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NOVEL APPROACH TO ISOINDOLO[2,1-a]QUINOLINES

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Abstract: An *N*-acyliminium ion approach towards the synthesis of isoindolo [2,1-a]quinolines by an intramolecular process is described.

During the course of our work concerning the synthesis of new fused polyheterocyclic compounds with potential therapeutic interest we described in previous papers the use of an *N*-acyliminium ion in the key cyclization step¹⁻³. We wish to report herein a novel approach to isoindolo[2,1-a]quinolines through an intramolecular cyclization using *N*-acyliminium ion tethered to *o*-vinylbenzene derivatives. Few examples of the use of substituted vinylbenzenes as the π -nucleophile reagent are reported⁴⁻⁵ in the literature, probably due to the possible polymerization reaction in an acidic medium.

Various approaches⁶⁻⁸ leading to isoindolo[2,1-a]quinoline derivatives are described but to our knowledge none use an *N*-acyliminium ion generated from an isoindole moiety. Thus we propose (Scheme 1) a novel approach to this tetracyclic system starting from suitable *o*-substituted aniline. To these compounds addition of a Grignard reagent (methylmagnesium iodide) or reduction (NaBH₄, CH₃OH) gave the corresponding alcohols **1a-c** (>95%). Treatment of **1a,b** by *p*-toluenesulfonic acid (PTSA) afforded the vinyl derivatives **2a,b** which directly reacted (one pot) with phthalic anhydride in the presence of triethylamine to furnish the phthalimides **3a,b** (>90%). Complete polymerization occurred during the acidic treatment of **1e**. According to our preceding work¹, reduction of **3a,b** using sodium borohydride or addition of a Grignard reagent led to the hydroxylactams **4a,b** (R₂ = H, >95%) and **5a,b** (R₂ = Me) respectively. The latter were very sensitive to dehydration since during work up, formation of the enamides **6a,b** (>95% for **5+6**) was observed.

Scheme 1

Submitted to PTSA in refluxing toluene with heteroazeotropic elimination of water the hydroxylactams **4a,b** (reaction time 30 minutes) or **5a,b** (reaction time 4 hours) gave compounds **13a** (93%), **13b** (65%, contaminated with **15**) or **12a,b** (>90%) respectively. To explain the selectivity observed during the formation of these quinolines **12** or **13** we can consider the carbocations **7a,b** and **8a,b** which would result from a π -nucleophilic attack of the vinylbenzene onto the *N*-acyliminium ion generated from the hydroxylactams **4** or **5**. In the case of **7a,b** ($\text{R}_2 = \text{H}$) regardless of R_1 (CH_3 , phenyl), elimination of the α proton led to the intermediate **11a,b** which was rapidly isomerized to the stable enamides **13a,b**. The possible compounds **9a**, **10a** and **11a,b** were not detected in the reaction mixture. Nevertheless, a reaction conducted with trifluoroacetic acid in dichloromethane at room temperature gave **11a,b** which transformed with time into the corresponding enamides **13a,b** (>90%, in this case **13b** was not contaminated with **15**). We have already mentioned that the formation of a

carbon-carbon double bond conjugated to the lactam function was very easy^{9,10}. Furthermore, compounds **14a,b** (consecutive to a 1,3 migration of a methyl group) have never been observed.

During the treatment of **4b**, another compound (**15**) was detected. It may result from the competitive π -aromatic attack of the benzene ring (R_1 = phenyl) upon the *N*-acyliminium ion to afford an isoindolo[a]dibenz[c,f]azepine analogous to the isoindolo[a]dibenz[c,e]azepine recently described by us². To confirm this observation, we undertook the synthesis of **18** (Scheme 2). The starting phthalimide **16** resulted from the condensation of phthalic anhydride with *o*-aminobenzophenone (93%). Reduction of the ketone group (triethylsilane, TFA) followed by a reduction of the imide function (NaBH_4 , CH_3OH) led to the hydroxylactam **17** (96%). This latter species with trifluoroacetic acid at room temperature furnished the expected isoindolo[a]dibenz[c,f]azepine **18** (95%). This excellent yield supports the hypothesis that in **4b**, the π -aromatic nucleophile can compete with the π -olefinic nucleophile during the attack of the *N*-acyliminium ion.

The structures of **12a,b**, **13a,b**, **18** were supported by their ir and nmr spectra as well as their microanalyses.

Scheme 2

Since the isoindolo[a]quinolines **11c** or **13c** ($R_1 = R_2 = \text{H}$) could not be obtained in a similar manner, two other routes have been investigated (Scheme 3). Reaction of **1c** with phthalic anhydride gave **19** (40%) which was successively dehydrated (PTSA, toluene) into **3c** (65%) then reduced (NaBH_4 , CH_3OH) to **4c** ($R_1 = R_2 = \text{H}$) (92%). Unfortunately, and as it could be expected this latter compound under acidic conditions (PTSA, toluene or TFA, CH_2Cl_2) gave rapid polymerization. Nevertheless alcohol **20**⁶ treated with PTSA in toluene with heteroazeotropic elimination of water gave **13c** in an excellent yield (99%). This compound has been previously prepared from a quinoline derivative⁷. The possible intermediate **11c** has not been detected and the dehydration was very fast (10 minutes).

Scheme 3

In conclusion, we have demonstrated that substituted vinylbenzenes can be used as precursors for a π -nucleophilic attack onto *N*-acyliminium ion in an intramolecular process. This reaction constitutes a novel approach to the isoindolo[a]quinoline system and applications of this cyclization reaction to the synthesis of heterocyclic analogs are under investigations.

EXPERIMENTAL

Melting points are uncorrected. The infrared spectra of solids (potassium bromide) were recorded on a Perkin Elmer FTIR paragon 1000 spectrometer. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200 (200 MHz) instrument in deuteriochloroform solution and chemical shift (δ) are expressed in ppm relative to internal TMS. 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.

Synthesis of phthalimides **3a,b**

To a 0.5 M solution of methylmagnesium iodide (120 mL for **3a**, 80 mL for **3b**) was added dropwise, with stirring, a solution of 10 mmol of the corresponding amine (1.65 g of ethyl *o*-aminobenzoate for **3a**, 1.97 g of *o*-aminobenzophenone for **3b**) 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 min (monitored by TLC). After cooling, triethylamine (2 mL) and phthalic anhydride (1.48 g, 10 mmol) were added, then the solution was refluxed (Dean-Stark apparatus) for 2 days. The solution was cooled, then was concentrated under reduced pressure. The residue was recrystallized from ethanol to afford pure phthalimides **3a,b**.

2-[2-(1-methylethenyl)phenyl]phthalimide (3a)

Yield 91%; mp 139°C; IR: 1710 (C=O) cm^{-1} ; ^1H NMR (CDCl_3): δ 1.97-2.10 (m, 3H, CH_3), 4.73-4.82 (m, 1H, $=\text{CH}_2$), 4.92-5.01 (m, 1H, $=\text{CH}_2$), 7.19-7.49 (m, 4H, H_{arom}), 7.70-7.82 (m, 2H, H_{arom}), 7.85-7.99 (m, 2H, H_{arom}); Anal. Calcd. For $\text{C}_{17}\text{H}_{13}\text{NO}_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.32; H, 5.01; N, 5.32.

2-[2-(1-phenylethenyl)phenyl]phthalimide (3b)

Yield 97%; mp 193°C; IR: 1723 (C=O) cm^{-1} ; ^1H NMR (CDCl_3): δ 5.41 (d, $J = 1$ Hz, 1H, $=\text{CH}_2$), 4.92-5.01 (d, $J = 1$ Hz, 1H, $=\text{CH}_2$), 6.80-7.73 (m, 13H, H_{arom}); Anal. Calcd. for $\text{C}_{22}\text{H}_{15}\text{NO}_2$: C, 81.21; H, 4.65; N, 4.31. Found: C, 80.94; H, 4.60; N, 4.33.

Synthesis of hydroxylactams 4a,b

General procedure: To a mixture of phthalimide **3a,b** (4 mmol) in dry methanol (40 mL) at 10°C were 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 (controlled 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 hydroxylactam **4a,b** was separated by filtration, washed with water, dried and recrystallized from ethanol.

2,3-Dihydro-3-hydroxy-2-[2-(1-methylethenyl)phenyl]-1*H*-isoindol-1-one (4a)

Yield 97%; mp 230°C; IR: 3260 (OH), 1661 (C=O) cm^{-1} ; ^1H NMR (CDCl_3): δ 1.99 (s, 3H, CH_3), 2.67 (s, 1H, OH), 4.97-5.02 (m, 1H, $=\text{CH}_2$), 5.04-5.10 (m, 1H, $=\text{CH}_2$), 6.14 (s, 1H, CH), 7.20-7.67 (m, 7H, H_{arom}), 7.86 (d, $J = 7$ Hz, 1H, H_{arom}); Anal. Calcd. for $\text{C}_{17}\text{H}_{15}\text{NO}_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.63; H, 5.70; N, 5.24.

2,3-Dihydro-3-hydroxy-2-[2-(1-phenylethenyl)phenyl]-1*H*-isoindol-1-one (4b)

Yield 96%; mp 113°C; IR: 3395 (OH), 1696 (C=O) cm^{-1} ; ^1H NMR (CDCl_3): δ 2.88 (d, $J = 10$ Hz, 1H, OH), 5.39 (s, 1H, $=\text{CH}_2$), 5.52 (s, 1H, $=\text{CH}_2$), 5.69 (d, $J = 10$ Hz, 1H, CH), 6.87-7.65

(m, 13H, H_{arom}); Anal. Calcd. for $\text{C}_{22}\text{H}_{17}\text{NO}_2$: C, 80.71; H, 5.23; N, 4.28. Found: C, 80.65; H, 5.17; N, 4.30.

Synthesis of isoindoloquinolines **12a,b**

First step: To a solution of imide **3a,b** (10 mmol) in dry dichloromethane (20 mL) was added a solution of methylmagnesium iodide (0.5 M in ether, 60 mL, 30 mmoles). The resulting mixture was stirred for 2 hours at room temperature, then poured into 200 mL of 1M ammonium chloride solution and extracted with dichloromethane. The organic layer was dried over magnesium sulfate and the solvent was removed under reduced pressure. Methylhydroxylactams **5a,b** were contaminated by their corresponding enamides **6a,b**.

Second step: A mixture of **5a-6a** (or **5b-6b**), a catalytic amount of *p*-toluenesulfonic acid and toluene were refluxed in a flask fitted with a Dean- Stark apparatus for 4 hours. The solution was cooled, washed with an aqueous solution of sodium hydrogen carbonate, dried over magnesium sulfate, then was concentrated under reduced pressure.

5,6a-Dimethylisoindolo[2,1-a]quinolin-11(6aH)-one (12a)

Yield 95% (oil); ^1H NMR (CDCl_3): δ 1.49 (s, 3H, CH_3), 2.05 (d, $J = 1$ Hz, 3H, CH_3), 6.00 (d, $J = 1$ Hz, 1H, H_6), 7.09-7.67 (m, 6H, H_{arom}), 7.90 (d, $J = 8$ Hz, 1H, H_{arom}), 7.99 (d, $J = 8$ Hz, 1H, H_{arom}); ^{13}C NMR: δ 18.7 (CH_3), 26.6 (CH_3), 62.9 (C), 120.9 (CH), 122.5 (CH), 124.0 (CH), 124.3 (CH), 124.7 (CH), 127.6 (C), 127.9 (CH), 128.1 (CH), 128.4 (CH), 130.4 (C), 130.8 (C), 132.5 (CH), 132.8 (C), 148.7 (C), 166.3 (CO).

5,6a-Methyl-5-phenylisoindolo[2,1-a]quinolin-11(6aH)-one (12b)

Yield 93%; mp 229°C (ethanol); IR: 1699 (C=O) cm^{-1} ; ^1H NMR (CDCl_3): δ 1.61 (s, 3H, CH_3), 6.15 (s, 1H, H_6), 7.07-7.66 (m, 11H, H_{arom}), 7.93 (d, $J = 8$ Hz, 1H, H_{arom}), 8.06 (d, $J = 8$ Hz, 1H, H_{arom}); ^{13}C NMR: δ 26.1 (CH_3), 63.0 (C), 121.0 (CH), 122.8 (CH), 124.4 (CH), 124.5 (CH), 126.7 (CH), 127.0 (C), 127.8 (CH), 128.2 (2CH), 128.3 (CH), 128.7 (2CH), 128.8 (CH), 129.2 (CH), 130.9 (C), 132.7 (CH), 133.2 (C), 137.6 (C), 138.3 (C), 148.4 (C), 166.2 (CO); Anal. Calcd. For $\text{C}_{23}\text{H}_{17}\text{NO}$: C, 85.42; H, 5.30; N, 4.33. Found: C, 85.17; H, 5.23; N, 4.19.

5-Methylisoindolo[2,1-a]quinolin-11(5H)-one (13a)

A mixture of **4a** (2.63 g, 10 mmol), a catalytic amount of *p*-toluenesulfonic acid and toluene were refluxed in a flask fitted with a Dean-Stark apparatus for 30 min. The solution was cooled, washed with an aqueous solution of sodium hydrogen carbonate, dried over magnesium sulfate, then was concentrated under reduced pressure. The residue was

recrystallized from ethanol. Yield 93%; mp 149°C; IR: 1679 (C=O) cm⁻¹; ¹H NMR (CDCl₃): δ 1.44 (d, J = 7 Hz, 3H, CH₃), 3.82 (qd, J = 7 and 5 Hz, 1H, H₅), 5.95 (d, J = 5 Hz, 1H, H₆), 7.07-7.72 (m, 6H, H_{arom}), 7.87 (d, J = 8 Hz, 1H, H_{arom}), 8.98 (d, J = 8 Hz, 1H, H_{arom}); ¹³C NMR: δ 25.3 (CH₃), 32.2 (CH), 109.4 (CH), 117.5 (CH), 119.3 (CH), 123.3 (CH), 124.8 (CH), 127.4 (CH), 127.9 (C), 128.4 (CH), 129.1 (CH), 130.2 (C), 132.0 (CH), 132.6 (C), 133.6 (C), 134.2 (C), 165.2 (CO); Anal. Calcd. for C₁₇H₁₃NO: C, 82.57; H, 5.30; N, 5.66. Found: C, 82.20; H, 5.25; N, 5.52.

5-Phenylisoindolo[2,1-a]quinolin-11(5H)-one (13b)

A solution of hydroxylactam **4b** (10 mmol), dichloromethane (50 mL), trifluoroacetic acid (5 mL) was stirred for 3 days at room temperature. After concentration under reduced pressure, the residue was dissolved into dichloromethane. The solution was washed with a solution of sodium hydrogen carbonate, dried, then concentrated. The residue was recrystallized from ethanol to afford pure **13b**. Yield 91%; mp 173°C; IR: 1699 (C=O) cm⁻¹; ¹H NMR (CDCl₃): δ 4.97 (d, J = 4 Hz, 1H, H₅), 6.02 (d, J = 4 Hz, 1H, H₆), 6.86-8.00 (m, 12H, H_{arom}), 9.05 (d, J = 8 Hz, 1H, H_{arom}); ¹³C NMR: δ 43.8 (CH), 107.4 (CH), 117.2 (CH), 119.3 (CH), 123.0 (CH), 124.6 (CH), 125.6 (C), 126.7 (CH), 127.4 (CH), 128.1 (2CH), 128.6 (2CH), 129.1 (CH), 129.8 (C), 129.9 (CH), 131.8 (C), 131.9 (CH), 133.4 (C), 134.0 (C), 144.8 (C), 165.0 (CO); Anal. Calcd. for C₂₂H₁₅NO: C, 85.41; H, 4.89; N, 4.53. Found: C, 85.10; H, 4.85; N, 4.38.

Isoindolo[2,1-a]quinolin-11(5H)-one (13c)

This compound was prepared from **20** in a similar manner as described for the synthesis of **13a**. Yield 99%. The physical data are identical to those reported in the literature⁷.

2-(2-benzoylphenyl)phthalimide (16)

A mixture of phthalic anhydride (1.48 g, 10 mmol), o-aminobenzophenone (1.97 g, 10 mmol), triethylamine (2 mL) and toluene was refluxed in a flask fitted with a Dean-Stark apparatus for 2 days. The solution was cooled, then was concentrated under reduced pressure. The residue was recrystallized from ethanol to afford pure phthalimide **16**. Yield 93%; mp 200°C; IR: 1709 (C=O), 1665 (C=O) cm⁻¹; ¹H NMR (CDCl₃): δ 7.07-7.82 (m, 13H, H_{arom}); Anal. Calcd. for C₂₁H₁₃NO₃: C, 77.06; H, 4.00; N, 4.28. Found: C, 76.82; H, 4.06; N, 4.31.

2,3-Dihydro-3-hydroxy-2-(2-(phenylmethyl)phenyl)-1H-isoindol-1-one (17)

A mixture of **16** (1.83 g, 10 mmol), triethylsilane (5 mL, 30 mmol), trifluoroacetic acid (30 mL) was stirred for 2 days at room temperature. The solution was concentrated under reduced pressure then methanol was added (100 mL) and reduction was accomplished with sodium borohydride with the same procedure than for the synthesis of **4a,b**. Yield 96%; mp 147°C;

IR: 3327 (OH), 1682 (C=O) cm^{-1} ; ^1H NMR (CDCl_3): δ 1.64 (s, 1H, CH), 3.91 (d, $J = 15$ Hz, 1H, CH_2), 4.06 (d, $J = 15$ Hz, 1H, CH_2), 5.63 (s broad, 1H, CH), 6.89-7.61 (m, 12H, H_{arom}), 7.80-7.88 (m, 1H, H_{arom}); Anal. Calcd. for $\text{C}_{21}\text{H}_{17}\text{NO}_2$: C, 79.98; H, 5.43; N, 4.44. Found: C, 79.92; H, 5.44; N, 4.47.

5*H*-Isoindolo[2,1-*a*]dibenz[*c,f*]azepin-14(9*bH*)-one (18)

A solution of **17** (1.85 g, 10 mmol) in trifluoroacetic acid (30 mL) was stirred overnight at room temperature. The solution was concentrated under reduced pressure then the residue was recrystallized from ethanol to afford pure **18**. Yield 95%; mp 183°C; IR: 1698 (C=O) cm^{-1} ; ^1H NMR (CDCl_3): δ 3.54 (d, $J = 14$ Hz, 1H, H_5), 4.22 (d, $J = 14$ Hz, 1H, H_5), 6.06 (s, 1H, H_{9a}), 6.93-7.72 (m, 11H, H_{arom}), 7.98 (d, $J = 7$ Hz, 1H, H_{arom}); ^{13}C NMR: δ 39.0 (CH_2), 64.5 (CH), 122.9 (CH), 124.2 (CH), 127.2 (CH), 127.8 (2CH), 128.0 (CH), 128.1 (CH), 128.4 (CH), 128.5 (2CH), 130.0 (CH), 131.4 (C), 132.2 (CH), 134.4 (C), 136.4 (C), 137.1 (C), 138.9 (C), 144.7 (C), 168.0 (CO); Anal. Calcd. for $\text{C}_{21}\text{H}_{15}\text{NO}$: C, 84.82; H, 5.08; N, 4.71. Found: C, 84.94; H, 4.97; N, 4.68.

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