5-Chloro Substituted 1,5-Dihydro-2*H*-pyrrol-2-ones as Intermediates for the Efficient Synthesis of 5-Alkylamino, 5-Azido, 5-Alkoxyamino, and 5-Alkoxy Derivatives

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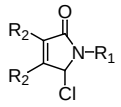
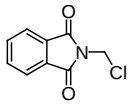
Abstract: 5-Hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones were converted to 5-chloro-1,5-dihydro-2*H*-pyrrol-2-ones **1a**−**d**. These compounds are shown to be useful intermediates for the preparation of various 5-alkoxy, 5-alkylamino, 5-alkoxyamino, and 5-azido derivatives in high yields.

Key words: pyrrolones, alkylations, heterocycles, azides

Substituted 1,5-dihydro-2*H*-pyrrol-2-ones are widely used as herbicide components[1] and as building blocks for total syntheses of natural compounds.[2] The preparation of the 5-hydroxy,[3] 5-alkoxy,[4] 5-cyano,[5] and 5-arylthio[6] derivatives of 1,5-dihydro-2*H*-pyrrol-2-ones is documented but the use of 5-halo substituted 1,5-dihydro-2*H*-pyrrol-2-ones **1** has rarely been employed,[1,2] even though some of these compounds (R_2+R_2 = fused benzene ring) are promising[7] intermediates to get 3-derivatives of the 3-alkylamino-2-alkyl-3-arylisoindolinone series (Figure). Some α-chlorinated imides such as *N*-chloromethylphthalimide (**2**) have recently been studied[8] in substitution reactions with several nucleophiles and good reactivity and selectivity was shown.



1



2

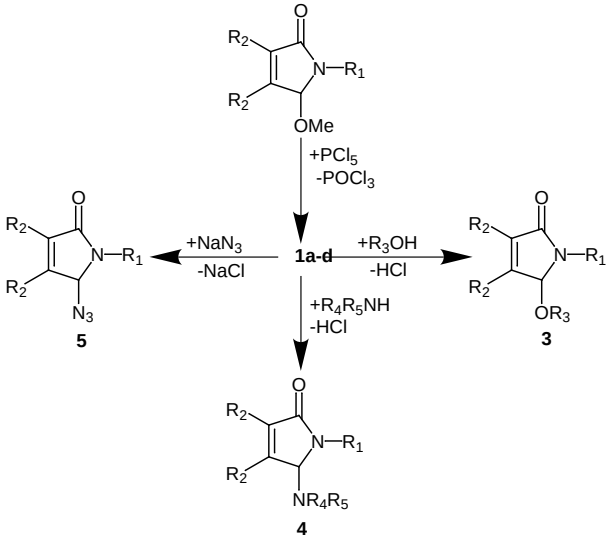
a R_1 = Bn, R_2+R_2 = fused benzene ring
b R_1 = Bn, R_2 = Me
c R_1 = Bu^t, R_2 = Me
d R_1 = -CMe_2-3,5-$Cl_2C_6H_3$, R_2 = Me

Figure

The preparation[1,2,7] of **1** typically involved substitution of the 5-hydroxy group using thionyl chloride. We used a two-step procedure: firstly, methoxylation of 5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones[4] or 3-hydroxy-1-isoindolinone (yields 95−100%) and, secondly PCl_5 methoxy group cleavage using *n*-hexane as solvent (yields 99−100%). This method avoids formation of hydrogen chloride.

Compounds **1a**−**d** are moisture sensitive, undergoing the hydrolytic chlorine substitution, and require anhydrous conditions for storage and handling. Their NMR, IR, and mass spectra fully confirm the monomeric molecular structure of **1**.

We studied the reactions of **1** with both oxygen and nitrogen nucleophilic reagents in order to obtain 5-alkoxy derivatives **3**, amines and alkoxyamines **4,** as well as azides **5** (Scheme). The use of nitrogen nucleophiles gives a facile route to the scarcely known 5-aminosubstituted 1,5-dihydro-2*H*-pyrrol-2-ones.



Scheme

Though alkoxylation of 5-hydroxypyrrolones is rather fast (using MeOH under acidic conditions) and has been reported elsewhere,[4] we found that some bulky alcohols or less nucleophilic phenols do not react at all. We used 5-chloropyrrolones **1** to introduce, in high yields, ethoxy, *tert*-butoxy, and phenoxy groups at the 5-position. These reactions were performed in acetonitrile as solvent in the presence of Et_3N as base under mild conditions (20 °C); the yields and spectral data are reported in Tables 1 and 2. The substitution of chlorine by alkoxy group proceeds quickly and one hour is sufficient for the reaction to be complete (see experimental).

The synthesis of 5-alkylaminopyrrolones **4** has not been reported previously, though 3-alkylaminoisoindolinones

Table 1 Preparation of Compounds **3**–**5**

Product	R_1	R_2	R_3	R_4	R_5	Yield, %
3a	Bn	Me	Et	–	–	94
3b	Bn	Me	Ph	–	–	84
3c	Bn	Me	*t*-Bu	–	–	78
4a	Bn	Me	–	Et	Et	88
4b	Bn	Me	–	H	DDB[a]	84
4c	Bn	Me	–	H	Bn	60
4d	Bn	Me	–	H	BnO	69
4e	Bn	Me	–	H	$ClCH_2CH_2$	80
4f	DDB	Me	–	H	BnO	74
4g	DDB	Me	–	H	Ph	73
4h	DDB	Me	–	Et	Et	73
4i	DDB	Me	–	H	3-FC_6H_4	79
4j	DDB	Me	–	H	3-Cl-4-FC_6H_3	80
4k	DDB	Me	–	H	Bn	61
4l	DDB	Me	–	H	DDB	84
4m	Bn	–[b]	–	H	BnO	77
5a	Bn	–[b]	–	–	–	78
5b	*t*-Bu	Me	–	–	–	77

[a] 1-(3,5-Dichlorophenyl)-1-methylethyl.
[b] $R_2 + R_2$ = Benzene.

were prepared[7] recently. We applied a two-fold excess of the reagent (alkylamine, arylamine, or *O*-benzylhydroxylamine) in acetonitrile in order to absorb the acid, released in the course of the substitution. A combination of the reagent with another base (Et_3N) can also be used. The reactivity of **1** in nucleophilic substitution is high enough for the reaction to be completed during addition of the reagent. Generally, the yields are high to excellent (Table 1); the products **4c**, **4d**, **4k** were obtained in good yields with benzylamine and *O*-benzylhydroxylamine.

The ^{1}H NMR chemical shift difference of the diastereotopic benzylic methylene protons provides reliable determination[7] of the position of the benzyl moiety in **4b**–**e**, **k**, **m.** In all cases, the position of the benzyl group corresponds to that of the initial 5-chloropyrrolone **1** used and no isomeric products were found. Our findings are in good accordance with the high substitution selectivity found in acetonitrile.[7]

The preparation of azides **5** has not been reported to the best of our knowledge. Starting from 5-chloropyrrolones **1** and sodium azide, azides **5a**, **b** can be readily prepared in dry acetonitrile at ambient temperature. The presence of water or alcohols leads to the formation of 5-alkoxy and 5-hydroxypyrrolones, a faster reaction than that leading to azide formation, and, therefore, must be avoided.

In summary, 5-chloro substituted pyrrolones and 3-chloro-1-isoindolinones **1** can be easily prepared in excellent yields and these compounds have been shown to be highly reactive towards nucleophiles. They serve as key intermediates for the facile and convenient preparation of 5-alkylamino-, 5-alkoxyamino-, 5-alkoxy, and 5-azido-1,5-dihydro-2*H*-pyrrol-2-ones and 1-isoindolinones **3**–**5** and may be suitable for parallel syntheses.

Commercially available reagents and solvents were used without further purification. Mps were measured with a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian GEMINI-200 using $CDCl_3$ as solvent. All chemical shifts (δ) are quoted in ppm downfield from TMS and coupling constants are given in Hz. Mass spectra were recorded on a Shimadzu GCMS-OP 1000 mass spectrometer. FT-IR spectra were recorded on a Mattson Genesis II spectrophotometer. Chromatographic separations were carried out on a silica gel column (Merck, 60 microns). Substituted 5-hydroxy and 5-methoxy-2,5-dihydropyrrol-2-ones were prepared by known procedures.[3,4]

3-Chloro-1-isoindolinones and 5-chloro-1,5-dihydro-2*H*-pyrrol-2-ones 1; General Procedure

To a suspension of substituted 5-methoxy-1,5-dihydro-2*H*-pyrrol-2-one (10 mmol) in *n*-hexane (20 mL) was added phosphorus pentachloride (2.09 g, 10 mmol) and the mixture heated under reflux for 2 h when PCl_5 was completely dissolved. The mixture was evaporated at reduced pressure (1 torr) to remove $POCl_3$ and to afford **1** as a glassy solid.

2-Benzyl-3-chloro-2,3-dihydro-(1*H*)-isoindol-1-one (1a)
Yield: 100%.

FTIR (KBr): ν = 1678 (C=O), 1439, 1065 cm^{-1}

^{1}H NMR ($CDCl_3$): δ = 4.27 (d, 1H, *J* = 14.7 Hz), 5.40 (d, 1H, *J* = 14.7 Hz), 6.16 (s, 1H), 7.30 −7.40 (m, 5H), 7.50−7.60 (m, 3H), 7.90 (m, 1H).

MS: *m/z* = 257 (M^+).

1-Benzyl-5-chloro-3,4-dimethyl-1,5-dihydro-2*H*-pyrrol-2-one (1b)
Yield: 98%.

FTIR (KBr): ν = 1685 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.88 (s, 3H), 1.99 (s, 3H), 4.15 (d, 1H, *J* = 14.8 Hz), 5.18 (d, 1H, *J* = 14.8 Hz), 5.45 (s, 1H), 7.30−7.40 (m, 5H).

MS: *m/z* = 235 (M^+).

1-*tert*-Butyl-5-chloro-3,4-dimethyl-1,5-dihydro-2*H*-pyrrol-2-one (1c)
Yield: 98%.

FTIR (KBr): ν = 1681 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.55 (s, 9H), 1.78 (s, 3H), 1.99 (s, 3H), 5.94 (s, 1H).

MS: *m/z* = 201 (M^+).

5-Chloro-1-[1-(3,5-dichlorophenyl)-1-methylethyl]-3,4-dimethyl-1,5-dihydro-2*H*-pyrrol-2-one (1d)
Yield: 100%.

FTIR (KBr): ν = 1680 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.77 (s, 3H), 1.78 (s, 9H), 1.87 (s, 3H), 2.07 (s, 3H), 6.04 (s, 1H), 7.10−7.40 (m, 3H).

MS: *m/z* = 333 ($M^{+,\ 37}Cl$).

1-Benzyl-5-alkoxy-3,4-dimethyl-1,5-dihydro-2*H*-pyrrol-2-ones 3a–c; General Procedure

To a solution of **1** (2.1 mmol) in dry MeCN (2 mL) under N_2 at 0 °C, the dry alcohol (2 mL) or phenol (2.2 mmol) was added followed by the addition of Et_3N (1 mL, 13 mmol), and the reaction mixture was stirred for 1 h at r.t. The solvent was evaporated under reduced pressure, H_2O (10 mL) was added, and the mixture was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried ($MgSO_4$), the solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (*n*-hexane/EtOAc) to obtain **3.** The characteristics of **3** are reported in Table 2.

Table 2 Characterization Data of Compounds **3**–**5**

Product (Formula)	Mp (°C)[a]	IR (KBr) ν (cm^{-1})	^{1}H NMR (200 MHz, $CDCl_3$/TMS) δ, *J* (Hz)	MS *m/z* (%)
3a ($C_{15}H_{19}NO_2$)	–	1698 (CO)	1.11 (t, 3 H, *J* = 4), 1.81 (s, 3 H), 1.87 (s, 3 H), 3.00–3.20 (m, 2 H), 4.10 (d, 1 H, *J* = 15), 4.87 (d, 1 H, *J* = 15), 4.93 (s, 1 H), 7.20–7.28 (m, 5 H)	245 (M^+, 21)
3b ($C_{19}H_{19}NO_2$)	68	1706 (CO)	1.86 (s, 3 H), 1.89 (s, 3 H), 4.10 (d, 1 H, *J* = 15), 5.07 (d, 1 H, *J* = 15), 5.53 (s, 1 H), 6.80–7.30 (m, 10 H)	294 (MH^+, 10)
3c ($C_{17}H_{23}NO_2$)	—	1680 (CO)	1.23 (s, 9 H, *t*-Bu), 1.85 (s, 3 H), 1.93 (s, 3 H), 4.27 (d, 1 H, *J* = 16), 5.06 (d, 1 H, *J* = 16), 5.12 (s, 1 H), 7.10–7.30 (m, 5 H)	273 (M^+, 18)
4a ($C_{17}H_{24}N_2O$)	–	1691 (CO)	0.92 (t, 6 H, *J* = 7.1), 1.82 (s, 6 H), 2.40–2.60 (m, 4H), 4.03 (d, 1 H, *J* = 15), 4.41 (s, 1 H), 5.06 (d, 1 H, *J* = 15), 7.00 (m, 2 H), 7.20–7.30 (m, 3 H)	272 (M^+, 14)
4b ($C_{22}H_{24}Cl_2N_2O$	–	3317 (NH), 1681 (CO)	1.40 (s, 3 H), 1.44 (s, 3 H), 1.64 (s, 1 H), 1.70 (s, 3 H), 1.81 (s, 3 H), 4.06 (d, 1 H, *J* = 16), 4.56 (s, 1 H), 4.96 (d, 1 H, *J* = 16), 7.00–7.30 (m, 8 H)	402 (M^+, 7).
4c ($C_{20}H_{22}N_2O$)	58	3345 (NH), 1666 (CO)	1.82 (s, 1 H), 1.87 (s, 6 H), 3.25 (d, 1 H, *J* = 14), 3.35 (d, 1 H, *J* = 14), 4.17 (d, 1 H, *J* = 15), 4.58 (s, 1 H), 4.97 (d, 1 H, *J* = 15), 7.10–7.30 (m, 10 H)	306 (M^+, 30)
4d ($C_{20}H_{22}N_2O_2$)	–	3233 (NH), 1671 (CO)	1.84 (s, 6 H), 4.25 (d, 1 H, *J* = 15), 4.60 (s, 2 H), 4.44 (s, 1 H), 5.04 (d, 1 H, *J* = 15), 5.55 (br s, 1 H), 7.10–7.30 (m, 10 H)	322 (M^+, 22)
4e ($C_{15}H_{19}ClN_2O$)	90	3332 (NH) 1655 (CO)	1.84 (s, 6 H), 2.10 (br s, 1 H), 2.40–2.60 (m, 2 H), 3.50 (t, 2 H, *J* = 5.6), 4.12 (d, 1 H, *J* = 15), 4.51 (s, 1 H), 5.00 (d, 1 H, *J* = 15), 7.20–7.40 (m, 5 H)	278 (M^+, 28)
4f ($C_{22}H_{24}Cl_2N_2O_2$)	–	3230 (NH), 1675 (CO)	1.73 (s, 9 H), 1.95 (s, 3 H), 4.57 (d, 1 H, *J* = 16), 4.63 (d, 1 H, *J* = 16), 4.85 (d, 1 H, *J* = 3), 5.53 (d, 1 H, *J* = 3), 7.10–7.30 (m, 8 H)	418 (M^+, 10)
4g ($C_{21}H_{22}Cl_2N_2O$)	192	3244 (NH), 1675 (CO)	1.72 (s, 6 H), 1.76 (s, 3 H), 1.87 (s, 3 H), 3.60–3.80 (br s, 1 H), 5.45 (s, 1 H), 6.55 (d, 2 H, *J* = 7.7), 6.79 (t, 1 H, *J* = 7.4), 7.10 (m, 5 H)	388 (M^+, 12)
4h ($C_{19}H_{26}Cl_2N_2O$)	60	1682 (CO)	0.95–1.20 (m, 6 H), 1.68 (s, 3 H), 1.73 (s, 3 H), 1.80 (s, 3 H), 1.91 (s, 3 H), 2.10–2.50 (m, 2 H), 2.80–3.05 (m, 2 H), 4.80 (s, 1 H), 7.20 (s, 3 H)	368 (M^+, 12)
4i ($C_{21}H_{21}Cl_2FN_2O$)	190	3244 (NH), 1677 (CO)	1.72 (s, 6 H), 1.76 (s, 3 H), 1.87 (s, 3 H), 3.82 (d, 1 H, *J* = 8.7), 5.40 (d, 1 H, *J* = 8.7), 6.20–6.30 (m, 2 H), 6.40–6.60 (m, 1 H), 7.10–7.30 (m, 4 H)	406 (M^+, 9)
4j ($C_{21}H_{20}Cl_3FN_2O$)	206	3262 (NH), 1683 (CO)	1.72 (s, 6 H), 1.76 (s, 3 H), 1.85 (s, 3 H), 3.72 (d, 1 H, *J* = 8), 5.29 (d, 1 H, *J* = 8), 6.20–6.40 (m, 1 H), 6.50 (m, 1 H), 6.90–7.00 (m, 1 H), 7.10–7.30 (m, 3 H)	442 (M^+, ^{37}Cl, 10)
4k ($C_{22}H_{24}Cl_2N_2O$)	110	3344 (NH), 1676 (CO)	1.76 (s, 3 H), 1.78 (s, 3 H), 1.86 (s, 3 H), 1.94 (s, 3 H), 3.37 (d, 1 H, *J* = 13), 3.62 (d, 1 H, *J* = 13), 5.10 (s, 1 H), 7.20–7.40 (m, 8 H)	402 (M^+, 12)
4l ($C_{24}H_{26}Cl_4N_2O$)	182	3424 (NH), 1676 (CO)	1.43 (s, 3 H), 1.47 (s, 3 H), 1.64 (s, 3 H), 1.73 (s, 3 H), 1.80 (s, 3 H), 1.81 (s, 3 H), 5.04 (s, 1 H), 7.10–7.50 (m, 6 H).	311 (M^+–187, 43)
4m ($C_{22}H_{20}N_2O_2$)	–	3232 (NH), 1698 (CO)	4.37 (d, 1 H, *J* = 14.9), 4.56 (s, 2 H), 5.18 (br s, 1 H), 5.24 (d, 1 H, *J* = 14.9), 5.72 (br s, 1 H), 7.10–7.30 (m, 10 H), 7.40–7.50 (m, 3 H), 7.80 (m, 1 H)	344 (M^+, 38)
5a ($C_{15}H_{12}N_4O$)	–	2102 (N_3), 1710 (CO)	4.35 (d, 1 H, *J* = 15), 5.28 (d, 1 H, *J* = 15), 5.31 (1 H), 7.30–7.40 (m, 5 H), 7.40–7.50 (m, 3 H), 7.80–7.90 (m, 1 H)	222 (M^+–42, 42)
5b ($C_{10}H_{16}N_4O$)	–	2102 (N_3), 1696 (CO)	1.50 (s, 9 H), 1.80 (s, 3 H), 1.94 (s, 3 H), 4.77 (s, 1 H)	166 (M^+–42, 40)

[a] Mp are not given for liquid and oily products.

5-Alkylamino-3,4-dimethyl-1,5-dihydro-2*H*-pyrrol-2-ones and 5-Benzyloxyamino-3,4-dimethyl-1,5-dihydro-2*H*-pyrrol-2-ones 4; General Procedure

To a solution of **1** (2 mmol) in dry MeCN (2 mL) under N_2 at 0 °C, the amine or *O*-benzylhydroxylamine (4 mmol) was added. The reaction mixture was stirred for 1 h at r.t. after which the solvent was evaporated. H_2O (10 mL) was then added, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), the solvent was evaporated under reduced pressure, and the residue was purified by column chromatography to obtain **4.** The characteristics of **4** are reported in Table 2.

5-Azido-3,4-dimethyl-1,5-dihydro-2*H*-pyrrol-2-ones 5a, b; General Procedure

A solution of **1** (1 mmol) in dry MeCN (3 mL) was added to sodium azide (5 mmol) under N_2. The reaction mixture was stirred for 2 h at r.t., the solvent was evaporated under reduced pressure, H_2O (10 mL) was added, and the mixture was extracted with EtOAc (2 × 5 mL). The combined organic layers were dried ($MgSO_4$), the solvent was evaporated under reduced pressure, and the residue was purified by column chromatography to obtain **5**. The characteristics of **5** are reported in Table 2.

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