

A CONVENIENT ROUTE TO 6-AMINOCYCLOPENTA[b]THIOPHENE DERIVATIVES

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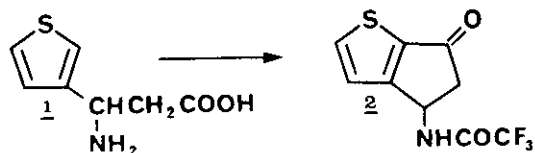
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Abstract - The intramolecular cyclization of 3-amino-3-(2-thienyl) propionic acid to 6-amino-5,6-dihydrocyclopenta[b] thiophene was achieved by Friedel-Crafts reaction.

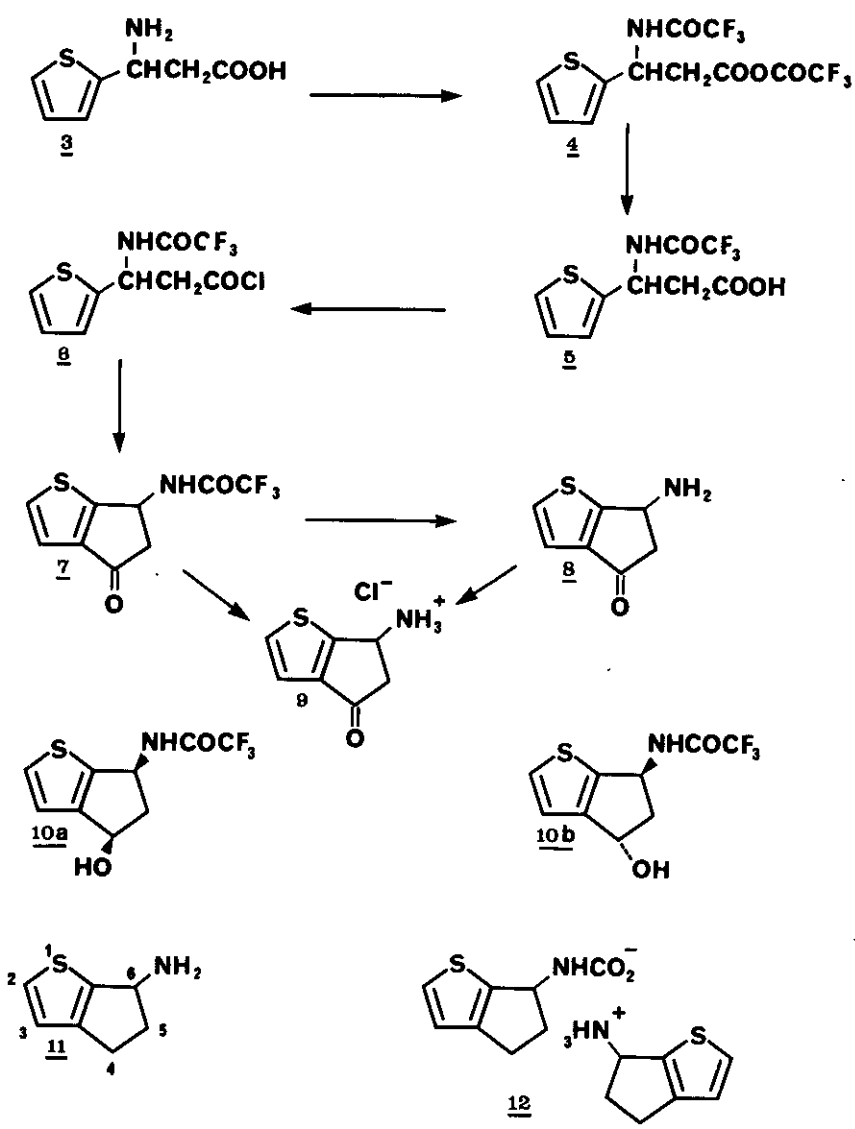
During the course of our work on the synthesis of new thiophenic compounds we have recently described the synthesis of 4-amino-4,5-dihydrocyclopenta[b]thiophen-6-one derivatives¹ and their ability to give aziridino compounds with potential DNA alkylating properties². We wish to describe herein the quite different synthesis of the isomeric structures : 6-amino-4,5-dihydrocyclopenta[b]thiophen-4-one derivatives.

Treatment of 3-amino-3-(3-thienyl)propionic acid 1 with a mixture of boiling trifluoroacetic acid and anhydride gave in one step the trifluoroacetaminopentanone 2.



When the same reaction is conducted starting with 3-amino-3-(2-thienyl)propionic acid 3, obtained from 2-thenaldehyde using the method of Rodionov³, it affords only in poor yield the unstable N-protected mixed anhydride 4, whose structure is deduced from its ir spectrum. Treatment of the latter with aqueous sodium hydrogen carbonate solution followed by acidic treatment gives the N-protected acid 5. However this one is better obtained in 50% yield by acylation of the amino-acid 3 with trifluoroacetic anhydride in ether at room temperature.

This lack of reactivity of the position 3 of the thiophene ring prompts us to investigate a Friedel-Crafts cyclization via the acid chloride 6 adapting the method described by Lozac'h in the preparation of some cyclopentathiophenes⁴.



The acid chloride 6 is obtained from 5 in 95% yield by treatment with thionyl chloride in refluxing benzene. After evaporation of the excess of reagent, the crude acid chloride is thoroughly washed with petroleum ether and dissolved in carbon disulfide in presence of aluminium chloride. The Friedel-Crafts reaction is run during 6 h at refluxing temperature, and the resulting mixture is worked up in a classical manner to give 7 in 23% yield.

All attempts of cyclization have showed that this reaction undergoes only in carbon disulfide, using benzene or toluene gives thienylpropiophenone derivatives while methylene chloride does not permit the reaction.

Hydrolysis of the N-protecting trifluoroacetyl group can be conducted in alkaline or acidic medium. The unstable β -aminoketone 8 is obtained in boiling N sodium hydroxide solution after extraction with chloroform. The ammonium chloride 9 can be obtained either by treatment of 8 with hydrochloric acid in anhydrous ether or by hydrolysis of 7 in boiling 6N aqueous hydrochloric acid.

Further, hydrogenation of the ketone 7 by sodium borohydride in methanol at room temperature gives a mixture of epimeric alcohols 10a (cis) and 10b (trans) in 10% and 90% yield respectively.

Furthermore the complete reduction is achieved by reduction of 10 with stannous chloride in refluxing aqueous hydrochloric acid to give the amine 11 as an unstable oil.

The latter, by exposure to air, conducts quickly by reaction with ambient carbon dioxide at room temperature to its own carbamate 12. This salt is stable and generates 11 in solution at room temperature.

Further studies concerning these and related compounds are in progress.

EXPERIMENTAL

General notes

Melting points are uncorrected. All new compounds gave satisfactory microanalysis. Ir spectra were recorded on a Perkin Elmer 257 G spectrometer and only noteworthy absorptions (cm^{-1}) are listed. Nmr spectra were recorded in DMSO- d_6 or CDCl_3 with TMS as international standard on a Jeol FX 200 spectrometer.

3-Trifluoroacetylamino-3-(2-thienyl)propionic Acid 5

Trifluoroacetic anhydride (20 ml) is added to a suspension of 3-amino-3-(2-thienyl)propionic acid 3 (17g, 0.1mole) in ether (200ml). The resulting solution is stirred at room temperature for 30 min. The solvent and the excess of reagent are then removed under reduced pressure. The white solid residue is recrystallized from ether (13.5g, 50%); mp 160°C; ir (KBr) ν max. NH: 3300 cm^{-1} , OH: 3200-2350 cm^{-1} , CO: 1700 cm^{-1} ; nmr (DMSO) δ ppm 9.97 (1H,d,NH), 7.38 (1H,dd, H5), 6.97 (2H,m,H3-H4), 5.47 (1H,q,CH), 2.95 (2H,d,CH₂).
Anal. Calc. for $\text{C}_9\text{H}_8\text{NO}_3\text{SF}_3$: C,40.45; H,3.02; N,5.24; S,12.00. Found: C,40.53; H,3.12; N,5.17; S,11.94.

3-Trifluoroacetylamino-3-(2-thienyl)propionic Acid Chloride 6

A solution of 3-trifluoroacetylamino-3-(2-thienyl)propionic acid 5 (13.5g, 0.05mole) and thionyl chloride (20 ml) in benzene (200ml) is refluxed for 30 min. The solvent and the excess of reagent are then removed under reduced pressure. The white solid obtained is washed with petroleum ether, filtered and dried (13.6g, 95%); mp 64°C (crude); ir (KBr) ν max. NH: 3280 cm^{-1} , CO: 1785 and 1700 cm^{-1} .

6-Trifluoroacetylamino-5,6-dihydrocyclopenta[b]thiophen-4-one 7

A suspension of compound 6 (8.5g, 0.03mole) and aluminum chloride (8g, 0.06mole) in carbon disulfide (500ml) is refluxed for 6 h. The solvent is then removed under reduced pressure. The residue is dissolved in ether (200ml) and the solution is stirred at room temperature for 10 min with 6 N aqueous hydrochloric acid solution. The organic layer is separated and washed twice with a saturated sodium hydrogen carbonate solution (100ml x 2), dried over magnesium sulfate and the solvent is removed under reduced pressure. The white solid obtained is recrystallized from ether (1.7g, 23%); mp 157°C; ir (KBr) ν max. NH: 3270 cm^{-1} , CO: 1700 cm^{-1} ; nmr (DMSO) δ ppm 10.0 (1H, s, NH), 7.78 (1H, d, H2), 7.15 (1H, d, H3), 5.55 (1H, m, H6), 3.37 (1H, dd, H5), 2.98 (1H, dd, H5).
Anal. Calc. for $\text{C}_9\text{H}_6\text{NO}_2\text{SF}_3$: C, 43.38; H, 2.43; S, 12.86; F, 22.87. Found: C, 43.31; H, 2.63; S, 12.63; F, 22.78.

6-Amino-5,6-dihydrocyclopenta[b]thiophen-4-one 8

A solution of compound 7 (2.5g, 0.01mole) in N aqueous sodium hydroxide solution (50ml) is refluxed for 30 min. The solution is then saturated with sodium chloride and extracted twice with chloroform (200ml x 2). The organic layer separated is dried over magnesium sulfate and the solvent is removed under reduced pressure to obtain an oily residue (0.5g, 32%); ir (KBr) ν max. NH₂: 3350 cm^{-1} and 3280 cm^{-1} , CO: 1700 cm^{-1} .

4-Oxo-4,5-dihydro-6H-cyclopenta[b]thiophen-6-ammonium Chloride 9

Method a

Hydrochloric acid is bubbled at room temperature during 1 min into a solution of compound 8 (1.5g, 0.01mole) in anhydrous ether (100ml). The precipitate solid is filtered, washed with ether, dried and recrystallized from isopropanol (1.85g, 98%); mp >260°C; ir (KBr) ν max. NH₃⁺: 3100-2750 cm^{-1} , CO: 1700 cm^{-1} ; nmr (DMSO) δ ppm 8.64 (3H, m, NH₃⁺); 7.79 (1H, d, H2); 7.14 (1H, d, H3); 4.97 (1H, m, H6); 3.36 (1H, dd, H5); 2.84 (1H, dd, H5).
Anal. Calc. for $\text{C}_7\text{H}_8\text{NOSCl}$: C, 44.33; H, 4.25; N, 7.39; S, 16.90. Found: C, 44.16; H, 4.29; N, 7.50; S, 16.78.

Method b

Compound 7 (2.5g, 0.01mole) is dissolved in a 6 N aqueous hydrochloric acid solution (50ml). The solution is then refluxed for 30 min and evaporated to dryness. The white solid obtained is recrystallized as above (1.58g,83%).

Trans 4-Hydroxy-6-trifluoroacetyl-amino-4,5-dihydro-6H-cyclopenta[b]thiophene10b

Sodium borohydride (1.52g, 0.04mole) is added to a solution of compound 7 (2.5g, 0.01mole) in methanol (50ml). The resulting mixture is stirred at room temperature for 1 h. The solvent is then removed under reduced pressure and the residue is dissolved in water (20ml). This solution is then extracted twice with ether (200ml x 2), the organic layer is dried over magnesium sulfate and the solvent is removed under reduced pressure. The white solid obtained (mixture of cis (10%) and trans (90%) epimers) is recrystallized from ether. The first crop of crystallization gives the trans epimer (1.8g, 82%); mp 152°C; ir (KBr) ν max. OH : 3270 cm^{-1} , CO : 1700 cm^{-1} ; nmr (CDCl_3) δ ppm 7.42 (1H,d,H2), 6.99 (1H,d,H3), 6.46 (1H,m,NH), 5.64 (1H,m,H4), 5.34 (1H,m,H6), 2.91 (1H,ddd,H5), 2.71 (1H,ddd,H5), 1.74 (1H,m,OH).

Anal. Calc. for $\text{C}_9\text{H}_8\text{NO}_2\text{SF}_3$: C, 43.03; H,3.21; N,5.58; F,22.69. Found : C, 42.85; H,3.35; N,5.59; F,22.37.

6-Amino-4,5-dihydro-6H-cyclopenta[b]thiophene11 and its Own Carbamate 12

Compound 10 (1.1g, 0.005mole) is dissolved in a solution of acetic acid (15ml) and hydrochloric acid (8ml). Stannous chloride (3g) is then added and the reaction mixture is stirred at room temperature overnight. Water (100ml) is then added. The resulting solution is alkalinized with sodium hydroxide (pellets, 5g) and extracted twice with ether (200ml x 2). The organic layer is dried over magnesium sulfate and the solvent is removed under reduced pressure. The residue is an unstable oil which by exposure to air gives very quickly its own carbamate 12 (0.6g, 37%); mp 105°C; ir (KBr) ν max. NH : 3330 cm^{-1} , NH_3^+ : 3100-2750 cm^{-1} , CO : 1625 cm^{-1} ; nmr (CDCl_3) δ ppm 7.26 (1H,d,H2); 6.78 (1H,d,H3); 4.52 (1H,m,H6); 2.84 (2H,m,H4); 2.69 (1H,m,H5), 2.14 (3H,m, H5-NH₂). Anal. Calc. for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_2\text{S}_2$: C,55.82; H,5.58; N,8.68; S,19.85. Found : C,55.77; H,5.43; N,8.71; S,19.68.

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