

SYNTHESIS OF 4-AMINOTHIENO[2,3-c]PYRID-7-ONE
FROM 4-AMINOCYCLOPENTA[b]THIOPHEN-6-ONE

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Abstract - 4-Aminothiено[2,3-c]pyrid-7-one derivatives are obtained selectively by ring enlargement of 4-aminocyclopenta[b]thiophen-6-one derivatives using Schmidt or Beckmann rearrangement. Ir and ¹H-Nmr spectra are described.

In continuation of our work on the synthesis and biological evaluation of new thiophenic compounds, we have recently described the synthesis of 4-amino-4,5-dihydrocyclopenta[b]thiophen-6-one 2 starting from 3-amino-3-(3-thienyl)propionic acid 1¹, and its ability to give aziridino derivatives². The present paper describes a convenient route to the yet unknown 4-amino-4,5,6,7-tetrahydrothieno-[2,3-c]pyrid-7-one 7 involving ring enlargement of the former system by Schmidt or Beckmann rearrangement.

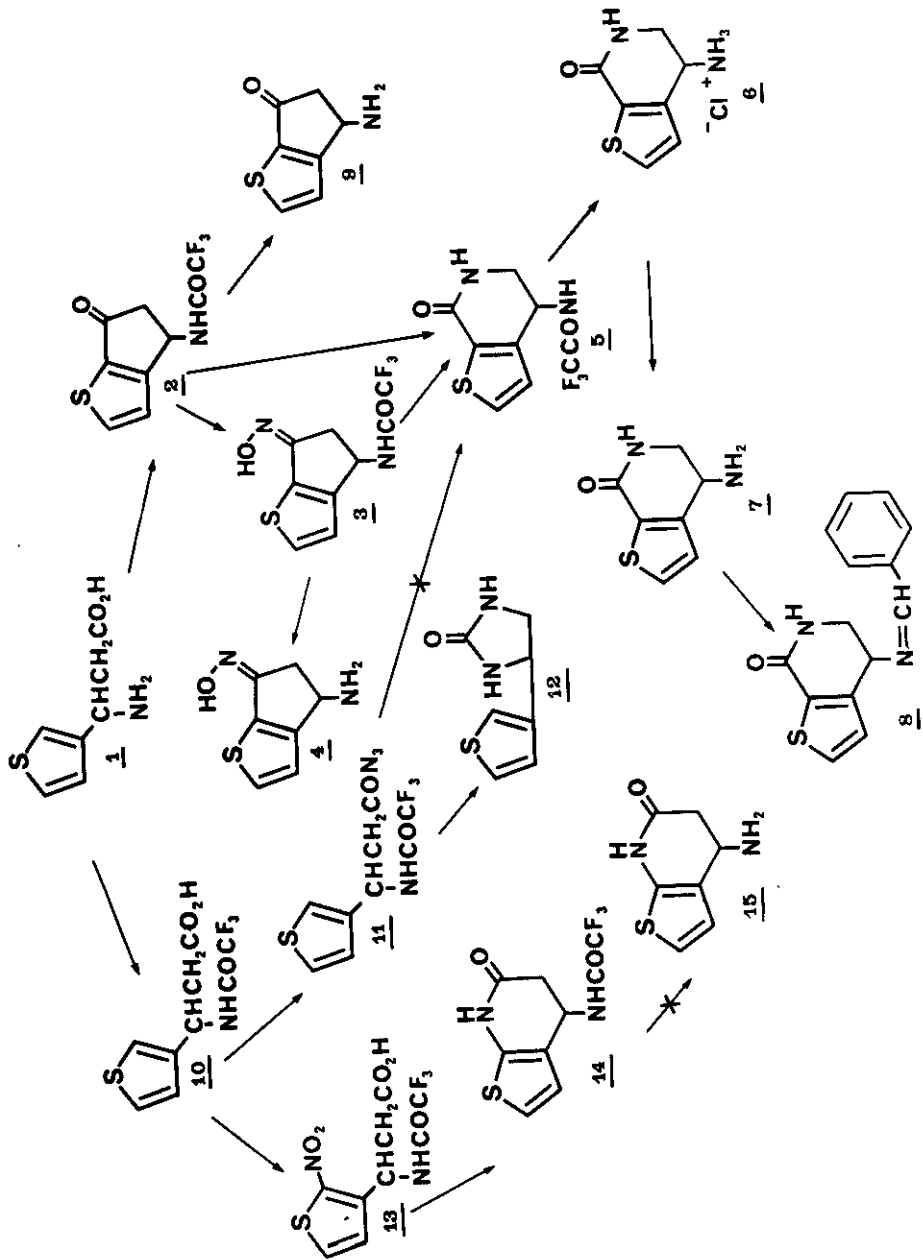
Treatment of cyclopentanone 2 with sodium azide in trifluoroacetic acid leads to a unique pyridone. Its ¹H-nmr spectrum which reveals the presence of a coupling constant, between the proton of the methylene group and the lactamic NH, which disappears after deuteration clearly establishes the thieno[2,3-c]pyridine structure 5 and excludes the isomeric [2,3-b] structure.

This surprising selectivity of the Schmidt reaction, which was not observed by Hurd³ with 2-acetylthiophene prompts us to investigate the Beckmann rearrangement starting from the oxime 3.

The latter is obtained in the usual manner using reaction of hydroxylamine hydrochloride with compound 2. ¹H-Nmr analysis of the crude product shows the presence of Z and E isomers in a ratio of 9:1. The major product Z can be isolated by crystallization. Comparison of the chemical shifts of the alpha thiophenic protons of the two isomers on the ¹H-nmr spectrum of the mixture clearly establishes the structure; thus minor E oxime presents a shielded H₂ alpha thiophenic proton (7.67 ppm) compared to the major Z oxime (7.80 ppm).

Treatment of the oxime 3Z with phosphorus pentachloride in tert-butyl methyl ether leads in poor yield as above to the [2,3-c]pyridone 5. This result is in agreement with theory of the Beckmann rearrangement and with the reactivity of thiaindanones described by Aparajithan⁴.

When the same reaction is run starting from a mixture of 3 E and Z isomers it leads to the pyridone 5 without any amount of the pyridone 14.



Further hydrolysis of the trifluoroacetyl group of 5 gives in acidic medium (1N ; HCl) the ammonium chloride 6 which leads to the free base 7 by treatment with aqueous 1N sodium hydroxide. The structure of this unstable amine is confirmed by formation of its benzylidene derivative 8. It must be pointed out that Schmidt and Beckmann rearrangements carried out starting from aminoketone 9 or aminooxime 4 do not provide the aminopyridone 7. The starting materials are recovered.

Furthermore, in order to confirm the structure of pyridones 5 and 14 by unambiguous synthesis, we have investigated their formation starting from N-TFA acid 10. However, application of the pyridone synthesis method of Eloy and Deryckere⁵ using N-TFA acid azide 11 fails and leads only to the imidazolidinone 12.

But on the other hand, synthesis of pyridone 14 was successful. This sequence needs at once a selective nitration of the N protected acid 10 in position 2 which is realized at 0°C with nitric acid in acetic anhydride. Then reduction and subsequent cyclization are achieved by hydrogenation of the nitro group under pressure in presence of palladium charcoal to give 14 whose trifluoroacetyl group can not be removed without deamination in acidic or alkaline medium. Comparison of the two samples 5 and 14 confirms the result described above.

Further reactions, chemical properties and biological evaluations of title and related compounds are under investigations.

EXPERIMENTAL

Oxime of 4,5-dihydro-4-trifluoroacetylaminocyclopenta[b]thiophen-6-one (3) (mixture of Z and E isomers in a ratio of 9:1)

To a solution of 4,5-dihydro-4 trifluoroacetylaminocyclopenta [b]thiophen-6-one (2 ; 3 g, 0.012 mol) in ethanol (10 ml) is added a solution of hydroxylammonium chloride (3.36 g, 0.048 mol) and sodium acetate (4 g, 0.048 mol) in water (15 ml). The resulting mixture is heated at reflux temperature for 1h, and then ethanol is removed under reduced pressure. After cooling, the precipitate produced is isolated by suction, washed with water and dried ; yield : 3 g (94 %) ; mp 236°C (mixture of E and Z isomers). First crop of crystallization from ether/ethyl acetate gives only the Z isomer ; yield : 1.7 g ; mp : 242°C.

$C_9H_7F_3N_2O_2S$ (264.23) Calc. C, 40.91 ; H, 2.67 ; N, 10.60 ; S, 12.14. Found : C, 41.07 ; H, 2.66 ; N, 10.49 ; S, 12.03.

Ir (KBr) : ν max 3260(NH) ; 3400-3100 (broad OH) ; 1690(C=O) ; 1635, 1545, 1215, 1180, 1145, 1000, 945, 745 cm^{-1} .

¹H-Nmr (90 MHz, DMSO-d₆/TMS) : 3E = 7.80(d,1H,H2) ; 6.95(d,1H,H3) ; 5.38(m,1H,H4) ; 3.52(dd,1H,H5 trans) ; 2.95(dd,1H,H5 cis) ; 10.97(s,1H,OH) ; 9.88 ppm(d,1H,NH). 3Z = idem except 7.67 ppm (d,1H,H2).

Oxime of 4-amino-4,5-dihydro cyclopenta[b]thiophen-6-one (4) (Z isomer)

A suspension of oxime 3Z (3g, 0.011 mol) in 1N aqueous solution of sodium hydroxide (30 ml) is heated at 60°C for 15 min. After cooling sodium chloride (10 g) is added and the resulting saturated solution is extracted twice with ethyl acetate (100 ml x 2). The organic layers are dried over magnesium sulfate and evaporated to dryness in vacuum : yield : 1.48 g (80 %) ; mp 160°C (from ether).

$C_7H_8N_2OS$ (168.22) Calc. C, 49.93 ; H, 4.79 ; N, 16.66 ; S, 19.06. Found : C, 50.03 ; H, 4.88 ; N, 16.47 ; S, 18.99.

Ir (KBr) : ν max : 3300, 3220 and 3140 (NH_2) ; 3100-2400 (broad OH), 1645, 1430, 1385, 1315, 1060, 925, 705 cm^{-1} .

1H -Nmr (90 MHz, $DMSO-d_6/TMS$) 7.67(d,1H,H2) ; 7.05(d,1H,H3) ; 4.33(m,1H,H4) ; 3.40(dd,1H,H5 trans) ; 2.65(dd,1H,H5 cis) ; 10.95(s,1H,OH) ; 3.38 ppm(m,2H, NH_2).

4,5,6,7-Tetrahydro-4-trifluoroacetylaminothieno[2,3-c]pyrid-7-one (5)

a) Beckmann rearrangement

To a solution of oxime 3Z (1 g, 0.0037 mol) in tert-butyl methyl ether (100 ml) cooled at 0°C with an ice bath is added by small portions of phosphorus pentachloride (2.08 g, 0.01 mol). The resulting mixture is stirred at room temperature overnight and then poured on to ice (50 g). The ethereal layer is decanted and the aqueous layer is extracted twice with ether (100 ml x 2). The organic layers are combined, washed with water (100 ml), dried over magnesium sulfate and decolorized with charcoal. The solvent is then removed under reduced pressure ; yield : 0.2 g (20 %) ; mp 260°C (from isopropanol).

$C_9H_7F_3N_2O_2S$ (264.23) Calc. C, 40.91 ; H, 2.67 ; N, 10.60 ; S, 12.14. Found : C, 40.75 ; H, 2.76 ; N, 9.95 ; S, 12.26.

Ir (KBr) : ν max 3280(NH) ; 3210(NH) ; 1715(C=O) ; 1650(C=O) ; 1550, 1480, 1340, 1210, 1180, 1150, 780, 745 cm^{-1} .

1H -Nmr (199.5 MHz, $DMSO-d_6/TMS$) 7.83(m,2H,H2, NH_6) ; 7.11(d,1H,H3) ; 5.19(ddd,1H,H4) ; 3.63(ddd,1H,H5 cis) ; 3.41(ddd,1H,H5 trans) ; 9.63 ppm(d,1H, NH_4).

b) Schmidt rearrangement

A solution of compound 2 (2.5 g, 0.01 mol) and sodium azide (1 g, 0.015 mol) in trifluoroacetic acid (30 ml) is heated at reflux temperature for 4 h. During the course of the reaction, sodium azide (0.5 g, 0.0075 mol) is added each hour.

The solvent is evaporated under reduced pressure and the residue is triturated with water (100 ml). The solid precipitate is isolated by suction and dried ; yield : 1.6 g (61 %).

7-Oxo-4,5,6,7-tetrahydrothieno[2,3-c]-4-pyridinyl ammonium chloride (6)

A solution of pyridone 5 (2.65 g, 0.01 mol) in aqueous hydrochloric acid (1N, 50 ml) is heated at reflux temperature for 2 h and then evaporated to dryness under reduced pressure. The resulting solid is recrystallized ; yield : 1.2 g (57 %) ; mp 260°C (from isopropanol).

$C_7H_9Cl_1N_2OS$ (204.67) Calc. C, 41.08 ; H, 4.43 ; N, 13.69 ; S, 15.66. Found : C, 41.17 ; H, 4.48 ; N, 13.82 ; S, 15.54.

Ir (KBr) : ν max 3280(NH) ; 3240-2700(NH_3^+) ; 1685(C=O) ; 1490, 1315, 1250, 1115 cm^{-1} .

1H -Nmr (199.5 MHz, $DMSO-d_6/TMS$) 7.95(d,1H,H2) ; 7.54(d,1H,H3) ; 5.42(m,1H,H4) ; 3.4(m,4H,H5 trans, NH_3) ; 2.44(m,1H,H5 cis) ; 8.7 ppm (broad, 1H, NH).

4-Amino-4,5,6,7-tetrahydrothieno[2,3]pyrid-7-one (7)

To a solution of aqueous sodium hydroxide (1N, 50 ml) is added with stirring ammonium chloride 6 (2 g). The resulting mixture is saturated with sodium chloride (10 g) and extracted with chloroform (100 ml x 3). The organic layer is dried over calcium chloride and evaporated under reduced

pressure to give an unstable oily residue ; yield : 0.54 g (32 %).

Ir (KBr mulls) ; ν max 3340, 3280, 3070(NH₂) ; 1650(C=O) ; 1470, 1430, 1335, 785 cm⁻¹.

¹H-Nmr (90 MHz, DMSO-d₆/TMS) 7.70(d,1H,H₂) ; 7.20(d,1H,H₃) ; 4.00(dd,1H,H₄) ; 3.41(ddd,1H,H₅ trans) ; 3.20(ddd,1H,H₅ cis) ; 3.0(m,2H,NH₂) ; 7.6 ppm (s,1H,NH).

4-Benzylidenamino-4,5,6,7-tetrahydrothieno[2,3-c]pyrid-7-one (8)

A solution of amine 7 (0.84 g, 0.005 mol) and benzaldehyde (0.53 g, 0.005 mol) in ethanol (30 ml) is heated at reflux temperature for 45 min. Ethanol is removed under reduced pressure and the solid residue is recrystallized ; yield : 1 g (76 %) ; mp 187°C (from isopropanol).

C₁₄H₁₂N₂O₅ (256.32) Calc. C, 65.60 ; H, 4.72 ; N, 10.93 ; S, 12.51. Found : C, 65.70 ; H, 4.68 ; N, 10.88 ; S, 12.47.

Ir (KBr) : ν max 3200(NH) ; 1660(C=O) ; 1635, 1470, 1430, 790, 770, 700 cm⁻¹.

¹H-Nmr (90 MHz, DMSO-d₆/TMS) 8.47(s,1H,CH) ; 7.7(m,4H,H₂,NH,2H arom.) ; 7.4(m,3H,arom.) ; 7.00(d,1H,H₃) ; 4.8(dd,1H,H₄) ; 3.60 ppm (m,2H,2H₅).

3-(3-Thienyl)-3-trifluoroacetylaminopropionyl azide (11)

To an ice cooled solution of acid 10 (4.34 g, 0.02 mol) in acetone (80 ml) is added dropwise with stirring triethylamine (2.3 g, 0.022 mol). After 15 min ethyl chloroformate (2.38 g, 0.022 mol) is added dropwise at such a rate that the temperature is kept below 5°C (15 min) ; after 30 min a solution of sodium azide (1.56 g, 0.024 mol) in water (5 ml) is added as above and the resulting mixture is stirred at 5°C for 1 h. It is then poured into ice (50 g) and the oily precipitate is extracted twice with methylene chloride (100 ml x 2). The organic layer is washed with water, dried over calcium chloride and the solvent is removed under reduced pressure. The unstable oily residue is used without further purifications in the subsequent step : yield : 3.9 g (66 %).

Ir (KBr) : ν max : 3270(NH) ; 2140(N₃) ; 1750, 1690, 1550, 1405, 1360, 1175, 800 cm⁻¹.

2-Oxo-4-(3-thienyl)-imidazolidine (12)

A solution of azide 11 (1 g) in dichloromethane (10 ml) is added to a solution of tributylamine (1 ml) in diphenyl ether (5 ml) and heated at 200°C. Heating is maintained for 30 min and the solution is cooled to room temperature. Ether (50 ml) is added to the resulting mixture and the solid precipitated is isolated by suction and dried ; yield : 0.4 g (68 %) ; mp 154°C (from isopropanol). The same result is obtained when ortho-dichlorobenzene, water or ethanol are used instead of diphenyl ether.

C₇H₈N₂O₅ (168.15) Calc. : C, 50.00 ; H, 4.80 ; N, 16.66 ; S, 19.03. Found : C, 50.15 ; H, 4.83 ; N, 16.71 ; S, 19.06.

Ir (KBr) : ν max 3200(NH), 1680(C=O) ; 1490, 1455, 1325, 1250, 1110, 865, 800, 775, 700 cm⁻¹.

¹H-Nmr (90 MHz, DMSO-d₆/TMS) 7.43(ddd,1H,H₅) ; 7.30(ddd,1H,H₂) ; 7.01(ddd,1H,H₄) ; 4.72(dd,1H,H_{4'}) ; 3.60(dd,1H,H₅) ; 3.10(dd,1H,H₅) ; 6.72 and 6.12 ppm (2s, 2H, 2NH).

3-(2-Nitro-3-thienyl)-3-trifluoroacetylaminopropionic acid (13)

A suspension of acid 10 (3 g, 0.011 mol) in acetic anhydride (20 ml) is cooled at 0°C and then

nitric acid ($d = 1.52$, 1.8 ml, 0.044 mol) is added dropwise. The ice bath is then removed and after 15 min the reaction mixture is poured on to water (300 ml). The resulting mixture is filtered and the filtrate is concentrated under reduced pressure to one third of the original volume and allowed to stand at 5°C for 1 h. The crystalline precipitate is isolated by suction and dried; yield: 1.2 g (35 %); mp: 213°C (from ether).

$C_9H_7F_3N_2O_5$ (312.22) Calc.: C, 34.62; H, 2.26; N, 8.97; S, 10.27. Found: C, 34.77; H, 2.31; N, 9.03; S, 10.23.

Ir (KBr): ν max 3290(NH); 1700(C=O); 1325, 1305, 1225, 1195, 1170 cm^{-1} .

1H -Nmr (199.5 MHz, DMSO- d_6 /TMS) 7.99(d,1H,H5); 7.20(d,1H,H4); 6.01(m,1H,CH); 2.74(m,2H,CH₂); 10.15(d,1H,NH); 2.5 ppm (s,1H,OH).

4,5,6,7-Tetrahydro-4-trifluoroacetylaminothieno[2,3-b]pyrid-6-one (14)

A suspension of nitroacid 13 (1.2 g, 0.0038 mol) and palladium charcoal (2 g) in ethanol (400 ml) is hydrogenated (50 psi) in a steel bomb at room temperature for 4 h. Palladium charcoal is filtered off and the filtrate is evaporated to dryness under reduced pressure. Residue is dissolved in ether (200 ml) and the solution is washed with a saturated solution of sodium hydrogen carbonate (100 ml), dried over magnesium sulfate and evaporated in vacuum; yield: 0.6 g (60 %); mp: 210°C (from isopropanol).

$C_9H_7F_3N_2O_2S$ (264.23) Calc.: C, 40.91; H, 2.67; N, 10.60; S, 12.14. Found: C, 41.07; H, 2.71; N, 10.72; S, 12.08.

Ir (KBr): ν max 3270(NH); 3210(NH); 1705(C=O); 1660(C=O); 1420, 1245, 1285, 1190, 1170, 1150 cm^{-1} .

1H -Nmr (199.5 MHz, $CDCl_3$ /TMS) = 6.76(d,1H,H2); 6.54(d,1H,H3); 5.29(dd,1H,H4); 3.03(dd,1H,H5 cis); 2.67(dd,1H,H5 trans); 10.99(s,1H,NH7); 9.01 ppm (d,1H,NH4).

REFERENCES AND A FOOT NOTE

This work was the subject of a poster communication at the One Day Pre-Grasmere Symposium on Thiophene - University of Salford (UK) - May 6, 1987.

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