

An Efficient Synthesis of Hexahydro Oxaisoindolo[2,1-*a*]Quinoline Derivatives via the Diels-Alder Reactions

Vladimir V. Kouznetsov^{*a§}, Fedor I. Zubkov^{*b}, Uriel Mora Cruz^c, Leonid G. Voskressensky^b, Leonor Y. Vargas Mendez^c, Luis Astudillo^a and Elena E. Stashenko^c

^aLaboratorio de Síntesis Orgánica, Instituto de Química de Recursos Naturales, Universidad de Talca, Chile, Casilla 747

^bOrganic Chemistry Department of the Russian Peoples Friendship University, 6, Miklukho-Maklayia St, Moscow, Russian Federation, 117198

^cLaboratorio de Síntesis Orgánica Fina, CIBIMOL, Escuela de Química, Universidad Industrial de Santander, A.A. 678, Bucaramanga, Colombia

Received July 20, 2003; Accepted August 30, 2003

Abstract. The straightforward synthesis of new carboxylic acids with hexahydro-oxaisoindolo[2,1-*a*]quinoline core from the 2,4-disubstituted 1,2,3,4-tetrahydroquinolines bearing a furan fragment via the intramolecular Diels-Alder reaction has been proposed. It was demonstrated that synthesis of key precursors can be realized with excellent level of diastereoselectivity either by imino-Diels-Alder reaction or multi-component condensation approach.

The chemistry of tetrahydroquinoline derivatives has long been an area of intense for organic chemists due to the presence of these scaffolds within the framework of numerous biologically interesting natural products and pharmaceutical agents. Many new methods for the synthesis of tetrahydroquinoline derivatives have been developed [1, 2]. The most attractive strategy for these derivatives is the acid-promoted imino-Diels-Alder reaction between *N*-aryldimines and electron-rich alkenes that has been a topic of continuing interest for forty years [3, 4]. The synthesis of such compounds by the three-component-reaction of substituted anilines, an aryl aldehydes, and an electron-rich olefins in the presence of different Lewis acid catalysts has also been reported recently [5]. On the other hand, the intramolecular Diels-Alder reaction with furan as the diene partner is a powerful synthetic tool for constructing rigid tricyclic nitrogen heterocycles [6]. With these facts in mind and taking into consideration that the 2-furyl-1,2,3,4-tetrahydroquinoline synthesis and its chemistry have been poorly explored, we consider that tetrahydroquinolines with furan moiety show interesting features that make them attractive for synthetic and pharmacological use. As part of our ongoing research program aiming at the search of bioactive polyheterocycles containing nitrogen atom from accessible aldimines [7], we were interested in an efficient synthesis of isoindolo[2,1-*a*]quinoline derivatives. Herein, we wish to report the straightforward synthesis of 1,3-

disubstituted 11-oxo-5-(2-oxopyrrolidinyl)-6,6a,9,10,10a,11-hexahydro-6b,9-oxaisoindolo[2,1-*a*]quinoline-10-carboxylic acids, from the 2,4-disubstituted 1,2,3,4-tetrahydroquinolines bearing a furan fragment via the intramolecular Diels-Alder reaction. Our approach to these oxaisoindolo[2,1-*a*]quinoline derivatives is based on the construction of key precursors, - 2,4-disubstituted 1,2,3,4-tetrahydroquinolines bearing a furan fragment, which can be easily prepared from readily available materials via two different procedures. One of the synthetic routes involves freshly distilled *N*-furfurylidenanilines (**1a-d**) that are easily obtained from various anilines and 2-furaldehyde. *N*-Vinylpyrrolidin-2-one (NVP) was used in the subsequent intermolecular imino-Diels-Alder reaction (scheme 1, route A).

Table 1. Synthesis of 2-(2-Furyl)-1,2,3,4-Tetrahydroquinolines (**2a-d**) Using Imino-Diels-Alder Reaction (Route A)

Entry	Substrate	R ¹	R ²	M.p. °C ^a	Cis:trans ^b	Yield (%) ^c
1	2a	H	H	94-95.5	97:3	98
2	2b	Me	H	194-194.5	96:4	96
3	2c	OMe	H	169-170	96:4	90
4	2d	OMe	OMe	178-179	98:2	94

a) Uncorrected

b) Crude reaction mixtures determined by GC-MS

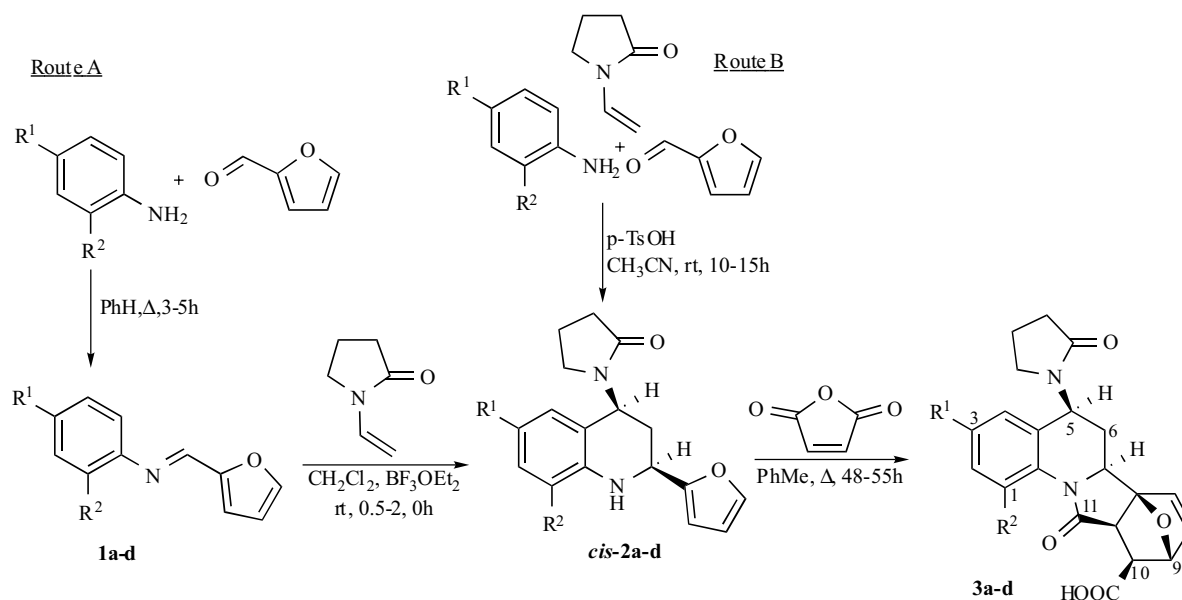
c) Isolated yield

*Address correspondence to this author at the ^aLaboratorio de Síntesis Orgánica, Instituto de Química de Recursos Naturales, Universidad de Talca, Chile, Casilla 747; E-mail: kouznet@uis.edu.co

^bOrganic Chemistry Department of the Russian Peoples Friendship University, 6, Miklukho-Maklayia St, Moscow, Russian Federation, 117198; E-mail: fzubkov@sci.pfu.edu.ru

[§]Short-term commission, Permanent address: Laboratorio de Síntesis Orgánica Fina, CIBIMOL, Escuela de Química, Universidad Industrial de Santander, A.A. 678, Bucaramanga, Colombia.

These reactions proceeded smoothly in the presence of BF₃ × Et₂O (20 mol %) at room temperature (23-25°C) in dichloromethane to give the corresponding 2-(2-furyl)-tetrahydroquinolines (**2a-d**) in high yields and selectivity. Isolated products are stable colorless crystalline substances (Table 1). Relative configuration of the newly created



Scheme 1.

stereocenters is *cis*, indicating on the *endo* approach of NVP. Their structure was elucidated by ^1H NMR. The relative *trans* orientation of H₂, H₃ and H₄ was established from the large vicinal coupling constants $J_{2,3}$, and $J_{3,4} = 10.0\text{--}11.5$ Hz [8].

Taking into consideration that the multi-component condensations have emerged as a powerful tool for delivering the needed molecular diversity in the combinatorial approaches for the preparation of bioactive compounds, we designed a synthesis of the same products by a convergent three-component reaction between anilines, 2-furaldehyde and NVP (scheme 1, route B). We tested various acid catalysts for the condensation of *p*-toluidine, 2-furaldehyde and NVP. This condensation proceeded smoothly in the presence of Lewis ($\text{BF}_3 \times \text{Et}_2\text{O}$, BiCl_3) and Brønsted (*p*-TsOH) acids (20 mol %). *p*-TsOH was found the best catalyst in this multi-component condensation to give the final product (**2b**) in 80% yield (10–15 h in acetonitrile at room temperature). The multi-component condensation between the chosen anilines, 2-furaldehyde and NVP under the specified conditions afforded the key tetrahydroquinoline precursors (**2a–c**) in good yields. However, in the case of the 2,4-dimethoxyaniline, the desired tetrahydroquinoline (**2d**) was obtained in very poor yield (Table 2).

Table 2. Synthesis of 2-(2-Furyl)-1,2,3,4-Tetrahydroquinolines (**2a–d**) Using Three-Component Condensation (Route B)

Entry	Substrate	R ¹	R ²	Yield (%) ^a
1	2a	H	H	65
2	2b	Me	H	80
3	2c	OMe	H	75
4	2d	OMe	OMe	10

a) Purified by column chromatography as *cis*-isomer

The *cis*-tetrahydroquinolines (**2a–d**) were easily converted into the corresponding 1,3-disubstituted 11-oxo-5-(2-oxopyrrolidinyl)-6,6a,9,10,10a,11-hexahydro-6b,9-oxaisoindolo[2,1-*a*]quinoline-10-carboxylic acids (**3a–d**). The N-acylation of 2-furyltetrahydroquinolines with maleic anhydride in boiling toluene and subsequent intramolecular Diels-Alder reaction with the furan moiety, provided the final polycyclic products in high yields and with an excellent level of selectivity, affording the *exo*-adducts (Scheme 1). These carboxylic acids are stable colorless crystalline substances, sparingly soluble in most organic solvents and with high melting points (Table 3). Homonuclear and inverse-detected 2D NMR experiments allowed the assignment of all the signals and correlations, corroborating the obtained oxaisoindolo[2,1-*a*]quinoline core. From of ^1H NMR spectra of compounds (**3a–d**), the configuration of the proton H-6a was judged to be axial.

The synthesis described herein provides oxaisoindolo[2,1-*a*]quinoline derivatives in a two- to three-step procedure with good yields from commercial and cheap reagents, such as NVP, anilines and 2-furaldehyde (or their respective aldimines). This method can be used for the preparation of interesting small drug-like molecules. Currently, a four-component-condensation to give these interesting molecules is under development in our laboratories and will be published in the near future.

Table 3. Synthesis of Oxaisoindolo[2,1-*a*]Quinoline Derivatives (**3a–d**) from Tetrahydroquinolines (**2a–d**)

Entry	Substrate	R ¹	R ²	M.p. °C ^a	Yield (%)
1	3a	H	H	264	80
2	3b	Me	H	300	83
3	3c	OMe	H	268	75
4	3d	OMe	OMe	243–244	70

a) Uncorrected

ACKNOWLEDGEMENTS

The authors are grateful for the financial support by Universidad de Talca (Proyecto: VAC 600-318) and Instituto Colombiano para el Desarrollo de la Ciencia y la Tecnología "Francisco José de Caldas" (COLCIENCIAS, Proyecto: 1102-05-11429).

REFERENCES

- [1] Katritzky, A.R.; Rachwal, S.; Rachwal, B. *Tetrahedron*, **1996**, *52*, 15031.
- [2] Kouznetsov, V.; Palma, A.; Ewert, C.; Varlamov, A. *J. Heterocycl. Chem.*, **1998**, *35*, 761.
- [3] Povarov, L.S. *Russ. Chem. Rev.*, **1967**, *36*, 656.
- [4] (a) Boger, D.L.; Weinreb, S.M. *Hetero Diels-Alder Methodology in Organic Synthesis*, Academic Press: San Diego, **1987**. (b) Weinreb, S.M. In *Comprehensive Organic Synthesis*; Trost, B.M.; Fleming, I., Eds.; Pergamon Press: Oxford, **1991**; Vol. 5, pp. 401-449.
- [5] (a) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.*, **1996**, *118*, 8977. (b) Mellor, J.M.; Merriman, G.D.; *Tetrahedron*, **1995**, *51*, 6115.
- [6] Paulvannan, K.; Jacobs, J.W. *Tetrahedron*, **1999**, *55*, 7433.
- [7] Puentes, C.O.; Kouznetsov, V.V. *J. Heterocyclic Chem.*, **2002**, *39*, 1.
- [8] Selective spectral and physical/chemical data for compound (**3a**): Yield 80%; mp. 264 °C; IR: ν_{COOH} 1733, $\nu_{\text{N=C=O}}$ 1693, $\nu_{\text{C=C}}$ 1639 cm^{-1} ; ^1H NMR (DMSO- d_6): δ 12.30 (1H, br.s, COOH), 8.64 (1H, d, $J = 9.0$ Hz, 1-H), 7.25 (1H, t, $J = 8.0$ Hz, 2-H), 7.08 (1H, t, $J = 8.0$ Hz, 3-H), 6.97 (1H, d, $J = 8.0$ Hz, 4-H), 6.61 (1H, d, $J = 5.0$ Hz, 8-H), 6.52 (1H, dd, $J = 5.0, 2.0$ Hz, 7-H), 5.48 (1H, br.dd, $J = 10.0, 6.0$ Hz, 5-H), 5.05 (1H, d, $J = 2.0$ Hz, 9-H), 4.88 (1H, dd, $J = 11.0, 3.0$ Hz, 6a-H), 3.25 (1H, q, $J = 8.0, 8.0$ Hz, 5'-HA), 3.13 (1H, d, $J = 9.0$ Hz, 10-H), 2.95 (1H, br.d, $J = 7.0$ Hz, 5'-HB), 2.59 (1H, d, $J = 9.0$ Hz, 10a-H), 2.46-2.30 (2H, m, 3'-H), 2.01-1.92 (4H, m, 6-H and 4'-H) ppm; ^{13}C NMR (DMSO- d_6): δ 175.0 (2'-C), 173.1 (10-COOH), 169.9 (11-C), 137.8 (+, 7-H), 137.4 (1a-C), 134.3 (+, 8-C), 127.9 (+, 2-C), 126.3 (+, 4-C), 123.6 (4a-C), 123.4 (+, 3-C), 118.1 (+, 1-C), 89.3 (6b-C), 81.0 (+, 9-C), 55.5 (+, 6a-C), 51.0 (+, 10-C), 47.4 (+, 5-C), 45.2 (+, 10a-C) 41.7 (-, 5'-C), 30.6 (-, 3'-C), 25.4 (-, 6-C), 17.8 (-, 4'-C). Anal. Calcd. For $\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}_5$: C, 66.31; H, 5.30; N, 7.36 %. Found: C, 66.25; H, 5.20; N, 7.50%.
- Selective spectral and physical/chemical data for compound (**3b**): Yield 83%; mp. 300 °C; IR: ν_{COOH} 1729, $\nu_{\text{N=C=O}}$ 1704, $\nu_{\text{C=C}}$ 1650 cm^{-1} ; ^1H NMR (DMSO- d_6): δ 12.28 (1H, br.s, COOH), 8.52 (1H, d, $J = 8.6$ Hz, 1-H), 7.06 (1H, dd, $J = 8.6, 1.7$ Hz, 2-H), 6.77 (1H, s, 4-H), 6.61 (1H, d, $J = 5.7$ Hz, 8-H), 6.52 (1H, dd, $J = 5.8, 1.8$ Hz, 7-H), 5.45 (1H, br.dd, $J = 11.1, 5.8$ Hz, 5-H), 5.04 (1H, d, $J = 1.8$ Hz, 9-H), 4.84 (1H, dd, $J = 11.6, 3.1$ Hz, 6a-H), 3.22 (1H, q, $J = 8.3, 7.8$ Hz, 5'-HA), 3.11 (1H, d, $J = 9.1$ Hz, 10-H), 2.96 (1H, br.q, $J = 7.6, 7.1$ Hz, 5'-HB), 2.58 (1H, d, $J = 9.1$ Hz, 10a-H), 2.46-2.31 (2H, m, 3'-H), 2.25 (3H, s, 3-CH₃), 2.05-1.93 (4H, m, 6-H and 4'-H) ppm; ^{13}C NMR (DMSO- d_6): δ 175.3 (2'-C), 173.4 (10-COOH), 169.9 (11-C), 138.0 (+, 7-C), 135.4 (1a-C), 134.6 (+, 8-C), 132.7 (3-C), 128.7 (+, 2-C), 126.8 (+, 4-C), 123.8 (4a-C), 118.4 (+, 1-C), 89.7 (6b-C), 81.3 (+, 9-C), 55.7 (+, 6a-C), 51.3 (+, 10-C), 47.7 (+, 5-C), 45.4 (+, 10a-C), 42.1 (-, 5'-C), 30.9 (-, 3'-C), 25.9 (-, 6-C), 20.9 (+, 3-CH₃), 18.2 (-, 4'-C) ppm. Anal. Calcd. For $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_5$: C, 66.99; H, 5.62; N, 7.10 %. Found: C, 66.65; H, 5.89; N, 7.37%.