Studies on Isocyanides and Related Compounds. Synthesis of Furan Derivatives and Their Transformation into Indole Derivatives

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Dedicated to the memory of our colleague and friend Ricardo Bossio

The intramolecular Knoevenagel condensation of *N*-cyclohexyl 3-aryl-2-(2-nitrophenyl)acetoxy-3-oxopropionamides **4** obtained from 2-nitrophenylacetic acid (**1**), arylglyoxals **2** and cyclohexyl isocyanide (**3**) afforded *N*-cyclohexyl 3-aryl-2,5-dihydro-2-(2-nitrophenyl)-5-oxofuran-2-carboxamides **6** which underwent reductive cleavage to *N*-cyclohexyl (*Z*)-3-aryl-2-hydroxy-3-(2,3-dihydro-2-oxoindol-3-ylidene)propionamides **8** probably *via* the labile intermediates **7**.

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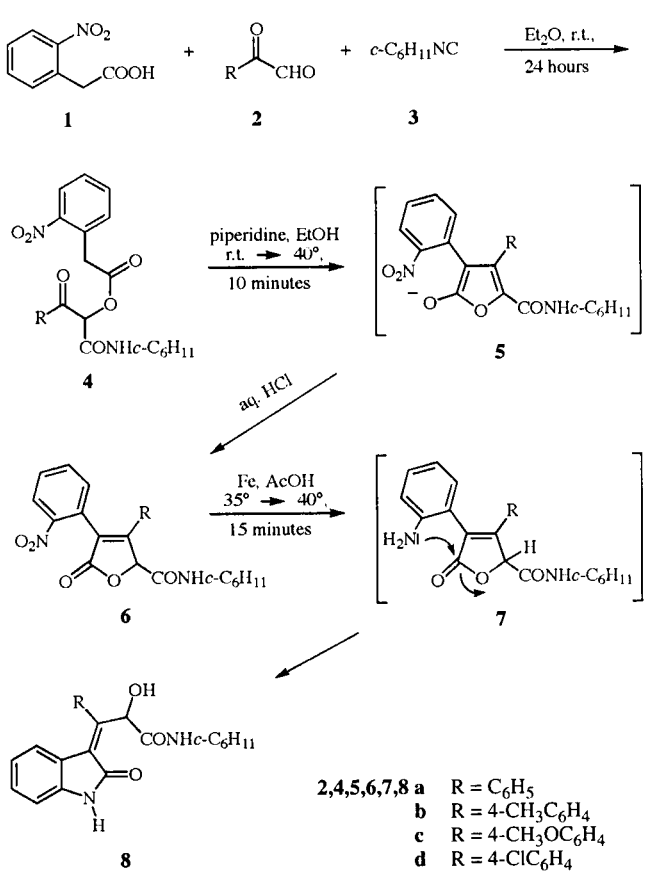
In continuation of our studies on the synthesis of heterocyclic compounds from isocyanides [I] we found that the Passerini three-component reaction between isocyanides, arylglyoxals, and cyanoacetic or arylsulfonylacetic acids affords a series of adducts which structure is suitable to give an intramolecular Knoevenagel condensation leading to furan derivatives having a substitution pattern which appears not easily achievable following other synthetic routes [2]. One of these derivatives, namely *N*-cyclohexyl 3-(4-chlorophenyl)-5-methoxy-4-phenylsulfonylfuran-2-carboxamide, showed antitumor activity in preliminary tests [3].

Keeping in mind the above results we decided to attempt the synthesis of a series of furan derivatives by employing 2-nitrophenylacetic acid (**1**) as the acid component in the Passerini reaction. The 2-nitrophenylacetic acid was chosen for two reasons: it is similar from the electronic point of view to both cyanoacetic and arysulfonylacetic acids, furthermore, the reduction of the nitro group may offer further synthetic possibilities.

The reaction between **1**, arylglyoxals **2**, and cyclohexyl isocyanide (**3**) took place smoothly at room temperature, giving the expected *N*-cyclohexyl 3-aryl-2-(2-nitrophenyl)acetoxy-3-oxopropionamides **4** in high yields. Compounds **4** were precipitated from the mother liquors in an almost pure form and were employed for the successive reaction without further purification.

Upon treatment of an ethanolic suspension of **4** with triethylamine, a deep violet, permanganate-like solution was obtained. This color, due to the high conjugation of the anion **5**, arising from the condensation between the carbonyl group and the methylene one, disappeared upon treatment with acids that led to the formation of the sparingly soluble, colorless *N*-cyclohexyl 3-aryl-2,5-dihydro-2-(2-nitrophenyl)-5-oxofuran-2-carboxamides **6**. It must be underlined that, whereas the Knoevenaael condensation is usually carried out with catalytic amounts of base, in this case stoichiometric amounts of base are required since it is consumed because of the formation of the salts **5**.



The reduction of compounds **6** was carried out in a satisfactory manner by employing iron in acetic acid, attempts to perform the reduction with zinc or tin gave poor results. In all of the runs the isolation of the amino derivatives **7** failed since the amino group gives a nucleophilic attack on the lactone carbonyl group with subsequent opening of the furan ring and formation of *N*-cyclohexyl (*Z*)-3-aryl-2-hydroxy-3-(2,3-dihydro-2-oxoindol-3-ylidene)propionamides (**8**) in good yields. To our knowledge a similar "ring switching" reaction has been reported recently [4].

EXPERIMENTAL

2-Nitrophenylacetic acid (**1**) was purchased from Aldrich, arylglyoxals **2a** [5], **2b** [6], **2c** [6], **2d** [6] and cyclohexyl isocyanide (**3**) [7] were prepared following literature procedures. Iron powder (150 μm) from Merck was employed in all of the reduction reactions.

Melting points were determined on a Büchi 512 melting point apparatus in open capillary tubes and are uncorrected. The ir spectra were taken on a Perkin-Elmer 881 spectrophotometer in potassium bromide pellets. The ^{1}H nmr spectra were recorded on a Varian Gemini 200 apparatus at 200 MHz. The mass spectra (ms) were recorded on a Carlo Erba QMD 1000 spectrometer operating at 70 eV.

Three-Component Reactions Between 2-Nitrophenylacetic Acid (**1**), Arylglyoxals **2**, and Cyclohexyl Isocyanide (**3**).

General Procedure.

A well-stirred suspension of 2-nitrophenylacetic acid (**1**) (3.81 g, 21 mmoles) in diethyl ether (70 ml) was treated with a solution of arylglyoxal **2** (21 mmoles) in diethyl ether (30 ml). A solution of cyclohexyl isocyanide (**3**) (2.29 g, 21 mmoles) in diethyl ether (10 ml) was added as soon as possible to the above suspension and the resulting mixture was stirred at room temperature for 24 hours. Adducts **4** were isolated by filtration.

N-Cyclohexyl 2-(2-Nitrophenyl)acetoxy-3-oxo-3-phenylpropionamide (**4a**).

This compound was obtained as white crystals in 77% yield, mp 130-131° from *i*-PrOH; ir: ν 3275 (NH), 1753 (CO-O), 1696 (CO), 1649 (CO-N), 1340 (NO_2) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.05-1.89 (m, 10H, cyclohexyl), 3.67 (m, 1H, 1-H cyclohexyl), 4.07 (d, J = 16.8 Hz, 1H, $COCH_2$), 4.28 (d, J = 16.8 Hz, 1H, $COCH_2$), 6.19 (d, J = 8.0 Hz, 1H, NH), 6.32 (s, 1H, COCHCO), 7.38-8.13 (m, 9H, aromatic).

Anal. Calcd. for $C_{23}H_{24}N_2O_6$: C, 65.08; H, 5.70; N, 6.60. Found: C, 65.25; H, 5.72; N, 6.41.

N-Cyclohexyl 3-(4-Methyphenyl)-2-(2-nitrophenyl)acetoxy-3-oxopropionamide (**4b**).

This compound was obtained as white crystals in 84% yield, mp 145-146° from EtOH; ir: ν 3294 (NH), 1757 (CO-O), 1693 (CO), 1650 (CO-N), 1343 (NO_2) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.03-1.89 (m, 10H, cyclohexyl), 2.37 (s, 3H, CH_3), 3.67 (m, 1H, 1-H cyclohexyl), 4.07 (d, J = 17.0 Hz, 1H, $COCH_2$), 4.29 (d, J = 17.0, 1H, $COCH_2$), 6.14 (d, J = 8.4 Hz, 1H, NH), 6.31 (s, 1H, COCHCO), 7.20-8.14 (m, 8H, aromatic).

Anal. Calcd. for $C_{24}H_{16}N_2O_6$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.52; H, 5.90; N, 6.50.

N-Cyclohexyl 3-(4-Methoxyphenyl)-2-(2-nitrophenyl)acetoxy-3-oxopropionamide (**4c**).

This compound was obtained as white crystals in 85% yield, mp 124-126° from EtOH; ir ν 3264 (NH), 1745 (CO-O), 1680 (CO), 1650 (CO-N), 1349 (NO_2) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.04-1.85 (m, 10H, cyclohexyl), 3.67 (m, 1H, 1-H cyclohexyl), 3.83 (s, 3H, CH_3), 4.07 (d, J = 16.8 Hz, 1H, $COCH_2$), 4.29 (d, J = 16.8 Hz, 1H, $COCH_2$), 6.15 (d, J = 8.2 Hz, 1H, NH), 6.29 (s, 1H, COCHCO), 6.86-8.14 (m, 8H, aromatic).

Anal. Calcd. for $C_{24}H_{26}N_2O_7$: C, 63.43; H, 5.77; N, 6.16. Found: C, 63.31; H, 5.91; N, 6.02.

N-Cyclohexyl 3-(4-Chlorophenyl)-2-(2-nitrophenyl)acetoxy-3-oxopropionamide (**4d**).

This compound was obtained as white crystals in 90% yield, mp 146-148° from EtOH; ir ν 3296 (NH), 1753 (CO-O), 1696 (CO), 1647 (CO-N), 1342 (NO_2) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.04-1.89 (m, 10H, cyclohexyl), 3.67 (m, 1H, 1-H cyclohexyl), 4.07 (d, J = 17.0 Hz, 1H, $COCH_2$), 4.29 (d, J = 17.0 Hz, 1H, $COCH_2$), 6.17 (d, J = 8.0 Hz, 1H, NH), 6.25 (s, 1H, COCHCO), 7.36-8.14 (m, 8H, aromatic).

Anal. Calcd. for $C_{23}H_{23}ClN_2O_6$: C, 60.20; H, 5.05; N, 6.10. Found: C, 60.15; H, 5.29; N, 5.96.

Cyclization of Compounds **4** to Furan Derivatives **6**.

General Procedure.

A well-stirred suspension of finely ground **4** (8 mmoles) in ethanol (50 ml) was treated dropwise at room temperature with piperidine (724 mg, 8.5 mmoles) and then heated at 40° for 10 minutes. The resulting deep violet solution was cooled and freed from a small amount of unreacted starting product by filtration. The filtrate was acidified with 6*N* hydrochloric acid until *p*H = 4. The cyclization products **6** were isolated by filtration.

N-Cyclohexyl 2,5-Dihydro-2-(2-nitrophenyl)-3-phenyl-5-oxofuran-2-carboxamide (**6a**).

This compound was obtained as white crystals in 71% yield, mp 176-177° from *i*-PrOH; ir: ν 3290 (NH), 1764 (CO-O), 1664 (CO-N), 1342 (NO_2) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.05-1.92 (m, 10H, cyclohexyl), 3.62 (m, 1H, 1-H cyclohexyl), 5.93 (s, 1H, 2-H furan), 6.15 (d, J = 7.8 Hz, 1H, NH), 7.05-8.27 (m, 9H, aromatic).

Anal. Calcd. for $C_{23}H_{22}N_2O_5$: C, 67.97; H, 5.46; N, 6.89. Found: C, 67.69; H, 5.60; N, 6.98.

N-Cyclohexyl 2,5-Dihydro-3-(4-methylphenyl)-2-(2-nitrophenyl)-5-oxofuran-2-carboxamide (**6b**).

This compound was obtained as white crystals in 74% yield, mp 174-175° from EtOH; ir: ν 3305 (NH), 1761 (CO-O), 1665 (CO-N), 1342 (NO_2) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.12-1.92 (m, 10H, cyclohexyl), 2.30 (s, 3H, CH_3), 3.62 (m, 1H, 1-H cyclohexyl), 5.90 (s, 1H, 2-H furan), 6.13 (d, J = 6.6 Hz, 1H, NH), 7.07-8.27 (m, 8H, aromatic).

Anal. Calcd. for $C_{24}H_{24}N_2O_5$: C, 68.56; H, 5.75; N, 6.66. Found: C, 68.50; H, 5.51; N, 6.79.

N-Cyclohexyl 2,5-Dihydro-3-(4-methoxyphenyl)-2-(2-nitrophenyl)-5-oxofuran-2-carboxamide (**6c**).

This compound was obtained as white crystals in 69% yield, mp 176-177° from EtOH; ir: ν 3350 (NH), 1746 (CO-O), 1674 (CO-N), 1343 (NO_2) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.06-

1.92 (m, 10H, cyclohexyl), 3.64 (m, 1H, 1-H cyclohexyl), 3.76 (s, 3H, CH_3), 5.90 (s, 1H, 2-H furan), 6.14 (d, J = 6.4 Hz, 1H, NH), 6.76-8.27 (m, 8H, aromatic).

Anal. Calcd. for $C_{24}H_{24}N_2O_6$: C, 66.05; H, 5.54; N, 6.42. Found: C, 66.31; H, 5.70; N, 6.21.

N-Cyclohexyl 3-(4-Chlorophenyl)-2,5-dihydro-2-(2-nitrophenyl)-5-oxofuran-2-carboxamide (**6d**).

This compound was obtained as white crystals in 76% yield, mp 212-213° from EtOH; ir: ν 3295 (NH), 1761 (CO-O), 1663 (CO-N), 1340 (NO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.08-1.92 (m, 10H, cyclohexyl), 3.63 (m, 1H, 1-H cyclohexyl), 5.89 (s, 1H, 2-H furan), 6.19 (d, J = 7.4 Hz, 1H, NH), 7.05-8.27 (m, 8H, aromatic).

Anal. Calcd. for $C_{23}H_{21}ClN_2O_5$: C, 62.66; H, 4.80; N, 6.35. Found: C, 62.77; H, 4.96; N, 6. 10.

Transformation of Furan Derivatives **6** into Indole Derivatives **8**.

General Procedure.

A well-stirred suspension of **6** (2.5 mmoles) in acetic acid (18 ml) was heated at 35 °C and treated with iron powder (2.5 g, 44.8 mmoles). When the exothermic reaction had subsided, the reaction mixture was heated at 60-65° for 15 minutes and then cooled at room temperature, stirred with chloroform (50 ml), and filtered. The filtrate was evaporated to dryness and treated again with chloroform (50 ml). The resulting solution was transferred to a separatory funnel and washed with two 50 ml portions of water. The organic layer was dried. over anhydrous sodium sulfate and evaporated to dryness to give the crude **8**. Purification of all of the compounds **8** was achieved by recrystallization from ethanol.

N-Cyclohexyl (Z)-3-(2,3-Dihydro-2-oxoindol-3-ylidene)-2-hydroxy-3-phenylpropionamide (**8a**).

This compound was obtained as white crystals in 82% yield, mp 226-227° from EtOH, ir: ν 3332 (OH), 3203 (NH), 1710 (CO indole), 1664 (CO-N) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 1.06-1.90 (m, 10H, cyclohexyl), 3.38-3.61 (m, 1H, 1-H cyclohexyl), 4.43 (d, J = 7.3 Hz, 1H, H-2), 5.17 (d, J = 7.3 Hz, 1H, OH), 6.85-7.43 (m, 9H, aromatic), 8.70 (d, J = 7.5 Hz, 1H, NH-cyclohexyl), 10.53 (s, 1H, NH indole); ms: *m/z* 376 (M^+).

Anal. Calcd. for $C_{23}H_{24}N_2O_3$: C, 73.38; H, 6.43; N, 7.44. Found: C, 73.32; H, 6.69; N, 7.3 1.

N-Cyclohexyl (Z)-3-(2,3-Dihydro-2-oxoindol-3-ylidene)-2-hydroxy-3-(4-methylphenyl)propionamide (**8b**).

This compound was obtained as white crystals in 88% yield, mp 240-241° from EtOH, ir: ν 3341 (OH), 3202 (NH), 1712 (CO indole), 1670 (CO-N) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 1.05-185 (m, 10H, cyclohexyl), 2.35 (s, 3H, CH_3), 3.45-3.70 (m, 1H, 1-H cyclohexyl), 4.42 (d, J = 7.0 Hz, 1H, H-2), 5.15 (d, J = 7.0 Hz, 1H, OH), 6.65-7.25 (m, 8H, aromatic), 8.69 (d, J = 8.3 Hz, 1H, NH-cyclohexyl), 10.51 (s, 1H, NH indole); ms: *m/z* 390 (M^+).

Anal. Calcd. for $C_{24}H_{26}N_2O_4$: C, 73.82; H, 6.71; N, 7.17. Found: C, 73.99; H, 6.91; N, 7.02.

N-Cyclohexyl (Z)-3-(2,3-Dihydro-2-oxoindol-3-ylidene)-2-hydroxy-3-(4-methoxylphenyl)propionamide (**8c**).

This compound was obtained as white crystals in 83% yield, mp 221-223° from EtOH; ir. ν 3341 (OH), 3231 (NH), 1712 (CO indole), 1672 (CO-N) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 1.03-1.85 (m, 10H, cyclohexyl), 3.82 (s, 3H, OCH_3), 4.40 (d, J = 7.3 Hz, 1H, H-2), 5.12 (d, J = 7.3 Hz, 1H, OH), 6.63-7.30 (m, 8H, aromatic), 8.67 (d, J = 8.1 Hz, 1H, NH-cyclohexyl), 10.48 (s, 1H, NH indole) [8]; ms: *m/z* 406 (M^+).

Anal. Calcd. for $C_{24}H_{26}N_2O_4$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.66; H, 6.31; N, 7.02.

N-Cyclohexyl (Z)-3-(4-Chlorophenyl)-3-(2,3-dihydro-2-oxoindol-3-ylidene)-2-hydroxypropionamide (**8d**).

This compound was obtained as white crystals in 91% yield, mp 242-243° from EtOH, ir: ν 3339 (OH), 3203 (NH), 1719 (CO indole), 1666 (CO-N) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 0.96-1.80 (m, 10H, cyclohexyl), 3.35-3.58 (m, 1H, 1-H cyclohexyl), 4.33 (d, J = 7.1 Hz, 1: H, H-2), 5.12 (d, J = 7.1 Hz, 1H, OH), 6.62-7.39 (m, 8H, aromatic), 8.53 (d, J = 8.0 Hz, 1H, NH-cyclohexyl), 10.43 (s, 1H, NH indole); ms: *m/z* 410 (M^+).

Anal. Calcd. for $C_{23}H_{23}ClN_2O_3$: C, 67.23; H, 5.64; N, 6.82. Found: C, 67.52; H, 5.71; N, 6.59.

REFERENCES AND NOTES

[1a] S. Marcaccini and T. Torroba, *Org. Prep. Proc. Int.*, **25**, 141 (19,93); [b] R. Bossio, S. Marcaccini, S. Papaleo, and R. Pepino, *J. Heterocvclic Chem.*, **31**, 397 (1994); [c] R. Bossio, S. Marcaccini, and R. Pepino, *Synthesis*, 765 (1994); [d] R. Bossio, S. Marcaccini, R. Pepino, and P. Paoli, *J. Heterocyclic Chem.*, **31**, 729 (1994); [e] R. Bossio, S. Marcaccini, and R. Pepino, *J. Heterocyclic Chem.*, **32**, 1115 (1995); [f] R. Bossio, S. Marcaccini, R. Pepino, and T. Torroba, *J. Chem. Soc. Perkin Trans. 1*, 229 (1996) ; [g] R. Bossio, S. Marcaccini, R. Pepino, and T. Torroba, *J. Org. Chem.*, **61**, 2202 (1996); [h] R. Bossio, C. F. Marcos, S. Marcaccini, and R. Pepino, *Tetrahedron Lett.*, **38**, 2519 (1997); [i] R. Bossio, C. F. Marcos, S. Marcaccini, and R. Pepino, *Heterocycles*, **45**, 1589 (1997); [j] R. Bossio, C. F. Marcos, S. Marcaccini, and R. Pepino, *Synthesis*, 1389 (1997); [k] R. Bossio, S. Marcaccini, R. Pepino, and T. Torroba, *Heterocycles*, **50**, 463 (1999).

[2a] R. Bossio, S. Marcaccini, R. Pepino, and T. Torroba, *Synthesis*, 783 (1993); [b] R. Bossio, S. Marcaccini, and R. Pepino, *Liebigs Ann. Chem.*, 527 (1994).

[3] S. Radtke, NCI, Bethesda, private communication.

[4] P. J. Murray, I. D. Starkey, and J. E. Davies, *Tetrahedron Lett.*, **39**, 6721 (1998).

[5] H. A. Riley and A. R. Gray, *Org. Synth., Coll. Vol. 2*, 509 (1948).

[6] F. Venien, A. Brault, and M. Kerfanto, *C. R. Acad. Sci., Ser. C*, **266**, 1650 (1968).

[7a] I. Ugi, R. Meyr, M. Lipinski, F. Bodesheim, and F. Rosendahl, *Org. Synth., Coll. Vol. 5*, 300 (1973); [b] G. W. Gokel, R. P. Widera, and W. P. Weber, *Org. Synth.*, **55**, 96 (1976).

[8] The signal of the H- I of cyclohexyl is not detectable because of the overlapping of the signal due to the water contained in deuterated solvent.