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## Diisoindolothieno[2,4]diazepines *via* a diastereoselective *N*-acyliminium ion cyclization

Pascal Pigeon and Bernard Decroix\*

*Laboratoire de Chimie, Faculté des Sciences et des Techniques de l'Université du Havre,  
25 rue Philippe Lebon, BP 540, 76058 Le Havre-Cédex, France*

New address: Université du Havre, URCOM, 25 rue Philippe Lebon, BP 1123, 76063 Le Havre cedex, France

\* Fax: (33)02.35.19.67.71

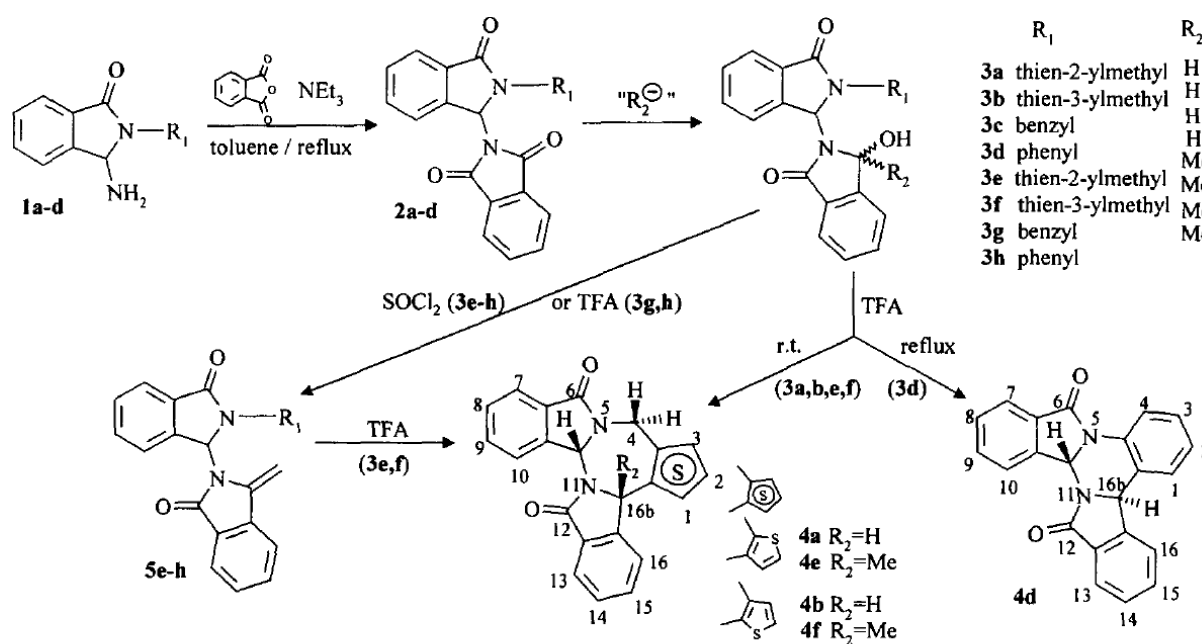
### Abstract

A high *syn* stereoselectivity, of the addition of an aromatic to the cyclic *N*-acyliminium ions generated from hydroxylactams **3a,b,e,f** leading to the thieno[2,4]diazepines **4a,b,e,f** is described.

*Keywords:* Iminium salts; Diazepines; Polycyclic heterocyclic compounds; Quinazolines.

Heterocyclic compounds containing phthalimidine (2,3-dihydroisoindol-1-one) skeleton have received a wide attention since a number of natural or synthetical products such as indoprofen [1,2] (antiinflammatory agent), DN-2327 [3] (anxiolytic agent) or batracyclin [4] (neoplasm inhibitor) possess biological activity. In the course of our continuing efforts towards the synthesis of [1,3]diazepines annulated to a benzene ring [5] or a heterocyclic ring [6,7] we focused our attention on a stereoselective access to diisoindolothieno[2,4]diazepine **4**. The nucleophilic addition to *N*-acyliminium ion constitutes a powerful tool for this purpose. Previous studies from our laboratory have shown that the reaction of this ion with an aromatic compound gave indolizines [8] or dibenzazepine derivatives [9]. In the present paper, we wish to report a stereoselective approach to **4** using asymmetric hydroxylactams **3a,b,e,f** as starting material.

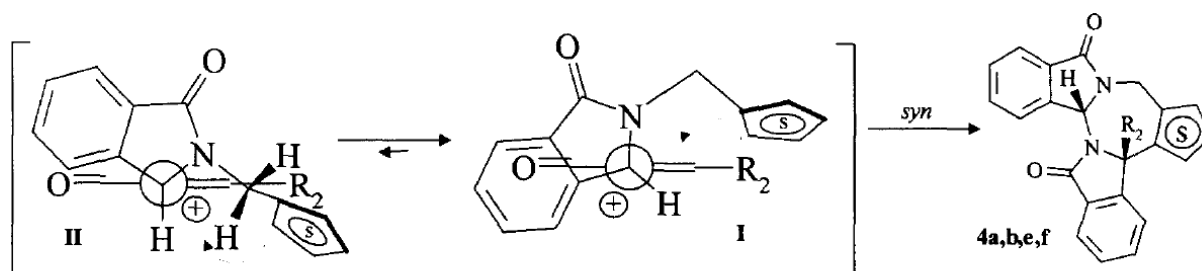
Aminolactams **1a-d** [10] were reacted with phthalic anhydride in refluxing toluene in the presence of triethylamine giving the phthalimidolactam derivatives **2a-d** in excellent yields (95-98%) (Scheme 1). Reduction of imides **2a-d** at 5-10°C with sodium borohydride in the presence of acid [8,11] afforded a mixture of hydroxylactams **3a-d** (97-99%). These hydride reductions gave a mixture of unseparable diastereomers with a low stereoselectivity (75/25 for **3a-e**, 55/45 for **3d**). In a recent work [12], Polniaszek has shown that the stereoselectivity of the hydride reduction of *N*-chiral benzylsuccinimides depends on the substitution of the aromatic ring connected to the chiral carbon. By the way, it is known that other succinimides substituted with a different chiral carbon fixed on the nitrogen atom have a similar behavior [13,14]. In our conditions the moderate stereoselectivity observed depends on the nature of the group (phenyl, benzyl, or thienylmethyl) bonded to the nitrogen atom of the isoindolone moiety. Similar results were observed when a Grignard reagent (methylmagnesium bromide, 95-98% yield) was used at room temperature instead of sodium borohydride since a mixture was obtained (75/25 for **3e,f**; 55/45 for **3h**; 62/38 for **3g**).



Scheme 1

The hydroxylactams **3a-h** were reacted with trifluoroacetic acid at room temperature. Under these conditions, the intermediate acyliminium ions (Scheme 2) were cyclized into **4a,b,e,f** in high yields (92-99%) (with R<sub>1</sub> = thienylmethyl). In the cases of **3c,d**, the starting material was recovered and **3g,h** gave the enamides **5g,h**. When the reactions were conducted under reflux **3d** gave **4d** (93%) and **3e,g,h** decomposed. The acyliminium ions **I** or **II** (Scheme 2) displayed a stereoselectivity in the cyclization reaction. The structures of the

cyclized products were supported by NMR ( $^1\text{H}$ ,  $^{13}\text{C}$ ) analyses. Moreover a NOESY spectrum of **4a** reveals a cross peak between the singlet of  $\text{H}_{10\text{b}}$  at 7.28 ppm and both the doublet of doublet of  $\text{H}_{4\text{p-ax}}$  at 4.53 ppm and the singlet of  $\text{H}_{16\text{b}}$  proton at 5.21 ppm. The  $^1\text{H}$  NMR spectrum of **4a** exhibits a broad singlet for  $\text{H}_{16\text{b}}$  and a doublet of doublet for  $\text{H}_{4\text{p-ax}}$  with coupling constants of 2 Hz ( $\text{H}_{16\text{b}}\text{-H}_{4\text{p-ax}}$ ) and 16 Hz ( $\text{H}_{4\text{p-ax}}\text{-H}_{4\text{p-eq}}$ ) characteristic of *gem* protons. Obviously the homoallylic long range coupling between  $\text{H}_{16\text{b}}$  and  $\text{H}_{4\text{p-ax}}$  is absent in **4e** since carbon  $\text{C}_{16\text{b}}$  is substituted with a methyl group. The high stereoselectivity observed during nucleophilic addition to the acyliminium ion containing the chiral isoindolone moiety may be ascribed to the preferred transition conformer **I** (Scheme 2), where the nitrogen atom of the isoindolone moiety adopts a perpendicular position to the plane of the  $\text{C}=\text{N}$  double bond due to a destabilizing  $\text{A}^{(1,3)}$  strain type interaction [12,13,15]. Similar observations were done in a study on *N*-(2-substituted pyrrolidin-1-yl) imides [16]. Thus, the thiophene ring of the conformer **I**, which acts as the nucleophile, approaches the iminium face providing the *syn* isomers **4a,b,e,f**. The alternative conformer **II**, which could lead to the *anti* isomer, suffers from non bonding interaction between the isoindolone system and the acyliminium group. On the contrary, **3d** led to **4d** with a *trans* configuration for  $\text{H}_{10\text{b}}$  and  $\text{H}_{16\text{b}}$ . This result is in accordance with those reported for relative compounds [17] and was confirmed by examination of the molecular model.



Scheme 2

Furthermore, we have shown that cyclization occurred when a substituted hydroxylactam was treated with thionyl chloride to form indolizidines [8]. In similar reaction conditions compounds **3e-h** did not give the expected diazepines **4e-h** but the methylene phthalimidine derivatives **5e-h** (96-98%) (Scheme 1) whereas **3a-d** did not react. However, cyclization into **4e,f** was accomplished when compounds **5e,f** were submitted to trifluoroacetic acid at room temperature (98-99%) while the less reactive benzenic derivatives **5g,h** did not react at room temperature and were decomposed under heating.

The high degree of selectivity of this amidoalkylation lead us to carry on our investigations in view of application to the synthesis of natural products.

## Experimental details

Physical data for **4a**: yield 99%; mp >270°C; IR: 1712 (C=O), 1687 (C=O) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 4.53 (dd, 1H, H<sub>4</sub>, J = 16 and 2 Hz), 5.21 (s broad, 1H, H<sub>16b</sub>), 5.33 (d, 1H, H<sub>4</sub>, J = 16 Hz), 7.07 (s, 2H, H<sub>1,2</sub>), 7.28 (s, 1H, H<sub>10b</sub>), 7.43-7.71 (m, 6H, H<sub>arom</sub>), 7.75-7.85 (m, 1H, H<sub>arom</sub>), 7.93 (d, 1H, H<sub>arom</sub>, J = 8 Hz); <sup>13</sup>C NMR: δ 39.2 (CH<sub>2</sub>), 57.5 (CH), 68.5 (CH), 123.4 (CH), 123.7 (CH), 123.9 (2CH), 124.4 (CH), 126.3 (CH), 128.7 (CH), 130.0 (CH), 131.1 (C), 132.1 (C), 132.4 (CH), 132.7 (CH), 134.0 (C), 136.2 (C), 142.1 (C), 145.0 (C), 167.8 (CO), 169.3 (CO); Anal. Calcd. for C<sub>21</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>S: C, 70.37; H, 3.94; N, 7.82. Found: C, 70.60; H, 3.82; N, 7.86.

Physical data for **4b**: yield 99%; mp >270°C; IR: 1716 (C=O), 1690 (C=O) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 4.41 (dd, 1H, H<sub>4</sub>, J = 16 and 2 Hz), 5.38 (s broad, 1H, H<sub>16b</sub>), 5.45 (d, 1H, H<sub>4</sub>, J = 16 Hz), 6.90 (d, 1H, H<sub>3</sub>, J = 5 Hz), 7.12 (d, 1H, H<sub>2</sub>, J = 5 Hz), 7.14 (s, 1H, H<sub>10b</sub>), 7.46-7.66 (m, 5H, H<sub>arom</sub>), 7.71-7.86 (m, 2H, H<sub>arom</sub>), 7.90 (d, 1H, H<sub>arom</sub>, J = 7 Hz); <sup>13</sup>C NMR: δ 40.7 (CH<sub>2</sub>), 56.3 (CH), 69.1 (CH), 123.6 (CH), 123.7 (CH), 123.9 (CH), 124.2 (CH), 124.4 (CH), 127.5 (CH), 129.0 (CH), 130.0 (CH), 131.4 (C), 131.6 (C), 132.3 (CH), 132.8 (CH), 134.7 (C), 136.3 (C), 142.2 (C), 144.9 (C), 167.5 (CO), 169.1 (CO); Anal. Calcd. for C<sub>21</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>S: C, 70.37; H, 3.94; N, 7.82. Found: C, 70.34; H, 4.16; N, 7.82.

Physical data for **4d**: yield 90%; mp 249°C; IR: 1717 (C=O), 1698 (C=O) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 5.36 (s, 1H, H<sub>16b</sub>), 6.53 (s, 1H, H<sub>10b</sub>), 7.86-7.17 (m, 9H, H<sub>arom</sub>), 7.88-8.00 (m, 2H, H<sub>arom</sub>), 8.09 (d, 1H, H<sub>arom</sub>, J = 7 Hz); <sup>13</sup>C NMR: δ 56.9 (CH), 67.8 (CH), 124.0 (2CH), 124.5 (CH), 124.7 (CH), 125.1 (CH), 125.5 (CH), 126.4 (CH), 129.0 (CH), 129.1 (CH), 129.8 (CH), 130.2 (C), 131.0 (C), 131.9 (CH), 132.4 (C), 133.3 (CH), 134.5 (C), 142.1 (C), 143.6 (C), 166.3 (CO), 168.5 (CO); Anal. Calcd. for C<sub>21</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>: C, 78.09; H, 4.17; N, 8.28. Found: C, 77.82; H, 4.13; N, 7.25.

Physical data for **4e**: yield 96%; mp >270°C; IR: 1690 (C=O) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.16 (s, 3H, CH<sub>3</sub>), 4.48 (d, 1H, H<sub>4</sub>, J = 16 Hz), 5.33 (d, 1H, H<sub>4</sub>, J = 16 Hz), 7.04 (d, 1H, H<sub>1</sub>, J = 5 Hz), 7.09 (d, 1H, H<sub>2</sub>, J = 5 Hz), 7.44 (s, 1H, H<sub>10b</sub>), 7.38-7.71 (m, 6H, H<sub>arom</sub>), 7.74-7.87 (m, 1H, H<sub>arom</sub>), 7.91 (d, 1H, H<sub>arom</sub>, J = 8 Hz); <sup>13</sup>C NMR: δ 28.7 (CH<sub>3</sub>), 38.7 (CH<sub>2</sub>), 67.7 (CH), 68.3 (C), 122.1 (CH), 123.3 (CH), 123.8 (CH), 123.9 (CH), 124.3 (CH), 126.9 (CH), 128.6 (CH), 129.4 (C), 129.7 (CH), 132.1 (C), 132.4 (CH), 132.7 (CH), 134.7 (C), 139.2 (C), 143.2 (C), 150.7 (C), 166.9 (CO), 168.8 (CO); Anal. Calcd. for C<sub>22</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>S: C, 70.95; H, 4.33; N, 7.52. Found: C, 71.35; H, 4.15; N, 7.44.

Physical data for **4f**: yield 92%; mp 238°C; IR: 1715 (C=O), 1682 (C=O) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.30 (s, 3H, CH<sub>3</sub>), 4.37 (d, 1H, H<sub>4</sub>, J = 16 Hz), 5.44 (d, 1H, H<sub>4</sub>, J = 16 Hz), 6.81 (d, 1H, H<sub>3</sub>, J = 5 Hz), 7.10 (d, 1H, H<sub>2</sub>, J = 5 Hz), 7.29 (s, 1H, H<sub>10b</sub>), 7.44-7.67 (m, 5H, H<sub>arom</sub>), 7.73-7.93 (m, 3H, H<sub>arom</sub>); <sup>13</sup>C NMR: δ 30.1 (CH<sub>3</sub>), 40.3 (CH<sub>2</sub>), 67.7 (C), 68.2 (CH), 122.2 (CH), 123.4 (CH), 123.7 (CH), 124.0 (2CH), 127.4 (CH), 128.8 (CH), 129.4 (C), 129.7 (CH), 131.7 (C), 132.5 (2CH), 134.9 (C), 140.8 (C), 143.5 (C), 151.1 (C), 166.9 (CO), 168.4 (CO); Anal. Calcd. for C<sub>22</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>S: C, 70.95; H, 4.33; N, 7.52. Found: C, 70.79; H, 4.03; N, 7.52.

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