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Transformations of 2,2-dimethyl-2,4-dihydro-3*H*-pyrrol-3-on-1-oxide derivatives in the Vilsmeier–Haack reaction conditions

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ABSTRACT

Enhydroxylaminones—2,2-dimethyl-2,4-dihydro-3*H*-pyrrol-3-on-1-oxides were shown to give various chlorinated products in the Vilsmeier–Haack reaction. The general sequence of the reaction steps is determined and the extent of the reaction was shown to be strongly dependent on the substrate structure.

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1. Introduction

β-Oxonitrones (enhydroxylaminones), in contrast to β-diketones and their nitrogen analogues–β-ketoimines or enaminones (in general, this tautomeric form is predominant), are on insufficiently explored class of organic compounds. There are a few reports concerning enhydroxylaminones where their reactions with some nucleophilic and electrophilic reagents were described. An electrophilic attack in these compounds is usually directed to the enamine carbon or oxygen of the hydroxyl group.[1] The behavior of enhydroxylaminones in the Vilsmeier–Haack reaction has not been previously studied. The derivatives of the isoxazolin-5-one that could be considered as topological *endo*-cyclic analogues of enhydroxylaminones are the most studied objects, and even for these compounds some of the reactions with electrophiles are ambiguous, and are the matter of a discussion among researchers. It was shown, in particular, that the direction of the reaction of isoxazoline-5-ones with the Vilsmeier reagent,[2–6] and the composition of the products depends noticeably on the structure of the substrate and on the reagents ratio. In contrast to the isoxazolin-5-one derivatives, the enhydroxylaminones derived from 2,2-dimethyl-2,4-dihydro-3*H*-pyrrol-3-on-1-oxide possesses an hydroxyl group—one more potential reaction center. In the present work, the behavior of these enhydroxylaminones in the Vilsmeier–Haack reaction has been studied.

2. Results and discussion

Pyrrolin-3-on-1-oxide derivatives **1** undergo a series of successive transformations in the reaction with the Vilsmeier reagent, which lead primarily to the 4-chloro-substituted enaminones **2** and then to the dichloro-substituted 2*H*-pyrrole derivatives **3**. The reaction of 5-methyl-substituted pyrrolin-oxide **1c** proceeds further to give enamide **4**; increasing the amount of the Vilsmeier reagent results in the formation of enaminoimine **5** as a main product and enaminoaldehyde **6**—as a by-product (Scheme 1).

The fact that enaminones **2** are the intermediates in the formation of dichloroderivatives **3** is confirmed by the reaction of **2a** with the Vilsmeier reagent, producing the corresponding dichloroderivative **3a** in a good yield.

The reaction progress of **1** depends on the character of the substituent at the fifth position of the pyrroline cycle. Thus, in the case of phenyl- and trifluoromethyl-substituted derivatives **1a**,**b**, the reaction could be stopped at the formation of enaminones **2**, while in the case of *tert*-butyl-substituted pyrroline **1d**, the only isolated product was dichloro-substituted compound **3d**. The corresponding enaminone **2d** was not obtained (Scheme 1).

Pyrroline **1c** transforms into enamide **4** under Vilsmeier–Haack reaction conditions, which exists in solution as an equilibrium mixture of two conformers (Scheme 2). ^{1}H NMR spectrum in DMSO-d_6 (30 °C) reveals the signals of methylene protons of conformer **A** at 5.84 and 4.80 ppm and of conformer **B** at 5.11 and 4.55 ppm; the signals of the aldehyde proton are at 8.94 and 8.79 ppm for **A** and **B**, respectively (molar ratio of conformers: **A**/**B**=1.2:1). An exchange between the protons at 5.84 and 5.11 ppm,

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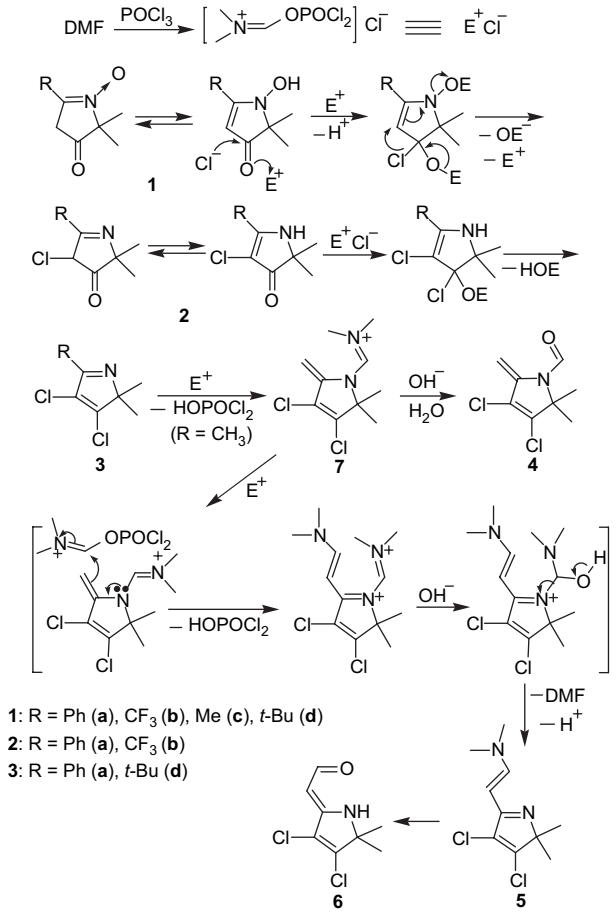
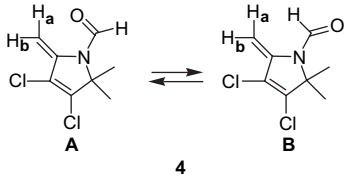


Scheme 1.

4.80 and 4.55 ppm, 8.94 and 8.79 ppm were observed when the temperature was increased to 80 °C. Decreasing the temperature back to 30 °C restores the initial spectrum.

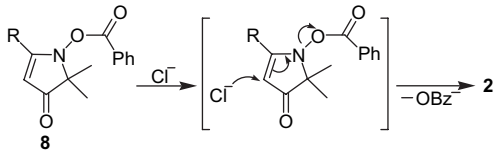


Scheme 2.

The reaction of **1c** with a larger excess of $POCl_3$ (see details in Section 4) gives enaminoimine **5** along with enaminoaldehyde **6**. Enaminoimine **5** was probably formed as the result of the electrophilic attack of one more equivalent of the Vilsmeier reagent at the methylene group in intermediate **7** (Scheme 1). Similar transformations were observed earlier for the Vilsmeier–Haack reaction of 3-oxyl-2,2,4,4-tetramethyl-5-methyleneimidazolidine-1-carbaldehyde derivatives.[7]

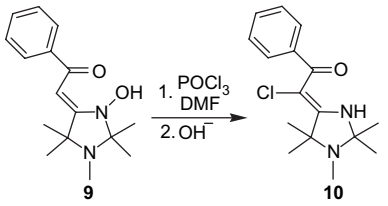
The probable scheme of the transformation of pyrrolines **1** into the products **2**–**4** includes initial nucleophilic attack of the chloride ion at the carbon of the carbonyl group facilitated by electrophilic catalysis by the Vilsmeier reagent. Further migration of the chlorine atom to position 4 of the heterocycle (intra- or intermolecular) accompanied by the removal of a good leaving group gives rise to enaminone **2**. At the next step, a nucleophilic attack of the chloride ion at the carbonyl carbon occurs for the second time, and subsequent elimination leads to the dichloro-substituted compound **3**. In the case of the methyl-substituted pyrroline, further electrophilic attack of the Vilsmeier reagent at nitrogen atom accompanied by the removal of a proton from methyl group gives an intermediate **7**. Its further hydrolysis affords the *N*-formylsubstituted product **4** (cf. Ref. 7) (Scheme 1).

The alternative route of the transformation of compounds **1** to **2** could be an electrophilic attack of the Vilsmeier reagent on the oxygen atom of *N*-hydoxylamino group followed by chloride ion attack on the carbon atom at the position 4 of heterocycle and simultaneous removal of a good leaving group from nitrogen atom to form product **2** (Scheme 3). An indirect argument against this way is the fact that the reaction of *N*-benzoyloxy-substituted compounds **8** either with ammonium chloride or with triethylbenzylammonium chloride in DMF yielding compounds **2** does occur, but proceeds very slowly (several weeks at room temperature).



Scheme 3.

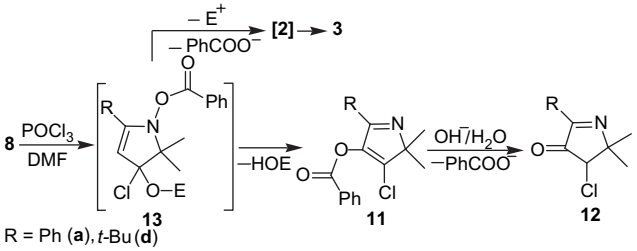
Of note is that the reaction of *exo*-cyclic enhydroxylaminone **9** with the Vilsmeier reagent proceeds in the same manner and leads to chloro-substituted compound **10** (Scheme 4). In other words, such a behavior in the Vilsmeier–Haack reaction seems to be quite general for enhydroxylaminones, at least at the first stages of the process.



Scheme 4.

One could suppose that the Vilsmeier–Haack reaction with pyrrolines **1** proceeds in this way due to the possibility of electrophilic attack of the Vilsmeier reagent at the oxygen atom of the hydroxylamino group. In order to suppress this route, *N*-benzoyloxy-substituted pyrroline derivatives **8** were involved into the reaction. Compounds **8** were synthesized by the acylation of compounds **1** with benzoyl chloride.[1]

It was found that the reaction of pyrrolines **8a**,**d** with the Vilsmeier reagent leads to the formation of 4-benzoyloxy-substituted 2*H*-pyrrole derivatives **11a**,**d**, dichloro-substituted derivatives **3a**,**d**, and iminoketones **12a**,**d**, respectively (Scheme 5). The structure of compound **11a** was proved by X-ray diffraction analysis (Fig. 1).



Scheme 5.

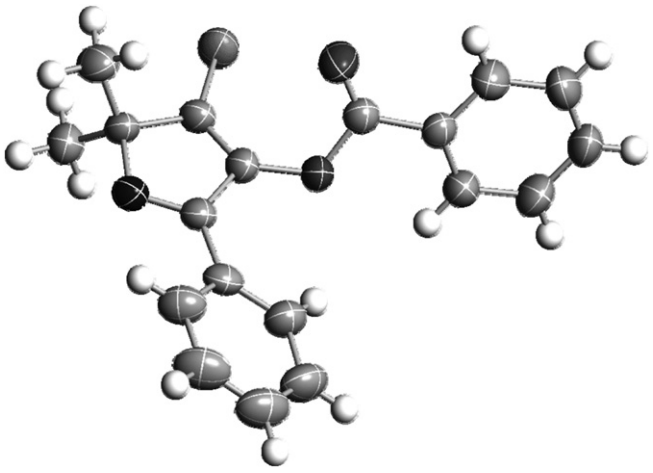
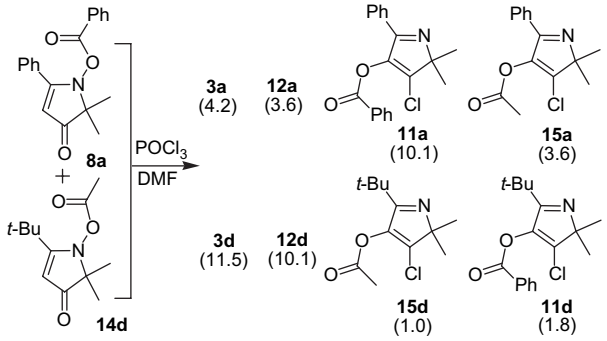


Figure 1. X-ray structure of **11a**.

The formation of these products is in line with the reaction scheme proposed above (Scheme 1). The first step of the transformation seems to be the formation of intermediate **13**. Then, either migration of chlorine atom with simultaneous removal of benzoyloxy group finally gives compound **3**, or migration of benzoyloxy group leading to ester **11** occurs. Hydrolysis of the latter gives product **12** on treatment of the reaction mixture. Isolation of individual compound **12** failed because it is chromatographically inseparable from compound **3**, but according to ^{1}H, ^{13}C NMR, and GC–MS data for the mixture of these products, compound **12** has the suggested structure.

A similar rearrangement was observed earlier while studying the acylation reaction of nitrones bearing at least one hydrogen atom at the β-carbon of the nitrone group.[8–12] The authors concluded that the rearrangement proceeds intramolecularly either as a sigmatropic shift (like Hetero-Oxy-Cope rearrangement) or via the ion-pair mechanism. The possibility of intermolecular rearrangement either was rejected on the base of kinetic study or wasn't considered at all. The realization of a cyclic planar transition state in the case of the intermediate **13** is impossible, which makes the probability of the rearrangement as a concerted process doubtful. The Vilsmeier–Haack reaction with an equimolar mixture of compounds **8a** and **14d** gives products **15a** and **11d**, as follows from GC–MS data. Obviously, these products can be formed exclusively as the result of intermolecular rearrangement (Scheme 6, the molar ratio of products is given in parentheses).

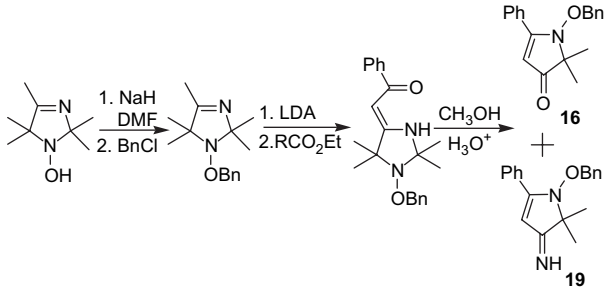


Scheme 6.

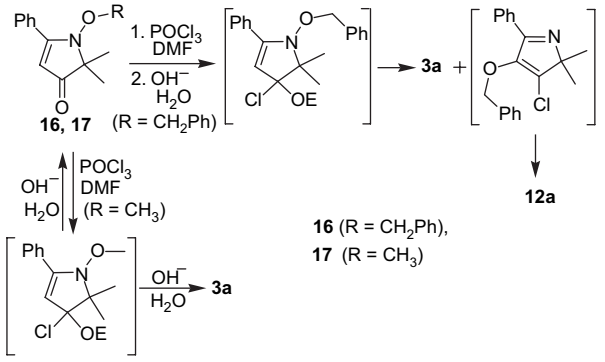
The migration of benzoyloxy group in compound **8** does not proceed even at heating up to 100 °C. This suggests that nitrogen–oxygen bond cleavage proceeds by heterolytic mechanism and conjugated electron-withdrawing carbonyl group hampers this process.

Thus, in the course of the Vilsmeier–Haack reaction, the acyloxy group is removed from the nitrogen atom and migrates to the position 4 of heterocycle; the migration can proceed intermolecularly.

Taking into account lower stability of the alkoxide anion in comparison to the acetate anion, the preservation of *N*-alkoxy group in *N*-alkoxyenaminone molecules **16** and **17** in the course of the Vilsmeier–Haack reaction could be expected. In fact, the reaction of compound **16**, derived according to Scheme 7, with the Vilsmeier reagent resulted in the formation of **12a** along with dichloro-substituted 2*H*-pyrrole **3a** and benzyl chloride. The formation of benzyl chloride probably occurs as a result of S_N2-type substitution with simultaneous formation of pyrroline **1a**, which can react further, as described above, to give dichloroderivative **3a** (Scheme 1). The formation of ketone **12a** seems to be a result of the sequence of transformations similar to those described above (Schemes 1 and 5) including the migration of benzyloxy group to the position 4 of heterocycle and hydrolysis of the migration product—the vinyl ether (Scheme 8).



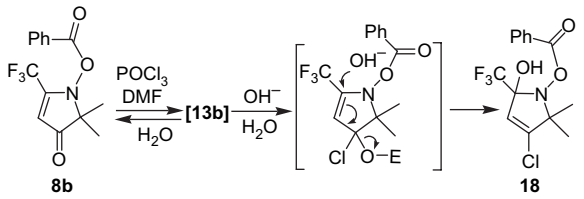
Scheme 7.



Scheme 8.

The reaction of *N*-methoxy-substituted compound **17** with the Vilsmeier reagent also leads to the formation of dichloro-substituted compound **3a**. Considerable amounts of the starting substrate were isolated along with **3a**, although the former has been completely consumed according to the TLC data of the reaction mixture (Scheme 8).

Trifluoromethyl-substituted derivative **8b** reacts differently to the other *N*-benzoyloxy-analogues. The *N*-substituent is retained and the main product of the reaction is compound **18** along with some amount (~35%) of the starting material, although it was not detected in the reaction mixture by TLC before its treatment. The probable scheme of the reaction includes the intermediate formation of **13b** and its further transformation either into **18**, or into initial compound **8b** on treating the reaction mixture (Scheme 9).



Scheme 9.

3. Conclusion

It was shown that the Vilsmeier–Haack reaction with enhydroxylaminones—the derivatives of 2,2-dimethyl-2,4-dihydro-3*H*-pyrrol-3-on-1-oxide—proceeds via the loss of *N*-substituent and leads to the chloro-substituted enaminones and then to the dichloro-substituted 2*H*-pyrrole derivatives. 4-Formyl-substituted products are not formed in all cases. The rearrangement of *N*-benzoyloxy-derivatives was observed and it was shown to proceed intermolecularly.

4. Experimental

4.1. General

IR spectra were recorded with Bruker IFS 66 spectrometer as KBr pellets (concentration 0.25%, thickness of a pellet 1 mm) or as solutions in CCl_4 (concentration 2%). UV spectra were measured with Specord M-40 spectrophotometer in EtOH. NMR spectra were recorded with Bruker WP 200 SY, Bruker AC 200, Bruker AV 300, and Bruker AM 400 spectrometers on 5% solutions in $CDCl_3$ or $(CD_3)_2CO$ with solvent as an internal standard at 25 °C. The composition of the reaction mixtures was found from GC–MS data using quadrupole MS (Hewlett–Packard MSD 5971) coupled to HP G1800A GC fitted with HP-5 fused silica gel column, injector and detector (MSD) temperatures were 280 and 170 °C, respectively, MSD was operated at 70 eV. High-resolution mass spectra were recorded with Finnigan MAT 8200 mass spectrometer with a direct sample injection and resolution of 10,000. Melting points were measured using 'Boetius' plate and are uncorrected. TLC monitoring was carried out on Silufol-254 or Alufol-254 plates. In all cases solvent evaporation was carried out under reduced pressure.

Compounds **2a**, **14d** were identified by comparing with ones synthesized previously.[1] Compounds **8a**,**c**, **17**,[1] **1a**–**d**,[13] and **9**[14] were synthesized as described.

4.2. Syntheses

*4.2.1. 1-(Benzoyloxy)-2,2-dimethyl-5-(trifluoromethyl)-1,2-dihydro-3H-pyrrol-3-one **8b***

Benzoyl chloride (0.45 mL, 3.84 mmol) was added dropwise to a well stirred solution of pyrroline **1b** (0.50 g, 2.56 mmol) and NaOH (0.26 g, 6.40 mmol) in water (15 mL) under argon. The reaction mixture was stirred for 30 min, then extracted with $CHCl_3$ (3×25 mL); combined extract was dried by $MgSO_4$ and then evaporated. The crude product **8b** was purified on a silica gel column (chloroform). Yield: 60%, mp 36–37 °C. R_f (3% MeOH/$CHCl_3$) 0.68. [Found: C 55.91, H 3.86, N 4.92. $C_{14}H_{12}F_3NO_3$ requires: C 56.19, H 4.01, N 4.68%.] δ_H (200 MHz, $(CD_3)_2CO$) 1.44 (6H, s, C^2–(CH_3)$_2$), 6.35 (1H, s, C^5=C^4–*H*), 7.5–7.8 (3H, m), 8.0–8.1 (2H, m, Ph). δ_C (50 MHz, $(CD_3)_2CO$) 22.3 (C^2–(CH_3)$_2$), 75.5 (C^2), 111.9 (C^4), 120.7 (q, *J* 303 Hz, CF_3), 127.7, 129.9, 130.6, 135.2 (Ph), 162.2 (q, *J* 37 Hz, C^5), 164.3 (O–C=O), 201.2 (C=O). ν_{max} (KBr) 1768 (O–C=O), 1724 (C=O), 1179, 1149 (CF_3) cm^{-1}. UV (ethanol): λ_{max} (lg ε)=232 (4.10), 283 nm (4.04).

*4.2.2. 1-(Benzoyloxy)-5-tert-butyl-2,2-dimethyl-1,2-dihydro-3H-pyrrol-3-one **8d***

Compound **8d** was synthesized by the method above, but the reaction time was 4 h. The precipitate of **8d** was filtered off, washed with 2 mL of cold water, dried, and purified by preparative TLC on silica gel ($CHCl_3$/CH_3OH (40:1)), yield: 0.13 g (41%). Mp 117–118.5 °C (hexane). R_f (3% MeOH/$CHCl_3$) 0.73. [Found C 71.23, H 7.41, N 4.88. $C_{17}H_{21}NO_3$ requires: C 71.08, H 7.32, N 4.88%.] δ_H (200 MHz, $CDCl_3$) 1.28 (9H, s, C–(CH_3)$_3$), 1.29 (3H, s), 1.35 (3H, s, C^2–(CH_3)$_2$), 5.46 (1H, s, C^4*H*), 7.4–7.7 (3H, m), 8.0–8.1 (2H, m, Ph). δ_C (100 MHz, $CDCl_3$) 23.9, 27.3 (C^2–(CH_3)$_2$), 28.7 (C–(CH_3)$_3$), 34.4 (*C*–(CH_3)$_3$), 73.7 (C^2), 104.9 (C^4H), 127.3 (*i*-Ph), 128.9, 129.7 (*o*,*m*-Ph), 134.0 (*p*-Ph), 164.2 (C^5), 186.7 (O–C=O), 202.1 (C^3=O). ν_{max} (KBr) 1751 (O–C=O), 1702 (C=O), 1649, 1565 (C=C) cm^{-1}. UV (ethanol): λ_{max} (lg ε)=232 (4.11), 283 nm (3.92).

*4.2.3. 1-(Acetyloxy)-5-tert-butyl-2,2-dimethyl-1,2-dihydro-3H-pyrrol-3-one **14d***

A solution of pyrroline **1d** (0.3 g, 1.64 mmol) and acetic anhydride (0.16 mL, 1.64 mmol) in $CHCl_3$ (3 mL) was kept for 5 days at room temperature then washed with aqueous solution of Na_2CO_3 (3 mL), dried ($MgSO_4$), and evaporated. Compound **14d** was isolated by silica gel column chromatography ($CHCl_3$). Yield: 0.22 g (82%), mp 79–81 °C (lit.[1] mp 78–80 °C). R_f ($CHCl_3$) 0.42.

*4.2.4. 1-(Benzyloxy)-2,2-dimethyl-5-phenyl-1,2-dihydro-3H-pyrrol-3-one **16***

2,2,4,5,5-Pentamethyl-2,5-dihydro-1*H*-imidazol-1-ol (2.0 g, 12.82 mmol) was added to a stirred suspension of NaH (0.6 g, 25.63 mmol) in *N*,*N*-dimethylformamide (10 mL) under argon. The mixture was stirred for 15 min and then benzyl chloride (1.77 mL, 15.38 mmol) was added dropwise. The stirring was continued for 4.5 h, then the reaction mixture was poured into brine (100 mL) and extracted with hexane (2×20 mL). The combined extract was washed with portion of water (10 mL) and then with brine (10 mL), dried ($MgSO_4$), and evaporated. 1-(Benzyloxy)-2,2,4,5,5-pentamethyl-2,5-dihydro-1*H*-imidazole was purified on an Al_2O_3 column (hexane, hexane/diethyl ether (1:1)). Yield: 2.3 g (75%), colorless oil. R_f (50% diethyl ether/hexane) 0.45. HRMS (EI): M^+, found: 246.1736. $C_{15}H_{22}N_2O$ requires: 246.1732. δ_H (300 MHz, $CDCl_3$) 1.19 (6H, s, C^5–(CH_3)$_2$), 1.33 (6H, s, C^2–(CH_3)$_2$), 1.88 (3H, s, C^4–(CH_3)), 4.74 (2H, s, OCH_2), 7.30–7.39 (5H, m, Ph). δ_C (62 MHz, $CDCl_3$) 16.2 (*C*H_3), 21.0, 23.8, 27.9, 31.1 (C^5–(*C*H_3)$_2$, C^2–(*C*H_3)$_2$), 72.4 (C^5), 78.6 (CH_2), 90.1 (C^2), 128.0 (*p*-Ph), 128.4, 129.0 (*o*,*m*-Ph), 138.1 (*i*-Ph), 174.9 (C^4). ν_{max} (CCl_4) 1651 (C=N) cm^{-1}.

A solution of 1-(benzyloxy)-2,2,4,5,5-pentamethyl-2,5-dihydro-1*H*-imidazole (1.3 g, 5.28 mmol) in diethyl ether (10 mL) was added dropwise to a well stirred ice-cold solution of LDA (prepared from lithium (0.15 g, 21.14 mmol), bromobenzene (1.22 mL, 11.62 mmol) and *N*,*N*-diisopropylamine (1.46 mL, 10.56 mmol) in anhydrous diethyl ether (20 mL)) under argon. The stirring was continued for 45 min and then the ethyl benzoate (1.13 mL, 7.93 mmol) was added to an ice-cold reaction mixture in two portions. The mixture was stirred for 1 h, then water (15 mL) was added. The ether layer was separated, the aqueous one extracted with $CHCl_3$ (15 mL). Combined organic extract was dried ($MgSO_4$) and evaporated. *2-(1-(Benzyloxy)-2,2,5,5-tetramethylimidazolidin-4-ylidene)-1-phenylethanone* was purified on a silica gel column ($CHCl_3$/CH_3OH (30:1)). Yield: 1.6 g (90%), mp 59.5–60.5 °C (hexane). R_f ($CHCl_3$) 0.19. HRMS (EI): M^+, found: 350.1990. $C_{22}H_{26}N_2O_2$ requires: 350.1994. δ_H (400 MHz, $CDCl_3$) 1.43 (12H, s, C^2–(CH_3)$_2$, C^5–(CH_3)$_2$), 4.82 (2H, s, CH_2), 5.62 (1H, s, =*CH*), 7.3–7.5 (8H, m), 7.8–7.9 (2H, m, Ph), 10.32 (1H, br s, N*H*). δ_C (100 MHz, $CDCl_3$) 23.3, 24.7, 28.9, 30.9 (C^5–(*C*H_3)$_2$, C^2–(*C*H_3)$_2$), 68.6 (C^5), 79.0 (C^2), 80.6 (CH_2), 83.3 (CH), 126.8, 128.0, 128.2, 128.6 (*o*,*m*-Ph), 127.9, 130.5 (*p*-Ph), 137.2, 140.1 (*i*-Ph), 169.3 (C^4), 189.4 (C=O). ν_{max} (CCl_4) 1623, 1622, 1600, 1583,

1539 (O=C–C=C–N) cm^{-1}. UV (ethanol): λ_{max} (lg ε)=242 (3.90), 331 nm (4.28).

A solution of *2-(1-(benzyloxy)-2,2,5,5-tetramethylimidazolidin-4-ylidene)-1-phenylethanone* (0.5 g) in a mixture methanol–20% HCl (1:1) was heated at 52 °C for 24 h, then it was evaporated nearly to half of the volume, neutralized by 5% NaOH, and extracted with $CHCl_3$ (3×15 mL). Combined extract was dried by $MgSO_4$ and evaporated. *1-(Benzyloxy)-2,2-dimethyl-5-phenyl-1,2-dihydro-3H-pyrrol-3-one* ***16*** and *1-(benzyloxy)-2,2-dimethyl-5-phenyl-1,2-dihydro-3H-pyrrol-3-imine* ***19*** were separated on a silica gel column ($CHCl_3$, $CHCl_3$/CH_3OH (15:1)). Yields of products **16** and **19** are 0.2 g (50%) and 0.1 g (25%), respectively.

Compound **16**: mp 61–63 °C. R_f ($CHCl_3$) 0.53. HRMS (EI): M^+, found: 293.1412. $C_{19}H_{19}NO_2$ requires: 293.1416. δ_H (300 MHz, $CDCl_3$) 1.50 (6H, s, C–(CH_3)$_2$), 5.06 (2H, s, CH_2), 5.56 (1H, s, C*H*), 7.12–7.22 (2H, m), 7.26–7.31 (3H, m), 7.40–7.50 (3H, m), 7.56–7.60 (2H, m, Ph). δ_C (75 MHz, $CDCl_3$) 23.4 (C–(CH_3)$_2$), 72.8 (*C*–(CH_3)$_2$), 79.0 (CH_2), 104.9 (C^4), 128.4, 128.6, 128.7, 128.8, 129.0, 131.1, 131.3, 135.1 (Ph), 177.6 (C^5), 202.3 (C^3=O). ν_{max} (KBr) 1694 (O=C–C=C) cm^{-1}. UV (ethanol): λ_{max} (lg ε)=256 (4.04), 301 nm (3.97).

Compound **19**: mp 166–169 °C. R_f (7% MeOH/$CHCl_3$) 0.07. HRMS (EI): M^+, found: 292.1574. $C_{19}H_{20}N_2O$ requires: 292.1576. δ_H (300 MHz, $CDCl_3$) 1.81 (6H, s, C–(CH_3)$_2$), 5.03 (2H, s, CH_2), 6.10 (1H, s, C^4H), 7.18–7.23 (2H, m), 7.28–7.35 (3H, m), 7.44–7.52 (2H, m), 7.54–7.62 (1H, m), 7.68–7.72 (2H, m, Ph), 10.27 (1H, br s, N*H*). δ_C (75 MHz, $CDCl_3$) 24.3 (C–(CH_3)$_2$), 74.3 (*C*–(CH_3)$_2$), 80.6 (CH_2), 95.0 (C^4), 128.0, 129.0, 129.1, 129.3 (2 signals), 129.5, 133.1, 133.4 (Ph), 174.8 (C^5), 183.2 (C^3). ν_{max} (KBr) 2877 (N–H), 1682,1600, 1581 (C=C–C=N) cm^{-1}. UV (ethanol): λ_{max} (lg ε)=272 (4.01), 350 nm (4.02).

4.2.5. Reaction with the Vilsmeier reagent (general method)

$POCl_3$ (0.19 mL, 2.00 mmol) was added dropwise to ice-cold *N*,*N*-dimethylformamide (2 mL). The solution was stirred for 10 min, compounds **1**, **2a**, **8**, **9**, **14d**, **16**, or **17** (1.00 mmol) were added and the stirring was continued for 3 h at 20 °C. The reaction mixture was poured into the saturated ice-cold solution of Na_2CO_3 (7 mL), the resulting mixture was kept at 20 °C for 30 min and then extracted either with diethyl ether or $CHCl_3$. Combined extract was thoroughly washed with water, dried by $MgSO_4$, and evaporated. The crude product was purified as described below.

4.2.5.1. 4-Chloro-2,2-dimethyl-5-phenyl-1,2-dihydro-3H-pyrrol-3-one ***2a***. Compound **2a** was extracted with ether (3×15 mL). The residue after evaporation was triturated with a small amount of diethyl ether, the resultant precipitate **2a** was filtered off and recrystallized from a mixture of hexane/EtOAc, yield: 33%, mp 190–191 °C (lit.[1] mp 190–191 °C). δ_C (50 MHz, $CDCl_3$) 24.2, 24.3 (C^2–(CH_3)$_2$), 63.9 (C^2), 101.1 (C^4), 127.9, 128.8, 129.5, 132.3 (Ph), 167.8 (C^5), 198.3 (C=O).

4.2.5.2. 4-Chloro-2,2-dimethyl-5-(trifluoromethyl)-1,2-dihydro-3H-pyrrol-3-one ***2b***. Compound **2b** was purified by sublimation at 2 mmHg and 40–50 °C. Yield: 25 %, mp 138–139 °C (hexane/EtOAc). [Found: C 40.10, H 3.30, N 6.63, Cl 16.56. $C_7H_7NOF_3Cl$ requires: C 39.34, H 3.28, N 6.56, Cl 16.63%.] HRMS (EI): M^+, found: 213.0167. $C_7H_7ClF_3NO$ requires: 213.0168. δ_H (200 MHz, $CDCl_3$) 1.37 (6H, s, C^2–(CH_3)$_2$), 6.28 (1H, br s, N*H*). δ_C (50 MHz, $CDCl_3$) 22.3, 23.6 (C^2–(CH_3)$_2$), 64.9 (C^2), 103.2 (C^4), 118.8 (q, *J* 275 Hz, CF_3), 156.2 (q, *J* 37 Hz, C^5), 199.0 (C=O). ν_{max} (KBr) 3181 (N–H), 1668 (C=O), 1569 (C=C), 1227, 1192, 1171, 1138 (CF_3) cm^{-1}. UV (ethanol): λ_{max} (lg ε)=335 nm (3.89).

4.2.5.3. 3,4-Dichloro-2,2-dimethyl-5-phenyl-2H-pyrrole ***3a***. Compound **3a** was extracted with ether (3×15 mL) and isolated on a silica gel column (diethyl ether), yield: 50%, mp 25.5–27 °C. R_f ($CHCl_3$) 0.36. HRMS (EI): M^+, found: 239.0272. $C_{12}H_{11}Cl_2N$ requires: 239.0269. δ_H (200 MHz, $CDCl_3$) 1.42 (6H, s, C^2–(CH_3)$_2$), 7.4–7.5 (3H, m), 7.85–7.95 (2H, m, Ph). δ_C (50 MHz, $CDCl_3$) 23.0 (C^2–(CH_3)$_2$), 75.9 (C^2), 122.4 (C^4), 128.3, 128.6, 130.5, 132.5 (Ph), 157.8 (C^3), 166.7 (C^5). ν_{max} (CCl_4) 1605, 1580, 1533 (C=C, C=N) cm^{-1}. UV (ethanol): λ_{max} (lg ε)=251 nm (4.12).

4.2.5.4. 5-tert-Butyl-3,4-dichloro-2,2-dimethyl-2H-pyrrole ***3d***. Compound **3d** was extracted with ether (3×15 mL) and purified on a silica gel column (mixtures of hexane/diethyl ether from 10:0 to 10:1), yield: 11%, mp 22–23 °C. R_f (50% diethyl ether/hexane) 0.58. HRMS (EI): M^+, found: 219.0582. $C_{10}H_{15}Cl_2N$ requires: 219.0582. δ_H (400 MHz, $CDCl_3$) 1.26 (6H, s, C^2–(CH_3)$_2$), 1.32 (9H, s, *t*-Bu). δ_C (100 MHz, $CDCl_3$) 23.0 (C^2–(*C*H_3)$_2$), 27.2 (C–(*C*H_3)$_3$), 35.9 (*C*–(CH_3)$_3$), 74.3 (C^2), 122.4 (C^4), 157.6 (C^3), 175.2 (C^5). ν_{max} (KBr) 1601, 1539 (C=C, C=N) cm^{-1}. UV (ethanol): λ_{max} (lg ε)=244 nm (3.61).

4.2.5.5. 3,4-Dichloro-2,2-dimethyl-5-methylene-2,5-dihydro-1H-pyrrole-1-carbaldehyde ***4***. Compound **4** was isolated by extraction with $CHCl_3$ (3×15 mL) and purified on a silica gel column (hexane/diethyl ether (10:1)). Yield of the isomers mixture: 53%, colorless oil. R_f ($CHCl_3$) 0.24. HRMS (EI): M^+, found: 205.0061. $C_8H_9Cl_2NO$ requires: 205.0061. δ_H (300 MHz, $CDCl_3$, 25 °C) 1.54 (6H, s, C^2–(CH_3)$_2$, **A**), 1.59 (6H, s, C^2–(CH_3)$_2$, **B**), 4.57 (1H, d, *J* 3.3 Hz, H_bCH_a, **B**), 4.67 (1H, d, *J* 3.3 Hz, H_aCH_b, **B**), 4.91 (1H, d, *J* 1.0 Hz, H_bCH_a, **A**), 5.95 (1H, d, *J* 1.0 Hz, H_aCH_b, **A**), 8.56 (1H, s, *H*C=O, **A**), 8.75 (1H, s, *H*C=O, **B**). δ_C (75 MHz, $CDCl_3$,) 22.9 (q, *J* 130.7 Hz, C^2–(CH_3)$_2$, **B**), 26.6 (q, *J* 129.2 Hz, C^2–(CH_3)$_2$, **A**), 67.8 (C^2–(CH_3)$_2$, **A**), 69.3 (C^2–(CH_3)$_2$, **B**), 83.7 (dd, *J* 166.1, 162.1 Hz, CH_2, **B**), 94.3 (dd, *J* 170.6, 160.5 Hz, CH_2, **A**), 122.5 (C^4, **B**), 124.1 (C^4, **A**), 135.4 (C^3, **A**), 139.3 (C^3, **B**), 140.5 (C^5, **A**), 142.5 (C^5, **B**), 156.9 (d, *J* 212.4 Hz, HC=O, **B**), 158.7 (d, *J* 196.2 Hz, HC=O, **A**). ν_{max} (CCl_4) 1755 (H–C=O), 1694, 1617 (C=C, C=N) cm^{-1}. The molar ratio of isomers is **A**/**B**=1:1.7.

4.2.5.6. N-[2-(3,4-Dichloro-2,2-dimethyl-2H-pyrrol-5-yl)vinyl]-N,N-dimethylamine ***5*** *and (3,4-dichloro-5,5-dimethyl-1,5-dihydro-2H-pyrrol-2-ylidene)acetaldehyde* ***6***. Compounds **5** and **6** were synthesized according to a general method using 3 mmol of $POCl_3$ (instead of 2 mmol). A mixture of products was extracted with $CHCl_3$ (3×15 mL) and the products were separated on an Al_2O_3 column ($CHCl_3$). Yields of compounds **5** and **6** are 11% and 3%, respectively.

Compound **5**: mp 70–73 °C (hexane). R_f ($CHCl_3$) 0.04. HRMS (EI): M^+, found: 232.0531. $C_{10}H_{14}Cl_2N_2$ requires: 232.0534. δ_H (300 MHz, $CDCl_3$) 1.30 (6H, s, C(*C*H_3)$_2$), 2.92 (6H, s, N(*C*H_3)$_2$), 4.95 (1H, d, *J* 13.2 Hz, *CH*), 7.60 (1H, d, *J* 13.2 Hz, *HC*–NMe_2). δ_C (75 MHz, $CDCl_3$) 24.1 (s, N(CH_3)$_2$, C(*C*H_3)$_2$), 74.2 (*C*(CH_3)$_2$), 84.9 (N^1=C^5–*C*=C–N), 123.4 (C^4), 147.0 (N^1=C^5–C=*C*–N), 153.9 (C^3), 165.2 (C^5). ν_{max} (KBr) 1641, 1602 (N=C–C=C–N) cm^{-1}. UV (ethanol): λ_{max} (lg ε)=253 (4.11), 350 nm (4.19).

Compound **6**: mp 101–104 °C. R_f ($CHCl_3$) 0.38. HRMS (EI): M^+, found: 205.0057. $C_8H_9Cl_2NO$ requires: 205.0061. δ_H (300 MHz, $CDCl_3$) 1.43 (6H, s, C(*C*H_3)$_2$), 5.39 (1H, d, *J* 2.1 Hz, *CH*), 9.26 (1H, d, *J* 2.1 Hz, *HC*=O), 9.50 (1H, br s, N*H*). ν_{max} (KBr) 3313 (NH), 1639, 1592, 1562 (O=C–C=C–N) cm^{-1}.

4.2.5.7. 2-Chloro-2-(1,2,2,5,5-pentamethylimidazolidin-4-ylidene)-1-phenylethanone ***10***. Compound **10** was extracted with $CHCl_3$ (3×15 mL) and purified on a silica gel column ($CHCl_3$), yield: 40%, mp 168.5–169 °C (hexane/EtOAc). R_f ($CHCl_3$) 0.68. [Found: C 65.46, H 7.28, N 9.58, Cl 12.11. $C_{16}H_{21}ClN_2O$ requires: C 65.64, H 7.18, N 9.57, Cl 12.14%.] δ_H (200 MHz, $CDCl_3$) 1.39 (6H, s, C^5–(CH_3)$_2$), 1.51 (6H, s, C^2–(CH_3)$_2$), 2.33 (3H, s, N–CH_3), 7.24 (3H, m), 7.36 (2H, m, Ph), 11.33 (1H, br s, N*H*). δ_C (75 MHz, $CDCl_3$) 22.8 (C^5–(CH_3)$_2$), 26.0 (N–CH_3), 27.1 (C^2–(CH_3)$_2$), 67.7 (C^5), 78.6 (C^2), 93.8 (C–Cl), 127.4, 127.6

(*o*,*m*-Ph), 129.2 (*p*-Ph), 140.7 (*i*-Ph), 167.2 (C^4), 191.4 (C=O). ν_{max} (KBr) 3223 (NH), 1595, 1538 (O=C–C=C–N), 1278 (C–N) cm^{-1}. UV (ethanol): λ_{max} (lg ε)=241 (3.59), 342 nm (4.03).

4.2.5.8. 3-Chloro-2,2-dimethyl-5-phenyl-2H-pyrrol-4-yl benzoate ***11a*** *and 4-chloro-5,5-dimethyl-2-phenyl-4,5-dihydro-3H-pyrrol-3-one* ***12a****.* A mixture of products **11a**, **3a**, and **12a** was extracted with ether (3×15 mL) and purified on a silica gel column (diethyl ether). The products were separated on a silica gel column ($CHCl_3$, $CHCl_3$/CH_3OH (100:1)). Yield of **11a**—30%, yield of a mixture of **3a** and **12a**—22%. Compound **12a** was not isolated in individual form because of its low stability upon chromatography.

Compound **11a**: mp 65–66.5 °C (hexane). R_f (3% MeOH/$CHCl_3$) 0.18. HRMS (EI): M^+, found: 325.0870. $C_{19}H_{16}ClNO_2$ requires: 325.0870. δ_H (400 MHz, $CDCl_3$) 1.50 (6H, s, C^2–(CH_3)$_2$), 7.3–7.4 (3H, m), 7.45–7.55 (2H, m), 7.6–7.7 (1H, m), 8.1–8.2 (2H, m), 8.8–8.9 (2H, m, 2 Ph). δ_C (100 MHz, $CDCl_3$) 23.1 (C^2–(CH_3)$_2$), 73.4 (C^2), 132.5 (C^3), 127.2, 128.0, 128.5, 128.7, 130.2, 130.5, 134.0, 139.3 (2Ph), 148.0 (C^4), 162.4 (C^5), 165.8 (O–C=O). ν_{max} (KBr) 1757 (O–C=O), 1644 (C=C–C=N) cm^{-1}. UV (methanol): λ_{max} (lg ε)=238 nm (4.40).

X-ray crystallography experiment. Data for compound **11a** (2θ<50°) were measured on a Bruker P4 single crystal diffractometer, with graphite monochromated Mo-K_α radiation. A correction for absorption was made by integration method (transmission 0.8166–0.9485). The structure was solved by the direct method using the SHELXS-97 program and refined in the full-matrix anisotropic (isotropic for H atoms) approximation by the SHELXL-97 program. The hydrogen atom positions were located geometrically. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-623496. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

X-ray structure data for ***11a***: $C_{19}H_{16}ClNO_2$, M=325.78, monoclinic, a=9.3024(12), b=34.622(4), c=10.3003(10) Å, β=90.315(10)°, V=3317.4(7) $Å^3$, space group $P2_1/c$, Z=8, d_c=1.305 g cm^{-3}, μ(Mo-K_α)=0.239 mm^{-1}, F(000)=1360. The final indexes are S=1.024, R_1=0.0512, wR_2=0.1155 for all 5818 independent reflections and R_1=0.0402, wR_2=0.1076 for 4720 $F_0>4\sigma$.

Compound **12a**: R_f ($CHCl_3$) 0.49. HRMS (EI): M^+, found: 221.0605. $C_{12}H_{12}ClNO$ requires: 221.0607. δ_H (400 MHz, $CDCl_3$) 1.39 (3H, s), 1.57 (3H, s, C^5–(CH_3)$_2$), 4.19 (1H, s, C^4H), 7.40–7.52 (3H, m), 8.15–8.20 (2H, m, Ph). δ_C (100 MHz, $CDCl_3$) 26.5, 27.9 (C^5–(CH_3)$_2$), 66.1 (C^4), 67.9 (C^5), 128.4, 128.8, 132.1, 132.5 (Ph), 163.6 (C^2), 196.2 (C^3).

4.2.5.9. 5-tert-Butyl-3-chloro-2,2-dimethyl-2H-pyrrol-4-yl benzoate ***11d*** *and 2-tert-butyl-4-chloro-5,5-dimethyl-4,5-dihydro-3H-pyrrol-3-one* ***12d****.* The reaction mixture was extracted with $CHCl_3$ (3×15 mL), a mixture of products was separated by preparative TLC on an Al_2O_3 (hexane). Yield of **11d**—6%, yield of chromatographically homogenous mixture of **3d** and **12d**—15%.

Compound **11d**: mp 123–124.5 °C (hexane). R_f (50% diethyl ether/hexane) 0.45. HRMS (EI): M^+, found: 305.1180. $C_{17}H_{20}ClNO_2$ requires: 305.1183. δ_H (400 MHz, $CDCl_3$) 1.29 (9H, s, *t*-Bu), 1.46 (6H, s, C^2–(CH_3)$_2$), 7.50–7.58 (2H, m, *m*-Ph), 7.63–7.69 (1H, m, *p*-Ph), 8.12–8.15 (2H, m, *o*-Ph). δ_C (100 MHz, $CDCl_3$) 23.1 (C^2–(CH_3)$_2$), 27.4 (C–(CH_3)$_3$), 35.8 (*C*–(CH_3)$_3$), 72.5 (C^2), 128.1 (s, C^3, *i*-Ph), 129.1, 130.5, 134.5 (*m*,*o*,*p*-Ph), 139.4 (C^4), 161.9 (s, C^5, O–C=O). ν_{max} (KBr) 1754 (O–C=O), 1645 (C=C–C=N) cm^{-1}. UV (ethanol): λ_{max} (lg ε)=233 nm (4.26).

Compound **12d**: R_f (50% diethyl ether/hexane) 0.58. GC–MS: found m/z=201: $C_{10}H_{16}ClNO$. δ_H (400 MHz, $CDCl_3$) 1.25 (12H, s, C–(CH_3)$_3$, C^5–(CH_3)), 1.44 (3H, s, C^5–(CH_3)), 3.95 (1H, s, C^4H). δ_C (100 MHz, $CDCl_3$) 26.4, 27.9 (C^5–(CH_3)$_2$), 27.0 (C–(CH_3)$_3$), 34.9 (*C*–(CH_3)$_3$), 66.0 (C^4), 67.0 (C^5), 175.3 (C^2), 196.0 (C^3).

4.2.5.10. A reaction of a mixture of compounds ***8a*** */* ***14d*** *with the Vilsmeier reagent.* The reaction was carried out according to the general method. The ratio of starting compounds **8a**/**14d** was 1:1. The reaction mixture was extracted with $CHCl_3$ (3×15 mL) and the resulting mixture was purified by filtration through silica gel layer using chloroform as solvent. Then the mixture was analyzed with GC–MS: found m/z=239: $C_{12}H_{11}Cl_2N$ (4.2), **3a**; m/z=219: $C_{10}H_{15}Cl_2N$ (11.5), **3d**; m/z=221: $C_{12}H_{12}ClNO$ (3.6), **12a**; m/z=201: $C_{10}H_{16}ClNO$ (10.1), **12d**; m/z=325: $C_{19}H_{16}ClNO_2$ (10.1), **11a**; m/z=243: $C_{12}H_{18}ClNO_2$ (1.0), **15d**; m/z=263: $C_{14}H_{14}ClNO_2$ (3.6), **15a**; m/z=305: $C_{17}H_{20}ClNO_2$ (1.8), **11d**, the molar ratio of products is given in parentheses.

4.2.5.11. A reaction of compound ***16*** *with the Vilsmeier reagent.* The reaction was carried out according to the general method. The reaction mixture was extracted with $CHCl_3$ (3×15 mL) and the products were separated on a silica gel column (hexane, mixtures hexane/diethyl ether with ratio from 10:1 to 1:2). Yields of benzyl chloride, compound **3a**, and compound **12a** are 14%, 22% and 50%, respectively.

4.2.5.12. A reaction of compound ***17*** *with the Vilsmeier reagent.* The reaction was carried out according to the general method. The reaction mixture was extracted with $CHCl_3$ (3×15 mL) and the products **17** and **3a** were separated on a silica gel column ($CHCl_3$). A conversion was 63%, yield of **3a**—21%.

4.2.5.13. 1-(Benzoyloxy)-4-chloro-5,5-dimethyl-2-(trifluoromethyl)-2,5-dihydro-1H-pyrrol-2-ol ***18****.* Compound **18** was extracted with ether (3×15 mL) and isolated on a silica gel column (hexane/diethyl ether (10:1)). A conversion was 65%, yield of **18**—40%, mp 128–129 °C (hexane/EtOAc). R_f (20% diethyl ether/hexane) 0.44. [Found: C 49.94, H 3.86, N 4.12, Cl 10.48. $C_{14}H_{13}ClF_3NO_3$ requires: C 50.07, H 3.87, N 4.17, Cl 10.58%.] δ_H (400 MHz, $(CD_3)_2CO$) 1.38 (3H, s), 1.50 (3H, s, C^2–(CH_3)$_2$), 6.10 (1H, s, C^4H), 6.6–6.7 (1H, br s, O*H*), 7.5–7.6 (2H, m), 7.65–7.69 (1H, m), 8.08–8.16 (2H, m, Ph). δ_C (100 MHz, $(CD_3)_2CO$) 23.2, 25.1 (C^2–(CH_3)$_2$), 73.1 (C^2), 93.4 (q, J 33 Hz, C^5), 120.0 (C^4), 123.7 (q, J 284 Hz, CF_3), 129.5, 129.6, 130.5, 134.4 (Ph), 146.2 (C^3), 165.2 (O–C=O). ν_{max} (KBr) 3379 (OH), 1736 (O–C=O), 1188 (CF_3) cm^{-1}. UV (ethanol): λ_{max} (lg ε)=229 (4.00), 275 (3.06), 282 (3.06), 316 nm (3.35).

References and notes

1. Reznikov, V. A.; Vishnivetskaya, L. A.; Volodarskii, L. B. *Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Transl.)* **1990**, *39*, 335–340.
2. Kallury, R. K. M. R.; Devi, P. S. U. *Tetrahedron Lett.* **1977**, *41*, 3655–3658.
3. Ashok, K.; Sridevi, G.; Umadevi, Y. *Synthesis* **1993**, 623–626.
4. Anderson, D. J. *J. Org. Chem.* **1986**, *51*, 945–947.
5. Beccalli, E. M.; Marchesini, A. *J. Org. Chem.* **1987**, *52*, 3426–3434.
6. Beccalli, E. M.; Marchesini, A.; Molinari, H. *Tetrahedron Lett.* **1986**, *27*, 627–630.
7. Reznikov, V. A.; Vishnivetskaya, L. A.; Volodarskii, L. B. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1988**, 504–508.
8. Cummins, C. H.; Coates, R. M. *J. Org. Chem.* **1983**, *48*, 2070–2076.
9. Demeunynck, M.; Tohme, N.; Lhomme, M.-F.; Mellor, J. M.; Lhomme, J. *J. Am. Chem. Soc.* **1986**, *108*, 3539–3541.
10. Gutteridge, N. J.; Dales, J. R. M. *J. Chem. Soc. C* **1971**, 122–125.
11. Gibson, N. J.; Forrester, A. R. *J. Chem. Soc., Perkin Trans. 1* **1995**, 491–499.
12. Black, D. St. C.; Strauch, R. J. *Aust. J. Chem.* **1989**, *42*, 71–78.
13. Reznikov, V. A.; Volodarskii, L. B. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1990**, *7*, 767–772.
14. Martin, V. V.; Volodarskii, L. B. *Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Transl.)* **1980**, *29*, 956–962.