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A novel pyrrole synthesis

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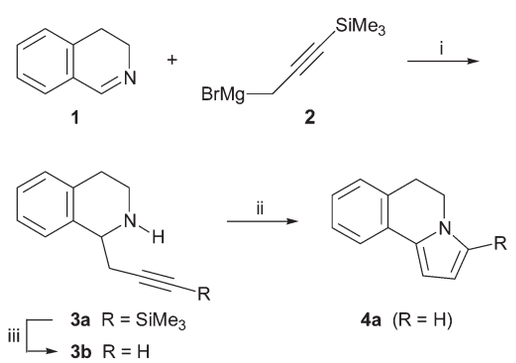
The silver(I)-promoted oxidative cyclization of homopropargylamines at room temperature provides a novel access to pyrroles. Homopropargylamines are readily available by the addition of a propargyl Grignard reagent to *Schiff* bases.

The pyrrole ring is a basic substructure of numerous biologically active alkaloids and pharmaceutical products.[1] Therefore, in addition to the classical *Hantzsch*, *Knorr* and *Paal–Knorr* syntheses many alternative syntheses of pyrroles by cyclization, multicomponent condensation and coupling reactions have been reported.[2] Herein, we describe a novel procedure for pyrrole annelation by silver(I)-promoted oxidative cyclization of homopropargylamines. Since the homopropargylamines are easily prepared by addition of a propargyl Grignard reagent to the appropriate *Schiff* base, our method consists of only two simple steps. The procedure is demonstrated for the oxidative annelation of a pyrrole ring at 3,4-dihydroisoquinoline (**1**) (Scheme 1).



Scheme 1 Synthesis of the dihydropyrrolo[2,1-*a*]isoquinoline **4a**. *Reagents and conditions*: (i) 1. BF_3–Et_2O, THF, −23 °C, 30 min; 2. **2**, Et_2O, −23 °C, 15 h, 80%; (ii) 1.1 eq. AgOAc, CH_2Cl_2, rt, 14 h, 72% from **3a**, 71% from **3b**; (iii) TBAF, THF, rt, 3 h, 87%.

The addition of 3-trimethylsilylpropargylmagnesium bromide (**2**) to 3,4-dihydroisoquinoline (**1**)[3] using Nakagawa's procedure (formation of a BF_3–imine complex prior to Grignard addition)[4] afforded 1-(3-trimethylsilylpropargyl)-1,2,3,4-tetrahydroisoquinoline (**3a**). Silver(I) salts form stable π-complexes with terminal acetylenes.[5] Therefore, we expected that the observed activation of the acetylene may be utilized for cyclization reactions by intramolecular nucleophilic attack onto the acetylene. Silver(I)-promoted cyclizations of substituted allenes to heterocyclic rings including 2,5-dihydropyrroles were reported previously.[6] Treatment of compound **3a** with silver acetate in dichloromethane solution at room temperature overnight resulted in a smooth oxidative cyclization forming the dihydropyrrolo[2,1-*a*]isoquinoline **4a** in 72% yield along with metallic silver. An extensive variation of the metal salt and its stoichiometry demonstrated that the reaction works best using 1.1 equivalents of silver acetate in dichloromethane or acetone at room temperature (Table 1). Application of a larger excess of the silver(I) salt does not improve the yield (entry 2) and since the reaction represents an oxidative cyclization, it is not catalytic in silver (entry 3). The results presented in Table 1 indicate the important role of the oxidation potential of the metal ion. Remarkably, cuprous acetate afforded a 56% yield of **4a**, in contrast to cupric acetate which led only to recovery of starting material (entries 4 and 5). Palladium(II) acetate gave a moderate yield of the anellated pyrrole **4a** (entry 6), while salts of more noble metals ($PtCl_2$, AuCl) were not useful (entries 7 and 8).

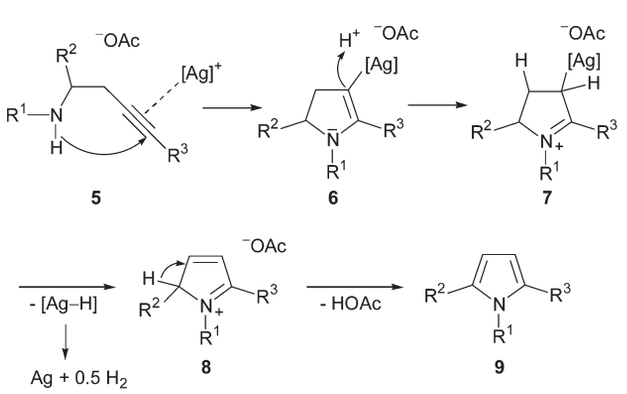
Table 1 Variation of metal salt and stoichiometry for cyclization of the homopropargylamine **3a** to the dihydropyrrolo[2,1-*a*]isoquinoline **4a**[a]

Entry	Metal salt	Equivalents	**4a**, Yield (%)
1	AgOAc	1.1	72
2	AgOAc	2.1	66
3	AgOAc	0.1	5
4	CuOAc	1.1	56
5	$Cu(OAc)_2$	1.1	—[b]
6	$Pd(OAc)_2$	1.1	18
7	$PtCl_2$	1.1	—
8	AuCl	1.1	Trace

[a] Reaction conditions: dry dichloromethane, room temperature, 14 h. [b] Complete recovery of starting material.

It was demonstrated that the oxidative cyclization of homopropargylamines to pyrroles works also for terminally unprotected alkynes (Scheme 1). Protodesilylation of compound **3a** provided 1-propargyl-1,2,3,4-tetrahydroisoquinoline (**3b**), which on treatment with silver acetate using the same reaction conditions gave the dihydropyrrolo[2,1-*a*]isoquinoline **4a** in 71% yield. Thus, it is concluded that on cyclization of **3a**, the trimethylsilyl group is removed by protodesilylation following the aromatization.

We tentatively propose the following mechanism for the silver(I)-promoted oxidative cyclization of homopropargylamines to pyrroles (Scheme 2). The coordination of the alkyne to the silver cation (**5**) initiates a nucleophilic attack of the amine at the alkyne, leading to intermediate **6**. Protonation of **6** affords the iminium ion **7** which on subsequent β-hydride elimination generates the pyrrylium ion **8** and metallic silver. Finally, proton loss of **8** provides the pyrrole **9**. For trimethylsilyl-substituted homopropargylamines **5** (R^3 = $SiMe_3$), the 1,2,5-trisubstituted pyrroles **9** (R^3 = $SiMe_3$) formed initially are protodesilylated by acetic acid to 1,2-disubstituted pyrroles **9** (R^3 = H). Preliminary experiments with internal alkynes **3** (R = Me, Ph) led to the corresponding 1,2,5-trisubstituted pyrroles **4** (R = Me, Ph).



Scheme 2 Proposed mechanism for the silver(I)-promoted oxidative cyclization of homopropargylamines to pyrroles.

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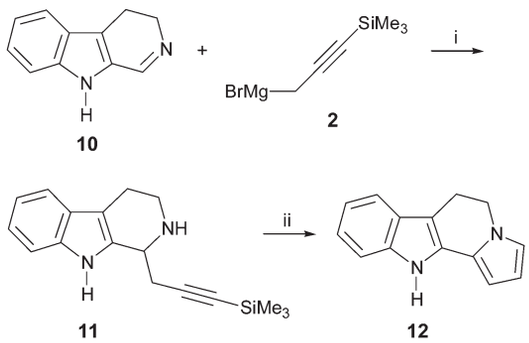
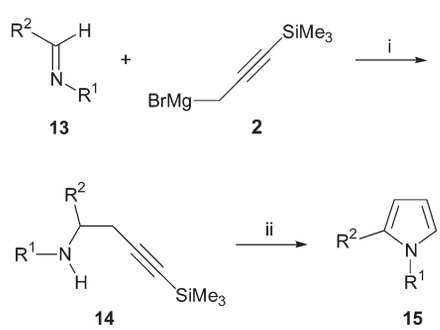
This method was applied to the annelation of pyrrole at 3,4-dihydro-β-carboline (**10**)[7] (Scheme 3). Addition of the propargyl Grignard reagent **2** to **10** afforded 1-(3-trimethylsilylpropargyl)-1,2,3,4-tetrahydro-β-carboline (**11**), which was used as a precursor in our iron-mediated total synthesis of the yohimbane alkaloid (±)-demethoxycarbonyldihydrogambirtannine.[8] The silver(I)-promoted oxidative cyclization of **11** afforded the dihydroindolizino[8,7-*b*]indole **12**, which represents a synthetic precursor for the indolizidino[8,7-*b*]indole alkaloid harmicine.[9]



Scheme 3 Synthesis of the dihydroindolizino[8,7-b]indole **12**. *Reagents and conditions*: (i) 1. BF_3–Et_2O, THF, −23 °C, 10 min; 2. **2**, Et_2O, −23 °C, 15 h, 68%; (ii) AgOAc, CH_2Cl_2, rt, 14 h, 77%.

Application of our procedure to *Schiff* bases generated from simple arylaldehydes afforded monocyclic pyrroles (Scheme 4, Table 2). An optimization of the reaction conditions has not been carried out for each case. However, the following result demonstrates that almost quantitative yields are feasible for the oxidative cyclization. Addition of the propargyl Grignard **2** to benzylidene-*p*-anisidine (**13a**) gave the homopropargylamine **14a**, which on silver(I)-promoted oxidative cyclization afforded almost quantitatively 1-(*p*-anisyl)-2-phenylpyrrole (**15a**). Analogously a broad variety of pyrroles can be prepared. It is noteworthy that conjugated double bonds of α,β-unsaturated imines are tolerated in this reaction. Thus, the imine **13c**, easily prepared from cinnamaldehyde and *p*-anisidine,[10] was transformed to the homopropargylamine **14c** and subsequently to 1-(*p*-anisyl)-2-cinnamylpyrrole (**15c**).



Scheme 4 Synthesis of the pyrroles **15**. *Reagents and conditions*: (i) 1. BF_3–Et_2O, THF, −23 °C, 30 min; 2. **2**, Et_2O, −23 °C, 15 h (conditions for **14c**: 1. 0 °C, 30 min; 2. 0 °C, 15 h); (ii) 1.1 eq. AgOAc, CH_2Cl_2, rt, 4 d.

Table 2 Synthesis of the monocyclic pyrroles **15a**–**c**

	R^1	R^2	**14**, Yield (%)	**15**, Yield (%)
a	4-$MeOC_6H_4$	C_6H_5	78	99
b	4-MeC_6H_4	4-$MeOC_6H_4$	80	85[a]
c	4-$MeOC_6H_4$	$C_6H_5CH{=}CH$	88	78

[a] 8% of starting material (**14b**) was recovered.

In conclusion, we have developed a novel two-step procedure for the synthesis of pyrroles by addition of a propargyl Grignard reagent to a *Schiff* base and subsequent silver(I)-promoted oxidative cyclization of the resulting homopropargylamine.

Experimental

General procedure for the silver(I)-promoted oxidative cyclization of homopropargylamines

Silver(I) acetate (1.1 eq.) was added to a solution of the homopropargylamine **3**, **11**, or **14** (1.0 eq.) in anhydrous CH_2Cl_2. In the absence of light, the solution was stirred at room temperature under an argon atmosphere for 14 h (compounds **3a**, **3b** and **11**) or 4 d (compounds **14a–c**). Filtration over a short path of neutral alumina (hexane–EtOAc) and removal of the solvent provided the pyrroles **4a**, **12**, or **15a–c**.

4a: Light yellow oil. UV (MeOH): λ = 293, 303 (sh) nm. IR (ATR): ν = 2927, 2879, 1689, 1606, 1577, 1550, 1494, 1460, 1427, 1413, 1334, 1316, 1245, 1230, 1200, 1167, 1102, 1070, 1045, 751, 706, 689, 673, 605 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.08 (t, J = 6.6 Hz, 2 H), 4.09 (t, J = 6.6 Hz, 2 H), 6.24 (dd, J = 3.5, 2.7 Hz, 1 H), 6.53 (dd, J = 3.5, 1.5 Hz, 1 H), 6.69 (m, 1 H), 7.11 (dt, J = 1.1, 7.4 Hz, 1 H), 7.18 (dd, J = 7.4, 0.4 Hz, 1 H), 7.24 (m, 1 H), 7.54 (dd, J = 7.4, 0.4 Hz, 1 H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 29.45 (CH_2), 44.08 (CH_2), 103.59 (CH), 108.53 (CH), 120.79 (CH), 122.36 (CH), 125.49 (CH), 127.07 (CH), 127.90 (CH), 129.56 (C), 129.79 (C), 130.27 (C). MS (EI): m/z (%) = 169 (100) [M^+], 168 (67), 167 (25), 166 (5), 154 (5), 141 (5), 84 (9). HRMS: m/z calcd for $C_{12}H_{11}N$ [M^+]: 169.0891; found: 169.0888.

12: Light green powder; mp: 161–163 °C. UV (MeOH): λ = 224, 281, 290 nm. IR (DRIFT): ν = 3425, 3383, 1624, 1603, 1480, 1438, 1369, 1353, 1332, 1320, 1307, 1272, 1244, 1234, 1070, 844, 747, 712 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.18 (t, J = 7.0 Hz, 2 H), 4.22 (t, J = 7.0 Hz, 2 H), 6.26 (dd, J = 3.4, 2.7 Hz, 1 H), 6.33 (dd, J = 3.4, 1.4 Hz, 1 H), 6.80 (dd, J = 2.7, 1.4 Hz, 1 H), 7.18 (m, 2 H), 7.39 (m, 1 H), 7.54 (m, 1 H), 8.10 (br s, 1 H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 21.25 (CH_2), 45.36 (CH_2), 101.87 (CH), 105.17 (C), 108.14 (CH), 110.93 (CH), 117.81 (CH), 119.94 (CH), 121.44 (CH), 121.77 (CH), 124.62 (C), 127.13 (C), 128.96 (C), 136.38 (C). MS (EI): m/z (%) = 208 (100) [M^+], 207 (68), 206 (18), 205 (3), 115 (4), 104 (3). HRMS: m/z calcd for $C_{14}H_{12}N_2$ [M^+]: 208.1000; found: 208.0994.

15a: Yellow oil. UV (MeOH): λ = 225, 277 nm. IR (ATR): ν = 1603, 1511, 1493, 1464, 1442, 1299, 1245, 1180, 1169, 1105, 1073, 1060, 1039, 946, 907, 884, 833, 798, 757, 725, 696, 664, 646, 617, 607 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.82 (s, 3 H), 6.38 (m, 1 H), 6.47 (dd, J = 3.5, 1.8 Hz, 1 H), 6.87 (d, J = 8.9 Hz, 2 H), 6.92 (m, 1 H), 7.13 (d, J = 8.9 Hz, 2 H), 7.16–7.19 (m, 3 H), 7.22–7.25 (m, 2 H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 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^+], 234 (47), 206 (5), 204 (5), 179 (6). HRMS: m/z calcd for $C_{17}H_{15}NO$ [M^+]: 249.1154; found: 249.1182.

15b: Yellow oil. UV (MeOH): λ = 226 (sh), 270 nm. IR (ATR): ν = 2924, 1675, 1598, 1510, 1460, 1420, 1366, 1304, 1246, 1168, 1109, 1024, 965, 902, 814, 714, 693, 632, 604 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.35 (s, 3 H), 3.77 (s, 3 H), 6.33 (m, 1 H), 6.34 (dd, J = 3.5, 1.9 Hz, 1 H), 6.76 (d, J = 8.8 Hz, 2 H), 6.88 (dd, J = 2.6, 1.9 Hz, 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), 125.52 (2 CH), 125.78 (C), 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^+], 248 (57), 220 (5), 189 (8), 135 (12). HRMS: m/z calcd for $C_{18}H_{17}NO$ [M^+]: 263.1310; found: 263.1313.

15c: Orange oil. UV (MeOH): λ = 228, 334 nm. IR (ATR): ν = 1629, 1598, 1512, 1459, 1418, 1298, 1248, 1180, 1147, 1106, 1040, 956, 893, 835, 801, 784, 747, 714, 692, 634, 613 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.88 (s, 3 H), 6.32 (m, 1 H), 6.64 (dd, J = 3.5, 1.6 Hz, 1 H), 6.78 (d, J = 16.3 Hz, 1 H), 6.84 (dd, J = 2.7, 1.6 Hz, 1 H), 6.86 (d, J = 16.3 Hz, 1 H), 6.99

(d, J = 8.9 Hz, 2 H), 7.17 (tt, J = 7.2, 1.2 Hz, 1 H), 7.25–7.29 (m, 2 H), 7.28 (d, J = 8.9 Hz, 2 H), 7.33 (m, 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), 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), 108 (56), 106 (85), 105 (89), 78 (27), 77 (100). HRMS: m/z calcd for $C_{19}H_{17}NO$ [M^+]: 275.1310; found: 275.1310.

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