Directed Ortho Metalation and Facile Anionic Rearrangement of 5-(Aryloxy)-1-phenyltetrazoles

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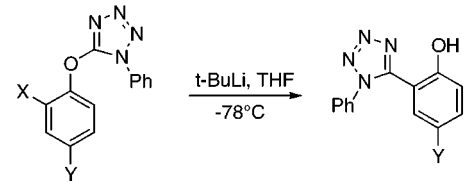
The tetrazole ring is well-known to medicinal chemists as a bioisostere for the carboxylic acid group.[1] The development of nonpeptide angiotensin II antagonists for the treatment of congestive heart failure,[2] in which the most biologically active compounds utilize the tetrazole group, provides impetus for the development of new synthetic methods for their preparation.[3] Currently, the most synthetically useful method for the preparation of aryltetrazoles involves addition of an azide source to either a benzimidoyl halide or a benzonitrile.[4] Directed metalation chemistry has expanded the chemist's ability to prepare highly functionalized aromatic systems.[5] However, little is known regarding the ortho-directing properties of the (aryloxy)tetrazole group. The details of the directed metalation ability and subsequent anionic 1,3-migration of ortho-lithiated (aryloxy)tetrazoles are the subject of this paper.

The first documented example of an anionic equivalent of the Fries rearrangement was reported by Sibi and Snieckus.[6] They found that *O*-arylcarbamates could be ortho-metalated with *s*-BuLi/TMEDA at −78 °C and 1,3-carbamoyl migration occurs upon warming to room temperature to provide salicylamides in good yield. At the same time, Chenard discovered that 2-(phenylthio)-4,4-dimethyloxazoline upon treatment with LDA undergoes smooth ortho-lithiation and subsequent rearrangement to yield 2-[(methylthio)phenyl]-4,4-dimethyloxazoline after alkylation with methyl iodide.[7]

The initial studies focused on the ability to generate the lithiated species by metal−halogen exchange, since the ortho-directing properties of the oxyphenyltetrazole substituent were unknown at the onset of this research. The starting materials **1a**−**e** were easily prepared by reaction of the appropriate phenol and 5-chloro-1-phenyltetrazole in refluxing acetone containing potassium carbonate.[8] Treatment of (aryloxy)tetrazole **1a** with 2.2 equiv of *t*-BuLi in THF at −78 °C followed by warming to room temperature produced, after aqueous workup, the phenolic tetrazole **2a** in 60% yield. However, if **1a** is lithiated with *t*-BuLi for 1−2 h at −78 °C and quenched with saturated ammonium chloride at this temperature, the yield of tetrazole **2a** is improved to 93%. The remaining examples (**1b** and **1c**) involving the metal−halogen exchange procedure were performed using the latter optimized conditions and provided the desired 5-(hydroxyaryl)-1-phenyltetrazoles in greater than 87% yield (see Table 1).

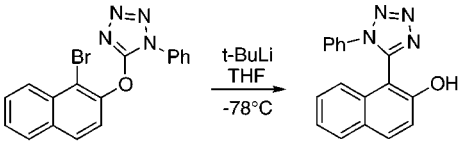
Table 1. Synthesis of 2-(1-Phenyl-5-tetrazolyl)Phenols by 1,3-Migration

substrate	product	yield (%)
1a	2a	93
1b	2b	99
1c	2c	87
1d	2a	85
1e	2e	84

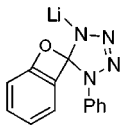


1a X=Br, Y=H
1b X=Br, Y=Cl
1d X=H, Y=H
1e X=H, Y=OMe

2a Y=H
2b Y=Cl
2a Y=H
2e Y=OMe



1c **2c**



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To determine whether the (aryloxy)tetrazole substituent supports directed metalation, **1d** was treated with *s*-BuLi/TMEDA at −78 °C to afford a 1:1 mixture of **1d** and **2a**. There was minimal improvement in the lithiation by increasing the amount of base. However, following the conditions of Chenard,[7] the ortho-metalation/rearrangement procedure was found to be more efficient with LDA at 0 °C, providing tetrazole **2a** in 85% yield. Similarily, 5-(4-methoxyphenoxy)-1-phenyltetrazole (**1e**) also rearranged under these conditions (LDA, 0 °C) to afford **2e** in high yield. Presumably, the reaction proceeds through a four-membered intermediate **3** such as suggested by Chenard's work describing the rearrangement of (phenylthio)oxazolines.[7]

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In summary, we have demonstrated, for the first time, the ortho directing group properties of the (aryloxy)tetrazole functionality and its rapid anionic rearrangement to provide 5-(hydroxyaryl)-1-phenyl-1*H*-tetrazoles. The newly generated phenol presumably could be used as a synthetic handle, in the form of a triflate, to further functionalize the aromatic ring via Suzuki or Stille-type couplings to prepare biaryl tetrazoles.[9]

Experimental Section

General Procedure. All metalation reactions were carried out under a positive atmosphere of nitrogen. Reagent-grade acetone was used as purchased. Tetrahydrofuran was dried and distilled over sodium benzophenone ketyl. Alkyllithium reagents were purchased from Aldrich and titrated with 2,5-dimethoxybenzyl alcohol.[10] Diisopropylamine was purchased from Aldrich and distilled from calcium hydride before use. Melting points are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ at 300 MHz relative to $CHCl_3$ (7.24 ppm). ^{13}C NMR were recorded in $CDCl_3$ at 75 MHz with the chemical shifts relative to $CHCl_3$ (77.0 ppm). (Aryloxy)tetrazoles **1d** and **1e** are known in the literature[11] and were prepared by the method of Gates.[8]

General Procedure for (Aryloxy)tetrazole Preparation. 5-(2-Bromophenoxy)-1-phenyl-1*H*-tetrazole (1a). To a solution of 5.0 g of 1-bromophenol (28.9 mmol) in acetone (250 mL) was added 6.0 g of K_2CO_3 (43.4 mmol) and 5.2 g of 5-chloro-1-phenyl-1*H*-tetrazole (28.9 mmol). The reaction mixture was heated at reflux for 14 h. After the mixture was cooled to room temperature, the precipitate was filtered and the filtrate concentrated. The crude (aryloxy)tetrazole was recrystallized from EtOAc to provide 7.7 g of pure **1a** (83%).

1a: mp 88−89 °C; ^{1}H NMR ($CDCl_3$) δ 8.53 (dd, J = 8.0, 1.6 Hz, 1H), 7.90 (m, 2H), 7.55 (m, 4H), 7.43 (dt, J = 8.6, 1.6 Hz, 1H), 7.34 (dt, J = 8.5, 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 159.0 (s), 150.4 (s), 134.0 (d), 133.0 (s), 129.8 (d), 129.6 (d), 129.2 (d), 128.3 (d), 122.3 (d), 122.0 (d), 114.3 (s); MS (EI) *m*/*z* 316 (4), 210 (12), 209 (100), 117 (46); IR (KBr) 1597, 1539, 1506, 1451, 1208, 756, 683 cm^{-1}. Anal. Calcd for $C_{13}H_9BrN_4O$: C, 49.23; H, 2.86; N, 17.67. Found: C, 49.49; H, 2.95; N, 17.67.

5-(2-Bromo-4-chlorophenoxy)-1-phenyl-1*H*-tetrazole (1b). 2-Bromo-4-chlorobenzene (5.0 g, 24.1 mmol), 4.4 g of 5-chloro-1phenyl-1*H*-tetrazole (24.1 mmol), and 6.7 g of K_2CO_3 (48.2 mmol) were combined with 100 mL acetone as in the general procedure for **1a** to afford after recrystallization from EtOAc 7.58 g of **1b** (89%).

1b: mp 132−133 °C; ^{1}H NMR ($CDCl_3$) δ 7.88 (m, 2H), 7.68 (d, J = 2.4 Hz, 1H), 7.51−7.63 (m, 5H), 7.41 (dd, J = 8.8, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 149.1, 133.6, 133.1, 129.8, 129.7, 129.3, 122.8, 122.3, 115.1; MS (EI) *m*/*z* 350 (10), 245 (32), 243 (96), 207 (58), 205 (45), 179 (32), 177 (24), 145 (20), 117 (100); IR (KBr) 3434, 1597, 1541, 1505, 1474, 1453, 1219, 1096, 1044, 756 cm^{-1}. Anal. Calcd for $C_{13}H_8BrClN_4O$: C, 44.41; H, 2.29; N, 15.94. Found: C, 44.66; H, 2.34; N, 16.06.

5-[(1-Bromo-2-naphthyl)oxy]-1-phenyl-1*H*-tetrazole (1c). A mixture of 1.61 g of 1-bromo-2-naphthol (7.19 mmol), 1.42 g pf 5-chloro-1-phenyl-1*H*-tetrazole (7.90 mmol), and 2.00 g of K_2CO_3 (14.4 mmol) was combined in 30 mL of acetone as in the general procedure for **1a** to afford after recrystallization from EtOAc 2.64 g of **1c** (99%).

1c: mp 193−194 °C; ^{1}H NMR ($CDCl_3$) δ 8.26 (d, J = 8.4 Hz, 1H), 7.89−7.96 (m, 4H), 7.51−7.69 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 159.0, 148.3, 132.9, 132.4, 132.4, 129.5, 129.4, 129.3, 128.1, 126.8, 122.0, 119.5, 113.2; MS (EI) *m*/*z* 368 (26), 366 (26), 287 (22), 259 (100), 221 (22), 193 (54), 195 (54), 117 (58); IR (KBr) 3434, 1597, 1547, 1505, 1451, 1221, 752, 681 cm^{-1}. Anal. Calcd for $C_{17}H_{11}BrN_4O$: C, 55.61; H, 3.02; N, 15.26. Found: C, 55.72; H, 3.05; N, 15.27.

General Procedure for the Anionic Fries Rearrangement via Metal−Halogen Exchange. 5-(2-Hydroxyphenyl)-1-phenyl-1*H*-tetrazole (2a). To 644 mg of (aryloxy)tetrazole **1a** (2.03 mmol) in 51 mL of THF at −78 °C was added 4.06 mL of *t*-BuLi (6.50 mmol) dropwise, and the solution was stirred at −78 °C for 3 h. Saturated ammonium chloride was added, and the reaction was warmed to room temperature. The layers were separated, and the aqueous layer was extracted with ethyl acetate and dried over $MgSO_4$. The crude reaction mixture was chromatographed (hexanes/EtOAc, 9:1) to afford 452 mg of hydroxytetrazole **2a** (93%).

2a: mp 147−148 °C; ^{1}H NMR ($CDCl_3$) δ 7.42−7.56 (m, 5H), 7.34 (ddd, J = 7.8, 7.1, 1.6 Hz, 1H), 7.16 (dd, J = 7.9, 1.6 Hz, 1H), 6.99 (dd, J = 8.3, 1 Hz, 1H), 6.79 (dt, J = 8.0, 1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 157.3, 152.2, 135.1, 133.1, 130.2, 129.7, 129.2, 124.6, 119.0, 117.7, 109.3; MS (EI) *m*/*z* 238 (100), 210 (29), 209 (95), 181 (20), 91 (24), 77 (25); IR (KBr) 3426, 3087, 1617, 1501, 1483, 1458, 1281, 766 cm^{-1}. Anal. Calcd for $C_{13}H_{10}N_4O\cdot 0.1H_2O$: C, 65.05; H, 4.28; N, 23.34. Found: C, 65.00; H, 4.28; N, 23.18.

5-(5-Chloro-2-hydroxyphenyl)-1-phenyl-1*H*-tetrazole (2b). Metalation of 2.64 g of **1b** (7.51 mmol) in 200 mL of THF with 9.7 mL of *t*-BuLi (16.52 mmol) as in the general procedure for **2a** gave 2.03 g of the desired phenol **2b** (99%), which was pure by TLC and ^{1}H NMR methods. A sample was recrystallized from EtOAc, which was used to obtain the analytical data shown below.

2b: mp 145−146 °C; ^{1}H NMR (DMSO-d_6) δ 10.3 (s, 1H), 7.42−7.54 (m, 6H), 7.38 (dd, J = 8.8, 2.7 Hz, 1H), 6.86 (d, J = 8.8 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 154.4 (s), 151.1 (s), 134.6 (s), 132.4 (d), 130.4 (d), 129.7 (d), 129.4 (d), 123.7 (d), 122.7 (s), 117.7 (d), 112.8 (s); MS (EI) *m*/*z* 272 (48), 243 (56), 181 (28), 77 (100); IR (KBr) 3420, 3077, 1485, 1456, 1435, 691. Anal. Calcd for $C_{13}H_9N_4OCl$: C, 57.26; H, 3.33. Found: C, 57.06; H, 3.69.

5-(2-Hydroxynaphthyl)-1-phenyl-1*H*-tetrazole (2c). Metalation of 3.72 g of **1c** (10.1 mmol) in THF (250 mL) with *t*-BuLi (32.3 mmol) as in the general procedure for **2a** provided the desired phenol **2c**. Purification by silica gel chromatograghy using 1/1 EtOAc−hexane gave 2.53 g of **2c** (87%).

2c: mp 217−218 °C; ^{1}H NMR ($CDCl_3$) δ 9.65 (s, 1H), 7.83 (d, J = 9.0 Hz, 1H), 7.79 (m, 1H), 7.25−7.44 (m, 8H), 7.15 (d, J = 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 154.8, 136.4, 133.2, 133.0, 129.4, 129.2, 128.3, 128.0, 127.8, 123.7, 123.3, 123.0, 118.1, 103.3; MS (EI) *m*/*z* 288 (84), 260 (100), 231 (18), 129 (24), 104 (28); IR (Kbr) 3422, 3067, 1591, 1495, 1439, 1248, 689. Anal. Calcd for $C_{17}H_{12}N_4O$: C, 70.82; H, 4.20; N, 19.43. Found: C, 70.59; H, 4.25; N, 19.11.

General Procedure for the Anionic Fries Rearrangement via Directed Metalation: 5-(2-Hydroxyphenyl)-1-phenyl-1*H*-tetrazole (2a). Diisopropylamine (1.89 mmol, 0.27 mL) was dissolved in THF (3 mL) and cooled to 0 °C, and *n*-BuLi (1.87 mmol, 2.33 M in hexane) was added dropwise. After 20 min, a solution of **1e** (1.26 mmol, 300 mg) in THF (10 mL) was added dropwise. The reaction was stirred for 30 min and then quenched with saturated ammonium chloride. The aqueous layer was extracted with EtOAc and dried over $MgSO_4$. The crude reaction mixture was concentrated and purified by column chromatography (hexane/EtOAc, 6:1) to provide 255 mg of **2a** (85%) as a white solid. The spectral data are identical to that of the product of the metal−halogen exchange procedure described above.

5-(5-Methoxy-2-hydroxyphenyl)-1-phenyl-1*H*-tetrazole (2e). LDA (3.17 mmol) was added to a solution consisting of 345 mg of **1e** (1.29 mmol) in THF (10 mL) as described in the general procedure for the synthesis of **2a**. The product was purified by flash chromatography (hexane/EtOAc, 6:1) to afford

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2e in 84% yield. A sample was recrystallized from EtOAc/ether to obtain the analytical data shown below.

2e: mp 136.6−137.3 °C; ^{1}H NMR ($CDCl_3$) δ 7.64−7.68 (m, 3H), 7.49−7.52 (m, 2H), 7.05 (d, J = 9.1 Hz, 1H), 6.95 (dd, J = 9.1, 3.0 Hz, 1H), 6.36 (d, J = 3.0 Hz, 1H), 3.33 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 152.3 (s), 152.1 (s), 152.9 (s), 135.0 (s), 131.3 (d), 130.3 (d), 126.5 (d), 121.5 (d), 119.5 (d), 110.1 (d), 106. 7 (s), 55. 2 (q); MS (EI) m/z 268 (63), 240 (92), 225 (97), 197 (76), 77 (100); IR (KBr) 3098, 1507, 1439, 1296, 762. Anal. Calcd for $C_{14}H_{12}N_4O_2$: C, 62.68; H, 4.51; N, 20.88. Found: C, 62.51; H, 4.48; N, 20.98.

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