Stereoselective Reduction of New Fused Azoninones with a Bridgehead Nitrogen

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The synthesis of methanothienoazoninones **5a,b** is described starting from 2(3)-halogenomethylthiophenes. Their reduction with sodium borohydride led to the corresponding aminoalcohols **6a,b** with a complete stereoselectivity.

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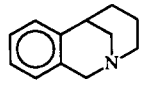
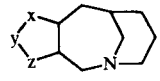
Substituted azepines or azocines fused to a benzene or an heterocycle ring are widely used and have been shown to exhibit potent antitumor activities, but azepines or azocines with their nitrogen atom at a bridgehead position are little explored. In a view of recent reports on the formation of azepines [1-3] or azocines of type I fused to a benzene ring [4] and in connection with other work in our laboratory [5-7] we wish to describe herein a simple route to methanothienoazonines of type II.



I

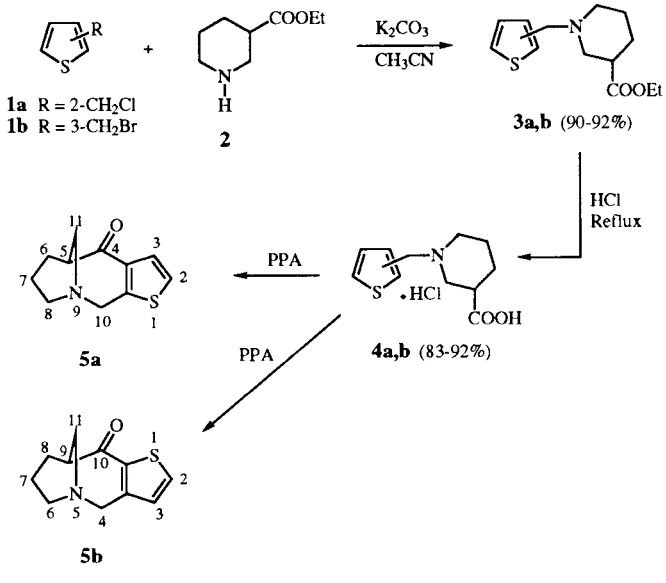


II

x, y, z = S, CH

We recently described the cyclization of *N*-thienylmethylpiperidine-2-carboxylic acid into piperidinothienoazepinones [7] and Heathcock [8] showed the formation of a methano bridge from a ketone in protic medium. From these results we propose a three step synthesis starting from the readily available ethyl (±)-nipecotate (**2**) and halogenomethylthiophenes **1a,b**.

Scheme 1



1a R = 2-CH_2Cl
1b R = 3-CH_2Br

2

3a,b (90-92%)

4a,b (83-92%)

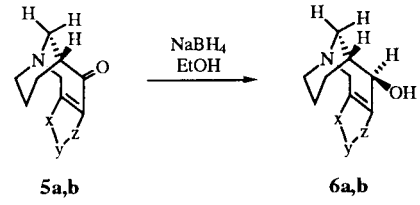
5a

5b

The *N*-alkylation of **2** occured in acetonitrile as the solvent and with potassium carbonate as the base. Acidic hydrolysis of the aminoesters **3a,b** gave directly the hydrochloride salts **4a** and **4b** in 83% and 92% yields, respectively. A Friedel-Crafts cyclization of these acids according to our previously reported work [6] did not lead to ketones **5a,b** but when the hydrochloride salts of the aminoacids **4a,b** were treated with polyphosphoric acid at 120-130°, the ketones **5a** (41%) and **5b** (63%) were obtained (Scheme 1).

The structures of these compounds were assigned on the basis of their microanalyses and nmr (^1H and ^{13}C) spectra. The CH_2-N protons in β-aminoesters **3a,b** and β-aminoacid **4b** appear as an AB system as in the corresponding α-substituted products [7] but with very close chemical shifts ($\Delta\delta$ = 0.05 ppm). In compound **4a** they appear as a singlet. For the ketones **5a,b** some features are interesting. The protons attached to the carbon located between the nitrogen atom and the thiophene ring (C_{10}-Hα and β) appear as an AB system with chemical shifts of 4.58 and 4.22 ppm **5a** or 4.48 and 4.13 ppm **5b**. The non-equivalence of the C_{10}-Hα and C_{10}-Hβ protons is similar to those observed in thienoquinolizidinones [7] with in addition a deshielding of about +0.5 ppm and a long range coupling constant of 0.7 Hz between C_{10}-Hα and C_{11}-Hβ. A non-equivalence of the C_{11}-Hα and C_{11}-Hβ protons for the ketone **5a** can be reported. The former

Scheme 2

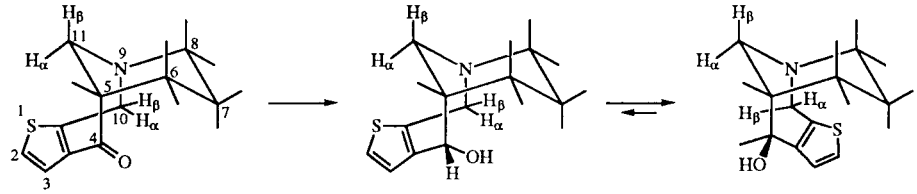


5a,b

6a,b

	5a, 6a	5b, 6b
x	S	CH
y	CH	CH
z	CH	S

Scheme 3



A B

is a doublet of doublet with coupling constants of J = 0.8 Hz (C_{11}-Hα, H_5) and J = 14.8 Hz (C_{11}-Hα, C_{11}-Hβ) and the other is a doublet of doublet of doublet with coupling constants of J = 0.7 (C_{11}-Hβ, C_{10}-Hα), J = 3.5 Hz (C_{11}-Hβ, H_5), J = 14.8 Hz (C_{11}-Hα, C_{11}-Hβ). Similar coupling constants are observed in the ^{1}H nmr spectrum of the ketone **5b**.

The above aminoketones **5a,b** represent a new tricyclic system with considerable hindrance. With respect to the substituted 1-azabicyclo[3,3,1]nonanes [9], we think that the predominant conformation is probably the chair (six membered ring)-twisted (seven membered ring) conformation **A** (Scheme 3). So, it was interesting to study the stereoselectivity of the reduction of these ketones. Actually, using sodium borohydride, the reduction (Scheme 2) led to the aminoalcohols **6a,b** in good yields (70% and 80%). Only one diastereomer was isolated in both cases. The attack of hydride proceeds from the sterically more accessible side of the carbonyl group and gives aminoalcohols with two asymmetric carbon atoms having an R*, R* (from R* nipecotate) or S*, S* (from S* nipecotate) relative configuration and a stable chair-chair conformation **B** of the nitrogen heterocycles in which the hydroxyl group have a stable pseudo-equatorial position.

As in the ketone **5a**, the ^{1}H nmr spectrum of the aminoalcohol **6a** shows a non-equivalence of the two protons attached to carbons C_{10} and C_{11}. The most significant difference between these two spectra is the shielding effect observed for the C_{11}-Hα proton (3.49 ppm for the ketone, 3.31 ppm for the aminoalcohol) and the deshielding effect observed for the C_{11}-Hβ proton (3.31 ppm for the ketone and 3.50 ppm for the aminoalcohol) due to the absence of anisotropic effect after the reduction of the carbonyl function. Finally, we observe a shielding effect for the C_7 protons (1.2 ppm for the ketone, 0.9 ppm for the aminoalcohol) due to the effect of the thiophene ring in the chair-chair conformation **B**.

In summary, we report an efficient synthesis of azoninones with a bridgehead nitrogen and the stereospecific reduction into the corresponding alcohols. Further investigation, molecular mechanics calculations, X-ray examination combined with solid-state ^{13}C nmr spectroscopic studies of the ketones and the aminoalcohols are in progress and the results will be published soon.

EXPERIMENTAL

Melting points were taken on a hot-stage apparatus and elemental analyses were obtained in the microanalysis laboratory of the Institut National des Sciences Appliquées, Rouen. ^{1}H and ^{13}C nmr spectra were recorded on a Brucker AC200 instrument and chemical shifts (δ) are expressed in ppm relative to internal TMS. Infrared spectra were measured with a Bruker IFS 48.

Ethyl *N*-Thien-2-ylmethylnipecotate (**3a**) and Ethyl *N*-Thien-3-ylmethylnipecotate (**3b**).

A solution of thienylmethyl halide **1a** or **1b** (0.1 mole) in 50 ml of acetonitrile was added dropwise (during 3 hours) to a stirred mixture of ethyl (±)nipecotate (15.7 g, 0.1 mole) and potassium carbonate (15 g, 0.13 mole) in 100 ml of acetonitrile at room temperature. The resulting suspension was additionally refluxed for 2 hours, then filtered and the solvent was removed in vacuum. Distillation of the oily residue under reduced pressure afforded the ester **3a** (23.3 g, 92%) or the ester **3b** (22.8 g, 90%).

Compound **3a** had $bp_{0.08}$ 150-153°; ir: 1730 (COOEt) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.20 (dd, J = 4.8, 1.4 Hz, 1H, H_5 thiophene), 6.85-6.95 (m, 2H, H_3 and H_4 thiophene), 3.73 (d, J = 11.6 Hz, 1H, CH_2N), 3.69 (d, J = 11.6 Hz, 1H, CH_2N), 2.98 (dd, J = 3.4, 10.4 Hz, 1H, H_2), 2.22 (dd, J = 10.4, 10.5 Hz, H_2), 2.70-2.85 (m, 1H, H_6), 2.05 (ddd, 1H, H_6), 2.45-2.65 (m, 1H, H_3), 1.80-1.95 (m, 1H, H_4), 1.30-1.75 (m, 3H, H_4, H_5, H_5), 4.09 (q, J = 7.1 Hz, 2H, CH_2 (CH_3)), 1.22 (t, J = 7.1 Hz, 3H, CH_3 (CH_2)).

Anal. Calcd. for $C_{13}H_{19}NO_2S$: C, 61.63; H, 7.56; N, 5.53. Found: C, 61.51; H, 7.28; N, 5.30.

Compound **3b** had $bp_{0.1}$ 170-175°; ir: 1725 (COOEt) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.24 (dd, J = 3.0, 4.8 Hz, 1H, H_5 thiophene), 7.05-7.10 (m, 1H, H_3 thiophene), 7.02 (dd, J = 1.4 Hz, 1H, H_4 thiophene), 3.54 (d, J = 11.6 Hz, 1H, CH_2N), 3.49 (d, J = 11.6 Hz, 1H, CH_2N), 2.60-2.75 (m, 1H, H_6), 2.92 (dd, J = 3.5, 10.6 Hz, 1H, H_2), 2.18 (dd, J = 10.3, 10.6 Hz, 1H, H_2), 1.95-2.10 (m, 1H, H_6), 1.80-1.95 (m, 2H, H_4), 1.30-1.80 (m, 3H, H_3, H_5, H_5), 4.10 (q, J = 7.2 Hz, 2H, CH_2 (CH_3)), 1.20 (t, J = 7.2 Hz, 3H, CH_3 (CH_2)).

Anal. Calcd. for $C_{13}H_{19}NO_2S$: C, 61.63; H, 7.56; N, 5.53. Found: C, 61.78; H, 7.31; N, 5.29.

N-Thien-2-ylmethylnipecotic Acid Hydrochloride (**4a**) and *N*-Thien-3-ylmethylnipecotic Acid Hydrochloride (**4b**).

A mixture of the ester **3a** or **3b** (10 g, 0.0395 mole) in 100 ml

of a 10 *N* hydrochloric acid solution was refluxed for 3 hours. The resulting dark solution was treated with charcoal and evaporated to dryness to give **4a** (8.6 g, 83%) or **4b** (9.5 g, 92%) as white hygroscopic crystals.

Compound **4a** had mp 163-165° (acetonitrile); ^{1}H-nmr (DMSO-d_6): δ 7.68 (d, J = 5.0 Hz, 1H, H_5 thiophene), 7.42 (d, J = 3.3 Hz, 1H, H_3 thiophene), 7.12 (dd, J = 3.5, 5.0 Hz, 1H, H_4 thiophene), 4.52 (s, 2H, CH_2N), 3.20-2.50 (m, 2H, H_2, H_6), 2.65-3.15 (m, 3H, H_2, H_6, H_3), 1.65-2.10 (m, 3H, H_4, H_5, H_5), 1.30-1.55 (m, 1H, H_4).

Anal. Calcd. for $C_{11}H_{16}ClNO_2S$: C, 50.47; H, 6.16; N, 5.35. Found: C, 50.27; H, 6.29; N, 5.10.

Compound **4b** had mp 179-182° (acetonitrile-ether); ^{1}H-nmr (DMSO-d_6): δ 7.80 (d, J = 2.7 Hz, 1H, H_2 thiophene), 7.62 (dd, J = 2.8, 4.9 Hz, 1H, H_5 thiophene), 7.41 (d, J = 4.9 Hz, 1H, H_4 thiophene), 4.32 (d, J = 11.8 Hz, 1H, CH_2N), 4.28 (d, J = 11.8 Hz, 1H, CH_2N), 3.15-3.50 (m, 2H, H_2, H_6), 2.65-3.15 (m, 3H, H_2, H_6, H_3), 1.70-2.10 (m, 3H, H_4, H_5, H_5), 1.25-1.55 (m, 1H, H_4).

Anal. Calcd. for $C_{11}H_{16}ClNO_2S$: C, 50.47; H, 6.16; N, 5.35. Found: C, 50.16; H, 6.40; N, 5.09.

5,6,7,8,9,10-Hexahydro-5,9-methanothieno[2,3-*c*]azonin-4-one (**5a**) and 4,5,6,7,8,9-Hexahydro-5,9-methanothieno[3,2-*c*]-azonin-10-one (**5b**).

The acid **4a** or **4b** (4 g, 0.0153 mole) was added portionwise to 80 g of stirred polyphosphoric acid. The mixture was stirred under nitrogen at 120-130° during 12 hours. The dark solution was poured slowly onto crushed ice and basified at 10° with 40% sodium hydroxide to *p*H = 7. The resulting suspension was extracted with ether (3 x 200 ml). The organic layer was dried over magnesium sulfate and evaporated to dryness to give an oily residue which was purified by flash chromatography on a silica gel column eluting with dichloromethane-methanol (9/1).

Ketone **5a** was obtained in 41% yield, 1.3 g of yellowish oil; ir: 1630 (C=O) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.41 (d, J = 5.3 Hz, 1H, H_2), 7.00 (dd, J = 0.7, 5.3 Hz, H_3), 4.58 (d, J = 18.1 Hz, 1H, H_{10}-β), 4.22 (dd, J = 0.7, 18.1 Hz, 1H, H_{10}-α), 3.49 (dd, J = 0.8, 14.8 Hz, 1H, H_{11}-α), 3.31 (ddd, J = 0.7, 3.5, 14.8 Hz, 1H, H_{11}-β), 3.0-3.25 (m, 2H, H_8), 2.76 (m, 1H, H_5), 1.2-2.0 (m, 4H, H_6, H_7); ^{13}C-nmr: δ 199.1 (C_4), 155.4 (C_{10a}), 140.5 (C_{3a}), 130.3 (C_2), 121.9 (C_3), 56.7 (C_{11}), 53.6 (C_{10}), 49.6 (C_8), 48.2 (C_5), 28.2 (C_6), 20.7 (C_7).

Anal. Calcd. for $C_{11}H_{13}NOS$: C, 63.73; H, 6.32; N, 6.96. Found: C, 63.64; H, 6.32; N, 6.70.

Ketone **5b** was obtained in 63% yield (2.0 g), mp 159-162° (toluene-heptane); ir: 1625 (C=O) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.46 (d, J = 5.1 Hz, 1H, H_2), 6.82 (d, J = 5.1 Hz, 1H, H_3), 4.48 (d, J = 14.7 Hz, 1H, H_4-β), 4.13 (dd, J = 0.8, 14.8 Hz, 1H, H_4-α), 3.43 (d, 14.8 Hz, 1H, H_{11}-α), 3.32 (ddd, J = 14.8, 3.4, 0.8 Hz, 1H, H_{11}-β), 3.0-3.15 (m, 2H, H_6), 2.76 (m, 1H, H_9), 1.2-2.15 (m, 4H, H_7, H_8); ^{13}C-nmr: δ 198.0 (C_{10}), 150.6 (C_{3a}), 141.9 (C_{10a}), 133.3 (C_2), 128.8 (C_3), 58.4 (C_{11}), 54.2 (C_4), 48.7 (C_6), 47.4 (C_9), 28.8 (C_7), 21.0 (C_8).

Anal. Calcd. for $C_{11}H_{13}NOS$: C, 63.73; H, 6.32; N, 6.96. Found: C, 63.81; H, 6.12; N, 6.71.

5,6,7,8,9,10-Hexahydro-4-hydroxy-5,9-methano-4*H*-thieno-[2,3-*c*]azonine (**6a**) and 4,5,6,7,8,9-Hexahydro-10-hydroxy-5,9-methano-4*H*-thieno[3,2-*c*]azonine (**6b**).

To a stirred solution of **5a** or **5b** (1 g, 0.048 mole) in ethanol (50 ml) was added sodium borohydride (0.5 g, 0.0132 mole) and the reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure. The solid residue was taken up with water (50 ml), heated to reflux, cooled and filtered to give the aminoalcohol **6a** (0.7 g, 70%) or **6b** (0.8 g, 80%).

Compound **6a** had mp 144-146° (toluene-heptane); ir (potassium bromide): 3420-3000 (OH) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.13 (d, J = 5.1 Hz, 1H, H_2), 7.04 (d, J = 5.1 Hz, 1H, H_3), 5.04 (d, J = 3.2 Hz, 1H, H_4), 4.21 (d, J = 16.4 Hz, 1H, H_{10}-β), 3.99 (d, J = 16.4 Hz, 1H, H_{10}-α), 3.50 (dd, 1H, J = 4.4, 14.4 Hz, H_{11}-β), 3.31 (d, 1H, J = 14.4 Hz, H_{11}-α), 2.99-3.05 (m, 2H, H-8), 2.03-2.14 (broad, 1H, OH), 1.89-2.03 (m, 1H, H-6), 1.80-1.88 (m, 1H, H_5), 1.52-1.73 (m, 1H, H-6), 0.73-0.94 (m, 2H, H-7); ^{13}C-nmr (DMSO-d_6): δ 144.3 (C_{10a}), 136.0 (C_{3a}), 129.1 (C_3), 120.8 (C_2), 72.6 (C_4), 55.5 (C_{11}), 54.0 (C_{10}), 50.9 (C_8), 35.7 (C_5), 21.8 (C_6), 19.3 (C_8).

Anal. Calcd. for $C_{11}H_{15}NOS$: C, 63.12; H, 7.22; N, 6.69. Found: C, 62.95; H, 7.05; N, 6.55.

Compound **6b** had mp 183-185° (toluene-heptane); ir (potassium bromide): 3300-3000 (OH) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.10 (d, J = 5.2 Hz, 1H, H_2), 6.80 (d, J = 5.2 Hz, 1H, H_3), 5.25 (d, J = 2.9 Hz, 1H, H_{10}), 4.13 (d, J = 16.2 Hz, 1H, H_4), 4.05 (d, J = 16.2 Hz, 1H, H_4), 3.56 (dd, J = 4.2, 14.4 Hz, 1H, H_{11}-β), 3.37 (d, J = 14.4 Hz, 1H, H_{11}-α), 2.97-3.16 (m, 2H, H-6), 2.60-2.90 (broad, 1H, OH), 2.08-2.17 (m, 1H, H-8), 1.92-1.97 (m, 1H, H-9), 1.60-1.73 (m, 1H, H-8), 0.92-1.04 (m, 2H, H-7); ^{13}C-nmr (DMSO-d_6): δ 146.0 (C_{3a}), 136.5 (C_{10a}), 129.0 (C_2), 121.7 (C_3), 72.5 (C_{10}), 55.5 (C_{11}), 54.9 (C_4), 51.2 (C_6), 35.8 (C_9), 21.9 (C_8), 19.3 (C_7).

Anal. Calcd. for $C_{11}H_{15}NOS$: C, 63.12; H, 7.22; N, 6.69. Found: C, 63.34; H, 7.10; N, 6.54.

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