

STUDIES ON ISOCYANIDES AND RELATED COMPOUNDS. A NOVEL SYNTHETIC ROUTE TO 1,6-DIHYDRO-6-OXOPYRIDINE-2-CARBOXYLIC ACID DERIVATIVES

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Abstract— The Ugi 4-CC between (*E*)-cinnamaldehyde (**2**), benzoylformic acid (**3**), cyclohexyl isocyanide (**4**) and amines (**5**) afforded the expected (*E*)-2-[*N*-benzoylformyl-*N*-arylamino]-4-phenylbut-3-enoic acid *N*-cyclohexylamides (**6**) which underwent a base-catalyzed cyclization to give the title compounds in high yields.

The 1,6-dihydro-6-oxopyridine-2-carboxylic acid moiety is contained in natural products such as acromelic acids.² The totally hydrogenated ring has been found in the amino acid tabtoxine δ -lactam, a metabolite of *Pseudomonas* species.³ Furthermore, some derivatives of 1,6-dihydro-6-oxopyridine-2-carboxylic acid are interesting because of their biological activities.⁴

The synthesis of these compounds has been achieved starting from suitable pyridine derivatives. Thus, the reaction of appropriate pyridine *N*-oxides with trifluoroacetic anhydride affords the desired hydroxylated compounds.⁵ An alternative method consists in the reaction of pyridinecarboxylic acids with fluorine.⁶ For this procedure a poor regioselectivity has been claimed, and a microbial hydroxylation of 2-picolinic acid has been proposed for a large-scale preparation of the parent compound.⁷ Another elegant approach is based on the cleavage of 4,6-dichloro-2-oxa-5-azabicyclo[2.2.2]oct-5-en-3-ones.⁴

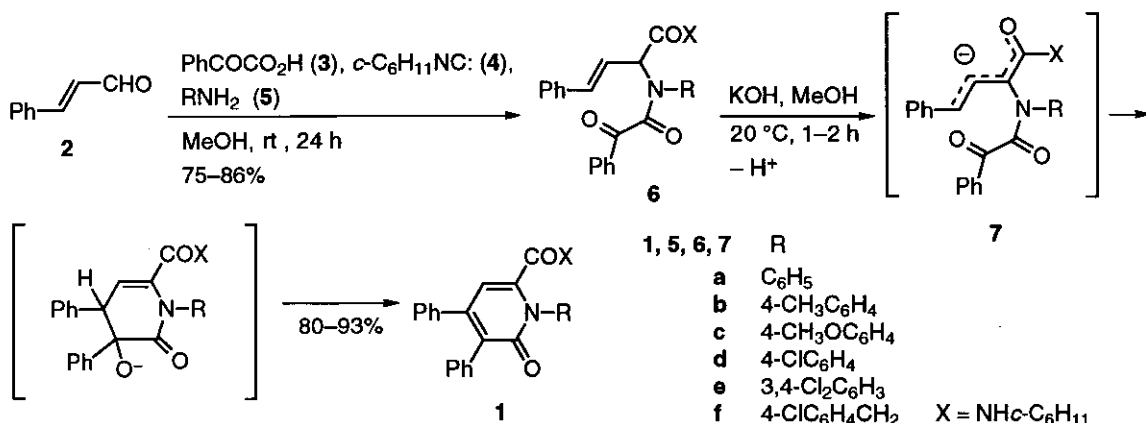
The present note, belonging to a series of articles on the synthetic utility of isocyanides,⁸ deals with a convenient two-step synthesis of 1-substituted *N*-cyclohexyl-1,6-dihydro-6-oxo-4,5-diphenylpyridine-2-carboxamides (**1**).

The first step of the synthesis consisted in the reaction between (*E*)-cinnamaldehyde (**2**), benzoylformic acid (**3**), cyclohexyl isocyanide (**4**), and amines (**5**). The reaction took place easily, giving the expected Ugi four-component condensation products⁹ (**6**) in high yields and in an almost pure form. Upon treatment with methanolic KOH, compounds (**6**) underwent a ring-closure reaction that afforded the pyridones (**1**) in very good yields.

The IR and ¹H NMR spectral data of compounds (**1**) were in agreement with the assigned structures. Thus, in the IR spectra of **1** a strong absorption due to the amide NH group was detected at about 3270 cm⁻¹. Furthermore, two absorptions at about 1670 and 1630 cm⁻¹ were detected due to the cyclic CO and to the amide

carbonyl group, respectively. In the ^1H NMR spectra of compounds (1) a singlet signal at about δ 6.5, due to the proton in position -3 of the pyridine ring, was clearly detected. Further evidence for the assigned structures (1) was provided by MS spectra. In fact, besides the molecular ion, the fragment ion ($\text{PhC}=\text{CPhCH}^+$) m/z 191 was always detected.

A possible reaction mechanism is reported in the Scheme 1. The key intermediate is the highly-stabilized anion (7) which behaves as a benzyl anion in the intramolecular nucleophilic attack on the oxo group.



Scheme 1

EXPERIMENTAL

All of the starting products were purchased from Aldrich and employed without further purification. IR spectra were recorded on a Perkin-Elmer 881 spectrophotometer, ^1H NMR spectra on a Varian Gemini 200 spectrometer, and MS spectra on a Carlo Erba QMD 1000 apparatus at 70 eV. Melting points are uncorrected.

(E)-2-[N-Benzoylformyl-N-phenylamino]-4-phenylbut-3-enoic acid N-cyclohexylamide (6a). General Procedure for the Synthesis of Compounds (6). A solution of aniline (5a) (1.32 g, 14 mmol) in MeOH (5 mL) was added to a well-stirred solution of benzoylformic acid (3) (2.11 g, 14 mmol) in MeOH (5 mL). The resulting solution was treated, as quickly as possible, with a solution of (E)-cinnamaldehyde (2) (1.85 g, 14 mmol) in MeOH (5 mL), and then with a solution of cyclohexyl isocyanide (4) (1.53 g, 14 mmol) in MeOH (5 mL). The resulting mixture was stirred for 24 h at rt and then filtered. The collected product was washed with a little *i*-PrOH and then with *i*-Pr₂O, and dried to give **6a** (5.43 g, 83%); mp 177–178 °C (EtOH); IR (KBr) 3341, 1671, 1659, 1641 cm^{-1} . *Anal.* Calcd for $\text{C}_{30}\text{H}_{30}\text{N}_2\text{O}_3$: C, 77.23; H, 6.48; N, 6.01. Found: C, 77.01; H, 6.63; N, 6.14.

(E)-2-[N-Benzoylformyl-N-(4-methylphenyl)amino]-4-phenylbut-3-enoic acid N-cyclohexylamide (6b): mp 170–171 °C (EtOH); yield 82 %; IR (KBr) 3320, 1677, 1648 cm^{-1} . *Anal.* Calcd for $\text{C}_{31}\text{H}_{32}\text{N}_2\text{O}_3$: C, 77.48; H, 6.71; N, 5.83. Found: C, 77.40; H, 6.76; N, 5.99.

(E)-2-[N-Benzoylformyl-N-(4-methoxyphenyl)amino]-4-phenylbut-3-enoic acid N-cyclohexylamide (6c): mp 153–154 °C (EtOH); yield 80 %; IR (KBr) 3357, 1673, 1657, 1640 cm^{-1} . *Anal.* Calcd for $\text{C}_{31}\text{H}_{32}\text{N}_2\text{O}_4$: C, 74.98; H, 6.50; N, 5.64. Found: C, 75.12; H, 6.51; N, 5.73.

(E)-2-[N-Benzoylformyl-N-(4-chlorophenyl)amino]-4-phenylbut-3-enoic acid N-cyclohexylamide (6d): mp 193–194 °C (EtOH); yield 86 %; IR (KBr) 3316, 1680, 1660, 1648 cm^{-1} . *Anal.* Calcd for $\text{C}_{30}\text{H}_{29}\text{N}_2\text{O}_3\text{Cl}$: C, 71.92; H, 5.84; N, 5.59. Found: C, 71.72; H, 5.59; N, 5.72.

(E)-2-[N-Benzoylformyl-N-(3,4-dichlorophenyl)amino]-4-phenylbut-3-enoic acid N-cyclohexylamide (6e): mp 174–175 °C (EtOH); yield 79 %; IR (KBr) 3326, 1675, 1655 cm^{-1} . *Anal.* Calcd for $\text{C}_{30}\text{H}_{28}\text{N}_2\text{O}_3\text{Cl}_2$: C, 67.30; H, 5.27; N, 5.23. Found: C, 67.21; H, 5.12; N, 5.36.

(E)-2-[N-Benzoylformyl-N-(4-chlorobenzyl)amino]-4-phenylbut-3-enoic acid N-cyclohexylamide (6f): mp 129–130 °C (EtOH); yield 75 %; IR (KBr) 3264, 1676, 1640 cm^{-1} . *Anal.* Calcd for $\text{C}_{31}\text{H}_{31}\text{N}_2\text{O}_3\text{Cl}$: C, 72.29; H, 6.07; N, 5.44. Found: C, 72.21; H, 6.25; N, 5.46.

N-Cyclohexyl-1,6-dihydro-6-oxo-1,4,5-triphenylpyridine-2-carboxamide (1a). General Procedure for the Synthesis of Compounds (1). Compound (6a) (3.04 g, 6.5 mmol) was added to a well-stirred solution of KOH (0.36 g, 6.5 mmol) in MeOH (10 mL). The resulting mixture was stirred at rt for 2 h and then cooled and filtered. The collected product was washed with water, and then with a little *i*-PrOH, and dried to give **1a** (2.51 g, 86%): mp 264–265 °C (EtOH); ^1H NMR (200 MHz, CDCl_3) δ 0.84–1.63 (m, 10 H), 3.48–3.69 (m, 1 H), 5.53–6.64 (m, 1 H), 6.61 (s, 1 H), 6.91–7.47 (m, 15 H); IR (KBr) 3267, 1667, 1659, 1631 cm^{-1} ; MS m/z 448 (M^+), 191 ($\text{PhC}=\text{CPhCH}^+$). *Anal.* Calcd for $\text{C}_{30}\text{H}_{28}\text{N}_2\text{O}_2$: C, 80.33; H, 6.29; N, 6.25. Found: C, 80.31; H, 6.09; N, 6.54.

N-Cyclohexyl-1,6-dihydro-1-(4-methylphenyl)-6-oxo-4,5-diphenylpyridine-2-carboxamide (1b): mp 260–261 °C (EtOH); yield 88%; ^1H NMR (200 MHz, CDCl_3) δ 0.86–1.67 (m, 10 H), 2.38 (s, 3 H), 3.54–3.66 (m, 1 H), 5.63–5.72 (m, 1 H), 6.57 (s, 1 H), 7.08–7.38 (m, 14 H); IR (KBr) 3252, 1671, 1631 cm^{-1} ; MS m/z 462 (M^+), 191 ($\text{PhC}=\text{CPhCH}^+$). *Anal.* Calcd for $\text{C}_{31}\text{H}_{30}\text{N}_2\text{O}_2$: C, 80.49; H, 6.54; N, 6.06. Found: C, 80.32; H, 6.72; N, 5.89.

N-Cyclohexyl-1,6-dihydro-1-(4-methoxyphenyl)-6-oxo-4,5-diphenylpyridine-2-carboxamide (1c): mp 265–266 °C (EtOH); yield 85%; ^1H NMR (200 MHz, CDCl_3) δ 0.88–1.64 (m, 10 H), 3.50–3.72 (m, 1 H), 3.82 (s, 3 H), 5.64–5.76 (m, 1 H), 6.55 (s, 1 H), 6.81–7.33 (m, 14 H); IR (KBr) 3255, 1665, 1633 cm^{-1} ; MS m/z 478 (M^+), 191 ($\text{PhC}=\text{CPhCH}^+$). *Anal.* Calcd for $\text{C}_{31}\text{H}_{30}\text{N}_2\text{O}_3$: C, 77.80; H, 6.32; N, 5.86. Found: C, 77.56; H, 6.30; N, 5.99.

1-(4-Chlorophenyl)-N-cyclohexyl-1,6-dihydro-6-oxo-4,5-diphenylpyridine-2-carboxamide (1d): mp 263–264 °C (EtOH); yield 93%; ^1H NMR (200 MHz, CDCl_3) δ 0.92–1.62 (m, 10 H), 3.56–3.68 (m, 1 H), 5.79–

5.89 (m, 1 H), 6.51 (s, 1 H), 7.10–7.43 (m, 14 H); IR (KBr) 3269, 1666, 1631 cm^{-1} ; MS m/z 482 (M^+), 191 ($\text{PhC}=\text{CPhCH}^+$). *Anal.* Calcd for $\text{C}_{30}\text{H}_{27}\text{N}_2\text{O}_2\text{Cl}$: C, 74.60; H, 5.64; N, 5.80. Found: C, 74.76; H, 5.51; N, 5.82.

1-(3,4-Dichlorophenyl)-N-cyclohexyl-1,6-dihydro-6-oxo-4,5-diphenylpyridine-2-carboxamide (1e): mp 261–262 °C (EtOH); yield 85%; ^1H NMR (200 MHz, CDCl_3) δ 1.01–1.71 (m, 10 H), 3.52–3.76 (m, 1 H), 5.87–5.98 (m, 1 H), 6.51 (s, 1 H), 7.16–7.54 (m, 13 H); IR (KBr) 3281, 1669, 1634 cm^{-1} ; MS m/z 516 (M^+), 191 ($\text{PhC}=\text{CPhCH}^+$). *Anal.* Calcd for $\text{C}_{30}\text{H}_{26}\text{N}_2\text{O}_2\text{Cl}_2$: C, 69.64; H, 5.07; N, 5.42. Found: C, 69.73; H, 5.21; N, 5.49.

1-(4-Chlorobenzyl)-N-cyclohexyl-1,6-dihydro-6-oxo-4,5-diphenylpyridine-2-carboxamide (1f): mp 224–225 °C (EtOH); yield 80%; ^1H NMR (200 MHz, CDCl_3) δ 0.98–1.86 (m, 10 H), 3.74–3.84 (m, 1 H), 5.55 (s, 2 H), 5.74–5.86 (m, 1 H), 6.36 (s, 1 H), 6.81–7.33 (m, 14 H); IR (KBr) 3351, 1633 cm^{-1} ; MS m/z 496 (M^+), 191 ($\text{PhC}=\text{CPhCH}^+$). *Anal.* Calcd for $\text{C}_{31}\text{H}_{29}\text{N}_2\text{O}_2\text{Cl}$: C, 74.91; H, 5.88; N, 5.64. Found: C, 75.06; H, 5.89; N, 5.49.

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