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Synthesis of 3-Halopyrroles

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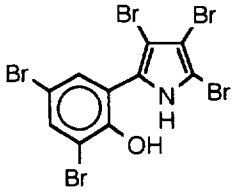
Abstract : 3-Chloro- and 3-bromo-2-arylpyrroles, which are potential physiologically active compounds in agrochemistry and pharmaceutical sciences, were efficiently prepared from the corresponding 2-aryl-1-pyrrolines by α,α-dihalogenation with N-halosuccinimides and subsequent base-induced monodehydrohalogenation using sodium methoxide in methanol.

INTRODUCTION

The chemistry of halogenated pyrroles has witnessed a phenomenal revival in the last decade because of the discovery of a large variety of functionalized azaheterocycles from natural sources, and the large area of physiological activities associated with these structures. 3-Halopyrroles especially have been shown to have pronounced physiological activities in agrochemistry and pharmaceutical sciences, although the 2-halopyrrole moiety is also often encountered as a part of the molecule. Pentabromopseudilin **1** is a brominated pyrrole



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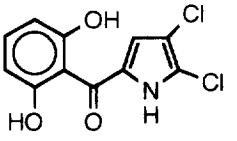

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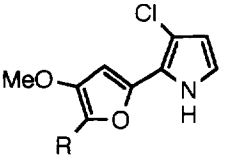

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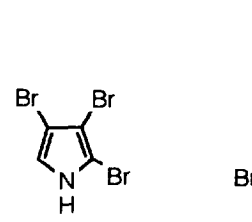
isolated from the marine bacterium *Alteromonas luteo-violaceus* which showed antibacterial and anti-tumor activity, in addition to being an enzyme inhibitor.[1] Pyoluteorin **2** is an antibacterial chlorinated pyrrole, isolated from *Pseudomonas aeruginosa*,[2] while roseophillin **3** is a 3-chloropyrrole-containing antileukemic

compound, isolated from *Streptomyces griseoviridis*.[3] 2,3,4-Tribromopyrrole **4** is an antibacterial compound isolated from the marine polychaete *Polyphysia crassa*,[4] and 4,5-dibromopyrrole-2-carboxylic acid **5** and agelongine have been isolated from the sponges *Agelas oroides*[5a] and *Agelas longissima*,[5b] respectively. Synthetic analogues of the latter halopyrroles were found to exhibit molluscicidal, insecticidal, nematocidal, fungicidal,[6,7] and herbicidal activity.[8] The antifungal and antibacterial pyrrolnitrin **6**, isolated from the bacterium *Pseudomonas pyrociniae*,[9] functioned as a lead for a number of fungicides, e.g. fenpiclonil **7**,[10]



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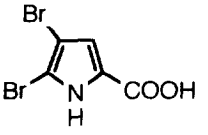

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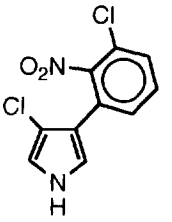

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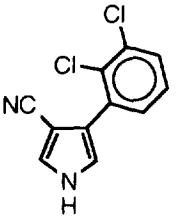

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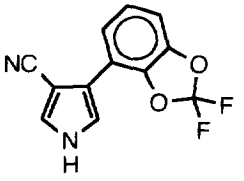

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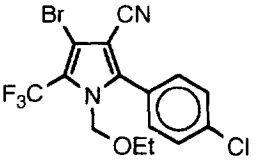

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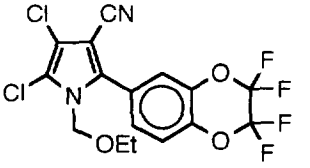

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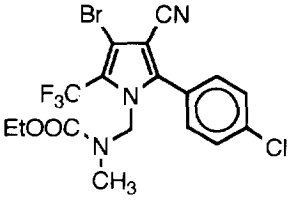
saphire® **8**,[11] insecticides,[12-14,16] nematicides[14] and molluscicides,[15] e.g. pyrroles, **9-12**. The manzacidines A-C are a class of 3-bromopyrrole derivatives **13**, isolated from the Okinawan sponge *Hymeniacidon sp.*[17] Other natural products containing the 3-halopyrrole nucleus are longamide[18] and pseudoceratidine.[19]



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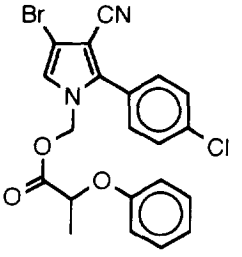

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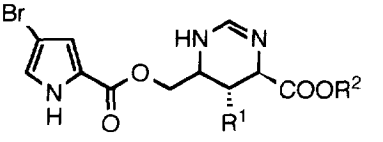

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The access to halopyrroles in a regiospecific way has been fairly limited, because of problems associated with the regiocontrol of halogenation of pyrroles, the problem of overhalogenation, the instability of reaction products and the formation of oxidation products.[20-27] The thermodynamically more stable 3-bromopyrroles are the major monobrominated products when bromine is used as brominating agent due

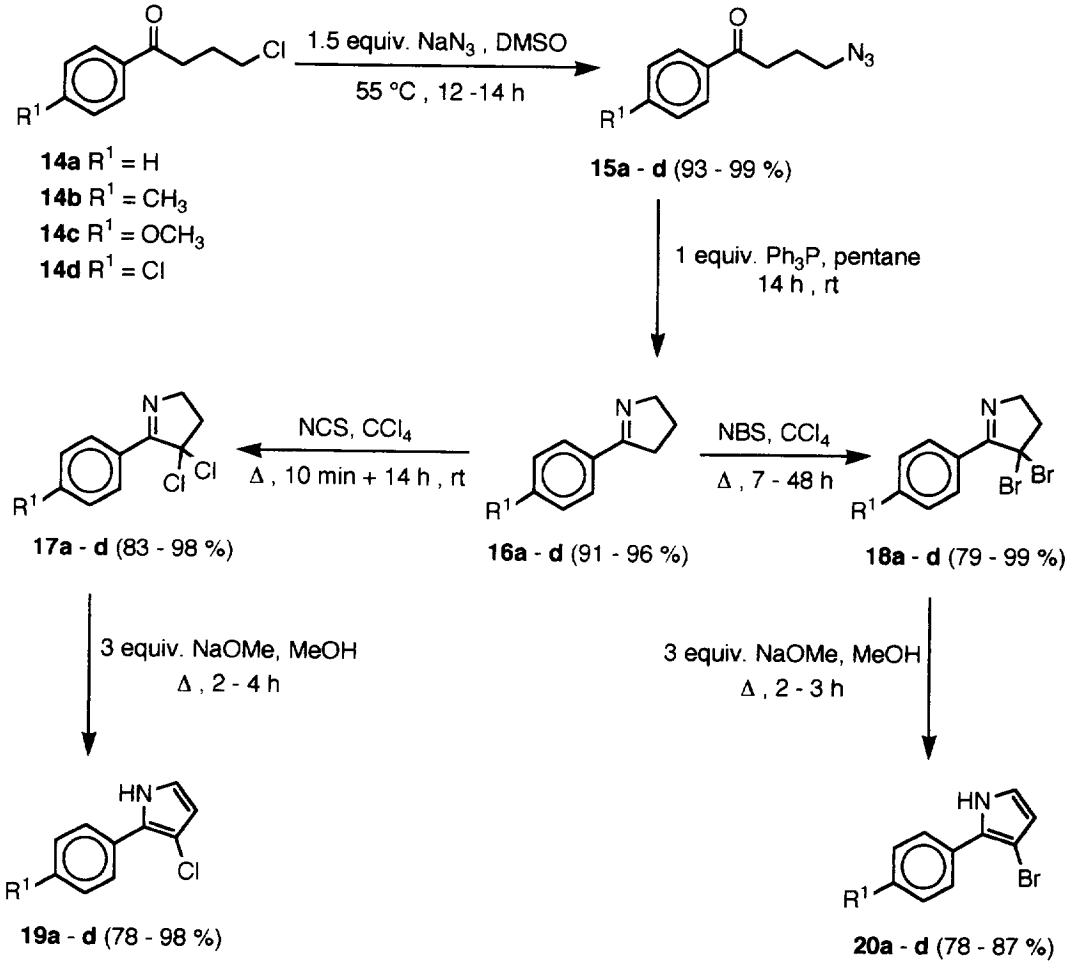
to the isomerization of 2-bromopyrroles with hydrogen bromide.[28] The regioselective introduction of a chloro substituent in pyrroles by N-chlorosuccinimide is highly dependent upon the solvent used.[28] The monohalogenation of pyrroles can be regioselectively directed to the 3-position using N-halosuccinimides in dimethylformamide[25] or in tetrahydrofuran, in the latter case with the directing triisopropylsilyl group as N-substituent.[29-31] Also the N-trityl group was found to be a suitable directing substituent for bromination at the 3-position.[32] By changing the 2-formyl substituent into the corresponding iminium salt, derived from pyrrolidine, the regioselectivity of the bromination of the pyrrole derivative could be considerably increased.[33] The enzymatic bromination of 2-arylpyrroles by chloroperoxidase and sodium bromide afforded a mixture of bromopyrroles.[34] An alternative regioselective synthesis of 3-chloropyrroles consists of the thermal rearrangement of 2,2-dichlorocyclopropanecarbaldehyde imines in polar solvents,[35,36] while 3-bromopyrroles are accessible from the reaction of 3-amino-2-yn-1-ones with hydrogen bromide.[37] 3-Fluoropyrroles have been prepared by cyclocondensation of γ-iodo-α,α-difluorocarbonyl compounds with ammonia,[38,39] by the fluorination of 3-bromopyrroles with N-fluorobenzenesulfonimide,[40] by dehydrofluorination and dehydratation of 3,3-difluoro-5-hydroxypyrrolidines,[41] and by dehydrofluorination of 3,3-difluoro-5-(trimethylsilyl)-1-pyrrolines.[39]

In the present report, an efficient regiospecific synthesis of 2-aryl-3-chloropyrroles **19** and 2-aryl-3-bromopyrroles **20** through dehydrohalogenation of 2-aryl-3,3-dihalo-1-pyrrolines **17** and **18** is disclosed.

RESULTS AND DISCUSSION

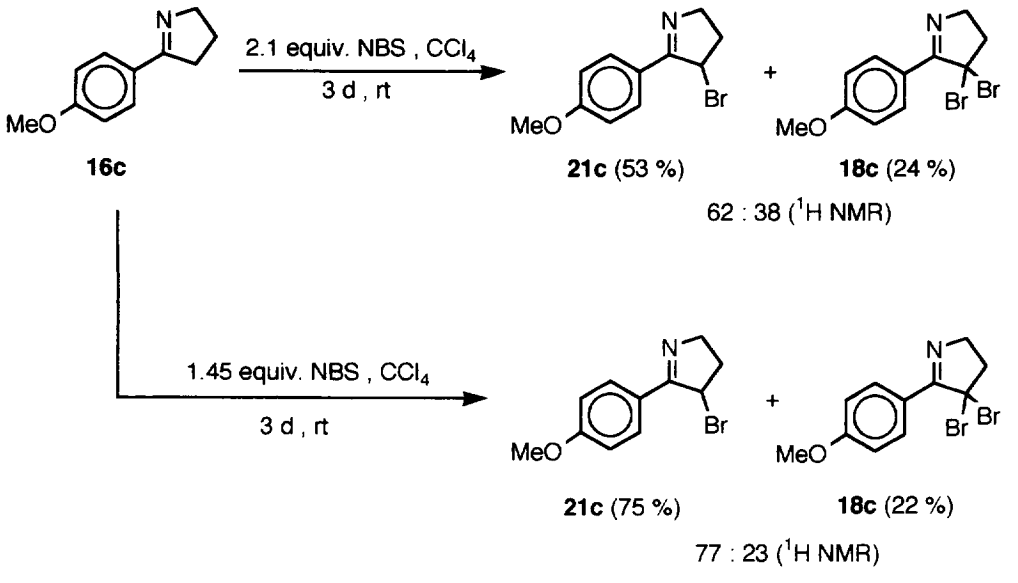
1-Aryl-4-chloro-1-butanones **14** were reacted with sodium azide in dimethylsulfoxide[42] to give 1-aryl-4-azido-1-butanones **15** in 93-99 % yield. The crude γ-azidoketones **15** (purity > 96 %) were cyclized to 2-aryl-1-pyrrolines **16** via an aza-Wittig type reaction[42,43] with triphenylphosphine in pentane at room temperature. Reaction of 2-aryl-1-pyrrolines **16** with 2.05-2.2 equivalents of N-chlorosuccinimide in carbon tetrachloride at reflux for a few minutes and further at room temperature for several hours afforded 2-aryl-3,3-dichloro-1-pyrrolines **17** in 83-98 % yield (Table 1). Similarly, 2-aryl-1-pyrrolines **16** reacted with N-bromosuccinimide in carbon tetrachloride for 7-48 h at 65°C or at reflux to give rise to 2-aryl-3,3-dibromo-1-pyrrolines **18** in 79-99 % yield (Table 1; Scheme 1). This α-bromination of 1-pyrrolines proceeded much slower than the corresponding α-chlorination. In addition, it was more difficult to let the α,α-dibromination reaction of 1-pyrrolines **16** go to completion, requiring to check the progress of the reaction by sampling and NMR-monitoring. At room temperature for 3 days, 2-(4-methoxyphenyl)-1-pyrroline **16c** reacted with 2.1 equivalents of N-bromosuccinimide in CCl_4 to give mainly the monobromination product, i.e. 3-bromo-2-(4-methoxyphenyl)-1-pyrroline **21c** (62 %) and some 3,3-dibromo-2-(4-methoxyphenyl)-1-pyrroline **18c** (38 %). The α-monobromination could not be performed with a very high specificity. On treatment of 1-pyrroline **16c** with 1.45 equivalents of N-bromosuccinimide at room temperature for 3 days, a monobromination : dibromination ratio of 77 : 23 was obtained (Scheme 2). 3-Bromo-1-pyrroline **21c** was separated (yield 75%) from 3,3-dibromo-1-pyrroline **18c** (yield 22 %) by flash chromatography on silica gel. Similar difficulties in the selective bromination of 1-pyrrolines have been observed previously in the literature.[44]

2-Aryl-3,3-dichloro-1-pyrrolines **17** and 2-aryl-3,3-dibromo-1-pyrrolines **18** were conveniently converted into 2-aryl-3-chloropyrroles **19** and 2-aryl-3-bromopyrroles **20**, respectively, by reaction with excess sodium methoxide in methanol under reflux for 2-4 h (Scheme 1). All 3-halopyrroles **19** and **20** were obtained almost free of side products except the 2-(4-methoxyphenyl)-3-halopyrroles **19c** and **20c** which were extra purified



Scheme 1

by flash chromatography. All other 3-halopyrroles **19** and **20** were obtained as pure oils (Table 2). Also 3-bromo-2-(4-methoxyphenyl)-1-pyrroline **21c** was easily dehydrobrominated with sodium methoxide in methanol under reflux to afford 2-(4-methoxyphenyl)pyrrole **22c** in 78 % yield (Scheme 3).

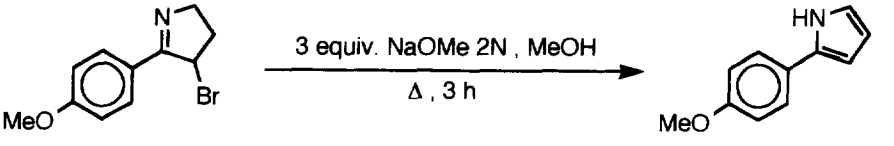


Scheme 2

Table 1. Synthesis of 2-Aryl-3,3-dichloro-1-pyrrolines **17** and 2-Aryl-3,3-dibromo-1-pyrrolines **18**

R^1	Compound **17**		Compound **18**	
	Reaction conditions[a]	Yield (%)	Reaction conditions[a]	Yield (%)
a: H	2.2 equiv. NCS, CCl_4, reflux, 10 min + rt, 7 h	90	2.2 equiv. NBS, CCl_4 65°C, 2 d	80
b: CH_3	2.05 equiv. NCS, CCl_4, reflux, 10 min + rt, 14h	83	2.2 equiv. NBS, CCl_4 reflux, 14 h	88
c: OCH_3	2.05 equiv. NCS, CCl_4, reflux, 10 min + rt, 14h	86	2.2 equiv. NBS, CCl_4 reflux, 7 h	99
d: Cl	2.2 equiv. NCS, CCl_4, reflux, 10 min + rt, 12h	98	2.2 equiv. NBS, CCl_4 65°C, 2 d	79

[a]Reaction of 1-pyrrolines **16** with N-halosuccinimides in CCl_4.



21c **22c** (78 %)

Scheme 3

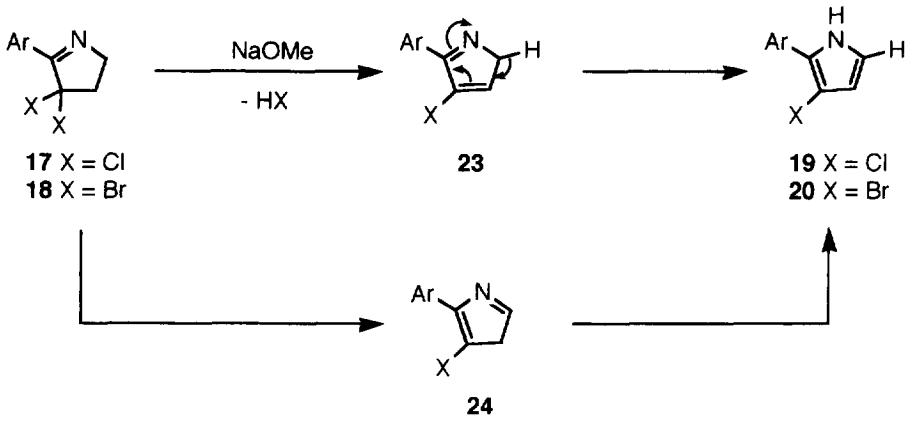
Table 2. Synthesis of 2-Aryl-3-chloropyrroles **19** and 2-Aryl-3-bromopyrroles **20**

R^1	2-Aryl-3-chloropyrroles **19**		2-Aryl-3-bromopyrroles **20**	
	Reaction conditions	Yield (%)	Reaction conditions	Yield (%)
a: H	3 equiv. 1N NaOMe, MeOH reflux, 2h	95	3 equiv. 1N NaOMe, MeOH reflux, 2h	85
b: CH_3	3 equiv. 2N NaOMe, MeOH reflux, 3h	98[a]	3 equiv. 2N NaOMe, MeOH reflux, 3h	82[a]
c: OCH_3	3 equiv. 2N NaOMe, MeOH reflux, 3h	78[a]	3 equiv. 2N NaOMe, MeOH reflux, 3h	78[a]
d: Cl	3 equiv. 2N NaOMe, MeOH reflux, 4h	95	3 equiv. 2N NaOMe, MeOH reflux, 3h	87

[a]purified by flash chromatography (silica gel; EtOAc : hexane 2:3).

From the mechanistic point of view, the base-induced conversion of 2-aryl-3,3-dihalo-1-pyrrolines **17** and **18** into 2-aryl-3-halopyrroles **19** and **20** is the result of a dehydrochlorination reaction, either in a 1,2-fashion via **23** or in a 1,4-fashion via **24**, and a final aromatization reaction by a deprotonation-protonation process. As there is no activating influence on the acidity of the hydrogens of the methylene function attached to nitrogen in 1-pyrrolines **17** and **18**, the 1,4-dehydrohalogenation process is less plausible, although this process is known for N-benzyl α-chloro imines.[46] The conversion of **17** and **18** into **19** and **20** shows some

similarity with the dehydrofluorination of 3,3-difluoro-1-pyrrolines,[39] the conversion of 2-aryl-4-cyano-3-(trifluoromethyl)-1-pyrrolines by bromination into 2-aryl-5-bromo-4-cyano-3-(trifluoromethyl)pyrrole,[45] and oxidative aromatization of ethyl 2-aryl-1-pyrrolinyl-5-carboxylates with NBS/AIBN.[44b]



Scheme 4

EXPERIMENTAL PART

^{1}H NMR spectra were recorded at 60 MHz (JEOL PMX 60 SI) or 270 MHz (JEOL JNM-EX 270) with $CDCl_3$ or CCl_4 as solvent. ^{13}C NMR spectra were recorded at 20 MHz (VARIAN FT-80) or 67.8 MHz (JEOL JNM-EX 270) with $CDCl_3$ as solvent. Mass spectra were obtained on a mass spectrometer (70 eV) using direct inlet or GC-MS coupling (RSL 200, 20 m glass capillary column, i.d. 0.53 mm, He carrier gas). Tetrachloromethane was distilled from CaH_2. Diethyl ether was distilled from sodium/benzophenone ketyl. The other solvents were used as such.

General Procedure for the Synthesis of 2-Aryl-1-pyrrolines 16

A solution of 0.3 mol of 1-aryl-4-chloro-1-butanone **14** in 100 ml of dimethylsulfoxide was treated with 29.25 g (0.45 mol) of sodium azide and a catalytic amount of sodium iodide (1.5 g). The suspension was warmed under stirring to 55°C (oil bath temperature) after which stirring was continued for 12 h behind a safety shield.[43] The reaction mixture was poured into 200 ml of water and extracted with ether (4 × 50 ml). The combined ethereal layers were washed with brine and dried ($MgSO_4$). After filtration and evaporation of the solvent, 1-aryl-4-azido-1-butanones **15** were obtained in 93-99 % yield.

For the synthesis of azidoketones **15b,c** (R^1=Me, OMe) no sodium iodide was used. The crude γ-azidoketones **15** thus obtained were sufficiently pure (> 96 %) for further use in the next step. These ketones **15** were characterized by ^{1}H NMR, ^{13}C NMR and IR spectroscopy.

A stirred solution of 0.28 mol of the γ-azidoketone **15**, obtained as above, in 1000 ml of dry pentane was treated portionwise with 0.28 mol of triphenylphosphine.[43] A few minutes after the addition of the first portions of triphenylphosphine, nitrogen gas evolved from the reaction mixture. If the reaction does not start after a few minutes, warming of the reaction mixture (± 35°C) may be necessary. However, the reaction is exothermic so that the temperature must be controlled. The suspension was stirred behind a safety shield for 14 h and then poured into 1000 ml of petroleum ether. The triphenylphosphin oxide was filtered off and washed with cold ether (0°C). The filtrate was evaporated and a mixture of ether/petroleum ether (50/50) was added again to the remaining oil. Filtration of the precipitated triphenylphosphin oxide and evaporation of the solvent led to the isolation of 2-aryl-1-pyrrolines **16** in 86-95 % overall yield from 1-aryl-4-chloro-1-butanones **14**. 2-Phenyl-1-pyrroline **16a** : yield 95 %. Bp. 125°C/14 mmHg; Lit. bp. 95-97°C/0.5 mmHg; Lit. mp. : ~ 30°C.[42b]

2-(4-Methylphenyl)-1-pyrroline **16b** : yield 84 %. Flash chromatography (silica gel): eluent EtOAc/Hexane 1/1, Rf = 0.29. Mp. 60 °C. Lit. mp. 63 °C.[47]

2-(4-Methoxyphenyl)-1-pyrroline **16c** : yield 81 %. Flash chromatography (silica gel): eluent EtOAc/Hexane 7/3, Rf = 0.17. Mp. 72°C. Lit. mp. 74 °C.[47]

2-(4-Chlorophenyl)-1-pyrroline[48] **16d** : yield 96 %.

General Procedure for the Synthesis of 2-Aryl-3,3-dihalo-1-pyrrolines 17 and 18

To a solution of 0.04 mol of 2-aryl-1-pyrroline in 50 ml of tetrachloromethane was added 0.088 mol (2.2 equiv.) of N-halosuccinimide. The reaction mixture was refluxed for ten minutes and stirred further at room temperature for 7-12 h. The succinimide was filtered off and washed with ice-cold tetrachloromethane. Evaporation of the solvent gave the pure 2-aryl-3,3-dihalo-1-pyrrolines **17** and **18** in excellent yields which could be used as such in the dehydrohalogenation step (purity > 96%).

3,3-Dichloro-2-phenyl-1-pyrroline **17a**

Yield : 90 % (crude mixture); 40 % (distilled); bp. 125-127°C/1 mmHg). ^{1}H NMR (CCl_4) δ 2.90 (2H, t, J=6 Hz, CH_2CCl_2); 4.03 (2H, t, J=6 Hz, CH_2N); 7.3-7.7 (3H, m, Ph); 8.1-8.4 (2H, m, Ph). ^{13}C NMR ($CDCl_3$) δ 48.86 (t, $\underline{C}H_2CCl_2$); 56.54 (t, CH_2N); 87.32 (s, CCl_2); 128.10 (d, CH); 128.73 (d, CH); 129.62 (s, C_{quat}); 130.82 (d, CH); 168.75 (s, C=N). IR (NaCl) : 1720 cm^{-1} (C=N). MS m/z (%) : 213/5/7 (22, M^+); 177/79/81(3); 178/80/82(2); 149(2); 142(2); 117(100); 115(8); 104(11); 91(7); 77(10); 75(8); 63(3); 51(5). Anal. Calcd. for $C_{10}H_9Cl_2N$: C 56.10%; H 4.24%; N 6.54%. Found C 56.22%; H 4.04%; N 6.29%.

3,3-Dibromo-2-phenyl-1-pyrroline **18a**

Yield : 80 % (crude mixture; decomposition on attempted distillation *in vacuo* or on flash chromatography).^{1}H NMR ($CDCl_3$) δ 3.16 (2H, t, J=6 Hz, CH_2CBr_2); 3.93 (2H, t, J=6 Hz, CH_2N); 7.1-7.5 (3H, m, Ph); 7.9-8.3 (2H, m, Ph). ^{13}C NMR ($CDCl_3$) δ 51.53 (t, $\underline{C}H_2CBr_2$); 56.95 (t, CH_2N); 58.04 (s, CBr_2); 127.96 (d, CH); 128.86 (d, CH); 129.82 (s, C_{quat}); 130.84 (d, CH); 170.29 (s, C=N). IR (NaCl) : 1720 cm^{-1} (C=N). MS m/z (%) 303/5 (1, M^+); 301(1); 222/4(3); 221/3(4); 143(6); 142(7); 117(100); 115(21); 104(13); 91(19); 77(13); 51(10).

3,3-Dichloro-2-(4-methylphenyl)-1-pyrroline **17b**

Yield : 83 % (crude mixture). To remove the last traces of triphenylphosphinoxide the crude product was purified by flash chromatography using Et_2O/Pentane 3/7, Rf = 0.39. ^1H NMR ($CDCl_3$) δ 2.39 (3H, s, Me); 2.98 (2H, t, J=6.10 Hz, CH_2CCl_2); 4.07 (2H, t, J=6.11 Hz, CH_2N); 7.24 (2H, d, J=7.91 Hz, Ar, H_{meta}); 8.05 (2H, d, J=8.58 Hz, Ar, H_{ortho}). ^{13}C NMR ($CDCl_3$) δ 21.49 (Me); 49.04 ($\underline{C}H_2CCl_2$); 56.66 (CH_2N); 87.29 (CCl_2); 126.84 (Ar); 128.71 (Ar, C_{ortho}); 128.98 (Ar, C_{meta}); 141.35 (Ar); 169.16 (C=N). IR (NaCl) : 1615 cm^{-1} (C=N). MS m/z (%) : 227/29/31 (12, M^+); 192/4(4); 157(3); 131(100); 118(7); 117(6); 116(4); 115(4); 105(6); 91(6); 90(2); 89(3); 75(4); 65(4); 63(2); 56(3); 44(2); 40(2). Anal. Calcd. for $C_{11}H_{11}Cl_2N$: C 57.92%; H 4.86%; N 6.14%. Found C 58.09%; N 4.78%; N 6.20%.

3,3-Dibromo-2-(4-methylphenyl)-1-pyrroline **18b**

Yield : 88 % (crude mixture). Flash chromatography (silica gel), eluent Et_2O/Pentane 3/7, Rf = 0.40. Mp. 50.5°C. ^1H NMR ($CDCl_3$) δ 2.47 (3H, s, Me); 3.32 (2H, t, J=5.94 Hz, CH_2CBr_2); 4.08 (2H, t, J=5.94 Hz, CH_2N); 7.32 (2H, d, J=8.25 Hz, Ar, H_{meta}); 8.17 (2H, d, J=8.25 Hz, Ar, H_{ortho}). ^{13}C NMR ($CDCl_3$) δ 21.53 (Me); 51.84 ($\underline{C}H_2CBr_2$); 57.16 (CH_2N); 58.24 (CBr_2); 127.26 (Ar); 128.93 (Ar, C_{ortho} and C_{meta}); 141.42 (Ar); 170.46 (C=N). IR (NaCl) : 1600 cm^{-1} (C=N). MS m/z (%) : no M^+; 235/7 (100, M^+-HBr); 156(55); 155(21); 154(18); 129(41); 128(24); 127(16); 78(33); 65(12); 51(8); 44(61). Anal. Calcd. for $C_{11}H_{11}Br_2N$: C 41.68%; H 3.50%; N; 4.42%. Found C 41.89%; H 3.65%; N 4.30%.

3,3-Dichloro-2-(4-methoxyphenyl)-1-pyrroline **17c**

Yield : 86 % (crude mixture). Flash chromatography (silica gel) , eluent Et_2O/Pentane 3/7, Rf = 0.36. Mp. 54.5°C. ^1H NMR ($CDCl_3$) δ 2.95 (2H, t, J=6 Hz, CH_2CCl_2); 3.79 (3H, s, OMe); 4.03 (2H, t, J=6 Hz, CH_2N); 6.93 (2H, d, J=8.91 Hz, Ar, H_{meta}); 8.12 (2H, d, J=8.91 Hz, Ar, H_{ortho}). ^{13}C NMR ($CDCl_3$) δ 49.00 ($\underline{C}H_2CCl_2$); 55.22 (OMe); 56.46 (CH_2N); 87.35 (CCl_2); 113.58 (Ar, C_{meta}); 122.01 ($\underline{C}C$=N); 130.46 (Ar, C_{ortho}); 161.70 ($\underline{C}$OMe); 168.39 (C=N). IR (KBr) : 1607 cm^{-1} (C=N). MS m/z (%) : 243/5/7 (22, M^+); 208/10(5); 193/5(4); 147(100); 133(11); 132(11); 121(8); 103(4); 102(4); 91(3); 90(2); 77(7); 75(5); 51(3); 44(8). Anal. Calcd. for $C_{11}H_{11}Cl_2NO$: C 54.12%; H 4.54%; N 5.74%. Found C 54.24%; H 4.33%; N 5.67%.

3,3-Dibromo-2-(4-methoxyphenyl)-1-pyrroline **18c**

Yield : 99 % (crude mixture). Flash chromatography (silica gel), eluent EtOAc/Hexane 4/6, Rf = 0.45. Mp. 63°C. ^1H NMR ($CDCl_3$) δ 3.26 (2H, t, J=5.94 Hz, CH_2CBr_2); 3.86 (3H, s, OMe); 4.00 (2H, t, J=5.94 Hz, CN_2N); 6.96 (2H, d, J=9.08 Hz, Ar, H_{meta}); 8.19 (2H, d, J=9.08, Ar, H_{ortho}). ^{13}C NMR ($CDCl_3$) δ 51.73 ($\underline{C}H_2CBr_2$); 55.20 (OMe); 56.93 (CH_2N); 58.36 (CBr_2); 113.42 (Ar, C_{meta}); 122.35 ($\underline{C}C$=N); 130.58 (Ar, C_{ortho}); 161.60 ($\underline{C}$OMe); 169.56 (C=N). IR (KBr) : 1600 cm^{-1} (C=N). MS m/z (%) : 331/3/5 (9, M^+); 288/90/92(2); 252/4(8); 237/9(5); 173(5); 159(5); 147(100); 135(7); 133(17); 132(6); 130(5); 129(4); 121(27); 103(7); 102(9); 91(6); 90(4); 77(11); 76(5); 75(5); 65(3); 64(3); 51(5); 50(3); 44(9); 43(5); 42(4); 41(3). Anal. Calcd. for $C_{11}H_{11}Br_2NO$: C 39.67%; H 3.33%; N 4.21%. Found C 39.76%; H 3.45%; N 4.14%.

2-(4-Chlorophenyl)-3,3-dichloro-1-pyrroline **17d**

Yield : 98 % (crude mixture). ^{1}H NMR ($CDCl_3$) δ 2.98 (2H, t, J=6 Hz, CH_2CCl_2); 4.21 (2H, t, J=6 Hz, CH_2N); 7.46 (2H, d, J=8.5 Hz, Ar); 8.19 (2H, d, J=8.5 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ 48.92 (t, $\underline{C}H_2CCl_2$); 56.65 (t, CH_2N); 87.04 (s, CCl_2); 128.04 (s, CCl); 128.37 (d, Ar); 130.13 (d, Ar); 137.04 (s, Ar); 167.04 (s, C=N). IR (NaCl) : 1610 cm^{-1} (C=N). MS m/z (%) : 247/49/51/53 (20, M^+); 212/4/6(20); 177/9(12); 151/3 (100); 141(8); 140(6); 139(4); 138(16); 137(10); 123(10); 116(8); 115(9); 114(8); 113(8); 111(12); 89(12); 75(20); 44(12).

2-(4-Chlorophenyl)-3,3-dibromo-1-pyrroline **18d**

Yield : 79 % (crude mixture). ^{1}H NMR ($CDCl_3$) δ 3.26 (2H, t, J=6 Hz, CH_2CBr_2); 4.05 (2H, t, J=8 Hz, CH_2N); 7.47 (2H, d, J=8.2 Hz, Ar); 8.24 (2H, d, J=8.5 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ 51.62 (t, CH_2CBr_2); 56.90 (t, CH_2N); 58.09 (s, CBr_2); 128.27 (s, =CCl); 128.53 (d, Ar); 130.31 (d, Ar); 137.16 (s, Ar); 168.97 (s, C=N). IR (NaCl) : 1720 cm^{-1} (C=N). No mass spectrum could be obtained due to decomposition.

3-Bromo-2-(4-methoxyphenyl)-1-pyrroline **21c**

To a solution of 2-(4-methoxyphenyl)-1-pyrroline **16c** (0.67 g; 3.8 mmol) in 10 ml of dry tetrachloromethane was added 1.45 equivalents of NBS (0.98 g; 5.5 mmol) at room temperature. The reaction mixture was stirred for 3 days at room temperature. After filtration and evaporation of the filtrate the resulting mixture of mono- and dibromo pyrrolines was separated by flash chromatography (silica gel; EtOAc/Hexane 4/6) to give 3,3-dibromo-2-(4-methoxyphenyl)-1-pyrroline **18c** (0.30 g, 22 %, Rf = 0.45) and 3-bromo-2-(4-methoxyphenyl)-1-pyrroline **21c** (0.77 g, 75 %, Rf = 0.26, mp. 48°C). Spectral data of compound **21c** : ^{1}H NMR ($CDCl_3$) δ 2.36-2.55 (2H, m, $C\underline{H}_2CHBr$); 3.85 (3H, s, OMe); 3.97-4.22 (2H, m, CH_2N); 5.22 (1H, d×d, J_1=6.27 Hz, J_2=1 Hz, CHBr); 6.95 (2H, d, J=8.91 Hz, Ar, H_{meta}); 7.89 (2H, d, J=8.91 Hz, Ar, H_{ortho}). ^{13}C NMR ($CDCl_3$) δ 36.23 ($\underline{C}H_2CHBr$); 48.64 (CHBr); 55.31 (OMe); 58.96 (CH_2N); 113.92 (Ar, C_{meta}); 124.02 ($\underline{C}C$=N); 129.86 (Ar, C_{ortho}); 161.76 ($\underline{C}OMe$); 170.65 (C=N). IR (KBr) : 1595 cm^{-1} (C=N). MS m/z (%) : 253/5 (26, M^+); 174(8); 173(7); 158(8); 147(100); 133(22); 132(9); 131(3); 130(6); 121(14); 115(3); 104(3); 103(7); 102(3); 91(5); 90(3); 87(4); 78(4); 77(12); 76(3); 75(2); 74(11); 63(4); 59(17); 58(4); 51(6); 50(2); 45(13); 44(10); 43(12); 42(4); 41(20). Anal. Calcd. for $C_{11}H_{12}BrNO$: C 51.99%; H 4.76%; N 5.51%. Found C 52.13%; H 4.68%; N 5.59%.

General Procedure for the Synthesis of 2-Aryl-3-halopyrroles 19 and 20

To a stirred solution of 12 mmol 2-aryl-3,3-dihalo-1-pyrrolines in 30 ml of methanol was added 36 ml (36 mmol) of sodium methoxide (1-2N) and the reaction mixture was refluxed for 2-4 h. After cooling, the mixture was poured into 100 ml of water, extracted with dichloromethane (4×20 ml) and dried ($MgSO_4$). After filtration and evaporation of the solvent *in vacuo*, the crude 2-aryl-3-halopyrroles **19** and **20** were obtained in good yield.

3-Chloro-2-phenylpyrrole **19a**

Reflux for 2 h. Yield : 95 % (by filtration from freshly distilled ether a yellow oil was obtained). ^{1}H NMR ($CDCl_3$) δ 6.13 (1H, t, J=2 Hz, CHCHCl); 6.46 (1H, t, J=2 Hz, CHNH); 7.0-7.6 (5H, m, Ph); 8.2 (1H, br s, NH). ^{13}C NMR ($CDCl_3$) δ 109.41 (s, CCl); 110.7 (d, CHCHCl); 117.80 (d, CHNH); 125.76 (d, CH); 126.54 (s, C_{quat}); 126.83 (d, CH); 128.64 (d, CH); 130.94 (s, CNH). IR (NaCl) : 3430 cm^{-1} (NH); 1609 cm^{-1}; 1500 cm^{-1} (pyrrole). MS m/z (%) 177/9 (87, M^+); 143(40); 115(100); 104(20); 88(60); 73(23); 70(33). Anal. Calcd. for $C_{10}H_8ClN$: C 67.62%, H 4.54%, N 7.89%. Found : C 67.76%, H 4.26%, N 7.93%.

3-Bromo-2-phenylpyrrole **20a**

Reflux for 2 h. Yield : 85 % (no purification possible due to rapid denaturation of the product upon standing). ^{1}H NMR ($CDCl_3$) δ 6.3 (1H, br s, CHCHBr); 6.66 (1H, br s, CHNH); 7.2-7.7 (5H, m, Ph); 8.5 (1H, br s, NH). ^{13}C NMR ($CDCl_3$) δ 94.48 (s, CBr); 113.29 (d, CHCHN); 118.65 (d, CHNH); 126.52 (d, CH); 127.08 (d, CH); 128.59 (d, CH); 128.64 (s, C_{quat}); 131.58 (s, CNH). IR (NaCl) : 3420 cm^{-1} (NH); 1600 cm^{-1}; 1490 cm^{-1} (pyrrole).

3-Chloro-2-(4-methylphenyl)pyrrole **19b**

Reflux for 3 h. Yield : 98 % (crude product). Purification by flash chromatography (silica gel) eluent 1/9 EtOAc/Hexane; Rf = 0.19. Mp. 65°C. ^{1}H NMR ($CDCl_3$) δ 2.36 (3H, s, Me); 6.23 (1H, t, J=3 Hz, CHCCl); 6.69 (1H, t, J=3 Hz, CHNH); 7.21 (2H, d, J=8.09 Hz, Ar, H_{meta}); 7.49 (2H, d, J=8.09 Hz, Ar, H_{ortho}); 8.14 (1H, br s, NH). ^{13}C NMR ($CDCl_3$) δ 21.19 (Me); 109.32 (CCl), 110.85 (CHCCl); 117.14 (CHNH); 126.97 (Ar); 128.34 (Ar); 129.43 (Ar); 136.85 (Ar). IR (KBr) : 3390 cm^{-1} (NH); 1495 cm^{-1}. MS m/z (%) : 191/3 (100, M^+); 156(32); 154(12); 141(3); 140(3); 130(3); 129(20); 128(14); 127(8); 126(3); 122(4); 116(3); 102(4); 95(10); 77(16); 75(7); 73(8); 63(7); 57(3); 56(9); 55(4); 44(3); 43(3); 40(8). Anal. Calcd. for $C_{11}H_{10}ClN$: C 68.93%; H 5.26%; N 7.31%. Found C 68.86%; H 5.35%; N 7.22%.

3-Bromo-2-(4-methylphenyl)pyrrole **20b**

Reflux for 3 h. Yield : 82 % (crude product). Pyrrole **20b** was purified by flash chromatography (silica gel), eluent EtOAc/Hexane 3/7, Rf = 0.48. Mp. (decomp.) 53°C. ^{1}H NMR ($CDCl_3$) δ 2.32 (3H, s, Me); 6.25 (1H, t, J=2.97 Hz, CHCBr); 6.63 (1H, t, J=2.97 Hz, CHNH); 7.15 (2H, d, J=7.92 Hz, Ar, H_{meta}); 7.44 (2H, d, J=7.92 Hz, Ar, H_{ortho}); 8.26 (1H, br s, NH). ^{13}C NMR ($CDCl_3$) δ 21.10 (Me); 93.96 (CBr); 113.02 (CHCBr); 118.26 (CHNH); 126.38 (Ar); 128.53 (Ar); 129.25 (Ar); 128.66 (Ar); 136.89 (Ar). IR (KBr) : 3405 cm^{-1} (NH). Neither GC-MS nor a direct inlet gave satisfactory mass spectra.

3-Chloro-2-(4-methoxyphenyl)pyrrole **19c**

Reflux for 3 h. Yield : 78 % (crude product). By flash chromatography (silica gel, eluent EtOAc/Hexane 4/6, Rf = 0.52) a yellow oil was obtained. ^{1}H NMR ($CDCl_3$) δ 3.79 (3H, s, OMe); 6.21 (1H, t, 3 Hz, CHCCl); 6.65 (1H, t, J=3 Hz, CHNH); 6.91 (2H, d, J=8.91 Hz, Ar, H_{meta}); 7.49 (2H, d, J=8.91 Hz, Ar, H_{ortho}); 8.16 (1H, br s, NH). ^{13}C NMR ($CDCl_3$) δ 110.64 (CHCCl); 114.18 (Ar, C_{meta}); 116.94 (CHNH); 123.90; 126.83; 127.51 (Ar, C_{ortho}); 158.58 (COMe). IR (NaCl) : 3260 cm^{-1} (NH); 1605 cm^{-1}. MS m/z (%) : 207/9

(100, M^+); 192/4(95); 172(7); 164/6(22); 129(6); 128(11); 102(13); 101(13); 75(11); 73(7); 63(5); 51(5); 50(3); 44(11). Anal. Calcd. for $C_{11}H_{10}ClNO$: C 63.62%; H 4.85%; N 6.74%. Found C 63.76%; H 4.79%; N 6.71%.

3-Bromo-2-(4-methoxyphenyl)pyrrole **20c**

Reflux for 3 h. Yield : 78 % (crude product). Purification by flash chromatography (silica gel), eluent EtOAc/Hexane 3/7, Rf = 0.41. Compound **20c** decomposed rapidly upon standing at room temperature but was stable in EtOAc or $CDCl_3$ solution. ^1H NMR ($CDCl_3$) δ 3.81 (3H, s, OMe); 6.29 (1H, t, J=2.97 Hz, CHCBr); 6.72 (1H, t, J=2.97 Hz, CHNH); 6.93 (2H, d, J=8.90 Hz, Ar, H_{meta}); 7.37 (2H, d, J=8.90 Hz, Ar, H_{ortho}); 8.34 (1H, br s, NH). ^{13}C NMR ($CDCl_3$) δ 56.19 (OMe); 94.72 (CBr); 113.98 (CHCBr); 114.97 (Ar, C_{meta}); 118.80 (CHNH); 125.21, 128.89 (Ar, C_{ortho}); 129.70, 159.66 (COMe). IR (NaCl) : 3465 cm^{-1} (NH); 1615 cm^{-1}. No mass spectrum could be taken due to the instability of this compound.

3-Chloro-2-(4-chlorophenyl)pyrrole **19d**

Reflux for 4 h. Yield : 95 %. ^1H NMR (CCl_4) δ 6.35 (1H, t, J=2 Hz, CHCCl); 6.84 (1H, t, J=2 Hz, CHN); 7.48 (2H, d, J=9.5 Hz, Ar); 7.66 (2H, d, J=9.5 Hz, Ar); 8.3 (1H br s, NH). ^{13}C NMR ($CDCl_3$) δ 110.35 (s, CCl); 111.27 (d, CHCCl); 117.88 (d, CHNH); 125.83 (s, =CCl); 127.26 (d, Ar); 128.84 (d, Ar); 129.70 (s, -C=CN); 132.78 (s, CNH). IR (NaCl) : 3440 cm^{-1} (NH); 1493 cm^{-1}. MS m/z (%) : 211/3/5 (100, M^+); 176/8(33); 149/51(3); 141(18); 140(10); 114(9); 113(11); 106(12); 105(18); 87(8); 75(9); 74(8); 73(14); 70(9); 63(9); 44(8). Anal. Calcd. for $C_{10}H_7Cl_2N$: C 56.63%; H 3.33%; N 6.60%. Found : C 56.72%; H 3.27%; N 6.56%.

3-Bromo-2-(4-chlorophenyl)pyrrole **20d**

Reflux for 3 h. Yield : 87 % (no purification possible due to the lability of the compound). ^1H NMR ($CDCl_3$) δ 6.33 (1H, t, J=3 Hz, CHCBr); 6.76 (1H, t, J=3 Hz, =CHN); 7.37 (2H, d, J=8.8 Hz, Ar); 8.58 (2H, d, J=8.8 Hz, Ar); 8.4 (1H, br s, NH). ^{13}C NMR ($CDCl_3$) δ 95.42 (s, CBr); 113.86 (d, CHCBr); 118.73 (d, CHNH); 127.93 (s, CCl); 128.01 (d, Ar); 129.38 (d, Ar); 129.63 (s, -C=CN); 132.42 (s, CNH). IR (NaCl) : 3320-3420 cm^{-1} (br, NH); 1493 cm^{-1}. MS m/z (%) : 255/7/9 (100, M^+); 176/8(57); 149/51(58); 141(59); 140(23); 128(26); 127(21); 114(31); 113(36); 88(19); 87(15); 86(13); 75(16); 70(46); 63(28).

2-(4-Methoxyphenyl)pyrrole **22c**

Reflux for 3 h. Yield : 78 % (crude product). Purification by flash chromatography (silica gel), eluent EtOAc/Hexane 2/8, Rf = 0.40. Mp. 154.°C. Lit. mp. 152 °C.[47] ^1H NMR ($CDCl_3$) δ 3.82 (3H, s, OMe); 6.26-6.29 (1H, m, CHCHCH); 6.39-6.42 (1H, m, CHCHCHNH); 6.82 (1H, t×d, J_1=1.65 Hz, J_2=2.64 Hz, CHNH); 6.91 (2H, d, J=8.90 Hz, Ar, H_{meta}); 7.39 (2H, d, J=8.90 Hz, Ar, H_{ortho}); 8.33 (1H, br s, NH). ^{13}C NMR ($CDCl_3$) δ 55.33 (OMe); 104.85 (CHCHCH); 109.90 (CHCAr); 114.32 (Ar, C_{meta}); 118.15 (CHNH); 125.26 (Ar, C_{ortho}); 125.89; 132.13, 158.22 (COMe). IR (KBr) : 3440 cm^{-1} (NH); 1605 cm^{-1}. MS m/z (%) : 173 (100, M^+); 158(79); 145(2); 130(13); 129(2); 128(2); 115(2); 103(6); 102(4); 86(7); 77(8); 76(3); 74(2); 63(2); 59(3); 58(4); 51(4); 45(3); 44(9); 43(10); 41(2). Anal. Calcd. for $C_{11}H_{11}NO$: C 76.28%; H 6.40%; N 8.09%. Found C 76.34%; H 6.51%; N 7.98%.

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