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Synthesis of pyrroles by silver(I)-promoted oxidative cyclization

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Dedicated to Professor Richard R. Schmidt on the occasion of his 78th birthday

Abstract
Condensation of aromatic aldehydes with arylamines to form Schiff bases, and subsequent addition of trimethylsilylpropargylmagnesium bromide, leads to homopropargylamines which on silver(I)-promoted oxidative cyclization affords 1,2-diarylpyrroles.

Keywords: Condensation, cyclization, Grignard addition, pyrroles, silver(I)

Introduction
The pyrrole ring system is a crucial structural unit which is found in many biologically active alkaloids and medicinal products. 2 Thus, a wide range of methods for the synthesis of pyrroles has been reported.3,4 In 2004, we described a novel synthesis of pyrroles based on a three-component coupling followed by a silver(I)-promoted oxidative cyclization of the resulting homopropargylamines.5 Our silver(I)-promoted oxidative cyclization of homopropargylamines was applied to the total synthesis of natural products containing annulated pyrroles,6 like the indolizino[8,7-b]indole alkaloid (±)-harmicine and the pyrrolo[2,1-a]isoquinoline alkaloid (±)-crispine A.7,8 In the present paper, we report full details of the silver(I)-promoted oxidative cyclization to 1,2-diarylpyrroles.

Results and Discussion
Condensation of aromatic aldehydes 1a–c with anilines 2 provides the previously known Schiff bases 3a–c (Scheme 1, Table 1).9,10 The addition of 3-trimethylsilylpropargylmagnesium bromide (4) requires an activation of the aldimines 3. Following Nakagawa’s procedure by generation of a preformed aldimine–BF3 complex,11 the homopropargylamines 5a–c were
available in yields ranging from 78–88%. The subsequent oxidative cyclization of the homopropargylamines 5a–c by reaction with 1.1 equivalents of silver(I) acetate under the exclusion of light afforded the pyrroles 6a–c and metallic silver. Control by thin layer chromatography indicated that the transformation was generally complete after 4 days at room temperature. Shorter reaction times at room temperature led to mixtures of starting material and product. Increasing the reaction temperature by performing the silver(I)-promoted oxidative cyclization in dichloromethane or 1,2-dichloroethane under reflux led to partial decomposition. The optimized procedure afforded the pyrroles 6a–c in 78–99% yield after 4 days at room temperature. Conjugated double bonds in the Schiff bases (compare compound 3c) are tolerated in this process. Thus, besides the 1,2-diarylpyrroles 6a and 6b, the corresponding 2-styryl derivative 6c resulting from cinnamaldehyde 1c could also be prepared. For the cyclization of 5c to 6c, further extension of the reaction time to 6 days did not provide a better result (72% yield).

![Scheme 1](image)

**Scheme 1.** Synthesis of pyrroles 6a–c. *Reagents and conditions:* (a) MgSO₄, EtOAc, r.t., 1–2 h; (b) BF₃·Et₂O, THF, –23 °C, 30 min; then: 4 in Et₂O, –23 °C 15 h; (c) 1.1 equiv AgOAc, CH₂Cl₂, r.t., 4 d.

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<th>Table 1. Coupling to the homopropargylamines 5 and silver(I)-promoted oxidative cyclization to 6</th>
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The silver(I)-promoted oxidative cyclization of homopropargylamines 5 to pyrroles 6 has been rationalized by the following proposed mechanism (Scheme 2). The interaction of silver(I) with terminal alkynes is known to provide silver(I)–alkyne π-complexes. The resulting
activation of the triple bond towards nucleophilic attack can be exploited for heterocyclization reactions.\textsuperscript{13} Thus, we propose that silver(I) acetate on reaction with the homopropargyamine 5 generates initially a silver(I)–alkyne π-complex 7. An intramolecular nucleophilic attack of the nitrogen atom at the electrophilic alkyne leads to the intermediate 2-pyrroline–silver(I) complex 8, which is formed in a 5-endo-dig cyclization.\textsuperscript{14} Obviously, the intramolecular nucleophilic attack at the silver(I)–alkyne π-complex 7 obviously is faster than its transformation into a silver(I) acetylide via protodesilylation.\textsuperscript{12b,15} Protonation of the enamine moiety in intermediate 8 to the iminium ion 9 is followed by β-hydride elimination to afford finally metallic silver and the pyrrylium ion 10. Aromatization by loss of a proton and protodesilylation provide the pyrrole 6.

\[
\text{Ag} + 0.5 \text{H}_2
\]

\text{(R}^1 = \text{aryl, aryl-CH=CH; R}^2 = \text{aryl})

\textbf{Scheme 2.} Proposed mechanism for the silver(I)-promoted oxidative cyclization of homopropargyamines 5.

It has been demonstrated that using the corresponding \textit{N}-tosylhomopropargylamines as substrates provide 2-pyrrolines as products of the cyclization. As silver(I) is not being reduced in the course of that process, the reaction can be performed using catalytic amounts of silver(I).\textsuperscript{16} This silver(I)-catalyzed cyclization of \textit{N}-tosylhomopropargylamines has been applied to the synthesis of 2-arylpyrroles and 2,2'-bipyrrroles.\textsuperscript{16,17}

\textbf{Conclusions}

The homopropargylamines which serve as starting materials for the silver(I)-promoted pyrrole synthesis are readily available by a simple process: condensation of an aromatic aldehyde and an aniline to the corresponding Schiff base followed by Lewis acid-promoted addition of trimethylsilylpropargylmagnesium bromide. The silver(I)-promoted oxidative cyclization of the
homopropargylamines provides 1,2-disubstituted pyrroles in good to excellent yields and can be applied to the total synthesis of natural products featuring a 2-arylpyrrole structural unit.

**Experimental Section**

**General.** All reactions were carried out under argon using dry solvents. Flash chromatography: flash silica gel 60 (40 μm). Melting points: heating plate H600. UV spectra: Perkin–Elmer Lambda 25 (UV/VIS spectrometer). IR spectra: Nicolet Avatar 360 (FT–IR). 1H NMR and 13C NMR spectra: Bruker DRX-500; internal standard: tetramethylsilane or the signal of the deuterated solvent; δ in ppm; coupling constants (J) in Hz. MS: Finnigan MAT-95; ionization potential: 70 eV.

**General procedure for the synthesis of the Schiff bases 3a–c.** The anilines 2 (50 mmol) and magnesium sulfate are added successively to a solution of the aldehydes 1a–c (50 mmol) in ethyl acetate. The reaction mixture is stirred until total conversion is detected by thin layer chromatography (1–2 h). Magnesium sulfate is removed by filtration and washed with ethyl acetate. Removal of the solvent provides the Schiff bases 3a–c.

*N*-Benzylidene-4-methoxyaniline (3a). Yield: 82%. Light yellow crystals; for spectroscopic data, see ref.9

*N*-(4-Methoxybenzylidene)-4-methylaniline (3b). Yield: 98%. Light yellow crystals; for spectroscopic data, see ref.9

4-Methoxy-*N*-[(*E*)-3-phenylallylidene]aniline (3c). Yield: 100%. Yellow-green crystals; for spectroscopic data, see ref.10

**General procedure for the synthesis of the homopropargylamines 5a–c.** Boron trifluoride-diethyl ether complex (8.0 mmol) is added to a solution of the Schiff bases 3a–c (8.0 mmol) in THF at –23 °C. After stirring for 30 min, a solution of freshly prepared 3-trimethylsilylpropargylmagnesium bromide (4) (24 mmol) in diethyl ether is added dropwise to this suspension. The reaction mixture is stirred for 15 min at –23 °C (for 3a and 3b) or at 0 °C (for 3c). Subsequently, the mixture is poured into a saturated aqueous solution of ammonium chloride and extracted with ethyl acetate. The combined organic layers are washed with water and dried over sodium sulfate. Evaporation of the solvent and flash chromatography (hexane/ethyl acetate, 5:1) of the residue on silica gel affords the homopropargylamines 5a–c.

4-Methoxy-*N*-[1-phenyl-4-(trimethylsilyl)but-3-ynyl]aniline (5a). Yield: 78%. Light yellow oil; UV (MeOH): λ 244, 311 nm; IR (ATR): ν 3393, 3063, 3029, 2956, 2899, 2831, 2174, 1927, 1620, 1509, 1453, 1408, 1295, 1237, 1179, 1121, 1038, 839, 818, 757, 699, 641 cm⁻¹; 1H NMR (500 MHz, CDCl₃): δ 0.30 (s, 9 H), 2.74 (dd, J 16.9, 7.2 Hz, 1 H), 2.83 (dd, J 16.9, 5.4 Hz, 1 H), 3.76 (s, 3 H), 4.36 (br s, 1 H), 4.53 (br t, J 6.3 Hz, 1 H), 6.62 (d, J 8.9 Hz, 2 H), 6.81 (d, J 8.9 Hz, 2 H), 7.33–7.36 (m, 1 H), 7.42 (t, J 7.5 Hz, 2 H), 7.50 (d, J 7.8 Hz, 2 H); 13C NMR and DEPT
(125 MHz, CDCl$_3$): $\delta$ –0.12 (3 CH$_3$), 29.56 (CH$_2$), 55.36 (CH$_3$), 57.42 (CH), 87.95 (C), 102.95 (C), 114.96 (2 CH), 126.29 (2 CH), 127.17 (CH), 128.34 (2 CH), 141.30 (C), 142.46 (C), 152.11 (C); MS (EI): $m/z$ 323 (5) [M$^+$], 212 (100), 180 (10), 179 (46), 128 (17), 112 (11), 107 (79), 97 (5), 79 (20), 77 (10), 75 (22), 73 (43); HRMS: $m/z$ calc. for C$_{20}$H$_{25}$NOSi: 323.1705, found: 323.1695.

**N-(1-(4-Methoxyphenyl)-4-(trimethylsilyl)but-3-ynyl)-4-methylaniline (5b).** Yield: 80%. Pale yellow solid; mp: 69–70 °C; UV (MeOH): $\lambda$ 227, 247, 283, 301 nm; IR (ATR): $\nu$ 3408, 3002, 2961, 2903, 2862, 2171, 1613, 1584, 1548, 1441, 1420, 1403, 1317, 1301, 1245, 1212, 1168, 1128, 1113, 1096, 1055, 1033, 1010, 834, 808, 761, 726, 703, 645, 602 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 0.16 (s, 9 H), 2.20 (s, 3 H), 2.63 (dd, $J$ 16.9, 7.2 Hz, 1 H), 2.72 (dd, $J$ 16.9, 5.4 Hz, 1 H), 3.79 (s, 3 H), 4.32 (br s, 1 H), 4.42 (br t, $J$ 6.2 Hz, 1 H), 6.47 (d, $J$ 8.2 Hz, 2 H), 6.87 (d, $J$ 8.6 Hz, 2 H), 6.92 (d, $J$ 8.6 Hz, 2 H), 7.31 (d, $J$ 8.6 Hz, 2 H); $^{13}$C NMR and DEPT (125 MHz, CDCl$_3$): $\delta$ –0.02 (3 CH$_3$), 20.34 (CH$_3$), 29.85 (CH$_2$), 55.20 (CH$_3$), 56.38 (CH), 88.10 (C), 103.02 (C), 113.86 (2 CH), 113.92 (2 CH), 126.85 (C), 127.41 (2 CH), 129.55 (2 CH), 134.62 (C), 145.05 (C), 158.77 (C); MS (EI): $m/z$ 337 (20) [M$^+$], 227 (77), 226 (100), 225 (5), 224 (7), 182 (8), 164 (5), 118 (18), 91 (20), 73 (23); HRMS: $m/z$ calc. for C$_{21}$H$_{27}$NOSi: 337.1862, found: 337.1845.

**N-(E)-4-Methoxy-N-(1-phenyl-6-(trimethylsilyl)hex-1-en-5-yn-3-yl)aniline (5c).** Yield: 88%. Light yellow oil; UV (MeOH): $\lambda$ 250, 285, 292 nm; IR (ATR): $\nu$ 3390, 3028, 2957, 2899, 2831, 2171, 1927, 1599, 1509, 1458, 1441, 1420, 1317, 1301, 1245, 1212, 1168, 1128, 1113, 1096, 1055, 1033, 1010, 834, 808, 761, 726, 703, 645, 602 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 0.17 (s, 9 H), 2.63 (d, $J$ 5.8 Hz, 2 H), 3.74 (s, 3 H), 3.83 (br s, 1 H), 4.08–4.15 (m, 1 H), 6.24 (dd, $J$ 15.2, 6.3, 1.4 Hz, 1 H), 6.64–6.68 (m, 3 H), 6.76 (dd, $J$ 8.8, 1.7 Hz, 2 H), 7.21–7.26 (m, 1 H), 7.31 (t, $J$ 7.6 Hz, 2 H), 7.37 (d, $J$ 7.9 Hz, 2 H); $^{13}$C NMR and DEPT (125 MHz, CDCl$_3$): $\delta$ 0.06 (3 CH$_3$), 27.13 (CH$_2$), 55.25 (CH), 55.71 (CH$_3$), 88.04 (C), 102.92 (C), 114.80 (2 CH), 115.61 (2 CH), 126.41 (2 CH), 127.50 (CH), 128.50 (2 CH), 130.57 (CH), 131.00 (CH), 136.77 (C), 141.20 (C), 152.53 (C); MS (EI): $m/z$ 349 (22) [M$^+$], 153 (8), 133 (100), 115 (17), 77 (9), 75 (14), 73 (16); HRMS: $m/z$ calc. for C$_{22}$H$_{27}$NOSi: 349.1862, found: 349.1883.

**General procedure for the silver(I)-promoted oxidative cyclization to the pyrroles 6a–c.** Silver(I) acetate (0.33 mmol) is added to a solution of the homopropargylamines 5a–c (0.30 mmol) in dichloromethane. The reaction mixture is stirred for 4 d at room temperature in the absence of light. Filtration over a short path of neutral alumina (hexane/ethyl acetate, 1:1) and removal of the solvent provide the pyrroles 6a–c.

**1-(4-Methoxyphenyl)-2-phenyl-1H-pyrrole (6a).** Yield: 99%. Light yellow oil; UV (MeOH): $\lambda$ 225, 277 nm; IR (ATR): $\nu$ 3061, 2956, 2835, 2244, 1670, 1603, 1511, 1493, 1464, 1442, 1342, 1299, 1245, 1180, 1169, 1105, 1073, 1060, 1039, 946, 907, 884, 833, 798, 757, 725, 696, 664, 646, 617, 607 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 3.82 (s, 3 H), 6.38 (t, $J$ 3.2 Hz, 1 H), 6.47 (dd, $J$ 3.5, 1.8 Hz, 1 H), 6.85–6.88 (m, 2 H), 6.92–6.93 (m, 1 H), 7.11–7.15 (m, 2 H), 7.16–7.19 (m, 3 H), 7.22–7.25 (m, 2 H); $^{13}$C NMR and DEPT (125 MHz, CDCl$_3$): $\delta$ 55.34 (CH$_3$), 108.81
(CH), 110.05 (CH), 114.06 (2 CH), 124.47 (CH), 126.08 (CH), 126.87 (2 CH), 127.97 (2 CH), 128.15 (2 CH), 132.98 (C), 133.66 (C), 133.82 (C), 158.13 (C); MS (EI): m/z 249 (100) [M']
(2 CH), 234 (47), 206 (5), 204 (5), 179 (6), 146 (5), 115 (6), 107 (7); HRMS: m/z calc. for C$_{17}$H$_{15}$NO: 249.1154, found: 249.1182.

2-(4-Methoxyphenyl)-1-p-tolyl-1H-pyrrole (6b). Yield: 85%. Light yellow oil; UV (MeOH): λ 226 (sh), 270 nm; IR (ATR): ν 2954, 2924, 2839, 1675, 1598, 1510, 1460, 1420, 1366, 1304, 1246, 1168, 1109, 1024, 902, 814, 714, 693, 632, 604 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): δ 2.35 (s, 3 H), 3.77 (s, 3 H), 6.32–6.35 (m, 2 H), 6.74–6.77 (m, 2 H), 6.88–6.89 (m, 1 H), 7.03–7.08 (m, 4 H), 7.11 (d, J 8.4 Hz, 2 H); $^{13}$C NMR and DEPT (125 MHz, CDCl$_3$): δ 20.99 (CH$_3$), 55.15 (CH$_3$), 108.79 (CH), 109.52 (CH), 113.48 (2 CH), 123.72 (CH), 125.32 (2 CH), 129.52 (2 CH), 129.56 (2 CH), 133.60 (C), 136.24 (C), 138.10 (C), 158.13 (C); MS (EI): m/z 263 (100) [M']
(2 CH), 248 (57), 220 (5), 189 (8), 135 (12); HRMS: m/z calc. for C$_{18}$H$_{17}$NO: 263.1310, found: 263.1313.

(E)-1-(4-Methoxyphenyl)-2-styryl-1H-pyrrole (6c). Yield: 78%. Orange oil; UV (MeOH): λ 228, 334 nm; IR (ATR): ν 3081, 3027, 2956, 2835, 1629, 1598, 1512, 1459, 1418, 1298, 1180, 1147, 1106, 1040, 956, 893, 835, 801, 747, 714, 693, 634, 613 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): δ 3.87 (s, 3 H), 6.31 (t, J 3.2 Hz, 1 H), 6.63 (dd, J 3.6, 1.5 Hz, 1 H), 6.83–6.84 (m, 2 H), 6.97–6.99 (m, 2 H), 7.17 (tt, J 7.2, 1.2 Hz, 1 H), 7.25–7.28 (m, 5 H), 7.32 (d, J 7.3 Hz, 2 H); $^{13}$C NMR and DEPT (125 MHz, CDCl$_3$): δ 55.54 (CH$_3$), 106.91 (CH), 109.29 (CH), 114.29 (2 CH), 118.04 (CH), 118.04 (CH), 123.68 (CH), 125.94 (3 CH), 126.88 (CH), 127.49 (2 CH), 128.53 (2 CH), 132.47 (C), 132.66 (C), 137.78 (C), 158.75 (C); MS (EI): m/z 275 (76) [M'], 274 (26), 260 (14), 201 (49), 167 (13), 158 (12), 149 (26), 108 (56), 106 (85), 105 (89), 78 (27), 77 (100), 74 (11); HRMS: m/z calc. for C$_{19}$H$_{17}$NO: 275.1310, found: 275.1310.

References


