Synthesis of Thienothiazocinoisoindolediones and Thienothiazinoisoindolones from Mercaptothiophenes and Chloromethylphthalimide

Pierre Netchitaïlo*, Mohamed Othman and Bernard Decroix

Laboratoire de chimie, Université Le Havre, 30 rue Gabriel Péri, 76600 Le Havre, France

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2-Thienylthiomethylphthalimides **3a,b** were synthesized by action of chloromethylphthalimide on 2-or 3-mercaptothiophene. Reduction of **3a,b** and Wittig reaction using carbethoxycarbonyltriphenylphosphorane gave the corresponding acetic acids **5a,b** which cyclized under Friedel and Crafts conditions to lead the thienothiazocinoisoindolediones **6a,b**. Thienothiazinoisoindolones **7a,b** were obtained from hydroxyisoindolones derivatives **4a,b** in acid conditions *via* an acyliminium ion.

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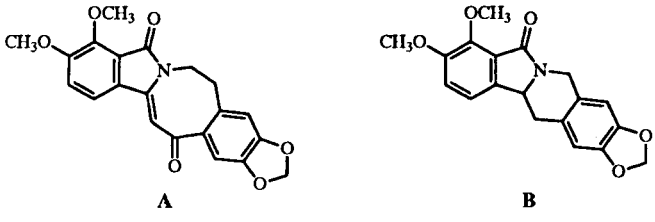
Recently, new alkaloïds have been isolated from the plant family *Berberidaceae*. These compounds exhibit various ring systems such as isoindolobenzazocine [1], isoindolobenzazepine [2], isoindoloisoquinoline [3] or isoquinolinobenzazepine [4].

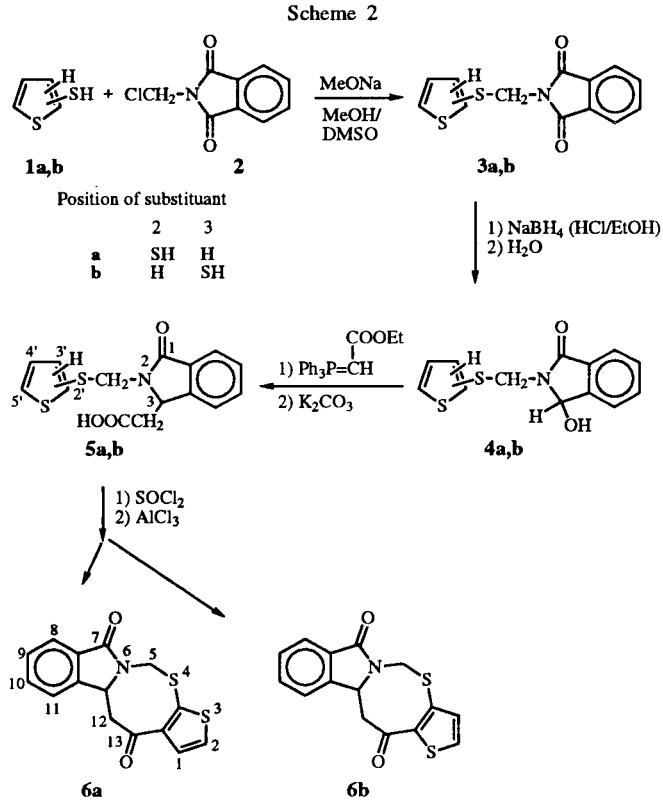
During our investigations on the synthesis of polyheterocycles containing the thiophene ring we described some thienodiazepines annelated to a pyrrole and pyrrolidine ring [5,6] and thienoazepinoisoindolediones [7]. In the present study, we report the synthesis of thienothiazocinoisoindolediones and thienothiazinoisoindolones which were respectively analogous to the isoindolobenzazocine alkaloid, magallanesine **A**, and the isoindoloisoquinoline alkaloid, nuevamine **B**.

Scheme 1



A **B**

Scheme 2



1a,b **2** **3a,b** **4a,b** **5a,b** **6a** **6b**

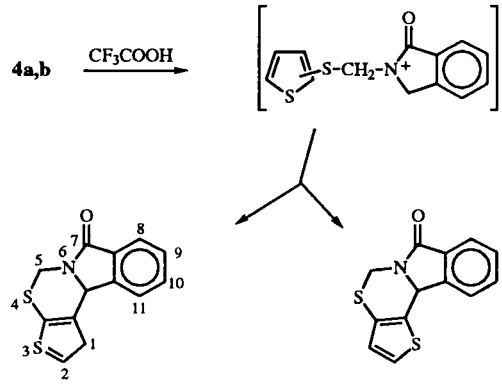
As indicated in Scheme 2, 2- or 3-mercaptothiophene **1a,b** was alkylated with chloromethylphthalimide **2** in DMSO using sodium methylate as basic reagent. Reduction of thienylthiomethylphthalimides **3a,b** with sodium borohydride at 0° in ethanolic-hydrochloric acid solution followed by hydrolysis with aqueous sodium bicarbonate led to the hydroxylactams **4a,b** in quantitative yields. A Wittig reaction using ethoxycarbonylmethylidene triphenylphosphorane on **4a,b** gave the isoindolone acetic acids **5a,b**.

The ^{1}H nmr spectra of **3a,b** showed that CH_2-N protons present a singlet with a chemical shift of 4.90 ppm. In contrast, they appear as two well resolved doublets of an AB system (J = 13-14 Hz) in compounds **4-5a,b** with a large difference of chemical shift which is close to 1 ppm for compounds **5a,b**. As expected, the H_3 proton appears as a doublet of doublet in **5** (5.25 ppm, J = 4.8, 6.9 Hz for **5a** and 5.21 ppm, J = 5.1, 6.7 Hz for **5b**) since the protons of the methylcarboxylic group in α position are not equivalent (J = 15 and 16.1 Hz, for **5a** and **5b**, respectively).

Cyclization of **5a,b** was performed using a Friedel and Crafts reaction. As previously described in the synthesis of thienoindolizines [8], aluminium trichloride of high purity gave the best yields. Acid chlorides, obtained from acids **5a,b** and thionylchloride, were treated with aluminium trichloride in dichloromethane at room temperature to lead the cyclic compounds **6a,b** in good yield for **6a** (78%) to moderate yield for **6b** (42%). The structure of these new polycyclic systems was supported by ir, ^{1}H nmr

spectroscopy and microanalysis. The ^1H nmr spectra of **6a** and **6b** showed an AB thiophene system with a coupling constant of 5.6 Hz for **6a** and 5.1 Hz for **6b**. As reported above, H_5 and H_{12} protons are not equivalent. In particular, H_5 protons exhibit a marked difference (1.5 ppm) in chemical shift, indicating that in such structures one of the two protons is strongly under the influence of the lone pair of the nitrogen. Finally, the proton H_{11b} in the α position of the non equivalent H_{12} protons appears as a doublet of a doublet (J = 3.5, 8.2 Hz) in compound **6a**.

Scheme 3



From the hydroxylactams **4a,b** in the presence of trifluoroacetic acid, at room temperature, we isolated the thienothiazinoisoindolones **7a,b** *via* the *N*-acyliminium ion cyclization [9]. The structure of **7a** and **7b** was supported by their ^1H nmr spectra. They show two AB systems corresponding to the disubstituted thiophene (J = 5.3 and 5.1 Hz, respectively) and CH_2 protons of the thiazine ring (J = 12.4 Hz). As reported in indolizine [8] or quinolizine [9] systems, the position of the axial proton is at higher magnetic field (4.60 ppm) than the equatorial proton (5.45 ppm). Finally, the signal of the H_{11b} proton is a singlet (δ = 5.85 ppm).

In summary, we have described the synthesis of thienothiazocinoindolediones and thienothiazinoisoindolones from mercaptothiophenes and readily available chloromethylphthalimide. Further investigations are in progress particularly to extend the use of *N*-acyliminium ions to the synthesis of azine systems containing another heteroatom.

EXPERIMENTAL

Melting points were taken on a hot stage apparatus, elemental analyses were obtained in the microanalysis laboratory of the Institut National des Sciences Appliquées, Rouen. The ^1H nmr spectra were recorded on a Brucker AC-200 instrument in deuteriochloroform solution and chemical shift (δ) are expressed in ppm relative to internal TMS. Infrared spectra were recorded with a Perkin Elmer FTIR paragon 1000 spectrometer. Starting chloromethylphthalimide **2** was synthesized as described elsewhere [10].

2-Thienylthiomethylphthalimides **3a,b**.

To a mixture of 2-or 3-mercaptothiophene (15 mmoles) in 10 ml of dry DMSO was slowly added 4 ml of a saturated solution of sodium methylate (3.8 *M*) in methanol. After 2 hours of stirring, chloromethylphthalimide (2.9 g, 15 mmoles) dissolved in 10 ml of dry DMSO was added dropwise over a period of 30 minutes. The solution was stirred at room temperature for 3 hours and then poured into 100 ml of ice-water. The precipitate was collected by filtration and dried. Recrystallization from methanol afforded 2-thienylthiomethylphthalimides **3a,b** as colourless crystals.

2-(Thien-2'-ylthiomethyl)phthalimide (**3a**).

This compound was obtained in a yield of 66%, mp 104°; ir: 1719 (C=O) cm^{-1}; ^1H nmr: δ 4.85 (s, 2H, CH_2-N), 6.92 (dd, 1H, $H_{4'}$, J = 3.6, 5.2 Hz), 7.10 (dd, 1H, $H_{3'}$, J = 1.4, 3.6 Hz), 7.38 (dd, 1H, $H_{5'}$, J = 1.4, 5.2 Hz), 7.67-7.76 (m, 2H, H arom), 7.77-7.86 (m, 2H, H arom).

Anal. Calcd. for $C_{13}H_9NO_2S_2$: C, 56.71; H, 3.29; N, 5.09. Found: C, 56.55; H, 3.52; N, 4.92.

2-(Thien-3'-ylthiomethyl) phthalimide (**3b**).

This compound was obtained in a yield of 62%, mp 117°; ir: 1723 (C=O) cm^{-1}; ^1H nmr: δ 4.90 (s, 2H, CH_2-N), 7.05 (dd, 1H, $H_{4'}$, J = 1.6, 4.8 Hz), 7.25-7.32 (m, 2H, $H_{2',5'}$), 7.65-7.74 (m, 2H, H arom), 7.76-7.85 (m, 2H, H arom).

Anal. Calcd. for $C_{13}H_9NO_2S_2$: C, 56.71; H, 3.29; N, 5.09. Found: C, 56.49; H, 3.42; N, 4.81.

2,3-Dihydro-3-hydroxy-2-(thienylthiomethyl)- 1*H*-isoindol-1-ones **4a,b**.

To a mixture of phthalimidothiomethylthiophene **3a,b** (10 mmoles) in dry methanol (50 ml) at 0° was added sodium borohydride (1.12 g, 30 mmoles) in several portions during 30 minutes and 3 drops of ethanolic-hydrochloric acid solution (99:1). After the solution became clear, the solvent was evaporated. The residue was carefully treated by cold water (20 ml) and diluted hydrochloric acid. The mixture was extracted with dichloromethane, then the organic layer was dried and evaporated. The hydroxylactams were recrystallized from benzene-hexane (**4a**) or methanol (**4b**).

2,3-Dihydro-3-hydroxy-2-(thien-2'-ylthiomethyl)-1*H*-isoindol-1 one (**4a**).

This compound was obtained in a yield of 95%, mp 120°; ir: 3343 (OH), 1684 (C=O) cm^{-1}; ^1H nmr: δ 4.23 (d, 1H, CH_2-N, J = 13.1 Hz), 4.78 (d, 1H, CH_2-N, J = 13.1 Hz), 5.95 (s, 1H, H_3), 6.85 (dd, 1H, $H_{4'}$, J =3.6, 5.2 Hz), 7.00 (dd, 1H, $H_{3'}$, J = 1.4, 3.6 Hz), 7.27 (dd, 1H, $H_{5'}$, J = 1.4, 5.2 Hz), 7.30-7.60 (m, 4H, H arom).

Anal. Calcd. for $C_{13}H_{11}NO_2S_2$: C, 56.30; H, 4.00; N, 5.05. Found C, 56.08; H, 3.87; N, 4.87.

2,3-Dihydro-3-hydroxy-2-(thien-3'-ylthiomethyl)-1*H*-isoindol-1 one (**4b**).

This compound was obtained in a yield of 96%, mp 87°; ir: 3270 (OH), 1670 (C=O) cm^{-1}; ^1H nmr: δ 3.75 (d, 1H, OH, J = 9.4 Hz), 4.36 (d, 1H, CH_2-N, J = 13.7 Hz), 4.95 (d, 1H, CH_2-N, J = 13.7 Hz), 5.92 (d, 1H, H_3, J = 9.4 Hz), 6.98 (dd, 1H, $H_{4'}$, J = 1.4, 4.8 Hz), 7.18-7.28 (m, 2H, $H_{2',5'}$), 7.35-7.60 (m, 4H, H arom).

Anal. Calcd. for $C_{13}H_{11}NO_2S_2$ C, 56.30; H, 4.00; N, 5.05. Found C, 56.42; H, 4.12; N, 4.89.

2,3-Dihydro-1-oxo-2-(thienylthiomethyl)-1*H*-isoindol-3-acetic Acids **5a,b**.

A solution of hydroxylactam **4a** or **4b** (0.55 g, 2 mmoles) and carbethoxycarbonyltriphenylphosphorane (0.85 g, 2.44 mmoles) in toluene (15 ml) was refluxed with stirring during 3 hours. The solvent was evaporated and a mixture of potassium carbonate (0.6 g), water (3 ml) and methanol (12 ml) was added to the residue. The solution was refluxed for 2 hours, concentrated under reduced pressure and then treated with water-dichloromethane (1:1). The organic layer was discarded and the aqueous layer was acidified with hydrochloric acid (10%). The gummy residue precipitated was extracted with dichloromethane. After removal of the solvent, crude compounds **5a** and **5b** were recrystallized from benzene-ethyl acetate (2:1).

2,3-Dihydro-1-oxo-2-(thien-2'-ylthiomethyl)-1*H*-isoindol-3-acetic Acid (**5a**).

This compound was obtained in a yield of 77%, mp 165°; ir: 2925 (OH), 1718 (COOH), 1663 (C=O) cm^{-1}; ^1H nmr: δ 2.62 (dd, 1H, CH_2-CO, J = 6.9, 15 Hz), 2.95 (dd, 1H, CH_2-CO, J = 4.8, 15 Hz), 4.36 (d, 1H, CH_2-N, 13.8 Hz), 5.25 (dd, 1H, H_3, J = 4.8, 6.9 Hz), 5.40 (d, 1H, CH_2-N, J = 13.8 Hz), 6.85 (dd, 1H, $H_{4'}$, J = 3.5, 5.4 Hz), 7.05 (dd, 1H, $H_{3'}$, J = 1.3, 3.5 Hz), 7.28 (dd, 1H, $H_{5'}$, J = 1.3, 5.4 Hz), 7.35-7.8 (m, 4H, H arom).

Anal. Calcd for $C_{15}H_{13}NO_3S_2$: C, 59.38; H, 4.32; N, 4.62. Found C, 59.14; H, 4.31; N, 4.69.

2,3-Dihydro-1-oxo-2-(thien-3'-ylthiomethyl)-1*H*-isoindol-3-acetic Acid (**5b**).

This compound was obtained in a yield of 62%, mp 171°; ir: 2944 (OH), 1716 (COOH), 1655 (C=O) cm^{-1}; ^1H nmr: δ 2.70 (dd, 1H, CH_2-CO, J = 6.7, 16.1 Hz), 2.96 (dd, 1H, CH_2,-CO, J = 5.1, 16.1 Hz), 4.47 (d, 1H, CH_2-N, J = 14.0 Hz), 5.21 (dd, 1H, H_3, J = 5.1, 6.7 Hz), 5.50 (d, 1H, CH_2-N, J = 14.0 Hz), 7.00 (dd, 1H, $H_{4'}$, J = 2.4, 3.5 Hz), 7.10-7.25 (m, 2H, $H_{2',5'}$), 7.35-7.50 (m, 3H, $H_{4,5,6}$), 7.72 (d, 1H, H_7, J = 6.9 Hz).

Anal Calcd for $C_{15}H_{13}NO_3S_2$: C, 59.38; H, 4.32; N, 4.62. Found C, 59.68; H, 4.57; N, 4.42.

Thienothiazocinoisoindolediones **6a,b**.

A mixture of compounds **5a,b** (2.5 mmoles) in dry dichloromethane (20 ml) and thionyl chloride (0.3 ml) was heated under reflux for 2 hours. The solution was evaporated under reduced pressure and the residue was dissolved in dry dichloromethane. This solution was slowly added to a stirred suspension of aluminium trichloride (99.99%, 1 g, 7.6 mmoles) in dry dichloromethane (30 ml). After the addition was complete, stirring was continued for 2 hours. Then 50 ml of ice-water was carefully added to the suspension and the solution was vigorously stirred. The aqueous layer was extracted with dichloromethane, the combinated organic phases were washed with water, dried over magnesium sulfate and evaporated. The residue was purified by chromatography on a silica gel column eluting with dichloromethane.

5,11b-Dihydro-12*H*-thieno[3',2':7,8]thiazocino[4,3-*a*]isoindole-7,13-dione (**6a**).

This compound was obtained in a yield of 78%, mp 212°; ir: 1684 (C=O), 1660 (C=O) cm^{-1}; ^1H nmr: δ 3.25 (dd, 1H, H_{12}, J = 3.5, 13.2 Hz), 4.20 (d, 1H, CH_2-N, J = 12.4 Hz), 4.80 (dd, 1H, H_{12}, J = 8.2, 13.2 Hz), 4.97 (dd, 1H, H_{11b}, J = 3.5, 8.2 Hz), 5.76 (d, 1H, CH_2-N, J = 12.4 Hz), 7.16 (d, 1H, H_2, J = 5.6Hz), 7.24 (d, 1H, H_1, J = 5.6Hz), 7.35-7.70 (m, 4H, H arom).

Anal Calcd for $C_{15}H_{11}NO_2S_2$: C, 59.78; H, 3.68; N, 4.65. Found C, 60.13; H, 3.34; N, 4.34.

5,11b-Dihydro-12*H*-thieno[2',3':7,8]thiazocino[4,3-*a*]isoindole-7,13-dione (**6b**).

This compound was obtained in a yield of 42%, mp 198°; ir: 1691 (C=O), 1662 (C=O) cm^{-1}; ^1H nmr: δ 3.26 (m, 1H, H_{12}), 4.25 (d, 1H, CH_2-N, J = 12.6 Hz), 4.95 (m, 2H, H_{11b}-H_{12}), 5 70 (d, 1H, CH_2-N, J = 12.6 Hz), 7.14 (d, 1H, H_3, J = 5.1 Hz), 7.35-7.75 (m, 5H, H_2-H arom).

Anal. Calcd. for $C_{15}H_{11}NO_2S_2$: C, 59.78; H, 3.68; N, 4.65. Found: C, 59.66; H, 3.40; N, 4.54.

Thienothiazinoisoindolones **7a,b**.

A solution of hydroxylactam **4a** or **4b** (2 mmoles) in trifluoroacetic acid (10 ml) was stirred overnight. The acid was evaporated and the residue was taken up with 20 ml of water-dichloromethane (1:1). The organic layer was neutralized with sodium hydrogen carbonate, dried over magnesium sulfate and evaporated to dryness. The solids were recrystallized from ethanol.

5-11b-Dihydrothieno[3',2':5,6]thiazino[4,3-*a*]isoindol-7-one (**7a**).

This compound was obtained in a yield of 72%, mp 166°; ir: 1717 (C=O) cm^{-1}; ^1H nmr: δ 4.60 (d, 1H, CH_2-N, J = 12.4 Hz), 5.45 (d, 1H, CH_2-N, J = 12.4 Hz), 5.85 (s, 1H, H_{11b}), 7.20 (d, 1H, H_1, J = 5.3 Hz), 7.25 (d, 1H, H_2, J = 5.3 Hz), 7.45-7.90 (m, 4H, H arom).

Anal. Calcd. for $C_{13}H_9NOS_2$ C, 60.21; H, 3.50; N, 5.40. Found: C, 60.24; H, 3.49; N, 5.26.

5-11b-dihydrothieno[2',3':5,6]thiazino[4,3-*a*]isoindol-7-one (**7b**).

This compound was obtained in a yield of 64%, mp 129°; ir: 1698 (C=O) cm^{-1}; ^1H nmr: δ 4.60 (d, 1H, CH_2-N, J = 12.4 Hz), 5.45 (d, 1H, CH_2-N, J = 12.4 Hz), 5.85 (s, 1H, H_{11b}), 6.70 (d, 1H, H_3, J = 5.1 Hz), 7.20 (d, 1H, H_2, J = 5.1 Hz), 7.30-7.80 (m, 4H, H arom).

Anal. Calcd. for $C_{13}H_9NOS_2$: C, 60.21; H, 3.50; N, 5.40. Found: C, 60.45, H; 3.27; N, 5.37.

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