Transition Metals in Organic Synthesis, Part 97:[1] Silver-Catalyzed Synthesis of Hexahalogenated 2,2′-Bipyrroles

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Abstract: We describe the synthesis of three hexahalogenated 1,1′-dimethyl-2,2′-bipyrroles using an efficient silver(I)-catalyzed cyclization as key step.

Key words: alkaloids, catalysis, cyclization, halogenation, pyrroles

The pyrrole ring is a pivotal substructure of many heterocyclic natural products.[2] Thus, a broad range of different methods for the construction of pyrroles has been developed.[3,4] In 2004, we reported a silver(I)-promoted oxidative cyclization of homopropargylamines leading to pyrroles.[5] This procedure was applied to the total synthesis of (±)-harmicine and (±)-crispine A.[6,7] More recently, we have used a silver(I)-catalyzed cyclization of *N*-tosylhomopropargylamines for the synthesis of the naturally occurring pentabromopseudilin and pentachloropseudilin and their synthetic analogues.[8] For our ongoing studies on polyhalogenated heterocycles,[9] we became interested in the synthesis and biological testing of the hexahalogenated 1,1′-dimethyl-2,2′-bipyrroles **1**–**3** (Figure 1).

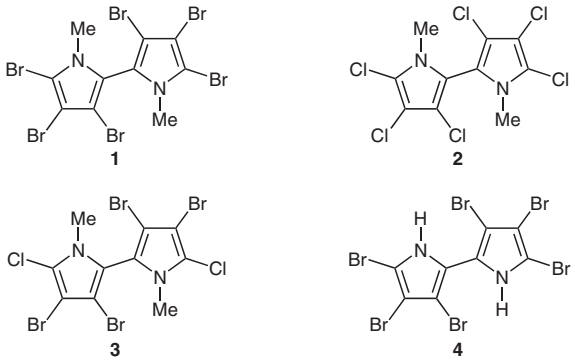

Figure 1 Hexahalogenated 1,1′-dimethyl-2,2′-bipyrroles **1**–**4**

The hexabromo-2,2′-bipyrrole **4** was found first by Faulkner et al. in 1974 in the marine bacterium *Chromobacter* I-L-33.[10a] In 1999, the hexahalogenated 2,2′-bipyrroles **1** and **3** were detected using mass spectrometry in seabird eggs and in samples of bald eagle liver.[10b] So far, the hexachloro derivative **2** has not been found in nature. Gribble et al. have confirmed the structural assignments by total synthesis of the 2,2′-bipyrroles **1**–**3** and subsequent X-ray crystal structure analysis.[11] The 2,2′-bipyrrole core structure is found in several pharmaceutically interesting natural products, e.g. prodigiosins,[12] streptorubin B[13] and tambjamines.[14] Diverse synthetic approaches to 2,2′-bipyrroles resulted from the strong interest in this structural unit.[15]

We have developed a short access to the compounds **1**–**3** by using our silver(I)-catalyzed cyclization as key step. Condensation of the commercially available aldehyde **5** with *p*-toluenesulfonamide (**6**) afforded the *N*-tosylaldimine **7** (Scheme 1).[16] Generally, unactivated aldimines need to be activated by a Lewis acid for alkylation with Grignard reagents.[17] In contrast, Grignard addition to *N*-tosylaldimines proceeds smoothly without further activation of the imine carbon atom by a Lewis acid.[18] Thus, alkylation of **7** with trimethylsilylpropargylmagnesium bromide provided the silyl-*N*-tosylhomopropargylamine **8**. Removal of the trimethylsilyl protecting group with tetrabutylammonium fluoride (TBAF) led to the terminal acetylene **9**. Subsequent cyclization of **9** using 10 mol% of silver(I) acetate afforded the 2,3-dihydro-1′-methyl-1-tosyl-2,2′-bipyrrole (**10**) in 95% yield.[19] The structure of the 2,3-dihydro-2,2′-bipyrrole **10** was confirmed by an X-ray crystal structure analysis (Figure 2).[20] Aromatization of the dihydropyrrole **10** was achieved by elimination of *p*-toluenesulfinic acid. Thus, treatment of the 2,3-dihydro-2,2′-bipyrrole **10** with potassium *tert*-butoxide in dimethyl sulfoxide followed by addition of iodomethane provided via N-alkylation of the intermediate anion 1,1′-dimethyl-2,2′-bipyrrole (**11**).[21] Alternative routes to compound **11** have been reported previously by other groups.[11,22]

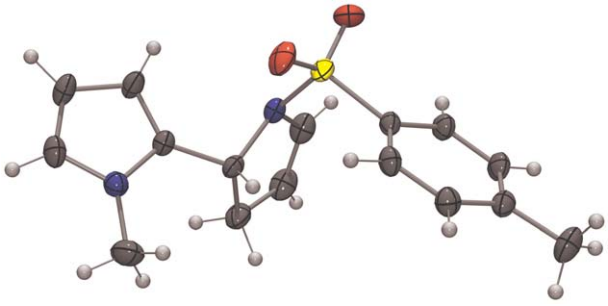

Figure 2 Molecular structure of the 2,3-dihydro-2,2′-bipyrrole **10** in the crystal

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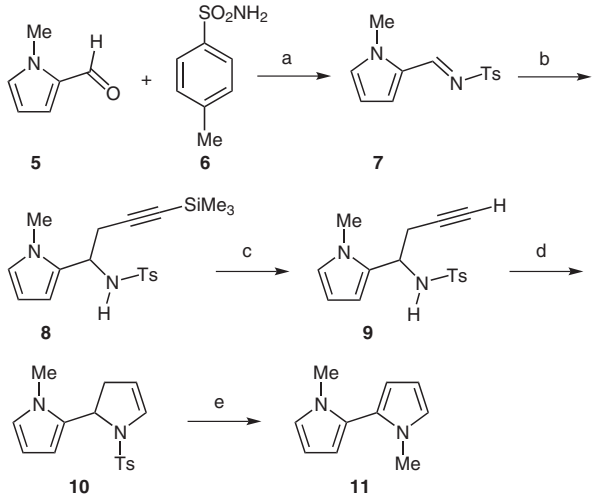
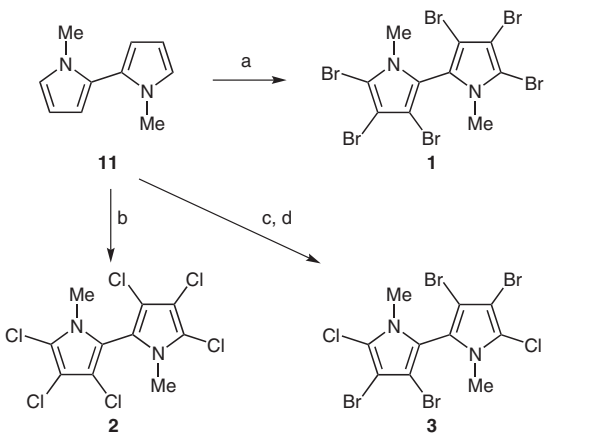


Scheme 1 Synthesis of 1,1′-dimethyl-2,2′-bipyrrole (**11**). *Reagents and conditions*: (a) **6** (1.0 equiv), $Si(OEt)_4$ (1.05 equiv), 160 °C, 6 h, 77%; (b) $BrMgCH_2C{\equiv}CSiMe_3$ (2.0 equiv), CH_2Cl_2, 25 °C, 15 h, 92%; (c) TBAF (1.1 equiv), THF, 25 °C, 16 h, 99%; (d) AgOAc (10 mol%), acetone, 56 °C, 3 d, 95%; (e) *t*-BuOK (5.2 equiv), DMSO, 50 °C, 4 h, then MeI (10.0 equiv), 25 °C, 15 h, 76%.

As demonstrated previously by Gribble and co-workers, the 1,1′-dimethyl-2,2′-bipyrrole (**11**) represents the crucial intermediate for the synthesis of the 2,2′-bipyrroles **1**–**3**.[11a] Electrophilic bromination of **11** using *N*-bromosuccinimide (NBS) provides the hexabromo derivative **1** in an improved yield of 91% (Scheme 2).[23] Chlorination of **11** with *N*-chlorosuccinimide (NCS) afforded the hexachloro derivative **2** in 82% yield. For an access to the mixed halogenated derivative **3**, the bipyrrole **11** was initially treated with two equivalents of NCS to generate 5,5′-dichloro-1,1′-dimethyl-2,2′-bipyrrole. After a short chromatographic purification over silica gel, this labile intermediate was exhaustively brominated with NBS (5 equiv) to afford the tetrabromodichloro derivative **3** in 63% yield over two steps. It is interesting to note that compound **3** due to its axial chirality could be separated by chiral HPLC into the stable atropisomers.[24] The spectroscopic data for the hexahalogenated 1,1′-dimethyl-2,2′-bipyrroles **1**–**3** were in full agreement with those reported previously.[10,11a,23]



Scheme 2 Synthesis of the 2,2′-bipyrroles **1**–**3**. *Reagents and conditions*: (a) NBS (7.0 equiv), MeCN, –40 °C to 25 °C, 15 h, 91%; (b) NCS (6.2 equiv), MeCN, –40 °C to 25 °C, 90 min, 82%; (c) NCS (2.0 equiv), MeCN, –40 °C to 25 °C, 4 h, 83%; (d) NBS (5.0 equiv), MeCN, –40 °C to 25 °C, 15 h, 76%.

In conclusion, the silver(I)-catalyzed pyrrole cyclization provides a facile access to 2,2′-bipyrroles. In order to demonstrate the utility of this chemistry for natural product synthesis, we have developed a short access to the hexahalogenated 1,1′-dimethyl-2,2′-bipyrroles **1**–**3**. Further applications of our methodology and biological studies with the compounds **1**–**3** are currently in progress.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(19) **Synthesis of 2,3-Dihydro-1′-methyl-1-tosyl-2,2′-bipyrrole (10) by Silver(I)-Catalyzed Cyclization of the *N*-Tosylhomopropargylamine 9**: Silver(I) acetate (6 mg, 35.9 μmol) was added to a stirred solution of compound **9** (105 mg, 347 μmol) in anhyd acetone (12 mL) and the resulting mixture was heated at reflux for 3 d. After cooling to r.t., the solvent was removed in vacuum. Purification of the crude product by flash chromatography (light petroleum ether–Et_2O, 5:1) on silica gel provided the 2,3-dihydro-2,2′-bipyrrole **10**; yield: 100 mg (95%); yellow crystals; mp 125 °C. UV (MeOH): λ = 221, 252, 277 nm. IR (ATR): 3099, 2925, 2857, 1619, 1597, 1494, 1451, 1344, 1295, 1160, 1089, 1049, 957, 911, 814, 706, 664 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.41 (s, 3 H), 2.60 (ddt, *J* = 16.7, 7.6, 2.4 Hz, 1 H), 2.84 (ddt, *J* = 16.7, 11.2, 2.4 Hz, 1 H), 3.54 (s, 3 H), 4.86 (dd, *J* = 11.2, 7.6 Hz, 1 H), 5.14 (m, 1 H), 6.00 (m, 2 H), 6.47 (m, 1 H), 6.50 (t, *J* = 2.2 Hz, 1 H), 7.24 (m, 2 H), 7.51 (d, *J* = 8.3 Hz, 2 H). ^{13}C NMR (DEPT; 125 MHz, $CDCl_3$): δ = 21.55 (Me), 34.47 (Me), 38.43 (CH_2), 56.76 (CH), 106.87 (CH), 108.74 (CH), 109.35 (CH), 123.51 (CH), 127.44 (2 × CH), 129.44 (2 × CH), 130.61 (CH), 130.92 (C), 134.30 (C), 143.49 (C). MS (EI): *m/z* (%) = 302 (33) [M^+], 147 (100), 107 (11). HRMS: *m/z* [M^+] calcd for $C_{16}H_{18}N_2O_2S$: 302.1089; found: 302.1078. Anal. Calcd for $C_{16}H_{18}N_2O_2S$: C, 63.55; H, 6.00; N, 9.26; S, 10.60. Found: C, 63.72; H, 5.97; N, 9.15; S, 10.49.

(20) Crystallographic Data for the 2,3-Dihydro-2,2′-bipyrrole **10**: $C_{16}H_{18}N_2O_2S$, M = 302.38 g mol^{-1}, crystal size: 0.70 × 0.55 × 0.30 mm^3, monoclinic, space group $P2_1/n$, a = 13.286 (1), b = 8.603 (1), c = 13.580 (1) Å, *V* = 1494.6 (2) $Å^3$, *Z* = 4, ρ_{calcd} = 1.344 g cm^{-3}, μ = 0.223 mm^{-1}, λ = 0.71073 Å, T = 198 (2) K, θ range = 3.04–30.00°, reflections collected: 73987, independent: 4349 (R_{int} = 0.0256), 192 parameters. The structure was solved by direct methods and refined by full-matrix least-squares on F^2; final *R* indices [$I > 2\sigma(I)$]: R_1 = 0.0353; wR_2 = 0.1005; maximal residual electron density: 0.302 e $Å^{-3}$. CCDC 829173 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(21) **Synthesis of 1,1′-Dimethyl-2,2′-bipyrrole (11) by Aromatization and Alkylation of 10**:
A solution of potassium *tert*-butoxide (926 mg, 8.25 mmol) and the 2,3-dihydro-2,2′-bipyrrole **10** (500 mg, 1.65 mmol) in dimethyl sulfoxide (35 mL) was stirred at 50 °C for 3 h. The solution was cooled to 0 °C, MeI (1.0 mL, 2.28 g, 16.1 mmol) was added and the reaction mixture was stirred at r.t. overnight. After addition of H_2O (50 mL), the reaction mixture was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with H_2O (2 × 25 mL) and dried over $MgSO_4$. Removal of the solvent and purification of the crude product by flash chromatography (light petroleum ether–Et_2O, 10:1) on silica gel afforded 1,1′-dimethyl-2,2′-bipyrrole (**11**) as a yellow oil; yield: 200 mg (76%). IR (ATR): 3101, 2926, 1514, 1484, 1447, 1410, 1359, 1312, 1282, 1234, 1203, 1088, 1062, 968, 781, 706 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.52 (s, 6 H), 6.16–6.17 (m, 2 H), 6.19–6.21 (m, 2 H), 6.73 (m, 2 H). ^{13}C NMR (DEPT; 125 MHz, $CDCl_3$): δ = 34.38 (2 × Me), 107.30 (2 × CH), 110.44 (2 × CH), 122.58 (2 × CH), 125.05 (2 × C). MS (EI): *m/z* (%) = 160 (100) [M^+], 159 (38), 145 (16), 118 (21), 117 (16). HRMS: *m/z* [M^+] calcd for $C_{10}H_{12}N_2$: 160.1000; found: 160.0995.

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(23) **Synthesis of 3,3′,4,4′,5,5′-Hexabromo-1,1′-dimethyl-2,2′-bipyrrole (1) by Bromination of 11**:
A solution of *N*-bromosuccinimide (449 mg, 2.52 mmol) in anhyd MeCN (10 mL) was added at –40 °C to a solution of 1,1′-dimethyl-2,2′-bipyrrole (**11**) (57.5 mg, 0.36 mmol) in MeCN (15 mL). The resulting green solution was warmed slowly to r.t. and stirred for 15 h. Removal of the solvent in vacuum and purification by flash chromatography (light petroleum ether–Et_2O, 7:1) on silica gel provided compound **1**; yield: 208 mg (91%).
Spectroscopic data for the 3,3′,4,4′,5,5′-Hexahalo-1,1′-dimethyl-2,2′-bipyrroles **1**–**3**:
3,3′,4,4′,5,5′-Hexabromo-1,1′-dimethyl-2,2′-bipyrrole (**1**): pale yellow solid; mp 237–238 °C. UV (MeOH): λ = 256 nm. IR (ATR): 2923, 2853, 1478, 1462, 1436, 1402, 1384, 1364, 1321, 1228, 1187, 1087, 1042, 971, 753, 733, 677, 613 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.46 (s, 6 H). ^{13}C NMR (DEPT; 125 MHz, $CDCl_3$): δ = 35.37 (2 × Me), 101.21 (2 × C), 103.31 (2 × C), 106.77 (2 × C), 122.17 (2 × C). MS (EI): *m/z* (%) = 640 (7), 638 (44), 636 (81), 634 (100), 632 (84), 630 (47), 628 (7) [M^+], 516 (10), 514 (23), 512 (24), 510 (11), 476 (29), 474 (46), 472 (31), 395 (15), 393 (15). HRMS: *m/z* [M^+] calcd for $C_{10}H_6Br_6N_2$: 627.5631; found: 627.5619.
3,3′,4,4′,5,5′-Hexachloro-1,1′-dimethyl-2,2′-bipyrrole (**2**): colorless crystals; mp 208–209 °C (dec.). UV (MeOH): λ = 230, 260 nm. IR (ATR): 2951, 2920, 2846, 1509, 1446, 1382, 1348, 1333, 1259, 1198, 1112, 1055, 1015, 981, 909, 794, 734, 708, 690, 627 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.41 (s, 6 H). ^{13}C NMR (DEPT; 125 MHz, $CDCl_3$): δ = 32.79 (2 × Me), 108.38 (2 × C), 113.52 (2 × C), 116.39 (2 × C), 116.51 (2 × C). MS (EI): *m/z* (%) = 370 (30), 368 (78), 366 (100), 364 (47) [M^+], 331 (11), 296 (16), 294 (17), 292 (16), 290 (26), 288 (16). HRMS: *m/z* [M^+] calcd for $C_{10}H_6Cl_6N_2$: 363.8662; found: 363.8658. Anal. Calcd for

$C_{10}H_6Cl_6N_2$: C, 32.74; H, 1.65; N, 7.64. Found: C, 32.76; H, 1.75; N, 7.44.

3,3′,4,4′-Tetrabromo-5,5′-dichloro-1,1′-dimethyl-2,2′-bipyrrole (**3**): yellow solid; mp 220 °C (dec.). UV (MeOH): λ = 232, 253 nm. IR (ATR): 2943, 2923, 2851, 1726, 1491, 1476, 1440, 1408, 1375, 1323, 1190, 1105, 1049, 978, 764, 681, 665, 620 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.43 (s, 6 H). ^{13}C NMR (DEPT; 125 MHz, $CDCl_3$): δ = 33.50 (2 × Me), 97.37 (2 × C), 102.89 (2 × C), 118.81 (2 × C), 120.25 (2 × C). MS (EI): *m/z* (%) = 550 (11), 548 (46), 546 (94), 544 (100), 542 (55), 540 (13) [M^+], 428 (12), 426 (38), 424 (57), 422 (43), 420 (12), 388 (19), 386 (56), 384 (63), 382 (25). Anal. Calcd for $C_{10}H_6Br_4Cl_2N_2$: C, 22.05; H, 1.11; N, 5.14. Found: C, 22.32; H, 1.21; N, 4.96.

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