A NEW TYPE OF TRIFLUOROACETYLAMINO ANCHIMERIC ASSISTANCE IN A CYCLOPENTANE RING.

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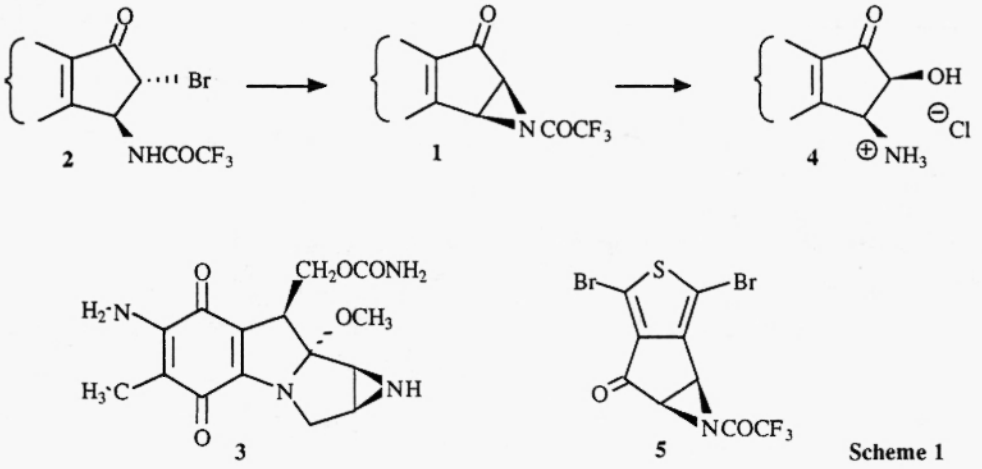
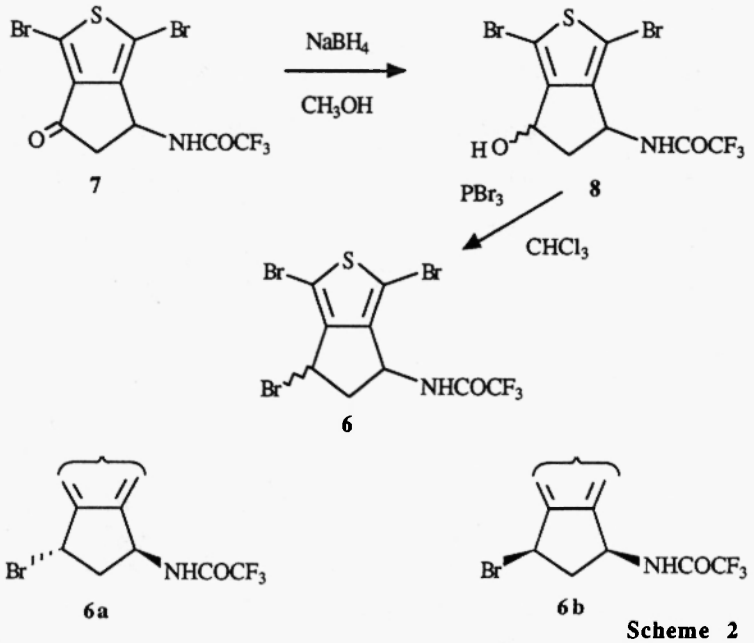
Abstract : Treatment in alkaline medium of a γ-bromotrifluoroacetylaminocyclopentane derivative affords a bridged oxazepine whose cleavage led selectively to *trans* substituted compounds. This anchimeric assistance reaction due to a trifluoroacetylamino group beared by a cyclopentane ring is similar to those observed with the opening of aziridines in homologous structures.

During the course of our work concerning the synthesis of new heterocyclic systems with potential therapeutic interest in the cancerology field, we described the access to several cyclopentatrifluoroacetylaziridinones **1** (1,2) synthesized by treatment of β-halotrifluoroacetamides **2** in alkaline medium (scheme 1). In relation with the biological behaviour of mitomycin **3** (3), a reference antimitotic compound, we clearly shown the ability of **1** to be cleaved in acidic medium leading regiospecifically to *cis* aminohydroxy compounds **4** (4,5) through an anchimeric assistance reaction due to the trifluoroacetyl group. Further we reported recently the interest of the dibromocyclopenta[*c*]thiophene series (6) whose aziridino derivative **5** and its related compounds exhibited a cytotoxic activity against L1210 leukemia (7). In order to investigate the biological potentialities of other cleavable cyclopentane derivatives, we studied the synthesis, starting from γ-halotrifluoroacetamides, of new bridged derivatives homologous to aziridines especially in the dibromocyclopenta [*c*]thiophene series.



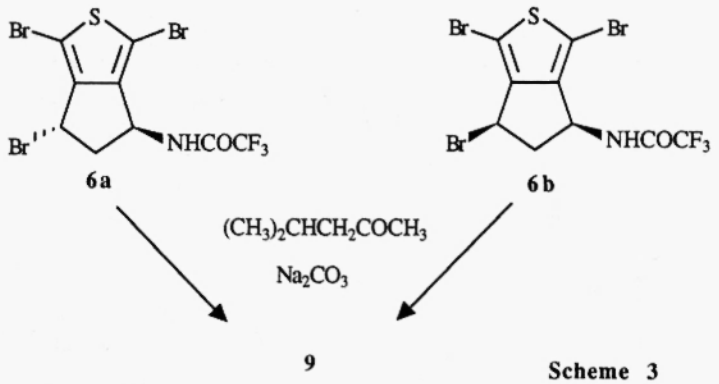
Scheme 1

Access to 1,3,4-tribromo-6-trifluoroacetylaminocyclopenta[*c*]thiophene **6**, was achieved by reduction, using sodium borohydride in methanol at room temperature, of its keto derivative **7** (6) (scheme 2). The reaction led to a mixture, in equal parts, of *cis* and *trans* hydroxy compounds **8** (8). Treatment of the mixture with phosphorus tribromide in chloroform at 0°C gave the expected bromo derivatives **6**. *Trans* **6a** and *cis* **6b** isomers were then separated by crystallization and their structures were elucidated by ^{1}H-NMR analysis (9,10).



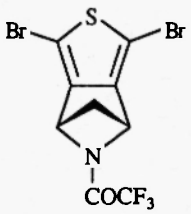
Scheme 2

Cyclization of **6** was achieved by treatment with sodium carbonate in refluxing isobutylmethylketone. All attempts, starting from **6a** or from **6b** led to an unique compound **9** (scheme 3).



Scheme 3

The ^{1}H-NMR spectrum of **9** (12) exhibited two singlets at 5.72 and 4.66 ppm and two doublets at 2.79 and 2.44 ppm with a coupling constant of 12 Hz. The symmetry of the thieno[*c*]pyrroline **10** (scheme 4) excluded such a spectrum which was rather in favor of the thieno[*c*]oxazepine **9**. This structure was confirmed by an analysis of the IR spectrum (11) which shows a weak absorption at 1660 cm^{-1} corresponding to a C=N bond which furthermore appeared in ^{13}C-NMR (11) as a quartet with a coupling constant of 38 Hz at 146.23 ppm (while the carbonyl signals of trifluoroacetylamino groups are centered on 155 ppm (12)).



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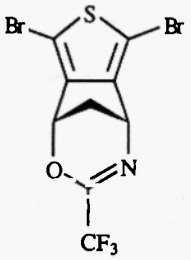


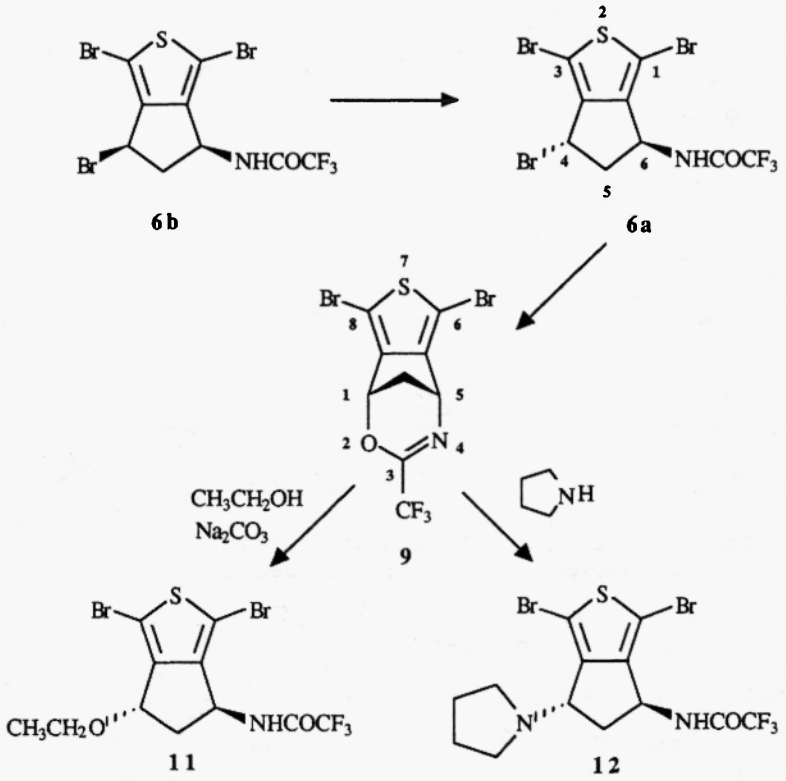
9

Scheme 4

To understand the formation of **9** starting from the *cis* bromotrifluoroacetylamino isomer **6b**, we studied the reaction in DMSO-d6 and we followed it using ^{1}H-NMR spectrometry. According to this experiment we pointed out an isomerisation reaction of **6b** into its *trans* form **6a** preceeding the synthesis of **9** due to a backside nucleophilic attack of the trifluoroacetylamino group on C-4 atom (scheme 5). We previously described some examples of such isomerisation reactions realized either in alkaline or in acidic medium (2,4,5).

The stability of **9** was tested in comparison with those of aziridines **1**. The cleavage of **9** needed more drastic conditions and was runned using nucleophilic agents as alkoxides or amines. It always led to *trans* derivatives like ethoxide **11** (13) and pyrrolidine derivative **12** (14).

Further investigations concerning the application of this anchimeric assistance between two groups in γ-positions in cycloalkyl derivatives and biological evaluation of the yielded products are currently in progress.



Scheme 5

References and notes

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(8) 8. (mixture *cis* / *trans*) mp 152°C; ^{1}H NMR (DMSO-d6, 200 MHz) δ 9.80 (d, J = 8 Hz, NH), 5.57 (d, J = 6 Hz, OH *cis*), 5.48 (d, J = 6 Hz, OH *trans*), 5.34 (m, H-4 *cis*), 5.02 (m, H-4 *trans*), 4.82 (m, H-6), 2.94 (m, H-5a *cis*), 2.51 (m, H-5a *trans* and H-5b), 2.17 (m, H-5b *cis*).

(9) 6a. mp 190°C; ^{1}H NMR (DMSO-d6, 200 MHz) δ 10.00 (d, J = 8 Hz, NH), 5.45 (d, J = 6 Hz, H-4), 5.31 (m, H-6), 2.91 (m, H-5a and H-5b).

(10) 6b. mp 195°C; ^{1}H NMR (DMSO-d6, 200 MHz) δ 10.04 (d, J = 8 Hz, NH), 5.24 (d, J = 6 Hz, H-4), 5.11 (m, H-6), 3.46 (m, H-5a), 2.69 (m, H-5b).

(11) 9. mp 118°C; ir (KBr) 1660 cm^{-1} (C=N); ^{1}H NMR (DMSO-d6, 200 MHz) δ 5.72 (s, H-1), 4.66 (s, H-5), 2.79 and 2.44 (2 d, J = 12 Hz, CH_2). ^{13}C NMR (DMSO-d6, 50 MHz) 148.74 (C-8), 146.23 (q, J = 38 Hz, C-3), 144.26 (C-6), 116.17 (q, J = 277 Hz, CF_3), 106.55 (C-8a), 102.97 (C-5a), 76.22 (C-1), 52.34 (C-5), 40.13 (CH_2).

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(13) 11. mp 170°C; ^{1}H NMR (DMSO-d6, 200 MHz) δ 9.84 (d, J = 8 Hz, NH), 5.22 (m, H-6), 4.62 (d, J = 6 Hz, H-4), 3.50 (q, J = 7 Hz, CH_2), 2.57 (m, H-5a and H-5b), 1.14 (t, J = 7 Hz, CH_3).

(14) 12. mp 134°C; ^{1}H NMR (DMSO-d6, 200 MHz) δ 9.80 (d, J = 8 Hz, NH), 5.05 (m, H-6), 4.23 (d, J = 6 Hz, H-4), 2.65 (m, 2 CH_2), 2.62 (m, H-5a and H-5b), 1.71 (m, 2 CH_2).

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