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First direct synthesis of pyrrolo[1,2-*a*]thieno[3,2-*e*]- or [2,3-*e*][1,4]diazepines, thiophene analogues of pyrrolo[2,1-*c*][1,4]benzodiazepines.

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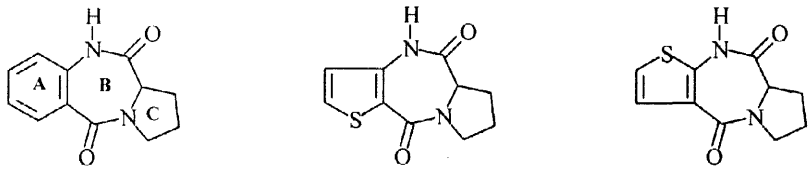
Abstract

Condensation of 2-thiaisatoic anhydride **1** or 3-thiasatoic anhydride **2** with proline **4a** or hydroxyproline **4b** led to the pyrrolo[1,2-*a*]thieno[3,2-*e*]- and [2,3-*e*][1,4]diazepine derivatives **5**, **6**, **10** and **11**.

Keywords: pyrrolo[2,1-c][1,4]benzodiazepines/thiaisatoic anhydrides/pyrrolo[1,2-a]thieno[3,2-e]- or [2,3-e][1,4]diazepines

The pyrrolo[2,1-*c*][1,4]benzodiazepine ring system PBD's (Scheme 1) is found in a number of natural products that recognize and bind to specific sequences of DNA. Such compounds have potential as therapeutic agents in the treatment of cancer[1]: consequently this area has recently been the subject of an exhaustive review[2] and is always a subject studied by several authors[3,4].

Scheme 1



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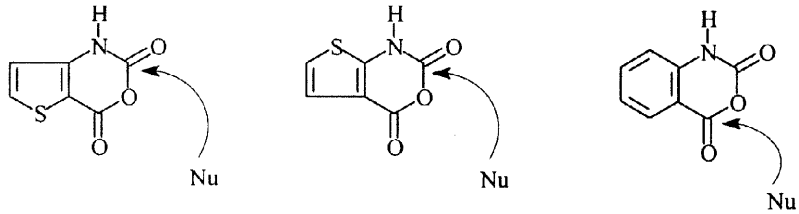
Owing to the interest taken in the synthesis of these tricyclic systems, we decided to synthesize their thiophene analogues PTD's (Scheme 1), compounds not or less[5] described in the literature up to now.

We recently reported the synthesis on broad scale of 2-thiaisatoic **1** and 3-thiaisatoic **2** anhydrides[6]. Moreover, we studied the reactivity of these two compounds towards various nucleophiles and came up to the conclusion that anhydrides **1** and **2** react in an opposite way to their benzene analogue, isatoic anhydride **3** (Scheme 2).

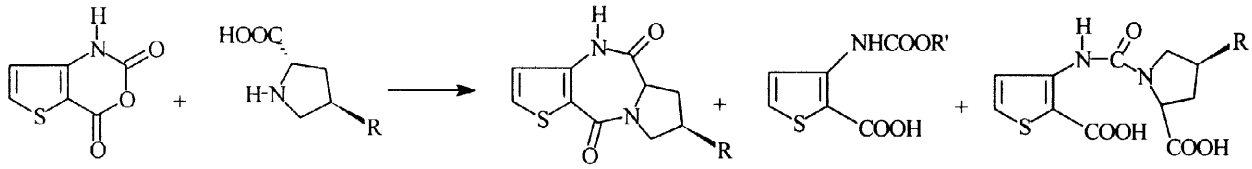
Scheme 2



1 **2** **3**

We first developed the condensation of 2-thiaisatoic anhydride **1** with L-proline **4a** or hydroxyproline **4b** in various conditions (Scheme 3 ; Table 1). According to our first results[6], it appeared that in normal conditions such as in DMF, 1,4-dioxane or THF (entries 1 and 2), only the diacids **8** or **9** resulting from the aminoacid attack at the C2 of anhydride **1** were formed quantitatively.

Scheme 3



1 **4a** R = H **4b** R = OH **5** R = H **6** R = OH **7** **8** R = H **9** R = OH

Table 1 : Condensation of anhydride **1** with proline **4a** in various conditions.

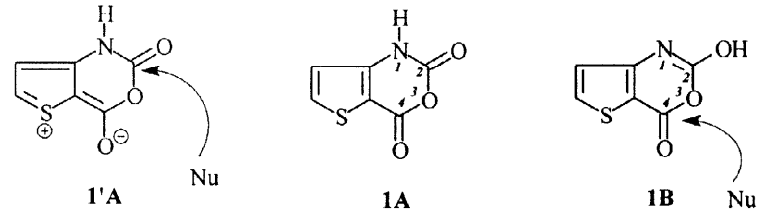
Entry	Solvent	**1**[a] (%)	**5**[a] (%)	**8**[a] (%)	**7**[a] (%)	Global yield[b] (%)
1	DMF or 1,4-dioxane			100		70
2	THF	50		50		40
3	Methanol		68	4	28	83
4	Ethanol		54	8	38	74
5	*tert*-butanol		55	45		64
6	1,4-dioxane/water (1/1)		92	8		81

a - Relative percentages calculated by ^{1}H NMR (%)**1**+(%)**5**+(%)**8**+(%)**7** = 100. b - Crude isolated product.

However in varying the solvent conditions, we highlighted that PTD **5** could be formed in various proportion in methanol (entry 3), ethanol (entry 4) or *tert*-butanol (entry 5). The use of these alcohols led also to the unavoidable formation of carbamate **7** resulting from the alcoholize of anhydride **1**. Finally, after numerous attempts, we found that the use of a mixture of 1,4-dioxane/water (1/1) was able to completely reverse the carbonyl reactivity (entry 6) of **1** allowing the exclusive formation of PTD **5**[7].

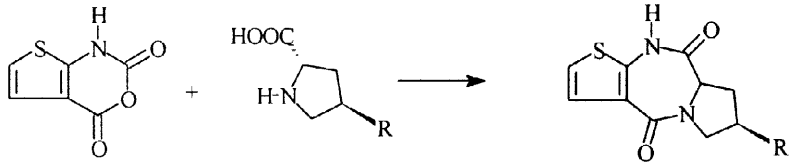
A reasonable explanation for this reverse reactivity could be the following: in protic solvents such as various alcohols or water, the mesomeric form **1B** of the anhydride (scheme 4) could be favoured leading to a preferential attack on the carbonyl in position 4, while in aprotic solvents the canonical form **1'A** predominates.

Scheme 4



We generalized this reaction with condensation of 3-thiaisatoic anhydride **2** with L-proline **4a** or hydroxyproline **4b** (Scheme 5), due to the same phenomenom we obtained similar results.

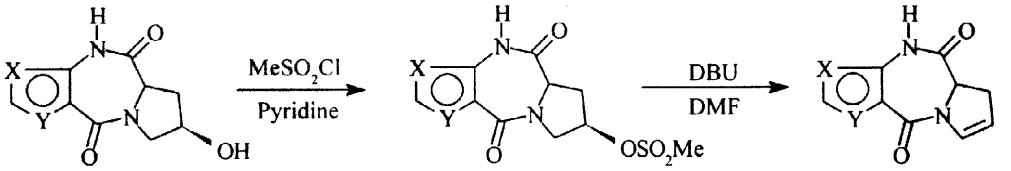
Scheme 5



Thus, after heating one hour in a mixture of 1,4-dioxane/water (1/1), the pyrrolo[1,2-*a*]thieno[2,3-*e*][1,4]diazepines **10**[5] or **11** were isolated with 55% and 35% yields respectively by washing with diethyl ether for compound **10**, by recrystallization from water for diazepine **11**.

Further, the mesylates **12** and **13** were synthezised at room temperature with 75% and 70% yields respectively (Scheme 6). After heating in dimethylformamide (DMF) in presence of 1,8-diazabicyclo[5.4.0]undecene (DBU), we isolated the corresponding alkenes **14** and **15**.

Scheme 6



6 X = C Y = S
11 X = S Y = C

12 X = C Y = S
13 X = S Y = C

14 X = C Y = S
15 X = S Y = C

In conclusion, the better knowledge of the reactivity of thiaisatoic anhydrides will allow to develop the synthesis of PTD's in the light of the chemistry described for PDB's and for instance, the synthesis of derivatives bearing the diazepine imine double bond.

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[7] A typical experiment is as follows for **5**: The mixture of anhydride **1** (1g; 6 mmol) and proline **4a** (0.69g; 6 mmol) was heating under classical conditions in 50 mL of dioxane/water (1/1) for one hour. The solvent was then removed under reduced pressure and the residue was taken up in a saturated solution of sodium hydrogenocarbonate. The precipitate of **5** was filtered and recrystallized from isopropyl alcohol. Yield: 70%. Mp: 248°C. [α]D = +173° (c = 1.3 in methanol). IR (KBr) 3200, 1702, 1684, 1632 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 1.96-2.03 (m, 2H, CH_2); 2.10 (m, 1H, CH_2); 2.80 (m, 1H, CH_2); 3.61-3.75 (m, 2H, CH_2); 4.16 (dd, 1H, CH_2-CH-CO); 6.81 (d, 1H, H-C=C, J=5.2Hz); 7.48 (d, 1H, H-C=C, J=5.2Hz); 9.50 (broad s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 23.8; 26.4; 47.2; 58.1; 121.5; 123.5; 130.7; 136.9; 161.6; 169.5; MS (m/z) 222 (M^+); Anal. *Calcd* for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.53; N, 12.60. *Found* C, 53.72; H, 4.56; N, 12.36.