Valuable Versatile Reactivity of Thiaisatoic Anhydrides: Expedient Solid-Phase Synthesis of Thieno[1,4]diazepine-2,5-diones

Yann Brouillette, Pascal Verdié, Jean Martinez, Vincent Lisowski*

Institut des Biomolécules Max-Mousseron, UMR 5247, CNRS, Universités Montpellier I et II, UFR de Sciences Pharmaceutiques et Biologiques, 15 Avenue Charles Flahault, 34093 Montpellier Cedex 5, France
Fax +33(4)67548654; E-mail: vincent.lisowski@univ-montp1.fr

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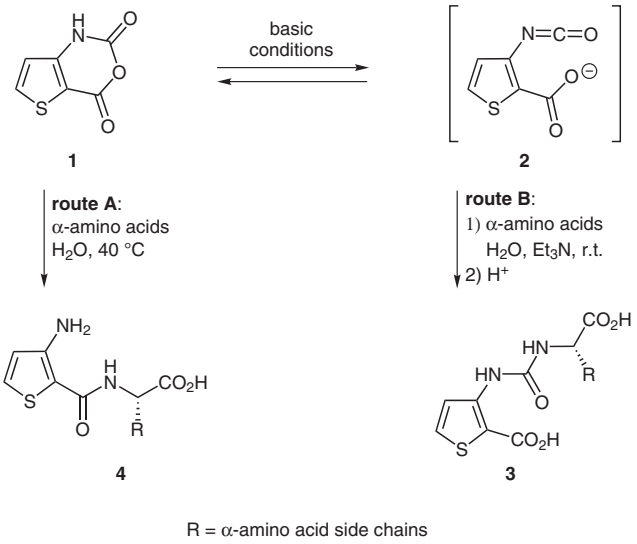
Abstract: An expedient route for the generation of substituted thieno[3,2-*e*][1,4]diazepine-2,5-dione analogues is described herein. It was demonstrated in solution that thiaisatoic anhydride and its N-alkylated equivalents react in opposite ways with amino acids in basic conditions. This versatile reactivity was used to develop an efficient strategy on solid support. Wang resin-bound thiaisatoic anhydride was coupled with N-alkylated α-amino acids, cyclocondensed and effectively cleaved from the polymer to provide a preliminary collection of thieno[3,2-*e*][1,4]diazepine-2,5-diones in 83–99% purity and 71–95% yield.

Key words: 1*H*-thieno[3,2-*d*][1,3]oxazine-2,4-dione, thiaisatoic anhydride, 3,4-dihydro-1*H*-thieno[3,2-*e*][1,4]diazepine-2,5-dione, thienodiazepines, solid-phase synthesis

The well-known diazepine-containing cholecystekinin (CCK) receptor antagonists (L364,718 and L365,260) were recently reported by our group to also inhibit the p38 mitogen-activated protein kinase (MAPK) activity with a possible interaction with its ATP binding site as demonstrated in dynamic docking studies.[1] The p38 MAP kinase has emerged as an attractive target for chemotherapy of rheumatoid arthritis and other inflammatory disorders, with several inhibitors currently undergoing clinical trials.[2–5] Therefore, part of our efforts is today directed towards the design of selective p38 MAPK heterocyclic-fused diazepine-based inhibitors. The diazepine scaffold is one of the classical examples of privileged structures which has proved its effectiveness in a number of pharmaceutical drugs and still continues to attract much interest today in medicinal chemistry.[6–12] In this context, the synthesis of combinatorial focused libraries is a valuable tool to explore structure–activity relationships and the main key for the success of such an approach is the use of parallel solid-phase organic synthesis. In this paper we report an expedient solid-supported synthesis of substituted thienodiazepinediones employing an N-polymer-bound thiaisatoic anhydride as starting material.

Since isatoic anhydrides[13] are versatile intermediates in medicinal and organic chemistry,[14–17] we recently reported regioselective ring opening of the isatoic anhydride isoster **1** by nucleophilic attack of α-amino acids to provide two libraries of optically pure thienylimidazolidinediones[18] and thienodiazepinediones.[19] In our previous studies, we demonstrated that 1*H*-thieno[3,2-*d*][1,3]oxazine-2,4-dione (**1**) reacts in an opposite way to isatoic anhydride when treated by α-amino acids (α-aa) in basic protic or aprotic conditions to afford ureidodiacid (**3**) by oxazine ring opening at the carbamic carbonyl (route B, Scheme 1).[18] Surprisingly, the selectivity of this nucleophilic attack can be satisfyingly reversed in favor of the carboxylic carbonyl to restore an isatoic anhydride-like reactivity in neutral protic conditions (amide **4**, route A, Scheme 1).[19] This unexpected result demonstrated that the basicity of the medium and the nature of the solvent have a great importance in the course of the reaction. Supported by a kinetic study of the reactions of amines with isatoic anhydride,[20] we hypothesized the existence of an isocyanate intermediate **2** for which the formation could be subordinated to ionization of oxazine **1** in basic conditions, directing the nucleophilic attack toward the formation of the ureidodiacid (**3**, Scheme 1).



Scheme 1 Known reactivity of anhydride **1** with α-amino acids

While many different solid-phase approaches exist for the benzodiazepine scaffold,[21] to the best of our knowledge, only one example has been described for the thiophene series in a five-step process from a resin-bound aldehyde.[22] The previously discussed postulate of the isocyanate intermediate formation in basic conditions led us to imagine that the alkylation of the thiaisatoic anhydride's nitrogen would impede the nucleophilic attack on the carbamic car-

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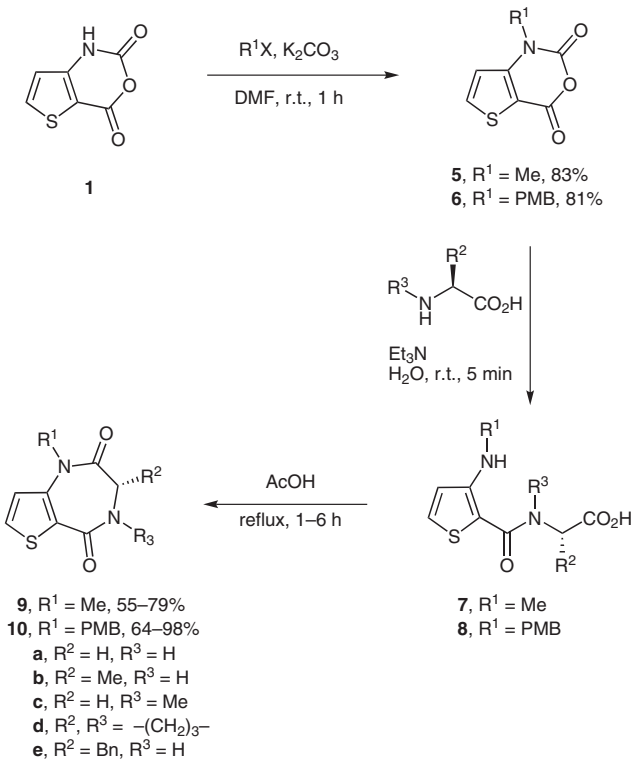
bonyl. Consequently, attaching thiaisatoic anhydride **1** on solid support by its nitrogen would allow its regioselective ring opening and afford the expected N-substituted thieno[3,2-*e*][1,4]diazepine-2,5-diones.

To validate our strategy, we first studied in solution the reactivity of the previously reported[23] *N*-methyl thiaisatoic anhydride (**5**) towards its reaction with cyclic (Pro), acyclic (Gly, Ala), bulky (Phe) and N-alkylated (Sar) amino acids in formerly described conditions (H_2O, 40 °C, 10 equiv α-aa).[19] As expected, a slow (8–24 h) but completely selective nucleophilic attack was observed to afford the amides **7** as detected by LC-MS. Reaction time can be drastically reduced to five minutes by a preactivation of the α-aa with Et_3N to afford at room temperature the same amides **7** with the same total selectivity (Scheme 2). Therefore, thiaisatoic anhydride **1** and its *N*-methyl counterpart **5**, submitted to the same aqueous basic conditions (route B, Scheme 1 for **1**; Scheme 2 for **5**), led to a complete opposite reactivity. The corresponding acquired amides **7** were then cyclized in refluxing AcOH for one to six hours to afford the thieno[3,2-*e*][1,4]diazepinedione analogues **9** (Scheme 2) in 55–79% yield from anhydride **5**. This favorable reactivity of *N*-methyl thiaisatoic anhydride (**5**), with no labile hydrogen, prompted us to continue our investigation for the application of this approach on solid support. Reactivity of the *N*-*p*-methoxybenzylthiaisatoic anhydride (**6**) was thus studied in solution as a mimic of the solid-supported Wang resin linker. Anhydride **6** was synthesized by alkylation of thiaisatoic anhydride **1** with *p*-methoxybenzyl chloride (PMBCl) in 81% yield, using an inorganic base (K_2CO_3) in anhydrous DMF at room temperature for one hour. The akin amides **8** were consequently obtained by ring opening of anhydride **6** with the same natural and synthetic α-amino acids in the presence of Et_3N in water at room temperature for five minutes. Addition of DMF drops was necessary for PMB-bearing compounds complete solubility. Accordingly, diazepines **10** were then obtained in 64–98% yield from anhydride **6** by cyclocondensation of amides **8** in refluxing AcOH for 4–6 h (Scheme 2). Interestingly, it was observed that in the case of N-alkylated amino acids such as Sar and Pro, heating in the previous step was sufficient to convert the precursors **7c**,**d** and **8c**,**d** into N-substituted diazepines **9c**,**d** and **10c**,**d**, respectively. As previously described for proline-containing peptides,[24] the N-alkylated amide bond of the pseudo-dipeptides **7c**,**d** and **8c**,**d** must have a *cis*/*trans* geometry which facilitates this cyclocondensation.

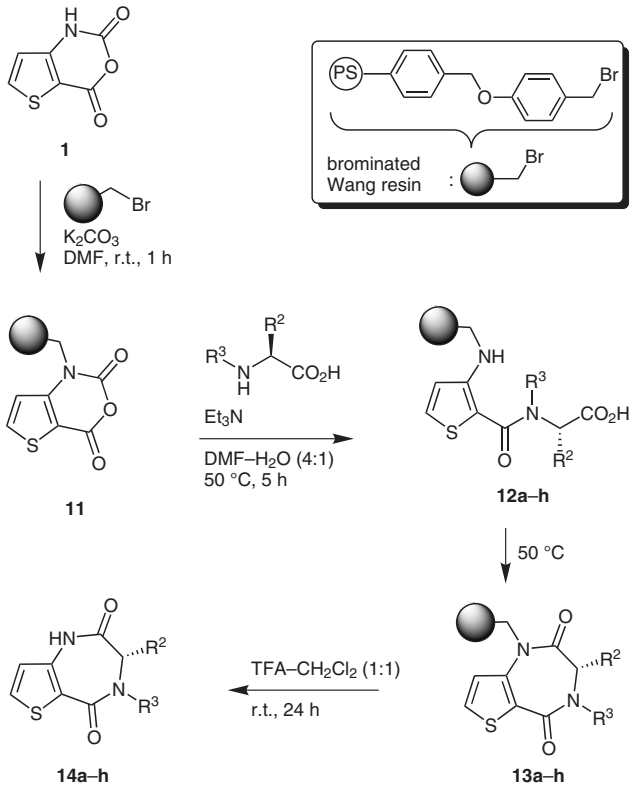
Our solution-phase protocol was adapted to the solid phase using the commercially affordable, widely used, and easily cleavable Wang resin.[25,26] Resin-bound thiaisatoic anhydride **11** was synthesized by attachment of anhydride **1** to 4-(bromomethyl)phenoxymethyl polystyrene (Wang bromide resin)[27–29] using K_2CO_3 in DMF at room temperature for one hour (Scheme 3).[30,31] Qualitatively, anchoring of the loaded resin **11** was indicated by IR spectroscopy of resin samples. Sharp indicative signals were observed for C=O stretching bands, respectively, at 1774



Scheme 2 Reactivity of N-substituted thiaisatoic anhydride

and 1721 cm^{-1}; moreover, the C–Br band at 592 cm^{-1} disappeared. Quantitatively, the loading of the resin was ascertained by treating a measured amount of the resin-bound anhydride **11** twice with 50% TFA in CH_2Cl_2 at room temperature for 30 minutes and evaluating its recovery. Resin-bound amides **12** were produced by treatment of anhydride **11** with a variety of amino acids (500 mol%) in the presence of Et_3N (1000 mol%), in a mixture of H_2O–DMF (1:4). The combination of DMF and water was necessary to allow decent swelling of the polystyrene resin and complete solubility of the amino acids. Glycine, alanine, and proline analogues as well as phenylalanine were chosen to attack the resin-bound anhydride **11**. Azetidine-2-carboxylic and pipecolic acids were also used to study the ring constraint of the following cyclocondensation. It was observed that heating at 50 °C was necessary for the total conversion of anhydride **11** into the corresponding resin-bound amide **12**.

Treatment of resin-bound anhydride **11** with natural α-aa (where R^3 = H), such as Ala (R^2 = Me) and Phe (R^2 = Bn), allowed the formation of the supported amides **12**. However, the solid-phase cyclocondensation to the diazepines using acidic conditions (AcOH, r.t. to 80 °C) or coupling reagents (such as DIC–HOBt, BOP–HOBt, HBTU–DIEA, and EDC) proved to be unsuccessful. Cleavage from the resin using TFA–CH_2Cl_2 (1:1) at room temperature for 30 minutes only delivered the uncyclized acids. In spite of this failure, the formation of the corresponding diazepines was pursued in solution by heating the acidic resin filtrates at reflux for 24 hours. Nonetheless, this alternative solid-phase approach with α-aa (where

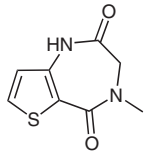
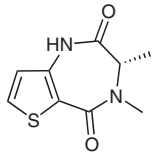
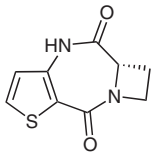
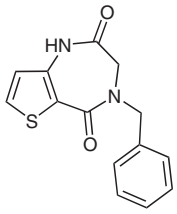
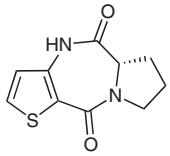
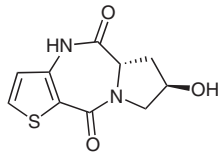
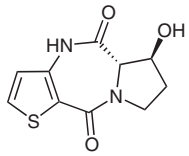
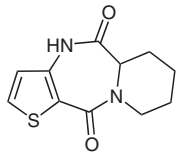


Scheme 3 Solid-phase synthesis of thienodiazepinedione analogues

R^3 = H) did not give higher yields and purities than our previously reported solution-phase protocol.[19] On the other hand, in accordance with our previous solution study with N-alkylated α-aa, simply heating the reaction mixtures of the solid-supported amides **12a–h** (where R^3 = alkyl) at 50 °C in DMF–H_2O (4:1) for five hours directly afforded the corresponding resin-bound thienodiazepines **13a–h**. These observations demonstrated that partial *cis* conformation induced by N-alkylation ($R^3 \neq$ H) is essential for a cyclization in nonacidic conditions, in both solution- and solid-phase approaches.

Cleavage of the products from the resin was effected by treating resins **13a–h** twice with TFA–CH_2Cl_2 (1:1) at room temperature for 30 minutes. A mixture of NH- and *N*-*p*-hydroxybenzyl thienodiazepines was obtained as inferred by LC-MS analysis. The N-hydroxybenzylated diazepines were presumed to originate from an anomalous cleavage of the benzyl ether bond through which *p*-hydroxybenzyl bromide was attached to Merrifield resin.[32–34] Although the use of a 2-(4-bromomethylphenoxy)ethyl polystyrene resin or HF cleavage are suggested to avoid formation of hydroxybenzylated byproduct arising from breakdown of the linker, these approaches are expensive or necessitate special equipment. In our case, the prolonged stirring in TFA–CH_2Cl_2 (1:1) for an extra 23 hours afforded the diazepines **14** as sole product after filtration of the resin, evaporation of the filtrate, and trituration with an Et_2O–pentane (1:1) mixture. In this manner, optically pure thienodiazepinediones **14** of high purity (83–99%) were obtained in 71–95% yield (Table 1).

Table 1 N-Substituted Thienodiazepinediones **14a–h** SPOS

Entry	Structure	Yield (%)[a]	Purity (%)[b]
1		95	92
2		90	83
3		80	99
4		95	90
5		86	98
6		79	83
7		88	95
8		71	86

[a] Based on ascertained loading of resin **11**.
[b] As determined by reversed-phase HPLC with monitoring at 214 nm.

These results prove the effectiveness of this methodology with cyclic and acyclic N-alkylated α-aa, and allow a consequent diversification (R^2, R^3) to design potential MAPK inhibitors.

In conclusion, we demonstrated that thiaisatoic anhydride **1** and its N-alkylated derivatives react in an opposite manner with α-amino acid nucleophiles in basic conditions, providing evidence of the isocyanate **2** equilibrium. This

finding was used to prepare in solution a library composed of ten N-substituted thieno[3,2-*e*][1,4]diazepine-2,5-dione analogues **9** and **10** in 55–98% yield.[35,36] Transposition of this protocol to the solid-phase allowed the initial synthesis of a series of eight 1*H*-thieno[3,2-*e*][1,4]diazepine-2,5-dione analogues **14** in purities and yields of 83–99% and 71–95%, respectively, in a three-step process.[37] The potential of this protocol is now being explored for preparing large libraries of structurally diverse thienodiazepines that may have beneficial uses in the MAPK inhibition field.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(35) **Typical Experimental Procedure for the Ring Opening of Thiaisatoic Anhydrides 5 and 6**
A stirring suspension of *N*-*p*-methoxybenzylthieno[3,2-*d*][1,3]oxazine-2,4-dione (**6**, 7.00 g, 24.22 mmol) and the corresponding α-amino acid (26.64 mmol) in H_2O (100 mL) was treated with Et_3N (7.43 mL, 53.29 mmol) at r.t. for 30 min. Drops of DMF can be added to favor complete solubility. The resulting solution was partitioned with EtOAc. The aqueous phase was extracted with EtOAc (3 × 40 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated to afford the corresponding product **8**.
Acid **8e**: white solid, mp 68–70 °C; $[\alpha]_D^{20}$ –18.7 (*c* 0.3, DMSO). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.57 (m, 2 H), 7.46 (d, 1 H, *J* = 5.4 Hz), 7.26 (m, 5 H), 7.22 (d, 2 H, *J* = 7.3

Hz), 6.87 (d, 2 H, *J* = 7.1 Hz), 6.74 (d, 1 H, *J* = 5.4 Hz), 4.52 (q, 1 H, *J* = 8.0), 4.31 (d, 2 H, *J* = 5.5), 3.71 (s, 3 H), 3.10 (d, 2 H, *J* = 8.0 HZ). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 173.4, 164.6, 158.3, 154.5, 138.3, 131.8, 129.1, 129.0, 128.4, 128.1, 126.3, 117.6, 113.9, 100.6, 55.0, 53.6, 47.5, 36.1. HRMS: *m/z* calcd for [M + H$^+$] $C_{22}H_{23}N_2O_4S$: 411.1379; found: 411.1360.

(36) **Typical Experimental Procedure for the Synthesis of Thieno[3,2-*e*][1,4]diazepinediones 9 and 10**

A solution of acid **8** in AcOH was magnetically stirred at reflux for 1–6 h. The resulting solution was concentrated under reduce pressure and triturated with Et_2O to afford the corresponding thienodiazepine **10**. This procedure can be directly applied to the crude mixture of acids **7** and **8**, after evaporation of volatile material, to attain a one-flask protocol directly to thienodiazepines **9** and **10**. The workup remains the same.

(*S*)-1-(4-Methoxybenzyl)-3-benzyl-3,4-dihydro-1*H*-thieno[3,2-*e*][1,4]diazepine-2,5-dione (**10e**): orange solid, mp 66–68 °C; $[\alpha]_D^{20}$ +27.5 (*c* 0.1, DMSO). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.50 (d, 1 H, *J* = 3.5 Hz), 7.81 (d, 1 H, *J* = 5.3 Hz), 7.37–7.20 (m, 6 H), 7.03 (d, 2 H, *J* = 8.5 Hz), 6.81 (d, 2 H, *J* = 8.6 Hz), 5.23 (d, 1 H, *J* = 15.5 Hz), 4.89 (d, 1 H, *J* = 15.5 Hz), 4.17 (m, 1 H), 3.68 (s, 3 H), 3.24 (dd, 1 H, *J* = 13.8, 5.3 Hz), 2.98 (dd, 1 H, *J* = 13.5, 9.0 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 168.6, 162.8, 158.4, 140.4, 137.8, 130.8, 129.5, 128.9, 128.4, 128.2, 126.5, 124.9, 122.7, 113.9, 55.0, 55.0, 48.6, 34.3. HRMS: *m/z* calcd for $C_{22}H_{21}N_2O_3S$ [M + H$^+$]: 393.1273; found: 393.1298; R_f = 0.4 ($CHCl_3$–EtOAc, 4:1).

(37) **General SPS Procedure**

Wang bromide resin (5.0 g, 1.6 mmol/g) was swollen in 50 mL of DMF, treated with anhydride **1** (2.03 g, 12.0 mmol) and K_2CO_3 (2.21 g, 16.0 mmol) for 1 h at r.t. and sequentially washed with H_2O, DMF, and CH_2Cl_2 to afford the beige resin-bound anhydride **11**. Thienodiazepine resin **13** was synthesized by treating a suspension of resin **11** (0.400 g, 0.56 mmol) in DMF–H_2O (10 mL, 4:1) with the respective amino acid (500 mol%) and Et_3N (1000 mol%) for 5 h at 50 °C, and then washed with DMF, H_2O, and CH_2Cl_2. Thienodiazepines **14** were obtained by treating diazepine resin **13** (0.400 g, 0.52 mmol) with TFA–CH_2Cl_2 (8 mL, 1:1) for 24 h.

(*S*)-3,4-Dihydro-3,4-dimethylthieno[3,2-*e*][1,4]diazepine-2,5-dione (**14b**): beige solid, mp 191–194 °C; $[\alpha]_D^{20}$ +51.6 (*c* 0.1, DMSO). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.91 (s, 1 H), 7.78 (d, 1 H, *J* = 5.1 Hz), 6.80 (d, 1 H, *J* = 5.1 Hz), 4.20 (q, 1 H, *J* = 6.9 Hz), 2.93 (s, 3 H), 1.34 (d, 3 H, *J* = 7.0). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 169.2, 162.5, 138.1, 131.4, 128.5, 121.3, 54.7, 30.8, 12.6. HRMS: *m/z* calcd for $C_8H_{11}N_2O_2S$ [M + H$^+$]: 211.0541; found: 211.0575.