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TETRAHEDRON

Synthesis of 2-Acyl-3-chloropyrroles : Application to the Synthesis of the Trail Pheromone of the Ant *Atta texana*

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Abstract : Alkyl 3-chloropyrrole-2-carboxylates and 2-alkanoyl-3-chloropyrroles are conveniently prepared from 2-alkyl-1-pyrrolines by tetra- and pentahalogenation with *N*-chlorosuccinimide, subsequent base-induced aromatisation with sodium alkoxides in the corresponding alcohol and final acid hydrolysis of the resulting orthoester or acetal functions into the 3-chloropyrrole. The developed strategy is applied to the synthesis of the trail pheromone of the ant *Atta texana*.

INTRODUCTION

Many natural products such as the bile pigments, porphyrins and related macrocycles contain the pyrrole ring as a characteristic subunit and play an important role in both the animal and plant kingdom.[1a] It is well known that many naturally occuring 3-halopyrroles and synthetic analogues exhibit strong antibacterial, antifungal and herbicidal activity.[2] Methyl 4-methylpyrrole-2-carboxylate is a trail pheromone from the Texan leaf-cutter ants *Atta texana*[3] and *Acromyrmex subterranous*.[4] Recently, a synthetic analogue of this compound, 4-dodecylpyrrole-2-carboxylate has been shown to have a potential application in the treatment of obesity and diabetes.[5]

Of the many pyrrole syntheses reported to date,[1b] also cyclic imines have been used for the synthesis of pyrroles.[6-17] Among the reported procedures are the oxidative aromatization of 2-substituted-1-pyrrolines with DDQ[6-8] or with palladium on carbon,[9,10] and a halogenation-dehydrohalogenation process, applied for the synthesis of 3-halopyrroles,[2,11,12] pyrroles[16,17] and indoles.[13] In addition, convenient access to 3-substituted pyrroles has been a long standing problem because kinetic electrophilic substitution of pyrroles predominantly takes place at the α-position(s).[1b]

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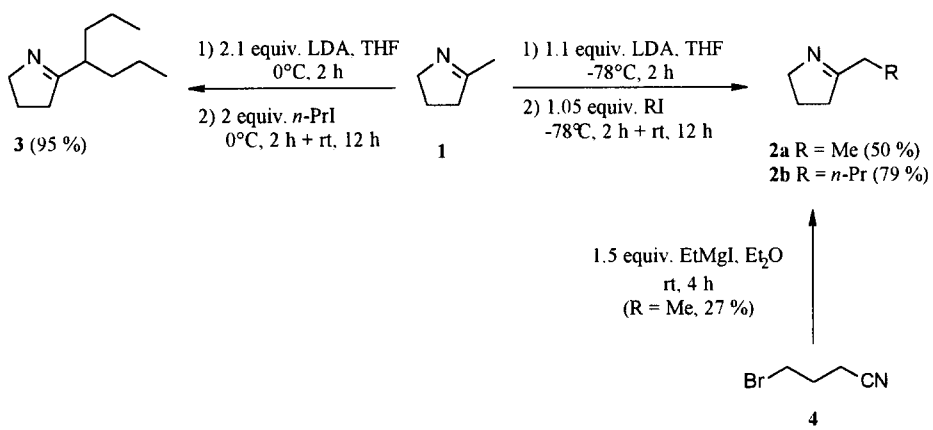
Recently, we have developed a general and practical method for the preparation of 3-halo-2-aryl-pyrroles, which belong to an important class of potential agrochemicals.[2] In the present report an efficient synthesis of 2-alkanoyl- and 2-alkoxycarbonyl-3-chloropyrroles will be disclosed.

RESULTS AND DISCUSSION

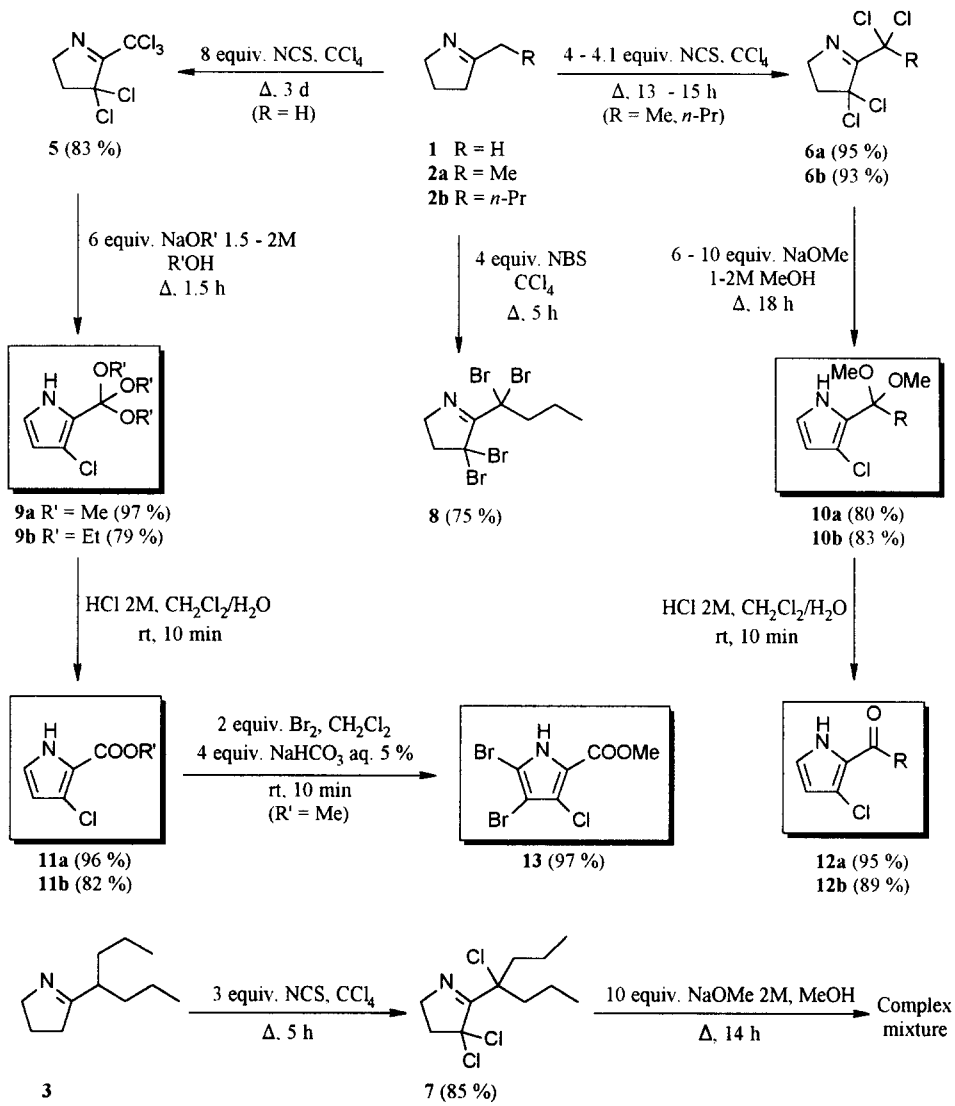
2-Ethyl-1-pyrroline **2a** and 2-butyl-1-pyrroline **2b** were prepared by α-lithiation of 2-methyl-1-pyrroline **1** with lithium diisopropylamide (LDA) and subsequent alkylation with iodomethane and 1-iodopropane at -78°C.[20] In the latter case, when the lithiation was performed with two equivalents of lithium diisopropylamide at 0°C and subsequent alkylation with two equivalents of 1-iodopropane the α,α-dialkylated product **3** was formed in excellent yield (Scheme 1). An analogous observation has been made in the literature when 2,4,4-trimethyl-1-pyrroline was alkylated with benzyl bromide.[18a] 2-Ethylpyrroline **2a** was alternatively prepared by the addition of ethylmagnesium iodide to γ-bromobutyronitrile **4** according to a literature procedure.[19] The low yields of this product are probably due to the volatility and water solubility of the 1-pyrroline.



Scheme 1

Chlorination of 2-methyl-1-pyrroline **1** with 8 equivalents of *N*-chlorosuccinimide (NCS) in carbon tetrachloride at reflux for three days afforded 2,2-dichloro-1-trichloromethyl-1-pyrroline **5** in 83 % yield. The same reaction of 2-ethyl- and 2-butyl-1-pyrroline **2a** and **2b** with 4 - 4.1 equivalents of NCS in carbon tetrachloride gave rise to $\alpha,\alpha,\alpha',\alpha'$-tetrachlorinated 1-pyrrolines **6** in very good yields (Scheme 2). Trihalogenation of **3** to give 3,3-dichloro-2-(1-chloro-1-propylbutyl)-1-pyrroline **7** could be executed without any problem with three equivalents of NCS. Several attempts were made to perform the halogenation in a regiospecific way. On treatment of 1-pyrroline **1** with 3 - 6 equivalents of NCS in CCl_4, the major compound formed was always

2-trichloromethyl-1-pyrroline (60 - 80 %) **22**, along with variable amounts of the tetrachloro derivative (15 - 40 %) **23**, showing that the exocyclic position was chlorinated first (Scheme 4). In a similar way, the reaction of 2-ethyl-1-pyrroline **2a** with 1.9 - 6.75 equivalents of NCS yielded complex mixtures of di-, tri- and tetrachlorinated 1-pyrrolines.

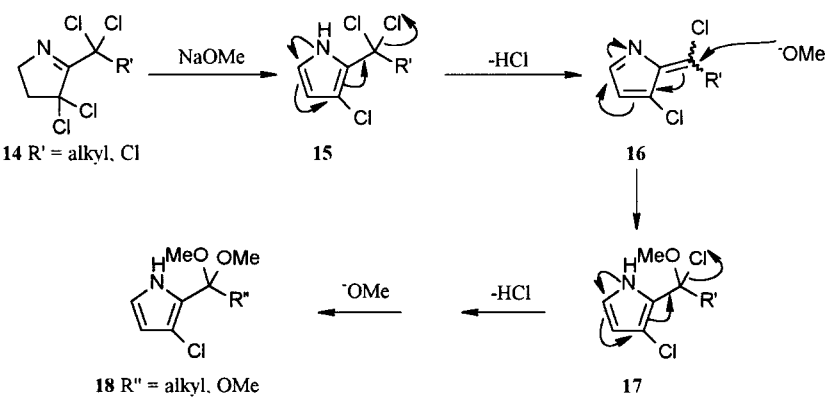


Scheme 2

The same difficulties were encountered in the literature with the chlorination of some steroidal 2-methylpyrrolines with *tert*-butyl hypochlorite.[20] In case of 2-butyl-1-pyrroline **2b**, the reaction with two equivalents of NCS in CCl_4 gave mainly 2-(1,1-dichlorobutyl)-1-pyrroline **19** (84 %) and some 3-chloro-2-(1,1-dichlorobutyl)-1-pyrroline **20** (11 %) (Scheme 4). Unfortunately, these compounds could not be separated, neither by flash chromatography, nor by vacuum destillation or preparative gas chromatography. Bromination of pyrrolines **1**, **2** with 1 - 5 equivalents of *N*-bromosuccinimide (NBS) in CCl_4 at reflux resulted in very complex and unseparable reaction mixtures which were not further analyzed. However, when 2-butyl-1-pyrroline **2b** was treated with 4 equiv. of NBS in CCl_4 at reflux, the tetrabromo pyrroline **8** was formed, which disproportionated instantaneously upon complete evaporation of the solvent, giving rise to a mixture of tribromo and dibromo-1-pyrrolines, which were inseparable by flash chromatography.

Pentachloro pyrroline **5** was conveniently converted into 3-chloro-2-(trialkoxymethyl)pyrroles **9** (79 - 97 % yield) by reaction with an excess of sodium methoxide in methanol or sodium ethoxide in ethanol under reflux for 90 minutes and subsequent non-aqueous workup. In a similar way, sodium methoxide treatment of 3,3-dichloro-2-(1,1-dichloroalkyl)-1-pyrrolines **6** resulted in 3-chloro-2-(1,1-dimethoxyalkyl)pyrroles **10** in 80 - 83 % yield (Scheme 2).

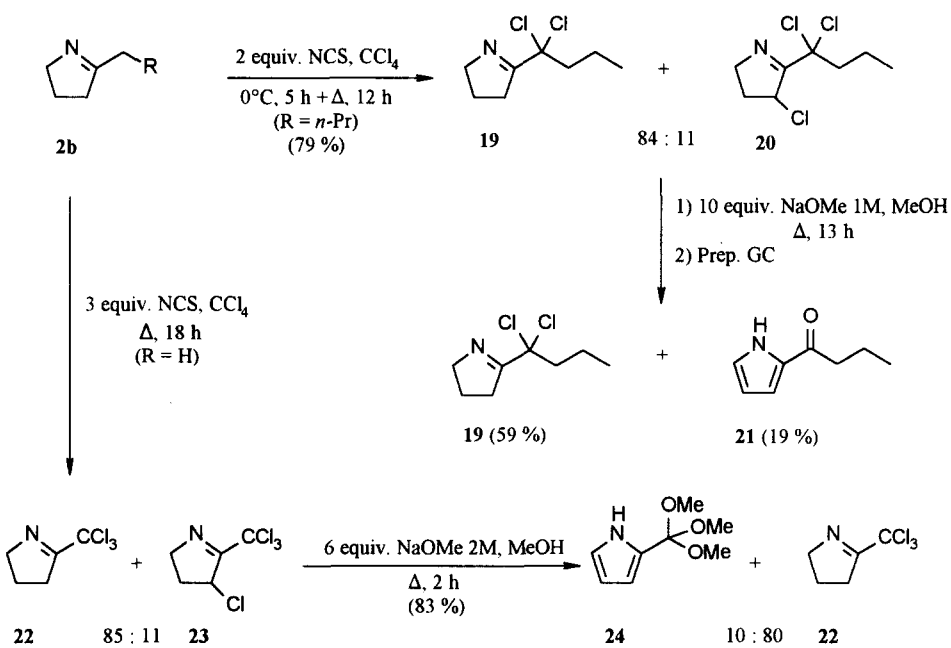
Acid treatment of pyrroles **9** and **10** led to 2-alkoxycarbonyl-3-chloropyrroles **11** (82 - 96 % yield) and 2-alkanoyl-3-chloropyrroles **12** (89 - 95 % yield). All 3-halogenated pyrroles **11** and **12** were purified by flash chromatography on silica gel except compound **11a** which was recrystallized from chloroform (-18°C). When the base-induced aromatization of 3,3-dichloro-2-(1-chloro-1-propylbutyl)-1-pyrroline 7 was performed with an excess sodium methoxide in methanol (10 equiv.; 2M) at reflux, only inseparable mixtures of pyrroles were obtained (not further investigated). Because of the extraordinary physiological properties of polyhalogenated pyrroles,[2a] 3-chloro-2-(methoxycarbonyl)pyrrole **11a** was treated with 2 equivalents of bromine in dichloromethane under alkaline conditions, yielding 4,5-dibromo-3-chloro-2-(methoxycarbonyl)pyrrole **13** as crystalline needles (97 %).



Scheme 3

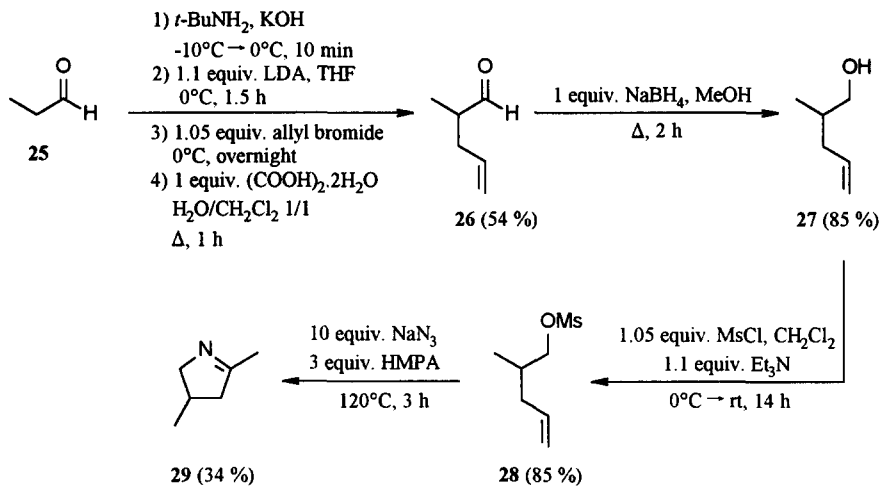
The mechanism of the base-induced dehydrochlorination of tetrachloropyrrolines **6** and pentachloropyrrolines **5** to form pyrroles **9** and **10**, respectively, is interpreted as starting with the aromatization of the pyrroline **14**, followed by expulsion of chloride, resulting in a 1-azafulvene **16** which is subsequently attacked by methoxide (Scheme 3). Repetition of the last two steps leads finally to the 2-(1,1-dialkoxyalkyl)- and 2-(trialkoxymethyl)pyrroles **18**. This sequence is comparable with a mechanism which has been postulated for the reduction of 2-alkanoylpyrroles to 2-alkylpyrroles with sodium borohydride.[21]

Some indirect proof for the above mechanism is delivered by the reaction of a mixture containing 84 % 2-(1,1-dichlorobutyl)-1-pyrroline **19** and 11 % of 3-chloro-2-(1,1-dichlorobutyl)-1-pyrroline **20** (originating from the chlorination of 1-pyrroline **2b**), with an excess of sodium methoxide in methanol under reflux. After preparative gas chromatography, unreacted **19** was isolated next to 2-butanoylpyrrole **21** (Scheme 4). This result is indicative for the slow methanolysis of the geminal dichloride, and of the faster methanolysis of the dichloride when the pyrrole moiety is present. A similar result was obtained by treatment of a mixture of 85 % trichloromethyl-1-pyrroline **22** and 10 % 3-chloro-2-trichloromethyl-1-pyrroline **23** with 6 equivalents of sodium methoxide (2M) in methanol under reflux (2 h). In addition to starting material **22** (80 %), 2-(trimethoxymethyl)pyrrole **24** (10 %) could also be distinguished.



Scheme 4

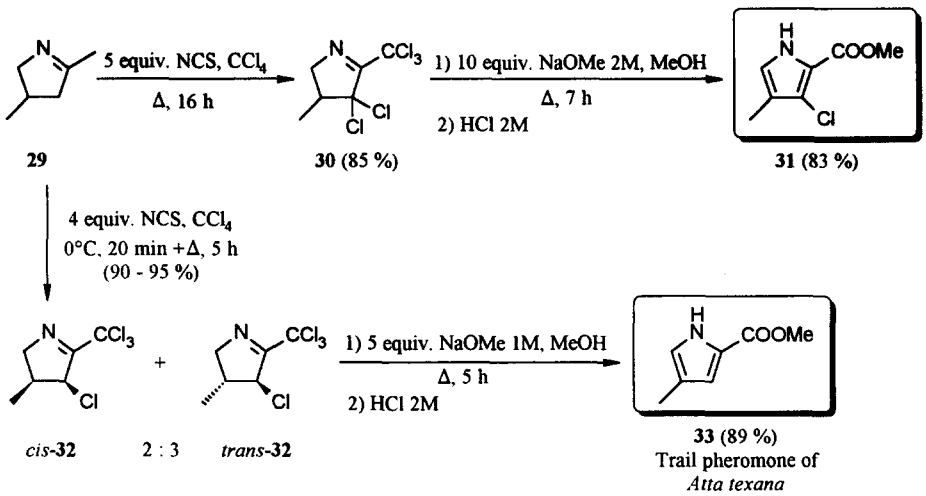
With a reliable route to 2-acylpyrroles secured, this methodology was applied to the synthesis of the trail pheromone of the ant *Atta texana*.[22-29] Therefore, it was necessary to synthesize the previously unreported 2,4-dimethyl-1-pyrroline **29**. 2-Methylpent-4-enal **26** was made accessible from propanal **25** in a three-step procedure, involving (1) imination with *t*-butylamine, (2) α-deprotonation with LDA and α-alkylation with allylbromide and (3) acid hydrolysis of the α-allylaldimine (Scheme 5).[30] Reduction of the aldehyde **26** with two equivalents of sodium borohydride in methanol at reflux and activation of the alcohol moiety of **27** as a mesylate function gave rise to the required precursor **28** for the synthesis of 2,4-dimethyl-1-pyrroline **29**. By heating the mesyloxyalkene **28** with 10 equivalents of sodium azide in an excess of HMPA or acetone during



Scheme 5

20 - 24 h only starting material could be isolated. However, when three equivalents of HMPA were used as solvent, heating at 120°C for 24 h afforded 2,4-dimethyl-1-pyrroline **29** in 34 % yield (Scheme 5). The low yield of 1-pyrroline **29** is certainly due to the very high volatility and solubility in water of this heterocyclic compound.

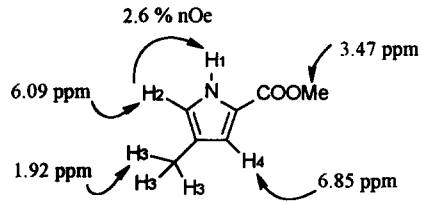
Intramolecular cycloadditions of an azide with an alkene are commonly used for the synthesis of azaheterocycles.[31] The reaction mechanism proceeds *via* an intermediate triazoline, which undergoes ring opening with expulsion of nitrogen. Chlorination of 2,4-dimethyl-1-pyrroline **29** with five equivalents of NCS in CCl_4, followed by base-induced dehydrochlorination of the pentachloropyrroline **30** using sodium methoxide in methanol



Scheme 6

(10 equivalents; 2M) and final acid workup yielded 3-chloro-2-methoxycarbonyl-4-methylpyrrole **31** in 74 % overall yield (Scheme 6). The selective tetrachlorination of 1-pyrroline **29** was executed with 4 equivalents of NCS in CCl_4 at 0°C and subsequently at reflux for 5 h. The resulting mixture consisted mainly (90 - 95 %) of *cis*- and *trans*-3-chloro-4-methyl-2-trichloromethyl-1-pyrroline **32** (*cis*/*trans* : 2/3). In most experiments about 5 - 10 % of the pentachloro derivative **30** also was present. Because it was not possible to separate the tetrachloro- and the pentachloro compounds by flash chromatography, the crude mixture was used as such in the next aromatization step towards the ant trail pheromone. The final reaction of the mixture of *cis*- and *trans*-isomers **32** with sodium methoxide in methanol under reflux furnished after acid workup, the natural product **33** in 89 % yield (Scheme 6). Methyl 4-methylpyrrole-2-carboxylate **33** was purified both by flash chromatography on silica gel and by recrystallization from *n*-hexane.

Some literature data describe the aromatic protons on the 3- and 5-position respectively as doublets at 6.73 and 6.70 ppm, each of them with a coupling constant of 1 Hz ($CDCl_3$, 300 MHz).[28] Another reference assigns the protons on the 3- and 5 positions to the two singlets at 6.72 and 6.78 ppm respectively ($CDCl_3$, 90 MHz).[26] Finally an article from 1989 mentions two doublets at 6.72 and 6.73 ppm corresponding with 3-H and 5-H ($CDCl_3$, 200 MHz).[25] Because of these remarkable differences in the literature a total ^1H NMR analysis of compound **33** was performed by means of spin-spin decoupling, COSY and difNOE-experiments. The latter technique showed that the 5-H proton resonates at a lower field than the 3-H proton, which is in clear contradiction with some literature data.[25,26] The observed coupling constants are summarized in Figure 1 and in the experimental section.



(C_6D_6, 270 MHz)

$^3J_{H(1),(2)} = 2.64$ Hz
$^4J_{H(5),(4)} = 1.65$ Hz
$^4J_{H(2),(3)} = 0.99$ Hz
$^4J_{H(1),(4)} = 2.31$ Hz
$^4J_{H(3),(4)} = 0.66$ Hz

Figure 1

EXPERIMENTAL PART

^1H NMR spectra were recorded at 270 MHz (JEOL JNM-EX 270) with $CDCl_3$ or C_6D_6 as solvent. ^{13}C NMR spectra were recorded at 67.8 MHz (JEOL JNM-EX 270) with $CDCl_3$ or C_6D_6 as solvent. Mass spectra were obtained on a mass spectrometer (VARIAN MAT 112, 70 eV) using GC-MS coupling, unless otherwise stated (RSL 200, 20 m glass capillary column, i.d. 0.53 mm, He carrier gas). Melting points are uncorrected (Büchi 535 melting point apparatus). IR spectra were measured with a Perkin Elmer 1310 spectrophotometer.

Tetrachloromethane and dichloromethane were dried over calciumhydride, diethylether was distilled from sodium wire, while tetrahydrofuran was distilled from sodium/benzophenone ketyl. Other solvents were used as received from the supplier.

General Procedure for the Alkylation of 2-Methyl-1-pyrroline 1

To a stirred and cooled (0°C) solution of diisopropylamine (0.12 mol) in dry THF (15% w/v) was added *n*-butyllithium (44 mL 2.5 M in hexane; 0.11 mol) under a nitrogen atmosphere. After 5 minutes the solution was cooled to -78°C and a solution of 2-methyl-1-pyrroline **1** (0.1 mol) in 30 mL of THF was slowly added *via* a syringe. The reaction mixture was stirred at -78°C for 1 h after which a solution of the alkyl iodide (0.105 mol) in 30 mL of THF was added *via* a syringe. Stirring was continued for 2 h at -78°C and, after warming up to room temperature, it was further stirred for 12 h. The solution was poured into a 1M aqueous NaOH solution (150 mL) and extracted with ether (2×150 mL, 1×50 mL). After drying of the combined organic extracts (K_2CO_3) the solvent was distilled off in a distillation apparatus in the case of 2-ethyl-1-pyrroline **2a** and continued further distillation of the residu yielded 4.82 g (50 %) of 2-ethyl-1-pyrroline **2a** (bp. 130 - 132°C; purity 96 %; GC). Lit.[32] bp. 135 - 140°C. In the case of 2-butyl-1-pyrroline **2b**, the organic layers, after drying

(K_2CO_3) were evaporated after which the crude product was distilled. Yield 9.84 g (79 %). Bp. 65 - 70°C/19 mm Hg. Flash chromatography (silica gel), eluent EtOAc/hexane 4/6, R_f =0.08. Lit.[33] bp. 84-86°C/27 mm Hg. For the dialkylation of 2-methyl-1-pyrroline **1** (0.05 mol), the deprotonation was performed with 2.2 equiv. of LDA (prepared from 0.11 mol of diisopropylamine and 0.105 mol of *n*-butyllithium in THF) at 0°C for 2 h. A solution of 0.1 mol of 1-iodopropane in 30 mL of THF was added *via* a syringe at 0°C. Stirring was continued for 2 h at 0°C after which the mixture was warmed up to room temperature and stirred for another 12 h. Workup was performed as described above for compound **2b**. Compound **3** was obtained as a colourless liquid in 95 % yield (crude mixture). Flash chromatography (silica gel), eluent EtOAc/hexane 4/6, R_f =0.17 (yield 87 %).

2-Ethyl-1-pyrroline **2a**

^{1}H NMR ($CDCl_3$) δ 1.16 (3H, t, J=7.4 Hz, CH_3); 1.80-1.92 (2H, m, $C\underline{H}_2CH_2N$); 2.35 (2H, q, J=7.4 Hz, $CH_3C\underline{H}_2$); 2.47 (2H, t, J=8 Hz, CH_2C=N); 3.77-3.83 (2H, m, CH_2N). ^{13}C NMR ($CDCl_3$) δ 10.69 (CH_3); 22.64 ($NCH_2\underline{C}H_2$); 26.92 and 37.00 (2 × CH_2C=N); 60.83 (CH_2N); 179.31 (C=N). IR (NaCl) : 1643 cm^{-1} (C=N). MS m/z (%) : 97(52, M^+); 96(48); 82(2); 70(9); 69(100); 68(14); 67(4); 56(36); 54(23); 42(32); 41(44).

2-Butyl-1-pyrroline **2b**

^{1}H NMR ($CDCl_3$) δ 0.92 (3H, t, J=7.26 Hz, CH_3); 1.35 (2H, sextet, J=7.3 Hz, $CH_3C\underline{H}_2$); 1.58 (2H, quintet, J=7.6 Hz, $CH_3CH_2C\underline{H}_2$); 1.86 (2H, quintet, J=7.8 Hz, $NCH_2C\underline{H}_2$); 2.34 (2H, t, J=7.8Hz, CH_2C=N); 2.46 (2H, t, J=8.1 Hz, CH_2C=N); 3.80 (2H, t×t, J_1=7.26 Hz, J_2=1.65 Hz, NCH_2). ^{13}C NMR ($CDCl_3$) δ 13.89 (CH_3); 22.57 ($NCH_2\underline{C}H_2$); 22.64 ($CH_3\underline{C}H_2$); 28.59 ($CH_3CH_2\underline{C}H_2$); 33.51 and 37.14 (2 × $\underline{C}H_2C$=N); 60.70 (NCH_2); 178.63 (C=N). IR (NaCl) : 1662 cm^{-1} (C=N). MS m/z (%) : 125 (1, M^+); 124(3); 110(5); 96(23); 84(11); 83(100); 82(20); 69(5); 68(5); 67(3); 59(2); 57(6); 56(3); 55(19); 54(6); 42(14); 41(20); 40(11).

2-(1-Propylbutyl)-1-pyrroline **3**

^{1}H NMR ($CDCl_3$) δ 0.89 (6H, t, J=7.26 Hz, 2 × CH_3); 1.15-1.35 (4H, m, 2 × $C\underline{H}_2CH_3$); 1.37-1.50 (4H, m, 2 × $C\underline{H}_2CH_2CH_3$); 1.76-1.89 (2H, m, $NCH_2C\underline{H}_2$); 2.39 (2H, t, J=8 Hz, CH_2C=N); 2.51 (1H, quintet, J=7.26 Hz, CH); 3.78 (2H, t, J=7.26 Hz, CH_2N). ^{13}C NMR ($CDCl_3$) δ 14.25 (2 × CH_3); 20.74 (2 × $\underline{C}H_2CH_3$); 22.52 ($NCH_2\underline{C}H_2$); 34.03 ($\underline{C}H_2C$=N); 35.44 (2 × $\underline{C}H_2CH$); 43.56 (CH); 60.36 (CH_2N); 181.33 (C=N). IR (NaCl) : 1638 cm^{-1} (C=N). MS m/z (%) : 166 (1, M^+-1); 138(7); 125(17); 110(3); 96(100); 95(2); 94(3); 83(7); 82(3); 81(2); 69(3); 68(4); 67(4); 57(4); 56(2); 55(5); 54(3); 53(2); 43(4); 42(5); 41(17). Anal. Calcd. for $C_{11}H_{21}N$: C 78.97 %; H 12.65 %; N 8.37 %. Found : C 78.90 %; H 12.75 %; N 8.41 %.

General Procedure for the Chlorination of 1-Pyrrolines 1, 2, 3 and 29

Unless otherwise stated, halogenation experiments were performed on a 2 - 5 mmole scale. To a stirred and cooled (0°C) solution of 2-alkyl-1-pyrroline in tetrachloromethane (5 %, w/v) was added portionwise *N*-chlorosuccinimide. The resulting suspension was either first stirred for an additional period at room temperature and subsequently heated under reflux, or immediately refluxed during 5 h - 3 days. Details of the chlorination conditions are given below, at the description of each reaction product. After this period, stirring was stopped and the mixture was cooled to 0°C. After succinimide was filtered off and washed twice with cold (0°C) CCl_4. Evaporation *in vacuo* afforded the crude chlorinated imines which were pure enough to use as such in the next steps.

3,3-Dichloro-2-trichloromethyl-1-pyrroline **5**

The title compound was prepared by reaction of 0.1 mol 2-methyl-1-pyrroline **1** with 8 equivalents of NCS (reflux for 3 days). Yield 98 % (crude product). After recrystallisation from pentane, dark purple crystals were obtained in 83 % yield. Mp. 48.5-50°C.

^{1}H NMR ($CDCl_3$) δ 3.07 (2H, t, J=6.94 Hz, CH_2CCl_2); 4.15 (2H, t, J=6.94 Hz, NCH_2). ^{13}C NMR ($CDCl_3$) δ 51.23 ($\underline{C}H_2CCl_2$); 55.94 (NCH_2); 84.01 (CCl_2); 89.70 (CCl_3); 168.51 (C=N). IR (NaCl) : 1730 cm^{-1} (C=N). MS m/z (%) : 253/5/7/9/61/63 (6, M^+); 218/20/2/4/6(6); 182/4/6/8/90(2); 157/9/61/3(14); 150(2); 148(4); 146(4); 144(3); 136(2); 122/4/6(11); 110/2/4(100); 96/8/100(6); 87(6); 86(7); 85(9); 84(4); 75/7(55); 66(4); 61(7); 52(5); 51(8); 50(6); 49(13). Anal. Calcd. for $C_5H_4NCl_5$: C 23.52 %; H 1.58 %; N 5.49 %. Found : C 23.36 %; H 1.45 %; N 5.72 %.

3,3-Dichloro-2-(1,1-dichloroethyl)-1-pyrroline **6a**

The title compound, a yellow oil, was synthesized from **2a** by reaction with 4 equivalents of NCS (reflux for 13 h). Yield : 95 % (crude product).

^{1}H NMR ($CDCl_3$) δ 2.56 (3H, s, CH_3); 2.96 (2H, t, J=5.8 Hz, CH_2CCl_2); 4.05 (2H, t, J=5.8 Hz, CH_2N). ^{13}C NMR ($CDCl_3$) δ 36.96 (CH_3); 50.48 ($\underline{C}H_2CCl_2$); 55.90 (CH_2N); 80.12 (CCl_2); 85.12 (CCl_2); 170.40 (C=N). IR (NaCl) : 1720 cm^{-1} (C=N). MS m/z (%) : 233/5/7/9 (7, M^+); 198/200/2/4 (22, M^+-Cl); 137/9/41(45); 110/12/14(100); 102(22); 99(14); 97(15); 77(29); 75(90); 73(9); 63(12); 61(9); 52(5); 51(10); 49(17); 41(17). HRMS (EI) : M^+, found 232.9340. $C_6H_7Cl_4N$ requires 232.9333.

3,3-Dichloro-2-(1,1-dichlorobutyl)-1-pyrroline **6b**

The title compound, a yellow oil, was prepared from **2b** by reaction with 4.1 equivalents of NCS (reflux for 15 h). Yield : 93 % (crude product).

^{1}H NMR ($CDCl_3$) δ 1.01 (3H, t, J=7.4 Hz, CH_3); 1.61-1.76 (2H, m, $C\underline{H}_2CH_3$); 2.60-2.67 (2H, m, $C\underline{H}_2CH_2CH_3$); 2.93 (2H, t, J=5.8 Hz, $C\underline{H}_2CH_2N$); 4.02 (2H, t, J=5.8 Hz, CH_2N). ^{13}C NMR ($CDCl_3$) δ 13.41 (CH_3); 18.56 ($CH_3\underline{C}H_2$); 49.16 ($CH_3CH_2\underline{C}H_2$); 50.46 ($\underline{C}H_2CH_2N$); 55.99 (CH_2N); 84.22 (CCl_2); 85.55 (CCl_2); 169.97 (C=N). IR (NaCl) : 1740 cm^{-1} (C=N). MS m/z (%) : no M^+; 219/21/23/25/27 (62; M^+-Pr); 190/2/4(9); 184/6/8(12); 164(10); 154(10); 138(12); 132(10); 130(31); 127(8); 125(8); 118(11); 114(12); 112(33); 110(48); 101(13); 91(14); 89(20); 77(35); 75(100); 69(15); 66(11); 65(15); 63(19); 53(11); 51(18); 49(18); 42(13); 41(27).

3,3-Dichloro-2-(1-chloro-1-propylbutyl)-1-pyrroline 7

By reaction of 3 equivalents of NCS. with the 1-pyrroline **3** for 5 h under reflux the title compound 7 was obtained, as a yellow oil, in 85 % yield (crude mixture).

^{1}H NMR ($CDCl_3$) δ 0.94 (6H, t, J=7.26 Hz, 2×CH_3); 1.35-1.55 (4H, m, 2 × $CH_3C\underline{H}_2$); 2.07-2.35 (4H, m, 2 × $CH_3CH_2C\underline{H}_2$); 2.87 (2H, t, J=5.94 Hz, CH_2CCl_2); 3.95 (2H, t, J=5.8 Hz, CH_2N). ^{13}C NMR ($CDCl_3$) δ 14.00 (2 × CH_3); 17.95 (2 × $CH_3\underline{C}H_2$); 43.86 (2 × $\underline{C}H_2CH_2CH_3$); 50.24 ($\underline{C}H_2CCl_2$); 55.88 (CH_2N); 73.57 (CCl); 87.13 (CCl_2); 172.15 (C=N). IR (NaCl) : 1710 cm^{-1} (C=N). MS m/z (%) : No M^+; 334/6 (32, M^+-Cl); 198/200/2(100); 197(24); 162(25); 154(28); 146(29); 144(47); 138(38); 114(20); 112(24); 110(24); 97(31); 77(19); 75(22); 55(38); 41(33).

3,3-Dibromo-2-(1,1-dibromobutyl)-1-pyrroline **8**

The title compound was prepared by reaction of 5 mmole of compound **2b** with 4 equivalents of *N*-bromosuccinimide (reflux for 5 h). A dark brown oil was obtained in 75 % yield. Due to the extreme lability of this product no ^{13}C spectra and mass spectra were recorded. After 10 minutes already considerable degradation could be observed in ^{1}H NMR. Flash chromatography (eluent 1/3 : EtOAc/Hexane) yielded still complex mixtures of tri- and -dibrominated pyrrolines.

^{1}H NMR ($CDCl_3$) δ : 1.06 (3H, t, J=7.6 Hz, CH_3); 1.7-1.8 (2H, m, $CH_3C\underline{H}_2$); 1.9-2.1 (2H, m, $C\underline{H}_2CH_2CH_3$); 3.05-3.15 (2H, m, $C\underline{H}_2CH_2N$); 3.9-4.0 (2H, m, $C\underline{H}_2N$). IR (NaCl) : 1712 cm^{-1} (C=N).

2-(1,1-Dichlorobutyl)-1-pyrroline **19**

By reaction of 2-butyl-1-pyrroline **2b** with 2 equiv. of NCS (reflux for 14 h) the title compound was obtained as a dark yellow oil in 84 % yield (crude mixture). Flash chromatography (silica gel) (eluent EtOAc/hexane 4/6, R_f =0.34) did not remove the trichlorinated side product **18**, present in 11 %.

^{1}H NMR ($CDCl_3$) δ 1.01 (3H, t, J=7.4 Hz, CH_3); 1.6-1.8 (2H, m, $CH_3C\underline{H}_2$); 1.9-2.1 (2H, m, $NCH_2C\underline{H}_2$); 2.4-2.5 (2H, m, CH_2CCl_2); 2.94 (2H, t×t, J_1=1.98 Hz, J_2=8.2 Hz, CH_2C=N); 3.98 (2H, t×t, J_1=1.98 Hz, J_2=7.26 Hz, CH_2N). ^{13}C NMR ($CDCl_3$) δ 13.57 (CH_3); 18.62 ($CH_3\underline{C}H_2$); 23.11 ($\underline{C}H_2CH_2N$); 33.71 ($\underline{C}H_2C$=N); 47.21

($\underline{C}H_2CCl_2$); 61.15 (CH_2N); 88.59 (CCl_2); 175.45 (C=N). IR (NaCl) : 1640-1730 cm^{-1} (C=N). MS m/z (%) : No M^+; 158/60 (45, M^+-Cl); 151/3/5(100); 150(21); 143(5); 130(8); 122(11); 117(6); 97(11); 96(16); 94(13); 80(7); 77(5); 68(5); 67(7); 66(6); 65(8); 63(5); 53(9); 51(8); 42(18); 41(12).

2-Trichloromethyl-1-pyrroline **22**

The title compound was obtained as a yellow oil by reaction of 2-methyl-1-pyrroline **1** with 3 equivalents of NCS (reflux for 18 h). Pyrroline **22** was present in 85 %, next to 10 % of the tetrachlorinated product **23**.

^1H NMR ($CDCl_3$) δ 2.19 (2H, quintet, J=8 Hz, $NCH_2C\underline{H}_2$); 3.03 (2H, t×t, J_1=8.25 Hz, J_2=2.0 Hz, CH_2C=N); 4.09 (2H, t×t, J_1=7.4 Hz, J_2=2.0 Hz, CH_2N). ^{13}C NMR ($CDCl_3$) δ 24.31 ($CH_2\underline{C}H_2CH_2$); 33.10 ($\underline{C}H_2C$=N); 61.02 ($\underline{C}H_2N$); 93.53 (CCl_3); 172.92 (C=N). IR (NaCl) : 1725 cm^{-1} (C=N). MS m/z (%) : 185/87/89/91 (M^+, 21); 150/2/4(100); 122/4/6(16); 119(6); 117(7); 116(7); 114(13); 98(9); 96(13); 88(14); 87(15); 86(12); 85(8); 78(8); 75(6); 68(16); 63(14); 61(11); 53(18); 51(22); 49(16); 42(69); 41(35). HRMS (EI): M^+, found 184.9558. $C_5H_6Cl_3N$ requires 184.9566.

3,3-Dichloro-4-methyl-2-trichloromethyl-1-pyrroline **30**

The title compound was prepared from **29** by reaction with 5 equiv. of NCS (reflux for 16 h). Yield 85 %. Flash chromatography on silica gel (eluent EtOAc/hexane 40/60, R_f =0.73) furnished the pure pyrroline **30** in 42 % yield, as a nearly colourless oil. Every fraction was analyzed by capillary GC because the product was invisible on TLC either under UV or by I_2-colouring or by H_2SO_4 treatment.

^1H NMR ($CDCl_3$) δ 1.33 (3H, d, J=6.60 Hz, CH_3); 2.9-3.0 (1H, m, $C\underline{H}CH_3$); 3.62 and 4.17 (2×1H, d×d×d, J_{gem}=16.6 Hz, J_1=6.4 Hz, J_2=7.8 Hz, CH_2N). ^{13}C NMR ($CDCl_3$) δ 11.52 (CH_3); 54.09 ($\underline{C}HCH_3$); 61.94 (CH_2N); 88.52 (CCl_2); 90.15 (CCl_3); 169.20 (C=N). IR (NaCl) : 1715 cm^{-1} (C=N). MS m/z (%) : 267/9/71 (3, M^+); 232/4/6/8 (2, M^+-Cl); 198/200/2(2); 162(5); 159(11); 157(12); 128(10); 126(61); 125(6); 124(100); 122(13); 111(9); 109(12); 99(5); 98(7); 96(11); 91(31); 89(95); 86(6); 75(5); 73(6); 63(7); 61(6); 53(11); 51(9); 49(14). Anal. Calcd. for $C_6H_6Cl_5N$: C 26.75 %; H 2.25 %; N 5.20 %. Found : C 25.62 %; H 2.36 %; N 5.42 %.

3-Chloro-4-methyl-2-trichloromethyl-1-pyrroline **32**

The title compound was obtained as a yellow oil by reaction of **29** with 4 equivalents of NCS (room temperature for 20 min, reflux for 5 h). Usually about 4 - 10 % of compound **30** was formed too. *Cis/trans* : 2/3 (^1H NMR).

Cis-**32** : ^1H NMR ($CDCl_3$) δ : 1.27 (3H, d, J=6.93 Hz, $C\underline{H}_3CH$); 2.6-2.8 (1H, m, $CH_3C\underline{H}$); 4.23 (1H, d×d, J_{gem}=16.7 Hz, J=6.27 Hz, NHC($\underline{H}$)); 4.37 (1H, d×d×d, J_{gem}=16.7 Hz, J_1=5.93 Hz, J_2≈1 Hz, N$\underline{H}$C(H)); 5.05

(1H, d×d, J_1=6.1 Hz, J_2≈1 Hz, CHCl). ^{13}C NMR ($CDCl_3$) δ 12.24 ($\underline{C}H_3CH$); 41.90 ($CH_3\underline{C}H$); 62.12 (CHCl); 64.71 (CH_2N); 91.70 (CCl_3); 172.76 (C=N).

Trans-**32** : ^{1}H NMR ($CDCl_3$) δ 1.11 (3H, d, J=7.59 Hz, $C\underline{H}_3CH$); 2.6-2.8 (1H, m, $CH_3C\underline{H}$); 3.80 (1H, d, J=1.98 Hz, NHC($\underline{H}$)); 3.86 (1H, d, J=1.65 Hz, N$\underline{H}$C(H)); 4.71 (1H, broad s, CHCl). ^{13}C NMR ($CDCl_3$) δ 17.54 ($\underline{C}H_3CH$); 45.88 ($CH_3\underline{C}H$); 63.05 (CHCl); 65.52 (CH_2N); 91.70 (CCl_3); 170.19 (C=N). IR (NaCl) : (*cis* + *trans*) 1715 cm^{-1} (C=N). MS (*cis* or *trans*): m/z (%) : No M^+; 157(45); 124/6 (100); 125(21); 122(33); 109(32); 91(64); 89(90); 86(28); 84(51); 49(67); 44(84); 40(85). MS (*trans* or *cis*): m/z (%) : No M^+; 235(24); 102(44); 200(29); 198(53); 86(42); 55(60); 54(22); 51(40); 49(35); 44(53); 40(100). Mp. (*cis* + *trans*) 118-124°C.

General Procedure for the Synthesis of 3-Chloro-2-(trialkoxymethyl)pyrroles 9, 3-Chloro-2-(1,1-dimethoxyalkyl)pyrroles 10, 2-(Alkoxycarbonyl)pyrroles 11, 31, 33 and 2-Alkanoyl-3-chloropyrroles 12.

The halogenated 1-pyrroline **5**, **6**, **19**, **20**, **30** or **32** was added to a 1-2 M solution of sodium methoxide in methanol or a 1.5 M solution of sodium ethoxide in ethanol at room temperature (see details on the reaction conditions below). The resulting mixture was refluxed for 1.5 - 18 h. For the synthesis of compounds **9** and **10**, the reaction mixture was cooled to room temperature after which the solvent was evaporated *in vacuo*. Ether (10 mL/mmol) was added to the residue and the mixture was stirred for an additional 30 minutes. Subsequently, the precipitated sodium chloride and unreacted alkoxides were filtered off, the filtrate was dried (K_2CO_3) and evaporated *in vacuo*, yielding the pyrroles **9** and **10**. Further acid workup with an aqueous hydrochloric acid solution (2M) and extraction with dichloromethane (3 times) gave rise, after drying ($MgSO_4$) and evaporation of the solvent, to the corresponding 2-alkoxycarbonyl-3-chloropyrroles **11** and 2-alkanoyl-3-chloropyrroles **12**. For the synthesis of compounds **31** and **33** the reaction mixture was poured into an aqueous HCl solution (2M) and extracted three times with dichloromethane. The extracts were dried ($MgSO_4$) and evaporation of the solvent afforded the crude pyrroles **31** and **33** in an acceptable yield.

3-Chloro-2-(trimethoxymethyl)pyrrole **9a**

6 Equivalents of sodium methoxide 2M in MeOH were reacted with 10 mmol of the halogenated 1-pyrroline **5** (reflux for 1.5 h). After recrystallisation from dichloromethane (-18°C) light brown crystals of **9a** were obtained (yield : 97 %, mp. 103-105°C).

^{1}H NMR ($CDCl_3$) δ 3.20 (9H, s, $C(OCH_3)_3$; 6.15 (1H, t, J=3.97 Hz, NCH=C$\underline{H}$); 6.67 (1H, t, J=3.97 Hz, NCH); 8.6 (1H, broad s, NH). ^{13}C NMR ($CDCl_3$) δ 49.72 ($C(O\underline{C}H_3)_3$) ; 110.12 (NCH=); 110.87 (CCl); 112.51 (NCH=$\underline{C}$H); 116.76 and 121.34 ($\underline{C}$HCCl and $C(OCH_3)_3$ or *vice versa*). IR (KBr) : 3313 cm^{-1} (NH). MS (direct inlet) m/z (%) : 205/7 (15, M^+); 174/6(100); 159/61(34); 143(6); 138(5); 128/30(54); 116(4);

115(8); 114(9); 105(9); 100/02(11); 94(9); 80(4); 75(7); 73(12); 66(4); 64(8); 59(13); 53(2); 51(2); 49(3); 45(2); 42(3). Anal. Calcd. for $C_8H_{12}ClNO_3$: C 46.73 %; H 5.88 %; N 6.81 %. Found : C 46.61 %; H 6.03 %; N 6.97 %.

3-Chloro-2-(triethoxymethyl)pyrrole **9b**

6 Equivalents of sodium ethoxide 1.5M in ethanol were reacted with 10 mmol of the halogenated 1-pyrroline **5** (reflux for 1.5 h). After recrystallisation from chloroform (-18°C), brown crystals of the pyrrole **9b** were obtained (yield : 79 %, mp. 70.2-71.3°C).

^{1}H NMR ($CDCl_3$) δ 1.21 (9H, t, J=7.26 Hz, ($C\underline{H}_3CH_2O)_3C$); 3.44 (6H, q, J=7.26 Hz, ($CH_3C\underline{H}_2O)_3C$); 6.11 (1H, t, J=2.97 Hz, C<u>H</u>=CHN); 6.67 (1H, t, J=2.97 Hz, CH<u>N</u>); 8.73 (1H, broad s, NH). ^{13}C NMR ($CDCl_3$) δ 14.56 (3 × CH_3); 57.43 (3 × OCH_2); 109.51 (<u>C</u>H=CHN); 109.85 ($C_{quat.}$); 110.96 ($C_{quat.}$); 116.17 (CHN); 122.95 (=CCl). IR (KBr) : 3420 cm^{-1} (NH). MS (direct inlet) m/z (%) : 247 (7, M^+); 202/4 (36, M^+-OEt); 201/3(21); 174/6(30); 175/7(22); 146/8(51); 145/7(30); 128/30(92); 127/9(100); 102(10); 101(21); 100(18); 73(17); 64(11); 45(15). Anal. Calcd. for $C_{11}H_{18}ClNO_3$: C 53.33 %; H 7.32 %; N 5.65 %. Found : C 53.50 %; H 7.47 %; N 5.51 %.

3-Chloro-2-(1,1-dimethoxyethyl)pyrrole **10a**

By reaction of 2.7 mmol of pyrroline **6a** with 6 equivalents of NaOMe 1M in methanol (reflux for 18 h) the the title compound was obtained in 80 % yield as a light brown oil.

^{1}H NMR ($CDCl_3$) δ 1.67 (3H, s, $C\underline{H}_3C(OCH_3)_2$); 3.17 (6H, s, $C(OCH_3)_2$); 6.06 (1H, d, J=2.7 Hz, C<u>H</u>=CHN); 6.54 (1H, d, J=2.97 Hz, CHN); 8.45 (1H, broad s, NH). ^{13}C NMR ($CDCl_3$) δ 22.79 ($\underline{C}H_3C(OMe)_2$); 48.66 ($C(O\underline{C}H_3)_2$); 98.87 ($\underline{C}(OCH_3)_2$); 110.03 (<u>C</u>H=CHN); 115.36 (CHN); 122.86 and 126.92 ($\underline{C}C(OMe)_2$ and =CCl). IR (NaCl) : 3380 cm^{-1} (NH); 2830 cm^{-1} (OCH_3). MS (direct inlet) m/z (%) : 189/91 (20, M^+); 174/6(7); 158/60(100); 157/9(97); 154(7); 143/5(23); 128/30(79); 127/9(83); 126(39); 125(13); 116(10); 114(18); 100(16); 94(11); 93(11); 92(32); 91(23); 90(15); 89(15); 75(16); 74(41); 73(23); 65(19); 64(14); 63(19); 59(59); 57(11); 52(12); 51(17); 45(46); 44(66); 43(60); 42(17); 41(19). HRMS (EI) : M^+, found 189.0551. $C_8H_{12}ClNO_2$ requires 189.0557.

3-Chloro-2-(1,1-dimethoxybutyl)pyrrole **10b**

By reaction of 2.2 mmole of pyrroline **6b** with 10 equivalents of NaOMe 2M in methanol (reflux for 17 h) the the title compound was obtained in 83 % yield as a dark yellow oil.

^{1}H NMR ($CDCl_3$) δ 0.83 (3H, t, J=7.01 Hz, $C\underline{H}_3CH_2$); 0.95-1.13 (2H, m, $CH_3C\underline{H}_2$); 2.0-2.1 (2H, m, $CH_3CH_2C\underline{H}_2$); 3.15 (6H, s, $O(OCH_3)_2$); 6.13 (1H, t, J=2.97 Hz, C<u>H</u>=CHN); 6.61 (1H, t, J=2.97 Hz, CH<u>N</u>); 8.59 (1H, broad s, NH). ^{13}C NMR ($CDCl_3$) δ 13.93 ($\underline{C}H_3CH_2$); 16.91 ($CH_3\underline{C}H_2$); 36.41 ($CH_3CH_2\underline{C}H_2$);

48.30 ($C(O\underline{C}H_3)_2$); 101.31 ($\underline{C}(OCH_3)_2$); 108.05 (C_{quat}); 109.90 ($\underline{C}H$=CHN); 115.61 (CHN); 125.78 (C_{quat}). IR (NaCl) : 3410 cm^{-1} (NH); 2835 cm^{-1} (OCH_3). MS m/z (%) : No M^+; 185/7 (81, M^+-HOMe); 107/2(100); 154(14); 153(11); 150(28); 140(15); 138(14); 135(31); 134(20); 130(13); 128(39); 127(12); 120(31); 118(26); 117(16); 116(15); 100(13); 91(14); 75(11); 73(14); 63(10); 59(10); 55(15); 51(12); 41(13).

2-Butanoylpyrrole **21**

By reaction of 5 mmole of the dichlorinated 1-pyrroline **19** with 10 equivalents of NaOMe 2M (reflux 13 h) a dark brown reaction mixture was obtained, which after preparative gaschromatography (temperature of the column: 120°C) yielded an analytically pure sample (colourless liquid) of compound **21**. The ^{13}C NMR data are in accordance with the literature.[35] For the sake of completeness the other spectral data are listed below.

^1H NMR ($CDCl_3$) δ 0.99 (3H, t, J=7.58 Hz, CH_3); 1.75 (2H, ~ quintet, J=7.3 Hz, $CH_3C\underline{H}_2$); 2.74 (2H, ~ t, J=7.3 Hz, $CH_3CH_2C\underline{H}_2$); 6.27 (1H, m, CH); 6.91 (1H, m, CH); 7.02 (1H, m, CH); 8.4 (1H, broad s, NH). ^{13}C NMR ($CDCl_3$) δ 13.98 (CH_3); 18.69 ($CH_3\underline{C}H_2$); 39.91 ($\underline{C}H_2C$=O); 110.56 (CH); 115.97 (CH); 124.27 (CH); 132.16 ($\underline{C}$-C=O); 191.03 (C=O). IR (NaCl) : 3240 cm^{-1} (NH); 1630 cm^{-1} (C=O). MS m/z (%) : 137 (32, M^+); 122(4); 109(23); 94(100); 93(2); 80(2); 67(7); 66(26); 64(2); 55(5); 50(1); 43(3); 42(2); 41(5).

3-Chloro-2-(methoxycarbonyl)pyrrole **11a**

The title compound was prepared starting from **9a**. Yield 96 % (crude product). Recrystallisation from chloroform (-18°C) yielded pure **11a** as light yellow crystals. Mp. 88.3-90.3°C (yield 81 %).

^1H NMR ($CDCl_3$) δ 3.90 (3H, s, OCH_3); 6.25 (1H, t, J=2.97 Hz, $C\underline{H}$=CHN); 6.87 (1H, t, J=3.1 Hz, CHN); 9.3 (1H, broad s, NH). ^{13}C NMR ($CDCl_3$) δ 51.72 (OCH_3); 111.88 ($\underline{C}H$=CHN); 118.11 and 119.39 (C_{quat}); 122.53 (CHN); 161.18 (C=O). IR (KBr) : 3390 cm^{-1} (NH); 1665 cm^{-1} (C=O). MS (direct inlet) m/z (%) : 159/61 (80, M^+); 128.30(100); 127/9(74); 100/2(31); 99(9); 75(9); 73(26); 66(5); 64(17); 49(8); 47(5). Anal. Calcd. for $C_6H_6ClNO_2$: C 45.16 %; H 3.79 %; N 8.78 %. Found : C 45.01 %; H 3.90 %; N 8.55 %.

3-Chloro-2-(ethoxycarbonyl)pyrrole **11b**

The title compound, a light yellow solid, was prepared starting from **9b**. Yield 82 % (crude product). Flash chromatography on silica gel (eluent EtOAc/hexane 1/9, R_f = 0.1) yielded the analytically pure product in 65 % yield.

^1H NMR ($CDCl_3$) δ 1.38 (3H, t, J=7.26 Hz, CH_3); 4.36 (2H, q, J=7.26 Hz, $OC\underline{H}_2CH_3$); 6.24 (1H, t, J=2.8 Hz, $C\underline{H}$=CHN); 6.85 (1H, t, J=3.1 Hz, CHN); 9.3 (1H, broad s, NH). ^{13}C NMR ($CDCl_3$) δ 14.31 (CH_3); 60.72 (CH_2O); 111.88 ($\underline{C}H$=CHN); 118.40 and 119.10 (2 × C_{quat}); 121.73 (CHN); 160.43 (C=O). IR (NaCl) : 3280 cm^{-1} (NH); 1665 cm^{-1} (C=O). MS m/z (%) : 173/5 (59, M^+); 145/7(30); 128/30(69); 127/9(100);

101/3(23); 100/2(19); 99(11); 75(7); 74(7); 66(6); 64(13); 49(9); 47(5); 45(5); 44(6); 41(4). Anal. Calcd. for $C_7H_8ClNO_2$: C 48.43 %; H 4.65 %; N 8.07 %. Found : C 48.62 %; H 4.75 %; N 8.01 %.

2-Acetyl-3-chloropyrrole **12a**

Yield 95 % (crude product). This compound was also obtained as a light purple oil by preparative GC of the corresponding acetal **10a**. Purification by flash chromatography (silica gel) : eluent EtOAc/hexane 1/9, R_f = 0.11.

^1H NMR ($CDCl_3$) δ 2.59 (3H, s, CH_3); 6.26 (1H, t, J=2.97 Hz, C<u>H</u>=CHN); 6.93 (1H, t, J=3.1 Hz, CHN); 9.4 (1H, broad s, NH). ^{13}C NMR ($CDCl_3$) δ 27.99 (CH_3); 112.16 (<u>C</u>H=CHN); 119.33 (C_{quat}); 123.09 (CHN); 127.90 (C_{quat}); 187.58 (C=O). IR (NaCl) : 3270 cm^{-1} (NH); 1630 cm^{-1} (C=O). MS m/z (%) : 143/5 (64, M^+); 128/30(100); 100/2(43); 89(3); 87(4); 84(5); 76(6); 75(10); 74(11); 73(21); 72(5); 66(7); 65(6); 64(11); 63(5); 53(5); 52(6); 51(13); 50(7); 49(15); 44(8); 43(21); 42(7); 41(6). Anal. Calcd. for C_6H_6ClNO : C 50.20 %; H 4.21 %; N 9.76 %. Found : C 50.36 %; H 4.10 %; N 9.88 %.

2-Butanoyl-3-chloropyrrole **12b**

The title compound was prepared in 89 % yield (crude product) from **10b**. Recrystallisation from EtOAc (-18 °C) gave rise to purple crystals (mp. 70.9-71.5°C).

^1H NMR ($CDCl_3$) δ 1.01 (3H, t, J=7.4 Hz, CH_3); 1.68-1.82 (2H, m, $CH_3C\underline{H}_2$); 2.93 (2H, t, J=7.4 Hz, CH_2CO); 6.25 (1H, t, J=2.64 Hz, C<u>H</u>=CHN); 6.91 (1H, t, J=2.8 Hz, CHN); 9.4 (1H, broad s, NH). ^{13}C NMR ($CDCl_3$) δ 13.96 (CH_3); 17.88 ($CH_3\underline{C}H_2$); 41.83 ($\underline{C}H_2CO$); 112.06 (<u>C</u>H=CHN); 119.05 (C_{quat}); 123.57 (CHN); 127.67 (C_{quat}); 190.98 (C=O). IR (KBr) : 3240 cm^{-1} (NH); 1634 cm^{-1} (C=O); MS (direct inlet) m/z (%) : 171/3 (23, M^+); 156/8(9); 143/5(44); 136(6); 128/30(100); 101/3(13); 100/2(21); 94(5); 75(5); 74(5); 73(11); 55(6); 51(5); 49(5); 43(5); 42(7); 41(8). Anal. Calcd. for $C_8H_{10}ClNO$: C 55.99 %; H 5.87 %; N 8.16 %. Found : C 55.77 %; H 5.92 %; N 8.05 %.

3-Chloro-2-methoxycarbonyl-4-methylpyrrole **31**

Reaction of 1 mmol of **30** with 10 equivalents of NaOMe 2M in methanol (reflux for 7 h) gave rise to the title compound in 83 % yield as a yellow oil (crude product; purity > 90 %, GC).

^1H NMR ($CDCl_3$) δ 2.05 (3H, s, CH_3C=); 3.88 (3H, s, OCH_3); 6.72 (1H, d, J=2.97 Hz, CHN); 9.5 (1H, broad s, NH). ^{13}C NMR ($CDCl_3$) δ 9.56 (<u>C</u>H_3C=); 51.61 (OCH_3); 117.77; 119.28 and 119.91 (3 × C_{quat}); 120.74 (NCH); 161.11 (C=O). IR (NaCl) : 3270 cm^{-1} (NH); 1690 cm^{-1} (C=O); MS m/z (%) : 173/5 (85, M^+); 142/4(71); 141/3(92); 114/6(14); 113/5(19); 112(12); 106(14); 89(8); 87(18); 79(11); 79(100); 76(8); 75(16); 53(11); 52(11); 51(30); 50(11); 49(11); 44(10); 42(7). HRMS (EI): M^+, found 173.0247. $C_7H_8ClNO_2$ requires 173.0244.

4-Methyl-2-(methoxycarbonyl)pyrrole **33**

Reaction of 3 mmol of **32** with 5 equivalents of 1M NaOMe in methanol (reflux for 5 h) yielded 89 % crude product. Purification by flash chromatography (silica gel) eluent EtOAc/hexane 1/9, R_f = 0.12. Mp. 67.1-68.7°C. Recrystallisation was performed in hexane (-18°C) and gave rise to white crystals (mp. 72.1-72.4°C, lit.[25,27] mp. 72-73°C).

^{1}H NMR ($CDCl_3$) δ 2.11 (3H, broad s, CH_3C=); 3.83 (3H, s, OCH_3); 6.72 (2H, 3 x s, C<u>H</u>=C-$COOCH_3$ and NC<u>H</u>); 9.0 (1H, broad s, NH). ^{13}C NMR ($CDCl_3$) δ 11.68 (<u>C</u>H_3C=); 51.37 (OCH_3); 116.08 (<u>C</u>H=C-$COOCH_3$); 120.95 (C_{quat}); 121.44 (NCH); 122.17 (C_{quat}); 161.74 (C=O). ^{1}H NMR (C_6D_6) δ 1.92 (3H, s, CH_3C); 3.47 (3H, s, OCH_3); 6.09 (1H, q×d×d, J_d=2.64, J_d=1.65, J_q=0.99 Hz, NCH); 6.85 (1H, t, J= 1.8 Hz, C<u>H</u>=C-$COOCH_3$); 8.48 (1H, broad s, NH). ^{13}C NMR (C_6D_6) δ 11.70 (<u>C</u>H_3C); 50.82 (OCH_3); 116.15 (<u>C</u>H=C-$COOCH_3$); 120.61 (C_{quat}); 121.44 (NCH); 122.77 (C_{quat}); 161.65 (C=O). IR (NaCl) : 3305 cm^{-1} (NH); 1683 cm^{-1} (C=O). MS m/z (%) : 139 (100, M^+); 108(96); 107(73); 106(29); 81(9); 80(45); 79(83); 78(21); 65(6); 54(8); 53(54); 52(48); 51(23); 50(13); 49(9); 44(8); 41(8).

Synthesis of 4,5-Dibromo-3-chloro-2-(methoxycarbonyl)pyrrole **13**

To a solution of 0.79 g (5 mmol) 3-chloro-2-(methoxycarbonyl)pyrrole **11a** in 30 mL dichloromethane was added 33.6 mL of a 5 % $NaHCO_3$ solution and 1.60 g (0.01 mol) bromine in dichloromethane (5 mL) at room temperature. After 10 minutes the organic phase was isolated and the alkaline waterlayer was extracted with dichloromethane (3 × 10 mL). The combined extracts were dried ($MgSO_4$) and evaporated, yielding 1.54 g (97 %) of the white crystalline 4,5-dibromo-3-chloro-2-(methoxycarbonyl)pyrrole **13**. Extra purification could be performed by recrystallisation of **13** from dichloromethane (-18°C). Mp. 202.1-203°C.

^{1}H NMR ($CDCl_3$) δ 3.94 (3H, s, OCH_3); 9.84 (1H, broad s, NH). ^{13}C NMR ($CDCl_3$) δ 52.34 (OCH_3); 102.96; 106.59; 120.03 and 120.09 (C_{quat} pyrrole); 159.51 (<u>C</u>$OOCH_3$). IR (NaCl) : 3320-3100 cm^{-1} (NH); 1665 cm^{-1} (C=O). MS m/z (%) : 315/7/9/21 (21, M^+); 283/5/7/9(44); 256/8/60/62(3); 233(6); 231(9); 229(4); 229/31/33(4); 205/7/9(2); 179(5); 178(23); 177(4); 176(17); 154(3); 152(10); 150(8); 131(3); 117(5); 115(4); 99(6); 98(6); 97(5); 86(4); 73(4); 71(11); 59(6); 47(3). Anal. Calcd. for $C_6H_4Br_2ClNO_2$: C 22.71 %; H 1.27 %; N 4.41 %. Found : C 22.83 %; H 1.20 %; N 4.52 %.

Synthesis of 2-Methylpent-4-en-1-ol **27**

To a stirred and cooled (0°C) solution of 2-methylpent-4-enal **26** (0.245 mol, 24.04 g) in methanol (0.5 L) was added, portionwise 9.31 g of sodium borohydride (0.245 mol). The resulting solution was refluxed for 2 h, after which stirring was stopped and the mixture was poured into 750 mL of a 1M aqueous NaOH solution and extracted four times with dichloromethane (4×150 mL). The combined extracts were dried ($MgSO_4$) and the

evaporation of the solvent afforded 20.33 g of the colourless alcohol **27** (83 %). No further purification was necessary (purity > 95 %, GC).

^{1}H NMR ($CDCl_3$) δ 0.93 (3H, d, J=6.60 Hz, CH_3); 1.5 (1H, broad s, OH); 1.6-1.8 (1H, m, $CH_3C\underline{H}$); 1.9-2.3 (2H, m, $C\underline{H_2}CH$=); 3.4-3.6 (2H, m, $C\underline{H_2}OH$); 4.9-5.1 (2H, m, $C\underline{H_2}$=CH); 5.7-5.9 (1H, m, CH_2=C$\underline{H}$). ^{13}C NMR ($CDCl_3$) δ 16.97 (CH_3); 35.60 ($CH_3\underline{C}H$); 37.84 ($\underline{C}H_2C$=); 67.91 (CH_2OH); 116.10 ($\underline{C}H_2$=CH); 136.98 ($\underline{C}H$=CH_2). IR (NaCl) : 3340 cm^{-1} (OH); 3075 cm^{-1}; 1642 cm^{-1} (C=C). MS m/z (%) : No M^+; 84 (67); 61(1); 51(32); 50(4); 49(100); 48(7); 47(12); 44(1); 43(1); 42(8); 41(10).

Synthesis of 1-Mesyloxy-2-methylpent-4-ene **28**

To a solution of 2-methylpent-4-en-1-ol **27** (20.33 g, 0.2 mol) and triethylamine (22.60 g, 0.22 mol) in dichloromethane (200 mL) were added slowly 1.05 equivalents of mesylchloride (24.05 g, 0.21 mol), dissolved in 20 mL CH_2Cl_2. The mixture was stirred at room temperature for 14 h during which time a white precipitate formed. The suspension was filtered and the filtrate was poured into a 0.5 M aqueous NaOH solution (100 mL) and extracted with dichloromethane. The aquous layer was extracted two additional times with CH_2Cl_2 (2×50 mL). The combined extracts were dried ($MgSO_4$), evaporated and the residue distilled to give 30.30 g of the colourless mesyloxyalkene **28** (85 %). Bp. 127-130°C/10 mm Hg.

^{1}H NMR ($CDCl_3$) δ 1.00 (3H, d, J=6.27 Hz, $C\underline{H_3}CH$); 1.9-2.2 (3H, m, $CH_3C\underline{H}$ and $C\underline{H_2}CH$=); 3.01 (3H, s, $C\underline{H_3}SO_3$); 4.03 (1H, d×d, J_{gem}=9.45 Hz, J=5.94 Hz, MsO($\underline{H}$)CH); 4.10 (1H, d×d, J_{gem}=9.45 Hz, J=5.4 Hz, MsO(H)C$\underline{H}$); 5.0-5.2 (2H, m, $C\underline{H_2}$=CH); 5.7-5.9 (1H, m, CH_2=C$\underline{H}$). ^{13}C NMR ($CDCl_3$) δ 17.90 ($\underline{C}H_3CH$); 34.56 ($\underline{C}HCH_3$); 38.82 ($\underline{C}H_3OSO_2$ and $\underline{C}H_2CH$=); 75.78 (CH_2O); 118.96 ($\underline{C}H_2$=CH); 137.11 (CH_2=$\underline{C}H$). IR (NaCl) : 3100 cm^{-1}; 1690 cm^{-1} (C=C). MS m/z (%) : no M^+; 136(1); 109(1); 83(4); 82(36); 81(9); 79(22); 69(9); 68(6); 67(100); 65(5); 59(6); 58(4); 57(5); 55(11); 54(10); 53(5); 43(5); 42(6); 41(51). Anal. Calcd. for $C_7H_{14}O_3S$: C 47.17 %; H 7.92 %. Found : C 47.02 %; H 8.07 %.

Synthesis of 2,4-dimethyl-1-pyrroline **29**

A stirred mixture of the mesyloxyalkene **28** (5.35 g, 0.03 mol), HMPA (16.0 g, 0.09 mol) and sodium azide (19.51 g, 0.3 mol) was heated at 120°C during 24 h behind a safety shield The reaction mixture was poured into 50 mL water and extracted four times with ether (4×50 mL). The combined extracts were washed with 20 mL of brine, dried (K_2CO_3) and distilled under atmospheric pressure. In addition to ether, the first fractions contained some 2,4-dimethyl-1-pyrroline **24** already (capillary GC). Further distillation yielded 1 g (34 %) of the title compound **29**, which appeared as a clear liquid. Bp. 117-121°C.

^{1}H NMR ($CDCl_3$) δ 1.01 (3H, d, J=6.93 Hz, $C\underline{H_3}CH$); 2.01 (3H, s, CH_3C=N); 2.09 (1H, d×d, J_{gem}=17 Hz, J=5.6 Hz, $\underline{H}C(H)C$=N); 2.65 (1H, d×d, J_{gem}=17 Hz, J=8.6 Hz, HC($\underline{H}$)C=N); 2.3-2.5 (1H, m, $CH_3C\underline{H}$); 3.3-3.4 (1H, m, N$\underline{H}$C(H)); 3.90 (1H, d×d×q, J_{gem}=15 Hz, J_1=7.8 Hz, J_2=1.98 Hz, NHC($\underline{H}$)). ^{13}C NMR ($CDCl_3$) δ

19.88 ($\underline{C}H_3C$=N); 20.31 ($\underline{C}H_3CH$); 31.61 ($CH_3\underline{C}H$); 46.88 ($\underline{C}H_2C$=N); 68.39 (CH_2N); 174.59 (C=N). IR (NaCl) : 1644 cm^{-1} (C=N). MS m/z (%) : 97 (28, M^+); 96(1); 82(4); 80(1); 70(1); 69(6); 68(1); 67(2); 56(53); 55(100); 54(13); 53(4); 52(2); 51(2); 50(1); 42(28); 41(34). Anal. Calcd. for $C_6H_{11}N$: C 74.17 %; H 11.41 %; N 14.24 %. Found : C 74.08 %; H 11.49 %; N 14.35 %.

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REFERENCES

1. a) Sundberg, R.J. in Comprehensive Heterocyclic Chemistry Vol. 4, p. 313. Katritzky, A.R.; Rees, C.W.; Eds.; Pergamon Press, New York 1984. b) Jones, R.A. Ed., Pyrroles, Part II, The Synthesis, Reactivity and Physical Properties of Substituted Pyrroles; J. Wiley, New York 1992.
2. De Kimpe, N.; Abbaspour Tehrani, K.; Stevens, C.; De Cooman, P. *Tetrahedron* **1996**, *53*, 3693-3706 and references cited therein.
3. Tumlinson, J.H.; Silverstein, R.M.; Moser, J.C.; Brownlee, R.G.; Ruth, J.M. *Nature (London)* **1971**, *234*, 348-349.
4. Do Nascimento, R.R.; Morgan, E.D.; Moreira, D.D.O.; Della Lucia, T.M.C. *J. Chem. Ecol.* **1994**, *20*, 1719-1724.
5. Mitsuya, M. *Jpn. Kokai Tokkyo Koho JP 08 12,573*, 1996; *Chem. Abstr.* **1996**, *124*, 250949.
6. Turro, N.J.; Cha, Y.; Gould, I.R.; Padwa, A.; Gasdaska, J.R.; Tomas, M. *J. Org. Chem.* **1985**, *50*, 4415-4417.
7. Padwa, A.; Gasdaska, J.R.; Tomas, M.; Turro, N.J.; Cha, Y.; Gould, I.R. *J. Am. Chem. Soc.* **1986**, *108*, 6739-6746.
8. Ezquerra, J.; Pedregal, C.; Rubio, A.; Valenciano, J.; Navio, J.L.G.; Alvarez-Builla, J.; Vaquero, J.J. *Tetrahedron Lett.* **1993**, *34*, 6317-6320.
9. Strell, M.; Kreis, F. *Chem. Ber.* **1954**, *87*, 1011-1018.
10. Severin, T.; Poehlmann, H. *Chem. Ber.* **1977**, *110*, 491-499.
11. ApSimon, J.W.; Durham, D.G.; Rees, A.H. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1588-1594.
12. a) Qiu, Z.-M.; Burton, D.J. *Tetrahedron Lett.* **1994**, *35*, 4319-4322. b) Qiu, Z.-M.; Burton, D.J. *Tetrahedron Lett.* **1995**, *36*, 5119-5122.

13. De Kimpe, N.; Keppens, M. *Tetrahedron* **1996**, *52*, 3705-3718.
14. Polyak, F.D.; Eremeev, B.V.; Gavars, M.; Gaukhman, A.P.; Mazheika, I. *Khim. Geterosikl. Soedin.* **1988**, 894-896; *Chem. Abstr.* **1989**, *110*, 173709.
15. Ueda, A.; Nagasaki, F.; Takakura, Y.; Kojima, S. *Jpn. Kokai Tokkyo Koho JP 59 78,160* 1984; *Chem. Abstr.* **1984**, *101*, 171083.
16. Haüsler, J.; Schmidt, U. *Liebigs Ann. Chem.* **1979**, 1881-1889.
17. Haüsler, J. *Liebigs Ann. Chem.* **1981**, 1073-1088.
18. a) Dannhardt, G.; Obergrusberger, R. *Arch. Pharm.* **1979**, *312*, 498-507. b) Fraser, R.R.; Bresse, M.; Chuaqui-Offermans, N.; Houk, K.N.; Rondan, N.G. *Can. J. Chem.* **1983**, *61*, 2729-2734.
19. Fry, D.F.; Fowler, C.B.; Dieter, R.K. *Synlett.* **1994**, 836-838.
20. Picot, A.; Dendane, M.; Lusinchi, X. *Tetrahedron* **1976**, *32*, 2899-2906.
21. Greenhouse, R.; Ramirez, C.; Muchowski, J.M. *J. Org. Chem.* **1985**, *50*, 2961-2965.
22. Nicolaus, R.A.; Mangoni, L.; Misti, D. *Ann. Chim.* **1956**, *46*, 847-864; *Chem. Abstr.* **1957**, *51*, 6599.
23. Rapoport, H.; Bordner, J. *J. Org. Chem.* **1964**, *29*, 2727-2731.
24. Sonnet, P.E. *J. Med. Chem.* **1971**, *15*, 97-98.
25. Walizei, G.H.; Breitmaier, E. *Synthesis* **1989**, 337-340.
26. Cornforth, J.; Hui, D.M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1459-1462.
27. Barton, D.H.R.; Kervagoret, J.; Zard, S.Z. *Tetrahedron* **1990**, *46*, 7587-7598.
28. Zimmer, R.; Collas, M.; Roth, M.; Reiβig, H.-U. *Liebigs Ann. Chem.* **1992**, 709-714.
29. Xiao, D.; Schreier, J.A.; Cook, J.H.; Seybold, P.G.; Ketcha, D.M. *Tetrahedron Lett.* **1996**, *37*, 1523-1526.
30. De Kimpe, N.; De Smaele, D.; Hofkens, A.; Dejaegher, Y.; Kesteleyn, B. *Tetrahedron* **1997**, *53*, 10803-10816 (1997).
31. a) Pearson, W.H.; Bergmeier, S.C.; Williams, J.P. *J. Org. Chem.* **1992**, *57*, 3977-3987 and references cited therein. b) Logothetis, A.L. *J. Am. Chem. Soc.* **1965**, *87*, 749-754.
32. Etienne, A.; Correia, Y. *Compt. Rend.* **1964**, *259*, 2660-2663; *Chem. Abstr.* **1965**, *62*, 2753.
33. Bielawski, J.; Brandänge, S.; Lindblom, L. *J. Heterocyclic Chem.* **1978**, *15*, 97-99.
34. Alonso Garrido, D.O.; Buldain, G.; Frydman, B. *J. Org. Chem.* **1984**, *49*, 2619-2622.