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 tabtoxinine 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]

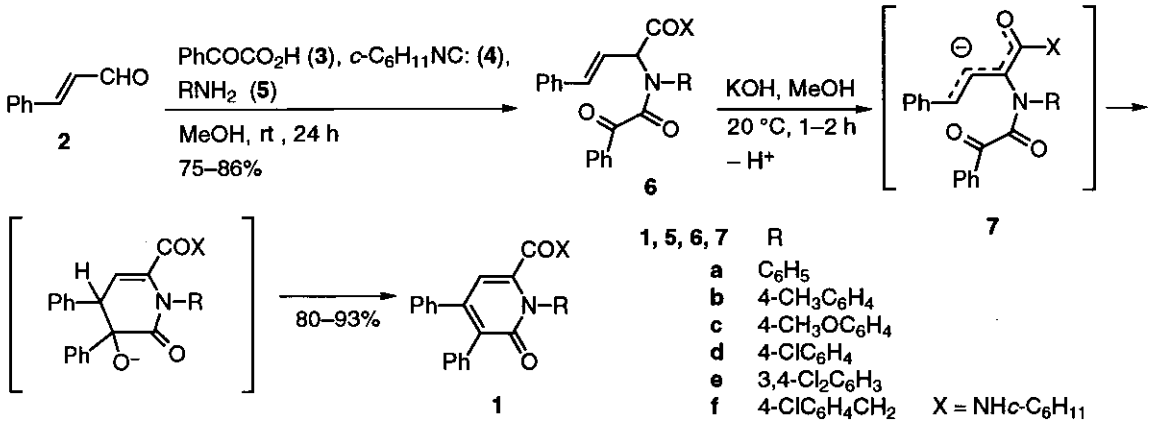
The present note, belonging to a series of articles on the synthetic utility of isocyanides,[8] deals with a convenient two-step synthesis of 1-substituted *N*-cyclohexyl-1,6-dihydro-6-oxo-4,5-diphenylpyridine-2-carboxamides (**1**).

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 products[9] (**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 ^{1}H 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 ^{1}H 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 (PhC=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, ^{1}H 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*-Pr$_2$O, 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 $C_{30}H_{30}N_2O_3$: 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 $C_{31}H_{32}N_2O_3$: 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 $C_{31}H_{32}N_2O_4$: 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 $C_{30}H_{29}N_2O_3Cl$: 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 $C_{30}H_{28}N_2O_3Cl_2$: 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 $C_{31}H_{31}N_2O_3Cl$: 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 ($PhC{=}CPhCH^+$). *Anal.* Calcd for $C_{30}H_{28}N_2O_2$: 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 ($PhC{=}CPhCH^+$). *Anal.* Calcd for $C_{31}H_{30}N_2O_2$: 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 ($PhC{=}CPhCH^+$). *Anal.* Calcd for $C_{31}H_{30}N_2O_3$: 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 ($PhC{=}CPhCH^+$). *Anal.* Calcd for $C_{30}H_{27}N_2O_2Cl$: 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 ($PhC{=}CPhCH^+$). *Anal.* Calcd for $C_{30}H_{26}N_2O_2Cl_2$: 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 ($PhC{=}CPhCH^+$). *Anal.* Calcd for $C_{31}H_{29}N_2O_2Cl$: C, 74.91; H, 5.88; N, 5.64. Found: C, 75.06; H, 5.89; N, 5.49.

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REFERENCES AND NOTES

1. Present address: Departamento de Química Orgánica, Facultad de Veterinaria, Universidad de Extremadura, E–10071 Cáceres, Spain.
2. K. Konno, H. Shirahama, and T. Matsumoto, *Tetrahedron Lett.*, 1983, **24**, 939; K. Yamano and H. Shirahama, *Chem. Lett.*, 1993, 21; K. Konno, K. Hashimoto, Y. Ohfune, H. Shirahama, and T. Matsumoto, *J. Am. Chem. Soc.*, 1988, **110**, 4807.
3. D. L. Lee and H. Rapoport, *J. Org. Chem.*, 1975, **40**, 3491.
4. K. J. Dubois, C. C. Fannes, F. Compernolle, and G. Hoornaert, *Tetrahedron*, 1996, **52**, 2591 and references therein.
5. K. Konno, K. Hashimoto, H. Shirahama, and T. Matsumoto, *Heterocycles*, 1986, **24**, 2169.
6. M. Van der Puy, D. Nalewajek, and G. E. Wicks, *Tetrahedron Lett.*, 1988, **29**, 4389.
7. A. Kiener, R. Glöckler, and K. Heinzmann, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1201.
8. S. Marcaccini and T. Torroba, *Org. Prep. Proced. Int.*, 1993, **25**, 141; R. Bossio, S. Marcaccini, and R. Pepino, *Synthesis* , 1994, 765; R. Bossio, S. Marcaccini, and R. Pepino, *Tetrahedron Lett.*, 1995, **36**, 2325; R. Bossio, S. Marcaccini, R. Pepino, and T. Torroba, *J. Org. Chem.*, 1996, **61**, 2202; R. Bossio, S. Marcaccini, R. Pepino, and T. Torroba, *J. Chem. Soc., Perkin Trans. 1*, 1996, 229; R. Bossio, S. Marcaccini, R. Pepino, and T. Torroba, *Heterocycles*, 1996, **43**, 471.
9. I. Ugi, A. Dömling, and W. Hörl, *Endeavour*, 1994, **18**, 115 and references therein.

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