SYNTHESIS OF 7-AMINO-4,5,6,7-TETRAHYDROTHIENO-[3,4-*c*]PYRID-4-ONES

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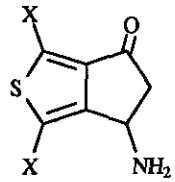
Abstract - Synthesis of 7-amino-4,5,6,7-tetrahydrothieno[3,4-*c*]pyrid-4-ones is achieved involving 6-amino-5,6-dihydro-4*H*-cyclopenta[*c*]thiophen-4-ones in Beckmann and Schmidt rearrangements .

During the course of our work concerning the access to new heterocycles with potential biological interest, we recently reported the synthesis [1] and the antineoplastic activity [2] of 6-amino-5,6-dihydro-4*H*-cyclopenta[*c*]thiophen-4-ones (**1a-c**) (Scheme 1).



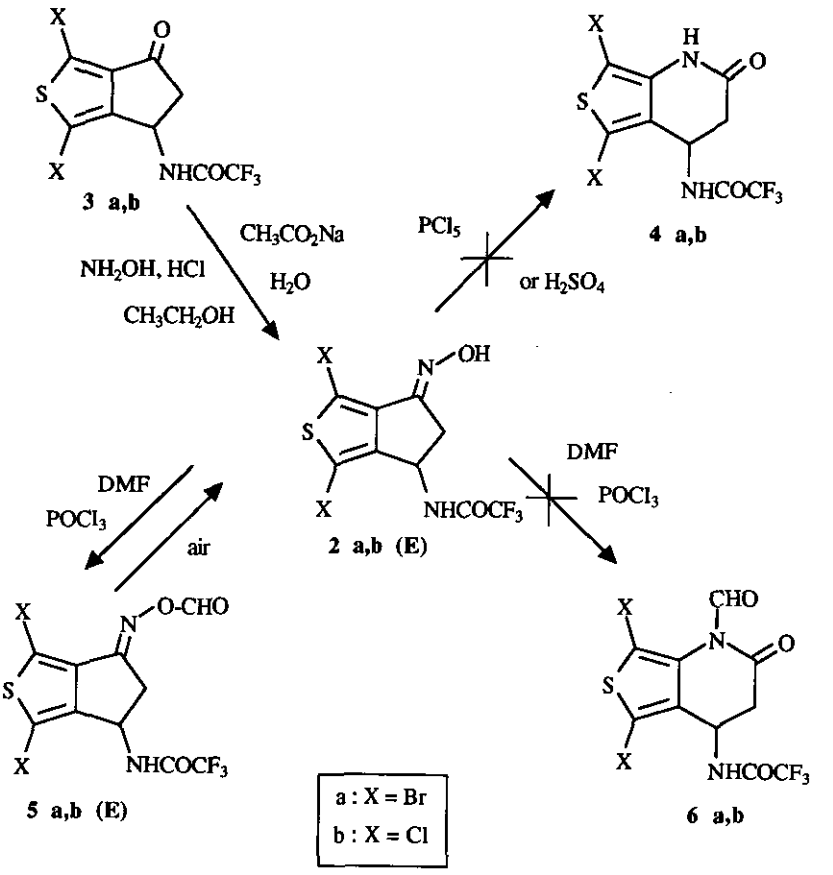
1 a-c

a : X = Br
b : X = Cl
c : X = H

Scheme 1

In order to well understand the structural requirements necessary to exert this antineoplastic activity, we studied the synthesis of homologous 7-amino-4,5,6,7-tetrahydrothieno[3,4-*c*]pyrid-4-ones involving Beckmann and Schmidt rearrangements. We wish to report herein the results of this study.

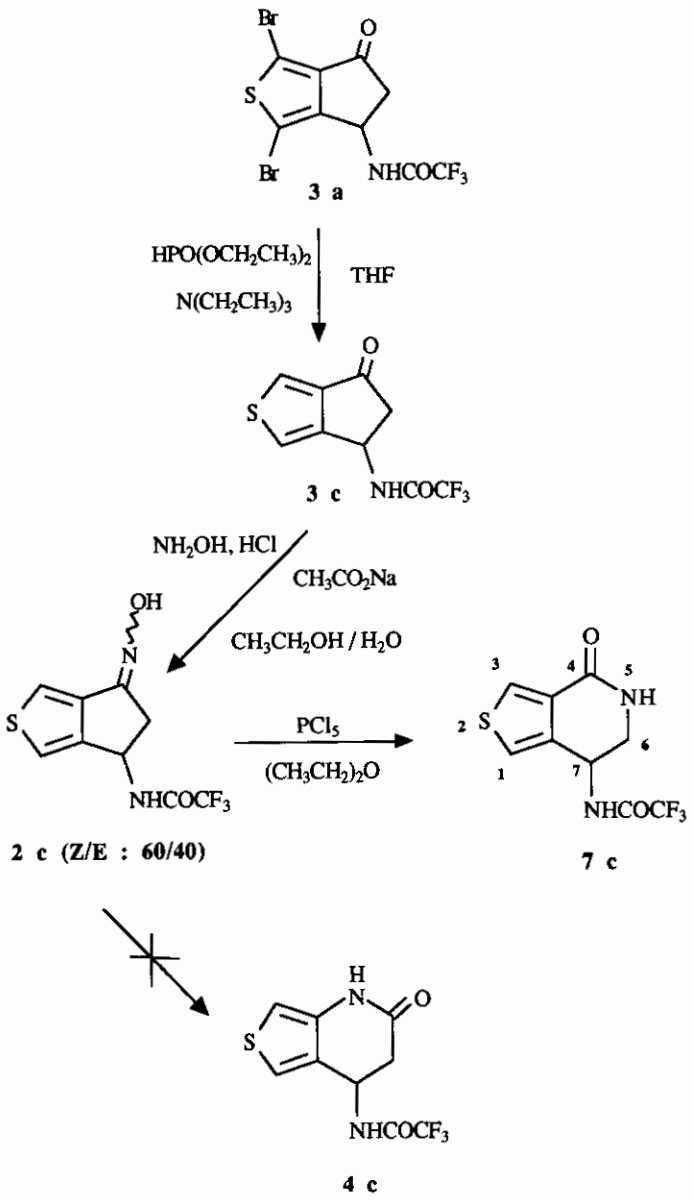
Beckmann rearrangement was first explored starting from the oximes (**2a,b**), easily available by treatment of the dihalo *N*-protected aminocyclopenta[*c*]thiophenones (**3a,b**) with hydroxylamine in ethanol (Scheme 2). This reaction led selectively to the unique isomers (**2a,b**) whose ^{1}H-NMR spectra were in favor of the expected E forms due to the steric hindrance of halogen atoms. However, all attempts aiming at rearrangement of **2a,b** with sulfuric acid or phosphorus pentachloride failed and only led to degradated materials, without traces of the expected aminothienopyridones (**4a,b**).
Further, the use of the Vilsmeier reagent was also inefficient since treatment of **2a,b** with phosphorus oxychloride in dimethylformamide gave only the *O*-formyloximes (**5a,b**) and not the formylpyridones (**6a,b**) contrarily to that was observed by Majo *et al.* in tetralone series. [3]



Scheme 2

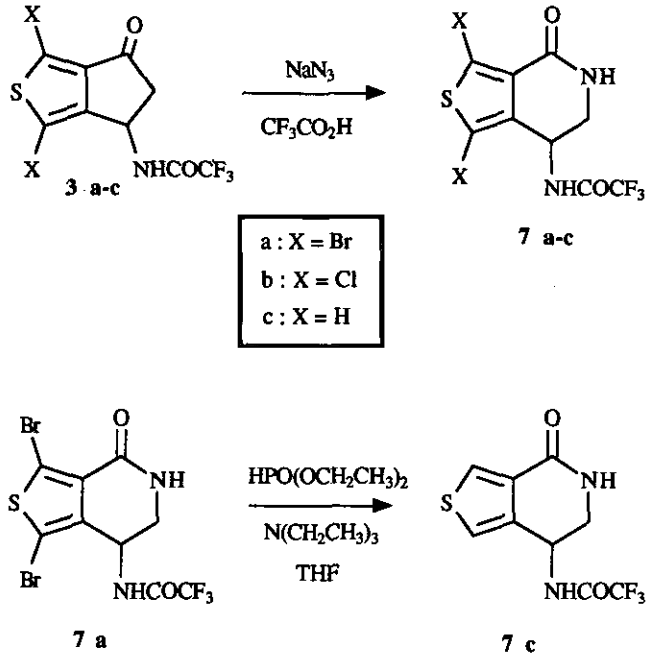
Structures of **5a,b** were assigned on the basis of ^{1}H NMR spectra and were confirmed by their deformylation into **2a,b** which quickly took place by exposure to the ambiant air .

These failures starting from the E forms of the oximes (**2a,b**) prompted us to study the reactivity of a Z form of this type of oxime. This synthesis needed dehalogenation of the dibromo compound (**3a**). Thus, as we previously described [1], bromine atoms of **3a** could be removed under treatment with zinc in refluxing acetic acid leading to the unsubstituted derivative (**3c**) (Scheme 3). The yield of the reaction was recently increased by using diethyl phosphite and triethylamine in tetrahydrofuran giving **3c** in 48 % yield. Treatment of **3c** with hydroxylamine in ethanol afforded an expected mixture of Z and E isomers (60/40) of the oxime (**2c**). Starting from this mixture, Beckmann rearrangement took place under phosphorus pentachloride treatment, in ether at room temperature, and gave in 52% yield selectively the trifluoroacetylaminothienopyridone (**7c**). The insertion of the nitrogen atom, in β position towards the thiophene ring, was deduced from the ^{1}H-^{1}H-COSY 2D NMR spectrum of **7c** which exhibited correlation signals between H-5 and H-6 excluding the isomer form (**4c**). This result was in favor of the sole reaction of the Z isomer of **2c**.



Scheme 3

Then after, we applied an useful Schmidt rearrangement we previously described in analogous series, [4, 5] using sodium azide in refluxing trifluoroacetic acid. Starting from the aminocyclopenta[*c*]thiophenones (**3a-c**), this method afforded in all cases the pyridones (**7a-c**) with 9%, 12% and 66% yields respectively (Scheme 4). Structure of **7c** was deduced by comparison with the Beckmann reaction product. Structure of **7a** was confirmed by its debromination leading to **7c** and finally structure of **7b** by NMR data analogy. No traces of **4a-c** were observed in these Schmidt reactions.



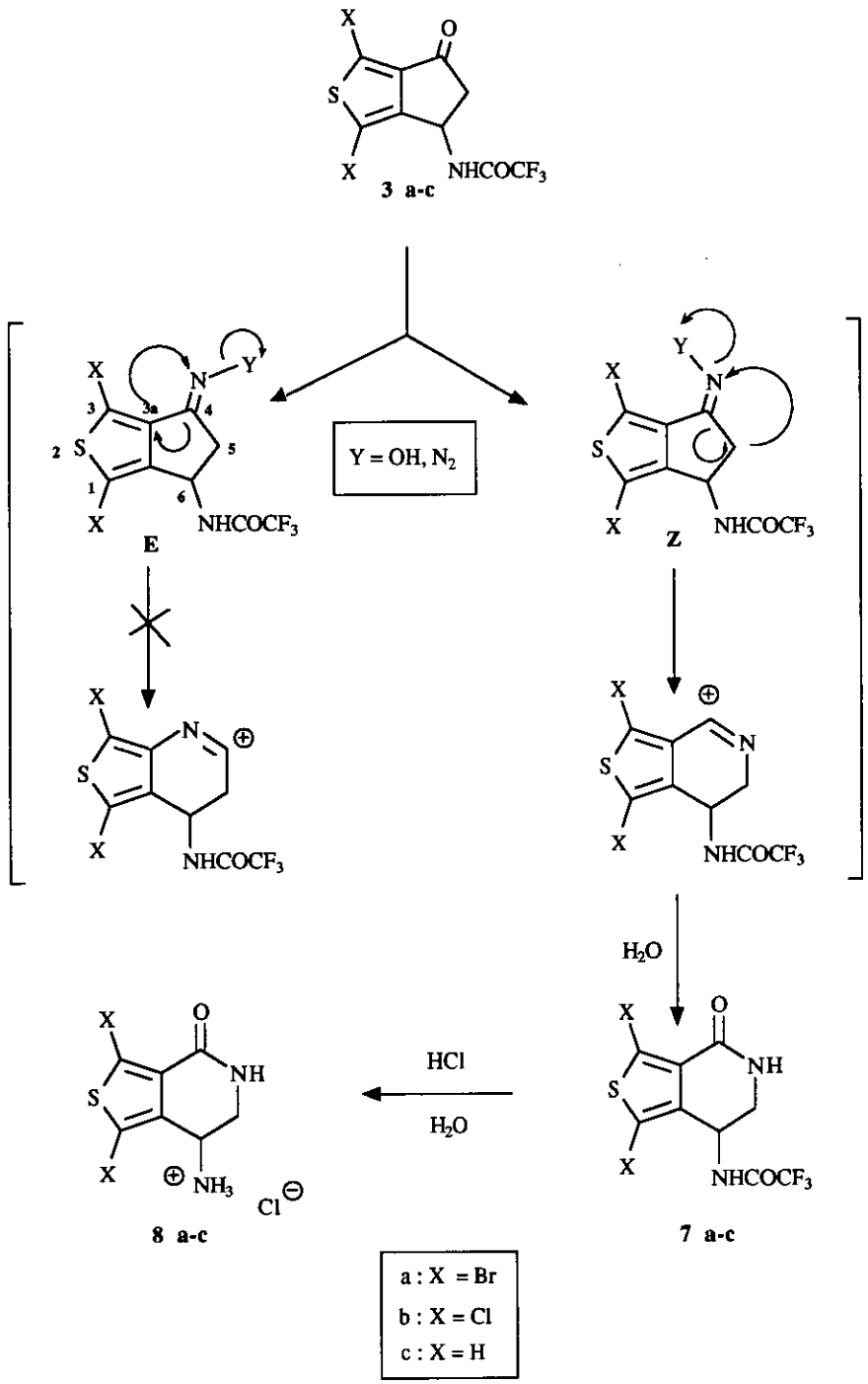
Scheme 4

The results and the yields of the Beckmann and Schmidt rearrangements applied to dihalo- and dehalocyclopentathiophenones (**3a-c**) led us to propose the following pathways (Scheme 5). The steric hindrance of the halogen atoms beared by the thiophene ring of **3a,b** orientated predominantly the structures of the oximes (**2a-c**) and of the intermediate azides towards their E form. However, the cleavage of the stabilized anti C-3a C-4 bond did not occur.

On the other hand, the lack of halogen atoms on the thiophene ring of **3c** led predominantly to the Z form of the oxime and of the intermediate azide which underwent the cleavage of the anti C-4 C-5 bond and gave, after aqueous treatment, the pyridones (**7a-c**).
Finally, acidic hydrolysis of **7a-c** gave in good yield the 4-oxo-4,5,6,7-tetrahydrothieno[3,4-*c*]pyrid-7-yl-ammonium chlorides (**8a-c**).

EXPERIMENTAL

General Methods. Melting points were taken on a Köfler bank and are uncorrected. IR spectra were recorded on a Mattson 1000 FTIR apparatus and only noteworthy absorptions (reciprocal centimeters) are listed. NMR spectra were recorded on a Jeol Lambda 400 spectrometer in DMSO-d_6 solution using TMS as an internal standard. Chemical shift are reported in ppm downfield (δ) from TMS.


X
O
S
X
NHCOCF3
3 a-c
Y = OH, N2
E
Z
H2O
HCl
H2O
NH3
Cl
8 a-c
7 a-c
a : X = Br
b : X = Cl
c : X = H

Scheme 5

1,3-Dibromo-6-trifluoroacetylamino-5,6-dihydro-4*H*-cyclopenta[*c*]thiophen-4-one oxime (E) (**2a**). To a solution of 1,3-dibromo-6-trifluoroacetylamino-5,6-dihydro-4*H*-cyclopenta[*c*]thiophen-4-one (**3a**) (2 g, 0.005 mol) in ethanol (75 mL), was added a solution of hydroxylamine hydrochloride (1.4 g, 0.02 mol) and sodium acetate (1.6 g, 0.02 mol) in water (15 mL). The reaction mixture was refluxed for 2 h and then evaporated to dryness under reduced pressure. The solid residue was triturated in water (50 mL), filtered, dried and recrystallized from ethanol to give **2a** as colorless crystals (1.3 g, 62%) : mp > 260°C; IR (KBr) 3625-3375 (NH, OH), 1702 (CO); ^{1}H-NMR 11.52 (s, OH), 9.96 (d, $J_{NH\ H\text{-}6}$ = 9 Hz, NH), 5.27 (m, H-6), 3.60 (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 $C_9H_5N_2O_2Br_2F_3S$: C, 25.62; H, 1.19; N, 6.64. Found : C, 25.66; H, 0.98; N, 6.56.

1,3-Dichloro-6-trifluoroacetylamino-5,6-dihydro-4*H*-cyclopenta[*c*]thiophen-4-one oxime (E) (**2b**). The pro-cedure described for the preparation of **2a** was followed using 1,3-dichloro-6-trifluoroacetylamino-5,6-dihydro-4*H*-cyclopenta[*c*]thiophen-4-one (**3b**) (1.6 g, 0.005 mol), hydroxylamine hydrochloride (1.4 g, 0.02 mol) and sodium acetate (1.6 g, 0.02 mol), ethanol (75 mL) and water (15 mL). The crude product was recrystallized from ethanol to give **2b** as colorless crystals (1.2 g, 74%) : mp > 260°C; IR (KBr) 3300 (NH, OH), 1690 (CO); ^{1}H-NMR 11.53 (s, OH), 9.98 (d, $J_{NH\ H\text{-}6}$ = 9 Hz, NH), 5.35 (m, H-6), 3.58 (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 $C_9H_5N_2O_2Cl_2F_3S$: C, 32.45; H, 1.51; N, 8.41. Found : C, 32.60; H, 1.42; N, 8.75.

6-Trifluoroacetylamino-5,6-dihydro-4*H*-cyclopenta[*c*]thiophen-4-one oxime (Z/E : 60/40) (**2c**). The procedure described for the preparation of **2a** was followed using 6-trifluoroacetylamino-5,6-dihydro-4*H*-cyclopenta[*c*]thiophen-4-one (**3c**) (1.2 g, 0.005 mol), hydroxylamine hydrochloride (1.4 g, 0.02 mol) and sodium acetate (1.6 g, 0.02 mol), ethanol (75 mL) and water (15 mL). The crude product was recrystallized from ethanol to give **2c** as an amorphous solid (0.9 g, 74%) : mp 202°C; IR (KBr) 3280 (NH, OH), 1702 (CO); ^{1}H-NMR 11.07 (s, OH (Z)), 10.92 (s, OH (E)), 9.95 (m, 2 NH), 7.94 (s, H-3 (Z)), 7.58 (s, H-3 (E)), 7.39 (s, H-1 (E)), 7.36 (s, H-1 (Z)), 5.28 (m, 2 H-6), 3.51 (m, 2 H-5a), 3.02 (m, 2 H-5b); Anal. Calcd for $C_9H_7N_2O_2F_3S$: C, 40.91; H, 2.67; N, 10.60. Found : C, 40.66; H, 2.61; N, 10.52.

1,3-Dibromo-6-trifluoroacetylamino-5,6-dihydro-4*H*-cyclopenta[*c*]thiophen-4-one *O*-formyloxime (E) (**5a**). To an ice-cooled solution of 1,3-dibromo-6-trifluoroacetylamino-5,6-dihydro-4*H*-cyclopenta-[*c*]thiophen-4-one oxime (E) (**2a**) (2.1 g, 0.005 mol) in dimethylformamide (8 mL), was added dropwise phosphorus oxychloride (3 mL, 0.03 mol). The reaction mixture was stirred at room temperature for 30 min, then refluxed for 3 h. The solution was poured into iced water (100 mL) and neutralised with an aqueous 10% sodium bicarbonate solution. The precipitate was filtered, washed with water (50 mL), dried and recrystallized from propan-2-ol to give **5a** as colorless crystals (1.6 g, 76%) : mp 178°C; IR (KBr) 3280 (NH), 1778, 1702 (CO); ^{1}H-NMR 9.99 (d, $J_{NH\ H\text{-}6}$ = 9 Hz, NH), 8.80 (s, CHO), 5.29 (m, H-6), 3.81 (dd, $J_{H\text{-}5a\ H\text{-}5b}$ = 19 Hz, $J_{H\text{-}5a\ H\text{-}6}$ = 8 Hz, H-5a), 3.17 (dd, $J_{H\text{-}5b\ H\text{-}5a}$ = 19 Hz, $J_{H\text{-}5b\ H\text{-}6}$ = 4 Hz, H-5b); Anal. Calcd for $C_{10}H_5N_2O_3Br_2F_3S$: C, 26.69; H, 1.12; N, 6.22. Found : C, 26.61; H, 1.09; N, 6.25.

1,3-Dichloro-6-trifluoroacetylamino-5,6-dihydro-4*H*-cyclopenta[*c*]thiophen-4-one *O*-formyloxime (E) (**5b**). The procedure described for the preparation of **5a** was followed using 1,3-dichloro-6-trifluoroacetylamino-5,6-dihydro-4*H*-cyclopenta[*c*]thiophen-4-one oxime (E) (**2b**) (1 g, 0.003 mol), phosphorus oxychloride (1.7 mL, 0.018 mol) and dimethylformamide (5 mL). The crude product was recrystallized from propan-2-ol to give **5b** as colorless crystals (1 g, 91%) : mp 164°C; IR (KBr) 3270 (NH), 1778, 1702 (CO); ^{1}H-NMR 10.00 (d, $J_{NH\ H-6}$ = 9 Hz, NH), 8.82 (s, CHO), 5.36 (m, H-6), 3.80 (dd, $J_{H-5a\ H-5b}$ = 19 Hz, $J_{H-5a\ H-6}$ = 8 Hz, H-5a), 3.17 (dd, $J_{H-5b\ H-5a}$ = 19 Hz, $J_{H-5b\ H-6}$ = 4 Hz, H-5b); Anal. *Calcd for* $C_{10}H_5N_2O_3Cl_2F_3S$: C, 33.26; H, 1.39; N, 7.76. Found : C, 33.33; H, 1.37; N, 8.02.

1,3-Dibromo-7-trifluoroacetylamino-4,5,6,7-tetrahydrothieno[3,4-*c*]pyrid-4-one (**7a**). Sodium azide (4.8 g, 0.075 mol) was added portionwise to a solution of 1,3-dibromo-6-trifluoroacetylamino-5,6-dihydro-4*H*-cyclopenta[*c*]thiophen-4-one (**3a**) (10 g, 0.025 mol) in trifluoroacetic acid (200 mL). The reaction mixture was refluxed for 10 h then stirred at room temperature for 12 h. The solution was evaporated to dryness under reduced pressure and the cooled residue was triturated in water (100 mL). The precipitate was filtered, washed with water (50 mL), dried and recrystallized from ether/petroleum ether to give **7a** as colorless crystals (0.9 g, 9%) : mp 216°C; IR (KBr) 3280 (NH), 1720, 1650 (CO); ^{1}H-NMR 10.19 (d, $J_{NH\ H-7}$ = 7 Hz, $NHCOCF_3$), 7.99 (m, NH), 5.06 (m, H-7), 3.51 (dd, $J_{H-6a\ H-6b}$ = 13 Hz, $J_{H-6a\ H-7}$ = 7 Hz, H-6a), 3.40 (dd, $J_{H-6b\ H-6a}$ = 13 Hz, $J_{H-6b\ H-7}$ = 5 Hz, H-6b); Anal. Calcd for $C_9H_5N_2O_2Br_2F_3S$: C, 25.62; H, 1.19; N, 6.64. Found : C, 25.59; H, 1.15; N, 6.60.

1,3-Dichloro-7-trifluoroacetylamino-4,5,6,7-tetrahydrothieno[3,4-*c*]pyrid-4-one (**7b**). The procedure described for the preparation of **7a** was followed using 1,3-dichloro-6-trifluoroacetylamino-5,6-dihydro-4*H*-cyclopenta[*c*]thiophen-4-one (**3b**) (10 g, 0.030 mol) and sodium azide (5.8 g, 0.09 mol). The crude product was washed with ether (50 mL), dried and recrystallized from propan-2-ol to give **7b** as colorless crystals (1.2 g, 12%) : mp 226°C; IR (KBr) 3285 (NH), 1739, 1677 (CO); ^{1}H-NMR 10.18 (d, $J_{NH\ H-7}$ = 7 Hz, $NHCOCF_3$), 8.00 (m, NH), 5.12 (m, H-7), 3.61 (dd, $J_{H-6a\ H-6b}$ = 13 Hz, $J_{H-6a\ H-7}$ = 7 Hz, H-6a), 3.40 (dd, $J_{H-6b\ H-6a}$ = 13 Hz, $J_{H-6b\ H-7}$ = 5 Hz, H-6b); Anal. Calcd for $C_9H_5N_2O_2Cl_2F_3S$: C, 32.45; H, 1.51; N, 8.41. Found : C, 32.73; H, 1.48; N, 8.34.

7-Trifluoroacetylamino-4,5,6,7-tetrahydrothieno[3,4-*c*]pyrid-4-one (**7c**).

Method A : Phosphorus pentachloride (1.7 g, 0.008 mol) was added portionwise to an ice-cooled solution of 6-trifluoroacetylamino-5,6-dihydro-4*H*-cyclopenta[*c*]thiophen-4-one oxime (Z/E : 60/40) (**2c**) (0.7 g, 0.003 mol) in ether (100 mL). The reaction mixture was stirred at room temperature overnight , then poured into water (50 mL) and stirred 2 h. The aqueous layer was separated, neutralized with sodium bicarbonate and extracted with ethyl acetate (2x100 mL). The organic layers were collected, dried over magnesium sulfate and solvent was removed under reduced pressure. The solid residue was recrystallized from ether/petroleum ether to give **7c** as colorless crystals (0.36 g, 52%) : mp 250°C; IR (KBr) 3260 (NH), 1727, 1677 (CO); ^{1}H-NMR 10.06 (d, $J_{NH\ H-7}$ = 7 Hz, $NHCOCF_3$), 8.13 (d, $J_{H-3\ H-1}$ = 3 Hz, H-3),

7.81 (m, NH), 7.52 (d, $J_{H\text{-}1\ H\text{-}3}$ = 3 Hz, H-1), 5.16 (m, H-7), 3.50 (dd, $J_{H\text{-}6a\ H\text{-}6b}$ = 13 Hz, $J_{H\text{-}6a\ H\text{-}7}$ = 7 Hz, H-6a), 3.42 (dd, $J_{H\text{-}6b\ H\text{-}6a}$ = 13 Hz, $J_{H\text{-}6b\ H\text{-}7}$ = 5 Hz, H-6b); Anal. Calcd for $C_9H_7N_2O_2F_3S$: C, 40.91; H, 2.67; N, 10.60. Found : C, 40.65; H, 2.34; N, 10.48.

Method B : The procedure described for the preparation of **7a** was followed using 6-trifluoroacetylamino-5,6-dihydro-4*H*-cyclopenta[*c*]thiophen-4-one (**3c**) (1 g, 0.004 mol) and sodium azide (0.78 g, 0.012 mol). The crude product was washed with water (50 mL), dried and recrystallized from ether/petroleum ether to give **7c** (0.7 g, 66%).

Method C : Triethylamine (8.3 mL, 0.06 mol) and diethyl phosphite (8 mL, 0.06 mol) were added to a solution of 1,3-dibromo-7-trifluoroacetylamino-4,5,6,7-tetrahydrothieno[3,4-*c*]pyrid-4-one (**7a**) (0.4 g, 0.001 mol) in tetrahydrofurane (30 mL). The reaction mixture was refluxed for 10 h, then stirred at room temperature for another 24 h and filtered. The filtrate was evaporated to dryness under reduced pressure and the cooled residue was poured into water (50 mL). The precipitate was filtered, dried and recrystallized from ether/petroleum ether to give **7c** (0.12 g, 48%).

1,3-Dibromo-4-oxo-4,5,6,7-tetrahydrothieno[3,4-*c*]pyrid-7-ylammonium chloride (**8a**). An aqueous hydrochloric acid solution (6N, 30 mL) was added to a solution of 1,3-dibromo-7-trifluoroacetylamino-4,5,6,7-tetrahydrothieno[3,4-*c*]pyrid-4-one (**7a**) (0.9 g, 0.0021 mol) in ethanol (100 mL). The reaction mixture was refluxed for 4 h, filtered and the filtrate was evaporated to dryness under reduced pressure. The solid residue was triturated in acetone (20 mL), filtered, dried and recrystallized from propan-2-ol to give **8a** as colorless crystals (0.48 g, 62%) : mp 230°C; IR (KBr) 3750-3200 ($^+NH_3$, NH), 1727 (CO); ^{1}H-NMR 12.00 (br, $^+NH_3$), 8.00 (s, NH), 4.19 (s, H-7), 3.50 (d, $J_{H\text{-}6a\ H\text{-}6b}$ = 14 Hz, H-6a), 3.35 (d, $J_{H\text{-}6b\ H\text{-}6a}$ = 14 Hz, H-6b); Anal. Calcd for $C_7H_7N_2OBr_2ClS$: C, 23.20; H, 1.95; N, 7.73. Found : C, 23.45; H, 1.98; N, 7.51.

1,3-Dichloro-4-oxo-4,5,6,7-tetrahydrothieno[3,4-*c*]pyrid-7-ylammonium chloride (**8b**). The procedure described for the preparation of **8a** was followed using 1,3-dichloro-7-trifluoroacetylamino-4,5,6,7-tetrahydrothieno[3,4-*c*]pyrid-4-one (**7b**) (1 g, 0.003 mol). The crude product was recrystallized from propan-2-ol to give **8b** as colorless crystals (0.7 g, 85%) : mp 190°C; IR (KBr) 3600-3200 ($^+NH_3$, NH), 1720 (CO); ^{1}H-NMR 8.85 (br, $^+NH_3$), 8.12 (s, NH), 4.56 (s, H-7), 3.63 (d, $J_{H\text{-}6a\ H\text{-}6b}$ = 14 Hz, H-6a), 3.47 (d, $J_{H\text{-}6b\ H\text{-}6a}$ = 14 Hz, H-6b); Anal. Calcd for $C_7H_7N_2OCl_3S$: C, 30.73; H, 2.58; N, 10.24. Found : C, 30.68; H, 2.70; N, 9.99.

4-Oxo-4,5,6,7-tetrahydrothieno[3,4-*c*]pyrid-7-ylammonium chloride (**8c**). The procedure described for the preparation of **8a** was followed using 7-trifluoroacetylamino-4,5,6,7-tetrahydrothieno[3,4-*c*]pyrid-4-one (**7c**) (1 g, 0.004 mol). The crude product was recrystallized from propan-2-ol to give **8c** as colorless crystals (0.65 g, 85%) : mp > 260°C; IR (KBr) 3600-3250 ($^+NH_3$, NH), 1727 (CO); ^{1}H-NMR 8.83 (br, $^+NH_3$), 8.18 (d, $J_{H\text{-}3\ H\text{-}1}$ = 3 Hz, H-3), 7.94 (s, NH), 7.78 (d, $J_{H\text{-}1\ H\text{-}3}$ = 3 Hz, H-1), 4.61 (m, H-7), 3.64

(d, $J_{H\text{-}6a\ H\text{-}6b}$ = 14 Hz, H-6a), 3.54 (d, $J_{H\text{-}6b\ H\text{-}6a}$ = 14 Hz, H-6b); Anal. Calcd for $C_7H_9N_2OClS$: C, 41.08; H, 4.43; N, 13.69. Found : C, 40.99; H, 4.51; N, 13.70.

REFERENCES

1. P. Dallemagne, A. Alsaïdi, M. Boulouard, S. Rault, and M. Robba, Heterocycles, 1993, 36, 287.

2. A. Alsaïdi, S. Al Shargapi, P. Dallemagne, F. Carreiras, P. Gauduchon, S. Rault, and M. Robba, Chem. Pharm. Bull., 1994, 42, 1605.

3. V.J. Majo, M. Venugopal, A.A.M. Prince, and P.T. Perumal, Synthetic Comm., 1995, 25, 3863.

4. P. Dallemagne, S. Rault, M. Cugnon de Sévricourt, and M.Robba, Heterocycles, 1988, 27, 1637.

5. P. Dallemagne, O.N. Tembo, S. Rault, and M. Robba, Bull. Soc. Chim. Fr., 1989, 1, 98.

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