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Synthesis of 2-aryl-4-chloropyrroles via ring expansion of 2-aryl-1-chlorocyclopropanecarbaldehydes

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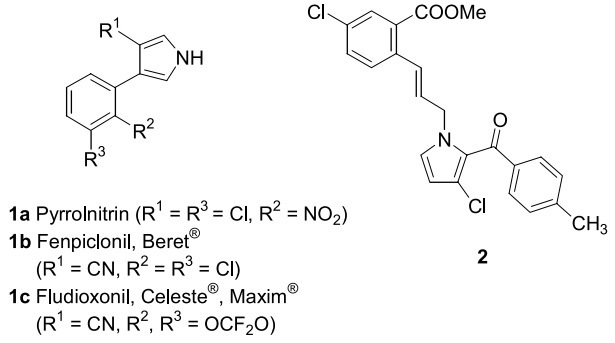
Abstract—An efficient electrophile-induced ring opening of 2-aryl-1-chlorocyclopropanecarbaldehydes is described towards halogenated butanals, which were converted to the corresponding imines. These α,α,γ-trichloroimines proved to be good substrates for a nucleophile-induced ring closure towards 2-pyrrolines as versatile synthons for the synthesis of pyrroles bearing physiologically interesting substitution patterns.

1. Introduction

In the unabated search for new physiologically active compounds, the study of substituted pyrroles still remains a subject of considerable importance. Halogenated pyrroles isolated from Nature, associated with diverse physiological activities, have served as lead structures to synthesize pyrroles with current use in agrochemistry (e.g., the antifungal pyrrolnitrin (**1a**) derivatives **1b**,**c**)[1] and medicine (e.g., 3-chloropyrrole **2**, a fibrosis inhibitor) (Fig. 1).[2]

Pentabromopseudilin **3** was first isolated from the marine bacterium *Alteromonas luteoviolaceus* and shows antitumor, antibacterial and antifungal activities. This polybrominated pyrrole (**3**) also inhibits various enzyme systems and the cholesterol biosynthesis.[3] Manzacidins A (**4a**) and B (**4b**) are alkaloids isolated from the Okinawan sponge *Hymeniacidon species*.[4] Roseophilin **5** is a 3-chloropyrrole found in *Streptomyces griseoviridis* and displays antibiotic and antileukemic properties.[5] More than 20 compounds of the 'oroidin' (**6**) family of β-brominated pyrroles (i.e., 4-bromo- and 4,5-dibromopyrrole-2-carboxamides) have been isolated from Nature and tested for physiological activities.[6] For instance, clathramides, isolated from *Agelas clathrodes*, possess antifungal properties,[7] while other oroidins show antiserotoninergic (keramadine), cytotoxic (agelastatin), antiviral (sceptrin), antihistaminergic (dispacamide) or antifouling (mauritiamine) activities.[6,8,9] With respect to this diversity of activities related to halogenated pyrroles, various synthetic methods to access these compounds have been developed, where each method displays its own advantages to access pyrroles with specific substitution patterns.[10] Of current interest for agrochemistry is the synthesis of 3-halogenated pyrroles bearing electron withdrawing groups (e.g., COOR, CN or CF_3) (Fig. 2).[11]



1a Pyrrolnitrin ($R^1 = R^3 = Cl$, $R^2 = NO_2$)
1b Fenpiclonil, Beret®
($R^1 = CN$, $R^2 = R^3 = Cl$)
1c Fludioxonil, Celeste®, Maxim®
($R^1 = CN$, R^2, $R^3 = OCF_2O$)

Figure 1.

Structure–activity relationship studies revealed that the presence of an aryl moiety at one pyrrole α-carbon is often responsible for specific biological activities, for example, 2-arylpyrrole **7** and derivatives are insecticidal compounds (100% mortality for *Spodoptera eridania* treated with **7** at 10 mg/L).[12] Related pyrroles **8** were recently patented for the protection of wood from termites.[13] In addition, substituted pyrroles with cyano- or carboxylic acid moieties at the α-carbon are important intermediates in the synthesis of porphyrins and other 'pigments of life'.[14]

Keywords: Ring expansion; Pyrroles; Cyclopropanes.
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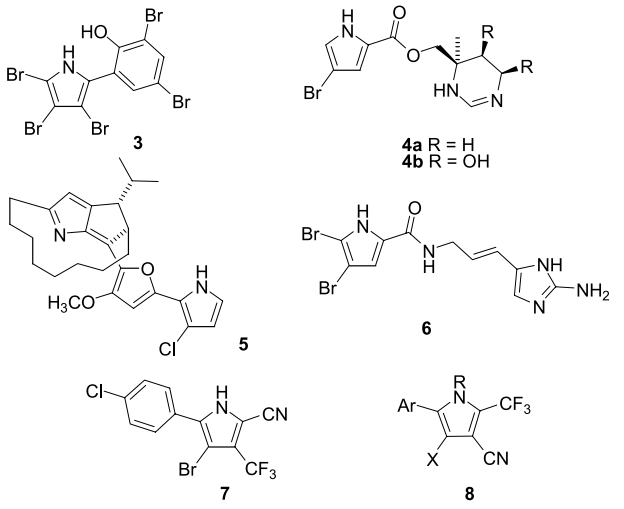


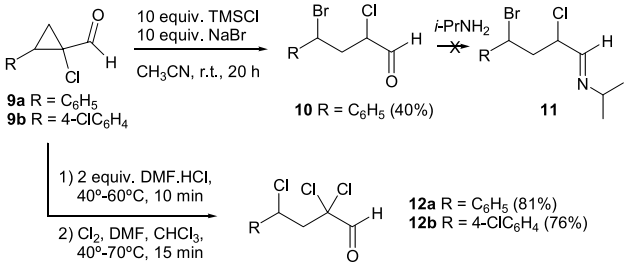
Figure 2.

In this article, an efficient synthesis of halogenated 2-arylpyrroles from 3-aryl-2,2-dichlorocyclobutanones via the intermediacy of 1-chlorocyclopropanecarbaldehydes is disclosed. Only a few publications report the use of cyclopropanecarbaldehydes as building blocks for pyrrole syntheses by thermal rearrangement of the corresponding imines.[15] In contrast, our approach deals with an initial ring opening of appropriate 1-chlorocyclopropane-1-carbaldehydes. Subsequent imination of the resulting γ-haloaldehydes followed by treatment with cyanide to induce a ring closure provides a new entry towards synthetically useful azaheterocyclic compounds.

2. Results and discussion

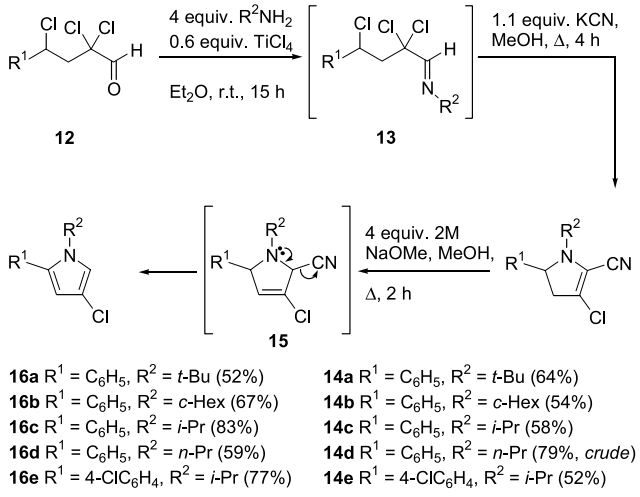
In continuation of the previously reported ring contraction of 2,2-dihalocyclobutanones towards 1-chlorocyclopropanecarbaldehydes **9**, [16] attempts were made to validate the latter compounds as useful synthons for the application in azaheterocyclic synthesis.

Analogous to earlier reported electrophile-induced ring opening reactions of cyclopropylketones under mild conditions,[17] α-chlorocyclopropanecarbaldehyde **9a** was treated with trimethylsilylchloride and sodium bromide to yield a diastereomeric mixture of γ-bromobutanals **10** (ratio 1:1) (Scheme 1). Compounds of this kind could be used to construct five-membered azaheterocycles after imination. Unfortunately, treatment of the aldehyde **10** with isopropylamine in the presence of $MgSO_4$ or $TiCl_4$ under various



Scheme 1.

reaction conditions did not result in the corresponding imines **11**. When an inverse imination procedure was applied, a mixture of cyclopropanecarbaldehyde **9a** and the corresponding imine was obtained due to α-deprotonation of **10** by isopropylamine. In order to eliminate the latter reaction, γ-bromo-α-chlorobutanal **10** was treated with chlorine gas to synthesize the α,α-dichlorinated analogue, which could be used as imine precursor. After chlorination, an inseparable mixture of reaction products was obtained. To overcome this problem an efficient synthesis of 4-aryl-2,2,4-trichlorobutanals **12** was developed by a HCl-induced ring opening and in situ chlorination of the obtained intermediate α-chloroaldehydes.[18] This procedure yielded compounds **12** in almost quantitative yield, which could be purified by distillation. Imination of compound **12** by the use of various amines in the presence of titanium(IV) chloride and subsequent treatment with potassium cyanide in methanol yielded 5-aryl-3-chloro-2-cyano-2-pyrrolines **14** in good yield (Scheme 2). The obtained intermediate imines **13** were not stable enough to purify by distillation or chromatography and were used directly after isolation from the reaction mixture. 2-Pyrrolines **14** proved to be stable at low temperatures (−20 °C) for several days.

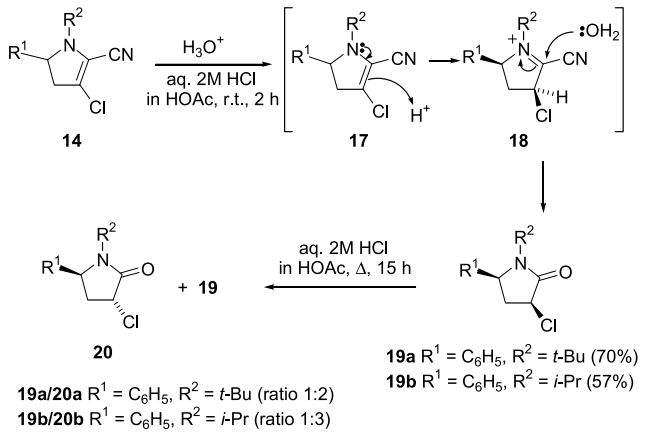


Scheme 2.

The treatment of 2-pyrrolines **14** with 4 equiv of 2 M sodium methoxide in methanol at reflux temperature for 2 h resulted in the formation of 3-chloropyrroles **16**.

The mechanism can be rationalized by an initial base induced isomerization towards 3-pyrrolines **15** and subsequent expulsion of cyanide. Further isomerization results in 2-aryl-4-chloropyrroles **16** in good yield (Scheme 2). With this procedure β-chloropyrroles can be synthesized on a multi-gram scale using cheap reagents and facile chemistry.

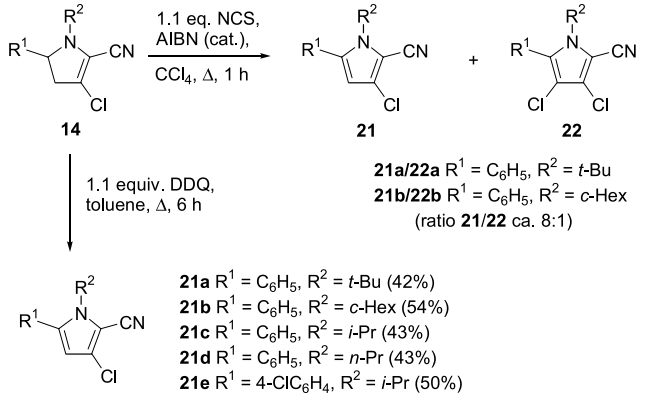
When handling pyrrolines **14** in wet solvents, often some hydrolysis product was formed. These products (**19**) were formed by electrophilic addition of a proton and subsequent attack of water, as shown in Scheme 3. In a more controlled manner, *cis*-substituted pyrrolidinones **19** could be obtained quantitatively by treatment of pyrrolines **14** with aqueous 2 M HCl in acetic acid at room temperature. When higher



Scheme 3.

temperatures were applied (Δ, 15 h), a partial isomerization of the *cis*-substituted pyrrolidinones **19** occurred towards the more stable *trans*-3-chloro-5-phenyl-pyrrolidinones **20** resulting in a mixture of isomers (ratios, see Scheme 3), which were separated by chromatography. The stereochemical assignments of **19** and **20** were performed by analysis of the coupling constants in ^{1}H NMR.

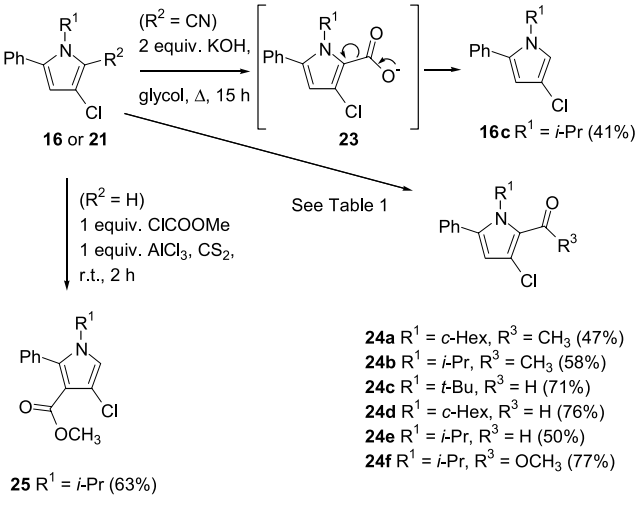
In order to synthesize 2-cyanopyrroles which form a class of compounds with specific physiological activities (e.g., insecticide **7**[12]), the pyrrolines **14** were reacted with NBS in tetrachloromethane to induce a radical bromination yielding halogenated pyrrolines as good precursors for pyrroles. Whereas the use of NBS only resulted in tarry reaction mixtures, the reaction with NCS at reflux temperatures in tetrachloromethane in the presence of a catalytic amount of AIBN yielded 2-cyanopyrroles **21a**,**b** in good yield. In the reaction mixture, also minor amounts of dichlorinated pyrroles **22** were detected (ratio **21**/**22** 8:1), which unfortunately could not be separated from the major pyrroles **21** by flash chromatography. During optimalization of the reaction by evaluation of various reaction conditions and follow up of the formed reaction products by GC-MS, it became clear that the formation of dichloropyrroles **22** started already at the early stage of the reaction, when still starting material is present. No improvement of the ratio **21**/**22** in favor of the monochloropyrrole **21** could be obtained (Scheme 4).



Scheme 4.

In a second approach, 2-pyrrolines **14** were oxidized towards the corresponding pyrroles using DDQ in toluene. This procedure yielded pyrroles in moderate yields. The presence of the cyano functionality at the 2-position leaves opportunities for functional group transformation to various other physiologically interesting pyrroles, for example, 2-acylpyrroles and derivatives. Attempts to hydrolyse the cyano function with aqueous base or acid did not result in pyrrole-2-carboxylate **23**. Starting material accompanied with decomposition products were recovered after treatment of **21c** with aq. 6 M HCl or 48% aq. HBr at reflux overnight. Alkaline treatment with 50% aq. KOH at various temperatures did not result in hydrolysis. Performing the reaction of **21c** with KOH in boiling glycol, hydrolysis of the cyano moiety and immediate decarboxylation occurred towards pyrrole **16c**.

To access 2-acylpyrroles **24a**,**b**, pyrroles **21b**,**c** were treated with methyllithium resulting in the corresponding methylimine, which was hydrolyzed by reaction with aq. 6 M HCl at room temperature (Scheme 5, Table 1). Pyrrole-2-carbaldehydes **24c–e** could be synthesized by electrophilic substitution of 2-unsubsituted pyrroles **16a–c**. Vilsmeier formylation of these pyrroles with DMF-$POCl_3$ yielded pyrrole-2-carbaldehydes **24c–e** together with a minor amount of the isomeric β-formylated pyrroles (10%–35%), which could be easily separated by flash chromatography. Due to the fact that the electrophilic substitution of pyrroles is kinetically driven to take place at the α-position, the major compounds were the 2-formylated pyrroles **24c–e**, as expected. Analogous reactions were evaluated to



Scheme 5.

Table 1. Synthesis of substituted 3-chloropyrroles **24** (Scheme 5)

Entry	Reaction conditions	Product
21b,**c** (R^2=CN)	(1) 1 equiv MeLi, THF, 0 °C, 30 min (2) excess aq. 6 M HCl, rt, 1 h	**24a**, **24b**
16a–c (R^2=H)	(1) 1.2 equiv $POCl_3$, DMF/CH_2Cl_2 (1:1), 0 °C, 5 h (2) excess aq. 1 M NaOH, rt, 15 min	**24c–e**[a]
16a (R^2=H)	1 equiv BuLi, 1 equiv ClCOOMe, THF, 0 °C, 2 h	**24f**

[a] Also the isomeric β-formylated pyrroles were formed (10–35%), which could easily be separated by flash chromatography.

synthesize pyrrole-2-carboxylates. Friedel-Crafts acylation using methyl chloroformate and aluminum(III) chloride in carbon disulfide yielded a mixture of carboxylated pyrroles **25** and **24f** with predominantly pyrrole **25** (ratio 1:4, resp.) Substitution at β-position of pyrroles has previously been observed when the nitrogen atom bears bulky groups.[19] Indeed, the carboxylation of pyrrole **16c** could be seen to be a little more sterically demanding as compared with the formylation, which shifts the ratio towards the 3-substituted pyrrole **25**. Also, under the used reaction conditions, rearrangements of pyrrole substituents are known to result in the thermodynamically most stable compounds (in casu pyrrole **25**).[19] The HSAB-theory as a rationale for selective acylations has only been demonstrated for pyrroles bearing electron withdrawing groups at nitrogen, where the use of a hard Lewis acid such as $AlCl_3$ promotes C-3 acylation.[20] However, *N*-alkyl- or *N*-unsubstituted pyrroles are generally acylated at C-2. To accomplish a carboxylation at C-2, deprotonation of the most acidic hydrogen of pyrrole **16c**, that is, the hydrogen at α-position, with BuLi and subsequent reaction with methyl chloroformate yielded exclusively methyl pyrrole-2-carboxylate **24f** in good yield.

In conclusion it can be stated that various interesting halogenated pyrroles can be synthesized in a straightforward manner from readily available 1-chlorocyclopropanecarbaldehydes.[16] In addition to the presence of a halogen at β-position of the synthesized pyrroles, other interesting substituents in relation to physiological activities, such as an aryl, cyano or carbonyl moiety at α-position were introduced to end up with highly substituted pyrroles with specific substitution patterns.

3. Experimental

^{1}H NMR spectra (270 MHz or 300 MHz) and ^{13}C NMR spectra (68 MHz or 75 MHz) were recorded with a Jeol JNM-EX 270 NMR spectrometer or a Jeol Eclipse FT 300 NMR spectrometer, respectively. Peak assignments were performed with the aid of the DEPT-technique, 2D-COSY and HETCOR spectra. IR assignments were obtained from a Perkin Elmer Spectrum One spectrophotometer. Mass spectra were recorded on an Agilent 1100 Series VL mass spectrometer (ES) or a HP 5973 MSD spectrometer (70 eV). Elemental analysis was performed on a Perkin Elmer 2400 Elemental Analyser and via a Callisto CF-Isotope Ratio Mass Spectrometer. Melting points were measured with a Büchi B-450 apparatus. Flash chromatography was carried out on a glass column with ACROS silica gel (particle size 0.035–0.07 mm, pore diameter ca. 6 nm). HRMS data were obtained with a VG Quattro II, ESI ionization (cone voltage 40 V).

3.1. Synthesis of 4-aryl-2,2,4-trichlorobutanals 12

As a representative example, the synthesis of 2,2,4-trichloro-4-phenylbutanal **12a** is described. A solution of 4.56 g (25.26 mmol) of 1-chloro-2-phenylcyclopropane-1-carbaldehyde **9a**[16] and 5.53 g (50.52 mmol, 2 equiv) of DMF-HCl in 5.00 g of DMF was heated to 40–60 °C. After reaction for 20 min, 10 mL of dry chloroform was added and chlorine gas was bubbled through the solution. During chlorination, the temperature was allowed to reach 65–70 °C. After 15–20 min, when no temperature increase was observed by addition of chlorine, the reaction was stopped and cooled down to room temperature. The reaction mixture was poured in 25 mL of concentrated HCl and extracted with chloroform (3×20 mL). The combined organic extracts were washed with an aqueous solution of sodium bisulfite and subsequently with concentrated HCl (20 mL). After drying ($MgSO_4$), filtration and evaporation of the solvent in vacuo, 2,2,4-trichloro-4-phenylbutanal **12a** was obtained which was purified by distillation (5.45 g, 81%).

3.1.1. 2,2,4-Trichloro-4-phenylbutanal 12a. Bp 80–85 °C, 0.05 mm Hg; yield 81%. ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.11 (1H, d×d, J=15.5, 5.6 Hz, CH_aH$_b$), 3.32 (1H, d×d, J=15.5, 7.9 Hz, CH$_a$$H_b$), 5.22 (1H, d×d, J=7.9, 5.6 Hz, CH), 7.29–7.45 (5H, m, C_6H_5), 9.14 (1H, s, CHO). ^{13}C NMR (68 MHz, $CDCl_3$): δ 51.3 (CH_2), 58.0 (CH), 85.9 (CCl_2), 2×127.0 (2×CH_{ar}), 2×128.8 (2×CH_{ar}), 129.0 (CH_{ar}), 139.3 (C_{quat}), 183.5 (C=O). IR (NaCl) ν_{max} 1738 cm^{-1}. MS (70 eV) *m/z* (%) 250/52/54/56 (M^+, 10); 151/53 (31); 138/40 (97); 125/27 (100); 115 (70); 91 (46); 77 (10).

3.1.2. 2,2,4-Trichloro-4-(4-chlorophenyl)butanal 12b. Bp 105–109 °C, 0.05 mm Hg; yield 76%. ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.07 (1H, d×d, J=15.2, 5.7 Hz, CH_aH$_b$), 3.28 (1H, d×d, J=15.2, 7.8 Hz, CH$_a$$H_b$), 5.20 (1H, d×d, J=7.8, 5.7 Hz, CH), 7.26–7.36 (4H, m, C_6H_4), 9.17 (1H, s, CHO). ^{13}C NMR (68 MHz, $CDCl_3$): δ 50.9 (CH_2), 57.3 (CH), 85.6 (CCl_2), 2×128.6 (2×CH_{ar}), 2×129.2 (2×CH_{ar}), 135.0 (C_{quat}), 138.1 (C_{quat}), 183.6 (C=O). IR (NaCl) ν_{max} 1742 cm^{-1}. MS (70 eV) *m/z* (%): no M+, 214/16/18 (M^+ −2Cl, 44); 173 (100); 150 (95); 126 (36).

3.2. Synthesis of 1-alkyl-5-aryl-3-chloro-2-cyano-2-pyrrolines 14

As a representative example, the synthesis of 3-chloro-2-cyano-1-isopropyl-5-phenyl-2-pyrroline **14c** is given. To a solution of 1.00 g (3.98 mmol) of 2,2,4-trichloro-4-phenylbutanal **12a** in 10 mL of dry diethyl ether was added 0.45 g (2.38 mmol, 0.6 equiv) of titanium(IV) chloride in 5 mL of dry pentane at 0 °C. After addition, the mixture was stirred for 15 min at 0 °C, followed by addition of 0.94 g (15.92 mmol, 4 equiv) of isopropylamine in 10 mL of dry diethyl ether. Cooling was stopped and the mixture was stirred for 15 h. Subsequently, the mixture was poured in 25 mL of aq. 1 M NaOH and rapidly extracted with diethyl ether (3×25 mL). The extract was dried (K_2CO_3/$MgSO_4$) and the solvent was removed in vacuo at 0–10 °C. The resulting aldimine **13** (R^1= C_6H_5, R^2= *i*-Pr) was used as such (without purification; purity >90%) to minimize decomposition. To 1.16 g (3.98 mmol) of *N*-(2,2,4-trichloro-4-phenyl-1-butylidene)isopropylamine in 20 mL of methanol was added 0.28 g (4.37 mmol, 1.1 equiv) of potassium cyanide and the mixture was heated under reflux for 4 h. After reaction, the mixture was poured in 20 mL of aq. 0.5 M NaOH and extracted with dichloromethane (3×20 mL). After drying ($MgSO_4$) and evaporation of the solvents, pyrroline **14c** was obtained and was purified by flash chromatography (0.57 g, 58%).

3.2.1. 1-*tert*-Butyl-3-chloro-2-cyano-5-phenyl-2-pyrroline 14a. Recrystallization (Et_2O/hexane, 1:3), yield 64%, mp 84–85 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.25 (9H, s, $C(CH_3)_3$), 2.49 (1H, d×d, J=17.8, 6.6 Hz, CH_aH_b), 3.43 (1H, d×d, J=17.8, 11.5 Hz, CH_aH_b), 4.67 (1H, d×d, J=11.5, 6.6 Hz, CH), 7.25–7.39 (5H, m, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): δ 3×28.3 ($C(CH_3)_3$), 45.2 (CH_2), 57.7 ($C(CH_3)_3$), 61.5 (NCH), 113.9 (CN), 119.8 (C_{quat}), 2×125.7 (2×CH_{ar}), 126.1 (C_{quat}), 127.2 (CH_{ar}), 2×128.8 (2×CH_{ar}), 145.7 (C_{quat}). IR (KBr) ν_{max} 2226 cm^{-1}. MS (70 eV) *m/z* (%): 260/62 (M^+, 12); 204/206 (100); 169 (41); 168 (12); 115 (11); 57 (85).

3.2.2. 3-Chloro-1-cyclohexyl-2-cyano-5-phenyl-2-pyrroline 14b. Flash chromatography (hexane/EtOAc 9:1, R_f=0.54), yield 54%. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.01–1.83 (10H, m, 5×CH_2), 2.61 (1H, d×d, J=17.3, 10.9 Hz, CH_aH_b), 2.85–3.07 (1H, m, NCH), 3.23 (1H, d×d, J=17.3, 11.5 Hz, CH_aH_b), 4.57 (1H, d×d, J=11.5, 10.9 Hz, NCH), 7.28–7.36 (5H, m, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): δ 25.4 (CH_2), 25.6 (CH_2), 25.9 (CH_2), 29.6 (CH_2), 30.4 (CH_2), 45.1 (CH_2CCl), 59.4 (NCH), 63.0 (NCH), 112.0 (CN), 120.7 (C_{quat}), 120.9 (C_{quat}), 2×126.5 (2×CH_{ar}), 127.6 (CH_{ar}), 2×128.6 (2×CH_{ar}), 143.1 (C_{quat}). IR (NaCl) ν_{max} 2228 cm^{-1}. MS (70 eV) *m/z* (%): 286/288 (M^+, 35); 243/245 (23); 204/206 (100); 169 (38); 83 (24); 55 (62).

3.2.3. 3-Chloro-2-cyano-1-isopropyl-5-phenyl-2-pyrroline 14c. Flash chromatography (hexane/EtOAc 4:1, R_f=0.60), yield 58%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (3H, d, J=6.9 Hz, CH_3), 1.23 (3H, d, J=6.9 Hz, CH_3), 2.63 (1H, dd, J=17.3, 11.5 Hz, CH_aH_b), 3.21 (1H, d×d, J=17.3, 11.2 Hz, CH_aH_b), 3.33 (1H, sept, J=6.9 Hz, $CH(CH_3)_2$), 4.48 (1H, d×d, J=11.2, 11.5 Hz, CH), 7.25–7.50 (5H, m, C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 2×19.3 (2×CH_3), 45.1 (CH_2), 50.8 ($CH(CH_3)_2$), 63.0 (CH), 112.1 (CN), 120.8 (C_{quat}), 121.4 (C_{quat}), 2×126.7 (2×CH_{ar}), 127.7 (CH_{ar}), 2×128.7 (2×CH_{ar}), 142.9 (C_{quat}). IR (NaCl) ν_{max} 2227 cm^{-1}. MS (70 eV) *m/z* (%): 246/48 (M^+, 55); 231/33 (98); 169 (46); 142 (25); 91 (100); 77 (17).

3.2.4. 3-Chloro-2-cyano-5-phenyl-1-propyl-2-pyrroline 14d. This compound was unstable and could not be completely purified by flash chromatography. The spectra still contained impurities (ca. 10%); crude yield 79%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.80 (3H, t, J=7.3 Hz, CH_3), 1.30–7.54 (2H, m, CH_2CH_3), 2.72 (1H, d×d, J=12.7, 17.1 Hz, $NCHCH_aH_b$), 2.83 (1H, t, J=6.6 Hz, NCH_aH_b), 2.85 (1H, t, J=6.6 Hz, NCH_aH_b), 3.15 (1H, d×d, J=11.0, 17.1 Hz, $NCHCH_aH_b$), 4.39 (1H, d×d, J=12.7, 11.0 Hz, $NCHCH_2$), 7.31–7.65 (5H, m, C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.5 (CH_3), 20.3 (CH_2), 45.2 (CH_2), 52.7 (NCH_2), 67.8 (NCH), 111.8 (CN), 120.0 (C_{quat}), 2×127.3 (2×CH_{ar}), 127.8 (C_{quat}), 128.3 (CH_{ar}), 2×128.9 (2×CH_{ar}), 141.1 (C_{quat}). IR (NaCl) ν_{max} 2229 cm^{-1}. MS (ES+) *m/z* (%): 238/40 ($M^+ - CN + H_2O$, 100).

3.2.5. 3-Chloro-5-(4-chlorophenyl)-2-cyano-1-isopropyl-2-pyrroline 14e. Flash chromatography (hexane/EtOAc 4:1, R_f=0.60), yield 52%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (3H, d, J=6.9 Hz, CH_3), 1.22 (3H, d, J=6.9 Hz, CH_3), 2.59 (1H, d×d, J=17.5, 11.1 Hz, CH_aH_b), 3.23 (1H, d×d, J=17.5, 11.4 Hz, CH_aH_b), 3.35 (1H, sept, J=6.9 Hz, $CH(CH_3)_2$), 4.49 (1H, d×d, J=11.1, 11.4 Hz, CH), 7.26–7.38 (4H, m, C_6H_4). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.3 (CH_3), 19.6 (CH_3), 45.2 (CH_2), 51.1 ($CH(CH_3)_2$), 62.2 (NCH), 112.1 (CN), 121.6 (C_{quat}), 2×128.3 (2×CH_{ar}), 128.5 (C_{quat}), 2×129.0 (2×CH_{ar}), 133.5 (C_{quat}), 141.8 (C_{quat}). IR (NaCl) ν_{max} 2213, 1453 cm^{-1}. MS (70 eV) *m/z* (%): 280/82/84 (M^+, 68); 265/67/69 (100); 238 (34); 203 (34); 125 (57).

3.3. Synthesis of 1-alkyl-2-aryl-4-chloropyrroles 16

As a representative example, the synthesis of 4-chloro-1-isopropyl-2-phenylpyrrole **16c** is described. To 5.00 g (20.28 mmol) of 3-chloro-2-cyano-1-isopropyl-5-phenyl-2-pyrroline **14c** was added 41 mL (81.13 mmol, 4 equiv) of 2 M NaOMe in MeOH at room temperature. The mixture was refluxed for 2 h, cooled and poured in 100 mL of water. After extraction with dichloromethane (3×50 mL), the extract was dried ($MgSO_4$) and the solvents evaporated in vacuo. The resulting pyrrole was purified by flash chromatography (3.96 g, 83%).

3.3.1. 1-*tert*-Butyl-4-chloro-2-phenylpyrrole 16a. Flash chromatography (hexane/EtOAc 95:5, R_f=0.58), yield 52%, mp 77 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.39 (9H, s, $C(CH_3)_3$), 5.95 (1H, d, J=2.3 Hz, NC=CH), 6.82 (1H, d, J=2.3 Hz, NCH=C), 7.32–7.36 (5H, m, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): δ 3×31.8 ($C(CH_3)_3$), 58.0 ($C(CH_3)_3$), 109.5 (C_{quat}), 111.5 (NC=CH), 116.0 (NCH=C), 2×127.5 (2×CH_{ar}), 127.9 (CH_{ar}), 2×131.7 (2×CH_{ar}), 133.8 (C_{quat}), 136.1 (C_{quat}). IR (KBr): ν_{max} 1368 cm^{-1}. MS (70 eV) *m/z* (%): 233/235 (M^+, 16); 178/180 (12); 177/179 (100); 57 (27). Anal. Calcd for $C_{14}H_{16}NCl$: C, 71.94; H, 6.90; N, 5.99. Found: C, 72.12; H, 7.09; N, 5.86.

3.3.2. 4-Chloro-1-cyclohexyl-2-phenylpyrrole 16b. Flash chromatography (hexane/EtOAc 95:5, R_f=0.56), yield 67%. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.14–1.98 (10H, m, 5×CH_2), 3.88–3.40 (1H, m, NCH), 6.05 (1H, d, J=1.9 Hz, NC=CH), 6.77 (1H, d, J=1.9 Hz, NCH=C), 7.29–7.44 (5H, m, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): δ 25.3 (CH_2), 2×25.8 (2×CH_2), 2×34.8 (2×CH_2), 55.6 (NCH), 108.1 (NC=CH), 111.6 (C_{quat}), 115.2 (NCH=C), 127.4 (CH_{ar}), 2×128.5 (2×CH_{ar}), 2×129.2 (2×CH_{ar}), 132.7 (C_{quat}), 133.7 (C_{quat}). IR (NaCl): ν_{max} 1495, 1448, 1395 cm^{-1}. MS (70 eV) *m/z* (%): 259/61 (M^+, 38); 178/180 (22); 177/179 (100); 115 (10); 55 (29); 41 (22). Anal. Calcd for $C_{16}H_{18}NCl$: C, 73.98; H, 6.98; N, 5.39. Found: C, 73.75; H, 7.11; N, 5.28.

3.3.3. 4-Chloro-1-isopropyl-2-phenylpyrrole 16c. Flash chromatography (hexane/EtOAc 95:5, R_f=0.50), yield 83%, mp 42–43 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.35 (6H, d, J=6.6 Hz, $CH(CH_3)_2$), 4.40 (1H, sept, J=6.6 Hz, $CH(CH_3)_2$), 6.05 (1H, d, J=1.9 Hz, NC=CH), 6.78 (1H, d, J=1.9 Hz, NCH=C), 7.30–7.43 (5H, m, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): δ 2×23.9 (2×CH_3), 47.7 (CH), 108.2 (NC=CH), 111.8 (C_{quat}), 114.3 (NCH=C), 127.6 (CH_{ar}), 2×128.5 (2×CH_{ar}), 2×129.3 (2×CH_{ar}), 132.7 (C_{quat}), 133.8 (C_{quat}). IR (KBr) ν_{max} 1497, 1463, 1394 cm^{-1}. MS (70 eV) *m/z* (%): 219/21 (M^+, 53); 178/80 (12); 177/79 (100); 115 (21). Anal. Calcd for $C_{13}H_{14}NCl$: C, 71.07; H,

6.42; N, 6.38. Found: C, 71.06; H, 6.48; N, 6.34. HRMS: Calcd for $C_{13}H_{14}NCl$, 220.0888; Found 220.0901.

3.3.4. 4-Chloro-2-phenyl-1-propylpyrrole 16d. Flash chromatography (hexane/EtOAc 98:2, R_f=0.35), yield 59%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.79 (3H, t, J=7.4 Hz, CH_3), 1.64 (2H, sext, J=7.4 Hz, CH_2CH_3), 3.80 (3H, t, J=7.4 Hz, NCH_2), 6.10 (1H, d, J=1.9 Hz, NC=CH), 6.69 (1H, d, J=1.9 Hz, NCH=C), 7.30–7.42 (5H, m, C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.3 (CH_3), 24.9 (CH_2), 49.2 (NCH_2), 108.8 (NC=*C*H), 111.7 (C_{quat}), 118.9 (NCH), 127.7 (CH_{ar}), 2×128.8 (2×CH_{ar}), 2×129.3 (2×CH_{ar}), 132.8 (C_{quat}), 134.5 (C_{quat}). IR (NaCl) ν_{max} 1603, 1500, 1475, 1324 cm^{-1}. MS (70 eV) *m/z* (%): 219/21 (M^+, 100); 190/92 (84); 177/79 (39); 155 (37); 142 (15); 115 (20). Anal. Calcd for $C_{13}H_{14}NCl$: C, 71.07; H, 6.42; N, 6.38. Found: C, 71.18; H, 6.60; N, 6.21. HRMS: Calcd for $C_{13}H_{14}NCl$, 220.0888; Found 220.0887.

3.3.5. 4-Chloro-2-(4-chlorophenyl)-1-isopropylpyrrole 16e. Flash chromatography (hexane/EtOAc 97:3, R_f=0.42), yield 77%, mp 61 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (6H, d, J=6.7 Hz, $CH(CH_3)_2$), 4.34 (1H, sept, J=6.7 Hz, $CH(CH_3)_2$), 6.04 (1H, d, J=1.9 Hz, NC=CH), 6.78 (1H, d, J=1.9 Hz, NCH=C), 7.21–7.26 (2H, m, 2×CH_{ar}), 7.34–7.39 (2H, m, 2×CH_{ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 2×24.0 (2×CH_3), 47.9 (CH), 108.6 (NC=*C*H), 112.1 (C_{quat}), 114.8 (N*C*H=C), 2×128.9 (2×CH_{ar}), 2×130.6 (2×CH_{ar}), 131.1 (C_{quat}), 132.6 (C_{quat}), 133.7 (C_{quat}). IR (KBr) ν_{max} 1495, 1415, 1288 cm^{-1}. MS (70 eV) *m/z* (%) 253/55/57 (M^+, 76), 211/13/15 (100), 176 (27), 149 (19). Anal. Calcd for $C_{13}H_{13}NCl_2$: C, 61.43; H, 5.16; N, 5.51. Found: C, 61.59; H, 5.30; N, 5.37.

3.4. Hydrolysis of 1-alkyl-5-aryl-3-chloro-2-cyano-2-pyrrolines 14

As a representative example, the hydrolysis of 3-chloro-2-cyano-1-isopropyl-5-phenyl-2-pyrroline **14c** is described. 3-Chloro-2-cyano-1-isopropyl-5-phenyl-2-pyrroline **14c** (0.50 g, 2.03 mmol) was dissolved in 10 mL of a 1:1 mixture of acetic acid and aq. 2 M HCl. The solution was stirred at room temperature in a well vented fume hood (CAUTION: formation of HCN!) for 2 h and subsequently poured in 25 mL of water and extracted with dichloromethane (3×25 mL). After drying ($MgSO_4$) and evaporation of the solvent in vacuo, *cis*-substituted pyrrolidinone **19b** was obtained after flash chromatography (0.27 g, 57%). When the reaction temperature was raised to reflux temperatures (15 h) a mixture of *cis*- (**19b**) and *trans*-substituted pyrrolidinones (**20b**) was obtained in a ratio 1:3, respectively. The two isomers were easily separated by flash chromatography.

3.4.1. *cis*-1-*tert*-Butyl-3-chloro-5-phenyl-2-pyrrolidinone 19a. Recrystallization (Et_2O/hexane 1:1), yield 75%, mp 130 °C. ^{1}H NMR ($CDCl_3$): δ 1.35 (9H, s, $C(CH_3)_3$), 2.09 (1H, d×t, J=14.8, 2.5 Hz, CH_aH_b), 2.99 (1H, d×t, J=14.8, 9.0 Hz, CH_aH_b), 4.37 (1H, d×d, J=9.0, 2.5 Hz, CH), 4.90 (d×d, J=9.0, 2.5 Hz, CHCl), 7.27–7.36 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$): δ 3×27.9 (3×CH_3), 38.4 (CH_2), 54.6 (CH), 56.3 ($C(CH_3)_3$), 61.2 (CHCl), 2×126.2 (2×CH_{ar}), 127.8 (CH_{ar}), 2×128.8 (2×CH_{ar}), 143.9 (C_{quat}), 171.1 (C=O). IR (KBr) ν_{max} 1677, 1495, 1457 cm^{-1}. MS (ES+) *m/z* (%) 252/54 ($M+H^+$, 60), 196/98 (100). Anal. Calcd for $C_{14}H_{18}NOCl$: C, 66.79; H, 7.21; N, 5.56. Found: C, 66.62; H, 7.38; N, 5.42.

3.4.2. *cis*-3-Chloro-1-isopropyl-5-phenyl-2-pyrrolidinone 19b. Flash chromatography (hexane/EtOAc 4:1, R_f=0.31), yield 57%, mp 110–112 °C. ^{1}H NMR ($CDCl_3$): δ 0.99 (3H, d, J=6.9 Hz, CH_3), 1.25 (3H, d, J=6.9 Hz, CH_3), 2.20 (1H, d×t, J=14.3, 6.3 Hz, CH_aH_b), 3.06 (1H, d×d×d, J=14.3, 9.1, 7.8 Hz, CH_aH_b), 3.85 (1H, sept, J=6.9 Hz, $CH(CH_3)_2$), 4.45 (1H, d×d, J=9.1, 6.3 Hz, CH), 4.62 (1H, d×d, J=7.8, 6.3 Hz, CH), 7.32–7.42 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$): δ 19.6 (CH_3), 20.3 (CH_3), 39.5 (CH_2), 46.8 ($CH(CH_3)_2$), 54.3 (NCH), 60.3 (CHCl), 2×127.5 (2×CH_{ar}), 128.6 (CH_{ar}), 2×129.0 (2×CH_{ar}), 141.2 (C_{quat}), 170.6 (C=O). IR (KBr) ν_{max} 1677, 1419 cm^{-1}. MS (70 eV) *m/z* (%) 237/39 (M^+, 9), 222/24 (30), 202 (100), 117(84). Calcd for $C_{13}H_{16}NOCl$: C, 65.68; H, 6.78; N, 5.89. Found: C, 65.84; H, 6.95; N, 5.70.

3.4.3. *trans*-1-*tert*-Butyl-3-chloro-5-phenyl-2-pyrrolidinone 20a. Flash chromatography (hexane/EtOAc 9:1, R_f=0.31), yield 70%, mp 81–82 °C. ^{1}H NMR ($CDCl_3$): δ 1.37 (9H, s, $C(CH_3)_3$), 2.41 (1H, d×d×d, J=12.7, 7.9, 1.4 Hz, CH_aH_b), 2.58 (1H, d×d×d, J=12.7, 10.2, 8.5 Hz, CH_aH_b), 4.67 (1H, d×d, J=10.2, 7.9 Hz, CH), 4.92 (1H, d×d, J=8.5, 1.4 Hz, CHCl), 7.17–7.40 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$): δ 3×27.8 (3×CH_3), 41.0 (CH_2), 55.0 (CH), 56.0 ($C(CH_3)_3$), 59.8 (CHCl), 2×125.26 (2×CH_{ar}), 127.9 (CH_{ar}), 2×129.2 (2×CH_{ar}), 142.7 (C_{quat}), 170.6 (C=O). IR (KBr) ν_{max} 1690, 1455, 1398 cm^{-1}. MS (ES+) *m/z* (%) 252/54 ($M+H^+$, 75), 196/98 (100). Calcd for $C_{14}H_{18}NOCl$: C, 66.79; H, 7.21; N, 5.56. Found: C, 66.67; H, 7.43; N, 5.39.

3.4.4. *trans*-3-Chloro-1-isopropyl-5-phenyl-2-pyrrolidinone 20b. Flash chromatography (hexane/EtOAc 4:1, R_f=0.06), yield 32%. ^{1}H NMR ($CDCl_3$): δ 0.99 (3H, d, J=6.8 Hz, CH_3), 1.27 (3H, d, J=6.8 Hz, CH_3), 2.44 (1H, d×d×d, J=14.0, 7.4, 5.3 Hz, CH_aH_b), 2.60 (1H, d×d×d, J=14.0, 7.4, 5.3 Hz, CH_aH_b), 3.89 (1H, sept, J=6.8 Hz, $CH(CH_3)_2$), 4.60 (1H, d×d, J=7.4, 5.3 Hz, CH), 4.79 (1H, d×d, J=7.4, 5.3 Hz, CH), 7.33–7.42 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$): δ 19.7 (CH_3), 20.0 (CH_3), 40.7 (CH_2), 46.4 ($CH(CH_3)_2$), 55.1 (NCH), 59.7 (CHCl), 2×126.8 (2×CH_{ar}), 128.5 (CH_{ar}), 2×129.1 (2×CH_{ar}), 140.8 (C_{quat}), 170.6 (C=O). IR (NaCl) ν_{max} 1699, 1495, 1456, 1222 cm^{-1}. MS (70 eV) *m/z* (%) 237/39 (M^+, 13), 222/24 (30), 202 (100), 117(88). Anal. Calcd for $C_{13}H_{16}NOCl$: C, 65.68; H, 6.78; N, 5.89. Found: C, 65.90; H, 6.95; N, 6.03.

3.5. Synthesis of 1-alkyl-5-aryl-3-chloro-2-cyanopyrroles 21

To a solution of 0.54 g (2.19 mmol) of 3-chloro-2-cyano-1-isopropyl-5-phenyl-2-pyrroline **14c** in 20 mL of dry toluene was added 0.55 g (2.41 mmol, 1.1 equiv) of DDQ. The resulting mixture was refluxed for 6 h. After reaction, the mixture was diluted with 20 mL of pentane and the formed heterogeneous mixture was filtered over Celite®. The filtrate was diluted with 50 mL of water and extracted with pentane (3×50 mL). The combined extracts were

dried ($MgSO_4$), filtered and the solvent was removed in vacuo. Purification of the synthesized pyrrole was performed by a fast flash chromatography over a short (5 cm) column of silica gel (0.23 g, 43%).

3.5.1. 1-*tert*-Butyl-3-chloro-2-cyano-5-phenylpyrrole 21a. Flash chromatography (hexane/EtOAc 9:1, R_f= 0.43), yield 42%, mp 119–120 °C. ^{1}H NMR ($CDCl_3$): δ 1.56 (9H, s, $C(CH_3)_3$), 5.96 (1H, s, CH), 7.26–7.46 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$): δ 3×32.3 (3×CH_3), 62.2 ($C(CH_3)_3$), 102.1 (CN), 112.4 (CH), 114.4 (C_{quat}), 125.4 (C_{quat}), 2×127.9 (2×CH_{ar}), 128.8 (CH_{ar}), 2×130.3 (2×CH_{ar}), 134.7 (C_{quat}), 139.8 (C_{quat}). IR (KBr) ν_{max} 2211, 1325 cm^{-1}. MS (70 eV) *m/z* (%) 258/60 (M^+, 5), 202/04 (100), 57 (20). Calcd for $C_{15}H_{15}N_2Cl$: C, 69.63; H, 5.84; N, 10.83. Found: C, 69.75; H, 5.96; N, 10.68.

3.5.2. 3-Chloro-1-cyclohexyl-2-cyano-5-phenylpyrrole 21b. Flash chromatography (hexane/EtOAc 4:1, R_f= 0.26), yield 54%, mp 125 °C. ^{1}H NMR ($CDCl_3$): δ 1.12–2.32 (10H, m, 5×CH_2), 4.05 (1H, t×t, J=12.4, 3.7 Hz, CHN), 6.12 (1H, s, CH), 7.26–7.32 and 7.41–7.51 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$): δ 24.7 (CH_2), 2×25.9 (2×CH_2), 2×32.6 (2×CH_2), 58.2 (CHN), 100.6 (CN), 109.5 (CH), 113.3 (C_{quat}), 124.7 (C_{quat}), 2×128.9 (2×CH_{ar}), 129.0 (CH_{ar}), 2×129.3 (2×CH_{ar}), 130.7 (C_{quat}), 139.4 (C_{quat}). IR (NaCl) ν_{max} 2212, 1333 cm^{-1}. MS (ES+) *m/z* (%) 285/87 ($M+H^+$, 100), 203/04 (15). Anal. Calcd for $C_{17}H_{17}N_2Cl$: C, 71.70; H, 6.02; N, 9.84. Found: C, 71.51; H, 6.14; N, 9.88.

3.5.3. 3-Chloro-2-cyano-1-isopropyl-5-phenylpyrrole 21c. Flash chromatography (hexane/EtOAc 95:5, R_f= 0.25), yield 43%, mp 68–71 °C. ^{1}H NMR ($CDCl_3$): δ 1.58 (6H, d, J=6.9 Hz, $CH(CH_3)_2$), 4.52 (1H, sept, J=6.9 Hz, $CH(CH_3)_2$), 6.11 (1H, s, NC=CH), 7.28–7.34 (2H, m, 2×CH_{ar}), 7.43–7.49 (3H, m, 3×CH_{ar}). ^{13}C NMR ($CDCl_3$): δ 2×22.5 (2×CH_3), 50.3 (NCH), 100.0 (CN), 109.6 (NC=*C*H), 113.2 (C_{quat}), 124.9 (C_{quat}), 2×128.8 (2×CH_{ar}), 129.2 (CH_{ar}), 2×129.6 (2×CH_{ar}), 130.7 (C_{quat}), 139.4 (C_{quat}). IR (KBr) ν_{max} 2211, 1454 cm^{-1}. MS (70 eV) *m/z* (%) 244/46 (M^+, 38), 202/4 (100), 166 (9), 140 (16). Calcd for $C_{14}H_{13}N_2Cl$: C, 68.71; H, 5.35; N, 11.45. Found: C, 68.88; H, 5.49; N, 11.30.

3.5.4. 3-Chloro-2-cyano-5-phenyl-1-propylpyrrole 21d. Flash chromatography (hexane/EtOAc 9:1, R_f=0.35), yield 43%. ^{1}H NMR ($CDCl_3$): δ 0.79 (3H, t, J=7.5 Hz, CH_3), 1.70 (2H, sext, J=7.5 Hz, CH_3CH_2), 3.98 (2H, t, J=7.5 Hz, NCH_2), 6.18 (1H, s, NC=*C*H), 7.32–7.49 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$): δ 10.9 (CH_3), 24.5 (CH_2), 48.7 (NCH_2), 103.5 (CN), 110.1 (NC=*C*H), 112.4 (C_{quat}), 123.1 (C_{quat}), 2×129.0 (2×CH_{ar}), 3×129.2 (2×CH_{ar} and C_{quat}), 130.6 (CH_{ar}), 139.7 (C_{quat}). IR (NaCl) ν_{max} 2217, 1460, 1337 cm^{-1}. MS (70 eV) *m/z* (%) 244/46 (M^+, 83), 202/4 (100), 190 (23), 180 (24), 166 (13), 140 (20). Anal. Calcd for $C_{14}H_{13}N_2Cl$: C, 68.71; H, 5.35; N, 11.45. Found: C, 68.59; H, 5.47; N, 11.37.

3.5.5. 3-Chloro-5-(4-chlorophenyl)-2-cyano-1-isopropylpyrrole 21e. Flash chromatography (hexane/EtOAc 97:3, R_f=0.19), yield 50%, mp 102 °C. ^{1}H NMR ($CDCl_3$): δ 1.59 (6H, d, J=6.9 Hz, $CH(CH_3)_2$), 4.46 (1H, sept, J=6.9 Hz, $CH(CH_3)_2$), 6.11 (1H, s, NC=CH), 7.22–7.28 (2H, m, 2×CH_{ar}), 7.40–7.48 (2H, m, 2×CH_{ar}). ^{13}C NMR ($CDCl_3$): δ 2×22.5 (2×CH_3), 50.5 (CH), 100.4 (CN), 109.8 (NC=*C*H), 113.0 (C_{quat}), 124.9 (C_{quat}), 129.0 (C_{quat}), 2×129.3 (2×CH_{ar}), 2×130.8 (2×CH_{ar}), 135.5 (C_{quat}), 138.1 (C_{quat}). IR (KBr) ν_{max} 2215, 1449, 1337 cm^{-1}. MS (70 eV) *m/z* (%) 278/80/82 (M^+, 54), 236/38/40 (100), 201/3 (16), 174 (21). Calcd for $C_{14}H_{12}N_2Cl_2$: C, 60.23; H, 4.33; N, 10.03. Found: C, 60.12; H, 4.50; N, 9.89.

3.6. Synthesis of 2-acetylpyrroles 24a,b

A solution of 1.6 M MeLi in diethyl ether (2.60 mL, 4.09 mmol, 1 equiv) was added to a solution of 1.00 g (4.09 mmol) of 3-chloro-2-cyano-1-isopropyl-5-phenylpyrrole **21c** in 50 mL of dry THF under N_2-atmosphere. After stirring for 2 h at room temperature, the reaction mixture was diluted with 50 mL of water and subsequently extracted with diethyl ether (3×25 mL). Drying of the solvents ($MgSO_4$/K_2CO_3), filtration and evaporation of the solvents in vacuo yielded a mixture of 2-acetylpyrrole **21c** and the corresponding imine. Separation of these two products was not possible, because the imine hydrolyzed towards **21c** during flash chromatography. The mixture was dissolved in 25 mL of dichloromethane and 10 mL of aq. 6 M HCl was added. The resulting biphasic solution was stirred at room temperature for 2 h and subsequently extracted with dichloromethane (3× 25 mL). Standard work up yielded 2-acetylpyrrole **24b**, which was purified by flash chromatography (0.62 g, 58%).

3.6.1. 2-Acetyl-3-chloro-1-cyclohexyl-5-phenylpyrrole 24a. Flash chromatography (hexane/EtOAc 4:1, R_f= 0.70), yield 47%. ^{1}H NMR ($CDCl_3$): δ 1.07–2.06 (10H, m, 5×CH_2), 2.66 (3H, s, CH_3), 4.32–4.34 (1H, m, NCH), 6.11 (1H, s, CH), 7.32–7.45 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$): δ 25.0 (CH_2), 2×26.3 (2×CH_2), 31.7 (CH_3), 2×32.4 (2×CH_2), 60.5 (CHN), 112.0 (CH), 121.2 (C_{quat}), 2×128.3 (2×CH_{ar}), 128.7 (CH_{ar}), 129.0 (C_{quat}), 2×129.8 (2×CH_{ar}), 132.9 (C_{quat}), 141.5 (C_{quat}), 189.2 (C=O). IR (NaCl) ν_{max} 1654 cm^{-1}. MS (ES+) *m/z* (%) 302/04 ($M+H^+$, 65), 220/22 (100). Anal. Calcd for $C_{18}H_{20}NOCl$: C, 71.63; H, 6.68; N, 4.64. Found: C, 71.86; H, 6.52; N, 4.60.

3.6.2. 2-Acetyl-3-chloro-1-isopropyl-5-phenylpyrrole 24b. Flash chromatography (hexane/EtOAc 97:3, R_f= 0.20), yield 58%, mp 42 °C. ^{1}H NMR ($CDCl_3$): δ 1.42 (6H, d, J=7.0 Hz, $CH(CH_3)_2$), 2.67 (3H, s, CH_3CO), 4.73 (1H, sept, J=7.0 Hz, $CH(CH_3)_2$), 6.12 (1H, s, NC=*C*H), 7.34–7.38 (2H, m, 2×CH_{ar}), 7.41–7.47 (3H, m, 3×CH_{ar}). ^{13}C NMR ($CDCl_3$): δ 2×22.4 (2×CH_3), 31.7 (CH_3), 51.8 (CH), 111.9 (NC=*C*H), 121.5 (C_{quat}), 2×128.5 (2×CH_{ar}), 128.9 (CH_{ar}), 2×129.9 (2×CH_{ar}), 132.7 (C_{quat}), 141.4 (C_{quat}), 189.0 (C=O). IR (KBr) ν_{max} 1651, 1445 cm^{-1}. MS (70 eV) *m/z* (%) 261/63 (M^+, 58), 219/21 (50), 204/6 (100), 149 (25). Anal. Calcd for $C_{15}H_{16}NOCl$: C, 68.83; H, 6.16; N, 5.35. Found: C, 69.01; H, 6.31; N, 5.54.

3.7. Synthesis of 2-formylpyrroles 24c,d,e

To a solution of 1.00 g (4.56 mmol) of 3-chloro-1-isopropyl-5-phenylpyrrole **16c** in 20 mL of DMF and 20 mL of dry dichloromethane was added a solution of 0.84 g (5.47 mmol, 1.2 equiv) of $POCl_3$ in 5 mL of dry

dichloromethane at 0 °C under N_2-atmosphere. After stirring for 5 h, the reaction mixture was diluted with 25 mL of aq. 1 M NaOH at 0 °C and stirred for 15 min at the same temperature. The mixture was poured in 25 mL of water and extracted with dichloromethane (3×30 mL). The extracts were dried over $MgSO_4$ and after filtration, the solvent was removed in vacuo. To remove residual DMF, additional evaporation at high vacuum (0.01 mm Hg) was applied. This procedure yielded a mixture of 2- and 4-formylated pyrroles (ratio 65:35, calculated from ^{1}H NMR spectra, which were easily separated by flash chromatography.

3.7.1. 1-*tert*-Butyl-3-chloro-2-formyl-5-phenylpyrrole 24c. Flash chromatography (hexane/EtOAc 9:1, R_f=0.36), yield 71%, mp 103 °C. ^{1}H NMR ($CDCl_3$): δ 1.52 (9H, s, $C(CH_3)_3$), 6.04 (1H, s, CH), 7.25–7.42 (5H, m, C_6H_5), 9.80 (1H, s, CHO). ^{13}C NMR ($CDCl_3$): δ 32.2 ($C(CH_3)_3$), 62.5 ($C(CH_3)_3$), 113.9 (CH), 2×128.1 (2×CH_{ar}), 128.3 (C_{quat}), 128.7 (CH_{ar}), 2×129.5 (2×CH_{ar}), 131.0 (C_{quat}), 135.6 (C_{quat}), 144.7 (C_{quat}), 177.3 (C=O). IR (KBr) ν_{max} 1655 cm^{-1}. MS (ES+) *m/z* (%) 262/64 ($M+H^+$, 5), 206/08 (100). Calcd for $C_{15}H_{16}NOCl$: C, 68.83; H, 6.16; N, 5.35. Found: C, 68.71; H, 6.32; N, 5.24.

3.7.2. 3-Chloro-1-cyclohexyl-2-formyl-5-phenylpyrrole 24d. Flash chromatography (hexane/EtOAc 9:1, R_f=0.35), yield 76%, mp 142-143 °C. ^{1}H NMR ($CDCl_3$): δ 0.81–2.42 (10H, m, 5×CH_2), 4.16–4.28 (1H, m, CHN), 6.19 (1H, s, CH), 7.29–7.36 (2H, m, 2×CH_{ar}), 7.44–7.48 (3H, m, 3×CH_{ar}), 9.79 (1H, s, CHO). ^{13}C NMR ($CDCl_3$): δ 24.5 (CH_2), 2×26.0 (2×CH_2), 2×31.0 (2×CH_2), 59.1 (CHN), 111.2 (CH), 126.1 (C_{quat}), 2×128.6 (2×CH_{ar}), 129.1 (CH_{ar}), 2×129.4 (2×CH_{ar}), 130.9 (C_{quat}), 131.7 (C_{quat}), 143.0 (C_{quat}), 176.9 (C=O). IR (KBr) ν_{max} 1667 cm^{-1}. MS (ES+) *m/z* (%) 288/90 ($M+H^+$, 100). Calcd for $C_{17}H_{18}NOCl$: C, 70.95; H, 6.30; N, 4.87. Found: C, 71.11; H, 6.48; N, 4.76.

3.7.3. 3-Chloro-2-formyl-1-isopropyl-5-phenylpyrrole 24e. Flash chromatography (hexane/EtOAc 9:1, R_f=0.54), yield 50%, mp 59 °C. ^{1}H NMR ($CDCl_3$): δ 1.49 (6H, d, J=6.9 Hz, $CH(CH_3)_2$), 4.64 (1H, sept, J=6.9 Hz, $CH(CH_3)_2$), 6.18 (1H, s, NC=CH), 7.33–7.37 (2H, m, 2×CH_{ar}), 7.43–7.50 (3H, m, 3×CH_{ar}), 9.80 (1H, s, CHO). ^{13}C NMR ($CDCl_3$): δ 2×21.4 (2×CH_3), 50.9 (CH), 111.1 (NC=*C*H), 126.1 (C_{quat}), 2×128.8 (2×CH_{ar}), 129.2 (C_{quat}), 129.3 (CH_{ar}), 2×129.5 (2×CH_{ar}), 131.6 (C_{quat}), 142.8 (C_{quat}), 176.7 (C=O). IR (KBr) ν_{max} 2845, 2806, 1655, 1450, 1207 cm^{-1}. MS (70 eV) *m/z* (%) 247/49 (M^+, 83), 205 (100), 149 (31), 140 (18), 115 (16). Anal. Calcd for $C_{14}H_{14}NOCl$: C, 67.88; H, 5.70; N, 5.65. Found: C, 68.01; H, 5.82; N, 5.67. HRMS: Calcd for $C_{14}H_{14}NOCl$, 248.0837; Found 248.0831.

3.8. Synthesis of methyl (3-chloro-1-isopropyl-5-phenylpyrrol-2-yl)carboxylate 24f

3-Chloro-1-isopropyl-5-phenylpyrrole **16c** (0.50 g, 2.28 mmol) was dissolved in 25 mL of dry THF and cooled to −78 °C. Under N_2-atmosphere, 0.92 mL (2.28 mmol, 1 equiv) of a 2.5 M BuLi solution in hexane was added and the mixture was stirred at 0 °C. After 30 min, 0.21 g (2.28 mmol, 1 equiv) of methyl chloroformate in 5 mL of dry THF was added via a syringe and the mixture was stirred for 2 h at 0 °C. After reaction, 25 mL of water was added, the organic phase was separated and the aqueous phase was extracted with diethyl ether (3×25 mL). After drying ($MgSO_4$) and evaporation of the solvents, compound **24f** was recrystallized yielding 0.49 g (77%) of pure compound.

3.8.1. Methyl (3-chloro-1-isopropyl-5-phenylpyrrol-2-yl)carboxylate 24f. Recrystallization (pentane), yield 77%, mp 66 °C. ^{1}H NMR ($CDCl_3$): δ 1.47 (6H, d, J=7.0 Hz, $CH(CH_3)_2$), 3.90 (3H, s, OCH_3), 4.71 (1H, sept, J=7.0 Hz, $CH(CH_3)_2$), 6.11 (1H, s, NC=CH), 7.33–7.38 (2H, m, 2×CH_{ar}), 7.40–7.47 (3H, m, 3×CH_{ar}). ^{13}C NMR ($CDCl_3$): δ 2×22.4 (2×CH_3), 51.4 and 51.5 (NCH and OCH_3), 111.5 (NC=*C*H), 119.3 (C_{quat}), 120.9 (C_{quat}), 2×128.5 (2×CH_{ar}), 128.8 (CH_{ar}), 2×129.9 (2×CH_{ar}), 132.7 (C_{quat}), 140.1 (C_{quat}), 161.5 (C=O). IR (KBr) ν_{max} 1697, 1454, 1223 cm^{-1}. MS (70 eV) *m/z* (%) 277/79 (M^+, 100), 246/48 (36), 235/37 (47), 204/6 (96). Calcd for $C_{15}H_{16}NO_2Cl$: C, 64.87; H, 5.81; N, 5.04. Found: C, 64.99; H, 6.03; N, 4.91.

3.9. Synthesis of methyl (4-chloro-2-phenylpyrrol-3-yl)-carboxylate 25

3-Chloro-1-isopropyl-5-phenylpyrrole **16c** (0.10 g, 0.45 mmol) was dissolved in 10 mL of carbon disulfide and cooled to 0 °C. To the cold solution, 45 mg (0.48 mmol, 1.05 equiv) of methyl chloroformate and 64 mg (0.48 mmol, 1.05 equiv) of aluminum(III) chloride were added under N_2-atmosphere and the mixture was allowed to reach room temperature. After stirring for 4 h, the mixture was diluted with 20 mL of water and extracted with dichloromethane (3×25 mL). After drying ($MgSO_4$), the solvents were removed in vacuo, in a fume hood (CS_2!) yielding a mixture of methoxycarbonylated pyrroles **25** and **24f** (ratio 1:4, resp.), which were separated by flash chromatography.

3.9.1. Synthesis of methyl 4-chloro-2-phenylpyrrol-3-yl carboxylate 25. Flash chromatography (hexane/EtOAc 9:1, R_f=0.23), yield 63%, mp 109 °C. ^{1}H NMR ($CDCl_3$): δ 1.30 (6H, d, J=6.7 Hz, $CH(CH_3)_2$), 3.60 (3H, s, OCH_3), 4.10 (1H, sept, J=6.7 Hz, $CH(CH_3)_2$), 6.79 (1H, s, NCH=C), 7.26–7.30 (2H, m, 2×CH_{ar}), 7.42–7.46 (3H, m, 3×CH_{ar}). ^{13}C NMR ($CDCl_3$): δ 2×23.7 (2×CH_3), 48.2 (OCH_3), 50.9 (CH), 110.4 (C_{quat}), 113.2 (C_{quat}), 115.3 (N*C*H=C), 2×128.2 (2×CH_{ar}), 128.7 (CH_{ar}), 2×130.5 (2×CH_{ar}), 131.7 (C_{quat}), 138.1 (C_{quat}), 164.1 (C=O). IR (KBr): ν_{max} 1695, 1543, 1478, 1256 cm^{-1}. MS (70 eV) *m/z* (%) 277/79 (M^+, 68), 246/48 (13), 235/37 (45), 203/5 (100), 140 (64). Calcd for $C_{15}H_{16}NO_2Cl$: C, 64.87; H, 5.81; N, 5.04. Found: C, 64.71; H, 5.95; N, 4.88.

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