Br (**5**) was isolated as a bright yellow powder.

M.p. >250 °C, decomposes. *Anal.* Calc. for $C_{23}H_{17}N_5O_3BrRe$: C, 40.77; H, 2.53; N, 10.34. Found: C, 40.96; H, 2.42; N, 10.24%.

^1H (300 MHz, CD_3COCD_3): δ 2.32 s (3H, CH_3), 5.72 s (2H, CH_2), 7.22 d (J = 9.1 Hz, 2H), 7.33 d (J = 9.1 Hz, 2H), 7.78 t (J = 6.0 Hz, 1H), 8.32 tm (1H), 8.71 m (3H), 8.82 s (1H), 9.13 d (J = 6.0 Hz, 1H), 9.59 s (1H); (400 MHz, CD_2Cl_2): δ 2.28 s (3H, CH_3), 5.51 s (2H, CH_2), 7.17 s (4H), 7.45 t (J = 6.0 Hz, 1H), 7.92 s (1H), 7.99 t (J = 7.2 Hz, 1H), 8.15 m (2H), 8.44 d (J = 8.0 Hz, 1H), 8.95 d (J = 5.2 Hz, 1H), 9.25 s (1H).

$^{13}C\{^1H\}$ (100.7 MHz, CD_2Cl_2): δ 23.05, 56.49, 123.76, 125.38, 125.60, 129.08, 130.31, 131.99, 132.30, 132.77, 133.29, 133.42, 137.36, 141.27, 144.24, 151.86, 155.26, 156.35.

IR (KBr) 2017 vs (ν_{CO}), 1926 s (ν_{CO}), 1889 vs (ν_{CO}), 640 w, 685 w, 730 w, 758 m, 790 m, 863 w, 979 w, 1042 w, 1234 w, 1315 w, 1346 w, 1442 m, 1456 m, 1470 m, 1603 m cm^{-1}.

UV/vis (CH_2Cl_2) λ_{max} = 264 (ε = 11,500), 326 (ε = 19,500), 394 (ε = 2200) nm.

2.6. *fac-[1-{m-Bromobenzyl}-4(5-bipyridyl)-1H-1,2,3-triazole]Re(CO)$_3$Br (**6**)*

A mixture of 209 mg (0.27 mmol) $[NEt_4]_2[Re(CO)_3Br_3]$ and 99.4 mg (0.26 mmol) **3** in 20 mL methanol was refluxed for 1 h precipitating a yellow solid. The product was collected by filtering, washed with 20 mL water and dried. 131 mg (68% yield) of *fac*-[1-{*m*-bromobenzyl}-4(5-bipyridyl)-1H-1,2,3-triazole]Re(CO)$_3$Br (**6**) was isolated as a bright yellow powder.

M.p. no changes observed up to 275 °C. *Anal.* Calc. for $C_{22}H_{14}N_5O_3Br_2Re$: C, 35.59; H, 1.90; N, 9.43. Found: C, 35.33; H, 1.96; N, 9.30%.

^1H (300 MHz, CD_3COCD_3): δ 5.82 s (2H, CH_2), 7.38, 7.41 overlapping t (2H), 7.56 dm (1H), 7.66 br s (1H), 8.32 tm (1H), 7.78 tm (1H), 8.33 tm (1H), 8.73 overlapping m (3H), 9.13 d (J = 5.7 Hz, 1H), 9.58 s (1H); (400 MHz, CD_2Cl_2): δ 5.54 s (2H, CH_2), 7.24 m (2H), 7.42 s (1H), 7.47 t (J = 6.4 Hz, 2H), 7.99 s (1H), 8.01 t (J = 6.4 Hz, 1H), 8.17 m (2H), 8.48 d (J = 8.4 Hz, 1H), 9.60 d (J = 4.8 Hz, 1H), 9.28 s (1H).

IR (KBr) 2017 vs (ν_{CO}), 1926 s (ν_{CO}), 1892 vs (ν_{CO}), 641 w, 678 w, 759 m, 779 m, 793 w, 864 w, 980 w, 1042 w, 1205 w, 1234 w, 1317 w, 1337 w, 1429 w, 1455 w, 1471 w, 1603 cm^{-1}.

UV/vis (CH_2Cl_2) λ_{max} = 266 (ε = 14,250), 325 (ε = 24,400), 395 (ε = 2375) nm.

2.7. *fac-(5-Ethynyl-2,2′-bipyridine)Re(CO)$_3$Br (**7**)*

A mixture of 400 mg (0.52 mmol) $[NEt_4]_2[Re(CO)_3Br_3]$ and 94 mg (0.57 mmol) 5-ethynylbipyridine in 25 mL methanol was refluxed for 2 h precipitating a tan solid. The crude product was collected by filtering, washed with 20 mL water and dried. The crude product was chromatographed on silica using a 2:1 mixture of CH_2Cl_2:ethyl acetate to elute a single yellow fraction. Evaporation of the solvent yielded 242 mg (88% yield) of *fac*-(5-ethynyl-2,2′-bipyridine)Re(CO)$_3$Br (**7**) as a bright yellow powder.

M.p. decomposes above 175 °C. *Anal.* Calc. for $C_{15}H_8N_2O_3Re$: C, 33.97; H, 1.52; N, 5.28. Found: C, 34.20; H, 1.93; N, 4.92%.

^1H (300 MHz, CD_3COCD_3): δ 4.32 s (1H, ≡CH), 7.82 t (J = 6 Hz, 1H), 8.35 m (2H), 8.74 d (J = 7.8 Hz, 2H), 9.15 s (2H).

IR (KBr) 2020 vs (ν_{CO}), 1894 vs (ν_{CO}), 725 w, 751 w, 790 w, 845, w, 1237 w, 1313 w, 1441 w, 1469 m (ν_{CC}), 1604 w cm^{-1}.

UV/vis (CH_2Cl_2) λ_{max} = 263 (ε = 17,900), 309 (ε = 29,000), 408 (ε = 4400) nm.

2.8. *fac-(6-Ethynyl-2,2′-bipyridine)Re(CO)$_3$Br (**8**)*

A mixture of 438 mg (0.57 mmol) $[NEt_4]_2[Re(CO)_3Br_3]$ and 103 mg (0.62 mmol) 6-ethynylbipyridine in 25 mL methanol was refluxed for 2 h precipitating a tan solid. The crude product was collected by filtering, washed with 20 mL water and dried. The crude product was chromatographed on silica using a 2:1 mixture of CH_2Cl_2:ethyl acetate to elute a single yellow fraction. Evaporation of the solvent yielded 278 mg (92% yield) of *fac*-(6-ethynyl-2,2′-bipyridine)Re(CO)$_3$Br (**8**) as a bright yellow powder.

M.p. decomposes above 180 °C. *Anal.* Calc. for $C_{15}H_8N_2O_3Re$: C, 33.97; H, 1.52; N, 5.28. Found: C, 34.15; H, 1.25; N, 5.13%.

^1H (300 MHz, CD_3COCD_3): δ 4.76 s (1H, ≡CH), 7.80 m (1H), 8.00 m (J = 8.1 Hz, 1H), 8.32 dd (J = 7.8, 8.1 Hz, 2H), 8.71 d (J = 8.1 Hz, 2H), 9.19 s (1H).

IR (KBr) 2020 vs (ν_{CO}), 1895 vs (ν_{CO}), 722 w, 748 w, 787 w, 843 w, 1002 w, 1028 w, 1072 w, 1119 m, 1184 m, 1405 m, 1437 m (ν_{CC}) w cm^{-1}.

UV/vis (CH_2Cl_2) λ_{max} = 283 (ε = 10,250), 309 (ε = 18,000), 402 (ε = 2250) nm.

2.9. *fac-(5-Bromo-2,2′-bipyridine)Re(CO)$_3$Br (**9**)*

A slurry of 218 mg (0.54 mmol) $Re(CO)_5Br$ and 107 mg (0.52 mmol) 3-bromobipyridine in 25 mL THF was heated to reflux under nitrogen for 20 h. Solvent was evaporated from the yellow solution under vacuum yielding 258 mg (86% yield) of *fac*-(5-bromo-2,2′-bipyridine)Re(CO)$_3$Br (**9**) as a yellow solid.

M.p. a sample of **9** remains unchanged upon heating to 250 °C. *Anal.* Calc. for $C_{13}H_7Br_2N_2O_3Re$: C, 26.77; H, 1.21; N, 4.80. Found: C, 27.07; H, 1.41; N, 4.97%.

^1H (300 MHz, CD_3COCD_3): δ 7.83 t or d (J = 1.2, 7.5 Hz, 1H), 8.35 t of d (J = 1.8, 8.7 Hz, 1H), 8.55 dd (2.4, 12 Hz, 1), 8.74 d (J = 8.7 Hz, 1H), 8.79 d (J = 8.1 Hz, 1H), 9.14 dd (J = 0.6, 5.4 Hz, 1H), 9.21 d (J = 2.4 Hz, 1H).

$^{13}C\{^1H\}$ (75.4 MHz, CD_3COCD_3): 126.12, 126.79, 129.57, 138.86, 141.38, 141.73, 151.02, 151.66, 155.04, 156.53, 180.78.

IR (KBr) 2015 vs (ν_{CO}), 1888 vs (ν_{CO}), 642 w, 689 w, 756 m, 788 m, 855 w, 913 w, 1040 w, 1065 w, 1094 w, 1105 w, 1120 w, 1134 w, 1166 w, 1237 w, 1279 w, 1306 w, 1369 w, 1427 w, 1463 w, 1592 cm^{-1}.

UV/vis (CH_2Cl_2) λ_{max} = 259 (ε = 27,200), 306 (ε = 28,375), 406 (ε = 4000) nm.

2.10. *fac*-(5-Ethynyl-2,2′-bipyridine)Re(CO)$_3$Br (**7**) from *fac*-(5-bromo-2,2′-bipyridine)Re(CO)$_3$Br (**9**)

A mixture of 158 mg (0.27 mmol) **9**, 9.1 mg (0.013 mmol, 5 mol%) $Pd(PPh_3)_2Cl_2$ and 13.2 mg (0.069 mmol) CuI were combined in 5 mL THF under a nitrogen atmosphere. A solution of 3 mL triethylamine containing 200 μL trimethylsilylacetylene was added leading to a color change from yellow to red. The mixture was heated at 60 °C for 3 h and then stirred at ambient temperature overnight. The mixture was filtered to remove a dark solid and the filtrate evaporated to a yellow-brown solid. Chromatography of the solid on silica using a 1:2 (v/v) mixture of ethyl acetate to dichloromethane slowly eluted an orange yellow band. Evaporation of the solvent followed by washing with hexane (5 mL) yielded 23 mg (14%) of yellow-orange solid *fac*-[5-(trimethylsilylethynyl)-2,2′-bipyridine]Re(CO)$_3$Br (**10**). The ^{1}H NMR spectrum of **10** was consistent with the formulation *fac*-[5-(trimethylsilylethynyl)-2,2′-bipyridine]Re(CO)$_3$Br but further purification and characterization was not attempted. Compound **10** was immediately used in the next step.

^{1}H NMR (300 MHz, CD_3COCD_3): d 0.30 s (9H, Me_3Si), 7.81 td (J = 1.2, 5.7 Hz, 1H), 8.33 d (J = 9.3 Hz, 2H), 8.70 t (J = 5.7 Hz, 2H), 9.12 d (J = 14.1, 3.9 Hz, 2H).

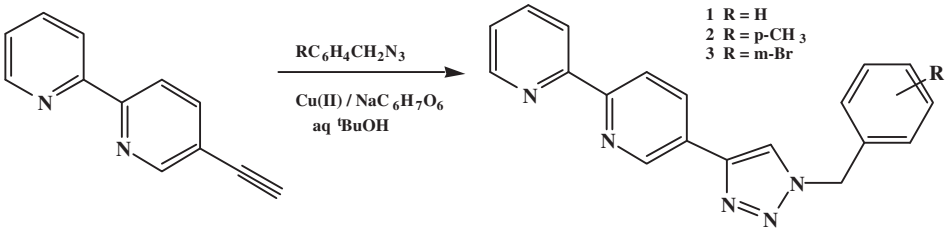
A 22 mg (0.037 mmol) sample of **10** was dissolved in 20 mL of 1:1 (v/v) THF:methanol to give a yellow-orange solution. Addition of 46.3 mg (0.80 mmol) KF did not lead to an observable color change after 3 h at ambient temperature. Evaporation of the solvent and chromatography on silica using 1:2 EtOAc:CH_2Cl_2 eluted a yellow band which upon evaporation, yielded 12 mg (62%) of **7**.

2.11. *fac*-[1-Benzyl-4-(5-bipyridyl)-1H-1,2,3-triazole]Re(CO)$_3$Br (**4**) from *fac*-(5-ethynyl-2,2′-bipyridine)Re(CO)$_3$Br (**7**)

A mixture of 48 mg (0.092 mmol) **7**, 28 mg (0.21 mmol) benzyl azide, 27 mg (0.11 mmol) $CuSO_4 \cdot 5\,H_2O$, and 38 mg (0.19 mmol) sodium ascorbate were reacted in 1:1 ^{t}BuOH:water (5 mL) at 90 °C for 3 h and then cooled to ambient temperature overnight. The yellow-green slurry was poured into 25 mL concentrated ammonia and extracted with 5 × 15 mL CH_2Cl_2. After work-up as described for **1**, 18 mg of a mixture containing 50%, **4** and 50%, **7** was isolated after crystallization from ethylacetate:hexane and comparison of the ^{1}H NMR spectrum with authentic samples.

3. Results and discussion

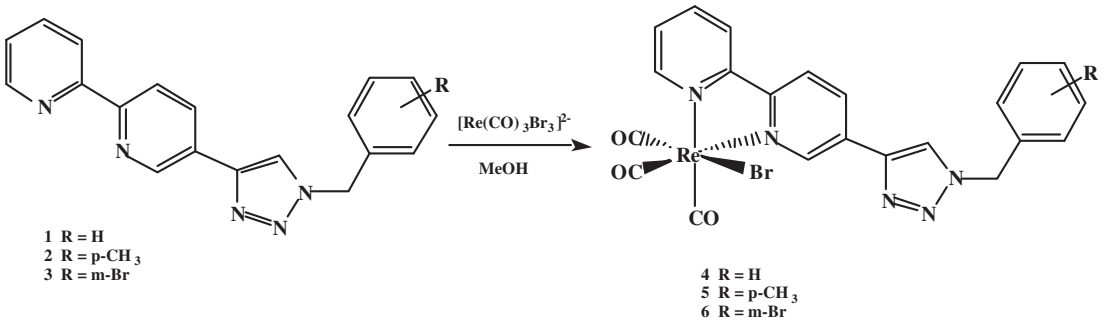
The synthesis of 1-benzyl-4-(5-bipyridyl)-1H-1,2,3-triazoles (**1**–**3**) proceeded in good yield (38–54%, Eq. (1)) after re-crystallization, provided that a stoichiometric (or near stoichiometric) amount of Cu(I) was used in the reaction. The copper was readily removed by washing with aqueous ammonia. Compounds **1**–**3** were characterized by ^{1}H and ^{13}C NMR spectroscopy and gave satisfactory elemental analyzes. Triazoles **1**–**3** are soluble in dichloromethane, chloroform, acetone and ethylacetate but the solubility of **3** in these polar solvents is significantly lower than for **1**–**2**. As noted earlier, bipyridine is an excellent chelating ligand, forming complexes with many transition metals, including Cu(II), the form of copper used as the catalyst precursor in the reaction [18]. The coordination of copper to the bipyridine moiety is a likely explanation for the low yields of triazoles observed when catalytic amount of $CuSO_4 \cdot 5H_2O$ are used in the reaction. A similar observation was reported in the preparation of roxatanes using Cu-catalyzed "click" chemistry [19] although no difficulties were reported in the reaction between 3-ethynyl-1,10-phenanthroline and azidophosphonates [20].



(1)

Triazoles **1**–**3** are assigned as the 1, 4-isomers by analogy to the literature of Cu-catalyzed [3+2] cycloaddition chemistry [21]. Efforts at preparing the 1, 5-isomer using catalytic amounts of $Cp^*Ru(PPh_3)_2Cl$ [22] were unsuccessful. No triazole products were isolated from the black reaction mixture. When followed by ^{1}H NMR in C_6D_6 solution, no reaction was observed between 5-ethynyl-2,2′-bipyridine and benzyl azide in the presence of 5 mol% $Cp^*Ru(PPh_3)_2Cl$. Substitution of PPh_3 by the 5-ethynyl-2,2′-bipyridine substrate may be responsible for the lack of reactivity in this case.

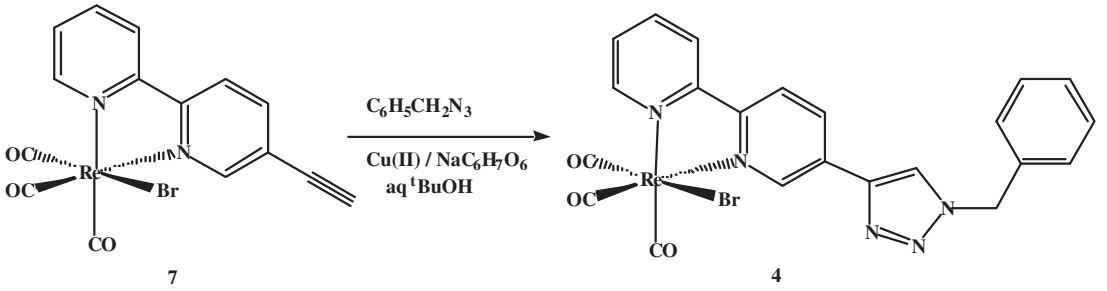
Reactions between triazoles **1**–**3** and $[NEt_4]_2[Re(CO)_3Br_3]$ yielded the corresponding Re(CO)$_3$Br coordination compounds **4**–**6** in good yield (70–80%, Eq. (2)). Compounds **4**–**6** precipitated out of methanol and required no further purification beyond washing with water to remove any alkyl ammonium salts. The rhenium compounds **4**–**6** are slightly soluble in acetone and DMSO but nearly insoluble in halocarbons or other polar solvents. Like **1**–**3**, compounds **4**–**6** gave satisfactory elemental analyzes and were characterized by ^{1}H NMR spectroscopy. The reactions appear to be very rapid in refluxing methanol with a characteristic color change from the tan hues of the starting materials to the bright yellow color of the rhenium carbonyl complexes noticeable even at room temperature in less than 30 s after mixing. The reactions were continued for 1–2 h, however, to ensure complete consumption of the starting materials. The observation of three strong $\nu_{(CO)}$ stretches between 1875 and 2025 cm^{-1} in the IR spectra of **4**–**6** are consistent with a *fac*-geometry for the carbonyl ligands and reflect the asymmetry of the triazole-substituted bipyridine [23] compared to the IR spectrum of *fac*-(5-bromobipyridine)Re(CO)$_3$Br (**9**). The IR spectra for **4**–**6** and **9** are similar to that for *fac*-(bipyridine)Re(CO)$_3$Br [24]. UV/vis spectra of **4**–**9** show a metal-to-ligand charge transfer band around 400 nm similar to that observed for *fac*-(bipyridine)Re(CO)$_3$Br [25].



(2)

We were also curious about whether or not click chemistry was possible using pre-formed $Re(CO)_3Br$ complexes of 5-ethynyl-2,2′-bipyridine. While such an approach is not useful for the preparation of BFCA's for imaging with short half-life radioisotopes, the reactions of (5-ethynyl-2,2′-bipyridine)$Re(CO)_3Br$ with benzyl azide acts as a test of the electronic effect of an electron withdrawing $Re(CO)_3Br$ group on the "click" reaction. Prior coordination of the $Re(CO)_3Br$ group also ties up the nitrogen lone pairs in 2,2′-bipyridine that proved to be problematic in the synthesis of **1**–**3**. Both 5-ethynyl (**7**) and 6-ethynyl-2,2′-bipyridine $Re(CO)_3Br$ (**8**) were prepared in nearly quantitative yield (>90%, Eq. (3)) by the same procedure used to synthesize **4**–**6**. In fact, **7** could also be prepared by a palladium-catalyzed Sonogashira reaction of 5-bromo-2,2′-bipyridine$Re(CO)_3Br$ with trimethylsilylacetylene followed by removal of the TMS group [15]. Yields of **7** by this route (9%) are considerably lower than from reactions between 5-ethynyl-2,2′-bipyridine and $[NEt_4]_2[Re(CO)_3Br_3]$ (88%) although no effort was expended at optimization of the former.

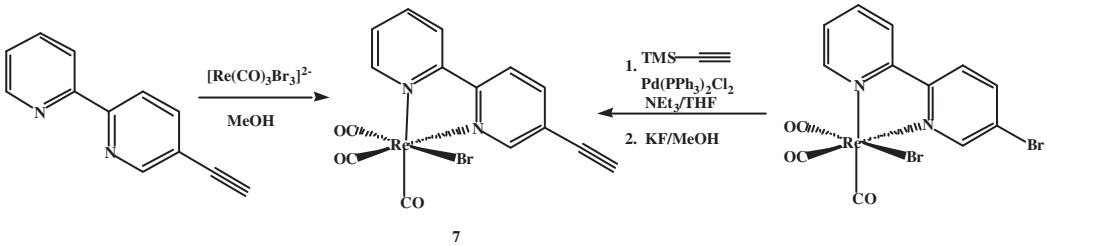
Reaction between **7** and benzyl azide in the presence of catalytic $CuSO_4{\cdot}H_2O$ (30 mol%) and sodium ascorbate at ambient temperature for 7 days failed to yield measurable amounts of **4**. Increasing the reaction time and temperature alone proved equally ineffectual. Increasing the catalyst concentration and heating at 90 °C for 3 h yielded a 1:1 mixture of **4** and unreacted **7** (Eq. (4)). While it is possible that further improvements to yield may be possible, it is clear that the best route to complexes such as **4**–**6** lies with introduction of the triazole functionality before coordination to $Re(CO)_3Br$.



(4)

4. Conclusions

We have successfully demonstrated the synthesis of a short series of 1-benzyl-4-(5-bipyridyl) -1H-1,2,3-triazoles starting from 5-ethynyl-2,2′-bipyridine and simple substituted benzyl azides as well as the preparation of the corresponding $Re(CO)_3Br$ complexes. The complexation of **1**–**3** to rhenium is rapid and proceeds in high



(3)

yield, important characteristics in the preparation of BFCA's. Nevertheless, the solubilities of **4**–**6** are low. An exploration of the [2+1] mixed ligand [26] approach to derivatives of **4**–**6** with greater biocompatibility and efforts at reacting 5-ethynylbipyridine with azide derivatives of biologically important molecules such as AZT and 11-β-oligoethyleneglycoloxy-substituted estradiol [27] are in progress.

Acknowledgments

We would like to thank Mr. Nisal Gajandeera for his assistance in the preparation of **2**, Professor Robert Hanson for helpful discussions and Northeastern University for support through the ENHANCE program.

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