New Synthesis of 3-Arylpyrroles

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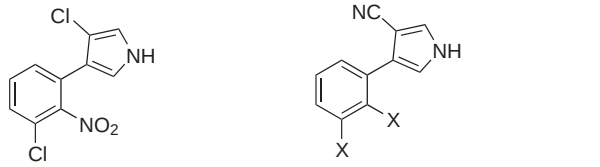
Abstract: 3-Arylpyrroles were synthesized by reduction of 3- and 4-pyrrolin-2-ones with 9-borabicyclo[3.3.1]nonane (9-BBN).

Key words: pyrroles, reductions, heterocycles, isomerizations, ring closure

Functionalized 3-arylpyrroles exhibit a wide range of agrochemical and pharmacological properties.[1–5] Pyrrolnitrin (**1**, Figure 1) is used in agriculture as crop protection agent because of its antifungal and antimycobacterial activity. Its derivatives fenpiclonil (**2a**) (Beret®), active against fungi on seeds, and fludioxonil (**2b**) (Saphire®), active against fungi on leafs, have already established their market position.[6–8] Pyrrolnitrin, isolated from the bacterium *Pseudomonas pyrociniae*, *P. cepacia* and *P. fluorescens* also revealed promising activity against *Mycobacterium avium* and *M. tuberculosis*, strains which acquired considerable resistance towards conventional antibiotics and cause problems in chemotherapy of numerous diseases (tuberculosis, AIDS, …).[9] Recently some halogenated 3-arylpyrroles were patented as herbicidal agents.[10]



1 pyrrolnitrin

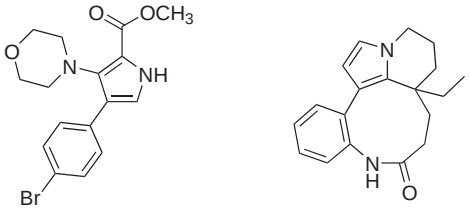
2a X = Cl
2b X = -O-CF_2-O-

fenpiclonil
fludioxonil

Figure 1

From a pharmacological point of view, the drug AWD 140-190 (**3**), proved to exert potent anticonvulsant activity, indicating that this substance has a potential for an antiepileptic therapy.[11] The natural alkaloid razinilam (**4**, Figure 2) is interesting because of its ability to mimic the cellular effects of the anticancer drug paclitaxel.[12] Many other 3-arylpyrroles exhibit antiinflammatory, analgesic, antiallergic and anti-HIV activities.[1,3]

According to the physiological importance of these pyrroles, substantial attention has been paid to develop efficient synthetic approaches. One of the synthetic pathways consists of the use of 3- and 4-pyrrolin-2-ones to obtain 2-oxygenated or 2-halogenated pyrroles.[13–16]



3 AWD 140-190

4 razinilam

Figure 2

To the best of our knowledge only one article has been published using a reductant (DIBALH) to synthesize 3-substituted pyrroles without the introduction of an additional functionality at the 2-position.[17] That publication deals only with 4-methoxy-3-pyrrolin-2-ones, which can be seen as enol ethers and, as a consequence, reveal different electronic properties as compared with the corresponding 4-arylpyrrolinones. In the present article, various reducing agents were evaluated for their ability to reduce 4-aryl-3-pyrrolin-2-ones and the isomeric 4-pyrrolinones towards 3-arylpyrroles. After evaluation of various reducing agents, only 9-borabicyclo[3.3.1]nonane (9-BBN) was found to yield pyrroles from pyrrolinones in good yield. In addition, 1-methyl-3-phenylsuccinimide was transformed direcly to the corresponding pyrrole using 9-BBN.

As it was found by us that 3- and 4-pyrrolin-2-ones were suitable substrates for conversion into pyrroles, efforts were done to develop a convenient route to these starting materials. 5-Methyl-4-phenyl-4-pyrrolin-2-one (**9a**) was synthesized by reacting phenylacetone with *t*-BuOK and chloroacetamide (**6a**) in DMSO.[18] Deprotonation of phenylacetone (**5a**) at C-1 and subsequent reaction with chloroacetamide yields 4-oxo-3-phenylpentanamide via nucleophilic substitution (Scheme 1). At the reaction temperature (80 °C) this intermediate cyclizes spontaneously and results in pyrrolinone **9a** after elimination of water. The same procedure was used to synthesize the *N*-propyl derivative **9b**, which isomerized towards the more stable 3-pyrrolin-2-one **10b** within three days at room temperature.

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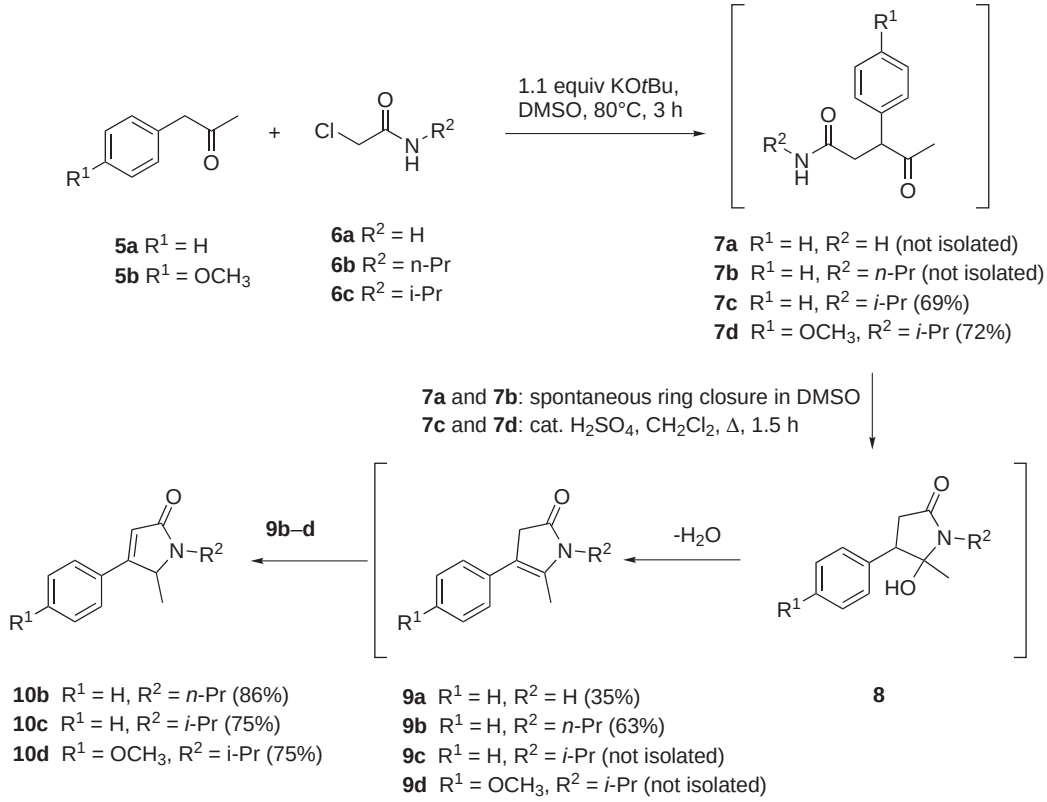


Scheme 1

With *N*-isopropyl-2-chloroacetamide (**6c**) as reactant to obtain 1-isopropylpyrrolinones **9c** and **9d**, no ring closure occurred due to the steric hindrance of the isopropyl moiety, resulting in *N*-isopropyl-3-aryl-4-oxopentanamides **7c** and **7d** (Scheme 1). To induce cyclization, the γ-ketoamides were dissolved in DMSO and heated at 100 °C for 1 hour. These reaction conditions however, yielded a mixture of 3-pyrrolinones **10** and 4-pyrrolinones **9**, which could be separated by column chromatography. When the ketoamides **7c**,**d** were refluxed in dichloromethane with a catalytic amount of sulfuric acid, only 3-pyrrolinones **10c**,**d** were formed in good yield.

In addition to the synthesis of the pyrrolinones outlined above, 1-methyl-4-phenyl-3-pyrrolin-2-one, 1-methyl-3-phenyl-3-pyrrolin-2-one, 1,4-dimethyl-3-pyrrolin-2-one and 1,3-dimethyl-3-pyrrolin-2-one (**12**, see Table 2, entries 1–4) were synthesized according to literature procedures.[19,20]

To synthesize pyrroles from the obtained 3- and 4-pyrrolin-2-ones, different reactions were evaluated using various reducing agents (Table 1). Reaction of pyrrolinone **10c** with $NaBH_4$ in diethyl ether, THF or toluene (0 °C or 25 °C or reflux) did not lead to pyrrole **15d**, but yielded mixtures of starting material **10c** and the isomeric 4-pyrrolinone **9c**. The use of $LiAlH_4$ in analogous reactions yielded more complex reaction mixtures, which also contained starting material and 4-pyrrolinone **9c**. The use of non-ionic reducing agents like borane (BH_3·THF) in THF at room temperature yielded complex reaction mixtures, which contained only traces of pyrrole **15d** (2–5%). No improvement was obtained when higher temperatures or more equivalents (up to 3 equiv) of borane were used. After reaction of pyrrolinone **10c** with 1 equivalent of BH_3 in toluene (reflux, 15 h), pyrrole **15d** was isolated in very low yield (9%) from the complex reaction mixture, which also contained pyrrolinones **10c** and **9c**.

Finally, 3-pyrrolinone **10c** was treated with 1.1 equivalents of 9-borabicyclo[3.3.1]nonane (9-BBN) in refluxing

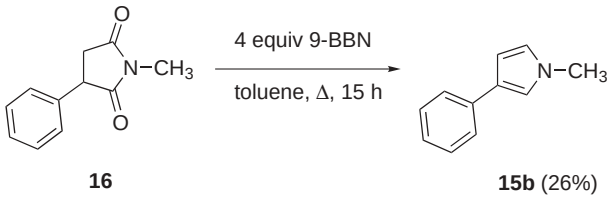
Table 1 Reduction of 3-Pyrrolin-2-one **10c** with 9-BBN

Reaction conditions (dry, under N_2-atmosphere)	Pyrrole **15d** (%)
1.1 equiv 9-BBN, THF, 25 °C, 24 h	0
1.1 equiv 9-BBN, THF, Δ, 4 h	19
1.1 equiv 9-BBN, THF, Δ, 15 h	25
1.1 equiv 9-BBN added in portions during 6 h, THF, Δ, 15 h	21
2.5 equiv 9-BBN, THF, Δ, 15 h	46
2.5 equiv 9-BBN added in portions during 6 h, THF, Δ, 15 h	39
2.5 equiv 9-BBN, dioxane, Δ, 15 h	22
2.5 equiv 9-BBN, toluene, Δ, 15 h	50
3 equiv 9-BBN, toluene, Δ, 15 h	53

THF for 15 hours. This procedure did not result in a complex reaction mixture, but yielded only pyrrole **15d**, pyrrolinone **10c** and **9c** in a ratio 25:45:30 (calculated from ^{1}H NMR data). In an attempt to optimize these surprising results, various reaction conditions were evaluated (see Table 1). The best yields were obtained using 3 equivalents of 9-BBN in refluxing toluene for 15 hours, under N_2-atmosphere using dry glassware and solvents. When more equivalents of 9-BBN were used, the yield did not increase and residual hydride was recovered [^{11}B NMR: δ = 27 ppm (R_2B-H)].[21] A decrease in yield was observed when less equivalents of 9-BBN were used and starting material **10c** and the isomeric pyrrolinone **9c** were partially recovered, even when the hydride was added in portions (5 × 0.2 equiv) with time intervals of 1.5 hours.

Using the optimized reaction conditions, various substituted 3-arylpyrroles were synthesized (Scheme 2, Table 2). Only in the case of 1,3-dimethylpyrrole (**15a**) the yields were very low, probably due to the volatility of the final product.

These results encouraged us to verify whether succinimides could be transformed directly to pyrroles by reduction with 9-BBN. 1-Methyl-3-phenylsuccinimide (**16**) was dissolved in toluene and treated with 4 equivalents of 9-BBN at reflux for 15 hours. The reaction indeed yielded 1-methyl-3-phenylpyrrole (**15b**), however, in rather low yield (see Scheme 3).



16 **15b** (26%)

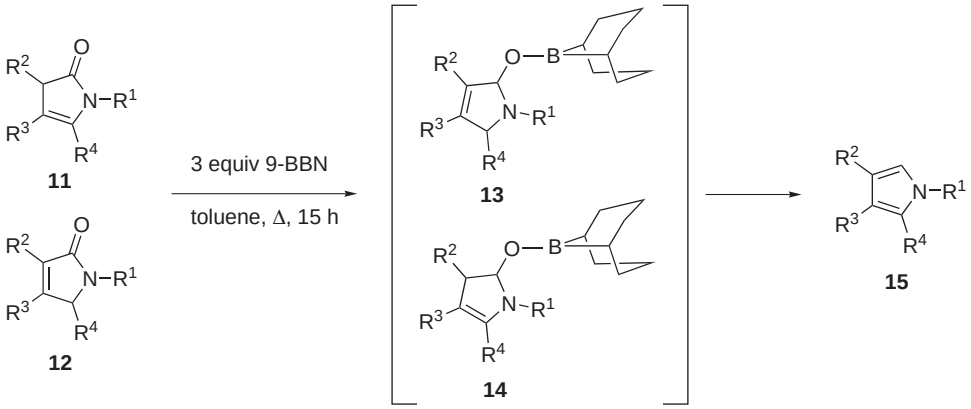
Scheme 3

In conclusion, various new 4-aryl-3-pyrrolin-2-ones, 4-aryl-4-pyrrolin-2-ones and succinimides were synthesized and reduced with 9-borabicyclo[3.3.1]nonane towards 3-arylpyrroles **15**, an interesting class of compounds with broad physiological importance.

***N*-Isopropyl-4-oxo-3-phenylpentanamide** (**7c**). To a solution of potassium *t*-butoxide (14.98 g, 133.48 mmol, 1.1 equiv) in 100 mL of DMSO was added slowly phenylacetone (16.26 g, 121.35 mmol) at r.t. Subsequently 1.1 equiv of *N*-isopropyl-2-chloroacetamide (18.09 g, 133.48 mmol), which was prepared from chloroacetylchloride and isopropylamine using a Schotten–Baumann procedure,

Table 2 Synthesis of Substituted Pyrroles **15** from Pyrrolin-2-ones **11** or **12** (Scheme 2)

Entry	Pyrrole	Starting material	R^1	R^2	R^3	R^4	Yield (%)
1	**15a**	**12**	CH_3	CH_3	H	H	15
2	**15a**	**12**	CH_3	H	CH_3	H	12
3	**15b**	**12**	CH_3	C_6H_5	H	H	48
4	**15b**	**12**	CH_3	H	C_6H_5	H	55
5	**15c**	**11**	H	H	C_6H_5	CH_3	21
6	**15d**	**11** or **12**	*i*-Pr	H	C_6H_5	CH_3	53
7	**15e**	**11** or **12**	*n*-Pr	H	C_6H_5	CH_3	50
8	**15f**	**11** or **12**	*i*-Pr	H	4-$CH_3OC_6H_4$	CH_3	58



11 **12** **13** **14** **15**

Scheme 2

was added portion wise. The reaction mixture was stirred at 80 °C during 3 hours. After cooling, the mixture was poured into ice water and the resulting suspension was extracted with chloroform (3 × 100 mL). The combined extracts were washed with water and after drying ($MgSO_4$) and evaporation of the solvent, 19.51 g (69%) of pentanamide **7c** was obtained, which was purified by column chromatography (hexane/EtOAc/Et_3N 13/7/1, R_f = 0.17). ^1H NMR ($CDCl_3$): δ = 1.02 (3 H, d, *J* = 6.6 Hz, $CHCH_{3a}CH_{3b}$), 1.10 (3 H, d, *J* = 6.6 Hz, $CHCH_{3a}CH_{3b}$), 2.11 (3 H, s, CH_3C=O), 2.34 (1 H, dd, *J* = 14.7 Hz, 5.4 Hz, CH_aH_b), 2.95 (1 H, dd, *J* = 14.7 Hz, 9.3 Hz, CH_aH_b), 3.94–4.02 [1 H, m, $CH(CH_3)_2$], 4.28 (1 H, dd, *J* = 5.4 Hz, 9.3 Hz, $CHCH_2$), 5.41 [1 H, d(br), *J* = 6.3 Hz, NH], 7.19–7.36 (5 H, m, CH_{ar}). ^{13}C NMR ($CDCl_3$): δ = 22.55 [$CH(CH_3)_2$], 29.08 (CH_3C=O), 39.53 (CH_2), 41.31 [$CH(CH_3)_2$], 55.24 ($CHCH_2$), 127.57 ($CH_{ar,para}$), 128.16 (2 × CH_{ar}), 129.06 (2 × CH_{ar}), 137.84 ($C_{ar,quat}$), 170.10 (CONH), 207.67 (CH_3C=O). IR (KBr): ν = 3300 (NH), 1714 (C=O), 1644 ($C=O_{amide}$), 1548 (C=C) cm^{-1}. MS: *m/z* (%) = 216 (100) [$M - H_2O + H^+$].

1-Isopropyl-5-methyl-4-phenyl-3-pyrrolin-2-one (**10c**) and **1-Isopropyl-5-methyl-4-phenyl-4-pyrrolin-2-one** (**9c**). One drop of concentrated sulfuric acid was added to a solution of 2 g (8.58 mmol) of pentanamide **7c** in 10 mL of toluene and the mixture was refluxed for 1.5 h. The resulting mixture of 3-pyrrolinone **10c** and 4-pyrrolinone **9c** was column chromatographed (hexane/EtOAc 16/4, $R_{f,\mathbf{10c}}$ = 0.07, $R_{f,\mathbf{9c}}$ = 0.25); $mp_{\mathbf{10c}}$ = 76 °C; $yield_{\mathbf{10c}}$ 62%, $yield_{\mathbf{9c}}$ 13%. Compound **10c**: ^1H NMR ($CDCl_3$): δ = 1.37 [6 H, d, *J* = 6.9 Hz, $CH(CH_3)_2$], 1.42 (3 H, d, *J* = 6.8 Hz, $CHCH_3$), 4.29 [1 H, sept, *J* = 6.9 Hz, $CH(CH_3)_2$], 4.65 (1 H, qd, *J* = 6.8 Hz, 0.9 Hz, $CHCH_3$), 6.28 (1 H, d, *J* = 0.9 Hz, CHC=O), 7.37–7.46 (5 H, m, CH_{ar}). ^{13}C NMR ($CDCl_3$): δ = 18.85 and 19.61 [$CH(CH_3)_2$], 21.04 ($CHCH_3$), 43.60 [$CH(CH_3)_2$], 56.46 ($CHCH_3$), 119.91 (C=CH-C=O), 126.13 (2 × CH_{ar}), 128.12 (2 × CH_{ar}), 128.86 ($CH_{ar,para}$), 130.91 ($C_{ar,quat}$), 159.57 (C=CH-C=O), 169.42 (C=O). IR (KBr): ν = 1671 (C=O) cm^{-1}. MS *m/z* (%) = 216 (100) [$M + H^+$]. Compound **9c**: ^1H NMR ($CDCl_3$): δ = 1.47 [6 H, d, *J* = 7.0 Hz, $CH(CH_3)_2$], 2.18 (3 H, t, *J* = 2.4 Hz, $=CCH_3$), 3.30 (2 H, q, *J* = 2.4 Hz, CH_2), 4.19 [1 H, sept, *J* = 7.0 Hz, $CH(CH_3)_2$], 7.17–7.40 (5 H, m, CH_{ar}). ^{13}C NMR ($CDCl_3$): δ = 11.86 (CH_3), 19.79 (2 × CH_3), 39.14 (CH_2), 44.17 (NCH), 112.49 (CH_2C=C), 125.32 ($CH_{ar,para}$), 126.67 (2 × CH_{ar}), 127.73 (2 × CH_{ar}), 134.48 (C=CCH_3), 135.78 ($C_{ar,quat}$), 175.45 (C=O). IR (KBr): ν = 1698 (C=O), 1496, 1405, 1355 cm^{-1}. MS: *m/z* (%) = 216 (100) [$M + H^+$].

1-Isopropyl-3-(4-methoxyphenyl)-2-methylpyrrole (**15f**). To a solution of pyrrolinone **12f** (1 g, 4.08 mmol) in 5 mL of dry toluene, was added 3 equiv (1.49 g, 20.24 mmol) 9-borabicyclo[3.3.1]nonane as a solid dimer. The mixture was allowed to reflux overnight (15 h) and was subsequently poured in 25 mL of water. Extraction with Et_2O (3 × 25 mL), drying ($MgSO_4$) and evaporation of the solvents in vacuo afforded pyrrole **15f**, which was purified by column chromatography (hexane/EtOAc 95/5, R_f = 0.25); yield 58%. ^1H NMR ($CDCl_3$): δ = 1.41 [6 H, d, *J* = 6.7 Hz, $CH(CH_3)_2$], 2.30 (3 H, s, CH_3), 3.78 (3 H, s, CH_3O), 4.28 [1 H, sept, *J* = 6.7 Hz, $CH(CH_3)_2$], 6.22 (1 H, d, *J* = 3.0 Hz, NCHCH), 6.70 (1 H, d, *J* = 3.0 Hz, NCHCH), 7.10 (2 H, d, *J* = 8.7 Hz, CH_{ar}), 7.30 (2 H, d, *J* = 8.7 Hz, CH_{ar}). ^{13}C NMR ($CDCl_3$): δ = 10.28 (CH_3), 23.22 (2 × CH_3), 46.65 [$CH(CH_3)_2$], 54.75 (CH_3O), 107.19 (NCHCH), 113.42 (2 × CH_{ar}), 114.32 (NCHCH), 121.06 (C_{quat}), 123.27 (C_{quat}), 128.90 (2 × CH_{ar}), 130.08 (C_{quat}), 157.07 (C_{ar}-OCH_3). IR (KBr): ν = 1612, 1559, 1508, 1459 (C=C), 1243 cm^{-1}. MS: *m/z* (%) = 230 (100) [$M + H^+$].

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