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TETRAHEDRON

Thiaisatoic Anhydrides : Efficient Synthesis under Microwave Heating Conditions and Study of their Reactivity.

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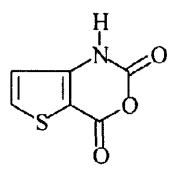
Abstract: 2-thiaisatoic anhydride **1** and 3-thiaisatoic anhydride **2** were synthesized in large scale under microwave heating conditions with 85% and 67% yields respectively. The reactivity of these two compounds was studied towards various nucleophiles and appeared to be generally different from that of isatoic anhydride : many new thiophene-2 and 3-carboxylic acids were isolated with good yields as potential new pharmacological scaffolds.

INTRODUCTION

The anthranilic acid and its cyclic anhydride, the isatoic anhydride, are raw materials widely used in the field of heterocyclic chemistry and their reactivity was extensively studied[1]. On the contrary, their thiophene analogues, the 3-amino-2-thiophene and the 2-amino-3-thiophene carboxylic acids as well as their two corresponding cyclic anhydrides, the 1*H*-thieno[3,2-*d*][1,3]oxazine-2,4-dione and the 1*H*-thieno[2,3-*d*][1,3]oxazine-2,4-dione that we name respectively "2-thiaisatoic" **1** and "3-thiaisatoic" **2** remain up to now scarcely studied and are not yet considered as building blocks in the chemistry of thiophene derivatives.



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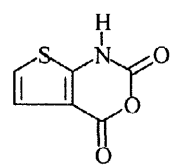

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The synthesis of 2-thiaisatoic anhydride **1** was described for the first time in a patent of Hunkler[2] in 1983. An improved procedure described in 1986 involves the hydrolysis of methyl-3-amino-2-thiophene carboxylate followed by reaction with phosgene[3]. The synthesis of 3-thiaisatoic anhydride **2** is older: it was first described by Baker in 1953 and involved the cyclization of the 2-azidocarbonyl-3-thiophene carboxylic acid[4]. More recently, another synthesis starting from ethyl-2-amino-3-thiophene carboxylate[3] was reported by Barker. A major problem with these syntheses is the instability of the thiophene *o*-aminoacides which easily

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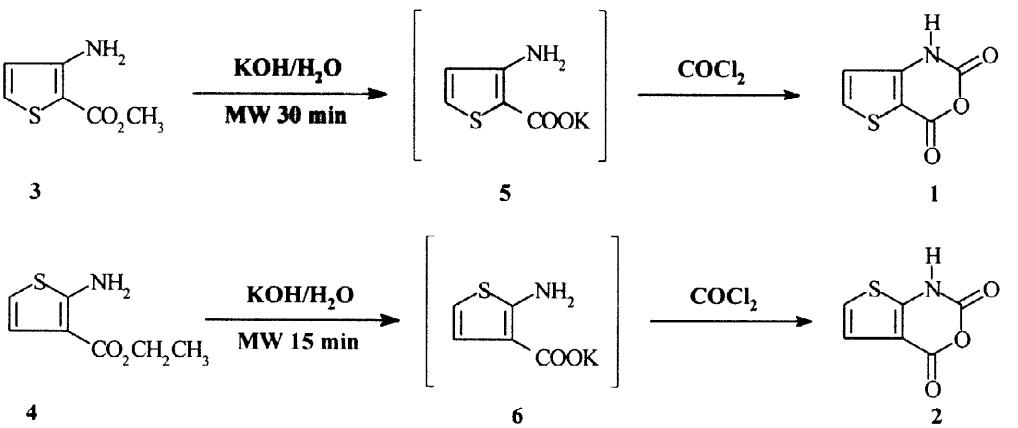
decarboxylate at room temperature to lead aminothiophenes which are themselves unstable[5] and have to be used as soon as they are prepared. Moreover, with large quantities of reactants, the hydrolysis step is not easy to perform because of the low reactivity of thiophene carboxylate[6]. Till now, no detailed studies of this reaction and reactivity of thiaisatoic anhydrides have been performed.

In the course of our work on the synthesis and the biological evaluation of new tricyclic compounds containing thiophene ring[7-12], we needed large amounts of these anhydrides. The aim of the present report is to describe an efficient synthesis of these thiaisatoic anhydrides and to study in detail their reactivity towards various nucleophiles.

RESULTS AND DISCUSSION

Synthesis of anhydrides 1 and 2

Our experience in the field of chemistry under microwave heating conditions[13-15] led us to study the alkaline hydrolysis of *o*-aminoesters **3** and **4** under these conditions in order to shorten the reaction time and to limit the formation of by-products. A detailed study of the experimental conditions of the reaction which was conducted in a multimode microwave oven Normatron® showed that it was possible to carry out this reaction in a few minutes on a large scale in water containing a slight excess of potassium hydroxide but without cosolvent (Scheme 1). When this reaction was run under classical heating conditions, it required longer time than under microwave heating conditions and led the formation of by-products and lower yields.



3 5 1

4 6 2

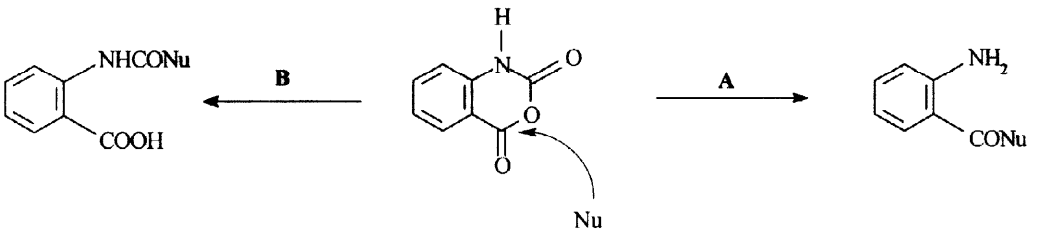
Scheme 1

The potassium carboxylates **5** and **6** could then be treated directly without isolation by bubbling phosgene in the aqueous solution or more classically by adding a solution of phosgene in toluene to yield the anhydrides **1** and **2** in 85 and 67% yields respectively with a purity higher than 90%.

Study of the reactivity of 1 and 2

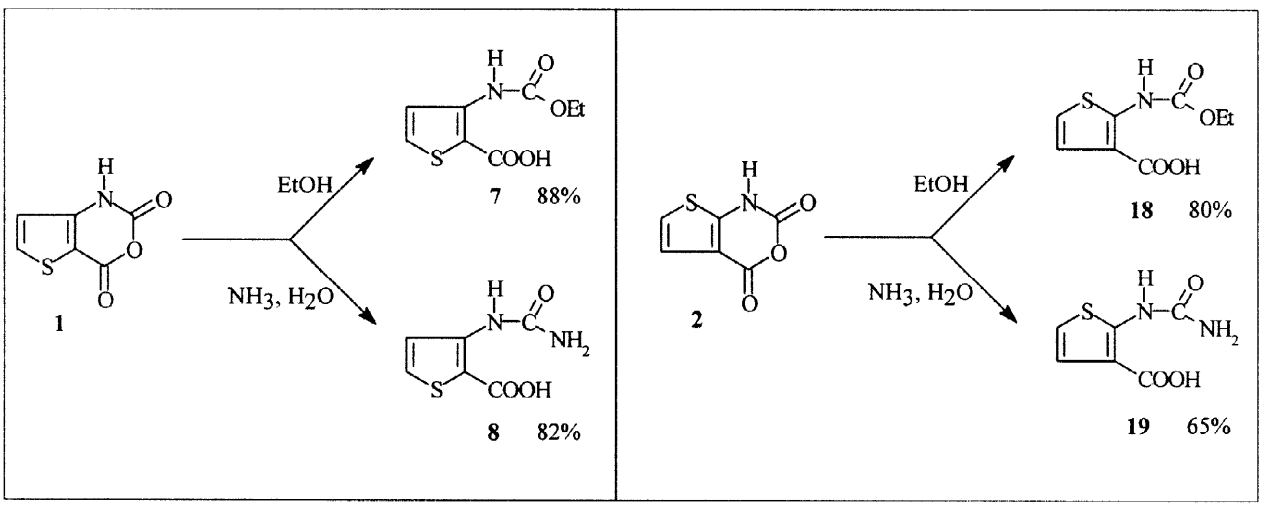
It is well-known that nucleophilic attack on isatoic anhydride generally takes place onto the carbonyl at position 4 (Scheme 2, way **A**). However, it was observed that *o*-ureidobenzoic acids could also be formed by using a large excess of amines or bulky amines such as *t*-butylamine[16]. In the same way, under high temperature

conditions, alcohols react **without base catalyst** preferentially on the C-2 carbonyl of isatoic anhydride **to give** alkyl isatoates instead of **anthranilates**[17] **(Scheme 2, way B)**.



Scheme 2

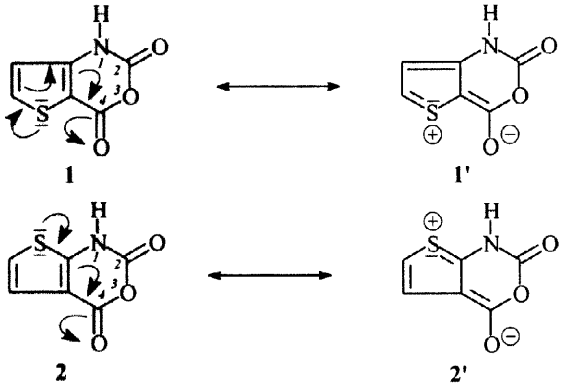
In an attempt to compare the reactivity of anhydrides **1** and **2** to that of isatoic anhydride, we first studied their behaviour towards both ethanol and an aqueous solution of ammonia. First of all, it appeared that heating thiaisatoic anhydrides **1** and **2** in ethanol led carbamates **7** or **18** without formation of the corresponding *o*-aminoesters (Scheme 3). The use of sodium ethoxide instead of ethanol gave the same results and did not modify the behaviour of **1** and **2**.



Scheme 3

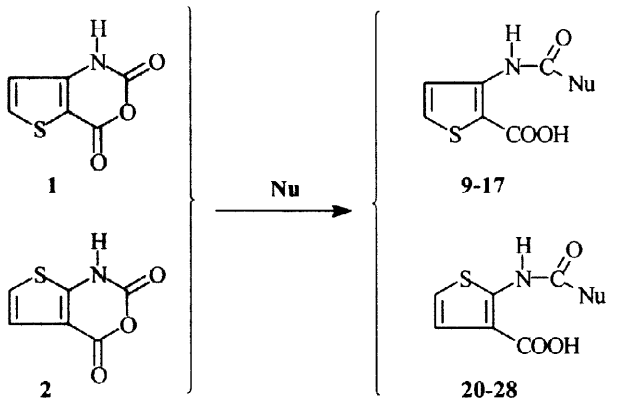
Similarly, compounds **1** and **2** were allowed to stand at room temperature for 15 minutes in aqueous ammonia to yield respectively ureidothiophene carboxylic acids **8** and **19** without formation of *o*-aminocarboxamides (Scheme 3).

It appeared that under these mild conditions the most reactive site of anhydrides **1** and **2** was the carbonyl group of the carbamate function and not that of the ester one. The lack of reactivity of the latter is readily explained by a mesomeric effect implying a low pair of electrons of the sulfur atom (Scheme 4).



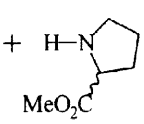
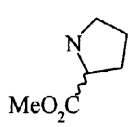
Scheme 4

A generalization of these observations is shown in Scheme 5 and Tables 1 and 2.



Scheme 5

Table 1. Thiophene-2-carboxylic acid derivatives **9-17**

Educts	Products	Nu	Solvent	T(°C)	Time	Yield %[a]
1 + $MeNH_2$	**9**	NHMe	THF	20	20min	51
1 + $PhNHNH_2$	**10**	NHNHPh	THF	20	2h	67
1 + $(Me)_2N(CH_2)_3NH_2$	**11**	$NH(CH_2)_3N(Me)_2$	THF	20	30min	87
1 + $PhNH_2$	**12**	NHPh	THF	20	15h	77
1 + $ClCH_2CH_2NH_2$	**13**	$NHCH_2CH_2Cl$	THF	20	30min	64
1 + 	**14**		THF	20	1h30	49
1 + $PhCH_2OH$	**15**	OCH_2Ph	no	90	8h	56
1 + $HSCH_2CO_2Me$	**16**	SCH_2CO_2Me	no	MW[b]	30min	43
1 + 	**17**		DMF	20	2h	71

a - Yield of isolated pure product. b - Microwave Heating (500W).

Table 2. Thiophene-3-carboxylic acid derivatives **20-28**

Educts	Products	Nu	Solvent	T(°C)	Time	Yield %[a]
2 + $MeNH_2$	**20**	NHMe	THF	20	4h	51
2 + $PhNHNH_2$	**21**	NHNHPh	THF	20	4h	73
2 + $(Me)_2N(CH_2)_3NH_2$	**22**	$NH(CH_2)_3N(Me)_2$	THF	20	15min	80
2 + $PhNH_2$	**23**	NHPh	THF	20	24h	40
2 + $(Me)_2NH$	**24**	$N(Me)_2$	THF	20	4h	78
2 + $CH_3(CH_2)_3OH$	**25**	$O(CH_2)_3CH_3$	no	20	48h	80
			no	110	2h	82
2 + $(CH_3)_3COH$	**26**	$OC(CH_3)_3$	no	80	2h	80
2 + $HSCH_2CO_2Me$	**27**	SCH_2CO_2Me	THF	60	10h	25
2 + $H_2NCH_2CO_2Me$	**28**	$NHCH_2CO_2Me$	DMF	20	2h	60
			DMF	150	1h	26

a - Yield of isolated pure product

It appeared that thiaisatoic anhydrides reacted at room temperature with primary amines (aliphatic or aromatic), secondary amines such as morpholine or dimethylamine, phenylhydrazine, alcohols or alkoxides and aminoacids esters. In some cases, reaction times were shortened by heating as illustrated by the reaction of benzyl alcohol which required heating at 90°C to be completed in 8 hours. However, in all cases, heating conditions were responsible for some degradation starting material and yields dropped. Thiaisatoic anhydrides **1** and **2** did not react at room temperature with methyl thioglycolate. In this case after a long period of heating with or without microwaves, thiocarbonylaminothiophene carboxylic acids **16** and **27** were only obtained in low yields.

CONCLUSION

This study has shown that thiaisatoic anhydrides **1** and **2** react with nucleophilic reagents differently from isatoic anhydride. These reactions allowed us new *o*-ureido and *o*-carbamoylthiophene carboxylic acids. These results associated with the description of an efficient synthesis of thiaisatoic anhydrides **1** and **2** make them very attractive as starting materials for new thiophenic scaffolds.

We are currently studying the reaction conditions of thiaisatoic anhydrides which could allow the preparation of *o*-aminothiophene carbonyl derivatives.

EXPERIMENTAL SECTION

General. Melting points were determined on a Kofler melting point apparatus and are uncorrected. IR spectra were taken with a Genesis Series FTIR spectrometer. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a JEOL Lambda 400 spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. The mass spectra (MS) were taken on a JEOL JMS GCMate spectrometer at a ionizing potentiel of 70eV. Elemental analyses were performed at the "Institut de Recherche en Chimie Organique Fine" (Rouen). Reaction times were monitored by TLC until no starting material remained. Thin-layer chromatography (TLC) were performed on 0.2-mm precoated plates of silica gel 60F-264 (Merck). Visualization was made with ultraviolet light. Reactions under microwave heating were

performed into Normatron® (Normalab) microwave reactor[18]. All solvents and reagents were purchased from Acros and Aldrich Chimie and used without further purification. 2-aminothiophene-3-carboxylic acid ethyl ester was prepared from a literature method[19].

Preparation of thiaisatoic anhydrides 1 and 2*

2-thiaisatoic anhydride (1)

Method A: 3-aminothiophene-2-carboxylic acid methyl ester **3** (40g; 0.25moles) was suspended in an aqueous solution of potassium hydroxide (21g; 0.375moles in 250mL of water). The mixture was then refluxed with stirring under microwave heating (500W) for 30min. After cooling the solution at 0°C, phosgene (1.6eq.; 210mL of 20% $COCl_2$ solution in toluene) was added dropwise with stirring. After addition, the mixture was allowed to stand at room temperature for one hour. The precipitate was filtered, washed with water and with a saturated sodium hydrogenocarbonate solution. After drying the product was washed with diethyl ether to give anhydride **1** with 85% yield (m.p 230°C dec.). Analytical data were in accordance with those cited in literature[3].

Method B: The procedure was the same but gaseous phosgene (40g) was gently bubbled in the aqueous solution instead of adding phosgene in a toluene solution.

3-thiaisatoic anhydride (2)

2-aminothiophene-3-carboxylic acid ethyl ester **4** (40g; 0.25moles) was suspended in an aqueous solution of potassium hydroxide (34g; 0.50moles in 500mL of water). The mixture was then heated under microwave heating (500W) for 15 minutes. After cooling the aqueous solution at 0°C, phosgene (1.6eq.; 210mL of 20% $COCl_2$ solution in toluene) was added dropwise with vigorous stirring. The mixture was allowed to stand at room temperature for one hour. The resulting precipitate was filtered and washed successively with water, hexane and petroleum ether. Anhydride **2** was obtained with 67% yield (m.p 232°C (dec.)). Analytical data were in accordance with those cited in literature[3].

Preparation of thiophene-2 and -3-carboxylic acids

General procedure for compounds 8, 9, 10, 12, 14, 19, 20, 21, 22, 23, 24

The "2- or 3-thiaisatoic" anhydride was diluted in 20mL of THF. After addition under stirring of the amine or hydrazine, the mixture was allowed to stand at room temperature. The solvent was then removed under reduced pressure and the product was taken up in a saturated $NaHCO_3$ solution. After filtration, the solution was acidified with concentrated HCl. The precipitate was collected under filtration and recrystallized from an appropriate solvent.

3-(ethoxycarbonylamino)thiophene-2-carboxylic acid (7)

The "2-thiaisatoic" anhydride **1** (1g; 6mmoles) was diluted in 20mL of ethanol. The mixture was then refluxed for two hours. The solvent was removed under reduced pressure and the solid residue taken up in a saturated $NaHCO_3$ solution. After filtration the solution was acidified with concentrated HCl and the precipitate collected by filtration. Recrystallization from isopropyl alcohol gave **7** as white crystals (88% yield; m.p 158°C (isopropyl alcohol). Analytical data were in accordance with those cited in literature[20].

* Thiaisatoic anhydrides **1** and **2** are now commercially available from SYNTHEVAL SA.

3-(ureido)thiophene-2-carboxylic acid (8)

See general procedure : "2-thiaisatoic" anhydride **1** (1g; 6mmoles), aqueous ammonia solution (excess), reaction time 15min. **8** : white crystals (82% yield ; m.p 238°C (CH_3CN, dec.)). (Found : C, 38.75; H, 3.21; N, 14.98. $C_6H_6N_2O_3S$ requires : C, 38.71; H, 3.25; N, 15.05). MS (m/z) : M^+ 186 (24), 169 ($-NH_3$, 8), 125 ($-CO_2$, 100). IR (cm^{-1}) : 3468 (NH) ; 3334, 3289, 3221 (NH_2) ; 1679 (CO) ; 1632 (CO). ^1H NMR (DMSO-d6) δ: 6.71 (broad s, 2H, NH_2); 7.67 (d, 1H, H-C=C, $^3J_{HH}$ = 5.3Hz); 7.90 (d, 1H, H-C=C, $^3J_{HH}$ = 5.3Hz); 9.28 (broad s, 1H, NH); 12.74 (broad s, 1H, COOH). ^{13}C NMR (DMSO-d6) δ: 107.6 (C=C-COOH); 122.1 (H-C=C); 131.6 (H-C=C); 146.1 (C=C-NH); 154.9 (NH-CO); 165.1 (COOH).

3-(3-methylureido)thiophene-2-carboxylic acid (9)

See general procedure : "2-thiaisatoic" anhydride **1** (1g; 6mmoles) gaseous methylamine (excess), reaction time 20 min. **9** : white crystals (51% yield ; m.p. 230°C (CH_3CN, dec.)). (Found : C, 41.81 ; H, 3.97 ; N, 13.87. $C_7H_8N_2O_3S$ requires : C, 41.99 ; H, 4.03 ; N, 13.99). MS (m/z) : M^+ 200 (25), 169 ($-NH_2CH_3$, 6), 125 ($-CO_2$, 100). IR (cm^{-1}): 3346 (NH) ; 3319 (NH) ; 1657 (CO) ; 1567. ^1H NMR (DMSO-d6) δ: 2.62 (s, 3H, NH-CH_3); 7.46 (broad s, 1H, NH-CH_3); 7.69 (d, 1H, H-C=C, $^3J_{HH}$ = 5.3Hz); 7.89 (d, 1H, H-C=C, $^3J_{HH}$ = 5.3Hz); 9.30 (broad s, 1H, NH); 12.5 (broad s, 1H, COOH). ^{13}C NMR (DMSO-d6) δ: 26.2 (CH_3); 107.1 (C=C-COOH); 121.8 (H-C=C); 131.6 (H-C=C); 146.1 (C=C-NH); 154.5 (NH-CO-NH); 165.1 (COOH).

3-(3-anilinoureido)thiophene-2-carboxylic acid (10)

See general procedure : "2-thiaisatoic" anhydride **1** (1g; 6mmoles) phenylhydrazine (0.97mL; 12mmoles), reaction time 2 hours. **10** : white crystals (67% yield; m.p 244°C (CH_3CN, dec.)). (Found : C, 52.27 ; H, 4.04 ; N, 15.27. $C_{12}H_{11}N_3O_3S$ requires : C, 51.98 ; H, 4.00 ; N, 15.15). MS (m/z) : M^+ 277 (10), 233 ($-CO_2$, 20); 169 ($-C_6H_5NHNH_2$, 18). IR (cm^{-1}): 3300 (NH) ; 3204 (NH) ; 3050 ; 1680 (CO) ; 1605 (CO). ^1H NMR (DMSO-d6) δ: 6.79 (m, 3H, HAr); 7.19 (m, 2H, HAr); 7.76 (d, 1H, H-C=C, $^3J_{HH}$ = 5.3Hz); 7.99 (d, 1H, H-C=C, $^3J_{HH}$ = 5.3Hz); 8.00 (broad s, 1H, NH); 8.69 (broad s, 1H, NH); 10.59 (broad s, 1H, NH); 13.00 (broad s, 1H, COOH). ^{13}C NMR (DMSO-d6) δ: 108.5 (C=C-COOH); 112.7 (2CAr); 119.7 (1 CAr); 121.2 (H-C=C); 129.0 (2 CAr); 132.0 (H-C=C); 145.1 (C=C-NH); 148.7 (CAr); 155.7 (NH-CO); 165.0 (COOH).

3-[3-(3-dimethylaminopropyl)ureido]thiophene-2-carboxylic acid (11)

The "2-thiaisatoic" anhydride **1** (1g; 6mmoles) was diluted in 20mL of tetrahydrofuran. 3,3-dimethylaminopropylamine (1.5mL; 6mmoles) was added in one portion to the solution. A precipitate was formed and the mixture was allowed to stand at room temperature for 30 minutes. The precipitate was filtered and washed with diethyl ether to give **11** as a white powder (87% yield; m.p 236°C). (Found : C, 48.85 ; H, 6.35 ; N, 15.70. $C_{11}H_{17}N_3O_3S$ requires : C, 48.69 ; H, 6.31 ; N, 15.49). MS (m/z) : M^+ 271 (3), 227 ($-CO_2$, 2), 169 ($-H_2N(CH_2)_3N(CH_3)_2$, 44). IR (cm^{-1}): 3287 (NH); 3233 (NH); 1696 (CO); 1645 (CO). ^1H NMR (DMSO-d6) δ: 1.83 (m, 2H, CH_2); 2.62 (s, 6H, $N(CH_3)_2$); 2.96 (m, 2H, CH_2); 3.20 (m, 2H, CH_2); 7.32 (d, 1H, H-C=C, $^3J_{HH}$ = 5.3Hz); 7.82 (d, 1H, H-C=C, $^3J_{HH}$ = 5.3z); 8.38 (broad s, 1H, NH); 10.29 (broad s, 1H, NH). ^{13}C NMR (D_2O) δ: 25.4 (CH_2); 37.2 (CH_2); 43.3 ($N(CH_3)_2$); 56.0 (CH_2); 118.0 (H-C=C); 122.1 (C=C-COOH); 129.4 (H-C=C); 141.8 (C=C-NH); 157.1 (NH-CO); 171.4 (COOH).

3-(3-phenylureido)thiophene-2-carboxylic acid (12)

See general procedure : "2-thiaisatoic" anhydride **1** (1g; 6mmoles), aniline (0.55mL; 6mmoles), reaction time 15 hours. **12** : white crystals (77% yield; m.p 248°C (CH_3CN, dec.)). (Found : C, 54.81 ; H, 3.85 ; N,

10.60. $C_{12}H_{10}N_2O_3S$ requires : C, 54.95 ; H, 3.84 ; N, 10.68). MS (m/z) : M^+ 262 (20), 218 ($-CO_2$, 63). IR (cm^{-1}): 3321 (NH) ; 1656 (CO) ; 1599. ^1H NMR (DMSO-d6) δ: 6.98 (dd, 1H, HAr); 7.28 (dd, 2H, HAr); 7.50 (d, 2H, HAr); 7.76 (d, 1H, H-C=C, $^3J_{HH}$ = 5.3Hz); 7.96 (d, 1H, H-C=C, $^3J_{HH}$ = 5.3Hz); 9.64 (broad s, 1H, NH); 9.97 (broad s, 1H, NH); 13.1 (broad s, 1H, COOH). ^{13}C NMR (DMSO-d6) δ: 108.6 (C=C-COOH); 118.6 (2 CAr); 121.9 (H-C=C); 122.3 (CAr); 128.8 (2 CAr); 131.7 (H-C=C); 139.6 (CAr); 145.1 (C=C-NH); 151.4 (NH-CO); 165.0 (COOH).

3-(2-chloroethylureido)thiophene-2-carboxylic acid (13)

0.7g (6mmoles) of 2-chloroethylamine hydrochloride were suspended in 20mL of THF. 0.83mL (6mmoles) of triethylamine were added to the suspension and the mixture was stirred for 30min. "2-thiaisatoic" anhydride **1** (1g 6mmoles) was then added and the mixture was allowed to stand at room temperature for 30min. The solvent was removed under reduced pressure and the residue was taken up in a saturated sodium hydrogenocarbonate solution. After filtration, the solution was acidified with concentrated hydrochloric acid and the precipitate was filtered. Recrystallization from acetonitrile gave **13** as white crystals (64% yield; m.p 216°C (dec.)). (Found : C, 38.70 ; H, 3.62 ; N, 11.34. $C_8H_9ClN_2O_3S$ requires : C, 38.64 ; H, 3.65 ; N, 11.26). MS (m/z) : M^+ 248 (15), 249 (M^+ +1, 2), 250 (M^+ +2, 6), 212 (-HCl, 71); 169 ($-C_2H_6ClN$, 18). IR (cm^{-1}): 3344 (NH) ; 1656 (CO). ^1H NMR (DMSO-d6) δ: 3.39 (m, 2H, $NHCH_2$); 3.62 (t, 2H, CH_2Cl); 7.69 (d, 1H, H-C=C, $^3J_{HH}$ = 5.3Hz); 7.88 (d, 1H, H-C=C, $^3J_{HH}$ = 5.3Hz); 7.98 (t, 1H, NH); 9.39 (broad s, 1H, NH); 13.0 (broad s, 1H, COOH). ^{13}C NMR (DMSO-d6) δ: 41.6 ($NHCH_2$); 44.3 (CH_2Cl); 107.9 (C=C-COOH); 122.0 (H-C=C); 131.8 (H-C=C); 145.8 (C=C-NH); 154.1 (NH-CO); 165.1 (COOH).

3-(4-morpholinocarbonylamino)thiophene-2-carboxylic acid (14)

See general procedure : "2-thiaisatoic" anhydride **1** (1g; 6mmoles), morpholine (0.52mL; 6mmoles), reaction time 1h30. **14** : white crystals (49% yield; m.p 204°C (CH_3CN, dec.)). (Found : C, 46.92 ; H, 4.72 ; N, 10.97. $C_{10}H_{12}N_2O_4S$ requires : C, 46.87 ; H, 4.72 ; N, 10.93). MS (m/z) : M^+ 256 (22), 212 ($-CO_2$, 18); 169 ($-C_4H_9NO$, 24). IR (cm^{-1}): 3129 (NH) ; 1688 (CO) ; 1648 (CO) ; 1573. ^1H NMR (DMSO-d6) δ: 3.39 (s, 4H, $N(CH_2)_2$); 3.62 (s, 4H, $O(CH_2)_2$); 7.76 (d, 1H, H-C=C, $^3J_{HH}$ = 5.3Hz); 7.86 (d, 1H, H-C=C, $^3J_{HH}$ = 5.3Hz); 9.98 (broad s, 1H, NH); 13.3 (broad s, 1H, COOH). ^{13}C NMR (DMSO-d6) δ: 43.6 ($N(CH_2)_2$); 65.8 ($O(CH_2)_2$); 108.1 (C=C-COOH); 121.3 (H-C=C); 132.2 (H-C=C); 146.2 (C=C-NH); 152.9 (NH-CO); 165.9 (COOH).

3-(benzyloxycarbonylamino)thiophene-2-carboxylic acid (15)

The "2-thiaisatoic" anhydride **1** (1g; 6mmoles) was diluted in 10mL of benzyl alcohol. The mixture was then heated at 90°C for eight hours. 80ml of a saturated sodium hydrogenocarbonate solution were added to the mixture. After 30min under stirring, the mixture was extracted twice with diethyl ether. The aqueous layer was then acidified with concentrated hydrochloric acid and the precipitate was filtered. Recrystallization from acetonitrile gave **15** as white crystals (56% yield; m.p 180°C). (Found : C, 56.52 ; H, 4.05 ; N, 5.36. $C_{13}H_{11}NO_4S$ requires : C, 56.31 ; H, 4.00 ; N, 5.05). MS (m/z) : M^+ 277 (7) ; 233 ($-CO_2$, 5). 169 ($-HOCH_2Ar$, 8). IR (cm^{-1}): 3346 (NH) ; 1738 (CO) ; 1658 (CO) ; 1571. ^1H NMR (DMSO-d6) δ: 2.06 (s, 2H, CO_2CH_2Ar); 7.38 (m, 5H, HAr); 7.73 (d, 1H, H-C=C, $^3J_{HH}$ = 5.3Hz); 7.83 (d, 1H, H-C=C, $^3J_{HH}$ = 5.3Hz); 9.68 (broad s, 1H, NH); 13.5 (broad s, 1H, COOH). ^{13}C NMR ($CDCl_3$) δ: 66.8 (CH_2); 110.0 (C=C-COOH); 120.7 (H-C=C); 128.2 (2CAr); 128.3 (CAr); 128.5 (CAr); 132.6 (H-C=C); 136.0 (CAr); 143.7 (C=C-NH); 152.1(NH-CO_2CH_2Ar); 165.0 (COOH).

3-methoxycarbonylmethylthiocarbonylamino-thiophene-2-carboxylic acid (16)

The "2-thiaisatoic" anhydride **1** (0.5g; 3mmoles) was diluted in 15mL of methyl thioglycolate. The mixture was heated under microwave irradiation (500W) for 30min. Methyl thioglycolate was then removed under reduced pressure and the residue was taken up in diethyl ether. The organic layer was then extracted three times with saturated $NaHCO_3$ solution. After acidification with concentrated hydrochloric acid, the precipitate was filtered. Recrystallization from acetonitrile gave **16** as white crystals (43% yield; m.p 164°C). (Found : C, 39.38; H, 3.32; N, 5.15. $C_9H_9NO_5S_2$ requires : C, 39.27; H, 3.30; N, 5.09). MS (m/z) : 169 (-$HSCH_2CO_2Me$, 42); . IR (cm^{-1}): 3294 (NH) ; 2900 ; 1746 (CO) ; 1703 (CO) ; 1648 (CO). ^1H NMR (DMSO-d6) δ: 3.65 (s, 3H, $CO_2\underline{CH_3}$); 3.86 (s, 2H, $\underline{CH_2}CO_2CH_3$); 7.66 (d, 1H, H-C=C, $^3J_{HH}$ = 5.3Hz); 7.83 (d, 1H, H-C=C, $^3J_{HH}$ = 5.3Hz); 10.4 (broad s, 1H, NH); 12.5 (broad s, 1H, COOH). ^{13}C NMR (DMSO-d6) δ: 31.8 ($CO_2\underline{CH_3}$); 52.5 ($\underline{CH_2}CO_2CH_3$); 112.4 (C=$\underline{C}$-COOH); 122.0 (H-$\underline{C}$=C); 132.6 (H-$\underline{C}$=C); 142.2 (C=$\underline{C}$-NH); 163.6 ($\underline{CO_2}CH_3$); 164.9 (NH-$\underline{CO}$); 169.2 ($\underline{COOH}$).

1-(2-carboxy-thiophene-3-ylcarbamoyl)pyrrolidine-2-carboxylic acid methyl ester (17)

Pyrrolidine-2-carboxylic acid methylester hydrochloride (1.99g; 12mmoles) was diluted in 20 mL of dimethylformamide. Triethylamine (1.68mL; 12mmoles) was added in the solution. After 5 minutes, the precipitate of triethylammonium chloride was filtered and the "2-thiaisatoic" anhydride **1** (2g, 12mmoles) was added to the solution. The mixture was then allowed to stand at room temperature for 2 hours. The solvent was then removed under reduced pressure and the product was taken up in a saturated sodium hydrogenocarbonate solution. After filtration, the solution was acidified with concentrated hydrochloric acid and the precipitate was filtered and washed with water. Recrystallization from diethyl ether/petroleum ether gave **17** as white crystals (71% yield; m.p 180°C). (Found : C, 48.51 ; H, 4.81 ; N, 9.52. $C_{12}H_{14}N_2O_5S$ requires : C, 48.32 ; H, 4.73 ; N, 9.39). MS (m/z) : M^+ 298 (12), 169 (-$C_6H_{11}NO_2$, 11). IR (cm^{-1}): 3232 (NH) ; 2963 ; 1747 (CO) ; 1669 (CO) ; 1632 (CO). ^1H NMR ($CDCl_3$) δ: 2.12 (m, 3H); 2.28 (m, 1H); 3.57 (m, 1H) 3.77 (s, 3H, CH_3); 3.77 (m, 1H); 4.58 (m, 1H); 7.48 (d, 1H, H-C=C, $^3J_{HH}$ = 5.3Hz); 8.02 (d, 1H, H-C=C, $^3J_{HH}$ = 5.3Hz); 9.73 (broad s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 24.4 ($\underline{CH_2}$) ; 29.8 ($\underline{CH_2}$) ; 46.1 ($\underline{CH_2}$) 52.4 ($CO_2\underline{CH_3}$) ; 58.9 ($\underline{CH}$) ; 107.5 (C=$\underline{C}$-COOH); 121.7 (H-$\underline{C}$=C) ; 132.6 (H-$\underline{C}$=C); 147.2 (C=$\underline{C}$-NH) ; 152.5 (NH-$\underline{CO}$); 168.1 ($\underline{COOH}$) ; 173.3 ($\underline{CO_2}CH_3$).

2-(ethoxycarbonylamino)thiophene-3-carboxylic acid (18)

The "3-thiaisatoic" anhydride **2** (1g; 6mmoles) was diluted in 20mL of ethanol. The mixture was then refluxed for two hours. The solvent was removed under reduced pressure and the solid residue was crystallized from acetonitrile to give **18** as white crystals (80% yield; m.p 190°C). (Found : C, 44.58; H, 4.18; N, 6.68. $C_8H_9NO_4S$ requires : C, 44.65; H, 4.21; N, 6.51). MS (m/z) : M^+ 215 (47), 169 (-C_2H_5OH, 8), 125 (-CO_2, 100). IR (cm^{-1}): 3320 (NH); 2600 (OH); 1720 (CO); 1640 (CO). ^1H NMR (DMSO-d6) δ: 1.26 (t, 3H, $CO_2CH_2\underline{CH_3}$); 4.21 (q, 2H, $CO_2\underline{CH_2}CH_3$); 6.92 (d, 1H, H-C=C); 7.10 (d, 1H, H-C=C); 10.29 (broad s, 1H, NH); 13.0 (broad s, 1H, COOH). ^{13}C NMR (DMSO-d6) δ: 14.2 ($CO_2CH_2\underline{CH_3}$); 62.2 ($CO_2\underline{CH_2}CH_3$); 112.5 (C=$\underline{C}$-COOH); 115.5 (H-$\underline{C}$=C); 124.6 (H-$\underline{C}$=C); 149.5 (C=$\underline{C}$-NH); 152.3 (NH-$\underline{CO_2}CH_2CH_3$); 166.4 ($\underline{COOH}$).

2-(ureido)thiophene-3-carboxylic acid (19)

The procedure was the same as for compound **8** starting from **2** (1g; 6mmoles) instead of **1**. (65% yield; m.p 242°C dec. (Lit[4].184°C dec.)). MS (m/z) : M^+ 186 (23), 169 (-NH_3, 13), 125 (-CO_2, 100). IR (cm^{-1}): 3620 (NH); 3300 (NH_2); 2500 (OH); 1660 (CO); 1640 (CO). ^1H NMR (DMSO-d6) δ: 6.71 (d, 1H, H-C=C, $^3J_{HH}$ = 6Hz); 6.98 (broad s, 2H, NH_2); 7.01 (d, 1H, H-C=C, $^3J_{HH}$ = 6Hz); 10.1 (broad s, 1H, NH); 12.61 (broad s,

1H, COOH). ^{13}C NMR (DMSO-d6) δ: 110.1 (C=C-COOH); 114.4 (H-C=C); 124.0 (H-C=C); 151.3 (C=C-NH); 154.4 (NH-CO); 166.1 (COOH).

2-(3-methylureido)thiophene-3-carboxylic acid (20)

The procedure was the same as for compound **9** : the methylamine was aqueous instead of gaseous and the reaction time was 4 hours (51% yield; m.p 242°C (dec.)). (Found : C, 41.75; H, 4.02; N, 13.72. $C_7H_8N_2O_3S$ requires : C, 41.99; H, 4.03; N, 13.99). MS (m/z) : M^+ 200 (27), 169 (-NH_2CH_3, 8), 125 (-CO_2, 100). IR (cm^{-1}): 3304 (NH); 2910 (OH); 1657 (CO); 1535 (CO). ^{1}H NMR (DMSO-d6) δ: 2.67 (s, 3H, NH-CH_3); 6.67 (d, 1H, H-C=C, $^3J_{HH}$ = 6Hz); 7.02 (d, 1H, H-C=C, $^3J_{HH}$ = 6Hz); 7.63 (broad s, 1H, NH-CH_3); 10.12 (broad s, 1H, NH); 12.5 (broad s, 1H, COOH). ^{13}C NMR (DMSO-d6) δ: 26.2 (CH_3); 109.9 (C=C-COOH); 114.0 (H-C=C); 123.9 (H-C=C); 151.5 (C=C-NH); 154.2 (NH-CO-NH); 166.1 (COOH).

2-(3-anilino-ureido)thiophene-3-carboxylic acid (21)

The procedure was the same as for compound **10** : **2** replaces **1** and the reaction time was 4 hours (73% yield; m.p ›260°C). (Found : C, 52.12; H, 3.92; N, 15.27. $C_{12}H_{11}N_3O_3S$ requires: C, 51.98; H, 4.00; N, 15.15). MS (m/z) : M^+ 277 (56), 233 (-CO_2, 13); 169 (-$C_6H_5NHNH_2$, 13). IR (cm^{-1}): 3349 (NH); 3206 (NH); 3090 (NH); 2906 (OH); 1708 (CO); 1644 (CO). ^{1}H NMR (DMSO-d6) δ: 6.79 (m, 3H, HAr); 6.80 (d, 1H, H-C=C, $^3J_{HH}$ = 5.8Hz); 7.04 (d, 1H, H-C=C, $^3J_{HH}$ = 5.8Hz); 7.19 (dd, 2H, HAr); 7.94 (broad s, 1H, NH); 8.97 (broad s, 1H, NH); 11.07 (broad s, 1H, NH); 12.53 (broad s, 1H, COOH). ^{13}C NMR (DMSO-d6) δ: 111.2 (C=C-COOH); 112.8 (CAr); 114.8 (H-C=C); 119.9 (2 CAr); 124.1 (H-C=C); 129.0 (2 CAr); 148.4 (CAr); 150.3 (C=C-NH); 155.5 (NH-CO); 166.1 (COOH).

2-[3-(3-dimethylaminopropyl)ureido]thiophene-3-carboxylic acid (22)

The procedure was the same as for compound **11**: **2** replaces **1** (80% yield; m.p 234°C). (Found : C, 48.89 ; H, 6.21 ; N,15.50. $C_{11}H_{17}N_3O_3S$ requires : C, 48.69; H, 6.31; N, 15.49). MS (m/z) : M^+ 271 (38), 227 (-CO_2, 35), 169 (-$H_2N(CH_2)_3N(CH_3)_2$, 26). IR (cm^{-1}): 3411 (NH); 3325 (NH); 2960 (OH); 1670 (CO); 1637 (CO). ^{1}H NMR (D_2O) δ: 1.78 (m, 2H, CH_2); 2.56 (s, 6H, $N(CH_3)_2$); 2.86 (m, 2H, CH_2); 3.21 (m, 2H, CH_2); 6.56 (d, 1H, H-C=C, $^3J_{HH}$ = 5.6Hz); 7.02 (d, 1H, H-C=C, $^3J_{HH}$ = 5.6Hz); 9.17 (broad s, 1H, NH); 11.22 (broad s, 1H, NH). ^{13}C NMR (D_2O) δ: 25.4 (CH_2); 37.3 (CH_2); 43.3 ($N(CH_3)_2$); 55.9 (CH_2); 114.4 (H-C=C); 118.3 (C=C-COOH); 126.4 (H-C=C); 147.7 (C=C-NH); 156.3 (NH-CO); 172.9 (COOH).

2-(3-phenylureido)thiophene-3-carboxylic acid (23)

See general procedure : "3-thiaisatoic" anhydride **2** (1g; 6mmoles), aniline (0.55mL; 6mmoles), reaction time 24 hours. The acidified solution was extracted with ethyl acetate. **23** : white crystals (40% yield; m.p 256°C (CH_3CN, dec.)). (Found : C, 54.59; H, 3.71; N, 10.89. $C_{12}H_{10}N_2O_3S$ requires : C, 54.95; H, 3.84; N, 10.68). MS (m/z) : M^+ 262 (43), 218 (-CO_2, 15). IR (cm^{-1}): 3332 (NH); 3291 (NH); 2560 (OH); 1650 (CO); 1598 (CO). ^{1}H NMR (DMSO-d6) δ: 6.80 (d, 1H, H-C=C, $^3J_{HH}$ = 5.8Hz); 7.01 (dd, 1H, HAr); 7.08 (d, 1H, H-C=C, $^3J_{HH}$ = 5.8Hz); 7.29 (dd, 2H, HAr); 7.49 (d, 2H, HAr); 10.08 (broad s, 1H, NH); 10.47 (broad s, 1H, NH); 12.5 (broad s, 1H, COOH). ^{13}C NMR (DMSO-d6) δ: 111.1 (C=C-COOH); 114.9 (H-C=C); 118.4 (2CAr); 122.5 (CAr); 124.1 (H-C=C); 128.9 (2CAr); 139.1 (CAr); 150.1 (C=C-NH); 151.2 (NH-CO); 166.1 (COOH).

2-(3,3-dimethylureido)thiophene-3-carboxylic acid (24)

See general procedure : "3-thiaisatoic" anhydride **2** (1g; 6mmoles) aqueous solution of dimethylamine (excess), reaction time 4 hours. **24** white crystals (78% yield; m.p 225°C (CH_3CN)). (Found : C, 44.75; H, 4.83; N, 12.98. $C_8H_{10}N_2O_3S$ requires : C, 44.85; H, 4.70; N, 13.08). MS (m/z) : M^+ 214 (16), 169 (-$NH(CH_3)_2$, 3). IR (cm^{-1}): 3390 (NH); 2936 (OH); 1660 (CO); 1549 (CO). ^1H NMR (DMSO-d6) δ: 2.96 (s, 6H, $N(CH_3)_2$); 6.76 (d, 1H, H-C=C, $^3J_{HH}$ = 6Hz); 7.06 (d, 1H, H-C=C, $^3J_{HH}$ = 6Hz); 10.78 (broad s, 1H, NH); 12.5 (broad s, 1H, COOH). ^{13}C NMR (DMSO-d6) δ: 35.7 ($N(CH_3)_2$); 110.7 (C=C-COOH); 114.6 (H-C=C); 123.8 (H-C=C); 151.7 (C=C-NH); 153.2 (NH-CO); 167.2 (COOH).

2-(butoxycarbonylamino)thiophene-3-carboxylic acid (25)

The "3-thiaisatoic" anhydride **2** (1g; 6mmoles) was diluted in 20mL of butanol-1. The mixture was then refluxed for two hours. The solvent was removed under reduced pressure and the solid residue was washed with diethyl ether to give **25** as white crystals (82% yield; m.p 146°C). (Found : C, 49.18; H, 5.37; N, 5.97. $C_{10}H_{13}NO_4S$ requires : C, 49.37; H, 5.38; N, 5.76). MS (m/z) : M^+ 243 (26). IR (cm^{-1}): 3328 (NH); 2961 (OH); 1727 (CO); 1641 (CO). ^1H NMR ($CDCl_3$) δ: 0.96 (t, 3H, $(CH_2)_3CH_3$); 1.45 (m, 2H, CH_2); 1.71 (m, 2H, CH_2); 4.26 (m, 2H, CH_2); 6.71 (d, 1H, H-C=C); 7.22 (d, 1H, H-C=C); 9.99 (broad s, 1H, NH); 11.5 (broad s, 1H, COOH). ^{13}C NMR ($CDCl_3$) δ: 13.7 (CH_3); 19 (CH_2); 30.8 (CH_2); 66.6 (CH_2); 110.8 (C=C-COOH); 115.2 (H-C=C); 124.7 (H-C=C); 152.7 (C=C-NH); 153.1 (NH-$CO_2(CH_2)_3CH_3$); 170.2 (COOH).

2-(tert-butoxycarbonylamino)thiophene-3-carboxylic acid (26)

The procedure was the same as for compound **25** : *tert*-butanol replaces butanol-1 (80% yield; m.p 186°C). (Found : C, 49.21; H, 5.48; N, 5.96. $C_{10}H_{13}NO_4S$ requires : C, 49.37; H, 5.38; N, 5.76). MS (m/z) : M^+ 243 (13), 187 (- $C(CH_3)_3$, 30). IR (cm^{-1}): 3320 (NH); 2980 (OH); 1720 (CO); 1660 (CO). ^1H NMR (DMSO-d6) δ: 1.48 (s, 9H, $C(CH_3)_3$); 6.90 (d, 1H, H-C=C); 7.08 (d, 1H, H-C=C); 10.16 (broad s, 1H, NH); 13.04 (broad s, 1H, COOH). ^{13}C NMR (DMSO-d6) δ: 27.8 ($CO_2C(CH_3)_3$); 81.9 ($CO_2C(CH_3)_3$); 112.1 (C=C-COOH); 115.3 (H-C=C); 124.5 (H-C=C); 149.6 (C=C-NH); 151.3 (NH-$CO_2C(CH_3)_3$); 166.4 (COOH).

2-(methoxycarbonylmethylthiocarbonylamino)thiophene-3-carboxylic acid (27)

The "3-thiaisatoic" anhydride **2** (1g; 6mmoles) was diluted in 20mL of tetrahydrofuran in the presence of triethylamine. After addition under stirring of methyl thioglycolate (0.54mL; 6mmoles), the mixture was refluxed for ten hours. The solvent was then removed under reduced pressure and the product was taken up in water. The aqueous layer was acidified with concentrated hydrochloric acid and extracted with ethyl acetate. After evaporation, the compound was crystallized from acetonitrile to give **27** as white crystals (25% yield; m.p 160°C). (Found : C, 39.45; H, 3.34; N, 5.33. $C_9H_9NO_5S_2$ requires : C, 39.27; H, 3.29; N, 5.09). MS (m/z) : M^+ 275 (3), 169 (-$HSCH_2CO_2Me$, 42). IR (cm^{-1}): 3213 (NH); 2934 (OH); 1709 (CO); 1679 (CO); 1655 (CO). ^1H NMR (DMSO-d6) δ: 3.67 (s, 3H, CO_2CH_3); 3.93 (s, 2H, $CH_2CO_2CH_3$); 7.01 (d, 1H, H-C=C, $^3J_{HH}$ = 6Hz); 7.12 (d, 1H, H-C=C, $^3J_{HH}$ = 6Hz); 11.3 (broad s, 1H, NH); 13.1 (broad s, 1H, COOH). ^{13}C NMR (DMSO-d6) δ: 31.8 ($CH_2CO_2CH_3$); 52.5 (CO_2CH_3); 114.2 (C=C-COOH); 116.6 (H-C=C); 124.4 (H-C=C); 146.9 (C=C-NH); 163.8 (CO_2CH_3); 165.9 (NH-CO); 169.0 (COOH).

2-(3-methoxycarbonylmethyl-ureido)thiophene-3-carboxylic acid (28)

The procedure was the same as for compound **17** starting from glycine methylester hydrochloride (0.76g; 6mmoles), triethylamine (0.90mL; 1.1eq.) and the "3-thiaisatoic" anhydride **2** (1g; 6mmoles). The precipitate

was filtered and washed with diethyl ether to give **28** as white crystals (60% yield; m.p 234°C). (Found : C, 41.76; H, 3.89 ; N,10.90. $C_9H_{10}N_2O_5S$ requires : C, 41.86; H, 3.90; N, 10.85). MS (m/z): M^+ 258 (10), 169 (-$H_2NCH_2CO_2Me$, 14). IR (cm^{-1}): 3211 (NH); 2960 (OH); 1723 (CO); 1682 (CO); 1662 (CO). ^1H NMR (DMSO-d6) δ: 3.64 (s, 3H, $CO_2\underline{CH_3}$); 3.91 (s, 2H, $\underline{CH_2}CO_2CH_3$); 6.75 (d, 1H, H-C=C, $^3J_{HH}$ = 6Hz); 7.04 (d, 1H, H-C=C, $^3J_{HH}$ = 6Hz); 8.37 (broad s, 1H, NH); 10.32 (broad s, 1H, NH); 12.70 (broad s, 1H, COOH). ^{13}C NMR (DMSO-d6) δ: 41.3 ($CO_2\underline{CH_3}$); 51.8 ($\underline{CH_2}CO_2CH_3$); 110.6 (C=$\underline{C}$-COOH); 114.5 (H-$\underline{C}$=C); 124.1 (H-$\underline{C}$=C); 150.7 (C=$\underline{C}$-NH); 153.9 ($\underline{C}O_2CH_3$); 166.0 (NH-$\underline{C}$O); 170.8 ($\underline{C}$OOH).

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