Intramolecular Diels–Alder Furan-Mediated Synthesis of 8-Aryl-3,4-dihydroisoquinolin-1(2*H*)-ones, Convenient Precursors of Indeno[1,2,3-*ij*]isoquinolines

Mónica Treus,[a,b] Laurence M. Harwood,*[b] Juan C. Estévez,[a] Cristian Salas,[c] Michael G. B. Drew,[b] Ramón J. Estévez*[a]

[a] Departamento de Química Orgánica and Centro Singular de Investigación en Química Biológica y Materiales Moleculares (CIQUS), Universidad de Santiago de Compostela, 15782 Santiago de Compostela, Spain
Fax +34(981)591014; E-mail: ramon.estevez@usc.es

[b] Department of Chemistry, University of Reading, Whiteknights, Reading RG6 6AD, UK
Fax +44(118)3786121; E-mail: l.m.harwood@reading.ac.uk

[c] Departamento de Química Orgánica, Pontificia Universidad Católica de Chile, 702843 Santiago de Chile, Chile

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Abstract: We describe herein preliminary studies on the intramolecular Diels–Alder furan-mediated synthesis of 8-aryl-3,4-dihydroisoquinolin-1(2*H*)-ones that constitutes a new, formal synthesis of indeno[1,2,3-*ij*]isoquinolines.

Key words: alkaloids, 8-arylisoquinolines, indeno[1,2,3-*ij*]isoquinolines, Bischler–Napieralski cyclization, intramolecular Diels–Alder furan reaction

The isoquinoline ring system is widely distributed in nature and many of the isoquinoline alkaloids isolated have important pharmacological properties.[1] For example, aporphines (**1**, Figure 1) exhibit a range of pharmacological activities, including antibiotical, antifungal, antimicrobial, and dopaminergic effects.[2] Of particular interest is the potent dopamine agonist apomorphine.[3] A second class of isoquinoline alkaloids is that of the indeno[1,2,3-*ij*]isoquinolines (**3**),[4] which differ from aporphines in the size of the C ring. These are attractive, because their pharmacological properties have not yet been studied, but some in vitro bioassays have shown that some of them inhibit the synthesis of RNA and DNA in mouse thymus cells.

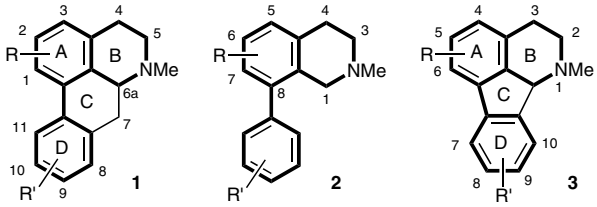

Figure 1

8-Aryltetrahydroisoquinolines **2** are mimetics of aporphines **1** and indeno[1,2,3-*ij*]isoquinolines **3** that maintain the integrity of the 8-phenyl-1,2,3,4-tetrahydroisoquinoline subunit, but the C ring of both tetracyclic isoquinolines derivatives **1** and **3** is absent.[5] They have been shown to be dopamine antagonists, probably due to the fact that the phenyl group is not restricted to the coplanar disposition of this group in both the aporphines and indeno[1,2,3-*ij*]isoquinolines. In addition, 8-aryltetrahydroisoquinolines have been used for the preparation of indeno[1,2,3-*ij*]isoquinolines **3**.[5c]

Isoquinoline alkaloids have been the subject of intensive research directed towards finding effective syntheses of these compounds.[3c,6] Classical methods for the generation of the isoquinoline framework (Bischler–Napieralski, Pictet–Spengler, and Pomeranz–Fritsch reactions) are of limited scope, because they consist of a ring closure to generate the nitrogen heterocycle. It involves an intramolecular electrophilic attack on an activated (substituted) benzene ring, but, in the absence of electron-releasing substituents, this cyclization step either fails or proceeds in low yield.

Searching for synthetic approaches not subject to the above limitations, we realized that the intramolecular Diels–Alder reaction of furan (IMDAF)[7] is a promising alternative for the synthesis of isoquinolines,[8] including 2-methyl-3,4-dihydroisoquinolin-1(2*H*)-one.[8e] In connection with our continuous interest on isoquinolines,[9] we considered that the IMDAF reaction appeared to be a suitable, not yet explored strategy for the preparation of 8-arylisoquinolines **8**. Our synthetic plan relied on the generation of the key starting building blocks **6** (Scheme 1). Further construction of the ABC ring system of these targets **8** was envisaged via an IMDAF reaction leading to adducts **7**, followed by aromatization of the B ring.

This strategy for the preparation of 8-arylisoquinolines **8** requires a substituent on the nitrogen atom of the Diels–Alder precursors **6** that facilitates the cycloaddition reaction.[8c] We chose a benzyl group as a protecting group for the nitrogen atom of these substrates **6**, which could be easily prepared by coupling different *trans*-cinnamoyl chorides **4** with 2-(2-furyl)ethylamine (**5**), itself readily obtained from furfuraldehyde.[10]

Reaction of this furylethylamine **5** with *trans*-cinnamoyl chloride **4a** in dichloromethane and pyridine at room temperature gave 98% yield of the desired amide **6a** as a colorless oil. After several unsuccessful attempts to promote

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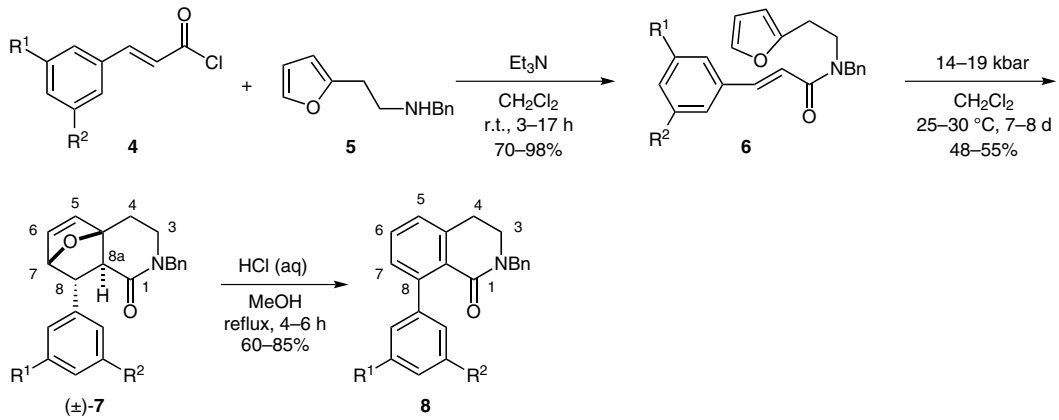

Scheme 1 a : $R^1 = R^2 = H$; **b**: $R^1 = R^2 = OMe$; **c**: $R^1 = H$, $R^2 = OMe$.

the IMDAF cyclization of **6a**,[11] which resulted in the recovery of the starting material, satisfactory results were achieved when a solution of this compound in dichloromethane was subjected to high pressure ($19 \cdot 10^3$ bar) for eight days. Under these conditions, a 49% yield of cycloadduct **7a** was obtained,[12] and a 25% of the starting material was recovered. The *exo* configuration expected for **7a** was confirmed by ^{1}H NMR, COSY, and NOE experiments.[13]

Finally, refluxing a solution of compound **7a** in methanol and aqueous hydrochloric acid for five hours produced a 85% yield of the desired *N*-benzylisoquinolin-1-one (**8a**),[14] as a result of the opening of the oxabicycle system and aromatization of the resulting material.

In order to explore the scope of this new approach to 8-arylisoquinolines **8**, we decided to attempt the preparation of substituted 8-arylisoquinolines **8b** and **8c**.

Thus, 2-(2-furyl)ethylamine (**5**) was reacted with *trans*-3,5-dimethoxycinnamoyl chloride (**4b**), in order to obtain cinnamoylamide **6b**. When a solution of **6b** in dichloromethane was subjected to high pressure ($14 \cdot 10^3$ bar) at 30 °C for eight days, a 48% yield of the expected racemic cycloadduct **7b** resulted, with 47% of starting material recovered. Finally, when oxabicyclo[2.2.1]heptene **7b** was subjected to the aromatization conditions applied for the transformation of **7a** into **8a**, the expected 8-arylisoquinolin-1-one **8b** resulted in 70% yield, as easily established from its spectroscopic and analytical data.[13]

Finally, once **6c** was obtained from **4c** and **5**, a solution of **6c** in dichloromethane was subjected to a pressure of $19 \cdot 10^3$ bar for seven days to give a 55% yield of cycloadduct **7c** after column chromatography, together with 30% of the recovered starting material.

The *exo* configuration expected for compound **7c** was unambiguously confirmed by single-crystal X-ray[15] analysis (Figure 2).

Aromatization of **7c** as before provided a 60% yield of the desired 8-arylisoquinoline **8c**.

To sum up, we report here preliminary results on the intramolecular Diels–Alder furan-mediated synthesis of 8-aryl-3,4-dihydroisoquinolin-1(2*H*)-ones, synthetic precursors of indeno[1,2,3-*ij*]isoquinolines. Accordingly, this constitutes a new, formal synthesis of these targets.

Work is now in progress aimed at the optimization of this promising IMDAF reaction, as a preliminary stage for its application to the preparation of a wide range of 8-substituted isoquinolines and related substrates, including 8-styrylisoquinolines and naphtho[1,2-*h*]isoquinolines.

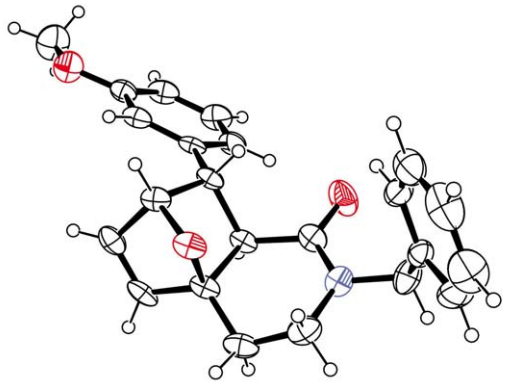

Figure 2 ORTEP diagram of **7c**

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(11) Unsuccessful conditions to promote the IMDAF cyclization of **6a** that resulted in the recovering of the starting material: (a) toluene, reflux, 5 d; (b) 145 °C, 21 h (no solvent); (c) $MgBr_2$, THF, MS, reflux, 21 h; (d) $AlCl_3$, THF, MS, reflux, 3 d; (e) $11 \cdot 10^3$ bar, CH_2Cl_2, 20 °C, 1 d.
(12) **Synthesis of (4a*R*,7*S*,8a*S*)-2-Benzyl-8-phenyl-2,3,4,7,8,8a-hexahydro-1*H*-4a,7-epoxyisoquinolin-1-one (7a)**
A solution of amide **6a** (60 mg, 0.181 mmol) in anhydrous CH_2Cl_2 (2 mL) was subjected to high pressure ($19 \cdot 10^3$ bar) at 27 ° C for 7 d. On depressurization, the solution was filtered through a plug of cotton wool to remove the solid matter, and the solvent was removed off under reduced pressure to afford 50 mg of crude material. Purification by column chromatography on silica (eluant: 1:1 light PE–Et_2O) furnished the cycloadduct **7a** as a colorless oil (29 mg, 49% yield) and 15 mg (25% yield) of recovered starting **6a** (64% yield of **7a** on the basis of recovered starting material).
(13) All new compounds gave satisfactory analytical and spectroscopic data.

Selected Physical and Spectroscopic Data

Compound 7a: ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 2.23–2.29 (m, 2 H, CH_2CN), 2.60 (d, 1 H, *J* = 4.9 Hz, H_{8a}), 3.19–3.27 (m, 1 H, CH_2-N), 3.44–3.56 (m, 1 H, CH_2N), 3.72 (t, 1 H, *J* = 4.7 Hz, H_8), 4.34 (d, 1 H, *J* = 14.7 Hz, CH_2Ph), 4.84 (d, 1 H, *J* = 14.7 Hz, CH_2Ph), 5.13 (d, 1 H, *J* = 4.6 Hz, H_7), 6.27 (s, 2 H, HC=CH), 7.12–7.41 (m, 10 H, 10 × ArH) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 26.0 (CH_2), 43.2 (CH_2), 50.3 (CH_2), 50.6 (CH), 50.7 (CH), 81.4 (CH), 87.5 (C), 126.5 (CH), 127.4 (CH), 128.0 (2 × CH), 128.1 (2 × CH), 128.3 (2 × CH), 128.6 (2 × CH), 136.5 (CH), 137.1 (CH + C), 139.8 (C), 171.2 (C=O) ppm. MS (CI): *m/z* (%) = 332 (53) [M + 1]$^+$, 131 (100). HRMS: *m/z* calcd for $C_{22}H_{22}NO_2$: 331.1572; found: 331.1580.

Compound 7b: ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 2.21–2.27 (m, 2 H, CH_2CN), 2.56 (d, 1 H, *J* = 4.8 Hz, H_{8a}), 3.18–3.24 (m, 1 H, CH_2N), 3.40–3.48 (m, 1 H, CH_2N), 3.65 (t, 1 H, *J* = 4.7 Hz, H_8), 3.70 (s, 6 H, 2 × OCH_3), 4.39 (d, 1 H, *J* = 14.7 Hz, CH_2Ph), 4.77 (d, 1 H, *J* = 14.7 Hz, CH_2Ph), 5.07 (dd, 1 H, *J* = 4.6, 1.4 Hz, H_7), 6.23–6.30 (m, 3 H, 3 × ArH), 6.44–6.46 (m, 2 H, HC=CH), 7.20–7.26 (m, 5 H, 5 × ArH) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 26.0 (CH_2), 43.2 (CH_2), 50.2 (CH_2), 50.6 (CH), 51.8 (CH), 55.2 (2 × OMe), 81.3 (CH), 87.4 (C), 98.3 (CH), 106.4 (2 × CH), 127.3 (CH), 127.9 (2 × CH), 128.6 (2 × CH), 136.5 (CH), 137.0 (CH + C), 142.2 (2 × C), 160.5 (2 × COMe), 171.1 (C=O). MS (CI): *m/z* (%) = 392 (100) [M + 1]$^+$. HRMS: *m/z* calcd for $C_{24}H_{25}NO_4$: 391.1783; found: 391.1778.

Compound 7c: mp 101–102 °C (MeOH). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 2.19–2.25 (m, 2 H, CH_2CN), 2.56 (d, 1 H, *J* = 4.9 Hz, H_{8a}), 3.14–3.23 (m, 1 H, CH_2N), 3.40–3.46 (m, 1 H, CH_2N), 3.67 (t, 1 H, *J* = 4.7 Hz, H_8), 3.69 (s, 3 H, OMe), 4.36 (d, 1 H, *J* = 14.7 Hz, CH_2Ph), 4.77 (d, 1 H, *J* = 14.7 Hz, CH_2Ph), 5.08 (1 H, dd, *J* = 4.8, 0.9 Hz, H_7), 6.22 (d, 1 H, d, *J* = 5.9 Hz, CH=CH), 6.25 (d, 1 H, *J* = 5.9 Hz, CH=CH), 6.64–6.67 (m, 1 H, m, ArH), 6.82–6.86 (m, 2 H, m, 2 × ArH), 7.07–7.24 (m, 6 H, 6 × ArH) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 26.4 (CH_2), 43.7 (CH_2), 50.7 (CH_2), 51.1 (CH), 52.1 (CH), 55.6 (OMe), 81.8 (CH), 87.9 (C), 112.2 (CH), 114.6 (CH), 120.9 (CH), 127.9 (CH), 128.6 (2 × CH), 128.9 (2 × CH), 129.6 (CH), 137.0 (CH), 137.6 (CH + C), 142.0 (C), 159.9 (COMe), 171.6 (C=O) ppm. MS (CI): *m/z* (%) = 362 (100) [M + 1]$^+$. Anal. Calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.87. Found: C, 76.30; H, 6.37; N, 3.83.

Compound 8a: mp 138–140 °C (MeOH). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 2.82 (t, 2 H, *J* = 6.3 Hz, CH_2CN), 3.45 (t, 2 H, *J* = 6.3 Hz, CH_2N), 4.63 (s, 2 H, CH_2Ph), 7.05–7.30 (m, 13 H, 13 × ArH) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 29.6 (CH_2), 44.9 (CH_2), 50.1 (CH_2), 126.1 (CH), 126.6 (CH), 127.3 (CH), 127.6 (2xCH), 127.8 (C), 128.0 (2 × CH), 128.2 (2 × CH), 128.5 (2 × CH), 130.4 (CH), 130.6 (CH), 137.8 (C), 139.8 (C), 142.9 (C), 144.1 (C), 163.8 (C=O) ppm. MS (CI): *m/z* (%) = 314 (100) [M + 1]$^+$. HRMS: *m/z* calcd for $C_{22}H_{19}NO$: 313.1467; found: 313.1466.

Compound 8b: ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 2.90 (t, 2 H, *J* = 6.2 Hz, CH_2CN), 3,52 (t, 2 H, *J* = 6.2 Hz, CH_2N), 3.80 (s, 6 H, 2 × OCH_3), 4.71 (s, 2 H, CH_2Ph), 6.45–6.48 (m, 3 H, 3 × ArH), 7.13–7.40 (m, 8 H, 8 × ArH) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 29.6 (CH_2), 45.2 (CH_2), 50.3 (CH_2), 55.2 (2 × OMe), 98.9 (CH), 106.7 (2 × CH), 126.2 (CH), 127.3 (CH), 128.0 (2 × CH + C), 128.5 (2 × CH), 130.3 (CH), 130.4 (CH), 137.9 (C), 139.8 (C), 143.9 (C), 145.0 (C), 159.9 (2 × COMe), 163.6 (C=O) ppm. MS (CI): *m/z* (%): 374 (100) [M + 1]$^+$. HRMS: *m/z* calcd for $C_{24}H_{23}NO_3$: 373.1678; found: 373.1677.

Compound 8c: ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 2.82 (t, 2 H, *J* = 6.4 Hz, CH_2CN), 3.45 (t, 2 H, *J* = 6.4 Hz, CH_2N), 3.75

(s, 3 H, OMe), 4.70 (s, 2 H, CH_2Ph), 6.70–6.82 (m, 3 H, 3 × ArH), 7.16–7.31 (m, 9 H, 9 × ArH) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 30.1 (CH_2), 45.5 (CH_2), 50.6 (CH_2), 55.6 (OMe), 112.5 (CH), 114.5 (CH), 121.4 (CH), 126.7 (CH), 127.8 (CH), 128.4 (2 × CH), 128.5 (3 × CH), 130.9 (CH), 131.0 (CH), 138.4 (C), 140.3 (C), 144.4 (C), 144.8 (C), 159.4 (COMe), 164.1 (C=O) ppm. MS (CI): *m/z* (%) = 344 (100) $[M + 1]^+$. HRMS: *m/z* calcd for $C_{22}H_{21}NO_2$: 343.1572; found: 343.1580.

(14) **Synthesis of 2-Benzyl-8-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one (8a)**
Concentrated HCl (0.1 mL) was added to a solution of cycloadduct **7a** (50 mg, 0.151 mmol) in MeOH (5 mL), and the mixture was refluxed for 4 h. The solution was neutralized with 2 M aq NaOH and extracted with CH_2Cl_2 (3 × 8 mL). The pooled organic extracts were washed with H_2O (15 mL) and dried (anhydrous sodium sulfate). Removal of the solvent under reduced pressure afforded a residue, which was purified by preparative TLC on silica (eluant: 1:1 light PE–Et_2O) to give 40 mg (85% yield) of isoquinoline **8a** as a white solid.

(15) The crystallographic data of compound **7c** have been included in the Supporting Information.

