JOC*Note*

Reactivity Study of 1*H*-Thieno[3,2-*d*][1,3]oxazine-2,4-dione toward the Synthesis of Bicyclic 3,4-Dihydro-1*H*-thieno[3,2-*e*][1,4]diazepine-2,5-dione Analogues

Yann Brouillette, Vincent Lisowski,* Pierre Fulcrand, and Jean Martinez

Laboratoire des Aminoacides, Peptides et Protéines (LAPP), CNRS UMR 5810, UMI-UMII, UFR des Sciences Pharmaceutiques et Biologiques, 15 Avenue Charles Flahault, 34093 Montpellier Cedex 5, France

vincent.lisowski@univ-montp1.fr

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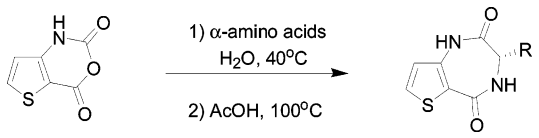

A series of 10 optically pure 3,4-dihydro-1*H*-thieno[3,2-*e*]-[1,4]diazepine-2,5-dione derivatives has been synthesized in 41−75% yields on treatment of 1*H*-thieno[3,2-*d*][1,3]oxazine-2,4-dione with different natural α-amino acids.

3,4-Dihydrobenzo[1,4]diazepine-2,5-diones are known as potential antitumor compounds,[1−4] antiamebics,[5] antithrombotics,[6] bactericides,[7] and herbicides.[8] 3,4-Dihydro[1,4]diazepine-2,5-diones fused with a heterocycle such as imidazole,[9−14] indole,[15] pyrrole,[16] pyridine,[17] isothiazole,[18] isoselenoazole,[18] quinoline,[19] furan,[16] benzothiophene,[20] or pyridothiophene[21] have been described in the literature. Although the thiophene ring is considered as a bioisoster of the benzene ring, the synthesis and chemistry of thiophene analogues of 3,4-dihydrobenzo[1,4]-diazepine-2,5-diones have been less studied. Nevertheless, the thieno[1,4]diazepine moiety is found in clotiazepam (Figure 1), an orally active anxiolytic and tenxiolytic drug.[22,23] Tricyclic structures derived from the later are further described[24−26] and include etizolam (Figure 1), an anticonvulsing and muscle relaxing agent,[27,28] and Y-24180 (Figure 1), a specific antagonist of platelet activating factor.[29,30]

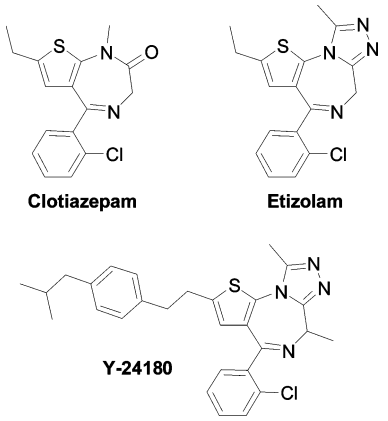

FIGURE 1. Representative examples of bioactive thienodiazepines.

While synthetic routes to bicyclic thieno[2,3-*e*][1,4]diazepine have been described,[31,32] mainly from (2-aminothiophen-3-yl)-

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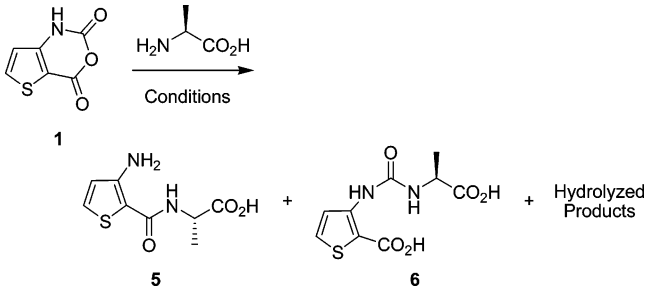
SCHEME 1. Synthesis of Amide 5



phenylmethanone intermediates,[33−35] access to the isomeric thieno[3,2-*e*][1,4]diazepine is a trickier chemical challenge. Few examples of bicyclic thieno[3,2-*e*][1,4]diazepine were prepared from (3-aminothiophen-2-yl)phenylmethanone intermediates but provided compounds of limited diversity.[36,37] Herein, we describe a general synthetic pathway to 3,4-dihydrothieno [3,2-*e*][1,4]diazepine-2,5-dione, a valuable scaffold in medicinal chemistry. To our knowledge, only one example of a bicyclic thieno[3,2-*e*][1,4]diazepine-2,5-dione derivative has been described and was synthesized on solid support in a five-step process from a resin-bound aldehyde.[17] In light of their significance as drug candidates, we propose an efficient methodology to obtain 3,4-dihydrothieno[3,2-*e*][1,4]diazepine-2,5-dione analogues by simple condensation of 1*H*-thieno [3,2-*d*][1,3]oxazine-2,4-dione (also known as thiaisatoic anhydride **1**) with various α-amino acids.

The reactivity of such thiaisatoic anhydride **1** was investigated toward various nucleophiles such as amines[38] and alcohols.[39] In an opposite way to isatoic anhydride,[40] its benzene analogue, the nucleophilic attack only proceeded on the carbonyl group of the carbamate function and not on the carboxylic carbonyl, leading respectively to ureido acids and carbamate derivatives. However, the synthesis of pyrrolothienodiazepines demonstrated that in the particular cases of proline and hydroxyproline, the nucleophilic attack can favorably be oriented toward the carboxylic carbonyl of the oxazinedione **1**.[41,42] The latest method describing condensation of thiaisatoic anhydride **1** with proline analogues, in a mixture of dioxane−water (1:1) at 100 °C for 1 h, is not suitable when acyclic α-amino acids were used. When L-alanine (Ala) was reacted under these conditions (entry a, Table 1), only amide **5** and urea **6** were recovered in equal amounts along with hydrolyzed products (Scheme 1). Partial hydrolysis of thiaisatoic anhydride **1** led to unstable *β*-amino acid **2**, which further reacted with another anhydride **1** to mainly form dimer **3** and amide **4** after decarboxylation, which were identified by MS and ^{1}H and ^{13}C NMR spectroscopy (Figure 2).

TABLE 1. Nucleophilic Opening Conditions of Thiaisatoic Anhydride 1

entry	solvent	*T* (°C)	time (h)	Ala (mol %)	**1**[a] (%)	**5**[a] (%)	**6**[a] (%)	**HP**[a,b] (%)
a	dioxane−H_2O (1:1)	100	2	150	0	21	29	50
b	dioxane−H_2O (1:1)	40	72	150	21	17	23	39
c	dioxane	100	14	150	59	0	41	0
d	dioxane	40	14	150	77	0	23	0
e	H_2O	100	4	150	0	0	0	100
f	H_2O	40	72	150	0	35	5	60
g	H_2O	40	40	500	0	75	12	13
h	H_2O	40	18	1000	0	75	15	10
i	H_2O−Et_3N (1:1)	rt	0.1	150	0	0	100	0
j	H_2O−AcOH (1:1)	40	36	150	100	0	0	0

[a] Yield determined by reversed-phase HPLC with monitoring at 214 nm. [b] Hydrolyzed products.

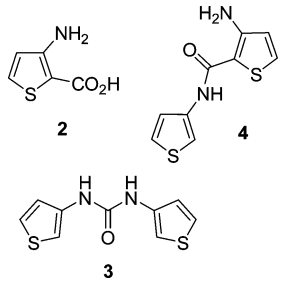


FIGURE 2. Major hydrolyzed products obtained from thiaisatoic anhydride **1**.

Obtention of amide **5** suggested a two-step process to form bicyclic thienodiazepinediones after optimization of the chemoselective nucleophilic attack conditions and cyclization. Amounts of hydrolyzed adducts in dioxane−water (1:1) could be reduced when the temperature was lowered to 40 °C. However, under these conditions, there was still no selectivity for the nucleophilic attack (entry b, Table 1). Influence of the aprotic solvent for the ring opening was confirmed when the reaction was performed only in dioxane at different temperatures (entries c and d, Table 1) because only the urea **6** and the starting material **1** were recovered. Even if a previous study described the synthesis of a library of 1180 ureido acids in aqueous media from an excess of various commercial amines,[38] we focused on a strategy in protic conditions using water as solvent to improve the amide **5**/urea **6** ratio. Thermal monitoring of the reaction showed that quantitative hydrolysis of thiaisatoic anhydride **1** occurred at temperatures higher than 60 °C (entry e, Table 1). Nucleophilic attack of Ala on thiaisatoic anhydride **1** was observed in an amide **5**/urea **6** ratio of 7:1 when heating was reduced to 40 °C in water. In this case, the reaction proceeded with slow kinetics (72 h), leading to the formation of great amounts of hydrolyzed products (entry f, Table 1). To favor the nucleophilic attack of Ala over water, the concentration of Ala was varied (entries g and h, Table 1). Finally, optimal conditions to synthesize amide **5** were found at 40 °C in a 1.0 M aqueous solution of amino acid (1000 mol %).

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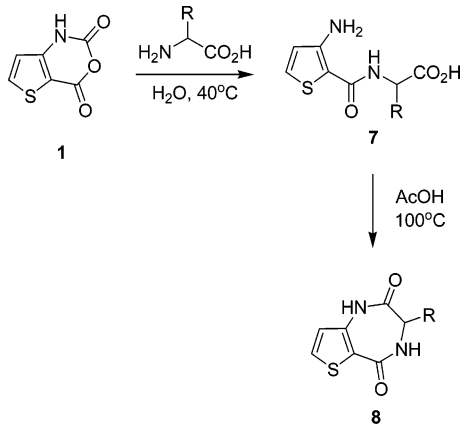
SCHEME 2. Synthesis of 3,4-Dihydro-1*H*-thieno[3,2-*e*][1,4]diazepine-2,5-dione Analogues



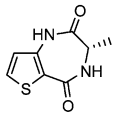
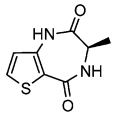
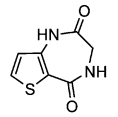
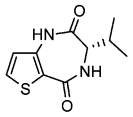
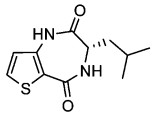
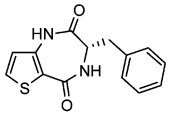
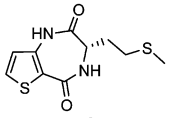
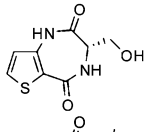
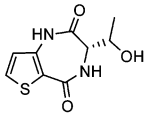
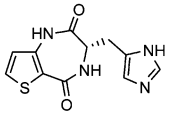
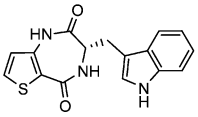
To explain this difference of reactivity in water and dioxane, the result reported in Table 1 (entry i) appears to be crucial because the use of triethylamine in water led to the unique formation of ureidoacid **6**. This result demonstrates that the basicity of the reaction mixture has a great importance in the course of the reaction. The pK_a of α-amino acids in dioxane and water could be different enough to permit the reaction to occur in different ways. One explanation could be the possible formation of an isocyanate intermediate in basic conditions (dioxane) directing the nucleophilic attack toward the formation of the ureido acid **6**. In less basic conditions (water), the isocyanate could not be predominantly formed and the attack would occur mainly on the other carbonyl, giving the amide **5**. The results published on the reactivity of isatoic anhydride defend this hypothesis.[43]

In the next step, 3,4-dihydro-3-methyl-1*H*-thieno[3,2-*e*][1,4]-diazepine-2,5-dione **8a** (Scheme 2) was synthesized by cyclization of amide **5** at a slow rate (120 h) in water at 100 °C. A more expedient procedure involving simple evaporation of water after amide **5** formation and heating in AcOH at 100 °C afforded the reaction to be complete within 2 h. Pure thienodiazepinedione **8a** (61% yield from thiaisatoic anhydride **1**) was obtained after extraction from water with EtOAc, evaporation of the volatile material, and trituration in Et_2O. The absence of racemization involved in the methodology was ascertained by the comparison of the optical rotation of thienodiazepinedione **8a** ($[\alpha]^{20}_D = 260$) and its enantiomer **8b** ($[\alpha]^{20}_D = -260$), and evaluation of the enantiomeric excess (>99%) in each synthesis by chiral HPLC.

To validate the method, natural amino acids bearing alkyl branched (Val, Leu), aromatic (Phe), sulfur-containing (Met), alcohol-containing (Ser, Thr), and heterocyclic (His, Trp) side chains were examined to provide a diverse series of thienodiazepinediones **8** in 41−75% yields (Table 2). Amide formation was the limiting step when longer reaction times were needed for the amino acids owning a bulky side chain (72 h). Histidine reacted on both sites of thiaisatoic anhydride **1** in a rapid manner (8 h), creating the corresponding amide and urea in 1:1 ratio. Lowering the temperature to 0 °C did not improve the His selectivity of attack. It was observed that in a mixture of water and base Ala instantly delivered urea **6** as the sole product (entry i, Table 1). Attempts to perform the corresponding nucleophilic reaction with Asp did not give the corresponding thienodiazepinedione as indicated by the complete recovery of starting material. The acidic conditions generated by the carboxylic acid functionality present on Asp side chain enabled the nucleophilic attack of the amino acid to take part. In the same way, mixtures of water and acid prevented any nucleophilic attack of Ala to take part on thiaisatoic anhydride **1** as observed by the complete recovery of the starting material (entry j, Table 1).

In conclusion, we have developed a straightforward inexpensive method for making 3,4-dihydro-thieno[3,2-*e*][1,4]-diazepine-2,5-dione analogues in 41−75% yields by condensation of thiaisatoic anhydride **1** with various α-amino acids, in a two-step, one-flask process. The potential of this protocol

TABLE 2. Synthesis of 3,4-Dihydro-1*H*-thieno[3,2-*e*][1,4]diazepine-2,5-dione Analogues 8a−k

entry	product (**8**)	isolated yield (%)[a]
a		61
b		60
c		64
d		58
e		51
f		54
g		75
h		52
i		51
j		41
k		56

[a] From thiaisatoic anhydride **1**.

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is now being explored toward the regioselective diversification of the diazepine amides and will offer a practical means for making novel libraries of these structurally diverse valuable compounds.

Experimental Section

Typical Experimental Procedure for 3,4-Dihydro-1*H*-thieno-[3,2-*e*][1,4]diazepine-2,5-dione (8) Synthesis. Thiaisatoic anhydride **1** (0.300 g, 1.78 mmol)[39] was treated with 18 mL of a 1.0 M solution of the corresponding α-amino acid in water. The suspension was heated at 40 °C under vigorous magnetic stirring for 8−72 h. Water was evaporated as much as possible. The residue was dissolved in 40 mL of acetic acid and heated under reflux for 1−12 h. The resulting solution was concentrated under reduce pressure and partitioned with water and EtOAc. The aqueous phase was extracted with EtOAc (30 mL × 3), and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, evaporated, and triturated with Et_2O to afford the corresponding thienodiazepinedione **8**, which was stored in stoppered flasks. The alcohol-containing **8h**,**i** and heterocyclic **8j**,**k** thienodiazepines products were partially soluble in water and therefore needed reversed-phase chromatographic purifications to afford higher yields.

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Supporting Information Available: Experimental details and ^1H and ^{13}C NMR spectral data for compounds **5**, **6**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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