

Acyliminium ion-olefin cyclization leading to isoindolo [2,1-a]quinoline derivatives

Pascal Pigeon, Mohamed Othman, Pierre Netchitaïlo, Bernard Decroix

▶ To cite this version:

Pascal Pigeon, Mohamed Othman, Pierre Netchitaïlo, Bernard Decroix. Acyliminium ion-olefin cyclization leading to isoindolo [2,1-a]quinoline derivatives. Journal of Heterocyclic Chemistry, 1999, 36 (3), pp.691-695. 10.1002/jhet.5570360319. hal-01230412

HAL Id: hal-01230412

https://hal.science/hal-01230412

Submitted on 9 Jan 2017

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers. L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Journal of Heterocyclic Chemistry (1999), 36(3), 691-695.

DOI: 10.1002/jhet.5570360319

Acyliminium Ion-Olefin Cyclization Leading to Isoindolo[2, 1-a]quinoline

Derivatives

Pascal Pigeon, Mohamed Othman, Pierre Netchitaïlo and Bernard Decroix*

URCOM, Université du Havre, 25 rue Philippe Lebon, BP 540, 76058 Le Havre Cedex,

France

Isoindolo[2,1-a]quinolines 10, 11, 12 were synthesized from hydroxylactams 8 or 9 via an N-

acyliminium ion- π -olefin nucleophile cyclization reaction.

Previous reports from our laboratory have described the synthesis of thienopyrroloisoindolones [1], benzothienoindolizinones [1], dibenz[c,e]azepine [2], thienothiazinoisoindolone [3], isoindoloquinolines [4] via an intramolecular α-amidoalkylation reaction. We wish to report herein the synthesis of isoindolo[2,1-a]quinolines through an intramolecular cyclization using N-acyliminium ion tethered to o-substituted vinylbenzene derivatives. These quinolines are analogous to the nuevamine alkaloid [5]. Some isoindolo[2,1a]quinolines [6-8] have been already synthesized but to our knowledge none has used an N-

acyliminium ion generated from an isoindole moiety.

The requisite phthalimides 3 and 6 were prepared as in Schemes I and II. Ethyl oaminobenzoate subjected to ethylmagnesium iodide gave the expected alcohol 1. Dehydration of 1 using p-toluenesulfonic acid as a catalyst in refluxing toluene furnished the vinyl derivatives 2 as a mixture of Z/E isomers. Condensation of 2 with phthalic anhydride led to the phthalimides 3 Z,E isomers (40/60). On the other hand, o-aminoacetophenone (Scheme II) treated with ethylmagnesium iodide gave alcohol 4. Dehydration of 4 led to three compounds: **5a, 5b** Z and **5b** E. Submitted to phthalic anhydride this mixture gave the corresponding phthalimides 6 Z (9%), 6 E (64%), 7 (27%). Interestingly, this mixture 6 + 7 treated with ptoluenesulfonic acid in refluxing toluene led to 6 Z (35%) and 6 E (65%). Indeed, the expected isomerization of 7 occurred and an equilibrium between 6 Z and 6 E was obtained after 48 hours

of heating. In similar conditions, the mixture 3 Z + E (40/60) isomerized to furnish a mixture

of $3 \ Z$ (71%) and $3 \ E$ (29%). The structures of 3 and 6 were supported by nmr (^{1}H , ^{13}C) spectroscopic analyses. NOE difference experiments were performed on 3 and 6 to determine the stereochemistry of the olefin part.

The phthalimides **3** and **6** were then reduced, by the action of sodium borohydride in methanol, into the hydroxylactams **9** (Z,E) and **8** (Z,E) with unchanged Z/E ratio. Under acidic conditions these hydroxylactams are precursors of N-acyliminium ions and an intramolecular cyclization could occur with the non aromatic π -nucleophile (olefin part). When **6** (Z + E) was

treated for 40 minutes with a catalytic amount of p-toluenesulfonic acid in refluxing toluene, three cyclic products were obtained, 10a (33%), 10b (33%), 10d (34%) (Scheme III). After 3 hours of reaction the percentages were 27%, 27%, 46% respectively and after 24 hours 10d was the only product observed. In the latter case, degradation occurred and 10d was obtained in a 48% yield. If the reaction was carried out with one equivalent of acid during 30 minutes 10d was obtained in a 75% yield as the lone product. Evolution of the reaction could be rationalized as depicted in Scheme III. The π -nucleophile attack upon the N-acyliminium ion, generated in situ, led to the intermediate carbocation A. Stabilization of A with loss of a proton gave the exocyclic olefins 10a (racemic form of $6R^*, 6aS^*$ relative configuration) and 10b (racemic form of 6S*,6aS* relative configuration), which were probably in equilibrium via the common isomer 10c (not detected). Izomerization of 10c furnished the stable enamide 10d. have already similar that we observed a thienoazepinoisoindolone [9]. In contrast to the reactivity of other olefins [10] the stereochemistry of the cyclization was not respected since the starting Z,E mixture (35/65) should give an equal trans/cis (35/65) mixture but gave a 50/50 mixture of 10a and 10b which turned in time to 10d. Intermediates compounds 10a and 10b could not be separated (fractional recrystallizations and column chromatographies where attempted) but their structures were well assigned from nmr studies (¹H and COSY experiments). Compound **10a** exhibited a trans coupling constant $J_{H6-H6a} = 11$ Hz and 10b revealed a cis coupling $J_{H6-H6a} = 3$ Hz. The spectrum of 10d revealed the absence of the H_{6a} proton, but the H_{5} proton appeared as a quadruplet (J_{H5} - $_{\text{Me}} = 7 \text{ Hz}$) with a chemical shift of $\delta = 3.52 \text{ ppm}$.

From these results it was interesting to study the reactivity of 9(Z,E) under similar conditions (Scheme IV). Thus, when hydroxylactams 9(Z/E, 71/29) were submitted to p-toluenesulfonic acid (catalytic amount) a mixture of 12(Z/E, 14%/14%), racemic form of 6R*,6aS* relative configuration), 11(E, 72%), racemic form of 6S*,6aS* relative configuration) was obtained in 90% yield after 40 minutes of reaction. A trace of compound 14 was observed but its quantity increased with a longer time reaction. When the reaction was carried out during 10 days the mixture consisted in 14(21%), 11E(57%), 12E(11%), 12Z(11%) and after 25 days in 14(42%), 11E(48%), 12E(5%), 12Z(5%). The slow isomerization of 11 and 12 was probably due to the higher stability of the substituted exocyclic double bond compared to the unsubstituted one in compounds 10a, (Scheme III). When the reaction was carried out with one equivalent of acid a mixture of 14(22%), 11E(68%), 12E(5%), 12Z(5%) was obtained after 1 hour but degradation products were also obtained and their amount was increasing with the reaction time. As intermediate 10c, the possible intermediate 13 has never been observed.

As described above for **8** (Z + E), the cyclization was not selective and the intermediate carbocation **B** stabilized with loss of a proton to furnish exocyclic olefins **11** and **12** and a small amount of **14**. The structures of these compounds were assigned on the basis of their nmr (1 H and 13 C) spectra. The configuration of **12** was supported by a coupling constant of 11 Hz characteristic of a *trans* relationship between H₆ and H_{6a}. Unfortunately it has not been possible to determine the geometry (Z or E) of the exocyclic double bond. The isoindoloquinoline **11** exhibits a *cis* coupling constant of 3 Hz (H₆-H_{6a}) and a E configuration (determined by NOE difference experiments). The oily mixture of **11**, **12** and **14** could not be separated by column chromatography.

In summary, we have demonstrated that disubstituted vinylbenzenes connected to hydroxylactam gave C_5 and C_6 substituted isoindolo[2,1-a]quinolines. The intramolecular cyclization was not selective and furnished a conjugate enamide **10d** in the case of vicinal dimethyl substituted vinyl derivatives **8** and an exocyclic double bond in the major isoindoloquinoline **11** with vicinal methylethylvinyl derivatives **9.** Further investigations are in progress particularly in order to obtain a selectivity during the cyclization step between the N-acyliminium ion and the π -olefin nucleophile.

EXPERIMENTAL

Melting points are uncorrected. The infrared spectra of solids (potassium bromide) were recorded on a Perkin Elmer FTIR paragon 1000 spectrometer. The 1 H and 13 C nmr spectra were recorded on a Bruker AC-200 (200 MHz) instrument in deuteriochloroform solution and the chemical shifts (δ) are expressed in ppm relative to internal tetramethylsilane. Ascending thin layer chromatography was performed on precoated plates of silica gel 60 F 254 (Merck) and the spots visualized using an ultraviolet lamp or iodine vapor. E. Merck silica gel 60 F (70-300 mesh) was used for column chromatography. The elemental analyses were carried out by the microanalysis laboratory of INSA at Rouen, F 76130 M t . S t . Aignan, France.

Phthalimides 3, 6.

To a 0.5M solution of ethylmagnesium iodide (120 ml for $\bf 3$, 80 ml for $\bf 6$) was added dropwise, with stirring, a solution of 10 mmoles of the corresponding amine (1.65 g of ethyl o-aminobenzoate for $\bf 3$, 1.35 g of o-aminoacetophenone for $\bf 6$) in 10 ml of dry ether. Stirring was continued overnight then the solution was carefully poured into 200 ml of 1M ammonium chloride solution. The organic layer was decanted and the aqueous layer was extracted with dichloromethane. The combination of the organic layers was evaporated, then toluene and a catalytic amount of p-toluenesulfonic acid were added. The flask was fitted with a Dean-Stark apparatus and the solution was refluxed for approximately 45 minutes (monitored by tlc). After cooling, triethylamine (2 ml) and phthalic anhydride (1.48 g, 10 mmoles) were added, then the solution was refluxed (Dean-Stark apparatus) for 2 days. The solution was cooled, then was concentrated under reduced pressure to give $\bf 3$ or a mixture of $\bf 6 + 7$.

Isomerization of phthalimides 6 Z, 6 E, 7 (9/64/27) into the mixture of 6 Z/E (35/65) was performed in refluxing toluene for 2 days with a catalytic amount of p-toluenesulfonic acid. The solution was cooled, washed with an aqueous solution of sodium hydrogen carbonate, dried over magnesium sulfate, then was concentrated under reduced pressure to afford the 35/65 mixture of isomers 6 Z/E.

Mixture of isomers 3 Z/E (40/60) could be partially isomerized to afford a 71/29 ratio by the above procedure.

N-[2-(l-Ethylprop-1-enyl)phenyl]phthalimides (3 Z,E).

The mixture of Z (71%) and E (29%) isomers recrystallized from ethanol was obtained in a yield of 96%.

Isomer Z had ¹H nmr: δ 0.89 (t, J = 7 Hz, 3H,CH₃), 1.41 (d, J = 7 Hz, 3H, =C-CH₃), 2.22 (q, J = 7 Hz, 2H, CH₂), 5.43 (q, J = 7 Hz, 1H, =CH), 7.13-7.49 (m, 4H, H_{arom}), 7.68-7.84 (m, 2H, H_{arom}), 7.85-7.98 (m, 2H, H_{arom}).

Isomer *E* had ¹H nmr: δ 0.91 (t, J = 7Hz, 3H,CH₃), 1.55 (d, J = 7 Hz, 3H, =C-CH₃), 2.23 (q, J = 7 Hz, 2H, CH₂), 5.40 (q, J = 7 Hz, 1H, =CH), 7.13-7.49 (m, 4H, H_{arom}), 7.68-7.84 (m, 2H, H_{arom}), 7.85-7.98 (m, 2H, H_{arom}).

Anal. Calcd. for C₁₉H₁₇NO₂: C, 78.33; H, 5.88; N, 4.81. Found: C, 77.92; H, 5.84; N, 4.83. *N*-[2-(1-Methylprop-l-enyl)phenyl]phthalimides (6 *Z,E*).

The mixture of Z (35%) and E (65%) isomers recrystallized from ethanol was obtained in a yield of 93%.

Isomer *Z* had ¹H nmr: δ 1.30 (d, J = 7 Hz, 3H, CH₃), 1.91 (s, 3H, CH₃), 5.42 (q, J = 7 Hz, 1H, =CH), 7.06-7.49 (m, 4H, H_{arom}), 7.68-7.82 (m, 2H, H_{arom}), 7.82-7.96 (m, 2H, H_{arom}). Isomer *E* had ¹H nmr: δ 1.49 (d, J = 7 Hz, 3H, CH₃), 1.85 (s, 3H, CH₃), 5.32 (q, J = 7 Hz, 1H, =CH), 7.06-7.49 (m, 4H, H_{arom}), 7.68-7.82 (m, 2H, H_{arom}), 7.82-7.96 (m, 2H, H_{arom}). *Anal.* Calcd. for C₁₈H₁₅NO₂: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.80; H, 5.42; N, 5.01. *N*-[2-(1-Ethylethenyl)phenyl]phthalimide (**7**).

Compound 7 had ¹H nmr: δ 0.98 (t, J = 7 Hz, 3H, CH₃), 2.30 (q, J = 7 Hz, 2H, CH₂), 4.85 (d, J = 1 Hz, 1H, =CH₂), 4.94 (d, J = 1 Hz, 1H, =CH₂), 7.06-7.49 (m, 4H, H_{arom}), 7.68-7.82 (m, 2H, H_{arom}), 7.82-7.96 (m, 2H, H_{arom}).

Hydroxylactams **8** *Z*,*E* and **9** *Z*,*E*.

General Procedure.

To a mixture of phthalimide 6 *Z,E* or 3 *Z,E* (4 mmoles) in dry methanol (40 ml) at 10° was added sodium borohydride by portions and 5 drops of ethanolic hydrochloric acid solution (prepared from 9 drops of concentrated hydrochloric acid in 15 ml of ethanol) at regular intervals (10 minutes) until the reaction was complete (monitored by tlc). The excess of sodium borohydride was decomposed by careful addition of diluted hydrochloric acid. Sodium hydrogen carbonate was added and the solvent was evaporated. The residue was triturated with water and the hydroxylactams 8 *Z,E* or 9 *Z,E* were separated by filtration, washed with water, dried and recrystallized from ethanol.

2,3-Dihydro-3-hydroxy-2-[2-(1-methylprop-1-enyl)phenyl]-lH-isoindol-1-one (**8** Z,E). A mixture of Z (35%) and E (65%) isomers was obtained in a yield of 92%.

Isomer Z had 1 H nmr: δ 1.44 (d, J = 7 Hz, 3H, CH₃), 1.86 (s, 3H, CH₃), 3.27 (s broad, 1H, OH), 5.52 (q, J = 7 Hz, 1H, =CH), 6.17 (s, 1H, CH), 7.03-7.65 (m, 7H, H_{arom}), 7.72 (d, J = 7 Hz, 1H, H_{arom}).

Isomer *E* had ¹H nmr: δ 1.59 (d, J = 7 Hz, 3H, CH₃), 1.79 (s, 3H, CH₃), 3.27 (s broad, 1H, OH), 5.52 (q, J = 7 Hz, 1H, =CH), 6.06 (s, 1H, CH), 7.03-7.65 (m, 7H, H_{arom}), 7.72 (d, J = 7 Hz, 1H, H_{arom}).

Anal. Calcd. for C₁₈H₁₇NO₂: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.31; H, 6.09; N, 5.06. 2,3-Dihydro-2-[2-(1-ethylprop-l-enyl)pheny l]-3-hydroxy-1*H*-isoindol-l-one (**9** *Z*,*E*).

A mixture of Z (71%) and E (29%) isomers was obtained in a yield of 88%.

Isomer Z had ¹H nmr: δ 0.85 (t, J = 7 Hz, 3H, CH₃), 1.64 (d, J = 7 Hz, 3H, =C-CH₃), 1.94-2.18 (m, 1H, CH₂), 2.21-2.47 (m, 1H, CH₂), 3.62 (s broad, 1H, OH), 5.49 (q, J = 7 Hz, 1H, =CH), 6.13 (s, 1H, CH), 7.04-7.61 (m, 7H, H_{arom}), 7.61-7.76 (m, 1H, H_{arom}).

Isomer *E* had ¹H nmr: δ 0.79-1.03 (m, 3H, CH₃), 1.76 (d, J = 7 Hz, 3H, =C-CH₃), 2.20-2.49 (m, 2H, CH₂), 3.60 (s broad, 1H, OH), 5.51 (q, J = 7 Hz, 1H, =CH), 6.15 (s, 1H, CH), 6.59-7.73 (m, 7H, H_{arom}), 7.89 (d, J = 7 Hz, 1H, H_{arom}).

Anal. Calcd. for C₁₉H₁₉NO₂: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.39; H, 6.59; N, 4.71. Isoindologuinolines **10a**,**b**,**d** and **11** (*E*), **12** (*Z*,*E*), **14**.

A mixture of **8** Z,E (or **9** Z,E), p-toluenesulfonic acid (catalytic amount or 1 equivalent) and toluene were refluxed in a flask fitted with a Dean-Stark apparatus for 30 minutes. The solution was cooled, washed with an aqueous solution of sodium hydrogen carbonate, dried over magnesium sulfate, then was concentrated under reduced pressure to afford an oily mixture of inseparable isomers (**10a**,**b**,**d** from **8** Z,E and **11** E + **12** Z,E + **14** from **9** Z,E). The mixture **11** + **12** + **14** did not give a good elemental analysis and was characterized by 1 H and 13 C nmr.

6H-5-Methylidene-6-methylisoindolo[2,1-a]quinolin-11(6aH)-one ($\mathbf{10a}$) ($6R^*$, $6aS^*$).

This unstable compound was detected in the crude product during the reaction and had ^{1}H nmr: δ 1.56 (d, J = 7 Hz, 3H, CH₃), 2.35-2.49 (m, 1H, H₆), 4.39 (d, J = 11 Hz, 1H, H_{6a}), 5.23 (d, J = 1 Hz, 1H, =CH₂), 5.71 (d, J = 1 Hz, 1H, =CH₂), 6.94-7.85 (m, 6H, H_{arom}), 7.89 (d, J = 7 Hz, 1H, H_{arom}), 8.47 (d, J = 8 Hz, 1H, H_{arom}).

6H-5-Methylidene-6-methylisoindolo[2,1–a]quinolin-11(6aH)-one (10b) (6S*,6aS*).

This compound was detected in the crude product during the reaction and had ^{1}H nmr: δ 0.54 (d, J = 7 Hz, 3H, CH₃), 3.23 (qd, J = 7 and 3 Hz, 1H, H₆), 4.92 (d, J = 3 Hz, 1H, H_{6a}), 5.12 (s,

1H, = CH_2), 5.60 (s, 1H, = CH_2), 6.94-7.85 (m, 6H, H_{arom}), 7.89 (d, J = 7 Hz, 1H, H_{arom}), 8.59 (d, J = 8 Hz, 1H, H_{arom}).

5,6-Dimethylisoindolo[2,1-a]quinolin-11(5H)-one (**10d**).

This compound was obtained, in 30 minutes using 1 equivalent of *p*-toluenesulfonic acid, as an oil, in a 75% yield and had 1 H nmr: δ 1.36 (d, J = 7 Hz, 3H, CH₃), 2.31 (s, 1H, CH₃), 3.52 (q, J = 7 Hz, 1H, H₅), 6.94-7.85 (m, 6H, H_{arom}), 7.89 (d, J = 7 Hz, 1H, H_{arom}), 8.95 (d, J = 8 Hz, 1H, H_{arom}); 13 C nmr: δ 17.4 (CH₃), 23.7 (CH₃), 39.8 (CH), 117.2 (CH), 122.1 (C), 122.3 (CH), 123.1 (CH), 124.5 (CH), 126.9 (CH), 127.4 (C), 127.7 (CH), 127.8 (CH), 128.1 (C), 130.3 (C), 131.8 (CH), 133.4 (C), 164.6 (CO).

Anal. Calcd. for C₁₇H₁₅NO: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.53; H, 6.15; N, 5.50. 5-Ethylidene-6-methylisoindolo[2,1-*a*]quinolin-11(6*aH*)-one (**11** *E*).

This compound had ${}^{1}H$ nmr: δ 0.50 (d, J = 7 Hz, 3H, CH₃), 1.91 (d, J = 7 Hz, 3H, =C-CH₃), 3.54 (qd, J = 7 and 3 Hz, 1H, H₆), 4.82 (d, J = 3 Hz, 1H, H_{6a}), 6.25 (q, J = 7 Hz, 1H, =CH), 6.81-8.04 (m, 7H, H_{arom}), 8.60 (d, J = 8 Hz, 1H, H_{arom}); ${}^{13}C$ nmr: δ 11.1 (CH₃), 13.1 (CH₃), 31.8 (CH), 61.6 (CH), 119.1 (CH), 119.8 (CH), 121.6 (CH), 123.9 (CH), 123.9 (CH), 124.1 (CH), 127.6 (CH), 127.8 (C), 128.4 (CH), 131.9 (CH), 133.3 (C), 134.0 (C), 135.4 (C), 142.6 (C), 166.4 (CO).

5-Ethylidene-6-methylisoindolo[2,1-*a*]quinolin-11(6a*H*)-one (**12** *Z/E*).

Compound 12 Z had 1 H nmr: δ 1.52 (d, J = 7 Hz, 3H, CH₃), 1.91 (d, J = 7 Hz, 3H, =C-CH₃), 2.93-3.17 (m, 1H, H₆), 4.36 (d, J = 9 Hz, 1H, H_{6a}), 6.25 (q, J = 7 Hz, 1H, =CH), 6.80-8.05 (m, 8H, H_{arom}).

Compound **12** E had ¹H nmr; δ 1.50 (d, J = 7 Hz, 3H, CH₃), 1.91 (d, J = 7 Hz, 3H, =C-CH₃), 2.30-2.48 (m, 1H, H₆), 4.46 (d, J = 10 Hz, 1H, H_{6a}), 6.25 (q, J = 7 Hz, 1H, =CH), 6.80-8.05 (m, 8H, H_{arom}).

5-Ethyl-6-methylisoindolo[2,1-a]quinolin-11(6aH)-one (**14**).

This compound had ${}^{1}\text{H}$ nmr: δ 0.60 (d, J = 7 Hz, 3H, CH₃), 1.68-1.85 (m, 2H, CH₂), 2.32 (s, 3H, =C-CH₃), 3.60 (t, 1H, J = 5 Hz, H_s), 6.81-8.04 (m, 7H, H_{arom}), 8.96 (d, J = 8 Hz, 1H, H₁₀); ${}^{13}\text{C}$ nmr: δ 8.4 (CH₃), 17.5 (CH₃), 28.8 (CH₂), 45.7 (CH), 117.0 (CH), 120.4 (C), 122.5 (CH), 123.3 (CH), 124.4 (CH), 126.3 (C), 127.0 (CH), 127.8 (CH), 127.9 (CH), 129.1 (C), 130.5 (C), 131.9 (CH), 133.4 (C), 134.8 (C), 164.8 (CO).

REFERENCES AND NOTES

- [1] M. Othman, P. Pigeon and B. Decroix, *Tetrahedron*, **53**, 2495 (1997).
- [2] P. Pigeon and B. Decroix, *Tetrahedron Letters*, **38**, 1041 (1997).
- [3] P. Netchitaïlo, M. Othman and B. Decroix, J. Heterocyclic Chem., 34, 321 (1997).
- [4] P. Pigeon and B. Decroix, *Synth. Commun.*, **28**, 2507 (1998).
- [5] E. Valencia, A. J. Freyer, M. Shamma and V. Fajardo, *Tetrahedron Letters*, **25**, 599 (1984).
- [6] Y. Ishihara, Y. Kiyota and G. Goto, Chem. Pharm. Bull.. 38, 3024 (1990).
- [7] Y. Abe, A. Ohsawa and H. Igeta, *Heterocycles*. **19**, 49 (1982).
- [8] H. Z. Alkhathlan, J. Chem. Res. (S), 260 (1992).
- [9] P. Pigeon and B. Decroix, *Bull. Soc. Chim. France*, **134**, 153 (1997).
- [10] H. Hiemstra and W. N. Speckamp, Comprehensive Organic Synthesis, Vol 2, B. M. Trost and I. Fleming, eds Pergamon, Oxford, 1991, pp 1047-1082.