STUDIES ON ISOCYANIDES AND RELATED COMPOUNDS. A FACILE SYNTHESIS OF 1-SUBSTITUTED 3-CYANO-2-METHOXY-3-PHENYL-PYRROLES

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Abstract— A simple one-pot synthesis of 1-substituted 3-cyano-1,2-dihydro-2-oxo-4-phenyl-2*H*-pyrroles (**8**) based on the isocyanide chemistry is described. Compounds (**8**) undergo a facile *O*-methylation with diazomethane to give the corresponding 1-substituted 3-cyano-2-methoxy-4-phenylpyrroles (**1**).

In our continuing research on the synthesis of heterocyclic compounds from isocyanides[1] we have shown that three- and four component condensations performed with reagents bearing additional functional groups are useful for the synthesis of furans,[2] pyrroles,[3] and other heterocyclic rings[4] with substitution patterns not easily achieved following other synthetic routes.

The present paper deals with a novel synthetic application of the Ugi four component condensation[5] which allowed us to obtain *N*-cyclohexyl-2-aryl-2-(3-cyano-2-methoxy-4-phenylpyrrol-1-yl)acetamides (**1**).

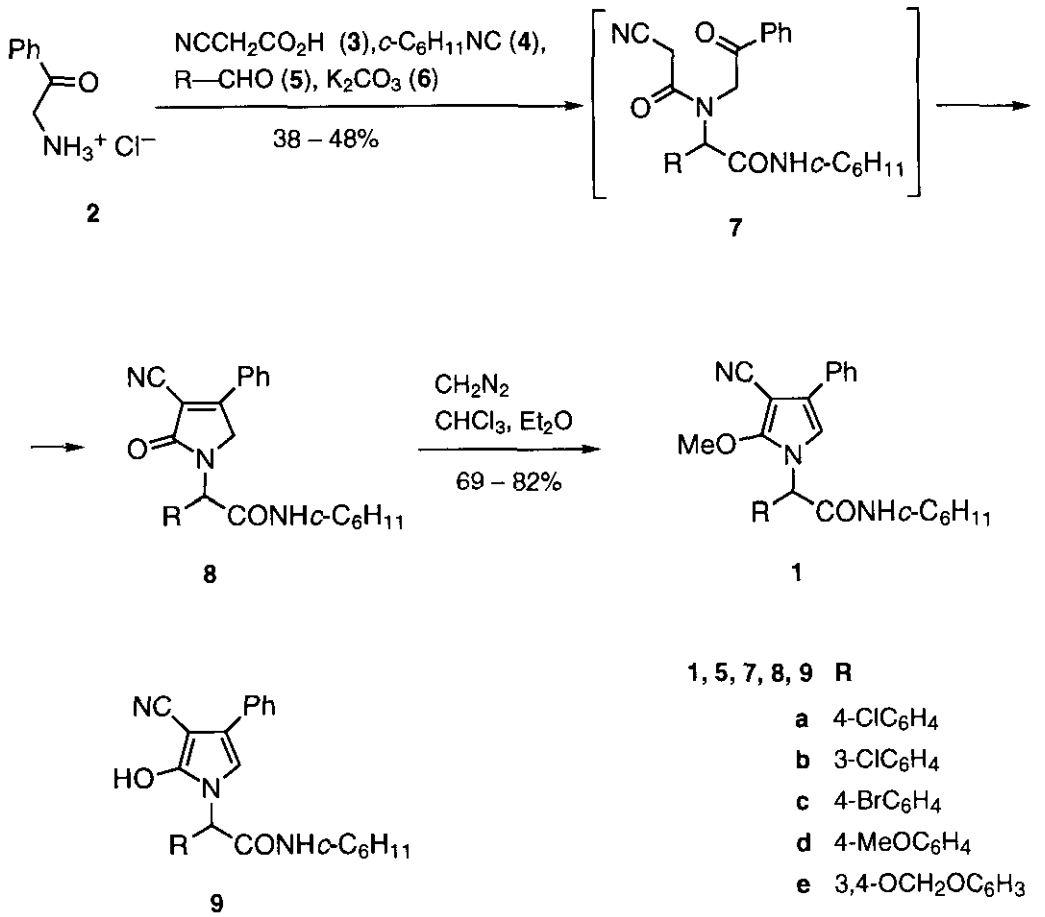
The first step of the synthesis consisted in a four component condensation (4-CC) between phenacylamine hydrochloride (**2**), cyanoacetic acid (**3**), cyclohexyl isocyanide (**4**), and aldehydes (**5**) in the presence of potassium carbonate (**6**). The reaction is much more slow than the usual Ugi 4-CCs, probably because of the low basic strength of phenacylamine that leads to a low concentration of immonium ions in the reaction medium. Nevertheless, by employing long reaction periods, pyrroles (**8**) were obtained in fair yields. We were unable to isolate the 4-CC adducts (**7**), owing to their tendency to cyclize spontaneously.

Evidence for the assigned structures (**8**) was provided by IR spectra: only two C=O absorptions at about 1690 and 1660 cm^{-1} due to the cyclic carbonyl group and to the exocyclic amide group were detected, being the ketone C=O group disappeared in the spontaneous Knoevenagel condensation. The ^1H NMR spectra of compounds (**8**) in DMSO-d_6 showed the existence of a tautomeric equilibrium between the prevalent oxo tautomer (**8**) and the 2-hydroxy tautomer (**9**).The signal of the OH proton of **9** was never detected, due to the rapid isotopic exchange with the solvent. Two exchangeable doublet signals due to the protons of the CH_2

group of **8** were detected at about δ 3.6 and 5.1. The coupling constant values (*ca.* 21 Hz) are in agreement with a geminal coupling. An exchangeable singlet signal at about δ 6.6 due to the H-5 of **9** was detected. Two not exchangeable singlet signals were detected at about δ 5.8 and 6.0, due to the CHCO proton of **8** and **9** , respectively. The integral of the above signals allowed us to determine the concentrations of the tautomers.

Upon treatment of compounds (**8**) with diazomethane in a chloroform/ether suspension a quick evolution of nitrogen was observed and compounds (**1**) were obtained in high yields.

Scheme



2 **7** **8** **1** **9**

1, 5, 7, 8, 9 **R**

- **a** 4-ClC_6H_4
- **b** 3-ClC_6H_4
- **c** 4-BrC_6H_4
- **d** 4-$MeOC_6H_4$
- **e** 3,4-$OCH_2OC_6H_3$

The structure of compounds (**1**) was confirmed by their analytical and spectral data. In the IR spectra, besides the signals of the cyano group at about 2210 cm^{-1} two strong absorptions at about 3290 and 1660 cm^{-1}, due to the NH and the CO of the amide group were detected. In the ^1H NMR spectra of **1** besides the aromatic proton signals, a singlet at about δ 4.24 due to the methoxy group was always detected. Furthermore a singlet signal due to the H-5 of the pyrrole nucleus was detected at about δ 6.24 and an exchangeable multiplet signal

at about δ 5.50 due to the NH proton which is coupled with the H-1 of the cyclohexane ring was detected.

EXPERIMENTAL

Phenacylamine hydrochloride (**2**) was purchased from Fluka, all the other chemicals were obtained from Aldrich and employed without further purification. IR spectra were recorded on a Perkin-Elmer 881 spectrophotometer, ^{1}H NMR spectra on a Varian Gemini 200 spectrometer for saturated solutions at 25 °C. Melting points were determined in open capillary tubes and are uncorrected.

***N*-Cyclohexyl-2-(4-chlorophenyl)-2-(3-cyano-1,2-dihydro-2-oxo-4-phenyl-2*H*-pyrrol-1-yl)acetamide (8a). General Procedure for the Synthesis of Compounds (8).** A solution of phenacylamine hydrochloride (**2**) (2.24 g, 13 mmol), cyanoacetic acid (**3**) (1.10 g, 13 mmol), and 4-chlorobenzaldehyde (**5a**) (1.83 g, 13 mmol) in MeOH (20 mL) was treated under stirring with finely ground K_2CO_3 (**6**) (8.98 g, 6.5 mmol). The resulting suspension was treated with cyclohexyl isocyanide (**4**) (1.42 g, 13 mmol) in MeOH (5 mL) and then with water (5 mL). The reaction mixture was stirred for 48 h at rt and then evaporated to dryness. The residue was stirred with a little *i*-Pr_2O and the resulting suspension filtered. The collected product was washed with water and then recrystallized from MeCN to give **8a** (2.54 g, 45%): mp 247-248 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ^6 0.98-1.82 (m, 10 H, cyclohexane), 3.42-3.70 (m, 1 H, H-1 cyclohexane), 4.39 (d, J = 22.6 Hz, Ha of CH_2), 5.09 (d, J = 22.6 Hz, Hb of CH_2), 5.89 (s, 0.82 H, CHCO of **8**), 6.01 (s, 0.18 H, CHCO of **9**), 6.63 (s, H-5), 7.20-7.95 (m, 9 H arom), 8.32-8.40 (m, NH of **8**), 8.42-8.50 (m, NH of **9**); IR (KBr) 3371, 3338 (NH), 2228 (CN), 1700 (CO), 1678 (CO) cm^{-1}. *Anal.* Calcd for $C_{25}H_{24}N_3O_2Cl$: C, 69.20; H, 5.57; N, 9.68. Found: C, 69.01; H, 5.50 ; N, 9.91.

***N*-Cyclohexyl-2-(3-chlorophenyl)-2-(3-cyano-1,2-dihydro-2-oxo-4-phenyl-2*H*-pyrrol-1-yl)acetamide (8b)**: mp 255-256 °C (EtOH/DMF); 40% yield; ^{1}H NMR (200 MHz, DMSO-d_6) δ^6 0.96-1.91 (m, 10 H, cyclohexane), 3.40-3.68 (m, 1 H, H-1 cyclohexane), 4.42 (d, J = 19.9 Hz, Ha of CH_2), 5.11 (d, J = 19.9 Hz, Hb of CH_2), 5.90 (s, 0.88 H, CHCO of **8**), 6.02 (s, 0.12 H, CHCO of **9**), 6.68 (s, H-5), 7.18-7.98 (m, 9 H arom), 8.27-8.52 (m, NH of **8** + NH of **9**); IR (KBr) 3271 (NH), 2227 (CN), 1700 (CO), 1687 (CO) cm^{-1}. *Anal.* Calcd for $C_{25}H_{24}N_3O_2Cl$: C, 69.20; H, 5.57; N, 9.68. Found: C, 69.15; H, 5.25; N, 9.83.

***N*-Cyclohexyl-2-(4-bromophenyl)-2-(3-cyano-1,2-dihydro-2-oxo-4-phenyl-2*H*-pyrrol-1-yl)acetamide (8c)**: mp 253-254 °C (MeCN); 42% yield; ^{1}H NMR (200 MHz, DMSO-d_6) δ^6 1.01-1.82 (m, 10 H, cyclohexane), 3.40-3.68 (m, 1 H, H-1 cyclohexane), 4.39 (d, J = 21.7 Hz, Ha of CH_2), 5.09 (d, J = 21.7 Hz, Hb of CH_2), 5.87 (s, 0.78 H, CHCO of **8**) 5.99 (s, 0.22 H, CHCO of **9**), 6.63 (s, H-5), 7.18-7.93 (m, 9 H arom), 8.33-8.41 (m, NH of **8**), 8.44-8.52 (m, NH of **9**); IR (KBr) 3292 (NH), 2233 (CN), 1687 (CO), 1656 (CO) cm^{-1}. *Anal.* Calcd for $C_{25}H_{24}N_3O_2Br$: C, 62.77; H, 5.06; N, 8.78. Found: C, 62.90; H, 4.81; N, 9.01.

***N*-Cyclohexyl-2-(3-cyano-1,2-dihydro-2-oxo-4-phenyl-2*H*-pyrrol-1-yl)-2-(4-methoxyphenyl)acetamide (8d)**: mp 164-165 °C (*i*-PrOH); 38% yield; ^{1}H NMR (200 MHz, DMSO-d_6) δ^6 0.99-1.85 (m, 10 H, cyclohexane), 3.35-3.65 (m, 1 H, H-1 cyclohexane), 3.74 (s, 3 H, CH_3), 4.26 (d, J = 20.7 Hz, Ha of CH_2), 5.10 (d, J = 20.7 Hz, Hb of CH_2), 5.92 (s, 0.84 H, CHCO of **8**), 5.95 (s, 0.16 H, CHCO of **9**), 6.50 (s, H-5), 6.80-7.91(m, 9 H arom), 8.18-8.41 (m, NH of **8** + NH of **9**); IR (KBr) 3281 (NH), 2227 (CN), 1708 (CO), 1648 (CO) cm^{-1}. *Anal.* Calcd for $C_{26}H_{27}N_3O_3$: C, 72.71; H, 6.34; N, 9.78. Found: C, 72.45; H, 6.44; N, 9.89.

***N*-Cyclohexyl-2-(3-cyano-1,2-dihydro-2-oxo-4-phenyl-2*H*-pyrrol-1-yl)-2-(3,4-methylenedioxyphenyl)-acetamide (8e)**: mp 227-228 °C (EtOH/DMF); 48% yield; ^{1}H NMR (200 MHz, DMSO-d_6) δ^6 1.01-1.82 (m, 10 H, cyclohexane), 3.36-3.70 (m, 1 H, H-1 cyclohexane), 4.36 (d, J = 22.8 Hz, Ha of CH_2), 5.10 (d, J = 22.8 Hz, Hb of CH_2), 5.79 (s, 0.81 H, CHCO of **8**) 5.88 (s, 0.19 H, CHCO of **9**), 6.01 (s, 2 H, O-CH_2-O) 6.50 (s, H-5), 6.70-7.95(m, 8 H arom), 8.18-8.35 (m, NH of **8**), 8.40-8.51 (m, NH of **9**); IR (KBr) 3266 (NH), 2226 (CN), 1689 (CO), 1689 (CO) cm^{-1}. *Anal.* Calcd for $C_{26}H_{25}N_3O_4$: C, 70.41; H, 5.68; N, 9.47. Found: C, 70.30; H, 5.85; N, 9.38.

***N*-Cyclohexyl-2-(4-chlorophenyl)-2-(3-cyano-2-methoxy-4-phenylpyrrol-1-yl)acetamide (1a). General Procedure for the Synthesis of Compounds (1).** A saturated solution of **8a** (1.04 g, 2.4 mmol) in $CHCl_3$ (10 mL) was treated with a large excess (*ca.* 4 : 1) of an ethereal solution of diazomethane. The resulting mixture was allowed to react for 12 h at rt and then evaporated to dryness to give **1a** (0.86 g, 80 %): mp 184-185 °C (*i*-PrOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.91-1.88 (m, 10 H, cyclohexane), 3.80-3.88 (m, 1 H, H-1 cyclohexane), 4.24 (s, 3 H, OCH_3), 5.58-5.63 (m, 1 H, NH), 5.73 (s, 1 H, CHCO), 6.26 (s, 1 H, H-5 pyrrole), 7.26-7.44 (m, 9 H arom); IR (KBr) 3288 (NH), 2209 (CN), 1663 (CO) cm^{-1}. *Anal.* Calcd for $C_{26}H_{26}N_3O_2Cl$: C, 69.71; H, 5.85; N, 9.38. Found: C, 69.90; H, 5.98; N, 9.21.

N-Cyclohexyl-2-(3-chlorophenyl)-2-(3-cyano-2-methoxy-4-phenylpyrrol-1-yl)acetamide (1b): mp 160-161 °C (EtOH); 71% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.87- 1.91 (m, 10 H cyclohexane), 3.81-3.86 (m, 1 H, H-1 cyclohexane), 4.25 (s, 3 H, OCH_3), 5.54-5.60 (m, 1 H, NH), 5.75 (s, 1 H, CHCO), 6.27 (s, 1 H, H-5 pyrrole), 7.18-7.55 (m, 9 H arom); IR (KBr) 3285 (NH), 2209 (CN), 1651 (CO) cm^{-1}. *Anal.* Calcd for $C_{26}H_{26}N_3O_2Cl$: C, 69.71; H, 5.85; N, 9.38. Found: C, 69.50; H, 5.99; N, 9.19.

***N*-Cyclohexyl-2-(4-bromophenyl)-2-(3-cyano-2-methoxy-4-phenylpyrrol-1-yl)acetamide (1c)**: mp 185-186 °C (*i*-PrOH); 77% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.86- 1.92 (m, 10 H, cyclohexane), 3.78-3.86 (m, 1 H, H-1 cyclohexane), 4.24 (s, 3 H, OCH_3), 5.50-5.56 (m, 1 H, NH), 5.73 (s, 1 H, CHCO), 6.23 (s, 1 H, H-5 pyrrole), 7.13-7.43 (m, 9 H arom); IR (KBr) 3293 (NH), 2213 (CN), 1659 (CO) cm^{-1}. *Anal.* Calcd for $C_{26}H_{26}N_3O_2Br$: C, 63.42; H, 5.32; N, 8.53. Found: C, 63.60; H, 5.05; N, 8.73.

***N*-Cyclohexyl-2-(3-cyano-2-methoxy-4-phenylpyrrol-1-yl)-2-(4-methoxyphenyl)acetamide (1d)**: mp 151-152 °C (*i*-PrOH); 69% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.86- 1.93 (m, 10 H, cyclohexane), 3.71-3.85 (m, 4 H, H-1 cyclohexane + CH_3OPh), 4.24 (s, 3 H, OCH_3), 5.48-5.57 (m, 1 H, NH), 5.72 (s, 1 H, CHCO), 6.20 (s, 1 H, H-5 pyrrole), 6.92-7.53 (m, 9 H arom); IR (KBr) 3283 (NH), 2213 (CN), 1650 (CO) cm^{-1}. *Anal.* Calcd for $C_{27}H_{29}N_3O_3$: C, 73.11; H, 6.59; N, 9.47. Found: C, 73.12; H, 6.70; N, 9.25.

***N*-Cyclohexyl-2-(3-cyano-2-methoxy-4-phenylpyrrol-1-yl)-2-(3,4-methylenedioxyphenyl)acetamide (1e)**: mp 170-171 °C (EtOH); 82% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88- 1.92 (m, 10 H, cyclohexane), 3.80-3.86 (m, 1 H, H-1 cyclohexane), 4.23 (s, 3 H, OCH_3), 5.43-5.50 (m, 1 H, NH), 5.67 (s, 1 H, CHCO), 5.98 (s, 2 H, CH_2), 6.24 (s, 1 H, H-5 pyrrole), 6.80-7.55 (m, 8 H arom); IR (KBr) 3310 (NH), 2213 (CN), 1656 (CO) cm^{-1}. *Anal.* Calcd for $C_{27}H_{27}N_3O_4$: C, 70.88; H, 5.95; N, 9.18. Found: C, 71.05; H, 5.81; N, 9.29.

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6. The integrals of the signals due to the following protons: CH_2 of **8** , H-5 of **9** , NH of **8** , NH of **9** are not reported because the isotopic exchange with the solvent makes these values useless for the determination of the concentrations of the tautomers.

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