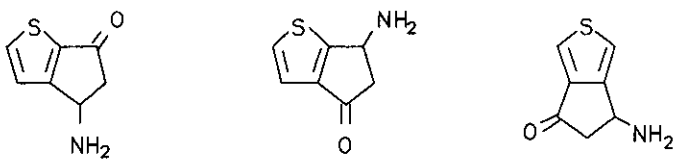
A CONVENIENT ROUTE TO 6-AMINOCYCLOPENTA[*c*]-THIOPHEN-4-ONE DERIVATIVES

Patrick Dallemagne, Abdellah Alsaïdi, M. Boulouard, Sylvain Rault, and Max Robba*

Laboratoire de Chimie Thérapeutique U.F.R. des Sciences Pharmaceutiques
1 rue Vaubénard - 14032 CAEN cedex, France

Abstract - Synthesis of 6-amino-5,6-dihydro-4*H*-cyclopenta[*c*]thiophen-4-one derivatives is achieved by cyclization of amino-2,5-dihalothienylpropionic acids and subsequent dehalogenation.

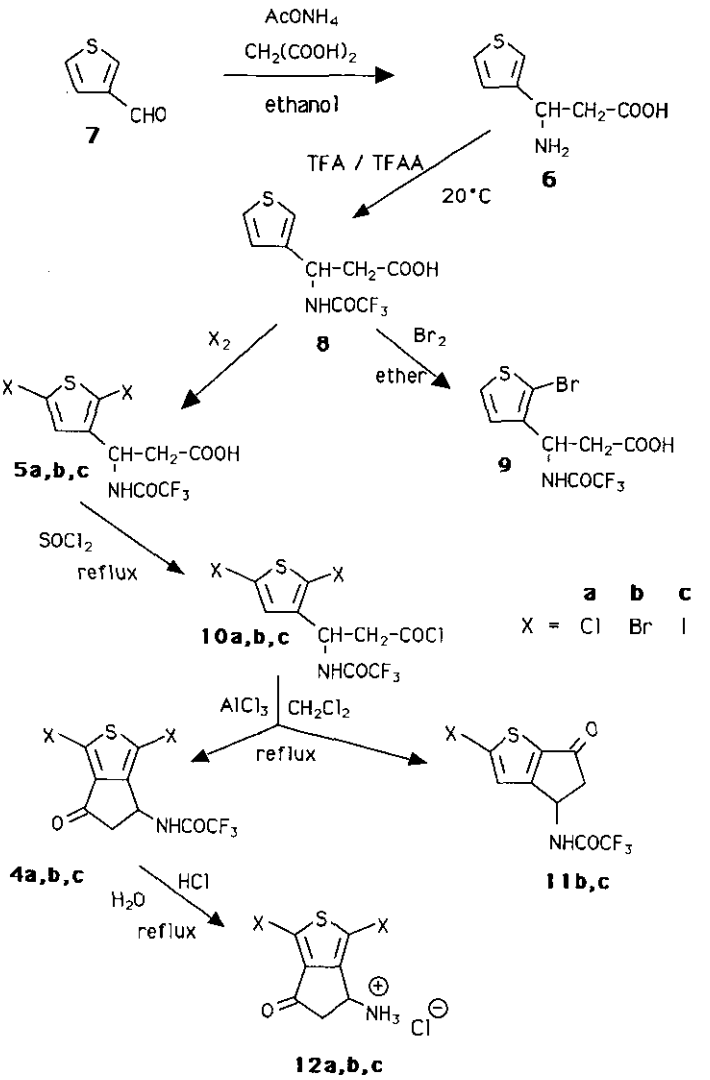
In continuation of our works concerning the formation of new heterocyclic systems with potential therapeutic interest, we recently described the synthesis of the 4-amino-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-6-one (**1**) [1-4] and 6-amino-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-4-one (**2**) series,[5] of which some derivatives revealed, *in vitro*, an antiviral activity against HIV.[6]
We wish to report herein a convenient route to the third and new isomeric thiophenic series : the 6-amino-5,6-dihydro-4*H*-cyclopenta[*c*]thiophen-4-one (**3**) derivatives (Scheme 1).



Scheme 1

The 6-trifluoroacetylaminocyclopenta[c]thiophen-4-ones (**4a,b,c**) are obtained by the cyclization of dihalotrifluoroacetylaminothienylpropionic acids (**5a,b,c**) (Scheme 2).

The 3-amino-3-(thien-3-yl)propionic acid (**6**) is synthesized from thiophene-3-carboxaldehyde (**7**) as previously described. [1] **6** is then treated, at room temperature, by a mixture of trifluoroacetic acid (TFA) and anhydride (TFAA), in order to protect its amino group, to give the 3-trifluoroacetylamino-3-(thien-3-yl)propionic acid (**8**). **8** is submitted to various halogenations with chlorine, bromine and iodine.



Scheme 2

Chlorination is conducted in chloroform. The solution is bubbled with a chlorine flow during 1 min and then refluxed for 15 min. The precipitate, appeared after cooling, is filtered and its ^{1}H nmr analysis reveals the 2,5-dichlorothiophenic structure (**5a**). Yield is about 70%.

Bromination is run in a similar manner with an excess of bromine. The precipitate formed is identified to be **5b**. Yield is about 50%. A selective monobromination can be realized in ether at 0°C with 1 equivalent of bromine. After 1 h, the reaction mixture is washed with water and the solvent is removed under reduced pressure to give the 3-trifluoroacetylamino-3-(2-bromothien-3-yl)propionic acid (**9**) with 76% yield.

Iodination is realized in carbon tetrachloride at 80°C for 5 h, with stoichiometric amounts of iodine and iodic acid, in the presence of diluted acetic and sulfuric acids. The reaction leads to the 2,5-diiodothiophene derivative (**5c**). Yield is about 69%.

The acid chlorides (**10a,b,c**) are quantitatively synthesized by treatment of **5** with thionyl chloride at reflux temperature for 5 min. They are cyclized in **4a,b,c**, in boiling dichloromethane for 5 min, in the presence of aluminium chloride. The yields are about 82% for **4a**, 65% for **4b** and 43% for **4c**. Cyclization of **10b** and **10c** leads also to the monobromo- and monoiodocyclopenta[*b*]thiophenones (**11b**) and (**11c**) which can be separated from **4b** and **4c** by fractional recrystallizations with 35% and 14% yield respectively. These secondary cyclizations, observed with **10b** and **10c**, are probably due to the steric hindrance of bromine and iodine atoms which is not in favour of the cyclization on the C-4 position.

The trifluoroacetamido groups of **4a,b,c** are, at last hydrolyzed with boiling hydrochloric acid to give the ammonium chlorides (**12a,b,c**).

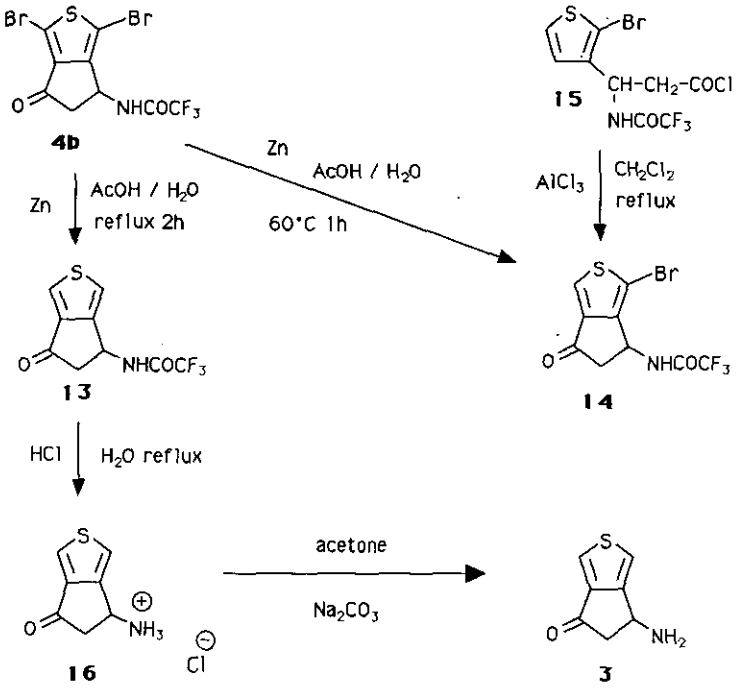
Dehalogenation is achieved in good conditions only starting from the dibromo series with zinc in diluted acetic acid (Scheme 3). At reflux temperature for 2 h, treatment of **4b** gives, after evaporation of the solvent, the dehalo compound (**13**) which is purified by chromatography on silica gel column. Yield is about 80%. When the debromination reaction is run at 60°C and for only 1 h, it gives a monobromo compound which precipitates from the reaction mixture by addition of water. ^{1}H Nmr analysis of this monobromo compound shows a thiophenic singulet at 8.22 ppm in favor of the structure (**14**) which is confirmed by Friedel-Crafts cyclization of the monobromotrifluoroacetylaminothienypropionic acid (**9**) , *via* the acid chloride (**15**), which selectively leads to **14**.

The ammonium chloride (**16**) is obtained by acidic hydrolysis of **13** as above. In alkaline medium, **16** leads to the title free base (**3**).

EXPERIMENTAL

General Methods. Melting points were taken on a Köfler bank and are uncorrected. Infrared spectra were recorded on a Philips PU 9716 apparatus and only noteworthy absorptions (reciprocal centimeters) are listed. Nmr spectra were recorded on a Jeol FX 200 in DMSO-d_6 solution using TMS as an internal standard. Chemical shift are reported in ppm downfield (δ) from TMS.

6-Amino-5,6-dihydro-4*H*-cyclopenta[*c*]thiophen-4-one (**3**). A suspension of ammonium chloride (**16**) (1.9 g, 0.01 mol) and sodium carbonate (3 g, 0.028 mol) in acetone (50 ml) was stirred at room temperature for 5 min. It was then filtered and the filtrate was evaporated to dryness under reduced pressure to give **3** as an unstable yellow oil (1.4 g, 89%): ir (KBr) 3340 and 3070 (NH_2), 1700 (CO); ^{1}H-nmr 8.17 (d, $J_{H3\ H1}$ = 2.5 Hz, H-3), 7.57 (d, $J_{H1\ H3}$ = 2.5 Hz, H-1), 5.42 (dd, $J_{H6\ H5a}$ = 8 Hz, $J_{H6\ H5b}$ = 4 Hz, H-6), 3.42 (dd, $J_{H5a\ H5b}$ = 19 Hz, $J_{H5a\ H6}$ = 8 Hz, H-5a), 2.94 (dd, $J_{H5b\ H5a}$ = 19 Hz, $J_{H5b\ H6}$ = 4 Hz, H-5b).



Scheme 3

3-Trifluoroacetylamino-3-(2,5-dichlorothien-3-yl)propionic acid (5a). A solution of trifluoroacetylaminothienylpropionic acid (8) (5g, 0.019 mol) in chloroform (100 ml) was bubbled for 1 min at room temperature with a chlorine flow. The reaction mixture was then refluxed for 15 min and left at room temperature. The precipitate appeared was filtered to give 5a (4.2 g 70%) : mp 162°C (ether); ir (KBr) 3295 (NH), 1700 (CO); ^{1}H-nmr 9.89 (d, $J_{NH\ H-3}$ = 8 Hz, NH), 7.14 (s, H-4 arom.), 5.33 (m, H-3), 3.5 (br, OH), 2.85 (dd, $J_{H-2a\ H-2b}$ = 16 Hz, $J_{H-2a\ H-3}$ = 9 Hz, H-2a), 2.72 (dd, $J_{H-2b\ H-2a}$ = 16 Hz, $J_{H-2b\ H-3}$ = 6 Hz, H-2b); Anal. Calcd for $C_9H_6NO_3Cl_2F_3S$: C, 32.16; H, 1.80; N, 4.17; S, 9.54. Found : C, 32.25; H, 1.71; N, 4.19; S, 9.39.

3-Trifluoroacetylamino-3-(2,5-dibromothien-3-yl)propionic acid (5b). A solution of trifluoroacetylaminothienylpropionic acid (8) (3g, 0.011 mol) in chloroform (60 ml) was added with bromine (1.8 ml, 0.033 mol). The reaction mixture was then refluxed for 15 min and left at room temperature. The precipitate appeared was filtered to give 5b (3.5 g 75%) : mp 180°C (ether); ir (KBr) 3290 (NH), 1700 (CO); ^{1}H-nmr 9.92 (d, $J_{NH\ H-3}$ = 8 Hz, NH), 7.23 (s, H-4 arom.), 5.31 (m, H-3), 3.7 (br, OH), 2.88 (dd, $J_{H-2a\ H-2b}$ = 16 Hz, $J_{H-2a\ H-3}$ = 9 Hz, H-2a), 2.71 (dd, $J_{H-2b\ H-2a}$ = 16 Hz, $J_{H-2b\ H-3}$ = 6 Hz, H-2b); Anal. Calcd for $C_9H_6NO_3Br_2F_3S$: C, 25.43; H, 1.42; N, 3.30; S, 7.54. Found : C, 25.52; H, 1.41; N, 3.19; S, 7.59.

3-Trifluoroacetylamino-3-(2,5-diiodothien-3-yl)propionic acid (5c). A stirred mixture of trifluoroacetylaminothienylpropionic acid (8) (15g, 0.056 mol), acetic acid (60 ml), water (22 ml), carbon tetrachloride (30 ml), sulphuric acid (0.9 ml), iodine (7 g, 0.028 mol) and iodic acid (5 g, 0.028 mol) was refluxed for 5 h. The reaction mixture was diluted with chloroform (300 ml).The organic layer was washed with a saturated sodium thiosulfate solution and then extracted with a saturated sodium bicarbonate solution. The aqueous layer was separated and adjusted to pH 1 with a concentrated aqueous solution of hydrochloric acid. The precipitate appeared was filtered, washed with water and dried to give 5c (20 g, 69%): mp 228°C (ether); ir (KBr) 3300 (NH), 1700 (CO); ^{1}H-nmr 12.4 (br, OH), 9.91 (d, $J_{NH\ H-3}$ = 8 Hz, NH), 7.21 (s, H-4 arom.), 5.14 (m, H-3), 2.78 (dd, $J_{H-2a\,H-2b}$ = 16 Hz, $J_{H-2a\,H-3}$ = 9 Hz, H-2a), 2.61 (dd, $J_{H-2b\,H-2a}$ = 16 Hz, $J_{H-2b\,H-3}$ = 6 Hz, H-2b); Anal. Calcd for $C_9H_6NO_3F_3I_2S$: C, 20.83; H, 1.17; N, 2.70; S, 6.18. Found : C, 20.66; H, 1.04; N, 2.63; S, 6.26.

3-Trifluoroacetylamino-3-(2-bromothien-3-yl)propionic acid (9). A solution of trifluoroacetylaminothienylpropionic acid (8) (3g, 0.011 mol) in ether (100 ml) was added with bromine (0.57 ml, 0.011 mol) and the reaction mixture was stirred for 90 min at 0°C. The organic layer was then washed twice with water, separated and dried over magnesium sulfate. The solvent was removed under reduced pressure to give 9 as white crystals (2.9 g, 76%) : mp 175°C (ether); ir (KBr) 3290 (NH), 1700 (CO); ^{1}H-nmr 9.88 (d, $J_{NH\ H-3}$ = 8 Hz, NH), 7.60 (d, $J_{H-5\ arom\ \ H-4\ arom}$ = 6 Hz, H-5 arom.), 7.07 (d, $J_{H-4\ arom\ \ H-5\ arom}$ = 6 Hz, H-4 arom.,), 5.34 (m, H-3), 3.3 (br, OH), 2.91 (dd, $J_{H-2a\,H-2b}$ = 16 Hz, $J_{H-2a\,H-3}$ = 9 Hz, H-2a), 2.69 (dd, $J_{H-2b\,H-2a}$ = 16 Hz, $J_{H-2b\,H-3}$ = 6 Hz, H-2b); Anal. Calcd for $C_9H_7NO_3BrF_3S$: C, 31.23; H, 2.04; N, 4.05; S, 9.26. Found : C, 31.31; H, 2.09; N, 4.11; S, 9.27.

3-Trifluoroacetylamino-3-(2,5-dihalo- and 2-bromothien-3-yl)propionic acid chlorides (10a,b,c) and (15)
General procedure : A solution of dihalo- or monobromotrifluoroacetylaminothienylpropionic acids (5a,b,c) or (9) (0.01 mol) in thionyl chloride (30 ml, 0.41 mol) was refluxed for 5 min. Thionyl chloride was then removed under reduced pressure to give 10a,b,c and 15 . The oily or solid residues were washed with petroleum ether and used without other purification.

3-Trifluoroacetylamino-3-(2,5-dichlorothien-3-yl)propionic acid chloride (10a) (starting material 5a) : yellow oil (76%) : ir (KBr) 3250 (NH), 1790 and1690 (CO).

3-Trifluoroacetylamino-3-(2,5-dibromothien-3-yl)propionic acid chloride (10b) (starting material 5b) : white crystals (80%) : mp 120°C (petroleum ether); ir (KBr) 3220 (NH), 1790 and1690 (CO).

3-Trifluoroacetylamino-3-(2,5-diiodothien-3-yl)propionic acid chloride (10c) (starting material 5c) : white crystals (90%) : mp 120°C (petroleum ether); ir (KBr) 3290 (NH), 1790 and1700 (CO).

3-Trifluoroacetylamino-3-(2-bromothien-3-yl)propionic acid chloride (15) (starting material 9) : yellow oil (70%); ir (KBr) 3300 (NH), 1800 and 1700 (CO).

1,3-Dihalo-6-trifluoroacetylamino-5,6-dihydro-4*H*-cyclopenta[*c*]thiophen-4-one (4a,b,c)
2-halo-4-trifluoroacetylamino-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-6-one (11b,c).
General procedure : A solution of dihalotrifluoroacetylaminothienylpropionic acid chlorides (10a,b,c) (0.01 mol) and aluminium chloride (4 g, 0.03 mol) in dichloromethane (50 ml) was refluxed for 5 min. The solvent was then removed under reduced pressure and the residual solid was triturated with water (150 ml). The insoluble crystals were filtered, washed with water and purified by recrystallization to give 4a,b,c and 11b,c.

1,3-Dichloro-6-trifluoroacetylamino-5,6-dihydro-4*H*-cyclopenta[*c*]thiophen-4-one **(4a)** (starting material **10a**): white crystals (82%) : mp 207°C (ether); ir (KBr) 3290 (NH), 1690 (CO); ^{1}H-nmr 10.02 (d, $J_{NH\ H\text{-}6}$ = 9 Hz, NH), 5.43 (ddd, $J_{H\text{-}6\ NH}$ = 9 Hz, $J_{H\text{-}6\ H\text{-}5a}$ = 8 Hz , $J_{H\text{-}6\ H\text{-}5b}$ = 4 Hz, H-6), 3.45 (dd, $J_{H\text{-}5a\ H\text{-}5b}$ = 19 Hz, $J_{H\text{-}5a\ H\text{-}6}$ = 8 Hz, H-5a), 2.86 (dd, $J_{H\text{-}5b\ H\text{-}5a}$ = 19 Hz, $J_{H\text{-}5b\ H\text{-}6}$ = 4 Hz, H-5b); Anal. Calcd for $C_9H_4NO_2Cl_2F_3S$: C, 33.98; H, 1.27; N, 4.40; S, 10.08 Found : C, 33.99; H, 1.38; N, 4.41; S, 9.97.

1,3-Dibromo-6-trifluoroacetylamino-5,6-dihydro-4*H*-cyclopenta[*c*]thiophen-4-one **(4b)** (starting material **10b**) : white crystals separated from **11b** by fractional recrystallizations (65%) : mp 230°C (ether / ethyl acetate); ir (KBr) 3330 (NH), 1700 (CO); ^{1}H-nmr 9.99 (d, $J_{NH\ H\text{-}6}$ = 9 Hz, NH), 5.36 (ddd, $J_{H\text{-}6\ NH}$ = 9 Hz, $J_{H\text{-}6\ H\text{-}5a}$ = 8 Hz, $J_{H\text{-}6\ H\text{-}5b}$ = 4 Hz, H-6), 3.45 (dd, $J_{H\text{-}5a\ H\text{-}5b}$ = 19 Hz, $J_{H\text{-}5a\ H\text{-}6}$ = 8 Hz, H-5a), 2.83 (dd, $J_{H\text{-}5b\ H\text{-}5a}$ = 19 Hz, $J_{H\text{-}5b\ H\text{-}6}$ = 4 Hz, H-5b); Anal. Calcd for $C_9H_4NO_2Br_2F_3S$: C, 26.56; H, 0.99; N, 3.44; S, 7.88 Found : C, 26.37; H, 0.93; N, 3.41; S, 7.90.

2-Bromo-4-trifluoroacetylamino-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-6-one **(11b)** (starting material **10b**). : white crystals separated from **4b** by fractional recrystallizations (35%) : mp 226°C (ether / petroleum ether); ir (KBr) 3290 (NH), 1700 (CO); ^{1}H-nmr 9.99 (d, $J_{NH\ H\text{-}4}$ = 8 Hz, NH), 7.50 (s, H-3), 5.44 (ddd, $J_{H\text{-}4\ NH}$ = 9 Hz, $J_{H\text{-}4\ H\text{-}5a}$ = 9 Hz , $J_{H\text{-}4\ H\text{-}5b}$ = 3 Hz, H-4), 3.45 (dd, $J_{H\text{-}5a\ H\text{-}5b}$ = 19 Hz, $J_{H\text{-}5a\ H\text{-}4}$ = 9 Hz, H-5a), 2.83 (dd, $J_{H\text{-}5b\ H\text{-}5a}$ = 19 Hz, $J_{H\text{-}5b\ H\text{-}4}$ = 3 Hz, H-5b); Anal. Calcd for $C_9H_5NO_2BrF_3S$: C, 32.95; H, 1.54; N, 4.27; S, 9.77 Found: C, 33.07; H, 1.53; N, 4.28; S, 9.66

1,3-Diiodo-6-trifluoroacetylamino-5,6-dihydro-4*H*-cyclopenta[*c*]thiophen-4-one **(4c)** (starting material **10c**) : white crystals separated from **11c** by fractional recrystallizations (43%) : mp 270°C (ether); ir (KBr) 3300 (NH), 1710 (CO); ^{1}H-nmr 9.86 (d, $J_{NH\ H\text{-}6}$ = 9 Hz, NH), 5.25 (ddd, $J_{H6\ NH}$ = 9 Hz, $J_{H6\ H\text{-}5a}$ = 8 Hz , $J_{H6\ H\text{-}5b}$ = 4 Hz, H-6), 3.46 (dd, $J_{H\text{-}5a\ H\text{-}5b}$ = 19 Hz, $J_{H\text{-}5a\ H6}$ = 8 Hz, H-5a), 2.80 (dd, $J_{H\text{-}5b\ H\text{-}5a}$ = 19 Hz, $J_{H\text{-}5b\ H\text{-}6}$ = 4 Hz, H-5b); Anal. Calcd for $C_9H_4NO_2F_3I_2S$: C, 21.58; H, 0.80; N, 2.80; S, 6.40 Found : C, 21.61; H, 0.85; N, 2.88; S, 6.50.

2-Iodo-4-trifluoroacetylamino-5,6-dihydro-4 *H*-cyclopenta[*b*]thiophen-6-one **(11c)** (starting material **10c**). : white crystals separated from **4c** by fractional recrystallizations (14%) : mp 226°C (ether / petroleum ether); ir (KBr) 3280 (NH), 1680 (CO); ^{1}H-nmr 9.95 (d, $J_{NH\ H\text{-}4}$ = 8 Hz, NH), 7.55 (s, H-3), 5.45 (ddd, $J_{H\text{-}4\ NH}$ = 9 Hz, $J_{H\text{-}4\ H\text{-}5a}$ = 9 Hz , $J_{H\text{-}4\ H\text{-}5b}$ = 3 Hz, H-4), 3.46 (dd, $J_{H\text{-}5a\ H\text{-}5b}$ = 19 Hz, $J_{H\text{-}5a\ H\text{-}4}$ = 9 Hz, H-5a), 2.80 (dd, $J_{H\text{-}5b\ H\text{-}5a}$ = 19 Hz, $J_{H\text{-}5b\ H\text{-}4}$ = 3 Hz, H-5b); Anal. Calcd for $C_9H_5NO_2F_3IS$: C, 28.82; H, 1.34; N, 3.73; S, 8.55 Found : C, 28.85; H, 1.29; N, 3.68; S, 8.66.

1,3-Dihalo-4-oxo-5,6-dihydro-4*H*-cyclopenta[*c*]thien-6-ylammonium chlorides **(12a,b,c)**
4-oxo-5,6-dihydro-4*H*-cyclopenta[*c*]thien-6-ylammonium chloride **(16)**

General procedure : A 6N aqueous solution of hydrochloric acid (30 ml) was added with a dihalotrifluoroacetylaminocyclopentanone **(4 a,b,c)** (0.005 mol). The reaction mixture was refluxed for 30 min and then evaporated to dryness under reduced pressure to give **12a,b,c**.

1,3-Dichloro-4-oxo-5,6-dihydro-4*H*-cyclopenta[*c*]thien-6-ylammonium chloride **(12a)** (starting material **4a**) : white crystals (81%) : mp > 260°C (isopropanol); ir (KBr) 3200-2600 ($^+NH_3$), 1720 (CO); ^{1}H-nmr 8.8 (br, $^+NH_3$), 4.82 (dd, $J_{H\text{-}6\ H\text{-}5a}$ = 8 Hz , $J_{H\text{-}6\ H\text{-}5b}$ = 4 Hz, H-6), 3.48 (dd, $J_{H\text{-}5a\ H\text{-}5b}$ = 19 Hz, $J_{H\text{-}5a\ H\text{-}6}$ = 8 Hz, H-5a), 2.98 (dd, $J_{H\text{-}5b\ H\text{-}5a}$ = 19 Hz, $J_{H\text{-}5b\ H\text{-}6}$ = 4 Hz, H-5b); Anal. Calcd for $C_7H_6NOCl_3S$: C, 32.52; H, 2.34; N, 5.42; S, 12.40 Found : C, 32.53; H, 2.37; N, 5.39; S, 12.46.

1,3-Dibromo-4-oxo-5,6-dihydro-4*H*-cyclopenta[*c*]thien-6-ylammonium chloride (**12b**) (starting material **4b**) : white crystals (47%) : mp > 260°C (isopropanol); ir (KBr) 3200-2600 ($^+NH_3$), 1700 (CO); ^{1}H-nmr 8.81 (broad, $^+NH_3$), 4.72 (dd, $J_{H\text{-}6\ H\text{-}5a}$ = 8 Hz , $J_{H\text{-}6\ H\text{-}5b}$ = 4 Hz, H-6), 3.47 (dd, $J_{H\text{-}5a\ H\text{-}5b}$ = 19 Hz, $J_{H\text{-}5a\ H\text{-}6}$ = 8 Hz, H-5a), 3.00 (dd, $J_{H\text{-}5b\ H\text{-}5a}$ = 19 Hz, $J_{H\text{-}5b\ H\text{-}6}$ = 4 Hz, H-5b); Anal. Calcd for $C_7H_6NOBr_2ClS$: C, 24.20; H, 1.74; N, 4.03; S, 9.23 Found : C, 24.53; H, 1.57; N, 4.09; S, 9.26.

1,3-Diiodo-4-oxo-5,6-dihydro-4*H*-cyclopenta[*c*]thien-6-ylammonium chloride (**12c**) (starting material **4c**) : white crystals (47%) : mp > 260°C (isopropanol); ir (KBr) 3200-2600 ($^+NH_3$), 1700 (CO); ^{1}H-nmr 8.7 (broad, $^+NH_3$), 4.54 (dd, H-6, $J_{H\text{-}6\ H\text{-}5a}$ = 8 Hz , $J_{H\text{-}6\ H\text{-}5b}$ = 4 Hz), 3.54 (dd, H-5a, $J_{H\text{-}5a\ H\text{-}5b}$ = 19 Hz, $J_{H\text{-}5a\ H\text{-}6}$ = 8 Hz), 2.96 (dd, H-5b, $J_{H\text{-}5b\ H\text{-}5a}$ = 19 Hz, $J_{H\text{-}5b\ H\text{-}6}$ = 4 Hz); Anal. Calcd for $C_7H_6NOCII_2S$: C, 19.05; H, 1.37; N, 3.17; S, 7.26 Found : C, 18.93; H, 1.29; N, 3.25; S, 7.29.

4-Oxo-5,6-dihydro-4*H*-cyclopenta[*c*]thien-6-ylammonium chloride (**16**) (starting material: **13**) : white crystals (77%) : mp > 260°C (ethanol / isopropanol); ir (KBr) 3250-2700 ($^+NH_3$), 1700 (CO); ^{1}H-nmr 8.8 (br, $^+NH_3$), 8.24 (d, $J_{H\text{-}3\ H\text{-}1}$ = 2.5 Hz, H-3), 7.90 (d, $J_{H\text{-}1\ H\text{-}3}$ = 2.5 Hz, H-1), 4.79 (dd, $J_{H\text{-}6\ H\text{-}5a}$ = 8 Hz , $J_{H\text{-}6\ H\text{-}5b}$ = 4 Hz, H-6), 3.31 (dd, $J_{H\text{-}5a\ H\text{-}5b}$ = 19 Hz, $J_{H\text{-}5a\ H\text{-}6}$ = 8 Hz, H-5a), 2.93 (dd, $J_{H\text{-}5b\ H\text{-}5a}$ = 19 Hz, $J_{H\text{-}5b\ H\text{-}6}$ = 4 Hz, H-5b); Anal. Calcd for C_7H_8NOClS: C, 44.33; H, 4.25; N, 7.39; S, 16.90 Found : C, 44.53; H, 4.32; N, 7.29; S, 17.01.

6-Trifluoroacetylamino-5,6-dihydro-4*H*-cyclopenta[*c*]thiophen-4-one (**13**) : A mixture of water (40 ml), zinc powder (0.95 g, 0.0145 mol) and acetic acid (5ml) was refluxed for 10 min with vigorous stirring and dibromocyclopentanone (**4b**) (1.5 g, 0.0037 mol) was added. After refluxing for 2 h, the reaction mixture was taken up in ether (150 ml) and washed with a saturated aqueous sodium bicarbonate solution. The organic layer was separated, dried over magnesium sulfate and the solvent was removed under reduced pressure to give an oily residue. The crude product was chromatographed on silica gel (Merck Silicagel 60 (0.040-0.063 mm)) with dichloromethane to give **13** as white crystals (0.65 g, 70%) : R_f 0.72 (10% MeOH in $CHCl_3$), mp 150°C (ether); ir (KBr) 3300 (NH), 1700 (CO); ^{1}H-nmr 10.0 (br, NH), 8.12 (d, $J_{H\text{-}3\ H\text{-}1}$ = 2.5 Hz, H-3), 7.58 (d, $J_{H\text{-}1\ H\text{-}3}$ = 2.5 Hz, H-1), 5.41 (dd, $J_{H\text{-}6\ H\text{-}5a}$ = 8 Hz, $J_{H\text{-}6\ H\text{-}5b}$ = 4 Hz, H-6), 3.41 (dd, $J_{H\text{-}5a\ H\text{-}5b}$ = 19 Hz, $J_{H\text{-}5a\ H\text{-}6}$ = 8 Hz, H-5a), 2.91 (dd, $J_{H\text{-}5b\ H\text{-}5a}$ = 19 Hz, $J_{H\text{-}5b\ H\text{-}6}$ = 4 Hz, H-5b); Anal. Calcd for $C_7H_6NO_2F_3S$: C, 43.38; H, 2.43; N, 5.62; S, 12.86 Found : C, 43.23; H, 2.26; N, 5.40; S, 12.88.

1-Bromo-6-trifluoroacetylamino-5,6-dihydro-4*H*-cyclopenta[*c*]thiophen-4-one (**14**).

Method A : The acid chloride (**15**) was treated in a similar way as the general procedure described to obtain **4a,b,c** to give **15** as white crystals (64%) : mp 176°C (ether / petroleum ether); ir (KBr) 3290 (NH), 1700 (CO); ^{1}H-nmr 9.97 (d, $J_{NH\ H\text{-}6}$ = 9 Hz, NH), 8.22 (s, H-3), 5.43 (m, H-6), 3.49 (dd, $J_{H\text{-}5a\ H\text{-}5b}$ = 19 Hz, $J_{H\text{-}5a\ H6}$ = 8 Hz, H-5a), 2.86 (dd, $J_{H\text{-}5b\ H\text{-}5a}$ = 19 Hz, $J_{H\text{-}5b\ H\text{-}6}$ = 4 Hz, H-5b); Anal. Calcd for $C_9H_5NO_2BrF_3S$: C, 32.95; H, 1.54; N, 4.27; S, 9.77 Found : C, 32.94; H, 1.61; N, 4.31; S, 9.88.

Method B : A solution of dibromocyclopentanone (**4b**) (2 g, 0.005mol) in water (15 ml) was added with acetic acid (15 ml) and zinc powder (1.3 g, 0.02 mol) and then heated at 60°C for 1 h. After cooling, the reaction mixture was filtered and the filtrate was poured into water (50 ml). The precipitate appeared was filtered and dried to give **14** with 38% yield.

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