Pergamon

Tetrahedron Letters 41 (2000) 6351–6353

TETRAHEDRON LETTERS

A novel C–N cleavage in isoquinolines allowing the first direct transformation of 1-benzylisoquinolines into benzo[*c*]phenanthridines and a new route to 2-phenyl-1,4-naphthoquinones

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Received 11 February 2000; accepted 20 June 2000

Abstract

Treatment of *N*-carbethoxy-1-benzylideneisoquinolines with LDA gives *N*-ethoxycarbonyl-1-amino-1-(2-vinylphenyl)-2-phenylethylenes, which can easily be transformed into *N*-carbethoxy-1-amino-2-phenylnaphthalenes. Bichler–Napieralski reaction of these latter compounds affords the corresponding benzo[*c*]phenanthridines, while their hydrolysis and subsequent oxidation constitutes a route to 2-phenyl-1,4-naphthoquinones.

Keywords: alkaloids; antitumour compounds; cleavage reactions; isoquinolines; quinones.

1-Benzylisoquinolines have received considerable chemical attention because they are the biogenetic precursors of a great variety of natural compounds of pharmacological interest,[1] including protoberberines, which are transformed into benzo[*c*]phenanthridines[2] such as fagaronine and nitidine; the considerable antileukemic activity of the latter[3] has been attributed to their conformationally rigid embedded 2-phenylnaphthalene subunit.[4] A number of syntheses of benzo[*c*]phenanthridines have been developed, including a biomimetic preparation from 1-benzylisoquinolines via protoberberines,[5,6] but no direct transformation of 1-benzylisoquinolines into benzo[*c*]phenanthridines has been hitherto described. Here we briefly sketch the first, which proceeds by an approach that is based on a novel C–N bond cleavage and provides a new route to 2-phenyl-1,4-naphthoquinones.

Treatment of the readily prepared *N*-ethoxycarbonylbenzylideneisoquinoline **1a**[7] for 30 min with LDA at 0°C resulted in cleavage of C_3–N bond, giving the styrylurethane **2a**[8] (easily identi-

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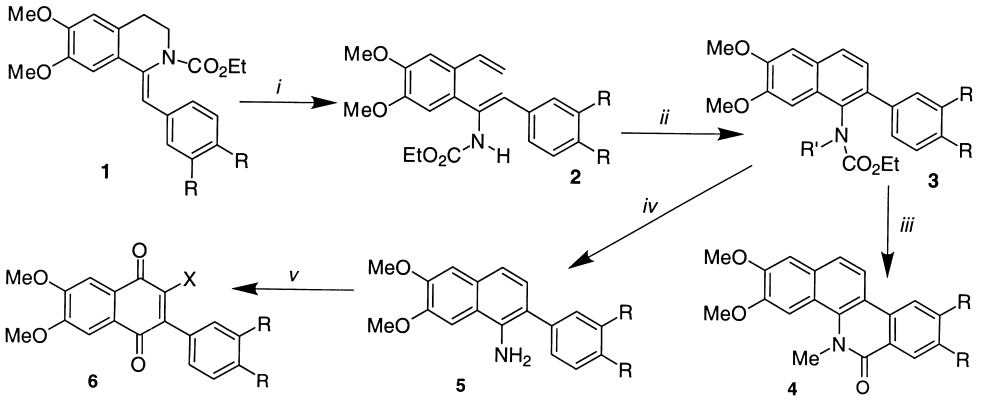
0040-4039/00/$ - see front matter
PII: S0040-4039(00)01052-2

fied from its analytical and spectroscopic data) (Scheme 1). Thermal electrocyclization of **2a** afforded the 2-phenylnaphthalene derivative **3a**, Bichler–Napieralski cyclization of the *N*-methyl derivative of which (**3b**) gave the expected benzo[*c*]phenanthridine **4a**. A similar sequence led to the tetrasubstituted benzo[*c*]phenanthridine **4b** via **2b**, **3c** and **3d**.



Scheme 1. Compounds **1**, **2**, **4** and **5**: (a) R = H; (b) R = OMe; compound **3**: (a) R = R′ = H; (b) R = H, R′ = Me; (c) R = OMe, R′ = H; (d) R = OMe, R′ = Me; compound **6**: (a) R = X = H; (b) R = H, X = OH; (c) R = OMe, X = H; (d) R = OMe, X = OH. Conditions: (*i*) LDA, THF, 0°C, 30 min–1 h (100% yield); (*ii*) (a) 10% Pd–C, *o*-xylene, reflux, 3–6 days (35–50% yield); (b) NaH, THF, rt, 30 min, MeI, rt, 40 min–1 h (74–75% yield); (*iii*) P_2O_5, $POCl_3$, reflux, 1.5–2.5 h (58–66% yield); (*iv*) KOH aq., EtOH, reflux, 14–19 h (93–100% yield); (*v*) (a) Fremy's salt, KH_2PH_4, 2:1 acetone:water, rt, 2 h (65% yield); (b) NaOH, 4:1 methanol:water, 4.5 h (90% yield)

In addition, hydrolysis of urethane **3a** gave 2-phenyl-1-amino naphthalene **5a**, which was easily and efficiently transformed into 2-phenyl-1,4-naphthoquinone **6a** by oxidation with Fremy's salt. Final treatment of **6a** with aq. sodium hydroxide easily gave the corresponding 3-hydroxy-2-phenyl-1,4-naphthoquinone **6b**, a member of a class of compounds that have received considerable attention[9] on account of their chemical and biological properties. The utility of this sequence was supported by the analogous transformation of urethane **3c** into hydroxynaphthoquinone **6d** via **5b** and **6c**.

A systematic study of this promising new C–N bond cleavage, including optimization of the new route to benzo[*c*]phenanthridines, is now in progress. Additionally, we are studying an application of the new direct route to naphthoquinones **6** to the preparation of derivatives of pharmacological interest, including 6,11-dihydrobenzo[*b*]naphtho[2,3-*d*]furan-6,11-diones, 7,12-dihydro-5*H*-dibenzo[*c*,*g*]chroman-5,7,12-triones and other similar antitumoral compounds.

Acknowledgements

We thank the Ministry of Education and Culture (DGES) and the Xunta de Galicia for financial support.

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8. All new compounds gave satisfactory analytical and spectroscopic data. Selected physical and spectroscopic data are as follows: Compound **2a**: Mp 106–109°C (ethyl ether); ^{1}H NMR (δ, ppm, Cl_3CD): 1.10 (m, 3H, $-CH_3$), 3.85 (s, 3H, $-OCH_3$), 3.91 (s, 3H, $-OCH_3$), 4.01 (q, J = 6.8 Hz, 2H, $-OCH_2-$), 5.13 (d, J = 11 Hz, 1H, $-C{=}CH_2$), 5.57 (d, J = 17.5 Hz, 1H, $-C{=}CH_2$), 5.90 (s, 1H, –N–C=CH–), 6.65 (bs, 1H, –NH–), 6.90 (s, 1H, Ar–H), 7.02 (dd, J = 11 and 17.5 Hz, 1H, $-CH-CH_2$), 7.04 (s, 1H, Ar–H), 7.21 (t, J = 7.5 Hz, 1H, Ar–H), 7.34 (t, J = 7.5 Hz, 2H, 2×Ar–H), 7.41 (d, J = 7.5 Hz, 2H, 2×Ar–H); MS (*m*/*z*, %): 353 (M^+, 22.97), 264 (100). Compound **2b**: mp 137–139°C (methanol); ^{1}H NMR (δ, ppm, Cl_3CD): 1.11 (t, J = 7.07 Hz, 3H, $-CH_3$), 3.87 (s, 3H, $-OCH_3$), 3.88 (s, 3H, $-OCH_3$), 3.90 (s, 3H, $-OCH_3$), 3.93 (s, 3H, $-OCH_3$), 4.04 (q, J = 7.07 Hz, 2H, $-OCH_2-$), 5.14 (d, J = 11 Hz, 1H, $-C{=}CH_2$), 5.56 (d, J = 17.4 Hz, 1H, $-C{=}CH_2$), 5.86 (s, 1H, –N–C=CH–), 6.45 (bs, 1H, –NH–), 6.81–6.88 (m, 2H, 2×Ar–H), 6.97–7.05 (m, 4H, 3×Ar–H and Ar–CH=CH_2); MS (*m*/*z*, %): 413 (M^+, 35.88), 262 (100). Compound **4a**: mp 193–195°C (methanol). ^{1}H NMR (δ, ppm, Cl_3CD): 4.00 (s, 3H, $-CH_3$), 4.01 (s, 3H, $-CH_3$), 4.02 (s, 3H, $-CH_3$), 7.13 (s, 1H, Ar–H), 7.51–7.57 (m, 3H, 3×Ar–H), 7.69–7.76 (m, 1H, Ar–H), 8.04 (d, J = 8.8 Hz, 1H, Ar–H), 8.20 (d, J = 8.8 Hz, 1H, Ar–H), 8.52 (dd, J = 7.9 Hz, J = 1.4 Hz, 1H, Ar–H); MS (*m*/*z*, %): 319 (M^+, 100). Compound **4b**: mp 220–250°C (acetonitrile, decomposition); ^{1}H NMR (δ, ppm, Cl_3CD): 4.04 (s, 9H, 3×$-CH_3$), 4.05 (s, 3H, $-CH_3$), 4.10 (s, 3H, $-CH_3$), 7.17 (s, 1H, Ar–H), 7.56–7.59 (m, J = 8.75 Hz, 3H, 3×Ar–H), 7.90 (s, 1H, Ar–H), 7.98 (d, J = 8.75 Hz, 1H, Ar–H); MS (*m*/*z*, %): 379 (M^+, 100).
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